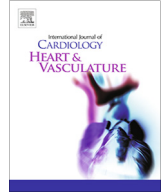




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## Apixaban versus Phenprocoumon: Oral AntiCoagulation plus antiplatelet therapy in patients with Acute Coronary Syndrome and Atrial Fibrillation (APPROACH-ACS-AF)



Rationale and design of the prospective randomized parallel-group, open-label, blinded-endpoint, superiority, multicenter-trial of a triple therapy versus a dual therapy in patients with Atrial Fibrillation and Acute Coronary Syndrome undergoing coronary stenting

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### ABSTRACT

**Background:** A regimen of dual (DAT) vs. triple (TAT) antithrombotic therapy reduces bleeding in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI). However, recent evidence suggests that DAT may be associated with an increased ischemic risk. This raises the question whether DAT rather than TAT should be recommended to AF patients that undergo PCI for acute coronary syndrome (ACS), carrying a particularly high risk of both bleeding and ischemic events, studied only as subgroups of previous trials.

**Abbreviations:** APT, anti-platelet therapy; DAT, dual antithrombotic therapy; SAPT, single antiplatelet therapy; TAT, triple antithrombotic therapy.

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**Keywords:**

Acute coronary syndrome  
 Atrial fibrillation  
 Apixaban  
 Antiplatelet therapy  
 Triple therapy  
 Anticoagulation

**Methods and design:** The APPROACH-ACS-AF-(DZHK-7) trial is a multicenter prospective, randomized, open-label, blinded endpoint (PROBE) trial which will include patients presenting with an ACS managed by PCI and requiring oral anticoagulation (OAC) due to AF. The trial will test, whether a DAT-regimen comprising clopidogrel plus the non-Vitamin-K-antagonist oral anticoagulant (NOAC) apixaban is superior to a TAT-regimen of vitamin-K-antagonist (VKA) plus dual anti-platelet therapy (APT) with respect to bleeding. A total of 400 patients will be randomized 1:1 to a control-arm with guideline-recommended TAT with VKA plus clopidogrel and acetylsalicylic-acid and a study arm receiving DAT comprising apixaban plus clopidogrel. Patients will be followed-up for 6 months. The primary endpoint of the study is the cumulative incidence of BARC type  $\geq 2$  bleeding, secondary endpoints include a composite clinical ischemic outcome and net clinical outcome.

**Conclusions:** APPROACH-ACS-AF is the first trial dedicated to ACS patients, testing whether in terms of bleeding a DAT with NOAC is superior to a TAT regimen with VKA in high-risk ACS patients with AF.

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## 1. Introduction

Patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) require a combination of oral anticoagulation (OAC) plus antiplatelet therapy to address the risk of stroke related to AF and the risk of recurrent myocardial ischemia after PCI [1,2]. Until recently, triple antithrombotic therapy (TAT) was the recommended antithrombotic regimen consisting of OAC with a vitamin K antagonist (VKA) plus dual antiplatelet therapy with acetylsalicylic-acid (ASA) plus P2Y12 inhibitor [3–6,7–9]. While effective in preventing recurrent ischemia, TAT is associated with increased bleeding complications, that have been reported to have a major impact on the prognosis of patients undergoing PCI [10,11]. Bleeding is also an economic challenge, since the annual health care costs per patient on OAC with intracranial bleeding, as well as major or minor gastrointestinal bleeding are as high as \$50,000 [12,13].

