Real-world effectiveness and adverse events caused by ACE inhibitors and ARBs for reduction in cardiovascular events with validation against the ONTARGET trial

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Declarations

I, Paris Jade Baptiste, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in this thesis.

Signed: P Baptiste

Date: 4th October 2023

Use of published work

One paper has been published, one paper is under revision and two papers plan to be submitted to peer-reviewed journals. Work for these papers were carried out as part of the PhD and during the period of registration. Paris Baptiste was lead author, prepared protocols, drafts of manuscripts, and carried out data analysis. Co-authors contributed to the study design question, provided advice and revised drafts prepared by Paris Baptiste. Work published is under the CC-BY license.

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Abstract

Background

Cardiovascular disease is a leading cause of death globally and medications to prevent cardiovascular outcomes are prescribed based on evidence from randomised controlled trials. However, generalisability of trial results to at-risk groups, who are often underrepresented in trials, is unknown.

Methods

This thesis used trial replication methods applied to the ONTARGET trial to validate findings from electronic health record data before extending inferences to trial underrepresented and excluded groups.

Results

Using a cohort of 137,155 patients in a propensity-score—weighted analysis conducted in the UK Clinical Practice Research Datalink (CPRD) GOLD I obtained comparable treatment effects to the ONTARGET trial for ARB compared to ACEi. After benchmarking findings to the ONTARGET trial results using a pre-specified validation criteria and aided with an increased sample size with more diverse characteristics, I extended findings to females, those aged ≥75 years and patients with chronic kidney disease and obtained consistent results. Consistent results were observed for Black and South Asian ethnic groups using CPRD Aurum. I observed a small increase in angioedema reported among Black individuals compared to White individuals. However, I observed ARBs were associated with a decreased risk of developing angioedema over a maximum follow-up of 5.5 years compared to ACEi in both Black and White ethnic groups despite clinical guidance recommending an ARB in preference of an ACEi in Black patients only. The replicability of the dual therapy comparison using an operational definition to capture dual users was explored and also led to comparable results.

Conclusion

When studying the use of ARBs and ACEi in high-risk individuals for the prevention of cardiovascular outcomes, applying trial replication methods to electronic health record data can add confidence to findings and provide evidence on treatment effects and risk in key at-risk groups who are often underrepresented in trials.

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Abbreviations

ACE	Angiotensin-converting enzyme
ACEi	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
BMI	Body-mass index
BP	Blood pressure
CAD	Coronary artery disease
CCB	Calcium channel blocker
CI	Confidence interval
CKD	Chronic kidney disease
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
EHR	Electronic health records
GFR	Glomerular filtration rate
GP	General practitioner
HES	Hospital Episode Statistics
HF	Heart failure
HR	Hazard ratio
IMD	Index of Multiple Deprivation
ITT	Intention-to-treat
MI	Myocardial infarction
ONS	Office for National Statistics
PAD	Peripheral artery disease
PS	Propensity score
RAAS	renin-angiotensin-aldosterone-system
RCT	Randomised controlled trial
RR	Relative risk
SBP	Systolic blood pressure
SIDIAP	The Information System for Research in Primary Care
UTS	up-to-standard

Chapter 1. Background information and rationale

Chapter summary

- Cardiovascular disease (CVD) is a leading cause of death globally and those with chronic kidney disease (CKD), older adults and Black and South Asian ethnic groups are at an increased risk.
- Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are commonly prescribed in the UK for treatment of conditions such as hypertension, diabetic nephropathy, CKD and to reduce the risk of cardiovascular events.
- Evidence for the effectiveness of these medications is often based on randomised controlled trials (RCTs) which can lack diversity and are not always representative of the population receiving these medications in everyday care.
- The use of observational data with validation against RCTs can bridge the gap in evidence, which can then be used to inform clinicians and policy makers ensuring patients are being prescribed optimal treatment.
- This thesis describes the application of trial replication methods applied to the ONTARGET trial in UK routinely collected data. As I was able to confirm replicability, analysis was extended to explore the effectiveness and risk of ARBs and ACEi in key at-risk groups who are often underrepresented in trials.

1.1 Cardiovascular disease

1.1.1 What is it?

CVD is a term for conditions that affect the heart or blood vessels.[1] It is a leading cause of death worldwide and responsible for nearly 18 million deaths globally each year.[2] Some of the main types of CVD are:

- Coronary heart disease – caused by a block or lack of blood flow to the heart and includes angina, heart attacks and heart failure among other conditions.
- Strokes and transient ischaemic attacks – caused by lack of blood flow to the brain.
- Peripheral artery disease (PAD) - caused by a block in the arteries to the limbs.

More than 4/5 of cardiovascular deaths are due to heart attacks or strokes.[2] Several behavioural factors increase the risk of CVD and include unhealthy diet, lack of exercise, smoking and alcohol use. These behavioural factors can later lead to hypertension, raised blood glucose, raised blood lipids, high body-mass index (BMI) and obesity. Addressing these factors can reduce the risk of cardiovascular events and for conditions like hypertension, type 2 diabetes and high blood lipids, treatment is required.

1.1.2 Specific risk groups

In addition to behavioural risk factors, specific groups of individuals are at an increased risk of developing CVD. CVD is most common in individuals aged over 50 years and risk increases with age. Both men and women are at risk of CVD. Men usually have a higher incidence than women, though women are thought to have a higher mortality.[3] Women are known to develop CVD at a later age than men due to the protective effects of oestrogen against coronary artery disease in pre-menopausal women.[4] During and after menopause, less oestrogen is produced in a woman's body increasing the risk of the coronary arteries narrowing.[5] Due to the later onset of CVD in women, they may be more likely to have other comorbidities, which could be a reason for higher mortality in women compared to

men. Ethnicity is also associated with CVD risk, with South Asian and Black African or African Caribbean individuals at an increased risk in the UK,[4] which is believed to be in part due to the increased risk of hypertension and type 2 diabetes in these ethnic groups. Those with CKD are also at an increased risk,[6] clinically defined as patients with glomerular filtration rate (GFR) <60 mL/min/1.73m^2 on at least two occasions 90 days apart.[7] This PhD will use the definition of CKD as GFR<60 mL/min/1.73m^2 without the time element to increase power.

1.2 ACE inhibitors and ARBs

1.2.1 What are they and how do they work?

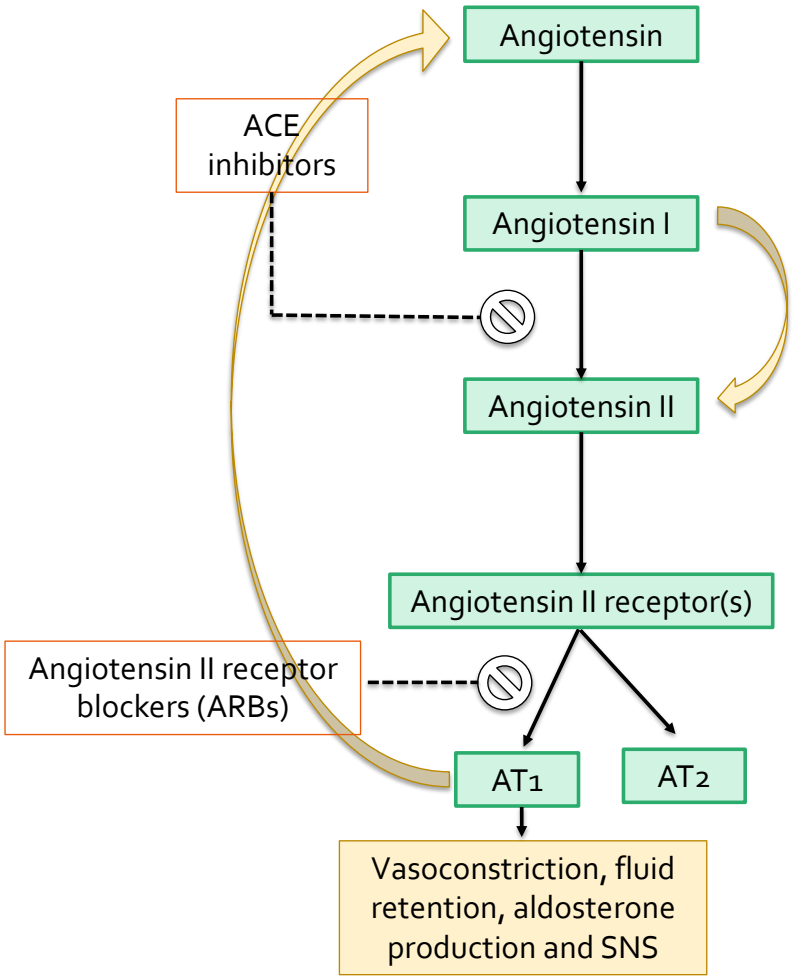
The renin-angiotensin-aldosterone-system (RAAS) is the system that regulates blood pressure and fluid balance.[8] Drugs affecting the RAAS are commonly used for treatment of conditions such as hypertension, diabetic nephropathy, CKD, congestive heart failure, and myocardial infarction (MI) and to reduce the risk of cardiovascular events occurring. These drugs are prescribed based on evidence from RCTs. The two main groups of RAAS-inhibitors are ACEis and ARBs. ACEi work by blocking the conversion of the angiotensin I hormone to angiotensin II, a substance which narrows blood vessels in the RAAS.[8] They also block the breakdown of bradykinin which also helps to contribute to the widening of blood vessels. However the increase in bradykinin is thought to be related to a side effect of ACEi-induced cough.[9] ARBs reduce the angiotensin II hormone, by blocking the angiotensin II receptors; this is displayed graphically in Figure ***1.1***. Both reduce blood pressure by widening or dilating blood vessels which further leads to reduction of risk of CVD and damage to the heart and kidneys.

Common types of ACEis and ARBs are displayed in Table ***1.1***.

Table 1.1 Common types of ACEi and ARB drugs, their licensed indications and percentage used in England in 2022/23.

ACEi		ARB	
Drug	**licensed indications**	**Drug**	**licensed indications**
Captopril	- Hypertension - HF - Diabetic nephropathy	Azilsartan	- Hypertension
Enalapril	- Hypertension - HF	Candesartan	- Hypertension - HF with impaired left ventricular systolic function when ACE inhibitor not tolerated or with an ACE inhibitor - Migraine prophylaxis
Fosinopril	- Hypertension - Congestive HF	Eprosartan	- Hypertension
Imidapril	- Hypertension - Hypertension in patients with HF, angina or cerebrovascular disease	Irbesartan	- Hypertension - Renal disease in hypertensive type 2 diabetes
Lisinopril	- Hypertension - Short term treatment following MI - Renal complications of diabetes - HF	Losartan	- Diabetic nephropathy - Chronic HF when ACE inhibitors unsuitable - Hypertension
Perindopril	- Hypertension - HF - Prophylaxis of cardiac events following MI or revascularisation in stable CAD	Olmesartan	- Hypertension
Quinapril	- Hypertension - HF	Telmisartan	- Hypertension - Prevention of CV events in patients with CVD or diabetes and target-organ damage
Ramipril	- Hypertension - HF - Prophylaxis after MI in patients with evidence of HF - Prevention of CV events in patients with CVD or diabetes and additional RF for CVD - Nephropathy	Valsartan	- Hypertension - HF when ACE inhibitors cannot be used or with an ACE inhibitor when a beta-blocker cannot be used - MI with left ventricular failure or left ventricular systolic dysfunction
Trandolapril	- Hypertension - Prophylaxis after MI in patients with left ventricular dysfunction		

ACEi		ARB	
Drug	**licensed indications**	**Drug**	**licensed indications**
HF= heart failure; MI= myocardial infarction; CV= cardiovascular disease; CAD= coronary artery disease.			



Notes: SNS= sympathetic nervous stimulation.

Figure 1.1 Diagram to show how angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers act on the renin-angiotensin-aldosterone system

1.2.2 Key trials of ACEi and ARB

The first RCT which explored the effects of an ACEi, specifically enalapril, on mortality in people with congestive heart failure (HF) was the CONSENSUS I trial (Co-operative North Scandinavian Enalapril Survival Study) in 1987.[10] This was a small study, including only

253 patients but showed promising signs of the cardio-protection of ACEis and later led to two large-scale trials in the same population.[11] These were SOLVD (Studies of Left Ventricular Dysfunction) 1 and 2 which explored the effects of enalapril on mortality and hospitalisation for congestive HF, and showed consistent results.[12, 13] Since then many other large-scale trials have been carried out exploring the effects of ACEis in different at-risk populations, including patients with hypertension, diabetes, and diabetic nephropathy, as well as patients post-MI. The effects of ACEis were also studied among high-risk cardiovascular patients in three landmark trials; HOPE (Heart Outcomes Prevention Evaluation),[14] EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease),[15] and PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition), and showed evidence of cardio-protection of ACEis.[16] These trials are summarised in Table ***1.2***.

The ELITE (Evaluation of Losartan in the Elderly) trial was one of the first studies to explore the comparative effects of ARBs and ACEis in 1997.[17] It compared losartan (ARB) to captopril (ACEi) in 722 patients with HF aged over 65 years. The study explored both renal safety and cardiovascular efficacy outcomes and showed a reduction in death or hospitalisation for HF in patients treated with losartan, but this was not significant (risk reduction: 32% (95% CI: -4%, 55%)). The risk reduction was shown to be due to a decrease in all-cause death (risk reduction: 46% (95% CI: 5%, 69%)). The results led to a larger study, the ELITE II trial in 2000 which examined the effects on morbidity and mortality in HF patients. The primary endpoint was all-cause death. The trial showed inconsistent results and showed no significant differences between the two medications (HR: 1.13 (95% CI: 0.95, 1.35). Significantly fewer patients in the losartan group discontinued due to adverse events compared to the captopril group (9.7% vs 14.7%).[18] Therefore, it was concluded that ARBs may be a beneficial treatment option when ACEis are not well-tolerated. Other large trials

supported this conclusion, including the landmark CHARM (Candesartan in Heart Failure Assessment of Mortality and Morbidity) program, which included 7601 patients in 2004.[19] The primary outcome in the trials included in the CHARM program was a composite of cardiovascular death or chronic heart failure hospitalisation. The CHARM Alternative Trial studied the effects of candesartan compared to placebo in patients with left ventricular ejection fraction who were intolerant of ACEis and showed candesartan reduced cardiovascular mortality and morbidity, HR for the primary outcome was 0.77 (95% CI: 0.67, 0.89). Discontinution rates were similar in the candesartan and placebo groups (30% vs 29%).[20] The CHARM Added Trial studied the effects of adding candesartan to patients already receiving an ACEi.[21] It showed some evidence to support the use of dual RAAS blockade but it has been suggested that results may have been influenced by low treatment doses (HR 0.85 (95% CI: 0.75, 0.96)).[11]

The results of CHARM led to two large-scale parallel studies, ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint) and TRANSCEND (Telmisartan Randomised Assessment Study in ACE-I Intolerant Subjects with CV Disease) in 2004 and 2008, respectively.[22-24] TRANSCEND studied the effects of telmisartan compared to placebo in high-risk cardiovascular patients who were intolerant of an ACEi and found further evidence to support the findings of CHARM Alternative. ONTARGET was the larger of the two trials and is summarised in the section 1.3.

Table 1.2 Summary of key trials for ACEis in high-risk cardiovascular patients

Trial	Year	Population	Intervention	Sample size	Result
HOPE (Heart Outcomes Prevention Evaluation Study)	2000	High-risk patients with vascular disease or diabetes without HF	Ramipril vs placebo	9297	Ramipril significantly reduced the risk of death, MI, stroke (RR 0.78 (95% CI: 0.70, 0.86)).
EUROPA (European Trial on Reduction of Cardiac events with Perindopril in Stable Coronary artery Disease)	2003	Patients with coronary heart disease without HF	Perindopril vs placebo	12,218	CV mortality, nonfatal MI and resuscitated cardiac arrest reduced by perinodopril use (RR reduction: 20% (95% CI: 9%, 29%)).
PEACE (Prevention of Events with ACE Inhibition Trial)	2004	Patients with stable coronary heart disease and preserved left ventricular function and receiving standard therapy	Trandolapril vs placebo	8290	No evidence addition of trandolapril provides benefit of CV death, MI or coronary revascularisation but rate of CV events lower than previous trials (HR 0.96 (95% CI: 0.88, 1.06)). Among patients assigned placebo proportion of cardiovascular deaths were 47% compared to 63% and 59% in the HOPE and EUROPA trials.

1.2.3 Underrepresentation of at-risk groups in trials

Despite the evidence provided by large-scale studies which have influenced the use of ARBs and ACEis in reducing the risk of CVD, most had limited inclusion of at-risk groups. The HOPE and EUROPA trials presented no ethnicity data and no data on the effects among

patients with CKD.[14, 15] The PEACE trial excluded patients with serum creatinine >177μmol/L which could have led to underrepresentation of those with CKD. In addition females of child-bearing potential were also excluded.[16] Despite displaying ethnicity data in the PEACE trial, ethnicity minority groups were largely underrepresented with 92% of participants being White.[16] Around a quarter of the patients included in these three studies were female and mean age was around 66 years, with 11% of participants in the PEACE trial aged over 75 years.[16]

Similarly for the CHARM study, 90% of participants were White, with 25% being female.[19]

TRANSCEND was a smaller study with 5926 patients included. However, the trial had a more even distribution of females (43.3% randomised to receive telmisartan) but included only 16% of participants aged ≥75 years and <2% of African origin.[24] The ONTARGET trial offered limited improvements in participant diversity which is discussed in section 1.3. Both ONTARGET and TRANSCEND excluded patients with serum creatinine >265μmol/L, which led to underrepresentation of patients with CKD included in the trials.

Trials which influence treatment guidelines and prescribing patterns often have a lack of representation of patients receiving these drugs in everyday care, particularly females, Black and South Asian ethnic groups, those with CKD and older adults. This is particularly an issue for those from Black ethnic groups, where Black/non-Black is a determinant of hypertension treatment choice in the UK.[25] Ethnic minority groups, particularly those from Black origin are often poorly represented in CVD trials.[26] One study carried out a meta-analysis of 28 RCTs, that had a primary outcome of CVD, of these 28 trials, only 16 had data regarding ethnicity and only 8 presented subgroup analyses by ethnicity. Due to this underrepresentation, guidance is often based on extrapolated evidence from trials which are not representative of the target population.

1.3 ONTARGET

1.3.1 Background

ONTARGET included patients across the globe who were ≥55 years old with a diagnosis of either coronary artery disease, peripheral artery disease, cerebrovascular disease, or diabetes mellitus with evidence of end-organ damage. Due to the large body of evidence of benefit already available, those with HF were excluded.[13, 20, 23]

The trial had two main treatment exposures, telmisartan 80 mg daily (ARB) and a combination of both telmisartan (ARB) and ramipril (ACEi), which were both compared to ramipril alone, 10 mg daily. The primary objectives of the trial were to determine (1) if the combination of the two therapies was more effective than ramipril alone; and (2) if telmisartan alone was at least as effective as ramipril alone.[23] The primary composite outcome was cardiovascular related death, MI, stroke or hospitalisation for HF.

1.3.2 Methods

Existing users of any ACEi or ARB were eligible to enter the trial if they met the inclusion criteria and were able to discontinue these medications. This was tested in a 3-week run in period where patients were blinded and were given:

1 Ramipril 2.5 mg + matching telmisartan placebo 40 mg for 3 days, then

2 Ramipril 2.5 mg + telmisartan 40 mg for 7 days, then

3 Ramipril 5 mg + telmisartan 40 mg for 11 to 18 days

Compliance was then checked before patients were randomised to receive either ramipril, telmisartan or dual therapy.

Primary study outcomes were reviewed by a central adjudicator and a random 10% of confirmed events were reviewed by the Events Adjudication Committee. All serious adverse events were reported to the Project Office and those deemed to be serious, related to the study

medications and unexpected were reported to the study sponsor and regulatory authorities.[23] These were all also reviewed by the independent Data and Safety Monitoring Board.

The study used a non-inferiority boundary based on results of the HOPE trial[27] where ramipril was compared to placebo and gave a HR=0.78 for the same primary composite outcome used in ONTARGET. Using a percentile of this estimate, it was calculated that if the upper limit of the 95% confidence interval for the hazard ratio of telmisartan vs. ramipril was below 1.13, this would ensure telmisartan retained at least half the effect of ramipril.[22] This comparison along with the test of superiority for dual therapy compared to ramipril alone was carried out using a Cox proportional hazards model.

1.3.3 Results

Recruitment started in 2001 and closed in July 2003.[23] By May 2004, 25,620 patients had been randomised by a computerised voice-activated telephone call, from 730 centres in 40 countries. Patients were followed for 3.5-5.5 years and had a median follow-up of 56 months.[22] ~70% of participants included had hypertension at baseline. The study had a mean age of 66 years, including only 15% participants aged ≥75 years. Like previous studies females and ethnic minority groups were underrepresented. 24% of patients had CKD[28] and mean creatinine was 94 μmol/L at baseline and those with creatinine >265 μmol/L were excluded. Key characteristics are shown in Table 1.3.

Table 1.3 Baseline characteristics from ONTARGET

Characteristic	**Ramipril (N=8576)**	**Telmisartan (N=8542)**	**Dual therapy (N=8502)**
Age - year	66.4 ± 7.2	66.4 ± 7.1	66.5 ± 7.3
Systolic BP – mm Hg[1]	141.8 ± 17.4	141.7 ± 17.2	141.9 ± 17.6
Diastolic BP - mm Hg[1]	82.1 ± 10.4	82.1 ± 10.4	82.1 ± 10.4
Body-mass index	28.1 ± 4.5	28.1 ± 4.6	28.0 ± 4.5

Characteristic	Ramipril (N=8576)	Telmisartan (N=8542)	Dual therapy (N=8502)
Female sex – no. (%)	2331 (27.2)	2250 (26.3)	2250 (26.5)
Cholesterol – mmol/l	4.9 ± 1.1	4.9 ± 1.1	5.0 ± 1.2
Triglycerides – mmol/l	1.7 ± 1.1	1.7 ± 1.1	1.7 ± 1.1
Glucose - mmol/l	6.7 ± 2.6	6.7 ± 2.5	6.7 ± 2.6
Creatinine - μmol/l	93.5 ± 22.8	93.8 ± 22.8	93.8 ± 22.8
Potassium – mmol/l	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.5
Ethnic group – no. (%)			
Asian	1182 (13.8)	1172 (13.7)	1167 (13.7)
Arab	102 (1.2)	106 (1.2)	106 (1.2)
African	206 (2.4)	215 (2.5)	208 (2.4)
European	6273 (73.1)	6213 (72.7)	6222 (73.2)
Native or aboriginal	747 (8.7)	756 (8.9)	728 (8.6)
Other	64 (0.7)	77 (0.9)	69 (0.8)
Missing	2 (<0.1)	3 (<0.1)	2 (<0.1)
Clinical history – no. (%)			
CAD	6382 (74.4)	6367 (74.5)	6353 (74.7)
MI	4146 (48.3)	4214 (49.3)	4189 (49.3)
Angina pectoris			
Stable	3039 (35.4)	2958 (34.6)	2960 (34.8)
Unstable	1257 (14.7)	1296 (15.2)	1264 (14.9)
Stroke or TIA	1805 (21.0)	1758 (20.6)	1779 (20.9)
PAD	1136 (13.2)	1161 (13.6)	1171 (13.8)
Hypertension	5918 (69.0)	5862 (68.6)	5827 (68.5)
Diabetes	3146 (36.7)	3246 (38.0)	3220 (37.9)
Microalbuminuria[2]	929 (13.1)	923 (13.2)	929 (13.3)
Previous procedures – no. (%)			
CABG	1862 (21.7)	1920 (22.5)	1893 (22.3)
PTCA	2527 (29.5)	2476 (29.0)	2434 (28.6)
Smoking status – no. (%)			
Current smoker	1062 (12.4)	1062 (12.4)	1101 (12.9)
Past smoker	4463 (52.0)	4468 (52.3)	4345 (51.1)
Medication – no. (%)			
Statin	5234 (61.9)	5294 (62.0)	5255 (61.8)
Beta-blocker	4847 (56.5)	4860 (56.9)	4876 (57.4)
Aspirin	6473 (75.5)	6469 (75.7)	6461 (76.0)
Clopidogrel/ticlopidine	927 (10.8)	966 (11.3)	931 (11.0)
Antiplatelet agent	6903 (80.5)	6926 (81.1)	6898 (81.1)
Diuretic	2454 (28.6)	2359 (27.6)	2351 (27.7)
CCB	2821 (32.9)	2787 (32.6)	2864 (33.7)

Characteristic	Ramipril (N=8576)	Telmisartan (N=8542)	Dual therapy (N=8502)
Notes: no. (%) are number (percent); x ± x are means ± standard deviation BP=blood pressure; CAD=coronary artery disease; MI=myocardial infarction; TIA=transient ischaemic attack; CABG=coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty; CCB=calcium-channel blocker. Ethnic group was self-reported. [1]A total of 13,386 patients had systolic blood pressure of more than 140 mm Hg. [2]Percentages are out of 21,074 patients who underwent baseline urinary analysis: 7073 in the ramipril group, 7013 in the telmisartan group, and 6988 in the dual-therapy group.			

Table 1.4 Results from the ONTARGET study for primary, secondary, and other outcomes

Outcome	**Ramipril (N=8576)**	**Telmisartan (N=8542)**	**Dual Therapy (N=8502)**	**Telmisartan vs Ramipril**	**Dual Therapy vs Ramipril**
	N (%)			*HR (95% CI)*	
Primary composite outcome[1]	1412 (16.5)	1423 (16.7)	1386 (16.3)	1.01 (0.94-1.09)	0.99 (0.92-1.07)
MI[2]	413 (4.8)	440 (5.2)	438 (5.2)	1.07 (0.94-1.22)	1.08 (0.94-1.23)
Stroke[2]	405 (4.7)	369 (4.3)	373 (4.4)	0.91 (0.79-1.05)	0.93 (0.81-1.07)
Hospitalisation for HF[2]	354 (4.1)	394 (4.6)	332 (3.9)	1.12 (0.97-1.29)	0.95 (0.82-1.10)
CV-related death	603 (7.0)	598 (7.0)	620 (7.3)	1.00 (0.89-1.12)	1.04 (0.93-1.17)
Main secondary outcome	1210 (14.1)	1190 (13.9)	1200 (14.1)	0.99 (0.91-1.07)	1.00 (0.93-1.09)
Non-CV-related death	411 (4.8)	391 (4.6)	445 (5.2)	0.96 (0.83-1.10)	1.10 (0.96-1.26)
All-cause death	1014 (11.8)	989 (11.6)	1065 (12.5)	0.98 (0.90-1.07)	1.07 (0.98-1.16)
Renal impairment[3]	871 (10.2)	906 (10.6)	1148 (13.5)	1.04 (0.96-1.14)	1.33 (1.22-1.44)
All dialysis, doubling, death[4]	1159 (13.4)	1147 (13.4)	1233 (14.5)	1.00 (0.92, 1.09)	1.09 (1.01, 1.18)
Doubling of creatinine[4]	140 (1.6)	155 (1.8)	166 (2.0)	1.11 (0.88, 1.39)	1.20 (0.96, 1.50)

Notes: N (%)=number (percent); HR= hazard ratio; CI=confidence interval; MI=myocardial infarction; HF=heart failure; CV=cardiovascular.

Primary composite outcome: cardiovascular-related death, MI, stroke, or hospitalisation for heart failure.

Main secondary outcome: composite of cardiovascular-related death, MI, or stroke.

Telmisartan vs ramipril was test of non-inferiority.

Dual therapy vs ramipril was test of superiority.

[1]Patients can have multiple events. The number of events were 2058 (24.0%) in the ramipril group, 2042 (23.9%) in the telmisartan group, and 2000 (23.5%) in the dual-therapy group.

[2]Patients could have multiple events in this category. This category includes both fatal and non-fatal events.

[3]No specific definitions were used. A determination of renal impairment was based on the clinical investigator's report of an event that led to the discontinuation of a study drug.

[4]Renal outcomes studied in the trial.

Results under an intention-to-treat (ITT) analysis are shown in Table 1.4. When investigating the first primary objective, dual therapy was shown not to be significantly better than ramipril alone, HR 0.99 (95% CI: 0.92, 1.07), in reducing the risk of CVD outcomes of interest and was also shown to significantly increase the risk of hypotension, syncope, renal dysfunction and hyperkalaemia. When looking at the second objective, the study showed that the upper boundary for the confidence interval (1.09) for the relative risk when comparing telmisartan to ramipril was significantly lower than the predefined non-inferiority boundary (1.13) and telmisartan was less likely to cause angioedema when looking at safety outcomes. Despite "conserving around 95% of the benefits of ramipril over placebo", as the authors state, the lower boundary gave evidence that telmisartan was not superior to ramipril, HR 1.01 (95% CI: 0.94, 1.09).[22] An analysis of renal outcomes showed dual therapy increased the risk of the primary composite renal endpoints of dialysis, doubling of creatinine, or death, HR 1.09 (95% CI: 1.01, 1.18) compared to the ramipril alone. This increase in risk was not observed for telmisartan compared to ramipril, HR 1.00 (95% CI: 0.92, 1.09).[29, 30] Telmisartan was better tolerated than ramipril with fewer patients discontinuing treatment due to cough (93 vs 360, telmisartan vs ramipril). Under the per-protocol (PP) analysis, for the primary outcome, telmisartan compared to ramipril and dual therapy compared to ramipril gave relative risks of 1.0 (95% CI: 0.92-1.09) and 0.98 (95% CI: 0.90-1.07), respectively.

Subgroup analyses were carried out and showed similar results for the each of the three treatment groups. There was no evidence of an interaction for any of the subgroups studied with males compared to females and age group comparisons (categorised as <65 years, ≥65 to <75 years and ≥75 years) giving P= 0.68 and P= 0.65 respectively for dual therapy compared to ramipril alone. Similarly, comparing telmisartan to ramipril p-values were 0.82 and 0.75 across sex and age comparison groups, respectively. Interactions for presence of cardiovascular disease, systolic blood pressure (SBP) (categorised as: ≤134 mm Hg, >134 to

≤150 mm Hg and >150 mm Hg) and diabetes were also tested and only SBP showed weak evidence of an interaction for telmisartan compared to ramipril (*P*= 0.10). Despite this, the study had low power to observe heterogeneity with only 26.8% females and 14.5% participants aged ≥75 years included in the trial.[22]

1.3.4 Strengths and limitations

Despite ONTARGET being a large global trial that was the first to demonstrate evidence for equivalent treatment effects of ARBs and ACEis for reduction in cardiovascular risk in high-risk patients, it had some limitations. Due to the particular focus on telmisartan, the generalisability of trial results to all ARBs is unknown. Despite approximately 49.6% of the world's population being female in 2004, with ~50.6% in North America and ~51.3% females in the European Union,[31] only 26.7% of people enrolled into the trial were female. Similarly, most of the trial population were made up of European ethnic groups, with <2.5% of people enrolled being from an African ethnic group in each of the 3 arms. In the US alone, 11.6% of the population are of Black or African American ethnicity based on the 2021 Census Bureau's American Community Survey (ACS).[32] A study analysed ONTARGET trial data and explored the risk of cardiovascular outcomes for telmisartan vs ramipril in Asians (including South Asian, Chinese, Japanese, Malay or Other Asian) vs non-Asians and showed equivalent treatment effects.[33] However, similar analysis has not been carried out for those from Black ethnic groups. Despite ONTARGET including a subgroup analysis based on age and sex the reliability of these results is questionable due to the low power as described above. Therefore, the true comparative effects of these medications in females, those aged ≥75 years and those from ethnic minority groups is unknown. Furthermore, the differences between Black ethnicity in the UK compared to the US, and specifically the ONTARGET trial categorising as African, also presents further questions on the generalisability of the results to Black individuals in the UK. This is also an issue for the

analysis conducted by Dans et al., exploring effects in Asian vs non-Asian individuals.[33] Despite the study showing equivalent treatment effects among Asian individuals, consistent with the trial, it was underpowered to explore if there was treatment effect heterogeneity among the individual Asian groups included, particularly among South Asian individuals who have an increased risk of CVD in the UK.

The trial included a subgroup analysis by CKD status (CKD: GFR<60 mL/min/1.73m^2 vs. no CKD: GFR≥60 mL/min/1.73m^2 at baseline) for the composite renal outcome of dialysis, doubling of creatinine or death and showed no evidence of heterogeneity for both telmisartan and dual therapy compared to ramipril alone.[30]. A post hoc analysis studied treatment heterogeneity for CKD for the risk of cardiovascular and renal outcomes. This was compared between dual users and users of ramipril or telmisartan (but not in combination) and failed to show evidence of heterogeneity, but the sample was small.[28] Time-limited follow-up means long-term treatment effects and adverse events were unable to be assessed in the trial population. Despite these limitations the trial provided key evidence to inform clinical decisions and change treatment recommendations.

1.3.5 Conclusions

Based on the findings from the ONTARGET trial in October 2009, telmisartan was approved as a treatment for cardiovascular risk reduction in patients intolerant to ACEis aged ≥55 years and with a high risk of cardiovascular events, after already having approval as an antihypertensive drug.

The trial also demonstrated no added benefit of dual therapy use and an increase in adverse events. Further meta-analysis of eight cardiovascular trials showed similar results indicating no evidence of superiority of dual therapy and an increase in adverse events.[34] However, there was some evidence that dual therapy could reduce heart failure admissions.[35] Due to lack of individual patient level data the meta-analysis was unable to conduct subgroup

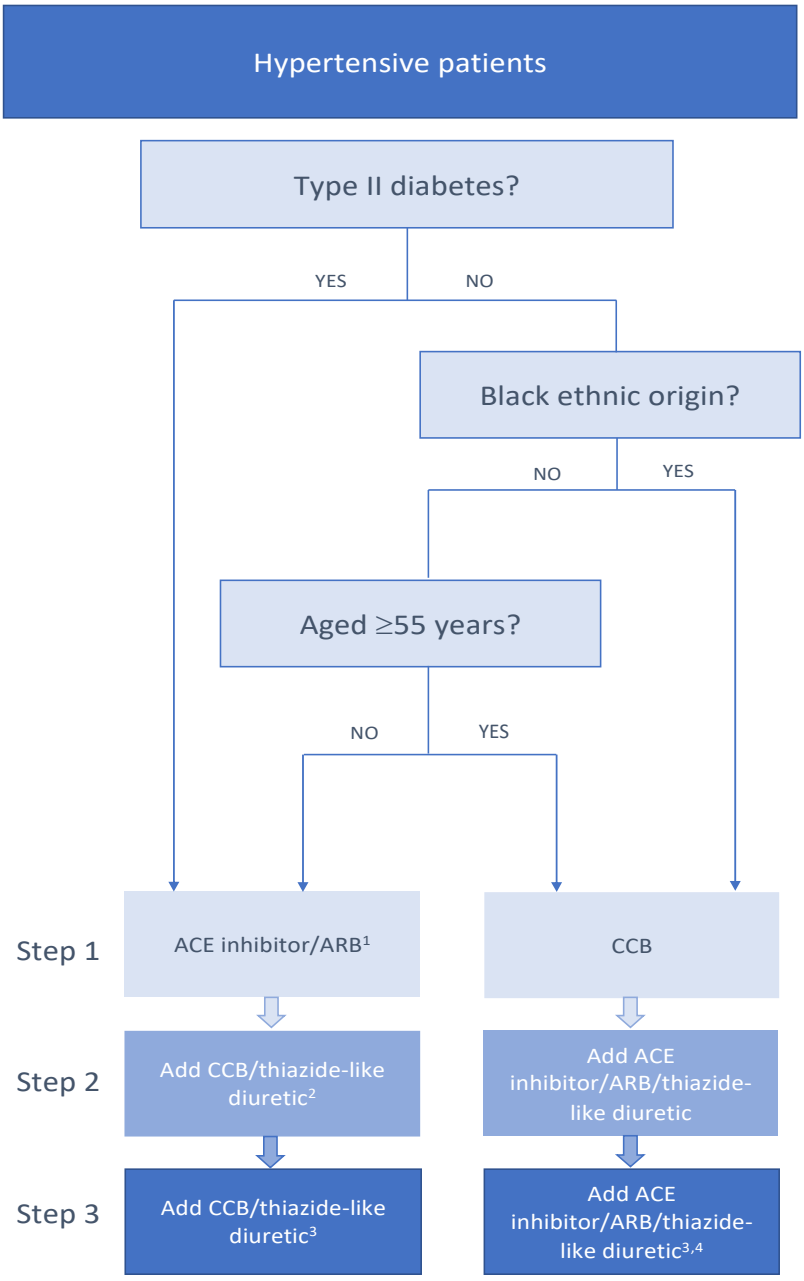
analyses for underrepresented groups. Based on the evidence from ONTARGET and the ALTITUDE and VA-Nephron-D studies, treatment prescribing changed and dual therapy was no longer recommended.[36] These conclusions are based on a population that may not be representative of the patients treated with these drugs in routine care and evidence on whether these results extend to trial-underrepresented groups is lacking.

Despite the ONTARGET study being large and geographically diverse it is not clear that drug effectiveness can be generalised to all populations due to the underrepresentation of key at-risk groups as shown in Table ***1.3*** and discussed in section 1.3.4. Therefore, gaps in the evidence provide a rationale to explore these clinical questions, as well as methodological issues related to trial replication techniques applied to this therapeutic area in this PhD.

1.4 ACE inhibitor and ARB use in the UK

As displayed in Table ***1.1***, two types of RAAS blockers licensed in the UK for prevention of cardiovascular events in high-risk patients are ramipril and telmisartan based on findings from the ONTARGET trial. By contrast all commonly used ACEis and ARBs are licensed for treatment of hypertension, which can in turn reduce the risk of cardiovascular endpoints. In addition to ACEi and ARB, other antihypertensives such as calcium channel blockers (CCBs), and diuretics are often used to treat hypertension. In England and Wales treatment for hypertension follows guidelines set out by the National Institute for Health and Care Excellence (NICE).[25] To achieve target blood pressure, multiple treatments are often considered in a stepwise manner (Figure ***1.2***), with anyone who is type 2 diabetic treated with an ACEi or ARB as first-line treatment regardless of age or ethnicity and those who are not type 2 diabetic but of Black African or African-Caribbean family origin (subsequently referred to as 'Black') receiving a CCB as first-line treatment. People who are not Black or are type 2 diabetic and aged <55 years are recommended to receive an ACEi or ARB and those aged ≥55 years also receiving a CCB. ARBs are recommended to be offered instead of

ACEi where ACEis are not tolerated, and where CCB are not tolerated thiazide-like diuretics are offered instead of CCBs.[37] In 2011 this guidance was updated to recommend an ARB in preference to an ACEi in Black populations based on evidence from the US ALLHAT trial which found an increased risk of angioedema in users of an ACEis compared to other antihypertensives (excluding ARBs). Significant differences were observed for lisinopril (ACEi) vs chlorthalidone (CCB). The study included 11,792 Black participants which made up 35% of the trial population with angioedema occurring in 49/33,357 (0.1%) of total participants.[38, 39]



Notes: [1]ARB preferred if Black ethnic origin; [2]thiazide-like diuretic preferred if no evidence of heart failure; [3]Add whichever was not added in Step 2; [4]either ACE inhibitor or ARB given but not given in combination; CCB= calcium channel blocker; Black ethnic origin= Black African or African-Caribbean family origin.

Figure 1.2 Graphical display of current treatment guidance for hypertension management (NG136) published 2019, updated 2022

1.5 Bridging the gap in evidence using trial replication methods

1.5.1 Benefits of RCTs

Large, well conducted, and analysed RCTs are the most reliable form of evidence for drug efficacy and safety. However, such studies can be time-consuming, expensive, and difficult to conduct. Since the length of follow-up in trials is limited, information on risk of medications may only be monitored over a relatively short period of time, therefore events that occur after this can be missed. In addition to this, older studies in particular can have limited inclusion of some subgroups and conclusions are drawn on only a small subset of the population. Therefore, general practitioners (GPs) choice of prescriptions in the wider population, largely informed by such trials, can lack information on the treatment effectiveness and risk in those patients that are being prescribed the medication.[40] It could be unethical and financially unappealing for pharmaceutical companies to now carry out larger trials, more representative of the general population, in key drugs that have been licenced for a long time. Therefore, the most reasonable approach to take would be to confirm this information using additional data sources, such as electronic health record (EHR) data.

1.5.2 What can observational research add?

Observational studies using existing routinely collected anonymised healthcare data can provide a quicker way to answer questions on treatment effectiveness compared to RCTs. Vast amounts of information are increasingly available based on routinely collected patient records from GP practices that are subsequently de-identified for research use in data sources such as the Clinical Practice Research Datalink (CPRD), which is largely representative of the UK population.[41] However, research using observational data can give rise to multiple sources of bias and confounding due to lack of randomisation, missing data, and misclassification of exposures and covariates. Ways to optimally address these biases in real-world settings are being investigated vigorously and include trial replication methodology.

1.5.3 Trial replication methodology

Trial replication is a method increasingly being used to validate results from observational studies against target trials, also known as “benchmarking”. This can provide confidence in the robustness of methods and data quality being harnessed using observational data to help answer causal questions. Replication of existing trials has been explored previously by Wing et al, Powell et al. and others in various therapeutic areas.[42-47] However, at the time of writing only two studies have explored these methods for antihypertensives in the area of cardiovascular disease. Both Fralick et al.,[45] and Wang et al.,[48] aimed to replicate the ONTARGET trial results in US health insurance claims data. However only the study by Fralick et al., led to comparable results and neither study included the dual therapy arm in analyses.[45] In comparison to longitudinal EHR data like CPRD, claims data are known to have some limitations. These include more restricted patient follow up to capture events of interest and often less available patient medical history. The data within CPRD may hold some advantages for trial replication within this therapeutic area compared to claims data, including capture of all previous patient medical history, longer average patient follow up and representativeness, since the National Health Service (NHS) is a health service free at the point of delivery. I therefore aimed to demonstrate the robustness of trial replication methods for both single and dual therapy within CPRD using the ONTARGET example.

There are a variety of approaches to trial replication and ability to replicate a trial may vary by therapeutic area but commonly the aim is to create a trial-eligible cohort in an observational data source. This is often achieved by applying trial inclusion and exclusion criteria and in some cases, where access to trial data is available, an additional step of matching observational exposure groups to trial arms can help ensure characteristics of the trial-eligible cohort are directly comparable to the target trial (the RCT).

Propensity scores or other similar methods are then used to ensure characteristics are balanced across exposure groups in the observational trial-eligible cohort.

By using a large healthcare database to create a sample representative of the trial, power is increased to study treatment effects in groups that were poorly represented, so it can be examined if trial results are generalisable to the population receiving such drugs. By relaxing some trial criteria, treatment effects in subgroups excluded from trials can be studied whilst still being confident methods have minimal bias and confounding by validating results from the trial-eligible cohort against the target trial.

Chapter 2. Aims and objectives

2.1 Research Aim 1

To investigate the comparative effectiveness of ARBs and ACEis for cardiovascular event reduction in populations excluded from or underrepresented in trials

- **Objective 1**

  Explore the replicability of the ONTARGET trial in a trial-eligible cohort using UK routinely collected data

- **Objective 2**

  Explore the comparative effectiveness and risk of ARBs and ACEis on cardiovascular event reduction among groups that would have been excluded from or were underrepresented in the ONTARGET trial

2.2 Research Aim 2

To investigate optimal methods to implement trial replication techniques in this therapeutic area

- **Objective 1**

  To assess the impact of choice of statistical approach to address confounding on the ability to replicate trial results in this therapeutic area

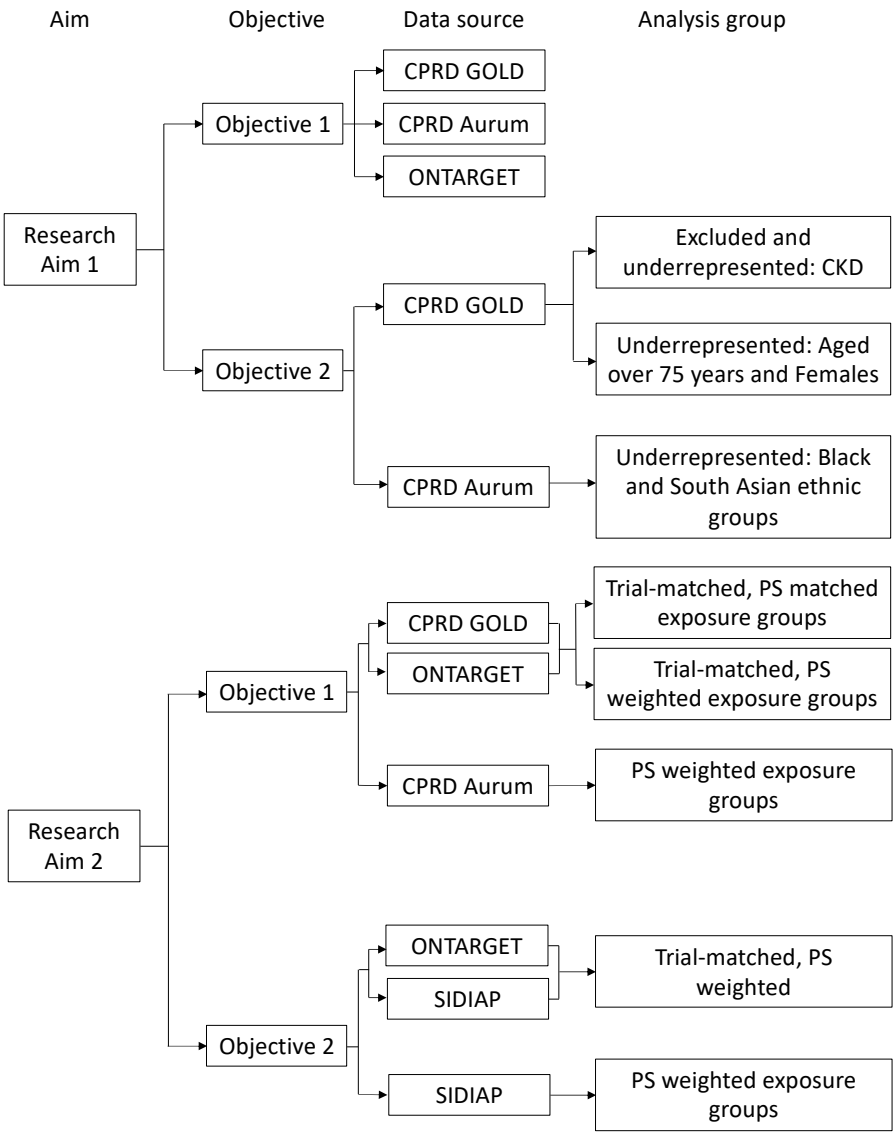
- **Objective 2**

  To explore whether trial replication methodology for this therapeutic area is transportable to alternate data sources (such as routinely collected data from outside of the UK)

2.3 Rationale

The results from this thesis will bridge the gap in evidence for effectiveness and risk of ARBs and ACEis at preventing cardiovascular outcomes in key at-risk populations. In addition to

this it will provide evidence on the feasibility of trial replication methods applied to UK electronic health records in the therapeutic area of cardiovascular disease and whether methods can be extended to dual therapy treatment arms.



Notes: Trial-matched= 1:1 matched EHR patients to ONTARGET trial participants, prior to balancing between exposure groups using PS weighting or PS matching. CPRD: UK Clinical Practice Research Datalink; SIDIAP: The Information System for Research in Primary Care, Catalonia.

Figure 2.1 Visual diagram of aims and objectives with corresponding data sources and resulting analysis groups

2.4 Organisation of thesis

This thesis is presented in research paper style format. Four manuscripts have been drafted as a result of this PhD. Each subsequent chapter included in this thesis is summarised below:

Chapter 3: Includes results from a literature search performed to identify (1) observational studies which have applied trial replication methodology and understand how these methods have been applied and (2) identify current evidence from observational studies on the comparative effectiveness of ARBs and ACEis at preventing cardiovascular outcomes.

Chapter 4: Describes the data sources used throughout this thesis.

Chapter 5: Outlines the methods used to address the research aims and objectives in this thesis including a peer-reviewed protocol paper published in BMJ Open.

Chapter 6: Includes a drafted manuscript submitted to the American Journal of Epidemiology, that I am currently responding to peer-reviewers' comments on. This research paper presents results from addressing Research Aim 1, exploring the replicability of the ONTARGET trial in CPRD GOLD and the results from extending the findings to the underrepresented at-risk groups of females, those aged ≥75 years and those with CKD (defined as GFR<60 mL/min/1.73m^2). A second drafted manuscript is included in this chapter which presents results from analysis conducted in CPRD Aurum, extending findings to Black and South Asian ethnic groups, who were also underrepresented in the trial. Finally, this chapter summarises the results from applying different trial replication techniques to find the optimal method, addressing Research Aim 2- Objective 1.

Chapter 7: Comprises a third drafted manuscript presenting results from replication of the ONTARGET trial dual therapy analysis.

Chapter 8: Presents work addressing Research Aim 2- Objective 2, including results from replication of the ONTARGET trial in the SIDIAP (the Information System for Research in Primary Care) database consisting of routinely-collected healthcare records for patients in Catalonia.

Chapter 9: The final chapter summarises and discusses the overall findings of this thesis in relation to the background, rationale, and implications of this work.

Chapter 3. Literature review

Chapter summary

- This chapter describes the methods applied and results from two focused literature searches.
- The objectives of these literature searches were to address two specific questions of interest. These were:
  1. In which settings has trial replication methodology been applied and how has it been implemented?
  2. What does current observational evidence conclude on the comparative effectiveness of ARBs and ACEis on preventing cardiovascular outcomes and how reliable is this evidence?

3.1 Literature search 1: Trial replication studies

3.1.1 Methods

I searched and screened both titles and abstracts using the search term in section 3.1.1.1 to identify observational studies which have applied trial replication methods. A full-text review was then carried out of the initially selected studies. The search was conducted by myself only, without a second reviewer.

3.1.1.1 Search terms and databases searched

Due to the relatively new use of these methods, a broad search term was used and was searched in PubMed and MEDLINE. Due to the terms ‘trial replication’ and ‘trial emulation’ being interchangeably used both were included in the search term. The search was carried out in October 2019 and was updated in February 2023. In February 2023 I included additional

terms to broaden the search based on terms such as “benchmarking” increasingly being used to describe trial replication studies. In February 2023 the updated search consisted of combining the initial search term and additional search term by “OR”.

Initial search term:

(“trial?replication” OR “trial?emulat*”)

Additional search term:

((("validated against"[tiab:~0]) OR ("validat* findings against"[tiab:~0]) OR ("validat* results against"[tiab:~0]) OR ("validation against"[tiab:~0]) OR ("bench?mark* against"[tiab:~0]) OR ("bench?mark* findings against"[tiab:~0]) OR ("bench?mark* results against"[tiab:~0])) AND (("RCT"[Title/Abstract]) OR ("randomi?ed control* trial"[tiab:~0]) OR ("randomi?ed trial"[tiab:~0]))))

3.1.1.2 Inclusion and exclusion criteria

Observational studies which included trial replication methodology were included. Studies returned that did not explicitly replicate a RCT and were instead an emulation of a hypothetical target trial, results from a RCT or studies without a clinical outcome were excluded. Additionally, any studies without published results, including protocols, guidelines, or reviews were excluded.

3.1.2 Results

The results from the literature search in February 2023 returned 206 studies, 197 studies were excluded due to not meeting the criteria after assessing the title and abstract. Despite not being identified in the literature search using the search terms in section 3.1.1.1 a replication of the ONTARGET trial by Fralick et al.[45] was identified when exploring literature related to the ONTARGET trial. This is summarised in Table ***3.1*** and additionally described in section

3.1.2.2, describing similarities and differences between the replication by Fralick et al.[45] and the replication in this PhD project.

3.1.2.1 Identified publications

Reasons for exclusion are shown in Figure ***3.1***. Nine publications were identified as meeting the inclusion and exclusion criteria after a full text review. Two related publications by Wing et al. were identified, and results were combined and displayed together in Table ***3.1*** at study entry 6.[49, 50]

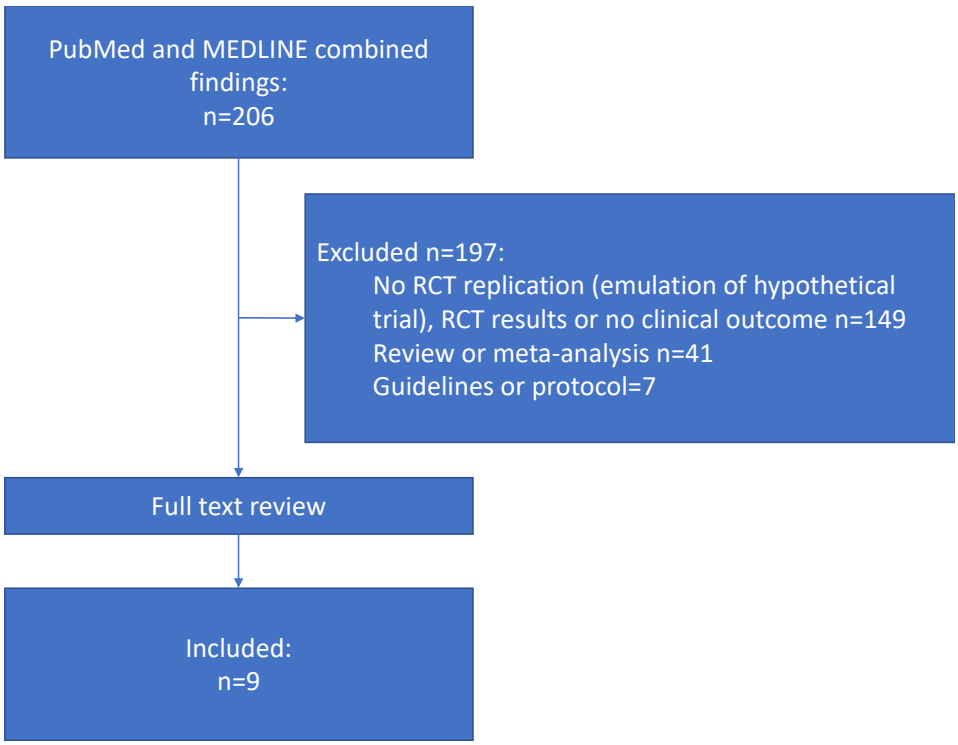


Figure 3.1 Flow chart of identified trial replication publications meeting inclusion and exclusion criteria from literature search 1.

Table 3.1 Identified trial replication studies from literature search 1.

Study no., authors, year	Target trial and therapeutic area	Population and data source, country	Statistical methods and pre-specified criteria	Success of replication
(1) Yiu et al., 2021[51]	CLEAR trial - secukinumab vs ustekinumab, psoriasis	BADBIR, a multicentre longitudinal pharmacovigilance register of patients with moderate to severe psoriasis in the UK and Republic of Ireland 2007-2019 Patients aged ≥18 years, had chronic plaque psoriasis and had at least 1 record of Psoriasis Area and Severity Index (PASI) of 12 or higher before their initiation to the two drugs of interest	PS 1:1 matched analysis and PS-weighted analysis Regulatory agreement (study replicates direction and statistical significance of RCT finding), estimate agreement (study estimate lies within 95% CI of the effect estimate in the RCT), standardised difference used to confirm replicability	Outcome: achieving psoriasis area and severity index of 2 or lower after 12 months of therapy. Trial result: RR 1.24 (95% CI: 1.11, 1.37); Replication result (PS-matched): RR 1.55 (95% CI: 1.19, 2.01); Replication result (PS-weighted): RR 1.28 (95% CI: 1.06, 1.55) Regulatory agreement and estimate agreement
(2) Merola et al., 2022[52]	PARSIFAL trial – fulvestrant and Palbociclib vs letrozole and palbociclib, breast cancer	Ontada iKnowMed (iKM) EHR database derived from outpatient oncology practices in the US Oncology Network (USON Women aged ≥18 years with diagnosis of metastatic breast cancer and no evidence of prior treatment for metastatic disease Combination therapy identified as drugs prescribed on the same day	Multiple imputation with chained equations, 50 imputed datasets. Model adjusted for confounders. For first imputed dataset, KM plot for the inverse probability of treatment weighted study population for comparison to overall survival curve of PARSIFAL trial. Standardised differences used to compare log HR of overall survival (>1.19) chosen as marker of incompatibility	Outcome: death. Trial result: HR 1.00 (95% CI: 0.68, 1.48); Replication result: HR 1.07 (95% CI: 0.86, 1.35) Similar estimates and reached same conclusion

Study no., authors, year	Target trial and therapeutic area	Population and data source, country	Statistical methods and pre-specified criteria	Success of replication
(3) Matthews et al., 2022[53]	TASTE trial – percutaneous coronary intervention (PCI) with and without thrombus aspiration in patients with (trial nested in SWEDEHEART registry), ST-elevation myocardial infarction	SWEDEHEART registry, national Swedish registry data. 2007-2016 (excluded June 2010 – March 2013 as period of TASTE) Eligibility of TASTE trial applied	In data source patients were randomised to treatment strategies so proceeded as if randomised After benchmarking to TASTE, extended follow up and explored effects in underrepresented subgroups Results informally benchmarked to 1-year results from TASTE	Outcome: death. Trial result: RR 0.94 (95% CI: 0.78, 1.15); replication result: RR 1.09 (95% CI: .96, 1.24) Results in emulated trial and TASTE were compatible with a similar range of hazard and risk.
(4) Matthews et al., 2021[54]	VALIDATE trial –bivalirudin vs heparin (nested in SWEDEHEART), ST-Segment and Non-ST-Segment	SWEDEHEART registry, national Swedish registry data. 2012-2014 (precedes period of VALIDATE) Eligibility of VALIDATE trial applied	Inverse probability weighting and outcome regression followed by standardisation used for adjustment No pre-specified replication criteria	Composite outcome: death, MI or major bleeding. Trial result: HR 0.96 (95% CI: 0.83, 1.10); replication result (weighted): RR 0.93 (95% CI: 0.77, 1.12); replication result (standardised): RR 0.92 (95% CI: 0.74, 1.14) Comparable for composite, risk of death or myocardial infarction

Study no., authors, year	Target trial and therapeutic area	Population and data source, country	Statistical methods and pre-specified criteria	Success of replication
	elevation myocardial infarction in patients on modern antiplatelet therapy			Could not replicable results for the outcome of bleeding which is suggested may be a result of intractable confounding early in follow-up or the inability to precisely emulate the trial's eligibility criteria
(5) Boyne et al., 2021[55]	IDEA trial, colon cancer	Dataset derived through record linkage of various provincial administrative databases via the Oncology Outcomes research initiative, Canada 2004-2015 Patients aged ≥18 years diagnosed with stage III colon cancer who initiated adjuvant chemotherapy at oncology clinics in Alberta, Canada. Eligibility of IDEA trial applied Different treatment strategy compared to that in IDEA but aligns with how IDEA trial findings are implemented in clinical practice (capecitabine + oxaliplatin chemotherapy or adjuvant 5-fluorouracil/leucovorin + oxaliplatin)	Patient duplicates were created and a copy of each was assigned to each treatment strategy then copies artificially censored when deviated from the assigned treatment strategy or discontinued earlier than assigned duration of chemotherapy. Time-varying inverse probability of censoring weights (IPCWs)	Outcome: overall survival Trial result: HR 0.96 (95% CI: 0.85, 1.08); replication result: HR 0.96 (95% CI: 0.43, 2.14) Obtained estimates that were similar in magnitude to the trial

Study no., authors, year	Target trial and therapeutic area	Population and data source, country	Statistical methods and pre-specified criteria	Success of replication
(6) Wing et al., 2021[49, 50]	TORCH trial – fluticasone propionate (FP)-salmeterol (SAL) vs SAL and FP-SAL vs placebo, chronic obstructive pulmonary disease (COPD)	UK Clinical Practice Research Datalink (CPRD) Patients aged between 40-80 with COPD registered in CPRD between 2000-2017 TORCH trial criteria applied. Trial-like selection with multiple potential follow-up periods available for inclusion.	1:1 matched to TORCH participants to get exposure groups and propensity-score matching between exposure groups. Additional analysis omitted trial matching step. Placebo selected as people eligible in CPRD who were not prescribed FP-SAL comparisons made between FP-SAL vs SAL and FP-SAL vs no FP-SAL. Pre-specified replicability criteria: FP-SAL vs SAL: 1. Effect size clinically comparable with TORCH, RR between 0.81 and 0.95; 2. 95% CI excluding 1. FP-SAL vs no FP-SAL: 1. RR between 0.65 and 0.9; 2. 95% CI excluding 1 After confirmation of replication, results extended to excluded subgroups	Outcome: exacerbation rate. FP-SAL vs SAL: Trial result: RR 0.88 (95% CI: 0.81, 0.95); replication result: RR 0.85 (95% CI: 0.74, 0.97) FP-SAL vs no FP-SAL: Trial result: RR 0.75 (95% CI: 0.69, 0.81); replication result: RR 1.30 (95% CI: 1.19, 1.42) Similar results for active-comparator analyses but unable to replicate placebo-controlled results. Results from omitting trial matching step gave similar results (FP-SAL vs SAL: RR 0.87 (95% CI: 0.81, 0.94)).
(7) Rizvi et al., 2017[56]	Hope for the Chronically Suicidal Patient – Dialectical behaviour therapy (DBT) vs general	50 adults aged aged ≥18 years with borderline personality disorder enrolled in a DBT training clinical program between 2010 and 2015.	Chi-squared test to compare rates of SA and NSSI from 6 months before and 6 months during treatment. For benchmarking compared effects sizes (Cohen's d) of pre-post symptom changes for BPD symptoms, global	Results comparable in effect size to the benchmarked RCT

Study no., authors, year	Target trial and therapeutic area	Population and data source, country	Statistical methods and pre-specified criteria	Success of replication
	psychiatric management		psychopathology, and depression symptomatology	
(8) Franklin et al., 2021[44]	N/A – initiative replicating multiple RCTs for cardiovascular outcomes of antidiabetic or antiplatelet medications. Results from first 10 replications.	US claims data from commercial and Medicare payers (Optum Clinformatics 2004-2019, IBM MarketScan 2003-2017, subset of Medicare Parts A, B and D 2011-2017). New users of exposure of interest identified. Trial criteria applied.	For placebo-controlled trials active comparator selected as a proxy for placebo. 1:1 propensity-score matching to control for >120 preexposure confounders. Success criteria for each replication prespecified as 3 binary agreement metrics: (1) regulatory agreement (study replicates direction and statistical significance of RCT); (2) estimate agreement (replication HR within 95% CI of RCT); (3) hypothesis tests for difference in findings using standardised differences.	Regulatory conclusions equivalent in 6/10 studies. Replications achieved HR within 95% CI of corresponding RCT in 8/10 studies. Either regulatory or estimate agreement success criteria fulfilled in 9/10 studies. 9/10 replications had standardised difference between effect estimates of replication and RCT of <2.
(9) Fralick et al., 2018[45]	ONTARGET trial – telmisartan vs ramipril, cardiovascular disease	Patients newly prescribed telmisartan or ramipril in 2002-2009 in US MarketScan health care database. ONTARGET trial criteria applied.	Propensity-score matching between exposure groups. No pre-specified replication criteria.	Outcome: composite of myocardial infarction, stroke, or hospitalisation for heart failure Trial result: HR 1.01 (95% CI: 0.94, 1.09) (included cardiovascular-related death in composite outcome); replication result: HR 0.99 (95% CI: 0.85, 1.14) Obtained estimates that were similar in magnitude to the trial

Study no., authors, year	Target trial and therapeutic area	Population and data source, country	Statistical methods and pre-specified criteria	Success of replication
Notes: Study 9, by Fralick et al.,[45] not identified using literature search terms described in 3.2.1.1				

3.1.2.2 Findings

A summary of the nine identified studies are presented in Table *3.1*. Studies identified applied methods to various therapeutic areas including skin conditions, specifically psoriasis, cancer, psychiatric management, COPD and cardiovascular disease. The work by Wing et al.,[49, 50] was the only identified study applying trial replication methods to UK routinely-collected data. A number of studies used US claims data and two used Swedish registry data. Publications identified benchmarked findings to the target trial after first applying trial criteria. Four out of the nine identified studies used propensity-score matching to address confounding with three using a weighting approach. One study compared both propensity-score matching and weighting approaches.[51] Only one of the identified publications, which studied medications for breast cancer, included a dual therapy arm.[52] This study categorised dual therapy users as those which received medications on the same day. However, in routine care this may not be the case as a second medication could be added later, particularly in the area of hypertension when treatments are added sequentially.[25] Therefore, pragmatic approaches need to be taken to categorise dual therapy users to avoid loss of sample size in the area of cardiovascular disease, which is explored in this PhD project.

All of the studies identified were able to replicate some of the results of the target trial, despite not all pre-specifying criteria for confirming replicability. The study by Franklin et al., achieved regulatory or estimate agreement in 9/10 studies.[44] Matthews et al., were able to replicate results for the composite outcome of death or myocardial infarction but was unable to replicate results for the outcome of bleeding.[54] Wing et al.,[49, 50] and Matthews et al.,[53] were the only studies to extend their analyses to trial underrepresented or excluded groups. Wing et al.,[49, 50] replicated the TORCH trial which studied medications for COPD and extended findings to excluded groups (including those aged >80 years, those with

concomitant asthma or those with substantial comorbidity) and underrepresented groups (e.g. people with mild COPD). Matthews et al.,[53] replicated the TASTE trial using the SWEDEHEART registry for patients with ST-elevation myocardial infarction. After benchmarking findings, follow-up was extended to 3 years and results were extended to underrepresented groups including females, older adults, those with diabetes or previous myocardial infarction or percutaneous coronary intervention. However despite Black and South Asian ethnic groups commonly being underrepresented in trials neither of these studies extended findings to explore effects in underrepresented ethnic groups. This thesis adds further evidence to this area of research on the use of real-world evidence to explore findings in underrepresented groups and will be the first to implement trial replication methods to look at underrepresented ethnic groups. Wing et al.,[49, 50] found similar results to the target RCT for active-comparator analyses of treatments for COPD both with and without first matching to the trial participants but was unable to replicate the placebo-controlled analyses.

This search identified a small number of trial replication studies. However due to increased interest in this methodology and the DUPLICATE initiative which recently published results, which are summarised below from replication of a further 20 completed and 2 ongoing trials, the body of evidence is rapidly increasing.

Studies identified since literature search performed

Recently further findings from the DUPLICATE initiative, funded by the FDA, were published and presented results from replication of 32 RCTs.[48] The initiative used a structured process to design real-world evidence studies emulating RCTs, without extension to underrepresented or excluded groups. It aimed to emulate 30 completed and 2 ongoing RCTs using three US health care claims data sources including Optum, IBM MarketScan and Medicare. The first results from the DUPLICATE initiative displayed in Table ***3.1***, and

included 7 placebo-controlled trials and chose active comparators as a proxy for placebo. The results presented in Table *3.1* by Franklin et al.,[44] concluded that 9/10 studies fulfilled regulatory or estimate agreement criteria and 9/10 studies had standardised difference between effect estimates of the replication and RCT of <2. However, the recent work by Wang et al.,[48] showed that 75% of the 30 completed RCTs replicated had statistical significance agreement (replication and RCT estimates and CIs on the same side of null), 66% had estimate agreement (estimates falling within 95% CI of RCT result) and 75% had standardised difference (SD) agreement (SDs |z| <1.96).

Replication of ONTARGET in US claims data

The study by Fralick et al.,[45] which was identified when exploring literature related to the ONTARGET trial, aimed to investigate whether real-world data analyses could confirm a supplemental indication using the main primary outcome of ONTARGET. Only those patients who had no prescriptions for any ACEi or ARB, including ramipril or telmisartan, at least 180 days prior to the index prescription were included. The study included a secondary analysis including patients with previous exposure to an ACEi or ARB which gave consistent results. After applying trial criteria and using propensity-score—matching to address confounding, 4665 new-user patients were included in the ramipril and telmisartan arms, respectively. The mean age in both groups was around 68 years and 67% were male. The study concluded similarity to the ONTARGET trial, despite not pre-specifying a replication criteria. The study also only included cardiovascular-related deaths in the primary composite outcome if they occurred during a hospitalisation for myocardial infarction, stroke, or heart failure but not outside of the hospital due to lack out-of-hospital death data. Therefore patients who did not die in hospital were not recorded as having an event.

New results from the DUPLICATE initiative described above emulated the ONTARGET trial, for the single therapy comparison only[48, 57] Of the three agreement metrics, replication of the ONTARGET trial in the DUPLICATE initiative met only partial statistical agreement, giving adjusted HR for telmisartan vs ramipril of 0.83 (95% CI: 0.77, 0.90) under an on-treatment analysis (HR 0.84 (95% CI: 0.78, 0.90) under intention-to-treat analysis).[48] These results were in contrast to the findings by Fralick et al, HR 0.99 (95% CI: 0.85, 1.14).[45]

Limited information was available on the methods used in the DUPLICATE initiative however replication of ONTARGET appeared to be conducted in the two commercial databases only (Optum and IBM MarketScan), with Medicare omitted. Despite ONTARGET including cardiovascular-related death as a component of the primary composite outcome it was noted that cause of death was not recorded, and all-cause death was used as a substitute. However, it was reported that out-of-hospital death was captured less completely in the two commercial databases which could provide an explanation for the difference in results between the DUPLICATE replication and the ONTARGET trial result.

Strengths and weaknesses compared with work of this PhD

Key components of the design choices implemented in the emulation of ONTARGET by Fralick et al., the DUPLICATE initiative and this PhD are summarised in Table ***3.2***. The study by Fralick et al., was large and gave evidence to support the ONTARGET trial findings in a US cohort. However, only a subset of trial exclusion criteria was applied as the researchers described some exclusion criteria were not readily identifiable in this specific data source.[45] As I had access to the individual patient level data from the ONTARGET trial I was able to match more closely to the ONTARGET trial participants and examine what impact this had on results. Using different data sources I was able to compare the findings in

a UK cohort to those observed by Fralick et al., and the newly published results by Wang et al.,[45, 48] using US data, whilst exploring what differences, if any, exist when using longitudinal EHR data as opposed to claims data. The two studies emulating ONTARGET in US claims data had a new-user design which is different to the ONTARGET trial which included prevalent users where participants could have previously taken an ARB or ACEi. This PhD replicated the trial design by including prevalent users which in turn meant additional steps were required to address biases which is useful for future replication studies of non-inferiority trials which often include prevalent users. By not restricting the cohort to new users this PhD was able to include multiple trial-eligible periods when creating the analysis cohort which emulates recruitment into an RCT by allowing a patient to meet trial criteria at multiple points in time. In addition to this, the study by Wang et al., included non-fatal events of MI and stroke only in the primary composite outcome which differs to the ONTARGET trial.[48]

Finally, by additionally using propensity-score—weighting to balance baseline characteristics which resulted in a cohort with more diverse characteristics I was able to extend methods to explore treatment effects in underrepresented and excluded groups after benchmarking results against the ONTARGET trial.

