Aspirin Use in Heart Failure

Is Low-Dose Therapy Associated With Mortality and Morbidity Benefits in a Large Community Population?

Margaret Bermingham, PhD; Mary Katherine Shanahan, MPharm; Eoin O'Connell, MLitt; Ian Dawkins, DPhil; Saki Miwa, MB; Rory O'Hanlon, MD; John Gilmer, PhD; Kenneth McDonald, MD; Mark Ledwidge, PhD

Background—Aspirin use in heart failure (HF) is controversial. The drug has proven benefit in comorbidities associated with HF; however, retrospective analysis of angiotensin-converting enzyme inhibitor trials and prospective comparisons with warfarin have shown increased risk of morbidity with aspirin use. This study aims to evaluate the association of low-dose aspirin with mortality and morbidity risk in a large community-based cohort.

Methods and Results—This was a retrospective cohort study of patients attending an HF disease management program. Aspirin use at baseline and its association with mortality and HF hospitalization in the population was examined. Of 1476 patients (mean age, 70.4±12.4 years; 63% men), 892 (60.4%) were prescribed aspirin. Low-dose aspirin (75 mg/d) was prescribed to 828 (92.8%) patients. Median follow-up time was 2.6 (0.8–4.5) years. During the follow-up period, 464 (31.4%) patients died. In adjusted analysis, low-dose aspirin use was associated with reduced mortality risk compared with nonaspirin use (hazard ratio=0.58; 95% confidence interval, 0.46–0.74), and this was confirmed by a propensity-matched subgroup analysis. Low-dose aspirin use was associated with reduced risk of HF hospitalization compared with nonaspirin use in the total population (adjusted hazard ratio=0.70; 95% confidence interval, 0.54–0.90). In adjusted analysis, there was no difference in mortality or HF hospitalization between high-dose aspirin users (>75 mg/d) and nonaspirin users.

Conclusions—In this study, low-dose aspirin therapy was associated with a significant reduction in mortality and morbidity risk during long-term follow-up. These results suggest that low-dose aspirin may have a continuing role in secondary prevention in HF and underline the need for more trials of low-dose aspirin use in HF. **(*Circ Heart Fail*. 2014;7:243-250.)**

Key Words: aspirin ■ heart failure ■ mortality

Aspirin use in heart failure (HF) is controversial. The drug has proven benefit in patients with established ischemic heart disease (IHD), a common comorbidity of HF. Aspirin is also recommended in diabetics at high risk of cardiovascular events and as second-line treatment of vascular disorders and atrial fibrillation—all frequently occurring comorbidities in an HF population. However, it has been reported that aspirin use may blunt the beneficial effect of renin–angiotensin–aldosterone system (RAAS) modifying therapy in patients with HF, and several trials have shown increased risk of HF hospitalization when using aspirin. Furthermore, older patients with HF may be at risk of adverse events related to aspirin use especially gastrointestinal hemorrhage.

Editorial see p 237
Clinical Perspective on p 250

Three prospective, randomized, controlled trials (Warfarin/Aspirin Study in Heart Failure [WASH], Warfarin and Antiplatelet Therapy in Chronic Heart Failure [WATCH], and Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction [WARCEF]) have been conducted in recent years to establish the role of aspirin use in HF and its relative benefit compared with warfarin.[1–3] All were performed in selected populations with low ejection fraction and in sinus rhythm, and 2 of these trials were underpowered.[1–3] Although the results of each of these trials demonstrate that there is no additional mortality benefit of warfarin use compared with aspirin in these patients, 2 of the trials[1,3] raised a concern of excess HF hospitalizations associated with aspirin use. Accordingly, the controversy about aspirin use in HF persists, and in the absence of large prospective, placebo-controlled outcome studies, several retrospective analyses of aspirin use in clinical trial or short-term follow-up of registry populations have been performed.[4–8] These studies have primarily focused on the interaction between aspirin use and effectiveness of RAAS modifying therapy and have not provided a consistent picture.

Received January 24, 2013; accepted January 28, 2014.

From the Heart Failure Unit, St. Vincent's University Hospital, Dublin, Ireland (M.B., M.K.S., I.D., K.M., M.L.); School of Medicine and Medical Science, University College Dublin, Dublin, Ireland (M.B., E.O., K.M., M.L.); School of Medicine, University College Cork, Cork, Ireland (S.M.); Centre for Cardiovascular Magnetic Resonance, Blackrock Clinic, County Dublin, Ireland (R.O.); and School of Pharmacy and Pharmaceutical Sciences, Trinity College, Dublin, Ireland (J.G.).

The Data Supplement is available at http://circheartfailure.ahajournals.org/lookup/suppl/doi:10.1161/CIRCHEARTFAILURE.113.000132/-/DC1.

Correspondence to Mark Ledwidge, PhD, Heart Failure Unit, St. Vincent's University Hospital, Dublin 4, Ireland. E-mail mark@heartbeat-trust.org

Circ Heart Fail **is available at http://circheartfailure.ahajournals.org** **DOI: 10.1161/CIRCHEARTFAILURE.113.000132**

The risk–benefit ratio of aspirin in HF may be dose related. It has been shown that the adverse renal and gastrointestinal effects of aspirin are more evident at doses >80 mg,[9,10] and the Antithrombotic Trialists group recommends aspirin at doses of 75 to 150 mg daily for cardiovascular protection because this dose is clinically effective and minimizes risk of adverse events.[11] However, the WASH, WATCH, and WARCEF studies used daily doses of 300, 162, and 325 mg, respectively.[1–3] Indeed, in one of the retrospective registry analyses of aspirin in HF to date, a large proportion of patients received aspirin at higher antiplatelet doses (325 mg/d),[7] and in other analyses, the dose used was not available, possibly explaining the adverse events and excess of HF hospitalizations observed.

There have been few large studies of aspirin use in real-world HF populations with lengthy follow-up times. This study aims to provide information on the association of low-dose aspirin with mortality and HF hospitalization risk in a large community-based cohort participating in a disease management program (DMP).