Several recent trials have therefore tested a de-escalated regimen, consisting in dual antithrombotic therapy (DAT) with single antiplatelet therapy (SAPT) comprising a P2Y12 inhibitor plus OAC preferably using non-Vitamin-K-antagonist oral anticoagulants (NOACs) instead of VKA [14–18]. Jointly, these trials showed a reduction in the primary outcome of bleeding [19]. There was no significant increase in ischemic outcomes in the individual trials; yet, none of the trials was sufficiently powered for this particular question. However, when the data of all landmark trials were pooled in a recent meta-analysis there was a significant increase in the rate of stent thrombosis with DAT compared to TAT [19–21]. This raises the important question whether it is indeed safe to recommend DAT rather than TAT to all AF patients undergoing PCI. In fact, the reduced efficacy in preventing ischemic events could be of particular relevance when treating high risk patients presenting with an ACS. On the other hand, annual bleeding rates of up to 44% have been reported in AF patients undergoing PCI; indicating that those patients might derive the greatest benefit from de-escalation [22,23].

Among AF patients undergoing PCI approximately 20–30% present with a clinical diagnosis of ACS [22–24]. While previous landmark trials comparing TAT versus DAT enrolled all-comers, a dedicated trial testing the efficacy of DAT compared to TAT in patients with ACS managed by PCI is lacking [14–17]. In addition, current evidence from large randomized controlled trials (RCTs) [14–17] mainly tested DAT against long-term TAT regimens that no longer represent guideline recommendations [8]. As a consequence, the bleeding rates observed in the TAT arms of previous trials and hence the benefit of de-escalation are potentially overestimated in these RCTs. This may be of particular relevance in ACS patients, that carry a high ischemic risk.

Hence, whether DAT rather than an initial (short-term) TAT should be recommended to the high-risk cohort of AF patients presenting with an ACS treated with PCI remains a matter of debate. We therefore designed the APPROACH-ACS-AF (APixaban versus PhenRocoumon: Oral AntiCoagulation plus antiplatelet tHerapy in patients with Acute Coronary Syndrome and Atrial Fibrillation) trial to test whether in AF patients with concomitant ACS managed by PCI a dual antithrombotic strategy is superior in terms of bleeding when compared to a guideline-conform triple regimen.

## 2. Study design

### 2.1. Study principle and study population

The APPROACH-ACS-AF study is an investigator initiated prospective randomized, parallel-group, open-labeled, blinded-endpoint, superiority, multicenter trial enrolling AF patients with an ACS managed with PCI. The planned study population will consist of 400 patients (200 per study arm). The study started in 2016 and is conducted in 17 investigational centers across Germany.

### 2.2. Hypothesis and objective

The main objective of the study is to evaluate whether DAT is superior to TAT in a high-risk group of AF patients with ACS managed by PCI. We hypothesize that a dual regimen, consisting of clopidogrel plus the factor Xa-inhibitor apixaban, compared to a triple treatment strategy consisting of VKA plus ASA plus clopidogrel reduces bleeding events (primary outcome), but is not associated with an increased ischemic risk (secondary outcome).

### 2.3. Primary and secondary study endpoints

#### 2.3.1. Primary endpoint

Bleeding is very frequent in ACS patients undergoing PCI and leads to increased mortality [22,23]. The primary objective of de-escalation from TAT to DAT is to reduce bleeding. Therefore, the rate of BARC type 2 or greater bleeding out to 6 months after randomization constitute the primary safety endpoint of this study [25]. The primary endpoint of BARC type 2 or greater bleeding was chosen since this bleeding category was shown to be associated with increased mortality in the context of PCI [11].

#### 2.3.2. Key secondary endpoint

The rate of a composite efficacy (ischemic) endpoint, comprising all-cause death, myocardial infarction, definite stent thrombosis, stroke/other systemic thromboembolism is the key secondary efficacy outcome of this study.

Additional secondary endpoints that will be assessed include:

- (1) Net clinical outcome: all-cause death, myocardial infarction, definite stent thrombosis (according to the academic research consortium [26]), stroke/other systemic thromboembolism [27] or BARC type > 3b bleeding [25];
- (2) Individual components of the composite secondary endpoint;
- (3) Cardiovascular death (acute myocardial infarction, sudden cardiac death, HF, stroke, cardiovascular procedure, cardiovascular hemorrhage, and other cardiovascular causes) [27];
- (4) Any bleeding episodes (according to Thrombolysis in Myocardial Infarction (TIMI) [28] and BARC criteria [25]).

