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CLINICAL COMMENTARIES
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Rivaroxaban after transcatheter aortic valve replacement: the GALILEO trial

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Transcatheter aortic valve replacement (TAVR) has been established as a standard of care for patients with severe aortic stenosis at high or prohibitive risk for surgery and is a viable alternative in patients at lower risk.[1–4] Since the pivotal trials that led to the commercial approval of TAVR, the antithrombotic regimens have been empiric and mostly based on expert consensus, observational studies, and small randomized controlled trials.[5–7] Patients who undergo TAVR remain at high risk of subsequent thrombo-embolic events, during both the early and late periods after the procedure. Subclinical bioprosthetic valve thrombosis has been identified as a potential substrate for thrombo-embolic events in these patients and has been shown in observational studies that it could be potentially prevented or reversed by oral anticoagulation.[8–10]

Within this background, the GALILEO trial was the first large randomized controlled trial investigating the efficacy and safety of oral anticoagulation with a factor Xa-inhibitor after successful (i.e. free from major periprocedural complications) TAVR in patients without an established indication for oral anticoagulation.[11,12] This was an international, open-label, event-driven randomized controlled trials comparing a rivaroxaban-based antithrombotic strategy vs. an antiplatelet-based strategy. In the rivaroxaban-based strategy, patients were treated with rivaroxaban 10 mg daily plus acetylsalicylic acid 75- to 100-mg daily for 3 months, followed by 10 mg daily rivaroxaban monotherapy. A dose of 10 mg rivaroxaban was chosen to provide a level of anticoagulation to prevent thrombus formation on the valve surface while mitigating the risk of bleeding complications. In the antiplatelet-based arm, patients received acetylsalicylic acid 75–100 mg daily plus clopidogrel 75 mg daily for 3 months, followed by acetylsalicylic acid monotherapy. The primary efficacy outcome of the study was the composite of all-cause death, or thrombo-embolic events including any stroke, myocardial infarction, symptomatic valve thrombosis, non-central nervous system systemic embolism, deep vein thrombosis, or pulmonary embolism. The primary safety outcome was the composite of major, disabling, or life-threatening bleeding. The primary hypothesis of the trial was that the rivaroxaban arm would be superior to the antiplatelet arm in reducing the risk of the primary efficacy outcome. The study was event-driven, i.e., based on a requirement for the number of patients reaching the primary efficacy endpoint.

After Data Safety Monitoring Board review, early termination of the trial was recommended due to safety concerns. A total of 1644 patients were randomized after successful TAVR in 136 centres in 16 countries. At a median follow-up time post-randomization of 17 months, in the intention-to-treat analysis, the primary efficacy outcome of death or first thrombo-embolic event occurred more frequently in the rivaroxaban arm compared with the antiplatelet arm [rates of 9.8 vs. 7.2 per 100 person-years, hazard ratio (HR) 1.35, 95% confidence interval (CI) 1.01–1.81; $P = 0.04$]. The primary safety outcome of major, disabling, or life-threatening bleeding, also tended to occur more frequently in the rivaroxaban arm compared to the antiplatelet arm (rates of 4.3 vs. 2.8 per 100 person-years, HR 1.50, 95% CI 0.95–2.37; $P = 0.08$). There were no significant differences in the rates of life-threatening or disabling bleeding. Bleeding rates according to other pre-specified definitions occurred more frequently in the rivaroxaban arm compared to the antiplatelet arm. Symptomatic valve thrombosis in the trial was rare and occurred only in three patients in the rivaroxaban arm and in seven patients in the antiplatelet arm.

There was an excess in all-cause mortality in the rivaroxaban arm compared with the antiplatelet arm (5.8 vs. 3.4 per 100 person-years, HR 1.69, 95% CI 1.13–2.53), mostly driven by greater rates of non-cardiovascular death (2.6 vs. 1.0 per 100 person-years HR 2.67, 95% CI 1.33–5.35) and sudden death. Of note, most of the deaths in both arms were rarely preceded within the prior 30 days by a non-fatal primary safety outcome or primary efficacy outcome; over 70% of deaths were never preceded by any such event.

The rates of premature permanent discontinuation of the study drug occurred more frequently in the rivaroxaban arm than in the antiplatelet arm, and most commonly due to adverse events. When evaluated in the per-protocol analysis, there were no significant differences in the rates of the primary efficacy outcome, primary safety outcome, and all-cause mortality. These results were consistent using an extended definition for the on-treatment analysis accounting for alternative formulations of the study drugs. Substantial number of deaths occurred after discontinuation of the study drug and were particularly different between the two groups beyond 100 days after study drug discontinuation.

Landmark analyses at 90 days, the timepoint of transition to monotherapy, were largely unrevealing with concordant trends observed in all intervals examined. The sole notable difference was the higher 90-day mortality with rivaroxaban plus aspirin vs. dual antiplatelet therapy.

Finally, the overall rate of new-onset atrial fibrillation was approximately 11% in both groups, and led to switching anticoagulation strategy in 60–80% of cases. Although the protocol allowed these patients to be

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kept in the study if per-protocol dose escalation (or switch from antiplatelet to warfarin in the control group) was employed, many exited the study due to utilization of other clinically driven regimens. The overall low rate of this arrhythmia and the variety of regimens opted limited any clinically meaningful comparisons.

The results of the main GALILEO trial need to be put into perspective with the ancillary GALILEO-4D study that evaluated the effect of a rivaroxaban-based strategy on subclinical leaflet-thickening and reduced leaflet motion of TAVR valves using four-dimensional computed tomography assessed at 90 days. In this study, a 10 mg rivaroxaban-based strategy was more effective than the antiplatelet strategy in preventing subclinical leaflet-thickening and motion abnormalities. This is notable given that the utilized dosage was lower than that prescribed for full anticoagulation for stroke prevention in atrial fibrillation.

Given the unfavourable risk–benefit trade-off the use of routine oral anticoagulation after TAVR in patients who do not otherwise have another specific indication for anticoagulation should not be recommended at the present time. Ongoing studies will further elucidate the optimal antithrombotic therapies after TAVR (NCT02247128; NCT02664649; NCT02943785).

Conflict of interest: none declared.

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