WILEY CLINICAL CARDIOLOGY

TRIAL DESIGNS

Design and Rationale of the RE-DUAL PCI Trial: A Prospective, Randomized, Phase 3b Study Comparing the Safety and Efficacy of Dual Antithrombotic Therapy With Dabigatran Etexilate Versus Warfarin Triple Therapy in Patients With Nonvalvular Atrial Fibrillation Who Have Undergone Percutaneous Coronary Intervention With Stenting

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Antithrombotic management of patients with atrial fibrillation (AF) undergoing coronary stenting is complicated by the need for anticoagulant therapy for stroke prevention and dual antiplatelet therapy for prevention of stent thrombosis and coronary events. Triple antithrombotic therapy, typically comprising warfarin, aspirin, and clopidogrel, is associated with a high risk of bleeding. A modest-sized trial of oral anticoagulation with warfarin and clopidogrel without aspirin showed improvements in both bleeding and thrombotic events compared with triple therapy, but large trials are lacking. The RE-DUAL PCI trial (NCT 02164864) is a phase 3b, a strategy of prospective, randomized, open-label, blinded-endpoint trial. The main objective is to evaluate dual antithrombotic therapy with dabigatran etexilate (110 or 150 mg twice daily) and a P2Y12 inhibtor (either clopidogrel or ticagrelor) compared with triple antithrombotic therapy with warfarin, a P2Y12 inhibitor (either clopidogrel or ticagrelor, and low-dose aspirin (for 1 or 3 months, depending on stent type) in nonvalvular AF patients who have undergone percutaneous coronary intervention with stenting. The primary endpoint is time to first International Society of Thrombosis and Hemostasis major bleeding event or clinically relevant nonmajor bleeding event. Secondary endpoints are the composite of all cause death or thrombotic events (myocardial infarction, or stroke/systemic embolism) and unplanned revascularization; death or thrombotic events; individual outcome events; death, myocardial infarction, or stroke; and unplanned revascularization. A hierarchical procedure for multiple testing will be used. The plan is to randomize ∼ 2500 patients at approximately 550 centers worldwide to try to identify new treatment strategies for this patient population.

KEYWORDS

Arrhythmia/all, management, Clinical trials, General clinical cardiology, Stroke prevention, Thrombosis/hypercoagulable states, Pharmacology, Anti platelet therapy, Cardiac, catheterization/diagnostic interventional

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1 | INTRODUCTION

Long-term treatment with oral anticoagulants (OACs) is indicated in patients with atrial fibrillation (AF) for the prevention of stroke and systemic embolism. Vitamin K antagonists (VKAs) such as warfarin have been the mainstay of therapy for such patients on the basis of evidence from placebo-controlled trials,[1,2] in which VKAs were superior to aspirin and to dual antiplatelet therapy (clopidogrel and aspirin).[3,4] In contrast, for patients undergoing percutaneous coronary intervention (PCI) with stent implantation, treatment with dual antiplatelet therapy (with a $P2Y_{12}$ inhibitor such as ticlopidine plus aspirin) was superior to oral anticoagulation.[5–8] The type of thrombosis that develops may explain this differential benefit: Stent thrombosis (ST) and coronary events are usually caused by platelet-rich thrombi, whereas in AF, low-shear stress thrombi can develop in the left atrium, which is a less platelet-dependent process.

Many patients with AF also have ischemic heart disease,[9] and most guidelines have, until recently, recommended triple antithrombotic therapy, comprising an anticoagulant plus dual antiplatelet therapy for such patients undergoing PCI. Not surprisingly, these potent regimens are associated with very high rates of major bleeding. Several large registries reported that the risk of major bleeding with triple antithrombotic therapy is 3-fold to 4-fold higher than with OAC

alone or single antiplatelet therapy.[10–13] In addition, major bleeding is associated with an up to 5-fold increased risk of death following an acute coronary syndrome (ACS).[14,15] As such, the search is underway for better treatment strategies that improve safety while preserving efficacy.

Two new promising approaches have emerged. First, non-VKA oral anticoagulants (NOACs) have been developed, the first being dabigatran etexilate. This oral direct thrombin inhibitor was tested in patients with nonvalvular AF in the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial.[16] RE-LY was a prospective, randomized, open-label (double-blind for the 2 dabigatran etexilate arms and open-label for warfarin), blinded-endpoint trial and involved 18 113 patients. Dabigatran 150 mg twice daily, when compared with warfarin, resulted in a lower rate of stroke or systemic embolism (1.12% vs 1.72%, respectively) and a similar rate of major bleeding events (3.40% vs 3.61%, respectively); dabigatran 110 mg twice daily resulted in similar rates of stroke or systemic embolism (1.54% vs 1.72%, respectively) and a lower rate of major bleeding events (2.92% vs 3.61%, respectively). Both doses of dabigatran reduced the risk of hemorrhagic stroke (150 mg, 0.10%; 110 mg, 0.12%; warfarin, 0.38%), whereas the 150-mg dose reduced the risk of ischemic stroke.[17] These benefits of dabigatran over warfarin were unchanged irrespective of whether patients had no concomitant

antiplatelet therapy or if they had a single or even dual antiplatelet therapy (Figure 1).[18] As such, the direct comparison of dabigatran vs warfarin has been made. There is, however, a need for prospective data on the use of dabigatran as part of an antithrombotic strategy in a stented population as compared with warfarin-antiplatelet strategies, which have been evolving.

