diabetesresearchandclinicalpractice 222 (2025) 112082

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Comparative effect of aspirin versus clopidogrel monotherapy on incident type 2 diabetes in patients with atherosclerotic cardiovascular diseases: A target trial emulation study

Chengsheng Ju [a,b,1], Xi Xiong [a,c,d,1], David T.W. Lui [e], Vincent K.C. Yan [c], Matthew Adesuyan [a], Ming Xu [f], Frederick K. Ho [g], Carlos K.H. Wong [d,h,i], Ian C.K. Wong [c,d,j,k], Esther W.Y. Chan [c,d,l,m,**], Li Wei [a,d,n,*]

[a] Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom
[b] Institute of Cardiovascular Science, University College London, London, United Kingdom
[c] Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China
[d] Laboratory of Data Discovery for Health ($D^2$4H), Hong Kong Science and Technology Park, Hong Kong, China
[e] Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China
[f] Department of Clinical Pharmacy, School of Preclinical Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, China
[g] School of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom
[h] Department of Family Medicine and Primary Care, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China
[i] Department of Infectious Disease Epidemiology & Dynamics, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom
[j] Aston Pharmacy School, Aston University, Birmingham, United Kingdom
[k] Advanced Data Analytics for Medical Science (ADAMS) Limited, Hong Kong, China
[l] Department of Pharmacy, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China
[m] The University of Hong Kong Shenzhen Institute of Research and Innovation, Shenzhen, China
[n] Centre for Medicines Optimisation Research and Education, University College London Hospitals NHS Foundation Trust, London, United Kingdom

ARTICLE INFO

Keywords:
Type 2 diabetes
Aspirin
Atherosclerotic cardiovascular disease
Target trial emulation

ABSTRACT

Aims: To compare the effects of low-dose aspirin and clopidogrel on the risk of incident type 2 diabetes among patients with ASCVD.
Methods: This target trial emulation study was performed using the IQVIA Medical Research Data UK primary care database, including adults with an incident first ASCVD event who initiated low-dose aspirin or clopidogrel between 2004 and 2021. We applied an overlap weighting approach to balance treatment groups. The observational analogues of intention-to-treat and per-protocol effects were estimated using pooled logistic regression.
Results: A total of 111,292 ASCVD patients who initiated aspirin (n = 78,012) or clopidogrel (n = 33,280) were included. In intention-to-treat analyses, aspirin and clopidogrel had similar risks of diabetes (Hazard ratio [HR] 1.02, 95 % Confidence interval [CI] 0.96 to 1.07), cardiovascular events (1.00, 0.95 to 1.05), and bleeding events (1.02, 0.97 to 1.08). In per-protocol analyses, risks remained comparable for diabetes (1.06, 0.97 to 1.15), cardiovascular events (0.96, 0.89 to 1.03), and bleeding events (1.01, 0.92 to 1.10).
Conclusions: Aspirin and clopidogrel have similar risks of incident diabetes, cardiovascular events, and bleeding events among patients with ASCVD. The choice between these agents may thus be influenced more by factors like cost, patient preference, or tolerance than by clinical outcomes alone.

* Corresponding author at: Research Department of Practice and Policy, UCL School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, United Kingdom.
** Corresponding author at: Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China.
E-mail addresses: ewchan@hku.hk (E.W.Y. Chan), l.wei@ucl.ac.uk (L. Wei).
[1] These authors share first authorship.

https://doi.org/10.1016/j.diabres.2025.112082
Received 23 January 2025; Received in revised form 19 February 2025; Accepted 3 March 2025
Available online 8 March 2025

1. Introduction

Aspirin is one of the most widely used medications globally, known primarily for its role in the secondary prevention of atherosclerotic cardiovascular disease (ASCVD) [1]. While low-dose aspirin has also been considered for primary prevention of CVD and colorectal cancer, the benefits are modest and must be balanced against an elevated bleeding risk [1]. Additionally, the anti-inflammatory properties of aspirin have led to interest in its potential for diabetes prevention [2]. A recent post-hoc analysis of the Aspirin in Reducing Events in the Elderly (ASPREE) trial revealed a 15 % lower risk of incident type 2 diabetes among older adults with no long term conditions, with daily low-dose aspirin use over six years [3]. However, widespread aspirin use for diabetes prevention should be cautioned due to the increased risk of major bleeding, resulting in limited net benefit [3,4]. Previous studies, such as the Physicians' Health Study (PHS) and the Women's Health Study (WHS), have reported inconsistent findings on aspirin's impact on diabetes incidence [5,6]. Notably, a key limitation of the ASPREE, PHS, and WHS trials is their exclusion of patients with baseline CVD. As a result, the potential effects of aspirin on diabetes incidence in individuals with existing CVD, who may benefit most from its cardiometabolic effects, remain unclear [4].

Aspirin and other antiplatelet agents, such as clopidogrel, are fundamental in secondary prevention of cardiovascular events in patients who experience coronary artery disease (CAD), ischaemic stroke/transient ischaemic attack (TIA), or peripheral arterial disease (PAD) [7,8]. Long-term monotherapy with either aspirin or clopidogrel is recommended in international guidelines for management of these conditions [9–12]. However, controversies remain in the choice of specific antiplatelet treatment strategies concerning to their comparative cost and effectiveness, and safety profiles in different patient populations [13–15]. Traditionally, aspirin and clopidogrel were compared using endpoints of cardiovascular and bleeding events. The ASPREE trial introduced a novel aspect in consideration of the risk of developing type 2 diabetes as a factor in determining the preferred antiplatelet treatment. This suggests that the choice of antiplatelet therapy might also need to consider potential metabolic effects, expanding the criteria beyond just cardiovascular outcomes and bleeding risks.

Recognising the existing gaps in evidence, we conducted this study to assess the effects of aspirin in comparison with clopidogrel on incident type 2 diabetes, cardiovascular events, and bleeding events in patients with ASCVD.

2. Material and methods

2.1. Study design

This cohort study applied a target trial framework to design and emulate a pragmatic clinical trial, comparing the effects of low-dose aspirin versus clopidogrel on the incidence of type 2 diabetes, cardiovascular events, and bleeding events in patients with ASCVD. The specifications of the key components of the target trial protocol and its emulation using observational data from the IQVIA Medical Research Data (IMRD) UK primary care database are presented in **Supplementary Table S1**. IMRD includes data from The Health Improvement Network (THIN), a Cegedim database, and comprises UK primary care records for approximately 18 million individuals from over 800 general practices, covering the period from 1987 to 2021. A previous study in 2011 demonstrated the validity of the database for pharmacoepidemiologic studies and its generalisability to the UK population [16]. This digital database provides comprehensive information, including sociodemographic and anthropometric data, lifestyle factors, details from general practitioner visits (such as disease diagnoses and drug prescriptions), diagnoses from specialist referrals and hospital admissions, and laboratory test results.

The study protocol was reviewed and approved by an independent Scientific Review Committee (reference number: 24SRC005). This study used de-identified data provided by patients as part of their routine primary care, and no informed consent was required for this study.

