Bleeding after Initiation of Multiple Antithrombotic Drugs, Including Triple Therapy, in Atrial Fibrillation Patients Following Myocardial Infarction and Coronary Intervention: A Nationwide Cohort Study

Running title: Lamberts et al.; Time of bleeding in MI/PCI patients with AF

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Abstract:

Background - Uncertainty remains over optimal antithrombotic treatment of patients with atrial fibrillation (AF) presenting with myocardial infarction (MI) and/or undergoing coronary intervention (PCI). We investigated the risk and time-frame for bleeding following MI/PCI in AF patients according to antithrombotic treatment.

Methods and Results - Patients with AF and admitted with MI or for PCI between 2000-2009 (11,480 subjects, mean age 75.6 years [SD±10.3], males 60.9%) were identified by individual level-linkage of nationwide registries in Denmark. Fatal or non-fatal (requiring hospitalization) bleeding was determined according to antithrombotic treatment regimen; Triple therapy (TT) with vitamin K antagonist (VKA) + aspirin + clopidogrel, VKA + antiplatelet (AP), and dual antiplatelet therapy (DAPT) with aspirin + clopidogrel. We calculated crude incidence rates, and adjusted hazard ratios by Cox regression models. Within 1-year, 728 bleeding events were recorded (6.3%); 79 were fatal (0.7%). Within 30 days, rates were 22.6, 20.3, and 14.3 bleeding events per 100 person-years for TT, VKA + AP, and DAPT, respectively. Both early (within 90 days) and delayed (90-360 days) bleeding risk with TT exposure in relation to VKA + AP was increased; hazard ratio 1.47 [1.04;2.08] and 1.36 [0.95;1.95], respectively. No significant difference in thromboembolic risk was observed for TT vs. VKA + AP; HR 1.15 [0.95;1.40].

Conclusions - High risk of bleeding is immediately evident with TT after MI/PCI in AF patients. A continually elevated risk associated with TT indicates no safe therapeutic window and TT should only be prescribed after thorough bleeding risk assessment of patients.

Key words: atrial fibrillation; myocardial infarction; percutaneous coronary intervention; antithrombotic treatment; triple therapy
Introduction

In patients with acute coronary syndrome the presence of atrial fibrillation (AF) raises a therapeutic challenge as treatment with both vitamin K antagonists (VKA) and antiplatelets is preferred to prevent stroke and further coronary events\(^1\)-\(^3\). However, rigorous antithrombotic treatment invariably raises the risk of bleeding adding to poorer prognosis with an estimated five-fold mortality increase following myocardial infarction (MI)\(^4\)-\(^8\). Existing recommendations (level C evidence) are based on small, single center studies mostly including patients treated with percutaneous coronary intervention (PCI) with stent implantation\(^9\). Inconsistent findings on the safety, and even the efficacy, of the recommended triple therapy (TT; with aspirin, clopidogrel and VKA) approach in these studies is of concern\(^10\)-\(^12\). Driven by this fact, guidelines endorse use of triple therapy for as short a time as possible, but the wisdom and safety of this practice is largely unknown. It is imperative to gain further knowledge on this topic as short treatment durations may raise false expectations for physicians and patients of increased safety.

We investigated the risk and time-aspect of bleeding in a nationwide cohort of AF patients with indication for dual antiplatelet therapy (due to MI or PCI) on top of VKA treatment. As our main objective, we focused on risk and time-frame of bleeding associated with TT compared to other treatment regimens, and as secondary objective the potential benefit on the thromboembolic risk.

Methods

Registries

The National Patient Registry has kept records of all hospital admissions since 1978. Each hospitalization is coded according to the International Classification of Diseases 8\(^{th}\) and 10\(^{th}\)
revisions (ICD-8 and ICD-10). The registry also includes operational classification codes since 1996 (The Nordic Medical Statistics Committees Classification of Surgical Procedures). Vital status and cause of death was obtained from the civil registration system through Statistics Denmark and the National Causes of Death Register, respectively. The latter holds information about the immediate, contributory and underlying causes of death. The Danish Registry of Medicinal Product Statistics (national prescription registry) contains information on all drug prescriptions dispensed from pharmacies in Denmark since 1995. All drugs are classified according to the international Anatomical Therapeutic Chemical (ATC) System. In Denmark all residents are provided with a unique and permanent civil registration number that enables linkage between these nationwide administrative registries.

**Population**

We identified subjects diagnosed with AF who had been hospitalized for MI or PCI between January 1, 2001 and December 31, 2009. Subjects were eligible for inclusion if their first MI/PCI event in the study period was not preceded by a MI/PCI event up to one year before the index date. To allow prescriptions to be claimed and exclude unmeasured complications related to index hospitalization, a seven-day quarantine period was defined after discharge. Thus, the inclusion date was seven days after discharge. Inclusion criteria were ongoing antithrombotic treatment in subjects alive, aged 30 years or older, and no registration with diagnosis of bleeding, MI or ischemic stroke during the quarantine period. Only individuals aged 10 years or older and alive January 1, 1997 were included. For overview see **Figure 1**. The PCI-only group resembles elective patients not having a MI prior to the procedure. The ICD codes used are available in **supplemental Table 1**.

**Antithrombotic treatment - Vitamin K antagonist, aspirin and clopidogrel**
Claimed prescriptions of VKA (warfarin and phenprocoumon), aspirin, and clopidogrel were used to classify the following five types of treatment regimen: single antiplatelet therapy (AP) with aspirin or clopidogrel; VKA monotherapy with only VKA; dual antiplatelet therapy (DAPT) with aspirin plus clopidogrel; VKA plus single AP with VKA plus aspirin or clopidogrel; or triple therapy (TT) including all three drugs. For each prescription dispensed the daily dosage was estimated for up to seven consecutive prescriptions, enabling us to calculate any treatment regimen at any given time. This method allows for dosages and exposure status to change through time and has previously been used\(^5\). Treatment regimen was set as a time-varying explanatory variable in the analyses. Ongoing treatment at inclusion for all seven possible combinations was defined as baseline treatment. The ATC codes of the identified therapies are listed in supplemental Table 2.

**Concomitant treatment**

Prescriptions filled up to six months prior to inclusion were recorded for the following drugs: renin-angiotensin system inhibitors; antiarrhythmic drugs (including beta-blockers, calcium channel blockers, digoxin, amiodarone and class 1C antiarrhythmic drugs); statins, glucocorticoids; non-steroidal anti-inflammatory drugs; and proton pump inhibitors.

**Comorbidities**

Previous bleeding was defined as any admission for intracranial bleeding, gastrointestinal bleeding (bleeding ulcer, hematemesis, melena and unspecified gastrointestinal bleeding), bleeding from the respiratory or urinary tract and anemia caused by bleeding within five years of inclusion.

Any previous diagnosis or operation for aortic or mitral valve disease was used to define potential valvular AF. Hypertension was defined as collection of at least two different
antihypertensive drugs at baseline as previously validated. A diagnosis of ischemic stroke and transient cerebral ischemia, systemic embolism, acute and chronic renal failure, peripheral arterial disease, alcohol abuse, liver disease, and malignancy within five years prior to inclusion was also determined. Diabetes was defined as treatment with glucose-lowering medication at baseline. Heart failure was defined as any admission for heart failure and use of loop diuretics as done previously.

HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke/thromboembolism, Bleeding history, Labile INR [international normalized ratio], Elderly [age>65 years], Drug consumption/alcohol abuse) scores were calculated from recorded co-morbidities as previously described. However, data on labile INRs was not available. Use of antiplatelet therapy was not included in the score because this was an explanatory variable in the analyses. CHADS2 score (Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, Stroke/Transient ischemic attack) for every patient were also calculated as done previously.

Outcomes

Primary outcome was non-fatal or fatal bleeding defined as either first admission with a diagnosis of non-fatal bleeding registered at discharge or as death from bleeding identified through the National Causes of Death Register. Occurrence and type of bleeding as recorded in hospital databases have shown a positive predictive value of 89-99%. If admission for non-fatal bleeding was followed by death due to bleeding within one week of admission, the bleeding was recorded as fatal. For secondary outcome we used thromboembolic events of cardiovascular death or ischemic stroke, non-fatal myocardial infarction or non-fatal ischemic stroke. For all outcomes under investigation only the first event was registered.

