Safety and efficacy of double vs. triple antithrombotic therapy in patients with atrial fibrillation with or without acute coronary syndrome undergoing percutaneous coronary intervention: a collaborative meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials

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Aims

Safety and efficacy of antithrombotic regimens in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) may differ based on clinical presentation. We sought to compare double vs. triple antithrombotic therapy (DAT vs. TAT) in AF patients with or without acute coronary syndrome (ACS) undergoing PCI.

Methods and results

A systematic review and meta-analysis was performed using PubMed to search for non-vitamin K antagonist (NOAC)-based randomized clinical trials. Data on subgroups of ACS or elective PCI were obtained by published reports or trial investigators. A total of 10,193 patients from four NOAC trials were analysed, of whom 5,675 presenting with ACS (DAT = 3,063 vs. TAT = 2,612) and 4,518 with stable coronary artery disease (SCAD; DAT = 2,421 vs. TAT = 2,097). The primary safety endpoint of ISTH major bleeding or clinically relevant non-major bleeding was reduced with DAT compared with TAT in both ACS (12.2% vs. 19.4%; RR 0.63, 95% CI 0.56–0.71; *P* < 0.0001; *I*² = 0%) and SCAD (14.6% vs. 22.0%; RR 0.68, 95% CI 0.55–0.85; *P* = 0.0008; *I*² = 66%), without interaction (*P*-int = 0.54). Findings were consistent for secondary bleeding endpoints, including intra-cranial haemorrhage. In both subgroups, there was no difference between DAT and TAT for all-cause death, major adverse cardiovascular events, or stroke. Myocardial infarction and stent thrombosis were numerically higher with
DAT or TAT based on clinical presentation

**Outcomes and Conclusions**

DAT vs. TAT consistently in ACS and SCAD (P-int = 0.60 and 0.86, respectively). Findings were confirmed by multiple sensitivity analyses, including a separate analysis on dabigatran regimens and a restriction to PCI population.

**Conclusions**

DAT, compared with TAT, is associated with lower bleeding risks, including intra-cranial haemorrhage, and a small non-significant excess of cardiac ischaemic events in both patients with or without ACS.

**Keywords**

Atrial fibrillation (AF) • Percutaneous coronary intervention (PCI) • Double therapy (DAT) • Triple therapy (TAT) • Non-vitamin K antagonist oral anticoagulant (NOAC) • Acute coronary syndrome (ACS)

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**Introduction**

The optimal antithrombotic strategy for patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) remains debated.1–5 Four multicentre trials, focusing on AF patients undergoing PCI or with acute coronary syndromes (ACS), showed that double antithrombotic therapy (DAT) consisting of a non-vitamin K antagonist (VKA) oral anticoagulant (NOAC) plus a P2Y12 inhibitor (essentially clopidogrel) reduced bleeding complications without apparent increase in ischaemic risk compared with triple antithrombotic therapy (TAT), consisting of a VKA and dual antiplatelet therapy (DAPT).6–9 However, individual trials were powered for safety and not for efficacy and a recent pooled analysis of these four trials observed that the bleeding benefit was counterbalanced by a significant increase of stent thrombosis (ST) and a trend towards higher risk of myocardial infarction (MI) with DAT.10 All these trials have enrolled a variable number of AF patients with ACS or stable coronary artery disease (SCAD). The bleeding and ischaemic risks, as well as the optimal antithrombotic therapy, might differ according to the clinical presentation. We therefore investigated the safety and efficacy of DAT vs. TAT in AF patients undergoing PCI or affected by ACS according to the clinical presentation among the four NOAC-based randomized clinical trials.

**Methods**

The present systematic review and meta-analysis integrates the previous one by adding a stratification based on clinical presentation (ACS vs. SCAD).10 Data on clinical events in these subgroups were extracted from published reports or provided by investigators. A full description of the methodology was previously published.10 Briefly, a systematic search was performed on PubMed and led to identify four NOAC-based randomized clinical trials comparing DAT vs. TAT in AF patients with ACS or undergoing PCI, including AUGUSTUS (Open-Label, 2 × 2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention), ENTRUST-AF PCI (Edoxaban vs. VKA in pPCI with AF undergoing PCI), PIONEER-AF PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention), and RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Non-valvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention). The protocol followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines and was registered on PROSPERO (CRD42019142779).