2.2. Eligibility criteria

Adults with incident first event of any one of the ASCVD conditions, i.e. CAD (myocardial infarction, angina, and related cardiac surgeries), stroke (excluding haemorrhagic stroke)/TIA, or PAD between 2004 and 2021 were eligible for the target trial. Patients would be excluded from the study if they met any of the following criteria: prior use of any antiplatelet within 365 days before the diagnosis of the index condition; a history of any types of diabetes or use of antidiabetic medications for at least two prescriptions; those who had never initiate either low-dose aspirin and clopidogrel monotherapy; lack of a one-year up-to-standard record history in the THIN database prior to the first event of ASCVD; or absence of follow-up time. Dual antiplatelet therapy (DAPT) is generally recommended for certain high-risk cases, such as acute coronary syndrome. Therefore, patients who received DAPT after the index condition, preceding the initiation of aspirin or clopidogrel monotherapy, were included. The end date of DAPT was defined as the discontinuation of one of the antiplatelets (having a 90-day gap between prescriptions of the same drug).

2.3. Treatment strategies

We compared two mutually exclusive treatment strategies of (1) initiation and continuous use of low-dose aspirin ($\leq$100 mg) monotherapy versus (2) initiation and continuous use of 75 mg clopidogrel monotherapy. Patients initiating aspirin or clopidogrel were assigned to the treatment strategy that they are compatible with at the baseline. Discontinuation was defined as the theoretical end date of a prescription plus a 90-day grace period without a new prescription. Patients were not considered as deviating from the assigned treatment strategies (i.e., switching between aspirin and clopidogrel or discontinuing aspirin or clopidogrel) if they experience a bleeding event.

2.4. Study outcomes

The primary study outcome was type 2 diabetes, defined as having a diagnostic code for type 2 diabetes, at least two prescriptions for an antidiabetic drug, fasting blood glucose $\geq$7.0 mmol/L, or haemoglobin A1c (HbA1c) level $\geq$6.5 % ($\geq$48 mmol/mol) [17]. The secondary study outcomes included cardiovascular events (myocardial infarction or stroke), and bleeding events (intracranial, gastrointestinal, and urogenital). They were identified by the read codes in the database (**Supplementary Table S2**).

2.5. Follow-up

The follow-up started from initiation of aspirin or clopidogrel monotherapy until the occurrence of outcome, death, or end of data collection in November 2021. In the per-protocol analysis, patients were additionally censored upon initiation on or switching to other antiplatelet treatment or discontinuing aspirin or clopidogrel. The follow-up time was divided into monthly intervals, during which exposure status, outcomes, censoring events, and time-varying covariates were updated.

2.6. Covariates

Study covariates measured at baseline were chosen based on clinical expertise and evidence from previous randomized controlled trials. These included demographic and health-related factors such age, sex, calendar year (grouped into 2004 to 2009, 2010 to 2015, 2016 to 2021), type of ASCVD, duration of ASCVD, DAPT preceding the aspirin or clopidogrel monotherapy, number of GP visits in the past year, and

influenza vaccination in the past year (as a proxy for health-seeking behaviour). Socioeconomic status was represented by the Townsend deprivation index. Body mass index (BMI) was categorised as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–24.9 kg/m^2), obese (≥30 kg/m^2), or unknown. Smoking status was classified as current, former, never, or unknown. Prediabetic status was indicated by baseline impaired fasting blood glucose (5.6–6.9 mmol/L) or HbA1c of 5.7 % to 6.4 % [17]. Measurements of these variables closest prior to the index date was taken as the baseline value. We also included a range of comorbidities that were ever recorded, including hypertension, dyslipidaemia, asthma, chronic obstructive pulmonary disease (COPD), atrial fibrillation (AF), heart failure (HF), venous thromboembolism (VTE), peptic ulcer, gastro-oesophageal acid reflux, cancer, chronic kidney disease (CKD), depression, psychosis. Recent medication use within the past 90 days was also documented, covering statins, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers, oral anticoagulants, proton pump inhibitors (PPIs), glucocorticoids, antidepressants, antipsychotics, non-steroidal anti-inflammatory drugs (NSAIDs). The covariates, except for age (due to collinearity with time), sex and calendar year, were also collected and updated during the follow-up at monthly intervals in the per-protocol analysis.

2.7. Statistical analysis

Baseline characteristics for the overall cohort and across treatment were presented as means with standard deviations (SD) for continuous variables and as counts with percentages for categorical variables. We assessed differences in baseline variables between groups using the standardized mean difference (SMD), with an SMD below 0.1 indicating a good balance between groups.

We estimated the observational analogues of the intention-to-treat effect and per protocol effect. Overlap weighting was applied to account for differences in baseline characteristics between patients in the real-world setting who used low-dose aspirin or clopidogrel. To construct the weights, we used logistic regression to estimate the probability of assignment to each treatment group based on all predefined covariates. The overlap weight for each participant was then calculated as the probability of receiving the opposite treatment, where patients using aspirin were weighted by the probability of receiving clopidogrel and vice versa, with possible values ranging from 0 to 1, without stabilization or trimming. Therefore, all patients were down-weighted by applying the overlap weights. This approach has demonstrated superior performance compared to inverse probability weighting for causal inference [18].

In the intention-to-treat analysis, we addressed baseline confounding by applying overlap weights, achieving exact balance on the mean of all measured covariates. For the per-protocol analysis, we also censored patients upon non-adherence to the assigned treatment strategy, defined as either discontinuation or switching of aspirin or clopidogrel. To address the potential selection bias introduced by artificial censoring due to treatment deviation, we estimated a time-varying non-stabilised inverse probability of censoring weight (IPCW) for treatment deviation. To calculate IPCWs for being uncensored, we used logistic regression models that incorporated baseline covariates and monthly time-varying covariates. The denominator was estimated using a time-dependent intercept (in linear and quadratic terms), baseline characteristics, and time-varying covariates [19]. The IPCW models were fitted separately for each treatment arm and extreme IPCWs were truncated at the 99th percentiles to minimise the undue influence of extreme weights. The final weight was calculated as a product between the baseline overlap weight and non-stabilised IPCW for treatment deviation.

Weighted pooled logistic regression models were used as the outcome model, which is a discrete-time hazard model that approximates Cox regression models for estimating hazard ratios (HRs) when outcomes are rare within each monthly time interval [20]. The outcome models included a treatment indicator and time since baseline (in both linear and quadratic terms), and was weighed by overlap weight. The robust sandwich variance estimator was used to estimate the 95 % confidence intervals (CIs) for the HRs. In addition, we estimated the absolute risks of each study outcome using the pooled logistic regression models. The model additionally included the product terms between treatment and follow-up time. The model estimated the discrete-time hazards at each time interval, and the 8-year absolute risks and risk differences (RDs) were calculated based on the cumulative discrete-time hazards [21]. Non-parametric bootstrapping with 200 full samples was used to generate percentile-based 95 % CIs for the absolute risks and risk differences.

2.8. Subgroup analysis

Primary and secondary outcomes were analyzed separately for each type of cardiovascular disease (CAD, stroke/TIA, and PAD). We also conducted pre-specified subgroup analyses, stratifying by age (65 years and older), sex, obesity, and prediabetes status. The weights were recalculated within each patient subgroup.

