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Temporary omission of oral anticoagulation in atrial fibrillation patients undergoing percutaneous coronary intervention: rationale and design of the WOEST-3 randomised trial

Ashley Verburg[1,2]*, MD; Wilbert L. Bor[1], MD; I. Tarik Küçük[3], MD; José P.S. Henriques[3], MD, PhD; Maarten A. Vink[4], MD, PhD; Willem-Peter T. Ruifrok[5], MD, PhD; Jacobus Plomp[6], MD; Ton A.C.M. Heestermans[7], MD, PhD; Carl E. Schotborgh[8], MD; Pieter J. Vlaar[9], MD, PhD; Michael Magro[10], MD, PhD; Sem A.O.F. Rikken[1,2], MD; Wout W.A. van den Broek[1], MD; Carlos A.G. van Mieghem[11], MD, PhD; Kristoff Cornelis[12], MD; Liesbeth Rosseel[13], MD; Karl S. Dujardin[14], MD; Bert Vandeloo[15], MD; Tom Vandendriessche[16], MD; Bert Ferdinande[17], MD; Arnoud W.J. van 't Hof[2,18,19], MD, PhD; Jan G.P. Tijssen[20], PhD; Ugo Limbruno[21], MD, PhD; Raffaele De Caterina[22,23], MD, PhD; Andrea Rubboli[24], MD; Dominick J. Angiolillo[25], MD, PhD; Tom Adriaenssens[26], MD, PhD; Willem Dewilde[27], MD, PhD; Jurrien M. ten Berg[1,18], MD, PhD

**Corresponding author: Department of Cardiology, St. Antonius Hospital, Koekoekslaan 1, 3435 CM, Nieuwegein, the Netherlands. E-mail: as.verburg@antoniusziekenhuis.nl*

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ABSTRACT

The optimal antithrombotic management of atrial fibrillation (AF) patients who require oral anticoagulation (OAC) undergoing percutaneous coronary intervention (PCI) remains unclear. Current guidelines recommend dual antithrombotic therapy (DAT; OAC plus $P2Y_{12}$ inhibitor – preferably clopidogrel) after a short course of triple antithrombotic therapy (TAT; DAT plus aspirin). Although DAT reduces bleeding risk compared to TAT, this is counterbalanced by an increase in ischaemic events. Aspirin provides early ischaemic benefit, but TAT is associated with an increased haemorrhagic burden; therefore, we propose a 30-day dual antiplatelet therapy (DAPT; aspirin plus $P2Y_{12}$ inhibitor) strategy post-PCI, temporarily omitting OAC. The study aims to compare bleeding and ischaemic risk between a 30-day DAPT strategy following PCI and a guideline-directed therapy in AF patients requiring OAC. WOEST-3 (ClinicalTrials.gov: NCT04436978) is an investigator-initiated, international, open-label, randomised controlled trial (RCT). AF patients requiring OAC who have undergone successful PCI will be randomised within 72 hours after PCI to guideline-directed therapy (edoxaban plus $P2Y_{12}$ inhibitor plus limited duration of aspirin) or a 30-day DAPT strategy ($P2Y_{12}$ inhibitor plus aspirin, immediately discontinuing OAC) followed by DAT (edoxaban plus $P2Y_{12}$ inhibitor). With a sample size of 2,000 patients, this trial is powered to assess both superiority for major or clinically relevant non-major bleeding and non-inferiority for a composite of all-cause death, myocardial infarction, stroke, systemic embolism or stent thrombosis. In summary, the WOEST-3 trial is the first RCT temporarily omitting OAC in AF patients, comparing a 30-day DAPT strategy with guideline-directed therapy post-PCI to reduce bleeding events without hampering efficacy.

KEYWORDS: ACS/NSTE-ACS; anticoagulant therapy; atrial fibrillation; bleeding; stable angina; stent thrombosis

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In patients with concomitant atrial fibrillation (AF) and coronary artery disease (CAD), it is crucial to achieve an optimal balance between the ischaemic risk associated with acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI), the cardioembolic risk associated with AF, and the haemorrhagic risk imposed by antithrombotic therapy[1,2]. AF, the most common cardiac arrhythmia worldwide, currently affects >10 million patients in Europe, and its prevalence continues to rise[3,4]. Given their shared risk factors, it often coexists with CAD[5]. Approximately 1 in 5 patients with AF undergo PCI, whereas 1 in 10 patients hospitalised with ACS or undergoing PCI develop new-onset AF[6].

