Patients with atrial fibrillation undergoing percutaneous coronary intervention

Current concepts and concerns: part I

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KEY WORDS
antithrombotic prophylaxis, atrial fibrillation, coronary artery disease, percutaneous coronary intervention

ABSTRACT
Atrial fibrillation (AF) and coronary artery disease (CAD) often coexist. Both conditions confer an increased risk of acute thrombotic complications. However, the pathogenesis of thrombus development in AF and CAD is different. Coagulation activation is the main pathway in AF, and platelet activation is the hallmark of coronary thrombosis. Antithrombotic prophylaxis is essential in both conditions.

In patients with AF undergoing percutaneous coronary intervention (PCI), a combination of oral anticoagulation and antiplatelet therapy is required, which elevates the risk of major bleeding. This has to be balanced against the risk of stroke and stent thrombosis.

In the first part of the present review, the prerequisites for antithrombotic management in AF patients undergoing PCI are discussed. We cover the epidemiology of concomitant presentation of AF and CAD as well as differences in the pathogenesis of thrombus formation in both conditions. We evaluate data regarding a variety of antithrombotic regimens including triple therapy in line with stroke and bleeding risk assessment.

Overall, triple therapy is often warranted but should be for the shortest possible duration. Although much of the current guidance comes from observational data, well designed, adequately powered randomized clinical trials are emerging to further inform practice in this challenging area.

Introduction
Atrial fibrillation (AF) and coronary artery disease (CAD) often coexist. The pattern of this comorbidity has not changed significantly over the last decade.¹⁻⁵ In 2 recent registries (the EURObservational Research Programme AF [EORP-AF] Pilot General Registry and PREvention of thromboembolic events—European Registry in AF [PREFER in AF]), which together collected prospective data from 16 participating European countries (over 10000 patients), approximately 20% to 35% of the patients were found to have CAD.¹⁻² This was consistent across different types of AF (eg, new onset, paroxysmal, persistent, and permanent).² Up to half of these patients have had myocardial infarction (MI) or undergone coronary revascularization or both.²⁻³ Both AF and CAD confer an increased risk of acute thrombotic complications, that is, stroke or systemic embolism in AF, and acute coronary syndrome, in CAD. In the latter, percutaneous coronary intervention (PCI) with stent implantation is the standard of care.⁶ It is also widely used in patients with stable CAD to relieve symptoms of myocardial ischemia due to flow-limiting coronary disease.⁶⁻⁸ Patients undergoing PCI are at risk of stent thrombosis, particularly in the case of first-generation drug-eluting stents.⁹ Antiproliferative substances profoundly inhibit the reparative response to arterial injury and delay endothelialization, thus leading to persistent prothrombotic and proinflammatory reactions as well as neointimal atherosclerotic change (neoatherosclerosis).¹⁰⁻¹¹

Pathogenesis of thrombosis in atrial fibrillation and coronary artery disease
The pathogenesis of thrombus development in AF and CAD is slightly
24,26-28 The first part of the present review discusses some concerns related to combination antithrombotic therapy in patients with AF who need PCI in the acute or chronic setting (ie, balancing the risk of ischemic and hemorrhagic complications) as well as opportunities to reduce the risks, for example, with a combination of OAC and single antiplatelet therapy in lieu of dual antiplatelet therapy.

Concomitant atrial fibrillation and coronary artery disease

New-onset AF, particularly if uncontrolled, may exacerbate preexisting CAD by causing an abrupt increase in myocardial oxygen demand, leading to ischemia that during sinus rhythm remains compensated. In turn, ion currents are particularly sensitive to oxygen supply, and hypoxia may cause ectopic flow in the atria and generate AF. 29,30 In several studies, either new-onset or pre-existing AF was shown to have a negative impact on prognosis in patients with CAD treated with PCI (TABLE 1). 31-35 AF may result in progressive deterioration of systolic function if heart rate is not controlled. It confers an increased stroke risk and requires OAC (with or without antiplatelets), which, in turn, is associated with a risk of hemorrhage. Despite adjustment for possible confounders, AF appeared to be an independent predictor of death, stroke, and other adverse events. Baseline characteristics of AF patients were usually different from patients in sinus rhythm (eg, older age, worse renal function, lower left ventricular ejection fraction). Hence, it is not always obvious different (FIGURE). Clot structure is known to be affected by the velocity of blood flow and wall shear rates, which vary widely along blood vessels of different caliber and type and were found to reach the highest levels in the arteries, particularly at sites of stenotic lesions. Coagulation activation against the background of low flow, blood stasis, and increased expression of procoagulant factors, leading to fibrin-rich thrombus formation is the main pathway in AF, and platelet activation at sites of vascular injury under high flow resulting in platelet-rich thrombus development is a hallmark of coronary thrombosis. 12-15

