Atrial fibrillation patients undergoing percutaneous coronary intervention: dual or triple antithrombotic therapy with non-vitamin K antagonist oral anticoagulants

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About 20% of all atrial fibrillation (AF) patients develop coronary artery disease, which requires coronary stenting [percutaneous coronary intervention (PCI)]. Thus, this subcohort of AF patients may require aggressive antithrombotic therapy encompassing vitamin K antagonist (VKA) or non-vitamin K antagonist oral anticoagulants (NOAC) plus aspirin and a P2Y12 inhibitor. At present, four clinical Phase IIIb trials using dabigatran, rivaroxaban, apixaban, or edoxaban, were published. These studies assessed the impact of NOACs as a part of DAT therapy vs. triple therapy. Compared with triple therapy, NOAC-based DAT has been shown to be associated with reduced major bleeding as well as intracranial haemorrhages. The benefit, however, is somewhat counterbalanced by a higher risk of stent-related ischaemia during the early phase of dual therapy. Thus, triple therapy after stenting is appropriate for at least 14 days with a maximum of 30 days. Thereafter, DAT including a NOAC is the therapy of choice in AF PCI patients to reduce the risk of bleeding during a 1 year of follow-up compared to VKA-based regimes. The present review summarizes the published study results and demonstrates differences in trial design and reported outcomes.

Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs) have been proven in patients with atrial fibrillation (AF) to prevent stroke and peripheral embolism.1 The risk for stroke in AF depends on concomitant clinical factors, which are represented in the CHA2DS2-Vasc risk score.2 In most patients with AF, the arrhythmia appears to be the consequence of an atrial cardiomyopathy, which triggers atrial thrombogenesis at the endocardium. The thrombogenic endocardial remodelling is characterized by expression of adhesion molecules and inflammatory markers in particular in the left atrial appendage.2,6 About 20% of all AF patients develop coronary artery disease, which may require coronary stenting [percutaneous coronary intervention (PCI)]. After coronary stenting dual antiplatelet therapy (aspirin and P2Y12 inhibitors; DAPT) is necessary to prevent stent thrombosis.7,9 In AF patients with recent stent implantation, triple antithrombogenic regime (TAT) encompassing vitamin K antagonist (VKA) or NOAC plus aspirin and P2Y12 inhibitor was considered to be therapy of choice to prevent stroke and stent thrombosis. Recently, the so called dual therapy (DAT) consisting of VKA/NOAC plus a P2Y12
inhibitor has been found as safe alternative in this clinical setting. At present, four clinical trials using dabigatran, rivaroxaban, apixaban, or edoxaban, were published. These trials assessed the impact of NOACs as a part of DAT therapy vs. TAT encompassing VKA. However, none of these studies was powered to assess the effect of treatment on mortality or ischaemic events (Table 1).

Study outcomes of atrial fibrillation percutaneous coronary intervention trials

The four NOAC AF PCI trials used safety parameters as main endpoint (Table 1). The primary bleeding endpoint was typically defined as major bleeding or clinically relevant non-major bleeding (CRNMB) at longest available follow-up. Secondary safety endpoints consisted of bleeding endpoints according to various definitions. Secondary efficacy endpoints included all-cause death; cardiovascular death; trial-defined major adverse cardiovascular event (MACE); myocardial infarction (MI); stroke; and stent thrombosis (ST).

PIONEER-AF PCI trial

The PIONEER-AF trial was an open-label, randomized, controlled, multicentre trial assessing two treatment strategies of rivaroxaban and a dose-adjusted VKA strategy in AF patients who undergo PCI. A total of 2124 AF patients were assigned after PCI to low-dose rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor for 12 months, very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months, or standard therapy with a dose-adjusted VKA plus DAPT for 1, 6, or 12 months. The rates of clinically significant bleeding were lower in the rivaroxaban groups compared to VKA-based TAT. The rates of death from cardiovascular causes, myocardial infarction, or stroke were 6.5% in the 15 mg rivaroxaban group, 5.6% in the 2.5 mg rivaroxaban group, and 6.0% in the VKA-triple therapy arm. Thus, the administration of either low-dose rivaroxaban plus a P2Y12 inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1, 6, or 12 months was associated with a lower rate of clinically significant bleeding than standard therapy with a VKA plus DAPT during follow-up.

