ORIGINAL RESEARCH

Aspirin Use and Cardiovascular Outcome in Patients With Type 2 Diabetes Mellitus and Heart Failure: A Population-Based Cohort Study

Charbel Abi Khalil, MD, PhD, FESC, FACC, FAHA; Omar M. Omar, MSc; Jassim Al Suwaidi, MBChB, FACC; Shahrad Taheri, MBBS, PhD, FRCP

***Background*—**Aspirin is of uncertain benefit for primary prevention in patients with type 2 diabetes mellitus (T2D). We assessed whether primary prevention with aspirin is beneficial in patients with T2D and heart failure (HF).

***Methods and Results*—**Data from The Health Improvement Network, a UK multicenter prospective primary care database, were analyzed. Those with T2D and HF, age ≥55 years, and no previous history of myocardial infarction and/or coronary artery disease, stroke, peripheral artery disease, or atrial fibrillation were included. We compared outcomes for those on aspirin to no aspirin after diagnosis of HF and T2D and assessed the role of a >75-mg dose. The primary outcome was a composite of all-cause mortality and hospitalization for HF; secondary outcomes were nonfatal stroke, nonfatal myocardial infarction, or major bleeding. There were 5967 participants on aspirin and 6567 not on aspirin. The mean age (SD) was 75.3 (9.6) years, 53.9% were men, and the mean follow-up (SD) was for 5 (4.2) years. After propensity-score matching and further multivariable adjustment, aspirin was significantly associated with a decrease in the primary outcome and all-cause mortality (hazard ratio=0.88, 95% confidence interval 0.82-0.93; 0.88, 0.83-0.94], respectively); and an increased risk of nonfatal myocardial infarction (hazard ratio=1.66; 95% confidence interval 1.49-1.85) and nonfatal stroke (hazard ratio=1.23, 1.01-1.50). Major bleedings and hospitalization for HF were not significantly higher with aspirin (hazard ratio=0.68, 0.45-1.03; 0.87, 0.66-1.15, respectively). There was no additional benefit for a dose >75 mg.

***Conclusions*—**Primary prevention with aspirin in patients with T2D and HF is associated with lower all-cause mortality.
(*J Am Heart Assoc*. 2018;7:e010033. DOI: 10.1161/JAHA.118.010033.)

Key Words: aspirin • death • diabetes mellitus • heart failure

Since ISIS-2 (the second International Study of Infarct Survival),[1] in which aspirin improved survival after myocardial infarction (MI), international guidelines have recommended aspirin as first line for the secondary prevention of MI and other atherosclerotic cardiovascular disease.[2-4] However, data regarding aspirin use in primary prevention of cardiovascular disease are conflicting. In a recent systematic review that included 11 randomized controlled trials, aspirin in primary prevention was associated with a modest reduction in nonfatal MI, but did not reduce mortality.[5]

From the Joan and Sanford I. Weill Department of Medicine (C.A.K., J.A.S., S.T.), Department of Genetic Medicine (C.A.K.), Clinical Research Core, Department of Medicine (O.M.O., S.T.), Weill Cornell Medicine, Doha, Qatar and NY; Adult Cardiology, Heart Hospital (C.A.K., J.A.S.), and Department of Medicine, Qatar Metabolic Institute (S.T.), Hamad Medical Corporation, Doha, Qatar.

Correspondence to: Charbel Abi Khalil, MD, PhD, FESC, FACC, FAHA, Weill Cornell Medicine, Doha, Qatar. E-mail: cha2022@med.cornell.edu

Received June 8, 2018; accepted September 21, 2018.

Patients with type 2 diabetes mellitus (T2D) are predisposed to a higher risk of cardiovascular events and increased mortality[6] because of several pathophysiological mechanisms, including hypercoagulability and higher platelet reactivity induced by insulin resistance and hyperglycemia.[7,8] However, aspirin has not been shown to be beneficial for primary cardiovascular disease prevention in T2D as demonstrated by several retrospective cohorts as well as in the 10-year follow-up of the randomized JPAD (Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes) trial.[9]

Heart failure (HF) is also associated with hypercoagulability,[10] but the benefit of aspirin in those with HF is controversial. Although some prospective cohorts have suggested that aspirin might reduce mortality in patients with HF,[11,12] randomized placebo-controlled trials have reported either a neutral or deleterious effect of aspirin in comparison to warfarin or placebo.[13-15] Nevertheless, aspirin has been used for secondary prevention because most patients with HF have a history of a cardiovascular event.

Emerging clinical trials have highlighted the important impact of heart failure in cardiovascular mortality in patients with diabetes mellitus. For example, the beneficial effects observed with sodium glucose transporter-2 inhibitors appear

Clinical Perspective

What Is New?

- This study assessed whether primary prevention with aspirin is beneficial in patients with heart failure and type 2 diabetes mellitus.
- A low dose of aspirin was significantly associated with a decrease in all-cause mortality.
- Major bleedings and hospitalization for heart failure were not significantly higher with aspirin.
- There was no additional benefit for a high dose.

What Are the Clinical Implications?

- Our study suggests that aspirin is beneficial in patients with type 2 diabetes mellitus and heart failure, aged ≥55 years, and with no previous history of myocardial infarction and/or coronary artery disease, stroke, peripheral artery disease, or atrial fibrillation.
- It might be reasonable to consider aspirin for the primary prevention of patients with diabetes mellitus and heart failure in the absence of other contraindications.

to be driven through a reduction in mortality in patients with diabetes mellitus and heart failure.[16] Therefore, there is a need for greater focus on patients with diabetes mellitus and heart failure. Evidence for aspirin use for patients with HF with a high cardiovascular risk such as T2D and no prior ischemic event is lacking, but a preventive role may be hypothesized. Therefore, the aim of the current study was to examine the impact of aspirin in the primary prevention of mortality and key cardiovascular outcomes for patients with T2D and HF in the primary care setting.

Methods

Study Population

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

The THIN (The Health Improvement Network) database is a large retrospective cohort of patients presenting to 546 UK primary care centers with a total of over 14 million patients contributing data, thus providing specific data regarding outcomes in actual clinical practice.[17] THIN is generalizable to the UK population by age, sex, death rates, and medical conditions. Information on THIN is collected during routine patient consultations with general practitioners from registers at a THIN-affiliated general practice. Symptoms and diagnosis of disease are recorded using Read codes. The Read codes are a very comprehensive coded clinical language. The codes include terms relating to observations (signs and symptoms), diagnosis, procedures, and investigations.