This results in differences to antithrombotic prevention, which is essential in both conditions. While patients with nonvalvular AF and 1 additional stroke risk factor (ie, the vast majority of AF population) clearly benefit from oral anticoagulation (OAC), 16-20 notwithstanding a sufficient protective effect of OAC in stable CAD, 21 those with ACS or stable CAD but undergoing stent implantation require antiplatelet therapy (FIGURE). 6

Thus, AF patients undergoing PCI require a period of treatment with OAC and either single or dual antiplatelet therapy to inhibit both pathways, the combination of which increases the risk of major bleeding. 22-25 This must be weighed against the risk of stroke and stent thrombosis. Recent studies have focused on finding the ideal combination of antithrombotic therapy while maintaining efficacy and safety for patients. 22,23

Current guidelines consist mainly of an expert opinion based on observational data, and prospective randomized clinical trials (RCTs) are warranted to inform modern clinical practice. 22,23 As a result, attempts to standardize antithrombotic therapy in AF patients undergoing PCI have proved difficult. 24,26-28

The first part of the present review discusses some concerns related to combination antithrombotic therapy in patients with AF who need PCI in the acute or chronic setting (ie, balancing the risk of ischemic and hemorrhagic complications) as well as opportunities to reduce the risks, for example, with a combination of OAC and single antiplatelet therapy in lieu of dual antiplatelet therapy.

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# TABLE 1  
Studies on impact of atrial fibrillation on prognosis of patients with coronary artery disease

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Population</th>
<th>Clinical outcomes</th>
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<tr>
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<td>death, %</td>
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<td>CV death, %</td>
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<td>MI, %</td>
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<td>TVR, %</td>
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<td>stent thrombosis, %</td>
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<td>ischemic stroke, %</td>
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<td>MACE, %</td>
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<td>major bleeding, %</td>
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<tr>
<td>Chan et al. 2012&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3307</td>
<td>prospective, multicentre</td>
<td>1 month</td>
<td>PCI, AF (prevalent) ACS 64.7%</td>
<td>9.9 / 2.2&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
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<td>Lopes et al. 2009&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5745</td>
<td>post hoc analysis of the APEX-AMI trial (prospective, double-blind, multicentre RCT)</td>
<td>90 days</td>
<td>STEMI, PCI AF (incident) 6.3%</td>
<td>1.81 (1.06–3.09)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lopes et al. 2012&lt;sup&gt;c&lt;/sup&gt;</td>
<td>69255</td>
<td>retrospective, multicentre, ACTION registry</td>
<td>in-hospital stay</td>
<td>STEMI, NSTEMI, AF (prevalent) 7.1% PCI 68.7%</td>
<td>9.9 / 4.2&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pilgrim et al. 2013&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6308</td>
<td>prospective, single-centre</td>
<td>4 years</td>
<td>PCI, DES AF (prevalent) 5.3% ACS 54.5%</td>
<td>22.5 / 9.6&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rene et al. 2014&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3281</td>
<td>post hoc analysis of the HORIZONS-AMI (prospective, open-label, multicentre RCT)</td>
<td>3 years</td>
<td>STEMI, PCI AF (incident) 4.5%</td>
<td>11.9 / 6.3&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
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*a*  event rate in patients with AF vs patients with sinus rhythm, hazard ratios (95% confidence interval) for significant associations when available  
*b*  various definitions across the studies  
*c*  significant difference in event rates  
*d*  in-hospital event rate  
*e*  trend toward between-group difference

Abbreviations: ACS, acute coronary syndrome; ACTION, National Cardiovascular Data Registry’s Acute Coronary Treatment and Intervention Outcomes Network Registry – Get With the Guidelines; AF, atrial fibrillation; APEX-AMI, Assessment of Pexelizumab in Acute Myocardial Infarction; CV, cardiovascular; DES, drug-eluting stents; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; MACE, major adverse cardiac events; MI, myocardial infarction; NR, not reported; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; STEMI, ST-segment elevation myocardial infarction; TVR, target vessel revascularization
whether AF directly affects the clinical course of CAD or merely reflects a poorer baseline state.

