Trial design: Rivaroxaban for the prevention of major cardiovascular events after transcatheter aortic valve replacement: Rationale and design of the GALILEO study

Stephan Windecker, MD,[a,b] Jan Tijssen, PhD,[b,c] Gennaro Giustino, MD,[d] Ana H. C. Guimarães, PhD,[e] Roxana Mehran, MD,[d] Marco Valgimigli, MD, PhD,[a,b] Pascal Vranckx, MD, PhD,[f,b] Robert C. Welsh, MD,[g] Usman Baber, MD,[d] Gerrit-Anne van Es, PhD,[b,e] Peter Wildgoose, PhD,[h] Albert A. Volkl, PharmD BCPS,[h] Ana Zazula, MD,[i] Karen Thomitzek, MD,[j] Melanie Hemmrich, MD,[j] and George D. Dangas, MD, PhD[d] *Bern, Switzerland; Rotterdam, Amsterdam, the Netherlands; NY, USA; Hasselt, Belgium; NJ, USA; Edmonton, Canada; São Paulo, Brazil; and Berlin, Germany*

Background Optimal antithrombotic treatment after transcatheter aortic valve replacement (TAVR) is unknown and determined empirically. The direct factor Xa inhibitor rivaroxaban may potentially reduce TAVR-related thrombotic complications and premature valve failure.

Design GALILEO is an international, randomized, open-label, event-driven, phase III trial in more than 1,520 patients without an indication for oral anticoagulation who underwent a successful TAVR (ClinicalTrials.gov NCT02556203). Patients are randomized (1:1 ratio), 1 to 7 days after a successful TAVR, to either a rivaroxaban-based strategy or an antiplatelet-based strategy. In the experimental arm, subjects receive rivaroxaban (10 mg once daily [OD]) plus acetylsalicylic acid (ASA, 75-100 mg OD) for 90 days followed by rivaroxaban alone. In the control arm, subjects receive clopidogrel (75 mg OD) plus ASA (as above) for 90 days followed by ASA alone. In case new-onset atrial fibrillation occurs after randomization, full oral anticoagulation will be implemented with maintenance of the original treatment assignment. The primary efficacy end point is the composite of all-cause death, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep venous thrombosis, and systemic embolism. The primary safety end point is the composite of life-threatening, disabling, and major bleeding, according to the Valve Academic Research Consortium definitions.

Conclusions GALILEO will test the hypothesis that a rivaroxaban-based antithrombotic strategy reduces the risk of thromboembolic complications post-TAVR with an acceptable risk of bleeding compared with the currently recommended antiplatelet therapy–based strategy in subjects without need of chronic oral anticoagulation. (Am Heart J 2017;184:81-7.)

Background

Degenerative aortic valve stenosis is the most common cause of aortic stenosis among adults in Europe and in the United States.[1] Aortic valve replacement is the most effective treatment to alleviate symptoms and improve survival in patients with critical aortic stenosis. Transcatheter aortic valve replacement (TAVR) has become the treatment of choice among patients at prohibitive-to-high surgical risk[1-4] and a valid alternative to surgical aortic valve replacement among patients at intermediate-to-high surgical risk.[5-8] Patients are at an increased risk of stroke and other thromboembolic events for several months after the TAVR procedure.[9]

Degenerative aortic stenosis leaflets contain large amounts of tissue factor and thrombin, which might contribute to the increased local inflammation and thrombogenicity[2] upon native leaflet disruption. During the TAVR procedure, exposure of leaflet content to the circulation with microembolization of valvular components has been reported, with >50% of cerebral emboli