For the composite clinical ischemic outcome myocardial infarction is defined according to the Third Universal Definition [29]; for the individual components of the secondary endpoint myocardial infarction is defined according to the Third Universal Definition and, in addition, according to earlier clinical trial definition [30].

### 3. Methods

#### 3.1. Study cohort

Patients with AF or atrial flutter with an indication for OAC (i.e. CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or greater) that present with an ACS which is successfully managed with PCI are eligible for study inclusion. APPROACH-ACS-AF is the only trial focusing on ACS patients including STEMI, NSTEMI and unstable angina pectoris. Table 1 gives an overview summarizing key characteristics of important conducted and ongoing clinical trials on treatment strategies in patients with indication for OAC.

#### 3.2. Inclusion and exclusion criteria

The APPROACH-ACS-AF study is a clinical trial enrolling only ACS patients with AF or atrial flutter, older than 18 years, undergoing successful PCI. Major exclusion criteria comprise patients with contraindications for chronic OAC and/or contraindications to one of the study drugs. Table 2 provides a detailed summary of all in- and exclusion criteria of the study.

#### 3.3. Randomization and treatment regimens

Eligible patients are randomized in a 1:1 fashion into one of the two study groups on the basis of an online randomization platform (provided by the Institut für Medizinische Informatik, Universitätsmedizin Göttingen). Patients were eligible for randomization at a minimum of 12 h after the index PCI out to the time of discharge from the primary care hospital, where the successful PCI procedure was performed. The treatment groups are studied concurrently. Patients are considered enrolled in the study and eligible for the final intention to treat analysis at the time of randomization.

Patients are randomized to the study groups (see Fig. 1), receiving either

DAT comprising apixaban plus clopidogrel (experimental arm of the study)

or

TAT consisting of ASA plus clopidogrel plus phenprocoumon (control arm of the study) with a duration of 1–6 months depending of the individual bleeding risk (see below), followed by DAT with clopidogrel plus phenprocoumon.

We recommended a duration of TAT in the control group depending on the individual bleeding risk of the patient, stratified

based on the patient's individual HAS-BLED score: HAS-BLED score ≤ 2: 6 months of concomitant ASA therapy; HAS-BLED score ≥ 3: 1 month of concomitant ASA therapy [3,5,6]. Our control regimen is in line with the ESC guidelines on revascularization published in 2018 [6], where the recommended duration of TAT depends on the individual bleeding risk of the patient. Fig. 1 illustrates the control and the experimental arm of the study.

#### 3.4. Rationale for triple therapy duration

The duration of TAT in the APPROACH-ACS-AF trial is 1–6 months depending on the individual bleeding risk (e.g. HAS-BLED-Score). This corresponds to the most recent guideline recommendation at the time of protocol finalization [5]. In contrast, previous trials test a dual regimen against longer or fixed TAT durations that go beyond the recommendations of both current and contemporarily valid ESC guidelines (see table 1) [14,15,17]. This may lead to over-estimation of the potential reductions in bleeding with DAT compared to TAT. The only exception is the ENTRUST-AF trial [16], which used a representative duration of TAT (with a mean duration of 66 days) in line with the current guideline recommendations (table 1). Yet, this latter trial showed a strong trend but failed to show a statistically significant reduction in bleeding events in the dual therapy arm compared to TAT.

#### 3.5. Rationale for choice of antithrombotic treatment

The PIONEER-AF-PCI [15] trial used a modified dosage of rivaroxaban [31]. In contrast, the RE-DUAL PCI [17], ENTRUST-AF-PCI [16], and AUGUSTUS [14] trials evaluated anticoagulant doses established in large trials. These latter trials allowed an evaluated use of the potent P2Y<sub>12</sub> inhibitors ticagrelor and prasugrel at the discretion of the physician, [5–8]. A substudy of the RE-DUAL PCI trial showed higher bleeding rates in patients treated with ticagrelor compared to patients treated with clopidogrel blunting some of the benefits of DAT [32], as a consequence use of ticagrelor and prasugrel is discouraged by the guidelines [4,6]. The APPROACH-ACS-AF protocol therefore follows guideline recommendations and allows only clopidogrel.