**Outcome measures**

The primary safety bleeding endpoint was defined as ISTH major bleeding or clinically relevant non-major bleeding (CRNMB) at longest available follow-up (between 6 and 14 months). Secondary safety outcomes included alternative bleeding definitions (trial-defined primary safety bleeding endpoint; ISTH major bleeding, ISTH CRNMB, TIMI major or minor bleeding, intra-cranial haemorrhage).

Secondary efficacy endpoints included all-cause death; trial-defined major adverse cardiovascular event (MACE), MI, stroke, and ST. Main endpoint definitions are displayed in Supplementary material online, Table S1.

**Statistical analysis**

Effect sizes in the overall population and ACS and SCAD subgroups were calculated with the Mantel–Haenszel random-effects estimator and expressed as risk ratios (RRs) and 95% CIs. Heterogeneity was assessed by I² tests, with substantial heterogeneity defined as I² >50%. Number needed to treat for benefit (NNTB) or harm (NNTH) were also calculated according to Cochrane’s recommendations: (1/ACR × (1-RR)), where ACR is the assumed control risk. Sensitivity analyses were performed to: (i) investigate the influence of individual trials on the results; (ii) test results with a fixed-effect model; (iii) investigate separately the doses of dabigatran 110 mg and 150 mg b.i.d. for the RE-DUAL PCI trial; and (iv) restrict the analysis to PCI only (due to the peculiar design of the AUGUSTUS trial, a secondary analysis on PCI population was also conducted by excluding patients presenting with ACS and managed medically).

As previously described, the methodological quality of the randomized trials was assessed by Cochrane’s Collaboration tool for assessing risk of bias (low, unclear, or high risk of bias) and no publication bias was assessed due to the small number of studies (<10) included. Statistical significance was set at P < 0.05 (2-tailed). Data analysis was performed with Reviewer Manager (RevMan, version 5.3; Cochrane).

**Results**

Overall 10 193 patients (DAT = 5484 vs. TAT = 4709) from the four trials were analysed, of whom 5675 presented with ACS (DAT = 3063 vs. TAT = 2612) and 4518 with SCAD (DAT = 2421 vs. TAT = 2097).

The characteristics of the four included trials and of patients are reported in Supplementary material online, Tables S1 and S2. All trials were of high quality (Supplementary material online, Table S3).
Safety endpoints

The primary safety bleeding endpoint of ISTH major bleeding or CRNMB was significantly reduced with DAT compared with TAT in both ACS (12.2% vs. 19.4%; RR 0.63, 95% CI 0.56–0.71; P < 0.0001; I² = 0%) and SCAD (14.6% vs. 22.0%; RR 0.68, 95% CI 0.55–0.85; P = 0.0008; I² = 66%) without interaction (interaction P = 0.54; Figure 1). In both ACS and SCAD subgroups, this benefit was consistently driven by reductions of both major (ACS: 3.9% vs. 6.4%; RR 0.60, 95% CI 0.48–0.75; P < 0.0001; I² = 0%; SCAD: 4.4% vs. 6.4%; RR 0.69, 95% CI 0.53–0.88; P = 0.004; I² = 0%; interaction P = 0.42) and CRNMB (ACS: 9.1% vs. 14.3%; RR 0.64, 95% CI 0.56–0.75; P < 0.0001; I² = 0%; SCAD: 11.5% vs. 16.6%; RR 0.71, 95% CI 0.57–0.90; P = 0.004; I² = 56%; interaction P = 0.48; Figures 1 and 2). The results remained consistent when alternative bleeding definitions were adopted (Figure 3). DAT was associated with a borderline 43% reduction of intra-cranial haemorrhage (P = 0.06, Figure 2) compared with TAT, with consistent effects among ACS (0.31% vs. 0.53%; RR 0.89–1.51; P = 0.26; I² = 0%) and SCAD patients (0.38% vs. 0.83%; RR 0.49, 95% CI 0.22–1.09; P = 0.08; I² = 0%; interaction P = 0.83; Figure 2).