From the [a]Bern University Hospital, Bern, Switzerland, [b]European Cardiovascular Research Institute (ECRI), Rotterdam, the Netherlands, [c]Academic Medical Center–University of Amsterdam, Amsterdam, the Netherlands, [d]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York City, [e]Cardialysis, Clinical Research Organization, Rotterdam, the Netherlands, [f]Hartcentrum Hasselt, Hasselt, Belgium, [g]Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Canada, [h]Janssen Pharmaceuticals Inc., Raritan, NJ, [i]Bayer, São Paulo, Brazil, and [j]Bayer Pharma AG, Berlin, Germany.
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Submitted August 31, 2016; accepted October 25, 2016.
Reprint requests: Stephan Windecker, MD, Department of Cardiology, Bern University Hospital, 3010 Bern, Switzerland.
E-mail: stephan.windecker@insel.ch
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during TAVR reported to include thrombotic material.[10] The insertion of the prosthesis without removal of the diseased aortic valve creates an irregular blood flow zone with the crushed native leaflets around the device metallic frame that may predispose to thrombus formation. This prothrombotic environment associated with platelet dysfunction and the occurrence of atrial arrhythmias among other associated comorbidities may predispose to thromboembolic events.

Recently, reduced leaflet motion was identified after successful TAVR[11] by computed tomography imaging as a hemodynamically silent phenomenon, with normal aortic valve gradients on echocardiography. A higher incidence of cerebrovascular events was observed in patients with possible subclinical valve thrombosis manifesting with reduced leaflet motion.[11] Reduced leaflet motion was less frequently observed among patients receiving oral anticoagulation (OAC) compared with those receiving no anticoagulation. Of note, initiation of oral anticoagulation once reduced leaflet motion was identified resolved the condition.[11] Thrombosis seems to be implicated in the reduced leaflet motion condition based on the hypoattenuating opacities observed on computed tomography analysis and on the resolution of the condition with anticoagulation.

Currently, dual-antiplatelet therapy with acetylsalicylic acid (ASA) and clopidogrel for 3 to 6 months (without an indication for chronic OAC) is an empirical, widely accepted strategy that has been incorporated into clinical practice and relevant recommendations.[12-16] However, these recommendations lack consistency regarding appropriate dosage and duration of therapy.[15,17,18]

Although it is not entirely clear whether thrombi produced during and after TAVR have a prevailing platelet- or thrombin-related origin, there is growing evidence that thrombin plays a major role in the pathophysiology of thromboembolic events. Mechanisms of platelet activation and coagulation are highly interdependent, with thrombin playing a central role in both pathways.[19] In addition, thrombin catalyzes the conversion of fibrinogen into fibrin, stabilizing the acutely formed thrombus playing a central role in arterial thrombosis, including in patients with an acute coronary syndrome.[20] Hence, it is reasonable to consider an antithrombotic regimen to reduce the long-term thromboembolic risk after TAVR.

Rivaroxaban is a non–vitamin K antagonist (VKA) oral anticoagulant that selectively and directly inhibits factor Xa, thereby inhibiting both thrombin formation and endovascular thrombosis.[21] Rivaroxaban was previously demonstrated to be effective in several indications, including the prevention of thromboembolic complications in patients with atrial fibrillation,[22] the prevention of recurrent venous thromboembolism (VTE),[23] the prevention of VTE in orthopedic surgery,[24] and the prevention of recurrent cardiac ischemic events after acute coronary syndrome.[25] This agent has the potential to reduce the risk of thromboembolic complications after TAVR and to optimize post-TAVR outcomes.

A strategy of rivaroxaban 10 mg once daily (OD) in combination with ASA for the first 90 days, followed by rivaroxaban 10 mg OD alone, might provide the best tradeoff between efficacy and safety (bleeding) in this population without an established indication for anticoagulation after TAVR. The rivaroxaban dose of 10 mg OD is approved for the prevention of VTE in major orthopedic surgery patients without dose adjustment in normal to moderate renal impairment.

The GALILEO study (ClinicalTrials.gov NCT02556203) is a multicenter, randomized, open-label, event-driven, international phase III trial, designed to assess the efficacy and safety of a rivaroxaban-based strategy after a successful TAVR in comparison to the current recommended antiplatelet-based strategy.[12,14-16]