#### 3.6. Study duration and follow-up

The planned total duration of the study is 52 months. 43 months are planned for enrolment of patients. All patients will receive the study treatment according to their assigned study group for a total of 6 months. The follow-up period is 6 months. Follow-ups are performed after 1 and 6 months by telephone call or in-office visits. The follow-up duration of 6 months was based on the guideline recommendations [5,6,8], which all consistently recommend a uniform dual antithrombotic regimen after 6 months post PCI, irrespective of the stent type. Patients are monitored for endpoint events and adverse events. Three months are required to finalize all study-related procedures with regard to documentations and reports for the enrolled patients.

#### 3.7. Statistical considerations

The sample size calculation of the APPROACH-ACS-AF trial is based on the reported bleeding rates of the ISAR-REACT 4 trial [33] and WOEST trial [23].

Adjusted to a shorter follow-up period our calculation is based on the assumption, that a 6-months bleeding probability of 27% in the control group is expected, which is significantly reduced to a 6-months bleeding probability of 15.5% by the experimental regimen. This assumption is also in line with the results and reported bleeding rates in the recently published PIONEER AF-PCI trial [15].

**Table 1**  
Major clinical trials on treatment strategies in patients with indication for OAC undergoing PCI.

APPROACH-ACS-AF (NCT02789917)	PCI patients (only ACS) with indication for OAC (100% AF)	400	VKA + ASA + Clopidogrel vs. Apixaban (full dose) + Clopidogrel	1–6 months according to bleeding risk	Randomized, multicenter, prospective	Dual (with NOAC) vs. triple therapy	BARC ≥ 2 bleeding during 6 months of FU
WOEST[23] (NCT02164864)	PCI patients (all comers) and indication for OAC (69% AF)	573	Warfarin + Clopidogrel + ASA vs. Warfarin + Clopidogrel	At least 1 month in BMS (32% of patients), 12 months in DES (65%)	Randomized, multicenter, prospective	Dual vs. triple therapy	Combined end point of minor, moderate or major bleeding complications during the initial hospitalization & 1 year of FU (TIMI & GUSTO criteria).
ISAR-TRIPLE[22] (NCT00776633)	PCI patients (all comers) and indication for OAC (100% AF)	614	VKA + ASA + Clopidogrel	6 weeks vs. 6 months	Randomized, multicenter, prospective	Triple therapy for different duration	composite of death, myocardial infarction, definite stent thrombosis, stroke or major bleeding (in 9 months of FU)
PIONEER -AF-PCI [15] (NCT01830543)	PCI patients (all comers) and indication for OAC (100% AF)	2124	Rivaroxaban 15 mg + Clopidogrel/ Prasugrel/ Ticagrelor vs. Rivaroxaban 2,5mg + ASA + Clopidogrel/ Prasugrel/ Ticagrelor vs. VKA + ASA + Clopidogrel/ Prasugrel/ Ticagrelor	1 (16% of patients) 6 (35%), 12 months (49%) according to randomization	Randomized, multicenter, prospective	Dual (with NOAC) vs. triple therapy in two different strategies (low dose NOAC vs. VKA)	number of participants with clinically significant bleeding (12 months of FU) Clinically significant bleeding is a composite of TIMI major and minor bleeding, and bleeding requiring medical attention.
AUGUSTUS[14] (NCT02415400)	PCI or ACS (with or without PCI) patients and indication for OAC (100% AF)	4614	Apixaban + Clopidogrel vs. VKA + Clopidogrel AND ASA vs. placebo	6 months	Randomized, multicenter, prospective	Dual therapy vs. triple therapy AND Apixaban vs. Warfarin	ISTH Major bleeding or clinically relevant non-major bleeding (in 6 months of FU)
RE-DUAL- PCI[17] (NCT02164864)	PCI patients (all comers) and indication for OAC (100% AF)	2725	Dabigatran 110 mg/ 150 mg + Clopidogrel/ Ticagrelor Vs. Warfarin + Clopidogrel/ Ticagrelor + ASA	1 month BMS (15% of patients), 3 months DES (83%)	Randomized, multicenter, prospective	Dual (with NOAC) vs. triple therapy	Time to first TIMI Major Bleeding Event or Clinically Relevant Non Major Bleeding Event
ENTRUST-AF-PCI [16] (NCT02866175)	PCI patients (all comers) and indication for OAC (100% AF)	1506	Edoxaban + Clopidogrel/ Prasugrel/ Ticagrelor Vs. Marcumar + Clopidogrel/ Prasugrel/ Ticagrelor + ASA	1–12 months (mean 66 days)	Randomized, multicenter, prospective	Comparison of two dual therapy regimes (Edoxaban vs. Marcumar)	Number of Major or Clinically Relevant non-major ISTH-defined Bleeding (MCRB) (in 12 months of FU)
MANJUSRI [36] (NCT02206815)	PCI patients (all comers) and indication for OAC (100% AF)	296	Ticagrelor + Warfarin Vs. Clopidogrel + ASA + Warfarin	6 months	Randomized, multicenter, prospective	Dual vs. triple therapy	Overall bleeding events (in 6 months of FU)
AVIATOR 2 Registry[37] (NCT02362659)	PCI patients (all comers) and indication for OAC (100% AF)	2500	At the physicians discretion	At the physicians discretion	multicenter, multinational, observational prospective registry	Comparison of different antithrombotic and anticoagulant regimes, at the physicians' discretion	-Number of participants with AE (MACCE at 1 year) -bleeding (BARC 2,3 or 5)