To prevent ischaemic stroke and systemic embolism, most AF patients require long-term oral anticoagulant (OAC) treatment[3]. In patients presenting with ACS or undergoing PCI, dual antiplatelet therapy (DAPT; $P2Y_{12}$ inhibitor plus aspirin) is the cornerstone to prevent coronary ischaemic events, i.e., stent thrombosis (ST) and myocardial infarction (MI)[7]. For both cardioembolic and coronary ischaemic event protection, patients with AF undergoing PCI thus have a theoretical need for a combination of OAC and antiplatelet therapy[3,7]. Triple antithrombotic therapy (TAT; OAC plus DAPT) has, therefore, been the default strategy for years. However, long-term TAT has a detrimental effect on haemorrhagic risk, whilst bleeding (especially major) is associated with mortality[8,9]. Several dual antithrombotic therapy (DAT; OAC plus $P2Y_{12}$ inhibitor) regimens have demonstrated that vitamin K antagonist (VKA) or non-vitamin K antagonist oral anticoagulant (NOAC) plus $P2Y_{12}$ inhibitor (clopidogrel was used in >90% of patients), omitting aspirin, reduced bleeding complications compared to conventional TAT[10-14]. Current international guidelines and consensus statements therefore recommend the use of a NOAC, instead of VKA, in combination with single antiplatelet therapy, preferably clopidogrel, and to limit the use of aspirin to ≤1 week, or ≤30 days in high ischaemic risk patients[7,15,16]. However, this reduction in bleeding complications has been counterbalanced by an increase in coronary ischaemic events (ST risk ratio [RR] 1.54, 95% confidence interval [CI]: 1.10-2.14; MI RR 1.23, 95% CI: 1.04-1.46)[17].

Given that coronary ischaemic risk peaks within the first month post-PCI, there is ongoing debate regarding the utilisation of aspirin during this critical period[1,2,18]. While aspirin seems to provide early ischaemic benefit, but given that TAT is associated with more bleeding, the WOEST-3 trial proposes a 30-day DAPT strategy post-PCI, temporarily omitting OAC, instead of guideline-directed TAT followed by DAT. The temporary omission of OAC not only aims to further decrease bleeding risk but also ensures optimal coronary protection against ischaemic events during the early post-PCI period.

Methods

What is the Optimal Antithrombotic Strategy in Patients With Atrial Fibrillation Having Acute Coronary Syndrome or Undergoing Percutaneous Coronary Intervention? (WOEST-3, ClinicalTrials.gov: NCT04436978) is an investigator-initiated, multicentre, open-label, randomised controlled trial (RCT) evaluating the bleeding risk (i.e., safety) and ischaemic risk (i.e., efficacy) of a 30-day DAPT strategy post-PCI versus guideline-directed therapy in AF patients who require OAC after undergoing successful PCI.

A total of 2,000 patients will be enrolled. Enrolment started in January 2023 and is expected to conclude in 2026. Currently, over 300 patients have been randomised. An overview of the participating clinical sites is provided in **Supplementary Appendix 1**.

This trial is being conducted in compliance with the study protocol, the Declaration of Helsinki, and Good Clinical Practice guidelines, as defined by the International Council on Harmonisation. Medical ethics committee approval is required at all participating sites prior to study initiation. A yearly progress and safety report will be submitted to the accredited medical research ethics committees of the concerned member states. Patient identification codes and randomisation numbers are in place to maintain patient confidentiality. Eligible patients will be informed, both orally and in writing, on the possible risks and benefits of trial participation as well as their rights and duties. Prior to randomisation, eligible patients must provide written informed consent. Patient data are entered into an electronic case report form.

STUDY POPULATION

Patients are eligible for inclusion if they are ≥18 years old, have undergone successful PCI, and have a history of or newly diagnosed AF or atrial flutter with a long-term (≥1 year) indication for OAC. Exclusion criteria include recent ischaemic stroke, history of haemorrhagic stroke, an indication for OAC other than AF or atrial flutter, a CHA_2DS_2-VASc score ≥7, or active bleeding. A more detailed overview of the in- and exclusion criteria is shown in **Table 1**.

RANDOMISATION AND TREATMENT

Eligible patients will be randomised and centrally allocated 1:1 to either the interventional or standard group via a computer-generated sequence, stratified by site and clinical presentation, i.e., ACS or elective PCI. Randomisation will be performed as early as possible, within 72 hours post-PCI. Patients in the

Abbreviations

ACS	acute coronary syndrome
AF	atrial fibrillation
CAD	coronary artery disease
DAPT	dual antiplatelet therapy
DAT	dual antithrombotic therapy
MI	myocardial infarction
NOAC	non-vitamin K antagonist oral anticoagulant
OAC	oral anticoagulant
PCI	percutaneous coronary intervention
ST	stent thrombosis
TAT	triple antithrombotic therapy
VKA	vitamin K antagonist

Table 1. In- and exclusion criteria.