All participants gave a written consent, and the study was conducted in accordance with the 1964 Declaration of Helsinki. Collected medical records were anonymized, and the study protocol was approved by the THIN independent scientific review committee (number 13-030). We conducted a retrospective cohort study of adults newly diagnosed with T2D from calendar year 2000. The recording of diabetes mellitus diagnoses is comprehensive in THIN, and any patient with a Read code for from January 1, 2000 onward was considered for this study. The first record was considered as the date of diagnosis. The inclusion criteria for this analysis were patients with T2D and HF, age ≥55 years, no previous history of MI and/or coronary artery disease, stroke, peripheral artery disease, or atrial fibrillation. Aspirin exposure was defined as a fixed intake of aspirin within 30 days of diagnosis of T2D and HF. Previous aspirin users before the diagnosis of heart failure and diabetes mellitus were excluded.

Patients remained in the cohort and were followed until transfer out of practice, death, or until the end of follow-up.

End Points

The primary end point was a composite of all-cause mortality or a first-time hospitalization for HF. The secondary outcomes were the time to death from any cause, first-time hospitalization for HF, nonfatal MI, nonfatal stroke, and major bleedings. All clinical diagnoses, patient-related variables, and outcomes were extracted using Read codes (a full list of Read codes is available on request). Major bleeding was defined as symptomatic bleeding in a critical area or an organ, or a bleeding causing a fall in hemoglobin level of 20 g/L or more or leading to transfusion of 2 or more units of whole blood or packed red blood cells.

Statistical Analysis

Demographic characteristics and outcome data are summarized as counts and percentages for categorical variables and means (standard deviations) for continuous variables. Paired t tests were used to compare differences between groups. For categorical variables, differences were assessed using the Pearson chi-squared test. Incidence rates and 95% confidence intervals (CI) for primary and secondary end points were calculated by dividing the number of incident cases by the total person-years at risk (PYAR). Kaplan-Meier curves accompanied by hazard ratios from Cox regression models were used to analyze time-to-event outcomes. The Cox model (with robust standard errors) was adjusted for smoking status, age, duration of diabetes mellitus, sex, hypertension, dyslipidemia, and baseline use of metformin, angiotensin-converting

enzyme inhibitors, β-blockers, and statins. In the event of nonproportional hazards, parametric survival analysis methods were used to confirm the results. The index date for aspirin users was the first date of aspirin prescription (within 30 days of T2D and HF diagnosis). For nonusers, the index date was when they were diagnosed with T2D/HF. For the outcomes hospitalization for HF, nonfatal MI, nonfatal stroke, and major bleeding, a competing risk analysis model was used. We further analyzed hospitalization, nonfatal MI, and nonfatal stroke using a win-ratio matched-pairs approach,[18] initially recommended by Finkelstein and Schoenfeld.[19] For composite outcomes, this method prioritizes fatal outcomes (all-cause mortality) over less severe outcomes (eg, hospitalization).

Sensitivity Analysis (Propensity-Score Matching)

Propensity score matching was used for sensitivity analysis. Propensity score matching involved building a logistic regression model to derive predictors of aspirin usage by using a 3-step approach. Propensity scores were developed by including sex, age, duration of diabetes mellitus, hypertension, and dyslipidemia in the logistic regression model. This logistic regression model was then combined with the PSMATCH2 command in Stata (Version 15; Statacorp, College Station, TX) to calculate propensity scores representing the estimated probability of using aspirin on each participant's baseline characteristics.[20] Aspirin users were matched to nonusers with the closest propensity score on a ratio of 1:1 using a nearest-neighbor algorithm with no replacement, and matching was restricted to within the common support region.[21] To ensure that the model was performing adequately, we checked the balance of means and variances of covariates after matching by examining the standardized mean differences between aspirin users and nonusers both before and after matching.

Results

Baseline Characteristics

Out of the total of over 14 million participants in the THIN database, 12 534 participants fulfilled the study inclusion criteria, of whom 5967 (47.6%) were on aspirin (5830 on a dose ≤75 mg, and 137 on a dose >75 mg), and 6567 (52.4%) were not. At inclusion, 2208 (44.1%) patients were already on a β-blocker. As shown in Table 1, the mean (SD) age of the study population was 75.3 (9.6), and 53.9% were male. Patients on aspirin were younger and had a shorter duration of diabetes mellitus but had a higher prevalence of hypertension and dyslipidemia. Of note, the aspirin-treated group were less often prescribed angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, diuretics, oral antidiabetic agents such as metformin, sulfonylureas, and dipeptidyl peptidase-4 inhibitors, aldosterone antagonists, and vitamin K antagonists. Patients on high-dose aspirin had a higher prevalence of hypertension and a shorter diabetes mellitus duration compared with low-dose aspirin users.

Outcomes

During the 5 (SD 4.2) years of follow-up, the primary composite event rate was 86.0 per 1000 PYAR for aspirin users compared with 73.2 per 1000 PYAR in non–aspirin users (crude hazard ratio [HR] in the aspirin group 0.86, 95% CI 0.82-0.91, $P<0.001$; Table 2, Figure 1A). The reduction in the primary outcome was mainly driven by a reduction in all-cause mortality in aspirin users (crude HR 0.86; 95% CI 0.82-0.91, $P<0.001$; Table 2, Figure 1B).

Of the patients receiving aspirin, hospitalization for HF rate was 2.6 per 1000 PYAR, compared with 2.4 per 1000 PYAR not receiving aspirin (crude HR 0.95, 95% CI 0.73-1.24; Table 2, Figure 2A). Of note, the nonfatal MI rate was 17.4 per 1000 PYAR in non–aspirin users, whereas this number was almost double in the aspirin group (28.4 per 1000 PYAR; crude HR 1.70, 95% CI 1.53-1.88, $P<0.001$; Table 2, Figure 2B). Additionally, the rate of nonfatal strokes was 6.0 per 1000 PYAR in aspirin users compared with 5.0 per 1000 PYAR in the nonaspirin group (crude HR 1.22, 95% CI 1.02-1.47, $P=0.03$; Table 2, Figure 2C). However, major bleeding was not different according to aspirin use (crude HR 0.77, 95% CI 0.52-1.13, Table 2, Figure 2D). Furthermore, there was no difference between low-dose and high-dose aspirin in any outcome.

Figure 3 shows the Cox regression analysis. Despite several adjustments, low-dose aspirin use was independently associated with a decrease in all-cause mortality risk (corrected HR 0.89, 95% CI 0.84-0.94). This was counteracted by a paradoxical increase in nonfatal MI and stroke (corrected HR 1.67, 95% CI 1.51-1.86; HR 1.25, 95% CI 1.03-1.50, respectively). Major bleedings were unaffected by aspirin (corrected HR 0.73, 95% CI 0.49-1.08).

Win-ratio analysis of the primary composite outcome, all-cause mortality, and hospitalization (Table 3) showed that, in 3558 pairs, we know in which subjects death occurred first. Death occurred in 1704 patients first if they took aspirin, compared with 1854 patients who did not take aspirin. Among the 2081 remaining pairs, 59 subjects were hospitalized for HF first if they took aspirin, compared with 62 who did not take aspirin. Hence, the win ratio for the composite of all-cause mortality and hospitalization due to heart failure was 1.09 (95% CI 1.02-1.16, $P=0.011$). Thirty-five percent of matched pairs (n=1960) were tied; hence, they had neither all-cause mortality or hospitalization due to HF.

