Platelet-activation and optimal inhibition in patients with Atrial Fibrillation undergoing LAA closure; The POPULAR-LAAO trial

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Primary ObjectiveThe goal of the study is to evaluate hemostasis (i.e. coagulation activation, platelet reactivity, overall thrombus formation and fibrinolysis) following LAAO in a longitudinal design for hypothesis-generating purposes. Several...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac arrhythmias
Study type	Observational non invasive

Summary

ID

NL-OMON49947

Source
ToetsingOnline

Brief title
POPULAR-LAAO

Condition

- Cardiac arrhythmias

Synonym
Afib, Atrial fibrillation

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis

Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Device-related thrombus, Hemostasis, Left Atrial Appendage Occlusion, Non-valvular AF

Outcome measures

Primary outcome

This study will capture the following (exploratory) primary endpoints:

• Coagulation activation: TAT (thrombin-antitrombin III complex), prothrombin 1+2, and factor XIIa

• Platelet reactivity as measured with multiple platelet function tests: Multiplate and Pselectin

• Overall thrombus formation and clot lysis assessment using T-TAS (total thrombus formation analysis system), TEG (thromboelastography), TGT (thrombin generation test, fibrinopeptide A+B, fibrinogen, vWF (von Willebrand factor), PT, APTT

• Fibrinolysis: d-dimer and plasmin inhibitor (i.e. alfa-2-antiplasmin)

• CYP2C19 polymorphism: carriers of one of the loss-of-function *2 and *3 alleles will be stratified as intermediate metabolizers, patients with 2 loss-of-function alleles will be stratified as poor metabolizers

Platelet function and thrombin generation testing will be performed in blood samples collected before the procedure, directly after LAAO, and after 14 days, 3 months and 6 months. The goal of the study is to evaluate platelet inhibition and thrombin generation after LAAO with regard to clinical endpoints and

patient characteristics such as CYP2C19 genotype and antithrombotic regimen. Procedural characteristics such as type of device and echographic parameters will also be taken into account.

Secondary outcome

In addition to coagulation endpoints and CYP2C19 genotype, secondary clinically oriented endpoints during 12-month follow-up will include:

• The composite of stroke (ischemic or hemorrhagic), TIA, systemic embolism and cardiovascular death.

• Ischemic stroke

• Disabling stroke

• Separate ischemic or hemorrhagic stroke, mortality (both cardiovascular and all-cause), TIA, systemic embolism

• Major bleeding event rate (according to BARC criteria), both procedural up to 7 days, as well as total

• Minor bleeding event rate, both procedural up to 7 days, as well as total

• Procedural efficacy of LAAO up to 30 days

• Adverse events rate at 30 days, and from 30 days until end of follow up

• LAA sealing efficacy according to manufacturer*s definitions at all the predefined LAA CT/TEE imaging moments

• Device related thrombus event rate

• Quality of life assessments at regular basis in follow up (SF-12, HADS, EQ5D5L)

Study description

Background summary

Atrial fibrillation (AF) is prevalent in the Netherlands in around 300.000 patients. Cardio-embolic AF related stroke is assumed in around 7500 patients annually. Stroke risk for non-valvular AF is estimated with the CHA2DS2-VASc score. When patients have no risk factors, no oral anticoagulation (OAC) is recommended with a Class III, loe B. With 1 risk factor in men and 2 in women, anticoagulation should be considered (class IIA, loe-B). When the CHA2DS2-VASc score is 2 or greater in men (3 or greater in women) anticoagulation is recommended in all with a Class I, loe-A, preferably with a NOAC (class I, loe-A). However, anticoagulant therapy is undesirable in a subgroup of patients because of a high risk of (recurrent) bleeding.

Mechanical occlusion of the Left Atrial Appendage (LAAO), which is the main source of cardio-embolism, has emerged strongly in the last decades as an alternative to prevention of ischemic stroke. Percutaneous LAAO using the Watchman device has been proven non-inferior to vitamin K antagonists regarding thrombo-embolic prevention. Moreover, the possibility of cessation of OAC over time after LAAO has a positive effect on major bleeding rates. In post hoc analyses of PROTECT-AF, PREVAIL, and the CAP registries, it was observed that after discontinuation of warfarin at 45 days, bleeding rates in the Watchman arm were only half of those in the warfarin arm, and dropped another 50% after discontinuation of DAPT. For AMPLATZER amulet and other LAAO devices there are no published RCT compared to either VKA or NOAC. The EWOLUTION all-comers registry data in over 1000 AF pts (73% unable to use (N)OAC, CHA2DS2-VASc 4.7) after WATCHMAN LAAO showed stroke and bleeding rates 80% and 46% lower than expected compared to historical data. In 2 similar AMPLATZER-AMULET LAAO registries of >1000 AF patients, stroke and bleeding rates were 50-60% lower.