RE-DUAL PCI

The RE-DUAL PCI trial was a randomized evaluation of DAT with dabigatran vs. triple therapy (TAT) with warfarin in patients with non-valvular AF undergoing PCI, in this multicentre trial, 2725 patients with AF who had undergone PCI to TAT with warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and aspirin (for 1–3 months) (TAT group) or dual therapy with dabigatran (110 or 150 mg twice daily) plus a P2Y inhibitor (clopidogrel or ticagrelor) and no aspirin (DAT groups). There was no individualized dabigatran dose adjustment in this trial. The primary endpoint occurred in 15.4% in the 110-mg DAT group as compared with 26.9% in the TAT group and in 20.2% in the 150-mg DAT group as compared with 25.7% in the corresponding TAT group. The incidence of the composite efficacy Endpoint was 13.7% in the two DAT groups combined as compared with 13.4% in the TAT group. Thus, among AF PCI patients, the risk of bleeding was lower among those who received DAT with dabigatran and a P2Y12 inhibitor than among those who were assigned to TAT with warfarin, a P2Y12 inhibitor, and aspirin.

AUGUSTUS trial

The AUGUSTUS trial was randomized controlled clinical trial to evaluate the safety of apixaban vs. VKA and aspirin vs. aspirin placebo in patients with AF and acute coronary syndrome and/or PCI. The AUGUSTUS trial had a two-by-two factorial design. Atrial fibrillation patients with an acute coronary syndrome (ACS) or PCI were randomly assigned to receive apixaban or a VKA and to receive aspirin or matching placebo for 6 months. The primary endpoint was major or CRNM bleeding. Secondary endpoints encompassed death or hospitalization and a composite of ischaemic events. However, the Augustus trial randomized patients 6.6 days after the coronary event. Thus, the first week of antithrombotic therapy was not covered in the trial. Furthermore, several AF patients did not receive a PCI and the follow-up was rather short (6 months), although TAT was applied for 6 months, which appears to be rather aggressive. Of note, there were no significant interactions between the two randomization factors on the primary or secondary outcomes. Major or CRNM bleeding was noted in 10.9% of the patients receiving apixaban, as compared with 14.7% of those receiving VKA. Bleeding events occurred in 16.1% of the patients receiving aspirin, as compared with 9.0% of those receiving placebo. Patients in the apixaban group had a lower incidence of death or hospitalization than those treated with VKA. Patients in the aspirin group had an incidence of death or hospitalization and of ischaemic events that was similar to that in the placebo group. The AUGUSTUS investigators concluded that an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischaemic events.

ENTRUST AF PCI trial

The Edoxaban TReatment versUS VKA in paTients with AF undergoing PCI (ENTRUST-AF PCI) trial examined the role of edoxaban in AF patients undergoing PCI with and without ACS. The study was a randomized, multicentre, open-label, non-inferiority Phase 3b trial with masked outcome evaluation. Atrial fibrillation patients were included in the study if they were at least 18 years, and had a successful PCI for stable coronary artery disease or acute coronary syndrome. Patients were randomly assigned from 4 h to 5 days after PCI to either edoxaban (60 mg once daily) plus a P2Y12 inhibitor for 12 months or a VKA in combination with a P2Y12 inhibitor and aspirin (100 mg once daily, for 1–12 months). A total of 1506 patients were enrolled. Time from PCI to randomization was rather short (median: 45.1 h). Major or CRNM bleeding events occurred in 17% of patients with the edoxaban and to 20% of patients with VKA. Thus, in AF PCI patients DAT with edoxaban was non-inferior for bleeding compared with VKA-based TAT.
Differences between non-vitamin K antagonist oral anticoagulant atrial fibrillation percutaneous coronary intervention trials