Methods

This is a retrospective cohort study of patients with HF attending a DMP in St Vincent's University Hospital, Dublin, Ireland. The study was approved by the Clinical Audit Committee of the hospital. Patients were recruited to the DMP from December 1, 1998, to October 1, 2010. Data collection for each patient was censored at the time point of their most recent contact with the DMP or date of death. The aim of the study was to evaluate the impact of aspirin use on mortality in an ambulatory HF population with long-term follow-up. The study population was subdivided into (1) those with low-dose aspirin use at baseline (low-dose aspirin users), (2) those with high-dose aspirin use at baseline (high-dose aspirin users), and (3) those without aspirin use at baseline (nonaspirin users). Low-dose aspirin use was defined as aspirin dose of 75 mg daily, and high-dose aspirin use was defined as aspirin dose >75 mg daily.

Patients

Patients were recruited to the DMP after an HF hospitalization or by referral in a nonacute state from general practitioner or from another hospital service. Demographic details, comorbidities, medications, clinical data, biochemical laboratory results including B-type natriuretic peptide (BNP) levels, and echocardiogram results were recorded electronically at baseline and updated where appropriate at subsequent visits. Medication details recorded were drug name, dose, and frequency. Outcome data were obtained from patient or carer report or hospital database records. Cause of hospitalization was determined from patient or carer report, hospital database records, discharge letter, or inpatient medical notes. Deaths were reported through the hospital's database system if the patient died as an inpatient or were notified by patients' general practitioner or a carer if death occurred outside the hospital.

End Points

The primary end point of the study was mortality. The effect of low-dose aspirin use compared with that of nonaspirin use on mortality was assessed using survival analysis with and without adjustment of key confounding variables at baseline. Secondary end points included the following: HF hospitalization and combined mortality and all-cause hospitalization (all-cause events) assessed in low-dose aspirin use compared with nonaspirin use. The effect of low-dose aspirin use compared with that of high-dose aspirin use and the effect of high-dose aspirin use compared with that of nonaspirin use on these outcomes were also examined. The effect of low-dose aspirin use compared with that of nonaspirin use on outcomes was also examined in the following patient subcohorts: (1) IHD; (2) no IHD; (3) IHD, peripheral vascular disease (PVD), and stroke; (4) no IHD, PVD, or stroke; (5) atrial fibrillation; and (6) no atrial fibrillation. The effect of aspirin initiation postbaseline was also examined.

Statistical Analysis

Continuous normally distributed variables were compared using 1-way ANOVA, and post hoc analysis was performed using Tukey test. Continuous non-normal variables were compared using Kruskal–Wallis analysis. Where the Kruskal–Wallis test resulted in a statistically significant P value, the Mann–Whitney U test was used for comparisons between pairs of groups. A Bonferroni correction was used, resulting in a significant threshold of α=0.017. χ^2 tests were performed, and standardized residuals were examined to compare categorical variables.

Univariable and multivariable survival analysis between cohorts was performed using the Cox proportional hazards method. The baseline factors adjusted for were as follows: age; sex; BNP; creatinine level; HF type; and comorbidities—IHD, atrial fibrillation, diabetes mellitus, hypertension, dyslipidemia, stroke, PVD, chronic obstructive pulmonary disease unless otherwise stated. The proportional hazards assumption was verified for all scenarios examined. Survival data were censored at 3000-day follow-up because of low numbers beyond that time.

Propensity Analysis

A subsample of patients was drawn from the low-dose aspirin users group to match the nonaspirin users group. The method for matching was closest Mahalanobis distance within propensity score calipers.[12] Age, sex, IHD, atrial fibrillation, diabetes mellitus, hypertension, and dyslipidemia were used for the propensity score and Mahalanobis distance calculation. In total, 503 pairs of patients (n=1006) comprised the final matched sample. The low-dose aspirin user and nonaspirin user arms in the full sample differed on age (Wilcoxon test, P<0.001), IHD (χ^2, P<0.001), atrial fibrillation (χ^2, P<0.001), diabetes mellitus (χ^2, P=0.006), hypertension (χ^2, P=0.006), and dyslipidemia (χ^2, P<0.001). The low-dose aspirin user and nonaspirin user arms in the matched sample did not differ on age (Wilcoxon test, P=0.082), sex (χ^2, P=0.950), IHD (χ^2, P=0.890), atrial fibrillation (χ^2, P=0.480), diabetes mellitus (χ^2, P=0.580), hypertension (χ^2, P=0.087), or dyslipidemia (χ^2, P=0.520). All tests were 2 sided where possible. Wilcoxon rank-sum test was used for the age variable because the age data were neither normally distributed nor transformable to normally distributed. Shapiro–Wilk test was used to test for normally distributed data at α=0.05.

Propensity-matched data were compared by paired t tests for continuous, normally distributed variables, Wilcoxon signed-rank test for continuous non-normally distributed variables, and McNemar test for categorical variables. Univariable and multivariable survival analysis between matched cohorts was performed using the Cox proportional hazards method, stratified by matched pairs. The baseline factors adjusted for were BNP, creatinine level, HF type, stroke, PVD, and chronic obstructive pulmonary disease. Survival data were censored at 3000-day follow-up. All analyses were performed using SPSS version 18.

Results

Patient Demographics

Data were available for 1476 patients with median follow-up time of 2.15 (0.81–4.54) years. Minimum follow-up time was 1 day, and maximum follow-up time was 11.93 years. The mean age of the population was 70.4±12.4 years, and 930 (63.0%) patients of the population were men. Aspirin was prescribed at baseline to 892 (60.4%) patients.

Of those patients prescribed aspirin, 828 (92.8%) were using a dose of 75 mg daily. A dose of 150 mg daily was used by 15 (1.7%) patients and a dose of 300 mg daily by 49 (5.5%)

patients. A second antiplatelet agent was prescribed concomitantly to 164 (18.4%) patients, warfarin was prescribed concomitantly with aspirin to 248 (27.8%) patients, and triple therapy was prescribed to 19 (2.1%) patients.