Efficacy endpoints

In both ACS and SCAD subgroups, there was no significant difference between DAT and TAT for all-cause death (ACS: 4.5% vs. 4.0%; RR 1.13, 95% CI 0.88–1.45; P = 0.34; I² = 0%; SCAD: 3.5% vs. 3.3%; RR 1.05, 95% CI 0.77–1.44; P = 0.75; I² = 0%; interaction P = 0.73; Figure 4), MACE (ACS: 9.6% vs. 8.9%; RR 1.08, 95% CI 0.92–1.27; P = 0.36; I² = 0%; SCAD: 7.3% vs. 6.9%; RR 1.06, 95% CI 0.86–1.32; P = 0.56; I² = 0%; interaction P = 0.92; Figure 4) and stroke (ACS: 1.3% vs. 1.3%; RR 0.93, 95% CI 0.55–1.56; P = 0.78; I² = 13%; SCAD: 0.9% vs. 0.8%; RR 1.15, 95% CI 0.59–2.21; P = 0.68; I² = 0%; interaction P = 0.62; Figure 4). The rates of MI and ST were slightly but not significantly higher with DAT in both ACS: (4.4% vs. 3.7%; RR 1.16, 95% CI 0.89–1.51; P = 0.26; I² = 0% and 1.1% vs. 0.7%; RR 1.59, 95% CI 0.89–2.87; P = 0.12; I² = 0%; respectively) and SCAD groups (2.8% vs. 2.1%; RR 1.31, 95% CI 0.89–1.93; P = 0.16; I² = 0%; interaction P = 0.60 and 0.8% vs. 0.6%; RR 1.46, 95% CI 0.70–3.06; P = 0.31; I² = 0%; respectively; interaction P = 0.86; Figure 5).

Additional analyses

Bleeding endpoints remained consistent across clinical presentation subgroups when dabigatran 110 or 150 mg were analysed separately (Supplementary material online, Figures S1–S6). Ischaemic endpoints showed consistent results when dabigatran 110 or 150 mg were analysed separately (Supplementary material online, Figures S7–S11), although DAT with dabigatran 110 mg seemed to be associated with somewhat greater MI and ST risks in ACS but not SCAD patients (Supplementary material online, Figures S10 and S11).

Results remained consistent when AUGUSTUS patients with ACS not undergoing PCI were excluded (Supplementary material online, Figures S12–S16), although the benefit of DAT in the ACS subgroup in terms of intra-cranial haemorrhage became greater (Supplementary material online, Figure S13) as the risk of MI, while the risk of ST slightly reduced (Supplementary material online, Figure S16).

When removing one study at a time, consistent results between ACS and SCAD subgroups were confirmed for the primary bleeding endpoint (Supplementary material online, Table S4). Results remained consistent when a fixed-effects model was adopted (Supplementary material online, Table S5).

The NNNT and NNTH were calculated for safety and efficacy endpoints in both ACS and SCAD (Supplementary material online, Table S6). We also calculated NNNT and NNTH for multiple risk strata for both ISTH major bleeding and MI and analysed the net benefit (NNNT<NNTH) or harm (NNNT>NNTH) in ACS and SCAD subgroups, observing that DAT had greater benefit than harm in ACS patients but not for SCAD patients in whom the bleeding benefit did not seem to exceed the higher MI rates (Figure 6; Supplementary material online, Tables S7 and S8).

Discussion

In the present meta-analysis of the four NOAC-based multicentre randomized clinical trials, we investigated the safety and efficacy profile of DAT vs. TAT in 10 193 AF patients undergoing PCI according to clinical presentation (ACS or SCAD).

Main findings are summarized as follows (Figure 7):

- There was no difference in the treatment effects with respect to primary and secondary bleeding endpoints between ACS and SCAD patients treated with DAT or TAT, confirming a consistent reduction of bleeding with DAT in patients with or without ACS.
- There was no difference in treatment effects with respect to any cardiac or cerebrovascular ischaemic outcome between ACS and SCAD patients treated with DAT vs. TAT, suggesting that the small numerically higher rates of non-fatal cardiac ischaemic events with DAT may occur irrespective of the clinical presentation.