2.9. Sensitivity analysis

We conducted several sensitivity analyses on the primary outcome of type 2 diabetes. Firstly, to address potential misclassification bias due to the use of multiple diagnostic criteria, we performed a sensitivity analysis defining diabetes solely by diagnostic records. Secondly, we excluded patients with a history of DAPT before the initiation of aspirin or clopidogrel monotherapy. Thirdly, we repeated the per-protocol analysis, truncating the inverse probability of censoring weights (IPCW) at the 99.5th percentile to manage extreme values and improve robustness.

Findings were considered statistically significant when the 95 % CIs for HRs did not cross 1. Missing data were analyzed as a separate data class. All statistical analyses were conducted using SAS version 9.4.

3. Results

A total of 111,292 patients met the eligibility criteria in this trial emulation, with 78,012 initiating low-dose aspirin and 33,280 initiating clopidogrel. The process of patient selection and exclusion is illustrated in Fig. 1. Aspirin users had more CAD and PAD but fewer stroke/TIA as the index condition, longer time since the diagnosis, longer duration of DAPT, initiated treatment earlier during the study period, were more tobacco smokers, had fewer dyslipidaemia, more HF, used more ACEIs and beta-blockers but fewer CCBs (Table 1). The median age for aspirin users was 66.5 years (IQR 57.8 to 75.8), compared to 68.3 years (IQR 58.1 to 77.8) for clopidogrel users, with 40.0 % of aspirin users and 45.5 % of clopidogrel users being female. After applying baseline overlap weight, all characteristics were exact balanced on the mean of every covariate between the two groups, with SMD of 0. Full baseline characteristics before weighting are detailed in Table 1, which also includes characteristics after weighting, where the effective sample size in each group was 16,892, representing the pseudo-population created through overlap weighting. Separate baseline characteristics for patients with CAD, stroke/TIA, and PAD are provided in **Supplementary Tables S3–S5**.

3.1. Risks of type 2 diabetes

In the intention-to-treat analysis, over a median follow-up of 4.3 (IQR 1.8 to 7.9) years for aspirin users, and 3.1 (IQR 1.3 to 5.9) years for clopidogrel users, 7,016 aspirin users and 2,237 clopidogrel users were diagnosed with incident type 2 diabetes. The intention-to-treat cumulative incidence under each treatment arm is presented in Fig. 2**A**. The 8-year cumulative incidence of type 2 diabetes was 13.3 % (95 % CI 12.9

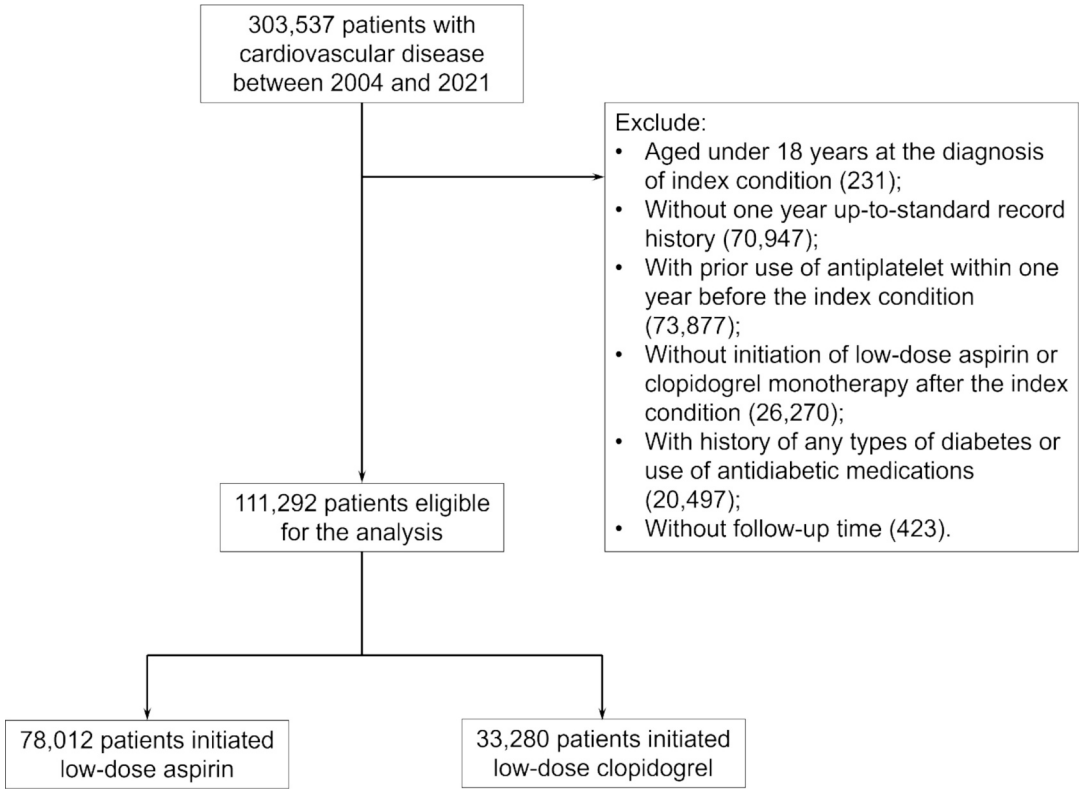

Fig. 1. Selection of patients from THIN for emulation of the target trial.

% to 13.7 %) with aspirin treatment versus 13.4 % (95 % CI 12.8 % to 14.0 %) with clopidogrel treatment. Compared to clopidogrel treatment, aspirin treatment was not associated with a significantly different risk of type 2 diabetes in the intention-to-treat analysis, with a HR of 1.02 (95 % CI 0.96 to 1.07) (Table 2).

In the per-protocol analysis, over a median follow-up of 1.5 (IQR 0.4 to 4.2) years for aspirin users and 1.3 (IQR 0.4 to 3.4) years for clopidogrel users, 4,368 aspirin users and 1,415 clopidogrel users were diagnosed with incident type 2 diabetes. The per-protocol cumulative incidence in each treatment arm is presented in Fig. 2**B**. The 8-year cumulative incidence of type 2 diabetes was 13.0 % (95 % CI 12.4 % to 13.6 %) on aspirin treatment versus 12.5 % (95 % CI 11.2 % to 13.5 %) on clopidogrel treatment. Compared to clopidogrel treatment, aspirin treatment was not associated with a significantly different risk of type 2 diabetes in the per-protocol analysis, with a HR of 1.06 (95 % CI 0.97 to 1.15) (Table 2).

When the analysis was done separately for each type of CVD, aspirin and clopidogrel had similar risk of incident type 2 diabetes in all CVD subtypes and all analyses (Table 2, Fig. 3). In patients with CAD, the HR for incident type 2 diabetes is 1.01 (95 % CI 0.94 to 1.10) with intention-to-treat analysis and 1.02 (95 % CI 0.88 to 1.20) with per-protocol analysis; in patients with stroke/TIA, the HR is 1.03 (95 % CI 0.94 to 1.14) with intention-to-treat analysis and 1.01 (95 % CI 0.88 to 1.15) with per-protocol analysis; in patients with PAD, the HR is 1.08 (95 % CI 0.92 to 1.29) with intention-to-treat analysis and 1.23 (95 % CI 0.96 to 1.60) with per-protocol analysis.