Both in the 2020 ESC and the 2019 AHA/ACC guidelines, LAAO has received a Class IIb, loe-B recommendation for stroke prevention in patients with AF that have non-reversible contra-indications for long-term anticoagulation. Randomized controlled trials comparing LAAO to direct oral anticoagulants (DOACs) are currently running. LAAO may also be a suitable option based on patient preference or AF-related ischemic events under OAC.

Administering OAC after LAAO procedure in the selection of patients ineligible for OAC is undesirable for obvious reasons. There is still no consensus on optical medical treatment after LAAO, despite multiple observational studies. In the Netherlands, dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and clopidogrel (CLOP) has emerged as the standard of care treatment directly after LAAO. However, this strategy is only based on expert opinion and no randomized controlled trials have been conducted regarding optimal medical approach to anticoagulation and platelet inhibition after LAAO.

Moreover, device-related thrombus (DRT) remains prevalent among patients undergoing LAAO. In the randomized Watchman device arms of the PROTECT-AF and PREVAIL combined with CAP-I and CAP-II registries, DRT occurred in 3.7% of 1739 patients. Similar numbers were found in the European EWOLUTION trial (2.5%) and the Asian-Pacific WASP registry (2.5%). For the Amplatzer device, similar DRT rates were found in the ACP registry, showing a DRT rate of 2.7%. In both devices an association of DRT and ischemic stroke, TIA, or systemic embolism have been reported. In a registry by Fauchier et al., risk factors for thrombus formation on the device included older age and previous ischemic stroke, while DAPT and OAC at discharge showed significantly lowered hazard ratios for DRT (0.10 (0.01-0.76) and 0.26 (0.09-0.77), respectively).Furthermore, suboptimal LAA occlusion, lower left ventricular ejection fraction (LVEF), larger LA size, greater spontaneous echocardiogram contrast (SEC) and lower peak LAA emptying velocity have been mentioned as possible risk factors.

The mechanism behind DRT remains uncertain. In the EWOLUTION registry, 34 of 835 patients with LAA imaging showed DRT. In these patients, no clear relation could be found regarding type of anticoagulation regimen. Both platelet activation and coagulation cascade could play a role in the pathogenesis of DRT. Rodés-Cabau et al. showed elevated biomarkers for coagulation activation 7 days after device implantation, without significant elevation of biomarkers for platelet activation. This suggests the possible importance of coagulation cascade above platelet activation in DRT.

Clopidogrel resistance might also play a role in observed DRT rates after LAAO. The efficacy of a genotype-based approach taking this phenomenon into account in primary percutaneous intervention in myocardial infarction has recently been described by Claassens et al. In this study, genetic clopidogrel resistance testing was performed in 1240 patients, of which 31% were intermediate to poor metabolizers based on genetic testing. A genotype-based approach to antiplatelet therapy was non-inferior with regard to thrombotic events and resulted in a lower incidence of bleeding. After LAAO, less data regarding clopidogrel resistance is available. In a case series by Ketter et al., 4/46 LAAO patients developed DRT. Of these DRT patients, 3 (75%) showed resistance to clopidogrel after platelet function testing. This suggests possible under treatment of a proportion of patients receiving clopidogrel.

Multiple tests have been developed regarding quantification of hemostasis. Prothrombin 1+2 and thrombin-antithrombin III complex (TAT) have proven to be valuable markers for coagulation activation.Platelet reactivity and aggregation can be assessed using flowcytometry for measuring the percentage platelet bound P-selectin expression. Whole blood multiple electrod aggregometry (MEA) is useful for measuring the magnitude of platelet reactivity by several agonist such as Adenosine Diphosphate- and Arachidonic Acid-induced platelet aggregation (ADP and AA), yielding information about the effectiveness of P2Y12-inhibitors (e.g. clopidogrel, ticagrelor) and acetylsalicylic acid (ASA) and the risk of ischemic events. Furthermore, thromboelastography (TEG), total

thrombus formation analysis (T-TAS) and thrombin generation test (TGT) can help clarify several hemostatic processes.
The aim of this study is to analyze changes in coagulation activation and platelet reactivity after LAAO in several subgroups in a hypothesis-generating manner.

