Title

Comparative clinical and cost effectiveness of non-ST elevation myocardial infarction management strategies in patients living with kidney impairment during the COVID-19 pandemic: protocol for a target trial emulation using English routinely collected health data

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ABSTRACT

Introduction

Recent national and international guidelines recommend an invasive cardiac investigation and treatment strategy for people at high risk of cardiovascular events, regardless of kidney function status. These guidelines are based on observational evidence suggesting that the benefits of invasive cardiac investigation and treatment versus conservative management for non-ST elevated myocardial infarction (NSTEMI) outweigh the risks for people with kidney impairment. Despite this, among people with kidney impairment there is substantial variation in the proportions who have early invasive versus conservative NSTEMI management across hospitals in England. The impact of the COVID-19 pandemic on this variation is unknown. This protocol describes a study to investigate this variation and any changes during the COVID-19 pandemic, and how this variation will be used to evaluate the comparative clinical and cost-effectiveness of alternative NSTEMI treatment strategies among people with reduced kidney function.

Methods and analysis

The CVD-COVID-UK/COVID-IMPACT British Heart Foundation (BHF) Data Science Centre Secure Data Environment, which contains nationally representative linked data on over 50 million people living in the United Kingdom, will be used to define a cohort of people hospitalised for NSTEMI. We will use linked secondary care data (Hospital Episode Statistics and National Institute for Cardiovascular Outcomes Research Audit) for cases with recent evidence of kidney impairment in primary care data (General Practice Extraction Service Data for pandemic planning and research) between 2019 and 2024. First, we will describe variation in early invasive versus conservative NSTEMI management at the hospital-level before and during the COVID-19 pandemic. Second, we will emulate a hypothetical trial using the target trial emulation framework to evaluate the comparative and cost-effectiveness of early invasive versus conservative NSTEMI management among people with reduced kidney function. We will use advanced

analytical methods (clone-censor-weighting and instrumental variable analyses) to minimise the risk of bias due to immortal time and confounding by indication.

Ethics and dissemination

This study was reviewed and approved by the BHF Data Science Centre Scientific and Public Panels. Results will be published in peer-reviewed journals, presented at conferences, and shared at patient and public panels. Analysis code will be shared in line with the BHF Data Science Centre's code-sharing procedures.

STRENGTHS AND LIMITATIONS

Strengths

- A large, nationally representative, linked dataset from the BHF Data Science Centre Secure Data Environment (SDE) will be used to more accurately capture NSTEMI hospitalisations across secondary care services in England.
- The target trial emulation framework combined with clone-censor-weighting and an instrumental variable analysis will reduce the risk of biases common in observational research, including immortal time bias and residual confounding.

Weaknesses

- NSTEMI management variation prior to 2019 cannot be studied since the SDE only includes follow-up time from 2019 onwards.
- Our analytical methods must assume either no unmeasured confounding (clone-censor-weight) or the instrumental variable assumptions (IV analysis).

ACRONYMS

2SRI: 2-Stage Residual Inclusion

AKI: Acute Kidney Injury

AMI: Acute Myocardial Infarction

APC: Admitted Patient Care

BHF: British Heart Foundation

CABG: Coronary Artery Bypass Graft

CCW: Clone-Censor-Weight

CI: Confidence Interval

CKD: Chronic Kidney Disease

COPD: Chronic Obstructive Pulmonary Disease

DAG: Directed Acyclic Graph

eGFR: estimated Glomerular Filtration Rate

GDPPR: General Practice Extraction Service Data for pandemic planning and research

HES-APC: Hospital Episode Statistics – Admitted Patient Care

HRQoL: Health-Related Quality of Life

ICD-10: International Classification of Diseases – 10th Revision

INB: Incremental Net Monetary Benefit

IPTW: Inverse Probability of Treatment Weighting

IV: Instrumental Variable

NSTEMI: Non-ST Elevation Myocardial Infarction

MINAP: Myocardial Ischaemia National Audit Project

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

NICOR: National Institute for Cardiovascular Outcomes Research Audit

NSTEMI: Non-ST Elevation Myocardial Infarction

PCI: Percutaneous Coronary Intervention

PPI: Patient and Public Involvement

QALY: Quality-Adjusted Life Year

RCT: Randomised Controlled Trial

SDE: Secure Data Environment

STEMI: ST Elevation Myocardial Infarction

UK: United Kingdom

INTRODUCTION

People with reduced kidney function are at increased risk of acute myocardial infarction (AMI) and poor outcomes post-AMI, including death.[1-3] Major advances in AMI treatment and improved outcomes have been driven by randomised controlled trials (RCTs) demonstrating the effectiveness of early invasive cardiac investigation (e.g., angiography) and treatment strategies (e.g., percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)) for most people hospitalised with AMI.[4-7] However, these RCTs usually underrepresent people with reduced kidney function,[8] who are at higher risk of poor AMI outcomes and are more likely to be older and living with multiple long-term conditions compared with the general population.[9]

Current National Institute for Health and Care Excellence (NICE) and international guidelines recommend timely invasive cardiac management among almost everyone presenting with ST-elevation myocardial infarction (STEMI), and those with non-ST-elevation myocardial infarction (NSTEMI) or unstable angina judged to be at high risk of subsequent adverse cardiovascular events.[4,10] People with reduced kidney function would be considered at high risk of adverse cardiovascular events post-NSTEMI hospitalisation; however, there is uncertainty as to the balance of benefits versus risks of early invasive NSTEMI management among this group, primarily due to the heightened risk of contrast-associated nephropathy and bleeding following angiography.[11,12] This uncertainty likely contributed to the substantial variation observed across hospitals in England pre-2018 in NSTEMI management in people with reduced kidney function.[13-15] It is unknown to what extent this variation persisted in more recent times, including during the COVID-19 pandemic, which had significant impacts on United Kingdom (UK) health care services for many non-communicable disease[16] including AMI hospitalisations and treatment pathways.[17]

Observational studies suggest that people with reduced kidney function benefit from early invasive NSTEMI management.[13,14,18,19] Thus, national and international guidelines published in 2022 and 2023[4,10] cautiously recommend early invasive NSTEMI management for people with reduced kidney function. However, the evidence that

supports these recommendations is prone to biases common in observational research such as immortal time bias[20] and unmeasured confounding.

Given the absence of RCT data and the inherent limitations of observational research, there is a need to apply advanced methodology and analysis strategies using high-quality observational data to gain more confidence in the comparative clinical and cost-effectiveness of alternative NSTEMI management strategies for people with reduced kidney function.

AIMS AND OBJECTIVES

This study aims to describe variation in NSTEMI management for people with reduced kidney function across hospitals in England through the COVID-19 pandemic, and use this variation to evaluate the comparative clinical and cost-effectiveness of alternative NSTEMI management strategies in this population. Specifically, we will:

(1) Describe NSTEMI management strategies among people with reduced kidney function hospitalised in England, and how the proportion receiving early invasive versus conservative management strategies may have changed during the COVID-19 pandemic;
(2) Evaluate the comparative clinical effectiveness of early invasive versus conservative NSTEMI management among people with reduced kidney function; and
(3) Evaluate the cost-effectiveness of early invasive versus conservative NSTEMI management among people with reduced kidney function.