3.2. Risks of cardiovascular and bleeding events

Aspirin and clopidogrel were associated with comparable risks of cardiovascular events across all analyses. In the intention-to-treat analysis, the HR was 1.00 (95 % CI 0.95 to 1.05), and in the per-protocol analysis, the HR was 0.96 (95 % CI 0.89 to 1.03). When the analyses were conducted separately for patients with CAD, stroke/TIA, and PAD, similar results were obtained (Supplementary Table S6, Supplementary Fig. S1).

Aspirin and clopidogrel were associated with similar risks of bleeding events in all analyses. The HR in the intention-to-treat analysis was 1.02 (95 % CI 0.97 to 1.08), and in the per-protocol analysis, the HR was 1.01 (95 % CI 0.92 to 1.10). Consistent results were also observed in subgroup analyses for patients with CAD, stroke/TIA, and PAD (Supplementary Table S7, Supplementary Fig. S2).

3.3. Subgroup analysis

Subgroup analyses by age (65 years or older), sex, obesity, and prediabetes status on type 2 diabetes, cardiovascular events, and bleeding events are presented in Supplementary Table S8–S10. Aspirin and clopidogrel were associated with similar risks of type 2 diabetes, cardiovascular events, and bleeding events across all subgroups with either intention-to-treat or per-protocol analysis.

3.4. Sensitivity analysis

Results from the sensitivity analyses are in Supplementary Table S11. All results are consistent with the results from primary analysis.

4. Discussion

In this observational emulation of a pragmatic clinical trial using the IMRD database in the UK, aspirin monotherapy was associated with comparable risks of incident type 2 diabetes, cardiovascular events, and bleeding events when compared with clopidogrel monotherapy in patients with ASCVD. These similar risks profiles were consistent among patients with CAD, stroke/TIA, or PAD, regardless of adherence to treatment strategies or other patient characteristics.

The effect of aspirin on incident diabetes has been previously

Table 1
Baseline characteristics between patients initiated low-dose aspirin or low-dose clopidogrel monotherapy, before and after overlap weight.

	Unweighted			Weighted		
	Aspirin N = 78,012	**Clopidogrel N = 33,280**	**SMD**	**Aspirin N = 16,892***	**Clopidogrel N = 16,892***	**SMD**
Age, years (SD)	66.6 (12.6)	67.7 (13.4)	−8.4	67.3 (6.1)	67.3 (9.4)	0
Female sex (%)	31,185 (40.0)	15,151 (45.5)	−11.2	7,366 (43.6)	7,366 (43.6)	0
Index ASCVD type (%)			86.3			0
CAD	43,979 (56.4)	7,991 (24)		6,544 (38.7)	6,544 (38.7)	
Stroke/TIA	22,277 (28.6)	22,646 (68)		8,342 (49.4)	8,342 (49.4)	
PAD	11,756 (15.1)	2,643 (7.9)		2,005 (11.9)	2,005 (11.9)	
Duration of ASCVD, days (SD)	250.5 (461.5)	151.9 (446.5)	21.7	207.8 (233.4)	207.8 (357.4)	0
DAPT (%)	25,901 (33.2)	5,552 (16.7)		4,066 (24.1)	4,066 (24.1)	0
Calendar year (%)			66.2			0
2004 to 2009	35,105 (45.0)	5,534 (16.6)		4,834 (28.6)	4,834 (28.6)	
2010 to 2015	28,623 (36.7)	16,258 (48.9)		7,913 (46.8)	7,913 (46.8)	
2016 to 2021	14,284 (18.3)	11,488 (34.5)		4,144 (24.5)	4,144 (24.5)	
Prediabetes (%)	8,191 (10.5)	3,856 (11.6)	−3.5	1,893 (11.2)	1,893 (11.2)	0
Townsend deprivation index (%)			3.1			0
1 (least deprived)	15,207 (19.5)	6,327 (19)		3,305 (19.6)	3,305 (19.6)	
2	15,205 (19.5)	6,492 (19.5)		3,323 (19.7)	3,323 (19.7)	
3	14,443 (18.5)	6,091 (18.3)		3,083 (18.3)	3,083 (18.3)	
4	13,261 (17.0)	5,593 (16.8)		2,861 (16.9)	2,861 (16.9)	
5 (most deprived)	10,041 (12.9)	4,232 (12.7)		2,130 (12.6)	2,130 (12.6)	
Unknown	9,855 (12.6)	4,545 (13.7)		2,189 (13.0)	2,189 (13.0)	
Smoking status (%)			10.0			0
Current	19,057 (24.4)	8,098 (24.3)		4,140 (24.5)	4,140 (24.5)	
Former	27,623 (35.4)	10,718 (32.2)		5,660 (33.5)	5,660 (33.5)	
Never	30,209 (38.7)	14,187 (42.6)		6,909 (40.9)	6,909 (40.9)	
Unknown	1,123 (1.4)	277 (0.8)		182 (1.1)	182 (1.1)	
BMI (%)			6.8			0
Underweight	1,727 (2.2)	882 (2.7)		442 (2.6)	442 (2.6)	
Normal weight	23,065 (29.6)	10,401 (31.3)		5,221 (30.9)	5,221 (30.9)	
Overweight	28,089 (36.0)	11,775 (35.4)		5,982 (35.4)	5,982 (35.4)	
Obese	16,591 (21.3)	7136 (21.4)		3,555 (21.0)	3,555 (21.0)	
Unknown	8,540 (10.9)	3086 (9.3)		1,691 (10.0)	1,691 (10.0)	
Healthcare utilisation						
Influenza vaccination (%)	44,370 (56.9)	17,459 (52.5)	8.9	9,130 (54.0)	9,130 (54.0)	0
No. of GP consultations (SD)	13 (10.9)	13.6 (11.0)	−5.1	13.7 (5.2)	13.7 (8)	0
Comorbidities (%)						
Hypertension	63,509 (81.4)	27,501 (82.6)	−3.2	13,890 (82.2)	13,890 (82.2)	0
Dyslipidaemia	40,166 (51.5)	19,308 (58)	−13.1	9,346 (55.3)	9,346 (55.3)	0
Asthma	8,931 (11.4)	4,381 (13.2)	−5.2	2,148 (12.7)	2,148 (12.7)	0
COPD	5,928 (7.6)	2,873 (8.6)	−3.8	1,445 (8.6)	1,445 (8.6)	0
AF	4,027 (5.2)	1,878 (5.6)	−2.1	1,094 (6.5)	1,094 (6.5)	0
HF	4,729 (6.1)	1,179 (3.5)	11.8	801 (4.7)	801 (4.7)	0
VTE	1,734 (2.2)	972 (2.9)	−4.4	467 (2.8)	467 (2.8)	0
Peptic ulcer	4,139 (5.3)	2,393 (7.2)	−7.8	1,179 (7.0)	1,179 (7.0)	0
GORD	8,303 (10.6)	4,192 (12.6)	−6.1	2,053 (12.2)	2,053 (12.2)	0
CKD	7,581 (9.7)	4,170 (12.5)	−9	1,965 (11.6)	1,965 (11.6)	0
Cancer	6,711 (8.6)	3,424 (10.3)	−5.8	1,638 (9.7)	1,638 (9.7)	0
Depression	16,419 (21)	7,610 (22.9)	−4.4	3,758 (22.2)	3,758 (22.2)	0
Psychosis	558 (0.7)	246 (0.7)	−0.3	125 (0.7)	125 (0.7)	0
Recent medications (%)						
Statins	59,621 (76.4)	26,648 (80.1)	−8.8	13,062 (77.3)	13,062 (77.3)	0
ACEIs	33,666 (43.2)	11,235 (33.8)	19.4	6,405 (37.9)	6,405 (37.9)	0
ARB	7,066 (9.1)	2,944 (8.8)	0.7	1,543 (9.1)	1,543 (9.1)	0
CCBs	15,228 (19.5)	8,331 (25.0)	−13.3	3,801 (22.5)	3,801 (22.5)	0
Beta-blockers	37,157 (47.6)	8,692 (26.1)	45.7	6,025 (35.7)	6,025 (35.7)	0
Oral anticoagulants	2,666 (3.4)	1,644 (4.9)	−7.6	908 (5.4)	908 (5.4)	0
PPIs	27,952 (35.8)	13,318 (40.0)	−8.6	6,690 (39.6)	6,690 (39.6)	0
Glucocorticoids	15,067 (19.3)	6,929 (20.8)	−3.8	3,519 (20.8)	3,519 (20.8)	0
Antidepressants	12,020 (15.4)	6,215 (18.7)	−8.7	2,952 (17.5)	2,952 (17.5)	0
Antipsychotics	1,337 (1.7)	633 (1.9)	−1.4	315 (1.9)	315 (1.9)	0
NSAIDs	7,169 (9.2)	2,530 (7.6)	5.7	1,359 (8.0)	1,359 (8.0)	0