Study objective

Primary Objective
The goal of the study is to evaluate hemostasis (i.e. coagulation activation, platelet reactivity, overall thrombus formation and fibrinolysis) following LAAO in a longitudinal design for hypothesis-generating purposes. Several factors will be taken into account, such as type of implantation device, CYP2C19 polymorphism and antithrombotic regimen.

Secondary Objective(s
In addition to coagulation endpoints, secondary clinically oriented endpoints during 12-month follow-up will include:
* Minor and major bleeding
* Device-related thrombus incidence
* Stroke, TIA, and systemic embolism

Study design

We propose a prospective observational study to identify the state of coagulation and platelet activity in patients after LAAO. Subjects may be on dual antiplatelet therapy (DAPT), single antiplatelet therapy (SAPT), oral anticoagulation (OAC) or use no anti-thrombotic agents at all. This will be at the discretion of the treating physician. Blood samples will be taken prior to LAAO, shortly after LAAO, and 14 days, 3 months and 6 months after the procedure. Genotype testing for CYP2C19 will be performed in all patients at baseline to asses prevalence of clopidogrel *non-responders* in the LAAO population. Implantations will be mainly be performed using the Watchman (FLX) device or AMULET device, but other devices are emerging and not excluded from this study. Subjects will receive quality of life questionnaires at baseline, 3 months, 6 months and 12 months after the procedure. Study follow-up will take place during 1 year per patient, followed by follow-up conform current standard of care. The total study duration is estimated to be 4 years.

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for deviation will be assessed. Blood samples will be taken prior to LAAO, shortly after LAAO, and 14 days, 3 months and 6 months after the procedure. Genotype testing for CYP2C19 will be performed in all patients at baseline to asses prevalence of clopidogrel *non-responders* in the LAAO population. Implantations will be mainly be performed using the Watchman (FLX) device or AMULET device, but other devices are emerging and not excluded from this study. Subjects will receive quality of life questionnaires at baseline and 3 months, 6 months and 12 months after the procedure.Study follow-up will take place during 1 year per patient, followed by follow-up conform current standard of care. The total study duration is estimated to be 4 years.

Study burden and risks

Study-related risks involve multiple venepunctures for diagnostic testing in an observational study-design. Potential risks of venepuncture involve bleeding/hematoma formation, infection, nerve damage and syncope.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- The subject is aged 18 years or older
- The subject is accepted/scheduled for left atrial appendage closure
- The subject has a CHA*DS*-VASc Score >=2 (male) or >=3 (female)
- The subject or legal representative is able to understand and is willing to provide written informed consent to participate in the trial.

Exclusion criteria

- Unable or unwilling to return for required follow-up visits and examinations
- Mechanical heart valves or valvular disease requiring surgery or interventional procedure
- Ongoing major bleeding or complicated or recent (<72hours) major surgery
- Known large oesophageal varices or decompensated liver disease (unless a documented positive opinion of a gastro-enterologist)
- Severe thrombocytopenia (<50,000/ml)
- High likelihood of being unavailable for follow-up or psycho-social condition making study participation impractical.
- Woman with child bearing potential who do not use an efficient method of contraception.
- Positive serum or urine pregnancy test for woman with child bearing potential
- Pregnancy or within 48 hours post-partum
- unsuitable LAA anatomy for closure or thrombus in the LAA at the time of procedure
- contraindications or unfavourable conditions to perform cardiac catheterization or TEE
- atrial septal malformations, atrial septal defect or a high-risk patient foramen ovale that may cause thrombo-embolic events
- atrial septal defect repair or closure device or a patent foramen ovale repair or any other anatomical condition as this may preclude an LAAO procedure
- Mitral valve regurgitation grade 3 or more
- Aortic valve stenosis (AVA<1.0 cm2 or Pmax>50 mmHg) or regurgitation grade 3 or more
- Planned CEA for significant carotid artery disease
- Life expectancy of less than 1 year

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-02-2021
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO Date:	08-12-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-02-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-01-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL75530.100.20