All trials were designed differently and used various treatment strategies encompassing low and very low dose of NOAC, different duration of TAT in the control arm, possibility to adjustment NOAC dose if appropriate and time points of randomization after PCI. Of note, not all patients in the NOAC AF PCI trials received a stent. In particular, the AUGUSTUS trial included a large group of patients with conservative management of an acute coronary syndrome.13 These differences must be considered if...
| Treatment | Rivaroxaban + P2Y₁₂-inhibitor | Rivaroxaban + DAPT | VKA + DAPT | Dabigatran + P2Y₁₂-inhibitor | VKA + DAPT | Apixaban + P2Y₁₂-inhibitor + aspirin | VKA + P2Y₁₂-inhibitor + aspirin | Edoxaban + P2Y₁₂-inhibitor | VKA + DAPT |
|-----------|-------------------------------|-------------------|------------|-------------------------------|------------|--------------------------------------|---------------------------------|------------------------|------------|
| N (randomization) | 709 | 709 | 706 | 763 | 764 | 2306 | 2308 | 751 | 755 |
| CHA₂DS₂-VASc | 3.7 | 3.8 | 3.8 | 3.3 | 3.6 | 3.9 | 4.0 | 3.9 | 3.9 |
| (SD) | n.a. | n.a. | n.a. | 1.5 | 1.5 | 1.6 | 1.6 | 1.7 | 1.5 |
| HAS-BLED score | 3.0 | 2.9 | 3.0 | 2.6 | 2.7 | 2.9 | 2.9 | 2.8 | 2.9 |
| (SD) | n.a. | n.a. | n.a. | 0.7 | 0.8 | 1.0 | 0.9 | 0.9 | 0.8 |
| Non-STEMI (%) | 130/701 | 129/703 | 123/691 | 179 | 151 | n.a. | n.a. | 163 | 157 |
| STEMI (%) | 86/701 | 97/703 | 74/691 | 114 | 112 | n.a. | n.a. | 133 | 132 |
| Unstable angina (%) | 145/701 | 148/703 | 164/691 | 126 | 138 | n.a. | n.a. | 112 | 123 |
| ACS and PCI (%) | n.a. | n.a. | n.a. | n.a. | 873/2297 | 841/2298 | 388/751 | 389/755 |
| Medically managed (%) | n.a. | n.a. | n.a. | n.a. | 38 | 37 | 52 | 52 |
| Elective PCI (%) | n.a. | n.a. | n.a. | n.a. | 877/2297 | 907/2298 | 363/751 | 366/755 |

VKA, vitamin K antagonist; HR, hazard ratio; CRNM, clinically relevant non-major bleeding; n.a., no information provided in primary publication of phase IIIb trial; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy (P2Y₁₂ inhibitor + aspirin).
### Table 3  Endpoints parameters provided by the main trial publication