In any scenario, AF forces amendments in the management of CAD patients, with the antithrombotic therapy for thromboprophylaxis perhaps being the most challenging area.

**Stroke and bleeding risk assessment** The impact of AF on stroke risk depends on the presence of other vascular risk factors, and appropriate risk stratification is important. The CHA

\[2\] -VASc score is now recommended by the European and other guidelines for decision making with respect to OAC in patients with non-valvular AF. Vascular disease in the CHA

\[2\] -VASc score includes peripheral artery disease, aortic plaque, and prior MI or coronary revascularization. Hence, patients with AF undergoing PCI are at a risk of stroke and require OAC with either a well-adjusted vitamin K antagonist (VKA) or one of novel OACs.

The CHA

\[2\] -VASc score reliably predicts all-cause mortality (hazard ratio [HR], 1.16; 95% confidence interval [CI], 1.02–1.32) and major adverse cardiac and cerebrovascular events (MACCE, defined as composite of all-cause death, MI, target vessel revascularization, definite/probable stent thrombosis, transient ischemic attack or stroke; HR, 1.17; 95% CI, 1.06–1.28) among AF patients undergoing PCI at a risk of stroke and require OAC with either a well-adjusted vitamin K antagonist (VKA) or one of novel OACs. Antithrombotic prevention, of any description is associated with an increased risk of hemorrhage. The HAS-BLED score (TABLE 2) is recommended for the assessment of risk of major bleeding with the score of 3 as a cut-off for high risk. It is important to note that a HAS-BLED score of 3 or higher alone should not be used as a reason to withhold OAC. An elevated HAS-BLED score rather highlights the requirement for closer monitoring (international normalized ratio [INR] in case of anticoagulation with VKAs, kidney function when NOACs are used) and correction of modifiable bleeding risk factors, for example, removal of unnecessary concomitant antiplatelet therapy / nonsteroidal anti-inflammatory drugs; TE, thromboembolism; TIA, transient ischemic attack; PAD, peripheral artery disease; others, see TABLE 1

| TABLE 2 | Stroke and bleeding risk stratification with the CHA

\[2\] -VASc and HAS-BLED scores |
|---|---|---|
| CHA

\[2\] -VASc | Score | HAS-BLED | Score |
| congestive heart failure/LV dysfunction | 1 | hypertension (systolic blood pressure > 160 mmHg) | 1 |
| hypertension | 1 | abnormal renal or liver function | 1 or 2 |
| age ≥75 years | 2 | stroke | 1 |
| diabetes mellitus | 1 | bleeding tendency or predisposition | 1 |
| stroke/TIA/TE | 2 | labile INRs (if on warfarin) | 1 |
| vascular disease (prior MI, PAD, or aortic plaque) | 1 | age (eg., >65, frail condition) | 1 |
| aged 65–74 years | 1 | drugs (eg, concomitant antiplatelet or NSAIDs) or alcohol excess/abuse | 1 or 2 |
| sex category (ie, female) | 1 | | |
| maximum score | 9 | 9 |

a CHA

\[2\] -VASc: heart failure (moderate-to-severe left ventricular systolic dysfunction refer to left ventricular ejection fraction ≤40% or recent decompensated heart failure requiring hospitalization), hypertension, age ≥75 years, diabetes, stroke/TIA, vascular disease (specifically, myocardial infarction, complex aortic plaque, and peripheral artery disease), age 65–74 years, female sex

b HAS-BLED: uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly patients (eg, age >65 years, frail condition), drugs (eg, antiplatelet, NOACs)/excessive alcohol

Abbreviations: INR, international normalized ratio; LV, left ventricular; NSAIDs, nonsteroidal anti-inflammatory drugs; TE, thromboembolism; TIA, transient ischemic attack; PAD, peripheral artery disease; others, see TABLE 1

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- The HAS-BLED score is simple, practical, and has been well-validated in multiple cohorts; however, in AF patients undergoing PCI, combined multiple antithrombotic drugs are likely to interfere with its predictive ability. Thus, it should be used for the assessment of baseline bleeding risk to define the most appropriate combination and duration of antithrombotic therapy.