METHODS AND ANALYSIS

Study design and data sources

We will conduct a cohort study using routinely collected, linked health data, to describe and compare NSTEMI management strategies among people with reduced kidney function hospitalised for NSTEMI in England. To identify and minimise the risk of important biases in our observational study, we will use the target trial emulation framework, which explicitly ties the design and analysis of an observational study to a hypothetical target trial which the observational study emulates; this target trial may be based on a real or hypothetical trial.[21,22] Our emulation will be based on a hypothetical trial since there is no real trial evaluating NSTEMI management strategies specifically in people with reduced kidney function. This trial emulation will use de-identified linked data from the CVD-COVID-UK/COVID-IMPACT Secure Data Environment (SDE) within the British Heart Foundation (BHF) Data Science Centre, hereafter referred to as the SDE.[23] The SDE obtained data from the National Cardiac Audit Programme provided by the National Institute for Cardiovascular Outcomes Research (NICOR).[24] We will repeat the main analyses in an additional data environment: the National Health Service (NHS) Data Lake, which is used for health commissioning and includes linkage to the UK Renal Registry.[25] **Table 1** summarises which datasets we will use in this study and for what purposes.

Table 1: Datasets and their purposes in the two data environments to be used in this study

Data type	Purpose in this study	Data environment	Dataset
Primary care	• Identify study population using the most recent eGFR measure to the index NSTEMI hospitalisation (derived from serum creatinine lab test results). • Measure confounders.	BHF SDE	GDPPR (primary care)
		NHS Data Lake	-
Secondary care routine hospital admission data	• Identify study population (people admitted to hospital for NSTEMI). • Measure confounders. • Define exposure status. • Define outcomes. • Collate main resource use measures (e.g. hospital length of stay, critical care bed-days).	BHF SDE	HES APC
		NHS Data Lake	SUS
Secondary care CVD audit data	• Identify study population (people admitted to hospital for NSTEMI). • Measure confounders. • Define exposure status. • Define outcomes.	BHF SDE	MINAP (NICOR)
		NHS Data Lake	MINAP (NICOR)

	• Collate main resource use measures (e.g. hospital length of stay, critical care bed-days).		
Secondary care kidney audit data	• Define subgroups (people receiving long-term dialysis, transplant recipients). • Define outcomes (AKI using dated AKI alerts, long-term dialysis).	BHF SDE	-
		NHS Data Lake	UKRR
Death data	• Define study population and outcomes.	BHF SDE	Civil Registry Deaths (death data)
		NHS Data Lake	Civil Registry Deaths (death data)

AKI: acute kidney injury; AMI: acute myocardial infarction; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; GDPPR: General Practice Extraction Service (GPES) Data for Pandemic Planning and Research; HES-APC: Hospital Episode Statistics – Admitted Patient Care; MINAP: Myocardial Ischaemia National Audit Project; NICOR: National Institute for Cardiovascular Outcomes Research; NHS: National Health Service; NSTEMI: non-ST segment elevation myocardial infarction

We will use the target trial emulation framework to clearly specify the inclusion/exclusion criteria, treatment strategies, assignment procedures, outcomes, follow-up, causal contrasts of interest, and analyses for the target trial and the observational emulation (**Table 2**).[21,22] Using this framework will help us identify and minimise the risk of biases impacting our comparative clinical and cost-effectiveness analyses.

Table 2: Description of the hypothetical target trial and observational emulation for the comparative- and cost-effectiveness analyses

	Target trial	**Observational emulation**
Eligibility criteria	People with CKD stages 3a-5D hospitalised for NSTEMI in England.	People with a latest eGFR<60mL/min/1.73m^2 measured in primary care prior to an index NSTEMI hospitalisation recorded in routine data in England.
Treatment strategies	Participants randomly assigned to: • Conservative management (i.e., no angiography and/or PCI or CABG within 7 days of admission) or • Early (within 7 days of admission) coronary angiography and, if indicated, coronary revascularisation (PCI or CABG) during the index NSTEMI hospitalisation.	Participants recorded as having either: • Conservative management (i.e., no record of angiography and/or PCI and/or CABG within 7 days of admission) or • Early (within 7 days of admission) coronary angiography and/or PCI and/or CABG recorded during the index NSTEMI hospitalisation.
Assignment procedures	Participants randomly assigned to one of two treatment strategies at NSTEMI admission (unblinded).	People are observed/recorded as receiving early invasive or conservative NSTEMI management during the first 7 days of the index NSTEMI hospitalisation. Conservative management if there is no record of early invasive NSTEMI management.
Follow-up	Follow-up begins on the NSTEMI admission date, synchronous with randomisation and eligibility evaluation. Follow-up ends at the earliest of the outcome event, migration out of England, or death (if not the outcome).	Follow-up begins on the NSTEMI admission date, synchronous with eligibility evaluation. Follow-up ends at the earliest of the outcome event, migration out of England, or death (if not the outcome).
Outcomes	**Primary:** All-cause mortality up to 1-year follow-up.	Same (but based on coded diagnoses in the health record, rather than adjudicated by clinicians).

	Target trial	Observational emulation
	Secondary: *Mortality* All-cause mortality up to 3-years follow-up. *Cardiovascular (adjudicated by clinicians)* 3-point MACE (recurrent MI, stroke, CVD-specific death) up to 1- and 3-years follow-up. Individual components of MACE up to 1- and 3-years follow-up. Heart failure hospitalisation up to 1- and 3-years follow-up. *Kidney (adjudicated by clinicians)* AKI up to 1- and 3-years follow-up. Dialysis up to 1- and 3-years follow-up. *Cost-effectiveness endpoints* Life-years at 1- and 3-years follow-up. QALYs at 1- and 3-years follow-up. Total costs at 1- and 3-years follow-up. Incremental net monetary benefit at 1- and 3-years follow-up.	
Causal contrasts of interest	Intention-to-treat effect for being randomised to either conservative or early invasive NSTEMI management. Average treatment effect.	Observational analogue of the intention-to-treat effect.[21] The IV analysis will use the 'tendency to manage' with early invasive versus conservative cardiac management strategy at the hospital in which the person is hospitalised for NSTEMI. The 'tendency to manage' is measured as the proportion of NSTEMI

	Target trial	Observational emulation
		cases in the 6-months prior managed with early invasive versus conservative NSTEMI management. Average treatment effect.
Statistical analysis	**Clinical effectiveness outcomes** Survival analysis using Cox proportional hazards regression for all time-to-event outcomes, adjusting for chance imbalances in covariates between treatment groups. Average treatment effect reported as the hazard ratio and survival differences, with 95% CI. **Cost-effectiveness outcomes** Generalised linear models with appropriate distributions and link functions based on the nature of the data, adjusting for chance imbalances in covariates between treatment groups.	**Clinical effectiveness outcomes** We will use (1) clone-censor-weight[26] and (2) IV analysis[27] to account for immortal time bias and confounding by indication. The clone-censor-weight analysis will use a Cox proportional hazards model to estimate the inverse probability of censoring weights, adjusting for all covariates measured at baseline which may predict censoring in the cloned dataset. The hazard ratios and survival differences will then be calculated using a second-stage Cox proportional hazards model, adjusted for measured confounders. We will calculate 95% CI using robust standard errors.[28] The IV analysis will use a two-stage residual inclusion (2SRI) analysis,[29] using the 'tendency to manage' as the instrument.[30] The hazard ratios will be calculated from the second-stage Cox proportional hazards model.[29] We will calculate 95% CI using nonparametric bootstrapping. **Cost-effectiveness outcomes** Generalised linear models with appropriate distributions and link functions based on the nature of the data will be used to compare life-years, quality adjusted life years (QALYs), total costs, and incremental net monetary benefit between the two NSTEMI management strategies. Treatment effects will be estimated from the clone-censor-weight analysis to reduce the risk of immortal time bias.