Descriptions of the total population, low-dose aspirin users, high-dose aspirin users, and nonaspirin users are given in Table 1.

Mortality

A total of 464 (31.4%) patients died during the follow-up period: 237 (28.6%) were low-dose aspirin users, 30 (46.9%) high-dose aspirin users, and 197 (33.7%) nonaspirin users.

In unadjusted analysis, there was a lower risk of mortality among low-dose aspirin users than nonaspirin users (hazard ratio [HR]=0.81; 95% confidence interval [CI], 0.67–0.98).

Table 1. Characteristics of (1) the Total Population, (2) Low-Dose Aspirin Users, (3) High-Dose Aspirin Users, and (4) Nonaspirin Users

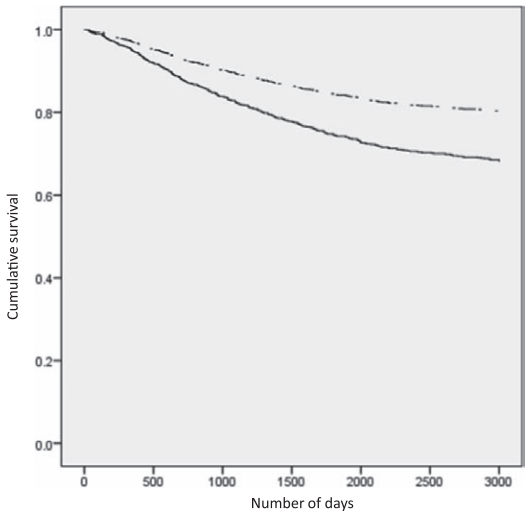
Characteristic	Total Population (N=1476)	Low-Dose Aspirin Users (n=828)	High-Dose Aspirin Users (n=64)	Aspirin Nonusers (n=584)
Demographics				
Age, y *†	70.4±12.4	71.9±11.3	71.9±9.8	68.1±13.8
Male	930 (63.0)	533 (64.4)	40 (62.5)	357 (61.1)
Clinical characteristics				
Systolic blood pressure, mm Hg	127.2±39.0	125.9±22.7	130.4±24.3	125.6±21.2
Diastolic blood pressure, mm Hg†‡	73.2±36.7	71.2±13.4	77.0±14.1	72.5±13.3
BNP, pg/mL*	317 (139–668)	352 (157–709)	262 (131–556)	274 (115–598)
Creatinine, μmol/L	103 (87–129)	105 (88–130)	103 (84–141)	101 (85–128)
Ejection fraction, %	40.2±14.5	39.9±14.0	40.2±15.3	40.5±15.1
HFrEF	797 (64.8)	464 (66.9)	37 (63.8)	296 (61.9)
Comorbidities				
Ischemic heart disease*	664 (45.0)	482 (58.2)	27 (42.2)	155 (26.5)
Atrial fibrillation	552 (37.4)	278 (33.6)	21 (32.8)	253 (43.3)
Chronic obstructive pulmonary disease	164 (11.1)	97 (11.7)	6 (9.4)	61 (10.4)
Dyslipidemia*	424 (28.7)	275 (33.2)	23 (35.9)	126 (21.6)
Diabetes mellitus	318 (21.5)	199 (24.0)	15 (23.4)	104 (17.8)
Hypertension	624 (42.3)	376 (45.4)	26 (40.6)	222 (38.0)
Peripheral vascular disease	18 (1.2)	12 (1.4)	0	6 (1.0)
Stroke	47 (3.2)	26 (3.1)	0	21 (3.6)
Medications				
Loop diuretic	1378 (93.3)	783 (94.6)	58 (90.6)	537 (92.0)
ACE inhibitor	1242 (84.1)	699 (84.4)	60 (93.8)	483 (82.7)
Angiotensin receptor blocker	403 (27.3)	217 (26.2)	24 (37.5)	162 (27.7)
β-Blocker	1247 (84.5)	719 (86.8)	49 (76.6)	479 (82.0)
Mineralocorticoid receptor antagonist	406 (27.5)	231 (27.9)	11 (17.2)	164 (28.1)
Digoxin*	658 (44.6)	302 (36.5)	31 (48.4)	325 (55.7)
Calcium channel blocker	348 (23.6)	211 (25.5)	21 (32.8)	116 (19.9)
Cholesterol-lowering agent*	532 (36.0)	361 (43.6)	15 (23.4)	156 (26.7)
Nonloop diuretic	606 (41.1)	331 (40.0)	33 (51.6)	242 (41.4)
Nitrate*	826 (56.0)	514 (62.1)	38 (59.4)	274 (46.9)
Proton pump inhibitor	698 (47.3)	415 (50.1)	23 (35.9)	260 (44.5)
Warfarin*	661 (44.8)	256 (30.9)	18 (28.1)	387 (66.3)

Continuous variables are expressed as mean±SD, where data are normally distributed and compared using 1-way ANOVA with post hoc analysis using Tukey test. Continuous variables are expressed as median (interquartile range), where data are non-normally distributed and compared using Kruskal–Wallis test with post hoc analysis using the Mann–Whitney *U* test. Categorical variables are summarized as frequencies and percentages and are compared using χ^2 test. ACE indicates angiotensin-converting enzyme; BNP, B-type natriuretic peptide; and HFrEF, heart failure with reduced ejection fraction.

For differences between patients prescribed low-dose aspirin at baseline and those with no aspirin use at baseline: *$P<0.05$.

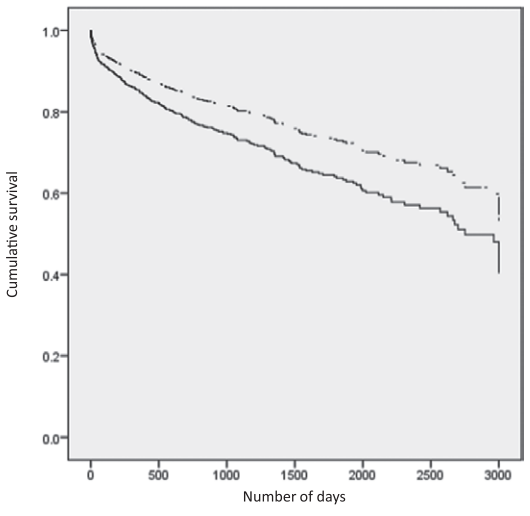
For differences between patients prescribed high-dose aspirin at baseline and those with no aspirin use at baseline: †$P<0.05$.