Statistical analysis
Patient characteristics according to treatment regimen at baseline are expressed as percentages or as means and standard deviations. Crude incidence rates of fatal, non-fatal bleeding, and thromboembolic events were determined within one year. Adjusted incidence rate ratios were calculated in a Poisson regression model. A Cox-proportional hazard model was used to estimate the risk of the primary outcomes in a landmark analysis in early (0-89 days) and delayed (90-360 days) time periods, and of the secondary outcome within one year. For both models was treatment regimen set as a time-varying covariate. This implied that subjects were only considered at risk when taking the corresponding antithrombotic drugs. For sensitivity, a model where baseline treatment regimen was used as non-time-dependent exposure was also constructed. All analyses were adjusted for age, gender, year of admission, and PCI as inclusion group, while HAS-BLED was used for bleeding outcomes and CHADS2 score for thromboembolic outcomes. Subjects were censored after 360 days from inclusion, when the follow-up period ended on December 31, 2009 or in case of death from other causes than the outcome under investigation. The interval 180-360 days from inclusion was used as reference when calculating the incidence rate ratios. For the Poisson and Cox model, we tested goodness-of-fit and the proportional hazard assumption, respectively. Both models were investigated for linearity of continuous variables and any significant interactions between the available covariates. None of the assumptions were violated, and no interactions were found. A two-sided significance level of 0.05 was used. All analyses were performed with SAS statistical package version 9.2. (SAS Institute Inc., Cary, NC, USA) and Stata statistical package version 11.0 (StataCorp LP, College Station, TX, USA).

**Ethics**

The Danish Data Protection Agency approved this study (ref. 2007-58-0015, int. ref: GEH-2010-
001), and data were made available such that individuals could not be identified. Retrospective register studies do not require ethical approval in Denmark.

Results

Population

Selection of the study population and baseline characteristics are summarized in Figure 1 and Table 1, respectively. Of 11,480 subjects in the study; 6,993 (60.9%) were males. Mean age was 75.6 years [standard deviation (SD) 10.3]. The group with MI as inclusion criteria consisted of 8,775 (76.4%) and hereof 1,521 (17.3%) had a PCI performed within 1 week, while the solitary PCI group comprised of 2,705 (23.6%). Males were approximately six years younger. Almost 10% had a history of bleeding before inclusion and mean HAS-BLED score was 2.1 (SD 0.9) while mean CHADS2 score was 1.5 (SD 1.5). All regimens containing clopidogrel were more common in patients having a PCI performed regardless of MI status.

Timing and risk of bleeding

Figure 2 demonstrates markedly raised crude incidence rates of bleeding immediately after initiation of TT, and TT bleeding rates were higher than for all other regimens regardless of time elapsed. Within 30 days, crude rates were 22.6, 20.3, and 14.3 major bleeding events per 100 person-years for TT, VKA plus single AP, and DAPT, respectively. The adjusted analysis of incidence rate ratios demonstrated that for all types of regimens, except for VKA monotherapy, the risk was frontloaded (Figure 3). An adjusted landmark analysis of risk in early (0-89 days from inclusion) and delayed (90-360 days) time periods also showed continually elevated bleeding risk with TT relative to VKA plus single AP or DAPT (Figure 4). Increased hazard ratios were also seen for TT compared to VKA plus clopidogrel but insignificant; early (HR 1.37
[0.81;2.31] and delayed (HR 1.07 [0.66;1.73]) time periods. A cross-sectional view of the study population at day 90 and 180 from discharge showed that 989 (out of 9,962 subjects at risk) and 719 (out of 9,076 subjects at risk) were treated with ongoing TT, respectively. Hence, the proportion of subjects on ongoing TT at inclusion, day 90 and 180 after discharge were 13.0%, 9.9%, and 7.9%, respectively.

**Bleeding, cardiovascular death, myocardial infarction and stroke during 360 days of follow-up**

During a mean follow-up of 288.1 days, 728 (6.3%) subjects experienced non-fatal or fatal bleeding (Table 2), and a total of 2,534 (22.1%) events of the combined endpoint of cardiovascular death, MI and ischemic stroke were observed. Nine out of ten fatal bleedings were intracranial or gastrointestinal of origin. Table 3 summarizes characteristics of bleeding events for each combination of therapy at 360 days of follow-up. Figure 5 shows crude incidence rates and number of thromboembolic and bleeding events. The highest bleeding rate was observed for TT (14.2 events per 100 person years) while the rate of the combined endpoint of cardiovascular death, MI and ischemic stroke were similar for TT and VKA plus single AP with rates of 20.1 and 19.4, respectively. The overall trend was that rates of bleeding increased while rates of thromboembolic events decreased with intensity of antithrombotic treatment regimen. The adjusted Cox model showed significant increased risk of bleeding for TT relative to VKA plus single AP at 1-year (HR 1.41 [1.10;1.81]) while the estimates for combined endpoint of cardiovascular death, MI and ischemic stroke showed no significant benefit with TT use; HR 1.15 [0.95;1.40].

**Sensitivity analyses**

Our main results of increased early bleeding risk for all regimens were shown to be consistent
when baseline treatment regimen was used as non-time-dependent exposure (supplementary Figure 1). We calculated adjusted incidence rate ratios of subgroups consisting of male/female, elderly (aged 75 years or older, and younger), inclusion status (MI or PCI) and CHADS\textsubscript{2} score $\geq 2$ (supplementary Figure 2 A-B). No interactions were found, i.e. the risk associated with each treatment regimen was not significant different between the various subgroups. For patients with a definite theoretical indication for VKA therapy (i.e. 7,240 patients with a CHADS\textsubscript{2} score $\geq 2$) crude incidence rates of bleeding were for all antithrombotic combinations similar (Table 3).

Discussion

Our main finding is that AF patients following MI or PCI are immediately at risk of clinically significant bleeding with recommended TT use. Although the risk decreased over time, the initial elevated risk associated with TT was sustained over time compared to less intensive antithrombotic regimens; indicating no safe therapeutic window of TT in respect to bleeding risk.

Studies of the time-dependent aspect of bleeding risk concerning ongoing combination antithrombotic therapy are scarce and show discrepant results. In 80 PCI patients treated with TT for 1 month, Porter et al concluded that TT did not show prohibitively increased bleeding risk\textsuperscript{10}. This is in contrast to our results and Rogacka et al who found that the majority of bleeding complications occurred within the first month\textsuperscript{17}. Similarly, in a large AF population treated with warfarin, the bleeding risk was greatest in the first month after initiation and then declined\textsuperscript{18}. Also longer term bleeding risk with antithrombotic combination therapy shows inconsistency. After follow-up of more than 1½ years Ruiz-Nodar et al did not find a substantial increase of bleeding in patients treated with coumarin combined with none, single or dual antiplatelets after
stent implantation compared to non-coumarin treated patients. As previously shown by our group and others, in predominately AF or MI populations, long-term follow-up of antiplatelets added to VKA are associated with more bleeds. In real-life AF patients suffering from an acute coronary event, the present study reveals a short-term hazard with TT and also VKA plus single AP use that seems most apparent during the first three months. Although patients treated with VKA plus clopidogrel had lower bleeding rates than TT, the adjusted analysis could not demonstrate a clear difference which is in concordance with our previous findings. Clinicians should be aware of a similar bleeding hazard for this combination.

In light of the lack of randomized trials, Paikin et al performed a meta-analysis of TT in AF patients treated with PCI, which supported the recommendation that short treatment duration should be maintained due to an assumed increased risk with time. The meta-analysis comprised of small and highly heterogeneous studies, and the total number of TT patients was smaller (n=1,349) than in our study. Our novel findings on contrary suggest that patients are immediately at risk on top of a continually threat with use of TT.

Our study reflects antithrombotic treatment regimens prescribed in everyday practice on a national level and showed that a large proportion of the patients were only prescribed monotherapy at baseline (43.6%). Former observational studies comprise small PCI-only populations with stringent inclusion criteria concerning antithrombotic treatment and hence show a high proportion of VKA plus mono or dual antiplatelet therapy subjects. This difference is readily explained by the additionally inclusion of MI patients in the present cohort, and the fact that all regimens including clopidogrel treatment were shown to be more prevalent when a PCI was performed. The latter indicating that a more intense treatment regimen is chosen when patients are seen by an interventional cardiologist. However, our subgroup analysis of PCI
subjects did not show these patients’ risks of early bleeding to be any different.

An expected favorable effect was seen for TT on crude incidence rates of combined endpoint of cardiovascular death, MI and ischemic stroke relative to monotherapies and DAPT but the combination of a VKA plus a single AP actually seemed to perform similar to TT. This was consistent in the adjusted analysis, and was also found in another observational study while a systematic review endorse TT because of a presumed protection of thromboembolic events. Findings are conflicting, and differences among the involved studies are prominent, most notably the focus on coronary stented AF patients in small single center registries, while the present study holds nationwide data on antithrombotic drug use and outcomes observed in everyday practice. A clear benefit of TT on thrombosis protection compared to VKA plus AP in these patients is questionable and further studies on the optimal treatment type and duration as well as patient selection are warranted.

