Antiplatelet Therapy for Stable Coronary Artery Disease in Atrial Fibrillation Patients Taking an Oral Anticoagulant: A Nationwide Cohort Study

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Background—The optimal long-term antithrombotic treatment of patients with coexisting atrial fibrillation and stable coronary artery disease is unresolved, and commonly, a single antiplatelet agent is added to oral anticoagulation. We investigated the effectiveness and safety of adding antiplatelet therapy to vitamin K antagonist (VKA) in atrial fibrillation patients with stable coronary artery disease.

Methods and Results—Atrial fibrillation patients with stable coronary artery disease (defined as 12 months from an acute coronary event) between 2002 and 2011 were identified. The subsequent risk of cardiovascular events and serious bleeding events (those that required hospitalization) was examined with adjusted Cox regression models according to ongoing antithrombotic therapy. A total of 8700 patients were included (mean age, 74.2 years; 38% women). During a mean follow-up of 3.3 years, crude incidence rates were 7.2, 3.8, and 4.0 events per 100 person-years for myocardial infarction/coronary death, thromboembolism, and serious bleeding, respectively. Relative to VKA monotherapy, the risk of myocardial infarction/coronary death was similar for VKA plus aspirin (hazard ratio, 1.12 [95% confidence interval, 0.94–1.34]) and VKA plus clopidogrel (hazard ratio, 1.53 [95% confidence interval, 0.93–2.52]). The risk of thromboembolism was comparable in all regimens that included VKA, whereas the risk of bleeding increased when aspirin (hazard ratio, 1.50 [95% confidence interval, 1.23–1.82]) or clopidogrel (hazard ratio, 1.84 [95% confidence interval, 1.11–3.06]) was added to VKA.

Conclusions—In atrial fibrillation patients with stable coronary artery disease, the addition of antiplatelet therapy to VKA therapy is not associated with a reduction in risk of recurrent coronary events or thromboembolism, whereas risk of bleeding is increased significantly. The common practice of adding antiplatelet therapy to oral VKA anticoagulation in patients with atrial fibrillation and stable coronary artery disease warrants reassessment. (Circulation. 2014;129:1577–1585.)

Key Words: antiplatelet agents ▪ atrial fibrillation ▪ hemorrhage ▪ myocardial infarction ▪ stroke

Optimal long-term antithrombotic treatment of patients with atrial fibrillation (AF) and stable coronary artery disease (CAD) is unresolved, and common practice is to add antiplatelet therapy to oral anticoagulation. The cornerstone of AF treatment should include oral anticoagulation if 1 or more stroke risk factors (such as vascular disease) are present,1 whereas initial preventive treatment after myocardial infarction (MI) or percutaneous coronary intervention (PCI) consists of drugs for platelet antiaggregation.2 American and European consensus documents (level C evidence) recommend the addition of 2 antiplatelet drugs to vitamin K antagonist (VKA) therapy arbitrarily from 1 month to 1 year after an acute coronary event, depending on degree of severity, type of stent implanted, and presumed bleeding risk.3,4 The risk of serious bleeding with multiple antithrombotic drugs is increased substantially5,6 even with only short-term initial therapy.7 For this reason, 1 antiplatelet drug should be removed when the risk of a recurrent coronary event and stent thrombosis has...
declined, and VKA alone is now recommended in AF patients who are >1 year from an acute coronary event or revascularization procedure. New data also suggest that MI risk could actually increase with the addition of multiple antiplatelets to oral anticoagulation treatment.

Both the need for an additional antiplatelet drug after the vulnerable period and the timing of VKA monotherapy are uncertain. In “real-life” AF patients surviving an acute coronary event, we investigated ongoing antithrombotic treatment and risk of new coronary events, thromboembolism, and serious bleeding. We tested the hypothesis that long-term antithrombotic treatment with VKA alone after 12 months with stable CAD versus the addition of a single antiplatelet agent to VKA would result in fewer serious bleeding events without an additional cost of increased risk of recurrent coronary events or thromboembolism.

Methods

Databases

From nationwide Danish administrative registries, we extracted information on healthcare and drug use that could be linked on the individual level to each resident. All admissions to hospitals are recorded by the National Patient Registry and by the International Classification of Diseases coding (8th revision until 1994 and 10th revision after that point). Diagnoses of MI (predictive value 94%), AF (predictive value 99%), and ischemic stroke (predictive value 97%) have been validated, and bleeding diagnoses have shown a positive predictive value of 89% to 99% in hospital databases. The Danish Registry of Medicinal Product Statistics (a national prescription registry) provides data on number of tablets, strength, and date of dispensing for all prescribed drugs classified according to the Anatomic Therapeutic Classification. Vital status and causes of death are obtainable through the civil registration system and the National Causes of Death Registry, respectively. The latter provides information from physicians on both the primary and potential contributing causes of death according to the International Classification of Diseases, 10th Revision classification. All International Classification of Diseases and Anatomic Therapeutic Classification codes used in the study are listed in Tables I and II in the online-only Data Supplement.

Population

All AF patients hospitalized for either MI or PCI between January 1, 2001, and December 31, 2011, were identified. To be eligible for inclusion, no subsequent hospitalization for MI or unstable or stable angina within 360 days was allowed (Figure 1). Patients with AF and stable CAD, defined as 360 days from the index coronary event (MI/PCI), were followed up from 2002 through the end of the study period on December 31, 2011. Only patients prescribed antithrombotic therapy were included. To ensure no recent MI/PCI episode occurred before an AF diagnosis, patients who were registered with any MI or PCI within 360 days before their MI/PCI hospitalization were also excluded.

Antithrombotic Treatment Regimens

We defined the following antithrombotic treatment regimens: Single-antiplatelet therapy (aspirin or clopidogrel), VKA monotherapy (warfarin or phenprocoumon), dual-antiplatelet therapy (aspirin and clopidogrel), VKA plus single antiplatelet (either aspirin or clopidogrel), and VKA plus dual-antiplatelet therapy. We calculated drug availability at any given time from claimed prescriptions, as described previously. A daily dosage was calculated for up to 3 prescription claims, which allowed the daily dose (for VKA only) to change with prescriptions claimed. A fixed dosing regimen was used for aspirin (75, 100, and 150 mg/d) and clopidogrel (75 mg/d). Treatment as of the date of inclusion in the study was defined as baseline treatment.

