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Rationale and design of a study exploring the efficacy of once-daily oral rivaroxaban (X-TRA) on the outcome of left atrial/left atrial appendage thrombus in nonvalvular atrial fibrillation or atrial flutter and a retrospective observational registry providing baseline data (CLOT-AF)

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Trial Designs

Rationale and design of a study exploring the efficacy of once-daily oral rivaroxaban (X-TRA) on the outcome of left atrial/left atrial appendage thrombus in non-valvular atrial fibrillation or atrial flutter and a retrospective observational registry providing baseline data (CLOT-AF)

RCT#s: NCT01839357 (X-TRA study), NCT01928979 (CLOT-AF registry)

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Abstract

There are still many unresolved issues concerning patient outcomes and prognostic factors in patients with atrial fibrillation (AF) and left atrial/left atrial appendage (LA/LAA) thrombi. Rivaroxaban (Xarelto®), a potent and highly selective, oral, direct factor Xa inhibitor, is a new therapeutic option in this setting. The planned study program will consist of a prospective interventional study (X-TRA) and a retrospective observational registry (CLOT-AF).

The primary objective of the X-TRA study is to explore the efficacy of rivaroxaban in the treatment of LA/LAA thrombi in patients with non-valvular AF or atrial flutter, scheduled to undergo cardioversion or AF ablation, in whom an LA/LAA thrombus has been found on transesophageal echocardiography (TEE) before the procedure. The primary endpoint is the complete LA/LAA thrombus resolution rate at 6 weeks of end-of-treatment confirmed by TEE. The secondary objectives are to describe: categories of thrombus outcome in patients (resolved, reduced, unchanged, larger, or new) confirmed on TEE at the end-of-treatment (after 6 weeks of treatment); incidence of the composite of stroke and non-central nervous system systemic embolism at the end-of-treatment and during follow-up; and incidence of all bleeding at the end-of-treatment and during follow-up.

The objective of the CLOT-AF registry is to provide retrospective thrombus-related patient outcome data following standard-of-care anticoagulant treatment in patients with non-valvular AF or atrial flutter, who have TEE-documented LA/LAA thrombi. The data will be utilized as a reference for the prospective X-TRA study.

In conclusion, X-TRA and CLOT-AF will provide some answers to the many unresolved issues concerning patient outcomes and prognostic factors in patients with AF and LAA thrombi. Results from this study program would provide the first prospective interventional study (X-TRA)

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and a large international retrospective observational registry (CLOT-AF) on the prevalence and natural history of LA/LAA thrombi. Unique data on clot resolution with rivaroxaban in a prospective cohort would be obtained in X-TRA.

Trial registration numbers: NCT01839357 (X-TRA study); NCT01928979 (CLOT-AF registry)

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Introduction

Atrial fibrillation (AF) predisposes to the development of atrial thrombi, most commonly in the left atrial appendage (LAA), which is the dominant source of embolism (>90%) in non-valvular AF.[1] Poor quality anticoagulation, especially where time in therapeutic range (international normalized ratio [INR] 2.0-3.0) is poor, or prior to establishment of effective oral anticoagulation, is associated with an increase in the risks of stroke and thromboembolism.[2,3] Unresolved thrombi in the LAA (identified in 10% of patients with AF and at high risk of thromboembolism) may result in an increased subsequent risk of thromboembolic events.[4–6] For example, during the initial control phase of the Ludwigshafen Observational Cardioversion Study, in the conventional approach (utilizing transthoracic echocardiography [TEE]), left atrial (LA)/LAA thrombus was found in the left atrium in 7.7% of cases and three thromboembolic events occurred in the first 4 weeks after cardioversion (CV; 0.8%), a rate similar to that observed in the prospective transesophageal echocardiographic group.[7]

TEE is well established as the gold standard for evaluation of the LA/LAA for the presence of thrombi.[8–11] If an LA/LAA thrombus is detected during TEE evaluation, current AF guidelines include treatment with vitamin K antagonist (VKA) therapy for 3 weeks, with an INR ranging from 2.0 to 3.0.[12] A follow-up TEE assessment at 3 weeks is recommended to ensure thrombus resolution.[12]