Table 1. Baseline Characteristics of the Study Participants

	Total Population (n=12 534)	Aspirin Nonusers (n=6567)	Low-Dose Aspirin Users (n=5830)	High-Dose Aspirin Users (n=137)
Male*, n (%)	6757 (53.9)	3468 (52.8)	3218 (55.2)	71 (51.8)
Age, y, mean (SD)*,†	75.3 (9.6)	75.7 (9.6)	75.0 (9.6)	73.6 (9.5)
Smoking status, n (%)				
Current smokers	1151 (9.4)	589 (9.2)	543 (9.5)	19 (13.9)
Ex-smokers	7144 (58.1)	3722 (58.0)	3339 (58.2)	83 (60.6)
Nonsmokers	3995 (32.5)	2107 (32.8)	1853 (32.3)	35 (25.5)
Duration of diabetes mellitus, y, median [IQR]*,†,‡	1.4 [0, 5.4]	2.0 [0, 6.0]	0.8 [0, 4.7]	0 [0, 2.0]
Hypertension, n (%)*,†	1391 (11.1)	659 (10.0)	708 (12.1)	24 (17.5)
Dyslipidemia, n (%)*	641 (5.1)	298 (4.5)	332 (5.7)	11 (8.0)
BMI, kg/m^2, mean (SD)*	31.3 (6.6)	31.4 (6.7)	31.1 (6.4)	31.5 (6.7)
Total cholesterol, mg/dL, mean (SD)	169.8 (43.3)	169.7 (43.7)	169.7 (42.9)	175.3 (40.2)
eGFR, mL/(min/1.73 m^2), mean (SD)	62.4 (22.0)	62.3 (22.3)	62.5 (21.8)	58.0 (17.6)
HbA_{1c}, %, mean (SD)	7.5 (1.6)	7.5 (1.6)	7.6 (1.6)	7.6 (1.4)
SBP, mm Hg (SD)*	138.0 (17.3)	137.5 (17.1)	138.6 (17.5)	138.3 (17.2)
DBP, mm Hg (SD)	75.5 (9.4)	75.3 (9.1)	75.6 (9.5)	76.0 (14.4)
ACE inhibitors, n (%)*	8543 (68.2)	4531 (69.0)	3915 (67.2)	97 (70.8)
β-Blockers, n (%)	6394 (51.0)	3377 (51.4)	2940 (50.4)	77 (56.2)
ARBs, n (%)*	2972 (23.7)	1662 (25.3)	1278 (21.9)	32 (23.4)
Statins, n (%)	8056 (64.3)	4268 (65.0)	3695 (63.4)	93 (67.9)
Diuretics, n (%)*	9337 (74.5)	5058 (77.0)	4171 (71.5)	108 (78.8)
Metformin, n (%)*	5864 (46.8)	3221 (49.1)	2585 (44.3)	58 (42.3)
Sulfonylureas, n (%)*,†	4502 (35.9)	2472 (37.6)	1990 (34.1)	40 (29.2)
Insulin, n (%)	1984 (15.8)	1063 (16.2)	898 (15.4)	23 (16.8)
GLP-1 analogues, n (%)*	151 (1.2)	98 (1.5)	53 (0.9)	0 (0)
DDP-4 inhibitors, n (%)*,†	550 (4.4)	338 (5.2)	211 (3.6)	1 (0.7)

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; DBP, diastolic blood pressure; DDP, dipeptidyl peptidase; eGFR, estimated glomerular filtration rate; GLP, glucacon-like peptide; HbA_{1c}, glycated hemoglobin; IQR, interquartile range; SBP, systolic blood pressure.
*P<0.05 for differences between patients prescribed low-dose aspirin at baseline and nonusers.
†P<0.05 for differences between patients prescribed high-dose aspirin at baseline and non–aspirin users.
‡P<0.05 for differences between patients prescribed low-dose aspirin and high-dose aspirin at baseline.

The win ratio of all-cause mortality and nonfatal MI (Table 4) showed that when all-cause mortality was prioritized, the win ratio for the composite was 0.95 (95% CI 0.89-1.00, P=0.057, and for the composite of all-cause mortality and nonfatal stroke, the win ratio was 1.07 (95% CI 1.00-1.14, P=0.037) (Table 5).

Subgroup Analysis

Subgroup analysis of all-cause mortality showed that aspirin decreases all-cause mortality in both men and women, in patients younger than 65 years and elderly patients, in obese patients as well as those with a body mass index <30 kg/m^2, and patients without a history of hypercholesterolemia or hypertension. However, the protection obtained from aspirin was less statistically obvious in hypercholesterolemic patients (HR 1.00, 95% CI 0.79-1.27; P for interaction of dyslipidemia subgroup=0.16), and in those with a history of hypertension (HR 0.86, 95% CI 0.73-1.01) despite the presence of a clear trend (Figure 4).

Sensitivity Analysis

We performed a sensitivity analysis by doing a propensity score match between aspirin users and non–aspirin users at baseline. In each group, 5639 patients were included, and the

Table 2. Primary and Secondary Outcomes

	Primary Composite Outcome			Secondary Outcomes		
	Composite of All-Cause Mortality or a First Hospitalization for Heart Failure	All-Cause Mortality	Hospitalization Due to Heart Failure	Nonfatal Myocardial Infarction	Nonfatal Stroke	Major Bleeding Episodes
	Number of Events Per 1000 Person Years at Risk (95% CI)	Number of Events Per 1000 Person Years at Risk (95% CI)	Number of Events Per 1000 Person Years at Risk (95% CI)	Number of Events Per 1000 Person Years at Risk (95% CI)	Number of Events Per 1000 Person Years at Risk (95% CI)	Number of Events Per 1000 Person Years at Risk (95% CI)
Aspirin use						
No	86.0 (82.7-89.4)	82.9 (79.7-86.2)	2.6 (2.1-3.1)	17.4 (16.0-18.8)	5.0 (4.4-5.8)	1.3 (1.0-1.7)
Yes	73.2 (70.3-76.2)	70.5 (67.7-73.4)	2.4 (1.9-2.9)	28.4 (26.6-30.2)	6.0 (5.3-6.7)	1.0 (0.7-1.3)
Aspirin dosage						
No aspirin	86.0 (82.7-89.4)	82.9 (79.7-86.2)	2.6 (2.1-3.1)	17.4 (16.0-18.8)	5.0 (4.4-5.8)	1.3 (1.0-1.7)
<75 mg/d	73.3 (70.4-76.3)	70.6 (67.7-73.5)	2.3 (1.9-2.8)	28.2 (26.4-30.1)	5.9 (5.2-6.7)	0.9 (0.7-1.2)
>75 mg/d	69.2 (54.3-88.3)	67.7 (53.0-86.5)	3.1 (1.2-8.4)	33.5 (23.3-48.2)	8.8 (4.7-16.3)	2.1 (0.7-6.4)