The other major development in this field came from the randomized What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST) study.[19] In this trial, 573 patients who were receiving anticoagulation with VKAs (mostly for AF) and needed PCI were randomized to standard triple antithrombotic therapy (anticoagulant, clopidogrel, and aspirin) vs dual antithrombotic therapy (anticoagulant and clopidogrel). The study showed that dual antithrombotic therapy significantly reduced the risk of bleeding and was also associated with a lower risk of death or thrombotic events than was triple antithrombotic therapy.[19] Data from registries support the WOEST findings.[19,20] More recently, the findings from the open-label ISAR-TRIPLE trial,[21] which involved 614 patients with an indication for OAC who were undergoing drug-eluting stent (DES) implantation, support a limited duration (6 weeks vs 6 months) of triple antithrombotic therapy.[22]

On the basis of these developments, a recent survey found that clinicians are interested in using NOACs as well as adopting a strategy of single antiplatelet therapy.[23] Indeed, a shift in practice guidelines is also emerging whereby the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines state that in patients with AF who underwent a recent PCI and have a CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 y, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 y, sex category [women]) score ≥2, it may be reasonable to use clopidogrel (75 mg once a day) concurrently with an OAC but without aspirin.[24] However, evidence supporting this recommendation is limited (class IIb, level of evidence B). The European Society of Cardiology, along with various other groups, released a joint consensus statement that also recommends dual antithrombotic therapy as an option in many patient groups, based on bleeding and thrombotic risk.[25] However, these recommendations are complex, derived from a single small trial,[19] and therefore relatively weak. Consequently, a single, 3-stage algorithm, applicable to a broad range of patients with coronary artery disease (CAD), has been proposed.[26]

Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) is a large, prospective, randomized trial that aims to test dual antithrombotic therapy and triple antithrombotic therapy with adequate power. The hypothesis is that, in patients with nonvalvular AF who have undergone PCI with stenting, dabigatran (110 or 150 mg twice daily) and clopidogrel or ticagrelor are noninferior to warfarin, clopidogrel or ticagrelor, and aspirin with respect to major bleeding events or clinically relevant nonmajor bleeding events over the duration of the trial. Of note, the reference arm is triple antithrombotic therapy for only 1 month or 3 months (depending on stent type), after which it too reverts to dual antithrombotic therapy, in keeping with the evolving guideline recommendations on triple antithrombotic therapy.

2 | METHODS

RE-DUAL PCI is a multicenter, prospective, randomized, open-label, blinded-endpoint, active-comparator, phase 3b, event-driven clinical trial that plans to enroll ~ 2500 patients at approximately 550 sites in 41 countries (see Appendix,). Patients are currently being recruited.

2.1 | Study Population

Study entry criteria are summarized in Table 1. Briefly, eligible adults have nonvalvular AF, are either treatment-naïve or receiving an OAC, have an ACS or stable CAD, and were successfully treated with PCI with bare-metal stent (BMS) or DES implantation. Nonvalvular AF could be paroxysmal, persistent, or permanent, but not secondary to a reversible disorder (eg, myocardial infarction [MI], pulmonary embolism, recent surgery, pericarditis, or thyrotoxicosis) unless long-term OAC is planned. Patients with implanted heart valves, severe renal insufficiency, and other major comorbidities will be excluded.

This study will be conducted in compliance with institutional review boards/institutional ethics committees, the principles laid down in the last revision of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and local laws and regulations relevant to the use of new

FIGURE 1 Data from the RE-LY trial[18]: Rates of major bleeding of warfarin vs dabigatran, with either no background antiplatelet therapy, single or dual antiplatelet therapy. As shown, in each group, the rates are higher as the number of antiplatelet agents increases, but rates tend to be highest with warfarin, then dabigatran 150 mg twice daily, and then dabigatran 110 mg twice daily. Abbreviations: RE-LY, Randomized Evaluation of Long-term Anticoagulation Therapy.
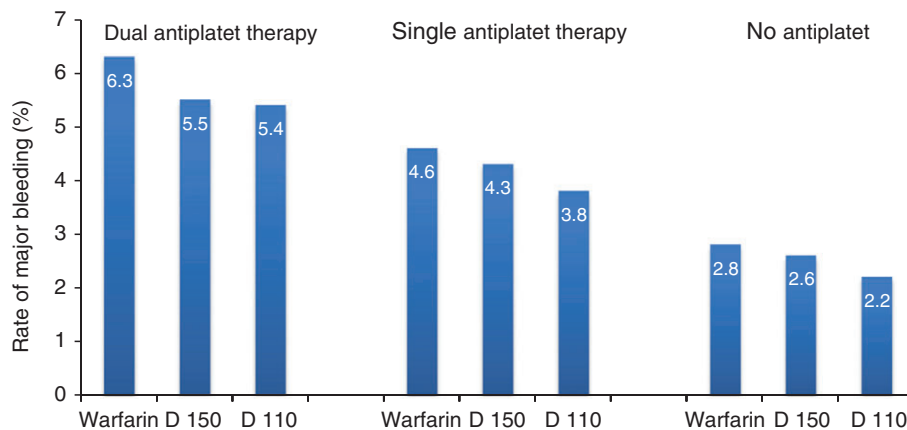
TABLE 1 Eligibility Criteria