Outcomes

Effectiveness outcomes were defined as MI/coronary death and fatal/nonfatal thromboembolism. Thromboembolism included ischemic stroke and systemic arterial embolism. The principal safety outcome was fatal/nonfatal bleeding. A secondary outcome of all-cause death was also defined. Nonfatal events were obtained from admissions in the National Patient Registry, and fatal events were recorded from the National Causes of Death Register. The diagnoses (eg, intracranial bleeding, gastrointestinal bleeding, anaemia from bleeding) used to characterize serious bleeding have been used previously. This category of serious bleeding would include most International Society of Thrombosis and Haemostasis major and clinically relevant nonmajor bleeds, although all events required hospitalization. For additional insight, we also categorized death attributable to bleeding as fatal bleeding directly and as death within 30 days of a nonfatal admission to the hospital because of bleeding. A composite outcome of MI, thromboembolism, bleeding, and all-cause mortality was also defined.

Concomitant Treatment and Comorbidity

Prescription claims 180 days before inclusion defined concomitant pharmacotherapy, and comorbidities were determined from any preceding diagnosis, as described previously. The CHA2DS2-VASc (congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke, vascular disease, age 65–75 years, and female sex) and modified HAS-BLED (hypertension, abnormal renal/liver function, stroke/thromboembolism, bleeding history, labile international normalized ratio, elderly [age >65 years], drug consumption/alcohol abuse) scores were calculated. For HAS-BLED, data on labile international normalized ratio were unavailable, and use of antiplatelet therapy was omitted from the HAS-BLED score because it is an explanatory variable. The scores have been shown to accurately predict risk of thromboembolism and bleeding in the Danish population.

Statistical Analyses

Characteristics according to antithrombotic treatment at inclusion are expressed as percentages or as means and SDs. Rates were all crude incidence rates, calculated by the number of events per 100 person-years with 95% confidence interval. The risk of outcomes associated with antithrombotic treatment was estimated by means of time-dependent Cox proportional-hazards models, with adjustment for changes in exposure (based on prescription claims) during follow-up. VKA as monotherapy was used as the reference. All models were adjusted for age, sex, inclusion year, and MI/PCI status at index event; pharmacotherapy; and comorbidity (including factors that are part of the CHA2DS2-VASc and HAS-BLED scores). Unadjusted estimates were also reported for the main models. To assess whether the risk of our effectiveness or safety outcomes changed over time, we performed landmark analyses for periods of 0 to 2 years and >2 years from inclusion in a Cox model for each outcome. Because of
low numbers, only aspirin monotherapy, dual-antiplatelet therapy, VKA plus aspirin, and VKA plus clopidogrel were explored. We also decided to report risks for patients who had a previous PCI performed at their index event to assess whether longer-term outcomes differed for patients who received invasive intervention (considered low-risk patients) compared with patients who received only pharmacotherapy (considered high-risk patients). We performed a sensitivity analysis as suggested by Schneeweiss\textsuperscript{18} to assess the impact of a potential unmeasured confounder for regimens of VKA and VKA plus aspirin because these were the most prevalent regimens that included VKA and because assessment of the relation of the addition of an antiplatelet agent to VKA was our main purpose. All patients were followed up until death or the end of the study period (December 31, 2011). We tested for fulfilment of the proportional hazards assumption, linearity of continuous variables, and lack of interactions for the Cox models, and no significant deviations from the assumptions were found. A 2-sided $P$ value $<0.05$ was considered to indicate statistical significance. Data were analyzed with SAS 9.2 (SAS Institute Corp, Cary, NC) and Stata 11.0 (StataCorp, College Station, TX).

Ethics

Ethical approval is not required for register-based studies in Denmark. The Danish Data Protection Agency approved the study (reference No. 2007-58-0015/Lauret No. 00916 GEH-2010-001). Anonymized data were made available to us so individuals could not be identified.

Results

Among 8700 AF patients with stable CAD (mean age, 74.2 years [SD, 10.4 years]; 38% women) included in the study, a total of 3243 (37%) were treated with VKA at inclusion (Table 1). Selection of the study population is shown in Figure 1. A total of 28,947 person-years were accumulated, and the groups that contributed the most with time at risk were aspirin monotherapy (45%), VKA plus aspirin (26%), and VKA monotherapy (14%). Figure 2 shows the crude incidence rates of MI/coronary death after the index coronary event.

Risk of MI/Coronary Death, Thromboembolism, and Serious Bleeding During Follow-Up

Within a mean follow-up of 3.3 years, 3457 patients (40%) died. The numbers of events coded as MI/coronary death, thromboembolism, and serious bleeding were 1978 (23%), 1040 (12.0%), and 1061 (12%), respectively. Corresponding crude incidence rates were 7.2, 3.8, and 4.0 events per 100 person-years. Table 2 shows the numbers and crude incidence rates for each outcome according to antithrombotic treatment group. Crude incidence rates of MI/coronary death were similar for VKA and VKA plus aspirin but higher for VKA plus dual-antiplatelet therapy. Adjusted hazard ratios for all outcomes are illustrated in Figure 3A through 3D. Relative to VKA monotherapy, there was no decrease in risk of MI/coronary death associated with the use of VKA plus a single antiplatelet (either aspirin or clopidogrel), and there was a higher risk with dual-antiplatelet therapy with or without VKA. A comparable risk of thromboembolism was present for regimens that included VKA, whereas non-VKA therapies were associated with greater risk than VKA monotherapy. Bleeding risk was greater in those who also took antiplatelet drugs (either aspirin or clopidogrel). Aspirin monotherapy showed a decrease in bleeding risk, whereas clopidogrel (with or without aspirin) showed comparable bleeding risk compared with VKA as monotherapy. The unadjusted hazard ratio estimates are provided as supplementary material (Table III in the online-only Data Supplement) and resemble the adjusted analyses. The combined outcome of MI, thromboembolism, bleeding, and all-cause mortality showed no beneficial effect of VKA plus a single antiplatelet compared with VKA monotherapy (Table 3).