CI indicates confidence interval.

characteristics of the 2 populations were well balanced (Table 6). Nevertheless, patients on aspirin had a slightly higher prevalence of hypertension and greater body mass index and were more often prescribed angiotensin receptor blockers and diuretics. Aspirin was also associated with a reduction in the primary composite outcome of all-cause mortality and HF and with the secondary outcome of all-cause mortality (Table 7). Hospitalization for HF was unaffected by aspirin use. However, there was an excess of nonfatal MI, nonfatal stroke (P<0.001). Cox regression analysis after adjustment for variables that were still statistically significant after propensity score matching confirmed the protection from all-cause mortality conferred by aspirin (HR 0.88, 95% CI 0.83-0.94), as well as the paradoxical increase in nonfatal MI and stroke (HR 1.66, 95% CI 1.49-1.85; HR 1.23, 95% CI 1.01-1.50, respectively) (Figure 5).

Discussion

This study, using actual clinical practice data from a large primary care cohort, demonstrated that aspirin use for primary prevention reduces mortality in patients with T2D and HF.

Platelet dysfunction, increased platelet aggregation, and aspirin insensitivity were reported to be more pronounced

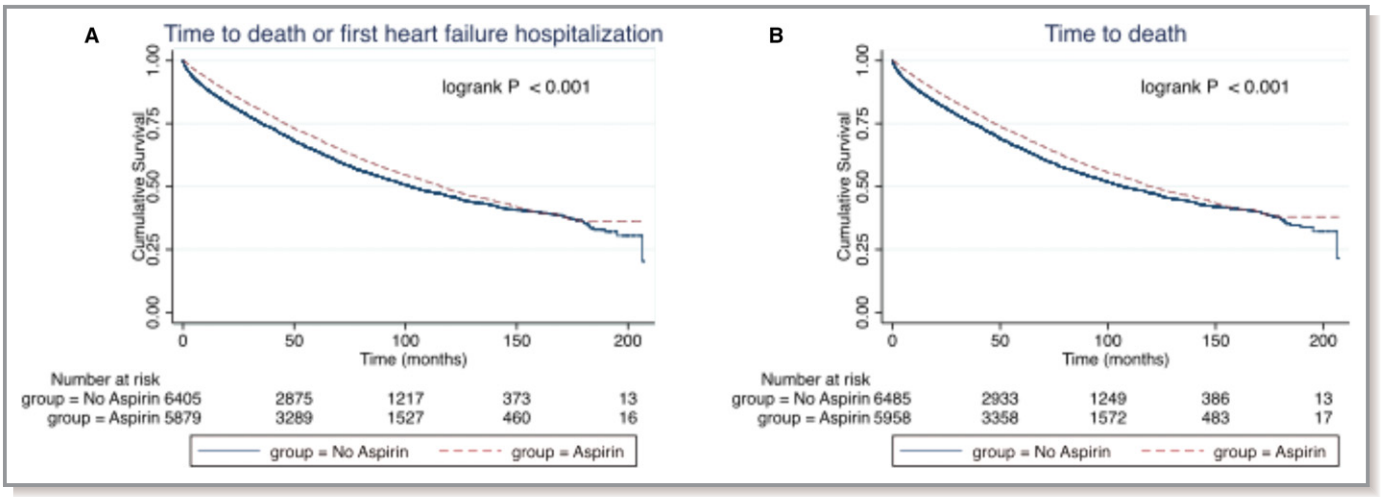


Figure 1. Kaplan-Meier curves comparing time to (A) death or first heart failure hospitalization and (B) time to death between aspirin users and non–aspirin users in patients with diabetes mellitus and heart failure.