Table 3.2 Comparison of design choices for two identified emulations of ONTARGET compared to this PhD

Study component	Fralick et al.	DUPLICATE - ONTARGET	This PhD
Data source	US MarketScan health care database provided by Truven (1/1/03-30/9/09)	US commercial Optum Clinformatics (2004-2019) and IBM MarketScan (2003-2017)	UK CPRD GOLD, Aurum (01/01/01-31/7/19) and SIDIAP (01/01/07-31/7/19)
Study population	Patients meeting trial criteria who filled a new prescription for telmisartan or ramipril (no fills for either drug or any other ARB/ACEi during prior 180 days). Had inclusion criteria diagnosis during 180 days prior.	Patients meeting trial criteria who were new users (limited info available specific to ONTARGET)	Patients meeting trial criteria receiving a prescription for an ARB/ACEi including prevalent users who could previously be exposed to an ARB/ACEi. Trial criteria assessed at time frame specified in trial.
Exposure	Telmisartan vs ramipril	Telmisartan vs ramipril	ARB vs ACEi (drug classes used to increase power and enable analysis to be conducted in underrepresented groups)
Main analysis	On-treatment analysis as main analysis censored when discontinued use of their initial medication, switched to the comparator, experienced study outcome, disenrolled from health plan, died or on 30/9/09.	On-treatment analysis as main analysis censored at treatment discontinuation, switched to comparator, initiation of disallowed drug or other event, nursing home admission, disenrollment from insurance, or end of study period.	Intention-to-treat as main analysis (as in trial) censored at outcome, death, last collection date, transferred out of practice data or end of study (5.5 years of follow up)
Method for confounding	Propensity-score matching with 74 characteristics	Propensity-score matching with >100 preexposure characteristics	Propensity-score matching and propensity-score weighting with variables considered as confounders based on clinical input, with and without first matching to the individual patient level data from the trial

Study component	Fralick et al.	DUPLICATE - ONTARGET	This PhD
Additional analyses	Allowed for past ACE inhibitor or ARB use other than telmisartan or ramipril in 180 days prior.	Intention-to-treat censored at outcome, death or disenrollment from database	On-treatment approach additionally censored at discontinuation of medication, switch to opposing medication or becomes dual user. Extended analysis to underrepresented and excluded groups including those with CKD, females, older adults and ethnic minority groups
Outcome	Composite of myocardial infarction, stroke, or hospitalisation for congestive heart failure. Cardiovascular deaths included in they occurred during a hospitalisation for myocardial infarction, stroke, or heart failure but not outside hospital. Non-fatal events of myocardial infarction or stroke included only.	Composite of myocardial infarction, stroke, or hospitalisation for congestive heart failure. Out of hospital death less completed and all-cause death used as substitute for cardiovascular death. Non-fatal events of myocardial infarction or stroke included only.	Composite of myocardial infarction, stroke, or hospitalisation for congestive heart failure, cardiovascular-related death.
CKD in this PhD will be defined as GFR<60 mL/min/1.73m^2 without the time element of the clinical definition which requires GFR measurements to fall below the threshold on at least two occasions 90 days apart. This was to allow analysis to be extended to the underrepresented group with sufficient power but could be a potential limitation.			

3.1.3 Summary

Trial replication methods have been applied to various therapeutic areas since 2017. Most of the identified studies applied methods to insurance claims data or the SWEDEHEART registry which has unique properties. In the two studies by Matthews et al.,[53, 54] the trials replicated were embedded in the SWEDEHEART registry which was used for replication so both the replication and the target trial were from the same population reducing sources of

bias. The study by Wing et al.,[49, 50] was the only identified study applying methods to UK routinely collected data.

Most of the studies identified were able to obtain comparable results after first applying trial criteria and applying methods to address confounding, commonly propensity score matching or weighting. However, the DUPLICATE initiative resulted in some differences, including significant differences between their emulation of ONTARGET and the RCT result.[48] Only two studies extended analyses to explore effects in underrepresented or excluded groups, with neither focussing on ethnicity despite being commonly underrepresented in trials. This thesis adds further evidence to support such methods being applied to UK data and investigates optimal methods to implement trial replication techniques in this therapeutic area.

3.2 Literature search 2: Observational studies comparing an ARB to an ACE inhibitor with a cardiovascular outcome

3.2.1 Methods

Titles and abstracts were searched using the search term in section 3.2.1.1 to identify observational studies which compare an ARB to an ACEi with a cardiovascular outcome.

3.2.1.1 Search terms and databases searched

As in literature search one, the search was carried out in October 2019 and was updated in February 2023. PubMed and MEDLINE was searched using the search term below:

((“ACE inhibitor*”) OR (ACEi*) OR (“angiotensin?converting enzyme*”) OR (“ramipril”)) AND ((“ARB”) OR (“ARBs”) OR (“angiotensin II receptor blocker*”) OR (“angiotensin receptor blocker*”) OR (“telmisartan”)) AND ((“cardiovascular disease”) OR (“CVD”)) AND ((“observational”) OR (“non?experimental”) OR (“non?interventional”) OR (“real?world”) OR (“cohort”))

3.2.1.2 Inclusion and exclusion criteria

Observational studies with a cardiovascular outcome and a comparison between ARBs and ACEis were included. Literature reviews, meta-analyses, protocol, or baseline results papers

only were excluded. One paper that appeared in the search was retracted and was subsequently excluded.

3.2.2 Results

The results from the updated literature search in February 2023 returned 160 publications, 155 studies were excluded due to not meeting the criteria after review of title and abstracts.

3.2.2.1 Identified publications

Reasons for exclusion are shown in Figure *3.2*. Five publications were identified as meeting the inclusion and exclusion criteria.

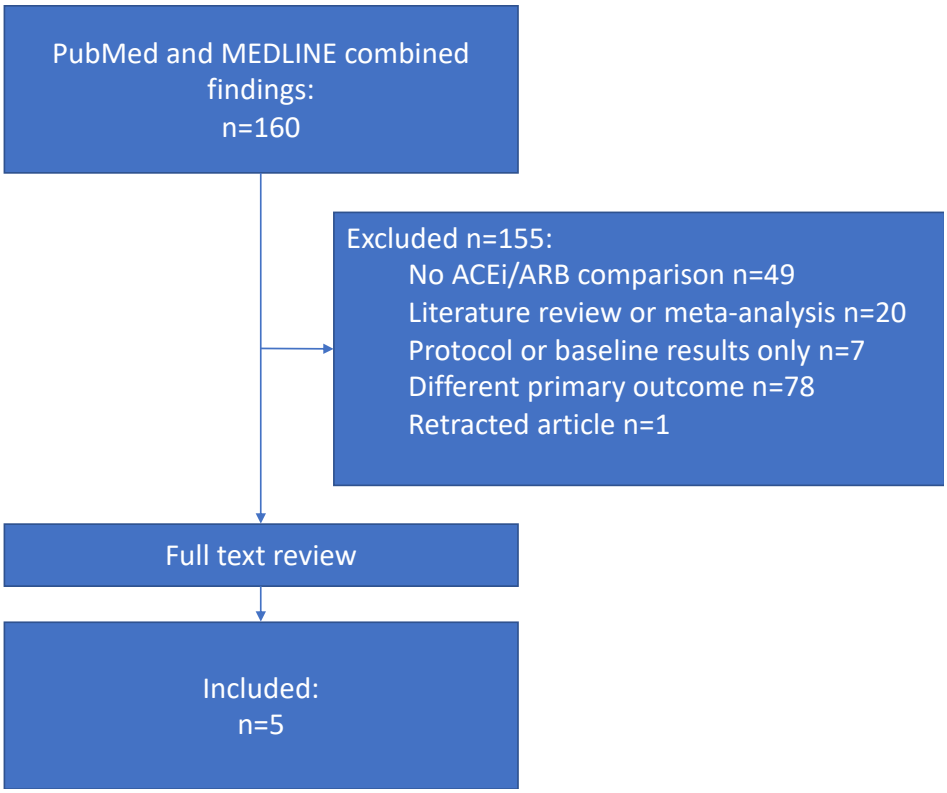


Figure 3.2 Flow chart of identified observational studies assessing effects of ARBs compared to ACE inhibitor with a cardiovascular outcome meeting inclusion and exclusion criteria from literature search 2.

3.2.2.2 Findings

A summary of the five identified studies after a full text review are presented in Table *3.2*.

Three of the identified studies explored effects of ARBs and ACEis in insurance claims

data.[58-60] This included US, Taiwan and French insurance data. Each of these three studies used different propensity score methods including adjustment, matching, and weighting. However, neither demonstrated comparative effects as observed in trial settings and each showed ARBs to reduce the risk of cardiovascular endpoints compared to ACEis.

Table 3.3 Identified observational studies comparing an ARB to an ACE inhibitor from literature search 2.

Study no., authors, year	**Outcome**	**Population and data source, country**	**Statistical methods and pre-specified criteria**	**Results**
(1) Padwal et al., 2016.[58]	All-cause hospital admission or death	Diabetic patients aged <20 years in US claims and integrated laboratory database.	Cox proportional hazards model with mortality risk score and adjusted for propensity score	ARB: 25,765; ACE inhibitor: 61,707 Mean age 52.1 years, 54.2% male ARB vs ACE inhibitor HR 0.90 (95% CI: 0.87, 0.94)
(2) Chien et al., 2015.[59]	All-cause mortality, hospitalisation for heart failure, hospitalisation for stroke, MI	Patients aged ≥70 years with hypertension between 2000-2009 in Taiwan's national health insurance research database (NHIRD). Patients with a history of cerebrovascular disease, MI, end-stage renal disease, kidney transplant recipients, received dialysis were excluded.	High-dimensional propensity score matching calculated using 1:1 nearest neighbour without replacement	ARB: 31,506; ACE inhibitor: 47,646 (12,347 in each group after matching) ARB vs ACE inhibitor: All-cause mortality HR 0.89 (95% CI: 0.85, 0.94) Hospitalisation for heart failure HR 0.93 (95% CI: 0.83, 1.04) Stroke HR 0.98 (95% CI: 0.90, 1.07) MI HR 0.92 (95% CI: 0.79, 1.06)
(3) Oger et al., 2022[60]	Overall mortality, cardiovascular-related death, major cardiovascular events	New ARB and ACE inhibitor users aged ≥50 years in 2009 in comprehensive French health insurance data (SNIIRAM/DCIR) linked to data from the French hospital discharge database (PMSI). Patients with a history of cancer, cardiovascular disease or chronic renal insufficiency were excluded.	Propensity scores (stabilised inverse probability of treatment weighting)	ARB: 233,682; ACE inhibitor: 174,133 ARB vs ACE inhibitor: All-cause mortality HR 0.88 (95% CI: 0.85, 0.90) Cardiovascular-related death HR 0.84 (95% CI: 0.80, 0.88)

Study no., authors, year	Outcome	Population and data source, country	Statistical methods and pre-specified criteria	Results
				Major cardiovascular event HR 0.89 (95% CI: 0.87, 0.91)
(4) Potier et al., 2017[61]	Composite of cardiovascular-related death, non-fatal MI, non-fatal stroke, or hospitalisation for cardiovascular reasons. Secondary outcomes were components of primary composite outcome and all-cause mortality	Patients aged >45 years with ≥3 risk factors for atherosclerosis and previous cardiovascular disease between 2003 and 2004 in the Reduction of Atherothrombosis for Continued Health registry.	Propensity score adjustment and propensity score matched	ARB: 12,036; ACE inhibitor: 27,589 ARB vs ACE inhibitor: Primary composite adjusted HR 0.90 (95% CI: 0.86, 0.95) Primary composite matched HR 0.91 (95% CI: 0.85, 0.97) Cardiovascular-related death HR 0.83 (95% CI: 0.75, 0.93) Non-fatal MI HR 0.97 (95% CI: 0.83, 1.12) Non-fatal stroke HR 0.94 (95% CI: 0.83, 1.07) Hospitalisation for cardiovascular reasons HR 0.91 (95% CI: 0.85, 0.96) All-cause mortality HR 0.89 (95% CI: 0.82, 0.97)
(5) Hasvold et al., 2014[62]	Cardiovascular disease	Hypertensive patients aged ≥18 years who were prescribed enalapril (ACE inhibitor) or candesartan (ARB) for the first time between 1999 and 2007 using Swedish primary medical records from primary care centres (database owned and managed by the Department of	Unadjusted, adjusted for covariates and propensity score matched	Candesartan: 4,265; Enalapril: 11,725 candesartan vs enalapril: Unadjusted HR 0.87 (95% CI: 0.76, 0.98) Adjusted for covariates HR 0.99 (95% CI: 0.87, 1.13)

Study no., authors, year	Outcome	Population and data source, country	Statistical methods and pre-specified criteria	Results
		Public Health and Caring Sciences, Uppsala University, Sweden). Patients with diagnosis of cardiovascular disease, diabetes, CKD or malignancy excluded.		Propensity score matched HR 0.83 (95% CI: 0.56, 1.24)

The study by Potier et al.,[61] included a similar composite outcome to the ONTARGET trial. As well as patients required to have previous cardiovascular disease as in ONTARGET, this study also included patients with risk factors for atherosclerosis using the Reduction of Atherothrombosis for Continued Health registry. The study used propensity score adjustment to address confounding however results were consistent with those obtained from exploring effects in insurance claims data.

The final study identified used Swedish primary medical records for new users of an ARB or ACEi who were hypertensive and aged ≥18 years.[62] This was the only study to explore different approaches to addressing confounding, presenting results from an adjusted, adjusted for covariates and propensity score matched analysis. Unadjusted analysis led to results consistent with the other identified studies, demonstrating a reduction in risk of the cardiovascular outcome for those treated with an ARB compared to an ACEi. Adjustment for covariates showed comparative effectiveness among ARBs and ACEis, HR 0.99 (0.87, 1.13). Propensity-score matching gave unreliable results, despite the CI containing 1 it was wide and was likely due to the small sample size after matching (n=1111 in each group).[62]

3.2.3 Summary

Almost all of the studies showed a reduction in risk of the cardiovascular outcome among ARB users in comparison to ACEi users and all had similar point estimates. These findings differ from the ONTARGET estimate for the primary composite outcome of 1.01, with a confidence interval containing 1. This could be due to sources of bias and residual confounding in observational studies such as ARBs generally being prescribed to a healthier, younger population in comparison to ACEis.[63] Since ARBs came into use after ACEis it is possible that many patients who were initially receiving an ACEi later switched to an ARB. All of the studies, except that by Potier et al.,[61] reported conducting an on-treatment analysis where patients who switched treatment were censored. It is not described whether

treatment switching under an intention-to-treat analysis is accounted for through statistical methods such as matching based on length of time exposed to each drug prior to the start of follow-up. Not appropriately handling treatment switchers in analysis may have led to bias in results.

Neither of the identified studies had the same outcome or directly comparable population to ONTARGET, a critical step in trial replication, with some looking at diabetic sub-populations while other studies focused on a younger or older population. Therefore, it is difficult to assess whether these studies provide evidence that supports or contradicts the findings of the RCT. The study by Hasvold et al.,[62] was the only study to show comparative effectiveness of candesartan (ARB) and enalapril (ACEi) for CVD risk when the analysis was adjusted for age, sex, index year and socio-economic status. This study was closest to ONTARGET in terms of drug-specific comparisons and primary outcome. Despite this, it excluded patients with previous CVD or diabetes which were inclusion criteria for ONTARGET and common indication for these medications. The studies gave little information on choice of variables included in propensity score models therefore it cannot be concluded that confounding was adequately addressed. The results presented by Hasvold et al.,[62] after propensity-score—matching was applied demonstrates that consideration needs to be given to the impact reduction in sample size may have on findings as a result of matching.

Chapter 4. Data sources

Chapter summary

- This chapter describes the data sources used in the subsequent chapters to address the research aims and objectives. This includes the target trial for replication and the routinely-collected healthcare data sources which were used for (1) ONTARGET trial replication and (2) exploration of the generalisability of trial findings to underrepresented and excluded subgroups.
- The format of the individual patient level data from the ONTARGET trial which was obtained from the trial sponsor is described.
- Strengths and limitations of the UK routinely-collected data sources are discussed and includes: the Clinical Practice Research Datalink (CPRD) GOLD, CPRD Aurum, hospital data from hospital episodes statistics (HES) and mortality and Index of Multiple Deprivation (IMD) data from Office for National Statistics (ONS).
- Finally, Catalonian routinely-collected data, the Information System for Research in Primary Care (SIDIAP) linked with minimum basic set of hospital discharge data (CMBD-AH) which is used to address Research Aim 2 is described.

4.1 ONTARGET trial data

Access was granted to the individual patient level data by the ONTARGET trial sponsor, the Population Health Research Institute.[23] This access complied with institutional review board approved informed consent forms provided by individuals from whom the data were collected. The data included patients baseline characteristics including age and sex, additional variables such as blood pressure and lab measurements including creatinine and potassium that were taken at the 3-week run-in. Information on clinical and medication history, alcohol

intake, and additional blood pressure measurements were collected at randomisation. Randomised treatment group was also included. Outcome data was not requested or provided. Trial participants were assigned a unique identifier and personal identifiers were removed prior to data transfer to ensure anonymity of participants.

4.2 Clinical Practice Research Datalink (CPRD)

4.2.1 Overview of CPRD

CPRD contains primary care electronic health records collected from GP practices across the UK.[64, 65] Data is fully-coded and anonymised using the Vision or EMIS clinical data capture software systems that are used by clinicians and other staff at GP practices. Due to data governance reasons, CPRD does not collect free text as these fields may contain identifiable patient information.[66] The two software systems define GOLD and Aurum and due to the differences in coding structure the records from the two systems are maintained in separate databases. Access to CPRD data is obtained via a licence agreement and anonymised patient datasets are extracted so researchers have no access to personally identifiable information. Access to CPRD data is granted based on approval of a study protocol submitted via CPRD's Research Data Governance Process.[67]

GP practices contribution to CPRD is endorsed by the Medicines and Healthcare products Regulatory Agency (MHRA), Royal College of General Practitioners (RCGP), NHS England and the National Institute for Health and Care Research (NIHR), with one in four practices in the UK contributing data.[68] In 2022, the data encompassed 60 million patients, including 16 million currently registered, and has been used for more than 30 years to facilitate research projects and inform clinical guidance. The database contains demographic data, diagnoses and symptoms along with drug exposures, tests and vaccines captured during clinical encounters. Medications prescribed and details of these are available in CPRD but

there is no information on whether these prescriptions were filled which is captured in data sources that provide information on medication dispensed.

4.2.2 Data structure of CPRD GOLD

CPRD GOLD includes data entered via the Vision system software. The data include several datasets relating to patients' clinical records, immunisation, and clinical tests as well as datasets containing information on the GP practice. Further detail on the structure of the data and the datasets included is displayed in Table *4.1*. Types of tests and medical history are coded using Read version 2 codes. Medications prescribed are coded using the Gemscript product code system including the brand and generic name.[69] Datasets within CPRD GOLD can be linked via the encrypted patient identifier and the last 5 digits of the patient identifier denote the identifier of the practice that the patient belongs to. In September 2022, CPRD GOLD contained 21,056,610 research acceptable patients with 3,020,188 patients currently registered with CPRD GOLD practices and 9,300,881 patients eligible for linkage. For the part of the project using CPRD GOLD, I used data from the July 2019 build, this contained data from 17,269,826 research acceptable patients and 8,910,255 patients eligible for linkage. This included 2,852,166 patients currently registered with 4.32% UK population coverage.[70]

Table 4.1 Data structure of CPRD GOLD

Dataset	Description
Patient	Contains unique patient identifier, sex, date of birth (dob), acceptable flag to determine if patient if research acceptable and met certain quality standards and information on registration with GP practice
Practice	Practice identifier, region of practice, when practice last collected information (last collection date) and when the practice was deemed to be of research quality, derived based on algorithm which uses practice death recording and gaps in recording (up to standard date)
Staff	Staff identifier, information on staff's sex, role
Consultation	Information on each individual consultation for each patient including date of consultation (both date of event discussed and date event entered into Vision), type of consultation (surgery, night, emergency etc) and identifier to link events to same consultation
Clinical	Information on each recorded clinical event including date occurred and date entered into Vision, type of consultation (diagnosis or system), medical code, additional identifier to link the additional dataset
Additional Clinical details	Contains additional information related to clinical event reported in clinical file links to clinical file using the additional identifier
Referral	Contains information on referrals that occurred, date of event and date entered into Vision, consultation type (management or administration), medical code associated with the event
Immunisation	Contains information on any immunisations that occurred, date and date entered into Vision, medical code associated with event, status of immunisation (advised, given, refusal), source where administered, reason for administration and method of administration
Test	Data on any tests that occurred including blood tests etc
Therapy	Data relating to any prescriptions, product code containing unique code for treatment selected, dosage information, quantity, number of days and packs prescribed, BNF code containing chapter and section from the British National Formulary for the product prescribed

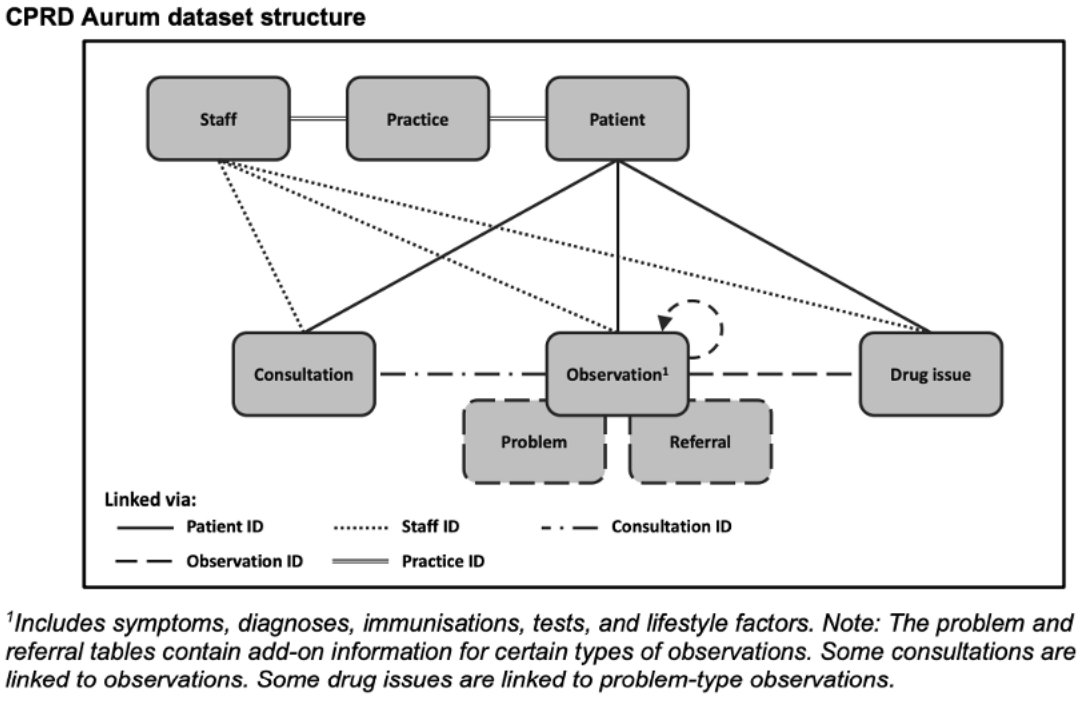
4.2.3 Data structure of CPRD Aurum

CPRD Aurum includes data entered via the EMIS Web electronic patient record system software and includes information on diagnoses, symptoms, prescriptions, referrals and tests. CPRD Aurum has been available for research since 2018 but clinical history for patients included in this data source extends to 1995.[66] As in CPRD GOLD, the data are separated

into different datasets: a patient file, practice file, staff and consultation file. However, information regarding the clinical records, tests and immunisations are collated into the observation file. Detail on prescriptions is given in the drug issue file. Further detail on the structure of the data and the datasets included is displayed in Figure ***4.1*** and Table **4.2**. Types of tests and medical history are coded using a combination of SNOMED, Read and local EMIS codes. Prescribed medications are coded using the Dictionary of Medicines and Devices (DM+D).[71] Datasets within CPRD Aurum can also be linked via the encrypted patient identifier and the last 5 digits of the patient identifier denote the identifier of the practice that the patient belongs to.

Figure 4.1 CPRD Aurum dataset structure

Duplication of patient data may occur if a practice is absorbed by another practice which also contributes to CPRD Aurum. As of August 2022, 29 practices are affected by this which is around 1% of practices in the database.[71] When a practice is absorbed despite the practice



Notes: Image from CPRD Aurum Data Specification.[1]

no longer contributing data, the current data remains in the database and patients from the absorbed database are assigned a new patient identifier and carry across their previous data to

the new database. To avoid these duplicates CPRD recommends excluding these 29 practices from research. Duplication of data can also occur when a patient moves to a new practice which contributes to the database. However, duplication of records can be avoided in this case by excluding data recorded before each individual's registration date.

In September 2022, CPRD Aurum contained 41,776,736 research acceptable patients with 13,775,799 research acceptable patients currently registered and 38,247,351 eligible for linkage. For this project I used data from the June 2021 data build, this included data from 40,000,297 research acceptable patients, with 13,375,774 currently registered with 20.02% UK population coverage.[72]

Table 4.2 Data structure of CPRD Aurum

Dataset	Description
Patient	Contains unique patient identifier, sex, dob, acceptable flag to determine if patient if research acceptable and met certain quality standards and information on registration with GP practice
Practice	Practice identifier, region of practice, when practice last collected information (last collection date) and when the practice was deemed to be of research quality, derived based on algorithm which uses practice death recording and gaps in recording (up to standard date)
Staff	Staff identifier, practice identifier, job category of staff member
Consultation	Information each individual patient consultation including date of consultation (both date of event and date event entered into EMIS), type of consultation (surgery, night, emergency etc) and patient, consultation, staff and practice identifier to link events to same consultation
Observation	Information on each recorded clinical event including date occurred and date entered into EMIS, value, unit of measure, medical code
Referral	Contains information on referrals that occurred, type of service referral relates to, referral urgency
Problem	Information on problem including end date, expected duration, last review date, status of the problem (active, past), significance of problem and parent problem identifier which can link to other problems in observation file
Drug issue	Data relating to any prescriptions, issue record identifier containing unique code for the issue record, drug record identifier, drug code containing unique code for the treatment selected, date issued and date entered into EMIS, quantity, unit and duration of treatment and estimated cost to the NHS

4.2.4 CPRD linked data

4.2.4.1 Overview of linked data

To maximise data completeness and availability of key exposures, outcomes and covariates primary care data from CPRD can be linked to several additional NHS datasets. Linkage of data is carried out by the Trusted Third-Party NHS Digital. Linked datasets can include HES Outpatient, Admitted Patient Care (APC), A&E, cancer registries and COVID-19 records. This project used data from HES APC, death registries and small area level data for Index of Multiple Deprivation (IMD) from ONS.[73] Cardiovascular events are commonly diagnosed in secondary care therefore this thesis used linked data from HES APC and cause of death as recorded on the death certificate collected by the ONS.

4.2.4.2 Linked Hospital Episode Statistics Admitted Patient Care data

HES APC contains data on patients' admissions or attendances at English NHS healthcare providers. All NHS healthcare providers in England including acute hospital trusts, primary care trusts and mental health trusts contribute data to HES APC. Data include admission and discharge dates, diagnoses coded using the International Classification of Diseases version 10 (ICD-10), and procedures undertaken coded using the Classification of Interventions and Procedures (OPCS) codes. CPRD has linked HES APC data from 1997, only a subset of patients included in CPRD are eligible for linkage and are linked using an algorithm based on NHS number, sex, date of birth and postcode.[73] Data in HES is categorised into unique hospitalisations, denoted as spells, and episodes and including data for events that are linked to specific episodes. Hospitalisations refer to the total time a patient stays in hospital and an episode is a time period within a hospitalisation which refers to the care received under one particular consultant. Therefore, each hospitalisation (spell) can have more than one episode. For each episode up to 20 diagnoses and 24 procedures may be recorded.[74] Ethnicity is

also available in HES data. Defining ethnicity using a combination of CPRD and HES is considered as the optimal approach.[75]

4.2.4.3 Linked Index of Multiple Deprivation (IMD) data

GP practice postcodes and eligible patient residence postcodes are used in CPRD to provide information of measures of deprivation at practice and patient level, respectively. These are commonly used as a proxy measure for socio-economic and socio-demographic data which are poorly recorded in primary care. Data related to deprivation are provided based on census geography and based on output areas (OS) built from adjacent postcodes. The lower layer super outcome area (LSOA) level area typically built from 4-6 OAs and have a minimum size of 300 households.[76] The IMD is a composite measure derived from measures including income, employment, education, health, housing, crime etc. The IMD is calculated as a weighted sum of domain indices. The first official indices of deprivation were provided in 2000 and have been updated since then. The indices used in this study relate to the 2015 update. Where patient level linkage is available it is preferred for use.

4.2.4.4 Linked Office for National Statistics (ONS) mortality data

ONS death registry also provides information on the official date and cause of death using ICD codes. Despite a high proportion of recording of death in CPRD, agreement on dates in CPRD and ONS is not always achieved. Therefore, linkage to the ONS registry is advised when outcomes of mortality, particularly cause-specific outcomes, are used.[77]

4.2.5 Data quality and completeness

To ensure data is of research quality standard CPRD provides two variables. These include the *acceptable* patient flag to determine if a patient has met certain research quality standards and the up-to-standard (UTS) practice date. It is often recommended to only use data for patients who have been registered at an UTS practices for at least 12 months and patients

who are deemed acceptable.[64] The acceptable research flag is based on registration status, recording of events and valid age and sex.[78] The UTS date is the date at which a practice is considered to be of continuous high-quality that is of research quality.[66] This is based on an algorithm that accesses completeness of recording and reporting of deaths. At present, the UTS date is not available for CPRD Aurum but is available to use for CPRD GOLD.

Due to the process of distributing prescriptions in UK primary care, therapy/drug issue files in CPRD are virtually complete. This is because the GP generates a prescription on a computer with the record automatically saved to the database. However, prescriptions issued in secondary care or medications bought over the counter (that do not require a prescription) are not captured.[79] Medical records and diagnoses however, can be subject to misclassification as these are recorded manually. The accuracy of coding has been assessed in a number of studies exploring the validity of diagnoses which often suggest a strong positive predictive value, specificity and sensitivity.[77, 79, 80]

In 2004 the Quality and Outcomes Framework encouraged the recording of key data such as smoking status by an incentive payment programme for English GPs.[81] From this, completeness of a large number of variables showed a significant improvement.[64] Despite this, it is acknowledged that missing data remains a challenge when analysing routinely collected data. Therefore, I linked the CPRD data to other NHS databases such as HES, to improve completeness, increase precision and reduce bias.[82] This is likely to improve the completeness of key variables, such as ethnicity.[75]

This thesis aimed to explore comparative effectiveness of medications to reduce cardiovascular events. A recent study which explored the validation of cardiovascular outcomes and risk factors in CPRD GOLD by using GP responses to questionnaires as gold standard showed strong positive predictive value for acute myocardial infarction.[80] However a study by Herrett et al,[82] exploring the completeness and diagnostic validation of

myocardial infarction in CPRD, HES, ONS and the Myocardial Ischaemia National Audit Project between 2003 and 2009 showed around 25-50% of MI events were missed in each data source but showed the positive predictive value of MI recording in primary care compared to the gold standard disease registry was 92.2%. The study recommended using linked data to obtain unbiased estimates. Throughout this PhD both CPRD and HES linked data was used, so only those patients who were eligible for HES linkage were included. If an event was recorded in both CPRD and HES, the date from HES would be preferred unless otherwise stated.

4.2.6 CPRD strengths and limitations

CPRD is a large data source containing vast amounts of data largely representative of the UK general population.[64, 65] Access to linked NHS databases increases data completeness and validity.[75, 77] As discussed in the previous section completeness and quality of data in CPRD is deemed to be high giving confidence to research which is generated using CPRD.[82] CPRD can provide access to long-term follow-up and detailed information on medication and diagnosis history. Despite these strengths, there are some limitations. These include a substantial proportion of missing data for key variables such as BMI and BP.[64] However, multiple imputation can be used to overcome this under the assumption of missing at random or missing completely at random.[83] In GP records, conditional on known factors likely to influence BP recording e.g., age, history of CVD and other variables it can be assumed that BP is missing at random. However, for BMI it is unlikely the data are missing at random as even in strata of patients who are similar in terms of demographics and medical history BMI is more likely to be recorded for someone who is overweight.[84] Some variables such as alcohol and smoking intake which are self-reported could be subject to bias and underreporting.[85] In addition to this some medication usage could be overestimated

due to no measure of adherence and the risk that prescription data may not accurately reflect the amount of drug taken.[86, 87]

4.3 Information System for Research in Primary Care (SIDIAP)

4.3.1 Overview of SIDIAP

Recalde et al.,[88] provided a summary of the SIDIAP data source in a recently published paper. The dataset includes primary care electronic health records from around 75% of the Catalonian population (~5.8 million). Similar, to the UK, Spain has a taxpayer-funded public health system which ensures high population coverage and representativeness of the SIDIAP data. Data are collected from over 30,000 healthcare professionals from 328 primary care centres and are entered into the SIDIAP database using the eCAP system software. SIDIAP was created in 2010, with data available from 2006 and is updated every 6 months with median follow-up time of 15.5 years.

4.3.2 Data structure of SIDIAP

Patients are automatically entered into SIDIAP if they are registered in the public health system and have been assigned to a primary care centre of the *Institut Català de la Salut* (ICS, Catalan Health Institute). As of June 2021, 83.9% of the SIDIAP population was of Spanish nationality and 75.3% resided in the Barcelona region.[88] Data are pseudo-anonymised and contains information on diagnoses, prescriptions and demographics as well as pharmacy dispensations and lab tests. Data are organised into different domains and linkage between domains is done via the individuals pseudo-anonymised identifier. Socio-economic status is measured via information on income, type of occupation and other variables. Data are coded using ICD-10CM codes and medications are coded using the Anatomical Therapeutic Chemical (ATC) Classification System. Further information on the some of the domains available in SIDIAP is shown in Table ***4.3***.

Table 4.3 Data structure of SIDIAP

Data type	Data domain	Description
Socio-demographics	Population	DOB, sex, data entry and exit date, reason for exit, nationality
	Socio-economic	Information including income, deprivation indices measured at the census tract level and health area level, etc
	Regional	Rural/urban living, province
	Complexity	Clinical risk group based on co-morbidities
Health conditions	Primary care diagnoses	Start and end date, ICD-10CM code and SIDIAP grouper (grouping multiple ICD-10CM codes with same meaning)
	Sick, maternity or paternity leave	Start and end date and code related to reason
Medications and vaccines	Prescriptions	ATC code, treatment family (e.g., hypertension), start and end date, frequency, dosage
	Dispensations	ATC code, start and end date (only month available), dosage
	Adverse reactions	ATC code, date
	Vaccinations	Code, date and dose and vaccine family
Lab tests	Analytical variables	Biomarker, measurement type (e.g., glucose), date, result and unit
	Serology	Serological test type (e.g., HIV), date and result
Clinical practice and lifestyle info	Clinical and lifestyle variables	Clinical measurements (e.g., BP, weight, height) or lifestyles variables (e.g., alcohol, smoking), date and value
Visits	Visits	Information on visit, including type of visit

4.3.3 SIDIAP linked data

Using a Trusted Third-Party and patients' personal identifier, data from SIDIAP can be linked to other data sources. Data in this project were linked to the public hospitalisations in Catalonia using the minimum basic set of hospital discharge data (CMBD-AH).[89] Linkage is through the *Programa d'analitica de dades per a la recerca I la innovació en salut* (PADRIS, Data Analysis Program for Health Research and Innovation) of the Catalan department of health. Information on date and cause of hospitalisation and discharge date and any codes that occurred during the hospitalisation are captured through ICD-10CM and ICD-10PCS codes. Data on hospital medication for outpatient dispensing was also available.[88]

4.3.4 Data quality and completeness

Internal and external validation checks are carried out at every data update which occurs every 6 months. Checks include stratifying the data by geographical regions and year to identify differences in data collection including changes in equivalent information capture recorded under different codes. Visual inspections are also carried out by week to identify temporal patterns. Based on these checks SIDIAP issues recommendations to researchers. External validation checks can include accessing the data recorded in SIDIAP through linkage to external gold standard data sources or analysing free text.[88] The use of SIDIAP data to assess vascular diseases was assessed by Ramos et al.,[90] and indicated a high level of validity for use in cardiovascular observational studies.

4.3.5 SIDIAP strengths and limitations

SIDIAP is a large database representative of the Catalonian population with regards to age, sex and geographic distribution providing information on socio-economic status and nationality. Unlike CPRD, drug exposure is provided from both prescriptions and dispensations so adherence to medication is better assessed. This PhD used only dispensation data. Although not included in this project due to time constraints, SIDIAP is linked to different common data models and has already been mapped to the international Observational Medical Outcomes Partnership-Common Data Model (OMOP-CDM), which facilitates multi-database studies. Such mapping can be useful for future studies using trial replication methods which would benefit from ease of transportability of methods to assess robustness of findings across data sources. Despite this, SIDIAP also has some limitations, these include the use of nationality as opposed to capturing information on ethnicity. The data source provides information on recorded death, however there is no information on cause of death. This limits the type of analyses that can be carried out in the SIDIAP data source.

Chapter 5. Methods

Chapter summary

- This chapter includes the peer-reviewed protocol that was published in BMJ Open. Methods described in the protocol relate to Research Aim 1, replication of the ONTARGET trial in CPRD GOLD data with results presented in Chapter 6 and Chapter 7.
- Additional detail on methods outlined in the published protocol are provided for developing the study population (elaborating on Step 4 and Step 5 in the published protocol) and extending analysis to underrepresented and excluded groups, including the use of CPRD Aurum data to further address Research Aim 1.
- Amendments to the protocol that were carried out to explore biases and improve consistency with trial methods are described in section 5.3.
- Detail on methods to address Research Aim 2 are given in section 5.4, including extension of methods to the SIDIAP database, with results presented in Chapter 8.

5.1 Trial replication methods in CPRD GOLD: Research paper 1 (published protocol)

5.1.1 Research paper 1

The protocol for analysis conducted in CPRD GOLD was peer-reviewed and published in BMJ Open. The paper relates to methods applied to address Research Aim 1. Supplementary material for this research paper are available in Appendix 1: Supplementary material from Research paper 1.

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<u>SECTION A – Student Details</u>

Student ID Number	1800205	**Title**	Miss
First Name(s)	Paris Jade		
Surname/Family Name	Baptiste		
Thesis Title	Real-world effectiveness and adverse events caused by ACE inhibitors and ARBs for reduction in cardiovascular events with validation against the ONTARGET trial		
Primary Supervisor	Laurie Tomlinson		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?	BMJ Open		
When was the work published?	30 January 2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	NA		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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Where is the work intended to be published?	
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author on this paper. I contributed to the study question and design and wrote the first draft of this protocol based on original scientific approval applications to ISAC that I contributed to. Myself and co-authors contributed to subsequent drafts and approval of the final manuscript for publication.

SECTION E

Student Signature	[redacted]
Date	7/6/23

Supervisor Signature	[redacted]
Date	7/6/23

BMJ Open

Effects of ACE inhibitors and angiotensin receptor blockers: protocol for a UK cohort study using routinely collected electronic health records with validation against the ONTARGET trial

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ABSTRACT

Introduction Cardiovascular disease is a leading cause of death globally, responsible for nearly 18 million deaths worldwide in 2017. Medications to reduce the risk of cardiovascular events are prescribed based on evidence from clinical trials which explore treatment effects in an indicated sample of the general population. However, these results may not be fully generalisable because of trial eligibility criteria that generally restrict to younger patients with fewer comorbidities. Therefore, evidence of effectiveness of medications for groups underrepresented in clinical trials such as those aged ≥75 years, from ethnic minority backgrounds or with low kidney function may be limited. Using individual anonymised data from the Ongoing Telmisartan Alone and the Ramipril Global Endpoint Trial (ONTARGET) trial, in collaboration with the original trial investigators, we aim to investigate clinical trial replicability within a real-world setting in the area of cardiovascular disease. If the original trial results are replicable, we will estimate treatment effects and risk in groups underrepresented and excluded from the original clinical trial.

Methods and analysis We will develop a cohort analogous to the ONTARGET trial within the Clinical Practice Research Datalink between 1 January 2001 and 31 July 2019 using the trial eligibility criteria and propensity score matching. The primary outcome is a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalisation for congestive heart failure. If results from the cohort study fall within pre-specified limits, we will expand the cohort to include under represented and excluded groups.

Ethics and dissemination Ethical approval has been granted by the London School of Hygiene & Tropical Medicine Ethics Committee (Ref: 22658). The study has been approved by the Independent Scientific Advisory Committee of the UK Medicines and Healthcare Products Regulatory Agency (protocol no. 20_012). Access to the individual patient data from the ONTARGET trial was obtained by the trial investigators. Findings will be submitted to peer-reviewed journals and presented at conferences.

Strengths and limitations of this study

- Large cohort study giving power to look at effects within subgroups under represented in the clinical trial and novelty of studying treatment effects of dual therapy in real-world settings.
- Access to individual patient level data from a landmark trial to support creation of a trial-analogous cohort.
- There may be differences between the trial population and the observational cohort due to the level of detail on inclusion/exclusion criteria provided by the trial and misclassification by primary care coding.
- Study of drug class effects as opposed to drug-specific effects may lead to differences in results.
- Despite efforts to eliminate confounding and bias, unlikely to remove entirely due to the data setting.

INTRODUCTION

Hypertension, age, diabetes and poor diet contribute to cardiovascular disease (CVD), a leading cause of death worldwide.[1] Men have a higher incidence than women, despite women having higher mortality.[2] Angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs) reduce blood pressure (BP) by targeting the renin–angiotensin system (RAS). They are commonly used drugs for the treatment of hypertension, stroke, heart failure, other CV outcomes and proteinuric kidney disease.[3]

Evidence underpinning the use of ACE inhibitors and ARBs comes from the results of landmark clinical trials. Although these international trials include a large number of participants, many have limited inclusion of subgroups, such as elderly patients, those from ethnic minority groups and people with impaired renal function, and thus have

limited power to look for interactions in drug effects.[4] Activity of the RAS and response to drugs that inhibit this system differ between patients, for example among different genders and ethnic groups.[5] In the management of hypertension, there is a longstanding theoretical model that people of black African or African-Caribbean family origin, (subsequently referred to as 'black') have lower levels of renin and that some drugs which block the RAS such as ACE inhibitors and ARBs are less effective in black populations.[6] Despite the evidence supporting this, it is increasingly recognised that there are no clear genetic causes of underlying health differences between ethnic groups, and differences may be due to factors such as differences in socio-economic status and access to healthcare, indicating a level of underlying structural racism.[7] Poor representation of black populations in clinical trials limits the ability to examine variation in drug effects by ethnicity.[8] Information regarding drug effects in these underrepresented populations is frequently only available from non-interventional studies,[9] often limited to select patient groups or heavily confounded. Trial replication is a technique which can be used to address this issue.[10] By creating a ('trial-analogous') observational cohort that has similar characteristics to a trial population that has been randomised, and accounting for confounders using propensity score methods, residual confounding can be reduced.[11] Validation of the results generated by a trial-analogous cohort against the target randomised controlled trial (RCT), allows us to determine if patient selection and methods used to address confounding and bias can produce comparable results. If data agreement is shown between the RCT and observational study, these methods can then be applied to the analysis of the treatment effects in populations who would have been excluded or underrepresented in the original trial, and populations over a longer follow-up period.

Recent studies by Wing *et al* and Powell *et al* have explored whether validation against RCTs can support conclusions drawn from observational studies carried out in electronic health records (EHRs).[12 13] We aim to explore the validity of such methods for assessing treatment effectiveness and risk in non-interventional settings in the therapeutic area of CVD, by matching individual patient data from the Ongoing Telmisartan Alone and the Ramipril Global Endpoint Trial (ONTARGET) to a trial-analogous cohort developed in UK primary care data. We will then apply our validated methods to the estimation of:

- Treatment effects and risk in groups that were excluded from the trial due to prior comorbidities.
- Treatment effects in people aged 75 years and over, of black/Asian ethnicity, those with low kidney function and females who were underrepresented in the trial.

Early findings from Franklin *et al* from the RCT DUPLICATE initiative, which replicated 10 RCTs have shown promising results.[14] However, it was shown agreement in results relies largely on the comparator studied. Those studies which had an active comparator with similar indications were shown to increase the validity of the real-world evidence. Similar work was done by Matthews *et al*, emulating the VALIDATE study using the SWEDEHEART register, here it is was shown that accurate effect estimates can be obtained using real-world data to emulate a target trial, but results are not always replicable.[15] It is thought that using a similar protocol in the observational study to that used in the trial and harmonisation of the data analysis can lead to more comparable results.[16]

AIMS AND OBJECTIVES

Aim

To measure the association between ACE inhibitors and ARBs and cardiovascular outcomes within a trial-analogous cohort and within patients excluded and underrepresented from the ONTARGET trial using trial-replication methods.

Primary objective

To validate the effects of ACE inhibitors and ARBs found in an RCT-analogous cohort from UK routine primary care against those obtained from a randomised clinical trial.

Secondary objectives

- To estimate treatment effectiveness and risk in patients excluded from trials using EHRs.
- To estimate treatment effectiveness and risk in patients under represented in trials using EHRs.
- To investigate long-term outcomes and adverse events of patients treated with ACE inhibitors or ARBs beyond the duration of trials.

METHODS AND ANALYSIS

Study design

A historic cohort design using prospectively collected data will be used with a trial-replication component.

Patient and public involvement

Patients were not involved in the design or conduct of the protocol. We plan to disseminate the results through peer review publication.

Settings/data sources

Data used in the study will be obtained from the RCT, ONTARGET, and the UK Clinical Practice Research Datalink (CPRD) GOLD (linked to Hospital Episode Statistics (HES) database and Office for National Statistics (ONS data.

Ongoing Telmisartan Alone and the Ramipril Global Endpoint Trial

The global landmark ONTARGET trial compared the non-inferiority of an ARB (telmisartan 80 mg daily) with an ACE inhibitor (ramipril 10 mg daily) and the superiority of a combination of both therapies compared with ramipril alone.[17] Patients had established vascular disease or were at high risk of vascular disease.

Table 1 Baseline characteristics from ONTARGET trial

Characteristic	Ramipril (N=8576)	Telmisartan (N=8542)	Combination therapy (N=8502)
Age—years	66.4±7.2	66.4±7.1	66.5±7.3
Female sex—n (%)	2331 (27.2)	2250 (26.3)	2250 (26.5)
Ethnic group—n (%)			
Asian	1182 (13.8)	1172 (13.7)	1167 (13.7)
Arab	102 (1.2)	106 (1.2)	106 (1.2)
African	206 (2.4)	215 (2.5)	208 (2.4)
European	6273 (73.1)	6213 (72.7)	6222 (73.2)
Native or aboriginal	747 (8.7)	756 (8.9)	728 (8.6)
Other	64 (0.7)	77 (0.9)	69 (0.8)
Missing	2 (<0.1)	3 (<0.1)	2 (<0.1)

Ethnic group was self-reported.
±, mean ± standard deviation; ONTARGET, Ongoing Telmisartan Alone and the Ramipril Global Endpoint Trial.

The primary outcome was a composite of: cardiovascular related death, non-fatal myocardial infarction (MI), non-fatal stroke or hospitalisation for heart failure.[18] Some baseline characteristics are displayed in table 1.

In the intention-to-treat (ITT) analysis, the trial found that telmisartan was non-inferior to ramipril in prevention of the primary composite outcome, hazard ratio (HR) 1.01, 95% CI 0.94 to 1.09) but was less likely to cause angioedema. In addition to this, it showed that combination therapy was no better than ramipril alone (HR 0.99, 95% CI 0.92 to 1.07) in preventing the primary composite outcome and significantly increased the risk of hypotension, syncope, renal dysfunction and hyperkalaemia. Similar results were shown under the per-protocol (PP) analysis.

Based on the findings of this trial and a smaller parallel trial, TRANSCEND, in October 2009 telmisartan was approved for cardiovascular risk reduction in patient's intolerant of ACE inhibitors, aged ≥55 years and with a high-risk of cardiovascular events, after already having been approved as an antihypertensive drug.

We assessed the bias present in the ONTARGET study using the Cochrane collaboration's tool for assessing risk of bias in randomised trials[19] and found the trial to have a low risk of bias. The results from the assessment are given in online supplemental material.

Clinical Practice Research Datalink

CPRD is an anonymised database of patient data from general practitioner (GP) practices across the UK. The data consist of 50 million patients with records dating back to 1987, of whom 14 million are currently registered at practices in the UK, ~20% of the UK population.[20] Patients have a median follow-up time of 10 years. The database contains demographic data, diagnoses and symptoms along with drug exposures, tests and vaccines. Linkage to Hospital Episode Statistics (HES) and other databases such as cancer registries and death registries from the ONS is also available. In August 2019, linkage data were available from ~74% of CPRD GOLD practices located in England and ~50% of practices in the UK, with 10 800 187 patients eligible for linkage.[21]

The validity of diagnoses captured in CPRD are described by Herrett *et al*.[22] In relevance to this study, the positive predictive value of acute MI recorded in primary care was 92.2% and 91.5% in HES data.[23] In 2004 the Quality and Outcomes Framework[24] encouraged the recording of key data such as smoking status by an incentive payment programme for English GPs. From this, completeness of a large number of variables showed a significant improvement.[25] Despite this, we acknowledge that missing data remains a challenge when analysing routinely collected data. Therefore, we will link the CPRD data to other databases to improve completeness, increase precision and reduce bias.[23] This is likely to improve the usage of key variables, such as ethnicity.[26] We also consider that part of this project is aiming to ascertain whether it is possible to obtain valid results using routinely collected data, despite the acknowledged challenges inherent in using such data.

Study population

Participants from CPRD with a prescription for an ACE inhibitor or ARB and eligible for HES linkage between 1 January 2001 and 31 July 2019 will be selected. To increase power, we will examine effects of drug classes, rather than specific drugs but we will report the proportion of each specific ACE inhibitor/ARB in our cohort. Prevalent users were included in the trial, and we will also include patients with previous prescriptions for ACE inhibitors or ARBs. Further detail related to the selection of participants for each objective is provided below.

Primary objective

To validate the effects of ACE inhibitors and ARBs found in an RCT-analogous cohort from UK routine primary

care against those obtained from a randomised clinical trial.

For this objective, users of ARBs will be compared with users of ACE inhibitors.

Step 1: selection of exposed time periods

Prescriptions for an ACE inhibitor or ARB received at least 12 months after the patient has been registered with a general practice that meet prespecified standards for research-quality data (ie, be 'up-to-standard') for at least 12 months will be considered as exposed time periods. Exposed time periods will be defined as periods of continuous therapy, that is, receiving a repeat prescription, >90 days without a prescription after the previous prescription ending will result in the exposure period ending. Prescription duration will be calculated using quantity and daily dose. If this is missing, the median will be imputed. Patients can contribute more than one exposed time period for each drug, with the earliest prescription in each exposed time period denoted as the first eligible prescription.

Step 2: application of inclusion criteria

Exposed time periods where patients are aged ≥55 years and ever received a diagnosis of one of the following prior to the first eligible prescription will be included. This represents the inclusion criteria used in the trial.

- Aged ≥55 years
- At least one of the following of:
  Coronary artery disease
  Peripheral artery disease
  Cerebrovascular disease
  High-risk diabetes (defined by evidence of end-organ damage)

Step 3: application of exclusion criteria

The trial exclusion criteria will then be applied and time periods with any of the following exclusion criteria prior to the first eligible prescription will be excluded:

- Symptomatic heart failure
- Significant valvular heart disease
- Pericardial constriction
- Complex congenital heart disease
- Uncontrolled hypertension (BP >160/100)
- Elevated potassium above 5.5 mmol/L
- Heart transplant recipient
- Stroke due to subarachnoid haemorrhage
- Significant renal disease (defined as patients with codes for renal artery stenosis or renal artery atherosclerosis; or serum creatinine concentration above 265 µmol/L)
- Hepatic dysfunction
- Primary hyperaldosteronism
- Hereditary fructose intolerance
- Other major noncardiac illness expected to reduce life expectancy or interfere with participation (cancer, drug or alcohol dependence, mental illness)
- Hypotension

Further information of how these criteria will be interpreted in EHR is available in online supplemental material and code lists are available for download: https://doiorg/1017037/DATA00002112. Due to some of the criteria not being fully assessable using CPRD read codes, exclusion criteria are analogous with ONTARGET criteria but we acknowledge they are not identical.

Periods where all inclusion and exclusion criteria are met will be referred to as trial eligible periods and the start date of these periods will be denoted as the eligible for trial inclusion date. The ACE inhibitor exposed cohort will include those periods where a prescription for an ACE inhibitor was received. The ARB exposed cohort will include those periods where a prescription for an ARB is received.

Step 4: matching to trial participants

Having obtained individual patient data for ONTARGET participants, we will match patients within the ONTARGET study to the CPRD ACE inhibitor trial eligible exposure period with the closest propensity score for the probability of being included in the trial. Variables for the propensity score will be chosen based on those known or suspected to influence the likelihood of the outcomes of interest (see Covariates section for further details).

Exact selection of matching variables will depend on the quality and completeness of the data available. Characteristics will be measured at the eligible for trial inclusion date for the ACE inhibitor trial eligible period. Once a trial participant is matched to an ACE inhibitor exposure period from CPRD all other ACE inhibitor exposure periods in CPRD for that participant will be dropped, ensuring a patient can only be matched and included once in the resulting ACE inhibitor trial-analogous cohort. We anticipate matching all or the majority of ONTARGET participants to a CPRD ACE inhibitor-exposed patient, giving us a pool of ONTARGET analogous ACE inhibitor-exposed patients, with similar baseline characteristics to the trial participants at the point of randomisation. This step is outlined in figure 1.

Step 5: matching trial-eligible exposure groups

The ACE inhibitor trial-analogous patients selected by step 4 will be matched 1:1 to the ARB trial-eligible periods from step 3 with the closest propensity score considering the same variables considered for the propensity score model in step 4. This matching step will ensure the ARB trial-eligible group has similar characteristics to the telmisartan ONTARGET group due to randomisation in the trial. It will also help us to understand whether trial outcomes can be investigated in non-interventional settings alone, when access to the trial data is not available. Once an ARB exposure period has been matched, any other ARB exposure periods for that patient will be excluded so an ARB patient is matched only once. If a patient ends up contributing eligible exposure periods to both the ARB and ACE inhibitor groups, a restriction

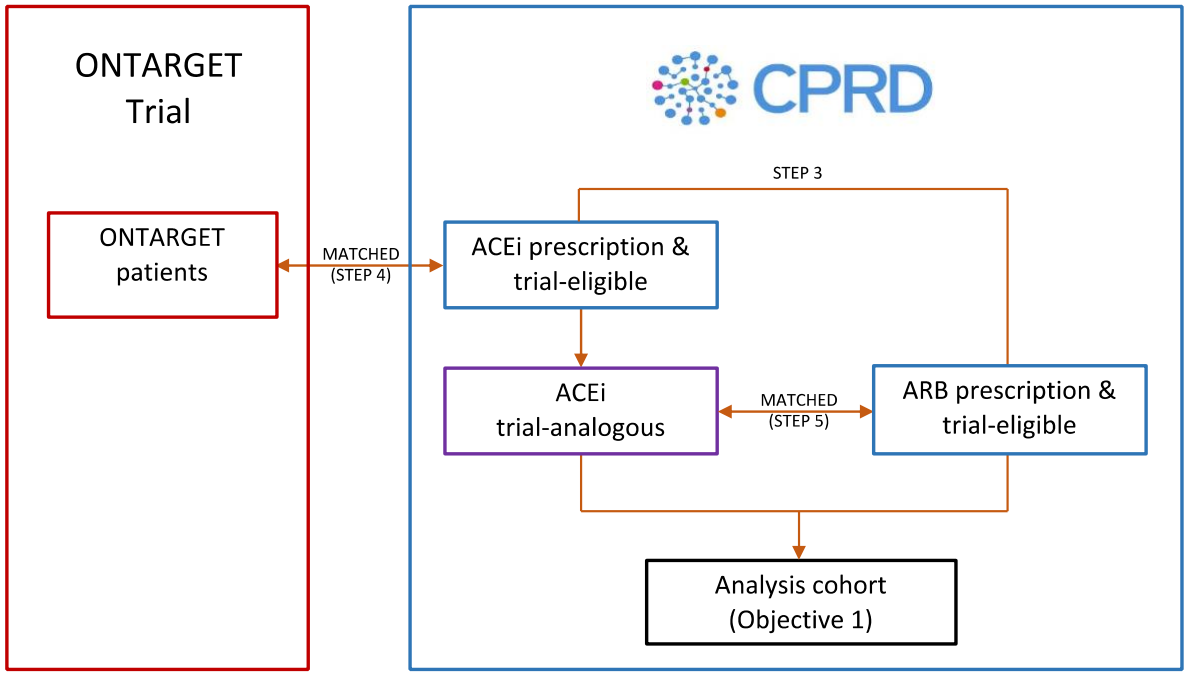

Figure 1 Simplified flow chart illustrating the planned steps in the selection of CPRD patients required to address the primary objective. Note double ended arrows denoted 'matched (step X)' indicates where two cohorts will be 1:1 matched using propensity score matching or some other similar method. ACEi, ACE inhibitor; ARBs, angiotensin II receptor blockers; CPRD, Clinical Practice Research Datalink; ONTARGET, Ongoing Telmisartan Alone and the Ramipril Global Endpoint Trial.

will be added that the patient cannot be matched to themselves.

The matched ACE inhibitor and ARB groups from step 5 will be the analysis cohort for the validation step.

To test the robustness of our findings, we will run the above propensity score model on the cohort of ARB and ACE inhibitor trial-eligible periods from step 3 (with removal of the trial-analogous ACE inhibitor group) and generate propensity scores. We will then run a propensity score weighted analysis to obtain the average treatment effects which will also be validated against the ONTARGET results. This will assess whether the trial-matching step is required in order to obtain results that are comparable to the trial.

Prior to the remaining objectives, we will check our findings from the validation step are generalisable to other settings. To do this we will repeat this step, matching the ACE inhibitor trial-analogous patients to the dual therapy trial-eligible group and see if results for the primary outcome are comparable with the trial. Dual therapy will be defined as explained in secondary objective 1.

Secondary objective 1

To estimate treatment effectiveness and risk in patients excluded from trials using EHRs.

Those patients who have one of the diagnoses listed in the trial diagnosis criteria in step 2, but who would have been excluded from the trial due to meeting specific exclusion criteria, such as those with significant renal disease. Exposure groups will be selected as in steps 1–3 with the inclusion/exclusion criteria modified to reflect that people with significant renal disease can be included. As the CPRD cohorts will include patients excluded from the trial, the cohorts will not be matched to the trial participants. The propensity score model developed in step 4 will be the basis for addressing confounding as validated in the primary objective.

Due to the difficulty of defining the dual therapy arm using routine data we will define dual ACE inhibitor/ARB users as patients with overlapping prescriptions who receive an additional prescription for the first agent after the second prescription for the second agent, this is shown in figure 2. Follow-up will then be started from the date of the first prescription of the second agent, with a sensitivity analysis planned where follow-up starts from the second prescription for the second agent (to evaluate the impact of using a prescription event occurring in the future for defining dual therapy users in the main analysis).

Secondary objective 2

To estimate treatment effectiveness and risk in groups underrepresented in trials using EHRs.

This will be applied as in secondary objective 1, with a focus on the groups of: black/Asian ethnicity, aged ≥75 years, and females who were underrepresented. All arms will be studied.

Secondary objective 3

To investigate long-term outcomes and adverse events of patients treated with ACE inhibitors or ARBs beyond the duration of trials.

Figure 2 Example timeline of dual therapy user with overlapping prescriptions for two agents with follow-up starting at date of first prescription for second agent.

Adverse events such as cough, angioedema and renal impairment will be studied over a longer duration than that in the trial. This will be studied in the same cohort developed in step 5 to address the primary objective.

EXPOSURES, OUTCOMES AND COVARIATES

Exposures

Exposures will be determined using prescribing records in CPRD and code lists developed for ACE inhibitors and ARBs.

For the primary objective, ARBs are the primary exposure and will be compared with ACE inhibitors.

For the secondary objectives, dual therapy will also be considered as an exposure compared with ACE inhibitors, and will be defined as explained in the 'study population' section.

Outcomes

Outcomes to be measured are:

- Primary outcome: composite of cardiovascular death, non-fatal MI, non-fatal stroke or hospital admission for congestive heart failure.
- Secondary outcomes:
  - Components of primary outcome: (separately) cardiovascular death; non-fatal MI; non-fatal stroke; hospital admission for congestive heart failure.
  - (Separately) newly diagnosed congestive heart failure; revascularisation procedures; nephropathy (defined as 1. 50% reduction in estimated glomerular filtration rate (eGFR) or start of renal replacement therapy or eGFR <15 mL/min (for sensitivity analysis requires 50% reduction in eGFR on two occasions at least 3 months apart) and 2. Development of eGFR <15 or start of renal replacement therapy (for sensitivity analysis requires eGFR <15 on two occasions at least 3 months apart))
- Other outcomes: (separately) all-cause mortality or microvascular complications of diabetes mellitus.
- Safety outcomes: cough, angioedema, hyperkalaemia or renal impairment.

Outcomes will be identified using read codes and ICD-10 codes in CPRD and HES. Code lists are available for download: https://doiorg/1017037/DATA00002112.

Covariates

The propensity score models in step 4 and step 5 of the 'study population' section will consider a large range of variables including the following ONTARGET baseline characteristics:

- Age
- Sex
- Ethnicity
- CVD (categorised into—coronary, peripheral, cerebrovascular)
- Diabetes
- Prior treatment with RAS blockers
- Baseline systolic and diastolic BP within 6 months
- Smoking status
- Body mass index
- Renal function

In the propensity score model in step 5 of the 'study population' section variables such as calendar period and healthcare utilisation (eg, GP consultations, hospital appointments, procedures) will also be considered.

SAMPLE SIZE

In ONTARGET, there were 8576 in the ramipril arm, 8542 in the telmisartan arm and 8502 in the combination arm so we estimate a minimum of 14 000 CPRD patients exposed to an ACE inhibitor or an ARB are required for the individual patient matching to provide any benefit.

In a previous study,[27] the following counts were obtained: ACE inhibitor alone: n=2 81 204, ARB alone: n=83 850, both ACE inhibitor and ARB at the same time: n=39 548 between April 1997 and March 2014. Using data from an ongoing study (ISAC Protocol 19_072, using CPRD GOLD alone), we estimate that 37% of ACE inhibitor/ARB users are aged ≥55 years with previous cardiovascular or cerebrovascular disease and/or diabetes at drug initiation.

We have assumed a sample size of 80 000, 20 000 and 14 000 in the ACE inhibitor, ARB and dual therapy groups, respectively. We have chosen sample sizes smaller than those obtained from 37% of the cohort sizes described in the study by Mansfield *et al*.[27] since these are more likely to reflect the numbers found after applying the trial exclusion criteria. We have taken the upper and lower confidence limits for the risk ratio for the primary outcome in ONTARGET and the baseline risk of 16.5% in the ramipril group.[18] From this, we estimate 87.4% power for a risk ratio of 0.94, and 99.6% power for a risk ratio of 1.09, when comparing the non-inferiority of ARBs versus ACE inhibitors. For the superiority of dual therapy versus

ACE inhibitors, we estimate 94.6% power for a risk ratio of 0.92, and 87.0% power for a risk ratio of 1.07.

STATISTICAL ANALYSIS

Propensity score for addressing confounding

Multivariable logistic regression (on probability of being included in the trial for step 4, and on exposure status for step 5) will be used to generate the propensity score, with the variables selected for inclusion in the initial multivariable logistic regression model based on expert/prior knowledge of association with outcome. Those provisional variables listed in the 'Covariates' section along with other variables will be considered.

The propensity score model developed in the validation step in the primary objective will be the basis for the model used in the secondary objectives.

Methods of analysis

An ITT analysis will be carried out for the validation of results in the primary objective, which was used in ONTARGET[18] and the remaining objectives.

For the secondary objectives, a PP analysis will be carried out (in addition to ITT) for all comparisons. Patients who discontinue or switch treatment or start dual therapy, data for original treatment will be included up to and including their calculated date of last dose of the initially prescribed treatment +60 days, to account for repeat prescriptions and ensure exposure groups are correctly categorised. Therefore, patients may contribute more than one exposure period. The two analysis populations are shown in figure 3. Patients will be censored up to the earliest of: outcome of interest, death, leaving general practice date, or last data collection date from the general practice, or the derived date of last dose of study drug when using the PP analysis. If these dates do not occur the patient will be censored after 5.5 years of follow-up (reflecting the maximum follow-up time in the trial).

A Cox proportional hazards model will be used to address the primary composite outcome of time to cardiovascular death, non-fatal MI, non-fatal stroke or hospitalisation for congestive heart failure. Point estimates and two-sided 95% CIs for HRs will be provided for all efficacy outcomes with the bootstrap method used to estimate standard errors. Safety outcomes will be studied using logistic regression. If variability between practices is observed, a mixed effects model will be considered to account for this. A summary table of our protocol compared with the ONTARGET protocol is given in table 2.

Validation of results against ONTARGET

In the primary objective, we will validate the findings from our primary analysis against ONTARGET by determining whether results of the CPRD analysis are comparable with the ONTARGET trial results. The ONTARGET trial demonstrated non-inferiority of telmisartan over ramipril for the primary outcome (HR 1.01, 95% CI 0.94 to 1.09)

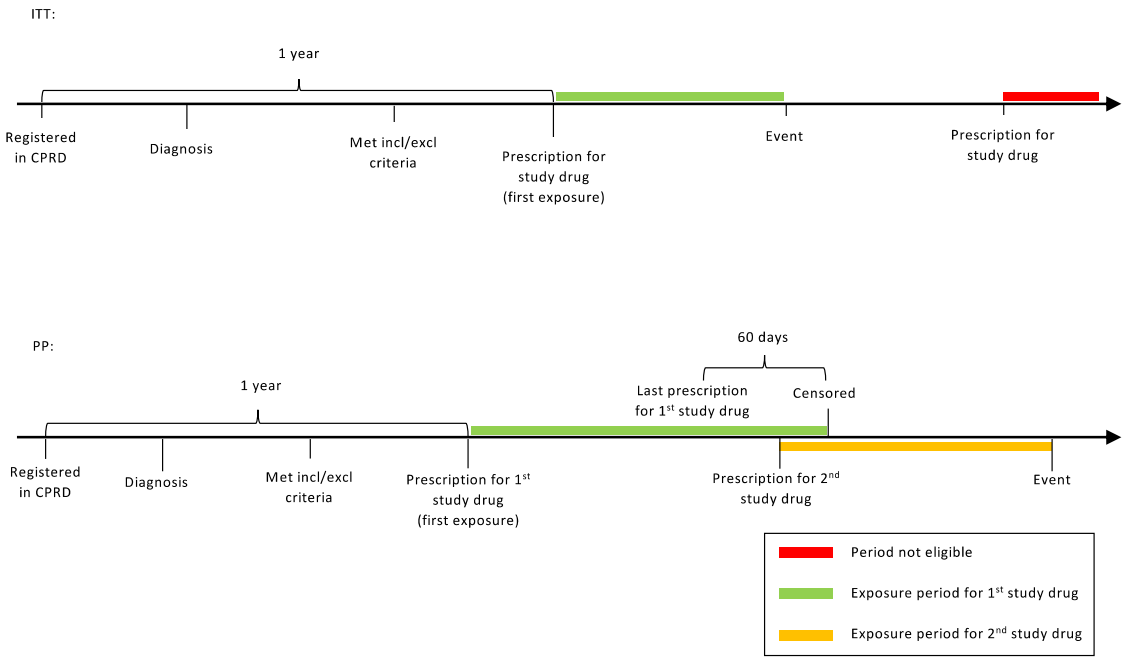

Figure 3 Figure illustration analysis groups to be used to address objectives. ITT timeline demonstrates order that criteria must be met for exposure period to be eligible, with patient no longer being able to contribute additional expose periods after being censored. PP timeline shows in green where patients exposure period can contribute to exposure group 1, then in yellow where a patient switches treatment and can contribute to second exposure group. There will be a small period of overlap, where the patient will contribute to both exposure groups as shown in the figure. CPRD, Clinical Practice Research Datalink; ITT, intention-to-treat; PP, per-protocol.

Table 2 Table of key design aspects of the ONTARGET trial and how these will be interpreted in our CPRD cohort

Protocol component	Description in ONTARGET	Description in CPRD
Eligibility criteria	Patients aged ≥55 years with coronary artery, peripheral vascular, or cerebrovascular disease or high-risk diabetes with end organ damage recruited up to 2004. No restriction on previous ACE inhibitor/ARB use except must be able to discontinue use.	Patients with a prescription for an ACE inhibitor or ARB between 01 January 2001 to 31 July 2019, eligible for HES linkage, aged ≥55 years with coronary artery, peripheral vascular, or cerebrovascular disease or high-risk diabetes.
Treatment strategies	Patients will enter 3-week single blind run-in period to check compliance then will be randomised to one of the three trial arms: ramipril 10 mg+telmisartan placebo, telmisartan 80 mg+ramipril placebo or ramipril 10 mg+telmisartan 80 mg.	Continuous courses of therapy with treatment gaps of <90 days. Dual therapy users defined as patients with overlapping prescriptions who receive additional prescription for the first agent after the second prescription for the second agent.
Assignment procedures	Randomly assigned and will receive a placebo for other drug so unaware which arm they are assigned to.	Based on prescriptions received. Patient can contribute to all three exposure groups at different timepoints.
Follow-up period	Follow-up starts at randomisation and ends at primary event, death, loss to follow-up or end of study. Close out planned in July 2007	Follow-up starts at start of trial-eligible period where exposure period meets trial inclusion/exclusion criteria. Ends at the earliest of: outcome of interest, death, transferred out of practice date, or last data collection from the general practice. If these dates do not occur the patient will be censored after 5.5 years of follow-up.
Outcome	Primary composite outcome of: cardiovascular death, non-fatal MI, non-fatal stroke, hospitalisation for heart failure	Primary composite outcome of: cardiovascular death, non-fatal MI, non-fatal stroke, hospitalisation for heart failure
Analysis plan	Primary analysis time-to-event counting first occurrence of any component of the composite outcome using Cox proportional hazards model.	Match to trial to obtain trial-analogous cohort then will match trial-eligible exposure groups. Cox proportional hazards model will be used for primary analysis.