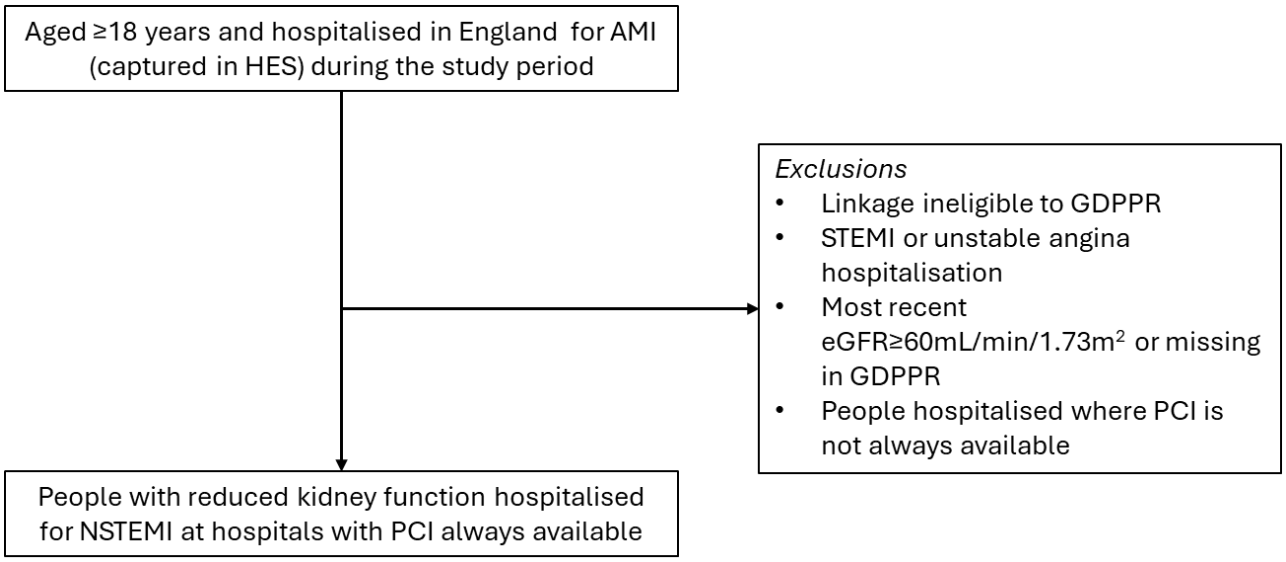
AKI: acute kidney injury; AMI: acute myocardial infarction; BHF: British Heart Foundation; CABG: coronary artery bypass graft; CKD: chronic kidney disease; CI: confidence interval; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; GDPPR: General Practice Extraction Service (GPES) Data for

Pandemic Planning and Research; HES: Hospital Episode Statistics; IV: instrumental variable; NICOR: National Institute for Cardiovascular Outcomes Research; NSTEMI: non-ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention; SDE: secure data environment

Study Population

We will include people aged ≥18 years with an incident NSTEMI hospitalisation captured in Hospital Episode Statistics Admitted Patient Care (HES-APC) on or after 1 November 2019 who are eligible for linkage to primary care data (**Figure 1**). The Myocardial Ischaemia National Audit Project (MINAP) data will be used to supplement HES-APC data for NSTEMI hospitalisations. Any events earlier than 1 November 2019 will not be included, since the General Practice Extraction Service data for pandemic planning and research (GDPPR), the primary care data source in the SDE, includes only people who were registered with a general practice in England and alive at this date. We will use International Classification of Diseases 10th revision (ICD-10) codes for NSTEMI (**Supplementary table 1**) in the first or second diagnostic position of the first episode in a spell to define an NSTEMI hospitalisation in HES-APC. Details on variables used to define NSTEMI in MINAP data are provided in **Supplementary table 2**.

Figure 1: Study population flow diagram for the planned cohort study.



AMI: acute myocardial infarction; HES: Hospital Episode Statistics; eGFR: estimated glomerular filtration rate; GDPPR: General Practice Extraction Service Data for pandemic planning and research; NSTEMI: non-ST elevation myocardial infarction; PCI: percutaneous coronary intervention

We will focus our analyses on those initially admitted to hospitals where PCI is always available (primary PCI hospitals). In England, hospitals have varying schedules for PCI service availability, ranging from never having PCI services available (requiring selective patient transfer to a hospital with PCI capability), to always having PCI services available. Pilot work using MINAP data[31] suggests that analyses will need to be restricted to people hospitalised where PCI is always available (primary PCI hospitals) in order to make fair comparisons for the comparative effectiveness of early invasive versus conservative NSTEMI management in routinely collected health data (**Supplementary table 3**).

Descriptive analyses on variation in NSTEMI management will include those hospitalised between 1 November 2019 to 30 September 2024. The comparative and cost-effectiveness analyses will further exclude people with an index NSTEMI hospitalisation between 1 November 2019 to 1 May 2020, since the lookback window to define the instrument for the IV analysis ('the tendency to manage') is 6 months.

We will define people with evidence of reduced kidney function, rather than those meeting the Kidney Disease Improving Global Outcomes (KDIGO) guidelines to define CKD with two eGFR measures <60mL/min/1.73m^2 separated by at least 90 days,[32] to avoid issues with missing data and survivor biases in selecting our sample within these routinely collected datasets.[33]

Subgroup populations of interest

There is considerable uncertainty as to the balance of benefits versus risks of early invasive versus conservative NSTEMI management for particular subgroups of people; namely, in people who are elderly,[34,35] who are more frail,[36] and in those with advanced kidney disease.[15,37] Thus, we pre-specify the following subgroups for which we will investigate treatment effect heterogeneity: (1) eGFR stages 3a, 3b, 4, and 5 (including those with a history of kidney replacement therapy); (2) age group (18-64, 65-74, 75-84, 85+); and hospital frailty risk score (low, intermediate, and high risk).[38]

Management strategies

The management strategies of interest are early invasive versus conservative NSTEMI management received during the index NSTEMI hospitalisation (**Table 3**). Early invasive

cardiac management will be defined as the individual being recorded as receiving at least one of: (1) invasive coronary angiography; (2) PCI; and (3) CABG within the first 7 days of the NSTEMI hospitalisation. While NICE guidelines recommend coronary angiography and follow-on PCI either immediately (for those whose condition is unstable) or within 72 hours of first admission for those at higher risk of adverse CVD events,[4] we allow for up to 7 days based on pilot data (**Supplementary figure 1**) and on the advice from our clinical collaborators. Those without records of early invasive NSTEMI management within 7 days of admission will be considered as receiving conservative management. **Supplementary table 4** describes the variables (MINAP) and Office of Population Censuses and Surveys (OPCS) codes (from HES) used to define early invasive cardiac management.