Novel anticoagulation agents have recently emerged. In competition with placebo in large trials of acute coronary syndrome patients, findings question the security of adding further anticoagulant drugs onto dual antiplatelet therapy. The Apixaban for Prevention of Acute Ischemic Events-2 (APPRAISE-2) trial had to be stopped early due to an increased bleeding rate while the highest dose of rivaroxaban in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS–TIMI 51) showed significant reduction of ischemic events but a more than 4-fold increase of major non-fatal bleedings. These findings on adding rivaroxaban in ACS patients resemble ours when comparing TT with DAPT (without VKA) on rates of bleeding and ischemic events. However, very-low-dose rivaroxaban showed promising results with no difference in fatal bleeding when compared to placebo. Short-term very-low-dose
rivaroxaban could be a safer choice as part of TT in ACS patients with AF, although a potential trade-off concerning lesser efficient thrombo-prophylaxis must be investigated.

**Strengths & limitations**

The study includes nationwide data, independent of socioeconomic status, race, employment status and participation in health insurance programs (minimizing selection bias). We did not have clinical information to define the severity of the bleeding episode, but using a definition of bleeding based on admissions, we presume that this event of bleeding is clinically severe enough to warrant hospitalization. Lastly, minor bleeding not causing hospitalization or death could not be identified, and therefore our results could underestimate the true risk associated with antithrombotic therapy. However, our study population reflects real-world patients, in contrast to patients enrolled in a randomized setting which are often highly selected in respect to low bleeding risk, and standardized management protocols are rigorously applied and may not mirror everyday practice\(^2^4\).

Data in the registries has previously been validated including diagnosis of MI, stroke and AF\(^2^5-2^7\). Several studies demonstrate that choice of antithrombotic treatment shows wide variability\(^2^8,2^9\) and in this present observational study the primary limitations consist of confounding by indication, i.e. we had no knowledge of reasons affecting the physicians´ choice of antithrombotic therapy and hence may confound outcomes. This bias is expected to affect our results on bleeding risk conservatively, i.e. more intensive antithrombotic therapy is most likely to be prescribed healthier patients at perceived lesser risk of bleeding. Furthermore we adjusted for prognostic factors for bleeding by the validated HAS-BLED score. Aspirin is available as over-the-counter and hence not recorded but chronic aspirin users collect financial reimbursement when prescribed and ensures high persistence\(^5\). We applied sensitivity analyses to
ensure robustness of our findings. To assess an effect of presumed physician’s choice of
treatment during admission, baseline treatment regimen was used as non-time-dependent
exposure, and we also found a similar early risk of bleeding in patients with a theoretical
indication of VKA therapy (CHADS$_2$ score 2 or larger). Unmeasured confounders e.g. INR
levels have not been determined and quality of treatment in real-life setting is difficult to
establish. In a controlled environment, time in therapeutic range in Denmark is high$^{30}$ but the
bias of residual confounding remains.

**Conclusion and clinical implications**

Our main finding is an immediately high risk of bleeding with recommended TT (with aspirin,
clopidogrel and VKA) after MI or PCI in AF patients that decreases over time. However, the risk
was continually elevated in comparison to less intense antithrombotic regimens. Our data of real-
life patients suggests even short-term TT is hazardous in regard to bleeding risk, and TT has no
safe therapeutic window. TT should only be prescribed after careful evaluation of bleeding risk.

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**Conflict of Interest Disclosures:** None.

**References:**

Management of antithrombotic therapy in atrial fibrillation patients presenting with acute
coronary syndrome and/or undergoing percutaneous coronary intervention/ stenting. *Thromb

2. Faxon DP, Eikelboom JW, Berger PB, Holmes DR, Jr., Bhatt DL, Moliterno DJ, Becker RC,


**Table 1. Baseline characteristics of the study population**

<table>
<thead>
<tr>
<th></th>
<th>Total (n=11,480)</th>
<th>Aspirin (n=3,388)</th>
<th>Monotherapy (n=768)</th>
<th>Dual therapy (n=3,144)</th>
<th>Triple therapy (n=1,495)</th>
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</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
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<tr>
<td>Age (males, years ± SD)</td>
<td>6,993 (60.9)</td>
<td>1,725 (50.9)</td>
<td>475 (61.9)</td>
<td>1,972 (62.7)</td>
<td>805 (64.5)</td>
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<tr>
<td>Age (males, years ± SD)</td>
<td>73.2 ± 10.2</td>
<td>76.5 ± 10.5</td>
<td>71.0 ± 10.7</td>
<td>73.5 ± 9.6</td>
<td>71.9 ± 10.7</td>
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<td>MI as inclusion criteria</td>
<td>8,775 (76.4)</td>
<td>3,166 (93.5)</td>
<td>491 (63.9)</td>
<td>2,203 (70.1)</td>
<td>1,147 (87.6)</td>
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<tr>
<td>With PCI within 1 day</td>
<td>1,085 (9.5)</td>
<td>99 (2.9)</td>
<td>95 (12.4)</td>
<td>35 (4.1)</td>
<td>507 (16.1)</td>
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<tr>
<td>With PCI within 2-7 days</td>
<td>436 (3.8)</td>
<td>37 (1.1)</td>
<td>46 (6.0)</td>
<td>10 (1.2)</td>
<td>194 (6.3)</td>
</tr>
<tr>
<td>PCI as inclusion criteria</td>
<td>2,705 (23.6)</td>
<td>222 (6.6)</td>
<td>277 (36.1)</td>
<td>88 (10.4)</td>
<td>941 (29.9)</td>
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<td>PCI with stent implanted</td>
<td>2,177 (19.0)</td>
<td>110 (3.3)</td>
<td>240 (31.3)</td>
<td>50 (5.9)</td>
<td>789 (25.1)</td>
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<td>Inclusion year (2001-2003)</td>
<td>3,724 (32.4)</td>
<td>1,573 (46.4)</td>
<td>235 (30.6)</td>
<td>336 (39.6)</td>
<td>692 (22.0)</td>
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<td>Inclusion year (2004-2009)</td>
<td>7,756 (67.6)</td>
<td>1,815 (53.6)</td>
<td>533 (69.4)</td>
<td>512 (60.4)</td>
<td>2,452 (78.0)</td>
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<td><strong>Co-morbidity</strong></td>
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<td>Previous ischemic stroke</td>
<td>1,374 (12.0)</td>
<td>451 (13.3)</td>
<td>83 (10.8)</td>
<td>135 (15.9)</td>
<td>308 (9.8)</td>
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<td>Previous bleeding</td>
<td>1,052 (9.2)</td>
<td>406 (12.0)</td>
<td>77 (10.0)</td>
<td>91 (10.7)</td>
<td>230 (7.3)</td>
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<td>Malignancy</td>
<td>1,032 (9.0)</td>
<td>356 (10.5)</td>
<td>65 (8.5)</td>
<td>77 (9.1)</td>
<td>284 (9.0)</td>
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<td>Heart failure</td>
<td>3,871 (29.5)</td>
<td>1,132 (33.4)</td>
<td>180 (23.4)</td>
<td>324 (38.2)</td>
<td>714 (22.7)</td>
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<td>Hypertension</td>
<td>8,532 (74.3)</td>
<td>2,324 (68.6)</td>
<td>552 (71.9)</td>
<td>638 (75.2)</td>
<td>2,324 (73.9)</td>
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<td>Diabetes mellitus</td>
<td>1,865 (15.3)</td>
<td>543 (16.0)</td>
<td>119 (16.6)</td>
<td>148 (17.5)</td>
<td>45b (14.3)</td>
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<td>Potential valve AF</td>
<td>1,312 (11.4)</td>
<td>348 (10.3)</td>
<td>77 (10.0)</td>
<td>143 (16.9)</td>
<td>310 (9.9)</td>
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<td><strong>CHADS2 score</strong></td>
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<tr>
<td>Low/intermediate (score 0-1)</td>
<td>4,240 (36.9)</td>
<td>1,108 (32.7)</td>
<td>332 (43.2)</td>
<td>282 (33.3)</td>
<td>1,368 (43.5)</td>
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<td>HAS-BLED score</td>
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<tr>
<td>Low (score 0-1)</td>
<td>2,828 (24.6)</td>
<td>791 (23.4)</td>
<td>227 (29.6)</td>
<td>195 (23.0)</td>
<td>887 (28.2)</td>
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<td>Intermediate (score 2)</td>
<td>5,410 (47.1)</td>
<td>1,522 (44.9)</td>
<td>333 (43.4)</td>
<td>391 (46.1)</td>
<td>1,455 (46.3)</td>
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<td>High (score ≥3)</td>
<td>3,242 (28.2)</td>
<td>1,075 (31.7)</td>
<td>208 (27.1)</td>
<td>262 (30.9)</td>
<td>802 (25.5)</td>
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<tr>
<td><strong>Concomitant Treatment</strong></td>
<td></td>
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<tr>
<td>RAS inhibitors</td>
<td>6,740 (58.7)</td>
<td>1,717 (50.7)</td>
<td>435 (56.6)</td>
<td>512 (60.4)</td>
<td>1,836 (58.4)</td>
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<td>Beta-blockers</td>
<td>8,445 (73.6)</td>
<td>2,175 (64.3)</td>
<td>561 (73.1)</td>
<td>557 (65.7)</td>
<td>2,498 (79.5)</td>
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<td>Statins</td>
<td>7,009 (61.1)</td>
<td>1,325 (39.1)</td>
<td>536 (69.8)</td>
<td>366 (43.2)</td>
<td>2,385 (75.9)</td>
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<td>Antiarrhythmic drugs*</td>
<td>10,694 (93.2)</td>
<td>3,028 (89.4)</td>
<td>716 (93.2)</td>
<td>791 (93.3)</td>
<td>2,955 (94.0)</td>
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<td>Steroids</td>
<td>1,203 (10.5)</td>
<td>434 (12.8)</td>
<td>82 (10.7)</td>
<td>92 (10.9)</td>
<td>321 (10.2)</td>
</tr>
<tr>
<td>NSAID</td>
<td>2,351 (20.5)</td>
<td>725 (21.4)</td>
<td>158 (20.6)</td>
<td>165 (19.5)</td>
<td>668 (21.3)</td>
</tr>
<tr>
<td>PPI</td>
<td>3,013 (26.3)</td>
<td>944 (27.9)</td>
<td>236 (30.7)</td>
<td>21.7 (184)</td>
<td>874 (27.8)</td>
</tr>
</tbody>
</table>