Previous PCI, Landmark Analyses, Death of Bleeding, and Sensitivity Analysis

Among 3393 patients with previous PCI, MI/coronary death, thromboembolism, and serious bleeding occurred in 512 (15%), 291 (9%) and 370 (11%), respectively. In patients with previous PCI, the crude rate of MI/coronary death was 4.5 per 100 person-years, whereas the corresponding crude rate in noninvasively treated patients was 9.1 per 100 person-years. A similar 2-fold greater rate was present for thromboembolism in non-PCI-treated patients (4.7 events per 100 person-years) compared with PCI-treated patients (2.8 events per 100 person-years). In the adjusted Cox models, the risks resembled those from the main analysis, with comparable risk of thrombosis between VKA with and without single-antiplatelet therapy, whereas bleeding risk was greater in those who also took an antiplatelet agent (either aspirin or clopidogrel). For further details of risks for PCI-treated and non–PCI-treated patients, please see Table IV in the online-only Data Supplement. The risk of MI/coronary death and thromboembolism was consistent and similar between VKA and VKA plus single-antiplatelet therapy in periods of 0 to 2 and $>$2 years (Figure IA through IC in the online-only Data Supplement). Of 951 patients admitted with a nonfatal bleeding episode, 507 died (53%), whereas of the 7749 patients who did not experience bleeding, 2950 died (38%), which corresponds to a hazard ratio of 2.14 (95% confidence interval, 1.94–2.37). No significant difference was observed for death attributable to bleeding between VKA and VKA plus a single antiplatelet drug, and only VKA plus dual-antiplatelet therapy was associated with a significantly increased risk of death related to bleeding (Table V in the online-only Data Supplement). When estimating the impact of an unmeasured confounder, we found that a potential confounder should be 3 times more prevalent in the exposed group (VKA plus aspirin) and should be associated with a 3-fold increase in risk of the outcome to explain a beneficial effect of VKA plus aspirin compared with VKA alone with regard to the outcome of MI. Regarding outcomes of thromboembolism, serious bleeding, and all-cause death, corresponding analyses indicated that an unmeasured confounder should be very unevenly distributed in the groups, with a very strong association with VKA plus aspirin therapy, and should also be very strongly associated with the outcome.

Discussion

In this nationwide observational study, the addition of antiplatelet therapy to VKA in patients with AF and stable CAD was not associated with any benefit, whereas serious bleeding increased significantly. Therapies that only included antiplatelet drugs (and not VKA therapy) were associated with an increased risk of all-cause death, with an appreciable risk of bleeding with the combination of aspirin and clopidogrel therapy. The study suggests that monotherapy with VKA may be the best choice in patients with AF and stable CAD.
Randomized clinical trials have demonstrated that both single- and dual-antiplatelet therapy are valuable after an MI and after a PCI procedure.\textsuperscript{19,20} There is also evidence from randomized trials for the benefit of long-term VKA therapy in selected patients with AF.\textsuperscript{21} We and others have previously examined the use of single and multiple antithrombotic

### Table 1. Patient Characteristics at Inclusion According to Antithrombotic Treatment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Not Including VKA</th>
<th>Aspirin Plus Clopidogrel</th>
<th>Including VKA</th>
<th>VKA Plus Aspirin</th>
<th>VKA Plus Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin (n=3273)</td>
<td>Clopidogrel (n=417)</td>
<td>VKA (n=950)</td>
<td>VKA Plus Aspirin (n=1471)</td>
<td>VKA Plus Clopidogrel (n=322)</td>
</tr>
<tr>
<td>Female</td>
<td>1494 (46)</td>
<td>161 (39)</td>
<td>659 (37)</td>
<td>360 (38)</td>
<td>460 (31)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>76.1 (10.9)</td>
<td>73.4 (10.9)</td>
<td>73.0 (10.8)</td>
<td>73.2 (10.0)</td>
<td>73.6 (9.0)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>2858 (87)</td>
<td>279 (67)</td>
<td>1159 (66)</td>
<td>804 (85)</td>
<td>1104 (75)</td>
</tr>
<tr>
<td>With PCI performed*</td>
<td>259 (9)</td>
<td>83 (30)</td>
<td>495 (43)</td>
<td>57 (79)</td>
<td>170 (15)</td>
</tr>
<tr>
<td>With stent implantation*</td>
<td>210 (7)</td>
<td>73 (26)</td>
<td>424 (37)</td>
<td>44 (5)</td>
<td>134 (12)</td>
</tr>
<tr>
<td>Previous PCI without MI</td>
<td>415 (13)</td>
<td>138 (33)</td>
<td>608 (34)</td>
<td>146 (15)</td>
<td>367 (25)</td>
</tr>
<tr>
<td>With stent implantation*</td>
<td>288 (69)</td>
<td>124 (90)</td>
<td>561 (92)</td>
<td>112 (77)</td>
<td>255 (69)</td>
</tr>
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<td>CHA\textsubscript{2}-VASc score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0)†</td>
<td>24 (1)</td>
<td>12 (1)</td>
<td>7 (1)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>Intermediate (1)</td>
<td>130 (4)</td>
<td>62 (4)</td>
<td>42 (4)</td>
<td>19 (6)</td>
<td></td>
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<tr>
<td>High (≥2)</td>
<td>3119 (95)</td>
<td>1397 (95)</td>
<td>901 (95)</td>
<td>303 (94)</td>
<td>396 (91)</td>
</tr>
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<td>HAS-BLED score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0–1)</td>
<td>900 (28)</td>
<td>315 (21)</td>
<td>237 (25)</td>
<td>55 (17)</td>
<td>106 (21)</td>
</tr>
<tr>
<td>Intermediate (2)</td>
<td>1325 (40)</td>
<td>658 (45)</td>
<td>380 (40)</td>
<td>135 (42)</td>
<td>218 (44)</td>
</tr>
<tr>
<td>High (≥3)</td>
<td>1048 (32)</td>
<td>498 (34)</td>
<td>333 (35)</td>
<td>132 (41)</td>
<td>176 (35)</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS inhibitors</td>
<td>1643 (50)</td>
<td>1109 (63)</td>
<td>537 (57)</td>
<td>951 (65)</td>
<td>236 (73)</td>
</tr>
<tr>
<td>Statins</td>
<td>1747 (53)</td>
<td>1345 (76)</td>
<td>628 (66)</td>
<td>1122 (76)</td>
<td>264 (82)</td>
</tr>
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<td>ß-Blockers</td>
<td>2151 (66)</td>
<td>221 (13)</td>
<td>182 (19)</td>
<td>273 (19)</td>
<td>51 (16)</td>
</tr>
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<td>Loop diuretics</td>
<td>1690 (52)</td>
<td>226 (15)</td>
<td>145 (15)</td>
<td>214 (15)</td>
<td>59 (18)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>453 (14)</td>
<td>182 (13)</td>
<td>121 (13)</td>
<td>273 (19)</td>
<td>51 (16)</td>
</tr>
<tr>
<td>Thiazide</td>
<td>530 (16)</td>
<td>287 (16)</td>
<td>145 (15)</td>
<td>214 (15)</td>
<td>59 (18)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>907 (28)</td>
<td>321 (18)</td>
<td>92 (22)</td>
<td>622 (42)</td>
<td>145 (45)</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>295 (9)</td>
<td>145 (8)</td>
<td>74 (8)</td>
<td>91 (6)</td>
<td>17 (5)</td>
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<tr>
<td>Proton pump inhibitors</td>
<td>840 (26)</td>
<td>484 (27)</td>
<td>194 (20)</td>
<td>310 (21)</td>
<td>73 (23)</td>
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<td>NSAID</td>
<td>506 (16)</td>
<td>271 (15)</td>
<td>128 (13)</td>
<td>187 (13)</td>
<td>47 (15)</td>
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<td>Comorbidity</td>
<td></td>
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<td></td>
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<tr>
<td>Ischemic stroke</td>
<td>527 (16)</td>
<td>251 (14)</td>
<td>171 (18)</td>
<td>278 (19)</td>
<td>58 (18)</td>
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<td>Diabetes mellitus</td>
<td>473 (14)</td>
<td>288 (16)</td>
<td>117 (12)</td>
<td>241 (16)</td>
<td>60 (19)</td>
</tr>
<tr>
<td>Arterial embolism</td>
<td>54 (2)</td>
<td>30 (2)</td>
<td>13 (11)</td>
<td>30 (2)</td>
<td>7 (2)</td>
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<td>Peripheral arterial disease</td>
<td>371 (11)</td>
<td>194 (11)</td>
<td>94 (10)</td>
<td>164 (11)</td>
<td>35 (11)</td>
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<td>Alcohol-related diseases</td>
<td>152 (5)</td>
<td>117 (7)</td>
<td>50 (5)</td>
<td>63 (4)</td>
<td>13 (4)</td>
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<tr>
<td>Liver disease</td>
<td>57 (2)</td>
<td>29 (2)</td>
<td>21 (2)</td>
<td>29 (2)</td>
<td>9 (3)</td>
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<tr>
<td>Chronic renal disease</td>
<td>266 (8)</td>
<td>121 (7)</td>
<td>97 (10)</td>
<td>102 (7)</td>
<td>22 (7)</td>
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<td>Previous bleeding</td>
<td>735 (22)</td>
<td>356 (20)</td>
<td>240 (25)</td>
<td>314 (21)</td>
<td>87 (27)</td>
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<td>Hypertension</td>
<td>1921 (59)</td>
<td>1212 (69)</td>
<td>607 (64)</td>
<td>1054 (72)</td>
<td>254 (79)</td>
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<tr>
<td>Malignancy</td>
<td>500 (15)</td>
<td>159 (17)</td>
<td>197 (13)</td>
<td>51 (16)</td>
<td>77 (15)</td>
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<tr>
<td>Congestive heart failure</td>
<td>966 (30)</td>
<td>403 (23)</td>
<td>317 (33)</td>
<td>478 (32)</td>
<td>102 (32)</td>
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</table>