Methods

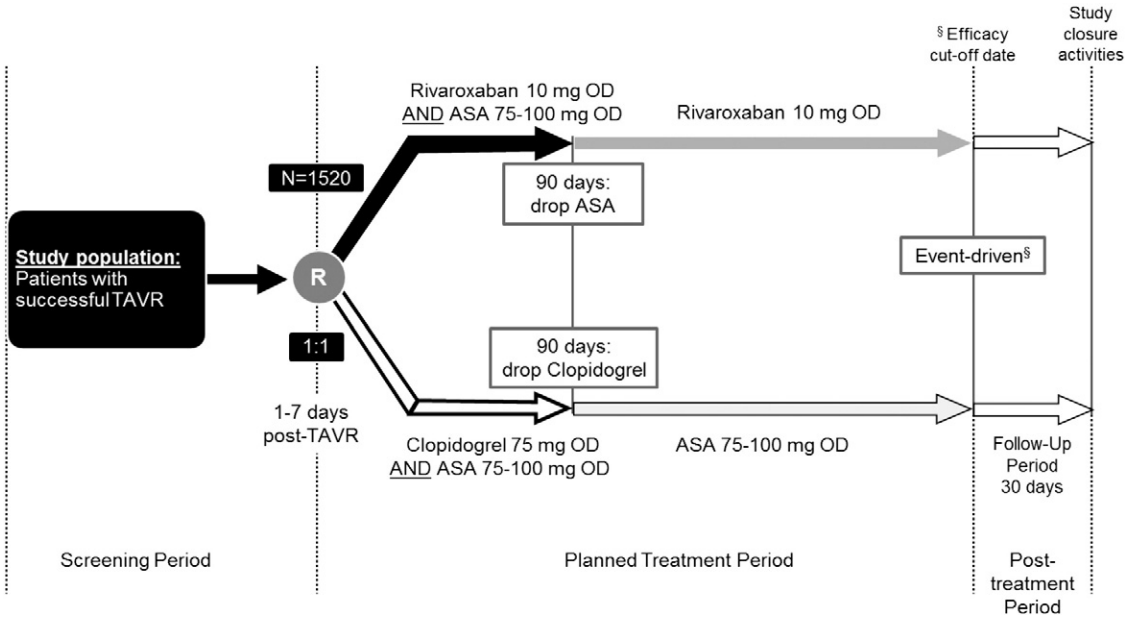
Study objectives

The primary objective of the GALILEO trial is to compare the efficacy of a rivaroxaban-based antithrombotic strategy with an antiplatelet-based antithrombotic strategy for the prevention of death or a thromboembolic event in patients without an indication for chronic OAC after successful TAVR. The primary safety objective is to compare the 2 antithrombotic strategies with regard to life-threatening, disabling, or major bleeding according to the Valve Academic Research Consortium (VARC-2)[26] criteria.

Study population and patient selection

Approximately 1,520 men and women 18 years or older with successful completion of a TAVR procedure (either native valve or valve-in-valve) by iliofemoral or subclavian access with any approved/marketed device were eligible for enrollment. A successful TAVR[26] is defined as (1) correct positioning of a single prosthetic heart valve into the proper anatomical location; (2) intended performance of the prosthetic heart valve with presence of all 3 of the following conditions post-TAVR: (*a*) mean aortic valve gradient <20 mm Hg, (b) peak transvalvular velocity <3.0 m/s, and (c) no severe or moderate aortic valve regurgitation; and (3) absence of periprocedural complications, such as (*a*) any type of stroke, (*b*) VARC-2–graded life-threatening bleeding, (*c*) acute coronary artery obstruction requiring intervention, (*d*) major vascular complication requiring intervention (including access-site vascular complications, any new ipsilateral peripheral ischemia, distal embolization from a vascular source, aortic dissection, aortic rupture, ventricular perforation, cardiac tamponade, and annulus rupture), (*e*) unresolved acute valve thrombosis, or (f) any requirement of a repeat procedure.

Figure 1



Study flow diagram GALILEO study. Successful TAVR as defined in the "Study population and patient selection" section. * The duration of the planned treatment period depends on the time needed to reach the efficacy cut-off date, that is, to collect the predefined number of efficacy end points. The expected duration of the treatment is 720 days, but may be adjusted depending on the rate of subject recruitment and efficacy event rates. On-site visits are planned at days 30, 90, and 360, and at every 180 days thereafter, and at the efficacy cut-off date. Telephone contacts are planned at day 180, and at 30 days after the last dose intake of the study assigned medication. R, randomization.

