is narrower for major bleeding than thromboembolism. Dose adjustment of edoxaban on the basis of clinical features obviates the need to measure drug levels or anticoagulant activity.

X-VeRT Results: Rivaroxaban Is Safe and Effective for Cardioversion in AF

Written by Nicola Parry

Riccardo Cappato, MD, Policlinico San Donato, San Donato Milanese, Italy, presented results from the Explore the Efficacy and Safety of Once-Daily Oral Rivaroxaban for the Prevention of Cardiovascular Events in Subjects With Nonvalvular Atrial Fibrillation Scheduled for Cardioversion trial [X-VeRT; Cappato R et al. *Eur Heart J*. 2014]. The data showed that oral rivaroxaban was as effective and safe as a vitamin K antagonist (VKA) when administered for only about a week prior to elective cardioversion for atrial fibrillation (AF).

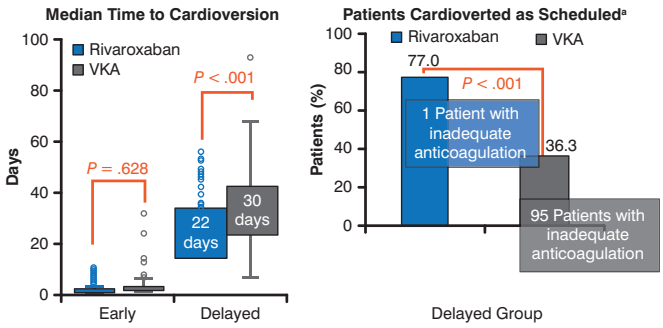
According to Prof Cappato, although cardioversion is commonly performed worldwide to restore normal rhythm in patients with AF [Hernández-Madrid A et al. *Europace* 2013], without appropriate anticoagulation therapy, the periprocedural risk of thromboembolism for this procedure is 5% to 7% [Stellbrink C et al. *Circulation* 2004], compared with 1% for patients who receive a VKA [Gallagher Mm et al. *J Am Coll Cardiol*. 2002], the current standard of care pre- and post-cardioversion [Camm AJ et al. *Eur Heart J*. 2013].

X-VeRT is the first prospective randomized study designed to compare the efficacy and safety of a novel oral anticoagulant (NOAC) with dose-adjusted VKAs in patients with AF undergoing elective cardioversion. This open-label, parallel-group, active-controlled phase 3b trial enrolled 1504 subjects with hemodynamically stable nonvalvular AF who were scheduled for cardioversion from 141 centers throughout 16 countries.

Patients were randomized 2:1 to rivaroxaban 20 mg once daily (15 mg if creatinine clearance was 30 to 49 mL/min) or international normalized ratio (INR)-adjusted VKA therapy, including warfarin. Local study investigators decided whether patients underwent an early (target period of 1 to 5 d post randomization) or delayed (3 to 8 weeks) cardioversion strategy.

The primary efficacy outcome was the composite of stroke and transient ischemic attack (TIA), non–central nervous system (CNS) systemic embolism, myocardial infarction, and cardiovascular death. The primary safety outcome was major bleeding, according to International Society on Thrombosis and Haemostasis recommendations.

Figure 1. Effects of Rivaroxaban and Vitamin K Antagonists on Time to Cardioversion



VKA, vitamin K antagonist; INR, international normalized ratio. [a]Reason for not performing cardioversion as first scheduled from 21–25 days primarily due to inadequate anticoagulation (indicated by drug compliance <80% for rivaroxaban or weekly INRs outside the range of 2.0–3.0 for 3 consecutive weeks before cardioversion for VKA).

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The primary efficacy outcome occurred in 0.51% of the rivaroxaban group and 1.02% of the VKA group (RR, 0.50; 95% CI, 0.15 to 1.73). In patients who underwent early cardioversion, the primary composite outcome occurred in 0.71% of the rivaroxaban group vs 1.08% of the VKA group, and in 0.24% vs 0.93% of those who underwent delayed cardioversion.

The incidence of major bleeding was similar in patients treated with rivaroxaban and VKAs (0.6% vs 0.8%; RR, 0.76; 95% CI, 0.21 to 2.67).

In patients selected for early cardioversion, time to cardioversion was similar in both treatment groups ($P = .628$), but in those selected for delayed cardioversion, it was significantly shorter in patients who received rivaroxaban compared with VKAs ($P < .001$; Figure 1).

Prof Cappato emphasized that differences in the primary efficacy and safety outcomes between the groups were not significant because this study was not powered to determine statistical significance. He concluded, however, that the results thus far suggest reassuring efficacy and safety profiles for rivaroxaban, and imply that this NOAC may represent a promising alternative to VKAs, allowing prompt, elective cardioversion in patients with AF.