Abbreviations: n (%), number (rounded column percent); SD, standard deviation; VKA, vitamin K antagonist; MI, myocardial infarction; PCI, percutaneous coronary intervention; AF, atrial fibrillation; CHADS2, score, Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke/Transient ischemic attack; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke/thromboembolism, Bleeding history, Labile INR, Elderly [age ≥ 65 years], Drug consumption/alcohol abuse; RAS, renin-angiotensin system; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitors
* Including beta-blockers, digoxin, class 1C antiarrhythmic drugs, calcium channel blockers, and amiodarone
Table 2. Distribution and type of non-fatal and fatal bleedings

<table>
<thead>
<tr>
<th></th>
<th>Non-fatal bleeding, n (%)</th>
<th>Fatal bleeding, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>38 (5.8)</td>
<td>36 (48.0)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>221 (33.8)</td>
<td>34 (45.3)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>109 (16.7)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Urogenital</td>
<td>120 (18.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Anaemia caused by bleeding</td>
<td>165 (25.3)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Total bleeding events</td>
<td>653</td>
<td>75</td>
</tr>
</tbody>
</table>

Table 3 - Characteristics and incidence rates of bleeding following MI or PCI in AF patients treated with different antithrombotic drug regimens

<table>
<thead>
<tr>
<th></th>
<th>Duration in treatment group until bleeding (person years)</th>
<th>Number of non-fatal and fatal bleedings</th>
<th>Proportion of no-fatal and fatal bleedings (%)</th>
<th>Time to non-fatal or fatal bleeding (days, median [IQR])†</th>
<th>Mean treatment duration until bleeding (days)‡</th>
<th>Crude incidence rate of non-fatal and fatal bleeding at 1-year [95% CI] §</th>
<th>Crude incidence rate of non-fatal and fatal bleeding at 1-year [95% CI] $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>2,591.6</td>
<td>181</td>
<td>25</td>
<td>42 [13-118]</td>
<td>138</td>
<td>7.0 [6.0;8.1]</td>
<td>7.7 [6.4;9.1]</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>548.7</td>
<td>36</td>
<td>5</td>
<td>34 [16-78]</td>
<td>71</td>
<td>6.6 [4.7;9.1]</td>
<td>8.9 [6.2;12.9]</td>
</tr>
<tr>
<td>VKA</td>
<td>646.9</td>
<td>45</td>
<td>6</td>
<td>45 [13-60]</td>
<td>99</td>
<td>7.0 [5.2;9.3]</td>
<td>7.9 [5.6;11.2]</td>
</tr>
<tr>
<td>Dual therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin + clopidogrel</td>
<td>2,292.2</td>
<td>160</td>
<td>22</td>
<td>41 [15-96]</td>
<td>162</td>
<td>7.0 [6.0;8.2]</td>
<td>9.1 [7.6;11.0]</td>
</tr>
<tr>
<td>VKA + aspirin</td>
<td>1,267.2</td>
<td>120</td>
<td>16</td>
<td>22 [13-39]</td>
<td>142</td>
<td>9.5 [7.9;11.3]</td>
<td>9.9 [8.0;12.3]</td>
</tr>
<tr>
<td>VKA + clopidogrel</td>
<td>367.4</td>
<td>39</td>
<td>5</td>
<td>8 [3-17]</td>
<td>92</td>
<td>10.6 [7.8;14.5]</td>
<td>11.2 [7.6;16.5]</td>
</tr>
<tr>
<td>Triple therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin + clopidogrel + VKA</td>
<td>803.1</td>
<td>114</td>
<td>16</td>
<td>18 [5-44]</td>
<td>121</td>
<td>14.2 [11.8;17.1]</td>
<td>16.0 [12.8;20.1]</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; CI, confidence interval; VKA, vitamin K antagonist; * number of bleedings in group ÷ 728 * 100, † Treatment is set as time-varying variable, and reported data is summed from inclusion, ‡ Treatment is set as time-varying variable, and reported data is given as mean without standard deviation due to right-censoring, § All crude incidence rates are number of events per 100 person years || Only patients with CHADS2≥2 (i.e. 7,240 patients)
Figure Legends:

Figure 1. Selection of the study population. Abbreviations: MI, myocardial infarction; PCI, percutaneous coronary intervention;

Figure 2. Crude incidence rates of fatal and non-fatal bleeding according to antithrombotic regimen in time periods following inclusion. Error bars show standard errors. Triple therapy includes aspirin, clopidogrel and vitamin K antagonists (VKA); VKA + single antiplatelet therapy includes VKA + aspirin or clopidogrel; dual antiplatelet therapy includes aspirin and clopidogrel; VKA monotherapy includes only VKA; single antiplatelet therapy includes aspirin or clopidogrel.

Figure 3. Adjusted incidence rate ratios for type of treatment regimen according to treatment interval. Adjusted for age, gender, year of admission, HAS-BLED-score (Hypertension, Abnormal renal/liver function, Stroke/thromboembolism, Bleeding history, Labile INR, Elderly [age>65 years], Drug consumption/alcohol abuse), and PCI inclusion status. Triple therapy includes aspirin, clopidogrel and vitamin K antagonists (VKA); VKA + single antiplatelet therapy includes VKA + aspirin or clopidogrel; dual antiplatelet therapy includes aspirin and clopidogrel; VKA monotherapy includes only VKA; single antiplatelet therapy includes aspirin or clopidogrel.

Figure 4. Risk of early and delayed bleeding in a landmark analysis following MI or PCI in AF patients comparing type of antithrombotic treatment regimen. Abbreviations: MI, myocardial
infarction; PCI, percutaneous coronary intervention; AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval. VKA, vitamin K antagonist; AP, antiplatelet (aspirin or clopidogrel).

Adjusted for age, gender, year of admission, HAS-BLED-score (Hypertension, Abnormal renal/liver function, Stroke/thromboembolism, Bleeding history, Labile INR, Elderly [age>65 years], Drug consumption/alcohol abuse), and PCI inclusion status.