ACS = acute coronary syndrome, AE = adverse event, AF = atrial fibrillation/flutter, ASA = acetylsalicylic acid, BARC = bleeding academic research consortium, FU = follow-up, GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries, MACCE = major adverse cardiac and cerebrovascular events, NOAC = new oral anticoagulation, OAC = oral anticoagulation, PCI = percutaneous coronary intervention, TIMI = Thrombolysis in Myocardial Infarction. VKA = vitamin K antagonist.

Each patient is intended to be followed for a total of 6 months and the exact time points of bleeding events are recorded during this period. The primary outcome is the time of the first bleeding event.

The critical values and the test characteristics of the group sequential test design were calculated for the O'Brien and Fleming design. The parameters are chosen to minimize the expected number of patients under a very conservative assumption: ASNH0 + ASNH1.

For specified one-sided alpha = 0,025, event rates  $\pi_{\text{control}} = 0.27$ ,  $\pi_{\text{experimental}} = 0.155$  at month 6 (hazard ratio = 0.535), the power 1 - beta is 80.0% if the logrank test is performed at the number of accumulated (pooled) events. The computation assumes an allocation ratio  $n_{\text{experimental}}/n_{\text{control}} = 1.0$ .

Assuming a follow-up time of 6 months per individual patient a total of 360 patients (180 patients per group) is expected to yield the necessary number of events. For comparison, the sample size in a fixed sample size design is  $n_1 + n_2 = 354$  (177 per group). In