Inclusion Criteria

- Age ≥18 years
- Nonvalvular AF: paroxysmal, persistent, or permanent, but not secondary to a reversible disorder (eg, MI, PE, recent surgery, pericarditis, or thyrotoxicosis) unless long-term OAC is planned
- Receiving OAC treatment (warfarin, another VKA or non-VKA OAC) or treatment naïve prior to PCI
- ACS (STEMI/NSTEMI/UA) successfully[a] treated by PCI and stenting (BMS or DES) or stable CAD with ≥1 lesion eligible for PCI that was successfully[a] treated by elective[b] PCI and stenting (BMS or DES)
- Ability to provide informed consent in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and local legislation and/or regulations

Exclusion Criteria

- Mechanical or biological heart valve prosthesis
- Cardiogenic shock during current hospitalization
- Use of fibrinolytic agents within 24 hours of randomization that could put patient at high risk of bleeding
- Stroke or major surgery within 1 month prior to screening visit
- Receipt of, or on waiting list for, an organ transplant
- History of intraocular, spinal, retroperitoneal, or traumatic intra-articular bleeding, unless causative factor has been permanently eliminated or repaired
- GI hemorrhage within 1 month prior to screening, unless cause has been permanently eliminated
- Major bleeding episode,[c] including life-threatening bleeding episode,[d] within 1 month prior to screening visit
- Hemorrhagic disorder or bleeding diathesis (eg, von Willebrand disease, hemophilia A or B or other hereditary bleeding disorder, history of spontaneous intra-articular bleeding or of prolonged bleeding after surgery/intervention)
- Anemia (Hb <10 g/dL) or thrombocytopenia (including heparin-induced; platelet count $<100 \times 10^9$/L) at screening
- Severe renal impairment (estimated CrCl <30 mL/min, calculated by Cockcroft-Gault equation) at screening
- Active liver disease (ie, ≥1 of prior and persistent ALT, AST, or AP >3× ULN); known active hepatitis A, B, or C
- Recent malignancy or radiation therapy (≤6 months) unless estimated life expectancy >36 months
- Need for continued treatment with systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus, dronedarone, rifampicin, phenytoin, carbamazepine, St. John's wort, or any cytotoxic/myelosuppressive therapy
- Need for continuous treatment with NSAIDs
- Known allergy to dabigatran etexilate or capsule excipients, or warfarin tablets or excipients
- Contraindication to OAC treatment, clopidogrel, ticagrelor, or ASA
- Premenopausal (last menstruation ≤1 year prior to screening) and: pregnant or breast feeding; not surgically sterile; of childbearing potential and not (planning to continue) practicing an acceptable method of birth control throughout the trial

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; ALT, alanine aminotransferase; AP, alkaline phosphatase; ASA, aspirin (acetylsalicylic acid); AST, aspartate transaminase; BMS, bare-metal stent; CAD, coronary artery disease; CrCl, creatinine clearance; DES, drug-eluting stent; GI, gastrointestinal; Hb, hemoglobin; MACE, major adverse cardiac events; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; NSTEMI, non–ST-segment elevation myocardial infarction; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; PE, pulmonary embolism; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; ULN, upper limit of normal; VKA, vitamin K antagonist.

[a]Achievement of <30% residual diameter stenosis of the target lesion assessed by visual inspection or quantitative coronary angiography and no in-hospital MACE (MI or repeat coronary revascularization of the target lesion). [b] Indication for elective PCI should be based on recent guidelines.[27,28] [c] Hb reduction of ≥2 g/dL, transfusion of ≥2 units of blood, or symptomatic bleeding in a critical area or organ. [d] Symptomatic intracranial bleeding; bleeding with Hb decrease of ≥5 g/dL; or bleeding requiring transfusion of ≥4 units of blood, inotropic agents, or surgery.

therapeutic agents. All patients will provide written informed consent.