Key exclusion criteria include any atrial fibrillation before or at the time of randomization, an ongoing indication for OAC, any other indication for continued treatment with any OAC, known bleeding diathesis, ongoing absolute indication for dual-antiplatelet therapy at time of screening that is unrelated to the TAVR procedure, clinically overt stroke within the last 3 months, planned coronary or vascular intervention or major surgery, severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1.73 m^2), dialysis, post-TAVR unresolved acute kidney injury and moderate and severe hepatic impairment, and any hepatic disease associated with coagulopathy. A full list of the exclusion criteria is provided in online Supplementary Table I.

Subjects provide written informed consent before randomization.

Randomization and treatment protocol

Consenting subjects are randomized in a 1:1 ratio to a rivaroxaban-based strategy or to an antiplatelet-based strategy 1 to 7 days after successful TAVR and before hospital discharge. Randomization is performed through an Interactive Web Response System and stratified by site. The study flow of the GALILEO trial is detailed in Figure 1.

In subjects randomized to the rivaroxaban-based strategy (experimental arm), rivaroxaban (10 mg OD, taken with or without food) is started at the time of randomization or within 1 to 3 days after last intake of clopidogrel. Acetylsalicylic acid (75-100 mg OD) is started immediately after randomization if not already being taken. In subjects randomized to the antiplatelet-based strategy (control arm), clopidogrel 75 mg OD and ASA 75-100 mg OD are continued unchanged or to be started at the time of randomization if not already being taken. In clopidogrel-naïve subjects, a single loading dose of at least 300 mg is administered and followed by clopidogrel 75 mg OD.

Under the rivaroxaban-based strategy, ASA is discontinued at 90 days and rivaroxaban 10 mg OD is continued as monotherapy. Under the antiplatelet-based strategy, clopidogrel is discontinued at 90 days and ASA 75-100 mg OD is continued as monotherapy. In this event-driven study, study treatments (rivaroxaban or ASA monotherapy) are continued until the efficacy cutoff date with an estimated median treatment duration of 540 days, but it may vary depending on the recruitment rate as well as on the incidence of the primary efficacy end point.

If new-onset of atrial fibrillation (NOAF) develops, study treatments are adapted as follows. Under the

rivaroxaban-based strategy, the rivaroxaban dose is raised from 10 to 20 mg OD, or to 15 mg OD for subjects with moderate renal impairment (ie, estimated glomerular filtration rate <50 and ≥30 mL/min per 1.73 m^2). If NOAF occurs within the first 90 days, ASA is discontinued at 90 days and either rivaroxaban is continued as monotherapy. Under the clopidogrel-based strategy, clopidogrel (≤90 days) or ASA monotherapy (>90 days) is replaced by a VKA to target an international normalized ratio of 2 to 3. If NOAF occurs within the first 90 days, ASA is discontinued at 90 days and VKA is continued as monotherapy. Because these treatment adaptations are integral parts of the study treatment regimens, events occurring under post-NOAF study treatments are retained in the primary study analysis (intention-to-treat). The timing of on-site visits and/or telephone assessments are kept unchanged until the efficacy cutoff date is reached as described earlier.

If a subject randomized to the rivaroxaban-based strategy needs to discontinue the assigned therapy permanently, ASA 75-100 mg OD for the remaining duration of the study is recommended in the absence of an indication for full anticoagulation and if the treating physician considers it safe and the clinical situation allows doing so.

On-site visits are planned at days 30, 90, and 360, and at every 180 days thereafter until the efficacy cutoff date. Telephone contacts are planned at day 180 and at 30 days after the last dose intake of the study assigned medication. All randomized subjects are clinically followed up until the efficacy cutoff date irrespective of possible deviations from the assigned treatment, and every effort is made to complete the clinical follow-up.