For differences between patients prescribed low-dose aspirin at baseline and those prescribed high-dose aspirin: ‡$P<0.05$.



Number at risk							
Nonaspirin users	584	505	457	430	402	393	195
Low-dose aspirin users	828	741	689	648	622	608	300

Figure 1. Kaplan–Meier survival curve comparing mortality among low-dose aspirin users with nonaspirin users in a Cox proportional hazards model adjusted for baseline age, sex, B-type natriuretic peptide, creatinine level, heart failure type, and comorbidities. Low-dose aspirin users (broken line) had a significantly reduced risk of mortality compared with nonaspirin users (unbroken line). Adjusted hazard ratio=0.58; 95% confidence interval, 0.46 to 0.74.



Number at risk							
Nonaspirin users	584	266	169	110	65	34	10
Low-dose aspirin users	828	384	248	148	81	41	14

Figure 2. Kaplan–Meier survival curve comparing heart failure hospitalization among low-dose aspirin users and nonaspirin users in a Cox proportional hazards model adjusted for baseline age, sex, B-type natriuretic peptide, creatinine level, heart failure type, and comorbidities. Low-dose aspirin users (broken line) had a lower risk of heart failure hospitalization than nonaspirin users (unbroken line). Adjusted hazard ratio=0.70; 95% confidence interval, 0.54 to 0.90.

In adjusted analysis, low-dose aspirin users had an even greater reduction in mortality compared with nonaspirin users (HR=0.58; 95% CI, 0.46–0.74; Figure 1). In a fully adjusted model including age, sex, BNP, creatinine, HF type, diastolic blood pressure, heart rate, smoking status, comorbidities, and medications, the mortality benefit of low-dose aspirin use remained significant (HR=0.65; 95% CI, 0.51–0.84).

In unadjusted analysis, there was no statistically significant difference in mortality between patients with high-dose aspirin use and those with no aspirin use (HR=1.40; 95% CI, 0.95–2.05). In multivariable analysis, there remained no statistically significant difference in mortality between these groups (HR=0.98; 95% CI, 0.59–1.63).

Patients with low-dose aspirin use had a lower mortality rate than high-dose aspirin users in unadjusted analysis (HR=0.58; 95% CI, 0.40–0.85), and mortality risk among low-dose aspirin users remained lower after multivariable adjustment (HR=0.57; 95% CI, 0.35–0.92).

HF Hospitalization and Combined Morbidity–Mortality

HF hospitalization was experienced by 364 (24.7%) patients, 202 (24.4%) low-dose aspirin users, 16 (25.0%) high-dose aspirin users, and 151 (25.9%) nonaspirin users. There was no statistically significant difference in risk of HF hospitalization between low-dose aspirin users and nonaspirin users in unadjusted analysis (HR=0.98; 95% CI, 0.79–1.20). However, in multivariable analysis, low-dose aspirin use was associated with a 30% lower risk of this event (HR=0.70; 95% CI, 0.54–0.90; Figure 2). There was no statistically significant difference in risk of HF hospitalization between high-dose aspirin users and nonaspirin users in univariable or multivariable analysis. Neither was there a statistically significant difference in HF hospitalization risk between low-dose aspirin users and high-dose aspirin users in univariable or multivariable analysis (Table 2).

There was no statistically significant difference between cohorts in risk of all-cause events in unadjusted or adjusted analyses (Table 2).

Indication for Aspirin Use, IHD, and Outcome

A definite indication for aspirin use (IHD or PVD or stroke) was present in 701 patients (47.5%) in the total population. Among aspirin users, 527 (59.1%) had a definite indication—500 (60.4%) low-dose aspirin users and 27 (42.2%) high-dose aspirin users (P=0.004 for difference between low- and high-dose aspirin users). Among nonaspirin users, 174 (29.8%) had a definite indication for aspirin use. Indication for low-dose aspirin use and outcomes adjusted for age, sex, BNP, creatinine level, and HF type are described in Table 3 and Figure 3.

Aspirin Discontinuation and Initiation

Aspirin was discontinued at some point by 169 (18.9%) patients: 159 (19.2%) low-dose aspirin users and 10 (15.6%) high-dose aspirin users (P=0.482). For all aspirin users, median follow-up time for aspirin persisters was 1.91 (0.65–4.26) years (11.2% less than median follow-up time for total population), whereas median follow-up time prescribed aspirin for non-persisters was 3.27 (1.58–5.04) years (52% greater than median follow-up time for total population). Among low-dose aspirin users, median follow-up time for persisters was 1.56 (0.53–3.61) years and median follow-up time prescribed aspirin for nonpersisters was 1.07 (0.31–2.46) years. The difference in follow-up time between persisters and nonpersisters was significant (P<0.001).

Table 2. Mortality, Heart Failure Hospitalization, and All-Cause Events

	Low-Dose Aspirin vs Nonaspirin Use	Low-Dose Aspirin vs High-Dose Aspirin Use	High-Dose Aspirin vs Nonaspirin Use
Mortality			
Univariable analysis	0.81 (0.67–0.98)	0.58 (0.40–0.85)	1.40 (0.95–2.05)
Multivariable analysis	0.58 (0.46–0.74)	0.57 (0.35–0.92)	0.98 (0.59–1.63)
Heart failure hospitalization			
Univariable analysis	0.99 (0.80–1.20)	1.31 (0.79–2.18)	0.76 (0.45–1.28)
Multivariable analysis	0.70 (0.54–0.90)	1.27 (0.70–2.30)	0.50 (0.27–0.92)
All-cause events			
Univariable analysis	0.98 (0.84–1.13)	1.03 (0.75–1.41)	0.96 (0.70–1.32)
Multivariable analysis	0.85 (0.71–1.02)	1.17 (0.79–1.73)	0.67 (0.44–1.01)

Mortality, heart failure hospitalization, and all-cause events adjusted for age, sex, B-type natriuretic peptide level, creatinine level, heart failure type, ischemic heart disease, atrial fibrillation, hypertension, diabetes mellitus, dyslipidemia, chronic obstructive pulmonary disease, peripheral vascular disease, and stroke. All values are presented as hazard ratio (95% confidence interval).