FAMOUS NSTEMI: FFR-Guided Management of NSTEMI Reduces PCI and CABG

Written by Emma Hitt Nichols, PhD

Guided management by fractional flow reserve (FFR) resulted in more patients with NSTEMI being allocated to medical therapy when compared with guided

management by angiography alone. Colin Berry, FRCP, PhD, University of Glasgow, Glasgow, United Kingdom, presented data from the Fractional Flow Reserve Versus Angiographically Guided Management to Optimise Outcomes in Unstable Coronary Syndromes study [FAMOUS NSTEMI; NCT01764334].

Currently, visual interpretation of diagnostic angiography is important in determining the need for revascularization in patients with NSTEMI. FFR has a class I recommendation in stable coronary artery disease, but there is insufficient evidence for a recommendation in acute coronary syndromes. Lesion-level ischemia is associated with increased risk of ischemic events, as prior studies have shown that lesions with an FFR ≤0.80 benefit from revascularization with either coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). The hypothesis of the multicenter FAMOUS NSTEMI trial was that routine FFR is not only feasible in patients with NSTEMI but adds diagnostic, clinical, and economic benefits when compared with the current standard: angiography-guided management [Berry C et al. *Am Heart J.* 2013].

The primary outcome of the study was the proportion of patients who were administered medical management only at baseline. Secondary outcomes were the feasibility and safety of routine FFR, association between FFR and severity of stenosis, major adverse cardiac events (MACEs), resource use, and quality of life [Berry C et al. *Am Heart J.* 2013].

In this prospective clinical trial, 350 patients with intermediate- to high-risk NSTEMI were randomized to management that was guided by both angiography and FFR or by angiography alone. In the angiography-guided group, FFR was measured but not disclosed to clinicians or patients. Treatment decisions for any patient were left to the discretion of the treating physician. FFR was successful in 100% of patients, with a 0.03% rate of wire dissections. The treatment plan was altered in 22% of patients after FFR was disclosed, which decreased the number of patients treated with revascularization and type 4 myocardial infarctions (MIs).

FFR-guided management increased the number of patients allocated to medical therapy at the time of angiography (22.7% vs 13.2%; $P=.02$). A similar relationship was seen at 1 year, although this did not achieve statistical significance.

The rate of MACEs at 1 year was similar in both arms (log rank $P=.79$). The rates of procedure-related type 4 MIs and spontaneous MIs were similar in both arms; however, there was evidence that procedure-related type 4 MIs were greater in the FFR-guided arm compared with the angiography-guided arm ($P=.12$).

In conclusion, Prof Berry stated that the data from the FAMOUS NSTEMI trial suggest that FFR is feasible and safe and that the results can influence clinical decision making for patients with NSTEMI. However, Prof Berry noted that a larger trial is needed to further evaluate the clinical outcomes and cost-effectiveness of FFR-guided management of patients with NSTEMI.

STABILITY: Darapladib and Lp-PLA$_2$ Levels in Treatment of Atherosclerosis

Written by Brian Hoyle

The Stability of Atherosclerotic Plaque by Initiation of Darapladib Therapy trial [STABILITY; NCT00799903] showed that darapladib, an oral inhibitor of lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$), compared with placebo, did not significantly reduce the composite primary end point of cardiovascular (CV) death, myocardial infarction (MI), and stroke (HR, 0.94; 95% CI, 0.85 to 1.03; $P=.20$) in 15 828 patients with stable coronary heart disease (CHD) on optimal medical therapy [White HD et al. *N Engl J Med.* 2014]. The mean follow-up duration was 3.7 years. The secondary end point of major coronary events (CHD death, MI, and urgent coronary revascularization) was significantly reduced with treatment versus placebo (HR, 0.90; 95% CI, 0.82 to 1.00; $P=.045$).

Lars Wallentin, MD, PhD, Uppsala Clinical Research Center, Uppsala, Sweden, presented data from a predefined analysis of STABILITY designed to examine factors that contribute to high levels of Lp-PLA$_2$ activity, whether its activity predicted outcomes or identified patients who would have a greater benefit with darapladib, and whether darapladib would provide persistent, long-term reduction of Lp-PLA$_2$ activity.

For this analysis, blood samples were collected at baseline from 14 500 patients; of these, samples were also collected at all follow-up visits (months 1, 3, 6, and 18 and end of treatment) in 100 patients. The mean activity level of Lp-PLA$_2$ was 172 nmol/min/mL, with a normal distribution in relation to baseline demographics. The patients were evenly divided by tertiles of Lp-PLA$_2$ activity (tertile 1, ≤153.6 nmol/min/mL; tertile 2, 153.7–192.5 nmol/min/mL; tertile 3, >192.5 nmol/min/mL).

The baseline characteristics and biomarkers that increased or decreased Lp-PLA$_2$ activity on multivariate analysis are shown in Table 1. In the subset of 100 patients, there was a 65% relative risk reduction in Lp-PLA$_2$ activity with darapladib that was seen 1 month after treatment began and persisted through the end of follow-up.