CV is one of the therapeutic options used to restore sinus rhythm; however, the procedure may result in dislodgment of LA thrombi or lead to new thrombus formation owing to atrial stunning after CV and is associated with an increased risk of stroke.[4,13,14] A treatment option is to perform immediate CV in patients with symptomatic AF after exclusion of LA thrombi with TEE under effective anticoagulation with short-acting anticoagulants. After a median of 4 weeks on warfarin therapy, the resolution rates of the thrombi on TEE were reported to be approximately 50 to

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90%.[4,7,9,14–16] The wide range of resolution rates were caused by different populations (e.g. those that did or did not include valvular AF; first diagnosed or persistent AF), different anticoagulation, and/or imaging strategies evaluated in relatively small observational studies.

Owing to the low incidence of LA/LAA thrombi in patients with AF, data are limited. In ROCKET AF, 321 patients underwent a total of 460 CV or AF ablation procedures.[17] Only small retrospective or prospective observational studies have been published (Supplemental document). In a post hoc analysis of the ARISTOTLE trial, no LA thrombi were found in 171 patients who underwent TEE.[18]

Data for the non-VKA oral anticoagulants (NOACs, previously called new or novel OACs) are presently limited[19] with regard to the treatment and outcome of patients with AF and LA/LAA thrombus, and these data largely comprise case reports. NOACs may offer several advantages in their relative efficacy, safety, and convenience, as well as fast onset of therapeutic anticoagulation when LA/LAA thrombus is detected.[20,21]

Several case reports with NOACs, however, indicate favorable outcomes in thrombus patients treated with NOACs, in which VKAs failed to resolve LA thrombi. In one case, LAA thrombus was resolved after 7 weeks' treatment with dabigatran. This patient failed to achieve INR >2 after 2 weeks of dose-adjusted VKA therapy before switching to dabigatran.[22] Results of a preliminary publication have shown that among 487 patients undergoing TEE before electrical CV or before AF ablation, when stratified by type of anticoagulation, dabigatran use was associated with a 4.6-times higher likelihood of LAA thrombi compared with warfarin (odds ratio 4.6 (1.6 to 21), $P = 0.003$) and 6.2-times higher likelihood compared with rivaroxaban (odds ratio 6.2 [1.9 to 31], $P = 0.002$).[23] After 4 weeks' treatment with rivaroxaban 15 mg once daily in a 64-year-old male, TEE showed a decrease in thrombus size; 6 weeks' treatment resulted in

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complete resolution of the LAA thrombus.[24] Additionally, Takasugi and colleagues described a set of three cases in which patients with non-valvular AF-related stroke had resolution of LAA thrombi within 8-33 days of rivaroxaban treatment.[25] Apixaban was also shown to completely resolve LA thrombus in a 72-year-old male, following 16 days of treatment.[26] In an 86-year-old male, 11 weeks of apixaban therapy led to almost complete resolution of LA thrombus.[27] Studies examining TEE detection and thrombus resolution are described in Supplementary Table I.

It is possible that the potential mechanism of action of NOACs allows for relatively higher thrombus resolution rates compared with the VKAs.[28] The current published case reports encourage further investigations in this field.

Rationale

There are still many unresolved issues concerning patient outcomes and prognostic factors in patients with AF and LA/LAA thrombi. Rivaroxaban (BAY 59-7939, Xarelto), a potent and highly selective, oral, direct factor Xa inhibitor, is a new therapeutic option in this setting.[29] The planned study program will consist of a prospective interventional study (X-TRA; **X**arelto – **T**h**R**ombus **A**ccelerated resolution) and a retrospective observational registry (CLOT-AF). The CLOT-AF registry was developed in light of the limited data on the prevalence and natural history of LA/LAA thrombi, and we wished to acquire center-specific data from the study sites undertaking X-TRA.