ARB, angiotensin II receptor blocker; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; MI, myocardial infarction; ONTARGET, Ongoing Telmisartan Alone and the Ramipril Global Endpoint Trial.

under an ITT analysis and showed similar results under a PP analysis giving HR 1.00 (95% CI 0.92 to 1.09).[18]

Since the primary outcome comparing telmisartan vs ramipril showed clear non-inferiority of telmisartan and the upper limit of the 95% CI was within the non-inferiority boundary of 1.13, this will be used to validate results when testing ARB vs ACE inhibitors in the CPRD population. To conclude that our results are comparable with the ONTARGET trial results we have two criteria that must be met.

- First, the effect size for the two exposure groups must be clinically comparable with the ONTARGET findings; the HR for the composite primary outcome (time to cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalisation for congestive heart failure) in the CPRD population under an ITT analysis must be between 0.9 and 1.12.
- Second, the 95% CI for the HR must contain 1.

Handling measurement of adherence to medication

A sensitivity analysis will be carried out to investigate the effect of a run-in period for compliance. The 3-week run-in period in the trial will be replicated by a 28-day period, reflecting a general prescription duration. Follow-up will be started from 28 days after first prescription and those patients who receive no subsequent prescriptions after 28 days will be excluded.

When using efficacy outcomes for validity we expect different adherence in routine clinical practice compared with the trial. Adherence will, therefore, be estimated in the CPRD cohort to enable comparisons with the trial and investigate the extent to which this may have influenced any observed differences in treatment effect. We will estimate the proportion of time covered by prescribing as a proxy measure for adherence in CPRD; this proxy measure assumes that all prescriptions are filled and that a patient takes all tablets in the prescription so is although not completely accurate, provides an indication of adherence.[28]

Missing data

CPRD data have few missing data for drug prescribing and mortality (partly through ONS linkage). Information on important comorbidity is also well recorded. Our approach for handling missing data in terms of the baseline characteristics will depend on the variable itself. Patients with variables missing that cannot be assumed to be missing at random will therefore be excluded from the trial-eligible cohort prior to step 4. In cases where missing data can be assumed to be missing at random or missing completely at random both a complete-case analysis and an analysis using multiple imputation in propensity score modelling to impute missing values will be used.[29]

ETHICS AND DISSEMINATION

Ethics

An application for scientific approval related to use of the CPRD data has been approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare

Products Regulatory Agency (protocol no. 20_012). CPRD are already approved via a National Research Ethnics Committee for purely non-interventional research of this type. Access to the secondary individual patient data from the ONTARGET trial was obtained by the trial investigators and complies with institutional review board approved informed consent forms provided by the individuals from whom the data were collected. Trial participants are identified by unique identifier and names and other personal identifiers other than age were not included in the data transfer.

Dissemination

The results of the study will be submitted to peer-reviewed journals and we anticipate three publications to arise directly from the planned work. Findings will also be presented at conferences such as the International Society for Pharmacoepidemiology Conference. Results will also be published on the London School of Hygiene & Tropical Medicine website and in the PhD thesis of the principal investigator. Results that may impact on treatment guidelines will be shared with policy-makers such as the Medicines and Healthcare products Regulatory Agency and the National Institute for Health and Care Excellence.

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Contributors PJB, LAT and KW contributed to the study question and design. PJB wrote the first draft of this protocol based on original scientific approval applications to ISAC that PJB, LAT, KW, JFEM and CC contributed to. PJB, LAT, KW, AYSW, CL, MC, AS, JFEM and CC contributed to further drafts and approved the final version.

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Competing interests PJB is funded by a GSK PhD studentship. CC has received consultation, advisory board membership or research funding from the Ontario Ministry of Health, Sanofi, Pfizer, Leo Pharma, Astellas, Janssen, Amgen, Boehringer-Ingelheim and Baxter. In 2018 she co-chaired a KDIGO potassium controversies conference sponsored at arm's length by Fresenius Medical Care, AstraZeneca, Vifor Fresenius Medical Care, relypsa, Bayer HealthCare and Boehringer Ingelheim. She co-chairs the cloth mask knowledge exchange, a stakeholder group that includes cloth mask manufacturers and fabric distributors. MC is an employee of, and own shares in, GSK.

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5.2 Additional detail of methods outlined in published protocol

In the subsequent subsections I provide additional detail on the steps taken to develop the study population in CPRD GOLD, relating to step 4 (matching to trial participants) and step 5 (matching trial-eligible exposure groups) in the published protocol. I also provide further detail on addressing the secondary objectives outlined in the protocol of extending findings to underrepresented and excluded groups.

5.2.1 Additional detail on Step 4: matching to trial participants

After applying trial inclusion and exclusion criteria as described in the published protocol in step 2 and 3, to ensure the cohort was closely representative of the ONTARGET trial population, propensity-score—matching was used.[91] The model used was achieved by appending ONTARGET individual patient level data, obtained from the trial sponsor, to the pool of trial-eligible ACEi exposed periods and mapping variables available in ONTARGET to those in CPRD GOLD. Multivariable logistic regression for the probability of being included in the trial was used, with ONTARGET participants inclusion status equal to 1 and CPRD patients inclusion status equal to 0.

All variables that were available in both ONTARGET and CPRD, and that were considered to be potentially associated with inclusion in the trial and outcomes studied in ONTARGET, were eligible for inclusion in the multivariable model.[92] Variables were then excluded if there were less than 10% of ONTARGET included patients in any of the categories or if the definition or capture was likely to differ across the two data sources, such as medication history as prescribing practices varied substantially across the two time periods studied, i.e., between the time period that the CPRD cohort was selected (01/01/01-31/07/19) and the date that the trial was performed (start date 2001, recruitment completed 2003, results published 2008). The form of continuous variables was chosen based on that which resulted in a linear association with trial inclusion status; a categorical form was chosen if linearity was not

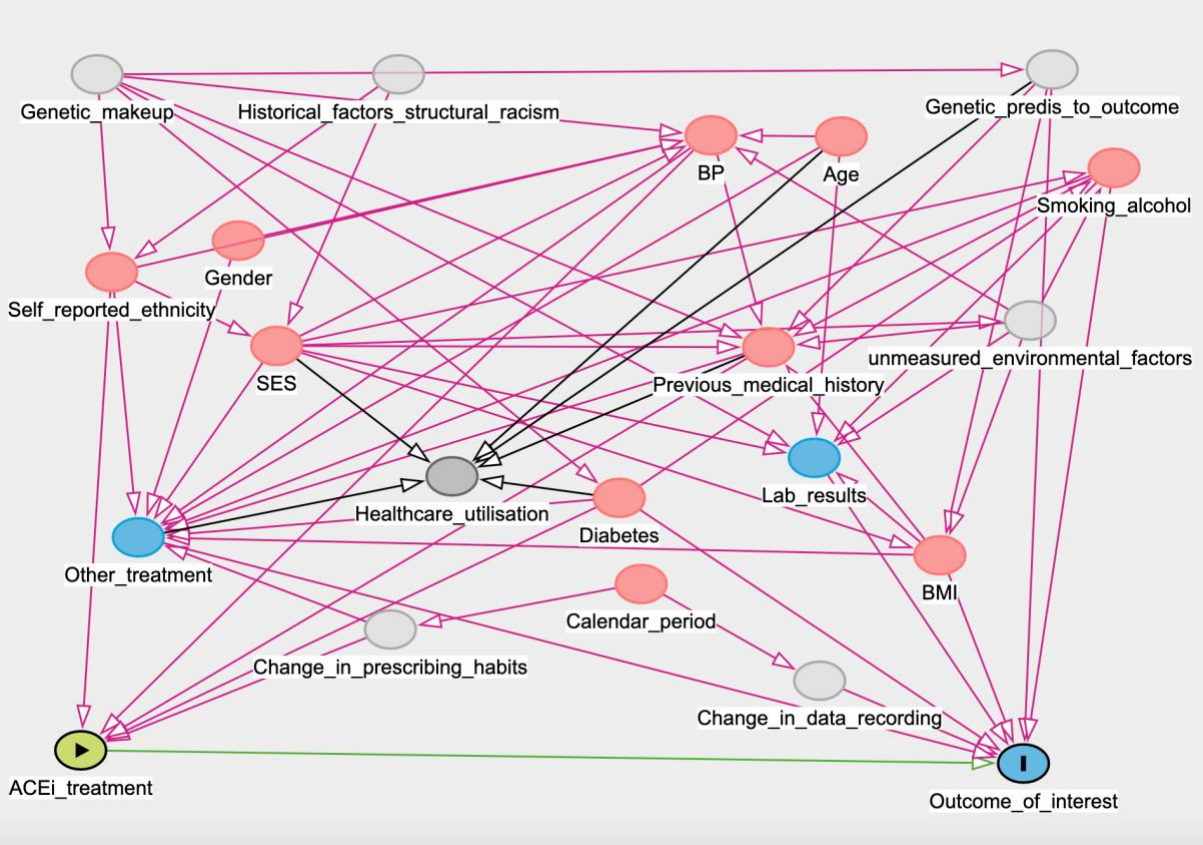
obtained. The requirement for higher order terms of continuous variables was tested using a likelihood ratio test. Using the propensity scores generated from the model each individual ONTARGET participant was then 1:1 matched to the closest trial-eligible ACEi exposed period, using a caliper of 0.25 x standard deviation of the propensity score. Once a trial-eligible period for a patient had been matched, all other trial-eligible periods for that patient were dropped, so a patient could only be included once. This resulted in a trial-matched ACEi exposed cohort. Kernel density plots and standardised differences (<0.1) were used to assess balance.[92].

5.2.2 Additional detail on Step 5: matching trial-eligible exposure groups

Appending the cohort of trial-matched ACEi patients (created from 1:1 matching ONTARGET patients to trial-eligible ACEi patients described in section 5.2.1) with trial-eligible ARB patients in CPRD GOLD, the second propensity score model was developed using multivariable logistic regression for the probability of receiving an ACEi. Using *a priori* knowledge and clinical input, all variables considered to be potentially associated with the choice of treatment and outcomes were included. This is displayed in the directed acyclic graph (DAG) in Figure 5.1. On creating the DAG it was recognised that self-reported ethnicity could be thought of as a proxy for a combination of genetic and non-genetic information including behaviour, cultural and lived experiences such as racism, which are not directly reported in the dataset. Additionally, by including variables such as BMI and lab results including BP it was assumed that unmeasured variables such as environmental factors were accounted for in analysis via these proxy variables. Due to the appended cohorts being from the same data source additional variables to those included in the first propensity score model (matching to ONTARGET) were available for selection and were included, such as socio-economic status indicators. As with the previous propensity score model, the form of continuous variables was chosen based on that which resulted in a linear association. In

addition, two-way interactions between inclusion criteria diagnoses (peripheral artery disease, coronary artery disease, cerebrovascular disease, high-risk diabetes), and key demographics and vital signs (ethnicity, age, sex, BMI, SBP, DBP) were also considered in a backwards selection approach.

The model developed in step 5 to balance between trial-eligible exposure groups was used to explore trial replicability in a propensity-score—matched analysis cohort where patients had comparable characteristics to those in ONTARGET and also a propensity-score—weighted analysis where patients were trial-eligible but possessed characteristics representative of those being prescribed these medications in the UK, therefore more diverse than trial



Notes: BP= blood pressure; SES= socio-economic status; BMI= body-mass-index

Figure 5.1 Directed acyclic graph for determining variables included in propensity score model

participants. Comparing these approaches enabled an assessment of whether trial results could be replicated in a trial-eligible cohort with patients with more diverse characteristics

and a larger sample, and in turn analyses could be extended to underrepresented and excluded groups.

5.2.3 Additional detail on extending findings to underrepresented and excluded groups

When extending to trial underrepresented and excluded groups, propensity-score weighting was used as the main analysis. This increased sample size and included more diverse users than the trial which was required to extend the findings to trial underrepresented and excluded groups. This approach provided sufficient power to examine any treatment heterogeneity by subgroups of interest.[93] This was achieved by fitting an interaction term between treatment and subgroup of interest to the Cox model for the propensity-score—weighted cohort. Balance of covariates after weighting was additionally checked within strata of subgroups and analysis was adjusted for any imbalanced variables. The underrepresented groups studied in CPRD GOLD were females, those aged over 75 years and those with CKD, defined as eGFR<60 ml/min/1.73m^2. For CKD, to increase the sample size the trial exclusion criteria of baseline serum creatinine >265μmol/L was removed.

5.2.4 Extension of methods to CPRD Aurum

To increase sample size, ONTARGET was also replicated in CPRD Aurum to enable Black and South Asian individuals to be studied as an underrepresented group. Since the ethnic groups of interest were Black, South Asian, and White individuals the cohort was restricted to include only patients from either of these three ethnic groups, excluding patients who had missing self-reported ethnicity. Methods in the published protocol were then applied omitting step 4 (matching to trial participants). Therefore, the propensity-score model in step 5 (balance trial-eligible exposure groups) was developed using ACEi trial-eligible patients as opposed to trial-matched ACEi patients. Furthermore, since diversity of patients was required and increased sample size, a propensity-score—weighted analysis was used as opposed to a

propensity-score matched analysis. As in CPRD GOLD, to explore treatment effect heterogeneity by ethnicity an interaction term between ethnicity and treatment was fitted.

5.3 Amendments to methods outlined in published protocol

Deviations from the published protocol are included in Appendix 2: Supplementary material from Research paper 2. Detail on amendments to the published protocol to assess bias introduced in the definition of dual users and the impact of time-related bias related to treatment switchers are described below.

5.3.1 Dual therapy definition

The definition of a dual user outlined in the published protocol was adapted to include a condition that the start of the second prescription for the first agent needed to fall within 90 days of the date of the second prescription for the second agent. This was implemented to ensure the definition captured dual users and not treatment switchers. Follow-up was then started from the date this criteria was met. Results from this analysis are presented in Chapter 7. To assess the impact of various biases introduced in the definition of a dual user, two alternate definitions were included. These are displayed in Figure 7.1 of the included Research paper 4 in Chapter 7.

5.3.2 Methods related to investigating biases introduced from treatment switching

Newer medications are often prescribed to healthier patients with less comorbidities,[94] which could potentially create a healthier group in the ARB exposure pool compared to ACEi users. Additionally, patients receiving an old medication are often switched to a newer medication therefore a patient would have had to survive up to the point of switching to be a switcher, introducing survivor bias. Figure ***5.2*** shows a bar chart for number of prescriptions

in CPRD Aurum for each treatment group. It can be seen that ARBs are still less prescribed than ACEis.

One suggested way to account for this bias and differences in prescribing often observed in observational studies including prevalent users is implementing a 'prevalent new user design' proposed by Suissa et al..[95] In this design eligible periods for the new drug (ARB) would have only been allowed to match to participants in their respective exposure set. Where the exposure set consists of eligible periods from the older drug (ACEi) that started within a specified time period related to the eligible period of interest. As well as this, variables such as time since first prescription and number of previous prescriptions for both the new drug of interest and the older comparator drug would be carefully matched within the exposure set. Despite the encouraging prospects of this design and the potential to address biases, this method can be computationally difficult to implement in large complex data sources. Therefore, after discussions with colleagues who implemented this method to large EHR cohorts and colleagues with experience of attempting to apply this method to ongoing trial replication analysis,[43] a second approach was developed which attempted to loosely replicate the methodology of the prevalent new user design. Here, similar variables to those that would have aided the exposure set were created. The time-related variables considered included calendar year of start of trial-eligible period, time since first trial-eligible period (irrespective of exposure group), number of prior ARB and ACEi trial-eligible periods prior to the trial-eligible period of interest. These variables were then added into the propensity score model and considered in two-way interactions when applying step 5 (balance between trial-eligible exposure groups) and matching among the CPRD exposure groups. This ensured treatment switchers were matched only to a patient in the opposing exposure group who had previously been treated for the same length of time and the period being matched was within the same year as the switch.

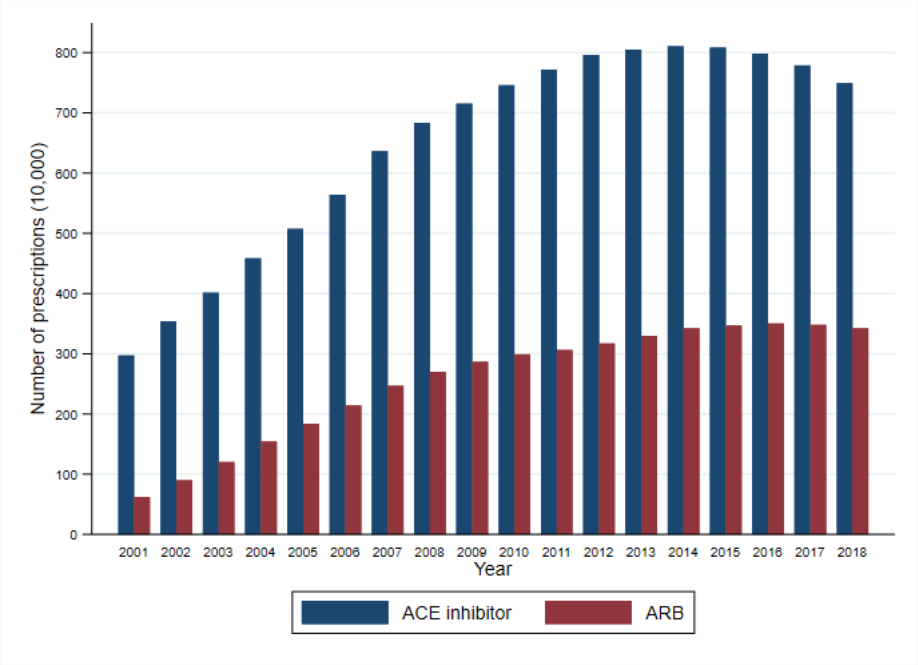


Figure 5.2 Bar graph of number of prescriptions for ARB and ACE inhibitor in CPRD Aurum from 2001 to 2018.

5.3.3 Safety outcomes

5.3.3.1 Methods related to investigating time-related biases in safety outcomes

Due to the concerns over time-related bias and treatment switchers, different scenarios were explored in addition to the original analysis described in the published protocol. First, the outcomes were analysed among a restricted cohort, including the first trial-eligible period for patients who had not switched treatment, i.e., had not had an eligible period contributing to the opposing treatment group prior to the eligible period of interest (denoted as non-switchers). Secondly, a time restriction was added that the outcome had to occur within 3 months of the start of the trial-eligible period, which is commonly seen in the reporting of adverse events. Thirdly, a combination of both restricting to non-switchers and the outcome occurring within 3 months.

5.3.3.2 Alternate analysis for assessing safety outcomes

Since ONTARGET referred to safety outcomes as reasons for permanent discontinuation, an alternate definition of a safety event was explored as an additional analysis. Events which occurred after the start of the trial-eligible period but prior to the end of an eligible period were classified as a safety event to denote a reason for discontinuation. Here the end of an eligible period i.e., the prescription end date prior to a gap of 90 days occurring was defined as discontinuation date. This is detailed in Research paper 2. For this alternate analysis of assessing safety outcomes (safety events as reasons for discontinuation) time-related bias was also explored by restricting the cohort to non-switchers.

5.4 Approach to addressing Research aim 2

5.4.1 Addressing Research aim 2 – objective 1

To investigate optimal methods to implement trial replication techniques, after applying trial criteria, different approaches were applied. These are described below with approach 1 having most restrictions and approach 3 having the least restrictions.

Approach 1 (conducted in CPRD GOLD):

1. ONTARGET trial criteria applied
2. ONTARGET trial participants 1:1 matched to closest ACEi trial-eligible period to create ACEi trial-matched cohort using propensity score model for probability of trial inclusion (requires access to ONTARGET trial data)
3. Second propensity score model developed using ACEi trial-matched cohort and ARB trial-eligible cohort for probability of receiving an ACEi
4. ACEi trial-matched patients 1:1 matched to closest ARB trial-eligible patients using propensity scores generated from model above (step 3) and used in propensity-score—matched analysis.

Approach 2 (conducted in CPRD GOLD):

1. ONTARGET trial criteria applied
2. ONTARGET trial participants 1:1 matched to closest ACEi trial-eligible period to create ACE inhibitor trial-matched cohort for probability of trial inclusion (requires access to ONTARGET trial data)
3. Second propensity score model developed using ACEi trial-matched cohort and ARB trial-eligible cohort for probability of receiving an ACEi
4. Propensity score weights generated for ACEi trial-eligible and ARB trial-eligible patients using model above (step 3) and used in propensity-score—weighted analysis.

Approach 3 (conducted in CPRD Aurum):

1. ONTARGET trial criteria applied
2. Propensity score model developed using ACEi trial-eligible and ARB trial-eligible cohort for probability of receiving an ACEi
3. Propensity score weights generated for ACEi trial-eligible and ARB trial-eligible patients using model above (step 2) and used in propensity-score—weighted analysis.

5.4.2 Addressing Research aim 2 – objective 2

Finally, to explore whether the proposed trial replication technique is transportable to alternate data sources the SIDIAP database was used. The optimal method from the approaches described in 5.4.1 (i.e., method that resulted in comparable results with least restrictions) was implemented in SIDIAP. Methods prior to step 4 followed those outlined in the published protocol. Data from SIDIAP has been available since 2006.[88] To ensure patients were registered at the practice for at least 1 year prior to the observation period, patients were selected who had a dispensation for an ARB or ACEi from 1/1/2007-31/7/2019. Dispensations were used in place of prescriptions to assess adherence by comparing results from the CPRD analysis which used prescription data only.

Chapter 6. Results from replication of the ONTARGET trial and treatment effectiveness in underrepresented and excluded groups using CPRD

Chapter summary

- This chapter includes Research paper 2 which presents the results from the replication of the ONTARGET single therapy comparison using CPRD GOLD as well as the results from extending the CPRD cohort to underrepresented and excluded groups of females, those aged ≥75 years and those with CKD, addressing Research Aim 1.
- I provide additional detail on the results from methods implemented to replicate the trial and provide a detailed summary of analysis related to safety outcomes and how time-related bias was explored.
- Section 6.2 includes Research paper 3 which presents results from extending analysis to the underrepresented groups of Black and South Asian individuals after first replicating ONTARGET in CPRD Aurum.
- Finally, I summarise the results from the various approaches taken to replicate the trial to address Research Aim 2– objective 1, concluding which approach is considered optimal to obtain results closely comparable to the ONTARGET trial.

6.1 Results from analysis in CPRD GOLD

6.1.1 Replication of ONTARGET in CPRD GOLD and extending methods to females, those with CKD and patients aged ≥75 years (Research paper 2)

6.1.1.1 Research paper 2

The research paper presenting results from replication of the ONTARGET trial in CPRD GOLD and extension of methods to the underrepresented and excluded groups of those with CKD, females and patients aged ≥75 years is available on the MedRxiv preprint server and I am currently preparing responses to peer-reviewers comments from submission to the American Journal of Epidemiology. The results presented in this paper relate to Research Aim 1. Supplementary material for this research paper are available in Appendix 2: Supplementary material from Research paper 2.

Further detail on developing the study cohort used in analysis, corresponding to the steps outlined in Chapter 5, and additional results from assessing safety outcomes are described in the subsequent sections.

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SECTION A – Student Details

Student ID Number	1800205	**Title**	Miss
First Name(s)	Paris Jade		
Surname/Family Name	Baptiste		
Thesis Title	Real-world effectiveness and adverse events caused by ACE inhibitors and ARBs for reduction in cardiovascular events with validation against the ONTARGET trial		
Primary Supervisor	Laurie Tomlinson		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	American Journal of Epidemiology
Please list the paper's authors in the intended authorship order:	Paris J Baptiste, Angel YS Wong, Anna Schultze, Catherine M Clase, Clémence Leyrat, Elizabeth Williamson, Emma Powell, Johannes FE Mann, Marianne Cunnington, Koon Teo, Shrikant I Bangdiwala, Peggy Gao, Laurie Tomlinson,

	Kevin Wing
Stage of publication	**Undergoing revision**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author on this paper. I contributed to the study question and design. I carried out data management and conducted the analysis for the work presented in this paper. I wrote the first draft of this mansucript and drafted subsequent versions.

SECTION E

Student Signature	[redacted]
Date	7/6/23

Supervisor Signature	[redacted]
Date	7/6/23

Cardiorenal effects of Angiotensin-converting enzyme inhibitors and Angiotensin receptor blockers in people underrepresented in trials: analysis of routinely collected data with validation against a target trial

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ABSTRACT

Cardiovascular disease (CVD) is a leading cause of death globally. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), compared in the ONTARGET trial, each prevent CVD. However, trial results may not be generalisable and their effectiveness in underrepresented groups is unclear.

Using trial replication methods within routine-care data to validate findings, we explored generalisability of ONTARGET results. For people prescribed an ACEi/ARB in the UK Clinical Practice Research Datalink GOLD from 1/1/2001-31/7/2019, we applied trial criteria and propensity-score methods to create an ONTARGET trial-eligible cohort. Comparing ARB to ACEi, we estimated hazard ratios for the primary composite trial outcome (cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure), and secondary outcomes. As the pre-specified criteria were met confirming trial replicability, we then explored treatment heterogeneity among three trial-underrepresented subgroups: females, those aged ≥75 years and those with chronic kidney disease (CKD).

In the trial-eligible population (*n*=137,155), results for the primary outcome demonstrated similar effects of ARB and ACEi, (HR 0.97 [95% CI: 0.93, 1.01]), meeting the pre-specified validation criteria. When extending this outcome to trial-underrepresented groups, similar treatment effects were observed by sex, age and CKD. This suggests that ONTARGET trial findings are generalisable to trial-underrepresented subgroups.

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of death globally, with older people and those with chronic kidney disease (CKD) at particularly high-risk.[6] Medications used to prevent cardiovascular events are prescribed based on evidence from randomised controlled trials. However, there is uncertainty whether trial evidence is generalisable to all patient groups because trials often restrict inclusion to younger patients with fewer comorbidities,[94, 96] and because trial patients are likely to have better adherence and monitoring. Observational studies using routinely-collected healthcare data can use trial-replication methods to validate findings against those from randomised trials, sometimes referred to as "benchmarking".[42, 44-46, 97-99] When similar findings are observed, we have more confidence that sources of bias and confounding are minimised, and aided by a large sample size and more diverse population, can then examine treatment effectiveness in trial underrepresented or excluded groups.[100]

ONTARGET was a large global trial with a follow-up of 3.5-5.5 years that compared the cardiovascular effects of angiotensin receptor II blocker (ARB) (telmisartan) to angiotensin-converting enzyme inhibitor (ACEi) (ramipril) among patients who had vascular disease or high-risk diabetes.[22, 30] Ramipril had previously been shown compared with placebo, to reduce the composite outcome of myocardial infarction, stroke or cardiovascular death by 22% (95% CI: 14-30%).[14] The findings of the ONTARGET trial of non-inferiority for telmisartan vs ramipril led to telmisartan's licensing for cardiovascular event reduction in 2009[101] and were a major contribution to perception of equivalent treatment effectiveness for ARB and ACEi. However, the relative effectiveness of ARB and ACEi for patients not included or underrepresented in ONTARGET remains uncertain.

The aims of this study were to demonstrate whether the primary and secondary outcome results of the ONTARGET trial could be replicated in UK routinely-collected data and, if so,

to examine treatment effects in females, those aged ≥75 years and those with CKD, all groups that were underrepresented in ONTARGET.

METHODS

The RCT

The secondary objective of the ONTARGET trial was to demonstrate the non-inferiority of telmisartan (ARB) vs. ramipril (ACEi) on reduction of cardiovascular events among patients who had vascular disease or high-risk diabetes but who did not have heart failure. The primary objective was to determine if dual therapy was superior to ACEi alone.[22] Patients were eligible if they were aged ≥55 years and had a history of either coronary artery, peripheral artery, or cerebrovascular disease or high-risk diabetes with end organ damage. Previous users of an ARB/ACEi were eligible but were excluded if they were unable to discontinue use. Recruitment for the trial closed in 2003 and 25 620 patients were recruited. The primary outcome of the trial was a composite of cardiovascular-related death, myocardial infarction (MI), stroke or hospitalisation for heart failure.

Study results

Among the participants included in the trial 26.7% were female and mean age was 66.4 years with 14.7% of participants aged ≥75 years. 23.6% of patients had CKD and mean creatinine at baseline was 94.2 μmol/l.[30] 8576 patients were randomised to receive ramipril and 8542 patients were randomised to receive telmisartan. The primary outcome occurred in 1412 (16.5%) patients in the ramipril group and 1423 (16.7%) patients in the telmisartan group. For the primary composite outcome for telmisartan vs ramipril, HR 1.01 (95% CI: 0.94, 1.09).[22]

The emulation using observational data

Data sources and study cohort

We aimed to replicate the ONTARGET trial by developing a propensity-score—weighted trial-eligible cohort in the UK Clinical Practice Research Datalink (CPRD) GOLD primary care dataset. As of 2019, patients currently contributing to UK practices covered 4.32% of the UK population and patients included were representative of the UK general population in terms of age, sex and ethnicity.[64, 70] Primary care data from CPRD were linked to hospitalisation data from Hospital Episode Statistics (HES) and death registrations from the Office for National Statistics (ONS), with ~52% of patients in CPRD GOLD eligible for linkage in 2019.[70]

Our study protocol has been published;[102] key components are detailed in Table ***6.1***, with deviations detailed in Table S1 of Appendix 2: Supplementary material from Research paper 2. Steps to create the study cohort are outlined below.

Table 6.1 Key design aspects of the ONTARGET trial, emulation protocol and deviations from protocol with implementation in CPRD GOLD data.

Protocol component	**ONTARGET**	**Trial emulation protocol**	**Implementation in CPRD Aurum**
Eligibility criteria	Patients aged ≥55 years with coronary artery, peripheral artery or cerebrovascular disease or high-risk diabetes with end organ damage recruited up to 2004. No restriction on previous ACEi/ARB use except must be able to discontinue use.	Patients with a prescription for an ACEi or ARB between 01 January 2001 to 31 July 2019, eligible for HES linkage, aged ≥55 years with coronary artery, peripheral vascular, or cerebrovascular disease or high-risk diabetes.	As in protocol.
Treatment strategies	Patients entered 3-week single blind run-in period to check compliance then randomised to one of three trial arms: ramipril 10 mg + telmisartan placebo,	Continuous courses of therapy with treatment gaps of <90 days.	As in protocol.

Protocol component	ONTARGET	Trial emulation protocol	Implementation in CPRD Aurum
	telmisartan 80 mg + ramipril placebo or ramipril 10 mg + telmisartan 80 mg.		
Assignment procedures	Randomly assigned and received placebo for other drug so unaware which arm assigned to	Based on prescriptions received. Patient can contribute to both exposure groups at different timepoints	As in protocol.
Follow-up period	Follow-up started at randomisation and ended at primary event, death, loss to follow-up or end of study. Close out was planned in July 2007.	Follow-up starts at start of trial-eligible period where exposure period meets trial inclusion/exclusion criteria. Ends at the earliest of: outcome of interest, death, transferred out of practice date, or last data collection from the general practice. If these dates do not occur the patient will be censored after 5.5 years of follow-up	As in protocol.
Outcome	Primary composite of: cardiovascular death, MI, stroke, hospitalisation for heart failure	As in ONTARGET, defined using ICD10, Read codes and death registries from ONS.	As in protocol.
Analysis plan	Primary analysis under time-to-event counting first occurrence of any component of the composite outcome using Cox proportional hazards model. Intention-to-treat as main analysis	Match to trial to obtain trial-analogous cohort then will match trial-eligible exposure groups. Cox proportional hazards model will be used for primary analysis.	Analysis conducted on one randomly selected trial eligible period per patient. Balance of covariates obtained by propensity score weighting for probability of receiving an ACEi and adjusted for any imbalanced variables for main analysis. Weighting as opposed to matching to increase sample size and diversity of cohort to enable inferences to be

Protocol component	ONTARGET	Trial emulation protocol	Implementation in CPRD Aurum
			extended to underrepresented groups. Cox proportional hazards model used for primary analysis. Propensity-score—matched analysis carried out as sensitivity.

- ***Step 1: Create exposed periods***

We selected patients who were ever prescribed any dose of an ACEi and/or an ARB from 1/1/2001-31/7/2019 and had been registered at an up-to-standard practice (meeting minimum data quality criteria[64]) for at least 12 months at the time of their first prescription (Figure S1 in Appendix 2: Supplementary material from Research paper 2). We defined 'exposed periods' as all continuous courses of therapy, with a calculated prescription gap of >90 days referred to as an 'unexposed period'. We did not restrict the study cohort to new users; therefore, we started their follow-up at the start of the selected exposed period for which they met trial criteria and were included in the cohort, thus emulating recruitment into the ONTARGET trial. Patients were not required to have a minimum length of exposure to be considered.

- ***Step 2: Create trial-eligible periods***

Using Read diagnostic and ICD-10 codes, we selected exposed periods that met the ONTARGET trial criteria. This resulted in a pool of trial-eligible exposed periods within individuals in CPRD. Specific diagnostic codes used for cohort identification are available for download: https://doi.org/10.17037/DATA.00002112. We have assumed the codes used to capture covariates in CPRD reflect the clinical covariates used in ONTARGET with minimal misclassification.

- ***Step 3: Balance across exposure groups***

The original trial coordinator, Population Health Research Institute, anonymised and provided access to the ONTARGET trial data. This allowed us to examine whether trial results could be replicated when the CPRD cohort had similar covariate distribution to the ONTARGET trial participants and when distribution differed. The latter enabled us to extend findings to underrepresented and excluded groups aided with a cohort with more diverse characteristics than the trial and more representative of the UK population receiving these medications in routine care.

In the main analysis, to ensure balance among CPRD groups used in analysis, we randomly selected one trial-eligible period per patient from the cohort of ARB and ACEi trial-eligible periods and generated propensity-scores and obtained inverse probability weights,[103] using a propensity score model for the probability of receiving an ACEi. Ensuring balance using propensity-score weights instead of matching, enabled us to maximise the number of participants included in the analysis. Patients could contribute to both ARB and ACEi exposed cohorts but trial-eligible periods in the two exposure groups that had prescription start dates on the same day were excluded from both groups. Additional detail on achieving balance between groups is available in Appendix 2: Supplementary material from Research paper 2.

Variables included in the propensity-score model were chosen based on *a-priori* knowledge of predictors of treatment with an ACEi and are displayed in Table S3 in Appendix 2: Supplementary material from Research paper 2. We considered comorbidities, medication history, demographics, and lifestyle factors. As our cohort included prevalent users, we also included variables associated with switching treatments, such as time since first trial-eligible period, and number of previous ARB/ACEi trial-eligible periods.[95]

Procedures

- ***Exposures and outcomes***

To maximise study power and generalisability, we compared outcomes between users of ARB and ACEi, rather than telmisartan and ramipril specifically. Outcomes were selected to replicate those in the ONTARGET trial.

- Primary outcome: composite of cardiovascular death, myocardial infarction (MI), stroke, or hospital admission for congestive heart failure
- Secondary outcomes:
    - Main secondary outcome: composite of cardiovascular death, MI, or stroke
    - Individual components of primary outcome
    - Death from non-cardiovascular causes
    - All-cause mortality
- Further secondary and other outcomes: (separately) newly-diagnosed congestive heart failure; revascularisation procedures; loss of glomerular filtration rate (GFR) or development of end-stage kidney disease (ESKD) (defined as: 50% reduction in estimated GFR (eGFR), start of kidney replacement therapy (KRT) or development of eGFR < 15ml/min/1.73m^2); development of ESKD (defined as: start of KRT or development of eGFR < 15ml/min/1.73m^2); microvascular complications of diabetes mellitus. GFR was calculated using the CKD-Epi equation 2009 without reference to ethnicity.[104]
- Safety outcomes: cough; angioedema; hyperkalaemia (potassium >5.5 mmol/L); ≥30% increase in serum creatinine.

Statistical analysis

- ***Benchmarking against the ONTARGET trial***

Using an intention-to-treat approach for the main analysis, we compared cohorts using a Cox proportional hazards model weighted by propensity-scores with robust standard errors. The Cox model was additionally adjusted for any variables that demonstrated imbalance after propensity-score—weighting, using standardised differences with <0.1 as a cut-off.[105] To replicate the trial per-protocol analysis, we also carried out an on-treatment analysis of ARB vs ACEi, additionally censoring at date of discontinuation of trial-eligible period, i.e., calculated end date of prescription when subsequent prescription gap of >90 days occurred, when a patient switched treatment or became a dual user.

Because ONTARGET reported relative risks for safety outcomes, we used a propensity-score—weighted log-binomial model with robust standard errors. Treatment cessation was defined as the end of an included trial-eligible exposed period (i.e., a prescription gap of >90 days after the calculated prescription end date). The last safety event which occurred before treatment cessation was considered as the reason for treatment cessation and these results were compared with ONTARGET.

We replicated the subgroup analyses carried out in ONTARGET using a propensity-score—weighted Cox proportional hazards model fitted with an interaction term for subgroup and treatment and used a Wald test to identify any effect modification. The subgroups studied were as in ONTARGET: sex, age (<65 years, 65-74 years, ≥75 years), systolic blood pressure (SBP) (≤134 mmHg, 135-150 mmHg, >150 mmHg), diabetes, and cardiovascular disease at study entry. For SBP the closest measurement prior to the start of the trial-eligible period but within 6 months was used. In addition, we included CKD status at baseline as a subgroup (CKD: eGFR <60 mL/min/1.73m^2).

- ***Validation criteria***

A priori, we defined replicability of the primary outcome of ONTARGET (HR 1.01 [95% CI: 0.94, 1.09]) if the HR estimates from the propensity-score—weighted analysis for ARB vs ACEi were between 0.9-1.12 and the 95% CI for the HR contained 1.0.[102]

Extending findings to trial-underrepresented groups

Conditional on the validation criteria being met, we examined whether there was treatment heterogeneity among the underrepresented groups using interaction terms for sex, age, and CKD status. For CKD status, we repeated methods to create the propensity-score—weighted cohort after removing the trial exclusion criteria of baseline serum creatinine >265 μmol/L.

Sensitivity analyses

Reasons for potential differences in effect estimates in the RCT and emulation that may lead to a false conclusion on replication due to cancelling out of biases was explored through design choices and sensitivity analyses described in Table S2 in Appendix 2: Supplementary material from Research paper 2. To explore any benefits to using a propensity-score—matched trial-eligible cohort, which ensured patient characteristics were comparable to trial participants, as opposed to a propensity-score—weighted trial-eligible cohort where patients were more diverse, we 1:1 propensity-score—matched ONTARGET participants to trial-eligible ACEi patients then matched this trial-matched ACEi cohort to the closest trial-eligible ARB period and repeated the analyses.[102] This is further detailed in Appendix 2: Supplementary material from Research paper 2.

To assess the impact of differential loss to follow-up in the trial and emulation we reanalysed excluding patients who were lost to follow-up in the first 12 months.

To examine the impact of including patients who may have only received one prescription for an ARB/ACEi, we started follow-up from 28 days after the start of the trial-eligible period, excluding patients if there were no prescriptions after 28 days.

We assessed the impact on the kidney outcomes of specifying sustained deterioration of kidney function. This required eGFR <15ml/min/1.73m^2 or 50% reduction in eGFR on two occasions at least 3 months apart for loss of eGFR or ESKD and development of ESKD outcomes.

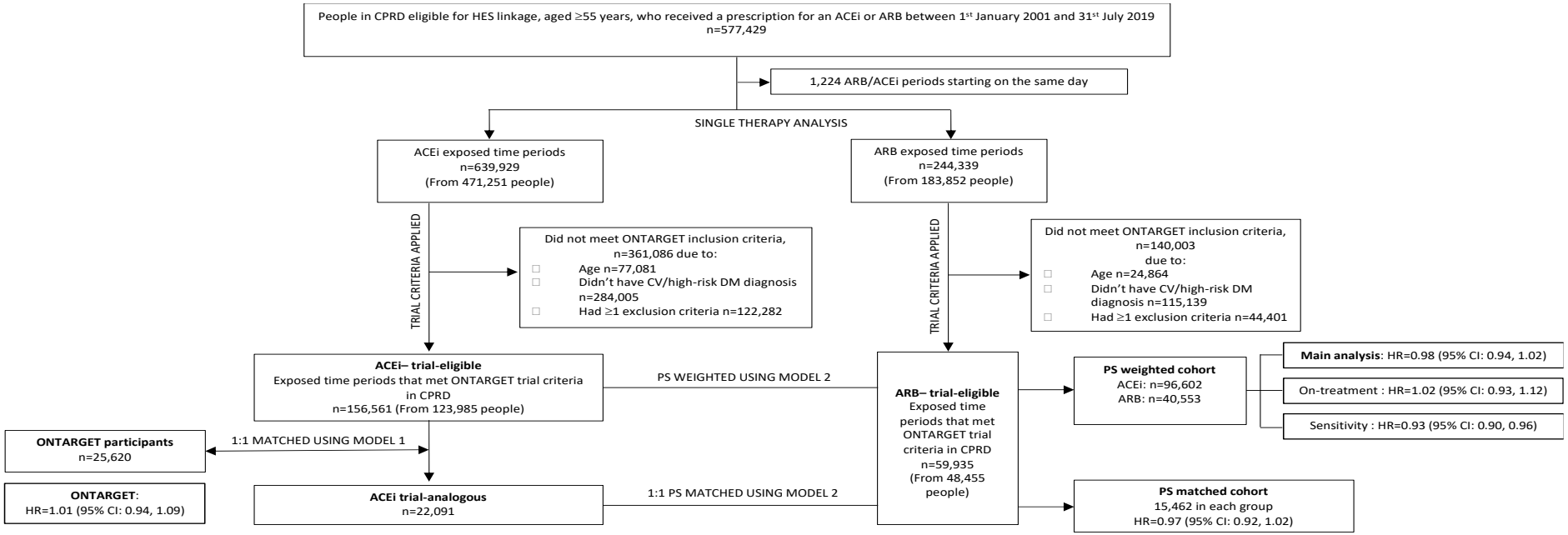
As a post-hoc sensitivity analysis, we assessed the impact of changing between medications in CPRD for safety outcomes by restricting the cohort to patients' first trial-eligible exposed period, and by excluding those with previous exposure to the alternative drug at any time before.

RESULTS

Baseline characteristics

After propensity-score—weighting, 96 602 ACEi and 40 553 ARB prescribed patients were included in the comparison of ARB vs ACEi users (Figure 6.1).

Mean age was similar across exposure groups (71 years), slightly older than in ONTARGET (66 years). There was a higher proportion of females across each exposure group (~51%) than in ONTARGET (27%) (Table ***6.2***). Balance before and after weighting is shown in Table S4 of Appendix 2: Supplementary material from Research paper 2. Imbalance remained for several time-related variables: time since first trial-eligible period, calendar year of trial-eligible period and number of prior ARB trial-eligible periods, so analysis was adjusted for these variables.



Notes: DM: diabetes mellitus; PS: propensity score. Model 1 is the propensity score model for the probability of being included in the trial. Model 2 is the propensity score model for probability of receiving an ACEi built using the cohort of ACEi trial-analogous patients appended to the ARB trial-eligible patients. The PS weighted analysis uses inverse PS weights generated from running Model 2 on 1 randomly selected trial-eligible ARB period per patient and 1 randomly selected trial-eligible ACEi period per patient. For the main analysis follow-up was from the start date of the trial-eligible period and patients were censored at the earliest date of: outcome, death, transferred out of practice, last practice data collection, or 5.5 years from the start of trial-eligible period, to reflect the maximum follow-up in the trial. In the on-treatment analysis, patients were additionally censored at the end of an eligible period, if they switched treatment or started dual therapy. This was denoted as date of last drug and patients were censored at this date +60 days. In the sensitivity analysis follow-up started from 28 days after the start of the eligible period (to reflect the typical length of prescription), excluding patients if there were no prescriptions after 28 days. 51,775 ACEi patients and 18,410 ARB patients were excluded for heart failure. PS weighted cohort included one randomly selected ACEi trial-eligible period and one randomly selected ARB trial-eligible per patient, among these patients 27,383 ACEi trial-eligible patients and 7,902 ARB trial-eligible patients were excluded from the analysis due to having missing values for variables included in the PS model.

Figure 6.1 Study profile

Table 6.2 Baseline characteristics of CPRD trial-eligible patients after applying trial criteria included in propensity-score—weighted analysis compared to ONTARGET

Characteristic	ACEi *n=96 602*	ARB *n=40 553*	ONTARGET *n=25 620*
Age - year	70.8 ± 9.0	71.2 ± 8.7	66.4 ± 7.2
Systolic BP– mmHg	147.4 ± 20.7	148.1 ± 20.7	141.8 ± 17.4
Diastolic BP – mmHg	80.1 ± 10.7	79.7 ± 10.5	82.1 ± 10.4
Body-mass index	28.3 ± 5.3	28.8 ± 5.4	28.2 ± 4.7
Cholesterol – mmol/l	4.8 ± 1.2	4.7 ± 1.1	4.9 ± 1.2
Triglycerides – mmol/l	1.7 ± 1.0	1.6 ± 0.9	1.7 ± 1.1
Glucose – mmol/l	6.5 ± 2.5	6.4 ± 2.4	6.7 ± 2.6
Creatinine - μmol/l	93.9 ± 25.0	94.3 ± 26.9	94.2 ± 24.4
Potassium – mmol/l	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.4
Female sex – no. (%)	45508 (47.1)	22690 (56.0)	6831 (26.7)
Ethnic group – no. (%)			
Black	1280 (1.3)	736 (1.8)	511 (2.5)
Other	1134 (1.2)	607 (1.5)	4901 (19.1)
South Asian	3026 (3.1)	1799 (4.4)	1375 (5.4)
Unknown	-	-	7 (<0.1)
White	91162 (94.4)	37411 (92.3)	18708 (73.0)
Clinical history – no. (%)			
CAD[a]	68009 (70.4)	28202 (69.5)	19102 (74.6)
MI	21997 (22.8)	7301 (18.0)	12549 (49.0)
Angina pectoris	31595 (32.7)	13205 (32.6)	11505 (44.9)
Cerebrovascular disease[b]	8695 (9.0)	3140 (7.7)	5342 (20.9)
PAD[c]	9999 (10.4)	4078 (10.1)	3468 (13.5)
Diabetes	43751 (45.3)	20003 (49.3)	9612 (37.5)
High-risk diabetes[d]	30736 (31.8)	14757 (36.4)	7151 (27.9)
Previous procedures – no. (%)			
CABG	6747 (7.0)	2912 (7.2)	5675 (22.2)
PTCA	10055 (10.4)	3823 (9.4)	7437 (29.0)
CKD (eGFR<60)	27608 (28.6)	13246 (32.7)	5470 (21.4)
Smoking status – no. (%)			
Non-smoker	34503 (35.7)	16470 (40.6)	9088 (35.5)
Current smoker	12921 (13.4)	3552 (8.8)	3225 (12.6)
Past smoker	49178 (50.9)	20531 (50.6)	13276 (51.8)
Unknown	-	-	31 (0.1)
Alcohol status – no. (%)			
Drinker	76756 (79.5)	31840 (78.5)	10345 (40.4)
Non-drinker	19846 (20.5)	8713 (21.5)	15261 (59.6)

Characteristic	ACEi *n=96 602*	ARB *n=40 553*	ONTARGET *n=25 620*
Unknown	-	-	14 (<0.1)
Medication[c] – no. (%)			
ACE inhibitor	78287 (81.0)	4659 (11.5)	14750 (57.6)
Alpha-blocker	6892 (7.1)	3202 (7.9)	1095 (4.3)
Oral anticoagulant agent	4613 (4.8)	1282 (3.2)	1939 (7.6)
Antiplatelet agent	12334 (12.8)	2482 (6.1)	2824 (11.0)
ARB	440 (0.5)	34579 (85.3)	2213 (8.6)
Aspirin	44011 (45.6)	9325 (23.0)	19403 (75.7)
Beta-blocker	34178 (35.4)	6756 (16.7)	14583 (56.9)
Calcium-channel blocker	28820 (29.8)	8515 (21.0)	8472 (33.1)
Digoxin	2533 (2.6)	600 (1.5)	865 (3.4)
Diuretics	32002 (33.1)	8838 (21.8)	7164 (28.0)
Diabetic treatment	20060 (20.8)	4910 (12.1)	8056 (31.4)
Nitrates	14862 (15.4)	3172 (7.8)	7523 (29.4)
Statins	52925 (54.8)	11474 (28.3)	15783 (61.6)

n= number of patients; no. (%)=number (percent); BP= blood pressure; CAD=coronary artery disease; MI=myocardial infarction; PAD=peripheral artery disease; CABG=coronary artery bypass graft; PTCA=percutaneous transient coronary angioplasty; CKD=chronic kidney disease (eGFR<60ml/min/1.73m^2)
One third of ONTARGET participants received both ramipril plus telmisartan.

[a] Includes diagnosis of: MI at least 2 days prior, angina at least 30 days prior, angioplasty at least 30 days prior, CABG at least 4 years prior

[b] Includes diagnosis of: stroke/TIA

[c] Includes diagnosis of: limb bypass surgery, limb/foot amputation, intermittent claudication

[d] Includes DM with: retinopathy, neuropathy, chronic kidney disease, proteinuria or other complication

[e] Within 3 months prior to eligible start date. Antiplatelet agent= clopidogrel/ticlopidine. In the categorisation of ethnicity in ONTARGET South Asian ethnic group included Other Asian and Black included Black African and Colored African as described in the trial CRF.

Follow-up and adherence

Among the propensity-score—weighted trial-eligible cohort, a total of 82 121 patients (ACEi: 58 553; ARB: 23 568) were followed until an event or 5.5 years of follow-up (maximum follow-up in the ONTARGET trial). 10 046 were censored at death, 32 034 patients were censored at the date the practice last contributed data to CPRD and 13 124 patients transferred out of practice. After one year, among patients in the ARB group 2.6% had switched to an ACEi and among patients in the ACEi group, 11% switched to an ARB.

Adherence was lower in CPRD, with 70% ACEi patients still on ACEi treatment after one year and 78% ARB patients still on ARB treatment after one year, compared to ONTARGET, where 92% ramipril patients were taking an ACEi and 94% telmisartan patients taking an ARB after one year.[22] However only small differences were observed between ARB and ACEi exposure groups in CPRD. (Table S5 in Appendix 2: Supplementary material from Research paper 2).

Benchmarking results

- ***Primary outcomes and validation***

Among the propensity-score—weighted trial-eligible cohort, the primary composite outcome occurred in 6287 (16%) in the ARB group and in 16 935 (18%) in the ACEi group (median follow-up 4.7 years), for event rates of 4.2 and 4.4 per 100 person-years, respectively. In ONTARGET, the number of events was 1423 (17%) and 1412 (17%) in the telmisartan and ramipril treatment groups, respectively, over median follow-up of 4.7 years. Comparing ARB users with ACEi users in the trial-eligible cohorts, the risk of the primary outcome was similar, HR 0.98 (95% CI: 0.94, 1.02) in the propensity-score–weighted, adjusted analysis. This was comparable to the ONTARGET primary outcome (HR 1.01 [95% CI: 0.94, 1.09]) and met the pre-specified validation criteria of trial replicability (Table ***6.3*** and Figure 6.2).

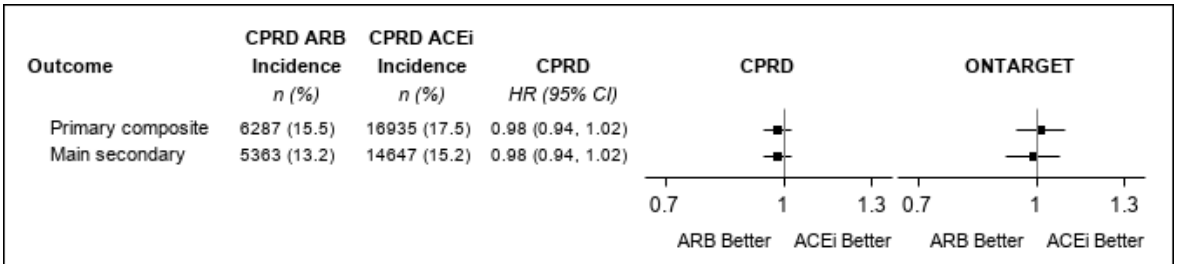
Table 6.3 Number of events for the primary outcome, its components, and death from any cause for a propensity-score—weighted analysis of ARB vs ACEi using CPRD data.

Outcome	**CPRD**			**ONTARGET**
	ACEi *n=96 602*	**ARB** *n=40 553*	**ARB vs ACEi** *n=137 155*	**Telmisartan vs ramipril** *n=17 118*
	Number (percent)		*Hazard ratio (95% CI)*	
Primary composite: Death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure	16935 (17.5)	6287 (15.5)	0.98 (0.94, 1.02)	1.01 (0.94, 1.09)
Main secondary outcome: Death from cardiovascular causes, myocardial infarction or stroke	5363 (13.2)	14647 (15.2)	0.98 (0.94, 1.02)	0.99 (0.91, 1.07)
Myocardial infarction	11617 (12.0)	4090 (10.1)	0.97 (0.92, 1.01)	1.07 (0.94, 1.22)
Stroke	3768 (3.9)	1573 (3.9)	1.04 (0.97, 1.12)	0.91 (0.79, 1.05)
Hospitalisation for heart failure	4028 (4.2)	1570 (3.9)	0.97 (0.90, 1.05)	1.12 (0.97, 1.29)
Death from cardiovascular causes	5194 (5.4)	1825 (4.5)	0.96 (0.90, 1.03)	1.00 (0.89, 1.12)
Death from non-cardiovascular causes	6984 (7.2)	2649 (6.5)	0.97 (0.92, 1.02)	0.96 (0.83, 1.10)
Death from any cause	12178 (12.6)	4474 (11.0)	0.97 (0.93, 1.01)	0.98 (0.90, 1.07)

Notes: CPRD weighted analysis includes 1 randomly selected trial-eligible period per patient. Propensity-score—weighted with robust standard errors. Analysis adjusted for time since first eligible period, number of prior ARB periods and calendar year.
Myocardial infarction and stroke include both fatal and non-fatal events.
55 015 (57.0%) of ACEi patients included received ramipril as the first prescription for the included trial-eligible exposed period. 1495 (3.7%) of ARB patients included received telmisartan as the first prescription for the included trial-eligible exposed period.
ONTARGET results are from published findings.

The Kaplan-Meier plot showed a lower risk among ARB users compared to ACEi users at 1, 2, 3, 4, and 5 years of follow-up (Figure S2 in Appendix 2: Supplementary material from Research paper 2). This differed to the ONTARGET results which showed a consistent risk at 1 year, with risk lower among ACEi users at 2, 3, 4, and 5 years. Results of the on-treatment

analysis showed ARBs were associated with a decreased risk of the primary composite outcome similar HR 0.90 (95% CI: 0.86, 0.94) for ARB vs ACEi.

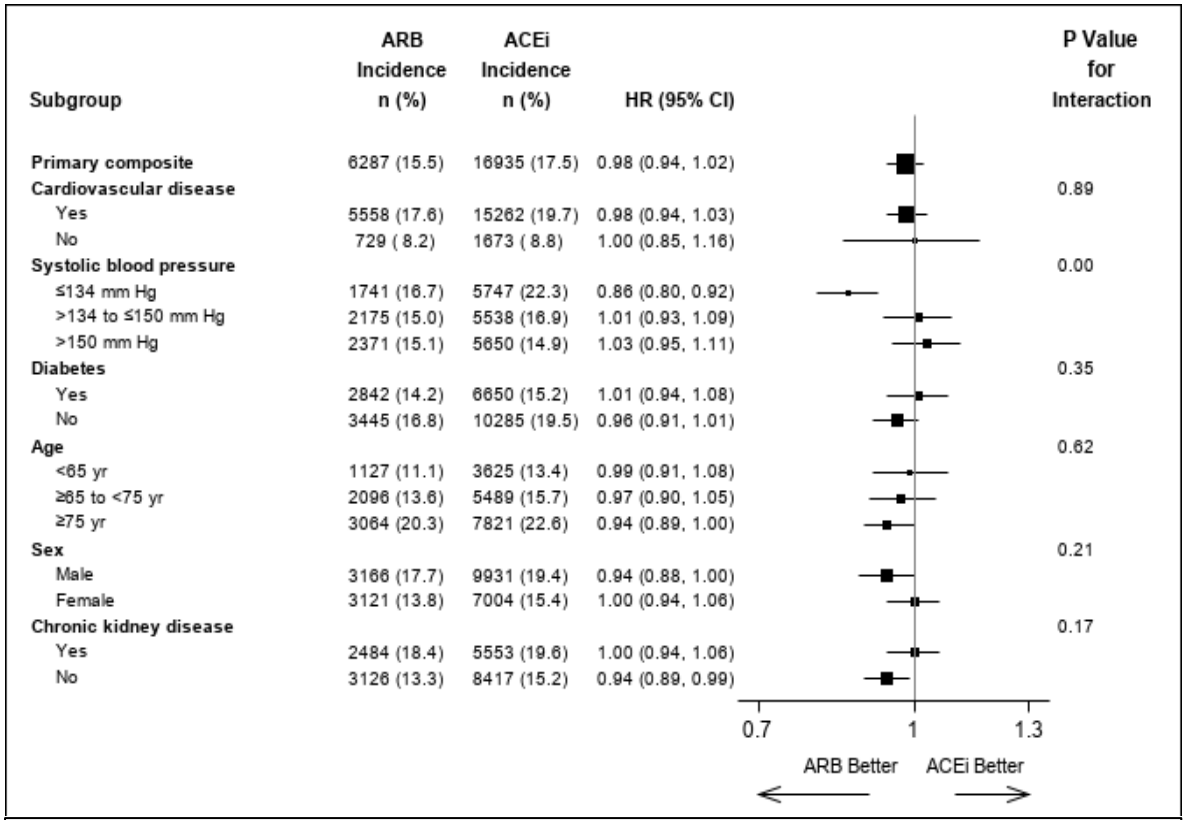


Notes: n (%)= number of events (percent). Primary composite outcome: cardiovascular death, myocardial infarction, stroke or hospitalisation for heart failure. Main secondary composite outcome: cardiovascular death, myocardial infarction or stroke.

Figure 6.2 Hazard ratios for the propensity-score—weighted and adjusted analysis of ARB vs ACEi for the primary composite outcome and main secondary outcome compared to comparison of telmisartan vs ramipril in ONTARGET.

- ***Secondary and other outcomes***

Results were consistent with ONTARGET for the main secondary composite outcome of cardiovascular death, MI, or stroke (Figure 6.2) and all other secondary outcomes, including development of ESKD (HR 1.06 [95% CI: 0.95, 1.19]) (Table S6 in Appendix 2: Supplementary material from Research paper 2). However, within the CPRD trial-eligible cohort the risk of the composite of loss of GFR or ESKD was higher for ARB users than for ACEi users (HR 1.11 [95% CI: 1.04, 1.19]), where ONTARGET observed similar treatment effects (Table ***6.3*** and Table S6 in Appendix 2: Supplementary material from Research paper 2).



Notes: n (%)= number of events (percent). P-value is the test of interaction between the treatment and each subgroup. Cardiovascular disease consists of patients with coronary artery disease, peripheral artery disease or cerebrovascular disease. Chronic kidney disease is defined as patients with eGFR<60ml/min/1.73m^2.

Figure 6.3 Hazard ratios in prespecified subgroups that were studied in ONTARGET (including underrepresented groups of females and aged over 75 years) along with those with CKD, for comparison of ARB vs ACEi for the primary composite outcome

- ***Safety outcomes***

In analyses of safety outcomes as reason for treatment cessation, cough was more common in ARB than in ACEi users (RR 1.29 [95% CI: 1.16, 1.43]) and angioedema was similar between groups, both in contrast with ONTARGET findings of reduced risk of cough and angioedema with ARB vs ACEi, however the number of events in our analysis was low, and our assessment was based on timing, whereas the ONTARGET reason for discontinuation was prospectively documented. Hyperkalaemia and ≥30% increase in serum creatinine were also more common in ARB users than in ACEi users RR 1.12 (95% CI: 1.06, 1.18) and RR

1.38 (95% CI: 1.34, 1.43), respectively (Table S7 in Appendix 2: Supplementary material from Research paper 2).

- ***Subgroup analysis***

Results of the primary outcome for ARB vs ACEi, stratified within the same subgroups as ONTARGET are shown in Figure 6.3. We observed evidence of effect modification by baseline SBP (P<0.01) with a lower risk among ARB users compared to ACEi in those with baseline SBP ≤134mmHg (HR 0.86 (95% CI: 0.80, 0.92). All other subgroups studied showed no strong evidence of treatment heterogeneity between groups, which was consistent with the findings in ONTARGET.

Underrepresented groups

For ARB vs ACEi for the primary composite outcome, there was no evidence to suggest treatment heterogeneity between males and females (male: HR 0.94 (95% CI: 0.88, 1.00) ; female: HR 1.00 (95% CI: 0.94, 1.06); P=0.21), by age group (<65 years: HR 0.99 (95% CI: 0.91, 1.08); 65- <75 years: HR 0.97 (95% CI: 0.90, 1.05); ≥75 years: HR 0.94 (95% CI: 0.89, 1.00); P=0.62) and by CKD status (no CKD: HR 0.94 (95% CI: 0.89, 0.99); CKD: HR 1.00 (95% CI: 0.94, 1.06); P=0.17), with all groups showing equivalent treatment effects of ARB and ACEi use. Among the trial-underrepresented groups of females, those aged ≥75 years and those with CKD, treatment effects for the primary composite outcome were consistent with ONTARGET (Figure 6.3).

For most secondary outcomes treatment effects were similar among males and females. However, there was some evidence of treatment heterogeneity for the outcomes of cardiovascular-related death (male: HR 1.02 (95% CI: 0.93, 1.12) ; female: HR 0.88 (95% CI: 0.80, 0.97); P=0.03), all-cause mortality (male: HR 1.00 (95% CI: 0.94, 1.06); female:

HR 0.91 (95% CI: 0.85, 0.97); *P*=0.04) and revascularisation procedures (male: HR 0.96 (95% CI: 0.91, 1.01); female: HR 1.06 (95% CI: 0.98, 1.15); *P*=0.03). Treatment effects were similar among ARB and ACEi users for men but among females ARB were associated with a lower risk of cardiovascular-related death and all-cause mortality compared to ACEi (Figure S3 in Appendix 2: Supplementary material from Research paper 2).

Similarly, by age group there was no evidence of treatment heterogeneity for most secondary outcomes. However, treatment effects differed for the outcomes of revascularisation procedures (<65 years: HR 0.91 (95% CI: 0.84, 0.98); 65- <75 years: HR 1.04 (95% CI: 0.97, 1.12); ≥75 years: HR 1.03 (95% CI: 0.95, 1.12); *P*=0.02) and loss of GFR or ESKD (<65 years: HR 1.42 (95% CI: 1.22, 1.66); 65- <75 years: HR 1.09 (95% CI: 0.97, 1.22); ≥75 years: HR 1.00 (95% CI: 0.91, 1.10); *P*<0.01). ARB and ACEi had similar treatment effects among users aged ≥65 years but among users aged <65 years, ARB were associated with a lower risk of revascularisation procedures and a higher risk of loss of GFR or ESKD, but event numbers were low (Figure S4 in Appendix 2: Supplementary material from Research paper 2).

For CKD, evidence of treatment heterogeneity was observed for MI (no CKD: HR 0.92 (95% CI: 0.86, 0.99); CKD: HR 1.05 (95% CI: 0.97, 1.14); *P*=0.02) and newly diagnosed heart failure (no CKD: HR 0.91 (95% CI: 0.84, 0.98); CKD: HR 1.02 (95% CI: 0.95, 1.10); *P*=0.03) and revascularisation procedures (no CKD: HR 0.95 (95% CI: 0.89, 1.00); CKD: HR 1.08 (95% CI: 0.99, 1.17); *P*=0.01). For these outcomes, treatment effectiveness was similar among ARB and ACEi users with CKD at baseline but ARB were associated with a lower risk among those without CKD at baseline (Figure S5 in Appendix 2: Supplementary material from Research paper 2).

Sensitivity analyses

The propensity-score—matched trial-eligible cohort, with similar covariate distribution to the ONTARGET trial participants included 15 462 patients in the ARB and ACEi exposure groups, respectively. Analysis of the propensity-score—matched trial-eligible cohort for ARB vs ACEi gave similar results to the propensity-score—weighted trial-eligible cohort for the primary outcome (HR 0.97 [95% CI: 0.92, 1.02], number of events: ARB=2453 (16%), ACEi=2539 (16%)) (Table 6.3 and Table S8 in Appendix 2: Supplementary material from Research paper 2). For all other outcomes, results had HRs close to 1.0 and 95% CI containing 1.0 (Table S8 in Appendix 2: Supplementary material from Research paper 2). Excluding patients who were lost to follow-up in the first 12 months gave consistent results, HR 0.96 (95% CI: 0.93, 1.00).

The risk of the primary outcome was lower among ARB users when follow-up was started from 28 days after the start of the trial-eligible period (HR 0.93 [95% CI: 0.90, 0.96], number of events: ARB=5966 (15%), ACEi=16 051 (16.8%)).

Specifying sustained deterioration of kidney function for loss of GFR or ESKD had no effect on results. However, among ARB users the risk of development of ESKD was increased (HR 1.16 [95% CI: 1.02, 1.32], number of events: ARB=626 (1.7%), ACEi=1016 (1.2%)).

Restricting to new users with no previous exposure to the opposite drug for safety outcomes, showed a lower risk of cough and angioedema as reason for treatment cessation for ARB vs ACEi, which was consistent with the trial findings (Table S9 in Appendix 2: Supplementary material from Research paper 2).

DISCUSSION

We emulated the ONTARGET randomised trial, using a large routinely-collected healthcare dataset. By applying the trial criteria and creating a propensity-score—weighted trial-eligible

cohort with balanced characteristics in each treatment arm, we showed similar risks among ARB and ACEi users for the composite of cardiovascular death, MI, stroke, or hospital admission for congestive heart failure, as well as further secondary outcomes. We attempted to replicate the ONTARGET per-protocol analysis using an on-treatment approach where we obtained inconsistent results. It was suspected that this was due to increased drug channelling in the early years with healthier patients prescribed the newer drug likely with better adherence, which introduced bias into results and differences in groups for measured and unmeasured confounders. This was assessed in a post-hoc analysis where we stratified by calendar year of start of trial eligible period and when restricting the cohort to eligible periods between 2010-2019, i.e., after ONTARGET was published, we observed consistent results with the main analysis, HR 1.06 (95% CI: 0.96, 1.17). Marked similarity between ONTARGET and our observational study was also found in subgroup analysis, with ARB users with the lowest baseline SBP at lower risk of the primary composite outcome compared to ACEi users. This could indicate that those with less severe hypertension may be given an ARB, which is commonly seen with new medications prescribed to healthier patients introducing some bias.

We subsequently extended analysis to females, those aged ≥75 years and patients with CKD (all underrepresented in ONTARGET), where we demonstrated consistency of treatment effects for most outcomes but saw some evidence to suggest ARB use associated with a lower risk of death-related outcomes among females.

Comparison to other studies

Our findings of similar effectiveness of ARB vs ACEi by sex and age for a composite cardiovascular outcome were consistent with previous comparative effectiveness studies.[59, 60] In line with the findings from a large Taiwanese cohort study,[106] we demonstrated no

difference between ARB vs ACEi in risk of kidney outcomes among those with and without CKD.

One recent ONTARGET replication study using United States insurance claims data performed a propensity-score—matched analysis of telmisartan vs ramipril and found HR 0.99 (95% CI: 0.85, 1.14) for the primary outcome.[45] The sample was small (9930 patients) and, unlike the trial, included new users only.

In contrast to other naïve observational studies that have shown a decreased risk among ARB users,[58, 61, 107] we observed equal treatment effectiveness of ARB and ACEi. This implies that using trial emulation techniques and propensity-score—weighting to obtain balance among exposure groups can adequately address confounding and bias and lead to results comparable to the target trial.

Strengths and Limitations

We were able to demonstrate that both a propensity-score—weighting approach and a propensity-score—matching approach yielded equivalent results to ONTARGET, providing evidence to support the use of a weighted approach in future trial replication studies where trial-eligible patients may have slightly different characteristics to participants included in the RCT (preferred, because weighting minimises the loss of participants involved in matching and enables greater power for examining rare outcomes such as ESKD). Having replicated the ONTARGET results, the increased sample size and diverse population in the propensity-score—weighted trial-eligible cohort allowed us to extend our analyses to trial-underrepresented groups. This included people with CKD where evidence from observational studies is limited. Among this group, we observed similar treatment effectiveness among ARB and ACEi users for the primary outcome and all other outcomes, including the outcomes of loss of GFR or ESKD and development of ESKD.

Despite overall similarity between ARB and ACEi users for most outcomes, we noted some discrepancies with ONTARGET. In the ONTARGET trial, ARB and ACEi users had comparable risk of kidney-related outcomes. In contrast, we found ARBs to be associated with a moderately greater risk of loss of GFR or ESKD compared with users of ACEi. This may reflect testing multiple outcomes, low numbers of outcomes in some strata or residual confounding by indication.

When dealing with comparisons between a new drug and a historic drug, careful considerations need to be given to handle treatment switchers and appropriately account for time trends in prescribing. We sought to account for such variables, including them as terms in our propensity-score model but it is not possible to exclude this as a source of residual confounding or bias. Starting follow-up from 28 days after the start of the trial-eligible period to assess the impact of including patients who only received one prescription led to a lower risk of the primary outcome among ARB users. This could indicate our main analysis may include patients who have briefly switched to an ARB before switching back to original treatment. Therefore the event captured may be incorrectly attributed to ARB use indicating equivalent treatment effects when in fact ARBs are associated with fewer events. This indicates some bias may still remain related to treatment switchers.

Discrepancy of safety outcomes is likely due to the close monitoring of adverse events in a trial setting compared with routine clinical care. Events such as cough are likely to be underreported in routine data. In addition to this, some confounding by indication may be present, particularly for patients with a history of cough or angioedema who may have been switched from an ACEi to an ARB. This was demonstrated in our sensitivity analysis, restricting the cohort to non-switchers, where we obtained results much closer to the ONTARGET trial. However, since ARB users who have not previously been exposed to an ACEi are likely to be healthier and less likely to experience cough, due to the known risk of

cough among ACEi users, we cannot be sure that restricting to non-switchers does not introduce further bias.