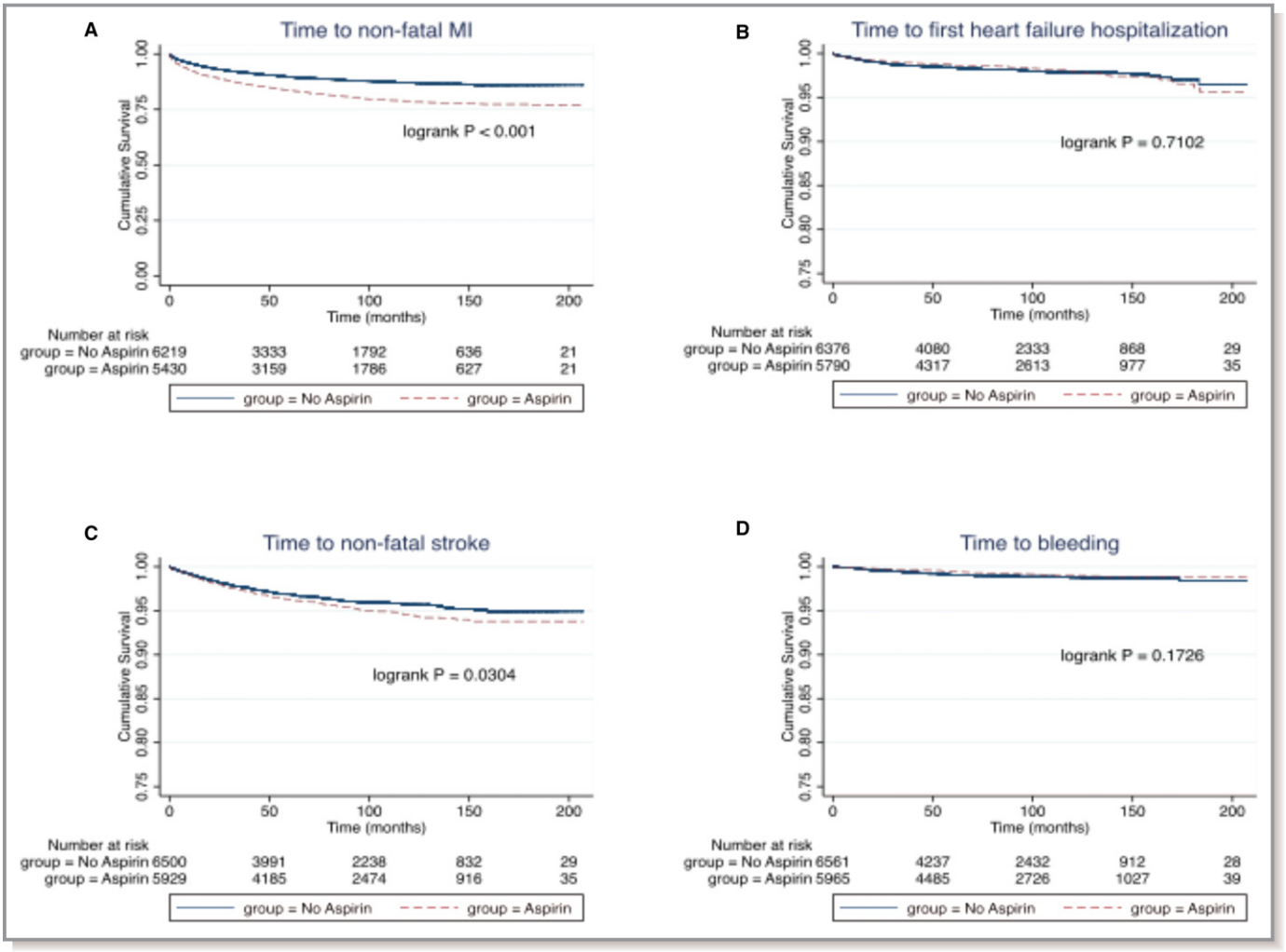
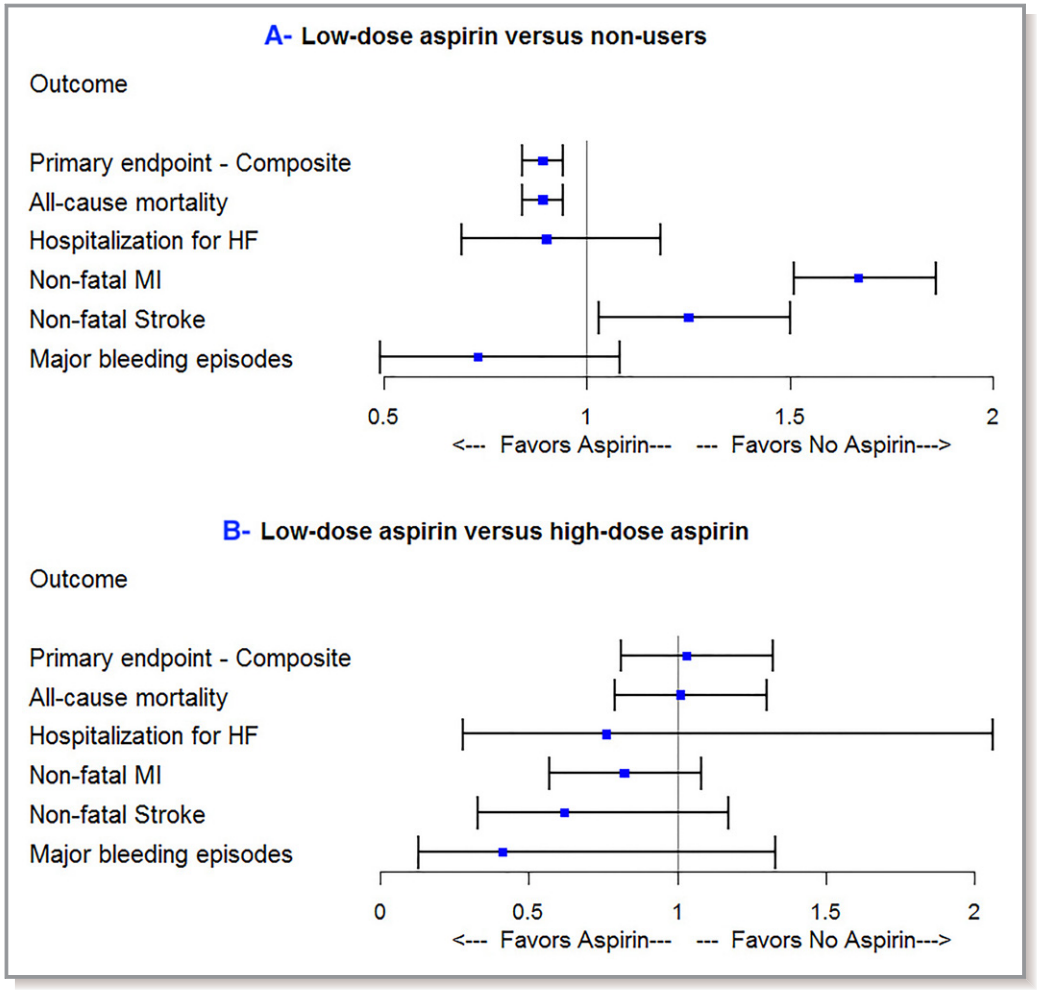


Figure 2. Kaplan-Meier curve comparing time to (A) first heart failure hospitalization, (B) nonfatal myocardial infarction, (C) nonfatal stroke, and (D) major bleeding between aspirin users and non–aspirin users in patients with type 2 diabetes mellitus and heart failure. MI indicates myocardial infarction.

in patients with T2D and no previous cardiovascular event, compared with nondiabetic individuals.[22] Moreover, chronic hyperglycemia promotes a prothrombotic state related to endothelial dysfunction, impaired fibrinolysis, increased levels of coagulation factors, and high platelet reactivity.[23] Because HF is also associated with an enhanced prothrombotic state,[24] we hypothesized that patients with T2D and HF would exceed the threshold of risk at which aspirin is assumed to become beneficial in terms of cardiovascular disease prevention, and thus, there would be benefit from aspirin in the primary prevention of cardiovascular events. Furthermore, the protection conferred by aspirin targeted both sexes, although it has already been established that cardiovascular risk in T2D is different in women compared with men. For example, in a recent analysis of the TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) study, which initially evaluated cardiovascular outcomes in patients with T2D on sitagliptin,[25] it was found that women experienced fewer cardiovascular events, although they had a worse baseline cardiovascular profile.[26]

In our initial analysis we found that aspirin intake is associated with a paradoxical increase in nonfatal MI and nonfatal stroke, although all-cause mortality was decreased. However, in our win-ratio analysis, which prioritized mortality over nonfatal events, we did not find a statistically significant excess of nonfatal MI in patients taking aspirin, which could be due to a shifting of events from fatal to nonfatal. Nevertheless, the win ratio analysis of nonfatal stroke confirmed an excess of cerebrovascular events under aspirin. One plausible explanation is that patients on aspirin are at a higher risk of experiencing nonfatal hemorrhagic strokes; however, the exact etiology of strokes was not recorded in our cohort.



Data supporting a beneficial effect of primary prevention with aspirin in patients with diabetes mellitus are lacking. JPAD was the first randomized placebo-controlled trial that assessed aspirin in patients with T2D without a prior cardiovascular event. In the initial follow-up (median 4.37 years), no benefit with aspirin was observed.[27] This was also confirmed in the long-term follow-up (median 10.3 years).[9] Additionally, aspirin was associated with a

Table 3. Win-Ratio Analysis of HF Hospitalization

Death on aspirin first	1704
Death on placebo first	1854
HF hospitalization on aspirin first	59
HF hospitalization on placebo first	62
None of the above	1960
Total no. of pairs	5639
Win ratio for composite	1.09
95% CI	1.02-1.16
z-score	2.52 (P=0.011)

CI indicates confidence interval; HF, heart failure.