SMD, standardised mean difference; SD, standard deviation; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; TIA, transient ischaemic attach; PAD, peripheral arterial disease; DAPT, dual antiplatelet therapy; BMI, body mass index; GP, general practice; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; HF, heart failure; VTE, venous thromboembolism; GORD, gastroesophageal reflux disease; CKD, chronic kidney disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug.

* The number reflects the effective sample size from overlap weighting, representing weighted contributions rather than actual patient counts.

investigated in three studies using data from randomised controlled trials (RCTs), yielding inconsistent results [3,5,6]. A recent post-hoc analysis of the ASPREE trial found that, among healthy older adults, daily administration of 100 mg aspirin was associated with a 15 % reduction in the risk of incident type 2 diabetes and a modest reduction in fasting plasma glucose concentrations compared to placebo [3]. In contrast, analyses from the PHS and WHS did not find that randomised aspirin treatment reduced the risk of incident type 2 diabetes among

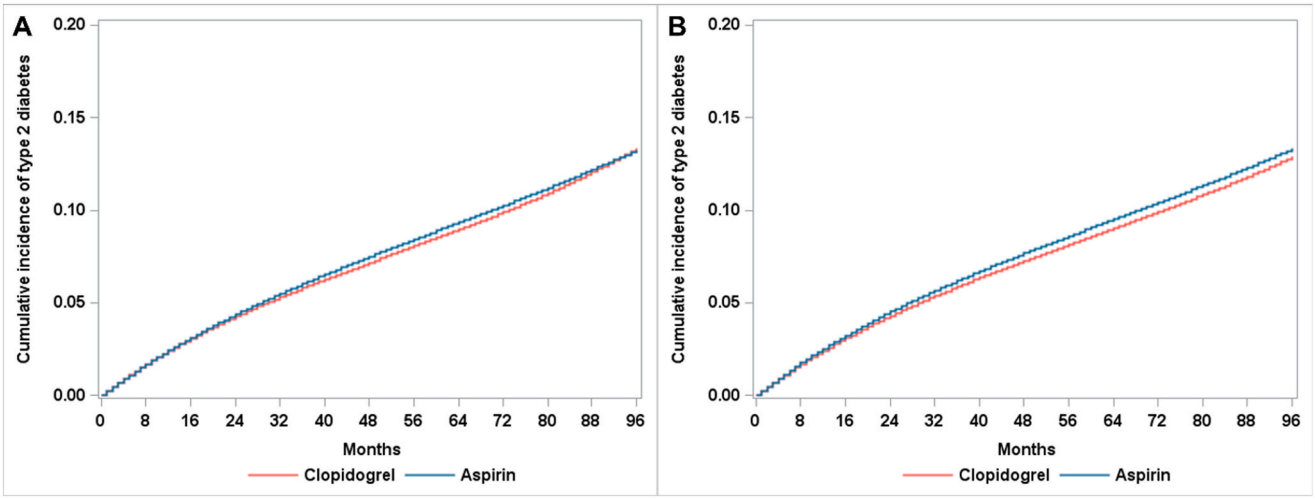

Fig. 2. Cumulative incidence of type 2 diabetes with aspirin or clopidogrel treatment among patients with ASCVD. (A) intention-to-treat analysis; (B) per-protocol analysis.

Table 2
8-year absolute risks, risk differences, and hazard ratios for type 2 diabetes comparing patients receiving low-dose aspirin versus low-dose clopidogrel monotherapy, overall and by ASCVD types.