We used propensity-score methods to achieve balance across CPRD exposure groups and have assumed the variables in the propensity score model sufficiently account for measured confounding. Due to lack of randomisation in observational studies we assumed no unmeasured confounding conditional on the measured confounders included in the propensity score model. We have also assumed consistency and no interference and examined the propensity score distribution to evaluate the positivity assumption. Some patients were excluded due to missing data for variables included in the propensity-score model. <0-5% of values were missing for most variables included in the propensity-score model. However ~14% of patients had missing blood pressure at baseline and were excluded. Therefore, our analysis is conditional on non-missing values for variables included in the propensity score model and we have assumed the 14% of patients with missing blood pressure were missing at random and had no effect on results.

In addition to unmeasured confounding and missing data, it is possible that other factors associated with study design and analysis could have biased results. Each factor could potentially bias results in different directions and subsequently balance out leading to a false conclusion on trial replicability. We sought to address these factors through design choices and sensitivity analyses described in Table S2 in Appendix 2: Supplementary material from Research paper 2).

For example, differences between the emulation and ONTARGET could be due to the treatment effect varying across groups that are unequally represented in the emulation and ONTARGET. Differences in study populations leading to differences in effect estimates may occur if not all the trial eligibility can be implemented in the observational data. Some criteria

were omitted such as planned cardiac surgery due to the risk of misclassification. However, the number of criteria not able to be applied was small.

In CPRD incidence of MI was higher than in ONTARGET which could have led to a difference in effect estimates. We explored adherence after treatment by calculating proportion of patients still receiving treatment at 1, 2, 3, 4 and 5,5 years, as done in the trial. For ARB users, adherence was similar to ONTARGET. However, for ACEi users, adherence differed to ONTARGET which is likely due to more patients switching to the newer drug. This is a limitation of studying a new vs old drug in observational data and in combination with residual confounding could explain why risk was lower among ARB users in the Kaplan-Meier plot compared to what was observed in ONTARGET.

Finally, some differences in estimates may be caused by the use of different causal contrasts. We attempted to replicate the trial per-protocol effect by additionally censoring patients at the end of a trial eligible period or when they switched treatment or started dual therapy and estimated the on-treatment effect. It is suggested the per-protocol effect should be re-estimated in the ONTARGET trial and emulation adjusting for pre- and post-baseline information associated with adherence.[53, 108, 109] However, since we did not have access to the outcome data from ONTARGET we were unable to estimate this in the RCT. Due to the nature of the data source we also unable to determine if patients discontinued for clinical reasons therefore informative censoring may have affected results. However, the number of patients who were additionally censored for discontinuation, switching or dual use was small.

Conclusion

In this emulation of the ONTARGET randomised trial using routinely-collected healthcare data, we closely replicated the primary and secondary outcomes and were able to demonstrate the generalisability of trial results to a cohort representative of patients receiving

prescriptions for ACEi or ARB in UK primary care. Subsequently we were able to provide evidence that trial results extend to trial-underrepresented subgroups where evidence is limited including females, those aged ≥75 years and patients with CKD. Benchmarking findings from observational studies against target trial results can add confidence to findings when using routinely-collected data to investigate the generalisability of trial findings to wider populations.

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Acknowledgments

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6.1.2 Additional results from applying step 4: matching to trial participants

The propensity score model used to achieve a cohort in CPRD analogous to ONTARGET participants included the variables displayed in Table ***6.4***. Characteristics and kernel density plots before and after matching trial participants to closest ACEi trial-eligible period are displayed in Table ***6.5*** and Figure ***6.4***. This cohort of trial-analogous ACEi patients was then used to inform the second propensity score model which was developed to achieve balance among exposure groups and comparability between patient profiles in CPRD and ONTARGET participants for all exposure groups.

Table 6.4 Covariates included in propensity score model used to ensure comparability between CPRD population and ONTARGET trial participants

Covariate	**Form**	**Higher order term**
Stroke/TIA	Binary	
Peripheral artery disease	Binary	
Coronary artery disease	Binary	
Diabetes	Binary	
High-risk diabetes	Binary	
Sex	Binary	
Ethnicity	Categorical (white, black, South Asian, other)	
Age	Continuous	
Body-mass-index	Continuous	
Systolic blood pressure	Continuous	+ quadratic
Diastolic blood pressure	Continuous	+ quadratic
Smoking status	Categorical (non, ex or current)	

Table 6.5 Standardised differences of baseline characteristics for trial-eligible ACE inhibitor exposed periods from CPRD GOLD and ONTARGET trial participants before and after 1:1 propensity score matching

Characteristic	Before matching			After matching		
	ACE inhibitor 123,523 (102,018)	ONTARGET 25,474	SMD	ACE inhibitor 22,091	ONTARGET 22,091	SMD
Age - year	70.8 ± 9.1	66.5 ± 7.2	0.537	66.5 ± 8.2	66.7 ± 7.2	0.028
Systolic BP – mmHg	147.1 ± 20.7	141.8 ± 17.4	0.276	141.7 ± 17.4	142.0 ± 17.6	0.019
Diastolic BP - mmHg	80.0 ± 10.7	82.1 ± 10.4	0.199	82.3 ± 10.4	82.0 ± 10.4	0.031
Body-mass index	28.3 ± 5.3	28.2 ± 4.7	0.037	28.3 ± 5.0	28.3 ± 4.8	0.004
Female sex – no. (%)[1]	47911 (47.0)	6788 (26.6)	0.431	5836 (26.4)	6121 (27.7)	0.029
Ethnic group – no. (%)[1]						
Black	1382 (1.4)	624 (2.4)	0.655	537 (2.4)	606 (2.7)	0.095
Other	1222 (1.2)	4885 (19.2)		1178 (5.3)	1656 (7.5)	
South Asian	3297 (3.2)	1366 (5.4)		1238 (5.6)	1343 (6.1)	
White	96117 (94.2)	18599 (73.0)		19138 (86.6)	18486 (83.7)	
Clinical history – no. (%)						
CAD[2,3]	86278 (69.8)	19001 (74.6)	0.106	16687 (75.5)	16557 (74.9)	0.014
Cerebrovascular disease[2,4]	11116 (9.0)	5308 (20.8)	0.333	4067 (18.4)	4173 (18.9)	0.012
PAD[2,5]	13161 (10.7)	3451 (13.5)	0.089	3049 (13.8)	3079 (13.9)	0.004
Diabetes[6]	57654 (46.7)	9560 (37.5)	0.186	7891 (35.7)	8325 (37.7)	0.041
High-risk diabetes[2,7]	41202 (33.4)	7107 (27.9)	0.119	5919 (26.8)	6197 (28.1)	0.028
Smoking status – no. (%)						
Non-smoker	44429 (36.0)	9042 (35.5)	0.041	7840 (35.5)	7748 (35.1)	0.014
Current smoker	17019 (13.8)	3208 (12.6)		2735 (12.4)	2830 (12.8)	
Past smoker	62075 (50.3)	13224 (51.9)		11516 (52.1)	11513 (52.1)	

ACE inhibitor cohort is developed from CPRD GOLD.

[1] % out of number of patients not number of eligible periods

[2] Any diagnosis prior to start of trial-eligible eligible period

[3] Includes diagnosis of: MI at least 2 days prior, angina at least 30 days prior, angioplasty at least 30 days prior, CABG at least 4 years prior

[4] Includes diagnosis of: stroke/TIA

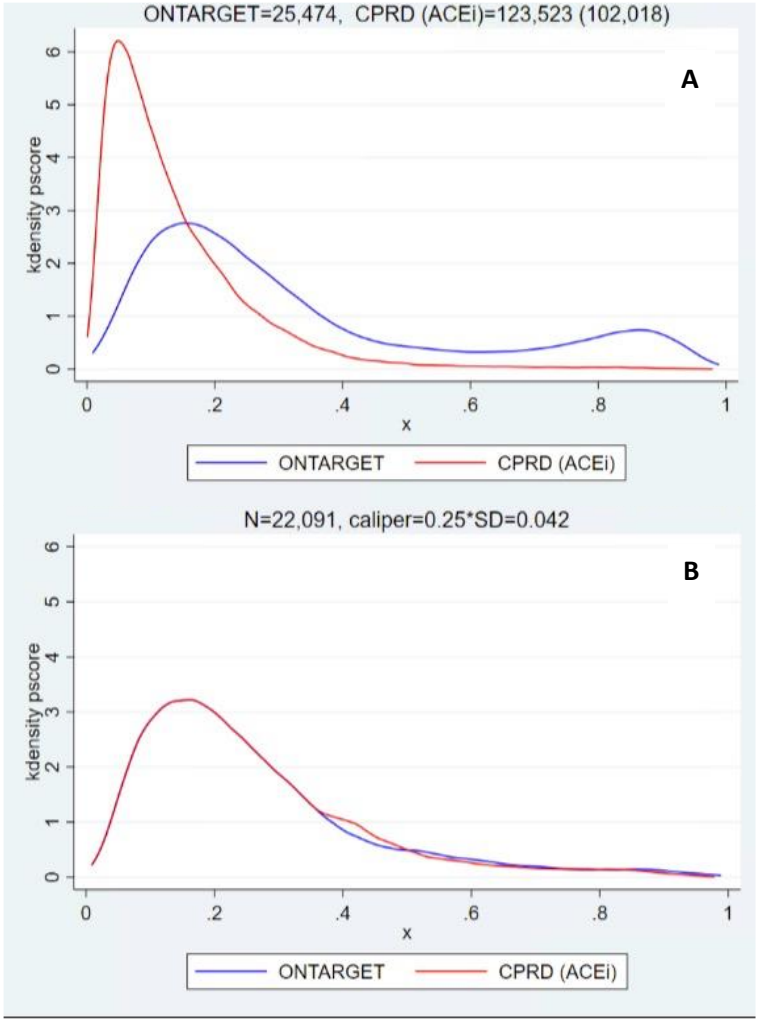
[5] Includes diagnosis of: limb bypass surgery, limb/foot amputation, intermittent claudication

[6] DM prior to start of eligible period

[7] Includes DM with: retinopathy, neuropathy, chronic kidney disease or proteinuria

Before matching column only includes periods/patients with non-missing propensity score. Some additional ONTARGET participants were excluded as they were <55 years.

N=x (x)=number of eligible periods (number of patients); no. (%)=number (percent); SMD=standardised mean difference; BP=blood pressure; CAD=coronary artery disease; PAD=peripheral artery disease.



Notes: A: before matching; B: after matching.

Figure 6.4 Kernel density plot before and after 1:1 propensity score matching ONTARGET trial participants to trial-eligible ACE inhibitor exposed patients.

6.1.3 Additional results from applying step 5: matching trial-eligible exposure groups

There was a disproportionate number of switchers in the two treatment groups, 46.7% of ACE inhibitor users switched to an ARB but only 2.8% of ARB users switched to an ACE inhibitor (percentages based on eligible periods). Therefore time-related variables described in section 5.3.2 of Chapter 5 were included in the propensity score model to achieve balance across exposure groups. The final choice of variables are displayed in Table ***6.6***.

Table 6.6 Covariates included in propensity score model used to ensure balance among ACE inhibitor and ARB trial-eligible exposure groups in CPRD GOLD

Covariate	Form	Higher order term
Stroke/TIA	Binary	
Peripheral artery disease	Binary	
Coronary artery disease	Binary	
Diabetes	Binary	
High-risk diabetes	Binary	
Sex	Binary	
Ethnicity	Categorical (white, black, South Asian, other)	
Age	Continuous	+ quadratic
Body-mass-index	Continuous	+ quadratic
Systolic blood pressure	Continuous	+ quadratic
Diastolic blood pressure	Continuous	
Smoke status	Categorical (non, ex or current)	
Alcohol consumption	Binary (yes, no)	
Index of multiple deprivation	Categorical (1-5)	
Statin use 3 months prior	Binary (yes, no)	
Nitrate use 3 months prior	Binary (yes, no)	
Diabetic treatment use 3 months prior	Binary (yes, no)	
Diuretic use 3 months prior	Binary (yes, no)	
Calcium channel blocker use 3 months prior	Binary (yes, no)	
Betablocker use 3 months prior	Binary (yes, no)	
Aspirin use 3 months prior	Binary (yes, no)	
Antiplatelet use 3 months prior	Binary (yes, no)	
Number of previous hospital admissions 6 months prior	Categorical (0, 1, 2+)	
Number of previous medications 6 months prior	Continuous	+ quadratic
Number of previous GP appointments 6 months prior	Square root	
Calendar year	Continuous	

Time since first trial-eligible period	Continuous	+ quadratic
Number of previous ARB periods	Square root	
Number of previous ACE inhibitor periods	Square root	
Interactions		
Ethnicity*Age		
Ethnicity*Sex		
Ethnicity*Peripheral artery disease		
Ethnicity*Coronary artery disease		
Ethnicity*Cerebrovascular disease		
Ethnicity*BMI		
Ethnicity*SBP		
Ethnicity*DBP		
Ethnicity*Time since first trial-eligible period		
Ethnicity*Number of previous ACE inhibitor periods (square root)		
Age*Sex		
Age*Calendar year		
Age*Coronary artery disease		
Age*Cerebrovascular disease		
Age*SBP		
Age*DBP		
Age*Number of previous ARB periods (square root)		
Sex*BMI		
Sex*DBP		
Calendar year*BMI		
Calendar year*SBP		
Calendar year* Number of previous ARB periods (square root)		
Calendar year* Number of previous ACE inhibitor periods (square root)		
Peripheral artery disease*cerebrovascular disease		
Peripheral artery disease* Number of previous ACE inhibitor periods (square root)		
Coronary artery disease*Time since first eligible period		
Coronary artery disease* Number of previous ARB periods (square root)		

Cerebrovascular disease*BMI
Cerebrovascular disease*Time since first eligible period
Cerebrovascular disease* Number of previous ACE inhibitor periods (square root)
High-risk diabetes*SBP
High-risk diabetes*Time since first eligible period
High-risk diabetes* Number of previous ARB periods (square root)
High-risk diabetes* Number of previous ACE inhibitor periods (square root)
BMI*DBP
SBP*DBP
SBP*Time since first eligible period
SBP*Number of previous ARB periods (square root)
SBP*Number of previous ACE inhibitor periods (square root)
DBP*Number of previous ARB periods (square root)
DBP*Number of previous ACE inhibitor periods (square root)
Time since first eligible period* Number of previous ARB periods (square root)
Time since first eligible period* Number of previous ACE inhibitor periods (square root)
Number of previous ARB periods (square root)*Number of previous ACE inhibitor periods (square root)

6.1.4 Additional results related to safety outcomes

6.1.4.1 Results for investigation into time-related biases in safety outcomes (in original analysis)

When I explored safety outcomes using a log-binomial model as described in the published protocol, results differed compared to those seen in ONTARGET where the risk of a safety event was lower among ARB users. The impact of time-related bias (due to more ACEi users switching to an ARB compared to ARB users switching to an ACEi, commonly seen after the introduction of a new medication) was explored using the methods described in Chapter 5, section 5.3.3.1.

Results from analysis of the propensity-score—weighted cohort are shown in Table ***6.7***, with 'any safety event' referring to the original analysis outlined in the published protocol, capturing safety events which occur after follow-up.

Table 6.7 Results from safety analysis using trial-eligible propensity score weighted cohort compared to ONTARGET

Safety outcome	**Trial-eligible propensity score weighted CPRD cohort**		
	ARB (N=40,553)	**ACE inhibitor** (N=96,602)	**ARB vs. ACE inhibitor**
	Number (percent)		*RR (95% CI)*
Any safety event (original analysis)			
Cough	1313 (3.2)	2230 (2.3)	1.16 (1.06, 1.27)
Angioedema	44 (0.1)	91 (0.1)	1.17 (0.77, 1.77)
Hyperkalaemia[1]	3983 (11.2)	9020 (11.4)	0.99 (0.95, 1.04)
≥30% increase in serum creatinine	7918 (21.7)	16284 (19.9)	1.10 (1.07, 1.14)
Occurs within 3 months			
Cough	750 (1.9)	424 (0.4)	3.08 (2.66, 3.57)
Angioedema	18 (0.04)	5 (0.01)	9.45 (3.21, 27.80)
Hyperkalaemia[1]	471 (1.3)	1187 (1.5)	0.83 (0.72, 0.95)
≥30% increase in serum creatinine	502 (1.4)	1327 (1.6)	0.92 (0.81, 1.05)
Non-switchers			
Cough	221 (1.9)	2063 (2.3)	0.72 (0.61, 0.85)
Angioedema	8 (0.1)	83 (0.1)	0.49 (0.22, 1.08)
Hyperkalaemia[1]	942 (10.6)	8317 (11.3)	0.96 (0.89, 1.03)
≥30% increase in serum creatinine	1900 (20.7)	15004 (19.7)	1.08 (1.03, 1.13)
Non-switchers and occurs within 3 months			
Cough	61 (0.5)	382 (0.4)	0.94 (0.67, 1.31)
Angioedema	1 (0.01)	5 (0.01)	0.51 (0.05, 4.80)
Hyperkalaemia[1]	86 (1.0)	1042 (1.4)	0.69 (0.53, 0.90)
≥30% increase in serum creatinine	114 (1.2)	1232 (1.6)	0.84 (0.67, 1.06)
ONTARGET			
Cough	93 (1.1)	360 (4.2)	0.26 (p<0.001)
Angioedema	10 (0.1)	25 (0.3)	0.4 (p=0.01)
Hyperkalaemia	-	-	-
≥30% increase in serum creatinine	-	-	-

Notes: RR=relative risk; p=p-value. Analysis adjusted for time since first eligible period, calendar year, number of prior ARB eligible periods. Non-switcher analysis adjusted for number of GP appointments within 6 months prior to start of eligible period. ONTARGET ARB group was telmisartan only (n=8542) and ACE inhibitor group was ramipril only (n=8576), results from ONTARGET presented as reasons for permanent discontinuation.

Hyperkalaemia and >30% increase in serum creatinine was not studied as reason for discontinuation in ONTARGET. ONTARGET presented relative risk (p value).

[1]Defined as potassium >5.5 mmol/l. Analysis out of number of people with non-missing potassium.

Renal outcome is out of the number of people with non-missing eGFR.

Non-switchers cohort includes 11,856 ARB patients and 90,597 ACE inhibitor patients.

ONTARGET results: Cough: Telmisartan 93 (1.1%), Ramipril 360 (4.2), RR 0.26 (p-value <0.01). Angioedema: Telmisartan 10 (0.1), Ramipril 25 (0.3), RR 0.4 (p-value 0.01)

When the restriction that safety events had to occur within 3 months of follow-up was introduced, risk of hyperkalaemia and renal impairment was reduced among ARB users. Results for risk of hyperkalaemia were not presented in ONTARGET but it was stated that combination therapy led to an increased risk compared to ACEis alone. However, in CPRD lower risk was observed among ARB users compared to ACEi users. For the remaining two safety outcomes, cough, and angioedema, an increased risk associated with ARBs was observed. This is in contrast to clinical evidence which shows an increased risk of cough and angioedema associated with ACEi use.[110, 111] Here, Read codes were used to define the outcomes whereas for the other outcomes where a lower risk was observed among ARB users, outcomes were defined by clinical measures i.e., hyperkalaemia was defined as potassium>5.5mmol/L. Therefore, it may be difficult to capture some safety events using Read codes. Additionally, the unexpected findings could be due differences in frequency and methods of monitoring in routine care versus that which would typically be seen in an RCT, particularly for outcomes such as cough, which are common and may be underreported in routine care. Another potential explanation could be due to inaccurate date of coding of a safety event leading to incorrectly attributing the event to the new (ARB) drug. This is supported by the risk of safety events decreasing among ARB users compared to ACEi users when switchers were excluded. The number of events identified were low in all of the sensitivity analyses therefore meaningful interpretation is difficult due to lack of precision and wide CIs. Additionally, bias may be present in results due to patients having to survive up

to the time of event and the statistical method not appropriately accounting for right-censoring.

6.1.4.2 Results for alternate analysis of assessing safety outcomes

Results from the alternate analysis for assessing safety outcomes, capturing safety events as reasons for permanent discontinuation consistent with the trial as presented in Research paper 2. Together with the corresponding investigation into assessing time-related bias related to treatment switchers, by restricting to non-switchers, described in chapter 5, section 5.3.3.2 are displayed in Table ***6.8***. Results were more similar to the trial when the cohort was restricted to people who did not switch between ARBs and ACE inhibitors.

Table 6.8 Results from safety analysis as reason for treatment discontinuation using trial-eligible propensity score weighted cohort

Reason for treatment discontinuation	**Trial-eligible propensity score weighted CPRD cohort**		
	ARB (N=40,553)	**ACE inhibitor** (N=96,602)	**ARB vs. ACE inhibitor**
	Number (percent)		*RR (95% CI)*
Events prior to end of eligible period (alternate analysis)			
Cough	949 (2.3)	1557 (1.6)	1.29 (1.16, 1.43)
Angioedema	37 (0.09)	83 (0.09)	1.14 (0.72, 1.80)
Hyperkalaemia[1]	2784 (7.8)	5836 (7.4)	1.12 (1.06, 1.18)
≥30% increase in serum creatinine	7222 (19.8)	12441 (15.2)	1.39 (1.34, 1.43)
Non-switchers			
Cough	178 (1.5)	1455 (1.6)	0.84 (0.70, 1.01)
Angioedema	10 (0.08)	77 (0.08)	0.72 (0.35, 1.48)
Hyperkalaemia[1]	685 (7.7)	5473 (7.4)	1.06 (0.97, 1.16)
≥30% increase in serum creatinine	1730 (18.8)	11781 (15.5)	1.25 (1.19, 1.32)
ONTARGET			
Cough	93 (1.1)	360 (4.2)	0.26 (p<0.001)
Angioedema	10 (0.1)	25 (0.3)	0.4 (p=0.01)
Hyperkalaemia	-	-	-
≥30% increase in serum creatinine	-	-	-

Notes: RR=relative risk; p=p-value. Treatment discontinuation is defined as the end date of the trial-eligible exposed period included in analysis (i.e., the date prior to a prescription gap of >90 days) and the latest event occurring prior to the end of the trial-eligible period is counted as the reason for treatment discontinuation.

Multiple reasons that occur on the same day are both counted. Analysis adjusted for time since first eligible period, calendar year, number of prior ARB eligible periods. Non-switcher analysis adjusted for number of GP appointments within 6 months prior to start of eligible period. ONTARGET ARB group was telmisartan only (n=8542) and ACE inhibitor group was ramipril only (n=8576), results from ONTARGET presented as reasons for permanent discontinuation. Hyperkalaemia and >30% increase in serum creatinine was not studied as reason for discontinuation in ONTARGET. ONTARGET presented relative risk (p value).

[1]Defined as potassium >5.5 mmol/l. Analysis out of number of people with non-missing potassium.

Renal outcome is out of the number of people with non-missing eGFR.

Non-switchers cohort includes 11,856 ARB patients and 90,597 ACE inhibitor patients.

ONTARGET results: Cough: Telmisartan 93 (1.1%), Ramipril 360 (4.2), RR 0.26 (p-value <0.01). Angioedema: Telmisartan 10 (0.1), Ramipril 25 (0.3), RR 0.4 (p-value 0.01)

6.1.4.3 Summary of replicating safety outcomes in CPRD GOLD

I was not able to replicate the safety outcomes observed in ONTARGET until I restricted the cohort to people who had not switched between medications. This is likely to indicate a difficulty of studying safety outcomes using routine care data when complete and non-differential capture requires active monitoring as occurs in randomised trials. The study by Fralick et al., successfully replicated the ONTARGET safety outcome of angioedema in US claims data, however it included new users only.[45] Therefore, it is unclear if the differences observed in this study could be due to the impact of time-related bias introduced by including prevalent users and/or due to capturing of safety events in UK routine care and a limitation of the CPRD database.

6.1.5 Other additional analysis

6.1.5.1 Reducing the cohort to be representative of the ONTARGET trial size

Despite meeting the validation criteria for replicability of the ONTARGET trial, results for the primary composite outcome had narrow confidence intervals, differing from the confidence intervals in ONTARGET. I hypothesised that this was due to increased precision as a result of greater sample size and I investigated this by reducing the cohort to be representative of the ONTARGET trial size (N=17,118). I randomly sampled 8,559 trial-

eligible periods by treatment and patient. Balance between treatment groups was achieved by running the same propensity score model that was used in the main analysis and generating inverse propensity score weights. Balance was assessed after weighting and analysis was adjusted for any variables that remained imbalanced. The HR for the primary composite outcome was 1.00 (95% CI: 0.91, 1.11) which was closely comparable to the ONTARGET result of HR 1.01 (95% CI:0.94, 1.09) for the comparison of telmisartan vs ramipril. This analysis provided further evidence that the small difference in point estimate and narrower confidence interval observed in the main analysis of the trial-eligible CPRD GOLD weighted cohort (N=137,155), which gave HR 0.98 (95% CI: 0.94, 1.02) was likely due to the increase in sample size.

6.2 Results from analysis in CPRD Aurum

6.2.1 Replication of ONTARGET in CPRD Aurum and extending methods to Black and South Asian individuals (Research paper 3)

6.2.1.1 Research paper 3

The findings from replicating ONTARGET in CPRD Aurum and exploration of treatment effects in Black and South Asian ethnic groups, who were underrepresented in the trial is presented in research paper 3. This paper is in draft format currently being revised by co-authors, which will be submitted to The BMJ. The results presented in this paper also relate to Research Aim 1. Supplementary material for research paper 3 are available in Appendix 3: Supplementary material from Research paper 3.

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SECTION A – Student Details

Student ID Number	1800205	**Title**	Miss
First Name(s)	Paris Jade		
Surname/Family Name	Baptiste		
Thesis Title	Real-world effectiveness and adverse events caused by ACE inhibitors and ARBs for reduction in cardiovascular events with validation against the ONTARGET trial		
Primary Supervisor	Laurie Tomlinson		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
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Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	The BMJ
Please list the paper's authors in the intended authorship order:	Paris J Baptiste, Angel YS Wong, Anna Schultze, Catherine M Clase, Clémence Leyrat, Elizabeth Williamson, Emma Powell, Johannes FE Mann, Marianne Cunnington, Koon Teo, Shrikant I Bangdiwala, Peggy Gao, Kevin Wing, Laurie

	Tomlinson
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author on this paper. I contributed to the study question and design. I carried out data management and conducted the analysis for the work presented in this paper. I wrote the first draft of this mansucript and drafted subsequent versions.

SECTION E

Student Signature	[redacted]
Date	7/6/23

Supervisor Signature	[redacted]
Date	7/6/23

Comparative effectiveness of ACE inhibitors and ARBs and risk of angioedema in among different ethnic groups in England: a cohort study using the Clinical Practice Research Datalink.

Authors

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Abstract

Background

Guidelines by the National Institute for Health and Care Excellence recommend an angiotensin receptor blocker (ARB) rather than an Angiotensin-converting enzyme (ACE) inhibitor for the treatment of hypertension for people of African and Caribbean descent, due to a lower risk of angioedema. However, the comparative effectiveness of these drugs in Black populations and the risk of angioedema in routine care is not known.

Methods

We aimed to explore the comparative effectiveness of these drugs in reducing cardiorenal outcomes in an ethnically diverse UK population benchmarking findings against the ONTARGET randomised clinical trial. We selected Black, South Asian and White patients who met the ONTARGET inclusion criteria and were prescribed an ARB or ACE inhibitor between 1/1/01-31/7/19 in the Clinical Practice Research Datalink Aurum. After selecting a trial eligible period for each individual, we fitted a propensity-score—weighted Cox-proportional hazards model both overall and with an interaction term between treatment and ethnicity to estimate a hazard ratio and 95% CIs for cardiovascular and kidney outcomes studied in the ONTARGET trial, and for the risk of developing angioedema.

Findings

Having closely replicated the results of the ONTARGET trial in the whole population, we found similar effectiveness of ARBs and ACE inhibitors at reducing the risk of the primary outcome in 19,020 Black patients (HR 1.06 (95% CI: 0.96, 1.17)) and other secondary outcomes. Angioedema was reported more commonly among Black patients compared to White patients but overall incidence was low, and risk was lower among ARB users compared to ACE inhibitors for both Black and White patients.

Interpretation

Despite observing a decreased risk of angioedema associated with ARB use, there is insufficient evidence that this association differs by ethnicity with similar treatment effects observed among Black and White patients.

Funding

GlaxoSmithKline

Introduction

Hypertension is associated with increased cardiovascular risk.[112, 113] Individuals of African and Caribbean descent, subsequently referred to as 'Black', and South Asian ethnic groups are disproportionately affected by hypertension in comparison to White individuals.[114] The extent to which these differences are related to genetics, differences in socio-economic status[115] and or factors such as differential access to healthcare [116-118] is uncertain.[119-121] Incidence and mortality from hypertension and stroke is increased among Black and South Asian ethnic groups and occurs at a younger age.[122-124]

In the UK, hypertensive patients are treated based on the National Institute for Health and Care Excellence (NICE) hypertension guidelines.[25] In contrast to other international guidelines, NICE include ethnicity as a determinant of treatment choice although the evidence underpinning this is uncertain.[125, 126] Among hypertensive patients with type 2 diabetes an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) is recommended as first-line treatment. Among non-diabetic hypertensive patients, an ACE inhibitor or ARB is recommended as initial treatment if the patient is aged <55 years and not Black, with those aged ≥55 years or those who are Black of any age being recommended a calcium channel blocker.

In 2011 guidelines were updated to recommend an ARB in preference to an ACE inhibitor for people who were Black.[38] The cited evidence was the ALLHAT trial which included 42,418 patients, with over a third of Black ethnicity,[111] and found that over half of people who developed angioedema in the trial were Black[39] and that the incidence of angioedema in Black individuals was higher among ACE inhibitor users compared to other antihypertensive drugs (not including ARBs), in contrast to non-Black participants. However, the absolute incidence was low with only 53 events during a follow-up of 4.9 years.

Trials demonstrating the comparative effectiveness of ARBs and ACE inhibitors which inform clinical guidance have provided limited data assessing the effects in Black or South Asian groups.[22, 127, 128] The ONTARGET trial, which demonstrated non-inferiority of telmisartan compared to ramipril in high-risk cardiovascular patients did not include subgroup analyses by ethnicity and included only 2% of Black patients (reported in the trial as Black African). This is consistent with the majority of clinical trials which have historically not reported any race or ethnicity data[129] and this can lead to extrapolation of trial results to ethnic minority populations without robust evidence, although initiatives have been put in place to improve diversity in clinical trials.[130, 131] A further approach to bridge this gap in evidence is to explore drug effects in diverse populations using observational studies in routine-care data. Trial replication methods can be used to benchmark findings against target trials providing confidence of the validity of the observational comparison before extending analyses to ethnic minority subgroups which can be adequately powered in the UK's diverse population.[44, 46, 53, 132]

Therefore, the comparative risk of angioedema and the overall effectiveness between ARB and ACE inhibitor users is uncertain among Black people. We sought to determine whether ARBs and ACE inhibitors were equally effective for reducing cardiovascular outcomes, and to quantify the risk of angioedema, among White, Black and South Asian people in the UK using routine healthcare data from the Clinical Practice Research Datalink (CPRD) Aurum, with replication of the ONTARGET trial to benchmark findings.

Methods

The RCT

The primary objective of the ONTARGET trial was to determine if dual use of telmisartan (ARB) and ramipril (ACE inhibitor) was superior to ramipril alone for reduction of

cardiovascular events among patients with vascular disease or high-risk diabetes, but without heart failure. The secondary objective aimed to determine if telmisartan (ARB) was non-inferior to ramipril (ACE inhibitor) in the same group of patients.[22] Patients were eligible if they were aged ≥55 years and had a history of either macrovascular disease or high-risk diabetes with end-organ damage. The primary outcome of the trial was a composite of cardiovascular-related death, myocardial infarction (MI), stroke or hospitalisation for heart failure.

Study results

Among the participants included in the trial 1.2% were of South Asian and 2% were of Black ethnicity. Just over 8500 patients were enrolled to receive each treatment arm of ramipril alone, telmisartan alone or dual treatments. The primary outcome occurred in 1412 (16.5%) patients in the ramipril group and 1423 (16.7%) patients in the telmisartan group. The primary composite outcome for the secondary objective of telmisartan vs ramipril showed HR 1.01 (95% CI: 0.94, 1.09).

The emulation using observational data

Eligibility criteria and treatment strategies

Methods are detailed in a previously published protocol and summarised in Figure S1 in Appendix 3: Supplementary material from Research paper 3.[102] Table S1 in Appendix 3: Supplementary material from Research paper 3 details protocol components from ONTARGET, the emulation protocol and deviations from the protocol that were carried out in CPRD Aurum. CPRD Aurum was used instead of GOLD to increase sample size and power.[126]

- ***Step 1: Create exposed periods***

To summarise, we selected self-reported Black, South Asian and White patients ever prescribed an ACE inhibitor and/or ARB between 1/1/01-31/7/19 in CPRD Aurum, with ethnicity defined using both CPRD and data from Hospital Episode Statistics (HES) to improve completeness.[75] As of June 2021, CPRD Aurum included primary care records for research acceptable patients (registered at currently contributing practices, excluding deceased patients) representative of around 20% of the UK population.[72] This was linked to hospitalisation and mortality data from HES and the Office for National Statistics (ONS). Courses of therapy were denoted as exposed periods, prescriptions of <90 days were combined; therefore, a patient could contribute multiple eligible exposed periods, as in a trial a patient could meet the trial criteria on more than one occasion.

- ***Step 2: Create trial-eligible periods***

We applied the ONTARGET trial criteria to the start of each exposed period to select high-risk patients aged ≥55 years with a previous cardiovascular diagnosis or diabetes with complications. Interpretation of trial criteria in CPRD is displayed in Table S9-S10 in Appendix 3: Supplementary material from Research paper 3.

Outcomes

Comparisons were made between ARB vs ACE inhibitor and outcomes replicated those studied in ONTARGET.

- Primary outcome: composite of cardiovascular death, myocardial infarction (MI), stroke, or hospital admission for congestive heart failure
- Secondary cardiovascular outcomes:
    - Main secondary outcome: composite of cardiovascular death, MI, or stroke

    - Individual components of primary outcome
    - Death from non-cardiovascular causes
    - All-cause mortality
- Secondary kidney outcomes:
    - Loss of glomerular filtration rate (GFR) or development of end-stage kidney disease (ESKD) (defined as: 50% reduction in estimated GFR (eGFR), start of kidney replacement therapy (KRT) or development of eGFR < 15ml/min/1.73m^2)
    - Development of ESKD (defined as: start of KRT or development of eGFR < 15ml/min/1.73m^2)
    - Doubling of serum creatinine

  GFR was calculated using the CKD-Epi equation 2009 without reference to ethnicity.[104]
- Safety outcome: angioedema

Statistical analysis

- ***Step 3: Balance across exposure groups***

From the trial eligible periods defined in step 2, we selected one random eligible period per patient and developed a propensity score model for the probability of receiving an ACE inhibitor. Variables considered in the propensity score model included demographics, medication and clinical history, and time-related variables to account for bias introduced in treatment switchers (Table S2 in Appendix 3: Supplementary material from Research paper 3). Treatment groups were weighted by propensity score to obtain balance of baseline characteristics and variables which remained imbalanced were adjusted for in the analysis.

- ***Benchmarking results***

We explored the replicability of the ONTARGET trial findings in our trial-eligible cohort by estimating a hazard ratio (HR) using the Cox-proportional hazards model weighted by propensity score for the primary composite trial outcome of cardiovascular death, MI, stroke or hospitalisation for heart failure and components of this outcome separately in addition to the main secondary outcome, all adjusted for any imbalanced covariates. Patients were followed from the start of the trial-eligible period until the first of outcome, death, transfer out of practice, last collection date or 5.5 years. We confirmed similarity to the trial if our results for the primary composite outcome met a pre-specified validation criteria of 1) HR between 0.92 and 1.13 and 2) 95% CI for the HR contained 1. No criteria were set to confirm replicability of the secondary outcomes but consistency with the primary outcome was deemed as comparable. These methods mirrored those that were implemented in an additional paper using CPRD GOLD.[102, 133]

Extending analysis to the underrepresented ethnic groups

We then explored treatment effect heterogeneity by ethnic group using a Wald test for an interaction between treatment and ethnic group in the Cox-proportional hazard model. Balance of covariates after weighting was assessed within ethnic groups and analysis was adjusted for imbalanced variables.

Angioedema events which occurred during the total follow-up period were assessed using a propensity-score—weighted Cox-proportional hazards model as for other outcomes studied.

Sensitivity analyses

Due to ONTARGET being a non-inferiority trial we confirmed our findings by comparing per-protocol results to the main analysis using an equivalent on-treatment analysis. This

involved additionally censoring patients if they ended treatment, switched, or became a dual user of ACE inhibitor/ARB. End of treatment was defined as the end of eligible period i.e., a treatment gap of >90 days occurred. Censor date was then date of last dose of study drug + 60 days.

To assess the bias introduced by including variables with missing values in our propensity-score model, we repeated analyses after multiple imputation of variables which could be assumed to be missing at random.[134, 135]

We assessed the impact of the 2011 treatment recommendation update,[38] recommending ARBs to Black patients in preference of an ACE inhibitor, may have had on results by restricting the cohort to trial-eligible periods prior to 2011. This was assessed for the primary outcome and development of angioedema over the total follow-up period.

Results

Baseline characteristics

In total 633,905 patients were included in the analysis of whom 71% were prescribed an ACE inhibitor. Among the cohort, 19,020 were Black, 33,337 were South Asian and 581,548 were White (Figure 6.5, Table ***6.9***). ACE inhibitors continued to be prescribed more than ARBs between 2001-2018 for all ethnic groups. After the 2011 treatment recommendation update,[38] a small increase in ARB prescriptions were observed among Black individuals. Prescribing patterns were similar among Black and South Asian individuals (Figure S2 in Appendix 3: Supplementary material from Research paper 3).

Table 6.9 Baseline characteristics of trial-eligible patients after applying trial criteria included in propensity-score—weighted analysis compared to ONTARGET

Characteristic	**ARB** N=452,886	**ACEi** N=181,019	**ONTARGET** N=25,620
Age – year	71.5 ± 9.2	70.9 ± 9.5	66.4 ± 7.2
Systolic BP – mmHg	142.9 ± 19.8	143.0 ± 20.2	141.8 ± 17.4
Diastolic BP – mmHg	78.3 ± 10.8	78.9 ± 11.0	82.1 ± 10.4
Body-mass index	29.3 ± 5.8	28.8 ± 5.8	28.2 ± 4.7
Creatinine - μmol/l	94.0 ± 29.6	92.9 ± 27.4	94.2 ± 24.4
Cholesterol – mmol/l	4.7 ± 1.2	4.8 ± 1.2	4.9 ± 1.2
Female sex – no. (%)	99532 (55.0)	212623 (47.0)	6831 (26.7)
Ethnic group – no. (%)			
Black	6613 (3.7)	12407 (2.7)	511 (2.0)
Other	0	0	5973 (23.3)
South Asian	11934 (6.6)	21403 (4.7)	303 (1.2)
Unknown	0	0	125 (<0.1)
White	162472 (89.8)	419076 (92.5)	18708 (73.0)
Clinical history – no. (%)			
CAD[a]	125818 (69.5)	321035 (70.9)	19102 (74.6)
Cerebrovascular disease[b]	19045 (10.5)	47980 (10.6)	5342 (20.9)
PAD[c]	16848 (9.3)	41651 (9.2)	3468 (13.5)
Diabetes	113559 (62.7)	272390 (60.2)	9612 (37.5)
High-risk diabetes[d]	91826 (50.7)	212396 (46.9)	7151 (27.9)
Smoking status – no. (%)			
Non-smoker	50809 (28.1)	118150 (26.1)	9088 (35.5)
Current smoker	41345 (22.8)	123576 (27.3)	3225 (12.6)
Past smoker	88865 (49.1)	211160 (46.6)	13276 (51.8)
Unknown	0	0	31 (0.1)
Alcohol status – no. (%)			
Drinker	112005 (61.9)	282967 (62.5)	10345 (40.4)
Unknown	14937 (8.3)	41235 (9.1)	14 (<0.1)
Medication[e] – no. (%)			
Alpha-blocker	21559 (11.9)	41810 (9.2)	1095 (4.3)
Oral anticoagulant agent	16288 (9.0)	38918 (8.6)	1939 (7.6)
Antiplatelet agent	15685 (8.7)	44603 (9.9)	2824 (11.0)
Aspirin	59571 (32.9)	161515 (35.7)	19403 (75.7)
Beta-blocker	56986 (31.5)	147999 (32.7)	14583 (56.9)
Calcium-channel blocker	63025 (34.8)	146287 (32.3)	8472 (33.1)
Digoxin	6468 (3.6)	18611 (4.1)	865 (3.4)

Characteristic	ARB N=452,886	ACEi N=181,019	ONTARGET N=25,620
Diuretics	76969 (42.5)	174522 (38.5)	7164 (28.0)
Diabetic treatment	46536 (25.7)	112718 (24.9)	8056 (31.4)
Nitrates	16552 (9.1)	48261 (10.7)	7523 (29.4)
Statins	96660 (53.4)	246879 (54.3)	15783 (61.6)

N= number of patients; no. (%)=number (percent); BP= blood pressure; CAD=coronary artery disease; PAD=peripheral artery disease; CKD=chronic kidney disease (eGFR<60ml/min/1.73m^2)

One third of ONTARGET participants received both ramipril plus telmisartan.

[a] Includes diagnosis of: MI at least 2 days prior, angina at least 30 days prior, angioplasty at least 30 days prior, CABG at least 4 years prior

[b] Includes diagnosis of: stroke/TIA

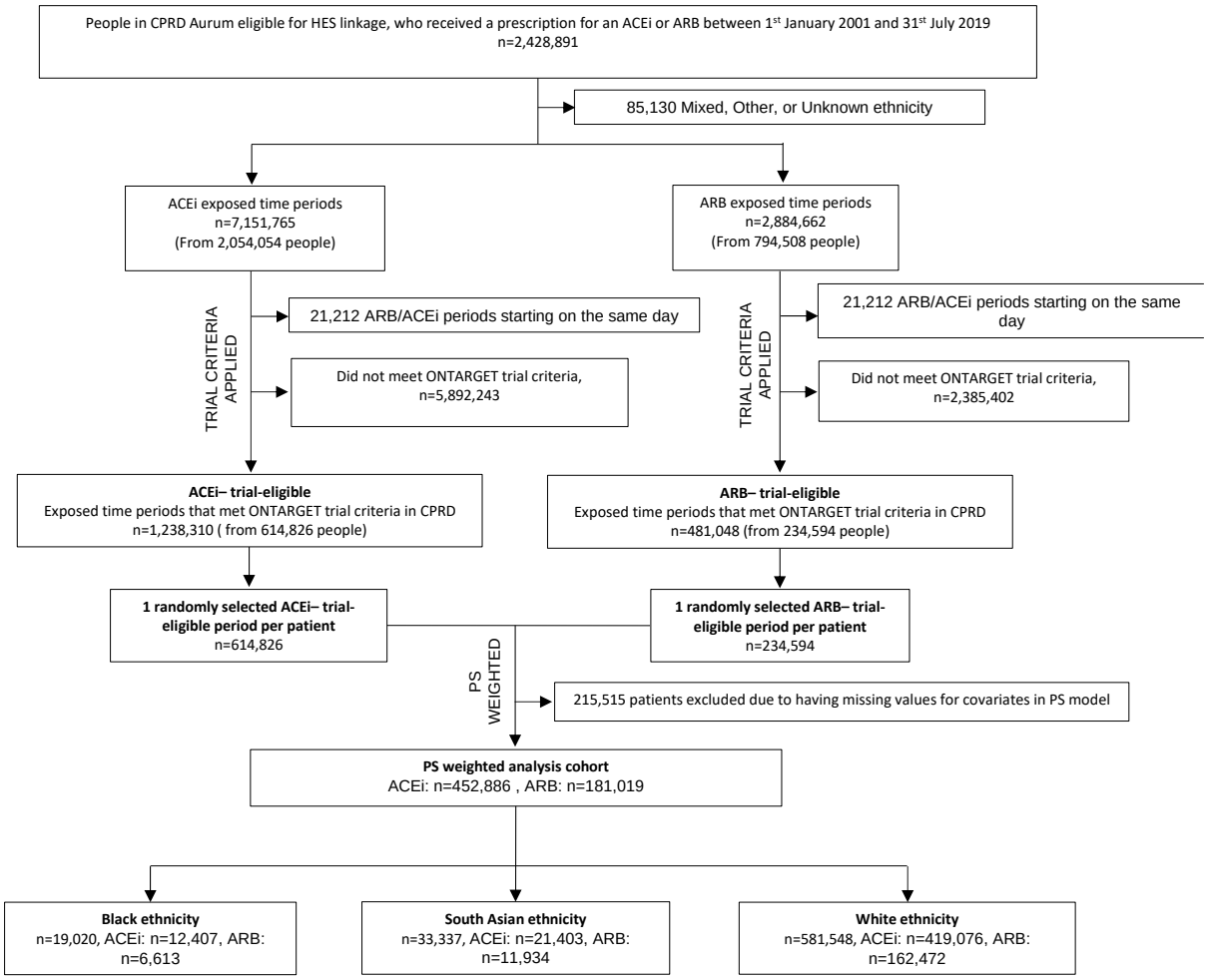
[c] Includes diagnosis of: limb bypass surgery, limb/foot amputation, intermittent claudication

[d] Includes DM with: retinopathy, neuropathy, chronic kidney disease, proteinuria or other complication

[e] Within 3 months prior to eligible start date. Antiplatelet agent= clopidogrel/ticlopidine

Black ethnic group presented for ONTARGET includes 'Black African' and White ethnic group presented for ONTARGET includes 'European/Caucasian' as described in trial CRF. South Asian ethnic group presented for ONTARGET includes Indian, Sri Lanka, Pakistan, Bangladesh, Afghanistan and Nepal. ONTARGET additionally included 'Colored African' ethnicity in the CRF which re-categorised to unknown.

South Asian individuals were younger with lowest baseline blood pressure of the three ethnic groups studied (Table S4-S6 in Appendix 3: Supplementary material from Research paper 3). A greater proportion of Black and South Asian individuals met the trial inclusion criteria due to high-risk diabetes in comparison to White individuals whose main reason for inclusion criteria was coronary artery disease. Black and South Asian individuals were less likely to smoke and drink with fewer hospital admissions and Black individuals most deprived (Table S3-S6 in Appendix 3: Supplementary material from Research paper 3)



Notes: ARB= angiotensin receptor blocker; ACEi= angiotensin-converting enzyme inhibitor; PS= propensity score.

Figure 6.5 Study diagram for people included in propensity-score—weighted analysis cohort using CPRD Aurum.

Benchmarking results to the ONTARGET trial

Baseline characteristics and standardised differences after weighting are shown in Tables S3-S6 in Appendix 3: Supplementary material from Research paper 3.

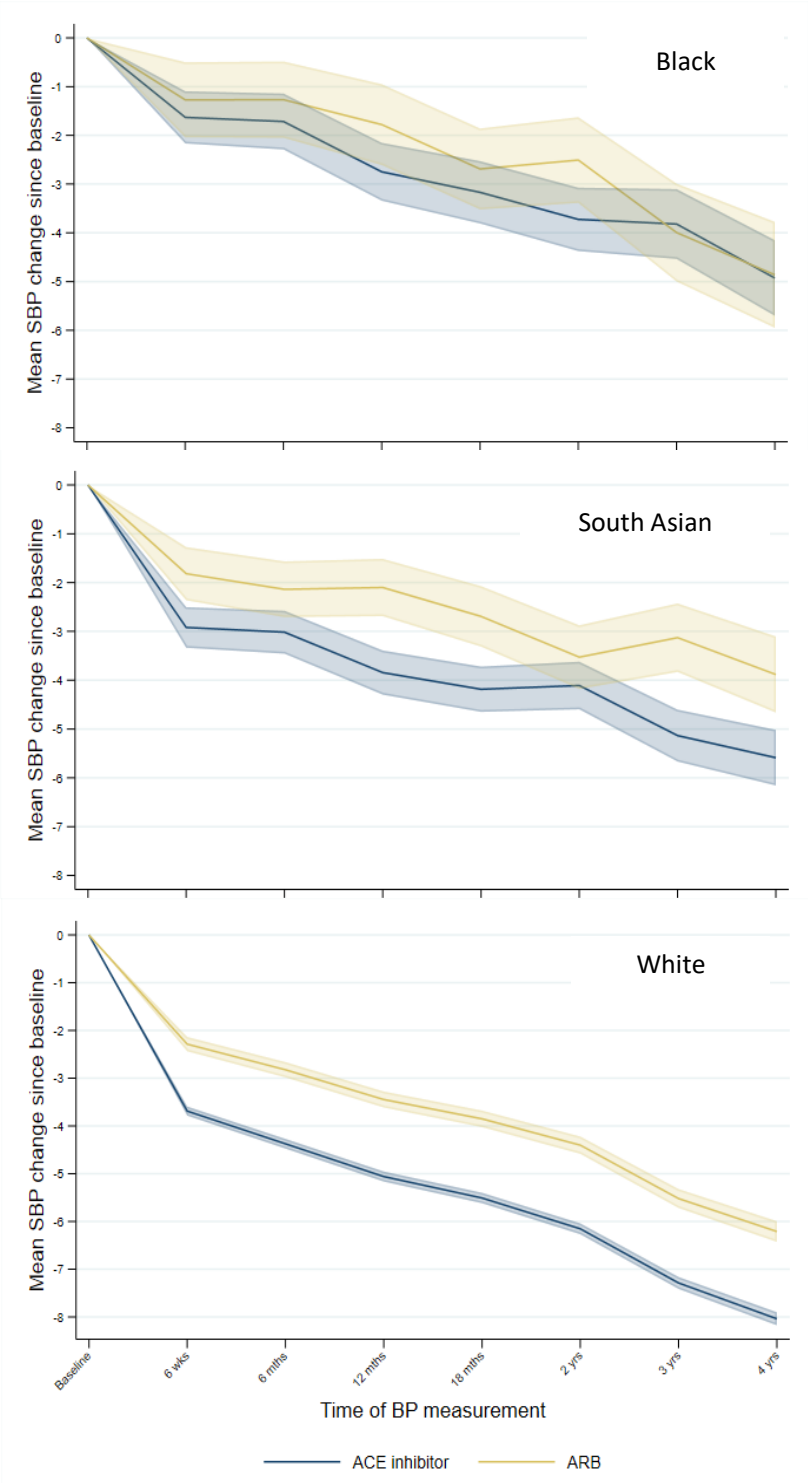
In the whole study population, the primary composite outcome occurred in 27,789 (15.4%) in the ARB group and in 73,914 (16.3%) in the ACE inhibitor group, representing event rates of 4.0 and 3.9 per 100 person-years respectively over a median follow-up of 5.0 years. The estimated HR was 1.00 (95% CI: 0.98, 1.02) for the comparison of ARB vs ACE inhibitor for

the primary composite outcome (Table S7 in Appendix 3: Supplementary material from Research paper 3), meeting the pre-specified validation criteria and confirming similarity to the ONTARGET trial (HR 1.01 (95% CI: 0.94, 1.09)). Results were consistent for secondary outcomes except for death-related outcomes including death from cardiovascular causes, death from non-cardiovascular causes and all-cause mortality where ARBs were associated with a lower risk than ACE inhibitors (although 95% CIs overlapped with ONTARGET). ARBs were associated with a small increased risk of hospitalisation for heart failure (Table S7 in Appendix 3: Supplementary material from Research paper 3).

Extending analysis to the underrepresented ethnic groups

- ***Blood pressure changes***

For people starting an ACE inhibitor there was a greater fall in systolic blood pressure compared to ARBs for South Asian and White individuals and no difference in treatment for Black patients, with the biggest reduction six weeks after the start of the trial-eligible period (Figure 6.6). Over 4 years of follow-up mean systolic blood pressure was reduced by 5, 5.5 and 8 mm Hg among Black, South Asian, and White patients, respectively.



Notes: BP: blood pressure; SBP: systolic blood pressure.

Baseline is closest measurement taken prior to start of trial-eligible period within 2 years.

Figure 6.6 Changes in systolic blood pressure (mm Hg) by treatment and ethnic group

- ***Primary composite outcome***

Among Black, South Asian, and White patients, the primary composite outcome occurred in 2,411 (12.7%), 5,077 (15.2%) and 94,215 (16.2%) people, respectively. Event rates for Black patients were 3.5 and 3.0 per 100 person-years for ARB and ACE inhibitor users, respectively. For South Asian patients, event rates were 3.9 and 3.7 per 100 person-years and for White patients, 4.0 per 100 person-years for both ARB and ACE inhibitor users. For the comparison of ARB vs ACE inhibitor for the primary composite outcome HR was 1.06 (95% CI: 0.96, 1.17) for Black patients, HR 0.98 (95% CI: 0.92, 1.05) for South Asian patients and HR 0.99 (95% CI: 0.97, 1.00) for White patients with no evidence of heterogeneity by ethnicity (*P*=0.365) (Table ***6.10***, Figure 6.7).

- ***Secondary outcomes***

There was no evidence of treatment heterogeneity by ethnicity for the majority of secondary outcomes (Table ***6.10***, Figure 6.7). However, there was evidence of heterogeneity for the death related outcomes including cardiovascular-related death (*P*=0.016) and all-cause mortality (*P*=0.035), with ARBs associated with reduced all-cause mortality compared to ACE inhibitors for White (HR 0.88 (95% CI: 0.87, 0.90)) and South Asian (HR 0.92 (95% CI: 0.85, 0.99)) patients but not for Black patients.(HR 1.01 (95% CI: 0.91, 1.12)), and ARBs associated with reduced cardiovascular death for White (HR 0.90 (95% CI: 0.87, 0.92)) but not Black patients (HR 1.13 (95% CI: 0.95, 1.34)) (Table ***6.10***, Figure 6.7).

Table 6.10 Treatment effect heterogeneity for the primary and secondary outcomes by ethnicity for ARB vs ACEi using a propensity-score—weighted and adjusted analysis of trial-eligible patients in CPRD Aurum.

Outcome	**Ethnic group**			**P value for interaction**
	Black (N=19,020)	**South Asian** (N=33,337)	**White** (N=581,548)	
	Hazard ratio (95% CI)			
Primary composite	1.06 (0.96, 1.17)	0.98 (0.92, 1.05)	0.99 (0.97, 1.00)	0.365
Main secondary outcome	1.04 (0.92, 1.18)	1.00 (0.92, 1.08)	0.98 (0.96, 1.00)	0.561
Myocardial infarction	1.11 (0.93, 1.33)	1.00 (0.91, 1.10)	0.99 (0.96, 1.02)	0.421
Stroke	1.01 (0.87, 1.18)	0.97 (0.85, 1.11)	0.98 (0.95, 1.01)	0.909
Hospitalisation for heart failure	1.07 (0.93, 1.23)	0.99 (0.89, 1.10)	1.00 (0.97, 1.03)	0.679
Death from cardiovascular causes	1.13 (0.95, 1.34)	0.96 (0.85, 1.09)	0.90 (0.87, 0.92)	0.016
Death from non-cardiovascular causes	0.93 (0.82, 1.07)	0.88 (0.79, 0.98)	0.88 (0.86, 0.90)	0.647
Death from any cause	1.01 (0.91, 1.12)	0.92 (0.85, 0.99)	0.88 (0.87, 0.90)	0.035
Loss of GFR or ESKD	1.15 (1.00, 1.31)	1.03 (0.93, 1.15)	1.05 (1.02, 1.08)	0.422
ESKD	1.09 (0.88, 1.35)	0.97 (0.80, 1.18)	0.99 (0.94, 1.04)	0.675
Doubling of serum creatinine	1.19 (1.00, 1.41)	1.03 (0.90, 1.18)	1.06 (1.02, 1.10)	0.409

ESKD: end-stage kidney disease; GFR: glomerular filtration rate.

Primary composite outcome: death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure.

Main secondary outcome: death from cardiovascular causes, myocardial infarction, or stroke.

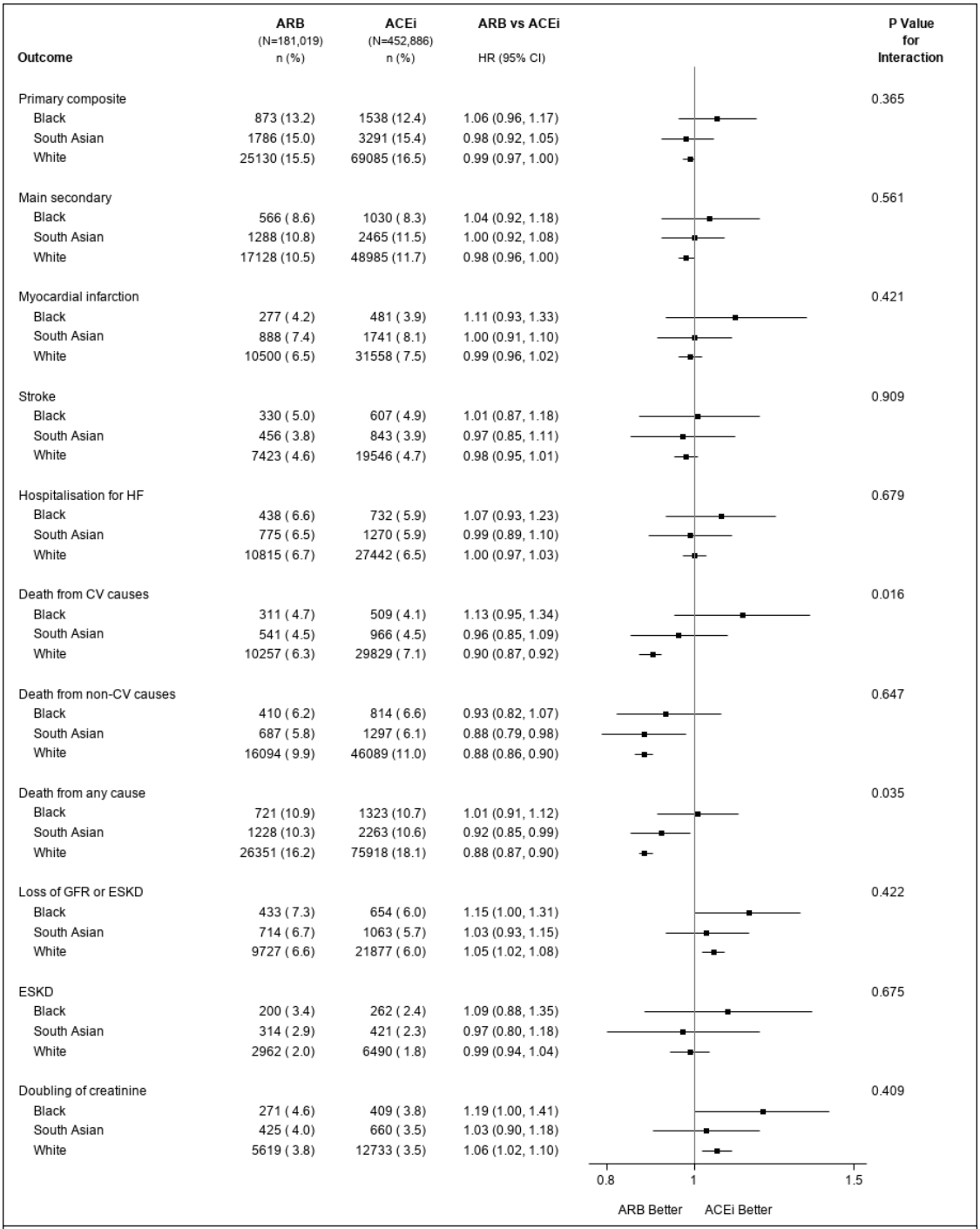
CPRD weighted analysis includes 1 randomly selected trial-eligible period per patient. Propensity-score—weighted with robust standard errors. Analysis adjusted for number of GP appointments 6 months prior, baseline creatinine and number of prior ARB periods.

Myocardial infarction and stroke include both fatal and non-fatal events.

Loss of GFR or ESKD defined as: 50% reduction in estimated glomerular filtration ratio (eGFR), start of kidney replacement therapy (KRT) or eGFR<15ml/min/1.73m^2.

ESKD defined as: start of KRT or eGFR<15ml/min/1.73m^2.

ONTARGET results are from published findings.

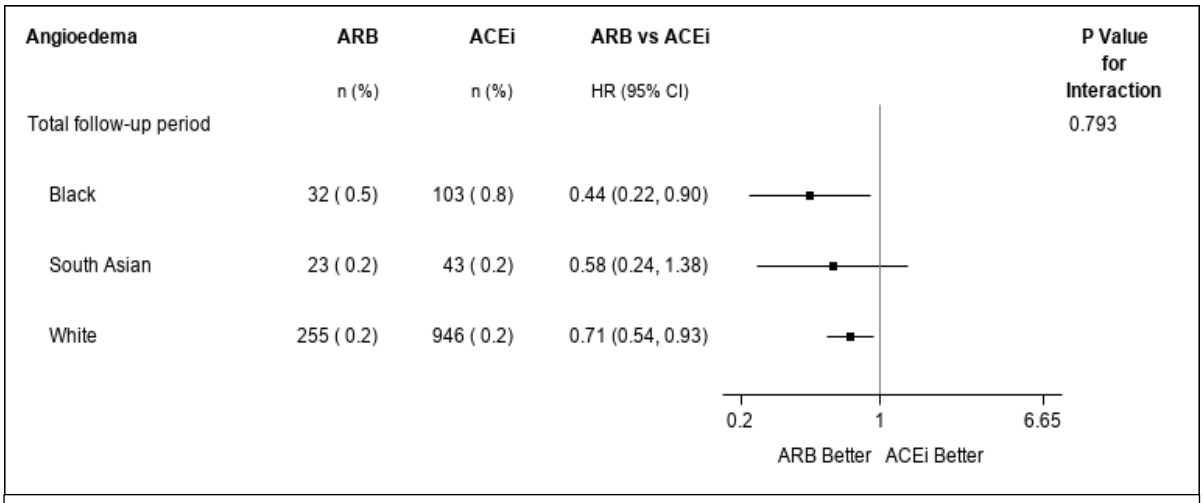


Notes: N (%)= number of events (percent); ESKD: end-stage kidney disease; GFR: glomerular filtration rate. Primary composite outcome: death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure. Main secondary outcome: death from cardiovascular causes, myocardial infarction, or stroke. Loss of GFR or ESKD defined as: 50% reduction in estimated glomerular filtration ratio (eGFR), start of kidney replacement therapy (KRT) or eGFR<15ml/min/1.73m^2. ESKD defined as: start of KRT or eGFR<15ml/min/1.73m^2. Analysis adjusted for number of GP appointments 6 months prior, baseline creatinine and number of prior ARB periods. P-value is test of interaction between ethnicity and treatment.

Figure 6.7 Treatment effect heterogeneity for the primary and secondary outcomes by ethnicity for ARB vs ACEi using a propensity-score—weighted and adjusted analysis of trial-eligible patients in CPRD Aurum.

- ***Angioedema***

The overall incidence of angioedema recorded in primary care data was 907 (0.14%) patients during the follow-up period of 5.5 years. 35% of angioedema events occurred within the first 12 months, compared to two thirds of events which in the ALLHAT trial.[39]. Over the total duration of follow-up (maximum 5.5 years) there was no association with treatment and the risk of developing angioedema for South Asian patients, HR 0.58 (95 CI: 0.24, 1.38). However, for Black and White patients ARB use was associated with a decreased risk of developing angioedema compared to ACE inhibitor use, HR 0.44 (95% CI: 0.22, 0.90) and RR 0.71 (95% CI: 0.54, 0.93), for Black and White patients, respectively (Figure 6.8). The angioedema rate per 10,000 person-years was 9.4 and 12.9 among Black ARB and ACE inhibitors users, respectively. 2.0 and 3.5 among South Asian ARB and ACE inhibitor users, respectively and 2.2 and 3.4 among White ARB and ACE inhibitor users, respectively.



Notes: N (%)= number of events (percent). Total follow-up period is a maximum follow-up of 5.5 years with patients censored at death, transferred out of practice date or last collection date as in main analysis.
Outcome assessed using propensity-score—weighted Cox proportional hazards model.
Analysis adjusted for number of GP appointments 6 months prior, baseline creatinine and number of prior ARB periods. P-value is test of interaction between ethnicity and treatment.

Figure 6.8 Treatment effect heterogeneity for the risk of angioedema by ethnicity for ARB vs ACEi using a propensity-score—weighted and adjusted analysis of trial-eligible patients in CPRD Aurum.

Sensitivity analyses

When we restricted to follow-up time on the original treatment (on-treatment analysis) results were consistent with the ONTARGET trial results for the whole population (HR 0.99 (95% CI: 0.97, 1.01)) and when extending analysis to Black and South Asian individuals for the primary composite outcome (Table S8 and Figure S3 in Appendix 3: Supplementary material from Research paper 3).

We used multiple imputation of missing covariates for variables included in the propensity score model to assess the bias introduced from a complete case analysis. After multiple imputation of missing covariates, for the primary composite outcome 781,551 patients were included in analysis. Results were consistent with the main analysis using complete records although confidence intervals were narrower strengthening an apparent association of lower risk among ARB users compared to ACEi users in White individuals for the primary composite outcome (HR 0.96 (95% CI: 0.95, 0.98)).

Assessing the impact of the 2011 treatment recommendation by restricting the cohort to trial-eligible periods prior to 2011 we observed consistent results for the primary outcome and angioedema (Figure S3-S4 in Appendix 3: Supplementary material from Research paper 3).

Discussion

Main findings

In this observational study reflecting current routine care in England, with inclusion of large numbers of South Asian and Black participants, we benchmarked findings of similar effectiveness of ACE inhibitors and ARBs against the ONTARGET randomised trial. We observed no evidence to suggest treatment heterogeneity by ethnic group. We also observed greater levels of blood pressure reduction after treatment initiation for White people

compared to Black and South Asian ethnic groups. Overall incidence of angioedema was low with 907 events occurring during a maximum follow-up of 5.5 years. This was compared to 53 events occurring in 4.9 years in the ALLHAT study.[39] Unlike other adverse events drug-related angioedema can occur years after treatment.[136] Therefore, we examined the risk of developing angioedema over the total follow-up period of 5.5 years. We observed more events occurred among ACE inhibitor users and ARB use was associated with a lower risk of angioedema for Black and White patients. Black patients were 3 times more likely to develop angioedema compared to White patients. Despite some evidence which support current UK treatment guidance that recommend an ARB in preference to an ACE inhibitor[111] due to the decreased risk of angioedema associated with ARB use, we observed no evidence that this differed by ethnicity.

Strengths and limitations

By aid of large sample size and using trial replication methods to add confidence to results we have been able to provide evidence supporting the comparative effectiveness of ARBs and ACE inhibitors at preventing cardiovascular and kidney outcomes in Black and South Asian populations, who are often underrepresented in trials. To our knowledge this is the first study exploring the risk of angioedema associated with ARB and ACE inhibitor treatment use among a large ethnically diverse population in the UK.

We excluded patients with missing ethnicity which could introduce some bias into our results but for this indication ethnicity is well-captured using combined CPRD Aurum and HES data so the number of patients who were excluded was low at 1.6%.

In agreement with other studies assessing the incidence of angioedema associated with ACE inhibitor use, incidence was low.[39, 111, 137] When assessing the risk of angioedema, we only included events reported in primary care. Therefore, the true number of events

experienced may be higher. Due to low incidence and wide confidence intervals, it is difficult to draw reliable conclusions for this outcome and results must be interpreted with caution. In addition to this, results observed may be due to multiple testing and despite observing an increased risk of angioedema in Black patients this could be influenced by potential differential misclassification by general practitioners (GP). Since angioedema is believed to be more prominent in Black populations and there is evidence to suggest increased risk associated with ACE inhibitor use, GPs may be more likely to diagnose angioedema and accurately record codes for Black patients or patients receiving an ACE inhibitor.

ACE inhibitors appeared to be most effective in reducing blood pressure for White and South Asian individuals, but no treatment differences were observed for Black patients. However, the treatment difference could be due to confounding by indication, with sicker patients with uncoded heart failure more likely to be prescribed an ACE inhibitor, which is supported by the increased risk of death associated with ACE inhibitor use among White and South Asian individuals. Additionally, differences observed in reductions in blood pressure could be due to potential ethnic differences in treatment duration and overall blood pressure management.[126]

We attempted to account for confounders such as socio-economic status that is known to differ by ethnicity by assessing balance of covariates across treatment groups within and between ethnic groups. We used propensity-score—weighting to account for measured confounders and assumed unmeasured confounding is small across the subgroups defined by the included covariates. However, this remains a limitation of observational data.

Comparison to literature

Few studies have explored the comparative effectiveness of ARBs and ACE inhibitors in Black and South Asian ethnic groups. Our results support the generalisability of the

ONTARGET trial results to ethnic minority populations and are consistent with other evidence demonstrating comparable effectiveness of ARBs and ACE inhibitors.[22, 138] Despite the subgroup analysis of the ALLHAT trial and other studies indicating increased incidence of angioedema among ACE inhibitor use for Black individuals compared to those who were non-Black the ALLHAT trial did not include a direct comparison between ARBs and ACE inhibitors.[39] In addition to this, current evidence has been from a US population.[139, 140] Despite our study showing an increase in incidence of developing angioedema among Black individuals compared to White individuals, ARBs were associated with a lower risk of angioedema over the total follow-up time in both White and Black ethnic groups.

Interpretations and conclusions

We have demonstrated equal treatment effects of ARBs and ACE inhibitors in preventing cardiovascular and kidney outcomes in high-risk patients in UK routinely collected data, consistent with the ONTARGET trial. These findings extend to South Asian and Black individuals who are often underrepresented in trials and for whom there is a lack of evidence of treatment effects.

Despite low numbers, we found incidence of angioedema was higher among Black individuals compared to South Asian and White patients. Over a follow-up of 5.5 years, we found no evidence of heterogeneity by ethnicity and observed ARBs were associated with a decreased risk of angioedema compared to ACE inhibitors in both Black and White patients. However, among South Asian individuals, treatment effects were similar, but events were low leading to wide confidence intervals.

UK hypertension treatment guidance recommends an ARB in preference to an ACE inhibitor in Black patients. Our results demonstrate similar relative increase in risk of angioedema

across ethnic groups suggesting that a recommendation to choose ARBs among Black patients only may not be appropriate.

Funding

This work was supported by the funding from a GlaxoSmithKline PhD studentship held by PB as part of an ongoing collaboration between GSK and the London School of Hygiene and Tropical Medicine.

6.2.2 Additional results from achieving balance across exposure groups in CPRD Aurum

Analysis in CPRD Aurum omitted step 4 of matching to trial participants, as outlined in the published methods paper (Research paper 1). Deviations from the protocol to extend analysis to CPRD Aurum are described in Chapter 5, section 5.2.4. In summary, I used propensity-score—weighting to achieve balance across trial-eligible exposure groups. The final choice of variables included in the propensity score model are displayed in Table ***6.11***.