Values are n (rounded column %) unless otherwise indicated. CHA\textsubscript{2}-VASc indicates score based on congestive heart failure, hypertension, age >75 y, diabetes mellitus, stroke, vascular disease, age 65 to 75 y, and female sex; HAS-BLED, score based on hypertension, abnormal renal/liver function, stroke/thromboembolism, bleeding history, labile international normalized ratio, elderly (age >65 y), and drug consumption/alcohol abuse; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PCI, percutaneous coronary intervention; RAS, renin-angiotensin system; and VKA, vitamin K antagonist.

*Group percentages given.
†Includes patients because PCI was not included in the score.
therapies after a recent coronary event. However, there is a lack of evidence for an optimal long-term antithrombotic treatment strategy in patients with AF and stable CAD.

The ineffectiveness of dual-antiplatelet therapy with regard to recurrent MI risk compared with VKA monotherapy was somewhat unexpected and was also present in patients treated with PCI. Because of the nonrandomized design of the study, this association could be based on the assumption that antiplatelet users were found ineligible for treatment with VKA and international normalized ratio monitoring and most likely comprise a group with a poorer outcome profile. A possible mechanistic explanation is that increased thrombogenesis in AF could play a role. AF has often been described as a prothrombotic state, and although the underlying mechanisms are not fully understood, clots (including coronary) in these patients could be fibrin rich (rather than platelet rich), which would lead to a more protective effect of anticoagulation.

Figure 2. Crude incidence rates of myocardial infarction/coronary death over time. Crude incidence rates of myocardial infarction/coronary death in atrial fibrillation patients after an episode of myocardial infarction or coronary intervention (index event). The study included patients at 360 days from the index event with stable coronary artery disease (ie, no admission for myocardial infarction, unstable angina, or stable angina defined stable coronary artery disease). The rate was calculated every 15 days for the first 720 days, and then every 30 days. The estimate at day 1440 included all remaining events.

Table 2. Comparison of Antithrombotic Treatment and Risk of Effectiveness and Safety Outcomes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration in Person-Years</th>
<th>Mean Treatment, d†</th>
<th>MI/Coronary Death</th>
<th>Thromboembolism</th>
<th>Serious Bleeding</th>
<th>All-Cause Death</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>No.</td>
<td>Crude Rate (95% CI)</td>
<td>No.</td>
<td>Crude Rate (95% CI)</td>
</tr>
<tr>
<td>VKA plus aspirin plus clopidogrel</td>
<td>264</td>
<td>102</td>
<td>16</td>
<td>7.8 (4.8–12.7)</td>
<td>9</td>
<td>3.6 (1.9–6.9)</td>
</tr>
<tr>
<td>VKA plus clopidogrel</td>
<td>262</td>
<td>163</td>
<td>17</td>
<td>4.4 (4.8–11.8)</td>
<td>11</td>
<td>4.6 (2.6–8.3)</td>
</tr>
<tr>
<td>VKA plus aspirin</td>
<td>7509</td>
<td>809</td>
<td>339</td>
<td>4.7 (4.2–5.2)</td>
<td>167</td>
<td>2.3 (2.0–2.7)</td>
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<tr>
<td>VKA</td>
<td>4107</td>
<td>544</td>
<td>188</td>
<td>4.7 (4.1–5.4)</td>
<td>118</td>
<td>3.0 (2.5–3.6)</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>1332</td>
<td>195</td>
<td>119</td>
<td>11.5 (9.6–13.7)</td>
<td>80</td>
<td>6.6 (5.3–8.3)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>667</td>
<td>236</td>
<td>55</td>
<td>9.0 (6.9–11.7)</td>
<td>35</td>
<td>5.8 (4.1–8.0)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>13079</td>
<td>732</td>
<td>1048</td>
<td>8.4 (7.9–8.9)</td>
<td>533</td>
<td>4.3 (3.9–4.7)</td>
</tr>
</tbody>
</table>

All rates are crude incidence rates (events per 100 person-years). CI indicates confidence interval; MI, myocardial infarction; and VKA, vitamin K antagonist.
†Total time at risk until death.
‡Treatment is set as a time-varying variable, and reported data are given as mean without SD because of right censoring.
risk of 1.58 is in accordance with the present findings (hazard ratio, 2.24). In the nonacute setting, the present data suggest that VKA is at least as effective as dual-antiplatelet therapy in preventing coronary events. Results from a recent controlled trial in a similar population (WOEST [What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting]) found a significantly increased risk of death and numerically more MI events in those given VKA plus dual-antiplatelet therapy (aspirin and clopidogrel) than in those treated with VKA plus clopidogrel therapy. The present data support these findings, that is, that antiplatelet therapy alone or added to VKA therapy is not associated with further protection against thrombosis; however, as an observational study, a causal treatment effect cannot be established. Further studies are warranted to explore this potential contradictory effect of antiplatelet therapy in anticoagulated patients.