Population and causal contrast	Treatment	Patients (n)	Events (n)	Median follow-up (IQR) (years)	Crude HR (95 % CI)*	Adjusted HR (95 % CI)*	Adjusted 8-year absolute risk (%)	Adjusted 8-year risk difference (%)
Overall								
Intention-to-treat								
	Aspirin	78,012	7,016	4.3 (1.8 to 7.9)	1.13 (1.08 to 1.19)	1.02 (0.96 to 1.07)	13.3 (12.9 to 13.7)	−0.1 (−0.9 to 0.5)
	Clopidogrel	33,280	2,237	3.1 (1.3 to 5.9)	Reference	Reference	13.4 (12.8 to 14.0)	Reference
Per-protocol								
	Aspirin	78,012	4,368	1.5 (0.4 to 4.2)	1.16 (1.09 to 1.23)	1.06 (0.97 to 1.15)	13.0 (12.4 to 13.6)	0.6 (−0.6 to 1.8)
	Clopidogrel	33,280	1,415	1.3 (0.4 to 3.4)	Reference	Reference	12.5 (11.2 to 13.5)	Reference
CAD								
Intention-to-treat								
	Aspirin	43,979	4,192	4.1 (1.7 to 7.7)	1.00 (0.93 to 1.08)	1.01 (0.94 to 1.10)	15.6 (14.5 to 16.9)	0.0 (−1.4 to 1.2)
	Clopidogrel	7,991	750	4.0 (1.5 to 7.5)	Reference	Reference	15.7 (15.1 to 16.3)	Reference
Per-protocol								
	Aspirin	43,979	2,723	1.7 (0.5 to 4.4)	1.02 (0.90 to 1.16)	1.02 (0.88 to 1.20)	14.7 (13.6 to 15.5)	0.4 (−2.3 to 2.6)
	Clopidogrel	7,991	265	0.5 (0.2 to 1.3)	Reference	Reference	14.3 (12.3 to 16.8)	Reference
Stroke/TIA								
Intention-to-treat								
	Aspirin	22,277	1,741	4.8 (1.9 to 7.9)	1.06 (0.98 to 1.13)	1.03 (0.94 to 1.14)	11.6 (11.0 to 12.3)	0.3 (−0.6 to 1.5)
	Clopidogrel	22,646	1,311	3.0 (1.3 to 5.4)	Reference	Reference	11.3 (10.4 to 12.0)	Reference
Per-protocol								
	Aspirin	22,277	1,012	1.3 (0.4 to 4.0)	1.02 (0.93 to 1.11)	1.01 (0.88 to 1.15)	10.9 (9.8 to 11.9)	−0.4 (−2.0 to 1.1)
	Clopidogrel	22,646	1,036	1.7 (0.6 to 3.8)	Reference	Reference	11.3 (10.3 to 12.6)	Reference
PAD								
Intention-to-treat								
	Aspirin	11,756	1,083	4.5 (2.0 to 7.7)	1.11 (0.95 to 1.30)	1.08 (0.92 to 1.29)	14.3 (13.1 to 15.2)	2.0 (0.3 to 3.9)
	Clopidogrel	2,643	176	2.9 (1.3 to 5.7)	Reference	Reference	12.3 (10.4 to 14.2)	Reference
Per-protocol								
	Aspirin	11,756	633	1.2 (0.4 to 3.6)	1.23 (1.01 to 1.50)	1.23 (0.96 to 1.60)	13.7 (12.1 to 15.3)	3.0 (−0.2 to 5.6)
	Clopidogrel	2,643	114	1.4 (0.4 to 3.4)	Reference	Reference	10.7 (8.4 to 13.1)	Reference

IQR, interquartile range; HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; TIA, transient ischaemic attach; PAD, peripheral arterial disease.
* Adjusted HRs are estimated using weighted pooled logistic regression models, while crude HRs are derived from unweighted models.

healthy men or women [5,6]. Although the observational analysis of 20-year follow-up data from the PHS suggested a 14 % reduction in the relative risk of diabetes, this result is likely influenced by confounding and selection bias [5]. The current study is the first in investigating the effect of aspirin on the risk of diabetes in patients with pre-existing CVD. Direct comparisons between our findings and those from ASPREE, WHS, or PHS are difficult due to differences in target populations and treatment regimens involving varied aspirin use. Nevertheless, existing evidence suggests that any potential benefits of aspirin on incident diabetes may be highly population specific. Further research is needed to clarify

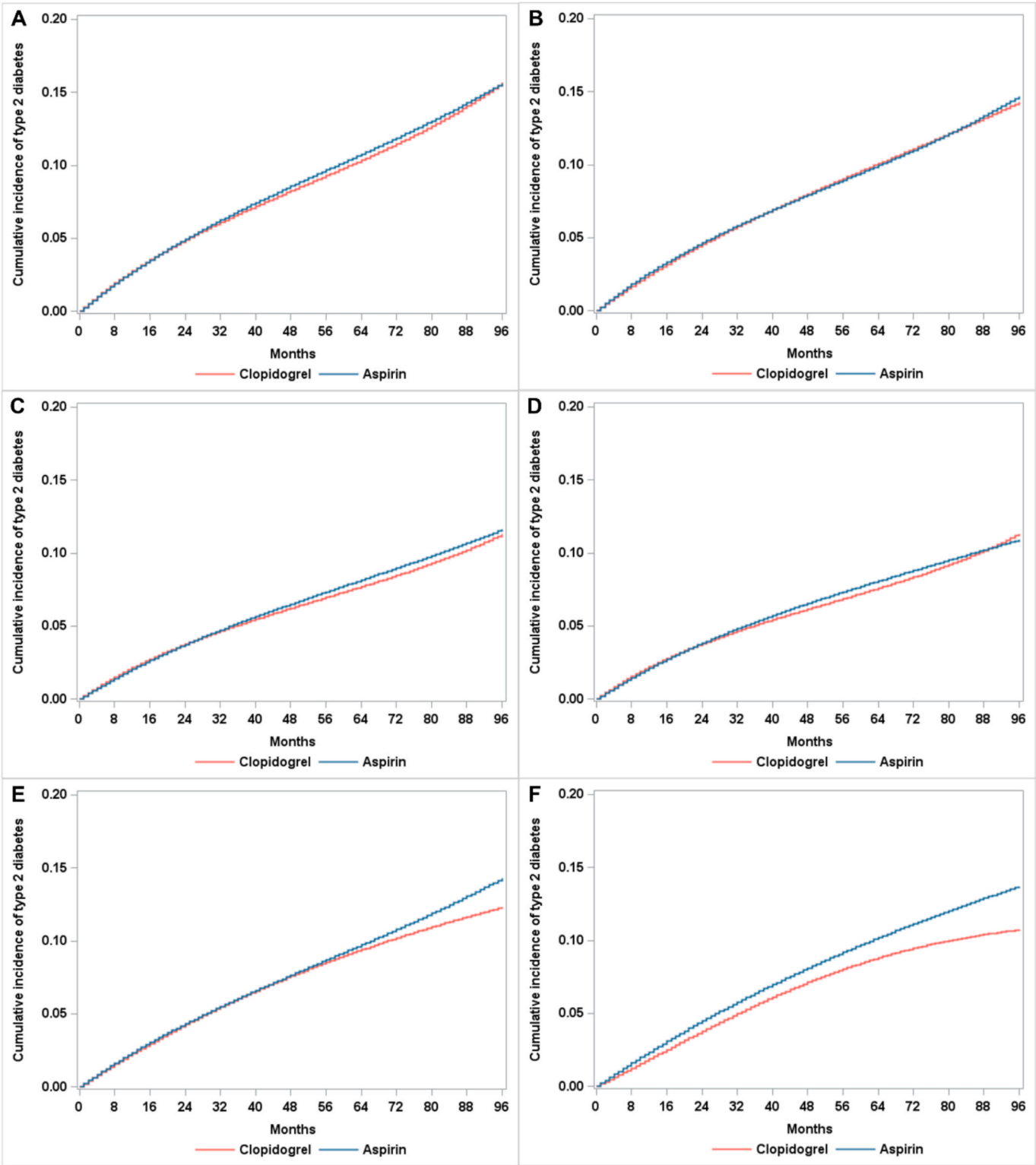

Fig. 3. Cumulative incidence of type 2 diabetes with aspirin or clopidogrel treatment. (A) intention-to-treat analysis among patients with CAD; (B) per-protocol analysis among patients with CAD; (C) intention-to-treat analysis among patients with stroke/TIA; (D) per-protocol analysis among patients with stroke/TIA; (E) intention-to-treat analysis among patients with PAD; (F) per-protocol analysis among patients with PAD.

the mechanisms by which aspirin may influence diabetes onset, putatively related to its anti-inflammatory properties [3], and to identify specific populations that might benefit from aspirin for diabetes prevention.