Table 6.11 Covariates included in propensity score model used to ensure balance among ACE inhibitor and ARB trial-eligible exposure groups in CPRD Aurum

Covariate	**Form**	**Higher order term**
Stroke/TIA	Binary	
Peripheral artery disease	Binary	
Coronary artery disease	Binary	
Diabetes	Binary	
High-risk diabetes	Binary	
Sex	Binary	
Age	Continuous	+ quadratic
Body-mass-index	Categoric	
Systolic blood pressure	Continuous	
Diastolic blood pressure	Continuous	+ quadratic
Smoke status	Categorical (non, ex or current)	
Index of multiple deprivation	Categorical (1-5)	
Statin use 3 months prior	Binary (yes, no)	
Nitrate use 3 months prior	Binary (yes, no)	
Diabetic treatment use 3 months prior	Binary (yes, no)	
Diuretic use 3 months prior	Binary (yes, no)	
Calcium channel blocker use 3 months prior	Binary (yes, no)	
Betablocker use 3 months prior	Binary (yes, no)	
Aspirin use 3 months prior	Binary (yes, no)	

Covariate	Form	Higher order term
Alpha-blocker use 3 months prior	Binary (yes, no)	
Anticoagulant use 3 months prior	Binary (yes, no)	
Antiplatelet use 3 months prior	Binary (yes, no)	
Number of previous hospital admissions 6 months prior	Continuous (log)	
Calendar year	Continuous	
Time since first trial-eligible period	Continuous	+ quadratic
Number of previous ACE inhibitor periods	Continuous	+ quadratic

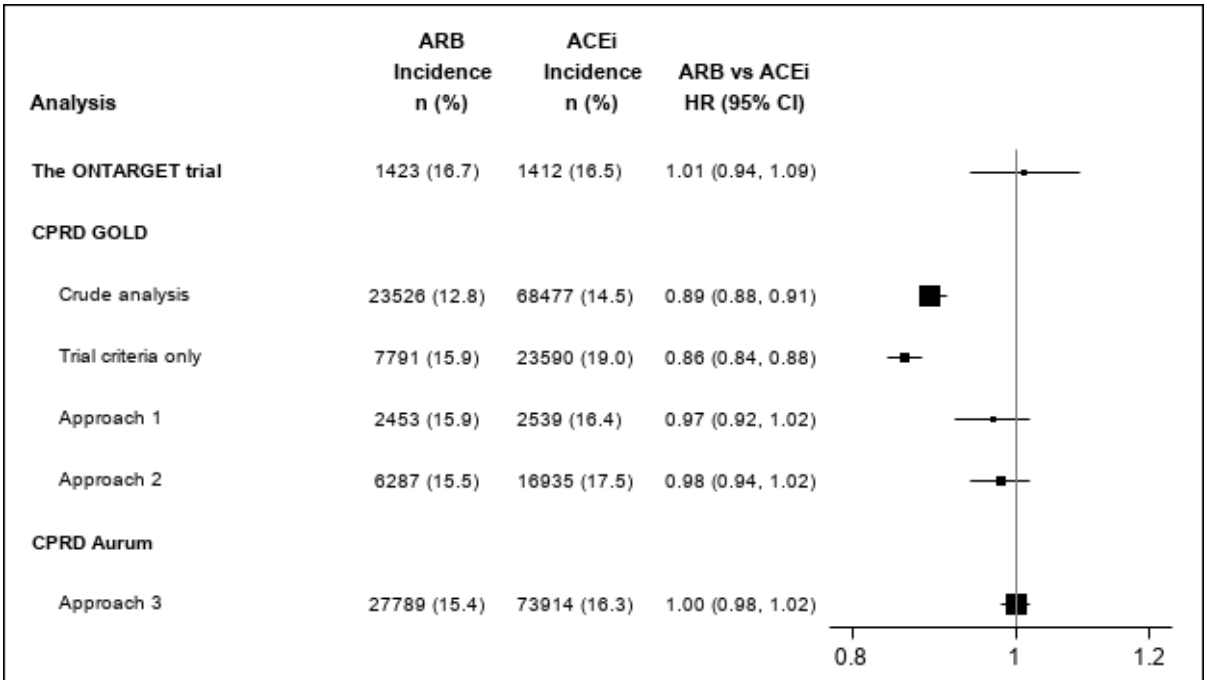
6.3 Summary of trial replication findings and crude results

The three approaches to trial replication to address Research Aim 2– objective 1, outlined in Chapter 5 were explored in CPRD GOLD and Aurum and are summarised below:

1. Trial-matched and trial-eligible ACEi patients 1:1 matched to closest ARB trial-eligible patient using propensity-score model developed for probability of receiving an ACEi using appended cohort of trial-matched and trial-eligible ACEi patients and trial-eligible ARB patients
2. Propensity score weighted trial-eligible ACEi and trial-eligible ARB patients using propensity-score model developed for probability of receiving an ACEi using appended cohort of trial-matched and trial-eligible ACEi patients and trial-eligible ARB patients
3. Propensity score weighted trial-eligible ACEi and trial-eligible ARB patients using propensity score model developed for probability of receiving an ACEi using appended cohort of trial-eligible ACEi patients and trial-eligible ARB patients (omitted trial-matching step)

I used both propensity score matching (approach 1) and weighting (approach 2) in CPRD GOLD to obtain balance of characteristics across exposure groups and both led to

comparable results. By using propensity score weighting the analysis cohort included patients with more diverse characteristics compared to those in the ONTARGET trial and prevented loss of sample size through matching. Approach 3 was implemented in CPRD Aurum. This method did not use the ONTARGET trial data to inform the propensity score model used to obtain balance across exposure groups in CPRD. This approach also led to results closely comparable to the ONTARGET trial results. Since approach 3 required the least restrictions (i.e., access to individual trial data was not required) and propensity-score—weighting increased sample size and allowed findings to be extended to underrepresented and excluded groups, this approach was deemed as optimal. Results from the three approaches are displayed in Figure 6.9. For comparison, I show two additional crude estimates. The first is from an unadjusted analysis including all patients who received prescriptions for the drugs of interest regardless of whether trial criteria were met, and the second is from an analysis of patients who met the trial criteria, without balancing characteristics across exposure groups, selecting one random period per patient and using Cox proportional hazards models to estimate the primary composite outcome without accounting for potential confounders by weighting, matching, or adjusting.



Notes: Analysis for primary composite outcome: cardiovascular-related death, myocardial infarction, stroke, or hospitalisation for heart failure. PS=propensity-score. Crude and trial criteria only analysis is unadjusted. PS-matched and PS-weighted analysis also adjusted for imbalanced variables. Approach 1: trial criteria applied and PS-matched; Approach 2: trial criteria applied and PS-weighted; Approach 3: trial criteria applied and PS – weighted. Approach 1 and Approach 2 in CPRD GOLD uses ACE inhibitor trial-analogous patients (generated after first 1:1 matching ONTARGET participants to closest ACE inhibitor trial-eligible period) to build PS model. Approach 3 in CPRD Aurum uses ACE inhibitor trial-eligible patients to build PS model omitting step 4 (matching to trial participants). Crude and trial criteria only analyses also carried out on first trial-eligible period per patient and gave HR 0.89 (95% CI: 0.88, 0.90) and HR 0.86 (95% CI: 0.83, 0.88), respectively.

Figure 6.9 Summary of results using different approaches to trial replication in CPRD

Chapter 7. Results from replication of the ONTARGET trial dual therapy analysis

Chapter summary

- This chapter aimed to investigate whether trial replication methods could be applied to emulate RCTs with dual therapy treatment arms
- The chapter includes a draft paper presenting findings from replicating the ONTARGET dual therapy analysis in CPRD Aurum
- I adapted the definition outlined in the published protocol to ensure dual users were captured as opposed to treatment switchers, as described in Chapter 5
- The impact of survivor and immortal time bias in the operational definition of a dual user was assessed in two sensitivity analyses
- Analysis showed the operational definition of a dual user gave results closely comparable to those presented in the ONTARGET trial, but confounding by indication could be present
- After benchmarking findings against the ONTARGET trial I extended analysis to explore treatment effect heterogeneity by CKD status for dual users compared to ACEi use along by fitting an interaction term

7.1 Results from dual therapy analysis in CPRD Aurum (Research paper 4)

7.1.1 Research paper 4

The included draft research paper presents results from conducting analysis to address Research Aim 1in CPRD Aurum, replicating the dual therapy analysis in ONTARGET. CPRD Aurum was used to increase sample size and methods followed those outlined in Chapter 5. Supplementary material relating to research paper 4 are available in Appendix 4: Supplementary material from Research paper 4.

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Student ID Number	1800205	**Title**	Miss
First Name(s)	Paris Jade		
Surname/Family Name	Baptiste		
Thesis Title	Real-world effectiveness and adverse events caused by ACE inhibitors and ARBs for reduction in cardiovascular events with validation against the ONTARGET trial		
Primary Supervisor	Laurie Tomlinson		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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	Tomlinson
Stage of publication	**Not yet submitted**

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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author on this paper. I contributed to the study question and design. I carried out data management and conducted the analysis for the work presented in this paper. I wrote the first draft of this mansucript and drafted subsequent versions.

SECTION E

Student Signature	[redacted]
Date	7/6/23

Supervisor Signature	[redacted]
Date	7/6/23

Cardiorenal effects of dual blockade with Angiotensin-converting enzyme inhibitors and Angiotensin receptor blockers: analysis of routinely collected data with validation against a target trial

Authors

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Abstract

Background

Trial replication methodology increasingly used to explore whether randomised trial results are generalisable to the wider population. However, treatment with two concurrent medications can be difficult to define in routine care data. This study aimed to explore the feasibility of these methods for studying the effects of dual therapy for the prevention of cardiovascular outcomes, with validation against the ONTARGET trial.

Methods

We selected people prescribed an angiotensin-converting enzyme inhibitor (ACEi) and/or an angiotensin receptor blocker (ARB) in the UK Clinical Practice Research Datalink (CPRD) Aurum from 1/1/2001-31/7/2019. We specified an operational definition of dual therapy ARB and ACEi users, applied ONTARGET trial criteria and generated a propensity-score—weighted analysis cohort of dual therapy and single-arm ACEi patients. Comparing dual therapy to ACEi, we used Cox-proportional hazards models to estimate the hazard ratios for the primary trial outcome – a composite of cardiovascular death, myocardial infarction, stroke, or hospital admission for heart failure – as well as a primary renal outcome of loss of GFR or end-stage kidney disease, and other secondary outcomes. We assessed the impact of bias in our operational definition of dual therapy users using two sensitivity analyses. Conditional on successfully benchmarking results against the ONTARGET trial, we explored treatment effects in those with chronic kidney disease (CKD) at baseline.

Findings

In the propensity-score—weighted analysis cohort (n=422,606), results for the primary cardiovascular outcome met pre-specified criteria for similarity to the ONTARGET trial (HR 0.99, 95% CI: 0.92, 1.07) and demonstrated similar effectiveness between dual therapy and ACEi, HR 0.97 (95% CI: 0.87, 1.08). However dual therapy use was associated with a greater

risk for the primary renal outcome, HR 1.18 (95% CI: 1.03, 1.34). Sensitivity analysis supported our operational definition of dual therapy users. Consistent results were observed for those with CKD at baseline.

Interpretation

We were able to closely replicate the results of the ONTARGET trial dual therapy comparison within routinely-collected healthcare. However, results were sensitive to how start of dual therapy treatment was defined.

Funding

GlaxoSmithKline

INTRODUCTION

Trial replication (also referred to as “benchmarking”) is methodology which can be used to add confidence to findings from observational studies.[42, 44, 46, 141] Such methods involve closely replicating a target randomised controlled trial (RCT) in a population of interest by applying the trial inclusion/exclusion criteria and using additional techniques such as propensity-score methods to address confounding. There is interest in the extent to which observational studies with trial replication methods can be used as an adjunct or alternative to RCTs to help with regulatory decision making and to provide evidence for supplemental indications.[48, 142, 143] Another application of these methods is to draw conclusions on treatment effects and risk in groups who are typically underrepresented in or excluded from trials.[50, 53] However, evidence on whether more complex interventions, such as dual therapy treatment arms, can be replicated in observational data is limited.

ONTARGET was a large global trial which compared the effects of a combination of ramipril (angiotensin-converting enzyme inhibitor (ACEi)) and telmisartan (angiotensin receptor blocker (ARB)) vs ramipril alone in high-risk cardiovascular patients.[30] Results from the trial, in conjunction with the ALTITUDE and VA-Nephron-D study,[144, 145] changed practice, leading to an end of recommendations for dual ACEi and ARB therapy in patients with kidney disease.[146] Despite these results there is still uncertainty about whether dual blockade of the renin-angiotensin system could be effective at reducing adverse renal outcomes in patients with chronic kidney disease (CKD).[147, 148] The effects of dual therapy in routine care have been little explored.

This study aimed to explore whether the primary and secondary outcome results of the target trial, ONTARGET, are replicable in UK routinely collected healthcare data for the comparison of dual therapy vs ACEi alone, and the extent to which the definition of dual therapy use altered these findings.

METHODS

The RCT

Trial design and analysis

The ONTARGET trial compared the effects of dual therapy of ramipril (ACEi) and telmisartan (ARB) vs. ramipril alone on reduction of cardiovascular events among patients who had vascular disease or high-risk diabetes but who did not have heart failure. The secondary objective of the trial was to determine whether telmisartan (ARB) was at least as effective as ramipril (ACEi).[22] Patients were eligible if they were aged ≥55 years and had a history of either macrovascular disease or high-risk diabetes with end organ damage. The primary outcome of the trial was a composite of cardiovascular-related death, myocardial infarction (MI), stroke or hospitalisation for heart failure. The study also investigated renal outcomes which included a composite dialysis, doubling of creatinine or death and individual components.

Study results

The trial included 17,078 patients of whom 8502 were randomised to receive dual therapy. 23.4% of patients had CKD at baseline and mean creatinine was in the normal range at 93.8 μmol/l. For the primary composite outcome there was no evidence of superiority of dual therapy compared to ACEi alone (HR of 0.99 (95% CI: 0.92, 1.07)), with evidence of an increase of adverse events in participants treated with dual therapy patients. For the primary composite renal outcome HR 1.09 (95% CI: 1.01, 1.18). For the renal primary composite renal outcome there was no evidence of treatment effect heterogeneity by CKD status (P=0.804).

Trial emulation using observational data

Eligibility criteria

Methods are detailed in a previously published protocol and summarised in Figure S1 in Appendix 4: Supplementary material from Research paper 4.[102] Key design aspects of the ONTARGET trial and this emulation are presented in Table S1 in Appendix 4: Supplementary material from Research paper 4.

- ***Step 1: Create exposed periods***

Patients who were ever prescribed an ACEi and/or an ARB from 1/1/2001-31/7/2019 were selected from CPRD Aurum linked to hospitalisation data from Hospital Episode Statistics (HES) and death registrations from the Office for National Statistics (ONS).[65, 74] CPRD Aurum was used to increase sample size and power to detect treatment effect heterogeneity. As of 2021, CPRD Aurum included 13 million alive patients currently registered at a contributing general practice. This represents ~20% of the UK population.[72] Patients were required to have been registered at an up-to-standard practice (ensuring adequate data quality) in CPRD for at least 12 months at the time of their first selected prescription.

- ***Step 2: Create trial-eligible periods***

Eligibility criteria were the same as the ONTARGET trial and assessed at the start of each exposed period for single therapy users and at the start of follow-up in the operational definition of dual users and the two alternate follow-up points.[102] Time periods starting at the point when patients met trial criteria were denoted as trial-eligible periods.

Treatment strategies

- ***Single therapy exposure***

Prescriptions for an ACEi with <90 days between the calculated end date and start of subsequent prescription were combined to create exposed periods. If a patient stopped and restarted treatment they could have multiple exposed periods. Therefore, any period could be selected which enabled a patient to be selected into the cohort at any point in time, similar to recruitment into a RCT such as in ONTARGET which included prevalent users.[23]

- ***Dual therapy exposure***

We defined dual therapy users as patients with overlapping prescriptions of an ACEi/ARB who had a subsequent prescription for the 1st agent within 90 days of the date of the 2nd prescription for the 2nd agent. Follow-up was then started from the date this operational definition was met, i.e., the date of the 2nd prescription for the 1st agent (Figure 7.1). Many patients switch between an ACEi and ARB during their treatment history. Therefore, we required patients to have a 2nd prescription for the 1st agent after the 2nd agent was added to avoid capturing people switching treatment as opposed to dual users. This definition requires "future-time" information, with time prior to meeting the definition not being included in analysis. Including only those who met this operational definition may potentially exclude those who die early during follow-up or who have early adverse events, introducing survivor bias. We assessed this bias through two alternate dual therapy definitions described below. However, by beginning follow-up from earlier on in the patient's history immortal time bias could be introduced.

Alternate definitions of dual therapy exposure to explore the impact of bias

- ***Alternate definition 1: Starting follow-up at the date of the 1st prescription for the 2nd agent***

To explore the impact of the bias from excluding those who may die early or have early adverse events, described above in the operational definition, we started follow-up at the date of 1st prescription for the 2nd agent (Figure 7.1). This reduced this element of survivor bias. However, due to only those patients who met the operational definition being included there would now be a period between the new start of follow-up and meeting the operational definition during which an event cannot occur, introducing immortal time bias.

- ***Alternate definition 2: Starting follow-up at the date of the 2nd prescription for the 2nd agent***

Additionally, to assess the trade-off between survivor and immortal time bias we started follow-up from the date of 2nd prescription for the 2nd agent (Figure 7.1). Despite immortal time bias still being present in this definition it was reduced compared to the alternate definition 1 and the form of survivor bias was also reduced compared to the operational definition.

Outcomes

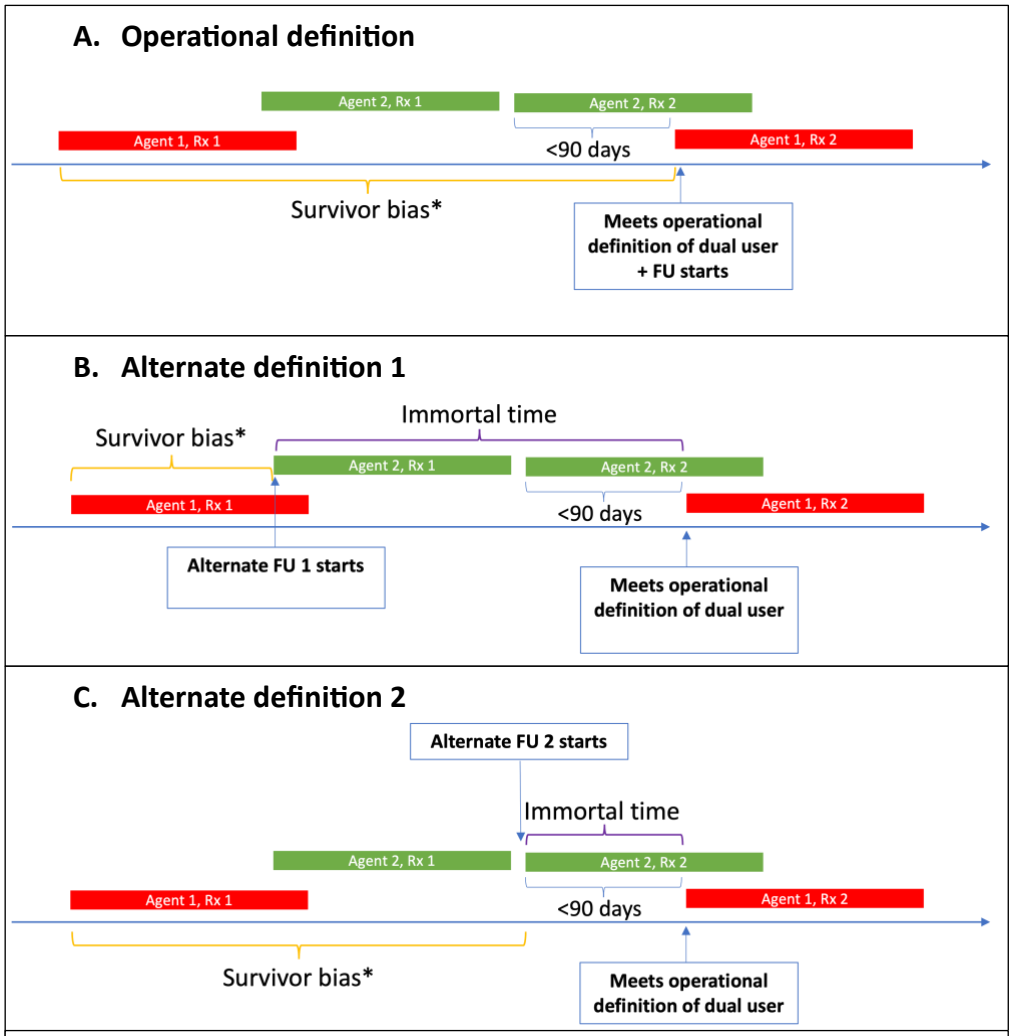
We compared primary and renal outcomes aligned with the clinical trial between dual users of ARB and ACEi vs. ACEi alone:[22] [30]

Cardiovascular outcomes:

- Primary outcome: composite of cardiovascular death, myocardial infarction (MI), stroke or hospital admission for congestive heart failure
- Main secondary outcome: composite of cardiovascular death, MI, or stroke

Renal outcomes

- Primary renal outcome: composite of loss of glomerular filtration rate (GFR) or development of end-stage kidney disease (ESKD) (defined as: 50% reduction in estimated GFR (eGFR), start of kidney replacement therapy (KRT) or development of eGFR < 15ml/min/1.73m^2). GFR was calculated using the CKD-Epi equation 2009 without reference to ethnicity.[104]
- Doubling of serum creatinine



Notes: Dual users are patients with overlapping prescriptions (<90 days between prescriptions) who have subsequent prescription for 1st agent within 90 days of 2nd prescription for 2nd agent. (A) operational definition: follow-up started from date patient meets definition of dual user; (B) Alternate definition 1: follow-up started from date of 1st prescription for 2nd agent; (C) Alternate definition 2: follow-up started from date of 2nd prescription for 1st agent. Agent=medication; Rx=prescription; FU=follow-up for dual user. Survivor bias* represents bias introduced from operational definition excluded patients who may have event or die early.

Figure 7.1 Illustration of operational definition of dual user and potential biases

Renal outcomes studied in ONTARGET were a mix of outcomes and adverse events, some of which were defined by the lead clinical investigators locally.[30] Therefore, the primary renal composite outcome assessed in this study was chosen as a mix of renal outcomes studied in ONTARGET and those which were deemed to be of clinical relevance based on discussions with the lead investigator of ONTARGET. Doubling of serum creatinine was assessed in ONTARGET.

Statistical analysis

- ***Step 3: Balance across exposure groups***

To preserve sample size, we used propensity-score—weighting to achieve balance among exposure groups using a logistic regression model for the probability of receiving an ACEi.[103] As with previous work,[133] we selected one random trial-eligible period per patient in the trial-eligible ACEi and dual therapy exposure groups. A random period was chosen as opposed to the first period as selecting the first period may bias results to new users.

Variables considered in the propensity-score model were chosen based on a-priori knowledge and included baseline demographics, socio-economic status, medication, and clinical history. To account for the potential time-related bias introduced by changing usage of dual blockade over time as a result of published trials and European Medicines Agency guidance,[36] we included time since first trial eligible period in our propensity-score model.[149] Included variables are displayed in Table S2 in Appendix 4: Supplementary material from Research paper 4.

- ***Benchmarking results***

Treatment effectiveness was assessed using a time-to-event analysis weighted by propensity-score, using robust standard errors in a Cox proportional hazards model, under an intention-to-treat approach. The Cox model was adjusted for variables that remained imbalanced after weighting.[105]

We pre-specified a validation criteria to confirm replicability of the ONTARGET trial for the single therapy comparison.[102] Results for the dual therapy comparison in ONTARGET were similar for the primary composite outcome.[22] We therefore also confirmed replicability if the same criteria were met, i.e., if the HR estimates from the observational study for dual therapy compared to ACEi were between 0.9-1.12 and the 95% CI for the HR contained 1.0.

Sensitivity analyses

We included a sensitivity analysis to assess the bias introduced from a complete case analysis of variables included in our propensity-score model that had missing data. We used multiple imputation of chained equations with inverse probability weighting to re-estimate treatment effects for the primary composite outcome[83, 135, 150]. Values were imputed for variables where the missing at random assumption could be assumed.

Extending analysis to trial- underrepresented group of those with CKD

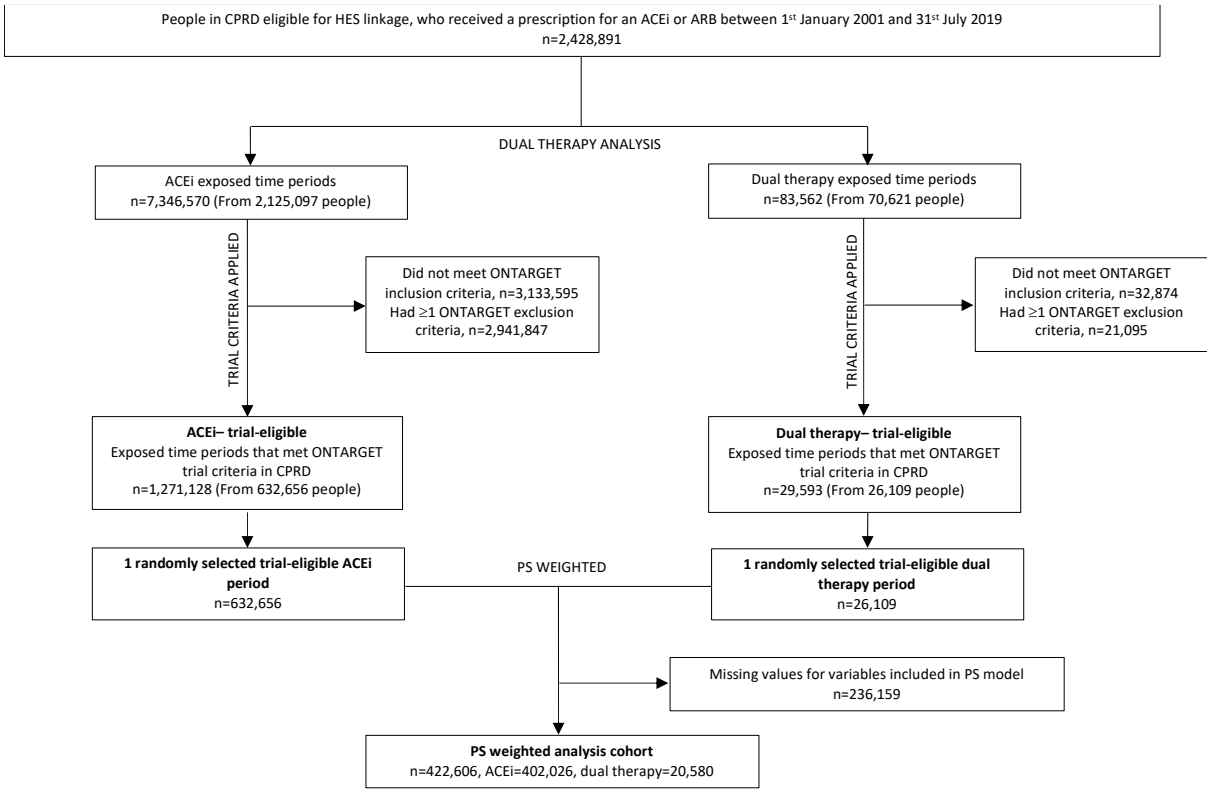
Conditional on the validation criteria being met, we examined whether there was evidence to suggest a benefit of dual blockade among patients with CKD in routine care. Aided by a larger sample size with more diverse characteristics than the ONTARGET trial and therefore a higher proportion of patients with CKD, we had sufficient power to detect treatment effect heterogeneity. This was assessed by fitting an interaction term between CKD at baseline and

treatment in the propensity-score—weighted analysis cohort that had previously been benchmarked against the trial results. The balance of characteristics was assessed within stratum of CKD at baseline and variables which remained imbalanced were adjusted for in the analysis.

Results

Baseline characteristics

After propensity-score—weighting, 402,026 ACEi and 20,580 dual therapy patients were included in the comparison (Figure 7.2). Prior to propensity-score—weighting patients receiving dual therapy treatment were more likely to have higher baseline blood pressure, higher creatinine and be from Black or South Asian ethnic groups compared to patients prescribed an ACEi alone (Table *7.1*). More patients receiving dual therapy had diabetes with proteinuria compared to patients receiving ACEi alone, 19.8% vs 11.9% in the dual therapy and ACEi exposure groups, respectively. Balance before and after propensity-score—weighting is displayed in Table S3 in Appendix 4: Supplementary material from Research paper 4.



Notes: PS=propensity-score; ACEi=ACE inhibitor. Weighted using inverse PS weights generated from propensity-score model for the probability of receiving an ACE inhibitor on 1 randomly selected trial-eligible dual therapy period per patient and 1 randomly selected trial-eligible ACE inhibitor period per patient

Figure 7.2 Dual therapy study profile

Primary outcomes and benchmarking results

The primary composite cardiovascular outcome occurred in 3226 (15.7%) and 65180 (16.2%) patients in the dual therapy and ACEi groups, respectively, similar to that seen in the ONTARGET study, 16.3% and 16.5% in the dual therapy and ramipril treatment groups, respectively.[22]. The risk of the primary cardiovascular outcome was similar among dual therapy and ACEi users, HR 0.97 (95% CI: 0.87, 1.08), consistent with the ONTARGET result (HR 0.99 (95% CI: 0.92, 1.07)) and met the validation criteria of trial replicability (Table *7.2*, Figure S2 in Appendix 4: Supplementary material from Research paper 4).

Table 7.1 Baseline characteristics of trial-eligible patients compared to ONTARGET

Characteristic	**Dual therapy** N=26,109	**ACEi** N=632,656	**ONTARGET** N=25,620
Age – year	70.4 ± 8.8	71.4 ± 9.9	66.4 ± 7.2
Systolic BP – mmHg	148.9 ± 20.5	143.0 ± 20.3	141.8 ± 17.4
Diastolic BP - mmHg	79.7 ± 10.8	78.9 ± 11.1	82.1 ± 10.4
Body-mass index	29.9 ± 6.0	28.7 ± 5.9	28.2 ± 4.7
Creatinine - µmol/l	99.0 ± 31.5	93.0 ± 27.6	94.2 ± 24.4
Female sex – no. (%)	13585 (52.0)	296411 (46.9)	6831 (26.7)
Ethnic group – no. (%)			
Black	1468 (5.6)	16396 (2.6)	629 (2.5)
Other	538 (2.1)	8079 (1.3)	4901 (19.1)
South Asian	2355 (9.0)	28253 (4.5)	1375 (5.4)
Unknown	259 (1.0)	9407 (1.5)	7 (<0.1)
White	21489 (82.3)	570521 (90.2)	18708 (73.0)
Clinical history – no. (%)			
CAD[a]	15654 (60.0)	453221 (71.6)	19102 (74.6)
Cerebrovascular disease[b]	2785 (10.7)	68105 (10.8)	5342 (20.9)
PAD[c]	2553 (9.8)	58626 (9.3)	3468 (13.5)
Diabetes	17464 (66.9)	346965 (54.8)	9612 (37.5)
High-risk diabetes[d]	16944 (64.9)	284914 (45.0)	7151 (27.9)
Smoking status – no. (%)			
Non-smoker	8178 (31.3)	172000 (27.2)	9088 (35.5)
Current smoker	6066 (23.2)	166730 (26.4)	3225 (12.6)
Past smoker	11185 (42.8)	276821 (43.8)	13276 (51.8)
Unknown	680 (2.6)	17105 (2.7)	31 (0.1)
Alcohol status – no. (%)			
Non-drinker	4960 (19.0)	93515 (14.8)	10345 (40.4)
Current drinker	14046 (53.8)	356096 (56.8)	14 (<0.1)
Past drinker	3231 (12.4)	72465 (11.5)	
Missing	3872 (14.8)	107580 (17.0)	
Medication[e] – no. (%)			
Alpha-blocker	4685 (17.9)	55831 (8.8)	1095 (4.3)
Oral anticoagulant agent	1509 (5.8)	55300 (8.7)	1939 (7.6)
Antiplatelet agent	2029 (7.8)	64026 (10.1)	2824 (11.0)
Aspirin	10493 (40.2)	225473 (35.6)	19403 (75.7)
Beta-blocker	8578 (32.9)	201254 (31.8)	14583 (56.9)
Calcium-channel blocker	10725 (41.1)	191828 (30.3)	8472 (33.1)
Digoxin	755 (2.9)	29455 (4.7)	865 (3.4)

Characteristic	Dual therapy N=26,109	ACEi N=632,656	ONTARGET N=25,620
Diuretics	12876 (49.3)	240047 (37.9)	7164 (28.0)
Diabetic treatment	10040 (38.5)	148687 (23.5)	8056 (31.4)
Nitrates	2239 (8.6)	67611 (10.7)	7523 (29.4)
Statins	15149 (58.0)	332421 (52.5)	15783 (61.6)

N= number of patients; no. (%)=number (percent); BP= blood pressure; CAD=coronary artery disease; PAD=peripheral artery disease; CKD=chronic kidney disease (eGFR<60ml/min/1.73m^2)

One third of ONTARGET participants received both ramipril plus telmisartan.

[a] Includes diagnosis of: MI at least 2 days prior, angina at least 30 days prior, angioplasty at least 30 days prior, CABG at least 4 years prior

[b] Includes diagnosis of: stroke/TIA

[c] Includes diagnosis of: limb bypass surgery, limb/foot amputation, intermittent claudication

[d] Includes DM with: retinopathy, neuropathy, chronic kidney disease, proteinuria or other complication

[e] Within 3 months prior to eligible start date. Antiplatelet agent= clopidogrel/ticlopidine.

In the categorisation of ethnicity in ONTARGET South Asian ethnic group included Other Asian and Black included Black African and Colored African as described in the trial CRF.

Table 7.2 Number of events for the primary outcome, main secondary outcome and renal outcomes for dual therapy vs ACEi using a propensity-score—weighted and adjusted analysis of trial-eligible patients in CPRD Aurum compared to ONTARGET.

Outcome	CPRD			ONTARGET
	Dual therapy (N=20,580)	ACEi (N=402,026)	Dual therapy vs ACEi (N=422,606	Dual therapy vs ramipril (N=17,078)
	Number (percent)		*Hazard ratio (95% CI)*	
Primary composite	3226 (15.7)	65180 (16.2)	0.97 (0.87, 1.08)	0.99 (0.92, 1.07)
Main secondary outcome	2332 (11.3)	45682 (11.4)	1.02 (0.91, 1.14)	1.00 (0.93, 1.09)
Primary renal outcome	1994 (9.7)	23826 (5.9)	1.18 (1.03, 1.34)	1.24 (1.01, 1.51)[1]
Doubling of creatinine	1224 (6.0)	13870 (3.5)	1.16 (0.96, 1.41)	1.20 (0.96, 1.50)

Primary composite outcome: death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure.

Main secondary outcome: death from cardiovascular causes, myocardial infarction, or stroke.

Main renal outcome: composite of loss of GFR or development of end-stage kidney disease (50% reduction in GFR, GFR<15 or start kidney replacement therapy).

CPRD weighted analysis includes 1 randomly selected trial-eligible period per patient. Propensity-score—weighted with robust standard errors. Analysis adjusted for number of GP appointments and hospital admissions 6 months prior and prior alpha-blocker and antiplatelet use.

Renal outcomes additionally adjusted for baseline serum creatinine.
ONTARGET results are from published findings.
[1]ONTARGET studied a composite renal outcome of dialysis or doubling of serum creatinine which differed to our primary renal composite outcome so results are not directly comparable.

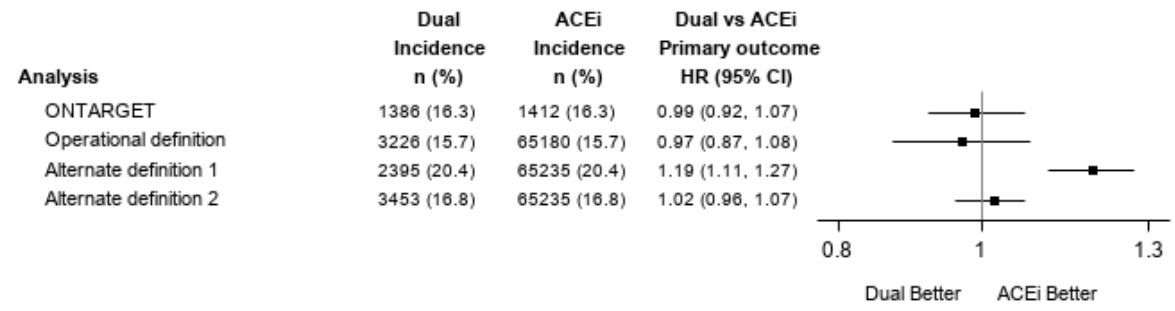
Secondary and renal outcomes

Results were consistent for the main secondary cardiovascular outcome of cardiovascular death, MI or stroke, HR 1.02 (95% CI: 0.91, 1.14) (Table *7.2*). For the renal primary composite outcome (loss of GFR or development of ESKD) results showed an increased risk among dual therapy users compared to ACEi alone for the propensity-score—weighted and adjusted analysis, HR 1.18 (95% CI: 1.03, 1.34). For doubling of creatinine results were consistent with the trial findings, HR 1.16 (95% CI: 0.96, 1.41), ONTARGET HR 1.20 (95% CI: 0.96, 1.50) (Table *7.2*).[30]

Alternate definitions of dual therapy exposure to explore the impact of bias

- ***Alternate definition 1: Starting follow-up at the date of the 1st prescription for the 2nd agent***

The risk of the primary composite cardiovascular outcome was increased among dual therapy users compared to ACEi users, HR 1.19 (95% CI: 1.11, 1.27) with similar findings for the main secondary outcome and the renal outcomes and different from the main analysis to and ONTARGET trial results (Figure 7.3).



Notes: Analysis for primary composite outcome (cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure). Dual therapy users defined as patients with overlapping prescriptions (<90 days between prescriptions) who have subsequent prescription for 1st agent within 90 days of 2nd prescription for 2nd agent. Operational definition: follow-up started from date definition met i.e., date of 2nd prescription for 1st agent. Alternate definition 1: follow-up started from date of 1st prescription for 2nd agent. Alternate definition 2: follow-up started from date of 2nd prescription for 2nd agent.

Figure 7.3 Forest plot of results for primary composite outcome for operational definition and alternate definitions of dual user

- ***Alternate definition 2: Starting follow-up at the date of the 2nd prescription for the 2nd agent***

Results for the primary composite cardiovascular outcome were consistent with the main analysis and the ONTARGET trial findings, HR 1.02 (95% CI: 0.96, 1.07). However, for the main secondary outcome, changing the start of follow up for the those in the dual therapy arm showed an increased risk among dual therapy users compared to ACEi users, HR 1.15 (95% CI: 1.08, 1.22), inconsistent with the main and ONTARGET trial results. Results for the renal outcome were also inconsistent with the operational definition analysis and the trial results (Figure 7.3).

Sensitivity analyses

After imputation of baseline blood pressure and creatinine and re-regeneration of propensity-score—weights, we estimated similar results for the primary composite cardiovascular

outcome for dual therapy vs ACEi as in the main analysis and ONTARGET trial, HR 1.09 (95% CI: 1.00, 1.19) and still met the validation criteria.

Extending analysis to trial- underrepresented group of those with CKD

Among those with non-missing baseline CKD status (99.9%), 8231 (40%) of patients had CKD in the dual therapy group and 125,968 (31%) patients had CKD in the ACE inhibitor exposure group. Imbalance remained for baseline creatinine, antiplatelet and alpha-blocker use in the 3 months prior to the start of the trial-eligible period, calendar year, and hospital and GP admissions in the 6 months prior to the start of the trial-eligible period, so analysis was adjusted for these variables.

Among those who had CKD at baseline, the primary outcome occurred in 1649 (20.0%) patients in the dual therapy group and 28,213 (22.4%) patients in the ACE inhibitor group. Among those who did not have CKD at baseline, the number of events for the primary composite outcome was 1560 (12.7%) in the dual therapy group and 36,967 (13.4%) in the ACE inhibitor group. There was no evidence of treatment effect heterogeneity by CKD status for the primary composite outcome (P=0.94). For dual therapy vs ACE inhibitor use, the effect estimates were HR 0.97 (95% CI: 0.80, 1.18) and HR 0.98 (95% CI: 0.85, 1.12) among those with and without CKD at baseline, respectively. Results were consistent for the main secondary outcome. For the primary renal composite outcome there was evidence of treatment heterogeneity by CKD status (P =0.01). The effect estimates were HR 1.46 (95% CI: 1.18, 1.80) and HR 0.93 (95% CI: 0.78, 1.10) among those with and without CKD at baseline, respectively. Similar results were observed for the outcome of doubling of creatinine (Figure 7.4).

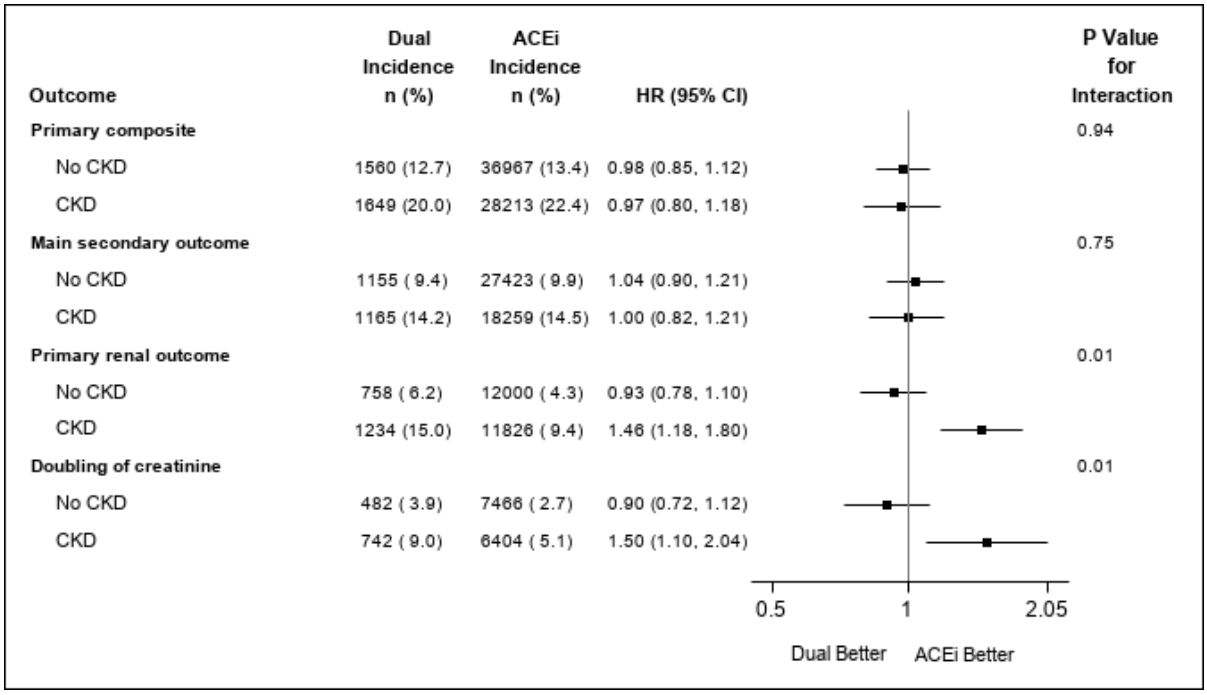


Figure 7.4 Forest plot of test for treatment effect heterogeneity by CKD status at baseline.

Discussion

In this emulation of the dual therapy arm of the ONTARGET randomised trial, using a large routinely-collected healthcare dataset we found comparative treatment effects of dual therapy and ACEi use for the primary and secondary composite cardiovascular outcomes that were very similar to the trial. In contrast, we found dual therapy was associated with an increased risk of a composite renal outcome of ESKD or 50% change in GFR, which despite different components was consistent with the findings of the composite renal outcomes studied in ONTARGET. We also found consistent results with the trial for the outcome of doubling of serum creatinine.

Despite the effects of dual therapy vs ACEi alone among those with CKD being of clinical interest, treatment effect heterogeneity by CKD was only assessed for the primary renal composite outcome in ONTARGET. After successfully benchmarking results for the primary composite cardiovascular outcome and aided by a greater power including an increased number of people with CKD at baseline, we were able to extend findings and examine for

treatment effect heterogeneity by baseline CKD status. We found that dual therapy was as effective at reducing the risk of cardiovascular outcomes as ACEi but for renal outcomes increased risk was observed only among those with baseline CKD.

We also examined the reliability of our operational definition of dual therapy use in routine care data by comparing results to those obtained in the ONTARGET trial. We started follow-up for dual therapy users at two additional timepoints and assessed the trade-off between a form of survivor bias and immortal time bias compared to the operational definition start point where immortal time bias was unlikely to be present.

Strengths and Limitations

After benchmarking findings against the ONTARGET trial, we observed that trial results for the primary and renal outcomes extended to patients with CKD at baseline who were underrepresented in ONTARGET.

Although prescribing of dual-therapy is no longer recommended uncertainty remains about the true balance of risks and benefits.[151] Understanding the potential harms of therapy in routine care, where patient monitoring is substantially less than in a clinical trial is therefore important. Due to the guidance recommending against dual RAS blockade in routine care the number of dual users in routine care is low, and many of these would not be detected by mandating initial prescriptions on the same day if the initial decision to start dual blockade did not result in simultaneous prescriptions, as would have occurred if patients were already taking one agent. Therefore, defining dual blockade by simultaneous prescriptions could create survivor bias by excluding early follow-up time. Our pragmatic definition of dual blockade users maximised power and avoided omitting this early follow-up time period but could have resulted in immortal time bias. Therefore, we robustly assessed the impact of our definition of dual users in sensitivity analyses. We identified that patients being prescribed

dual therapy were more ethnically diverse, with higher blood pressure, higher baseline creatinine and a higher proportion of high-risk diabetics compared to those prescribed an ACEi alone. Despite this, by using an operational definition were able to replicate the primary and secondary outcomes of ONTARGET in our emulation, providing confidence that the RCT results are generalisable to this wider routine care population. We also demonstrated an increased risk of renal outcomes among dual therapy compared to ACEi users, adding further evidence to support the ONTARGET trial findings. This is consistent with previous study findings and supports the recommendation for discontinuation of dual therapy.[30, 145] However, it is was observed that a greater proportion of patients who met trial criteria receiving dual therapy were being treated for diabetic proteinuria (19.8%) compared to patients receiving ACEi alone (11.9%), supported by increased creatinine in the dual therapy group. While these results contradict the belief that dual therapy may provide renal protection in those with CKD at baseline, they may also be due to confounding by indication. Observed baseline differences in indication may have contributed to the higher risk of the composite renal outcome observed in the dual therapy arm, since dual blockade was indicated for treatment of progressive proteinuria CKD for much of the time period of this study.[152-154] Our results from benchmarking against the trial were consistent with ONTARGET findings where confounding by indication was not present due to randomisation.

In addition, we have also demonstrated that the results are sensitive to how dual therapy use is defined in routine care data. This indicates that potential sources of bias, which will be specific to individual therapeutic areas, need to be carefully considered by research teams undertaking trial emulation.

There was a substantial amount of missing data for blood pressure and creatinine which could have led to bias. However, we assessed this using multiple imputation under the assumption

these variables were missing at random which provided results consistent with the main analysis.

Comparison to other studies

Although an increasing number of studies have used trial replication methods, few have looked at how to define dual therapy use in routine data. A study exploring treatment for breast cancer using trial replication methods by Merola et al., included dual users as patients who received prescriptions for both drugs on the same day.[52]

Fralick et al.[45] used US insurance claims data to replicate ONTARGET results for the single therapy comparison and led to results closely comparable to the trial for 9330 patients. However, they omitted the dual therapy analysis from their replication. To our knowledge this is the first study exploring the feasibility of trial replication methods applied to dual therapy treatment arms for cardiovascular disease, suggesting a practical proxy definition of a dual user when the sample of actual dual therapy users is small and survivor bias may be introduced when restricting the cohort to users with simultaneous prescriptions.

Contrary to belief, we found evidence to suggest dual therapy use was associated with an increased risk of renal outcomes compared to ACEi alone. These findings agree with a smaller study by Caravaca-Fontán et al., which found dual therapy use to be associated with a faster decline of renal function in patients with CKD.[155]

Conclusion

In this emulation of the dual therapy arm of the ONTARGET randomised trial using routinely-collected healthcare data, we confirmed similar effectiveness of dual therapy compared to ACEi alone at reducing risk of a composite of cardiovascular death, MI, stroke or hospital admission for congestive heart failure. Also consistent with the trial we observed

increased risk for the outcome of doubling of serum creatinine, and for a renal composite outcome of loss of GFR or ESKD, among dual therapy users compared to ACEi users alone. Cardiovascular results extended to patients with CKD at baseline who were underrepresented in the trial. However, this increased risk was observed only among patients with CKD at baseline.

In addition this study demonstrates that a target trial which includes a dual therapy arm can be replicated using observational data but highlights the importance of considering potential sources of confounding and bias in how dual therapy is defined which are specific to the therapeutic area and research question. Defining a dual user with minimal immortal time bias led to results comparable to the trial for this therapeutic area.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data and take final responsibility for the decision to submit for publication.

7.1.2 Additional results from applying step 5: matching trial-eligible exposure groups

Due to the small number of patients meeting the dual therapy user operational definition, only propensity-score—weighting was used to achieve balance between the trial-eligible ACE inhibitor and dual therapy patients as opposed to propensity-score—matching which often results in a loss of sample size. The choice of variables included in the propensity score model are displayed in **Table *7.3***.

Table 7.3 Covariates included in propensity score model used to ensure balance among ACE inhibitor and dual therapy trial-eligible exposure groups in CPRD Aurum

Covariate	**Form**	**Higher order term**
Stroke/TIA	Binary	
Peripheral artery disease	Binary	
Coronary artery disease	Binary	
Diabetes	Binary	
High-risk diabetes	Binary	
Sex	Binary	
Ethnicity	Categorical (white, black, South Asian, other)	
Age	Continuous	+ quadratic
Body-mass-index	Continuous	+ quadratic
Systolic blood pressure	Continuous	+ quadratic
Diastolic blood pressure	Continuous	+ quadratic
Smoke status	Categorical (non, ex or current)	
Index of multiple deprivation	Categorical (1-5)	
Statin use 3 months prior	Binary (yes, no)	
Nitrate use 3 months prior	Binary (yes, no)	
Diabetic treatment use 3 months prior	Binary (yes, no)	
Diuretic use 3 months prior	Binary (yes, no)	
Calcium channel blocker use 3 months prior	Binary (yes, no)	
Betablocker use 3 months prior	Binary (yes, no)	

Covariate	Form	Higher order term
Aspirin use 3 months prior	Binary (yes, no)	
Number of previous hospital admissions 6 months prior	Continuous (log)	
Calendar year	Continuous	
Time since first trial-eligible period	Continuous	+ quadratic
Baseline creatinine	Continuous	

Chapter 8. Exploring whether trial replication methodology for this therapeutic area is transportable to the SIDIAP database

Chapter summary

- This chapter presents results from implementing the analytical method of trial emulation as described in Chapter 6, to the SIDIAP data source (primary care records of patients in Catalonia) to address Research Aim 2– objective 2, to explore if trial replication methodology for this therapeutic area is transportable to a data source outside the UK
- Additional detail on methods are first described in section 8.1.
- Results from implementing the chosen approach to trial replication in the SIDIAP data source, representative of 75% of the Catalonian population, are presented in section 8.2

8.1 Summary of methods

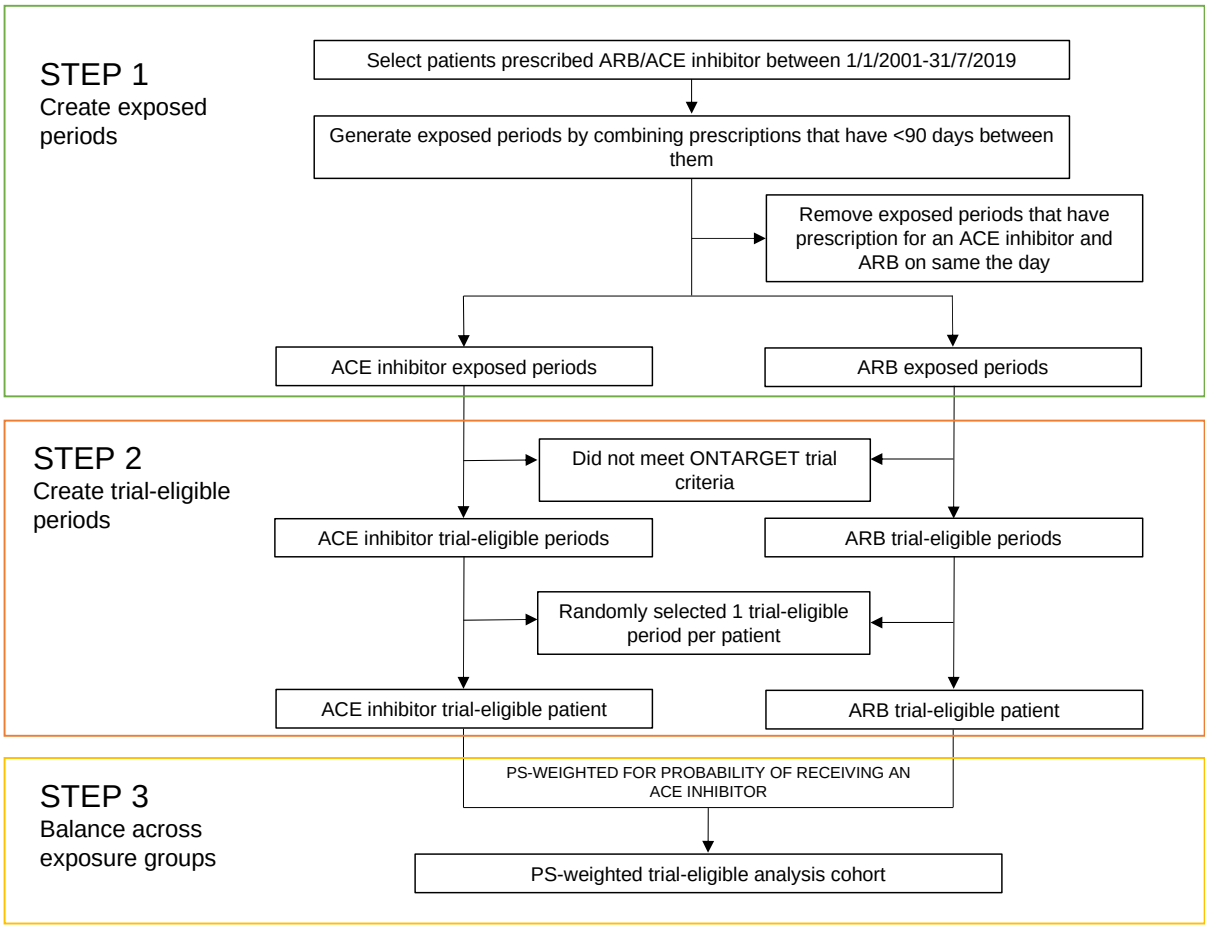
The proposed optimal technique that was identified in Chapter 6 is outlined in Figure ***8.1***. As described in Chapter 5, dispensations were used instead of prescriptions in the SIDIAP data source and patients with a dispensation for an ACEi and/or ARB between 1/1/2007-31/7/2019 were selected. This was due to ensure patients had been registered for at least 1 year, with SIDIAP data becoming available from 2006.

Code lists used to apply to trial criteria and identify outcomes in the SIDIAP analysis are available in Appendix 5: Supplementary material from SIDIAP analysis.

The impact of missing data on results was assessed using a sensitivity analysis, imputing values for variables included in the propensity score model that could be assumed to be

missing at random. This was done for 20 imputations using chained equations and estimates were combined using Rubin's rules.[135, 150]

Outcomes studied were the same efficacy outcomes as in ONTARGET and the CPRD replication of ONTARGET. The SIDIAP database does not record information on cause of death so an operational definition for cardiovascular death was used. This was defined as a death code recorded within 30 days of a cardiovascular event code. In addition to this definition, cardiac arrest (ICD-10CM code I46*) was also considered as cardiovascular-related death. The validation criteria were defined as for the main analysis using the CPRD which was 1) HR for the primary composite outcome needed to be between 0.9 and 1.12 and, 2) the CI for the HR needed to contain 1.



Notes: PS= propensity-score

Figure 8.1 Proposed optimal technique for replication of the ONTARGET trial using electronic health record data.

8.2 Results

8.2.1 Baseline characteristics

There was a greater number of covariates with substantial proportion of missing data in SIDIAP compared to CPRD. Percentages of missing data for variables considered as confounders are displayed in Table ***8.1***. Due to the large proportion of missing data for alcohol, BMI and QMEDEA (the socio-economic status proxy variable equivalent to IMD in CPRD) in SIDIAP, these variables were omitted from the propensity score model. Despite the substantial amount of missing data for baseline SBP and DBP, these variables were deemed to be important confounders and could be assumed to be missing at random. Therefore these variables were included in the propensity score model and were imputed in a sensitivity analysis.[84] After examination of baseline characteristics after applying the trial criteria there was a difference in baseline creatinine between exposure groups which was not observed in CPRD (Table ***8.2***). Therefore, I decided to also account for this variable in the propensity score model.

Table 8.1 List of covariates considered and included in propensity-score model for SIDIAP analysis

Covariates	**Included in model?**	**Reason for not including**
Stroke/TIA	✓	
Peripheral artery disease	✓	
Coronary artery disease	✓	
Diabetes	✓	
High-risk diabetes	✓	
Age (years)	✓	
Sex	✓	
Nationality		Numbers too small, 66% European and 32% missing
BMI		19% missing and cannot assume MAR
SBP	✓	
DBP	✓	
Baseline creatinine	✓	

Covariates	Included in model?	Reason for not including
QMEDEA (equivalent to Index of multiple deprivation)		22% missing
Smoke status	✓	
Alcohol use		23% missing and cannot assume MAR
Statin use	✓	
Nitrate use	✓	
Diabetic treatment use	✓	
Diuretic use	✓	
CCB use	✓	
Betablocker use	✓	
Aspirin use	✓	
Antiplatelet use	✓	
Digoxin use		Numbers too small <10% number of events
Anticoagulant use		Numbers too small <10% number of events
Alphablocker use		Numbers too small <10% number of events
No. of hospital admissions within 6 months prior	✓	
No. of GP appointments within 6 months prior	✓	
No. of medications within 6 months prior	✓	
Year of start of eligible period	✓	
Time since first eligible period (days)	✓	
No. of previous ACE inhibitor eligible periods		Too much variation in distribution between exposure groups which led to other variables being imbalanced when included
No. of previous ARB eligible periods	✓	

Notes: TIA: transient ischaemic attack; BMI: body-mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Variables are measured at start of trial-eligible period or before.

Peripheral artery disease includes limb bypass surgery or angioplasty, limb/foot amputation, or intermittent claudication.

Coronary artery disease includes previous MI, angina, coronary angioplasty, or CABG.

SBP and DBP are measured within 6 months prior to start of trial-eligible period.

Medication use is within 3 months prior to start of trial-eligible period.

Variables that had <10% missing were included (smoke status had 9.3% missing).

Variables that had >10% missing but could be assumed to be missing at random (MAR) were included and imputed in sensitivity analysis (DBP/SBP had 37% missing, creatinine had 15% missing).

Table 8.2 Baseline characteristics of one randomly selected period per patient meeting trial criteria in SIDIAP compared to ONTARGET

Characteristic	**ACEi** N=63,939	**ARB** N=28,534	**ONTARGET** N=25,620
Age - year	73.7 ± 10.0	74.2 ± 9.4	66.4 ± 7.2
Blood pressure – mmHg	138.4 ± 17.3 / 75.1 ± 10.3	138.3 ± 17.6 / 74.4 ± 10.2	141.8 ± 17.4 / 82.1 ± 10.4
Body-mass index	28.7 ± 4.6	29.3 ± 4.7	28.2 ± 4.7
Creatinine - μmol/l	90.6 ± 27.1	95.5 ± 31.3	94.2 ± 24.4
Potassium – mmol/l	4.5 ± 0.4	4.5 ± 0.4	4.4 ± 0.4
Female sex – no. (%)	45508 (47.1)	22690 (56.0)	6831 (26.7)
Nationality – no. (%)			
African/Caribbean	510 (0.8)	144 (0.5)	-
American/Australian/NZ	330 (0.5)	154 (0.5)	-
Asian	271 (0.4)	68 (0.2)	-
European	42296 (66.2)	18743 (65.7)	-
Unknown	20532 (32.1)	9425 (33.0)	-
Clinical history – no. (%)			
CAD[1]	25319 (39.6)	11279 (39.5)	19102 (74.6)
MI	11042 (17.3)	4225 (14.8)	12549 (49.0)
Angina pectoris	7197 (11.3)	3553 (12.5)	11505 (44.9)
Cerebrovascular disease[2]	19440 (30.4)	8381 (29.4)	5342 (20.9)
PAD[3]	8970 (14.0)	3619 (12.7)	3468 (13.5)
Diabetes	32561 (50.9)	15449 (54.1)	9612 (37.5)
High-risk diabetes[4]	21668 (33.9)	10877 (38.1)	7151 (27.9)
Previous procedures – no. (%)			
CABG	185 (0.3)	52 (0.2)	5675 (22.2)
PTCA	1246 (2.0)	460 (1.6)	7437 (29.0)
CKD (eGFR<60)	20325 (31.8)	11041 (38.7)	5470 (21.4)
Smoking status – no. (%)			
Low risk	49147 (76.8)	22543 (79.0)	-
High risk	9103 (14.2)	3095 (10.9)	-
Unknown	5689 (8.9)	2896 (10.2)	31 (0.1)
Alcohol status – no. (%)			
Low risk	30700 (48.0)	14071 (49.3)	-
High risk	19018 (29.7)	7511 (26.3)	-
Unknown	14221 (22.2)	6952 (24.4)	14 (<0.1)
Medication[5] – no. (%)			
ACE inhibitor	40733 (63.7)	630 (2.2)	14750 (57.6)
Alpha-blocker	5458 (8.5)	22667 (9.4)	1095 (4.3)
Oral anticoagulant agent	4860 (7.6)	2240 (7.8)	1939 (7.6)

Characteristic	ACEi N=63,939	ARB N=28,534	ONTARGET N=25,620
Antiplatelet agent	9355 (14.6)	3310 (11.6)	2824 (11.0)
ARB	154 (0.2)	21504 (75.4)	2213 (8.6)
Aspirin	24582 (38.5)	8611 (30.2)	19403 (75.7)
Beta-blocker	12812 (20.0)	4818 (16.9)	14583 (56.9)
Calcium-channel blocker	10300 (16.1)	5914 (20.7)	8472 (33.1)
Digoxin	1276 (2.0)	563 (2.0)	865 (3.4)
Diuretics	13126 (20.5)	6178 (21.7)	7164 (28.0)
Diabetic treatment	15606 (24.4)	6146 (21.5)	8056 (31.4)
Nitrates	7965 (12.5)	2984 (10.5)	7523 (29.4)
Statins	25674 (40.2)	9420 (33.0)	15783 (61.6)

N= number of patients; no. (%)=number (percent); NZ=New Zealand; CAD=coronary artery disease; MI=myocardial infarction; PAD=peripheral artery disease; CABG=coronary artery bypass graft; PTCA=percutaneous transient coronary angioplasty; CKD=chronic kidney disease (eGFR<60mmol/L)

One third of ONTARGET participants received both ramipril plus telmisartan.

[1] Includes diagnosis of: MI at least 2 days prior, angina at least 30 days prior, angioplasty at least 30 days prior, CABG at least 4 years prior

[2] Includes diagnosis of: stroke/TIA

[3] Includes diagnosis of: limb bypass surgery, limb/foot amputation, intermittent claudication

[4] Includes DM with: retinopathy, neuropathy, chronic kidney disease, proteinuria or other complication

[5] Within 3 months prior to eligible start date. Antiplatelet agent= clopidogrel/ticlopidine.

In the categorisation of ethnicity in ONTARGET South Asian ethnic group included Other Asian and Black included Black African and Colored African as described in the trial CRF.

After applying the steps to create the study cohort as outlined in Table ***8.1***, 15,801 and 34,882 patients were included in the ARB and ACEi trial-eligible weighted exposure groups, respectively (Figure 8.2). The covariates considered and included in the propensity score model are displayed in Table ***8.1***. Balance before and after propensity score weighting is shown in Table ***8.3***. All variables were balanced after propensity-score weighting, including number of prior ACEi periods despite being omitted from the propensity score model and baseline creatinine which was different among exposure groups prior to weighting. Median follow-up time was 5.5 years and event rates were 2.5 and 2.8 per 100 person-years in the ARB and ACEi groups, respectively.

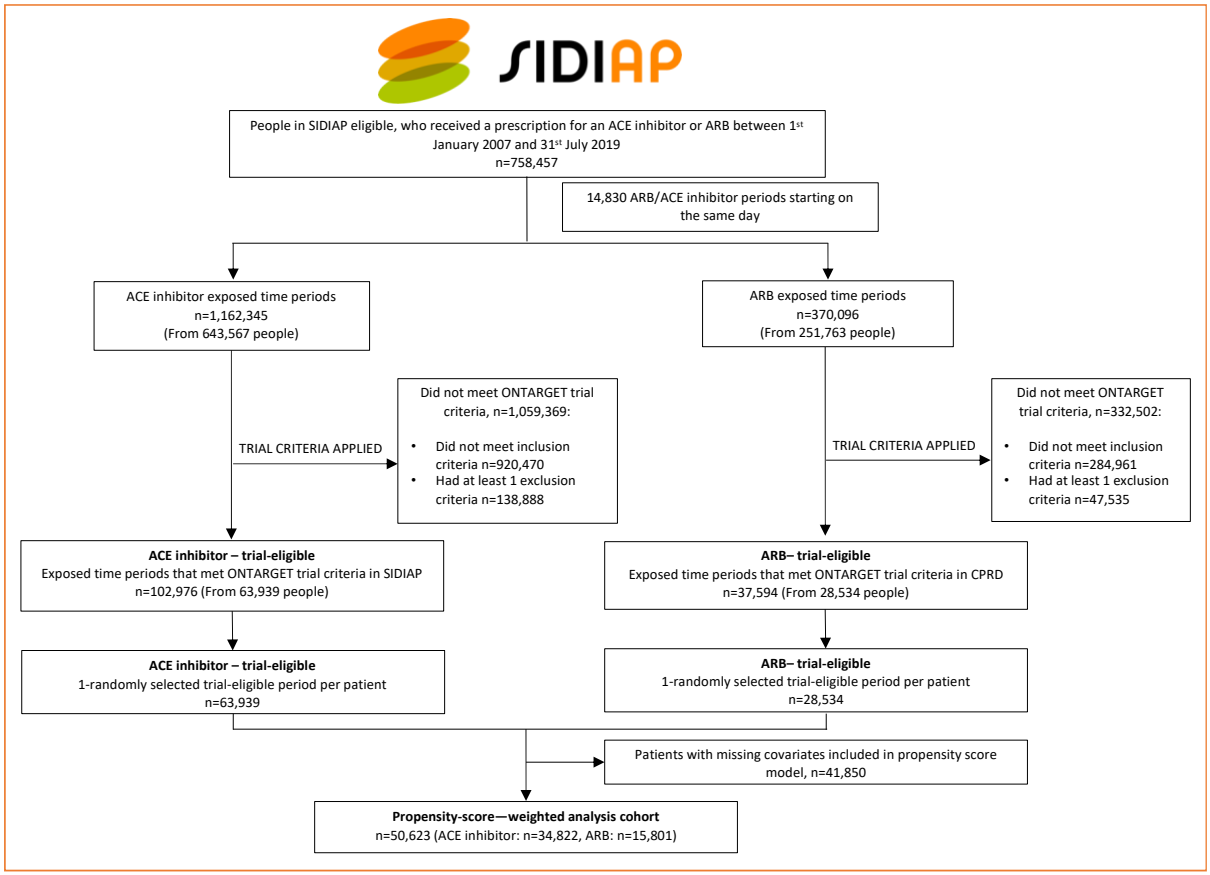


Figure 8.2 SIDIAP study profile

Table 8.3 Assessment of balance of covariates before and after propensity-score weighting in SIDIAP

Characteristic	Before propensity-score—weighting			After propensity-score—weighting		
	ACEi N=34,822	ARB N=15,801	SMD	ACEi N=34,822	ARB N=15,801	SMD
Age - year	74.2 ± 9.5	74.5 ± 9.1	0.036	74.2 ± 9.5	74.5 ± 9.1	0.018
Blood pressure – mmHg	138.3 ± 17.1 / 75.0 ± 10.3	138.2 ± 17.4 / 74.3 ± 10.2	0.006 / 0.063	138.3 ± 17.1 / 74.7 ± 10.3	138.3 ± 17.4 / 74.7 ± 10.3	0.002 / 0.004
Body-mass index (kg/m²)	28.8 ± 4.5	29.4 ± 4.7	0.125	28.9 ± 4.5	29.2 ± 4.6	0.078
Creatinine - µmol/l	90.8 ± 27.2	95.6 ± 31.8	0.162	92.6 ± 29.1	92.9 ± 29.2	0.008
Potassium – mmol/l	4.5 ± 0.4	4.5 ± 0.4	0.031	4.5 ± 0.4	4.5 ± 0.4	0.059
Female sex – no. (%)	13024 (34.4)	7009 (44.4)	0.142	20237 (39.8)	20159 (40.2)	0.009
Clinical history – no. (%)						
CAD[1,2]	12916 (37.1)	5859 (37.1)	0.000	18862 (37.1)	18492 (36.9)	0.004
Cerebrovascular disease[1,3]	9873 (28.4)	4281 (27.1)	0.028	14253 (28.0)	14093 (28.1)	0.002
PAD[1,4]	4841 (13.9)	2018 (12.8)	0.033	6898 (13.6)	6794 (13.5)	0.000

Characteristic	Before propensity-score—weighting			After propensity-score—weighting		
	ACEi N=34,822	ARB N=15,801	SMD	ACEi N=34,822	ARB N=15,801	SMD
Diabetes[5]	20391 (58.6)	9651 (61.1)	0.051	30253 (59.4)	29995 (59.8)	0.007
High-risk diabetes[1,6]	14242 (40.9)	7138 (45.2)	0.086	21586 (42.4)	21454 (42.8)	0.007
Smoking high risk – no. (%)	4669 (13.4)	1667 (10.6)	0.088	6340 (12.5)	6158 (12.3)	0.005
Alcohol status – no. (%)						
Low risk	18987 (54.5)	9069 (57.4)	0.058	28193 (55.4)	28117 (56.1)	0.013
High risk	11536 (33.1)	4624 (29.3)	0.084	16176 (31.8)	15535 (31.0)	0.017
Unknown	4299 (12.4)	2108 (13.3)	0.030	6526 (12.8)	6510 (13.0)	0.005
Medication[7] – no. (%)						
Antiplatelet agent	4568 (13.1)	1637 (10.4)	0.086	6222 (12.2)	6179 (12.3)	0.003
Aspirin	12918 (37.1)	4436 (28.1)	0.193	17414 (34.2)	17566 (35.0)	0.017
Beta-blocker	6982 (20.1)	2575 (16.3)	0.097	9661 (19.0)	9803 (19.5)	0.014
Calcium-channel blocker	5825 (16.7)	3338 (21.1)	0.112	9373 (18.4)	9591 (19.1)	0.018
Diuretics	7540 (21.7)	3542 (22.4)	0.018	11335 (22.3)	11856 (23.6)	0.032
Diabetic treatment	9734 (28.0)	3641 (23.0)	0.113	13464 (26.5)	13744 (27.4)	0.021
Nitrates	4044 (11.6)	1519 (9.6)	0.065	5618 (11.0)	5698 (11.4)	0.010
Statins	14017 (40.3)	4966 (31.4)	0.185	19084 (37.5)	19277 (38.4)	0.019
QMEDEA – no.(%)						
1 (least deprived)	3981 (11.4)	2011 (12.7)	0.040	5774 (11.4)	6652 (13.3)	0.058
2	4173 (12.0)	1921 (12.2)	0.006	6071 (11.9)	6249 (12.5)	0.016
3	4529 (13.0)	2033 (12.9)	0.004	6571 (12.9)	6501 (13.0)	0.001
4	4706 (13.5)	2100 (13.3)	0.006	6804 (13.4)	6626 (13.2)	0.005
5 (most deprived)	4399 (12.6)	1841 (11.7)	0.030	6380 (12.5)	5598 (11.2)	0.043
Rural	5664 (16.3)	2476 (15.7)	0.016	8302 (16.3)	7761 (15.5)	0.023
Unknown	7370 (21.2)	3419 (21.6)	0.012	10992 (21.6)	10775 (21.5)	0.003
Health utilisation[8]						
No. of hospital admissions	4.6 ± 6.0	4.9 ± 6.0	0.051	4.7 ± 6.1	4.7 ± 5.8	0.005
No. of GP apt.	4.8 ± 3.7	5.3 ± 3.9	0.126	5.0 ± 3.8	5.0 ± 3.8	0.002
No. of different drug types	2.7 ± 2.1	2.6 ± 1.9	0.052	2.7 ± 2.0	2.8 ± 2.1	0.034
Time-related variables						
Time since first eligible period (days)	247.9 ± 622.9	330.5 ± 699.6	0.125	276.2 ± 653.1	265.2 ± 644.7	0.017

Characteristic	Before propensity-score—weighting			After propensity-score—weighting		
	ACEi N=34,822	ARB N=15,801	SMD	ACEi N=34,822	ARB N=15,801	SMD
No. of prior ARB periods	0.09 ± 0.4	0.1 ± 0.5	0.148	0.1 ± 0.4	0.1 ± 0.4	0.020
No. of prior ACEi periods	0.3 ± 0.9	0.4 ± 0.7	0.114	0.3 ± 0.9	0.3 ± 0.7	0.017
Calendar year	2013 ± 3.6	2013 ± 3.6	0.114	2013 ± 3.6	2013 ± 3.7	0.019

Notes: SMD: standardised mean difference.
Cohort includes 1 randomly selected eligible period per patient in each group
[1] Any diagnosis prior to start of eligible period
[2] Includes diagnosis of: MI at least 2 days prior, angina at least 30 days prior, angioplasty at least 30 days prior, CABG at least 4 years prior
[3] Includes diagnosis of: stroke/TIA
[4] Includes diagnosis of: limb bypass surgery, limb/foot amputation, intermittent claudication
[5] DM prior to start of eligible period
[6] Includes DM with: retinopathy, neuropathy, chronic kidney disease or proteinuria
[7] Within 3 months prior to eligible start date. Antiplatelet agent= clopidogrel/ ticlopidine
[8] Within 6 months prior to eligible start date.
no. (%)=number (percent); CAD=coronary artery disease; MI=myocardial infarction; PAD=peripheral artery disease.
Some variables not included in propensity score model but assessment of balance still checked

8.2.2 Primary and secondary outcomes

For ARB vs ACEi for the primary composite outcome, the estimated HR was 0.91 (95% CI: 0.86, 0.97). This met the first validation criteria of estimate between 0.9 and 1.12 but the CI did not contain 1. Further examination of individual components of the primary composite outcome showed the risk of MI was lower among ARB users compared to ACEi users in the propensity-score—weighted cohort, HR 0.84 (95% CI: 0.76, 0.94) (Table ***8.4***).