Aspirin has represented for decades the cornerstone for antipla-
ischaemic events compared with SCAD patients and benefit more from prolonged DAPT duration, suggesting that a more potent and/or prolonged DAPT is beneficial among ACS patients.13 Thus, clinical presentation is an important driver for the decision-making on type and duration of DAPT.4 In patients with AF undergoing PCI, who require oral anticoagulation for the prevention of thrombo-embolic complications, the balance of benefits and risks of different antithrombotic regimens is more complex and the supporting evidence

### ISTH MAJOR OR CLINICALLY RELEVANT NONMAJOR BLEEDING

| Study or Subgroup | DAT | TAT | Risk Ratio | Risk Ratio |
|-------------------|-----|-----|------------|------------|
|                  | Events | Total | Events | Total | Weight | M–H, Random, 95% CI | M–H, Random, 95% CI |
| ACS               |       |       |       |       |       |                   |                   |
| AUGUSTUS          | 115   | 1410  | 194   | 1378  | 15.0%  | 0.58 [0.47, 0.72]  |                     |
| ENTRUST AF–PCI    | 59    | 388   | 79    | 389   | 9.7%   | 0.75 [0.55, 1.02]  |                     |
| PIONEER AF–PCI    | 56    | 355   | 88    | 359   | 10.0%  | 0.64 [0.48, 0.87]  |                     |
| RE–DUAL PCI       | 155   | 900   | 132   | 475   | 16.2%  | 0.62 [0.51, 0.76]  |                     |
| Subtotal (95% CI) | 3053  | 2601  | 51.0% | 0.63 [0.56, 0.71] |                     |
| Total events      | 385   | 493   |       |       |                   |                   |
| Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.83, df = 3 (P = 0.61); I^2 = 0% |
| Test for overall effect: Z = 7.42 (P < 0.00001) |

| SCAD              |       |       |       |       |       |                   |                   |
| AUGUSTUS          | 89    | 864   | 170   | 888   | 13.6%  | 0.54 [0.42, 0.68]  |                     |
| ENTRUST AF–PCI    | 69    | 363   | 73    | 366   | 10.3%  | 0.95 [0.71, 1.28]  |                     |
| PIONEER AF–PCI    | 51    | 334   | 77    | 324   | 9.2%   | 0.64 [0.47, 0.88]  |                     |
| RE–DUAL PCI       | 150   | 844   | 132   | 505   | 16.0%  | 0.68 [0.55, 0.84]  |                     |
| Subtotal (95% CI) | 2405  | 2083  | 49.0% | 0.68 [0.55, 0.85] |                     |
| Total events      | 359   | 452   |       |       |                   |                   |
| Heterogeneity: Tau^2 = 0.03; Chi^2 = 8.81, df = 3 (P = 0.03); I^2 = 66% |
| Test for overall effect: Z = 3.37 (P = 0.0008) |

### ISTH MAJOR BLEEDING

| Study or Subgroup | DAT | TAT | Risk Ratio | Risk Ratio |
|-------------------|-----|-----|------------|------------|
|                  | Events | Total | Events | Total | Weight | M–H, Random, 95% CI | M–H, Random, 95% CI |
| ACS               |       |       |       |       |       |                   |                   |
| AUGUSTUS          | 37    | 1410  | 58    | 1378  | 17.5%  | 0.62 [0.42, 0.94]  |                     |
| ENTRUST AF–PCI    | 21    | 388   | 24    | 389   | 8.9%   | 0.88 [0.50, 1.55]  |                     |
| PIONEER AF–PCI    | 14    | 355   | 23    | 359   | 6.8%   | 0.62 [0.32, 1.18]  |                     |
| RE–DUAL PCI       | 51    | 900   | 55    | 475   | 21.6%  | 0.40 [0.34, 0.70]  |                     |
| Subtotal (95% CI) | 3053  | 2601  | 54.8% | 0.60 [0.48, 0.75] |                     |
| Total events      | 123   | 160   |       |       |                   |                   |
| Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.96, df = 3 (P = 0.40); I^2 = 0% |
| Test for overall effect: Z = 4.40 (P < 0.00001) |

| SCAD              |       |       |       |       |       |                   |                   |
| AUGUSTUS          | 28    | 864   | 50    | 888   | 14.0%  | 0.58 [0.37, 0.91]  |                     |
| ENTRUST AF–PCI    | 24    | 363   | 24    | 366   | 9.6%   | 1.01 [0.58, 1.74]  |                     |
| PIONEER AF–PCI    | 13    | 334   | 23    | 324   | 6.5%   | 0.55 [0.28, 1.06]  |                     |
| RE–DUAL PCI       | 41    | 844   | 35    | 505   | 15.0%  | 0.70 [0.45, 1.09]  |                     |
| Subtotal (95% CI) | 2405  | 2083  | 45.2% | 0.69 [0.53, 0.88] |                     |
| Total events      | 106   | 132   |       |       |                   |                   |
| Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.93, df = 3 (P = 0.40); I^2 = 0% |
| Test for overall effect: Z = 2.91 (P = 0.004) |