- Once combination therapy has been started, the HAS-BLED score appears to be less useful and shows inconsistent performance. In a retrospective analysis of a cohort with ACS who received OAC in addition to dual antiplatelet therapy due to various indications (predominantly AF and apical akinesia), the HAS-BLED score reliably predicted spontaneous bleeding events with a c statistic of 0.67 (95% CI, 0.54–0.79). More contemporary data from the AFCAS registry showed no statistically significant difference in hemorrhage between distinct risk strata as classified via the HAS-BLED score as well as other
available bleeding risk assessment schemes (eg, HEMORR.HAGES, ATRIA, etc.)]. This is not unexpected since the HAS-BLED score was derived and validated in cohorts of “stable” anticoagulated AF patients.36,37

ACS-specific risk scores such as the GRACE 2.0 ACS Risk Calculator44-46 for predicting death or death/MI following an initial ACS, CRUSADE score47,48 for bleeding risk assessment, and stent thrombosis scores36,37 may be used; however, they have not been validated in AF cohorts and do not impact on decision making with respect to antithrombotic management in AF patients undergoing PCI.

Overall, the vast majority of AF patients undergoing PCI have a high risk both for stroke and major bleeding.31 Thus, antithrombotic therapy in this group of patients has to carefully balance thromboembolism versus bleeding.

Triple antithrombotic therapy: is there an alternative? Triple antithrombotic therapy (namely OAC in combination with dual antiplatelet therapy) for patients with AF undergoing PCI developed as a result of OAC is indicated for AF patients, and dual antiplatelet therapy is indicated for ACS patients.7,8,16,22,24 It is also supported by the pathology of clot formation and is generally deemed to be appropriate but until recently has not been tested in an RCT.12-15

However, adding antiplatelet agents on top of OAC inevitably results in elevation of bleeding risk.52-54 In a large analysis from the nationwide Danish registry including over 80,000 AF patients, HRs of fatal or nonfatal bleeding were as follows: 1.66 (95% CI, 1.34–2.04) for dual antiplatelet therapy; 1.83 (95% CI, 1.72–1.96) for warfarin and aspirin; 3.08 (95% CI, 2.32–3.91) for warfarin and clopidogrel, and 3.70 (95% CI, 2.89–4.76) for triple therapy versus warfarin monotherapy as a reference.52 Consistent results were obtained in the meta-analysis included 18 studies with patients receiving triple therapy after PCI and stenting: odds ratio (OR), 2.38; 95% CI, 1.05–5.38 at 30 days, and 2.87; 95% CI, 1.47–5.62 at 6 months compared with dual antiplatelet therapy.53

Studies on triple therapy in AF patients undergoing PCI are mostly observational, often retrospective, single-centre, and hence underpowered to reveal a difference in event rates between groups with different strategies of antithrombotic therapy. The proportion of AF and ACS patients included, event definitions and follow-up duration also varied widely. In the absence of robust evidence finding the equilibrium between the risk of serious bleeding on the one hand, and stroke, recurrent cardiac ischemia, stent thrombosis on the other, is particularly challenging.

There have been plenty of such studies weighing pros and cons of triple antithrombotic therapy against other antithrombotic regimens (Supplementary material online, Table S1) as well as a few meta-analyses (Table 3) that have been published.

Dual antiplatelet therapy with aspirin and clopidogrel is inferior to triple antithrombotic therapy in AF patients undergoing PCI particularly for ischemic stroke. Strokes in AF are usually severe and associated with poorer outcomes compared with non-AF-related strokes. Thus, OAC cannot be omitted. OAC was beneficial even in patients with high bleeding risk (HAS-BLED score ≥5) and octogenarians: subsets of patients in whom OAC is often withheld by clinicians for fear of bleeding complications, particularly intracranial hemorrhage, even in chronically anticoagulated patients with no need for combination antithrombotic therapy.51,56

The choice between triple therapy and OAC plus single antiplatelet is less well-defined. The WOEST trial (What is the Optimal antiplatE-let and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) was open-label, intention-to-treat RCT, in which triple therapy was compared with double therapy of OAC and clopidogrel (thus omitting aspirin).58