In addition to this, the number of events of hospitalisation for heart failure and death from cardiovascular causes was much lower than figures observed in ONTARGET and CPRD (hospitalisation for heart failure: SIDIAP 1.7% vs CPRD 4.1% vs ONTARGET 4.4%; cardiovascular-related death: SIDIAP 1.4% vs CPRD 5.1% vs ONTARGET 7.0%).[22]

Table 8.4 Number of events for the primary outcome, its components, and death from any cause for ARB vs ACEi propensity-score—weighted analysis cohort with one randomly selected trial eligible period per patient

Outcome	**SIDIAP**			**ONTARGET**
	ACEi (N=34,822)	**ARB** (N=15,801)	**ARB vs ACEi** (50,623)	**Telmisartan vs ramipril** (N=17,118)
	Number (percent)		*Hazard ratio (95% CI)*	
Primary composite: Death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure	4364 (12.5)	1832 (11.6)	0.91 (0.86, 0.97)	1.01 (0.94, 1.09)
Main secondary outcome: Death from cardiovascular causes, myocardial infarction, or stroke	4037 (11.6)	1666 (10.5)	0.91 (0.86, 0.97)	0.99 (0.91, 1.07)
Myocardial infarction	1467 (4.2)	536 (3.4)	0.84 (0.76, 0.94)	1.07 (0.94, 1.22)
Stroke	2426 (7.0)	1061 (6.7)	0.96 (0.89, 1.03)	0.91 (0.79, 1.05)
Hospitalisation for heart failure	586 (1.7)	280 (1.8)	0.90 (0.78, 1.05)	1.12 (0.97, 1.29)
Death from cardiovascular causes	497 (1.4)	215 (1.4)	0.89 (0.75, 1.06)	1.00 (0.89, 1.12)
Death from non-cardiovascular causes	7200 (20.7)	3123 (19.8)	0.92 (0.88, 0.96)	0.96 (0.83, 1.10)
Death from any cause	7679 (22.1)	3333 (21.1)	0.92 (0.88, 0.96)	0.98 (0.90, 1.07)
Notes: Myocardial infarction and stroke include both fatal and non-fatal events. ONTARGET results are from published findings.				

8.2.3 Sensitivity analysis

A sensitivity analysis using multiple imputation to impute missing values for variables included in the PS model which could be assumed to be missing at random was carried out. These included creatinine, SBP and DBP and were imputed with 20 imputations using chained equations with estimates combined using Rubin's rules.[83, 135] Three separate approaches to handle missing data for smoking status which could not be assumed to be missing at random were considered. These were:

1. Impute creatinine, SBP, DBP for patients with non-missing smoking status;
2. Impute creatinine, SBP, DBP and recategorize missing smoking status values as low risk;
3. Impute creatinine, SBP, DBP and recategorize missing smoking status values as high risk.

These three approaches were compared to the main analysis which used a complete case approach where results were conditional on people having non-missing creatinine, SBP, DBP and smoking status at baseline. The results from the sensitivity analysis for the primary composite outcome are displayed in Table ***8.5*** and showed consistency with the complete case analysis (HR 0.91 (95% CI: 0.86, 0.97)).

Table 8.5 Results from multiple imputation of variables which can be assumed to be MAR for 20 imputations using chained equations for the primary composite outcome

Imputation approach	**Primary composite outcome** **ARB vs ACE inhibitor** *HR (95% CI)*
Approach 1: People with non-missing smoking status (n=83,820)	0.91 (0.87, 0.95)
Approach 2: Missing smoking status as low risk (n=92,387)	0.90 (0.86, 0.94)
Approach 3: Missing smoking status as high risk (n=92,387)	0.90 (0.86, 0.94)
Notes: Values imputed for DBP, SBP and creatinine under the MAR assumption. 20 imputations using chained equations and estimates combined using Rubin's rules. Approach 1: Values imputed for people with non-missing smoking status; Approach 2: Values imputed and those with missing smoking status recategorized to low-risk smoking status; Approach 3: Values imputed and those with missing smoking status recategorized to high-risk smoking status	

8.2.4 Post-hoc analysis

To further examine the differences between results in SIDIAP and CPRD, a post-hoc analysis was carried out restricting the cohort to non-switchers, i.e., patients could not have previously prescribed the alternate drug. This reduced the sample substantially and despite resulting in estimates closer to the ONTARGET trial, the CIs were wide so the reliability of these results is uncertain (Table ***8.6***).

It is possible that in the early years after drug licensing, ARBs were likely to be prescribed to healthier, younger populations and that this 'channelling' of prescribing was not fully captured in the covariates leading to residual confounding. To assess the impact of this potential time-related bias on results an additional post-hoc analysis was carried out. Analysis was stratified by calendar year of start of trial-eligible period using the 75th percentile as a cut-off. In the first years of the study period, 2007-2016, the risk of the primary outcome was

reduced among ARB users compared to ACEi use as observed in the overall study result (HR 0.89, (95% CI: 0.83, 0.94)). However, when restricting to 2017-2019, a null effect was observed and results were consistent with the ONTARGET trial meeting both criteria for replicability, HR 1.05 (0.91, 1.20) for years 2017-2019 (Table ***8.7***). For comparability this was also undertaken in the CPRD GOLD analysis. In CPRD GOLD stratifying by time period showed similar results to SIDIAP although the effect estimate was higher in the earlier years for CPRD compared to SIDIAP: 2001-2010: HR 0.94 (95% CI: 0.90, 0.98), 2011-2019 HR 1.01 (95% CI: 0.89, 1.14). This demonstrated that time-related bias related to channelling of a new drug was a possible explanation for the differences between the SIDIAP and CPRD results.

Table 8.6 Number of events for the primary outcome, its components, and death from any cause for ARB vs ACEi propensity-score—weighted analysis cohort with one randomly selected trial eligible period per patient sensitivity analysis (restricting to non-switchers)

Outcome	**SIDIAP**			**ONTARGET**
	ACEi (N=2,918)	**ARB** (N=1,460)	**ARB vs ACEi** (4,378)	**Telmisartan vs ramipril** (N=17,118)
	Number (percent)		*Hazard ratio (95% CI)*	
Primary composite: Death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure	366 (12.5)	194 (13.3)	0.98 (0.79, 1.21)	1.01 (0.94, 1.09)
Main secondary outcome: Death from cardiovascular causes, myocardial infarction, or stroke	344 (11.8)	172 (11.8)	0.93 (0.75, 1.15)	0.99 (0.91, 1.07)
Myocardial infarction	119 (4.1)	48 (3.3)	0.89 (0.59, 1.33)	1.07 (0.94, 1.22)
Stroke	219 (7.5)	113 (7.7)	0.90 (0.70, 1.15)	0.91 (0.79, 1.05)
Hospitalisation for heart failure	38 (1.3)	39 (2.7)	1.54 (0.81, 2.93)	1.12 (0.97, 1.29)
Death from cardiovascular causes	38 (1.3)	27 (1.9)	0.99 (0.58, 1.71)	1.00 (0.89, 1.12)
Death from non-cardiovascular causes	572 (19.6)	293 (20.1)	0.92 (0.77, 1.09)	0.96 (0.83, 1.10)
Death from any cause	607 (20.8)	320 (21.9)	0.93 (0.79, 1.09)	0.98 (0.90, 1.07)
Notes: Myocardial infarction and stroke include both fatal and non-fatal events. ONTARGET results are from published findings. Analysis adjusted for number of prior ACE inhibitor periods				

Table 8.7 Number of events for the primary outcome for ARB vs ACEi propensity-score—weighted analysis cohort with one randomly selected trial eligible period per patient sensitivity analysis (stratified by year of start of trial-eligible period) for SIDIAP

Outcome	SIDIAP		
	Primary composite outcome		
	ACEi	ARB	ARB vs ACEi
Main analysis (n=50,623)	4364 (12.5)	1832 (11.6)	0.91 (0.86, 0.97)
2007-2016 (n=40,078)	3595 (13.1)	1506 (11.9)	0.89 (0.83, 0.94)
2017-2019 (n=10,545)	769 (10.4)	326 (10.5)	1.05 (0.91, 1.20)
Notes: Analysis adjusted for number of prior ARB periods and age.			

8.3 Potential reasons for observed differences in results

Some differences were noted between the CPRD and SIDIAP cohorts: those in SIDIAP met trial inclusion criteria primarily due to being high-risk diabetic, while in CPRD and ONTARGET the main reason for inclusion was coronary artery disease. This could contribute to differences in results. In addition to this the population in SIDIAP was older, but with lower blood pressure than on average in CPRD. Therefore, unlike patients in UK routine care, patients in Catalonia were likely to receive these treatments regardless of having blood pressure in the hypertensive range. In SIDIAP, differences in patient characteristics between the treatment groups were observed that were not seen in CPRD. For example, patients in SIDIAP who were treated with an ARB had higher creatinine at baseline than those treated with an ACEi, while conversely those treated with an ACEi were more likely to have previously had an MI (Table ***8.2***). I was not able to identify any differences in treatment guidelines after discussion with local clinicians, but it appears there are differences between prescribing patterns for these medications which are not seen in the UK which may have contributed to the difference in risk observed for MI. The lower number of events observed for heart failure hospitalisation and cardiovascular-related death in SIDIAP could be due to the differences in capturing reasons for hospitalisation between the two data sources and the

proxy used for cardiovascular-related death in SIDIAP. However in an additional post-hoc analysis, attributing all deaths as cardiovascular-related deaths had little effect on the primary composite outcome (HR 0.91 (95% CI: 0.88, 0.94)).

The impact of using medication dispensations from pharmacies to create trial-eligible periods in SIDIAP as opposed to the use of prescriptions in CPRD could be a further reason for the differences observed in the two data sources. Due to dispensations more closely reflecting patients taking the medications the results obtained using the SIDIAP data source could reflect more accurate identification of patients taking these medications in routine care. To explore this further I would need to repeat these analyses in SIDIAP using prescription data. Additionally, SIDIAP analysis included patients from 2007 whereas the study conducted in CPRD started in 2001, reflecting the time period of the ONTARGET study more closely. Therefore, the differences between the populations could also be impacted by the differences in incidence of these cardiovascular outcomes over time.

8.4 Conclusion

Overall, in replication of the ONTARGET study using SIDIAP data, with very similar methods to that used in CPRD I observed a point estimate for the HR that met one of the pre-specified criteria, but as confidence intervals did not contain 1 (with ARB use associated with a decreased risk of the outcomes), full replication was not achieved. A number of differences between the data sources may underlie this finding. Restricting the cohort to recent years, reducing potential channelling of ARBs to healthier populations meant that both criteria for trial replicability was met. This suggests that despite attempting to account for time-related bias by including time-related variables in the propensity score model in some cases a more sophisticated approach such as the prevalent new user design proposed by Suissa et al., may be required.[95]

Chapter 9. Discussion

Chapter summary

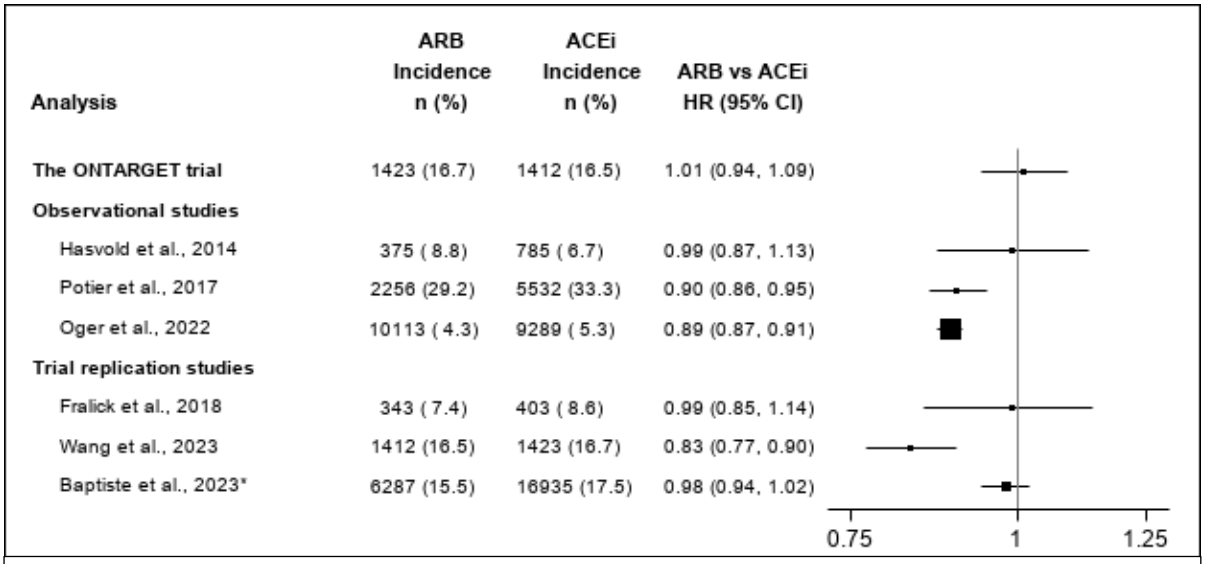
- The research presented in this thesis investigates whether trial replication methods can be applied to UK electronic health record data to obtain treatment effects in underrepresented and excluded groups
- The outputs include two research papers replicating the ONTARGET trial comparison of ARBs vs ACEis in CPRD before extending results to the underrepresented groups of females, those aged ≥75 years, those with CKD and Black and South Asian ethnic groups (Chapter 6). A third draft research paper aimed to replicate the ONTARGET trial dual therapy comparison in CPRD Aurum using an operational definition of dual users (Chapter 7). The final analysis conducted in this thesis aimed to explore whether trial replication methods could be transported to the SIDIAP data source which included primary care records for patients in Catalonia (Chapter 8)
- This work demonstrates that observational studies with validation against target trials can provide evidence for key trial-underrepresented and excluded groups. Findings of the ONTARGET trial were generalisable to UK patients receiving ARB and ACE inhibitors in routine care
- Implementing different approaches to trial replication methods I found propensity-score –weighting without access to individual level patient data from the target trial was sufficient to achieve results closely comparable to the trial using CPRD data whilst preserving sample size

9.1 Summary of findings

This thesis has applied trial replication methods to UK routinely collected data to explore treatment effects and risk in groups that were underrepresented and excluded from the ONTARGET trial. It demonstrates the benefits of using electronic health record data with validation against randomised controlled trials to bridge gaps in evidence. In the following sections I provide a brief overview of the main findings related to the research aims and objectives assessed in this thesis. I conclude with a section outlining the key strengths and limitations of this research.

9.2 Research aim 1 – objective 1 (replication of ONTARGET)

Trial replication methods are increasingly being implemented in various therapeutic areas to add confidence to findings from observational studies.[48, 50, 53] Two studies explored the replicability of the ONTARGET trial in US claims data and showed conflicting results.[45, 48] This thesis demonstrates how trial replication methods can be applied to UK electronic health record data to obtain estimates comparable to the ONTARGET trial, in agreement with the findings by Fralick et al.,[45] (Figure 9.1). Few studies have explored the feasibility of these methods to replicate trials which include a dual therapy arm.[52] This thesis demonstrated how an operational definition of a dual user can be used when the true sample of dual users is small which can led to results comparable to the dual therapy analysis observed in the ONTARGET trial. But substantial bias can be introduced depending on how dual therapy users are defined.



Notes: Composite outcome: CV-death, MI, stroke hospitalisation for heart failure. Hasvold et al., 2014 had primary outcome of CVD and included hypertensive patients aged 18 years and over who were new users. Potier et al., 2017 had same outcome as ONTARGET and included those with CVD and atherosclerosis. Oger et al., 2022 had primary outcome of major cardiovascular event and included new users and excluded those with CVD. Fralick et al., 2018 and Wang et al., 2023 included new users.

Figure 9.1 Forest plot of studies exploring comparative effects of ARBs compared to ACE inhibitors compared to ONTARGET trial findings

9.3 Research aim 2- objective 2 (extension to underrepresented and excluded groups)

Females, people with CKD, older adults and ethnic minority groups are commonly underrepresented in trials. Other than women, these groups are at increased risk of cardiovascular events.[4, 6] After first benchmarking findings from a trial-eligible cohort in CPRD against the ONTARGET trial results I was able to extend findings to explore treatment effects in these key at-risk groups that were underrepresented. This was aided by using propensity-score—weighting to balance characteristics between exposure groups which resulted in a cohort with increased sample size and more diverse characteristics than trial participants. Below I summarise key findings related to the underrepresented groups studied.

9.3.1 Females

ONTARGET included 4,581 (27%) females, whereas this thesis explored findings in a cohort with 68,198 (50%) females. Trial findings of comparative effectiveness of ARBs and ACEis associated with the risk of cardiovascular outcomes extended to females in UK routine care.

9.3.2 Aged ≥75 years

Similarly, trial findings were also replicated for UK patients aged ≥75 years. This analysis cohort included 49,621 (36%) patients aged ≥75 years, compared to 2,489 (15%) included in ONTARGET.

9.3.3 CKD

Among patients with CKD, results observed in CPRD were consistent with those observed in the ONTARGET trial. Extending analysis of the dual therapy comparison provided evidence to suggest no added benefit of dual use compared to ACEi alone at reducing cardiovascular endpoints and was associated with an increased risk of renal outcomes among dual therapy users although this may represent confounding by indication.

9.3.4 Black and South Asian ethnicity

Despite Black and South Asian groups being at increased risk of cardiovascular disease these groups are often poorly represented in trials. This is particularly an issue for Black patients who are recommended different treatments for hypertension compared to other ethnic groups in the UK.[25] I observed that ARBs and ACEis had comparable effects in Black, South Asian and White individuals.

The replication of ONTARGET in US claims data by Fralick et al.,[45] replicated the increased risk of angioedema observed in ONTARGET. In addition, the US ALLHAT trial

showed increased risk of angioedema among Black patients,[39, 156] and the findings of this trial later led to an update in UK hypertension guidance recommending an ARB in preference to an ACEi.[38] These studies showed an increased risk of angioedema among ACEi users in US populations. I observed an increased risk of angioedema among Black patients, with Black patients 3 times more likely to develop angioedema compared to White patients. However, I found that ARBs were associated with lower risk of angioedema in both Black and White individuals compared to ACEis. I observed no statistical association with treatment and angioedema among South Asian individuals but confidence intervals were wide.

9.4 Research aim 2 – objective 1 (optimal method for replication)

Chapter 6 investigated three different approaches to trial replication. I showed that by applying trial criteria and using propensity-score—weights to address confounding comparable trial results could be obtained providing consideration is given to the protocol of the emulation. This approach did not require access to the trial data and matching to the trial was omitted. This meant patients in the observational cohort had more diverse characteristics than the trial participants maximum sample size, which enabled results to be extended to underrepresented and excluded groups.

9.5 Research aim 2 – objective 2 (transportability of methods to data sources outside the UK)

The optimal trial replication technique identified in Chapter 6 was applied to SIDIAP data which was representative of ~75% the Catalonian population.[88] Close comparability was not achieved. A number of different sources of bias were identified and analysis restricting to recent years led to comparable results to the ONTARGET trial.

9.6 Strengths

Evidence to support use of trial replication methods in CPRD data

This thesis provides strong evidence that supports the use of CPRD data to add validation to observational studies by implementing trial replication methods.

Different approaches to trial replication explored

With access to the individual level patient data from the ONTARGET trial, I was able to explore if this provided added benefit to obtaining results closely comparable to the trial. From investigating different approaches to trial replication which had differing number of restrictions I was able to conclude that propensity-score—weighting and applying trial criteria without first matching to trial data was sufficient to replicate trial results and enable inferences to be extended to underrepresented and excluded groups.

Explores suitability of SIDIAP data for use of trial replication methods

This thesis explored the suitability of trial replication methods applied to the SIDIAP data source. Differences in characteristics and prescribing patterns were seen between Catalonia and the UK and in the main analysis I was not able to replicate the ONTARGET trial. Therefore, comparability between different data sources is not always achievable if country-wide differences are present. Potential reasons for differences are discussed in Chapter 8.

Replication of a dual therapy treatment arm

When only a small proportion of routine care patients were taking both ACEi and ARB, I demonstrated that an operational definition can be used to estimate treatment effects in patients receiving dual therapy in routine care.

Representative sample

By the application of trial replication methods to CPRD data representative of patients receiving these medications in the UK to validate findings, this thesis provides evidence on the population as treated in routine healthcare as well as key at-risk groups often underrepresented in trials.

9.7 Limitations

Despite the benefits of using routine data to obtain conclusions regarding generalisability of trial results several limitations exist and are discussed below.

Adherence

Use of prescriptions to estimate medication exposure could introduce information bias into results as the true number of patients filling prescriptions may be less than those prescribed. However, in this situation, whether patients take their prescribed medication is unlikely to differ between exposure groups. I calculated proportion of patients still receiving assigned medication at 1, 2, 3, 4 and 5.5 years and compared to the ONTARGET trial. Despite observing some differences between in CPRD and ONTARGET there were only small differences between exposure groups in CPRD. ACEi users were more likely to switch to an ARB which is commonly observed when comparing a new drug vs an old drug however this did not appear to impact relative rates.

Confounding bias

Despite using propensity score methods to address confounding, unmeasured confounding may still be present and this work is based on the assumption that the effect of unmeasured

cofounders is minimal in the subgroups of the covariates of measured confounders included in the model. Residual confounding can more difficult to identify in studies that do not benchmark findings. However, obtaining similar results to the trial after careful design approaches have been applied and pre-specified sensitivity analyses provides an indication that residual confounding is likely to be minimal. Despite this, multiple sources of bias may be present in observational studies that could affect the results in different directions and subsequently cancel each other out. Therefore, sensitivity analyses should be used to appropriately account for these situations.

Time-related bias

Due to including prevalent users in analysis and studying a newly licensed drug vs a well-established treatment, time-related biases such as channelling to healthier patients are known issues. This was observed in the analysis using SIDIAP data (Chapter 8). Methods such as the prevalent new user design proposed by Suissa et al.,[95] can be used to account for such bias and could be an extension to this work.

Generalisability

By applying the ONTARGET trial criteria, results may not be generalisable to the wider UK population receiving these medications but instead to a subset who would have met the trial criteria.

Information bias

Read and ICD10 codes were used to assess covariates, exposure status and outcomes in analysis. These are reliant on such codes being recorded by healthcare professionals and could be subject to misclassification. As drugs for similar indications are being compared, the

probability of events being misclassified in the exposure is likely to be similar across groups in the study. Therefore, the information bias is likely to be non-differential. For measures such as GFR biochemical data is used with patients who are diabetic or in poorer health more likely to be monitored and have regular measurements taken. This could subsequently lead to acute drops in GFR being detected more commonly.

In some cases, a proxy was required to capture outcomes, such as cardiovascular death in SIDIAP data which is a limitation of the data source.

Immortal time bias

Identification of the time when people begin taking concurrent medications in routine care data can be difficult, especially when, as with the medications studied in this analysis, people also often switch between them. Immortal time bias is likely to be present in the operational definition of dual users, since patients had to receive a subsequent prescription for the first agent after the second prescription for the second agent to ensure dual users were captured as opposed to switchers. However, starting follow up from an earlier time point would introduce survivor bias due to a patient having to survive up to the point of meeting the operational definition. Despite attempting to assess the impact this had using sensitivity analyses as described in Chapter 7, due to the trial observing a null effect it is possible that the effect observed in my work is due to sources of bias in different directions balancing out with an overall null effect.

Missing data

Missing data was present for some key variables including baseline blood pressure. Missing data was substantially higher in the SIDIAP data source. The effect of this was explored using multiple imputation but assumed such variables were missing at random. Variables with

large amounts of missing data for which this assumption could not be assumed were excluded from the propensity score model despite being potential confounders. Balance of such variables were checked after applying propensity score methods, but nonetheless may have impacted findings.

Inability to replicate safety outcomes

I was unable to obtain estimates for safety outcomes that were comparable to the ONTARGET trial. Therefore, it is unknown whether the estimates I observed are the true reflection of safety events occurring among patients receiving these medications in the UK or if results are affected by underreporting or misclassification leading to bias.

Ethnicity results conditional on non-missing ethnicity

Despite providing key evidence on treatment effects and risk of these medications in routine care among Black patients the analysis is conditional on patients having ethnicity recorded at baseline which could have led to bias in results. Missing ethnicity is unlikely to be missing at random and those with ethnicity recorded may have more contact with health professionals and therefore poorer health. However, ethnicity is generally well-recorded for this indication so this was likely to have minimal effect on results.

9.8 Future directions

The results from Research paper 3 (ethnic differences) aimed to determine if there were ethnic differences in the effectiveness of ARBs and ACEis. The use of routinely-collected data provides a unique tool to answer important questions based on key subgroups understudied in trials due to lack of power. It also provides the opportunity to explore the generalisability of trial results in real-world settings and explore whether there is sufficient

evidence to support ethnicity-based treatment guidelines. Further studies exploring whether equivalent conclusions on the effects of ARB/ACEi by ethnicity are obtained would be beneficial. Of particular interest is further evidence exploring if the risk of angioedema differs by ARB and ACEi use and by ethnicity as studies to date have not been able to provide reliable results due to the small number of events. Routine data in combination with genetic data could be used to see if potential differences are due to biological differences or underlying structural racism leading to poorer baseline health in ethnic minority groups which may be difficult to adequately account for using traditional statistical methods. Data arising from the Genes and Health Study will provide an opportunity to address questions relating specifically to South Asian ethnic groups. Therefore, similar data sources representative of the Black population would be largely beneficial to address these questions.

This thesis explored the use of an operational definition of dual users when the true number of dual users is small. This provided promising results, however elements of bias may still be present. Further work to explore the feasibility of such methods through simulation studies would be useful to aid in the use of trial replication methods to explore treatment effects for dual therapy treatment arms.

Routinely-collected data provides an opportunity for the near real-time monitoring of the safety of drugs. However, a better understanding of how such events are recorded in primary care data is needed to ensure conclusions are free from misclassification and the extent to which events are underreported. I was unable to replicate the safety outcomes observed in the ONTARGET trial, despite these being successfully replicated in the study by Fralick et al..[45] Most trial replication studies aim to replicate efficacy outcomes only, therefore it would be useful to further explore the feasibility of replicating safety outcomes particularly in electronic health record data where reporting of events may differ in this setting compared to claims data.

SIDIAP data was used to investigate if methods could be transported to a data source outside of the UK. This cohort had characteristics which differed to those in CPRD and ONTARGET which could have impacted results. Extension to other data sources could determine whether the differences observed in SIDIAP are due to the healthcare system, nature of the data collected or due to the lack of generalisability of methods. More broadly, implementation of structured trial replication methods to multiple data sources provides the opportunity to identify strengths and weaknesses of different data sources for addressing specific research questions and therapeutic areas. Structured trial replication methods applied to multiple data sources could be a solution to low power when addressing questions around small population subgroups. Differences in patient profiles within data sources could be addressed through weighting methods of key characteristics.

9.9 Conclusions

With cardiovascular disease being a leading cause of death globally and key at-risk groups underrepresented in trials there is uncertainty about the real-world effects of medications to prevent cardiovascular outcomes. This thesis demonstrates the generalisability of the ONTARGET trial findings to key subgroups in the UK. It provides evidence to suggest ARBs are associated with a lower risk of angioedema compared to ACEi among Black and White patients despite the current UK treatment guidelines recommending an ARB as preference for Black patients only. This work shows how observational data can be used to bridge the gap in evidence for the effectiveness of ARBs and ACEis in preventing cardiovascular outcomes by validating findings against target trials before extending inferences to underrepresented and excluded groups.

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Appendix

1.1 Appendix 1: Supplementary material from Research paper 1

SUPPLEMENTARY MATERIAL

Table of trial diagnoses (inclusion criteria) and interpretation in CPRD.

ONTARGET/TRANSCEND	**CPRD GOLD (HES + ONS Linked) READ or ICD 10 code for:**
Aged ≥55 years	Aged ≥55 years prior to prescription of drug
Coronary artery disease	
Previous myocardial infarction (>2 days post uncomplicated MI)	MI at least 2 days prior to prescription of drug
Stable angina or unstable angina >30 days before informed consent and with documented evidence of multivessel coronary artery disease	Angina/stable angina/unstable angina at least 30 days before prescription of drug and previous coronary artery disease diagnosis
Multi-vessel PTCA >30 days before informed consent	Read, ICD-10 or OPCS code for coronary angioplasty at least 30 days before prescription of drug
Multi-vessel CABG surgery >4 years before informed consent, or with recurrent angina following surgery	Read, ICD-10 or OPCS code for CABG at least 4 years before prescription of drug or with angina after CABG
Peripheral artery disease	
Previous limb bypass surgery or angioplasty	Read, ICD-10 or OPCS code for limb bypass surgery or angioplasty
Previous limb or foot amputation	Read, ICD-10 or OPCS code for limb/foot amputation

Intermittent claudication, with ankle:arm BP ratio <=0.80 on at least 1 side	Intermittent claudication
Significant peripheral artery stenosis (>50%) documented by angiography or non-invasive test	Not applicable
Cerebrovascular disease	
Previous stroke	Stroke before prescription of drug
Transient ischemic attacks >7 days and <1 year before informed consent	Transient ischemic attacks before prescription of drug
High-risk diabetes with evidence of end-organ damage	
High-risk diabetes	Specific codes for diabetes with retinopathy, neuropathy, chronic kidney disease or proteinuria before prescription of drug or diabetes defined by diabetes codes or diabetes therapy with CKD defined as eGFR<60 or proteinuria defined as ACR>3

Notes: Where dates are used as criteria dates from both CPRD and HES will be used, but if available HES will be preferred.

Table of trial exclusion criteria and interpretation in CPRD.

ONTARGET/TRANSCEND exclusion criteria	**CPRD GOLD (HES + ONS Linked) READ or ICD 10 code (prior to eligible for inclusion date, unless otherwise specified) for:**
Inability to discontinue ACE inhibitors or ARB	Not applicable
Known hypersensitivity or intolerance to ACE inhibitors or ARB	Not applicable
Symptomatic congestive heart failure	Heart failure or left ventricular dysfunction
Hemodynamically significant primary valvular or outflow tract obstruction	Aortic or pulmonary stenosis or previous valve replacement
Constrictive pericarditis	Constrictive pericarditis
Complex congenital heart disease	Congenital heart disease
Syncopal episodes of unknown etiology <3 months before informed consent	Not applicable
Planned cardiac surgery or PTCA <3 months of informed consent	Not applicable
Uncontrolled hypertension on treatment (e.g. BP >160/100 mm Hg)	Last recorded BP >160/100 mmHg for patients on treatment with other antihypertensives prior to ACEI/ARB initiation
Heart transplant recipient	Read, ICD-10 or OPCS code for heart transplant recipient
Stroke due to subarachnoid haemorrhage	Previous cerebral haemorrhage

Significant renal artery disease	Codes for renal artery stenosis or renal artery atherosclerosis; or serum creatinine concentration above 265μmol/L
Hepatic dysfunction	Cirrhosis or other documented liver disease
Uncorrected volume or sodium depletion	Not applicable
Primary hyperaldosteronism	Primary hyperaldosteronism/ Conn's syndrome
Hereditary fructose intolerance	Hereditary fructose intolerance
Other major noncardiac illness expected to reduce life expectancy or interfere with study participation	Recorded solid organ or metastatic malignancy within the last 5 years, drug, alcohol dependence or mental illness.
Simultaneously taking another experimental drug	Not applicable
Significant disability precluding regular follow-up visits	Not applicable
Unable or unwilling to provide written informed consent	Not applicable
Elevated potassium above 5.5mmol/L	Elevated potassium above 5.5mmol/L
Hypotension	SBP <90 mm Hg

Notes: Where dates are used as criteria dates from both CPRD and HES will be used, but if available HES will be preferred. Not applicable used when anticipated there will be extensive missing data or risk of misclassification.

Table of results from the Cochrane collaboration's tool for assessing risk of bias in ONTARGET trial.

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Low	Stratified according to site with use of permuted blocks through central automated telephone service.
Allocation concealment (selection bias)	Low	24-hour service computerized voice-activated telephone call
Selective reporting (reporting bias)	Unclear	Some mentioned secondary and other outcomes not displayed in table of results in main results paper, could be presented elsewhere
Other bias	Low	No other sources of bias identified
Blinding of participants and researchers (performance bias)	Unclear	underwent double blinding using telephone service, after 3 week single-blind run-in. No detail given on whether blinding was effective
Blinding of outcome assessment (detection bias)	Low	All main outcomes adjudicated by central committee whose study members were unaware of study group assignments
Incomplete outcome data (attrition bias)	Low	Information given on number discontinued, loss to follow up and numbers in intervention groups

1.2 Appendix 2: Supplementary material from Research paper 2

Supplementary Material

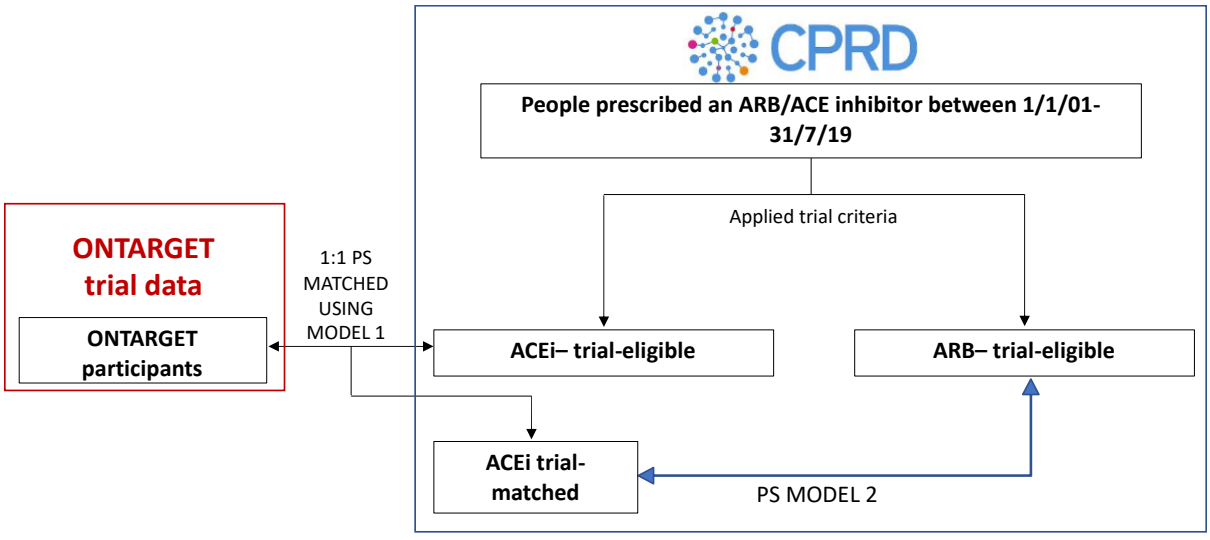
Supplementary material A. Additional details on Step 3: Balance across exposure groups

As we had access to individual patient level data from the ONTARGET trial we aimed to carry out analysis on two cohorts and examine if this provided any benefit to obtaining results consistent with the trial. The analysis cohorts used were:

1) Main analysis: propensity-score—weighted trial-eligible groups which resulted in covariate distribution more diverse than the trial

2) Sensitivity analysis: propensity-score—matched trial-matched ACEi cohort to trial-eligible ARB cohort which resulted in covariate distribution similar to the trial

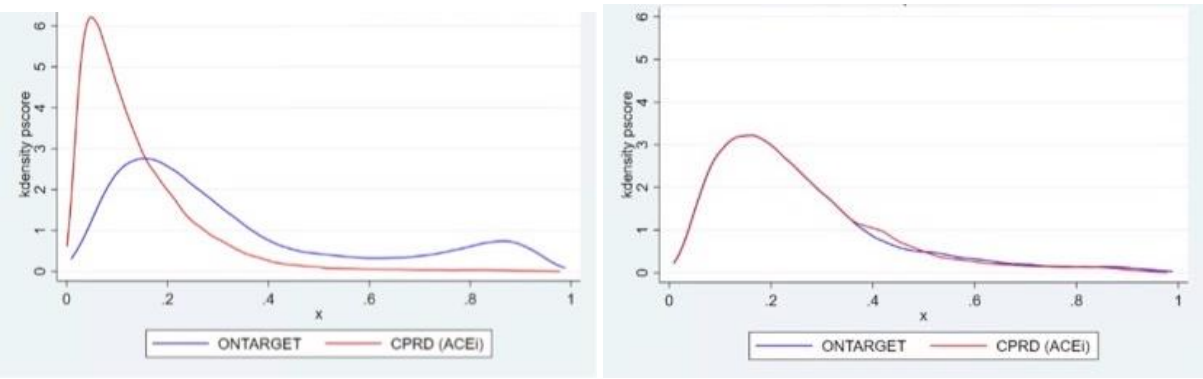
For efficiency the propensity score model used to achieve balance across CPRD exposure groups for the probability of receiving an ACEi in both the propensity-score—weighted and propensity-score—matched cohorts listed above was the same and was developed using an appended cohort of trial-matched ACEi patients and trial-eligible ARB periods. This is



Supplementary Figure A1. Steps to develop propensity score models used to achieve balance across CPRD exposure groups. PS=propensity-score; PS model 1: probability of being in the trial; PS model 2: probability of receiving an ACEi

displayed graphically in Supplementary Figure A1.

To develop the trial-matched ACEi cohort, which was used to ensure covariate distribution was consistent with the trial, the trial data were combined with the CPRD cohort of trial-eligible ACEi exposed periods. We then 1:1 matched each ONTARGET trial participant to one trial-eligible ACEi exposed period, without replacement, on closest propensity-score, using a propensity-score model for the probability of being included in the trial. Variables considered in the propensity score model were those available in both the ONTARGET and CPRD data and thought to be associated with trial inclusion and outcome and based on clinical input. Variables that were likely to differ across the data sources i.e., previous medication use due to changes over time were excluded. The chosen variables were: history



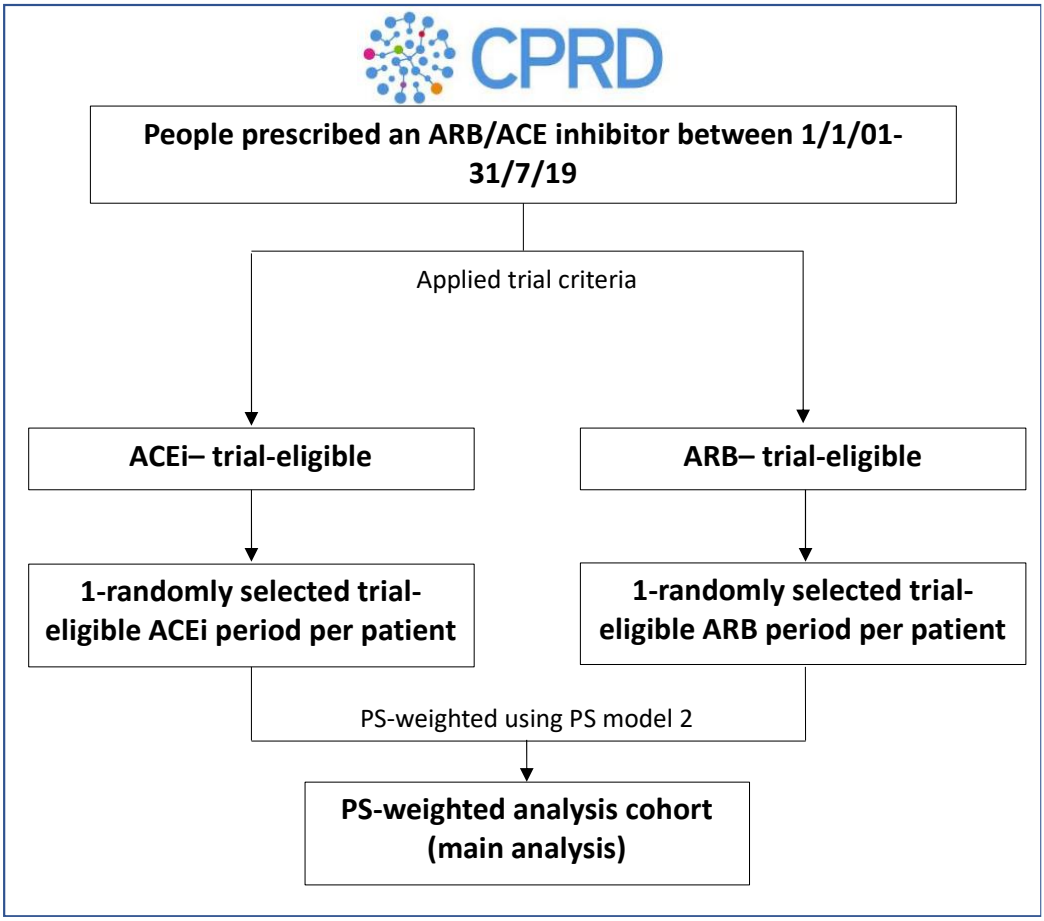
Supplementary Figure A2. Kernel density plots before and after matching ONTARGET participants to trial-eligible ACEi patients. Left: before matching; right: after matching.

of cerebrovascular disease, peripheral artery disease, coronary artery disease, diabetes, high-risk diabetes, age, sex, ethnicity, BMI, systolic and diastolic blood pressure and smoking status at baseline. We used a caliper of 0.25 of the standard deviation of the logit of the propensity-score, with the restriction that only one ACEi trial-eligible exposed period per patient could be matched. We used standardised differences (<0.1) and kernel density plots to assess the quality of matches which are presented in Supplementary Figure A2. Matching resulted in 22,091 trial-matched ACEi patients.

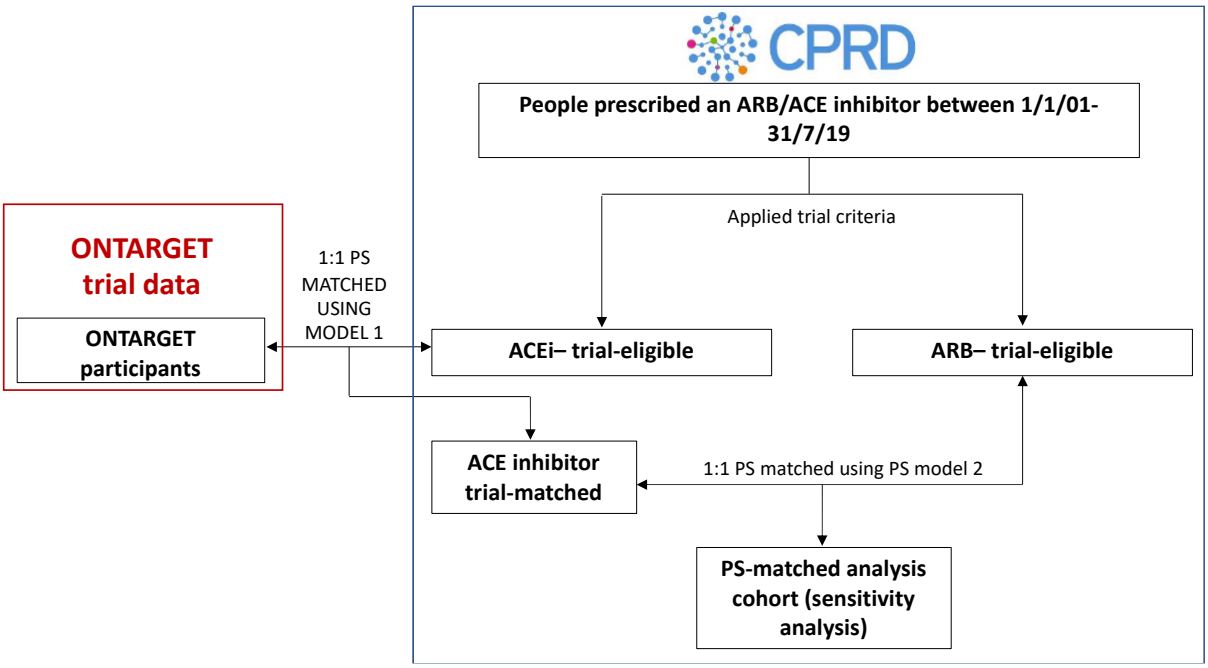
To develop the model used to balance exposure groups in CPRD we appended the trial-matched ACEi cohort with the trial-eligible ARB cohort and developed a second propensity score model for the probability of receiving an ACEi.

In the propensity-score—weighted analysis, which was the main analysis presented in the paper, which allowed us to extend findings to underrepresented groups, we applied this model to a cohort of one-randomly selected trial eligible period per patient from the trial-eligible ARB and ACEi exposure groups and generated inverse probability weights from propensity scores (Supplementary Figure A3). Using the trial-eligible cohorts and not the trial-matched cohort enabled characteristics to be more diverse than the trial. We selected one random period as opposed to the first period to avoid the possibility of biasing results towards new users, since the trial included prevalent users.

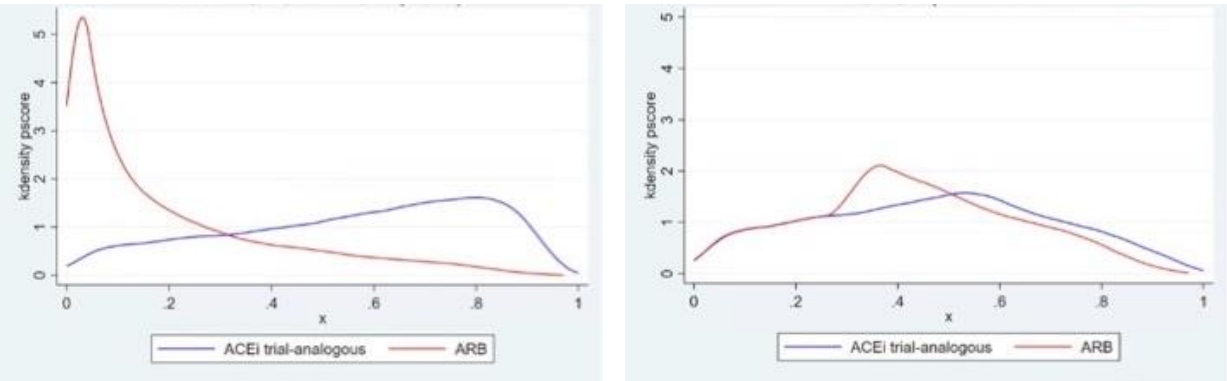
In the propensity-score—matched analysis, which was carried out as a sensitivity analysis, we 1:1 matched the trial-matched ACEi patients to one-randomly selected trial-eligible period per patient from the trial-eligible ARB exposure group using propensity scores generated from the model described above (probability of receiving an ACEi), with the restriction that only one ARB trial-eligible exposed period per patient could be matched (Supplementary Figure A4). This analysis allowed us to explore if there was an added benefit of matching to the trial data and using a cohort with covariate distribution consistent with the trial. We used standardised differences (<0.1) and kernel density plots to assess the quality of matches which are displayed in Supplementary Figure A5 and Supplementary Table A1.



Supplementary Figure A3. Steps to achieve balance across exposure groups in main analysis using propensity-score—weighting. PS=propensity-score; PS model 2: probability of receiving an ACEi



Supplementary Figure A4. Steps to achieve balance across exposure groups in sensitivity analysis using propensity-score—matching. PS=propensity-score; PS model 1: probability of being in the trial; PS model 2: probability of receiving an ACEi



Supplementary Figure A5. Kernel density plots before and after matching trial-matched ACEi patients to trial-eligible ARB patients. Left: before matching; right: after matching.

Supplementary Table A1. Assessment of balance of variables included in propensity-score model for ARB vs ACEi sensitivity analysis after matching compared to ONTARGET

Characteristic	Propensity-score—matched analysis cohort			ONTARGET
	ACEi	ARB	SMD	*n=25620*
	n=15,462	*n=15,462*		
Age - year	67.4 ± 8.3	67.8 ± 8.4	0.047	66.4 ± 7.2
Systolic BP– mmHg	143.1 ± 17.7	143.8 ± 17.9	0.035	141.8 ± 17.4
Diastolic BP– mmHg	82.1 ± 10.3	81.8 ± 10.3	0.028	82.1 ± 10.4
Body-mass index (kg/m^2)	28.6 ± 5.2	28.8 ± 5.3	0.037	28.2 ± 4.7
Female sex – no. (%)	5026 (32.5)	5554 (35.9)	0.072	6831 (26.7)
Ethnic group – no. (%)				
Black	409 (2.6)	429 (2.8)	0.008	629 (2.5)
Other	623 (4.0)	483 (3.1)	0.049	4901 (19.1)
South Asian	922 (6.0)	913 (5.9)	0.002	1375 (5.4)
Unknown	-	-	-	7 (<0.1)
White	13508 (87.4)	13637 (88.2)	0.025	18708 (73.0)
Clinical history – no. (%)				
CAD[a,b]	11474 (74.2)	11275 (72.9)	0.029	19102 (74.6)
Cerebrovascular disease[a,c]	2287 (14.8)	1902 (12.3)	0.073	5342 (20.9)
PAD[a,d]	1992 (12.9)	1856 (12.0)	0.027	3468 (13.5)
Diabetes[e]	6255 (40.5)	6647 (43.0)	0.051	9612 (37.5)
High-risk diabetes[a,f]	4675 (30.2)	4947 (32.0)	0.038	7151 (27.9)
Smoking status – no. (%)				
Non-smoker	5666 (36.6)	5799 (37.5)	0.019	9088 (35.5)
Current smoker	1765 (11.4)	1655 (10.7)	0.022	3225 (12.6)
Past smoker	8031 (51.9)	8008 (51.8)	0.002	13276 (51.8)
Alcohol status – no. (%)				
Drinker	12421 (80.3)	12317 (79.7)	0.017	10345 (40.4)

Supplementary Table A1. Assessment of balance of variables included in propensity-score model for ARB vs ACEi sensitivity analysis after matching compared to ONTARGET

Characteristic	**Propensity-score—matched analysis cohort**			**ONTARGET**
	ACEi *n=15,462*	**ARB** *n=15,462*	**SMD**	*n=25620*
Medication[g] – no. (%)				
Antiplatelet agent	1875 (12.1)	1577 (10.2)	0.061	2824 (11.0)
Aspirin	5987 (38.7)	5685 (36.8)	0.040	19403 (75.7)
Beta-blocker	4429 (28.6)	4169 (27.0)	0.038	14583 (56.9)
Calcium-channel blocker	4010 (25.9)	4115 (26.6)	0.015	8472 (33.1)
Diuretics	4128 (26.7)	4223 (27.3)	0.014	7164 (28.0)
Diabetic treatment	2615 (16.9)	2735 (17.7)	0.021	8056 (31.4)
Nitrates	1936 (12.5)	1761 (11.4)	0.035	7523 (29.4)
Statins	7450 (48.2)	7128 (46.1)	0.042	15783 (61.6)
Index of multiple deprivation (IMD) – no.(%)				
1 (least deprived)	3237 (20.9)	3358 (21.7)	0.020	
2	3474 (22.5)	3525 (22.8)	0.007	
3	3330 (21.5)	3293 (21.3)	0.005	
4	2932 (19.0)	2902 (18.8)	0.005	
5 (most deprived)	2489 (16.1)	2384 (15.4)	0.019	
Health utilisation[h]				
No. of hospital admissions	0.40 ± 0.87	0.36 ± 0.90	0.040	
No. of GP apt.	23.2 ± 26.4	23.4 ± 27.9	0.006	
No. of different drug types	8.5 ± 4.5	8.7 ± 4.5	0.045	
Time-related variables				
Time since first eligible period (days)	241.1 ± 628.0	241.0 ± 631.7	0.001	
No. of prior ARB periods	0.07 ± 0.32	0.04 ± 0.27	0.089	
No. of prior ACEi periods	0.30 ± 0.79	0.29 ± 0.66	0.010	

Supplementary Table A1. Assessment of balance of variables included in propensity-score model for ARB vs ACEi sensitivity analysis after matching compared to ONTARGET

Characteristic	Propensity-score—matched analysis cohort			ONTARGET
	ACEi	ARB	SMD	*n=25620*
	n=15,462	*n=15,462*		

Notes: SMD=standardised mean difference; BP=blood pressure.

Cohort includes 1 randomly selected eligible period per patient in each group

[a] Any diagnosis prior to start of eligible period

[b] Includes diagnosis of: MI at least 2 days prior, angina at least 30 days prior, angioplasty at least 30 days prior, CABG at least 4 years prior

[c] Includes diagnosis of: stroke/TIA

[d] Includes diagnosis of: limb bypass surgery, limb/foot amputation, intermittent claudication

[e] DM prior to start of eligible period

[f] Includes DM with: retinopathy, neuropathy, chronic kidney disease or proteinuria

[g] Within 3 months prior to eligible start date. Antiplatelet agent= clopidogrel/ ticlopidine

[h] Within 6 months prior to eligible start date.

no. (%)=number (percent); CAD=coronary artery disease; MI=myocardial infarction; PAD=peripheral artery disease. In the categorisation of ethnicity in ONTARGET South Asian ethnic group included Other Asian and Black included Black African and Colored African as described in the trial CRF.

Supplementary Table S1. Deviations from protocol

Deviation	Reason
Using propensity-score—weighting as opposed to propensity-score—matching (with propensity-score—matching carried out as an additional analysis)	To obtain average treatment effect as opposed to average treatment effect on treated and increase sample size
Underrepresented group analysis on propensity-score—weighted sample as opposed to propensity-score—matched cohort	This was to increase sample size as comparison between both analyses gave almost identical results
Primary outcome: including both fatal and non-fatal events for stroke and myocardial infarction	Consistency with trial
Included additional outcome- main secondary outcome: composite of cardiovascular-related death, myocardial infarction, or stroke	Consistency with trial
Angina inclusion criteria: Removed condition that needed to have previous coronary artery disease diagnosis	Misclassification
CABG Inclusion criteria: Removed condition that could be with angina	Only included events where CABG was within 4 years prior to avoid due to potential of capturing old events
Comparing reason for discontinuation to safety outcomes in trial as opposed to events occurring within 3 months	Consistency with safety outcomes reported in trial
Objective of extending follow-up for safety events	Have not yet addressed this objective due to difficulty replicating safety trial results
Renal function omitted from propensity-score model	Due to large amounts of missingness
Adherence assessed differently and instead reported proportions of patients receiving each drug at different timepoints	Consistency with trial
Additional subgroups studied	To further demonstrate trial replicability and quantify effect modification
On-treatment (per-protocol) analysis for secondary objectives 1 and 2 (extending findings to trial-underrepresented and excluded groups)	Not deemed necessary as on-treatment analysis was sufficiently comparable to ITT for primary outcome
Previously mentioned that patients had to meet inclusion and exclusion criteria prior to start of first exposed period instead trial criteria assessed at start of all exposed periods	Incorrect wording in protocol this reduces bias by assessing at start of follow up
Referred to analysis group as trial-analogous now analysis groups will be labelled as propensity-score—weighted trial-eligible for main analysis and propensity-score—matched trial-eligible for sensitivity analysis	To avoid confusion as only the ACEi trial-eligible cohort is trial-matched

Naming of nephropathy outcomes	Changed from nephropathy 1 and nephropathy 2 to loss of eGFR or ESKD and ESKD
Nephropathy 1 sensitivity analysis requiring 2 measurements at least 3 months apart for both eGFR<15 and 50% reduction in eGFR	Previously stated this is only required for 50% reduction in eGFR which was incorrect

Supplementary Table S2. Explanation for potential differences in estimates from ONTARGET and the emulation in CPRD after mapping protocol components

Protocol component	Potential remaining differences	Examples	Approach to address	Result
Eligibility criteria	Differences in study population	Groups unequally represented in the emulation and ONTARGET, i.e., ONTARGET including fewer females.	Sensitivity analysis PS-matching trial-eligible ACEi patients to ONTARGET trial participants then PS-matching trial-matched ACEi patients to trial-eligible ARB periods to ensure CPRD analysis cohort has similar covariate distribution to ONTARGET	Consistent with PS-weighted approach. Main analysis (PS-weighted): HR 0.98 (95% CI: 0.94, 1.02); sensitivity analysis (PS-matched): HR 0.97 (95% CI: 0.92, 1.02)
Treatment strategies	Differences in treatment uptake	Individuals in ONTARGET may be more adherent than patients in CPRD	Compare adherence in ONTARGET to that in CPRD	Adherence similar for ARB users, differed for ACEi users with more patients in ACEi exposure group switching to an ARB
Assignment procedures	Confounding by indication	Patients who started ARB in CPRD may be healthier than those receiving an ACEi	Compared Kaplan-Meier curves in ONTARGET and emulation at 1, 2, 3, 4 and 5 years	Risk appears slightly lower for ARB users in CPRD at 1, 2, 3, 4 and 5 years compared to ONTARGET where risk is similar among telmisartan and ramipril users until 1.5 years where risk is lower among ramipril users at 2, 3 and 4 years.
Follow-up period	Differential loss to follow-up	Patients lost to follow-up in CPRD may have worse prognosis	Reanalyse as sensitivity excluding patients who were lost	Consistent with main analysis, HR 0.96 (95% CI: 0.93, 1.00)

			to follow-up in the first 12 months	
Outcome	Differences in incidence of outcome	ONTARGET was a global trial and emulation on UK population so incidence of outcome may differ by country	Include individual components of composite outcome and compare incidence between CPRD and ONTARGET	Incidence similar for most outcomes but in CPRD incidence of MI was higher than in ONTARGET

Supplementary Table S3. List of variables considered and included in propensity-score model used to achieve balance across exposure groups

Variables included in propensity-score model	**Propensity score model for probability of receiving an ACEi**
Stroke/TIA	✓
Peripheral artery disease	✓
Coronary artery disease	✓
Diabetes	✓
High-risk diabetes	✓
Age (years)	✓
Sex	✓
Ethnicity	✓
BMI	✓
SBP	✓
DBP	✓
Index of Multiple Deprivation (IMD)	✓
Smoke status	✓
Alcohol use	✓
Statin use	✓
Nitrate use	✓
Diabetic treatment use	✓
Diuretic use	✓
CCB use	✓
Betablocker use	✓
Aspirin use	✓
Antiplatelet use	✓
Digoxin use	
Anticoagulant use	
Alpha-blocker use	
No. of hospital admissions within 6 months prior	✓
No. of GP appointments within 6 months prior	✓
No. of medications within 6 months prior	✓
Year of start of eligible period	✓
Time since first eligible period (days)	✓
No. of previous ACE inhibitor eligible periods	✓
No. of previous ARB eligible periods	✓
Notes: TIA: transient ischaemic attack; BMI: body-mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure. Variables are measured at start of trial-eligible period or before.	

Peripheral artery disease includes limb bypass surgery or angioplasty, limb/foot amputation, or intermittent claudication.

Coronary artery disease includes previous MI, angina, coronary angioplasty, or CABG.

SBP and DBP are measured within 6 months prior to start of trial-eligible period.

Medication use is within 3 months prior to start of trial-eligible period.

Supplementary Table S4. Assessment of balance of variables included in propensity-score model for ARB vs ACEi analysis before and after weighting

Characteristic	Before propensity-score—weighting			After propensity-score—weighting		
	ACEi *n=96 602*	ARB *n=40 553*	**SMD**	**ACEi** *n=96 602*	**ARB** *n=40 553*	**SMD**
Age - year	70.8 ± 9.0	71.2 ± 8.7	0.047	71.2 ± 8.9	71.1 ± 9.0	0.009
Systolic BP– mmHg	147.4 ± 20.7	148.1 ± 20.7	0.035	147.4 ± 20.3	148.2 ± 20.8	0.041
Diastolic BP– mmHg	80.1 ± 10.7	79.7 ± 10.5	0.041	79.5 ± 10.7	80.1 ± 10.7	0.054
Body-mass index (kg/m^2)	28.3 ± 5.3	28.8 ± 5.4	0.097	28.3 ± 5.7	28.6 ± 5.4	0.044
Female sex – no. (%)	45508 (47.1)	22690 (56.0)	0.178	75304.7 (51.8)	68530.9 (50.5)	0.026
Ethnic group – no. (%)						
Black	1280 (1.3)	736 (1.8)	0.039	2064.1 (1.4)	2053.2 (1.5)	0.008
Other	1134 (1.2)	607 (1.5)	0.028	1742.9 (1.2)	1747.3 (1.3)	0.008
South Asian	3026 (3.1)	1799 (4.4)	0.068	8632.0 (5.9)	5073.8 (3.7)	0.103
White	91162 (94.4)	37411 (92.3)	0.028	132818.6 (91.4)	126718.0 (93.5)	0.076
Clinical history – no. (%)						
CAD[a,b]	68009 (70.4)	28202 (69.5)	0.019	100440.6 (69.2)	94474.9 (69.7)	0.011
Cerebrovascular disease[a,c]	8695 (9.0)	3140 (7.7)	0.046	12626.5 (8.7)	11840.2 (8.7)	0.001
PAD[a,d]	9999 (10.4)	4078 (10.1)	0.010	14359.7 (9.9)	14463.3 (10.7)	0.026
Diabetes[e]	43751 (45.3)	20003 (49.3)	0.081	69713.4 (48.0)	64739.6 (47.8)	0.005
High-risk diabetes[a,f]	30736 (31.8)	14757 (36.4)	0.097	50469.3 (34.7)	46151.9 (34.0)	0.015
Smoking status – no. (%)						
Non-smoker	34503 (35.7)	16470 (40.6)	0.101	55849.7 (38.5)	50717.2 (37.4)	0.022
Current smoker	12921 (13.4)	3552 (8.8)	0.148	16659.7 (11.5)	16627.5 (12.3)	0.024
Past smoker	49178 (50.9)	20531 (50.6)	0.006	72748.3 (50.1)	68247.6 (50.3)	0.005
Alcohol status – no. (%)						

Supplementary Table S4. Assessment of balance of variables included in propensity-score model for ARB vs ACEi analysis before and after weighting

Characteristic	**Before propensity-score—weighting**			**After propensity-score—weighting**		
	ACEi *n=96 602*	ARB *n=40 553*	**SMD**	**ACEi** *n=96 602*	**ARB** *n=40 553*	**SMD**
Drinker	76756 (79.5)	31840 (78.5)	0.023	116186.3 (80.0)	106324.0 (78.4)	0.039
Medication[g] – no. (%)						
Antiplatelet agent	12334 (12.8)	2482 (6.1)	0.229	14649.6 (10.1)	13131.5 (9.7)	0.014
Aspirin	44011 (45.6)	9325 (23.0)	0.489	53048.8 (36.5)	50799.3 (37.5)	0.020
Beta-blocker	34178 (35.4)	6756 (16.7)	0.437	40751.5 (28.1)	38741.4 (28.6)	0.012
Calcium-channel blocker	28820 (29.8)	8515 (21.0)	0.204	38254.1 (26.3)	37864.7 (27.9)	0.036
Diuretics	32002 (33.1)	8838 (21.8)	0.256	40789.2 (28.1)	41887.5 (30.9)	0.062
Diabetic treatment	20060 (20.8)	4910 (12.1)	0.235	25257.7 (17.4)	25561.6 (18.9)	0.038
Nitrates	14862 (15.4)	3172 (7.8)	0.238	17721.7 (12.2)	16577.2 (12.2)	0.001
Statins	52925 (54.8)	11474 (28.3)	0.558	64630.3 (44.5)	61779.5 (45.6)	0.021
Index of multiple deprivation (IMD) – no.(%)						
1 (least deprived)	19805 (20.5)	8996 (22.2)	0.041	32568.7 (22.4)	28190.3 (20.8)	0.040
2	21977 (22.8)	9603 (23.7)	0.022	34344.3 (23.6)	30971.3 (22.8)	0.019
3	20644 (21.4)	8674 (21.4)	0.001	30255.9 (20.8)	28911.6 (21.3)	0.012
4	18462 (19.1)	7312 (18.0)	0.028	26032.4 (17.9)	25280.3 (18.6)	0.019
5 (most deprived)	15714 (16.3)	5967 (14.7)	0.043	22056.5 (15.2)	22238.8 (16.4)	0.033
Health utilisation[h]						
No. of hospital admissions	0.42 ± 1.0	0.31 ± 0.9	0.118	0.38 ± 0.9	0.36 ± 0.9	0.017
No. of GP apt.	27.9 ± 27.3	15.2 ± 25.4	0.482	22.8 ± 26.9	24.3 ± 29.5	0.058
No. of different drug types	8.5 ± 4.3	9.7 ± 4.6	0.273	9.2 ± 4.5	9.0 ± 4.6	0.035
Time-related variables						
Time since first eligible period (days)	131.3 ± 496.5	377.6 ± 759.1	0.384	544.7 ± 1444.4	223.6 ± 625.4	0.501
No. of prior ARB periods	0.04 ± 0.3	0.1 ± 0.5	0.163	0.1 ± 0.4	0.1 ± 0.4	0.117

Supplementary Table S4. Assessment of balance of variables included in propensity-score model for ARB vs ACEi analysis before and after weighting

Characteristic	**Before propensity-score—weighting**			**After propensity-score—weighting**		
	ACEi *n=96 602*	ARB *n=40 553*	**SMD**	**ACEi** *n=96 602*	**ARB** *n=40 553*	**SMD**
No. of prior ACEi periods	0.1 ± 0.5	0.6 ± 0.7	0.739	0.3 ± 0.8	0.3 ± 0.6	0.053
Calendar year	2007.1 ± 4.0	2007.6 ± 4.1	0.131	2007.9 ± 4.6	2007.3 ± 4.1	0.152

Notes: SMD=standardised mean difference; BP=blood pressure.