Study end points

The primary efficacy end point is death or a thromboembolic event, defined as the composite of all-cause death, any stroke, myocardial infarction (MI), symptomatic valve thrombosis, pulmonary embolism (PE), deep venous thrombosis (DVT), and non–central nervous system (CNS) systemic embolism.[27] The primary safety end point is the composite of life-threatening, disabling, or major bleeding. All components of the primary efficacy and safety end points are blindly adjudicated by an independent Clinical Event Committee (CEC). All-cause death, stroke, MI, symptomatic valve thrombosis, and all bleeding events are adjudicated according to VARC-2 definitions.[26,28] Pulmonary embolism, DVT, and non-CNS systemic embolism are adjudicated according to Buller et al.[27]

Secondary efficacy end points include the following: (1) the composite of cardiovascular death, any stroke, MI, symptomatic valve thrombosis, PE, DVT, or non-CNS systemic embolism; and (2) the net clinical benefit, defined as the composite of all-cause death, any stroke, MI, symptomatic valve thrombosis, PE, DVT, non-CNS systemic embolism, and life-threatening, disabling or major bleeding. Secondary safety end points include bleeding complications according to the following definitions: (*a*) composite of Thrombolysis In Myocardial Infarction major and minor bleeding, (*b*) International Society of Thrombosis and Haemostasis major bleeding, and (*c*) composite of Bleeding Academic Research Consortium scale 2, 3, or 5 bleeding. Other end points include the separate components of the primary efficacy and safety end points, and the mean transaortic valve pressure gradient at approximately 360 days after randomization as measured by echocardiogram.

Statistical considerations

The primary efficacy and safety analyses are conducted on the full analysis set of all randomized patients according to the intention-to-treat principle using end points adjudicated by the CEC. The primary analysis compares the time from randomization to first occurrence of any element of the primary composite end point between patients randomized to the rivaroxaban regimen vs those randomized to the antiplatelet regimen. Follow-up is censored at the last date of known outcome status or at the efficacy cutoff date (when 440 subjects have experienced a positively adjudicated primary efficacy end point), whichever comes first.

For the primary efficacy end point, the null hypothesis is that there is no difference between randomized treatments on the event rates over time. The rivaroxaban-based regimen is declared superior to the antiplatelet-based regimen if the 1-sided *P* value for the log-rank test falls below .025. This testing of superiority is hierarchically preceded by a test for noninferiority of the rivaroxaban-based strategy vs the antiplatelet-based regimen. The rivaroxaban-based regimen is declared noninferior to the antiplatelet regimen if the upper boundary of the 95% CI for the hazard ratio (adapted log-rank test) falls below 1.20. Noninferiority testing is performed on the basis of an on-treatment analysis, in which follow-up is censored at 2 days after permanent discontinuation of the randomized treatment strategy. Kaplan-Meier curves are used to describe the occurrence of the primary efficacy end point over time. Hazard ratios and 95% CIs are generated.

In all primary analyses, switches to full-dose anticoagulation are treated as an integral part of the treatment strategy. Pre-NOAF analyses, with censoring at the time of the switch to anticoagulation therapy, are carried out as exploratory analyses. Post-NOAF analyses, starting at the time of the treatment switch precipitated by NOAF, are carried out as exploratory analyses.

The prespecified subgroup analyses include but are not limited to gender, age, weight, body mass index, valve type, valve-in-valve procedure, Society of Thoracic Surgeons risk score and EuroSCORE II, renal function, hypertension, diabetes mellitus, prior stroke or non-CNS systemic embolism, prior MI, previous revascularization,

$CHADS_2$ and CHA_2DS_2-VASc scores, HAS-BLED, and frailty.

The sample size determination for the study was driven by requirements for testing superiority of the rivaroxaban-based strategy over the antiplatelet-based strategy. The expected day 540 event rate of the primary efficacy end point is 33.0%.[5-7,29] The target relative risk at day 540 is 0.80; that is, a reduction of the day 540 event rate from 33.0% under antiplatelet-based regimen to 26.4% under the rivaroxaban-based regimen, which corresponds to a hazard ratio of 0.7654 under an exponential distribution. Based on these assumptions, it was estimated that a total of 440 primary efficacy end points would provide 80% power at a 5% significance level. Randomization of 1,520 subjects with a minimum follow-up of 360 days and a median of 540 days is anticipated to allow accrual of approximately 440 primary adjudicated efficacy end points. Follow-up continues until the target number of end points is achieved. The Executive Committee (EC) monitors the overall rate of the primary efficacy end points and may alter the trial to preserve adequate power within reasonable trial duration. An independent data safety monitoring board (DSMB) has responsibility for monitoring safety during the trial.