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA plus aspirin plus clopidogrel</td>
<td>1.76 [1.05-2.94]</td>
</tr>
<tr>
<td>VKA plus clopidogrel</td>
<td>1.53 [0.93-2.52]</td>
</tr>
<tr>
<td>VKA plus aspirin</td>
<td>1.12 [0.94-1.34]</td>
</tr>
<tr>
<td>VKA</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>2.24 [1.76-2.84]</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1.73 [1.27-2.34]</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1.73 [1.48-2.02]</td>
</tr>
</tbody>
</table>

**Figure 3.** Risk of myocardial infarction/coronary death (A), thromboembolism (B), bleeding (C), and all-cause death (D). Forest plots show adjusted hazard ratios with error bars indicating 95% confidence interval (CI). HR indicates hazard ratio; and VKA, vitamin K antagonist.
Although the Thrombosis Prevention Trial\textsuperscript{25} focused on primary prevention of coronary events in high-risk subjects, comparing the effect of low-intensity warfarin versus aspirin, the investigators concluded that warfarin per se reduced fatal coronary events compared with aspirin but that the combination of both was most effective in primary prevention of ischemic heart disease. The Warfarin-Aspirin Reinfarction (WARIS) II study investigated the effect of aspirin, warfarin, or both for secondary prevention after MI and found that warfarin alone or with aspirin was superior to aspirin alone for a combined end point of death, nonfatal reinfarction, and stroke\textsuperscript{22}; however, when comparing warfarin versus warfarin plus aspirin, no difference in either the combined end point or event-free survival was demonstrated. For reinfarctions only, there was a significant protective effect of warfarin monotherapy and warfarin plus aspirin compared with aspirin only, but no analyses on reinfarctions were provided for warfarin versus warfarin plus aspirin. This latter issue is important in patients with CAD and coexisting AF, in whom an oral anticoagulant is needed for thromboprophylaxis, and warfarin could also protect against MI.

We confirmed previous results showing the inadequacy of single- or dual-antiplatelet therapy compared with VKA\textsuperscript{21} and furthermore showed that any addition of antiplatelet medication to VKA did not result in additional thromboembolic protection. Notably, bleeding risk was increased with more intense antithrombotic treatment, and in accordance with previous studies, we found a significant increase for VKA plus a single antiplatelet medication relative to VKA only.\textsuperscript{26} In peripheral artery disease, the combination of VKA plus aspirin provided no benefit with regard to thromboembolism but substantially increased the risk of major bleeding.\textsuperscript{27} Although a bleeding episode raised the subsequent risk of death >2-fold, we did not find a difference in death attributable to bleeding when a single antiplatelet agent was added to VKA. Hence, the addition of an antiplatelet agent to VKA does not confer any added benefit for the prevention of thrombosis but notably is associated with an increased risk of bleeding.

Long-term secondary prevention of CAD with aspirin is recommended in most patients (without AF). Still, interpretation of data on aspirin use in primary prevention has linked aspirin to poorer prognosis and has associated it with sudden death, hence masking MI events.\textsuperscript{28,29} Also, the main benefit of aspirin with regard to mortality after MI is seen early (<30 days), after which the event-free survival curves for aspirin and placebo are comparable.\textsuperscript{19} However, many of these older studies were in the era before contemporary management of acute coronary syndrome with early coronary intervention and use of stents and other secondary prevention measures, such as statins and renin-angiotensin system inhibitors. For the primary outcomes, crude rates were lower in patients treated with PCI than in those who were not. In either group, the findings from the adjusted analyses resembled those from the main analyses. In addition, the

Table 3. Risk of the Combined Outcome of Myocardial Infarction, Thromboembolism, Bleeding, and All-Cause Mortality

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Events</th>
<th>Crude Rate</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA plus aspirin plus clopidogrel</td>
<td>39</td>
<td>20.8</td>
<td>1.33 (0.96–1.84)</td>
<td>1.70 (1.22–2.36)</td>
</tr>
<tr>
<td>VKA plus clopidogrel</td>
<td>39</td>
<td>19.0</td>
<td>1.28 (0.92–1.77)</td>
<td>1.42 (1.02–1.97)</td>
</tr>
<tr>
<td>VKA plus aspirin</td>
<td>298</td>
<td>13.8</td>
<td>1.00 (0.90–1.12)</td>
<td>1.15 (1.03–1.29)</td>
</tr>
<tr>
<td>VKA</td>
<td>490</td>
<td>13.8</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>243</td>
<td>26.3</td>
<td>1.71 (1.46–2.00)</td>
<td>1.63 (1.39–1.91)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>111</td>
<td>20.4</td>
<td>1.43 (1.16–1.75)</td>
<td>1.29 (1.04–1.59)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>2222</td>
<td>19.4</td>
<td>1.39 (1.26–1.53)</td>
<td>1.35 (1.22–1.49)</td>
</tr>
</tbody>
</table>

All rates are crude incidence rates (events per 100 person-years). Adjusted analyses were controlled for sex, age, inclusion year, percutaneous coronary intervention status, pharmacotherapy, and comorbidity (including factors comprising the CHA\textsubscript{2}-DS\textsubscript{2}-VASc and HAS-BLED scores). CI indicates confidence interval; HR, hazard ratio; and VKA, vitamin K antagonist.
protective effect of VKA on thrombosis was unchanged after 2 years compared with VKA plus a single antiplatelet agent.

For the indication of stroke prophylaxis in AF, all approved new oral anticoagulants (eg, apixaban, rivaroxaban, and dabigatran) show a similar or better overall effect than VKA. Even with these new anticoagulants, combination therapy is associated with greater bleeding risk and no appreciable effect on thromboembolism. Whether these new anticoagulants can replace VKA in AF patients with coexisting CAD is unknown, and further investigation is warranted. Of note, recent data indicate that dabigatran could increase MI risk compared with warfarin.

Clinical Implications

Although the present study was purely observational, some of the conclusions are backed up by a subgroup analysis of the ACTIVE W trial and the recent WOEST trial described above. Given that there is no evidence of benefit from long-term combination of VKA with platelet inhibition, but certainty of some risk with bleeding, we find that the use of VKA only in patients with AF, an indication for VKA, and stable CAD is a valid consideration.