| Treatment | Rivaroxaban + P2Y12-inhibitor | VKA + DAPT | Dabigatran + P2Y12-inhibitor | VKA + DAPT | Apixaban + P2Y12-inhibitor + aspirin | VKA + P2Y12-inhibitor + aspirin | Edoxaban + P2Y12-inhibitor | VKA + DAPT |
|-----------|-------------------------------|-----------|-------------------------------|-----------|-------------------------------------|----------------------------------|-----------------------------|-----------|
| N (in analysis) | 696 | 697 | 763 | 764 | 2290 | 2259 | 751 | 755 |
| Major bleeding (ISTH) | 27 (3.9) | 48 (6.9) | 43 (5.6) | 64 (8.4) | 69 (3.0) | 104 (4.6) | 45 (6.0) | 48 (6.4) |
| Event rate/year (%) | 6.7 | 7.2 | 6.7 | 7.2 | 6.7 | 7.2 | 6.7 | 7.2 |
| HR (95% CI) | n.a. | n.a. | 0.64 (0.43–0.94) | 0.64 (0.47–0.86) | 0.95 (0.63–1.42) | 0.95 (0.63–1.42) | 0.83 (0.64–1.09) | 0.83 (0.64–1.09) |
| CRNM bleeding (%) | 90 (12.9) | 130 (18.7) | 180 (7.9) | 246 (10.9) | 97 (12.9) | 114 (15.1) | 15.3 | 18.7 |
| Event rate/year (%) | 18.2 | 26.1 | 18.2 | 26.1 | 15.3 | 18.7 | 116 (15.4) | 125 (16.6) |
| HR (95% CI) | n.a. | 0.69 (0.57–0.84) | n.a. | n.a. | 0.93 (0.72–1.20) | n.a. | 19.0 | 20.8 |
| Minor bleeding (%) | 123 (17.7) | 163 (23.4) | 116 (15.4) | 125 (16.6) | 19.0 | 20.8 |
| Event rate/year (%) | 0.72 (0.61–0.84) | n.a. | n.a. | n.a. | 0.84 (0.70–1.01) | n.a. | n.a. | n.a. |

VKA, vitamin K antagonist; HR, hazard ratio; CRNM, clinically relevant non-major bleeding; n.a., no information provided in primary publication of phase IIIb trial; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy (P2Y12 inhibitor + aspirin).

### Table 4  Key secondary efficacy outcomes provided by the main trial publication

| Treatment | Rivaroxaban + P2Y12-inhibitor | VKA + DAPT | Dabigatran + P2Y12-inhibitor | VKA + DAPT | Apixaban + P2Y12-inhibitor + aspirin | VKA + P2Y12-inhibitor + aspirin | Edoxaban + P2Y12-inhibitor | VKA + DAPT |
|-----------|-------------------------------|-----------|-------------------------------|-----------|-------------------------------------|----------------------------------|-----------------------------|-----------|
| N (in analysis) | 694 | 695 | 763 | 764 | 2306 | 2308 | 751 | 755 |
| Stroke | 8 | 7 | 9 (1.2) | 8 (1.0) | 13 (0.6) | 26 (1.1) | 10 (1.3) | 12 (1.6) |
| Event rate/year (%) | 1.3 | 1.2 | 1.3 | 1.2 | 1.3 | 1.2 | 1.2 | 1.2 |
| HR (95% CI) | 1.07 (0.39–2.96) | 1.09 (0.42–2.83) | 0.50 (0.26–0.97) | 0.50 (0.26–0.97) | 0.84 (0.36–1.95) | n.a. | 1.2 | 1.8 |
| Myocardial infarction | 19 | 21 | 26 (3.4) | 22 (2.9) | 72 (3.1) | 80 (3.5) | 29 (3.9) | 23 (3.0) |
| Event rate/year (%) | 3.0 | 3.5 | 6.6 | 7.4 | 4.3 | 3.4 | 4.3 | 3.4 |
| HR (95% CI) | 0.86 (0.46–1.59) | 1.16 (0.66–2.04) | 0.89 (0.65–1.23) | 0.89 (0.65–1.23) | 1.26 (0.73–2.17) | n.a. | 8 (1.1) | 6 (0.8) |
| Definite stent thrombosis | 5 | 4 | 7 (0.9) | 7 (0.9) | 8 (1.1) | 6 (0.8) | 1.2 | 0.9 |
| Event rate/year (%) | 0.8 | 0.7 | n.a. | n.a. | 1.32 (0.46–3.79) | n.a. | n.a. | n.a. |

VKA, vitamin K antagonist; HR, hazard ratio; CRNM, clinically relevant non-major bleeding; n.a., no information provided in primary publication of Phase IIIb trial; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy (P2Y12 inhibitor + aspirin).
trials and trial results are compared with each other (Tables 2, 3, and 4). Time in therapeutic range (TTR) during VKA therapy differed between trials (RE-Dual PCI TTR: mean 64%, PIONEER AF-PCI TTR: mean 65 ± 25%; AUGUSTUS TTR: mean 56 ± 31%; ENTRUST AF PCI TTR: mean 60 ± 21%), which may have contributed to differences in bleeding events.