2.2 | Treatment Protocol

The trial schema is shown in Figure 2. Patients with nonvalvular AF undergoing planned PCI will be identified as possible candidates during a prescreening period. All antithrombotic treatment for the PCI will be given according to standard guidelines, which call for loading doses of P2Y$_{12}$ inhibitors and aspirin.[27,28] Formal screening will be initiated after successful PCI. Eligible patients who consent to participate will be randomized to 1 of 3 treatment arms: (1) dabigatran etexilate 110 mg twice daily plus either clopidogrel or ticagrelor ("110 mg DE-DAT"); (2) dabigatran etexilate 150 mg twice daily plus either clopidogrel or ticagrelor ("150 mg DE-DAT"); or (3) warfarin plus one of clopidogrel or ticagrelor, plus aspirin ≤100 mg once daily ("warfarin–triple

antithrombotic therapy"). In the warfarin arm, aspirin will be discontinued after 1 month in patients implanted with a BMS and after 3 months in patients implanted with a DES, thus becoming a dual antithrombotic therapy strategy for most of the trial duration.

Randomization will be stratified in permuted blocks, dynamically stratified by aged (<80 or ≥80 years; <70 or ≥70 years for patients enrolled in Japan) and region (United States, Japan, and rest of the world). Patients age <80 years (for Japan <70 years) and all patients in the United States will be randomly assigned to 110 mg DE-DAT, 150 mg DE-DAT, or warfarin–triple antithrombotic therapy in a 1:1:1 ratio. Non-US patients aged ≥80 years (for Japan ≥70 years) will be assigned to 110 mg DE-DAT or warfarin–triple antithrombotic therapy in a 1:1 ratio (to be consistent with the labeling of dabigatran in elderly patients in non-US countries). The first dose of the study drug will be administered ≥6 hours after sheath removal and after hemostasis has been assured, up to 120 hours after successful PCI (but
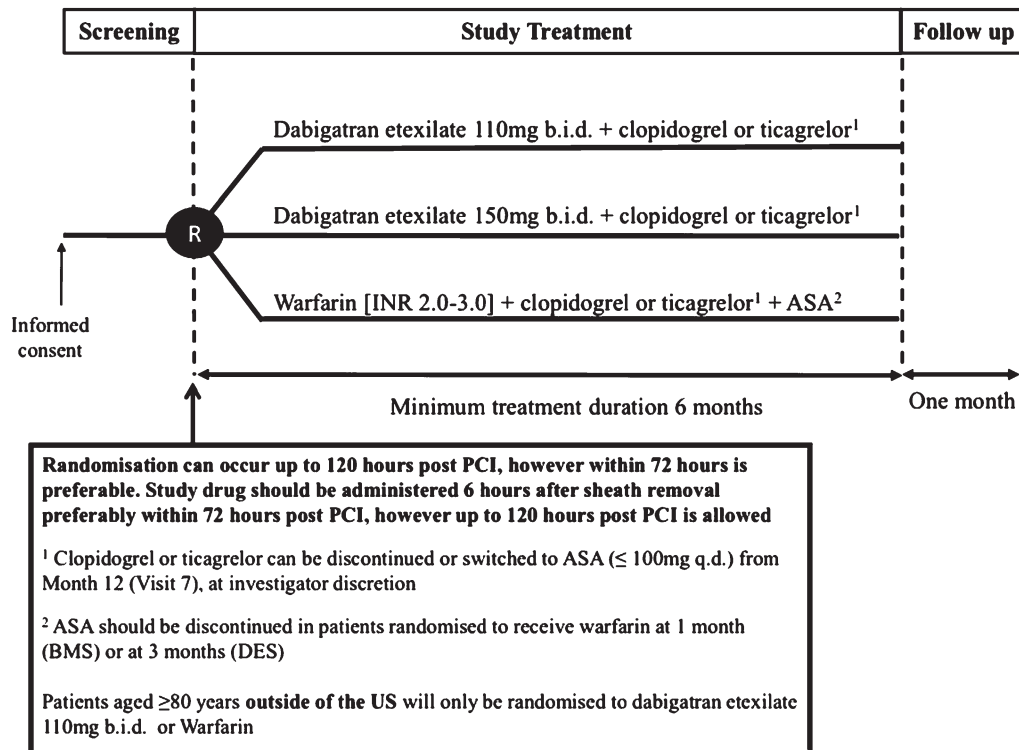
FIGURE 2 Treatment schema. Patients who meet the study entry criteria will be assigned to 1 of 3 treatment arms. First administration of study treatment will be at visit 2, between 6 hours after sheath removal and up to 120 hours after successful PCI with stenting. All patients will remain on study treatment until the last patient entered has completed ≥6 months of study treatment. Patients will have a 4-week follow-up visit. Telephone follow-ups will be conducted at 15, 21, and 27 months (not shown). Dabigatran etexilate dosage is 110 mg twice daily or 150 mg twice daily; clopidogrel dosage is 75 mg once daily; ticagrelor dosage is 90 mg twice daily; warfarin dosage is 1 mg, 3 mg, or 5 mg once daily, individually managed by study investigators to a target INR of 2.0 to 3.0; and ASA dosage is ≤100 mg once daily. Abbreviations: ASA, aspirin (acetylsalicylic acid); b.i.d., twice a day; BMS, bare-metal stent; DES, drug-eluting stent; INR, international normalized ratio; PCI, percutaneous coronary intervention; q.d., once a day; R, randomization; US, United States.

preferably within 72 hours). Patients may receive bridging therapy with a parenteral anticoagulant according to local practice before switching to the trial medication.