At 1-year follow-up, lower bleeding and mortality rates were revealed in the warfarin-plus-clopidogrel arm compared with the triple-therapy arm (HR, 0.36; 95% CI, 0.26–0.50, and HR, 0.39; 95% CI, 0.16–0.93, respectively) with no significant differences in the rate of thrombotic events.58 However, the WOEST trial had many limitations. First, the lower bleeding rate with dual therapy was driven by a reduction of minor bleeding

### Table 3: Meta-analyses on efficacy and safety of triple antithrombotic therapy versus dual antiplatelet therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention with stent implantation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of studies included</th>
<th>Clinical outcomes, odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gao et al. 2011</td>
<td>9</td>
<td>MACE: 0.29 (0.15–0.58), ischemic stroke: 0.84 (0.57–1.23), MI: 1.20 (0.63–2.27), all-cause death: 1.60 (0.42–0.86), major bleeding: 2.00 (1.41–2.83)</td>
</tr>
<tr>
<td>Saheb et al. 2013</td>
<td>10</td>
<td>MACE: 0.76 (0.54–1.07), ischemic stroke: 0.27 (0.13–0.57), MI: 0.57 (0.22–1.50), all-cause death: NR, major bleeding: 0.57 (0.22–1.78)</td>
</tr>
<tr>
<td>Zhao et al. 2011</td>
<td>9</td>
<td>MACE: 0.60 (0.42–0.86), ischemic stroke: 0.38 (0.12–1.22), MI: NR, all-cause death: 0.59 (0.39–0.90), major bleeding: 2.12 (1.05–4.29)</td>
</tr>
</tbody>
</table>

Abbreviations: MACE, major adverse cardiovascular events (composite of death, myocardial infarction/reinfarction, stent thrombosis, target vessel revascularization, stroke, and bleeding); others, see Table 1

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**Review Article**

Patients with atrial fibrillation undergoing percutaneous coronary intervention...
Supplementary material online Supplementary material online is available with the online version of the paper at www.pamw.pl.

REFERENCES


REFERENCES

1. Patients with atrial fibrillation undergoing percutaneous coronary intervention...


ARTYKUŁ POGŁĄDOWY

Przezskórne interwencje wieńcowe u chorych z migotaniem przedsionków

Aktualne koncepcje i obawy: część 1

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SŁOWA KLUCZOWE
choroba wieńcowa,
migotanie
przedsionków,
profilaktyka
przeciwcarkowowa,
przezskórna
interwencja
wieńcowa

STRESZCZENIE
Migotanie przedsionków (atrial fibrillation – AF) i choroba wieńcowa (coronary artery disease – CAD) często współistnieją. Oba stany niosą zwiększone ryzyko ostrych powikłań zakrzepowych, jednak patogeneza powstawania zakrzepu w AF i w CAD jest odmienna. W AF głównym szlakiem jest aktywacja kaskady krzepnięcia, natomiast w zakrzepicy wieńcowej kluczową rolę odgrywa aktywacja płytek. W obu stanach podstawowe znaczenie ma profilaktyka przeciwzakrzepowa.

U chorych z AF poddawanych przeszkórnej interwencji wieńcowej (percutaneous coronary intervention – PCI) konieczne jest kojarzenie doustnych antykoagulantów i leków przeciwpłytkowych, co zwiększa ryzyko poważnego krwawienia. Trzeba je odnieść do ryzyka udaru i zakrzepicy w stenie.

W części 1 niniejszego przeglądu przeanalizowano wymogi leczenia przeciwzakrzepowego u chorych z AF poddawanych PCI. Omówiono epidemiologię współwystępowania AF i CAD, a także różne w patogenezie zakrzepicy w obu stanach. Poddano ocenie dane dotyczące różnych wariantów leczenia przeciwzakrzepowego, w tym terapii potrójnej, w aspekcie oceny ryzyka krwawienia i udaru.