Table 3. Description of early invasive and conservative cardiac management, derived from NICE guideline NG185[4]

Management strategy	**Details**
Conservative management	• Offer ticagrelor plus aspirin as dual antiplatelet therapy (low bleeding risk) • Consider clopidogrel plus aspirin as dual antiplatelet therapy or aspirin alone (high bleeding risk) • Consider ischaemia testing prior to discharge
Early invasive cardiac intervention	• Offer immediate angiography if condition is unstable • Consider dual antiplatelet therapy • Offer angiography and follow-on PCI (if indicated) within 72 hours • Offer systemic unfractionated heparin in catheter laboratory if having PCI • Offer a drug-eluting stent if stenting indicated

NICE: National Institute for Health and Care Excellence; PCI: percutaneous coronary intervention

Outcomes

The primary outcome will be death up to 1-year follow-up (**Table 4**). Death at 3-years follow-up will be a secondary outcome. We will use the death date from the Civil Registry of Deaths to define mortality in the SDE.

Additional secondary outcomes are grouped as cardiovascular-specific and kidney-specific outcomes, and all up to 3-years follow-up. The cardiovascular-specific outcomes will include 3-point MACE (recurrent MI, stroke, CVD-specific death), the individual components of MACE, and heart failure hospitalisation. The kidney-specific outcomes are acute kidney injury (AKI) and new dialysis (chronic or acute).

Several health economic outcomes will also be investigated, including life-years, quality adjusted life years (QALYs), total costs, and incremental net monetary benefit. These will all be reported for 1-year follow-up, consistent with the main clinical analysis. We will also run sensitivity analyses to investigate whether the results are robust according to the choice of time horizon (3-years vs 1-year).

Table 4. Outcomes included in this study

Category	**Outcome**	**Type of outcome**	**Definition**
Clinical effectiveness: Mortality	All-cause mortality up to 1-year follow-up.	Time-to-event	Death date in the Civil Registry of Deaths.
	All-cause mortality up to 3-years follow-up.	Time-to-event	Death date in the Civil Registry of Deaths.
	CVD-specific mortality up to 3-years follow-up.	Time-to-event	Death date and cause of death in the Civil Registry of Deaths.
Clinical effectiveness: Cardiovascular	3-point MACE (recurrent AMI, stroke, CVD-specific death) and it's individual components up to 3-years follow-up.	Time-to-event	Death date and cause of death in the Civil Registry of Deaths. HES-APC admission with a diagnosis for AMI (STEMI or NSTEMI) or stroke in the first or second diagnostic position of any episode within a spell following the index NSTEMI hospitalisation. MINAP admission with a diagnosis for AMI (STEMI or NSTEMI) following the index NSTEMI hospitalisation.
	Heart failure hospitalisation up to 3-years follow-up.	Time-to-event	HES-APC admission with a diagnosis for heart failure in the first or second diagnostic position of any episode within a spell following the index NSTEMI hospitalisation.

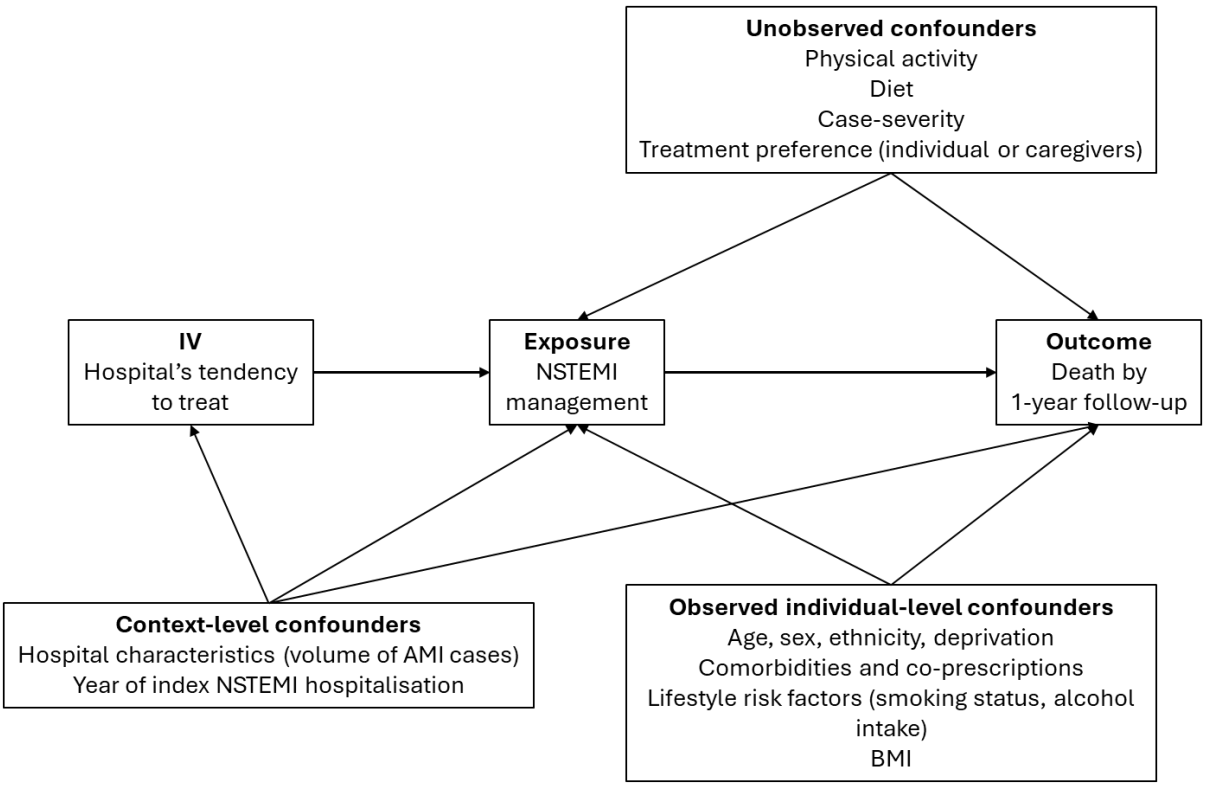
Clinical effectiveness: Kidney	AKI up to 3-years follow-up.	Time-to-event	UK Renal Registry AKI alert (NHS Data Lake only). AKI coded using ICD-10 codes in the first or second diagnostic position in any episode following the index NSTEMI admission date in HES-APC data.
	Dialysis up to 3-years follow-up.	Time-to-event	UK Renal Registry chronic dialysis start date (NHS Data Lake only). Dialysis coded using OPCS codes in any episode following the index NSTEMI admission date in HES-APC data.
Cost-effectiveness	Life-years at 1- and 3-years follow-up.	Continuous	Years of life gained following the intervention.
	QALYs at 1- and 3-years follow-up.	Continuous	Years of life gained adjusted for quality of life.
	Total costs at 1- and 3-years follow-up.	Continuous	Calculated by combining each resource use item with its corresponding unit cost, focusing on items anticipated to be the major drivers of incremental costs including cardiac intervention. Unit costs are sourced from national cost databases.
	Incremental net monetary benefit at 1- and 3-years follow-up.	Continuous	Calculated by multiplying the incremental QALYs by the willingness-to-pay threshold and subtracting the incremental cost.