The dose of warfarin will be adjusted to ensure the patient's international normalized ratio (INR), measured locally, is maintained at 2.0 to 3.0, ideally targeted at 2.0 to 2.5. For patients initiating warfarin, INR will be measured at least every 2 weeks for the first 3 months to obtain target INR as soon as possible to avoid overdosing or underdosing. The quality of warfarin therapy for each patient will be assessed by reporting the number of INR values within the ranges of 2.0 to 3.0 and 2.0 to 2.5, as well as those above and below these ranges. The Rosendaal method[29] will be used to provide another evaluation of percentage of time a patient's INR is within these target ranges. Good-quality anticoagulation control with VKAs, with attention to the time in therapeutic range, will be undertaken, given the relationship of time in therapeutic range to thromboembolism and bleeding.[30]

All patients will receive either clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily according to the local label for ≥12 months following randomization, with the choice of agent at the discretion of the investigator. Discontinuation of clopidogrel or ticagrelor or switching to aspirin (≤100 mg once daily) after 12 months of treatment will also be at the discretion of the investigator, allowing investigators to discontinue antiplatelet therapy as

suggested by a European consensus.[25] The use of prasugrel is not allowed based on a study showing that prasugrel was associated with a 4-fold increase in major bleeding when used in the setting of triple antithrombotic therapy in patients with evidence of clopidogrel resistance.[31]

Regarding aspirin therapy, all patients will have received aspirin at the time of PCI and daily before randomization. Patients randomized to either dabigatran arm will discontinue aspirin at the time of randomization before administration of trial drug. Patients randomized to receive warfarin will only receive aspirin (≤100 mg once daily) for 1 month or 3 months for those implanted with a BMS or DES, respectively. The duration of aspirin treatment for DES patients was discussed extensively by the executive steering committee and was a balance of using triple antithrombotic therapy for a reasonable duration for efficacy, but recognizing the desire to reduce bleeding over time. In the absence of anticoagulation, the recent dual antiplatelet therapy trial showed benefit of 30 months over 12 months of dual antiplatelet therapy,[32] and one might therefore consider longer triple therapy, but the ongoing risk of bleeding would limit this.

All patients will remain on study treatment until the last patient randomized has received a minimum of 6 months of study treatment. The maximum treatment duration is expected to be 30 months, although the study may conclude earlier if an adequate number of events is reported, or it may conclude later (or enroll additional

patients) if more time (or patients) may be needed to observe the minimum number of required events.

Some local amendments were incorporated. In the United States, the US Food and Drug Administration (FDA) requires that genetic testing for CYP2C19 be carried out, in accordance with the US label for clopidogrel. A pharmacokinetic substudy will be carried out in Germany. In Japan, an age cutoff of 70 years was chosen for the 150-mg dose of dabigatran, in accordance with local guideline recommendations, regulatory requirements, and clinical practice. In the initial protocol, a sample size of 8520 was planned to allow for an efficacy primary endpoint of thrombotic events; the feasibility of enrolling patients in a timely fashion did not allow this.

2.3 | Study Endpoints

The primary endpoint is time to first major (defined as per the International Society of Thrombosis and Hemostasis major criteria[33]) or clinically relevant nonmajor bleeding event. A clinically relevant nonmajor bleeding event is defined as a clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to ≥1 of the following: hospital admission for bleeding; physician-guided medical or surgical treatment for bleeding; and physician-guided change, interruption, or discontinuation of study drug.

The secondary endpoints (assessed by time to first event) are the composite of death or thrombotic event, comprising all-cause death (cardiovascular, noncardiovascular, and undetermined), MI, or stroke/systemic embolism, and unplanned revascularization (PCI/coronary artery bypass grafting); death or thrombotic event; individual outcome events (all-cause death, MI, stroke, systemic embolism, ST); the composite endpoint of death, MI, or stroke; and unplanned revascularization by PCI or coronary artery bypass grafting.

Endpoints will be adjudicated by an independent committee blinded to treatment assignment. Subgroup analyses are planned across major subgroups by medical history, baseline medication use, baseline risk of stroke and/or bleeding, type of stent, and clinical presentation at baseline.

2.4 | Statistical Design and Analysis

This study is designed to test 2 safety hypotheses in patients with nonvalvular AF who have undergone successful PCI with stenting: (1) 110 mg DE-DAT is noninferior to warfarin–triple antithrombotic therapy with respect to major bleeding events/clinically relevant nonmajor bleeding events over the duration of the trial; and (2) 150 mg DE-DAT is noninferior to warfarin–triple antithrombotic therapy with respect to major bleeding events/clinically relevant nonmajor bleeding events over the duration of the trial.