Similarly, aspirin was initiated after baseline by 114 patients (7.7% of total population or 19.5% of nonaspirin users at baseline), and there was little difference in the Cox proportional hazards models to compare groups with regards to mortality (adjusted HR=0.64; 95% CI, 0.50–0.84), HF hospitalization (adjusted HR=0.66; 95% CI, 0.51–0.87), and all-cause events (adjusted HR=0.86; 95% CI, 0.71–1.05) when repeated with aspirin initiators censored at the time that they commenced the drug.

Propensity-Matched Subgroup Analysis

Propensity analysis was performed on a matched subsample of 1006 patients from the total population: 503 low-dose aspirin users and 503 nonaspirin users. Characteristics of the matched population are presented in Table I in the Data Supplement. Significant differences between the groups in age and prescription of β-blockers, nitrates, cholesterol-lowering agents, and warfarin remained despite matching. Cox regression analysis of the mortality and all-cause outcomes in the propensity-matched sample confirmed the results obtained in the entire, unmatched population; however, in this matched population, a significant reduction in HF hospitalizations was not observed (data presented in Table II in the Data Supplement).

A description of all events in the total population and propensity-matched populations is given in Table III in the Data Supplement.

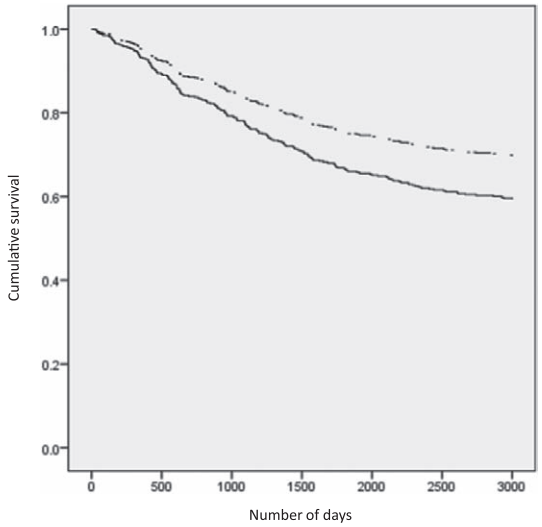
Discussion

This retrospective cohort study of 1476 patients with HF in a DMP shows that 60% were aspirin users and that low-dose aspirin use (75 mg daily) was associated with an adjusted reduction in mortality of 42% and was confirmed by analysis of a propensity-matched subsample of >1000 patients. A 30% reduction in HF hospitalization was also observed in the total population, although this reduction did not achieve statistical significance in the matched subsample. These results are set in contrast to several prospective and retrospective studies of higher dose aspirin in HF. Furthermore, in our study, the beneficial association between aspirin use and outcome was only observed in those on low doses (75 mg daily) and not in those on higher doses. It is also evident in patients with and without a definite indication for aspirin. Aspirin discontinuation rate among low-dose aspirin users during the follow-up period was surprisingly low at 19.2% and was not associated with increased risk. Although this subanalysis is limited to a relatively small number of patients, it may be explained by the low doses used, high use of gastrointestinal protective therapies, and because on average discontinuation occurred late in the follow-up period. The results of the present study add to the controversy on aspirin use in HF by presenting reassuring results on low-dose aspirin use in a clinical practice population. They challenge the belief that aspirin should be avoided in secondary prevention patients who go on to develop HF and suggest that patients on higher antiplatelet doses may benefit

Table 3. Indication for Low-Dose Aspirin Use and Adjusted Risk of (1) Mortality, (2) Heart Failure Hospitalization, and (3) All-Cause Events

Indication for Low-Dose Aspirin Use	Mortality HR (95% CI)	Heart Failure Hospitalization HR (95% CI)	All-Cause Events HR (95% CI)
IHD	0.65 (0.47–0.89)	0.72 (0.52–0.99)	0.84 (0.65–1.07)
No IHD	0.56 (0.39–0.81)	0.67 (0.45–1.02)	0.84 (0.65–1.09)
IHD, PVD, or stroke	0.69 (0.51–0.95)	0.83 (0.60–1.14)	0.92 (0.72–1.17)
No IHD, PVD, or stroke	0.54 (0.37–0.78)	0.59 (0.38–0.90)	0.80 (0.61–1.04)
Atrial fibrillation	0.51 (0.34–0.77)	0.89 (0.60–1.31)	0.92 (0.70–1.23)
No atrial fibrillation	0.70 (0.53–0.93)	0.79 (0.57–1.08)	0.87 (0.70–1.09)

All results adjusted for age, sex, B-type natriuretic peptide level, creatinine level, and heart failure type. CI indicates confidence interval; HR, hazard ratio; IHD, ischemic heart disease; and PVD, peripheral vascular disease.



Number at risk							
Nonaspirin users	174	150	130	118	105	102	51
Low-dose aspirin users	500	438	404	376	359	346	170

Figure 3. Kaplan–Meier survival curve comparing mortality risk of low-dose aspirin users with nonaspirin users among heart failure patients with ischemic heart disease, peripheral vascular disease, or stroke in a Cox proportional hazards model adjusted for baseline age, sex, B-type natriuretic peptide, creatinine level, and heart failure type. There was a significant reduction in mortality risk among low-dose aspirin users (broken line) compared with nonaspirin users (unbroken line). Adjusted hazard ratio=0.69; 95% confidence interval, 0.51 to 0.95.

from dose reduction. Prospective, randomized studies of low-dose aspirin use in HF populations are warranted.