**Meta-analyses**

A recent meta-analysis encompassing all patients (10 234 AF patients) from the four AF PCI trials showed that there was no significant difference between DAT and TAT in terms of all-cause death, cardiovascular death, MACE, and stroke, while DAT was associated with a border-line higher risk of MI, and a higher risk of coronary stent thrombosis.\(^8,9\) Of note, the results were still consistent when the analysis was restricted to NOAC-based DAT vs. VKA-based TAT (Figures 1, 2, and 3). Another, meta-analysis, which included the WOEST trial plus the four AF PCI trials showed included a total of 11 542 patients.\(^14\) The primary safety outcome of that study was thrombolysis in myocardial infarction (TIMI) major bleeding and the primary efficacy outcome was trial-defined major adverse cardiovascular events (MACE). Compared with VKA plus dual antiplatelet therapy (TAT), odds ratios for TIMI major bleeding were

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**Table 1** Main bleeding endpoints in dual antithrombotic therapy vs. triple antithrombotic therapy. Random-effects risk ratios for main bleeding endpoints. DAT, dual antithrombotic therapy; ISTH, International Society on Thrombosis and Haemostasis; M–H, Mantel-Haenszel; TAT, triple antithrombotic therapy. With permission Gargiulo et al.\(^9\)

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**Table 2** Clinically relevant nonmajor bleeding

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**Table 3** Intracranial haemorrhage

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**Table 4** Intracranial haemorrhage

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**Figure 1** Main bleeding endpoints in dual antithrombotic therapy vs. triple antithrombotic therapy. Random-effects risk ratios for main bleeding endpoints. DAT, dual antithrombotic therapy; ISTH, International Society on Thrombosis and Haemostasis; M–H, Mantel-Haenszel; TAT, triple antithrombotic therapy. With permission Gargiulo et al.\(^9\)
0.57 for VKA plus P2Y12 inhibitor, 0.69 for NOAC-based TAT, and 0.52 for NOAC-based DAT. The findings of this meta-analysis suggest that VKA-based TAT should be avoided, because DAT in which aspirin is discontinued lowers bleeding rates without an increase in ischaemic risk. Therefore, the use of a NOAC-based DAT without aspirin was considered to be the favourable treatment in AF patients undergoing PCI.

Thus, the four NOAC AF PCI trials show that DAT, compared to VKA-TAT, reduces major and CRNM bleeding. Furthermore, NOAC-based DAT are associated with reduced rates of intracranial haemorrhage. DAT is not associated with higher rates of trial-defined MACE, all-cause or cardiovascular death, and stroke as compared with TAT throughout the follow-up period. However, the risk of myocardial infarction and stent thrombosis is increased in AF patients if aspirin therapy (despite ongoing therapy with clopidogrel) is stopped early after stenting. Thus, TAT is of importance in all AF patients after coronary artery stenting for some weeks to prevent stent thrombosis.8,9,15 The mechanism through which early aspirin discontinuation exposes AF patients to more ischaemic events remains unknown. Whether ticagrelor or prasugrel reduce the ischaemic risks in DAT warrants further investigations. Nevertheless, the results of the four AF PCI trials will