Table 4. Win-Ratio Analysis of Nonfatal MI

Death on aspirin first	1704
Death on placebo first	1854
Nonfatal MI on aspirin first	635
Nonfatal MI on placebo first	357
None of the above	1089
Total no. of pairs	5639
Win ratio for composite	0.95
95% CI	0.89-1.00
z-score	−1.90 (P=0.057)

CI indicates confidence interval; MI, myocardial infarction.

Table 5. Win-Ratio Analysis of Nonfatal Stroke

Death on aspirin first	1704
Death on placebo first	1854
Nonfatal stroke on aspirin first	136
Nonfatal stroke on placebo first	114
None of the above	1818
Total no. of pairs	5639
Win ratio for composite	1.07
95% CI	1.00-1.14
z-score	2.08 (P=0.037)

CI indicates confidence interval.

higher risk of gastrointestinal hemorrhage.[9] However, serious hemorrhage rates were not reported in JPAD other than hemorrhagic stroke, which was not different between groups. In our study we did not have access to nonmajor hemorrhages, and major bleeding events were not increased in either our initial analysis or in our sensitivity analysis, even after cofounding factors had been taken into consideration. The POPAD (Prevention of Progression of Arterial Disease and Diabetes) trial, which randomized patients with diabetes mellitus and asymptomatic peripheral arterial disease in a bifactorial design to receive aspirin and an antioxidant, also failed to demonstrate any benefit of aspirin.[28] However, in a meta-analysis of patients with diabetes mellitus, aspirin was associated with a modest decrease in cardiovascular events, driven mostly by a reduction in MI and stroke.[29,30] Two randomized controlled trials are currently evaluating aspirin versus placebo in primary prevention among patients with diabetes mellitus. The ongoing ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes) trial aims to evaluate the safety and efficacy of aspirin at the dose of 100 mg in 5170 diabetic patients.[31] The ASCEND (A Study of Cardiovascular Events in Diabetes) trial aims to evaluate the effect of aspirin in more than 15 000 diabetic patients (clinical trial number NCT00135226). The initial results of the ASCEND trial suggest a beneficial effect of aspirin in primary prevention of diabetes mellitus that comes at a price of an excess gastrointestinal bleeding.[32]

Aspirin use in HF patients is controversial. Three retrospective randomized controlled trials have previously examined the benefit of aspirin in patients with HF compared with warfarin or placebo in patients without a formal recommendation of anticoagulation. The WASH (Warfarin/Aspirin Study in Heart Failure) trial that randomized patients to aspirin, warfarin, or a placebo reported a deleterious effect of aspirin

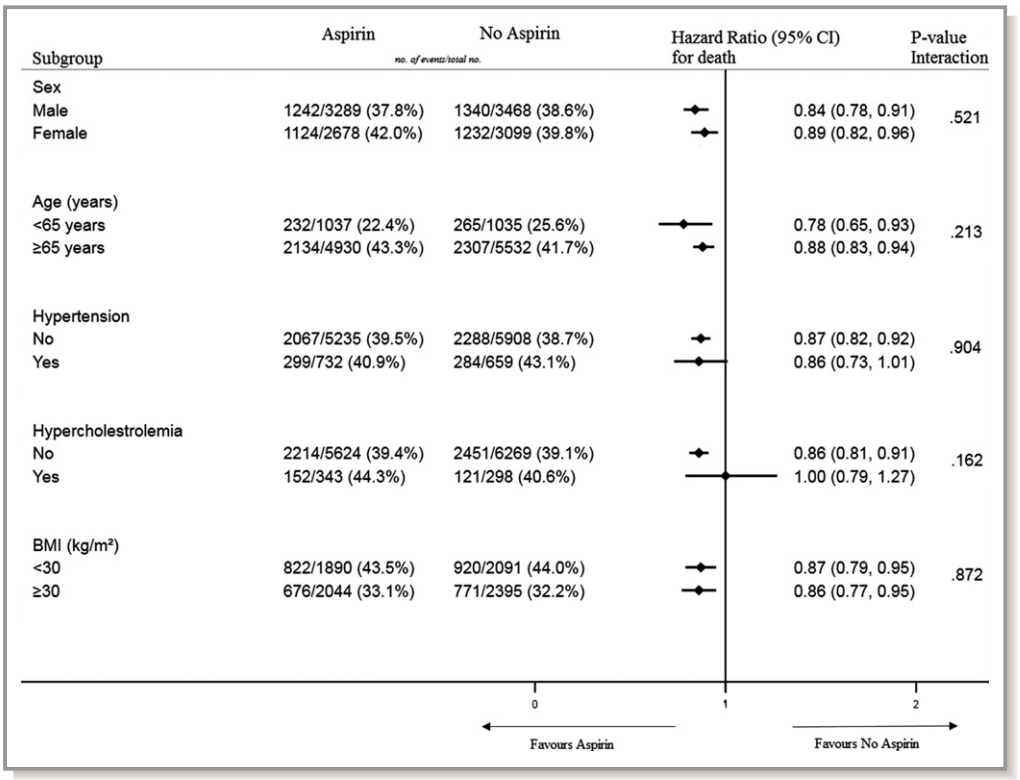


Figure 4. Subgroup analysis of all-cause mortality. BMI inidicates body mass index; CI, confidence interval.

Table 6. Baseline Characteristics and Medications of Propensity-Matched Patients

	Aspirin Nonusers (n=5639)	Low-Dose Aspirin Users (n=5639)
Male, n (%)	3073 (54.5)	3058 (54.2)
Age, y, mean (SD)	75.2 (9.6)	75.3 (9.5)
Smoking status, n (%)		
Current smoker	499 (9.1)	511 (9.2)
Ex-smoker	3212 (58.4)	3226 (58.2)
Nonsmoker	1790 (32.5)	1809 (32.6)
Duration of diabetes mellitus, y, median [IQR]	1.1 [0, 4.7]	1.0 [0, 4.9]
Hypertension, n (%)	638 (11.3)	553 (9.8)
Dyslipidemia, n (%)*	290 (5.1)	231 (4.1)
BMI (kg/m^2), mean (SD)*	31.5 (6.7)	31.1 (6.4)
Total cholesterol (mg/dL), mean (SD)	171.3 (43.9)	169.0 (42.6)
eGFR, mean (SD)	62.4 (22.2)	62.4 (21.8)
HbA_{1c}, mean (SD)	7.5 (1.6)	7.6 (1.6)
SBP, (SD)*	137.5 (17.2)	138.5 (17.4)
DBP, (SD)	75.6 (9.2)	75.5 (9.4)
ACE-inhibitors, n (%)	3862 (68.5)	3810 (67.6)
β-Blockers, n (%)	3377 (51.4)	2940 (50.4)
ARBs, n (%)*	1391 (24.7)	1261 (22.4)
Statins, n (%)	3559 (63.1)	3609 (64.0)
Diuretics, n (%)*	4324 (76.7)	4054 (71.9)
Metformin, n (%)	2594 (46.0)	2530 (44.9)
Sulfonylureas, n (%)	2004 (35.5)	1952 (34.6)
Insulin, n (%)	867 (15.4)	877 (15.5)
GLP-1 analogues, n (%)	70 (1.2)	53 (0.9)
DDP-4 inhibitors, n (%)	252 (4.5)	210 (3.7)