Study objectives and endpoints

X-TRA

The primary objective of this study (ClinicalTrials.gov identifier NCT01839357) is to explore the efficacy of rivaroxaban in the treatment of LA/LAA thrombi in patients with non-valvular AF or

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atrial flutter, scheduled to undergo CV or AF ablation, in whom an LA/LAA thrombus has been found on TEE before procedure. The primary endpoint is the complete LA/LAA thrombus resolution rate at 6 weeks of end-of-treatment confirmed by TEE. The term non-valvular AF is used to imply that AF is not related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves.[21]

The secondary objectives of the study are to describe: categories of thrombus outcome in patients (resolved, reduced, unchanged, larger, or new) confirmed on TEE at the end-of-treatment (after 6 weeks of treatment); incidence of the composite of stroke and non-central nervous system systemic embolism at the end-of-treatment and during follow-up; and incidence of all bleeding (major and non-major) events at the end-of-treatment and during follow-up.

The exploratory objectives of the study in the VKA/NOAC naïve/untreated subgroup are to evaluate biomarkers of: prothrombotic status (plasma prothrombin fragment 1+2 and thrombin–antithrombin complexes); inflammatory response (high-sensitivity interleukin-6; high-sensitivity C-reactive protein); thrombogenesis (D-dimers); fibrinolysis (plasminogen activator inhibitor type-1 [PAI-1] antigen); and endothelial damage/dysfunction (von Willebrand factor [vWF]).

CLOT-AF

The objective of this registry (ClinicalTrials.gov identifier NCT01928979) is to provide retrospective thrombus-related patient outcome data following standard-of-care anticoagulant treatment in patients with non-valvular AF or atrial flutter, who have TEE-documented LA/LAA thrombi. The data will be utilized as a reference for the prospective X-TRA study.

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The primary outcome of interest is thrombus resolution rate confirmed on TEE after 3-12 weeks of anticoagulant treatment based on the routine practice of the centers. Secondary endpoints are stroke or non-central nervous system systemic thromboembolism rate and all bleeding (major, non-major, unknown severity) rates.

External data evaluation bodies

X-TRA

A Steering Committee will be involved periodically in the planning, review, oversight of design, conduct, and study progress. The Study Outcome Committee (SOC) will apply the protocol definitions (to be provided in the SOC Manual) and will centrally adjudicate TEE results in a blinded fashion regarding pre- or post-treatment, but will not otherwise be involved in the study. Assessment of the SOC is the basis for the analysis of the efficacy endpoint.

CLOT-AF

In a subset of patients (at least 20% of sites), source data verification will be conducted. The purpose is to review documented data for completeness and plausibility, adherence to study protocol, and verification with source documents. Depending on the local legal and ethical regulations as well as data protection laws, the reviewer will compare data in the case report form with data in the source. TEE data in CLOT-AF will not be centrally adjudicated.

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Study design

X-TRA

The X-TRA study is a prospective, single-arm, open-label, multicenter study. Owing to the expected low incidence of LA/LAA thrombi in patients with AF, the proposed study will be explorative in nature but will be the first prospective interventional study with a NOAC in this setting.

The study will be designed as described in Figure 1. At the end of the treatment period, TEE will be repeated and centrally adjudicated by the SOC. An additional TEE should be encouraged at the post-treatment follow-up visit for patients with residual thrombi.