Cohort includes 1 randomly selected eligible period per patient in each group

[a] Any diagnosis prior to start of eligible period

[b] Includes diagnosis of: MI at least 2 days prior, angina at least 30 days prior, angioplasty at least 30 days prior, CABG at least 4 years prior

[c] Includes diagnosis of: stroke/TIA

[d] Includes diagnosis of: limb bypass surgery, limb/foot amputation, intermittent claudication

[e] DM prior to start of eligible period

[f] Includes DM with: retinopathy, neuropathy, chronic kidney disease or proteinuria

[g] Within 3 months prior to eligible start date. Antiplatelet agent= clopidogrel/ ticlopidine

[h] Within 6 months prior to eligible start date.

no. (%)=number (percent); CAD=coronary artery disease; MI=myocardial infarction; PAD=peripheral artery disease.

Supplementary Table S5. Medication adherence to assigned exposure group

Years of follow-up	**ACEi patients** *n=96 602*		**ARB patients** *n=40 553*	
	Receiving		**Receiving**	
	ACEi	**ARB**	**ARB**	**ACEi**
1	67347 (69.7)	10805 (11.2)	31661 (78.1)	1039 (2.6)
2	57188 (59.2)	12177 (12.6)	27381 (67.5)	1483 (3.7)
3	48991 (50.7)	12148 (12.6)	23487 (57.9)	1718 (4.2)
4	41583 (43.1)	11523 (11.9)	19950 (49.2)	1828 (4.5)
5.5	31769 (32.9)	10060 (10.4)	15210 (37.5)	1764 (4.4)

Supplementary Table S6. Secondary and other outcomes after propensity-score—weighted analysis using CPRD data

Outcome	**ACEi** *n=96 602*	**ARB** *n=40 553*	**ARB vs ACEi**
	Number (percent)		*Hazard ratio (95% CI)*
Newly diagnosed congestive heart failure	10232 (10.6)	4017 (9.9)	0.99 (0.94, 1.04)
Revascularisation procedures	14132 (14.6)	5250 (13.0)	1.00 (0.96, 1.04)
Loss of GFR or ESKD	4217 (5.2)	2205 (6.1)	1.11 (1.04, 1.19)
ESKD	1460 (1.8)	822 (2.3)	1.06 (0.95, 1.19)
Microvascular complications of diabetes mellitus	2261 (17.4)	757 (14.4)	0.95 (0.85, 1.05)

Notes: ESKD: end-stage kidney disease.

CPRD weighted analysis includes 1 randomly selected eligible period per patient. Propensity-score—weighted with robust standard errors. ARB vs ACEi also adjusted for time since first eligible period, calendar year and number of prior ARB periods.

Loss of GFR or ESKD defined as: 50% reduction in estimated glomerular filtration ratio (eGFR), start of kidney replacement therapy (KRT) or eGFR<15.

ESKD defined as: start of KRT or eGFR<15.

Kidney outcomes only include those subjects who have an eGFR measurement before start of the eligible period but within 6 months and adjusted for baseline serum creatinine.

Microvascular complications of diabetes mellitus outcome only include patients who are diabetic but non-high risk.

Supplementary Table S7. Reason for treatment cessation using trial criteria and propensity-score—weighting for ARB vs ACEi compared to ONTARGET

Reason for cessation	**CPRD**			**ONTARGET**
	ARB *n=40 553*	**ACEi** *n=96 602*	**ARB vs ACEi**	**telmisartan vs ramipril**
	Number (percent)		*Relative risk (95% CI)*	*Relative risk (P value)*
Cough	949 (2.3)	1557 (1.6)	1.29 (1.16, 1.43)	0.26 (<0.001)
Angioedema	37 (0.09)	83 (0.09)	1.14 (0.72, 1.80)	0.4 (0.01)
Hyperkalaemia[a]	2784 (7.8)	5836 (7.4)	1.12 (1.06, 1.18)	
≥30% increase in serum creatinine	7222 (19.8)	12441 (15.2)	1.38 (1.34, 1.43)	1.14 (0.46)[b]

Notes: In CPRD, treatment cessation is defined as the end date of the trial-eligible exposed period included in analysis (i.e., the date prior to a prescription gap of >90 days) and the latest event occurring prior to end of trial-eligible period is counted as the reason for treatment cessation. Multiple reasons that occur on the same day are both counted.

Analysis is adjusted for time since first eligible period, calendar year and number of prior ARB eligible periods.

[a]Defined as potassium >5.5 mmol/l. Analysis out of number of people with non-missing potassium.

[b]Definition of renal impairment as reason for discontinuation in ONTARGET is not stated so results are not directly comparable to CPRD

Kidney outcomes are adjusted for baseline serum creatinine and are out of the number of people with non-missing eGFR in CPRD.

ONTARGET did not present 95% CI.

Supplementary Table S8. Number of events in the primary outcome, its components, and death from any cause for ARB vs ACEi using a propensity-score—matched analysis of patients in CPRD (sensitivity analysis)

Outcome	**CPRD: Propensity-score—matched**			**ONTARGET**
	ACEi *n=15 462*	**ARB** *n=15 462*	**ARB vs ACEi**	**Telmisartan vs Ramipril**
	Number (percent)		*Hazard ratio (95% CI)*	
Primary composite: Death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure	2539 (16.4)	2453 (15.9)	0.97 (0.92, 1.02)	1.01 (0.94, 1.09)
Main secondary outcome: Death from cardiovascular causes, myocardial infarction, or stroke	2234 (14.5)	2173 (14.1)	0.98 (0.92, 1.04)	0.99 (0.91, 1.07)
Myocardial infarction	1806 (11.7)	1721 (11.1)	0.96 (0.90, 1.03)	1.07 (0.94, 1.22)
Stroke	535 (3.5)	591 (3.8)	1.10 (0.98, 1.24)	0.91 (0.79, 1.05)
Hospitalisation for heart failure	542 (3.5)	513 (3.3)	0.94 (0.83, 1.06)	1.12 (0.97, 1.29)
Death from cardiovascular causes	655 (4.2)	649 (4.2)	0.98 (0.88, 1.09)	1.00 (0.89, 1.12)
Death from non-cardiovascular causes	852 (5.5)	856 (5.5)	0.99 (0.90, 1.09)	0.96 (0.83, 1.10)
Death from any cause	1507 (9.8)	1505 (9.7)	0.99 (0.92, 1.06)	0.98 (0.90, 1.07)

Notes: Propensity-score—matched cohort developed using trial-matched ACEi patients 1:1 matched to closest trial-eligible ARB period.
Myocardial infarction and stroke include both fatal and non-fatal events.
ONTARGET results are from published findings.

Supplementary Table S9. Safety outcomes assessed among non-switchers using trial criteria and propensity-score—weighting for ARB vs ACEi (sensitivity analysis)

Safety outcome	**CPRD**			**ONTARGET**
	Reason for treatment cessation			
	ARB	**ACEi**	**ARB vs ACEi**	**telmisartan vs ramipril**
	n=11 856	*n=90 597*		
	Number (percent)		*Relative risk (95% CI)*	*Relative risk (P value)*
Cough	178 (1.5)	1455 (1.6)	0.84 (0.70, 1.01)	0.26 (<0.001)
Angioedema	10 (0.08)	77 (0.08)	0.72 (0.35, 1.48)	0.4 (0.01)
Hyperkalaemia[a]	685 (7.7)	5473 (7.4)	1.06 (0.97, 1.16)	
≥30% increase in serum creatinine	1730 (18.8)	11781 (15.5)	1.25 (1.18, 1.31)	1.14 (0.01)[b]

Notes: In CPRD, treatment cessation is defined as the end date of the trial-eligible exposed period included in analysis (i.e., the date prior to a prescription gap of >90 days) and the latest event occurring prior to end of trial-eligible period is counted as the reason for treatment cessation. Multiple reasons that occur on the same day are both counted.

Reason for treatment cessation represents the main analysis which is compared to ONTARGET and events occurring within 3 months represents the additional analysis exploring safety events which occur within 3 months of the start of eligible period.

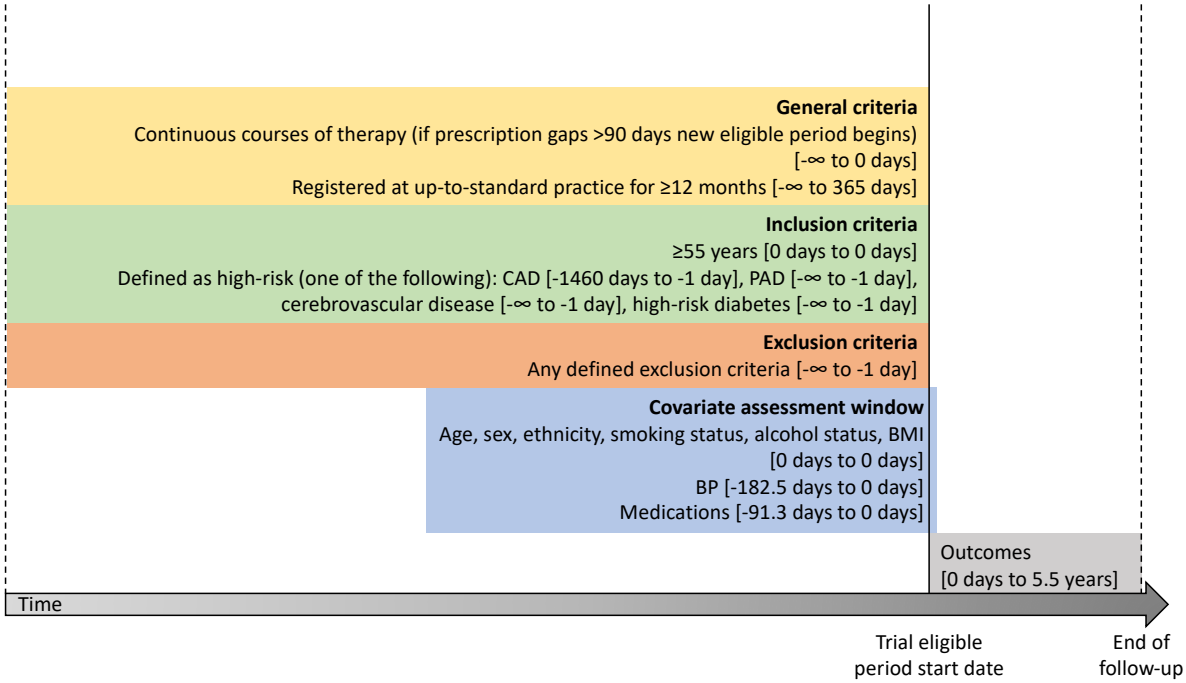
Non-switchers include first trial-eligible period per patient and excludes patients with previous exposure to opposing drug at any time prior to start of included trial-eligible period.

Both analyses are adjusted for number of previous GP appointments within 6 months prior.

[a]Defined as potassium >5.5 mmol/l. Analysis out of number of people with non-missing potassium.

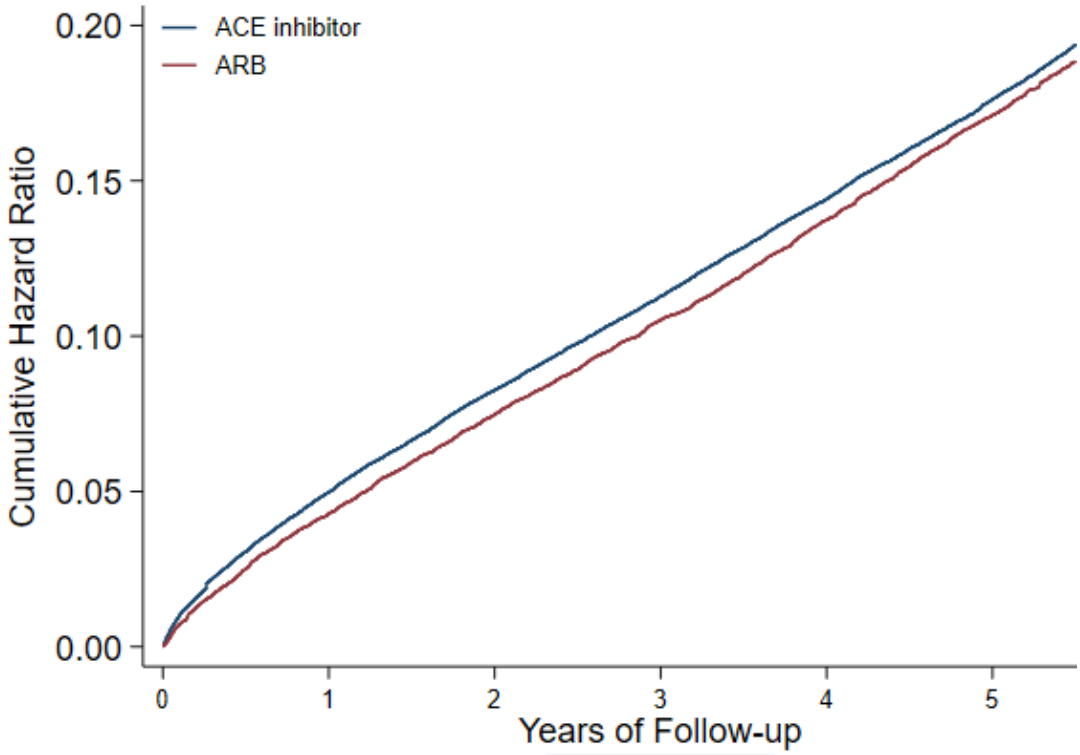
[b]Definition of renal impairment in ONTARGET is not stated so results are not directly comparable to CPRD Kidney outcomes are adjusted for baseline serum creatinine and are out of the number of people with non-missing eGFR in CPRD.

ONTARGET did not present 95% CI.

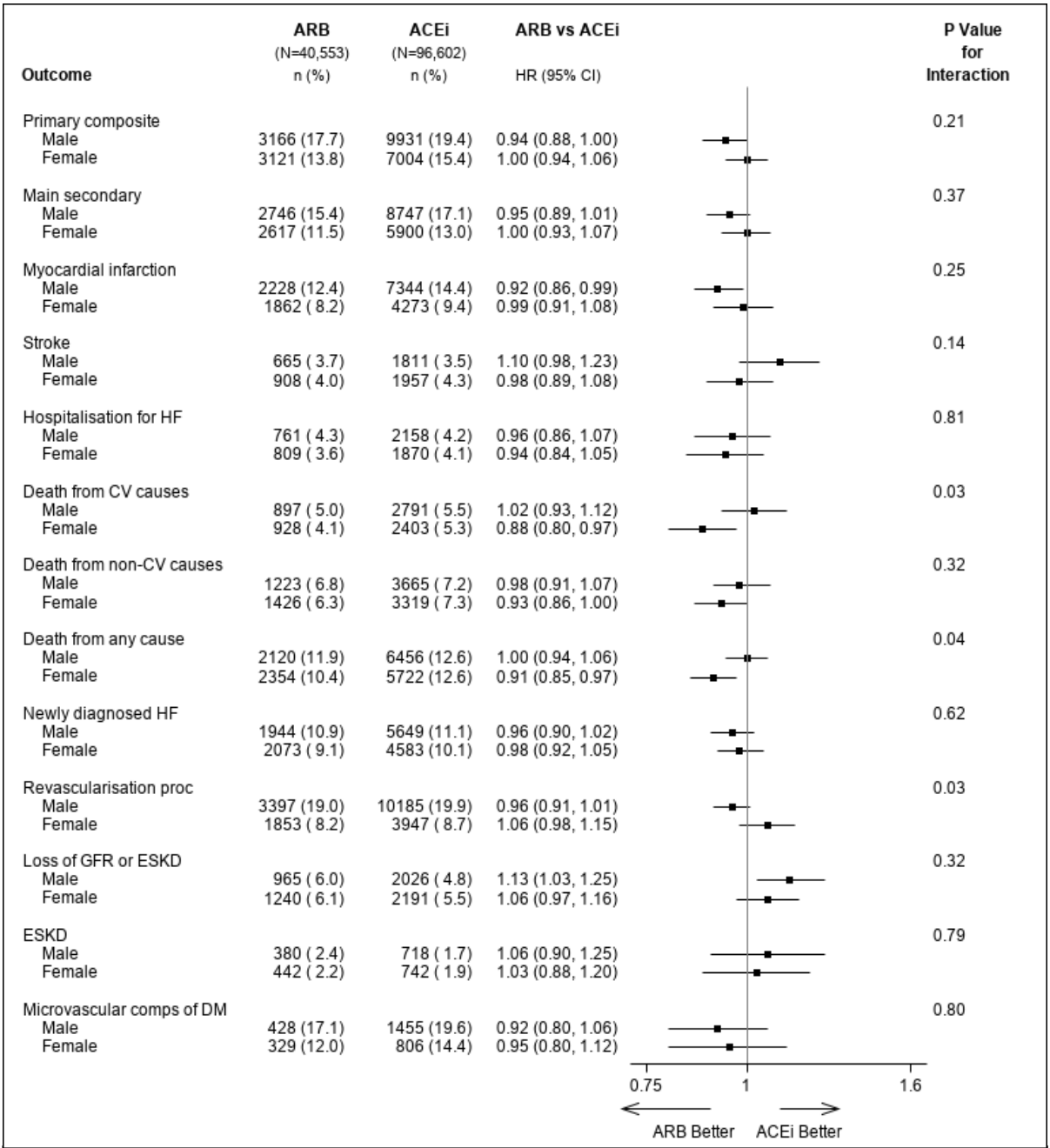


Supplementary Figure S1. Study diagram

End of follow-up was earliest of date of outcome, transferred out of practice date, death date, date of last collection, or 5.5 years from the start of eligible period. Trial eligible periods are defined as exposed periods where all trial criteria are met prior to the start of the exposed period. An exposed period is defined as periods of continuous courses of therapy (<90 days between prescriptions). CAD=coronary artery disease, PAD=peripheral artery disease. Details of how inclusion and exclusion criteria were defined are published previously. An up-to-standard practice is one that meets minimum data quality criteria based on continuity of recording and recorded number of deaths.

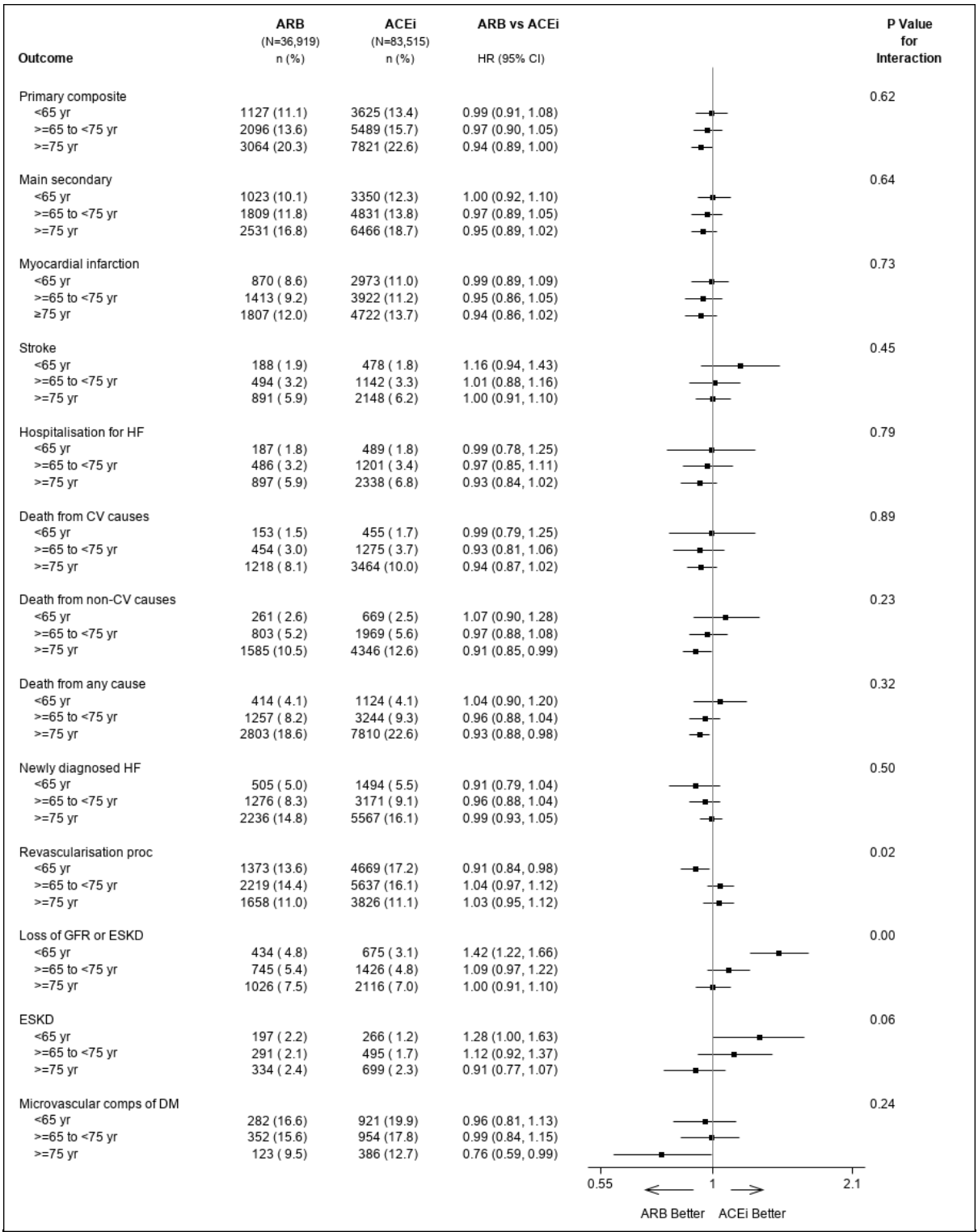


Supplementary Figure S2. Kaplan-Meier curves for the Primary composite outcome for ARB and ACEi users.



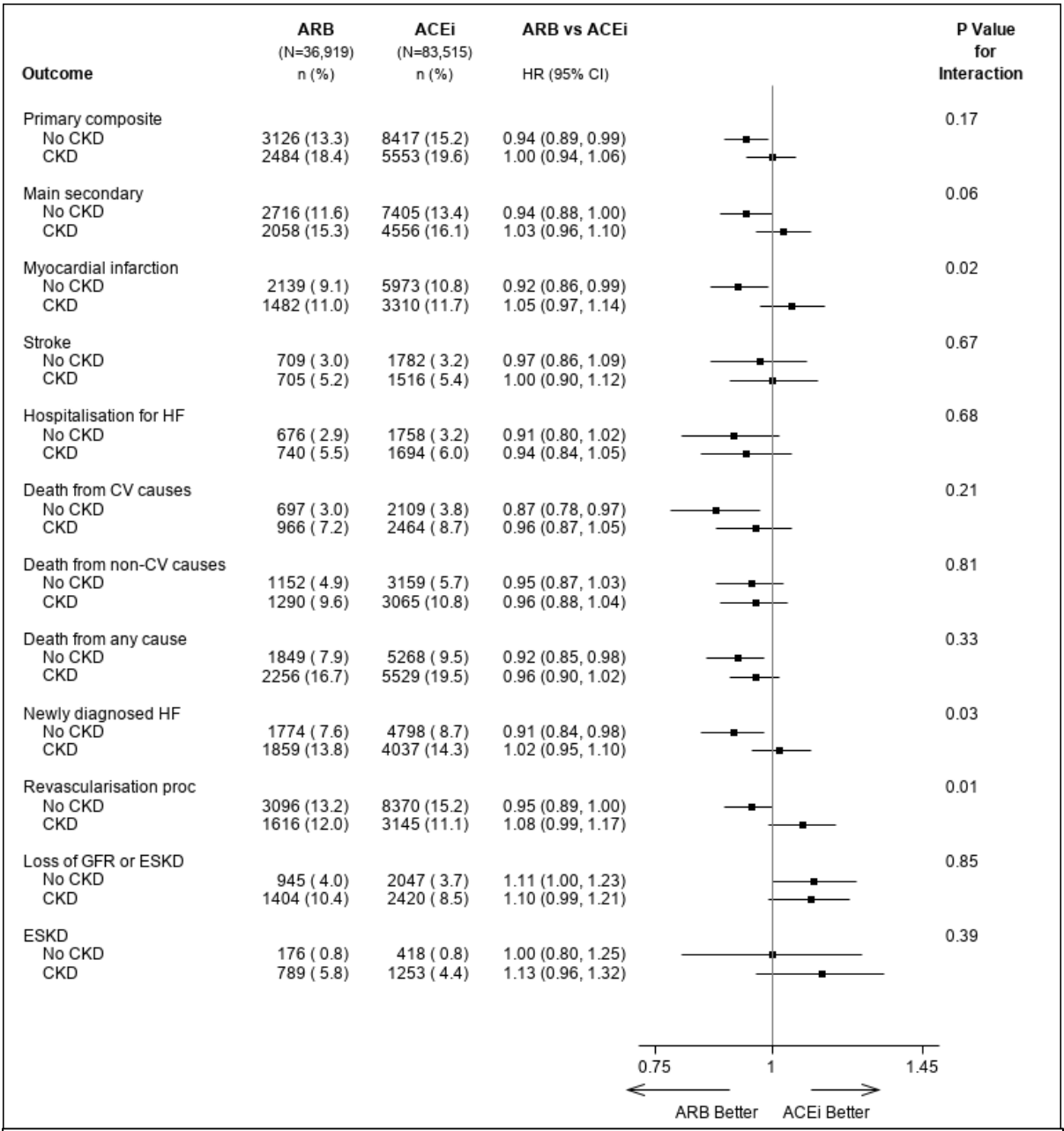
Supplementary Figure S3. Treatment heterogeneity by sex for all outcomes for comparison of ARB vs ACEi.

n (%)= number of events (percent). P-value is the test of interaction between the treatment for each outcome. ESKD: end-stage kidney disease. Analysis is propensity-score—weighted with robust standard errors. Analysis adjusted for number of previous GP appointments and medications within 6 months prior, time since first eligible period and number of prior ARB periods. Loss of GFR or ESKD defined as: 50% reduction in estimated glomerular filtration rate (GFR), start of kidney replacement therapy (KRT) or eGFR<15. ESKD defined as: start of KRT or eGFR<15. Kidney outcomes only include those subjects who have an eGFR measurement before start of the eligible period but within 6 months and adjusted for baseline serum creatinine. Microvascular complications of diabetes mellitus outcome only include patients who are diabetic but non-high risk.



Supplementary Figure S4. Treatment heterogeneity by age group for all outcomes for comparison of ARB vs ACEi.

P-value is the test of interaction between the treatment for each outcome. Analysis is propensity-score—weighted with robust standard errors. Analysis adjusted for number of previous medications within 6 months prior, time since first eligible period, number of prior ARB and ACEi periods, age and DBP. Loss of GFR or ESKD defined as: 50% reduction in GFR, start of KRT or eGFR<15. ESKD defined as: start of KRT or eGFR<15. Kidney outcomes only include those subjects who have an eGFR measurement before start of the eligible period and adjusted for baseline serum creatinine. Microvascular complications of diabetes mellitus outcome only include patients who are diabetic but non-high risk.



Supplementary Figure S5. Treatment heterogeneity by CKD status for all outcomes for comparison of ARB vs ACEi.

CKD: estimated GFR <60 mL/min/1.73m^2; ESKD: end-stage kidney disease. n (%)= number of events (percent). P-value is the test of interaction between the treatment for each outcome. Analysis is propensity-score—weighted with robust standard errors. Analysis adjusted for time since first eligible period. Loss of GFR or ESKD defined as: 50% reduction in estimated glomerular filtration rate (eGFR), start of kidney replacement therapy (KRT) or eGFR<15. ESKD defined as: start of KRT or eGFR<15. Kidney outcomes only include those subjects who have an eGFR measurement before start of the eligible period but within 6 months and adjusted for baseline serum creatinine.

1.3 Appendix 3: Supplementary material from Research paper 3

Supplementary Table S1. Key design aspects of the ONTARGET trial and emulation protocol and deviations from protocol with implementation in CPRD Aurum data

Protocol component	**ONTARGET**	**Trial emulation protocol**	**Implementation in CPRD Aurum**
Eligibility criteria	Patients aged ≥55 years with coronary artery, peripheral artery or cerebrovascular disease or high-risk diabetes with end organ damage recruited up to 2004. No restriction on previous ACEi/ARB use except must be able to discontinue use.	Patients with a prescription for an ACE inhibitor or ARB between 01 January 2001 to 31 July 2019, eligible for HES linkage, aged ≥55 years with coronary artery, peripheral vascular, or cerebrovascular disease or high-risk diabetes.	As in protocol but restricted to patients who were self-reported Black, South Asian or White.
Treatment strategies	Patients entered 3-week single blind run-in period to check compliance then randomised to one of three trial arms: ramipril 10 mg + telmisartan placebo, telmisartan 80 mg + ramipril placebo or ramipril 10 mg + telmisartan 80 mg.	Continuous courses of therapy with treatment gaps of <90 days.	As in protocol.
Assignment procedures	Randomly assigned and received placebo for other drug so unaware which arm assigned to	Based on prescriptions received. Patient can contribute to both exposure groups at different timepoints	As in protocol.
Follow-up period	Follow-up started at randomisation and ended at primary event, death, loss to follow-up or end of study. Close out was planned in July 2007.	Follow-up starts at start of trial-eligible period where exposure period meets trial inclusion/exclusion criteria. Ends at the earliest of: outcome of interest, death, transferred out of practice date, or last data collection from the general practice. If these dates do not occur the patient will be censored after 5.5 years of follow-up	As in protocol.

Supplementary Table S1. Key design aspects of the ONTARGET trial and emulation protocol and deviations from protocol with implementation in CPRD Aurum data

Protocol component	**ONTARGET**	**Trial emulation protocol**	**Implementation in CPRD Aurum**
Outcome	Primary composite of: cardiovascular death, MI, stroke, hospitalisation for heart failure	As in ONTARGET, defined using ICD10, Read codes and death registries from ONS.	As in protocol.
Analysis plan	Primary analysis under time-to-event counting first occurrence of any component of the composite outcome using Cox proportional hazards model. Intention-to-treat as main analysis	Match to trial to obtain trial-analogous cohort then will match trial-eligible exposure groups. Cox proportional hazards model will be used for primary analysis.	Analysis conducted on one randomly selected trial eligible period per patient. Balance of covariates obtained by propensity score weighting for probability of receiving an ACEi and adjusted for any imbalanced variables. Weighting as opposed to matching to increase sample size and diversity of cohort to enable inferences to be extended to underrepresented groups of Black and South Asian individuals. Cox proportional hazards model used for primary analysis.

Supplementary Table S2 List of variables considered and included in propensity-score model

Potential confounders	**Selected into propensity-score model**	**Reason for omitting**
Stroke/TIA	✓	
Peripheral artery disease	✓	
Coronary artery disease	✓	
Diabetes	✓	
High-risk diabetes	✓	
Age (years)	✓	
Sex	✓	
Ethnicity		Stratified variable
BMI	✓	
SBP	✓	
DBP	✓	
Creatinine		19% missing
Cholesterol		25% missing
Index of Multiple Deprivation (IMD)	✓	
Smoke status	✓	
Alcohol use		16% missing
Statin use	✓	
Nitrate use	✓	
Diabetic treatment use	✓	
Diuretic use	✓	
CCB use	✓	
Betablocker use	✓	
Aspirin use	✓	
Antiplatelet use	✓	
Digoxin use		Insufficient number of events
Anticoagulant use	✓	
Alpha-blocker use	✓	
No. of hospital admissions within 6 months prior	✓	
No. of GP appointments within 6 months prior		Variation between treatment groups too extreme to achieve balance for all other variables
Year of start of eligible period	✓	
Time since first eligible period (days)	✓	

Supplementary Table S2 List of variables considered and included in propensity-score model

Potential confounders	Selected into propensity-score model	Reason for omitting
No. of previous ACE inhibitor eligible periods	✓	
No. of previous ARB eligible periods		Variation between treatment groups too extreme to achieve balance for all other variables

Notes: TIA: transient ischaemic attack; BMI: body-mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Variables are measured at start of trial-eligible period or before.

Peripheral artery disease includes limb bypass surgery or angioplasty, limb/foot amputation, or intermittent claudication.

Coronary artery disease includes previous MI, angina, coronary angioplasty, or CABG.

SBP and DBP are measured within 6 months prior to start of trial-eligible period.

Medication use is within 3 months prior to start of trial-eligible period.

SBP and DBP had 22% missing but this variable was included as believed to be an important confounder.

Balance after weighting was assessed for all variables listed including those not included in the propensity-score model but could be assumed to be missing at random. If imbalance remained analysis was adjusted for these variables.

Supplementary Table S3 Baseline characteristics and standardised differences of trial-eligible patients after applying trial criteria included in propensity-score—weighted analysis before and after weighting

Characteristic	Before weighting		After weighting		
	ARB N=181,019	ACEi N=452,886	ARB N=181,019	ACEi N=452,886	SMD
Age – year	71.5 ± 9.2	70.9 ± 9.5	71.1 ± 9.4	71.1 ± 9.4	0.001
Systolic BP – mmHg	142.9 ± 19.8	143.0 ± 20.2	143.4 ± 20.2	143.1 ± 20.1	0.017
Diastolic BP - mmHg	78.3 ± 10.8	78.9 ± 11.0	78.9 ± 11.1	8.7 ± 11.0	0.013
Body-mass index	29.3 ± 5.8	28.8 ± 5.8	29.0 ± 5.8	28.9 ± 5.9	0.013
Creatinine – μmol/l	94.0 ± 29.6	92.9 ± 27.4	94.9 ± 29.7	92.7 ± 27.5	0.076
Cholesterol – mmol/l	4.7 ± 1.2	4.8 ± 1.2	4.7 ± 1.2	4.8 ± 1.2	0.051
Female sex – %	99532 (55.0)	212623 (47.0)	314752 (49.1)	311570 (49.2)	0.003
Ethnic group – %					
Black	6613 (3.7)	12407 (2.7)	22587 (3.5)	17810 (2.8)	0.041
South Asian	11934 (6.6)	21403 (4.7)	42378 (6.6)	30265 (4.8)	0.079
White	162472 (89.8)	419076 (92.5)	576017 (89.9)	584768 (92.4)	0.089
Clinical history – %					
CAD[a]	125818 (69.5)	321035 (70.9)	451577(70.5)	446152 (70.5)	0.001
Cerebrovascular disease[b]	19045 (10.5)	47980 (10.6)	67462 (10.5)	66870 (10.6)	0.002
PAD[c]	16848 (9.3)	41651 (9.2)	58979 (9.2)	58404 (9.2)	0.001
Diabetes	113559 (62.7)	272390 (60.2)	391349 (61.1)	385284 (60.9)	0.004
High-risk diabetes[d]	91826 (50.7)	212396 (46.9)	309940 (48.4)	304068 (48.1)	0.006
Smoking status – %					
Non-smoker	50809 (28.1)	118150 (26.1)	169719 (26.5)	168657 (26.7)	0.004
Current smoker	41345 (22.8)	123576 (27.3)	166024 (25.9)	164622 (26.0)	0.003
Past smoker	88865 (49.1)	211160 (46.6)	305238 (47.6)	299565 (47.3)	0.006
Alcohol drinker – %	112005 (61.9)	282967 (62.5)	402476 (62.8)	392517 (62.0)	0.016
Medication[e] – %					
Alpha-blocker	21559 (11.9)	41810 (9.2)	64464 (10.1)	63459 (10.0)	0.001
Oral anticoagulant agent	16288 (9.0)	38918 (8.6)	57216 (8.9)	55331 (8.7)	0.006
Antiplatelet agent	15685 (8.7)	44603 (9.9)	61748 (9.6)	60197 (9.5)	0.004
Aspirin	59571 (32.9)	161515 (35.7)	223027 (34.8)	220643 (34.9)	0.001
Beta-blocker	56986 (31.5)	147999 (32.7)	208661 (32.6)	204751 (32.4)	0.004
Calcium-channel blocker	63025 (34.8)	146287 (32.3)	214476 (33.5)	209533 (33.1)	0.007
Digoxin	6468 (3.6)	18611 (4.1)	23823 (3.7)	25826 (4.1)	0.019
Diuretics	76969 (42.5)	174522 (38.5)	256204 (40.0)	251353 (39.7)	0.005
Diabetic treatment	46536 (25.7)	112718 (24.9)	162502 (25.4)	159158 (25.2)	0.005
Nitrates	16552 (9.1)	48261 (10.7)	66087 (10.3)	64751 (10.2)	0.003
Statins	96660 (53.4)	246879 (54.3)	347138 (54.2)	341870 (54.0)	0.003

Supplementary Table S3 Baseline characteristics and standardised differences of trial-eligible patients after applying trial criteria included in propensity-score—weighted analysis before and after weighting

Characteristic	Before weighting		After weighting		
	ARB N=181,019	**ACEi** N=452,886	**ARB** N=181,019	**ACEi** N=452,886	**SMD**
Time-related variables					
Time since trial-eligible period	614.0 ± 1175.8	352.9 ± 899.2	434.9 ± 1038.0	426.3 ± 995.6	0.008
Number of prior ARB eligible periods	2.1 ± 3.9	0.2 ± 1.2	1.8 ± 3.4	0.2 ± 1.3	0.533
Number of prior ACEi eligible periods	1.5 ± 2.7	2.1 ± 3.8	2.1 ± 4.0	1.9 ± 3.6	0.051
Calendar year	2011 ± 5.3	2010 ± 5.3	2010 ± 5.3	2010 ± 5.3	0.006
Healthcare utilisation[f]					
Number of GP appointments	5.4 ± 23.7	10.7 ± 33.6	5.7 ± 24.4	10.6 ± 33.3	0.170
Number of hospital admissions	2.9 ± 10.7	3.4 ± 11.3	3.5 ± 12.0	3.3 ± 11.1	0.018
Index of multiple deprivation - %					
1 (least)	37323 (20.6)	85981 (19.0)	124429 (19.4)	123048 (19.4)	0.000
2	38296 (21.2)	92378 (20.4)	131458 (20.5)	130428 (20.6)	0.003
3	35644 (19.7)	88479 (19.5)	125756 (19.6)	123878 (19.6)	0.001
4	35949 (19.9)	93148 (20.6)	131220 (20.5)	128968 (20.4)	0.002
5 (most)	33807 (18.7)	92900 (20.5)	128118 (20.0)	126522 (20.0)	0.000

N= number of patients; no. (%)=number (percent); SMD=standardised mean difference; BP= blood pressure; CAD=coronary artery disease; PAD=peripheral artery disease; CKD=chronic kidney disease (eGFR<60ml/min/1.73m^2)

One third of ONTARGET participants received both ramipril plus telmisartan.

[a] Includes diagnosis of: MI at least 2 days prior, angina at least 30 days prior, angioplasty at least 30 days prior, CABG at least 4 years prior

[b] Includes diagnosis of: stroke/TIA

[c] Includes diagnosis of: limb bypass surgery, limb/foot amputation, intermittent claudication

[d] Includes DM with: retinopathy, neuropathy, chronic kidney disease, proteinuria or other complication

[e] Within 3 months prior to eligible start date. Antiplatelet agent= clopidogrel/ticlopidine

[f] Within 6 months prior to eligible start date.

Supplementary Table S4 Baseline characteristics and standardised differences of trial-eligible Black patients after applying trial criteria included in propensity-score—weighted analysis before and after weighting

Characteristic	Black ethnic group				
	Before weighting		After weighting		
	ARB N=12,407	ACEi N=6,613	ARB N=12,407	ACEi N=6,613	SMD
Age – year	68.8 ± 8.9	68.4 ± 8.9	68.4 ± 9.0	68.6 ± 8.9	0.030
Systolic BP – mmHg	144.3 ± 19.1	144.0 ± 18.9	144.7 ± 19.5	144.0 ± 18.8	0.036
Diastolic BP - mmHg	80.0 ± 10.8	80.5 ± 10.7	80.8 ± 11.7	80.3 ± 10.6	0.047
Body-mass index	30.6 ± 5.9	29.8 ± 5.7	30.1 ± 5.8	30.0 ± 5.7	0.020
Creatinine – µmol/l	98.8 ± 32.3	96.7 ± 29.0	99.9 ± 32.9	96.5 ± 29.2	0.110
Cholesterol – mmol/l	4.7 ± 1.1	4.7 ± 1.2	4.7 ± 1.1	4.7 ± 1.2	0.060
Female sex – %	3865 (58.5)	6277 (50.6)	11717 (51.9)	9498 (53.3)	0.029
Clinical history – %					
CAD[a]	4316 (65.3)	8368 (67.5)	144799 (65.5)	11934 (67.0)	0.031
Cerebrovascular disease[b]	650 (9.8)	1254 (10.1)	2213 (9.8)	1799 (10.1)	0.010
PAD[c]	608 (9.2)	1097 (8.8)	2044 (9.1)	1574 (8.8)	0.007
Diabetes	5176 (78.3)	9774 (78.8)	17387 (77.0)	14131 (79.3)	0.057
High-risk diabetes[d]	3950 (59.7)	7190 (58.0)	9349 (41.4)	7765 (43.6)	0.045
Smoking status – %					
Non-smoker	2716 (41.1)	4980 (40.1)	8734 (38.7)	7286 (40.9)	0.046
Current smoker	1292 (19.5)	2965 (23.9)	5103 (22.6)	4010 (22.5)	0.002
Past smoker	2605 (39.4)	4462 (36.0)	8751 (38.7)	6514 (36.6)	0.045
Alcohol drinker – %	2945 (44.5)	5759 (46.4)	10336 (45.8)	8111 (45.5)	0.004
Medication[e] – %					
Alpha-blocker	1243 (18.8)	1735 (14.0)	3649 (16.2)	2740 (15.4)	0.021
Oral anticoagulant agent	238 (3.6)	421 (3.4)	808 (3.5)	614 (3.5)	0.007
Antiplatelet agent	371 (5.6)	676 (5.5)	1324 (5.9)	956 (5.4)	0.021
Aspirin	1804 (27.3)	3352 (27.0)	6315 (28.0)	4786 (26.9)	0.024
Beta-blocker	1468 (22.2)	2612 (21.1)	5131 (22.7)	3743 (21.0)	0.041
Calcium-channel blocker	3363 (50.9)	5940 (47.9)	11025 (48.8)	8750 (49.1)	0.006
Digoxin	72 (1.1)	114 (0.9)	268 (1.2)	160 (0.9)	0.028
Diuretics	2758 (41.7)	4465 (36.0)	8805 (39.0)	6686 (37.5)	0.030
Diabetic treatment	2771 (41.9)	5354 (43.2)	9349 (41.4)	7765 (43.6)	0.045
Nitrates	340 (5.1)	626 (5.1)	1286 (5.7)	869 (4.9)	0.036
Statins	3018 (45.6)	5734 (46.2)	10350 (45.8)	8289 (46.5)	0.014
Time-related variables					

Supplementary Table S4 Baseline characteristics and standardised differences of trial-eligible Black patients after applying trial criteria included in propensity-score—weighted analysis before and after weighting

Characteristic	**Black ethnic group**				
	Before weighting		**After weighting**		
	ARB N=12,407	**ACEi** N=6,613	**ARB** N=12,407	**ACEi** N=6,613	**SMD**
Time since trial-eligible period	538.8 ± 1069.8	341.0 ± 871.5	274.9 ± 899.7	430.1 ± 983.4	0.057
Number of prior ARB eligible periods	2.1 ± 3.8	0.3 ± 1.5	1.8 ± 3.4	0.4 ± 1.6	0.475
Number of prior ACEi eligible periods	1.4 ± 2.6	1.9 ± 3.5	2.0 ± 4.0	1.9 ± 3.2	0.090
Calendar year	2012 ± 5.3	2011 ± 5.3	2011 ± 5.3	2011 ± 5.3	0.037
Healthcare utilisation[f]					
Number of GP appointments	7.0 ± 26.8	12.6 ± 35.2	7.2 ± 26.9	12.3 ± 34.9	0.163
Number of hospital admissions	3.1 ± 12.6	2.9 ± 11.1	3.6 ± 13.5	2.8 ± 10.8	0.070
Index of multiple deprivation - %					
1 (least)	170 (2.6)	338 (2.7)	546 (2.4)	496 (2.8)	0.023
2	416 (6.3)	713 (5.8)	1339 (5.9)	1034 (5.8)	0.005
3	1017 (15.4)	1808 (14.6)	3402 (15.1)	2646 (14.9)	0.006
4	2355 (35.6)	4513 (36.4)	8066 (35.7)	6513 (36.6)	0.018
5 (most)	2655 (40.2)	5035 (40.6)	9235 (49.9)	7122 (40.0)	0.018

N= number of patients; no. (%)=number (percent); SMD=standardised mean difference; BP= blood pressure; CAD=coronary artery disease; PAD=peripheral artery disease; CKD=chronic kidney disease (eGFR<60ml/min/1.73m^2)

One third of ONTARGET participants received both ramipril plus telmisartan.

[a] Includes diagnosis of: MI at least 2 days prior, angina at least 30 days prior, angioplasty at least 30 days prior, CABG at least 4 years prior

[b] Includes diagnosis of: stroke/TIA

[c] Includes diagnosis of: limb bypass surgery, limb/foot amputation, intermittent claudication

[d] Includes DM with: retinopathy, neuropathy, chronic kidney disease, proteinuria or other complication

[e] Within 3 months prior to eligible start date. Antiplatelet agent= clopidogrel/ticlopidine

[f] Within 6 months prior to eligible start date.

Supplementary Table S5 Baseline characteristics and standardised differences of trial-eligible South Asian patients after applying trial criteria included in propensity-score—weighted analysis before and after weighting

Characteristic	South Asian ethnic group				
	Before weighting		After weighting		
	ARB N=21,403	ACEi N=11,934	ARB N=21,403	ACEi N=11,934	SMD
Age – year	67.7 ± 8.5	67.0 ± 8.6	67.3 ± 8.6	67.3 ± 8.5	0.002
Systolic BP – mmHg	139.9 ± 18.9	140.7 ± 19.2	140.1 ± 19.2	140.8 ± 19.2	0.038
Diastolic BP - mmHg	77.9 ± 10.6	78.7 ± 10.8	78.4 ± 10.9	78.5 ± 10.8	0.008
Body-mass index	28.2 ± 5.0	27.6 ± 5.0	27.8 ± 4.9	27.8 ± 5.1	0.002
Creatinine – µmol/l	91.2 ± 31.4	88.9 ± 28.1	92.6 ± 31.7	88.7 ± 28.4	0.131
Cholesterol – mmol/l	4.4 ± 1.1	4.5 ± 1.2	4.4 ± 1.1	4.5 ± 1.2	0.082
Female sex – %	6238 (52.3)	9699 (45.3)	19189 (45.3)	14542 (48.1)	0.055
Clinical history – %					
CAD[a]	7958 (66.7)	14599 (68.2)	28605 (67.5)	20507 (67.8)	0.005
Cerebrovascular disease[b]	1143 (9.6)	2123 (9.9)	4000 (9.4)	2969 (9.8)	0.013
PAD[c]	1091 (9.1)	1931 (9.0)	3873 (9.1)	2729 (9.0)	0.004
Diabetes	9527 (79.8)	16907 (79.0)	33565 (79.2)	24029 (79.4)	0.005
High-risk diabetes[d]	6802 (57.0)	11596 (54.2)	23446 (55.3)	16773 (55.4)	0.002
Smoking status – %					
Non-smoker	5314 (44.5)	9151 (42.8)	17712 (41.8)	13166 (43.5)	0.032
Current smoker	2389 (20.0)	5061 (23.7)	9905 (23.4)	6765 (22.4)	0.024
Past smoker	4231 (35.5)	7191 (33.6)	14761 (34.8)	10334 (34.2)	0.014
Alcohol drinker – %	3660 (30.7)	6809 (31.8)	13679 (32.3)	9463 (31.3)	0.022
Medication[e] – %					
Alpha-blocker	1450 (12.2)	1971 (9.2)	4403 (10.4)	3038 (10.0)	0.012
Oral anticoagulant agent	395 (3.3)	598 (2.8)	1342 (3.2)	864 (2.9)	0.018
Antiplatelet agent	1176 (9.9)	2054 (9.6)	4643 (11.0)	2819 (9.3)	0.054
Aspirin	4353 (36.5)	8020 (37.5)	16373 (38.6)	11151 (36.9)	0.037
Beta-blocker	3360 (28.2)	5833 (27.3)	12519 (29.5)	8160 (30.0)	0.057
Calcium-channel blocker	4266 (35.8)	6820 (31.9)	14328 (33.8)	10000 (33.0)	0.016
Digoxin	124 (1.0)	245 (1.1)	477 (1.1)	345 (1.1)	0.001
Diuretics	3815 (32.0)	5610 (26.2)	12663 (29.9)	8312 (27.5)	0.053
Diabetic treatment	5828 (48.8)	10444 (48.8)	20760 (49.0)	14823 (49.0)	0.000
Nitrates	1265 (10.6)	2324 (10.9)	4976 (11.7)	3185 (10.5)	0.039
Statins	7289 (61.1)	12826 (59.9)	26284 (62.0)	18125 (59.9)	0.044
Time-related variables					

Supplementary Table S5 Baseline characteristics and standardised differences of trial-eligible South Asian patients after applying trial criteria included in propensity-score—weighted analysis before and after weighting

Characteristic	South Asian ethnic group				
	Before weighting		After weighting		
	ARB N=21,403	ACEi N=11,934	ARB N=21,403	ACEi N=11,934	SMD
Time since trial-eligible period	539.9 ± 1079.0	323.9 ± 852.3	359.6 ± 898.8	411.2 ± 966.7	0.053
Number of prior ARB eligible periods	1.8 ± 3.4	0.3 ± 1.2	1.6 ± 3.1	0.3 ± 1.4	0.470
Number of prior ACEi eligible periods	1.3 ± 2.3	1.7 ± 3.1	1.8 ± 3.4	1.6 ± 2.9	0.078
Calendar year	2012 ± 5.1	2011 ± 5.2	2011 ± 5.2	2011 ± 5.2	0.013
Healthcare utilisation[f]					
Number of GP appointments	6.7 ± 26.7	11.5 ± 34.3	6.9 ± 26.9	11.3 ± 34.2	0.143
Number of hospital admissions	3.1 ± 11.9	3.2 ± 12.2	3.8 ± 13.8	3.1 ± 12.0	0.061
Index of multiple deprivation - %					
1 (least)	1314 (11.0)	2091 (9.8)	4355 (10.3)	3042 (10.1)	0.008
2	1815 (15.2)	2822 (13.2)	6099 (14.4)	4072 (13.5)	0.027
3	2601 (21.8)	4357 (20.4)	9078 (21.4)	6217 (20.5)	0.022
4	3272 (27.4)	6172 (28.8)	11902 (28.1)	8676 (28.7)	0.013
5 (most)	2931 (24.6)	5961 (27.9)	10943 (25.8)	8259 (27.3)	0.033

N= number of patients; no. (%)=number (percent); SMD=standardised mean difference; BP= blood pressure; CAD=coronary artery disease; PAD=peripheral artery disease; CKD=chronic kidney disease (eGFR<60ml/min/1.73m^2)

One third of ONTARGET participants received both ramipril plus telmisartan.

[a] Includes diagnosis of: MI at least 2 days prior, angina at least 30 days prior, angioplasty at least 30 days prior, CABG at least 4 years prior

[b] Includes diagnosis of: stroke/TIA

[c] Includes diagnosis of: limb bypass surgery, limb/foot amputation, intermittent claudication

[d] Includes DM with: retinopathy, neuropathy, chronic kidney disease, proteinuria or other complication

[e] Within 3 months prior to eligible start date. Antiplatelet agent= clopidogrel/ticlopidine

[f] Within 6 months prior to eligible start date.

Supplementary Table S6 Baseline characteristics and standardised differences of trial-eligible White patients after applying trial criteria included in propensity-score—weighted analysis before and after weighting

Characteristic	White ethnic group				
	Before weighting		After weighting		
	ARB N=162,472	ACEi N=419,076	ARB N=162,472	ACEi N=419,076	SMD
Age – year	71.9 ± 9.2	71.2 ± 9.5	71.5 ± 9.4	71.4 ± 9.4	0.013
Systolic BP – mmHg	143.1 ± 19.9	143.1 ± 20.2	143.6 ± 20.3	143.1 ± 20.2	0.022
Diastolic BP - mmHg	78.3 ± 10.8	78.8 ± 11.0	78.8 ± 11.1	78.7 ± 11.0	0.013
Body-mass index	29.3 ± 5.9	28.8 ± 5.9	29.0 ± 5.8	28.9 ± 5.9	0.016
Creatinine – µmol/l	94.0 ± 29.4	93.0 ± 27.2	94.9 ± 29.4	92.8 ± 27.4	0.073
Cholesterol – mmol/l	4.8 ± 1.2	4.8 ± 1.2	4.8 ± 1.2	4.8 ± 1.2	0.043
Female sex – %	89429 (55.0)	196647 (46.9)	283846 (49.3)	287530 (49.2)	0.002
Clinical history – %					
CAD[a]	113544 (69.9)	298068 (71.1)	408172 (70.9)	413712 (70.8)	0.002
Cerebrovascular disease[b]	17252 (10.6)	44603 (10.6)	61249 (10.6)	62102 (10.6)	0.000
PAD[c]	15149 (9.3)	38623 (9.2)	53062 (9.2)	54102 (9.3)	0.001
Diabetes	98856 (60.8)	245709 (58.6)	340397 (59.1)	347123 (59.4)	0.005
High-risk diabetes[d]	81074 (49.9)	193610 (46.2)	273336 (47.5)	276765 (47.3)	0.002
Smoking status – %					
Non-smoker	42779 (26.3)	104019 (24.8)	143273 (24.9)	148206 (25.3)	0.011
Current smoker	37664 (23.2)	115550 (27.6)	151017 (26.2)	153946 (26.3)	0.002
Past smoker	82029 (50.5)	199507 (47.6)	281727 (48.9)	282716 (48.4)	0.011
Alcohol drinker – %	105400 (64.9)	270399 (64.5)	378461 (65.7)	374943 (64.1)	0.032
Medication[e] – %					
Alpha-blocker	18866 (11.6)	38104 (9.1)	56411 (9.8)	57681 (9.9)	0.002
Oral anticoagulant agent	15655 (9.6)	37899 (9.0)	55065 (9.6)	53853 (9.2)	0.012
Antiplatelet agent	14138 (8.7)	41873 (10.0)	55780 (9.7)	56422 (9.7)	0.001
Aspirin	53414 (32.9)	150143 (35.8)	200339 (34.8)	204706 (35.0)	0.005
Beta-blocker	52158 (32.1)	139554 (33.3)	191011 (33.2)	192847 (33.0)	0.004
Calcium-channel blocker	55396 (34.1)	133527 (31.9)	189123 (32.8)	190783 (32.6)	0.004
Digoxin	6272 (3.9)	18252 (4.4)	23078 (4.0)	25321 (4.3)	0.016
Diuretics	70396 (43.3)	164447 (39.2)	234736 (40.8)	236355 (40.4)	0.007
Diabetic treatment	37937 (23.4)	96920 (23.1)	132393 (23.0)	136570 (23.4)	0.009
Nitrates	14947 (9.2)	45311 (10.8)	59825 (10.4)	60696 (10.4)	0.000
Statins	86353 (53.2)	227319 (54.2)	310503 (53.9)	315456 (54.0)	0.001
Time-related variables					

Supplementary Table S6 Baseline characteristics and standardised differences of trial-eligible White patients after applying trial criteria included in propensity-score—weighted analysis before and after weighting

Characteristic	White ethnic group				
	Before weighting		After weighting		
	ARB N=162,472	ACEi N=419,076	ARB N=162,472	ACEi N=419,076	SMD
Time since trial-eligible period	622.5 ± 1186.4	354.7 ± 902.3	442.8 ± 1043.5	427.1 ± 997.5	0.015
Number of prior ARB eligible periods	2.2 ± 3.9	0.2 ± 1.1	1.8 ± 3.4	0.2 ± 1.3	0.538
Number of prior ACEi eligible periods	1.5 ± 2.8	2.1 ± 3.9	2.1 ± 4.0	2.0 ± 3.6	0.051
Calendar year	2011 ± 5.3	2010 ± 5.3	2010 ± 5.3	2010 ± 5.3	0.001
Healthcare utilisation[f]					
Number of GP appointments	5.3 ± 23.4	10.7 ± 33.4	5.6 ± 24.1	10.6 ± 33.3	0.173
Number of hospital admissions	2.9 ± 10.6	3.4 ± 11.2	3.5 ± 11.8	3.3 ± 11.1	0.013
Index of multiple deprivation - %					
1 (least)	35839 (22.1)	83552 (19.9)	119528 (20.8)	119511 (20.4)	0.008
2	36065 (22.2)	88843 (21.2)	124021 (21.5)	125322 (21.4)	0.002
3	32026 (19.7)	82314 (19.6)	113276 (19.7)	115015 (19.7)	0.000
4	30322 (18.7)	82463 (19.7)	111252 (19.3)	113778 (19.5)	0.004
5 (most)	28220 (17.4)	81904 (19.5)	107940 (18.7)	111142 (19.0)	0.007

N= number of patients; no. (%)=number (percent); SMD=standardised mean difference; BP= blood pressure; CAD=coronary artery disease; PAD=peripheral artery disease; CKD=chronic kidney disease (eGFR<60ml/min/1.73m^2)

One third of ONTARGET participants received both ramipril plus telmisartan.

[a] Includes diagnosis of: MI at least 2 days prior, angina at least 30 days prior, angioplasty at least 30 days prior, CABG at least 4 years prior

[b] Includes diagnosis of: stroke/TIA

[c] Includes diagnosis of: limb bypass surgery, limb/foot amputation, intermittent claudication

[d] Includes DM with: retinopathy, neuropathy, chronic kidney disease, proteinuria or other complication

[e] Within 3 months prior to eligible start date. Antiplatelet agent= clopidogrel/ticlopidine

[f] Within 6 months prior to eligible start date.

Supplementary Table S7 Number of events for the primary outcome, its components, main secondary outcome and death from any cause for ARB vs ACEi using a propensity-score—weighted and adjusted analysis of trial-eligible patients in CPRD Aurum compared to ONTARGET

Outcome	**CPRD**			**ONTARGET**
	ARB (N=181,019)	**ACEi** (N=452,886)	**ARB vs ACEi** (N=633,905)	**Telmisartan vs ramipril** (N=17,118)
	Number (percent)		*Hazard ratio (95% CI)*	
Primary composite	27789 (15.4)	73914 (16.3)	1.00 (0.98, 1.02)	1.01 (0.94, 1.09)
Main secondary outcome	18982 (10.5)	52480 (11.6)	0.99 (0.97, 1.01)	0.99 (0.91, 1.07)
Myocardial infarction	11665 (6.4)	33780 (7.5)	0.99 (0.97, 1.02)	1.07 (0.94, 1.22)
Stroke	8209 (4.5)	20996 (4.6)	0.99 (0.96, 1.02)	0.91 (0.79, 1.05)
Hospitalisation for heart failure	12028 (6.6)	29444 (6.5)	1.03 (1.01, 1.06)	1.12 (0.97, 1.29)
Death from cardiovascular causes	11109 (6.1)	31304 (6.9)	0.93 (0.91, 0.96)	1.00 (0.89, 1.12)
Death from non-cardiovascular causes	17191 (9.5)	48200 (10.6)	0.90 (0.88, 0.92)	0.96 (0.83, 1.10)
Death from any cause	28300 (15.6)	79504 (17.6)	0.91 (0.90, 0.93)	0.98 (0.90, 1.07)

Primary composite outcome: death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure.

Main secondary outcome: death from cardiovascular causes, myocardial infarction, or stroke.

CPRD weighted analysis includes 1 randomly selected trial-eligible period per patient. Propensity-score—weighted with robust standard errors. Analysis adjusted for number of GP appointments 6 months prior and number of prior ARB periods.

Myocardial infarction and stroke include both fatal and non-fatal events.

ONTARGET results are from published findings.

Supplementary Table S8 Treatment effect heterogeneity for the primary and secondary outcomes by ethnicity for ARB vs ACEi using a propensity-score—weighted and adjusted analysis of trial-eligible patients in CPRD Aurum with an on-treatment approach.

Outcome	**Ethnic group**			**P value for interaction**
	Black (N=19,020)	**South Asian** (N=33,337)	**White** (N=581,548)	
	Hazard ratio (95% CI)			
Primary composite	1.05 (0.95, 1.16)	0.97 (0.90, 1.04)	0.98 (0.96, 1.00)	0.380
Main secondary outcome	1.04 (0.91, 1.17)	0.99 (0.91, 1.07)	0.98 (0.95, 1.00)	0.627
Myocardial infarction	1.11 (0.92, 1.33)	0.99 (0.89, 1.09)	0.98 (0.95, 1.01)	0.426
Stroke	1.00 (0.85, 1.18)	0.96 (0.84, 1.10)	0.98 (0.95, 1.01)	0.912
Hospitalisation for heart failure	1.07 (0.92, 1.24)	0.97 (0.87, 1.08)	0.99 (0.97, 1.02)	0.568
Death from cardiovascular causes	1.10 (0.92, 1.31)	0.93 (0.82, 1.05)	0.89 (0.86, 0.91)	0.051
Death from non-cardiovascular causes	0.93 (0.81, 1.06)	0.87 (0.78, 0.97)	0.87 (0.85, 0.89)	0.679
Death from any cause	1.00 (0.89, 1.11)	0.89 (0.82, 0.97)	0.88 (0.86, 0.89)	0.083
Loss of GFR or ESKD	1.11 (0.96, 1.28)	1.02 (0.91, 1.14)	1.03 (1.00, 1.06)	0.586
ESKD	1.05 (0.84, 1.32)	0.97 (0.79, 1.18)	0.97 (0.92, 1.02)	0.762
Doubling of serum creatinine	1.16 (0.97, 1.39)	1.00 (0.87, 1.15)	1.04 (1.00, 1.08)	0.417

Primary composite outcome: death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure. Main secondary outcome: death from cardiovascular causes, myocardial infarction, or stroke. Loss of GFR or ESKD defined as: 50% reduction in estimated glomerular filtration ratio (eGFR), start of kidney replacement therapy (KRT) or eGFR<15ml/min/1.73m^2. ESKD defined as: start of KRT or eGFR<15ml/min/1.73m^2.

CPRD weighted analysis includes 1 randomly selected trial-eligible period per patient. Propensity-score—weighted with robust standard errors. Analysis adjusted for number of GP appointments 6 months prior, baseline creatinine and number of prior ARB periods.

Myocardial infarction and stroke include both fatal and non-fatal events.

Under on-treatment analysis, patients were additionally censored at the end of an eligible period, if they switched treatment or started dual therapy. This was denoted as date of last drug and patients were censored at this date +60 days.

Supplementary Table S9. Table of trial diagnoses (inclusion criteria) and interpretation in CPRD.

ONTARGET/TRANSCEND	**CPRD Aurum (HES + ONS Linked)** **READ or ICD 10 code for:**
Aged ≥55 years	Aged ≥55 years prior to prescription of drug
Coronary artery disease	
Previous myocardial infarction (>2 days post uncomplicated MI)	MI at least 2 days prior to prescription of drug
Stable angina or unstable angina >30 days before informed consent and with documented evidence of multivessel coronary artery disease	Angina/stable angina/unstable angina at least 30 days before prescription of drug and previous coronary artery disease diagnosis
Multi-vessel PTCA >30 days before informed consent	Read, ICD-10 or OPCS code for coronary angioplasty at least 30 days before prescription of drug
Multi-vessel CABG surgery >4 years before informed consent, or with recurrent angina following surgery	Read, ICD-10 or OPCS code for CABG at least 4 years before prescription of drug or with angina after CABG
Peripheral artery disease	
Previous limb bypass surgery or angioplasty	Read, ICD-10 or OPCS code for limb bypass surgery or angioplasty
Previous limb or foot amputation	Read, ICD-10 or OPCS code for limb/foot amputation
Intermittent claudication, with ankle:arm BP ratio <=0.80 on at least 1 side	Intermittent claudication
Significant peripheral artery stenosis (>50%) documented by angiography or non-invasive test	Not applicable
Cerebrovascular disease	
Previous stroke	Stroke before prescription of drug
Transient ischemic attacks >7 days and <1 year before informed consent	Transient ischemic attacks before prescription of drug
High-risk diabetes with evidence of end-organ damage	

High-risk diabetes	Specific codes for diabetes with retinopathy, neuropathy, chronic kidney disease or proteinuria before prescription of drug or diabetes defined by diabetes codes or diabetes therapy with CKD defined as eGFR<60 or proteinuria defined as ACR>3

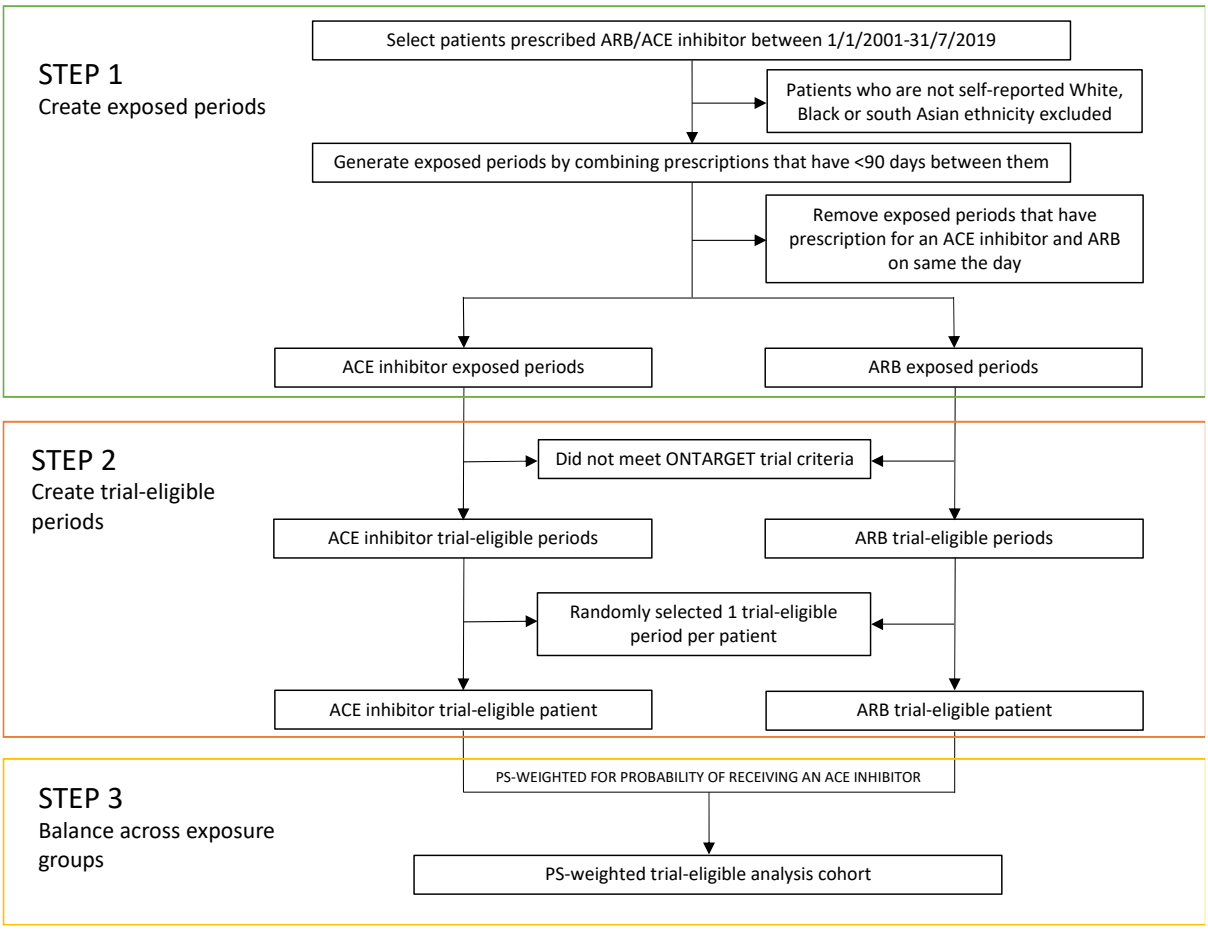
Notes: Where dates are used as criteria dates from both CPRD and HES will be used, but if available HES will be preferred.

Supplementary Table S10. Table of trial exclusion criteria and interpretation in CPRD.

ONTARGET/TRANSCEND exclusion criteria	**CPRD Aurum (HES + ONS Linked) READ or ICD 10 code (prior to eligible for inclusion date, unless otherwise specified) for:**
Inability to discontinue ACE inhibitors or ARB	Not applicable
Known hypersensitivity or intolerance to ACE inhibitors or ARB	Not applicable
Symptomatic congestive heart failure	Heart failure or left ventricular dysfunction
Hemodynamically significant primary valvular or outflow tract obstruction	Aortic or pulmonary stenosis or previous valve replacement
Constrictive pericarditis	Constrictive pericarditis
Complex congenital heart disease	Congenital heart disease
Syncopal episodes of unknown etiology <3 months before informed consent	Not applicable
Planned cardiac surgery or PTCA <3 months of informed consent	Not applicable
Uncontrolled hypertension on treatment (e.g. BP >160/100 mm Hg)	Last recorded BP >160/100 mmHg for patients on treatment with other antihypertensives prior to ACEI/ARB initiation
Heart transplant recipient	Read, ICD-10 or OPCS code for heart transplant recipient
Stroke due to subarachnoid haemorrhage	Previous cerebral haemorrhage
Significant renal artery disease	Codes for renal artery stenosis or renal artery atherosclerosis; or serum creatinine concentration above 265µmol/L
Hepatic dysfunction	Cirrhosis or other documented liver disease
Uncorrected volume or sodium depletion	Not applicable
Primary hyperaldosteronism	Primary hyperaldosteronism/ Conn's syndrome

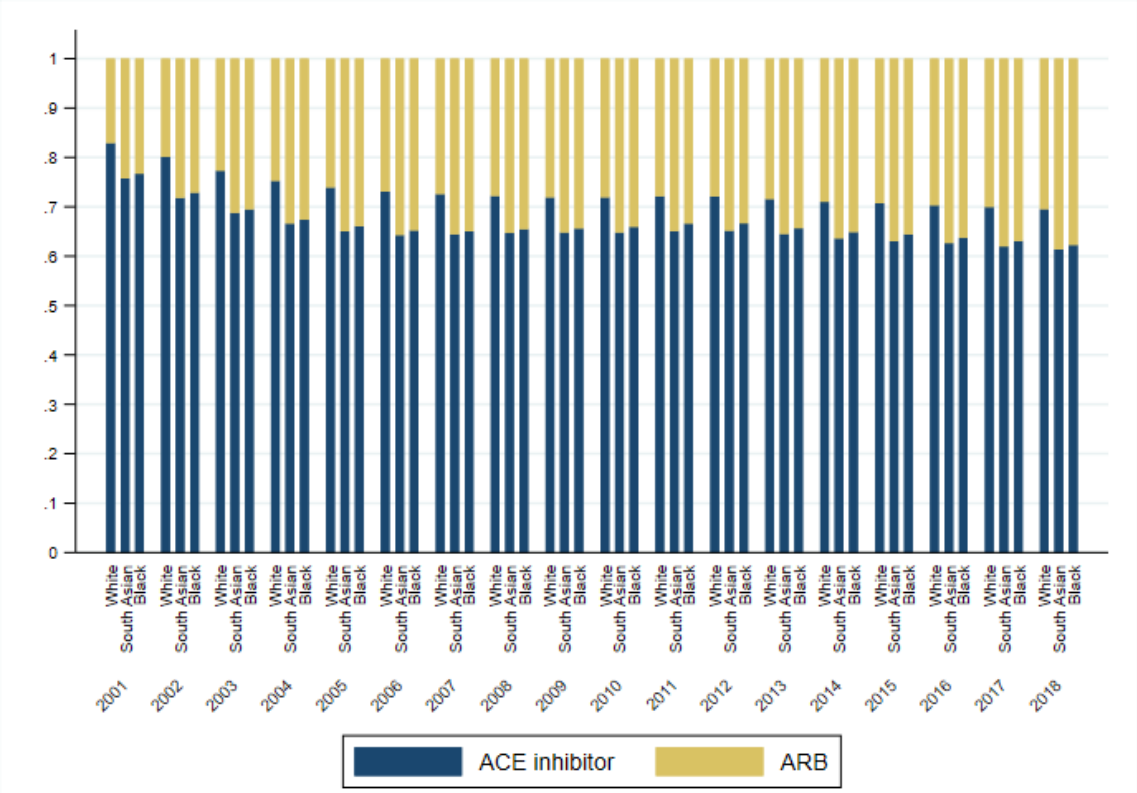
Hereditary fructose intolerance	Hereditary fructose intolerance
Other major noncardiac illness expected to reduce life expectancy or interfere with study participation	Recorded solid organ or metastatic malignancy within the last 5 years, drug, alcohol dependence or mental illness.
Simultaneously taking another experimental drug	Not applicable
Significant disability precluding regular follow-up visits	Not applicable
Unable or unwilling to provide written informed consent	Not applicable
Elevated potassium above 5.5mmol/L	Elevated potassium above 5.5mmol/L
Hypotension	SBP <90 mm Hg

Notes: Where dates are used as criteria dates from both CPRD and HES will be used, but if available HES will be preferred. Not applicable used when anticipated there will be extensive missing data or risk of misclassification.