### Figure 1
Main bleeding endpoints in double antithrombotic therapy vs. triple antithrombotic therapy according to clinical presentation. Random-effects risk ratios and 95% confidence intervals for main bleeding endpoints. DAT, double antithrombotic therapy; ISTH, International Society on Thrombosis and Haemostasis; M–H, Mantel–Haenszel; TAT, triple antithrombotic therapy.
CLINICALLY RELEVANT NONMAJOR BLEEDING

| Study or Subgroup | DAT | TAT | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|-------------------|-----|-----|--------|-------------------------------|-------------------------------|
| **ACS**           |     |     |        |                               |                               |
| AUGUSTUS          | 81  | 1410| 1378   | 15.0%                         | 0.55 [0.42, 0.71]             |
| ENTRUST AF–PCI    | 45  | 388 | 389    | 9.6%                          | 0.74 [0.52, 1.06]             |
| PIONEER AF–PCI    | 44  | 355 | 359    | 9.9%                          | 0.65 [0.46, 0.93]             |
| RE–DUAL PCI       | 120 | 900 | 91     | 16.0%                         | 0.70 [0.54, 0.89]             |
| Subtotal (95% CI) | 2053| 2601| 50.5%  | 0.64 [0.56, 0.75]             |                               |
| **Total events**  | 290 | 365 |        |                               |                               |
| Heterogeneity: Tau² = 0.00; Chi² = 2.50, df = 3 (P = 0.48); I² = 0% |
| Test for overall effect: Z = 5.88 (P < 0.00001) |

| **SCAD**          |     |     |        |                               |                               |
| AUGUSTUS          | 67  | 864 | 888    | 13.7%                         | 0.54 [0.41, 0.72]             |
| ENTRUST AF–PCI    | 52  | 363 | 366    | 9.8%                          | 0.99 [0.69, 1.41]             |
| PIONEER AF–PCI    | 43  | 334 | 324    | 9.4%                          | 0.72 [0.50, 1.03]             |
| RE–DUAL PCI       | 121 | 844 | 102    | 16.8%                         | 0.71 [0.56, 0.90]             |
| Subtotal (95% CI) | 2405| 2083| 49.5%  | 0.71 [0.57, 0.90]             |                               |
| **Total events**  | 283 | 340 |        |                               |                               |
| Heterogeneity: Tau² = 0.03; Chi² = 6.89, df = 3 (P = 0.08); I² = 56% |
| Test for overall effect: Z = 2.89 (P = 0.004) |

| **Total (95% CI)** | 5458 | 4684 | 100.0% | 0.68 [0.60, 0.77] |                               |
| **Total events**   | 573  | 705  |        |                               |                               |
| Heterogeneity: Tau² = 0.01; Chi² = 9.98, df = 7 (P = 0.19); I² = 30% |
| Test for overall effect: Z = 6.11 (P < 0.00001) |
| Test for subgroup differences: Chi² = 0.50, df = 1 (P = 0.48), I² = 0% |

**Figure 2** Clinically relevant non-major bleeding and intracranial haemorrhage in double antithrombotic therapy vs. triple antithrombotic therapy according to clinical presentation. Random-effects risk ratios and 95% confidence intervals clinically relevant non-major bleeding and intracranial haemorrhage.

more limited. In a sub-analysis of the PIONEER-AF PCI, Kerneis et al.14 observed consistent findings in several subgroups including those who required urgent revascularization, although a specific sub-analysis for ACS vs. SCAD was not performed. In the sub-analysis from the RE-DUAL trial, Oldgren et al.15 found that the benefits of both dabigatran 110 and 150 mg DAT compared with warfarin TAT in reducing bleeding risks were consistent across subgroups of patients with or without ACS, as were the results on ischaemic
endpoints. Windecker et al.,\textsuperscript{16} recently reported AUGUSTUS trial results stratified by clinical presentation (ACS managed medically, ACS undergoing PCI, elective PCI) demonstrating that the superior safety and similar efficacy of DAT was consistent across subgroups. Also, Vranckx et al.,\textsuperscript{17} recently reported that the edoxaban-based regimen provided consistent safety and similar efficacy irrespective of