Ogólnie – terapia potrójna jest często uzasadniona, ale powinna być stosowana jak najkorzej. Większość aktualnych zaleceń opiera się na danych obserwacyjnych, ale pojawiają się dobrze zaplanowane, o odpowiedniej mocy badania z randomizacją, które pozwolą nam poszerzyć wiedzę w tej trudnej dziedzinie.
| Study | Fit | Design | Follow-up | Population | Compared regimes | Clinical outcomes* | TT/DAPT | TT/DAPT/OAC+ASA | TT/DAPT/OAC+ATe | TT/DAPT vs. DAPT | TT/DAPT/OAC+ASA vs. DAPT | TT/DAPT/OAC+ATe vs. DAPT | TT-OAC+ATe vs. OAC+ATe | TT-OAC+ATe vs. TT/DAPT | TT-OAC+ATe vs. TT/DAPT/OAC+ASA | TT-OAC+ATe vs. TT/DAPT/OAC+ASA | TT-OAC+ATe vs. TT/DAPT/OAC+ASA | TT-OAC+ATe vs. TT/DAPT/OAC+ASA | TT-OAC+ATe vs. TT/DAPT/OAC+ASA | TT-OAC+ATe vs. TT/DAPT/OAC+ASA |
|-------|-----|--------|-----------|------------|------------------|-------------------|--------|----------------|----------------|-----------------|----------------------|---------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Bernard et al. 2013† | 417 | retrospective, single-center | 650 days | AF, PCI-S | ACS 61.9% | OAC+no OAC at discharge | 6.3/4 | NR | NR | 5.2/11.0 | NR | 5.2/13.4 | NR | 5.2/9.1 | 23.7/15.9 | 0.58 (0.21–1.50) |
| Caballero et al. 2013† | 604 | retrospective, two-center | 17 months | AF, PCI-S | ACS 75.8% | octetage 15.1% | 20.9/21.2 | 9.7/15.4 | NR | 22.2/24.4 | 3.79 (0.83–14.50) | NR | 20.6/25.0 | NR | NR | NR | 8.9/18.8 | 28.9/34.2 | 4.30 (1.26–14.56) |
| Ceballos et al. 2013† | 104 | prospective, single-center | 1 year | AF, PCI-S | ACS NR | TT/DAPT | 11.1/16.9 | 27.6/10.3 | 38.8/17.2 | 0.138 | NR | 2.2/19.4 | NR | 0/0 | NR | NR | NR | 8.9/18.8 | 28.9/34.2 | 4.30 (1.26–14.56) |
| De Witte et al. 2013‡ | 573 | retrospective, multicenter | 1 year | PO-S | AF 69% | ACS NR | TT/DAPT/clopidogrel | 5.6/3.2 | NR | 44.9/14.8 | 0.36 (0.26–0.50) | 6.3/5.0 | 0.39 (0.16–0.53) | 2.5/1.1 | 3.4/11.1 | 0.6/7.2 | 3.2/1.4 | 0.0 | 2.05 (0.05–1.17) | NR | NR | 94.2/20.9 |
| Fowler et al. 2013¶ | 1948 | retrospective, multicenter | 1 year | AF, NSTEMI, PO-S | TT/DAPT | 15.5/12.8 | 1.29 (0.96–1.74) | NR | NR | 12.6/13.3 | NR | 4.6/3.2 | NR | NR | 1.6/2.2 | NR | NR |
| Ge et al. 2010 †‡ | 622 | prospective, single-center | 1 year | AF, DES | ACS NR | TT/DAPT+AS/A † | 2.9/1.2 | 2.8/3.5 | 11.6/5.1 | 11.6/5.7 | 4.4/5.8 | NR | 2.3/3.8 | NR | 5.9/4.2 | NR | NR |
| Giard et al. 2009† | 359 | prospective, single-center | 1 year | PO-S | AF 69% | ACS NR | TT/DAPT | 5.6/2.1 | NR | 18.4/10.6 | 85.6 | 4.0/2.4 | 2.85/4.5 | 8.0 | 1.6/1.7 | 0.83 | 0.6/0 | NR |
| He et al. 2013‡ | 602 | retrospective, two-center | 2 years | AF, PCI-S | ACS NR | TT/DAPT | 24.2/20.4 | NR | NR | 16.5/3 | (CHADS2 <2) | 11.4/10.3 | (CHADS2 >2) | 5.0/4.3 | NR | NR | NR | NR |
| Mulheren et al. 2012‡ | 640 | prospective, single-center | 1 year | AF, PCI-S | ACS NR | TT/DAPT | 5.4 | NR | NR | 64.1 | 3.9 | 8.4/0 | NR | NR | NR | 1.1/1.3 | NR | 12.7/3 |