Inclusion criteria
1. ≥18 years of age
2. Successful PCI
3. History of or newly diagnosed (<72 hours after PCI/ACS) atrial fibrillation or flutter with a long-term (≥1 year) indication for OAC
Exclusion criteria
1. Contraindication to edoxaban, aspirin or all $P2Y_{12}$ inhibitors (e.g., kidney failure [eGFR <15 mL/min] or allergy)
2. Any stroke <12 months
3. History of intracranial haemorrhage
4. Current indication for OAC besides atrial fibrillation/flutter (e.g., venous thromboembolism, mechanical heart valve prosthesis, intracardiac thrombus or apical aneurysm requiring OAC)
5. Moderate to severe mitral valve stenosis (MVA ≤1.5 cm^2)
6. Life expectancy <1 year
7. Active liver disease (ALT, ASP, AP >3x ULN or active hepatitis A, B or C)
8. Active malignancy with metastases or undergoing non-curative treatments (e.g., palliative chemotherapy)
9. Known coagulopathy
10. Active bleeding on randomisation
11. History of intraocular, spinal, retroperitoneal, or traumatic intra-articular bleeding, unless the causative factor has been permanently resolved
12. Recent (<1 month) gastrointestinal haemorrhage, unless the causative factor has been permanently resolved
13. Severe anaemia requiring blood transfusion or thrombocytopaenia <50×10^9/L
14. Pregnancy or breastfeeding women
15. BMI >40 or bariatric surgery
16. Poor LV function (LVEF <30%) with proven slow flow
17. CHA_2DS_2-VASc score ≥7
18. Oral anticoagulant other than NOAC or acenocoumarole (e.g., phenprocoumon)

ACS: acute coronary syndrome; ALT: alanine aminotransferase; AP: alkaline phosphatase; ASP: aspartate aminotransferase; BMI: body mass index; CK: creatinine kinase; eGFR: estimated glomerular filtration rate; LV: left ventricle; LVEF: left ventricular ejection fraction; MVA: mitral valve area; NOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulation; PCI: percutaneous coronary intervention; ULN: upper limit of normal

interventional group will be treated with 30 days of DAPT, i.e., aspirin plus a $P2Y_{12}$ inhibitor, immediately discontinuing OAC. After 30 days, patients will be switched to standard therapy, i.e., NOAC and a $P2Y_{12}$ inhibitor. Patients in the standard therapy group will be treated with guideline-directed therapy, i.e., NOAC plus a $P2Y_{12}$ inhibitor plus a limited duration of aspirin, up to a maximum of 30 days at the discretion of the treating physician. A schematic overview of the study design is presented in **Figure 1**.

Edoxaban is the NOAC of choice for the sake of uniformity, as well as its once-daily dosing, and, together with apixaban, its association with fewer gastrointestinal bleeding events[15]. The recommended dose is 60 mg once daily unless one or more of the following criteria for the reduced dose of 30 mg once daily are met: moderate-to-severe kidney dysfunction (estimated glomerular filtration rate 15-50 ml/min/1.73 m^2), low body weight (<60 kg) or concomitant use of one of the following P-glycoprotein inhibitors: ciclosporin, dronedarone, erythromycin or ketoconazole.

Selection of the $P2Y_{12}$ inhibitor is at the discretion of the treating physician. Genotyping or platelet-function testing may be used to guide decision-making. Permissible daily doses of $P2Y_{12}$ inhibitors include clopidogrel 75 mg once daily, ticagrelor 90 mg twice daily, and prasugrel 10 mg once daily, or a reduced dose of 5 mg in patients aged ≥75 years or patients with low body weight (<60 kg). The daily aspirin dose is 75-100 mg.

The antithrombotic strategy before or during PCI – including the administration of glycoprotein IIb/IIIa inhibitors, bivalirudin or heparin – as well as invasive diagnostics and PCI techniques, are all at the treating physician's discretion.

PATIENT FOLLOW-UP

Efficacy and safety endpoints will be evaluated at 6 weeks, 3 months, and 6 months after randomisation and recorded in an electronic case report form. Endpoint evaluation will be conducted remotely through medical file reviewing and patient questionnaires on clinical events, self-reported adherence to study medication, and the EuroQol 5-dimension 5-level (EQ-5D-5L) quality of life questionnaire. If necessary, patients may be contacted by phone.

STUDY ENDPOINTS

The primary safety endpoint is major or clinically relevant non-major bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH), at 6 weeks after randomisation. The co-primary efficacy endpoint is a composite of all-cause death, MI, stroke, systemic embolism, or (probable or definite) ST at 6 weeks after randomisation.