AKI: acute kidney injury; AMI: acute myocardial infarction; CVD: cardiovascular; GDPPR: General Practice Extraction Service (GPES) Data for Pandemic Planning and Research; HES-APC: Hospital Episode Statistics-Admitted Patient Care; MACE: major adverse cardiovascular event; NSTEMI: non-ST segment elevation myocardial infarction; OPCS: Office of Population Censuses and Surveys; QALYs: quality adjusted life years

Potential confounders

Our simplified directed acyclic graph (DAG) informs the identification of several potential confounders, both measured and unmeasured (**Figure 2**). We will describe several measured potential confounders at the individual-level in our analyses. These include age, sex, ethnicity, deprivation (measured using the Index of Multiple Deprivation[39]), comorbidities (including history of AMI, chronic obstructive pulmonary disease (COPD), heart failure, hypertension, peripheral vascular disease, stroke, type 2 diabetes mellitus, unstable angina), baseline eGFR measured in primary care, history of kidney replacement therapy, history of AKI, and lifestyle risk factors (smoking status, alcohol intake, body-mass index).

Figure 2: Directed acyclic graph (DAG) illustrating the causal relationship between the instrumental variable, exposure, and primary outcome



AMI: acute myocardial infarction; BMI: body-mass index; IV: instrumental variable; NSTEMI: non-ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention

Measured context-level confounders will also be described, including year of index NSTEMI, since NSTEMI management and outcomes may have changed over the study time period. This will also account for year-on-year changes in NSTEMI management during the COVID-19 pandemic. Hospital-specific characteristics, like volume of AMI cases seen in the past year, are also context-level confounders and likely influence the tendency of the hospital to manage conservatively versus early invasively (i.e., the instrument), the exposure, and the outcome. Unmeasured potential confounders include diet, physical activity, case-severity, and patient and caregivers' preference for treatment. The clone-censor-weight[26,40] analyses assume no unmeasured confounding after adjusting for measured confounders. The IV analysis will reduce the risk of confounding by unmeasured confounders subject to the IV assumptions.[27]

Analysis

Description of NSTEMI management variation in England

We will first describe the baseline study population, overall and split by pre-COVID (November 2019 to 15 March 2020), COVID (COVID 16 March 2020 to 17 April 2022) and post-COVID (18 April 2022 to maximum follow-up) time periods.[41] Variation in the proportion of people receiving early invasive versus conservative NSTEMI management across English hospitals during these time periods will be described. These analyses will offer insight as to the extent of NSTEMI management variation among people hospitalised for NSTEMI with reduced kidney function, and to what extent this variation is explained by individual- and context-level characteristics. The unexplained variation across hospitals will be used in the target trial emulation to compare NSTEMI management strategies.

We will also describe the time taken from arrival to admission and to invasive NSTEMI management (earliest record of angiography, PCI, or CABG) and whether this changed during the COVID pandemic.

Comparative clinical effectiveness analysis

Our observational emulation is prone to two major forms of bias common in observational studies: immortal time bias and unmeasured confounding. We will use clone-censor-weighting to remove immortal time bias and an instrumental variable analysis to reduce the risk of unmeasured confounding bias. To our knowledge, clone-censor-weighting and instrumental variable analyses have never been combined in a single analysis. Because this would require significant methodological work, we will conduct these analyses separately. In an additional analysis, we will conduct a propensity score analysis with inverse probability of treatment weighting. Treatment effect estimates across the clone-censor-weighting with inverse probability of censoring weighting, the instrumental variable analysis, and the propensity score analysis will be compared to consider the impact of immortal time and confounding bias in this study.

Clone-censor-weight to address immortal time bias

Immortal time bias arises when there is a delay between the treatment decision and its actual initiation, creating an 'immortal' period during which people must survive to receive treatment, can lead to an overestimation of the treatment effect.[20,26] In this study, people hospitalised for NSTEMI and who are selected for early invasive management do not necessarily receive this management on the same day as admission. NICE guidelines recommend early invasive NSTEMI management within 3 days of admission.[4] Our pilot data show that this can be up to 7 days after admission (**Supplementary figure 1**). Because of the high proportion of deaths observed in the first 7 days of NSTEMI hospitalisation also observed in our pilot data (**Supplementary figure 2**), we are at risk of overestimating the effect of early invasive versus conservative management. We will use a clone-censor-weight analysis, which ensures that comparisons between the NSTEMI management strategies are fair to avoid inflating survival estimates for the early invasive management group (**Supplementary methods 1**).[26] These analyses will use Cox proportional hazards models in both the censoring step (to calculate inverse probability of censoring weights[26]) and the treatment effect estimation step (which will account for informative censoring in the cloned dataset) (**Supplementary methods 1**).

Instrumental variable analysis to understand the impact of residual confounding

Confounding by indication, where indications for early invasive versus conservative NSTEMI management also affect the outcome, is also of concern in this study. Most observational comparative effectiveness studies adjust for measured confounders using multivariable regression models (including propensity score models). These analyses assume there are no unmeasured confounders biasing the treatment effect. In this study, we anticipate unmeasured or imperfectly measured confounders like frailty and case-severity to bias our treatment effect estimates. In addition to clone-censor-weighting, we will conduct an IV analysis to reduce the risk of confounding bias, subject to the IV assumptions (**Supplementary methods 2**).[27] The 'tendency to manage' patients with early invasive versus conservative NSTEMI management at the hospital-level in the 6-months prior to each person's hospitalisation will be used as the instrument (**Figure 2**). Like the first alternative analysis (propensity score), this analysis will also be subject to immortal time bias, since the NSTEMI management strategy will be defined across the initial 7 days of NSTEMI hospitalisation. We will compare the treatment effect estimates from this analysis with those from the propensity score analysis to understand the impact of residual confounding for this treatment comparison.