**Table 2**

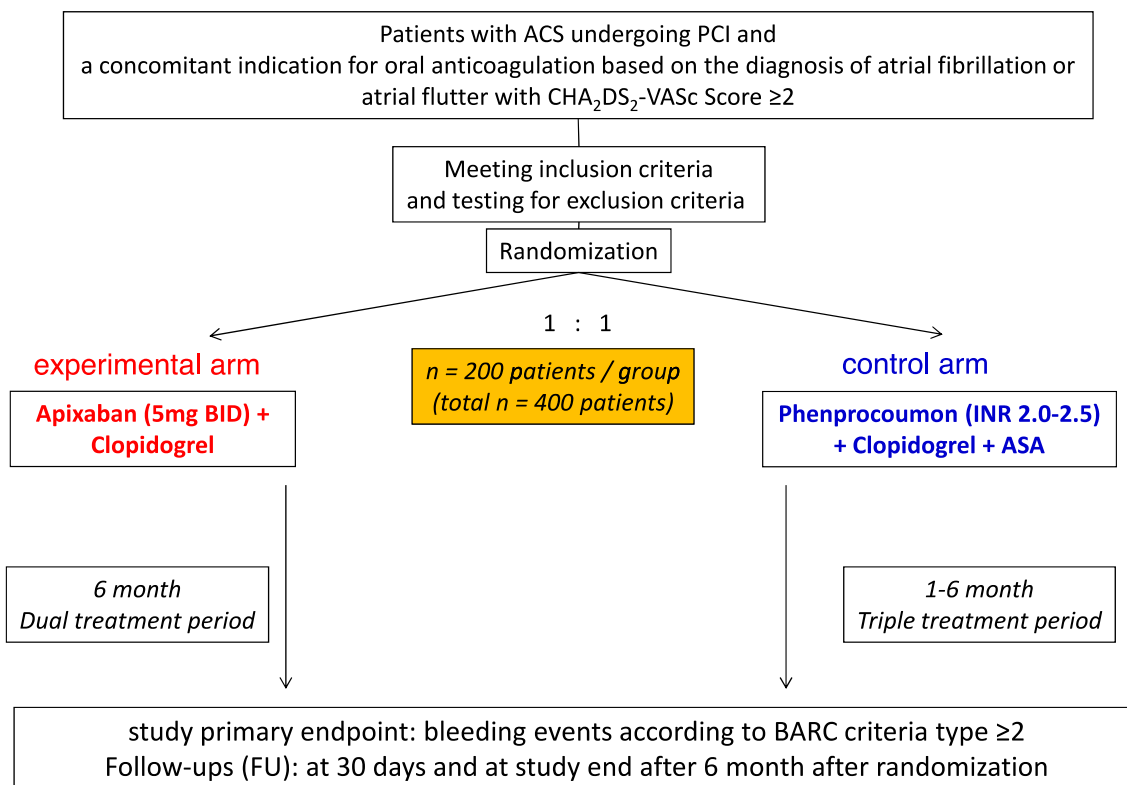
Study inclusion and exclusion criteria. The table lists all inclusion and exclusion criteria of the trial as stated in the latest version of the trial protocol.

**Inclusion Criteria:**

- Signed written informed consent
- Patients with an ACS after successful percutaneous coronary intervention
- Indication for oral anticoagulation due to non-valvular atrial fibrillation or atrial flutter (CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥ 2)
- Males and females, ages ≥ 18
- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 h prior to the start of study drug
- Women must not be breastfeeding
- WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus 30 days (duration of ovulatory cycle) post-treatment completion. However, they must still undergo pregnancy testing