Substudies

Prespecified substudies that are planned in subjects randomized in selected countries include measurement of neurocognitive function, cerebral imaging, and imaging of leaflet motion restriction.

Study organization

The trial is being conducted in 15 countries over 143 sites, in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice guidelines, and applicable regulatory requirements. The final study protocol and informed consent have been reviewed and approved by the ethics boards/institutional review boards and corresponding health authorities for all participating study sites.

GALILEO is funded by Bayer Pharma AG and Janssen Pharmaceuticals. The executive committee is composed of members of the academic leadership of the trial and members from each sponsoring company. The academic leadership of the trial came forth from a partnership between Mount Sinai and European Cardiovascular Research Institute, which designed the GALILEO in cooperation with the trial sponsors. The EC provides oversight of trial conduct and data analysis and oversees publication. Data analyses will be conducted by Cardialysis with validation by the trial sponsor. The academic leadership partners will have free and complete access to all trial data and will submit these results for publication in a peer-reviewed medical journal. The steering committee composed of academic experts and National Lead Investigators (online supplement) is responsible for the implementation of the protocol.

The DSMB is composed of 3 members (online supplement) who are not directly involved in the conduct of the trial. The DSMB will review the study (including reported serious adverse events) on a periodic basis, as detailed in the DSMB charter, and provides recommendations to the EC. An independent, blinded CEC applies the protocol definitions as detailed in the CEC charter and adjudicates all suspected study end points.

Conclusion

GALILEO is the first randomized clinical trial of an optimized direct acting OAC-based antithrombotic regimen after TAVR. The first patient was enrolled in December 2015, and 362 patients have been enrolled until mid-October 2016. GALILEO will provide randomized evidence of the efficacy and safety of a rivaroxaban-based strategy compared with an antiplatelet-based regimen after successful TAVR in the absence of an established indication for OAC.

Contributorship

SW, JT, AHCG, MV, PV, RCW, GAvE, MH, AZ, PW, AAV, and GDD contributed to the trial design; PV, MH, AZ, and KT contributed to protocol development; JT contributed to the statistical analysis and actively participated in the writing of the statistical sections of the manuscript; all authors critically reviewed the manuscript and approved the final version.

Disclosures

Stephan Windecker works at an institution that has received research grants from Abbott, Biotronik, Boston Scientific, Edwards Lifesciences, Guerbet, Johnson & Johnson, The Medicines Company, Medtronic, Merck Sharp and Dohme, Novartis, Sorin, St. Jude, and Symetis. Jan Tijssen has received an honorarium for serving on the Executive Committee of the present study and has also served on Data Safety Monitoring Boards of other Bayer studies. Roxana Mehran has worked as a consultant for Osprey, Janssen, and Medscape, and works at an institution that has received research grants from Abbott, AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi Sankyo Inc, Lilly, The Medicines Company, and Novartis. Marco Valgimigli has received speaker's fees from AstraZeneca, Biosensors, and Terumo, and has received institutional research grants from AstraZeneca, The Medicines Company, and Terumo. Pascal Varanckx has received speaking or consulting fees from AstraZeneca, Bayer Health Care, Boehringer-Ingelheim, Daiichi-Sankyo, and The Medicines Company, and is an unpaid executive committee member of trials funded by Biosensors and Biotronik. Robert Welsh is a consultant for Bayer,

Pfizer/Bristol-Myers Squibb, and Amgen Canada; has received research grants from AstraZeneca, Bayer and Boerhinger-Ingelheim; and has received honoraria from AstraZeneca and Bayer. Ana Zazula, Karen Thomitzek, and Melanie Hemmrich have received financial remuneration from Bayer Pharma AG as employees of the sponsor. Peter Wildgoose has received financial remuneration from Janssen as an employee of Janssen Scientific Affairs. Albert Volkl has received financial remuneration from Janssen as an employee of Janssen Medical Affairs. George Dangas has worked as a consultant to Bayer and Janssen.

Appendix. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2016.10.017.

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