To control the type I error rate at a 1-sided 0.025 level, a hierarchical procedure for multiple testing will be used to test the safety hypotheses, as outlined in Table 2; additional testing for safety and efficacy endpoints will be included. If any of the steps fails to meet statistical significance, the testing procedure will stop and subsequent tests will not be performed. The noninferiority margin used for major bleeding events/clinically relevant nonmajor bleeding events will be 1.38 (on the relative hazard ratio [HR] scale), as was used by the FDA for ximelagatran, apixaban, rivaroxaban, and dabigatran to preserve ≥50% of the relative reduction (on the log scale) in the risk of stroke or systemic embolism associated with warfarin in 6 previous randomized trials.[34] The same noninferiority margin has been applied to major bleeding events/clinically relevant nonmajor bleeding events, as it was considered the most clinically relevant available reference in the absence of any other type of data. The upper bound of the Wald confidence interval (CI) of the HR of DE-DAT vs warfarin-triple antithrombotic therapy (1-sided 97.5%) will be compared with this noninferiority margin for the noninferiority testing.

The study will employ a time-to-first-event analysis. The primary endpoint will be compared across treatments using the stratified Cox proportional hazards regression model stratified by age (<80 or ≥80 years [Japan, <70 or ≥70 years]). The primary analysis will be performed under the intent-to-treat framework on the full analysis set, which will include all randomized patients, regardless of whether they receive treatment. The robustness of the primary analyses will be assessed by an on-treatment analysis, which will only count events that occur while a patient is taking study medication (including the residual effect period of 6 days).

TABLE 2 Hierarchical Procedure for Multiple Testing (Safety Hypotheses)

Step	Test
1	Noninferiority of 110 mg DE-DAT to warfarin–triple antithrombotic therapy in major bleeding events/clinically relevant nonmajor bleeding events
2	Noninferiority of 150 mg DE-DAT to warfarin–triple antithrombotic therapy in major bleeding events/clinically relevant nonmajor bleeding events
3	Noninferiority of 150 mg DE-DAT and 110 mg DE-DAT combined to warfarin–triple antithrombotic therapy in death or thrombotic event and unplanned revascularization by PCI/CABG
4	Superiority of 110 mg DE-DAT to warfarin–triple antithrombotic therapy in major bleeding events/clinically relevant nonmajor bleeding events
5	Noninferiority of 150 mg DE-DAT and 110 mg DE-DAT combined to warfarin–triple antithrombotic therapy in death or thrombotic event
6	Superiority of 150 mg DE-DAT to warfarin–triple antithrombotic therapy in major bleeding events/clinically relevant nonmajor bleeding events. If any of the above steps fails to meet statistical significance, the testing procedure will stop and subsequent tests will not be performed.

Abbreviations: CABG, coronary artery bypass grafting; DE-DAT, dabigatran etexilate dual antithrombotic therapy; PCI, percutaneous coronary intervention.

The trial data are reviewed by an independent data monitoring committee, which will be allowed to recommend stopping the study (or an arm in the study) for safety. In addition, the chair of the data monitoring committee will review unblinded data every 2 months, or more frequently if needed, to ensure the safety of patients in the trial.

The overall sample size is driven by the noninferiority comparison of major bleeding events/clinically relevant nonmajor bleeding events between 110 mg DE-DAT or 150 mg DE-DAT and warfarin–triple antithrombotic therapy. With $\alpha = 0.025$ (1-sided) and assuming 14% of patients with ≥1 event at 1 year, 334 patients with ≥1 major bleeding event/clinically relevant nonmajor bleeding event in each pair of treatment groups (ie, 167 patients with major bleeding events/clinically relevant nonmajor bleeding events per treatment group) are required to achieve 83.6% power for this endpoint, yielding a final sample size estimated at 834 patients in each treatment group (ie, 2502 randomized patients in total). Therefore, approximately 500 patients with ≥1 major bleeding event/clinically relevant nonmajor bleeding event are required in total across the 3 treatment groups. An estimation of the anticipated power for the thrombotic endpoint analysis in the hierarchical testing, evaluating noninferiority with the same margins as the primary endpoint (NI margin 1.38) of the combined 2 dabigatran groups vs warfarin, is approximately 70%.

3 | DISCUSSION

In patients with AF undergoing PCI, the issue of how to balance the need for multiple antithrombotic drugs for prevention of thrombosis against the high risk of bleeding has remained a conundrum for clinicians for the past decade. A recent registry analysis[35] as well as a survey[23] found that physician practices vary widely regarding the perceived optimal antithrombotic strategy.