Figure 5. Thromboembolic and bleeding outcomes following MI or PCI in AF patients according to type of antithrombotic treatment regimen. Error bars show standard errors. *Triple therapy* includes aspirin, clopidogrel and vitamin K antagonists (VKA); *VKA + single antiplatelet therapy* includes VKA + aspirin or clopidogrel; *dual antiplatelet therapy* includes aspirin and clopidogrel; *VKA monotherapy* includes only VKA; *single antiplatelet therapy* includes aspirin or clopidogrel.
Atrial fibrillation subjects eligible for inclusion with admission for either MI (n=13,970) or PCI (n=2,909) with no PCI/MI events one year prior from January 1, 2001 to December 31, 2009 (total n=16,879)

Excluded (n=5,399)
- Fatal or non-fatal bleeding during quarantine period (224)
- Fatal or non-fatal stroke during quarantine period (354)
- Coronary death or non-fatal MI during quarantine period (2,491)
- Death from other causes (423)
- Not receiving antithrombotic therapy at inclusion (1,901)
- Age below 30 years (6)

Fulfilling inclusion criteria after seven day quarantine period after discharge and included in the study (n=11,480)

Aspirin (n=3,388)  Clopidogrel (n=768)  VKA (n=848)  Aspirin + clopidogrel (n=3,144)  Aspirin + VKA (n=1,310)  Clopidogrel + VKA (n=527)  Aspirin + clopidogrel + VKA (n=1,495)
The diagram illustrates the hazard ratios and confidence intervals for different treatments and time periods.

- **Early time period (0-89 days):**
  - VKA plus single AP (reference): Hazard ratio [95% CI] = 1.47 [1.04; 2.08]
  - Delayed time period (90-360 days): Hazard ratio [95% CI] = 1.36 [0.95; 1.95]
  - Triple therapy: Hazard ratio [95% CI] = 2.20 [1.58; 3.08]

- **Delayed time period (90-360 days):**
  - Dual antiplatelet therapy (reference): Hazard ratio [95% CI] = 1.93 [1.35; 2.77]
  - Triple therapy: Hazard ratio [95% CI] = 1.50 [1.08; 2.09]

- **VKA plus AP:** Hazard ratio [95% CI] = 1.42 [1.05; 1.92]
Bleeding after Initiation of Multiple Antithrombotic Drugs, Including Triple Therapy, in Atrial Fibrillation Patients Following Myocardial Infarction and Coronary Intervention: A Nationwide Cohort Study

Morten Lamberts, Jonas Bjerring Olesen, Martin Huth Ruwald, Carolina Malta Hansen, Deniz Karasoy, Søren Lund Kristensen, Lars Køber, Christian Torp-Pedersen, Gunnar Hilmar Gislason and Morten Lock Hansen

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### SUPPLEMENTAL TABLES

**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>Comorbidity</th>
</tr>
</thead>
</table>
| Atrial fibrillation Defined from diagnosis | *ICD8:* 42793, 42794  
*ICD10:* I48 |
| Myocardial infarction Defined from diagnosis | *ICD10:* I21, I22 |
| Percutaneous coronary intervention Defined from procedure performed | *NCSP:* KFNG |

#### Comorbidity

| Stroke Defined from diagnosis of ischemic stroke, transient ischemic attack and unspecified stroke. | *ICD10:* I63, I64, G458, G459 |
| Arterial embolism Defined from diagnosis | *ICD10:* I74 |
| Peripheral arterial disease Defined from diagnosis | *ICD10:* I702-I709 |
| Alcohol abuse Defined from diagnosis and adverse alcohol consumption reported during hospitalization | *ICD10:* E244, E52, F1, G312, G621, G721, I426, K292, K70, K860, L278A, O354, T51, Z714, Z721 |
| Liver disease Defined from diagnoses of liver cancer, chronic liver disease, liver surgery, cirrhosis, and hepatitis | *ICD10:* B15-B19, C22, D684C, I982B, K70-K77, DQ618A, Z944  
*NCSP:* KJJ |
| Diabetes mellitus Defined from treatment | *Treatment:* Glucose-lowering medication |
| Heart failure Defined from diagnosis plus treatment | *ICD10:* I110, I42, I50, J819  
*Treatment:* Loop-diuretics |
<p>| Acute renal failure Defined from diagnosis of acute tubular necrosis, uraemia without | <em>ICD10:</em> N17, N19, R34 |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>ICD10</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Defined from combination treatment with at 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>I60-162, I690-I692, J942, K250, K254, K260, K264, K270, K280, K920-K922, N02, R04, R31, S064-S066</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>Defined from diagnoses of cancer (non-benign)</td>
<td>C00-C97</td>
<td></td>
</tr>
<tr>
<td>Potential valvular atrial fibrillation</td>
<td>Defined from any diagnoses or operation of aortic or mitral valve disease including invasive antiarrythmic procedures</td>
<td>394, 395, 396, 4240, 4241</td>
<td>I05, I06, I34, I35</td>
</tr>
<tr>
<td>NCSP: KFK, KFM, KFP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Primary outcome**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Description</th>
<th>ICD10</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>Death from or diagnosis of gastrointestinal, intracranial, respiratory, and urinary tract bleedings; and anemia caused by bleeding.</td>
<td>I60-I62, I690-I692, J942, K250, K254, K260, K264, K270, K280, K920-K922, N02, R04, R31, S064-S066, D500, D62</td>
<td></td>
</tr>
</tbody>
</table>

**Secondary outcome**
<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Non-fatal myocardial infarction or ischaemic stroke from hospital admission and death from diagnosis of coronary disease or ischaemic stroke.</th>
<th>ICD10: I21-I22 (myocardial infarction), I63-I64 (ischaemic stroke), I20-I25 (coronary death)</th>
</tr>
</thead>
</table>

ICD8: 8th revision of the International Classification of Diseases system  
ICD10: 10th revision of the International Classification of Diseases system  
NCSP: The Nordic Medical Statistics Committees Classification of Surgical Procedures
**Supplemental Table 2 – ATC codes**
Pharmacotherapy used for defining the population, and comorbidity.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ATC:</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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>Vitamin K antagonists</td>
<td>BO11AA0</td>
<td>Including: warfarin, phenprocoumon</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>Calcium channel blockers</td>
<td>C08</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>C01AA05</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>C01BD01</td>
<td></td>
</tr>
<tr>
<td>Class 1 C antiarrhythmic drugs</td>
<td>C01BC</td>
<td>Including: flecainid, propafenon</td>
</tr>
<tr>
<td>Sotalol</td>
<td>C07AA07</td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>C07, C08, C01AA05, C01BD01, C07AA07, C01BC</td>
<td>Including: beta-blockers, calcium channel blockers, digoxin, amiodarone, sotalol, Class 1C drugs</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></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>H02AB</td>
<td>Including: prednisol</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>M01A</td>
<td></td>
</tr>
</tbody>
</table>

ATC: Anatomical Therapeutic Chemical (ATC) system
**SUPPLEMENTAL FIGURES AND FIGURE LEGENDS**

**Supplemental Figure 1** – Title: Adjusted incidence rate ratios for baseline treatment regimen according to treatment interval

Legend: Adjusted for age, gender, year of admission, HAS-BLED-score (Hypertension, Abnormal renal/liver function, Stroke/thromboembolism, Bleeding history, Labile INR, Elderly [age>65 years], Drug consumption/alcohol abuse), and PCI inclusion status.
Supplemental Figure 2A-B - Adjusted incidence rate ratios for subgroups according to treatment interval
Legends: All models adjusted for age, gender, year of admission, HAS-BLED-score (Hypertension, Abnormal renal/liver function, Stroke/thromboembolism, Bleeding history, Labile INR, Elderly [age>65 years], Drug consumption/alcohol abuse), and PCI inclusion status. In a particular subgroup the variable of interest was excluded in the adjusted analysis e.g. in the subgroup consisting of females the variable of gender was excluded.
SUPPLEMENTAL REFERENCES

심방세동 환자에서 심근경색이나 스텐트 시술 후의 항혈전 삼제요법은 이득에 비해 출혈 부작용이 훨씬 크다

최 기 준 교수 서울아산병원 심장내과

Summary

배경
심근경색이나 경피적 관상동맥성형술을 시행 받은 환자가 심방세동이 있는 경우 항혈전치료를 어떻게 해야 하는가에 대해서는 아직 이견이 많고, 확실한 치료방법이 확정되지 않은 상태이다.

방법 및 결과
덴마크의 국가등록 데이터 중 2000-2009년 사이에 심근경색으로 입원하거나 경피적 관상동맥성형술을 시행 받기 위해 입원했던 심방세동 환자군 11,480명을 대상으로 연구를 시행하였고, 평균 연령은 75.6세, 남성은 60.9%였다. 환자들의 항혈전치료 방법에 따라 삼제요법(1군: 와파린+아스피린+클로피도그렐), 와파린+하나의 항혈소판제(2군), 두 가지의 항혈소판제(3군: 아스피린+클로피도그렐) 치료군으로 나누어 출혈 발생을 분석하였다. 출혈률을 조사하였으며, Cox 회귀모델을 이용하여 보정된 위험률(hazard ratio, HR)을 구하였다.