Strengths and Limitations

The present observational nationwide study includes a real-life, unselected cohort of patients with AF and CAD, which is often characterized as being at higher risk for adverse events than patients in controlled trials, which often apply restrictive inclusions criteria for subjects that make extrapolation to everyday patients difficult. Furthermore, we did have the ability to continually update ongoing antithrombotic treatment and thus also investigate therapies given in day-to-day practice, which do not necessarily adhere to guidelines. Diagnoses of MI, AF, and ischemic stroke have shown high validity in the registries. Confounding by indication, that is, that patients at higher risk are treated with more intense antithrombotic therapy, could be present, and patients treated with aspirin plus clopidogrel with or without VKA were at higher risk of MI/coronary death and all-cause death. Because the present findings were consistent (adjusted and unadjusted main and landmark analyses), and we controlled for a wide range of known risk factors, we do not believe this alters our interpretation of an overall beneficial effect of VKA versus VKA plus single-antiplatelet therapy. Possible unmeasured confounders were smoking status, body mass index, information on coronary anatomy, type of AF (ie, paroxysmal, persistent, or permanent), international normalized ratio values, and patient/physician preference for VKA therapy. The estimation of the impact of a potential unmeasured confounder on the outcomes investigated suggests that it is very unlikely such a confounder alone could have driven the results. The registry holds no data on type of stent implanted. Over-the-counter aspirin use was not registered, but because patients are reimbursed for prescribed aspirin and persistent use of aspirin is high in MI patients in Denmark, such use is unlikely to affect our conclusions.

Conclusions

In AF patients with stable CAD, the addition of antiplatelet therapy (either aspirin or clopidogrel) to VKA therapy is not associated with a greater reduction in risk of recurrent coronary events or thromboembolism, whereas risk of bleeding is increased significantly. Thus, VKA might be considered as monotherapy for AF patients with stable CAD (12 months after a coronary event). The common practice of adding antiplatelet therapy to oral anticoagulation in patients with AF and stable CAD warrants reassessment.

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Disclosures

None.

References


Antiplatelet Therapy for Stable Coronary Artery Disease in Atrial Fibrillation Patients Taking an Oral Anticoagulant: A Nationwide Cohort Study
Morten Lamberts, Gunnar H. Gislason, Gregory Y.H. Lip, Jens Flensted Lassen, Jonas Bjerring Olesen, Anders P. Mikkelsen, Rikke Sørensen, Lars Køber, Christian Torp-Pedersen and Morten Lock Hansen

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Supplemental Table 1. ICD codes

Diagnoses, surgical procedures, and pharmacotherapy used for defining the study population, comorbidity, and outcomes

<table>
<thead>
<tr>
<th>Study population</th>
<th>Definition</th>
<th>ICD8</th>
<th>ICD10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Defined from diagnosis</td>
<td>42793, 42794</td>
<td>148</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Defined from diagnosis</td>
<td>41009, 14099</td>
<td>121, 122</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>Defined from procedure performed</td>
<td>NCSP: KFNG (KFNG05, stent implantation)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Definition</th>
<th>ICD8</th>
<th>ICD10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism</td>
<td>Defined from diagnosis including ischemic stroke, transient ischemic attack, systemic thromboembolism</td>
<td>433-8, 444, 450</td>
<td></td>
</tr>
<tr>
<td>Vascular disease</td>
<td>Defined from diagnosis including myocardial infarction, aortic plaque and peripheral arterial disease.</td>
<td>1700, 1702-1709</td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>Defined from diagnosis and adverse alcohol consumption reported during hospitalization</td>
<td>E244, E52, F1, G312, G621, G721, I426, K292, K70, K860, L278A, O354, T51, Z714, Z721</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>Defined from diagnoses of liver cancer, chronic liver disease, liver surgery, cirrhosis, and hepatitis</td>
<td>B15-B19, C22, D684C, I982B, K70-K77, DQ618A, Z944</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Defined from diagnosis</td>
<td>164, 164, G458, G459</td>
<td></td>
</tr>
<tr>
<td>Arterial embolism</td>
<td>Defined from diagnosis</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Defined from treatment</td>
<td>Treatment: Glucose-lowering medication</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Defined from combination treatment with a least two classes of antihypertensive drugs. This definition of hypertension has a positive predictive value of 80.0% and a specificity 94.7%¹</td>
<td>Treatment: Adrenergic α-antagonist, non-loop-diuretics, vasodilators, beta- blockers, calcium channel blockers, and renin-angiotensin system inhibitors.</td>
<td></td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>Defined from diagnosis</td>
<td>1702-1709</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Definition</td>
<td>ICD8/ICD10</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>Defined from diagnosis</td>
<td>ICD10: I110, I142, I150, J819</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Defined from diagnosis plus treatment</td>
<td>ICD8: 425, 4270-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment: Loop-diuretics</td>
<td></td>
</tr>
</tbody>
</table>

**Outcomes**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
<th>ICD8/ICD10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction / Coronary death</td>
<td>Diagnosis of myocardial infarction or coronary death</td>
<td>ICD10: I21-I22 (I20-I25 Coronary death)</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>Death from or diagnosis of ischemic stroke, transient ischemic attack and systemic arterial embolism</td>
<td>ICD10: I63-I64, G458-G459, I74</td>
</tr>
<tr>
<td>Serious bleeding</td>
<td>Death from or diagnosis of gastrointestinal, intracranial, respiratory, and urinary tract bleedings; and anemia caused by bleeding.</td>
<td>ICD10: I60-I62, I690-I692, J942, K250, K254, K260, K264, K270, K280, K920-K922, N02, R04, R31, S064-S066,</td>
</tr>
</tbody>
</table>

**References**

## Supplemental Table 2. ATC codes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ATC Code(s)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulants</td>
<td>BO11AA03-4</td>
<td>Vitamin K antagonists including warfarin and phenprocoumon</td>
</tr>
<tr>
<td>Aspirin</td>
<td>BO1AC06, NO2BA01</td>
<td>Acetylsalicylic acid</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>BO1AC04</td>
<td></td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>M01A</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>C10A</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>C07</td>
<td></td>
</tr>
<tr>
<td>Renin angiotensin system inhibitors</td>
<td>C09</td>
<td>Including: angiotensin-converting-enzyme inhibitors, angiotensin-II receptor blockers</td>
</tr>
<tr>
<td>Loop-diuretics</td>
<td>C03C</td>
<td></td>
</tr>
<tr>
<td>Thiazides</td>
<td>C03A</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>C03DA01</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>C01AA05</td>
<td></td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>A02BC</td>
<td></td>
</tr>
<tr>
<td>Oral glucose-lowering drugs</td>
<td>A10</td>
<td>Defines diabetes mellitus</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>H02AB</td>
<td>Including: prednisolon</td>
</tr>
</tbody>
</table>