A unique aspect of the current study is its focus on patients with ASCVD for whom aspirin is used for secondary prevention, potentially making our findings more applicable to current clinical practice in managing ASCVD with low-dose aspirin. In contrast, previous studies have largely examined healthy populations, where low-dose aspirin is not recommended for primary CVD prevention due to heightened bleeding risks [22,23]. Findings from the ASPREE trial support this caution, showing that any potential reduction in diabetes risk with

aspirin use is outweighed by an increased risk of major bleeding, thus reinforcing the absence of support for routine aspirin use in primary prevention [3,4]. Given the well-established role of aspirin as the standard-of-care for patients with CVD [24], coupled with overlapping risk factors for diabetes and CVD, individuals using aspirin for secondary CVD prevention are more likely to benefit from its potential cardiometabolic properties. Our findings, which show comparable risks of type 2 diabetes, recurrent cardiovascular events, and bleeding events between aspirin and clopidogrel, offer valuable insights for the reappraisal of guidelines on antiplatelet selection after ASCVD, as recently suggested in the literature [25,26]. Overall, this study supports the view that aspirin and clopidogrel monotherapy can serve as alternatives for managing ASCVD.

Our study also highlights two critical, unresolved questions. First, our analysis does not assess the net effect of aspirin on diabetes onset in the target population. Instead, it focuses solely on comparing the relative risks of aspirin versus clopidogrel, leaving the effect of clopidogrel alone on diabetes onset remaining largely unknown. While aspirin's proposed role in diabetes prevention is tied to its anti-inflammatory properties, evidence suggests that clopidogrel may also have anti-inflammatory effects [27,28]. Thus, it is possible that both aspirin and clopidogrel could similarly reduce diabetes risk. Therefore, our current approach cannot determine the net effect of either aspirin or clopidogrel on diabetes onset. Second, our analysis excludes patients with pre-existing diabetes, although aspirin's potential cardiometabolic benefits may be especially relevant to this group. Patients with diabetes face have a two- to threefold higher risk of vascular events than those without diabetes [29], and prior trials on aspirin for secondary prevention have included 15 to 43 % of patients with diabetes at baseline [30]. Future research are needed to explore the effect of aspirin on the progression of diabetes and associated risks among patients with pre-existing diabetes.

The comparative effectiveness of aspirin versus clopidogrel monotherapy following CVD has been investigated in previously RCTs [30], providing useful benchmarks for our findings. The CAPRIE trial was the first to examine the relative efficacy of clopidogrel (75 mg once daily) compared with aspirin (325 mg once daily) for reducing cardiovascular events in patients with a recent ischemic stroke, MI, or PAD [31]. Our results align well with those of the CAPRIE trial, showing comparable cardiovascular event risks between aspirin and clopidogrel in patients with MI or stroke. In PAD patients, the CAPRIE trial found a 23.8 % (95 % CI, 8.9 % to 36.2 %) relative risk reduction with clopidogrel, closely matching the point estimate from our intention-to-treat analysis for aspirin versus clopidogrel (HR = 1.18, 95 % CI 0.98 to 1.43), though our results did not reach statistical significance probably due to lower statistical power with lower sample size in the PAD subgroup. Similarly, the CAPRIE trial reported comparable bleeding rates between aspirin and clopidogrel, regardless of severity, which aligns with our conclusions. Other RCTs, such as CADET, STOPDAPT-2, and STOPDAPT-3 trials, have also compared aspirin and clopidogrel monotherapy following MI, both with and without surgical interventions or DAPT. Consistent with our findings, these trials showed no significant differences in effectiveness and safety between the two medications [32–34]. However, our results differ from those of the HOST-EXAM trial, which demonstrated clopidogrel to be superior to aspirin, with fewer cardiovascular events and major bleeding [35]. These differences may be attributed to variations in study populations (such as ethnicity, prevalence of CYP2C19 polymorphism, and use of percutaneous coronary intervention and DAPT) and differences in outcomes definitions, such as the inclusion of ACS as an endpoint in HOST-EXAM trial.

4.1. Strengths and limitations

This study is the first to examine aspirin use and the risk of incident diabetes, specifically in patients with ASCVD. Confirming the potential cardiometabolic benefits of aspirin in this population is particularly relevant to the current practice of using aspirin for CVD management. Aspirin and clopidogrel are commonly prescribed as alternative therapies for secondary prevention of CVD events, providing an ideal context to compare their effectiveness. In addition to diabetes incidence, we analysed cardiovascular and bleeding events as endpoints, allowing us to benchmark our findings against existing RCTs. Our study included a comprehensive set of potential confounders related to antiplatelet therapy and cardiometabolic outcomes. By using a target trial emulation framework with an active-comparator design, we aimed to minimise bias and improve the reliability of our results. We also assessed absolute and relative risks, offering observational analogues of intention-to-treat and per-protocol effects to enhance the clarity and interpretability of our findings. To address potential time-varying selection bias due to treatment deviations in the per-protocol analysis, we updated relevant variables in monthly intervals allowing us to capture changes in metabolic and clinical risk factors that may introduce time-varying confounding. This approach further strengthens our ability to draw meaningful conclusions about the long-term effectiveness and safety of aspirin and clopidogrel in this high-risk population.

However, this study has several limitations. First, our emulation of treatment assignment and adherence relied solely on prescription records, without information on whether prescriptions were redeemed or consumed. This limitation could result in exposure misclassification, potentially biasing our findings toward the null. Second, while our focus was on the relative risk of aspirin compared to clopidogrel, the specific impact of clopidogrel on the risk of incident diabetes remains largely unknown. Although we were unable to emulate a placebo-controlled trial to assess the absolute benefit of aspirin, our findings still offer valuable insights into antiplatelet choices for patients with ASCVD, likely more applicable in practice than comparisons with no antiplatelet therapy. Third, diabetes diagnoses were identified through diagnostic codes, antidiabetic medication records, blood glucose, and HbA1c levels; some cases may have been misclassified or missed. Fourth, we could not categorise bleeding events according to Bleeding Academic Research Consortium (BARC) criteria, which are used in prior RCTs as an endpoint. Lastly, as an observational study, we cannot fully eliminate the impact of residual confounding. Despite using an active comparator and overlap weights to closely approximate randomisation, residual confounding may be more prominent in analysing cardiovascular and bleeding events, as risk factors for these outcomes could influence the choice of antiplatelet therapy in clinical settings. Certain unmeasured factors, such as dietary intake, physical activity, and family history of diabetes, were not available in the database. These factors may influence diabetes incidence. However, given that our study compared two active treatment groups, we expect that their distribution was likely similar between groups, minimising the potential impact of residual confounding. Future prospective studies incorporating lifestyle or genetic information, or randomised controlled trials would be valuable to further validate our findings.