Key prespecified secondary endpoints are the primary safety and efficacy outcomes at 6 months after randomisation. Other secondary endpoints include the individual components of the 2 primary endpoints, as well as quality of life, and a net clinical

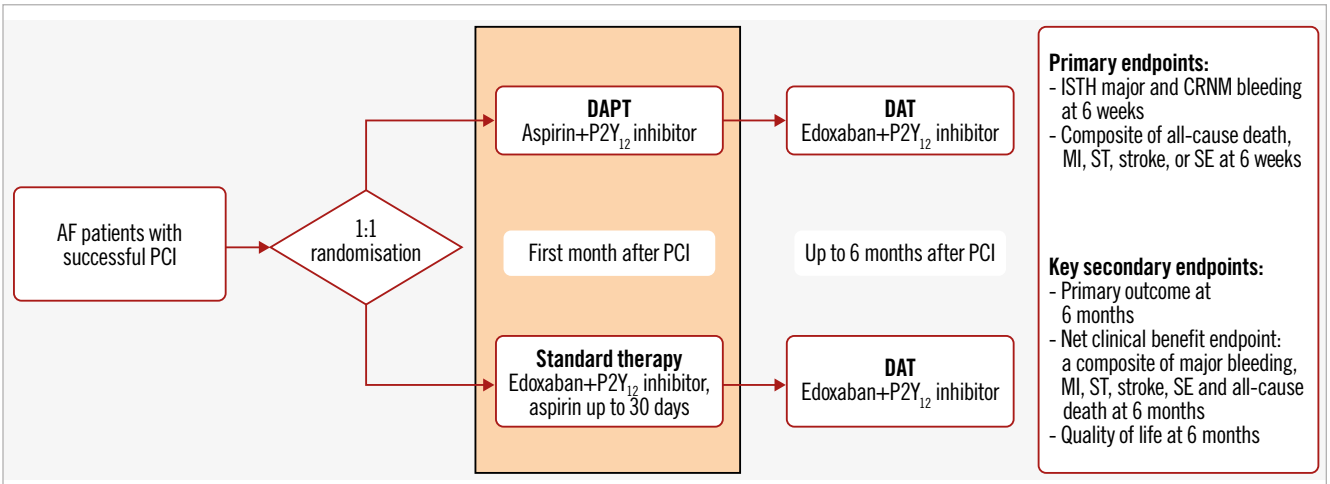

Figure 1. *Study design and outcome measures. AF patients with a successful PCI will be randomised in a 1:1 ratio to DAPT (aspirin+P2Y$_{12}$ inhibitor) versus standard therapy (edoxaban+P2Y$_{12}$ inhibitor+aspirin up to 30 days) in the first month after PCI, followed by DAT (edoxaban+P2Y$_{12}$ inhibitor). AF: atrial fibrillation; CRNM: clinically relevant non-major; DAPT: dual antiplatelet therapy; DAT: dual antithrombotic therapy; ISTH: International Society on Thrombosis and Haemostasis; MI: myocardial infarction; PCI: percutaneous coronary intervention; SE: systemic embolism; ST: stent thrombosis*

benefit endpoint comprising major bleeding, stroke, systemic embolism, all-cause death, MI, and (probable or definite) ST at 6-week, 3-month, and 6-month follow-up. Bleeding is defined according to the ISTH and Bleeding Academic Research Consortium (BARC) bleeding classifications to ensure comparability with prior and forthcoming publications. Detailed definitions of the components of the primary endpoints are provided in **Supplementary Appendix 2**.

SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS

This study is designed to test both safety and efficacy hypotheses in AF patients requiring OAC and undergoing PCI: a 30-day DAPT regimen post-PCI followed by DAT is (1) superior to guideline-directed therapy in reducing bleeding risk and (2) non-inferior to guideline-directed therapy in the composite ischaemic endpoint. Since 2 co-primary endpoints are being utilised, statistical correction will be applied for the dual assessment. Trial success will be defined by the fulfilment of both hypotheses.

We used a web-based power calculator based on "Sample Size Calculations in Clinical Research" by Chow et al[19]. Based on the AUGUSTUS trial, the anticipated bleeding rate in the standard treatment group is 7.45% at 30 days after ACS or elective PCI[14]. Hansen et al showed a hazard ratio of 1.88 for bleeding events in patients treated with OAC plus clopidogrel versus DAPT[20]. Therefore the assumed incidence for bleeding in the DAPT group is 4.01%. To achieve 80% power for superiority of the primary bleeding endpoint, 1,962 patients will be included, using a 1-sided significance level of 0.025.

This sample size will also ensure sufficient power to establish non-inferiority for the composite ischaemic endpoint. Based on the AUGUSTUS trial, the expected ischaemic event rate at 30 days is 1.66% in the interventional group and 2.57% in the standard group. If there is a true difference in favour of the experimental treatment of 1% (2.5% vs 1.5%), then 1,538 patients are required in order to be 80% sure that the upper limit of a 1-sided 97.5% CI will exclude a difference in favour of the standard group of more than 1%. To account for dropout, we will include 2,000 patients.

An intention-to-treat analysis will be performed for the primary endpoints. Per-protocol analysis will be used as a sensitivity analysis. Primary and secondary endpoint analyses will be based on the time of randomisation to the first occurrence of any event in the composite endpoint using Kaplan-Meier cumulative event-free curves and compared by means of the log-rank test.