1년 사이에 728건의 출혈이 발생하였는데(6.3%), 이 중에서 79건(0.7%)은 생명에 지장을 줄 정도로 치명적이었다. 최초 30일 사이에 100 person-year당 출혈이 각각의 그룹에서 22.6(1군), 20.3(2군), 14.3(3군)건이 발생하였다. 조기출혈(90일 이내)과 지연출혈(90일-1년)의 위험 모두 삼제요법군인 1군에서 2군에 비해 증가하였는데, HR은 1.47(1.04-2.08)과 1.36(0.95-1.95)이었다. 혈전색전증의 위험도에서는 1군과 2군에서 뚜렷한 차이가 없었다[HR 1.15(0.95-1.40)].

결론
심방세동 환자에서 심근경색이나 경피적 관상동맥성형술 시술 직후에 삼제요법을 사용한 경우에는 초기에 출혈 위험이 뚜렷하게 증가한다. 또한, 삼제요법은 초기 이후에도 지속적으로 출혈 위험을 증가시키므로 환자의 출혈 위험도를 충분히 고려한 후에 조심스럽게 처방하여야 한다.
심방세동 환자 또는 심근경색나 관상동맥성형술을 시행 받은 후의 항혈전치료에 대한 각각의 가이드라인은 마련되어 있으나, 두 가지 적응증을 같이 가지고 있는 경우, 즉 심방세동 환자가 심근경색이 있거나 관상동맥성형술을 받고 난 후에 항혈전치료를 어떻게 하여야 하는지에 대해서는 아직 정확한 가이드라인이 없는 상태이다. 현재 대규모 연구에 의한 증거는 부족한 상태이며, 다만 전문가 권고안(level C evidence)에서는 가능한 한 짧은 기간 동안만 와파린과 아스피린, 클로피드로그렐 삼제요법을 시행하는 것을 추천하고 있다. 한 예로 2010년 유럽 심장학회 가이드라인에서는 심방세동 환자가 스텐트 시술을 받은 경우, 출혈 위험이 아주 높지 않은 경우에는 비약물방출성 스텐트일 때 삼제요법을 1개월, 약물방출성 스텴트일 때는 삼제요법을 3-6개월 사용할 것을 권장하였고, 급성 관상동맥증후군의 경우에는 스텴트 종류에 관계없이 6개월 간의 삼제요법을 권장하였다. 이러한 유럽 심장학회 가이드라인은 비슷한 시기에 Lip 등이 발표한 최초의 컨센서스 보고를 근거로 마련된 것으로, 여기에서 짧은 기간의 삼제요법의 필요성과 함께 가능한 약물방출성 스텴트 사용의 자제를 강조하였다. 본 연구에서는 범 국가적인 코호트에서 다양한 항혈전요법들의 출혈 위험을 비교해보았다는 데 의의가 있다. 연구 결과, 삼제요법을 사용하면 초기(최초 30일 정도)에 출혈 위험이 가장 높고 시간이 지남에 따라 조금씩 감소하기는 하지만, 다른 군들에 비해 지속적으로 출혈 위험이 높음을 보여주어 삼제요법이 그 리 안전하지 않으며, 더욱이 심혈관관련 사망, 심근경색, 허혈성 뇌졸중 등의 복합적인 혈전색전증의 위험도 측면에서도 삼제요법의 이득이 크지 않을음을 보여주었다. 따라서 대규모의 무작위배정 연구 결과가 나올 때까지는 삼제요법의 사용은 상당히 조심스럽게 행해야 할 것이다.

이번 연구의 또 다른 특징은 덴마크에서는 국가 전체의

References

Bleeding After Initiation of Multiple Antithrombotic Drugs, Including Triple Therapy, in Atrial Fibrillation Patients Following Myocardial Infarction and Coronary Intervention

A Nationwide Cohort Study

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Background—Uncertainty remains over optimal antithrombotic treatment of patients with atrial fibrillation presenting with myocardial infarction and/or undergoing percutaneous coronary intervention. We investigated the risk and time frame for bleeding following myocardial infarction/percutaneous coronary intervention in patients with atrial fibrillation according to antithrombotic treatment.

Methods and Results—Patients with atrial fibrillation and admitted with myocardial infarction or for percutaneous coronary intervention between 2000 and 2009 (11,480 subjects, mean age 75.6 years [SD 10.3], males 60.9%) were identified by individual level linkage of nationwide registries in Denmark. Fatal or nonfatal (requiring hospitalization) bleeding was determined according to antithrombotic treatment regimen: triple therapy (TT) with vitamin K antagonist (VKA) + aspirin + clopidogrel, VKA + antiplatelet, and dual antiplatelet therapy with aspirin + clopidogrel. We calculated crude incidence rates and adjusted hazard ratios by Cox regression models. Within 1 year, 728 bleeding events were recorded (6.3%); 79 were fatal (0.7%). Within 30 days, rates were 22.6, 20.3, and 14.3 bleeding events per 100 person-years for TT, VKA + antiplatelet, and dual antiplatelet therapy, respectively. Both early (within 90 days) and delayed (90–360 days) bleeding risk with TT exposure in relation to VKA + antiplatelet was increased; hazard ratio 1.47 (1.04;2.08) and 1.36 (0.95;1.95), respectively. No significant difference in thromboembolic risk was observed for TT versus VKA + antiplatelet; hazard ratio, 1.15 (0.95;1.40).

Conclusions—High risk of bleeding is immediately evident with TT after myocardial infarction/percutaneous coronary intervention in patients with atrial fibrillation. A continually elevated risk associated with TT indicates no safe therapeutic window, and TT should only be prescribed after thorough bleeding risk assessment of patients. (Circulation. 2012;126:1185-1193.)

Key Words: anticoagulants ■ atrial fibrillation ■ hemorrhage ■ myocardial infarction ■ percutaneous coronary intervention ■ antithrombotic treatment ■ triple therapy

In patients with acute coronary syndrome the presence of atrial fibrillation (AF) raises a therapeutic challenge because treatment with both vitamin K antagonists (VKAs) and antiplatelets is preferred to prevent stroke and further coronary events.1-3 However, rigorous antithrombotic treatment invariably raises the risk of bleeding, adding to a poorer prognosis with an estimated 5-fold mortality increase following myocardial infarction (MI).4-8 Existing recommendations (level C evidence) are based on small, single-center studies mostly including patients treated with percutaneous coronary intervention (PCI) with stent implantation.9 Inconsistent findings on the safety, and even the efficacy, of the recommended triple therapy (TT; with aspirin, clopidogrel, and VKA) approach in these studies is of concern.10-12 Driven by this fact, guidelines endorse use of TT for as short a time as possible, but the wisdom and safety of this practice is largely unknown. It is imperative to gain further knowledge on this topic because short treatment durations may raise false expectations for physicians and patients of increased safety.

Clinical Perspective on p 57

We investigated the risk and time aspect of bleeding in a nationwide cohort of AF patients with an indication for dual
antiplalet treatment (because of MI or PCI) on top of VKA treatment. As our main objective, we focused on risk and time frame of bleeding associated with TT in comparison with other treatment regimens, and, as our secondary objective, we focused on the potential benefit on the thromboembolic risk.

**Methods**

**Registries**

The National Patient Registry has kept records of all hospital admissions since 1978. Each hospitalization is coded according to the International Classification of Diseases, 8th and 10th revisions. The registry has also included operational classification codes since 1996 (The Nordic Medical Statistics Committees Classification of Surgical Procedures). Vital status and cause of death was obtained from the civil registration system through Statistics Denmark and the National Causes of Death Register, respectively. The latter holds information about the immediate, contributory, and underlying causes of death. The Danish Registry of Medicinal Product Statistics (national prescription registry) contains information on all drug prescriptions dispensed from pharmacies in Denmark since 1995. All drugs are classified according to the international Anatomic Therapeutic Chemical System. In Denmark, all residents are provided with a unique and permanent civil registration number that enables linkage between these nationwide administrative registries.

**Population**

We identified subjects diagnosed with AF who had been hospitalized for MI or PCI between January 1, 2001 and December 31, 2009. Subjects were eligible for inclusion if their first MI/PCI event in the study period was not preceded by a MI/PCI event up to 1 year before inclusion. Any previous diagnosis or operation for aortic or mitral valve disease was used to define potential valvular AF. Hypertension was defined as the collection of at least 2 different antihypertensive drugs at baseline as previously validated.23 A diagnosis of ischemic stroke and transient cerebral ischemia, systemic embolism, acute and chronic renal failure, peripheral arterial disease, alcohol abuse, liver disease, and malignancy within 5 years before inclusion was also determined. Diabetes mellitus was defined as treatment with glucose-lowering medication at baseline. Heart failure was defined as any admission for heart failure and use of heart failure medications as previously described.15 However, data on labile INRs was not available. The use of antithrombotic therapy was not included in the procedure. The ICD codes used are available in online-only Data Supplement Table I.

