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

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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.

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Key Words: aspirin • death • diabetes mellitus • heart failure
to be driven through a reduction in mortality in patients with diabetes mellitus and heart failure.\textsuperscript{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.\textsuperscript{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 diabetes mellitus is diagnosed. We included 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 $\geq 55$ 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.

#### 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 $\geq 55$ 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.

#### 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, beta-blockers, statins, thiazolidinediones, and aspirin.
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, initially recommended by Finkelstein and Schoenfeld. 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. 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. 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.
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/m², 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 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/m², 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 m², mean (SD)                      | 62.4 (22.0)                 | 62.3 (22.3)               | 62.5 (21.8)                     | 58.0 (17.6)                    |
| HbA1c, %, 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, glucagon-like peptide; HbA1c, 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.
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 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 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...
in patients with T2D and no previous cardiovascular event, compared with nondiabetic individuals. Moreover, chronic hyperglycemia promotes a prothrombotic state related to endothelial dysfunction, impaired fibrinolysis, increased levels of coagulation factors, and high platelet reactivity. Because HF is also associated with an enhanced prothrombotic state, 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, it was found that women experienced fewer cardiovascular events, although they had a worse baseline cardiovascular profile.

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.

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.
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. This was also confirmed in the long-term follow-up (median 10.3 years). Additionally, aspirin was associated with a

**Figure 3.** Cox regression analysis of primary and secondary outcomes of (A) low-dose aspirin vs no aspirin and (B) low-dose aspirin vs high-dose aspirin. HF indicates heart failure; MI, myocardial infarction.

**Table 3.** Win-Ratio Analysis of HF Hospitalization

| Outcome                               | Event Count |
|---------------------------------------|-------------|
| 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

| Outcome                               | Event Count |
|---------------------------------------|-------------|
| 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.
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 5,170 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

### Table 5. Win-Ratio Analysis of Nonfatal Stroke

| Event          | No. of pairs | Win ratio | 95% CI   | P-value |
|----------------|--------------|-----------|----------|---------|
| Death on aspirin first | 1704         | 1.07      | 1.00-1.14 | .037    |
| 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         |           |          |         |

CI indicates confidence interval.

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

| Subgroup          | Aspirin | No Aspirin | Hazard Ratio (95% CI) | P-value |
|-------------------|---------|------------|-----------------------|---------|
| Sex               |         |            |                       |         |
| Male              | 1242/3269 (37.6%) | 1340/3468 (38.6%) | 0.84 (0.79, 0.91) | .521    |
| Female            | 1124/2678 (42.0%) | 1232/3099 (39.8%) | 0.89 (0.82, 0.96) |         |
| Age (years)       |         |            |                       |         |
| <65 years         | 232/1037 (22.4%) | 265/1055 (25.6%) | 0.78 (0.66, 0.93) | .213    |
| ≥65 years         | 2134/9330 (43.3%) | 2307/8532 (41.7%) | 0.88 (0.83, 0.94) |         |
| Hypertension      |         |            |                       |         |
| No                | 2067/5235 (39.5%) | 2288/5908 (38.7%) | 0.87 (0.82, 0.92) | .904    |
| Yes               | 289/732 (40.9%) | 284/659 (43.1%) | 0.86 (0.73, 1.01) |         |
| Hypercholesterolemia |         |            |                       |         |
| No                | 2214/5524 (39.4%) | 2451/6269 (39.1%) | 0.86 (0.81, 0.91) | .162    |
| Yes               | 152/349 (44.3%) | 121/286 (40.8%) | 1.00 (0.79, 1.27) |         |
| BMI (kg/m²)       |         |            |                       |         |
| <30               | 622/1890 (43.5%) | 920/2091 (44.0%) | 0.87 (0.79, 0.95) | .872    |
| ≥30               | 676/2044 (33.1%) | 771/2386 (32.2%) | 0.88 (0.77, 0.96) |         |