Prespecified subgroup analyses of the primary and secondary endpoints will be performed to investigate the consistency of treatment effects across subgroups of clinical importance, including type of AF, type of index event, type and dose of P2Y$_{12}$ inhibitor, the presence of CYP2C19 loss-of-function alleles, NOAC dose, (planned) duration of TAT and DAT, medical history, sex, and procedural characteristics (e.g., number of diseased vessels, number of stents, and total stent length) including high-risk characteristics (e.g., left main stenting, treatment of a chronic total occlusion or bifurcation with 2 stents implanted) according to the European Society of Cardiology guidelines[21].

STUDY ORGANISATION

WOEST-3 is an investigator-initiated clinical trial sponsored by the St. Antonius Hospital Research Fund and Daiichi Sankyo. The Executive Committee is solely responsible for the design, conduct, analysis and reporting of this study.

DATA SAFETY MONITORING BOARD

An independent data and safety monitoring board (DSMB) has been established to assess the accumulating study data for safety. The DSMB reviewed the study protocol, may decide to perform an interim analysis, and may recommend early termination of the trial if interim findings convincingly favour or oppose a trial arm.

CLINICAL EVENT COMMITTEE

Clinical event classifications of the following study endpoints will be adjudicated by a blinded clinical endpoint committee prior to presentation of the data to the DSMB: death, bleeding, stroke, MI, ST, systemic embolism, and coronary revascularisation.

Discussion

The What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing (WOEST) trial was the first study to demonstrate that, compared to TAT, DAT (VKA plus clopidogrel) was associated with a significantly lower rate of bleeding, with no apparent increase in ischaemic events[10]. More recently, NOACs replaced VKA in AF patients owing to their safer bleeding profile and similar efficacy[3]. The subsequent, pivotal NOAC-based DAT trials demonstrated reduced bleeding complications compared to conventional TAT[11-14]. Notably, none of these trials were powered to assess ischaemic endpoints. Although several meta-analyses concluded that DAT reduced bleeding risk, this was counterbalanced by an increase in coronary ischaemic events[17,22]. A *post hoc* analysis of the AUGUSTUS trial revealed that most ST occurred in the first month post-PCI[18] and that the beneficial effect of aspirin is confined to this first month, after which its continued use caused more severe bleeding events but did not reduce severe coronary ischaemic events[23]. These findings carry important clinical implications and sparked debate on its use and duration in the early post-PCI phase.

The temporary omission of OAC in WOEST-3 allows for DAPT in the post-PCI phase, offering 2 major benefits. Firstly, we know that bleeding risk is significantly lower on DAPT than DAT, leading to a reduction in bleeding events in the post-PCI phase[20,24]. Secondly, DAPT stands as the cornerstone treatment post-PCI, ensuring optimal coronary protection against ischaemic events during the critical 30-day period, which coincides with the peak occurrence of coronary events.

Omitting OAC in AF patients may be controversial, since the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) W parallel trial showed that warfarin was superior to DAPT for major cardiovascular event prevention (RR 1.44, 95% CI: 1.18-1.76)[25]. However, from the Stroke Preventions in Atrial Fibrillation (SPAF) and the ACTIVE A trials we know that aspirin versus placebo and DAPT versus aspirin, respectively, are both effective in reducing stroke risk in AF patients[26,27]. Since the annual incidence of ischaemic stroke and systemic embolism remain low using DAPT, the annual risk difference between OAC and DAPT in the ACTIVE W trial was only 1%, and OAC interruption will be limited to only 30 days, we hypothesise that a short course of DAPT, rather than guideline-directed therapy, is non-inferior concerning stroke or systemic embolism.

The Bridging Anticoagulation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial has already shown that completely omitting OAC for 1 week was non-inferior compared to bridging with heparin in patients on warfarin undergoing surgery[28]. Moreover, this temporary interruption of OAC will allow for the use of aspirin in the first month post-PCI, when both coronary and haemorrhagic risks are greatest[23,29]. As stroke risk is continuous over time and both bleeding and ischaemic risk are highest within the first 30 days but decline thereafter, the risk of bleeding or ischaemic events on TAT followed by DAT probably outweighs the risk of stroke on DAPT within the first month.

Several ongoing trials are currently exploring the optimal antithrombotic strategy in AF-PCI patients. The ADONIS-PCI trial (ClinicalTrials.gov: NCT04695106) and OPTIMA-4 substudy (NCT03234114) are investigating the impact of more potent $P2Y_{12}$ inhibitors in NOAC-based DAT on bleeding and ischaemic risk. The EPIDAURUS trial (NCT04981041) investigates de-escalation of an early intensive antithrombotic strategy. Notably, the MATRIX-2 trial (NCT05955365) shares a similar rationale with our trial, albeit more innovative, treating patients with 1 month of $P2Y_{12}$ inhibitor monotherapy followed by NOAC monotherapy.