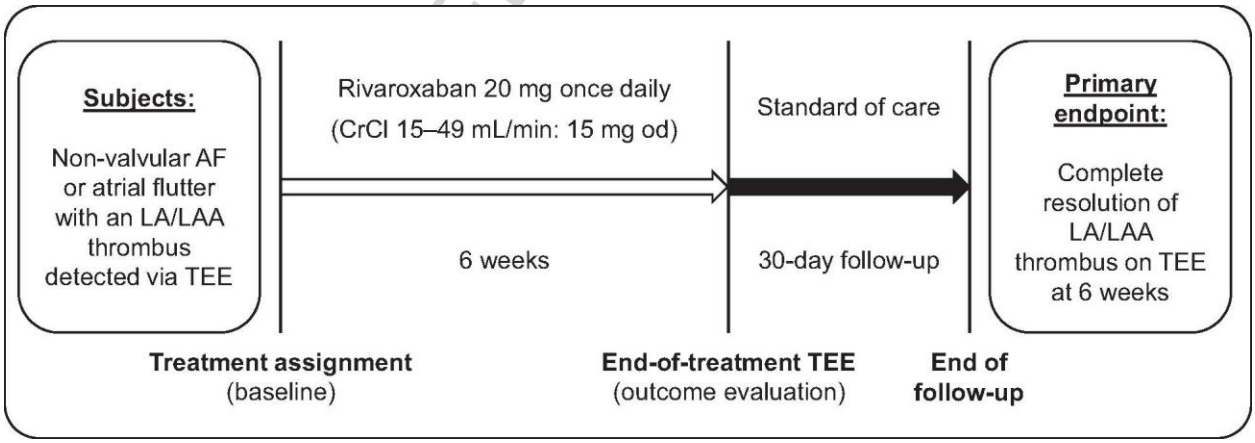

Figure 1. X-TRA study design.

AF, atrial fibrillation; CrCl, creatinine clearance; LA, left atrial; LAA, left atrial appendage; od, once daily; TEE, transesophageal echocardiogram

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CLOT-AF

CLOT-AF, a retrospective registry independent from the prospective interventional study, is planned in parallel to collect baseline data and outcome information from patients with non-valvular AF or atrial flutter who received VKA treatment based on standard of care and have LA/LAA thrombus confirmed on TEE. This retrospective registry will be set up at the same study sites participating in the X-TRA study to collect thrombus outcome data during 2011–2012 as a historical baseline of standard of care.

Retrospective patient data was collected from May 2013 to May 2014. The observation of each patient covers the period from the diagnosis of an LA/LAA thrombus until the end-of-treatment TEE following the 3-12-week standard-of-care anticoagulation therapy (Figure 2). If no end-of-treatment TEE has been performed during 3-12 weeks of anticoagulant therapy, the observational period will end at 12 weeks after diagnosis, at the latest. If more than one TEE was performed during treatment, the thrombus outcome will be collected from the last TEE performed within 12 weeks of treatment start.

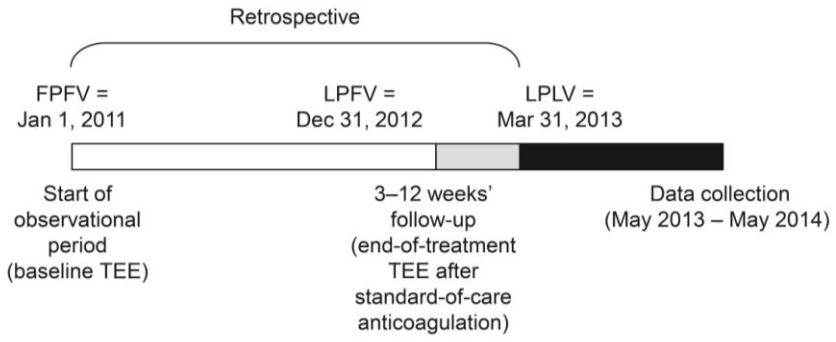

Figure 2 Overview of CLOT-AF registry.

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FPFV, first patient, first visit; LPFV, last patient, first visit; LPLV, last patient, last visit; TEE, transesophageal echocardiography

Eligible patients during the period from January 1, 2011 to December 31, 2012 to be identified via screening and review of medical records, for inclusion in registry. This retrospective screening and review will occur between May 2, 2013 and May 2, 2014. The observation of each patient will cover the period from diagnosis of a LA/LAA thrombus until the end-of-treatment TEE following the 3-12-week standard-of-care anticoagulation therapy.

Ethics approval

For both X-TRA and CLOT-AF, documented approval from the appropriate Independent Ethics Committees/Institutional Review Boards will be obtained for all participating centers before the start of the study according to good clinical practice and local laws, regulations, and organizations.

Patient population

X-TRA study

Men or women aged ≥18 years with hemodynamically stable non-valvular AF or atrial flutter in whom LA/LAA thrombus has been documented at baseline by TEE up to 72 hours prior to the start of study drug treatment are eligible for inclusion. Eligible patients must be VKA/NOAC-naïve or untreated within 1 month prior to signing the informed consent form (treatment of up to 72 hours with VKA, heparin, or a low molecular weight heparin is allowed before the start of study drug treatment); or VKA-pretreated but under ineffective INR levels (<2.0, documented

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with at least two consecutive measurements that are at least 24 hours apart) within the last 6 weeks.