Briefly, we will use the two stage residual inclusion (2SRI) method[29] for the IV analysis to estimate average treatment effects. The first stage propensity score model will estimate the probability of early invasive versus conservative NSTEMI management, conditional on the instrument and measured confounders. The generalised residuals from the first stage model will then be included as an independent variable in the second stage outcome model to reduce the risk of bias from unmeasured confounders.[29,44] We will then estimate treatment effects for clinical outcomes using Cox proportional hazards models. To calculate standard errors and 95% confidence intervals (CI), we will use nonparametric bootstrapping with replacement.[45] Further details are provided in **Supplementary methods 2.**

Propensity score analysis to understand the impact of immortal time bias

In this alternative analysis, we will estimate the treatment effect using a propensity score model with inverse probability of treatment weighting (**Supplementary methods 3**). Propensity scores will be estimated using logistic regression and inverse probability of treatment weights (IPTW) derived thereafter. Two approaches to estimated treatment effects will be applied: 1) IPTW outcome model [42] (**Supplementary methods 3**) and 2) IPTW with regression adjustment (weighted regression), both approaches will consider stabilised and non-stabilised weights. The weighted regression is doubly robust, as it will yield consistent estimates provided either the propensity score or the outcome regression model is correctly specified.[43]

This analysis will be subject to immortal time bias, since the propensity for early invasive versus conservative NSTEMI management will be calculated as a binary 'treatment' variable over the first 7-days of the NSTEMI hospitalisation. We will compare the treatment effect estimates from the clone-censor-weight model with the propensity score model to understand the impact of immortal time bias in our alternative analysis.

Cost-effectiveness analysis

We will evaluate the cost-effectiveness of early invasive versus conservative NSTEMI management among people with reduced kidney function (**Supplementary methods 4**). This analysis will take the same standpoints as the comparative effectiveness analysis, in reporting costs and outcomes over a 1-year interval for all people in the study using the same data sources.

In addition to the total life years, we will report QALYs up to one year by combining each person's survival time with appropriate health-related quality of life (HRQoL) estimates from literature. The unit costs will be taken from the NHS reference costs and Personal Social Services Research Unit costs and will be combined with each individual's resource use measures to calculate total hospital costs per person up to 1-year. Evidence suggests that major costs following invasive NSTEMI management are primarily incurred within the first year, and that for people who don't have a subsequent hospital admission, HRQoL is stable from 6- to 12-months post invasive NSTEMI management.[46-48]

We will report the incremental net monetary benefit, by calculating the incremental QALYs at 1-year of the conservative versus invasive NSTEMI management strategies, valuing these at NICE recommended levels of willingness to pay for a QALY gain (£20,000 and £30,000) and subtracting from this, the incremental costs of conservative versus invasive NSTEMI management.

Sensitivity analyses

For the comparative effectiveness analyses, we will repeat the instrumental variable analysis using an alternative data source, the NHS Data Lake, which includes linkage to the UK Renal Registry.[25] This linkage, unavailable in the SDE at the time of writing this protocol, is critical to accurately capture kidney-related outcomes, including AKI, dialysis, and ESKD.

Further, we will evaluate how changing the window (1) to define early invasive NSTEMI management (from 7 days to 3 days) and (2) to define the instrumental variable (from 6-month lookback to 1-year lookback) may change treatment effect estimates.

For the cost-effectiveness analyses, we will extend the time horizon to 3-years to capture potential longer-term impacts (e.g., from receipt of renal replacement therapy).

Patient and Public Involvement (PPI)

This study has benefited from PPI since inception. The study was designed in collaboration with two PPI representatives. These representatives reviewed and contributed to the grant being successful. This study's protocol for the BHF Data Science Centre approvals process was also presented to a PPI panel prior to being approved. PPI representatives made valuable comments on the protocol, which were integrated into the updated version ultimately approved by the BHF Data Science Centre review committee. These representatives will also critically review study results and future manuscripts and be co-authors on peer-reviewed publications. They will also help advise how best to disseminate these study results.

ETHICS AND DISSEMINATION

Ethics

This study's protocol was reviewed and approved by the BHF Data Science Scientific and Public Panels: https://bhfdatasciencecentre.org/projects/ccu066-changes-in-acute-cardiac-care-of-patients-with-reduced-kidney-function-during-the-covid-19-pandemic-2/, as well as the London School of Hygiene & Tropical Medicine Ethics Committee (reference 28740). The CVD-COVID-UK/COVID-IMPACT programme, led by the BHF Data Science Centre (https://bhfdatasciencecentre.org/), received approval to access data in NHS England's SDE service for England from the Independent Group Advising on the Release of Data (IGARD) (https://digital.nhs.uk/about-nhs-digital/corporate-information-and-documents/independent-group-advising-on-the-release-of-data) via an application made in the Data Access Request Service (DARS) Online system (ref. DARS-NIC-381078-Y9C5K) (https://digital.nhs.uk/services/data-access-request-service-dars/dars-products-and-services). The CVD-COVID-UK/COVID-IMPACT Approvals & Oversight Board (https://bhfdatasciencecentre.org/areas/cvd-covid-uk-covid-impact/) subsequently granted approval to this project to access the data within NHS England's SDE service for England.

The UK Renal Registry is owned and operated by the UK Kidney Association (a trading name of the Renal Association). The latest privacy notice for patients can be found on the UKKA website, which not only covers the UK Renal Registry but all uses of patient data at the UK Kidney Association. Sharing with NHS England is covered in the section "Who does the UKKA share data with? And why? starting on pg 7: https://ukkidney.org/sites/renal.org/files/UKKA%20Patient%20Privacy%20Notice%20May%202024.pdf. The UK Renal Registry holds Section 251 permission for both audit and research. There are no specific conditions applied as part of the approvals.

Dissemination

We will publish findings from this study in peer-reviewed journals. Re-usable code will also be developed and published on Github, in line with standards and regulations set

out by the BHF Data Science Centre. This work will add to the small evidence base of observational studies which currently suggests that invasive cardiac investigation and treatment has a net benefit for people with kidney impairment.[13,14] This work will also highlight the need for more sustainable linkages of disparate health data, as well as randomised evidence addressing this important clinical question, as the prevalence of multimorbidity, in particular co-morbid cardiovascular and kidney disease grows in the UK and throughout the world.