ATC: Anatomical Therapeutic Chemical (ATC) system
### Supplemental Table 3. Unadjusted and adjusted analysis of primary outcomes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MI/Coronary death</th>
<th>Thromboembolism</th>
<th>Serious bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted HR</td>
<td>Adjusted HR</td>
<td>Unadjusted HR</td>
</tr>
<tr>
<td>VKA plus aspirin plus clopidogrel</td>
<td>1.43 [0.86-2.39]</td>
<td>1.76 [1.04-2.94]</td>
<td>1.05 [0.53-2.07]</td>
</tr>
<tr>
<td>VKA plus clopidogrel</td>
<td>1.41 [0.86-2.32]</td>
<td>1.53 [0.93-2.52]</td>
<td>1.70 [0.75-2.61]</td>
</tr>
<tr>
<td>VKA plus aspirin</td>
<td>0.99 [0.83-1.17]</td>
<td>1.12 [0.94-1.34]</td>
<td>0.77 [0.61-0.98]</td>
</tr>
<tr>
<td>VKA</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>2.14 [1.69-2.70]</td>
<td>2.24 [1.76-2.84]</td>
<td>1.98 [1.48-2.64]</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1.83 [1.35-2.47]</td>
<td>1.73 [1.27-2.34]</td>
<td>1.82 [1.24-2.65]</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1.74 [1.49-2.04]</td>
<td>1.73 [1.48-2.02]</td>
<td>1.39 [1.14-1.70]</td>
</tr>
</tbody>
</table>

Unadjusted and adjusted hazard ratios (HR) with 95% confidence intervals (CI) of primary outcomes. Adjusted analyses were controlled for gender, age, inclusion year, PCI status, pharmacotherapy and comorbidity (including factors comprising the CHA2DS2-VASc and HAS-BLED scores.

Abbreviations: VKA, vitamin K antagonist; HR, hazard ratio; CI, confidence interval, PCI, percutaneous coronary intervention. CHA2DS2-VASc and HAS-BLED, please see text.
Supplemental Table 4. Risk of effectiveness and safety outcomes in AF patients with and without previous PCI

<table>
<thead>
<tr>
<th>Treatment with previous PCI</th>
<th>MI/Coronary death (total 512 events)</th>
<th>Thromboembolism (total 291 events)</th>
<th>Serious bleeding (total 370 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate [95% CI]</td>
<td>HR [95% CI]</td>
<td>Rate [95% CI]</td>
</tr>
<tr>
<td>VKA plus aspirin plus clopidogrel</td>
<td>4.2 [1.9-9.3]</td>
<td>1.02 [0.43-2.42]</td>
<td>3.1 [1.3-7.5]</td>
</tr>
<tr>
<td>VKA plus clopidogrel</td>
<td>3.9 [1.7-8.6]</td>
<td>0.89 [0.38-2.08]</td>
<td>4.5 [2.1-9.4]</td>
</tr>
<tr>
<td>VKA plus aspirin</td>
<td>3.3 [2.7-3.9]</td>
<td>0.92 [0.66-1.29]</td>
<td>1.8 [1.4-2.3]</td>
</tr>
<tr>
<td>VKA</td>
<td>3.8 [2.9-5.0]</td>
<td>Reference</td>
<td>2.2 [1.5-3.2]</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>8.8 [6.5-11.8]</td>
<td>2.18 [1.42-3.35]</td>
<td>4.6 [3.2-6.8]</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>4.9 [2.9-8.2]</td>
<td>1.34 [0.74-2.44]</td>
<td>3.9 [2.1-7.0]</td>
</tr>
<tr>
<td>Aspirin</td>
<td>4.7 [4.1-5.4]</td>
<td>1.46 [1.06-2.00]</td>
<td>2.8 [2.3-3.3]</td>
</tr>
<tr>
<td></td>
<td><strong>MI/Coronary death (total 1,466 events)</strong></td>
<td><strong>Thromboembolism (total 749 events)</strong></td>
<td><strong>Serious bleeding (total 691 events)</strong></td>
</tr>
<tr>
<td>Treatment without previous PCI</td>
<td>Rate [95% CI]</td>
<td>HR [95% CI]</td>
<td>Rate [95% CI]</td>
</tr>
<tr>
<td>VKA plus clopidogrel</td>
<td>14.1 [7.8-25.4]</td>
<td>2.42 [1.30-4.49]</td>
<td>4.9 [1.8-13.0]</td>
</tr>
<tr>
<td>VKA plus aspirin</td>
<td>6.2 [5.4-7.1]</td>
<td>1.22 [0.98-1.51]</td>
<td>2.9 [2.4-3.5]</td>
</tr>
<tr>
<td>VKA</td>
<td>5.1 [4.4-6.1]</td>
<td>Reference</td>
<td>3.5 [2.8-4.3]</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>14.0 [11.2-17.6]</td>
<td>2.25 [1.68-3.02]</td>
<td>8.4 [6.4-11.0]</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>12.6 [9.3-17.1]</td>
<td>1.94 [1.36-2.76]</td>
<td>7.4 [5.0-11.1]</td>
</tr>
<tr>
<td>Aspirin</td>
<td>10.5 [9.8-11.2]</td>
<td>1.83 [1.52-2.20]</td>
<td>5.2 [4.7-5.7]</td>
</tr>
</tbody>
</table>

Effectiveness and safety outcomes in 3,393 atrial fibrillation patients with previous PCI treatment, and 5,307 without previous PCI treatment. All rates are crude incidence rates (events per 100 person-years). HRs reported are adjusted estimates. Abbreviations: VKA, vitamin K antagonist; HR, hazard ratio; CI, confidence interval, PCI, percutaneous coronary intervention.
### Supplemental Table 5. Risk of death from bleeding