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin reception blockers; BMI, body mass image; DBP, diastolic blood pressure; DDP, dipeptidyl peptidase; eGFR, estimated glomerular filtration rate; GLP, glucacon-like peptide; HbA_{1c}, glycated hemoglobin; IQR, interquartile range; SBP, systolic blood pressure.
*$P<0.05$ for differences between patients prescribed low-dose aspirin at baseline and non–aspirin users.

on cardiovascular events, especially worsening of HF.[13] The WASH trial failed to demonstrate any superiority of warfarin or clopidogrel over aspirin in patients with left ventricular dysfunction and sinus rhythm.[15] Finally, the WARCEF (Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction) trial did not show any superiority of warfarin over aspirin, other

Table 7. Primary and Secondary Outcomes in Propensity-Scored Individuals

	Aspirin Nonusers (n=5639)	Low-Dose Aspirin Users (n=5639)	HR (95% CI)	*P* Value
Primary composite outcome, number of events per 1000 person years at risk				
All-cause mortality or a first hospitalization for HF	6.87 (6.59-7.16)	6.13 (5.88-6.38)	0.90 (0.85-0.95)	<0.001
All-cause mortality	6.62 (6.34-6.90)	5.90 (5.66-6.15)	0.90 (0.85-0.95)	<0.001
Hospitalization due to HF	0.23 (0.19-0.27)	0.19 (0.16-0.24)	0.89 (0.68-1.17)	0.410
Secondary outcomes, number of events per 1000-person years at risk				
Nonfatal MI	1.40 (1.28-1.52)	2.29 (2.14-2.45)	1.64 (1.47-1.83)	<0.001
Nonfatal stroke	0.39 (0.34-0.45)	0.48 (0.42-0.54)	1.26 (1.03-1.53)	0.022
Major bleeding episodes	0.12 (0.09-1.15)	0.07 (0.05-0.10)	0.66 (0.43-0.99)	0.049

CI indicates confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

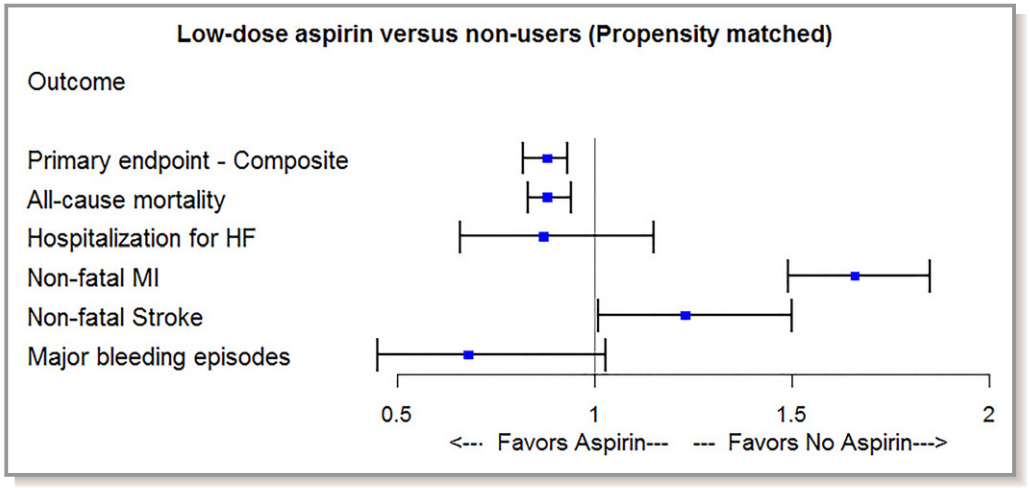


Figure 5. Cox regression analysis of primary and secondary outcomes of low-dose aspirin vs no aspirin after propensity score matching. HF indicates heart failure; MI, myocardial infarction.

than a reduced risk of ischemic stroke that was counterbalanced with an increased risk of major hemorrhage under warfarin.[14] Hospitalization for HF was not increased in either study group.[33]

Our results are aligned with recent data from a retrospective Irish cohort of HF patients, 21% of whom had diabetes mellitus, as low-dose aspirin was associated with a reduction in mortality during a follow-up of almost 3 years.[11] Concordant with our study, aspirin was also beneficial for patients without a history of a cardiovascular event (adjusted HR of mortality 0.69, 95% CI 0.51-0.95), but not on hospitalization for HF.[11] However, other end points such as MI and stroke were not investigated. Consistent with our findings, the SOLVD (Studies of Left Ventricular Dysfunction) investigators also reported a reduction in all-cause mortality and in the composite end point of mortality and hospitalization for HF.[12] Nevertheless, patients on primary prevention with aspirin were not analyzed separately.

Although our study included a large primary cohort of patients and used actual clinical practice data, we acknowledge the presence of several limitations in our study. Like any observational study, we cannot exclude unaccounted confounding factors. The daily dose of aspirin was recorded but not the number of administrations per day, nor adherence to therapy, nor aspirin exposure over time. In addition, the decision to prescribe aspirin in primary prevention could have been for different factors that we could not account for in our analysis. For example, aspirin could have been prescribed to patients with diabetes mellitus, HF, and other comorbid factors not recorded in this database such as dilated cardiomyopathy, hypertrophic cardiomyopathy, or valvular heart disease. Also, the left ventricular ejection fraction was not recorded, so we could not determine whether the outcome associated with aspirin differs according to the type of HF. Most importantly, cardiovascular death was not recorded separately; hence, all-cause mortality could not reflect cardiovascular mortality accurately.

Conclusion

In conclusion, our study supports aspirin use in primary prevention in those with T2D and HF, as it decreased all-cause mortality. However, there was an increased risk of nonfatal MI that might reflect a shifting of events from fatal to nonfatal and/or an excess of nonfatal stroke of unknown etiology. These results persisted after correction for confounding factors and performance of propensity score matching. Our retrospective analysis of data from a large UK National Health Service primary healthcare cohort needs confirmation in heart failure cohorts. If similar results are observed, then a randomized placebo-controlled trial assessing primary prevention of aspirin in patients with diabetes mellitus and heart failure is warranted.