In conclusion, this study comparing aspirin and clopidogrel monotherapy in patients with atherosclerotic CVD found similar risks for incident type 2 diabetes, cardiovascular events, and bleeding outcomes between the two treatments. While both drugs are widely used as antiplatelet agents, our findings suggest that their impacts on cardiometabolic profiles are comparable. This information may support clinicians in selecting antiplatelet therapy based on patient preference, cost, and individual risk factors rather than significant differences in cardiometabolic outcomes.

CRediT authorship contribution statement

Chengsheng Ju: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xi Xiong:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **David T.W. Lui:**

Writing – review & editing, Methodology. **Vincent K.C. Yan:** Writing – review & editing. **Matthew Adesuyan:** Writing – review & editing. **Ming Xu:** Writing – review & editing. **Frederick K. Ho:** Writing – review & editing. **Carlos K.H. Wong:** Writing – review & editing. **Ian C.K. Wong:** Writing – review & editing. **Esther W.Y. Chan:** Writing – review & editing, Resources, Project administration. **Li Wei:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Funding

This study was supported by the Laboratory of Data Discovery for Health ($D^2$4H) funded by the AIR@InnoHK administered by the Innovation and Technology Commission. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2025.112082.

References

[1] Guirguis-Blake JM, Evans CV, Perdue LA, Bean SI, Senger CA. Aspirin use to prevent cardiovascular disease and colorectal cancer: updated evidence report and systematic review for the US preventive services task force. JAMA 2022;327:1585–97.
[2] Rumore MM, Kim KS. Potential role of salicylates in type 2 diabetes. Ann Pharmacother 2010;44:1207–21.
[3] Zoungas S, Zhou Z, Owen AJ, Curtis AJ, Espinoza SE, Ernst ME, et al. Daily low-dose aspirin and incident type 2 diabetes in community-dwelling healthy older adults: a post-hoc analysis of efficacy and safety in the ASPREE randomised placebo-controlled trial. Lancet Diabetes Endocrinol 2024;12:98–106.
[4] Ostrominski JW, Aroda VR. Aspirin and diabetes prevention among healthy older adults-practice-changing or hypothesis-generating? Lancet Diabetes Endocrinol 2024;12:84–5.
[5] Hayashino Y, Hennekens CH, Kurth T. Aspirin use and risk of type 2 diabetes in apparently healthy men. Am J Med 2009;122:374–9.
[6] Pradhan AD, Cook NR, Manson JE, Ridker PM, Buring JE. A randomized trial of low-dose aspirin in the prevention of clinical type 2 diabetes in women. Diabetes Care 2009;32:3–8.
[7] NICE. Stroke and transient ischaemic attack in over 16s: diagnosis and initial management, NICE guideline [NG128]. 2019.
[8] NICE. Peripheral arterial disease: diagnosis and management, Clinical guideline [CG147]. 2012.
[9] Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. Stroke 2021;52:e364–467.
[10] Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e686–725.
[11] Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407–77.
[12] Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;39:763–816.
[13] Faxon DP, Freedman JE. Facts and controversies of aspirin and clopidogrel therapy. Am Heart J 2009;157:412–22.
[14] Kumbhani DJ, de Lemos JA. The optimal antiplatelet agent for secondary prevention of coronary artery disease: ring out the old? J Am Coll Cardiol 2023;82:106–8.
[15] Hwang D, Kim HL, Koo BK, Rhee TM, Yang DW, Seo Y, et al. Cost-effectiveness of clopidogrel vs aspirin monotherapy after percutaneous coronary intervention: results from the HOST-EXAM study. JACC Asia 2023;3:198–207.
[16] Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. Inform Prim Care 2011;19:251–5.
[17] Lyu H, Zhao SS, Zhang L, Wei J, Li X, Li H, et al. Denosumab and incidence of type 2 diabetes among adults with osteoporosis: population based cohort study. BMJ 2023;381:e073435.
[18] Cheng C, Li F, Thomas LE, Li FF. Addressing extreme propensity scores in estimating counterfactual survival functions via the overlap weights. Am J Epidemiol 2022;191:1140–51.
[19] Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550–60.
[20] Thompson Jr WA. On the treatment of grouped observations in life studies. Biometrics 1977;33:463–70.
[21] Dickerman BA, Garcia-Albeniz X, Logan RW, Denaxas S, Hernan MA. Avoidable flaws in observational analyses: an application to statins and cancer. Nat Med 2019;25:1601–6.
[22] Force USPST, Davidson KW, Barry MJ, Mangione CM, Cabana M, Chelmow D, et al. Aspirin use to prevent cardiovascular disease: US preventive services task force recommendation statement. JAMA 2022;327:1577–84.
[23] National Institue for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. NICE guideline [NG238] 2023.
[24] Byrne RA, Colleran R. Aspirin for secondary prevention of cardiovascular disease. Lancet 2020;395:1462–3.
[25] Jacobsen AP, Raber I, McCarthy CP, Blumenthal RS, Bhatt DL, Cusack RW, et al. Lifelong aspirin for all in the secondary prevention of chronic coronary syndrome: still sacrosanct or is reappraisal warranted? Circulation 2020;142:1579–90.
[26] Brass EP, Hiatt WR. Aspirin monotherapy should not be recommended for cardioprotection in patients with symptomatic peripheral artery disease. Circulation 2017;136:785–6.
[27] Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Sabate M, Jimenez-Quevedo P, et al. Clopidogrel withdrawal is associated with proinflammatory and prothrombotic effects in patients with diabetes and coronary artery disease. Diabetes 2006;55:780–4.
[28] Molero L, Lopez-Farre A, Mateos-Caceres PJ, Fernandez-Sanchez R, Luisa Maestro M, Silva J, et al. Effect of clopidogrel on the expression of inflammatory markers in rabbit ischemic coronary artery. Br J Pharmacol 2005;146:419–24.
[29] Emerging Risk Factors C, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215–22.
[30] Chiarito M, Sanz-Sanchez J, Cannata F, Cao D, Sturla M, Panico C, et al. Monotherapy with a P2Y(12) inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. Lancet 2020;395:1487–95.
[31] Committee CS. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee Lancet 1996;348:1329–39.
[32] Woodward M, Lowe GD, Francis LM, Rumley A, Cobbe SM, Investigators CS. A randomized comparison of the effects of aspirin and clopidogrel on thrombotic risk factors and C-reactive protein following myocardial infarction: the CADET trial. J Thromb Haemost 2004;2:1934–40.
[33] Watanabe H, Morimoto T, Natsuaki M, Yamamoto K, Obayashi Y, Nishikawa R, et al. Clopidogrel vs aspirin monotherapy beyond 1 year after percutaneous coronary intervention. J Am Coll Cardiol 2024;83:17–31.
[34] Watanabe H, Natsuaki M, Morimoto T, Yamamoto K, Obayashi Y, Nishikawa R, et al. Aspirin versus clopidogrel monotherapy after percutaneous coronary intervention: 1-year follow-up of the STOPDAPT-3 trial. Eur Heart J 2024;45(47):5042–54.
[35] Koo BK, Kang J, Park KW, Rhee TM, Yang HM, Won KB, et al. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. Lancet 2021;397:2487–96.