| Palleschi et al. 2007‡ | 478 | prospective, multicenter | 1 year | PO-S | AF 35% | ACS 53.8% | TT/DAPT | 8.3/2.9 | 3.3/1.3 | 8.4/0 | NR | NR | NR | NR | NR | NR | 11.0/7.5 | 4.1/1.3 | 3.22/1.6 | 3.0 (8.8–12.1) | NR | NR |
| Lamberti et al. 2013‡ | 12195 | retrospective, nationwide | 1 year | AF, PCI-S | ACS 77.4% | TT/DAPT+ASA | 14.3/6.9 | 70.9 | 2.0/0.6 | 6.61 (0.47–10.75) | 0.54 (0.35–0.76) | 2.5/7.5/3.9 | 10.14/8.4 | 2.2 (1.0–4.3) | NR | NR | 4.1/6.2 | 0.8 (0.46–0.98) | 0.81 (0.81–1.00) | 0.05 (0.28–0.95) | NR | NR |
| Reusen et al. 2008‡ | 254 | prospective, single-center | 18 months | PO-S | AF 66% | ACS 78% | TT/DAPT | 2.9 | 7/2.9 | 10.8/6 | 2.9/1.0 | 1/1 | 16.2/21.3/7.9 | 10.9/11.0 | 0.83 (0.68–1.00) | 0.78 (0.68–0.89) | 0.56 (0.46–0.79) | NR | NR | 13.0/26.4 | 2.1 (3.3–8.3) |
| Rabbioli et al. 2012‡ | 632 | prospective, single-center | 1 year | PO-S | AF 50% | ACS 69% | TT/DAPT+ASA | 5.0/2.0 | 2/8 | NR | 9.8/5.1 | 0.10 | 2/2 | 12.3/10.3 | 11.9 | 2.7/1.2 | 11.4/1.1 | 1.0/1.1 | NR | NR |
| Rico-Posel et al. 2008‡ | 426 | retrospective, two-center | 644 days | PO-S | ACS 83.8% | TT/DAPT | 14.0/9.5 | 12.6/0.0 | NR | 17.6/2.7 | NR | 11.3/5.9 | 7/1.8 | 1.2/1.3 | NR | NR | 1.18/0.9 | NR | 26.5/21.7 | 4.9 (2.17–11.09) |
| Rico-Posel et al. 2012‡ | 426 | retrospective, two-center | 1 year | AF, PCI-S | ACS 83.6% | TT/DAPT | 11.0/4.0 | 3.3/1 (2.7–3.8) | NR | NR | 9.5/1.0 | 0.10 | 9.4/10.9 | NR | NR | NR | NR | NR | 13.0/26.4 | 0.48 (0.29–0.77) |
| Sambo et al. 2009‡ | 405 | prospective, single-center | 6 months | PO-S | AF 67% | ACS NR | TT/DAPT+ASA | 4.5/1.2 | 11.2/2.6 | 5.5/3.7 | 11.5/3.7 | 4.6/7 | 3.9/4.3 | 4.6/8.7 | 0.21/2.2 | 3.2/1/2.2 | 0.3/1/2.2 | 7.8/12.7 |
| Smith et al. 2012‡ | 318 | retrospective, single-center | 1 year | ACS, PCI-S | AF 19.5% | TT/DAPT | 13.4/3.0 | NR | NR | 4.5/2.5 | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Uchida et al. 2010‡ | 575 | prospective, single-center | 458 days | DES | AF 5% | ACS 39.1% | TT/DAPT | 20.2 | 7.8 | 0.02 (3.34–19.15) | 20.8 | 19.8 | 0.8 | NR | NR | NR | NR | NR | NR | NR |

**Note:** For a list of references, see the main article.

**Abbreviations:** ACS, acute coronary syndrome; AT, single antiplatelet therapy; AF, atrial fibrillation; ASA, acetylsalicylic acid; CHADS2, congestive heart failure, hypertension, age, diabetes, stroke; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; MAG/CIE, major adverse cardiac (and cerebral) events; MI, myocardial infarction; NR, not reported; NSTEVA, non-ST-segment elevation myocardial infarction; OAC, oral anticoagulation; PCI-S, percutaneous coronary intervention (with stenting); RCT, randomized controlled trial; SE, systemic embolism; TT, triple antithrombotic therapy; TVR, target vessel revascularization.