| Study or Subgroup | NOAC_DAT | VKA_TAT | Risk Ratio | Risk Ratio |
|-------------------|----------|---------|------------|------------|
| EVENTS | TOTAL | EVENTS | TOTAL | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| AUGUSTUS | 23 | 62 | 62 | 1132 | 22.2% | 0.16 [0.23, 0.58] | 0.16 [0.23, 0.58] |
| ENTRUST AF-PCI | 45 | 751 | 48 | 755 | 25.2% | 0.19 [0.36, 1.04] | 0.19 [0.36, 1.04] |
| PIONEER AF-PCI | 27 | 696 | 48 | 697 | 22.6% | 0.56 [0.36, 0.89] | 0.56 [0.36, 0.89] |
| RE-DUAL PCI | 92 | 1744 | 90 | 981 | 30.0% | 0.57 [0.43, 0.76] | 0.57 [0.43, 0.76] |
| Total (95% CI) | 4334 | 5556 | 100.0% | 0.59 [0.41, 0.83] | 0.59 [0.41, 0.83] |

Figure 2: Main bleeding endpoints in non-vitamin K antagonist oral anticoagulant-based dual antithrombotic therapy vs. vitamin K antagonist-based triple antithrombotic therapy. Random-effects risk ratios for main bleeding endpoints. DAT, dual antithrombotic therapy; ISTH, International Society on Thrombosis and Haemostasis; M-H, Mantel-Haenszel; TAT, triple antithrombotic therapy; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist. With Gargiulo et al.9
influence clinical routine (Figure 4). Further sub-studies are warranted to access differences between various sub-
groups of AF patients like ACS and stable coronary artery
disease. A post hoc study from AUGUSTUS suggests that as-
pirin should be provided up to 30 days in AF patients at high
risk for stent thrombosis. Of note, many patients stent in
the AUGUSTUS trial did not receive a, and therefore, stent
thrombosis is not a good outcome parameter for the total
study population. In addition, a recent substudy from
AUGUSTUS could show that incidence of bleeding events
tend to differ between patients undergoing elective PCI
and ACS patients with AF. Furthermore, the ENTRUST AF
PCI trial suggests that rates of bleeding after PCI differ
between radial and femoral artery puncture. The periproce-
dural antithrombotic regime might address this aspect: in
case of femoral artery puncture, VKA and NOACs might be
paused 24 h prior to the procedure. Re-initiation of therapy
might start about 24 h after the procedure to reduce bleed-
ing from the femoral access site. This temporary pause of
VKA/NOACs might not be necessary if the radial route is
used for PCI.

In addition to the NOAC AF PCI trials, all other published
Phase III trials (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-
TIMI 48, ENSURE AF, X-VERT, and PIONEER AF-PCI) have also
shown that NOACs are not inferior to VKA therapy. Nevertheless, the study results are based on the correct in-
take of the NOACs. Thus, adherence and persistence to
medical therapy appears of major importance for adequate
anticoagulation. Recently, Andrade et al. published a
study on self-reported adherence to various NOACs. Non-
adherence, however, is likely to be a significant problem
and a reason for concern when prescribing NOACs for long-
term anticoagulation.

**Conclusion**

Compared with TAT, NOAC-based DAT has been shown to be
associated with reduced major bleeding as well as intracra-
nial haemorrhages. The benefit is somewhat counterbal-
ced by a higher risk of stent-related ischaemia during the
early phase of DAT. Thus, TAT after stenting is appropri-
ate for at least 14 days with a maximum of 30 days.
Thereafter, DAT including a NOAC is the therapy of choice
in AF PCI patients to reduce the risk of bleeding during a 1
year of follow-up (Figure 4).
Therapy with proton pump inhibitor for GI-protection

Figure 4  Antithrombotic therapy in atrial fibrillation patients after successful percutaneous coronary intervention. NOAC, non-vitamin K antagonist; full AF dose, dose of non-vitamin K antagonist oral anticoagulant approved by Phase III trials to prevent stroke in atrial fibrillation patients (AF); PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; CCS, chronic coronary syndrome.

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Data availability

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