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number</th>
<th>Rate [95% CI]</th>
<th>HR [95% CI]</th>
<th>Number</th>
<th>Rate [95% CI]</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA plus aspirin plus clopidogrel</td>
<td>4</td>
<td>1.5 [0.6-4.0]</td>
<td>3.67 [1.23-10.95]</td>
<td>6</td>
<td>2.3 [1.0-5.1]</td>
<td>3.69 [1.52-8.99]</td>
</tr>
<tr>
<td>VKA plus clopidogrel</td>
<td>2</td>
<td>0.8 [0.2-3.1]</td>
<td>1.78 [0.41-7.72]</td>
<td>3</td>
<td>1.1 [0.4-3.6]</td>
<td>1.75 [0.53-5.79]</td>
</tr>
<tr>
<td>VKA plus aspirin</td>
<td>53</td>
<td>0.8 [0.5-0.9]</td>
<td>1.67 [0.99-2.83]</td>
<td>68</td>
<td>0.9 [0.7-1.1]</td>
<td>1.37 [0.89-2.11]</td>
</tr>
<tr>
<td>VKA plus aspirin</td>
<td>19</td>
<td>0.5 [0.3-0.7]</td>
<td>1.00 (reference)</td>
<td>15</td>
<td>0.7 [0.5-1.0]</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>12</td>
<td>0.9 [0.5-1.6]</td>
<td>1.58 [0.75-3.31]</td>
<td>30</td>
<td>1.1 [0.7-1.9]</td>
<td>1.27 [0.67-2.40]</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1</td>
<td>0.1 [0.0-1.1]</td>
<td>0.28 [0.04-2.08]</td>
<td>3</td>
<td>0.4 [0.1-1.4]</td>
<td>0.53 [0.16-1.73]</td>
</tr>
<tr>
<td>Aspirin</td>
<td>63</td>
<td>0.5 [0.4-0.6]</td>
<td>0.91 [0.54-1.52]</td>
<td>92</td>
<td>0.7 [0.6-0.9]</td>
<td>0.83 [0.55-1.26]</td>
</tr>
</tbody>
</table>

All rates are crude incidence rates (events per 100 person-years). HRs reported are adjusted estimates. Due to low number of events the models were controlled for age, gender, inclusion year and PCI status. Abbreviations: VKA, vitamin K antagonist; HR, hazard ratio; CI, confidence interval.
Supplemental Figure 1 A-C – Landmark analyses: Risk of MI/coronary death, thromboembolism and serious bleeding

A: Risk of myocardial infarction/coronary death

<table>
<thead>
<tr>
<th>Landmark</th>
<th>Treatment</th>
<th>HR [95% CI]</th>
<th>IR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 years</td>
<td>VKA plus clopidogrel</td>
<td>1.43 [0.76-2.68]</td>
<td>7.2 [3.9-12.9]</td>
</tr>
<tr>
<td></td>
<td>VKA plus aspirin</td>
<td>1.11 [0.86-1.43]</td>
<td>5.3 [4.6-6.2]</td>
</tr>
<tr>
<td></td>
<td>VKA</td>
<td>1.00 (reference)</td>
<td>5.4 [4.4-6.6]</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>1.68 [1.34-2.10]</td>
<td>9.6 [8.9-10.4]</td>
</tr>
<tr>
<td>&gt;2 years</td>
<td>VKA plus clopidogrel</td>
<td>1.80 [0.79-4.14]</td>
<td>7.7 [3.4-17.0]</td>
</tr>
<tr>
<td></td>
<td>VKA plus aspirin</td>
<td>1.14 [0.88-1.47]</td>
<td>4.2 [3.6-4.9]</td>
</tr>
<tr>
<td></td>
<td>VKA</td>
<td>1.00 (reference)</td>
<td>4.2 [3.4-5.1]</td>
</tr>
<tr>
<td></td>
<td>Aspirin plus clopidogrel</td>
<td>2.21 [1.64-2.98]</td>
<td>9.7 [6.7-14.2]</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>1.77 [1.41-2.20]</td>
<td>7.2 [6.5-7.8]</td>
</tr>
</tbody>
</table>

Hazard Ratio

(Horizontal bars indicate 95% confidence interval)
### B: Risk of thromboembolism

<table>
<thead>
<tr>
<th>Landmark</th>
<th>Treatment</th>
<th>HR [95% CI]</th>
<th>IR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 years</td>
<td>VKA plus clopidogrel</td>
<td>1.54 [0.73-3.25]</td>
<td>5.1 [2.6-10.2]</td>
</tr>
<tr>
<td></td>
<td>VKA plus aspirin</td>
<td>0.84 [0.60-1.17]</td>
<td>2.6 [2.1-3.2]</td>
</tr>
<tr>
<td></td>
<td>VKA</td>
<td>1.00 (reference)</td>
<td>3.4 [2.7-4.5]</td>
</tr>
<tr>
<td></td>
<td>Aspirin plus clopidogrel</td>
<td>1.95 [1.35-2.81]</td>
<td>7.8 [6.1-10.0]</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>1.36 [1.03-1.83]</td>
<td>4.6 [4.1-5.2]</td>
</tr>
</tbody>
</table>

| >2 years | VKA plus clopidogrel           | 1.57 [0.49-5.03] | 3.7 [1.2-11.3] |
|          | VKA plus aspirin               | 0.86 [0.61-1.20] | 2.1 [1.7-2.6] |
|          | VKA                            | 1.00 (reference) | 2.7 [2.1-3.5] |
|          | Aspirin plus clopidogrel       | 1.24 [0.70-2.21] | 4.0 [2.4-6.6] |
|          | Aspirin                        | 1.36 [1.02-1.82] | 3.9 [3.5-4.5] |

Hazard Ratio
(Horizontal bars indicate 95% confidence interval)
C: Risk of serious bleeding

<table>
<thead>
<tr>
<th>Landmark</th>
<th>Treatment</th>
<th>HR [95% CI]</th>
<th>IR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 years</td>
<td>VKA plus clopidogrel</td>
<td>1.69 [0.87-3.31]</td>
<td>7.2 [3.9-12.9]</td>
</tr>
<tr>
<td></td>
<td>VKA plus aspirin</td>
<td>1.70 [1.29-2.23]</td>
<td>5.3 [4.6-6.2]</td>
</tr>
<tr>
<td></td>
<td>VKA</td>
<td>1.00 (reference)</td>
<td>5.4 [4.4-6.6]</td>
</tr>
<tr>
<td></td>
<td>Aspirin plus clopidogrel</td>
<td>1.03 [0.70-1.53]</td>
<td>12.1 [9.8-14.8]</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>0.68 [0.52-0.90]</td>
<td>9.6 [8.9-10.4]</td>
</tr>
<tr>
<td>&gt;2 years</td>
<td>VKA plus clopidogrel</td>
<td>2.36 [1.08-5.16]</td>
<td>8.5 [4.0-17.8]</td>
</tr>
<tr>
<td></td>
<td>VKA plus aspirin</td>
<td>1.29 [0.98-1.70]</td>
<td>4.4 [3.8-5.2]</td>
</tr>
<tr>
<td></td>
<td>VKA</td>
<td>1.00 (reference)</td>
<td>3.6 [2.9-4.5]</td>
</tr>
<tr>
<td></td>
<td>Aspirin plus clopidogrel</td>
<td>0.94 [0.53-1.66]</td>
<td>3.3 [2.0-5.6]</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>0.74 [0.56-0.98]</td>
<td>2.6 [2.2-3.0]</td>
</tr>
</tbody>
</table>

(Horizontal bars indicate 95% confidence interval)