A wide spectrum of strategies can be considered for use in this population (Figure 3). With many different $P2Y_{12}$ inhibitors available in current practice, and 4 NOACs, some with different doses, more than 25 possible drug combinations are available. In addition, different durations of antiplatelet therapy can be used, leading to hundreds of possible treatment strategies. Although this variety offers great options for patients and physicians, very few data support any of them other than the standard triple antithrombotic therapy with aspirin, clopidogrel, and warfarin. As noted above, antiplatelet monotherapy is not sufficient for stroke prevention, nor is dual antiplatelet therapy alone (although this has not been tested with the more potent drugs). On the other end of the spectrum, use of triple antithrombotic therapy for 1 year has an unacceptable increased risk of bleeding.[13,20,36]

The RE-DUAL PCI trial aims to study several new strategies for antithrombotic treatment in these patients, and 3 regimens across the spectrum of intensity have been selected. The 2 dual antithrombotic therapy regimens will include a NOAC—dabigatran etexilate—at both of the doses shown to be effective and approved (worldwide). These doses of dabigatran offer a sufficient level of anticoagulation, providing a similar (110 mg) or superior (150 mg) effect to warfarin for stroke prevention.[16] RE-DUAL PCI will not seek to re-prove the efficacy of dabigatran for stroke prevention, but rather will look at the overall balance of safety and efficacy as part of the dual antithrombotic strategy.

The 2 dabigatran arms in RE-DUAL PCI will fully adopt the dual antithrombotic therapy approach, with immediate discontinuation of aspirin at the time of randomization before administration of trial drug. As such, RE-DUAL PCI will be a large follow-up study to test a WOEST[19]-like strategy in an adequately powered manner. With
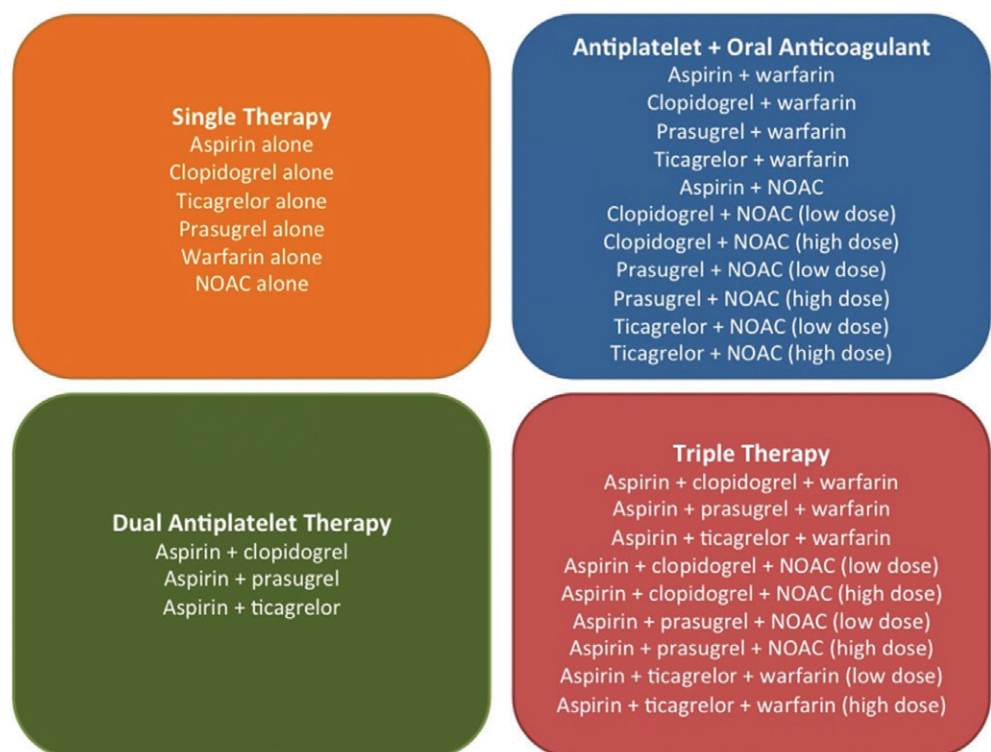
FIGURE 3 Options for antithrombotic regimens in patients with AF undergoing PCI. Additional nuances of these strategies could be applied by changing the duration of antiplatelet therapy. Abbreviations: AF, atrial fibrillation; NOAC, non–vitamin K antagonist oral anticoagulant; PCI, percutaneous coronary intervention.

Single Therapy
Aspirin alone
Clopidogrel alone
Ticagrelor alone
Prasugrel alone
Warfarin alone
NOAC alone

Antiplatelet + Oral Anticoagulant
Aspirin + warfarin
Clopidogrel + warfarin
Prasugrel + warfarin
Ticagrelor + warfarin
Aspirin + NOAC
Clopidogrel + NOAC (low dose)
Clopidogrel + NOAC (high dose)
Prasugrel + NOAC (low dose)
Prasugrel + NOAC (high dose)
Ticagrelor + NOAC (low dose)
Ticagrelor + NOAC (high dose)

Dual Antiplatelet Therapy
Aspirin + clopidogrel
Aspirin + prasugrel
Aspirin + ticagrelor

Triple Therapy
Aspirin + clopidogrel + warfarin
Aspirin + prasugrel + warfarin
Aspirin + ticagrelor + warfarin
Aspirin + clopidogrel + NOAC (low dose)
Aspirin + clopidogrel + NOAC (high dose)
Aspirin + prasugrel + NOAC (low dose)
Aspirin + prasugrel + NOAC (high dose)
Aspirin + ticagrelor + warfarin (low dose)
Aspirin + ticagrelor + warfarin (high dose)

dabigatran, the risk of MI was not statistically higher than with warfarin in RE-LY, whereas all thrombotic events (MI, stroke/embolism, revascularization, unstable angina, or cardiac death) were statistically significantly lower with dabigatran 150 mg.[37] In addition, the recent FDA analysis found no increase in MI.[38] Of note, as patients will have received standard doses of aspirin for the PCI, the antiplatelet effect of aspirin will remain for 5 to 7 days, covering the early post-PCI period, when patients are at highest risk of thrombotic events.