Limitations

It is important to acknowledge limitations within our trial. Firstly, the NOAC used in this study is edoxaban, which may limit the generalisability of our findings to other NOACs. Secondly, the choice of $P2Y_{12}$ inhibitor is left to the discretion of the investigator (although clopidogrel is the preferred drug), potentially introducing variability in treatment regimens. A prespecified subgroup analysis will be performed on the choice of $P2Y_{12}$ inhibitor. Despite these limitations, the insights gained from our trial will contribute valuable knowledge to the ongoing pursuit of the optimal antithrombotic strategy in AF-PCI.

Conclusions

The WOEST-3 trial is the first randomised controlled, multicentre trial assessing the safety and efficacy of a 30-day DAPT strategy post-PCI in patients with AF and a long-term indication for OAC. Although recent RCTs demonstrated significantly fewer bleeding events with DAT when compared to TAT, bleeding rates remain high, and the omission of aspirin may lead to an increase in the incidence of ST and MI. Therefore, in WOEST-3, temporary OAC omission allows for a short course of DAPT. This may not only decrease bleeding risk but also provides optimal coronary protection against ischaemic events during the first 30 days post-PCI.

Authors' affiliations

1. Department of Cardiology, St. Antonius Hospital, Nieuwegein, the Netherlands; 2. Cardiovascular Research Institute Maastricht (CARIM), Maastricht, the Netherlands; 3. Department of Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; 4. Department of Cardiology, OLVG, Amsterdam, the Netherlands; 5. Department of Cardiology, Treant Zorggroep, Emmen, the Netherlands; 6. Department of Cardiology, Tergooi MC, Blaricum, the Netherlands; 7. Department of Cardiology, Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands; 8. Department of Cardiology, Haga Hospital, Den Haag, the Netherlands; 9. Department of Cardiology, Catharina

Hospital, Eindhoven, the Netherlands; 10. Department of Cardiology, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands; 11. Department of Cardiology, AZ Groeninge, Kortrijk, Belgium; 12. Department of Cardiology, AZ Maria Middelares, Gent, Belgium; 13. Department of Cardiology, Algemeen Stedelijk Hospital, Aalst, Belgium; 14. Department of Cardiology, AZ Delta, Roeselare, Belgium; 15. Department of Cardiology, University Hospital Brussels, Brussels, Belgium; 16. Department of Cardiology, University Hospital Antwerpen, Antwerpen, Belgium; 17. Department of Cardiology, Hospital Oost-Limburg, Genk, Belgium; 18. Department of Cardiology, University Medical Centre Maastricht, Maastricht, the Netherlands; 19. Department of Cardiology, Zuyderland Medical Centre, Heerlen, the Netherlands; 20. Department of Clinical Epidemiology and Biostatistics, Amsterdam UMC, Amsterdam, the Netherlands; 21. Cardioneurovascular Department, Azienda USL Toscana Sud Est, Grosseto, Italy; 22. Cardio-Thoracic and Vascular Department, Pisa University Hospital, Pisa, Italy and University of Pisa, Pisa, Italy; 23. Fondazione Villaserena per la Ricerca, Città Sant'Angelo, Italy; 24. Department of Cardiology, Ospedale S. Maria delle Croci, Ravenna, Italy; 25. Division of Cardiology, University of Florida College of Medicine, Jacksonville, FL, USA; 26. Department of Cardiology, University Hospitals Leuven, Leuven, Belgium; 27. Department of Cardiology, Imelda Hospital, Bonheiden, Belgium

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Conflict of interest statement

The authors have no specific conflicts of interest to declare with respect to this manuscript.

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Supplementary data

Supplementary Appendix 1. Clinical trial sites.
Supplementary Appendix 2. Clinical event definitions.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00100

Supplementary data

Supplementary Appendix 1. Clinical trial sites.

The Netherlands

St. Antonius Hospital, Nieuwegein, the Netherlands

Amsterdam University Medical Centre, Amsterdam, the Netherlands

OLVG, Amsterdam, the Netherlands

Treant, Emmen, the Netherlands

Tergooi Medical Centre, Hilversum, the Netherlands

Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands

Haga Hospital, Den Haag, the Netherlands

Catharina hospital, Eindhoven, the Netherlands

Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands

Medisch Spectrum Twente, Enschede, the Netherlands

Zuyderland Medical Centre, Heerlen, the Netherlands

Belgium

University Hospitals Leuven, Leuven, Belgium

AZ Maria Middelares, Gent, Belgium

AZ Delta, Roeselare, Belgium

Imelda Hospital, Bonheiden, Belgium

AZ Groeninge, Kortrijk, Belgium

Hospital Oost-Limburg, Genk, Belgium

University Hospital Antwerpen, Antwerpen, Belgium

University Hospital Brussel, Brussel, Belgium

Algemeen Stedelijk Hospital, Aalst, Belgium

Italy

Ospedale S. Maria delle Croci, Ravenna, Italy

Pisa University Hospital and University of Pisa, Pisa, Italy

Azienda USL Toscana Sudest, Grosseto, Italy

Sant' Andrea Hospital, La Spezia, Italy

University Hospital of Parma, Parma, Italy

Ospedale Maggiore, Bologna, Italy

Azienda USL – IRCCS Reggio Emilia, Reggio Emilia, Italy

AUSL della Romagna, Morgagni-Pierantoni Hospital, Forlì, Italy

Ospedale Infermi, Rimini, Italy

M. Bufalini Hospital, Cesena, Italy

Azienda Ospedaliero Universitaria Careggi, Firenze, Italy

Supplementary Appendix 2. Clinical event definitions.