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

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

| Table 6. Baseline Characteristics and Medications of Propensity-Matched Patients |
|---------------------------------|---------------------------------|---------------------------------|
| **Aspirin Nonusers (n=5639)**   | **Low-Dose Aspirin Users (n=5639)** |
| Male, n (%)                     | Male, n (%)                     |
| 3073 (54.5)                     | 3058 (54.2)                     |
| Age, y, mean (SD)               | Age, y, mean (SD)               |
| 75.2 (9.6)                      | 75.3 (9.5)                      |
| Smoking status, n (%)           | Smoking status, n (%)           |
| Current smoker                  | Current smoker                  |
| 499 (9.1)                       | 511 (9.2)                       |
| Ex-smoker                       | Ex-smoker                       |
| 3212 (58.4)                     | 3226 (58.2)                     |
| Nonsmoker                       | Nonsmoker                       |
| 1790 (32.5)                     | 1809 (32.6)                     |
| Duration of diabetes mellitus, y, median [IQR] | Duration of diabetes mellitus, y, median [IQR] |
| 1.1 [0, 4.7]                    | 1.0 [0, 4.9]                    |
| Hypertension, n (%)             | Hypertension, n (%)             |
| 638 (11.3)                      | 553 (9.8)                       |
| Dyslipidemia, n (%)*            | Dyslipidemia, n (%)*            |
| 290 (5.1)                       | 231 (4.1)                       |
| BMI (kg/m²), mean (SD)*         | BMI (kg/m²), mean (SD)*         |
| 31.5 (6.7)                      | 31.1 (6.4)                      |
| Total cholesterol (mg/dL), mean (SD) | Total cholesterol (mg/dL), mean (SD) |
| 171.3 (43.9)                    | 169.0 (42.6)                    |
| eGFR, mean (SD)                 | eGFR, mean (SD)                 |
| 62.4 (22.2)                     | 62.4 (21.8)                     |
| HbA1c, mean (SD)                | HbA1c, mean (SD)                |
| 7.5 (1.6)                       | 7.1 (1.6)                       |
| SBP, (SD)*                      | SBP, (SD)*                      |
| 137.5 (17.2)                    | 138.5 (17.4)                    |
| DBP, (SD)                       | DBP, (SD)                       |
| 75.6 (9.2)                      | 75.5 (9.4)                      |
| ACE-inhibitors, n (%)           | ACE-inhibitors, n (%)           |
| 3862 (68.5)                     | 3810 (67.6)                     |
| β-Blockers, n (%)               | β-Blockers, n (%)               |
| 3377 (51.4)                     | 2940 (50.4)                     |
| ARBs, n (%)*                    | ARBs, n (%)*                    |
| 1391 (24.7)                     | 1261 (22.4)                     |
| Statins, n (%)                  | Statins, n (%)                  |
| 3559 (63.1)                     | 3609 (64.0)                     |
| Diuretics, n (%)*               | Diuretics, n (%)*               |
| 4324 (76.7)                     | 4054 (71.9)                     |
| Metformin, n (%)                | Metformin, n (%)                |
| 2594 (46.0)                     | 2530 (44.9)                     |
| Sulfonylureas, n (%)            | Sulfonylureas, n (%)            |
| 2004 (35.5)                     | 1952 (34.6)                     |
| Insulin, n (%)                  | Insulin, n (%)                  |
| 867 (15.4)                      | 877 (15.5)                      |
| GLP-1 analogues, n (%)          | GLP-1 analogues, n (%)          |
| 70 (1.2)                        | 53 (1.9)                        |
| DPP-4 inhibitors, n (%)         | DPP-4 inhibitors, n (%)         |
| 252 (4.5)                       | 210 (3.7)                       |

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass image; DBP, diastolic blood pressure; DDP, dipeptidyl peptidase; eGFR, estimated glomerular filtration rate; GLP, glucacon-like peptide; HbA1c, 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.

| Table 7. Primary and Secondary Outcomes in Propensity-Scored Individuals |
|---------------------------------|---------------------------------|---------------------------------|
| **Aspirin Nonusers (n=5639)**   | **Low-Dose Aspirin Users (n=5639)** | **HR (95% CI)**  |
| All-cause mortality or a first hospitalization for HF | All-cause mortality or a first hospitalization for HF |
| 6.87 (6.59-7.16)                 | 6.13 (5.68-6.38)                 | 0.90 (0.85-0.95)  |
| All-cause mortality              | All-cause mortality              |
| 6.62 (6.34-6.90)                 | 5.90 (5.66-6.15)                 | 0.90 (0.85-0.95) |
| Hospitalization due to HF        | Hospitalization due to HF        |
| 0.23 (0.19-0.27)                 | 0.19 (0.16-0.24)                 | 0.89 (0.68-1.17)  |
| Secondary outcomes, number of events per 1000-person years at risk |
| Nonfatal MI                      | Nonfatal MI                      |
| 1.40 (1.28-1.52)                 | 2.29 (2.14-2.45)                 | 1.64 (1.47-1.83)  |
| Nonfatal stroke                  | Nonfatal stroke                  |
| 0.39 (0.34-0.45)                 | 0.48 (0.42-0.54)                 | 1.26 (1.03-1.53)  |
| Major bleeding episodes          | Major bleeding episodes          |
| 0.12 (0.09-1.15)                 | 0.07 (0.05-0.10)                 | 0.66 (0.43-0.99)  |

CI indicates confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.
than a reduced risk of ischemic stroke that was counterbalanced with an increased risk of major hemorrhage under warfarin. Hospitalization for HF was not increased in either study group.

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. 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. 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. 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.

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**Disclosures**

None.
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