REFERENCES

1. Santopinto JJ, Fox KA, Goldberg RJ, et al. Creatinine clearance and adverse hospital outcomes in patients with acute coronary syndromes: findings from the global registry of acute coronary events (GRACE). *Heart (British Cardiac Society)*. Sep 2003;89(9):1003-8. doi:10.1136/heart.89.9.1003
2. Sofia Sederholm L, Joakim A, Karolina S, Mats F, Eva S. Prevalence and prognostic impact of chronic kidney disease in STEMI from a gender perspective: data from the SWEDEHEART register, a large Swedish prospective cohort. *BMJ Open*. 2015;5(6):e008188. doi:10.1136/bmjopen-2015-008188
3. Hanna EB, Chen AY, Roe MT, Saucedo JF. Characteristics and in-hospital outcomes of patients presenting with non-ST-segment elevation myocardial infarction found to have significant coronary artery disease on coronary angiography and managed medically: stratification according to renal function. *Am Heart J*. Jul 2012;164(1):52-7.e1. doi:10.1016/j.ahj.2012.04.009
4. NICE guideline [NG185]: Acute coronary syndrome. Web. NICE. Accessed March 10, 2022. https://www.nice.org.uk/guidance/ng185
5. Grines CL, Browne KF, Marco J, et al. A Comparison of Immediate Angioplasty with Thrombolytic Therapy for Acute Myocardial Infarction. *New England Journal of Medicine*. 1993;328(10):673-679. doi:doi:10.1056/NEJM199303113281001
6. A Clinical Trial Comparing Primary Coronary Angioplasty with Tissue Plasminogen Activator for Acute Myocardial Infarction. *New England Journal of Medicine*. 1997;336(23):1621-1628. doi:doi:10.1056/NEJM199706053362301
7. Teixeira R, Gonçalves L, Gersh B. Acute myocardial infarction — Historical notes. *International Journal of Cardiology*. 2013/09/01/ 2013;167(5):1825-1834. doi:https://doi.org/10.1016/j.ijcard.2012.12.066
8. Konstantinidis I, Nadkarni GN, Yacoub R, et al. Representation of Patients With Kidney Disease in Trials of Cardiovascular Interventions: An Updated Systematic Review. *JAMA internal medicine*. Jan 2016;176(1):121-4. doi:10.1001/jamainternmed.2015.6102
9. Tonelli M, Wiebe N, Guthrie B, et al. Comorbidity as a driver of adverse outcomes in people with chronic kidney disease. *Kidney Int*. Oct 2015;88(4):859-66. doi:10.1038/ki.2015.228
10. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes: Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). *European heart journal*. 2023;44(38):3720-3826. doi:10.1093/eurheartj/ehad191
11. Barrett BJ, Parfrey PS. Clinical practice. Preventing nephropathy induced by contrast medium. *The New England journal of medicine*. Jan 26 2006;354(4):379-86. doi:10.1056/NEJMcp050801
12. Rear R, Bell RM, Hausenloy DJ. Contrast-induced nephropathy following angiography and cardiac interventions. *Heart (British Cardiac Society)*. 2016;102(8):638. doi:10.1136/heartjnl-2014-306962
13. Shaw C, Nitsch D, Lee J, Fogarty D, Sharpe CC. Impact of an Early Invasive Strategy versus Conservative Strategy for Unstable Angina and Non-ST Elevation Acute

Coronary Syndrome in Patients with Chronic Kidney Disease: A Systematic Review. *PLOS ONE*. 2016;11(5):e0153478. doi:10.1371/journal.pone.0153478
14. Shaw C, Nitsch D, Steenkamp R, et al. Inpatient coronary angiography and revascularisation following non-ST-elevation acute coronary syndrome in patients with renal impairment: a cohort study using the Myocardial Ischaemia National Audit Project. *PLoS One*. 2014;9(6):e99925. doi:10.1371/journal.pone.0099925
15. Scott J, Bidulka P, Taylor DM, et al. Management and outcomes of myocardial infarction in people with impaired kidney function in England. *BMC Nephrology*. 2023/11/02 2023;24(1):325. doi:10.1186/s12882-023-03377-x
16. Mansfield KE, Mathur R, Tazare J, et al. Indirect acute effects of the COVID-19 pandemic on physical and mental health in the UK: a population-based study. *The Lancet Digital Health*. 2021/04/01/ 2021;3(4):e217-e230. doi:https://doi.org/10.1016/S2589-7500(21)00017-0
17. Wu J, Mamas M, Rashid M, et al. Patient response, treatments, and mortality for acute myocardial infarction during the COVID-19 pandemic. *European Heart Journal - Quality of Care and Clinical Outcomes*. 2020;7(3):238-246. doi:10.1093/ehjqcco/qcaa062
18. Fox CS, Muntner P, Chen AY, et al. Use of evidence-based therapies in short-term outcomes of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction in patients with chronic kidney disease: a report from the National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network registry. *Circulation*. Jan 26 2010;121(3):357-65. doi:10.1161/circulationaha.109.865352
19. Bhatia S, Arora S, Bhatia SM, et al. Non-ST-Segment-Elevation Myocardial Infarction Among Patients With Chronic Kidney Disease: A Propensity Score-Matched Comparison of Percutaneous Coronary Intervention Versus Conservative Management. *J Am Heart Assoc*. Mar 10 2018;7(6)doi:10.1161/jaha.117.007920
20. Yadav K, Lewis RJ. Immortal Time Bias in Observational Studies. *Jama*. 2021;325(7):686-687. doi:10.1001/jama.2020.9151
21. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol*. 2016;183(8):758-764. doi:10.1093/aje/kwv254
22. Hernán MA, Wang W, Leaf DE. Target Trial Emulation: A Framework for Causal Inference From Observational Data. *Jama*. 2022;328(24):2446-2447. doi:10.1001/jama.2022.21383
23. Wood A, Denholm R, Hollings S, et al. Linked electronic health records for research on a nationwide cohort of more than 54 million people in England: data resource. *BMJ (Clinical research ed)*. Apr 7 2021;373:n826. doi:10.1136/bmj.n826
24. National Institute for Cardiovascular Outcomes Research (NICOR): Home. Web. NICOR. Accessed 12 September, 2023. https://www.nicor.org.uk/
25. UK Renal Registry (UKRR): Home. Web. UKRR. Accessed 12, 2023. https://ukkidney.org/about-us/who-we-are/uk-renal-registry
26. Maringe C, Benitez Majano S, Exarchakou A, et al. Reflection on modern methods: trial emulation in the presence of immortal-time bias. Assessing the benefit of major surgery for elderly lung cancer patients using observational data. *International Journal of Epidemiology*. 2020;49(5):1719-1729. doi:10.1093/ije/dyaa057

27. Baiocchi M, Cheng J, Small DS. Instrumental variable methods for causal inference. *Stat Med*. Jun 15 2014;33(13):2297-340. doi:10.1002/sim.6128
28. Limozin JM, Seaman SR, Su L. Inference procedures in sequential trial emulation with survival outcomes: comparing confidence intervals based on the sandwich variance estimator, bootstrap and jackknife. *asXiv*. 2024;
29. Terza JV, Basu A, Rathouz PJ. Two-stage residual inclusion estimation: Addressing endogeneity in health econometric modeling. *Journal of Health Economics*. 2008/05/01/ 2008;27(3):531-543. doi:https://doi.org/10.1016/j.jhealeco.2007.09.009
30. Brookhart MA, Schneeweiss S. Preference-based instrumental variable methods for the estimation of treatment effects: assessing validity and interpreting results. *The international journal of biostatistics*. 2007;3(1):Article 14. doi:10.2202/1557-4679.1072
31. Bidulka P, Weston C, de Belder M, et al. Acute myocardial infarction treatment variation and disparities by kidney function: a cross-sectional study using the Myocardial Ischaemia National Audit Project (MINAP).
32. Stevens PE, Levin A. Evaluation and Management of Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline. *Annals of Internal Medicine*. 2013/06/04 2013;158(11):825-830. doi:10.7326/0003-4819-158-11-201306040-00007
33. Iwagami M, Tomlinson LA, Mansfield KE, et al. Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared with national survey and registry data in the United Kingdom. *Nephrol Dial Transplant*. Apr 1 2017;32(suppl_2):ii142-ii150. doi:10.1093/ndt/gfw318
34. Kotanidis CP, Mills GB, Bendz B, et al. Invasive vs. conservative management of older patients with non-ST-elevation acute coronary syndrome: individual patient data meta-analysis. *European heart journal*. 2024;45(23):2052-2062. doi:10.1093/eurheartj/ehae151
35. Kunadian V, Mossop H, Shields C, et al. Invasive Treatment Strategy for Older Patients with Myocardial Infarction. *New England Journal of Medicine*. 2024;391(18):1673-1684. doi:doi:10.1056/NEJMoa2407791
36. Sanchis J, Bueno H, García-Blas S, et al. Invasive Treatment Strategy in Adults With Frailty and Non–ST-Segment Elevation Myocardial Infarction: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Network Open*. 2024;7(3):e240809-e240809. doi:10.1001/jamanetworkopen.2024.0809
37. Majmundar M, Ibarra G, Kumar A, et al. Invasive Versus Medical Management in Patients With Chronic Kidney Disease and Non‐ST‐Segment‐Elevation Myocardial Infarction. *Journal of the American Heart Association*. 2022;11(12):e025205. doi:doi:10.1161/JAHA.121.025205
38. Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *Lancet (London, England)*. May 5 2018;391(10132):1775-1782. doi:10.1016/s0140-6736(18)30668-8
39. National statistics: English indices of deprivation 2019. Web. Ministry of Housing, Communities & Local Government. Accessed 10 June, 2024. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019
40. Gaber CE, Ghazarian AA, Strassle PD, et al. De-Mystifying the Clone-Censor-Weight Method for Causal Research Using Observational Data: A Primer for Cancer