**Exclusion Criteria:**

- Age < 18 years
- Active bleeding
- History of TIMI major bleeding according to TIMI and/or type ≥ 3b BARC criteria in the last 6 months
- History of intracranial bleeding
- History of peptic ulcer in the last 6 months
- Subjects with a history of a complicated or prolonged cardiogenic shock in the last two weeks prior to randomization. A complicated or prolonged cardiogenic shock is defined by a cardiogenic shock that required mechanical ventilation or the cardiovascular support with positive inotropic drugs (i.v. catecholamine) for ≥ 7 days
- Planned major surgery during the study course with planned discontinuation of antithrombotic therapy
- Expected life expectancy of less than a year and/or severe illness (e.g. malignancy)
- Mechanical valve replacement
- Valvular atrial fibrillation
- Severe renal insufficiency (creatinine clearance < 30 ml/min)
- Severe liver insufficiency (Child-Pugh-class C) or elevated hepatic transaminases > 2 times the upper limit of normal
- Patient's inability to fully comply with the study protocol
- Known or persistent abuse of medication, drugs or alcohol reliable by the investigator in individual cases
- Subjects with known contraindications to apixaban, phenprocoumon, clopidogrel or ASA treatment, which are hypersensitive to the drug substance or any component of the product
- Relevant hematologic deviations: platelet count < 50 G/L or platelet count > 600 G/L
- Current or planned pregnancy or nursing women, women 90 days after childbirth. Females of childbearing potential, who do not use and are not willing to use medically reliable methods of contraception for the entire study duration (such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices) unless they are surgically sterilized / hysterectomized or there are any other criteria considered sufficiently



**Fig. 1.** Study flow chart and treatment groups. The figure illustrates the control arm and the experimental arm of the study. 1:1 randomization is done after PCI and before discharge of patients. The primary endpoint is bleeding events according to BARC criteria type ≥ 2. Follow-ups will be performed at 30 days and at 6 months after randomization.



order to compensate a loss to follow up of 10% a total of 400 patients are included into the study.

In case of the optimistic assumption (6-months bleeding probability of 27% in the control group and a 6-months bleeding probability of 10% in the experimental group) a total of 178 patients is needed to show the assumed difference on a one-sided significance level of 0.0082 with a power of 80%.

The primary analysis is performed on an intention to treat basis for the primary endpoint. The main hypothesis will be assessed via the difference in the cumulative bleeding incidences (cumulative hazard functions over the first 6 months) between both treatment groups using time-to-event methodology: Kaplan-Meier-Estimates and stratified Cox-Regression. The stratified Cox-Regression allows to calculate a 95% CI for the hazard ratio, which represents the treatment effect. The analyses will be stratified with respect to the HAS-BLED score  $< 3$  /  $\geq 3$ .

### 3.8. Organizational structure

Project management and monitoring of the trial are conducted by the Münchner Studienzentrum (MSZ, Klinikum Rechts der Isar) as an independent clinical research organization. The steering committee is responsible for overseeing the good execution and administrative progress of the protocol. An independent Safety Monitoring Board (SMB) is responsible for making risk-benefit assessment and making recommendations regarding endpoint analysis and any potential problems. Events will be reported to the SMB. It is also responsible for reviewing the final results of the clinical study regarding the analysis. The independent Event Adjudication Committee (EAC) will adjudicate the clinical events within the trial. All members of the committee will be blinded to the primary results of the trial and will be blinded to the randomized treatment for any adjudicated patient.

### 3.9. Status quo

The first patient in APPROACH-ACS-AF was enrolled in July 2016. As per February 2020, recruitment was completed for the trial. Follow-up has been completed recently. Reporting of trial results is currently planned for the second or third quarter of 2021.

### 3.10. Ethical and regulatory aspects

The sponsor (Ludwig-Maximilians-University, Munich, Germany) has the overall responsibility for the conduct of the study, including assurance that the study is conducted in accordance with the provisions of the Declaration of Helsinki as amended in Seoul (2008), with the International Conference on Harmonization "Good Clinical Practices" and the relevant national regulations.

## 4. Discussion

The results of the randomized WOEST-trial [23] first tested the hypothesis that a dual therapy regimen omitting ASA could be an alternative to TAT in a mixed cohort of triple patients including patients with AF undergoing PCI. As a consequence, a series of four large RCTs was designed to test a dual regimen (mostly including a NOAC instead of VKA) against a TAT (including Warfarin as OAC) in AF patients undergoing PCI. Three out of these four trials demonstrated that DAT is superior to TAT with respect to bleeding events. They were not sufficiently powered to show or exclude differences in ischemic events between TAT and DAT [14,16]. However, in a sub-analysis of the AUGUSTUS trial ischemic myocardial events (myocardial infarction, stent thrombosis, urgent revascularization) tended to be higher in DAT compared to in the TAT strategy