Patients who meet any of the following cardiac-related criteria will be excluded: previous intracardiac thrombus; free-floating ball thrombus; intracardiac tumor (e.g. known presence of atrial myxoma); known left ventricular or aortic thrombus; or active endocarditis. Patients with the following will be also excluded: calculated creatinine clearance <15 mL/minute at the screening visit; hepatic disease that is associated with coagulopathy leading to a clinically relevant bleeding risk; or any severe condition that would limit life expectancy to <3 months (e.g. advanced malignancy). Complete inclusion and exclusion criteria are described in Supplementary Table II.

CLOT-AF

Retrospective registry of men or women aged ≥18 years with hemodynamically stable non-valvular AF or atrial flutter in whom LA/LAA thrombus has been documented at baseline by TEE are eligible for inclusion.

Patients who meet any of the following cardiac-related criteria will be excluded: valvular AF (European Society of Cardiology 2012 definition);[21] a history of cardiac thrombus confirmed on TEE; intracardiac tumors (e.g. known presence of atrial myxoma); or active endocarditis.

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Study drug

X-TRA study

Patients will be treated with 6 weeks of rivaroxaban 20 mg once daily, with a dose reduction to 15 mg once daily for patients with moderate to severe renal impairment (i.e. creatinine clearance of 15-49 mL/min, inclusive) at screening.

CLOT-AF registry

Owing to the retrospective, observational nature of the CLOT-AF registry, the choice of anticoagulant was left to the discretion of the treating physician.

Transesophageal echocardiography

TEE will be performed according to standard procedures at screening and at the end of treatment. If a residual or new thrombus is confirmed on the end-of-treatment TEE, performance of an additional TEE should be encouraged at the end of the follow-up period. TEE data obtained prior to the screening visit will be collected on DVD or in electronic format for review by the SOC as baseline. In the X-TRA study, TEE images will be recorded by the investigator for the SOC to adjudicate the primary endpoint and confirm the presence of a thrombus. The results of the third TEE (if performed) will be reported in the electronic case report form by the investigators.

Data to be collected include number, size, location, mobility of thrombus/thrombi for primary outcome, and evolution of the LA/LAA thrombus, e.g. resolved, reduced in size, stable (unchanged size), or worsened (increased in size or new thrombus). All examinations should be

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recorded for adjudication and to differentiate thrombus from severe (“sludge”) left atrial spontaneous echo contrast (LASEC).

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Biomarkers

The effect of rivaroxaban will be explored in the study population with respect to coagulation, inflammatory response, fibrinolysis, and endothelial damage/dysfunction. A blood sample will be obtained only in the VKA/NOAC-naïve/untreated subgroup at screening and at the end of treatment (or at the time of early discontinuation of study drug treatment if blood sampling can occur within 24 hours after the last dose of study drug).

In several studies, coagulation biomarkers, such as fibrin D-dimers, were elevated in patients with AF and those with LA thrombi.[30–33] A sufficient anticoagulant effect is mirrored by a significant decrease of coagulation biomarkers.[34,35] LA thrombi presence is associated with elevated plasma C-reactive protein levels[36] and the pro-inflammatory cytokine IL-6 is suspected to have a role in thrombogenesis.[37,38] It has been shown that plasma IL-6 levels are related to markers of pro-thrombotic state of patients with AF.[30] PAI-1 inhibits endogenous fibrinolysis, and plasma PAI-1 levels are increased in patients with AF.[39] Expression of PAI-1 has been shown to be upregulated in the left atrium in AF and could have a role in thrombogenesis.[40] Further investigations revealed that PAI-1 decreases significantly upon anticoagulation therapy.[41]

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Plasma vWF plays an important role in platelet adhesion to the subendothelium. Furthermore, vWF regulates thrombus formation by interacting with glycoprotein complexes.[42] It is an established biomarker of endothelial damage and/or dysfunction. It was found that high vWF was associated with future adverse cardiovascular events and mortality in patients with permanent AF.[43] Patients with AF and LAA thrombus had higher vWF antigen activity compared with those without LAA thrombus.[44] Several other studies have emphasized the use of plasma vWF to stratify risk and predict outcome in AF.[45,46]