For the control arm, patients start with standard triple antithrombotic therapy (warfarin, aspirin, and either clopidogrel or ticagrelor), but this will be altered in line with newer data and guidelines to lead to an "enhanced" standard of care. The duration of dual antiplatelet therapy has been shortened, in keeping with the overall trend suggested by WOEST[19]; but instead of stopping the P2Y$_{12}$ inhibitor (as has been the standard in prior guidelines and practice), aspirin will be stopped. As such, the triple antithrombotic therapy strategy will revert to a dual antithrombotic therapy approach for most of the study period.

All 3 arms in RE-DUAL PCI will allow the use of ticagrelor, given the benefits seen in reducing risk of death and the lack of increase in major bleeding, when analyzed in intent-to-treat, compared with clopidogrel in the Platelet Inhibition and Platelet Outcomes (PLATO) trial.[39] It should also be noted that there are sparse data on the use of ticagrelor in nonvalvular AF patients who have undergone PCI. As such, patients will be monitored carefully, with special focus by the data monitoring committee throughout the trial.

3.1 | Prior Studies Supporting Dual Antithrombotic Therapy

The concept of a dual antithrombotic therapy approach has support from previous studies in terms of efficacy and safety. Indeed, because blockade of P2Y$_{12}$ receptor–mediated signaling with clopidogrel is associated with greater platelet-inhibitory effects than cyclooxygenase-1 inhibition with aspirin, as well as the established role of P2Y$_{12}$ receptor blockade on recurrent thrombotic events, clopidogrel might be expected to be more effective than aspirin at reducing risk of ST, with a potentially lower rate of gastrointestinal bleeding as well.[40] A few retrospective cohorts have observed a lower incidence of ST with clopidogrel plus warfarin dual antithrombotic therapy,[13,20,41] and clopidogrel, aspirin, and warfarin triple antithrombotic therapy,[42] compared with warfarin and aspirin dual antithrombotic therapy.

The WOEST study[19] demonstrated lower rates of bleeding and ischemic events for patients receiving dual antithrombotic therapy (warfarin and clopidogrel) compared with triple antithrombotic therapy (warfarin, clopidogrel, and aspirin). One-year follow-up data showed that bleeding episodes were observed in 19.4% of patients receiving dual antithrombotic therapy vs 44.4% receiving triple antithrombotic therapy (HR: 0.36, 95% CI: 0.26, 0.50, $p < 0.0001$). However, this study was not powered to assess efficacy and can therefore only be considered hypothesis-generating. In the ISAR-TRIPLE study,[21] in which patients were randomized to 6 weeks or 6 months of clopidogrel on top of aspirin and OAC after DES implantation, no difference was apparent between groups in the primary

endpoint of death, MI, ST, stroke, or Thrombolysis In Myocardial Infarction major bleeding (HR: 1.14, 95% CI: 0.68, 1.91, $p = 0.63$) at 9-month follow-up. Furthermore, there were no differences in the combined secondary endpoint (cardiac death, MI, ST, or ischemic stroke; HR: 0.93, 95% CI: 0.43, 2.05, $p = 0.44$) or in Thrombolysis In Myocardial Infarction major bleeding (HR: 1.35, 95% CI: 0.64, 2.84, $p = 0.87$). These data suggest that physicians should balance patients' risk of ischemic events against their bleeding risk when selecting the shorter or longer duration of triple therapy.

With these emerging provocative data, clinical guidelines[24] are already being adjusted, with dual antithrombotic therapy being given a class IIb recommendation in this patient population. In the latest European Society of Cardiology consensus statement,[25] dual antithrombotic therapy is recommended over triple antithrombotic therapy in AF patients with low stroke risk, high bleeding risk, stable CAD, and PCI; is an option in most other situations; but is not suggested as an early treatment option in patients with low bleeding risk and an ACS. However, prospective clinical data with any new dual antithrombotic therapy or triple antithrombotic therapy regimen with dabigatran etexilate or other NOACs in nonvalvular AF patients undergoing PCI would be helpful.[41]

4 | CONCLUSION

RE-DUAL PCI is designed to provide clinicians with robust, much-needed information regarding treatment for nonvalvular AF patients who have undergone PCI with stenting.

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APPENDIX

Countries participating in RE-DUAL

Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Ireland, Israel, Italy, Japan, Korea, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Russia, Singapore, Slovakia, Slovenia, Spain, Sweden, Taiwan, Thailand, Turkey, UK, US.

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