**Antithrombotic Treatment: VKA, Aspirin, and Clopidogrel**

Claimed prescriptions of VKA (warfarin and phenprocoumon), aspirin, and clopidogrel were used to classify the following 5 types of treatment regimen: single antiplatelet therapy (AP) with aspirin or clopidogrel; VKA monotherapy with only VKA; dual antiplatelet therapy (DAPT) with aspirin plus clopidogrel; VKA plus single AP with VKA plus aspirin or clopidogrel; or TT including all 3 drugs. For each prescription dispensed, the daily dosage was estimated for the following drugs: renin-angiotensin system inhibitors; antiarhythmic drugs (including β-blockers, calcium channel blockers, digoxin, amiodarone, and class 1C antiarrhythmic drugs); statins, glucocorticoids; nonsteroidal anti-inflammatory drugs; and proton pump inhibitors.

**Concomitant Treatment**

Prescriptions filled up to 6 months before inclusion were recorded for the following drugs: renin-angiotensin system inhibitors; antiarhythmic drugs (including β-blockers, calcium channel blockers, digoxin, amiodarone, and class 1C antiarrhythmic drugs); statins, glucocorticoids; nonsteroidal anti-inflammatory drugs; and proton pump inhibitors.

**Comorbidities**

Previous bleeding was defined as any admission for intracranial bleeding, gastrointestinal bleeding (bleeding ulcer, hematoma, melena, and unspecified gastrointestinal bleeding), bleeding from the respiratory or urinary tract, and anemia caused by bleeding within 5 years of inclusion. A previous diagnosis or operation for aortic or mitral valve disease was used to define potential valvular AF. Hypertension was defined as the collection of at least 2 different antihypertensive drugs at baseline as previously validated.23 A diagnosis of ischemic stroke and transient cerebral ischemia, systemic embolism, acute and chronic renal failure, peripheral arterial disease, alcohol abuse, liver disease, and malignancy within 5 years before inclusion was also determined. Diabetes mellitus was defined as treatment with glucose-lowering medication at baseline. Heart failure was defined as any admission for heart failure and use of loop diuretics as done previously.14 HAS-BLED (Hypertension, Abnormal renal/liver function, Strokethromboembolism, Bleeding history, Labile INR [international normalized ratio], Elderly [age ≥65 years], Drug consumption [alcohol abuse] scores were calculated from recorded comorbidities as previously described.15 However, data on labile INRs was not available. The use of antiplatelet therapy was not included in the score because this was an explanatory variable in the analyses. CHADS2 score (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke/transient ischemic attack) for every patient were also calculated as done previously.13
Outcomes
Primary outcome was nonfatal or fatal bleeding defined as either first admission with a diagnosis of nonfatal bleeding registered at discharge or as death from bleeding identified through the National Causes of Death Register.\(^4,^5\) Occurrence and type of bleeding as recorded in hospital databases have shown a positive predictive value of 89% to 99%.\(^6\) If admission for nonfatal bleeding was followed by death due to bleeding within 1 week of admission, the bleeding was recorded as fatal. For secondary outcome, we used thromboembolic events of cardiovascular death or death from ischemic stroke, nonfatal MI, or nonfatal ischemic stroke. For all outcomes under investigation, only the first event was registered.

Statistical Analysis
Patient characteristics according to treatment regimen at baseline are expressed as percentages or as means and standard deviations. Crude incidence rates of fatal bleeding, nonfatal bleeding, and thromboembolic events were determined within 1 year. A adjusted incidence rate ratios were calculated in a Poisson regression model. A Cox proportional hazards model was used to estimate the risk of the primary outcomes in a landmark analysis in early (0–89 days) and delayed (90–360 days) time periods, and of the secondary outcome within 1 year. For both models treatment regimen was set as a time-varying covariate. This implied that subjects were only considered at risk when taking the corresponding antithrombotic drugs. For sensitivity, a model in which the baseline treatment regimen was used as non–time-dependent exposure was also constructed. All analyses were adjusted for age, sex, year of admission, and PCI as inclusion group, whereas HAS-BLED score was used for bleeding outcomes and CHADS\(_2\) score was used for thromboembolic outcomes. Subjects were censored after 360 days from inclusion, when the follow-up period ended on December 31, 2009 or in the case of death from other causes than the outcome under investigation. The interval 180 to 360 days from inclusion was used as reference when calculating the incidence rate ratios. For the Poisson and Cox model, we tested goodness-of-fit and the proportional hazard assumption, respectively. Both models were investigated for linearity of continuous variables and any significant interactions between the available covariates. None of the assumptions were violated, and no interactions were found. A 2-sided significance level of 0.05 was used. All analyses were performed with SAS statistical package version 9.2 (SAS Institute Inc, NC) and Stata statistical package version 11.0 (StataCorp LP).

Ethics
The Danish Data Protection Agency approved this study (ref: 2007-58-0015, int ref: GEH-2010-001), and data were made available such that individuals could not be identified. Retrospective register studies do not require ethical approval in Denmark.

Results
Population
Selection of the study population and baseline characteristics are summarized in Figure 1 and Table 1, respectively. Of 11 480 subjects in the study, 6993 (60.9%) were males. Mean age was 75.6 years (SD 10.3). The group with MI as inclusion criteria consisted of 8775 (76.4%) subjects, and hereof 1521 (17.3%) had a PCI performed within 1 week, and the solitary PCI group comprised 2705 (23.6%) subjects. Males were ~6 years younger. Almost 10% had a history of bleeding before inclusion, and the mean HAS-BLED score was 2.1 (SD 0.9), and the mean CHADS\(_2\) score was 1.5 (SD 1.5). All regimens containing clopidogrel were more common in patients having a PCI performed regardless of MI status.

Timing and Risk of Bleeding
Figure 2 demonstrates markedly raised crude incidence rates of bleeding immediately after initiation of TT, and TT bleeding rates were higher than for all other regimens regardless of time elapsed. Within 30 days, crude rates were 22.6, 20.3, and 14.3 major bleeding events per 100 person-years for TT, VKA plus single AP, and DAPT, respectively. The adjusted analysis of incidence rate ratios demonstrated that for all types of regimens, with the exception of VKA monotherapy, the risk was frontloaded (Figure 3). An adjusted landmark analysis of risk in early (0–89 days from inclusion) and delayed (90–360 days) time periods also showed continually elevated bleeding risk with TT relative to VKA plus single AP or DAPT (Figure 4). Increased hazard ratios were also seen for TT in comparison with VKA plus clopidogrel but insignificant; early (hazard ratio [HR] 1.37 [0.81;2.31]) and delayed (HR 1.07 [0.66;1.73]) time periods. A cross-sectional view of the study population at days 90 and 180 from discharge showed that 989 (of 9962 subjects at risk) and 719 (of 9076 subjects at risk) were treated with ongoing TT, respectively. Hence, the proportion of subjects on ongoing TT at inclusion, day 90, and day 180 after discharge were 13.0%, 9.9%, and 7.9%, respectively.

Bleeding, Cardiovascular Death, MI, and Stroke During 360 Days of Follow-Up
During a mean follow-up of 288.1 days, 728 (6.3%) subjects experienced nonfatal or fatal bleeding (Table 2), and a total of 2534 (22.1%) events of the combined end point of cardiovascular death, MI, and ischemic stroke showed no significant benefit with TT use (HR 1.15 [0.95;1.40]). Sensitivity Analyses
Our main results of increased early bleeding risk for all regimens were shown to be consistent when baseline treatment regimen was used as non–time-dependent exposure (online-only Data Supplement Figure I). We calculated adjusted incidence rate ratios of subgroups consisting of male/female, elderly (aged >75 years/<75 years), inclusion status (MI or PCI) and CHADS\(_2\) score ≥2 (online-only Data Supplement Figure IIA and IIB). No interactions were found, ie, the risk associated with each treatment regimen was not significantly different between the various subgroups. For
patients with a definite theoretical indication for VKA therapy (ie, 7240 patients with a CHADS2 score ≥2) crude incidence rates of bleeding were similar for all antithrombotic combinations (Table 3).

**Discussion**

Our main finding is that AF patients following MI or PCI are immediately at risk of clinically significant bleeding with recommended TT use. Although the risk decreased over time, the initial elevated risk associated with TT was sustained over time compared to less intensive antithrombotic regimens; indicating no safe therapeutic window of TT in respect to bleeding risk.