![PRIMARY BLEEDING ENDPOINT TRIAL-DEFINED](image)

**Figure 3** Alternative bleeding definitions in double antithrombotic therapy vs. triple antithrombotic therapy according to clinical presentation. Random-effects risk ratios and 95% confidence intervals for primary bleeding endpoint trial-defined and thrombolysis in myocardial infarction major or minor bleeding.
Figure 4 Death, major adverse cardiovascular events, and stroke in double antithrombotic therapy vs. triple antithrombotic therapy according to clinical presentation. Random-effects risk ratios and 95% confidence intervals for all-cause death, major adverse cardiovascular events, and stroke.
clinical presentation. However, these individual sub-analyses have limited power to identify whether clinical presentation is a treatment modifier for the effects of DAT vs. TAT.

Patients with ACS are at higher risks of ST and recurrent MI after PCI. Therefore, despite the absence of supporting evidence, multiple international guidelines or position papers have suggested caution in

**Figure 5** Myocardial infarction and stent thrombosis in double antithrombotic therapy vs. triple antithrombotic therapy according to clinical presentation. Random-effects risk ratios and 95% confidence intervals for myocardial infarction and stent thrombosis. Note: stent thrombosis definition was definite ST for the RE-DUAL PCI, ENTRUST-AF PCI and PIONEER-AF PCI trials, and definite or probable ST for AUGUSTUS.
selecting a DAT instead of a TAT regimen early after intervention in this patient population. While there is large consensus that

Figure 6

Figure 7

the trade-off between predicted ischaemic and bleeding risks should guide the early vs. late adoption of a DAT regimen in AF patients undergoing PCI, some guidelines and position statements endorsed ACS presentation per se among the drivers for a TAT instead of a DAT regimen. Although several meta-analyses have been conducted on patients with AF undergoing PCI, this is the first one to specifically address the subgroups of ACS and SCAD and does not support this position for two main observations. First, ACS patients also suffer from heightened major bleeding risk and they derived, in this pooled analysis, slightly greater absolute risk benefit with DAT instead of TAT, resulting in a slightly lower number needed to treat for benefit compared with SCAD patients. Secondly, the absolute risk difference as well as the relative risk increase for MI or ST with DAT compared with TAT was not higher in ACS compared with SCAD patients. These observations were unexpected and might reflect the synergistic role of NOACs, when administered at full doses, with a P2Y12
inhibitor monotherapy for the prevention of coronary ischaemic events. Interestingly, the only signal that DAT was associated with higher MI (RR: 1.87; 95% CI 1.04–3.36) and ST (RR: 3.73; 95% CI 1.06–13.15) risks compared with TAT was observed in patients treated with dabigatran 110 mg, but not dabigatran 150 mg.

Hence, ACS or SCAD presentation per se does not justify the default adoption of a given post-PCI antithrombotic regimen in patients taking NOAC at FDA approved stroke prevention regimens, rather concurs, together with other established ischaemic, and bleeding risk factors, to the decision-making on the optimal secondary prevention antithrombotic regimens.

**Study limitations**

This is a study-level meta-analysis without access to individual patient data, which carries well-known inherent limitations. Due to missing information on ACS or SCAD presentation, the present analysis excluded 41 (0.4%) among the 10 234 originally included patients across the four selected trials, which explains the apparently inconsistent findings on ST in this compared with a prior meta-analysis.19

Randomization was stratified according to clinical presentation only in the ENTRUST-AF PCI and AUGUSTUS trials. Finally, our results mainly apply to a clopidogrel-based therapy (>90% of patients received this P2Y12 inhibitor), therefore, whether the use of strategies to identify poor-responders (such as genotype or platelet function tests or risk score application)22,24 or the use of alternative P2Y12 inhibitors, such as ticagrelor or prasugrel, might reduce thrombotic risks while preserving the bleeding benefit remains to be investigated.

**Conclusions**

DAT is associated with a reduction in bleeding complications, including major and intra-cranial haemorrhages compared with TAT, irrespective of clinical presentation and is associated with a small increase of non-fatal cardiovascular ischaemic events in both ACS and SCAD patients.

**Supplementary material**

**Supplementary material** is available at European Heart Journal – Cardiovascular Pharmacotherapy online.

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**Data availability**

The data underlying this article are available in the article and in its online supplementary material.

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