Bleeding according to ISTH definition

Major bleeding

Having a symptomatic presentation and:

- Fatal bleeding, and/or
- Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in haemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.

Clinical relevant non-major bleeding

Any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:

- Requiring medical intervention by a healthcare professional
- Leading to hospitalization or increased level of care
- Prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

Minor

Bleeding episodes not requiring any medical attention and therefore not meeting the criteria for major of clinically relevant non-major bleeding

Bleeding according to BARC definition

Type 0

No bleeding

Type 1

Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.

Type 2

Any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:

- requiring nonsurgical, medical intervention by a healthcare professional,
- leading to hospitalization or increased level of care, or
- prompting evaluation

Type 3a

- Overt bleeding plus haemoglobin drop of 3 to <5 g/dL (=1.86 to < 3.10 mmol/L)* (provided haemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b

- Overt bleeding plus haemoglobin drop ≥5 g/dL(≥ 3.10 mmol/L) * (provided haemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/ nasal/ skin/ haemorrhoid)
- Bleeding requiring intravenous vasoactive agents

Type 3c

- Intracranial haemorrhage (does not include micro bleeds or haemorrhagic transformation, does include intraspinal)
- Subcategories confirmed by autopsy or imaging or lumbar puncture
- Intraocular bleed compromising vision

Type 4
CABG-related bleeding

- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period. *Cell saver products are not counted.*
- Chest tube output ≥2L within a 24-h period

Type 5a
Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b
Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Stroke according to VARC-2 definition

Diagnostic criteria

- Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
- **Stroke:** duration of a focal or global neurological deficit≥24 h; OR<24 h if available neuroimaging documents a new haemorrhage or infarct; OR the neurological deficit results in death
- **TIA:** duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new haemorrhage or infarct
- No other readily identifiable non-stroke cause for the clinical presentation, to be determined by or in conjunction with the designated neurologist
- Confirmation of the diagnosis by at least one of the following
    - Neurologist or neurosurgical specialist
    - Neuroimaging procedure (CT scan or brain MRI), but stroke maybe diagnosed on clinical grounds alone

Stroke classification
Ischaemic without haemorrhagic transformation: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue
Ischaemic with haemorrhagic transformation: haemorrhage may be consequence of a ischaemic stroke. In this situation, the stroke is an ischaemic stroke with haemorrhagic transformation and not a haemorrhagic stroke
Haemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage
Undetermined: a stroke may be classified as undetermined if there is insufficient information to allow categorization as ischaemic or haemorrhagic

Stroke definitions
Disabling stroke: an mRS score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline
Non-disabling stroke: an mRS score of <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline

Systemic embolism according to ENTRUST-AF PCI definition

A SEE is defined as an abrupt episode of arterial insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation). Arterial embolic events involving the CNS (including the eye), coronary, and pulmonary arterial circulation are not considered SEEs, but correspond respectively to stroke/TIA, myocardial infarction, and pulmonary embolism. In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusion.

SEE will be further classified according to the affected location: Upper extremity, lower extremity, abdominal excluding renal, or renal.

Fatal SEEs are defined as those that lead to death within 7 days.

Myocardial infarction according to the 4th Universal Definition of Myocardial Infarction

Type 1 MI

Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and with at least 1 of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.*

**Postmortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial haemorrhage, meets the type 1 MI criteria regardless of cTn values.*

Type 2 MI

Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis, requiring at least 1 of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic etiology

Type 3 MI

Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

Type 4a MI

Coronary intervention–related MI is arbitrarily defined by an elevation of cTn values >5 times the 99th percentile URL in patients with normal baseline values.

In patients with elevated preprocedure cTn in whom the cTn level are stable (≤20% variation) or falling, the postprocedure cTn must rise by >20%. However, the absolute postprocedural value must still be at least 5 times the 99th percentile URL. In addition, 1 of the following elements is required:

- New ischaemic ECG changes;
- Development of new pathological Q waves*;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic etiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization.†

**Isolated development of new pathological Q waves meets the type 4a MI criteria if cTn values are elevated and rising but <5 times the 99th percentile URL.*
†Postmortem demonstration of a procedure-related thrombus in the culprit artery, or a macroscopically large circumscribed area of necrosis with or without intra-myocardial haemorrhage meets the type 4a MI criteria.

Type 4b MI

Stent thrombosis as documented by angiography or autopsy using the same criteria utilized for type 1 MI.