Studies of the time-dependent aspect of bleeding risk concerning ongoing combination antithrombotic therapy are scarce and show discrepant results. In 80 PCI patients treated with TT for 1 month, Porter et al10 concluded that TT did not show prohibitively increased bleeding risk. This is in contrast to our results and those of Rogacka et al17 who found that the TT using 1 mg daily showed prohibitive increased bleeding risk. This is in contrast to our results and those of Rogacka et al17 who found that the TT using 1 mg daily showed prohibitive increased bleeding risk.
month. Similarly, in a large AF population treated with warfarin, the bleeding risk was greatest in the first month after initiation and then declined.\textsuperscript{18} Also longer-term bleeding risk with antithrombotic combination therapy shows inconsistency. After follow-up of \(\geq 1\frac{1}{2}\) years, Ruiz-Nodar et al\textsuperscript{12} did not find a substantial increase of bleeding in patients treated with coumarin combined with none, single, or dual antiplatelets after stent implantation in comparison with non-coumarin-treated patients. As previously shown by our group and others, in predominately AF or MI populations,
long-term follow-up of antiplatelets added to VKA are associated with more bleeds.4,5,19 In real-life AF patients experiencing an acute coronary event, the present study reveals a short-term hazard with TT and also VKA plus single AP use that seems most apparent during the first 3 months. Although patients treated with VKA plus clopidogrel had lower bleeding rates than TT, the adjusted analysis could not demonstrate a clear difference that is in concordance with our previous findings. Clinicians should be aware of a similar bleeding hazard for this combination.

In light of the lack of randomized trials, Paikin et al20 performed a meta-analysis of TT in AF patients treated with PCI, which supported the recommendation that short treatment duration should be maintained because of an assumed increased risk with time. The meta-analysis comprised small and highly heterogeneous studies, and the total number of TT patients was smaller (n = 1349) than in our study. Our novel findings, on the contrary, suggest that patients are immediately at risk on top of a continuing threat with the use of TT.

Our study reflects antithrombotic treatment regimens prescribed in everyday practice on a national level and shows that a large proportion of the patients were only prescribed monotherapy at baseline (43.6%). Former observational studies comprise small PCI-only populations with stringent inclusion criteria concerning antithrombotic treatment and, hence, show a high proportion of VKA plus mono or dual antiplatelet therapy subjects.12,21 This difference is readily explained by the additional inclusion of MI patients in the present cohort, and the fact that all regimens including clopidogrel treatment were shown to be more prevalent when a PCI was performed. The latter indicates that a more intense treatment regimen is chosen when patients are seen by an interventional cardiologist. However, our subgroup analysis of PCI subjects did not show these patients’ risks of early bleeding to be any different.

An expected favorable effect was seen for TT on crude incidence rates of the combined end points of cardiovascular death, MI, and ischemic stroke relative to monotherapies and DAPT, but the combination of a VKA plus a single AP actually seemed to perform similarly to TT. This was consistent in the adjusted analysis and was also found in another observational study,21 whereas a systematic review9 endorses TT because of a presumed protection of thromboembolic events. Findings are conflicting, and differences among the included studies are prominent, most notably the focus on AF patients with coronary stents in small single-center registries, whereas the present study holds nationwide data on antithrombotic drug use and outcomes observed in everyday practice. A clear benefit of TT on thrombosis protection in comparison with VKA plus AP in these patients is questionable, and further studies on the optimal treatment type and duration, and patient selection, as well, are warranted.

Table 2. Distribution and Type of Nonfatal and Fatal Bleedings

<table>
<thead>
<tr>
<th>Nonfatal Bleeding, n (%)</th>
<th>Fatal Bleeding, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>38 (5.8)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>221 (33.8)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>109 (16.7)</td>
</tr>
<tr>
<td>Urogenital</td>
<td>120 (18.4)</td>
</tr>
<tr>
<td>Anemia caused by bleeding</td>
<td>165 (25.3)</td>
</tr>
<tr>
<td>Total bleeding events</td>
<td>653</td>
</tr>
</tbody>
</table>

Figure 4. Risk of early and delayed bleeding in a landmark analysis following MI or PCI in AF patients comparing type of antithrombotic treatment regimen. Adjusted for age, sex, year of admission, HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke/thromboembolism, Bleeding history, Labile INR, Elderly [age > 65 years], Drug consumption/alcohol abuse), and PCI inclusion status. MI indicates myocardial infarction; INR, international normalized ratio; PCI, percutaneous coronary intervention; AF, atrial fibrillation; VKA, vitamin K antagonist; and AP, antiplatelet (aspirin or clopidogrel).
reduction of ischemic events but a >4-fold increase of major nonfatal bleedings. These findings on adding rivaroxaban in patients with acute coronary syndrome resemble ours when comparing TT with DAPT (without VKA) on rates of bleeding and ischemic events. However, very-low-dose rivaroxaban showed promising results with no difference in fatal bleeding in comparison with placebo. Short-term very-low-dose rivaroxaban could be a safer choice as part of TT in AF patients with acute coronary syndrome, although a potential trade-off concerning lesser efficient thromboprophylaxis must be investigated.

Strengths and Limitations
The study includes nationwide data, independent of socioeconomic status, race, employment status, and participation in health insurance programs (minimizing selection bias). We did not have clinical information to define the severity of the bleeding episode, but by using a definition of bleeding based on admissions, we presume that this event of bleeding is clinically severe enough to warrant hospitalization. Last, minor bleeding not causing hospitalization or death could not be identified, and therefore our results could underestimate the true risk associated with antithrombotic therapy. However,
ever, our study population reflects real-world patients, in contrast to patients enrolled in a randomized setting who are often highly selected with respect to low bleeding risk, and standardized management protocols are rigorously applied and may not mirror everyday practice.24

Data in the registries have previously been validated, including diagnosis of MI, stroke, and AF.25–27 Several studies demonstrate that choice of antithrombotic treatment shows wide variability.28,29 and, in this present observational study, the primary limitations consist of confounding by indication, ie, we had no knowledge of reasons affecting the physicians’ choice of antithrombotic therapy and hence may confound outcomes. This bias is expected to affect our results on bleeding risk conservatively, ie, more intensive antithrombotic therapy is most likely to be prescribed to healthier patients at a perceived lesser risk of bleeding. Furthermore, we adjusted for prognostic factors for bleeding by the validated HAS-BLED score. Aspirin is available as over the counter and hence not recorded, but chronic aspirin users collect financial reimbursement when prescribed, ensuring high persistence.30 We applied sensitivity analyses to ensure the robustness of our findings. To assess an effect of presumed physician’s choice of treatment during admission, baseline treatment regimen was used as non-time-dependent exposure, and we also found a similar early risk of bleeding in patients with a theoretical indication of VKA therapy (CHADS2 score ≥2). Unmeasured confounders, eg, INR levels, have not been determined, and quality of treatment in a real-life setting is difficult to establish. In a controlled environment, time in therapeutic range in Denmark is high,30 but the bias of residual confounding remains.

**Conclusions**

Our main finding is an immediately high risk of bleeding with recommended TT (with aspirin, clopidogrel, and VKA) after MI or PCI in AF patients that decreases over time. However, the risk was continually elevated in comparison with less intense antithrombotic regimens. Our data of real-life patients suggests that even short-term TT is hazardous in regard to the risk was continually elevated in comparison with less

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**Disclosures**

None.

**References**


CLINICAL PERSPECTIVE

Uncertainty remains regarding optimal antithrombotic treatment of patients with atrial fibrillation presenting with myocardial infarction or undergoing coronary intervention. Present expert statements (Level C evidence) recommend triple therapy with aspirin, clopidogrel, and vitamin K antagonist, with treatment limited to as short a time as possible because of a perceived greater risk of bleeding with prolonged treatment. In the current study, we examined the risk of bleeding associated with different antithrombotic treatment regimens in a nationwide real-life cohort of patients with atrial fibrillation and myocardial infarction and/or coronary intervention. We demonstrated an immediately high risk of bleeding with triple therapy that decreases over time. Nevertheless, the risk was continually elevated in comparison with less intense antithrombotic regimens, which suggests that triple therapy has no safe therapeutic window. No benefit was present for a combined thromboembolic end point of cardiovascular death, myocardial infarction, and ischemic stroke for triple therapy relative to vitamin K antagonist plus a single antiplatelet agent. Until data from randomized trials are available, our results suggest that triple therapy should only be prescribed after careful evaluation of bleeding risk.