Researchers. *Cancer Medicine*. 2024;13(23):e70461. doi:https://doi.org/10.1002/cam4.70461
41. Edouard Mathieu HR, Lucas Rodés-Guirao, Cameron Appel, Charlie Giattino, Joe Hasell, Bobbie Macdonald, Saloni Dattani, Diana Beltekian, Esteban Ortiz-Ospina, Max Roser. Coronavirus Pandemic (COVID-19). Web. Our World in Data. Accessed 25 October, 2024. https://ourworldindata.org/covid-stringency-index#citation
42. Stürmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. *Journal of internal medicine*. Jun 2014;275(6):570-80. doi:10.1111/joim.12197
43. Wooldridge JM. Inverse probability weighted estimation for general missing data problems. *Journal of Econometrics*. 2007/12/01/ 2007;141(2):1281-1301. doi:https://doi.org/10.1016/j.jeconom.2007.02.002
44. Basu A, Coe NB, Chapman CG. 2SLS versus 2SRI: Appropriate methods for rare outcomes and/or rare exposures. *Health Econ*. Jun 2018;27(6):937-955. doi:10.1002/hec.3647
45. Basu A. Person-centred treatment (PeT) effects: Individualized treatment effects using instrumental variables. *The Stata Journal*. 2015;15(2):397-410.
46. Siriyotha S, Pattanaprateep O, Srimahachota S, Sansanayudh N, Thakkinstian A, Limpijankit T. Factors associated with health-related quality of life in patients undergoing percutaneous coronary intervention: Thai PCI registry. *Front Cardiovasc Med*. 2023;10:1260993. doi:10.3389/fcvm.2023.1260993
47. Lee MMY, Petrie MC, Rocchiccioli P, et al. Invasive Versus Medical Management in Patients With Prior Coronary Artery Bypass Surgery With a Non-ST Segment Elevation Acute Coronary Syndrome. *Circ Cardiovasc Interv*. Aug 2019;12(8):e007830. doi:10.1161/circinterventions.119.007830
48. Nam J, Briggs A, Layland J, et al. Fractional flow reserve (FFR) versus angiography in guiding management to optimise outcomes in non-ST segment elevation myocardial infarction (FAMOUS-NSTEMI) developmental trial: cost-effectiveness using a mixed trial- and model-based methods. *Cost Eff Resour Alloc*. 2015;13:19. doi:10.1186/s12962-015-0045-9

AUTHOR CONTRIBUTIONS

PB, MdB, CW, DA, RG, DN conceived the study. PB, ZZ, and ZL wrote the first draft of the manuscript. RKH, JT, JS, SS, AJ, JD, MdB, CW, DA, RG, DN reviewed and commented on the manuscript.

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COMPETING INTERESTS STATEMENT

PB, ZZ, ZL, JT, JS, AJ and RG have nothing to declare. RKH has a contract with NHS England and has received financial support from NHS England to attend meetings/travel. SS declares previous grants or contracts from AstraZeneca, Johnson & Johnson, and CSL Vifor, consulting fees from AstraZeneca, CSL Vifor, and Boehringer-Ingelheim, payment or honoraria from AstraZeneca, Bayer, Menarini, Boehringer-Ingelheim, and CSL Vifor, and support for attending meetings from AstraZeneca, Novartis, and CSL Vifor. JD has received contracts from Alzheimer's Research UK (2022-2025) and British Heart Foundation (2019-2022), has received consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk, and Bayer, and received honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk, and Bayer. MdB declares membership of the executive committee of the DAPA-MI trial sponsored by AstraZeneca. CW has received personal payments for participation in educational events from Astra Zeneca, is an unpaid chair of a data safety monitoring board for Novo Nordisk Ltd, and is the clinical lead of the

Myocardial Ischaemia National Audit Project. DA is supported by Cancer Research UK and British Heart Foundation, and has received grants from Health Data Research UK, NIHR UK, Abbot Vascular for unrelated work, received royalties for ECG made Practical and ECG Problems books, has two patents planned, issued or pending (EP3277337A1 (cardiac assist device) and 2211616.4 (heart failure shunt device)), and is chair of the ESC-ACVC SCAD Study Group. DN is the UK Kidney Association Director of Informatics Research.

DATA AVAILABILITY

Pilot data to inform this protocol are from the NHS Data Lake. These data were accessed by RKH for health services audit. Researchers can request access to versions of these data by applying to the Health Quality Improvement Partnership (MINAP data) or NHS Research Ethics Committee (for HES data).

This protocol also describes future analyses which will use data from the NHS England's Secure Data Environment (SDE) service for England. Restrictions apply so that these data are not publicly available (https://digital.nhs.uk/services/secrue-data-enivronment-service). The CVD-COVID-UK/COVID-IMPACT programme, led by the BHF Data Science Centre (https://bhfdatasciencecentre.org/), received approval to access data in NHS England's SDE service for England from the Independent Group Advising on the Release of Data (IGARD) (https://digital.nhs.uk/about-nhs-digital/corporate-information-and-documents/independent-group-advising-on-the-release-of-data) via an application made in the Data Access Request Service (DARS) Online system (ref. DARS-NIC-381078-Y9C5K) (https://digital.nhs.uk/services/data-access-request-service-dars/dars-products-and-services). The CVD-COVID-UK/COVID-IMPACT Approvals & Oversight Board (https://bhfdatasciencecentre.org/areas/cvd-covid-uk-covid-impact/) subsequently granted

approval to this project to access the data within NHS England's SDE service for England. The de-identified data to be used in future work for this study will be made available to accredited researchers only. Those wishing to gain access to the data should contact bhfdsc@hdruk.ac.uk in the first instance.