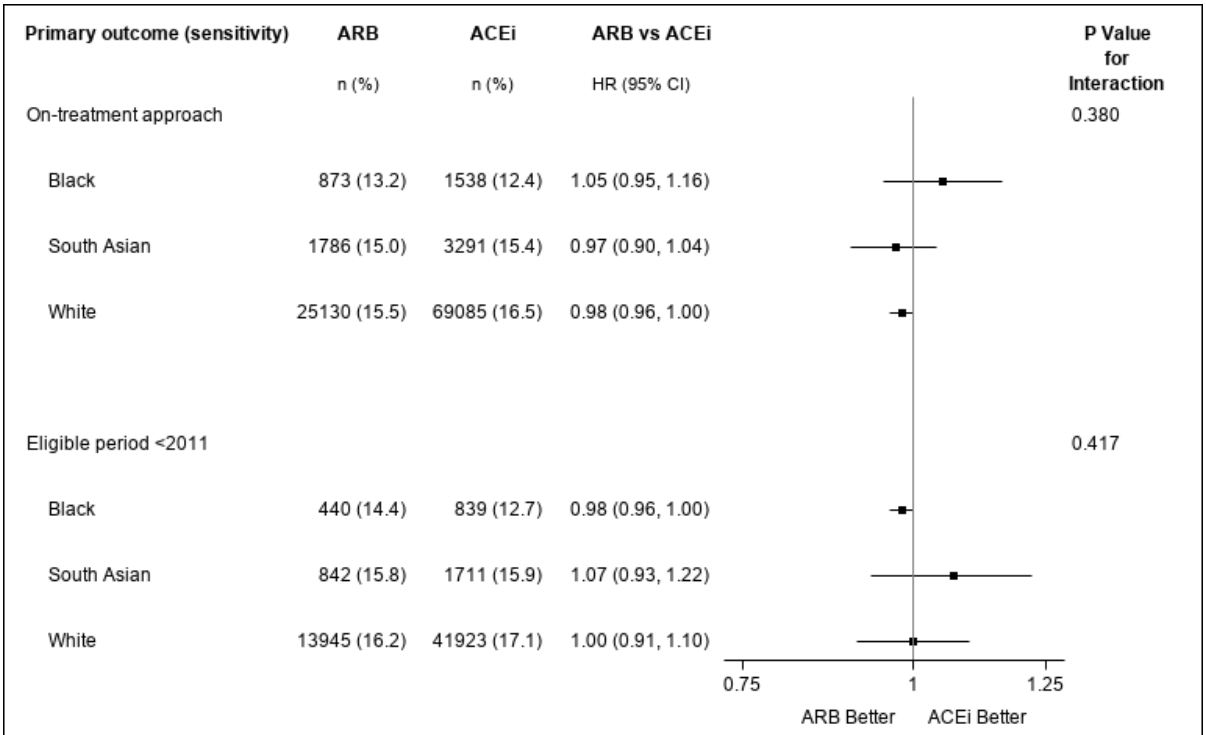


Supplementary Figure S1. Steps to define analysis cohort.

Rx=prescription

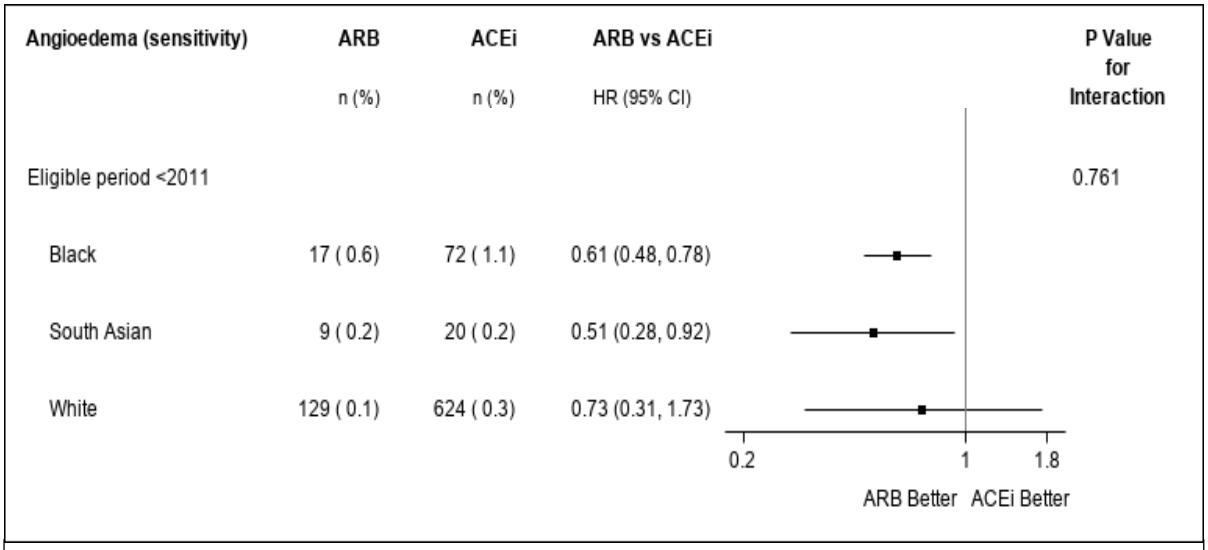


Supplementary Figure S2. Proportion of ARB and ACE inhibitor prescriptions prescribed each year out of total number prescribed within each ethnic group.



Supplementary Figure S3. Forest plot of sensitivity analysis for ARB vs ACE inhibitor use for primary composite outcome.

Primary composite outcome is cardiovascular related death, myocardial infarction, stroke, or hospitalisation for heart failure. On-treatment approach censored at treatment discontinuation (i.e., treatment gap of >90 days), switch treatment or start of dual use +60 days. Eligible period <2011 is analysis restricted to start of trial-eligible periods prior to 2011. P value is test for interaction between treatment and ethnicity. Analysis is propensity-score—weighted and adjusted analysis using Cox proportional hazards model adjusted for number of prior ARB periods, number of GP appointments and baseline creatinine.



Supplementary Figure S4. Forest plot of sensitivity analysis for ARB vs ACE inhibitor use for the risk of developing angioedema.

Angioedema that occurs during maximum follow-up of 5.5 years included. On-treatment approach censored at treatment discontinuation (i.e., treatment gap of >90 days), switch treatment or start of dual use +60 days. Eligible period <2011 is analysis restricted to start of trial-eligible periods prior to 2011. P value is test for interaction between treatment and ethnicity. Analysis is propensity-score—weighted and adjusted analysis using Cox proportional hazards model adjusted for number of prior ARB periods, number of GP appointments and baseline creatinine.

1.4 Appendix 4: Supplementary material from Research paper 4

Supplementary Table S1. Table of key design aspects of the ONTARGET trial dual analysis and emulation in CPRD Aurum

Protocol component	**ONTARGET**	**Trial emulation protocol**	**Implementation in CPRD Aurum**
Eligibility criteria	Patients aged ≥55 years with coronary artery, peripheral artery or cerebrovascular disease or high-risk diabetes with end organ damage recruited up to 2004. No restriction on previous ACEi/ARB use except must be able to discontinue use.	Patients with a prescription for an ACE inhibitor or ARB between 01 January 2001 to 31 July 2019, eligible for HES linkage, aged ≥55 years with coronary artery, peripheral vascular, or cerebrovascular disease or high-risk diabetes.	As in protocol.
Treatment strategies	Patients entered 3-week single blind run-in period to check compliance then randomised to one of three trial arms: ramipril 10 mg + telmisartan placebo, telmisartan 80 mg + ramipril placebo or ramipril 10 mg + telmisartan 80 mg.	Continuous courses of therapy with treatment gaps of <90 days. Dual therapy users defined as patients with overlapping prescriptions who received a subsequent prescription for the 1st agent after the 2nd prescription for the 2nd agent.	As in protocol with condition added for dual therapy definition that subsequent prescription for 1st agent must occur within 90 days of 2nd prescription for 2nd agent to avoid capturing treatment switchers, i.e., patients with overlapping prescriptions who received a subsequent prescription for the 1st agent with 90 days of the 2nd prescription for the 2nd agent.
Assignment procedures	Randomly assigned and received placebo for other drug so unaware which arm assigned to	Based on prescriptions received. Patient could contribute to both exposure groups at different timepoints	As in protocol.
Follow-up period	Follow-up started at randomisation and ended at primary event, death, loss to follow-up or end of study.	Follow-up started at start of trial-eligible period where exposure period met trial inclusion/exclusion criteria. For dual users follow-up	As in protocol but for dual users follow-up started at date meets criteria for dual user, i.e., the date of the 2nd prescription for the

Supplementary Table S1. Table of key design aspects of the ONTARGET trial dual analysis and emulation in CPRD Aurum

Protocol component	**ONTARGET**	**Trial emulation protocol**	**Implementation in CPRD Aurum**
	Close out was planned in July 2007.	started at date of 1st prescription for 2nd agent. Ended at the earliest of: outcome of interest, death, transferred out of practice date, or last data collection from the general practice. If these dates did not occur the patient was censored after 5.5 years of follow-up	1st agent, conditional on meeting the trial criteria. Impact of this choice of start of follow-up assessed in sensitivity analysis.
Outcome	Primary composite of: cardiovascular death, MI, stroke, hospitalisation for heart failure	As in ONTARGET, defined using ICD10, Read codes and death registries from ONS.	As in protocol.
Analysis plan	Primary analysis under time-to-event counting first occurrence of any component of the composite outcome using Cox proportional hazards model. Intention-to-treat as main analysis	Match to trial to obtain trial-analogous cohort then will match trial-eligible exposure groups. Cox proportional hazards model used for primary analysis.	Analysis conducted on one randomly selected trial eligible period per patient. Balance of covariates obtained by propensity score weighting for probability of receiving an ACEi and adjusted for any imbalanced variables. Weighting as opposed to matching to increase sample size and methods trialled and led to comparable results in replication of single therapy analysis. Cox proportional hazards model used for primary analysis.

Supplementary Table S2. List of variables considered and included in propensity-score model

Potential confounders	**Selected into propensity-score model**	**Reason for omitting**
Stroke/TIA	✓	
Peripheral artery disease	✓	
Coronary artery disease	✓	
Diabetes	✓	
High-risk diabetes	✓	
Age (years)	✓	
Sex	✓	
Ethnicity	✓	
BMI	✓	7.6% missing
SBP	✓	22.5% missing
DBP	✓	22.5% missing
Creatinine	✓	19.5% missing
Index of Multiple Deprivation (IMD)	✓	0.1% missing
Smoke status	✓	2.7% missing
Alcohol use		16.9% missing
Statin use	✓	
Nitrate use	✓	
Diabetic treatment use	✓	
Diuretic use	✓	
CCB use	✓	
Betablocker use	✓	
Aspirin use	✓	
Antiplatelet use		Insufficient number of events
Digoxin use		Insufficient number of events
Anticoagulant use	✓	
Alpha-blocker use		Insufficient number of events
No. of hospital admissions within 6 months prior	✓	
No. of GP appointments within 6 months prior		Variation between treatment groups too extreme to achieve balance for all other variables
Year of start of eligible period	✓	
Time since first eligible period (days)	✓	

Notes: TIA: transient ischaemic attack; BMI: body-mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Variables are measured at start of trial-eligible period or before.

Peripheral artery disease includes limb bypass surgery or angioplasty, limb/foot amputation, or intermittent claudication.

Coronary artery disease includes previous MI, angina, coronary angioplasty, or CABG.

SBP and DBP are measured within 6 months prior to start of trial-eligible period.

Medication use is within 3 months prior to start of trial-eligible period.

SBP and DBP had 22.5% missing but this variable was included as believed to be an important confounder. Similarly, baseline creatinine had 19.5% missing but due to the known differences in prescribing based on baseline creatinine this variable was also included in the model.

Balance after weighting was assessed for all variables listed including those not included in the propensity-score model but could be assumed to be missing at random. If imbalance remained analysis was adjusted for these variables.

Supplementary Table S3. Baseline characteristics and standardised differences of trial-eligible patients after applying trial criteria included in propensity-score—weighted analysis before and after weighting using operational definition of dual user

Characteristic	Before weighting		After weighting		
	Dual therapy N=20,580	ACEi N=402,026	Dual therapy N=20,580	ACEi N=402,026	SMD
Age – year	70.3 ± 8.7	71.1 ± 9.5	71.5 ± 9.9	71.1 ± 9.5	0.046
Systolic BP – mmHg	148.4 ± 20.2	142.7 ± 19.9	143.1 ± 19.5	142.9 ± 20.0	0.010
Diastolic BP - mmHg	79.4 ± 10.8	78.6 ± 11.0	79.1 ± 11.1	78.7 ± 10.9	0.037
Body-mass index	30.0 ± 6.0	28.8 ± 5.8	28.5 ± 5.8	28.9 ± 5.9	0.054
Creatinine – µmol/l	98.9 ± 31.3	92.8 ± 27.4	92.6 ± 27.3	93.1 ± 27.6	0.016
Female sex – %	10749 (52.2)	189148 (47.1)	232063 (50.7)	199959 (47.3)	0.068
Ethnic group – %					
Black	1166 (5.7)	10987 (2.7)	12418 (2.7)	12145 (2.9)	0.010
South Asian	1905 (9.3)	18683 (4.7)	22121 (4.8)	20576 (4.9)	0.002
White	17102 (83.1)	367488 (91.4)	417390 (91.3)	384578 (91.0)	0.009
Other	407 (2.0)	4868 (1.2)	5439 (1.2)	5268 (1.3)	0.005
Clinical history – %					
CAD[a]	12107 (58.8)	280945 (69.9)	313956 (68.6)	293038 (69.4)	0.015
Cerebrovascular disease[b]	2159 (10.5)	42052 (10.5)	48597 (10.6)	44212 (10.5)	0.006
PAD[c]	1974 (9.6)	36447 (9.1)	37667 (8.2)	38416 (9.1)	0.030
Diabetes	14783 (71.8)	256991 (63.9)	290116 (63.4)	271706 (64.3)	0.018
High-risk diabetes[d]	13879 (67.4)	198040 (49.3)	236740 (51.8)	211881 (50.1)	0.032
Smoking status – %					
Non-smoker	6198 (30.1)	99061 (24.6)	122672 (26.8)	105288 (24.9)	0.043
Current smoker	4949 (24.1)	108955 (27.1)	116474 (25.5)	113873 (27.0)	0.034
Past smoker	9433 (45.8)	194010 (48.3)	218222 (47.7)	203406 (48.1)	0.009
Alcohol status – %					
Non-drinker	4023 (19.6)	60117 (15.0)	77165 (16.9)	64108 (15.2)	0.046
Current drinker	11853 (57.6)	256124 (63.7)	273403 (59.8)	268233 (63.5)	0.076
Past drinker	2936 (14.3)	57448 (14.3)	61868 (13.5)	60348 (14.3)	0.022
Missing	1768 (8.6)	28337 (7.1)	44932 (9.8)	29878 (7.1)	0.099
Medication[e] – %					
Alpha-blocker	3872 (18.8)	38168 (9.5)	71454 (15.6)	40412 (9.6)	0.183
Oral anticoagulant agent	1169 (5.7)	35582 (8.9)	43658 (9.6)	36778 (8.7)	0.029
Antiplatelet agent	1652 (8.0)	39000 (9.7)	75538 (16.5)	40192 (9.5)	0.209
Aspirin	8580 (41.7)	142816 (35.5)	175405 (38.4)	151363 (35.8)	0.052
Beta-blocker	6955 (33.8)	130831 (32.5)	166030 (36.3)	137776 (32.6)	0.078
Calcium-channel blocker	8860 (43.1)	132710 (33.0)	143287 (31.3)	141510 (33.5)	0.046
Digoxin	575 (2.8)	16556 (4.1)	22398 (4.9)	17253 (4.1)	0.040

Supplementary Table S3. Baseline characteristics and standardised differences of trial-eligible patients after applying trial criteria included in propensity-score—weighted analysis before and after weighting using operational definition of dual user

Characteristic	Before weighting		After weighting		
	Dual therapy N=20,580	**ACEi** N=402,026	**Dual therapy** N=20,580	**ACEi** N=402,026	**SMD**
Diuretics	10380 (50.4)	154743 (38.5)	181614 (39.7)	165087 (39.1)	0.013
Diabetic treatment	8468 (41.2)	106401 (26.5)	114983 (25.1)	114778 (27.2)	0.046
Nitrates	1809 (8.8)	42369 (10.5)	56651 (12.4)	44187 (10.5)	0.061
Statins	12611 (61.3)	223841 (55.7)	254551 (55.7)	236374 (55.9)	0.006
Time-related variables					
Time since trial-eligible period	332.7 ± 793.7	357.8 ± 896.0	352.2 ± 935.4	356.5 ± 891.2	0.005
Calendar year	2008 ± 4.2	2011 ± 5.2	2011 ± 4.7	2011 ± 5.2	0.014
Healthcare utilisation[f]					
Number of GP appointments	0.9 ± 3.8	11.4 ± 35.3	2.4 ± 7.3	11.4 ± 35.2	0358
Number of hospital admissions	0.5 ± 3.4	3.6 ± 11.7	7.6 ± 19.6	3.4 ± 11.4	0.484
Index of multiple deprivation - %					
1 (least)	3852 (18.7)	76303 (19.0)	95712 (20.9)	80167 (19.0)	0.049
2	4094 (19.9)	81884 (20.4)	89210 (19.5)	85976 (20.4)	0.021
3	4191 (20.4)	78730 (19.6)	91060 (19.9)	82911 (19.6)	0.007
4	4365 (21.2)	83030 (20.7)	92643 (20.3)	87375 (20.7)	0.010
5 (most)	4078 (19.8)	82079 (20.4)	88743 (19.4)	86138 (20.4)	0.025

N= number of patients; no. (%)=number (percent); SMD=standardised mean difference; BP= blood pressure; CAD=coronary artery disease; PAD=peripheral artery disease; CKD=chronic kidney disease (eGFR<60ml/min/1.73m^2)

One third of ONTARGET participants received both ramipril plus telmisartan.

[a] Includes diagnosis of: MI at least 2 days prior, angina at least 30 days prior, angioplasty at least 30 days prior, CABG at least 4 years prior

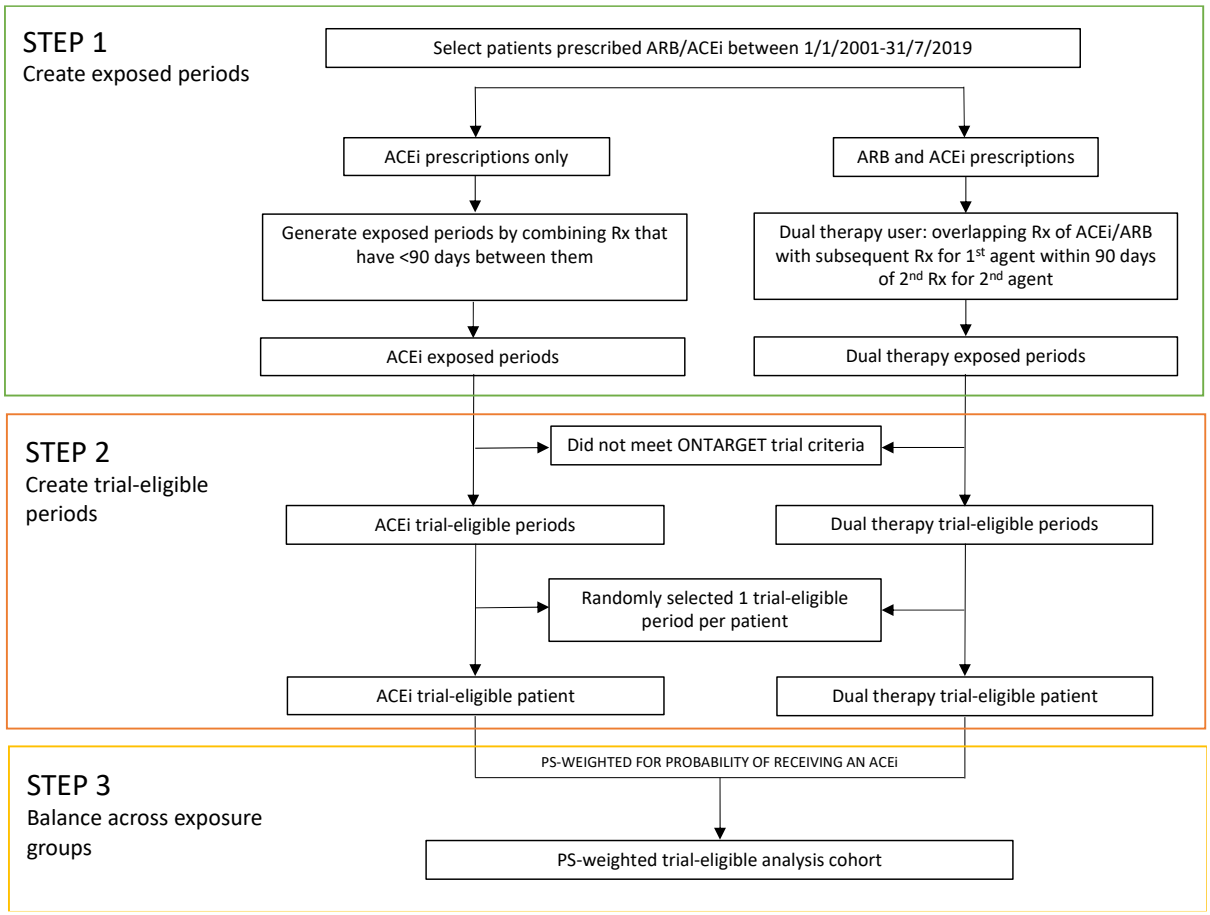
[b] Includes diagnosis of: stroke/TIA

[c] Includes diagnosis of: limb bypass surgery, limb/foot amputation, intermittent claudication

[d] Includes DM with: retinopathy, neuropathy, chronic kidney disease, proteinuria or other complication

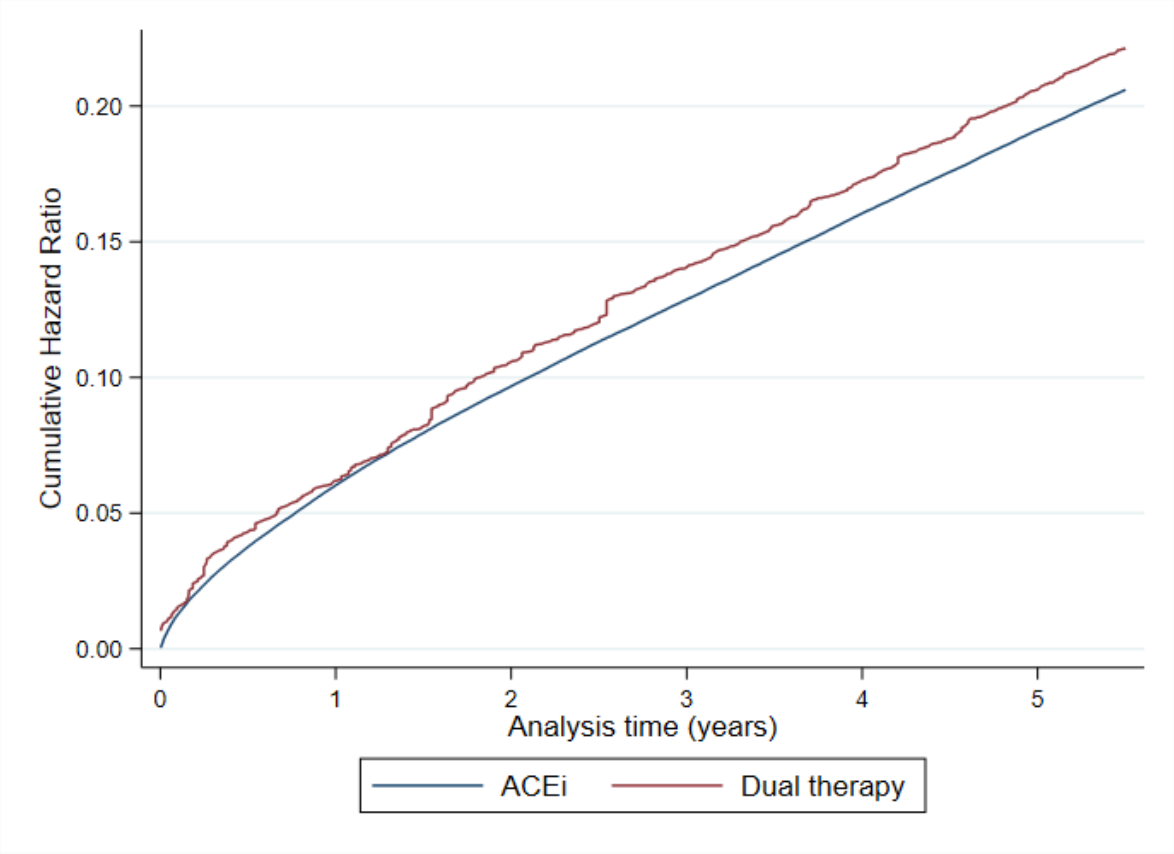
[e] Within 3 months prior to eligible start date. Antiplatelet agent= clopidogrel/ticlopidine

[f] Within 6 months prior to eligible start date.



Supplementary Figure S1. Steps to define analysis cohort.

Rx=prescription



Supplementary Figure S2. Kaplan-Meier curves for the primary composite outcome for dual therapy vs ACEi using the operational definition of a dual user

1.5 Appendix 5: Supplementary material from SIDIAP analysis

INCLUSIONS ICD-10CM			
code	**Description**	**Group**	**Subgroup**
I20*	Angina	CAD	Angina
I21*	Acute myocardial infarction	CAD	MI
I22	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	CAD	MI
I22.0	Subsequent ST elevation (STEMI) myocardial infarction of anterior wall	CAD	MI
I22.1	Subsequent ST elevation (STEMI) myocardial infarction of inferior wall	CAD	MI
I22.8	Subsequent ST elevation (STEMI) myocardial infarction of other sites	CAD	MI
I22.9	Subsequent ST elevation (STEMI) myocardial infarction of unspecified site	CAD	MI
I23	Certain current complications following acute myocardial infarction	CAD	MI
I23.0	Haemopericardium as current complication following acute myocardial infarction	CAD	MI
I23.1	Atrial septal defect as current complication following acute myocardial infarction	CAD	MI
I23.2	Ventricular septal defect as current complication following acute myocardial infarction	CAD	MI
I23.3	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction	CAD	MI
I23.4	Rupture of chordae tendineae as current complication following acute myocardial infarction	CAD	MI
I23.5	Rupture of papillary muscle as current complication following acute myocardial infarction	CAD	MI
I23.6	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction	CAD	MI
I23.8	Other current complications following acute myocardial infarction	CAD	MI
I24	Other acute ischaemic heart diseases	CAD	CAD
I24.0	Coronary thrombosis not resulting in myocardial infarction	CAD	CAD
I24.1	Dressler syndrome	CAD	CAD
I24.8	Other forms of acute ischaemic heart disease	CAD	CAD
I24.9	Acute ischaemic heart disease, unspecified	CAD	CAD
I25	Chronic ischemic heart disease	CAD	CAD
I25.1*	Atherosclerotic heart disease of native coronary artery	CAD	CAD
I25.2	Old myocardial infarction	CAD	MI
I25.3	Aneurysm of heart	CAD	CAD
I25.4*	Coronary artery aneurysm and dissection	CAD	CAD
I25.5	Ischemic cardiomyopathy	CAD	CAD
I25.6	Silent myocardial ischaemia	CAD	MI
I25.7	Atherosclerosis of coronary artery bypass graft and coronary artery of transplanted heart with angina pectoris	CAD	CABG
I25.70*	Atherosclerosis of coronary artery bypass graft unspecified, with other forms of angina pectoris	CAD	CABG
I25.71*	Atherosclerosis of autologous vein coronary artery bypass graft with angina pectoris	CAD	CABG
I25.72*	Atherosclerosis of autologous artery coronary artery bypass graft with angina pectoris	CAD	CABG
I25.73*	Atherosclerosis of nonautologous biological coronary artery bypass graft with unstable pectoris	CAD	CABG

INCLUSIONS ICD-10CM			
code	**Description**	**Group**	**Subgroup**
I25.76*	Atherosclerosis of bypass graft of coronary artery of transplanted heart with angina pectoris	CAD	CABG
I25.79*	Atherosclerosis of other coronary artery bypass graft with angina pectoris	CAD	CABG
I25.8*	Other forms of chronic ischemic heart disease	CAD	CAD
I25.9	Chronic ischemic heart disease, unspecified	CAD	CAD
T82.21*	Mechanical complication of coronary artery bypass graft	CAD	CABG
T82.7*	Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts	CAD	CABG
T82.8*	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	CAD	CABG
T82.9*	Unspecified complication of cardiac and vascular prosthetic device, implant and graft	CAD	CABG
Z95.5	Presence of coronary angioplasty implant and graft	CAD	Angioplasty
Y83.5	Amputation of limb(s)	PAD	limb or foot amputation
I70.2*	atherosclerosis of arteries of extremities	PAD	PAD
I72.4	Aneurysm of artery of lower extremity	PAD	PAD
I73.8*	Other specified peripheral vascular disease	PAD	PAD
I73.9	Peripheral vascular disease, unspecified	PAD	PAD
I74.3	Embolism and thrombosis of arteries of lower extremities	PAD	PAD
I74.4	Embolism and thrombosis of arteries of extremities, unspcified	PAD	PAD
I74.2	embolism and thrombosis of arteries of upper extremities	PAD	PAD
I74.5	embolism and thrombosis of iliac artery	PAD	PAD
I79.8	peripheral angiopathy in diseases classified elsewhere	PAD	PAD
E10.5*	insulin dependent diabetes mellitus with peripheral circulatory complications	PAD	PAD
E11.5*	non-insulin dependent diabetes mellitus with peripheral circulatory complications	PAD	PAD
I70.31*	atherosclerosis of unspecified type of bypass graft of the extremities with intermittent claudication	PAD	intermitten claudication
I70.41*	atherosclerosis of autologous vein bypass graft of the extremities with intermittent claudication	PAD	intermittent claudication
I70.51*	atherosclerosis of nonautologous biological bypass graft of the extremities with intermittent claudication	PAD	intermittent claudication
I70.61*	atherosclerosis of nonbiological bypass graft of the extremities with intermittent claudication	PAD	intermittent claudication
I70.71*	atherosclerosis of other type of bypass graft of the extremities with intermittent claudication	PAD	intermittent claudication
G45.0	Vertebro-basilar artery syndrome	cerebrovascular	stroke/TIA
G45.1	Carotid artery syndrome (hemispheric)	cerebrovascular	stroke/TIA
G45.2	Multiple and bilateral precerebral artery syndromes	cerebrovascular	stroke/TIA
G45.8	Other transient cerebral ischaemic attacks and related syndromes	cerebrovascular	stroke/TIA
G45.9	Transient cerebral ischaemic attack, unspecified	cerebrovascular	stroke/TIA
G46*	Vascular syndromes of brain in cerebrovascular diseases	cerebrovascular	stroke/TIA
I60*	Nontraumatic subarachnoid hemorrhage	cerebrovascular	stroke/TIA

INCLUSIONS ICD-10CM			
code	**Description**	**Group**	**Subgroup**
I61*	Nontraumatic intracerebral haemorrhage	cerebrovascular	stroke/TIA
I62.0*	Nontraumatic subdural hemorrhage	cerebrovascular	stroke/TIA
I62.9	Nontraumatic intracranial hemorrhage, unspecified	cerebrovascular	stroke/TIA
I63*	cerebral infarction	cerebrovascular	stroke/TIA
I65*	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	cerebrovascular	stroke/TIA
I66*	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction	cerebrovascular	stroke/TIA
I67.8*	Other specified cerebrovascular diseases	cerebrovascular	stroke/TIA
I67.9	Cerebrovascular disease, unspecified	cerebrovascular	stroke/TIA
I69*	Sequelae of cerebrovascular disease	cerebrovascular	stroke/TIA
E08.0*	Diabetes mellitus due to underlying condition with hyperosmolarity	high-risk DM	other comps
E08.1*	Diabetes mellitus due to underlying condition with ketoacidosis	high-risk DM	other comps
E08.2*	Diabetes mellitus due to underlying condition with kidney complications	high-risk DM	CKD
E08.3*	Diabetes mellitus due to underlying condition with ophthalmic complications	high-risk DM	retinopathy
E08.4*	Diabetes mellitus due to underlying condition with neurological complications	high-risk DM	neuropathy
E08.5*	Diabetes mellitus due to underlying condition with cirulatory complications	high-risk DM	other comps
E08.6*	Diabetes mellitus due to underlying condition with other specified complications	high-risk DM	other comps
E08.8*	Diabetes mellitus due to underlying condition with unspecified complications	high-risk DM	other comps
E08.9*	Diabetes mellitus due to underlying condition without complications	DM only	
E09.0*	Drug or chemical induced diabetes mellitus with hyperosmolarity	high-risk DM	other comps
E09.1*	Drug or chemical induced diabetes mellitus with ketoacidosis	high-risk DM	other comps
E09.2*	Drug or chemical induced diabetes mellitus with kidney complications	high-risk DM	CKD
E09.3*	Drug or chemical induced diabetes mellitus with ophthalmic complications	high-risk DM	retinopathy
E09.4*	Drug or chemical induced diabetes mellitus with neurological complications	high-risk DM	neuropathy
E09.5*	Drug or chemical induced diabetes mellitus with circulatory complications	high-risk DM	other comps
E09.6*	Drug or chemical induced diabetes mellitus with other specified complications	high-risk DM	other comps
E09.8	Drug or chemical induced diabetes mellitus with unspecified complications	high-risk DM	other comps
E09.9	Drug or chemical induced diabetes mellitus with without complications	DM only	
E10.1*	Type 1 diabetes mellitus with ketoacidosis	high-risk DM	other comps
E10.2*	Type 1 diabetes mellitus with kidney complications	high-risk DM	CKD
E10.3*	Type 1 diabetes mellitus with ophthalmic complications	high-risk DM	retinopathy

INCLUSIONS ICD-10CM			
code	**Description**	**Group**	**Subgroup**
E10.4 *	Type 1 diabetes mellitus with neurological complications	high-risk DM	neuropathy
E10.5 *	Type 1 diabetes mellitus with cirulatory complications	high-risk DM	other comps
E10.6 *	Type 1 diabetes mellitus with other specified complications	high-risk DM	other comps
E10.8	Type 1 diabetes mellitus with unspecified complication	high-risk DM	other comps
E10.9	Type 1 diabetes mellitus without complications	DM only	
E11.0 *	Type 2 diabetes mellitus with hyperosmolarity	high-risk DM	other comps
E11.1 *	Type 2 diabetes mellitus with ketoacidosis	high-risk DM	other comps
E11.2 *	Type 2 diabetes mellitus with kidney complications	high-risk DM	CKD
E11.3 *	Type 2 diabetes mellitus with ophthalmic complications	high-risk DM	retinopathy
E11.4 *	Type 2 diabetes mellitus with neurological complications	high-risk DM	neuropathy
E11.5 *	Type 2 diabetes mellitus with cirulatory complications	high-risk DM	other comps
E11.6 *	Type 2 diabetes mellitus with other specified complications	high-risk DM	other comps
E11.8	Type 2 diabetes mellitus with unspecified complication	high-risk DM	other comps
E11.9	Type 2 diabetes mellitus without complications	DM only	
E13.0 *	Other specified diabetes mellitus with hyperosmolarity	high-risk DM	other comps
E13.1 *	Other specified diabetes mellitus with ketoacidosis	high-risk DM	other comps
E13.2 *	Other specified diabetes mellitus with kidney complications	high-risk DM	CKD
E13.3 *	Other specified diabetes mellitus with ophthalmic complications	high-risk DM	retinopathy
E13.4 *	Other specified diabetes mellitus with neurological complications	high-risk DM	neuropathy
E13.5 *	Other specified diabetes mellitus with circulatory complications	high-risk DM	other comps
E13.6 *	Other specified diabetes mellitus with other specified complications	high-risk DM	other comps
E13.8	Other specified diabetes mellitus with unspecified complications	high-risk DM	other comps
E13.9	Other specified diabetes mellitus without unspecified complications	DM only	

Exclusions ICD-10CM		
code	**Description**	**Group**
I11.0	hypertensive heart disease with heart failure	heart failure
I13.0	hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	heart failure

Exclusions ICD-10CM		
code	**Description**	**Group**
I13.2	hypertensive heart and chronic kidney disease with heart failure and stage 5 chronic kidney disease, or end stage renal disease	heart failure
I50*	Heart failure	heart failure
I97.13*	postprocedural heart failure	heart failure
I09.81	rheumatic heart failure	heart failure
I06.0	rheumatic aortic stenosis	valve obstruction
I06.2	rheumatic aortic stenosis with insufficiency	valve obstruction
I08.0	Disorders of both mitral and aortic valves	valve obstruction
I08.2	Disorders of both aortic and tricuspid valves	valve obstruction
I08.3	Combined disorders of mitral, aortic and tricuspid valves	valve obstruction
I08.8	Other multiple valve diseases	valve obstruction
I35.0	nonrheumatic aortic (valve) stenosis	valve obstruction
I35.2	nonrheumatic aortic (valve) stenosis with insufficiency	valve obstruction
I37.0	nonrheumatic pulmonary valve stenosis	valve obstruction
I37.2	nonrheumatic pulmonary valve stenosis	valve obstruction
Q22.1	congenital pulmonary valve stenosis	valve obstruction
Q22.3	Other congenital malformations of pulmonary valve	valve obstruction
Q23.0	congenital stenosis of aortic valve	valve obstruction
Q23.8	other congenital malformations of aortic and mitral valves	valve obstruction
Q25.6	stenosis of pulmoary artery	valve obstruction
Q24.3	pulmonary infundibular stenosis	valve obstruction
Q24.4	congenital subaortic stenosis	valve obstruction
Q27.1	congenital renal artery stenosis	valve obstruction
I31.1	Chronic constrictive pericarditis	constrictive pericarditis
Q22.3	Other congenital malformations of pulmonary valve	heart disease
Q24.8	Other specified congenital malformations of heart	heart disease
Q24.9	Congenital malformation of heart, unspecified	heart disease
T86.2*	Heart transplant failure and rejection	heart transplant
T86.3*	Heart-lung transplant failure and rejection	heart transplant
Z94.1	Heart transplant status	heart transplant
Z94.3	Heart and lungs transplant status	heart transplant
I60*	Nontraumatic subarachnoid hemorrhage	stroke
I61*	Nontraumatic intracerebral haemorrhage	stroke
I62.0*	Nontraumatic subdural hemorrhage	stroke
I62.9	Nontraumatic intracranial hemorrhage, unspecified	stroke
I69*	Sequelae of cerebrovascular disease	stroke
S06.6	traumatic subarachnoid hemorrhage	stroke
S06.5	traumatic subdural hemorrhage	stroke
Q27.1	congenital renal artery stenosis	renal artery stenosis
Q27.2	Other congenital malformations of renal artery	renal artery stenosis
I70.1	Atherosclerosis of renal artery	renal artery stenosis

Exclusions ICD-10CM		
code	**Description**	**Group**
B16*	Acute hepatitis B	liver disease
B17*	Other acute viral hepatitis	liver disease
B18*	chronic viral hepatitis	liver disease
B19*	unspecified viral hepatitis	liver disease
I85.0*	Esophageal varices	liver disease
I86.4	Gastric varices	liver disease
K70*	alcoholic liver disease	liver disease
K71*	toxic liver disease	liver disease
K72*	Hepatic failure, not elsewhere classified	liver disease
K73*	Chronic hepatitis, not elsewhere classified	liver disease
K74*	Fibrosis and cirrhosis of liver	liver disease
K75.2	Nonspecific reactive hepatitis	liver disease
K75.3	Granulomatous hepatitis, not elsewhere classified	liver disease
K75.4	Autoimmune hepatitis	liver disease
K75.8*	Other specified inflammatory liver diseases	liver disease
K75.9	Inflammatory liver disease, unspecified	liver disease
K76.2	Central haemorrhagic necrosis of liver	liver disease
K76.3	Infarction of liver	liver disease
K76.4	Peliosis hepatis	liver disease
K76.5	Hepatic veno-occlusive disease	liver disease
K76.6	Portal hypertension	liver disease
K76.7	Hepatorenal syndrome	liver disease
K76.8*	Other specified diseases of liver	liver disease
K76.9	Liver disease, unspecified	liver disease
K77	Liver disorders in diseases classified elsewhere	liver disease
O98.4*	Viral hepatitis complicating pregnancy, childbirth and the puerperium	liver disease
K91.82	Postprocedural hepatic failure	liver disease
E26.0*	primary hyperaldosteronism	primary hyperaldosteronism
E26.8*	other hyperaldosteronism	primary hyperaldosteronism
E26.9	Hyperaldosteronism, unspecified	primary hyperaldosteronism
E74.12	hereditary fructose intolerance	hereditary fructose intolerance
C00*	Malignant neoplasm of lip	discontinuation reason: cancer
C01*	Malignant neoplasm of base of tongue	discontinuation reason: cancer
C02*	Malignant neoplasm of other and unspecified parts of tongue	discontinuation reason: cancer
C03*	Malignant neoplasm of gum	discontinuation reason: cancer
C04*	Malignant neoplasm of floor of mouth	discontinuation reason: cancer

Exclusions ICD-10CM		
code	**Description**	**Group**
C05*	Malignant neoplasm of palate	discontinuation reason: cancer
C06*	Malignant neoplasm of other and unspecified parts of mouth	discontinuation reason: cancer
C07*	Malignant neoplasm of parotid gland	discontinuation reason: cancer
C08*	Malignant neoplasm of other and unspecified major salivary glands	discontinuation reason: cancer
C09*	Malignant neoplasm of tonsil	discontinuation reason: cancer
C10*	Malignant neoplasm of oropharynx	discontinuation reason: cancer
C11*	Malignant neoplasm of nasopharynx	discontinuation reason: cancer
C12*	Malignant neoplasm of pyriform sinus	discontinuation reason: cancer
C13*	Malignant neoplasm of hypopharynx	discontinuation reason: cancer
C14*	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx	discontinuation reason: cancer
C15*	Malignant neoplasm of esophagus	discontinuation reason: cancer
C16*	Malignant neoplasm of stomach	discontinuation reason: cancer
C17*	Malignant neoplasm of small intestine	discontinuation reason: cancer
C18*	Malignant neoplasm of colon	discontinuation reason: cancer
C19*	Malignant neoplasm of rectosigmoid junction	discontinuation reason: cancer
C20*	Malignant neoplasm of rectum	discontinuation reason: cancer
C21*	Malignant neoplasm of anus and anal canal	discontinuation reason: cancer
C22*	Malignant neoplasm of liver and intrahepatic bile ducts	discontinuation reason: cancer
C23*	Malignant neoplasm of gallbladder	discontinuation reason: cancer
C24*	Malignant neoplasm of other and unspecified parts of biliary tract	discontinuation reason: cancer
C25*	Malignant neoplasm of pancreas	discontinuation reason: cancer
C26*	Malignant neoplasm of other and ill-defined digestive organs	discontinuation reason: cancer
C30*	Malignant neoplasm of nasal cavity and middle ear	discontinuation reason: cancer
C31*	Malignant neoplasm of accessory sinuses	discontinuation reason: cancer
C32*	Malignant neoplasm of larynx	discontinuation reason: cancer
C33*	Malignant neoplasm of trachea	discontinuation reason: cancer
C34*	Malignant neoplasm of bronchus and lung	discontinuation reason: cancer
C37*	Malignant neoplasm of thymus	discontinuation reason: cancer
C38*	Malignant neoplasm of heart, mediastinum and pleura	discontinuation reason: cancer

Exclusions ICD-10CM		
code	**Description**	**Group**
C39*	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs	discontinuation reason: cancer
C40*	Malignant neoplasm of bone and articular cartilage of limbs	discontinuation reason: cancer
C41*	Malignant neoplasm of bone and articular cartilage of other and unspecified sites	discontinuation reason: cancer
C43*	Malignant melanoma of skin	discontinuation reason: cancer
C44*	Other and unspecified malignant neoplasm of skin NOT: C44.01, C44.11, C44.21, C44.31, C44.41, C44.51, C44.61, C44.71, C44.81, C44.91 (Basal cell skin cancers)	discontinuation reason: cancer
C4A*	Merkel cell carcinoma	discontinuation reason: cancer
C45*	Mesothelioma	discontinuation reason: cancer
C46*	Kaposi's sarcoma	discontinuation reason: cancer
C47*	Malignant neoplasm of peripheral nerves and autonomic nervous system	discontinuation reason: cancer
C48*	Malignant neoplasm of retroperitoneum and peritoneum	discontinuation reason: cancer
C49*	Malignant neoplasm of other connective and soft tissue	discontinuation reason: cancer
C50*	Malignant neoplasm of breast	discontinuation reason: cancer
C51*	Malignant neoplasm of vulva	discontinuation reason: cancer
C52*	Malignant neoplasm of vagina	discontinuation reason: cancer
C53*	Malignant neoplasm of cervix uteri	discontinuation reason: cancer
C54*	Malignant neoplasm of corpus uteri	discontinuation reason: cancer
C55*	Malignant neoplasm of uterus, part unspecified	discontinuation reason: cancer
C56*	Malignant neoplasm of ovary	discontinuation reason: cancer
C57*	Malignant neoplasm of other and unspecified female genital organs	discontinuation reason: cancer
C58*	Malignant neoplasm of placenta	discontinuation reason: cancer
C60*	Malignant neoplasm of penis	discontinuation reason: cancer
C61*	Malignant neoplasm of prostate	discontinuation reason: cancer
C62*	Malignant neoplasm of testis	discontinuation reason: cancer
C63*	Malignant neoplasm of other and unspecified male genital organs	discontinuation reason: cancer
C64*	Malignant neoplasm of kidney, except renal pelvis	discontinuation reason: cancer
C65*	Malignant neoplasm of renal pelvis	discontinuation reason: cancer
C66*	Malignant neoplasm of ureter	discontinuation reason: cancer
C67*	Malignant neoplasm of bladder	discontinuation reason: cancer
C68*	Malignant neoplasm of other and unspecified urinary organs	discontinuation reason: cancer

Exclusions ICD-10CM		
code	**Description**	**Group**
C69*	Malignant neoplasm of eye and adnexa	discontinuation reason: cancer
C70*	Malignant neoplasm of meninges	discontinuation reason: cancer
C71*	Malignant neoplasm of brain	discontinuation reason: cancer
C72*	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system	discontinuation reason: cancer
C73*	Malignant neoplasm of thyroid gland	discontinuation reason: cancer
C74*	Malignant neoplasm of adrenal gland	discontinuation reason: cancer
C75*	Malignant neoplasm of other endocrine glands and related structures	discontinuation reason: cancer
C7A*	Malignant neuroendocrine tumors	discontinuation reason: cancer
C7B*	Secondary neuroendocrine tumors	discontinuation reason: cancer
C76*	Malignant neoplasm of other and ill-defined sites	discontinuation reason: cancer
C77*	Secondary and unspecified malignant neoplasm of lymph nodes	discontinuation reason: cancer
C78*	Secondary malignant neoplasm of respiratory and digestive organs	discontinuation reason: cancer
C79*	Secondary malignant neoplasm of other and unspecified sites	discontinuation reason: cancer
C80*	Malignant neoplasm without specification of site	discontinuation reason: cancer
C81*	Hodgkin lymphoma	discontinuation reason: cancer
C82*	Follicular lymphoma	discontinuation reason: cancer
C83*	Non-follicular lymphoma	discontinuation reason: cancer
C84*	Mature T/NK-cell lymphomas	discontinuation reason: cancer
C85*	Other specified and unspecified types of non-Hodgkin lymphoma	discontinuation reason: cancer
C86*	Other specified types of T/NK-cell lymphoma	discontinuation reason: cancer
C88*	Malignant immunoproliferative diseases and certain other B-cell lymphomas	discontinuation reason: cancer
C90*	Multiple myeloma and malignant plasma cell neoplasms	discontinuation reason: cancer
C91*	Lymphoid leukemia	discontinuation reason: cancer
C92*	Myeloid leukemia	discontinuation reason: cancer
C93*	Monocytic leukemia	discontinuation reason: cancer
C94*	Other leukemias of specified cell type	discontinuation reason: cancer
C95*	Leukemia of unspecified cell type	discontinuation reason: cancer
C96*	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue	discontinuation reason: cancer
D00*	Carcinoma in situ of oral cavity, esophagus and stomach	discontinuation reason: cancer

Exclusions ICD-10CM		
code	**Description**	**Group**
D01*	Carcinoma in situ of other and unspecified digestive organs	discontinuation reason: cancer
D02*	Carcinoma in situ of middle ear and respiratory system	discontinuation reason: cancer
D03*	Melanoma in situ	discontinuation reason: cancer
D04*	Carcinoma in situ of skin	discontinuation reason: cancer
D05*	Carcinoma in situ of breast	discontinuation reason: cancer
D06*	Carcinoma in situ of cervix uteri	discontinuation reason: cancer
D07*	Carcinoma in situ of other and unspecified genital organs	discontinuation reason: cancer
D09*	Carcinoma in situ of other and unspecified sites	discontinuation reason: cancer
D37*	Neoplasm of uncertain behavior of oral cavity and digestive organs	discontinuation reason: cancer
D38*	Neoplasm of uncertain behavior of middle ear and respiratory and intrathoracic organs	discontinuation reason: cancer
D39*	Neoplasm of uncertain behavior of middle ear and respiratory and intrathoracic organs	discontinuation reason: cancer
D40*	Neoplasm of uncertain behavior of male genital organs	discontinuation reason: cancer
D41*	Neoplasm of uncertain behavior of urinary organs	discontinuation reason: cancer
D42*	Neoplasm of uncertain behavior of urinary organs	discontinuation reason: cancer
D43*	Neoplasm of uncertain behavior of brain and central nervous system	discontinuation reason: cancer
D44*	Neoplasm of uncertain behavior of endocrine glands	discontinuation reason: cancer
D45*	Polycythemia vera	discontinuation reason: cancer
D46*	Myelodysplastic syndromes	discontinuation reason: cancer
D47*	Other neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue	discontinuation reason: cancer
D48*	Neoplasm of uncertain behavior of other and unspecified sites	discontinuation reason: cancer
D49*	Neoplasms of unspecified behavior	discontinuation reason: cancer
F01*	Vascular dementia	discontunation reason: mental illness
F02*	dementia in other diseases classified elsewhere	discontunation reason: mental illness
F03*	unspecified dementia	discontunation reason: mental illness
F04*	amnestic disorder due to known physiological condition	discontunation reason: mental illness
F05*	delirium due to known physiological condition	discontunation reason: mental illness
F06*	other mental disorders due to known physiological condition	discontunation reason: mental illness
F07*	personality and behavioral disorders due to known physiological condition	discontunation reason: mental illness
F09*	unspecified mental disorder due to known physiological condition	discontunation reason: mental illness

Exclusions ICD-10CM		
code	**Description**	**Group**
F10*	alcohol related disorders	discontunation reason: mental illness
F11*	opioid related disorders	discontunation reason: mental illness
F12*	cannabis related disorders	discontunation reason: mental illness
F13*	sedative, hypnotic, or anxiolytic related disorders	discontunation reason: mental illness
F14*	cocaine related disorders	discontunation reason: mental illness
F15*	other stimulant related disorders	discontunation reason: mental illness
F16*	hallucinogen related disorders	discontunation reason: mental illness
F18*	inhalant related disorders	discontunation reason: mental illness
F19*	other psychoactive substance related disorders	discontunation reason: mental illness
F20*	Schizophrenia	discontunation reason: mental illness
F21*	Schizotypal disorder	discontunation reason: mental illness
F22*	delusional disorders	discontunation reason: mental illness
F23*	brief psychotic disorder	discontunation reason: mental illness
F24*	shared psychotic disorder	discontunation reason: mental illness
F25*	schizoaffective disorders	discontunation reason: mental illness
F28*	other psychotic disorder not due to a substance or known physiological condition	discontunation reason: mental illness
F29*	unspecified psychosis not due to a substance or known physiological condition	discontunation reason: mental illness
F30*	manic episode	discontunation reason: mental illness
F31*	bipolar disorder	discontunation reason: mental illness
F32*	depressive episode	discontunation reason: mental illness
F33*	major depressive disorder, recurrent	discontunation reason: mental illness
F34*	persistent mood (affective) disorders	discontunation reason: mental illness
F39*	Unspecified mood (affective) disorder	discontunation reason: mental illness
F40*	phobic anxiety disorders	discontunation reason: mental illness
F41*	other anxiety disorders	discontunation reason: mental illness
F42*	obsessive-compulsive disorder	discontunation reason: mental illness
F43*	reaction to severe stress, and adjustment disorders	discontunation reason: mental illness
F44*	dissociative and conversion disorders	discontunation reason: mental illness
F45*	sematoform disorders	discontunation reason: mental illness

Exclusions ICD-10CM		
code	**Description**	**Group**
F48*	Other nonpsychotic mental disorders	discontunation reason: mental illness
F50*	eating disorders	discontunation reason: mental illness
F53*	mental and behavioral disorders associated with the puerperium, not elsehwere classified	discontunation reason: mental illness
F54*	psychological and behavioral factors associated with disorders or diseases classified elsewhere	discontunation reason: mental illness
F55*	abuse of non-psychoactive substances	discontunation reason: mental illness
F59*	unspecified behavioral syndromes associated with physiological disturbances and physical factors	discontunation reason: mental illness
F60*	specific personality disorders	discontunation reason: mental illness
F63*	impulse disorders	discontunation reason: mental illness
F71*	moderate intellectual disabilities	discontunation reason: mental illness
F72*	severe intellectual disabilities	discontunation reason: mental illness
F73*	profound intellectual disabilities	discontunation reason: mental illness
F78*	other intellectual disabilities	discontunation reason: mental illness
F79*	unspecified intellectual disabilities	discontunation reason: mental illness
F99	Mental disorder, not otherwise specified	discontunation reason: mental illness
G31.2	Degeneration of nervous system due to alcohol	discontunation reason: alcohol dependence
G62.1	Alcoholic polyneuropathy	discontunation reason: alcohol dependence
G72.1	Alcoholic myopathy	discontunation reason: alcohol dependence
I42.6	Alcoholic cardiomyopathy	discontunation reason: alcohol dependence
K29.2*	Alcoholic gastritis	discontunation reason: alcohol dependence
O35.4*	Maternal care for (suspected) damage to fetus by alcohol	discontunation reason: alcohol dependence
O35.5*	Maternal care for (suspected) damage to fetus by drugs	discontunation reason: drug dependence
O99.34*	other mental disorders and diseases of the nervous system complicating pregnancy, childbirth and the puerperium	discontunation reason: mental illness
O99.31*	alcohol use complicating pregnancy, childbirth and the puerperium	discontunation reason: alcohol dependence
099.32*	drug use complicating pregancy, childbirth and the puerperium	discontunation reason: drug dependence

Exclusions ICD-10CM		
code	**Description**	**Group**
P04.12	newborn affected by maternal cytotoxic drugs	discontunation reason: drug dependence
P04.14	newborn affected by mternal use of opiates	discontunation reason: drug dependence
P04.15	newborn affected by maternal use of antidepressants	discontunation reason: drug dependence
P04.16	newborn affected by maternal use of amphetamines	discontunation reason: drug dependence
P04.17	newborn affected by maternal use of sedative-hypnotics	discontunation reason: drug dependence
P04.1A	newborn affected by maternal use of anxiolytics	discontunation reason: drug dependence
P04.3	newborn affected by maternal use of alcohol	discontunation reason: alcohol dependence
P04.4*	newborn affected by maternal use of drugs of addiction	discontunation reason: drug dependence
P04.8*	newborn affected by other maternal noxious subtances	discontunation reason: drug dependence
P04.9	newborn affected by maternal noxious subtances, unspecified	discontunation reason: drug dependence
P96.1	Neonatal withdrawal symptoms from maternal use of drugs from addiction	discontunation reason: drug dependence
P96.2	Withdrawal symptoms from therapeutic use of drugs in newborn	discontunation reason: drug dependence
R78*	Findings of drugs and other substances, not normally found in blood	discontunation reason: drug dependence
E13.3*	encounter for screening examination for mental health and behavioral disorders	discontunation reason: mental illness
E71.41	alcohol abuse counselling and surveillance of alcoholic	discontunation reason: alcohol dependence
E71.51	drug abuse counselling and surveillance of drug abuser	discontunation reason: drug dependence
K85.2*	alcohol induced acute pancreatitis	discontunation reason: alcohol dependence
K86.0	alcohol-induced chronic pancreatitis	discontunation reason: alcohol dependence
K85.3*	drug induced acute pancreatitis	discontunation reason: drug dependence

Outcomes ICD-10CM		
Code	**Definition**	**Group**
I21*	Acute myocardial infarction	MI
I22	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	MI
I22.0	Subsequent ST elevation (STEMI) myocardial infarction of anterior wall	MI
I22.1	Subsequent ST elevation (STEMI) myocardial infarction of inferior wall	MI
I22.8	Subsequent ST elevation (STEMI) myocardial infarction of other sites	MI
I22.9	Subsequent ST elevation (STEMI) myocardial infarction of unspecified site	MI
I23	Certain current complications following acute myocardial infarction	MI
I23.0	Haemopericardium as current complication following acute myocardial infarction	MI
I23.1	Atrial septal defect as current complication following acute myocardial infarction	MI
I23.2	Ventricular septal defect as current complication following acute myocardial infarction	MI
I23.3	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction	MI
I23.4	Rupture of chordae tendineae as current complication following acute myocardial infarction	MI
I23.5	Rupture of papillary muscle as current complication following acute myocardial infarction	MI
I23.6	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction	MI
I23.8	Other current complications following acute myocardial infarction	MI
I60*	Subarachnoid haemorrhage	stroke
I61*	Intracerebral haemorrhage	stroke
I62*	Other nontraumatic intracranial haemorrhage	stroke
I69.0*	Sequelae of subarachnoid haemorrhage	stroke
I69.1*	Sequelae of intracerebral haemorrhage	stroke
I69.2*	Sequelae of other nontraumatic intracranial haemorrhage	stroke
S06.6	Traumatic subarachnoid haemorrhage	stroke
I50*	Heart failure	heart failure
I11.0	Hypertensive heart disease with (congestive) heart failure	heart failure
I13.0	Hypertensive heart and renal disease with (congestive) heart failure	heart failure
I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	heart failure
I97.13*	Postprocedural heart failure	heart failure
I09.81	Rheumatic heart failure	heart failure
I46*	cardiac arrest	cardiovascular-related death
R99	Death all-cause	Death

Medications (ATC -WHOcode)		
ATC code	**Medication**	**Category for use**
C09AA*	ACE inhibitors	Exposure
C09CA*	ARB	Exposure
A10AB*	Diabetes medications	Covariates
A10AC*	Diabetes medications	Covariates
A10AD*	Diabetes medications	Covariates
A10AE*	Diabetes medications	Covariates
A10AF*	Diabetes medications	Covariates
A10BA*	Diabetes medications	Covariates
A10BB*	Diabetes medications	Covariates
A10BC*	Diabetes medications	Covariates
A10BD*	Diabetes medications	Covariates
A10BF*	Diabetes medications	Covariates
A10BG*	Diabetes medications	Covariates
A10BH*	Diabetes medications	Covariates
A10BJ*	Diabetes medications	Covariates
A10BK*	Diabetes medications	Covariates
A10BX*	Diabetes medications	Covariates
A10XA*	Diabetes medications	Covariates
C02CA*	Alphablocker	Covariates
G04CA*	Alphablocker	Covariates
B01AC*	Antiplatelet therapy	Covariates
B01AC06	Aspirin	Covariates
C07AA*	Betablocker	Covariates
C07AB*	Betablocker	Covariates
S01ED*	Betablocker	Covariates
C08CA*	Calcium channel blocker	Covariates
C08CX*	Calcium channel blocker	Covariates
C08DA*	Calcium channel blocker	Covariates
C08DB*	Calcium channel blocker	Covariates
C08EA*	Calcium channel blocker	Covariates
C08EX*	Calcium channel blocker	Covariates
C01AA*	Digoxin	Covariates
C03AA*	Diuretics	Covariates
C03BA*	Diuretics	Covariates
C03BC*	Diuretics	Covariates
C03BD*	Diuretics	Covariates
C03BX*	Diuretics	Covariates
C03CA*	Diuretics	Covariates
C03CC*	Diuretics	Covariates
C03CD*	Diuretics	Covariates

Medications (ATC -WHOcode)		
ATC code	**Medication**	**Category for use**
C03CX*	Diuretics	Covariates
C03XA*	Diuretics	Covariates
C01DA*	Nitrate	Covariates
C10AA*	Statin	Covariates
B01AA*	Anticoagulant	Covariates
B01AB*	Anticoagulant	Covariates

Inclusions ICD-10PCS			
code	**Description**	**Group**	**Subgroup**
0210*	coronary artery bypass, one artery	CAD	CABG
0211*	coronary artery bypass, two arteries	CAD	CABG
0212*	coronary artery bypass, three arteries	CAD	CABG
0213*	coronary artery bypass, four or more arteries	CAD	CABG
02703*	dilation, percutaneous, coronary artery, one artery	CAD	PTCA
02713*	dilation, percutaneous, coronary artery, two arteries	CAD	PTCA
02723*	dilation, percutaneous, coronary artery, three arteries	CAD	PTCA
02733*	dilation, percutaneous, coronary artery, four or more arteries	CAD	PTCA
02704*	dilation, percutaneous endoscopic, coronary artery, one artery	CAD	PTCA
02714*	dilation, percutaneous endoscopic, coronary artery, two arteries	CAD	PTCA
02724*	dilation, percutaneous endoscopic, coronary artery, three arteries	CAD	PTCA
02734*	dilation, percutaneous endoscopic, coronary artery, four or more arteries	CAD	PTCA
041C*	bypass, common iliac artery right	PAD	limb bypass/angioplasty
041D*	bypass, common iliac artery left	PAD	limb bypass/angioplasty
041E*	bypass, internal iliac artery right	PAD	limb bypass/angioplasty
041F*	bypass, internal iliac artery left	PAD	limb bypass/angioplasty
041H*	bypass, external iliac artery right	PAD	limb bypass/angioplasty
041J*	bypass, external iliac artery left	PAD	limb bypass/angioplasty
041K*	bypass, femoral artery, right	PAD	limb bypass/angioplasty
041L*	bypass, femoral artery left	PAD	limb bypass/angioplasty
041M*	bypass, popliteal artery right	PAD	limb bypass/angioplasty
041N*	bypass, popliteal artery left	PAD	limb bypass/angioplasty
041P*	bypass, anterior tibial artery right	PAD	limb bypass/angioplasty
041Q*	bypass, anterior tibial artery left	PAD	limb bypass/angioplasty
041R*	bypass, posterior tibial artery right	PAD	limb bypass/angioplasty

Inclusions ICD-10PCS			
code	**Description**	**Group**	**Subgroup**
041S*	bypass, posterior tibial artery left	PAD	limb bypass/angioplasty
041T*	bypass, peroneal artery right	PAD	limb bypass/angioplasty
041U*	bypass, peroneal artery left	PAD	limb bypass/angioplasty
041V*	bypass, foot artery right	PAD	limb bypass/angioplasty
041W*	bypass, foot artery left	PAD	limb bypass/angioplasty
047C3*	dilation, percutaneous, common iliac artery right	PAD	limb bypass/angioplasty
047D3*	dilation, percutaneous, common iliac artery left	PAD	limb bypass/angioplasty
047E3*	dilation, percutaneous, internal iliac artery right	PAD	limb bypass/angioplasty
047F3*	dilation, percutaneous, internal iliac artery left	PAD	limb bypass/angioplasty
047H3*	dilation, percutaneous, external iliac artery right	PAD	limb bypass/angioplasty
047J3*	dilation, percutaneous, external iliac artery left	PAD	limb bypass/angioplasty
047K3*	dilation, percutaneous,femoral artery, right	PAD	limb bypass/angioplasty
047L3*	dilation, percutaneous, femoral artery left	PAD	limb bypass/angioplasty
047M3*	dilation, percutaneous, popliteal artery right	PAD	limb bypass/angioplasty
047N3*	dilation, percutaneous, popliteal artery left	PAD	limb bypass/angioplasty
047P3*	dilation, percutaneous, anterior tibial artery right	PAD	limb bypass/angioplasty
047Q3*	dilation, percutaneous, anterior tibial artery left	PAD	limb bypass/angioplasty
047R3*	dilation, percutaneous, posterior tibial artery right	PAD	limb bypass/angioplasty
047S3*	dilation, percutaneous, posterior tibial artery left	PAD	limb bypass/angioplasty
047T3*	dilation, percutaneous, peroneal artery right	PAD	limb bypass/angioplasty
047U3*	dilation, percutaneous,peroneal artery left	PAD	limb bypass/angioplasty
047V3*	dilation, percutaneous, foot artery right	PAD	limb bypass/angioplasty
047W3*	dilation, percutaneous, foot artery left	PAD	limb bypass/angioplasty
047Y3*	dilation, percutaneous, lower artery	PAD	limb bypass/angioplasty
047C4*	dilation, percutaneous endoscopic, common iliac artery right	PAD	limb bypass/angioplasty
047D4*	dilation, percutaneous endoscopic, common iliac artery left	PAD	limb bypass/angioplasty
047E4*	dilation, percutaneous endoscopic, internal iliac artery right	PAD	limb bypass/angioplasty
047F4*	dilation, percutaneous endoscopic, internal iliac artery left	PAD	limb bypass/angioplasty
047H4*	dilation, percutaneous endoscopic, external iliac artery right	PAD	limb bypass/angioplasty

Inclusions ICD-10PCS			
code	**Description**	**Group**	**Subgroup**
047J4*	dilation, percutaneous endoscopic, external iliac artery left	PAD	limb bypass/angioplasty
047K4*	dilation, percutaneous endoscopic,femoral artery, right	PAD	limb bypass/angioplasty
047L4*	dilation, percutaneous endoscopic, femoral artery left	PAD	limb bypass/angioplasty
047M4*	dilation, percutaneous endoscopic, popliteal artery right	PAD	limb bypass/angioplasty
047N4*	dilation, percutaneous endoscopic, popliteal artery left	PAD	limb bypass/angioplasty
047P4*	dilation, percutaneous endoscopic, anterior tibial artery right	PAD	limb bypass/angioplasty
047Q4*	dilation, percutaneous endoscopic, anterior tibial artery left	PAD	limb bypass/angioplasty
047R4*	dilation, percutaneous endoscopic, posterior tibial artery right	PAD	limb bypass/angioplasty
047S4*	dilation, percutaneous endoscopic, posterior tibial artery left	PAD	limb bypass/angioplasty
047T4*	dilation, percutaneous endoscopic, peroneal artery right	PAD	limb bypass/angioplasty
047U4*	dilation, percutaneous endoscopic,peroneal artery left	PAD	limb bypass/angioplasty
047V4*	dilation, percutaneous endoscopic, foot artery right	PAD	limb bypass/angioplasty
047W4*	dilation, percutaneous endoscopic, foot artery left	PAD	limb bypass/angioplasty
047Y4*	dilation, percutaneous endoscopic, lower artery	PAD	limb bypass/angioplasty
0Y62*	detachment, hindquarter right	PAD	limb/foot amputation
0Y63*	detachment, hindquarter left	PAD	limb/foot amputation
0Y64*	detachment, hindquarter bilateral	PAD	limb/foot amputation
0Y67*	detachment, femoral region right	PAD	limb/foot amputation
0Y78*	detachment, femoral region left	PAD	limb/foot amputation
0Y6C*	detachment, upper leg right	PAD	limb/foot amputation
0Y6D*	detachment, upper leg left	PAD	limb/foot amputation
0Y6F*	detachment, knee region right	PAD	limb/foot amputation
0Y6G*	detachment, knee region left	PAD	limb/foot amputation
0Y6H*	detachment, lower leg right	PAD	limb/foot amputation
0Y6J*	detachment, lower leg left	PAD	limb/foot amputation
0Y6M*	detachment, foot right	PAD	limb/foot amputation
0Y6N*	detachment, foot left	PAD	limb/foot amputation

EXCLUSIONS ICD-10 PCS
02YA* heart transplant