Statistical analysis plan

Statistical analyses will be exploratory and descriptive, and are not powered to test any specific hypothesis. The estimated sample size is based on the expected presence of an LA/LAA thrombus detected on TEE in the study sites participating in the enrollment period. The reported incidence of LA/LAA thrombus is varied and low, in the region of 5-15%.[12] Supplementary Table I describes the incidence of LA/LAA thrombus in published literature, with the majority of studies identifying LA/LAA thrombi in less than 60 patients. One study identified LAA thrombi in 151 patients out of 9,058 patients. Therefore, it's determined the target enrollment for the X-TRA study is 60 patients.

The primary outcome measure is the complete resolution of LA/LAA thrombus. This will be evaluated on a per-patient basis. The definition of complete thrombus resolution for a patient refers to being completely thrombus-free in the left atrium. This will be based on the end-of-treatment TEE as determined by independent adjudication by the SOC. The primary analysis will evaluate this outcome on the modified intent-to-treat population (patients with LA thrombus at baseline who have an evaluable end-of-treatment TEE after six weeks of treatment). Sensitivity analysis of the primary outcome will be based on the intent-to-treat population, in which patients without an evaluable TEE will be considered to still have a thrombus in this

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summary. Exact (Clopper-Pearson) 95% confidence intervals for the probability of a present thrombus in the LA/LAA will be calculated.

The secondary outcome measure will evaluate the outcome of thrombi after 6 weeks' treatment relative to patients observed at study entry. For this evaluation, patients will be categorized according to the worst change in thrombus noted on the end-of-treatment TEE compared with the baseline TEE. Individual thrombi will be evaluated (in increasing order of severity) as resolved, reduced, unchanged, or enlarged since baseline, or new as compared with baseline, and patients will be categorized according to the most severe category into which any thrombus falls. Rates will be provided for each category and 95% confidence intervals for the probability of belonging to the combined categories of resolved/reduced and unchanged/enlarged/new will be calculated.

Discussion

NOACs are increasingly being used for the prevention and treatment of thrombi formation owing to the inherent limitations of VKAs, such as difficulty in maintaining patients within a narrow therapeutic range and the need for regular INR measurements.[47,48] The NOACs work by directly inhibiting either thrombin or factor Xa, reducing thrombus formation. The differences in the mechanisms of action may be a factor in resolution of LA/LAA thrombi in patients with AF. Direct thrombin inhibitors such as dabigatran prevent thrombin from activating fibrinogen into fibrin. Conversely, rivaroxaban, apixaban, and edoxaban target factor Xa, preventing it from activating prothrombin to thrombin. Factor Xa is considered to be a particularly appropriate target for thrombus inhibition because of its convergent position between the intrinsic and extrinsic coagulation pathways,[49] with one molecule of factor Xa also responsible for the generation of more than 1000 thrombin molecules.[50] Additionally, direct thrombin inhibitors may downregulate

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protein C to a greater extent than factor Xa inhibitors[51] and consequently downregulate protein C-mediated anticoagulant pathways.[52]

X-TRA and CLOT-AF will provide some answers to the many unresolved issues concerning patient outcomes and prognostic factors in patients with AF and LAA thrombi. Results from this study program would provide the first data on the prevalence and natural history of LA/LAA thrombi. In addition, unique data on clot resolution with rivaroxaban in a prospective cohort would be obtained in X-TRA.

Acknowledgements and disclosures

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Conflicts of interest

G. L. has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola and Böhringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Böhringer Ingelheim, Daiichi-Sankyo, Medtronic and Sanofi Aventis. C. H. receives research grants from Sanofi-Aventis and speaker honoraria from Bayer Healthcare, Böhringer Ingelheim, and Pfizer. F.M. has received funding for research, consultancy, and lecturing from Abbott, Boston Scientific, Bayer, Astra Zeneca, Daiichi-Sankyo, BMS/Pfizer, and

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