A significant dilemma for clinicians treating patients with HF arises from the absence of clear evidence on the role of aspirin. The majority of patients with HF have a prior indication where aspirin has well-established benefit in the secondary prevention of cardiovascular events. This is reflected in our study in which just less than two thirds of patients were receiving chronic low-dose aspirin on entry into an HF DMP. Once the diagnosis of HF is established, European guidelines do not give conclusive recommendations on aspirin therapy[13] and American guidelines are equivocal, indicating that individual physicians may interpret the available evidence differently and may choose to remove aspirin in patients with HF.[14] The WASH, WATCH, and WARCEF prospective, randomized studies have compounded the concern regarding use of aspirin in HF populations with low ejection fraction and in sinus rhythm when comparing it with warfarin.[1–3] The WARCEF trial did not demonstrate a benefit of aspirin compared with warfarin use in this population.[2] The WASH and WATCH trials identified an increased risk of cardiovascular and HF events in aspirin users compared with warfarin users.[1,3] In all 3 trials, patients were only eligible if there was no definite indication for antiplatelet therapy and no concomitant anticoagulant or second antiplatelet agent.

However, the dose of aspirin used in these trials ranged from 162 to 325 mg daily, far in excess of the dose of 75 mg daily recommended by European guideline bodies and more commonly used in Europe for secondary prevention than in the United States. Juhlin et al[9] have demonstrated dose-dependent adverse renal effects of aspirin at doses >80 mg, which may be of particular concern in an HF population. A registry study of the dose-related effects of aspirin in patients with HF showed that patients prescribed an angiotensin-converting enzyme (ACE) inhibitor and high-dose aspirin (≥325 mg/d) had a significantly raised mortality risk compared with patients with ACE inhibitor and no aspirin use, whereas there was no increased risk in patients with ACE inhibitor and low-dose aspirin (≤160 mg/d).[15] Elsewhere, in the Platelet Inhibition and Patient Outcomes (PLATO) Trial of ticagrelor compared with clopidogrel in acute coronary syndrome, an interaction between higher aspirin dose (≥300 mg/d) and poorer outcome was observed.[16] Furthermore, although 2 studies have shown an adverse effect of aspirin therapy compared with clopidogrel therapy on natriuretic peptide levels in patients with HF treated with ACE inhibitors,[17,18] in both studies doses of aspirin >75 mg were used. The first of these studies showed that N-terminal pro-BNP increased in both groups but by a magnitude of 8 times greater in the aspirin-treated group. Patients were prescribed aspirin 100 mg or clopidogrel 75 mg daily for 8 weeks.[17] The second study showed a significant increase in BNP levels during 14 days in patients taking aspirin 325 mg daily, whereas there was no increase in BNP in those taking clopidogrel 75 mg daily.[18] By comparison to previous studies, our work reflects a more typical HF outpatient population and includes patients with atrial fibrillation and with indications for aspirin use including ischemic, vascular, and cerebrovascular disease. In our patient population, aspirin was used at a dose of 75 mg daily by 93% of patients, and clinical benefit was associated with aspirin use at 75 mg but not at higher doses. Furthermore, these patients also received concomitant anticoagulant and antiplatelet therapy as indicated. Finally, although the WASH and WATCH studies have particularly short follow-up times of <2 years because of poor recruitment and early discontinuation of the trials,[1,3] our patients have a mean follow-up of almost 3 years with low discontinuation rate.

Another mechanism that has been postulated as responsible for any negative effects of aspirin in HF is an attenuation of the benefits of ACE inhibitor effects possibly attributable to adverse renal effects. In the Studies of Left Ventricular Dysfunction (SOLVD) trial,[4] among those patients randomized to treatment, use of aspirin in combination with enalapril was associated with significant increase in mortality. Similarly, in a subanalysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II) trial, aspirin use was seen to reduce the beneficial effect of enalapril.[8] Aspirin inhibits its synthesis of vasodilatory and antithrombotic prostaglandins and thromboxanes in a dose-dependent manner.[19,20] ACE inhibitors, on the contrary, increase production of prostaglandins primarily through a reduction in degradation of bradykinin which is of benefit in HF.[21] However, aspirin use in the SOLVD and CONSENSUS II trials was not randomized, and there may be significant differences between aspirin users and those not prescribed aspirin including rates of β-blocker use and history of myocardial infarction.[22] A systematic review of 6 large randomized controlled trials of ACE inhibitor therapy in HF, comprising data for >22 000 patients, found that there was a "significant, substantial, and clinically important" reduction on composite outcome of major vascular events (including

mortality) in both users and nonusers of aspirin.[22] A retrospective review of data from the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) study found that there was no difference in the effect of angiotensin receptor blocker candesartan on the combined end point of cardiovascular death or HF hospitalization among aspirin users or controls.[5] Also, a recent retrospective study of aspirin use on short-term outcomes in recently discharged patients with HF in the Organized Program to Facilitate Life-Saving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry found that mortality was reduced in patients with IHD using RAAS modifying therapy along with aspirin compared with nonaspirin users and there was no difference in mortality in patients without IHD using RAAS modifying therapy along with or without aspirin.[6] The dose of aspirin used was not available in either of these retrospective studies. Finally, a large retrospective study of events in patients with HF in their first year postdischarge showed no increase in mortality or HF hospitalization among aspirin users compared with controls in the overall population or among subgroups of patients prescribed ACE inhibitor or not and patients with or without coronary artery disease.[7] In our study, only 80 (5.4%) patients did not receive ACE inhibitor or angiotensin receptor blocker therapy during the follow-up period and so it was not possible to study the effect of aspirin on the population split by use of RAAS therapy.