Type 4c MI

Focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL, using the same criteria utilized for type 1 MI.

Type 5 MI

CABG-related MI is arbitrarily defined as elevation of cTn values >10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated preprocedure cTn in whom cTn levels are stable (≤20% variation) or falling, the postprocedure cTn must rise by >20%. However, the absolute postprocedural value still must be >10 times the 99th percentile URL. In addition, 1 of the following elements is required:

- Development of new pathological Q waves*;
- Angiographic documented new graft occlusion or new native coronary artery occlusion;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic etiology.

**Isolated development of new pathological Q waves meets the type 5 MI criteria if cTn values are elevated and rising but <10 times the 99th percentile URL.*

Stent thrombosis according to ARC-2 definition

Definite stent/scaffold thrombosis

Definite stent/scaffold thrombosis is considered to have occurred by either angiographic or pathological confirmation

- Angiographic confirmation of stent/scaffold thrombosis
  The presence of a thrombus that originates in the stent/scaffold or in the segment 5 mm proximal or distal to the stent/scaffold or in a side branch originating from the stented/scaffolded segment and the presence of at least one of the following criteria:
  - Acute onset of ischaemic symptoms at rest
  - New electrocardiographic changes suggestive of acute ischaemia
  - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction)
- Pathological confirmation of stent/scaffold thrombosis
  - Evidence of recent thrombus within the stent/scaffold determined at autopsy
  - Examination of tissue retrieved following thrombectomy (visual/histology)

Probable stent/scaffold thrombosis

Regardless of the time after the index procedure, any myocardial infarction that is related to documented acute ischaemia in the territory of the implanted stent/scaffold without angiographic confirmation of stent/scaffold thrombosis and in the absence of any other obvious cause.

Silent stent/scaffold occlusion

The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered stent thrombosis

Timing of stent thrombosis (duration after stent implantation)

- Acute 0–24 h
- Subacute >24 h–30 d
- Late >30 d–1 y
- Very late >1

0h defined as the moment the patients is undraped and taken off the catheterization table
Early stent thrombosis is 0-30 days (acute plus subacute stent thrombosis)

Death according to ARC-2 and SCTI definitions

All-cause death: death of any cause, which is further categorised in:

Cardiovascular Death

Death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular (CV) procedures, death due to CV haemorrhage, and death due to other CV causes. Deaths related to the procedure or concomitant treatment are always classified as cardiovascular.

Non-Cardiovascular Death

Any death with a specific cause that is not thought to be CV in nature, as defined above. This may be one of, but not limited to, the following: pulmonary, renal, gastrointestinal, hepatobiliary, pancreatic, infection, inflammatory, haemorrhage that is neither CV bleeding or a stroke, non-CV procedure or surgery, trauma, suicide, (non-)

prescription drug reaction or overdose, neurological (excluding CV death from ischaemic or haemorrhagic stroke or undetermined cause of stroke or CV haemorrhage of central nervous system), malignancy.

Undetermined Cause of Death
Death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information or when there is insufficient supporting information or detail to assign the cause of death. In general, most death should be classifiable as CV or non-CV, and the use of this category of death, therefore, should be avoided and should apply to few patients. Such deaths will be classified as cardiovascular for end point determination.

Coronary revascularization according to ARC-2 and SCTI definitions

Target lesion revascularization

- The target lesion is defined as the treated segment including the 5-mm margin proximal and distal to the stent/scaffold.
- Target lesion revascularization is defined as a repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion.

Target vessel revascularization

- The target vessel is defined as the entire major intervened coronary vessel, including side branches.
- Target vessel revascularization is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel including the target lesion.

Target vessel non-target lesion revascularization

- Target vessel non-target lesion revascularization is defined as any repeat percutaneous intervention or surgical bypass of the target vessel for pre-existing disease, disease progression or other reasons unrelated to the target lesion as defined above.

Elective:
The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of myocardial infarction (MI) or death. For stable in-patients, the procedure is being performed during this hospitalization for convenience and ease of scheduling and NOT because the patient's clinical situation demands the procedure prior to discharge.

Urgent:
The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns that there is risk of myocardial ischaemia, MI, and/or death. Patients who are outpatients or in the emergency department at the time that the cardiac revascularization is requested would warrant hospital admission based on their clinical presentation.

Emergency:
The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischaemia and/or MI could lead to death. "As soon as possible" refers to a patient who is of sufficient acuity that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours.

Salvage:
The procedure is a last resort. The patient is in cardiogenic shock when the PCI begins (i.e., the time at which the first guide wire or intracoronary device is introduced into a coronary artery or bypass graft for the purpose of mechanical revascularization) OR within the last ten minutes prior to the start of the case or during the diagnostic portion of the case, the patient has also received chest compressions or has been on unanticipated circulatory support (e.g., intra-aortic balloon pump, extracorporeal membrane oxygenation, or cardiopulmonary support).