Sources of Funding

This study was supported by the Biomedical Research Program (BMRP) at Weill Cornell Medicine—Qatar, a program funded by the Qatar Foundation. The funders had no role in the study design, data collection and analysis, decision to publish, or in preparation of the manuscript. Dr Abi Khalil's lab is funded by the Qatar National Research Funds(QNRF), NPRP Grant 9-169-3-024.

Disclosures

None.

References

1. ISIS-2 (second international study of infarct survival) collaborative group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet*. 1988;2:349–360.
2. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P; ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177.
3. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S; ESC Scientific Document Group. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315.
4. Jneid H, Addison D, Bhatt DL, Fonarow GC, Gokak S, Grady KL, Green LA, Heidenreich PA, Ho PM, Jurgens CY, King ML, Kumbhani DJ, Pancholy S. 2017 AHA/ACC clinical performance and quality measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circ Cardiovasc Qual Outcomes*. 2017;2017:10.
5. Guirguis-Blake JM, Evans CV, Senger CA, O'Connor EA, Whitlock EP. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2016;164:804–813.
6. Abi Khalil C, Roussel R, Mohammedi K, Danchin N, Marre M. Cause-specific mortality in diabetes: recent changes in trend mortality. *Eur J Prev Cardiol*. 2012;19:374–381.
7. Bornfeldt KE, Tabas I. Insulin resistance, hyperglycemia, and atherosclerosis. *Cell Metab*. 2011;14:575–585.
8. Huang D, Refaat M, Mohammedi K, Jayyousi A, Al Suwaidi J, Abi Khalil C. Macrovascular complications in patients with diabetes and prediabetes. *Biomed Res Int*. 2017;2017:7839101.
9. Saito Y, Okada S, Ogawa H, Soejima H, Sakuma M, Nakayama M, Doi N, Jinnouchi H, Waki M, Masuda I, Morimoto T; JPAD Trial Investigators. Low-dose aspirin for primary prevention of cardiovascular events in patients with type 2 diabetes mellitus: 10-year follow-up of a randomized controlled trial. *Circulation*. 2017;135:659–670.
10. Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. *J Am Coll Cardiol*. 1999;33:1424–1426.
11. Bermingham M, Shanahan MK, O'Connell E, Dawkins I, Miwa S, O'Hanlon R, Gilmer J, McDonald K, Ledwidge M. Aspirin use in heart failure: is low-dose therapy associated with mortality and morbidity benefits in a large community population? *Circ Heart Fail*. 2014;7:243–250.
12. Al-Khadra AS, Salem DN, Rand WM, Udelson JE, Smith JJ, Konstam MA. Antiplatelet agents and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction (SOLVD) trial. *J Am Coll Cardiol*. 1998;31:419–425.
13. Cleland JG, Findlay I, Jafri S, Sutton G, Falk R, Bulpitt C, Prentice C, Ford I, Trainer A, Poole-Wilson PA. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J*. 2004;148:157–164.
14. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, Mohr JP, Massie BM, Labovitz AJ, Anker SD, Lok DJ, Ponikowski P, Estol CJ, Lip GY, Di Tullio MR, Sanford AR, Mejia V, Gabriel AP, del Valle ML, Buchsbaum R; WARCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med*. 2012;366:1859–1869.
15. Massie BM, Collins JF, Ammon SE, Armstrong PW, Cleland JG, Ezekowitz M, Jafri SM, Krol WF, O'Connor CM, Schulman KA, Teo K, Warren SR; WATCH Trial Investigators. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation*. 2009;119:1616–1624.
16. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia*. 2018;61:2108–2117.
17. Vision. The Health Improvement Network (THIN). Available at: https://www.Visionhealth.Co.uk/portfolio-items/the-health-improvement-network-thin/. Accessed November 17, 2017.
18. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J*. 2012;33:176–182.
19. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. *Stat Med*. 1999;18:1341–1354.
20. Leuven E, Sianesi B. PSMATCH2: Stata module to perform full mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing. 2003.
21. Augurzky B, Kluve J. Assessing the performance of matching algorithms when selection into treatment is strong. Discussion paper no 1301. 2004.
22. Mylotte D, Kavanagh GF, Peace AJ, Tedesco AF, Carmody D, O'Reilly M, Foley DP, Thompson CJ, Agha A, Smith D, Kenny D. Platelet reactivity in type 2 diabetes mellitus: a comparative analysis with survivors of myocardial infarction and the role of glycaemic control. *Platelets*. 2012;23:439–446.
23. Lemkes BA, Hermanides J, Devries JH, Holleman F, Meijers JC, Hoekstra JB. Hyperglycemia: a prothrombotic factor? *J Thromb Haemost*. 2010;8:1663–1669.
24. Zannad F, Stough WG, Regnault V, Gheorghiade M, Deliargyris E, Gibson CM, Agewall S, Berkowitz SD, Burton P, Calvo G, Goldstein S, Verheugt FW, Koglin J, O'Connor CM. Is thrombosis a contributor to heart failure pathophysiology? Possible mechanisms, therapeutic opportunities, and clinical investigation challenges. *Int J Cardiol*. 2013;167:1772–1782.
25. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373:232–242.
26. Alfredsson J, Green JB, Stevens SR, Reed SD, Armstrong PW, Angelyn Bethel M, Engel SS, McGuire DK, VAN de Werf F, Hramiak I, White HD, Peterson ED, Holman RR; TECOS Study Group. Sex differences in management and outcomes of patients with type 2 diabetes and cardiovascular disease: a report from TECOS. *Diabetes Obes Metab*. 2018;20:2379–2388.
27. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes Trial I. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2008;300:2134–2141.
28. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepherd J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N, Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R; Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Edinburgh. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ*. 2008;337:a1840.
29. Pignone M, Williams CD. Aspirin for primary prevention of cardiovascular disease in diabetes mellitus. *Nat Rev Endocrinol*. 2010;6:619–628.
30. Xie M, Shan Z, Zhang Y, Chen S, Yang W, Bao W, Rong Y, Yu X, Hu FB, Liu L. Aspirin for primary prevention of cardiovascular events: meta-analysis of randomized controlled trials and subgroup analysis by sex and diabetes status. *PLoS One*. 2014;9:e90286.
31. De Berardis G, Sacco M, Evangelista V, Filippi A, Giorda CB, Tognoni G, Valentini U, Nicolucci A; ACCEPT-D Study Group. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. *Trials*. 2007;8:21.
32. ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med*. 2018. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa1804988. Accessed October 10, 2018.
33. Teerlink JR, Qian M, Bello NA, Freudenberger RS, Levin B, Di Tullio MR, Graham S, Mann DL, Sacco RL, Mohr JP, Lip GYH, Labovitz AJ, Lee SC, Ponikowski P, Lok DJ, Anker SD, Thompson JLP, Homma S; WARCEF Investigators. Aspirin does not increase heart failure events in heart failure patients: from the WARCEF trial. *JACC Heart Fail*. 2017;5:603–610.