There are limitations to this study that must be acknowledged. First, this is a retrospective cohort study, and although we have conducted multivariable analyses and propensity-matched analyses taking account of many covariates, we cannot exclude the possibility that other unrecorded covariates may have influenced the results. Furthermore, without randomized, prospective analyses, the potential benefits of low-dose aspirin use in patients with HF cannot be stated definitively. Second, the information on patient medication profile is dependent on the prescription information and patient self-report recorded, and we have no definitive information on patient adherence in this population. Third, we did not routinely collect data on the medication history with respect to aspirin before recruitment onto the DMP and cannot exclude the possibility that some nonaspirin users were self-selected as being aspirin intolerant, potentially confounding the results herein. Finally, the possible interaction between low-dose aspirin and RAAS modifying therapy, especially ACE inhibitor therapy, is postulated as the mechanism by which aspirin use may be detrimental in HF, and we were unable to compare the effects of low-dose aspirin in a cohort of RAAS agent users and others because 95% of patients in our population were treated with an ACE inhibitor or angiotensin receptor blocker.

Conclusions

Unlike previous prospective studies in highly selected populations and retrospective cohort studies that have raised concerns about higher antiplatelet doses of aspirin in HF, the present study demonstrates a significant reduction in risk of mortality and morbidity associated with the use of low-dose aspirin in patients with HF when adjusted for clinically relevant variables. These benefits extend to patients with and without indication for the drug, and the mortality benefits are confirmed by propensity-matched subgroup analysis. These results suggest that low-dose aspirin may have a continuing role in secondary prevention once patients are diagnosed with HF and underline the need for more, preferably prospective, trials of low-dose aspirin use in HF.

Acknowledgments

The authors thank Kieran Smyth, School of Pharmacy and Pharmaceutical Sciences, Trinity College, Dublin, Ireland, for his assistance with data collection for this work.

Sources of Funding

This work was supported by the Heartbeat Trust, a registered charity in Ireland (CHY15398).

Disclosures

Drs Gilmer, Ledwidge, and McDonald are founders of Solvotrin Therapeutics which is developing an aspirin-niacin prodrug for treatment of type III hyperlipoproteinemia, a rare dyslipidemia. The other authors report no conflicts.

References

1. 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.
2. 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.
3. 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.
4. 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.
5. Chang SM, Granger CB, Johansson PA, Kosolcharoen P, McMurray JJ, Michelson EL, Murray DR, Olofsson B, Pfeffer MA, Solomon SD, Swedberg K, Yusuf S, Dunlap ME; CHARM Investigators. Efficacy and safety of angiotensin receptor blockade are not modified by aspirin in patients with chronic heart failure: a cohort study from the Candesartan in Heart failure–Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur J Heart Fail*. 2010;12:738–745.
6. Levy PD, Nandyal D, Welch RD, Sun JL, Pieper K, Ghali JK, Fonarow GC, Gheorghiade M, Gheorgiade M, O'Connor CM. Does aspirin use adversely influence intermediate-term postdischarge outcomes for hospitalized patients who are treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers? Findings from Organized Program to Facilitate Life-Saving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J*. 2010;159:222–230.e2.
7. McAlister FA, Ghali WA, Gong Y, Fang J, Armstrong PW, Tu JV. Aspirin use and outcomes in a community-based cohort of 7352 patients discharged after first hospitalization for heart failure. *Circulation*. 2006;113:2572–2578.
8. Nguyen KN, Aursnes I, Kjekshus J. Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *Am J Cardiol*. 1997;79:115–119.
9. Juhlin T, Jönsson BA, Höglund P. Renal effects of aspirin are clearly dose-dependent and are of clinical importance from a dose of 160 mg. *Eur J Heart Fail*. 2008;10:892–898.
10. Yokoyama H, Yaguchi T, Suzuki Y, Tokuoka K, Watanabe M, Kitagawa Y, Yamada Y. Theoretical investigation of aspirin dosage regimen to exhibit optimal antiplatelet effects and decrease risk of upper gastrointestinal lesions. *Biol Pharm Bull*. 2012;35:2112–2118.

11. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71–86.
12. Rosenbaum PR, Rubin DB. The bias due to incomplete matching. *Biometrics*. 1985;41:103–116.
13. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33:1787–1847.
14. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:e391–e479.
15. Guazzi M, Brambilla R, Reina G, Tumminello G, Guazzi MD. Aspirin-angiotensin-converting enzyme inhibitor coadministration and mortality in patients with heart failure: a dose-related adverse effect of aspirin. *Arch Intern Med*. 2003;163:1574–1579.
16. Mahaffey KW, Wojdyla DM, Carroll K, Becker RC, Storey RF, Angiolillo DJ, Held C, Cannon CP, James S, Pieper KS, Horrow J, Harrington RA, Wallentin L; PLATO Investigators. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation*. 2011;124:544–554.
17. Jug B, Sebestjen M, Sabovic M, Keber I. Clopidogrel is associated with a lesser increase in NT-proBNP when compared to aspirin in patients with ischemic heart failure. *J Card Fail*. 2006;12:446–451.
18. Meune C, Wahbi K, Fulla Y, Cohen-Solal A, Duboc D, Mahé I, Simoneau G, Bergmann JF, Weber S, Mouly S. Effects of aspirin and clopidogrel on plasma brain natriuretic peptide in patients with heart failure receiving ACE inhibitors. *Eur J Heart Fail*. 2007;9:197–201.
19. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol*. 1971;231:232–235.
20. Patrono C, Ciabattoni G, Patrignani P, Pugliese F, Filabozzi P, Catella F, Davì G, Forni L. Clinical pharmacology of platelet cyclooxygenase inhibition. *Circulation*. 1985;72:1177–1184.
21. Cleland JG, Bulpitt CJ, Falk RH, Findlay IN, Oakley CM, Murray G, Poole-Wilson PA, Prentice CR, Sutton GC. Is aspirin safe for patients with heart failure? *Br Heart J*. 1995;74:215–219.
22. Teo KK, Yusuf S, Pfeffer M, Torp-Pedersen C, Kober L, Hall A, Pogue J, Latini R, Collins R; ACE Inhibitors Collaborative Group. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet*. 2002;360:1037–1043.