independent of the type of anticoagulant [34]. The results of the ENTRUST-AF PCI trial despite showing a strong trend failed to show a statistical superiority of DAT compared to TAT with respect to the primary bleeding endpoint, but confirmed the trend towards more ischemic events. A consecutive meta-analysis including all four RCTs for the first time revealed a significant increase in the risk of stent thrombosis with DAT compared to TAT in the combined analysis of 10,234 patients [19]. Another meta-analysis including those RCTs focusing on ACS patients showed a non-significant increase of stent thrombosis and myocardial infarctions [35]. This casts doubts whether a deescalated dual antithrombotic treatment strategy should be the preferred choice also for patients with AF undergoing PCI carrying a high ischemic risk, such as patients presenting with an ACS. The APPROACH-ACS-AF trial will address this question by testing whether a dual regimen with a NOAC (Apixaban) and P2Y12 inhibitor (Clopidogrel) is superior with respect to prevention of bleeding events when compared to guideline-recommended bleeding-risk adjusted TAT in AF patients undergoing PCI for management of an ACS.

## 5. Conclusion

Based on current lacking evidence it remains still unclear if ACS patients with AF carrying a high ischemic and bleeding risk should receive DAT or TAT. The APPROACH-ACS-AF trial is designed to test whether a dual therapy strategy including a NOAC compared to a bleeding-risk adjusted TAT including VKA is superior with respect to bleeding events in a high-risk ACS cohort. Along with the findings obtained from previous all-comers studies, the results of the APPROACH-ACS-AF trial will provide important insights regarding the equipoise of bleeding and ischemia in high risk AF patients presenting with ACS.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: D.M.L reports grants from Deutsches Zentrum für Herz-Kreislaufforschung (DZHK), Bayer AG, AstraZeneca, Novartis, Abbott Vascular, Biotronik and Sahajanand Medical Technologies Pvt Ltd. (SMT) and personal fees from Bayer AG, Daiichi Sankyo, Amgen, B. Braun, Abbott Vascular, Boehringer Ingelheim, Boston, Sahajanand Medical Technologies Pvt Ltd. (SMT), Medtronic, Bayer AG, Vifor, Novartis and AstraZeneca; T.G. reports a research grant from Abbott Vascular and neovasc, lecture/consulting fees from Abbott Vascular, Neovasc, Boston Scientific, Daiichi-Sankyo, Bayer, Astra Zeneca, BMS, SMT, Eli Lilly, Pfizer, all outside the submitted work; I.A. reports personal fees from Daiichi Sankyo, Pfizer/BMS, Boston Scientific, GORE Medical; A.A.M. reports personal fees from AMGEN, AstraZeneca, BAYER, Berlin Chemie, Daiichi Sankyo outside the submitted work; M.B. received personal fees from Bayer, Boehringer-Ingelheim, Boston-Scientific, Daiichi-Sankyo, Medtronic, ZOLL CMS; F.E. reports grants from German Research Foundation (DFG), grants from German Ministry of Education and Research, during the conduct of the study; personal fees and non-financial support from Novartis, grants and personal fees from Boehringer Ingelheim, personal fees from CVRx, Pfizer, Medtronic, grants and personal fees from Servier, personal fees from MSD/Bayer, personal fees from Bayer, personal fees from Resmed, personal fees from Berlin Chemie, grants from Thermo Fischer, personal fees from Vifor Pharma, personal fees from PharmaCosmos, personal fees from Merck, outside the submitted work; N.S. received travel grants from BMS/Pfizer outside the submitted work; D.S. reports grants from Roche Diagnostics, grants from Daiichi Sankyo, personal fees from Bayer, personal fees from Astra Zeneca, personal fees from Daiichi Sankyo,

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