CLINICAL PERSPECTIVE

Controversy surrounds the use of aspirin in patients with heart failure (HF). The practical dilemma for clinicians is that although aspirin is indicated for secondary prevention of cardiovascular events, once HF is diagnosed, several data sets have raised concerns about excess hospitalizations associated with aspirin. However, most of these reports used aspirin at higher antiplatelet doses. This retrospective cohort study describes a population of 1476 patients with HF attending a disease management program and followed up for a median of 2.15 (0.81–4.54) years. Aspirin was prescribed to 892 (60.4%) patients at program baseline, was continued in the majority during the follow-up period, and 93% used low-dose aspirin (75 mg/d). In multivariable analysis, use of low-dose aspirin was associated with a 42% reduction in mortality risk compared with no aspirin use (hazard ratio=0.58; 95% confidence interval, 0.46–0.74). Low-dose aspirin users also experienced a 30% reduction in HF hospitalization (hazard ratio=0.70; 95% confidence interval, 0.54–0.90). Use of low-dose aspirin was also associated with reduced mortality risk in patients with ischemic heart disease, patients with atrial fibrillation, patients without an indication for aspirin therapy, and in a propensity-matched subsample of 503 low-dose aspirin users and 503 nonaspirin users. These data suggest that most patients continue with low-dose aspirin once HF is diagnosed and that low-dose aspirin may have a continuing role in secondary prevention in this setting. They also underline the need for more, preferably prospective, trials of low-dose aspirin use in HF.

Aspirin Use in Heart Failure: Is Low-Dose Therapy Associated With Mortality and Morbidity Benefits in a Large Community Population?

Margaret Bermingham, Mary Katherine Shanahan, Eoin O'Connell, Ian Dawkins, Saki Miwa, Rory O'Hanlon, John Gilmer, Kenneth McDonald and Mark Ledwidge

Circ Heart Fail. 2014;7:243-250; originally published online February 3, 2014;
doi: 10.1161/CIRCHEARTFAILURE.113.000132
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3289. Online ISSN: 1941-3297

SUPPLEMENTAL MATERIAL

Supplemental Tables

Supplementary Table I. Characteristics of total population, low-dose aspirin users and non-aspirin users in the propensity matched subgroup analysis.

Characteristic	**Total population (n=1006)**	**Low-dose aspirin users (n=503)**	**Aspirin non-users (n=503)**
Demographics			
Age (years)†	70.6±12.1	71.5±11.6	69.9±12.5
Male	632 (62.8)	317 (63.0)	315 (62.6)
Clinical characteristics			
Systolic blood pressure (mmHg)	126.2±21.9	125.9±22.3	126.5±21.5
Diastolic blood pressure (mmHg)	72.1±13.5	71.6±13.6	72.5±13.4
BNP (pg/ml)	317 [137:670]	345 [143:698]	291 [128:611]
Creatinine (μmol/L)	103 [86:131]	102 [87:130]	104 [86:132]

Ejection fraction (%)	40.5±15.0	40.1±14.9	40.9±15.0
HFrEF	527 (64.1)	273 (66.4)	254 (61.8)
Co-morbidities			
Ischemic heart disease	313 (31.1)	158 (31.4)	155 (30.8)
Atrial fibrillation	406 (40.4)	197 (39.2)	209 (41.6)
Chronic obstructive pulmonary disease	118 (11.7)	61 (12.1)	57 (11.3)
Dyslipidemia	256 (25.4)	133 (26.4)	123 (24.5)
Diabetes	204 (20.3)	106 (21.1)	98 (19.5)
Hypertension	446 (44.3)	237 (47.1)	209 (41.6)
Peripheral vascular disease	11 (1.1)	5 (1.0)	6 (1.2)
Stroke	38 (3.8)	20 (4.0)	18 (3.6)
Medications			
Loop diuretic	937 (93.1)	470 (93.4)	467 (92.8)
ACE inhibitor	850 (84.5)	430 (85.5)	420 (83.5)
Angiotensin receptor	263 (26.1)	128 (25.4)	135 (26.8)

blocker			
Beta-blocker *	842 (83.7)	431 (85.7)	411 (81.7)
Mineralocorticoid receptor antagonist	259 (25.7)	127 (25.2)	132 (26.2)
Digoxin	479 (47.6)	195 (38.8)	284 (56.5)
Calcium channel blocker	227 (22.6)	115 (22.9)	112 (22.3)
Cholesterol lowering agent†	333 (33.1)	194 (38.6)	139 (27.6)
Non-loop diuretic	404 (40.2)	189 (37.6)	215 (42.7)
Nitrate*	543 (54.0)	288 (57.3)	255 (50.7)
Proton pump inhibitor *	479 (47.6)	246 (48.9)	233 (46.3)
Warfarin *	501 (49.8)	167 (33.2)	334 (66.4)

Continuous variables are expressed as mean±standard deviation for normally distributed data and are compared using paired t-tests. Continuous variables are expressed as median [interquartile range] for non-normally distributed data and are compared using the Wilcoxon signed rank test. Categorical variables are summarised as frequencies and percentages and are compared using McNemar's test. Abbreviations: BNP, B-type natriuretic peptide; HFrEF, heart failure with reduced ejection fraction.

For differences between low-dose aspirin users and non-aspirin users, *p-value of <0.05 and †p-value of <0.001.

Supplementary Table II. Unadjusted and adjusted outcome analysis for propensity matched subsample of low-dose aspirin users compared with non-aspirin users.

	Low-dose aspirin users vs. non-aspirin users **Hazard ratio (95% confidence interval)**
Mortality	
Univariable analysis	0.73 (0.57–0.94)
Multivariable analysis	0.67 (0.47–0.96)
Heart failure hospitalization	
Univariable analysis	0.77 (0.55–1.08)
Multivariable analysis	0.77 (0.48–1.23)
All-cause events	
Univariable analysis	0.88 (0.70–1.11)
Multivariable analysis	0.94 (0.68–1.30)

Supplementary table III. Events in total population and propensity matched subsample.

Event	Total population (n=1476) n, %	Matched population (n=1006) n, %
Mortality	464 (31.4)	316 (31.4)
Heart failure hospitalisation	364 (24.7)	230 (22.9)
All-cause	776 (52.6)	518 (51.5)