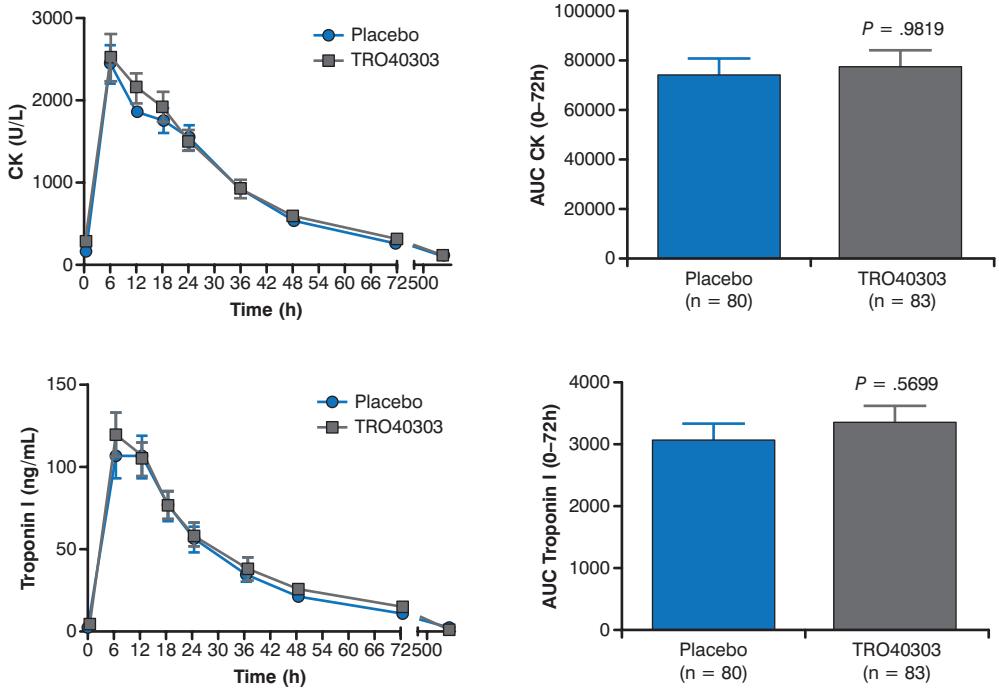
Figure 1. Effect of TRO40303 on CK and Troponin I Levels



AUC, area under the curve; CK, creatine kinase.
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The rate of adverse events was similar between the TRO40303 and placebo arms. However, 25% of patients experienced at least 1 adverse event in the TRO40303 arm, compared with 10% in the placebo arm ($P = .01$). For example, more patients in the TRO40303 group required repeat revascularization.

In conclusion, Prof Atar stated that the MITOCARE trial showed that TRO40303 does not reduce infarct size in patients with STEMI.

ENGAGE AF-TIMI 48: Tailoring Edoxaban Dose Preserves Drug Efficacy and Safety

Written by Brian Hoyle

The Effective Anticoagulation With Factor Xa Next Generation in the Atrial Fibrillation–TIMI 48 trial [ENGAGE AF-TIMI 48; Giugliano RP et al. *N Engl J Med*. 2013] of 21 105 patients with atrial fibrillation and $CHADS_2$ scores ≥2 reported the noninferiority of the oral factor Xa inhibitor edoxaban 30 and 60 mg once daily versus warfarin and dose-related decreases in major bleeding. Christian T. Ruff, MD, MPH, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented the results of a subanalysis showing that the protocol-driven dose adjustments in ENGAGE AF maintained the efficacy of edoxaban and reduced bleeding.

By way of background, the novel oral anticoagulants (NOACs), such as edoxaban, unlike warfarin, seem to provide fixed dosing therapeutic anticoagulation without the need for routine monitoring. However, an emerging question is whether the drug concentration or anticoagulant activity should be measured to optimize the risk/benefit ratio of a NOAC. Therefore, this subanalysis correlated the trough plasma concentrations of edoxaban in 6780 study patients and the anti–factor Xa activity in 2865 of the 6780 patients, measured 1 month after randomization with the edoxaban dose. The efficacy and safety outcomes were compared in the no dose reduction (NDR) and dose reduction (DR) groups in the edoxaban arms against warfarin.

The primary efficacy outcome was stroke or systemic embolic events (SEEs), and the primary safety outcome was major bleeding defined by International Society on Thrombosis and Haemostasis criteria. At baseline, or if any factors developed during the trial, doses in both edoxaban arms were reduced by 50% for patients with

reduced renal function (creatinine clearance 30–50 mL/min), those with lower weight (≤ 60 kg), and those coprescribed a potent P-glycoprotein inhibitor, which are indicators of increased bleeding risk or increased exposure to edoxaban.

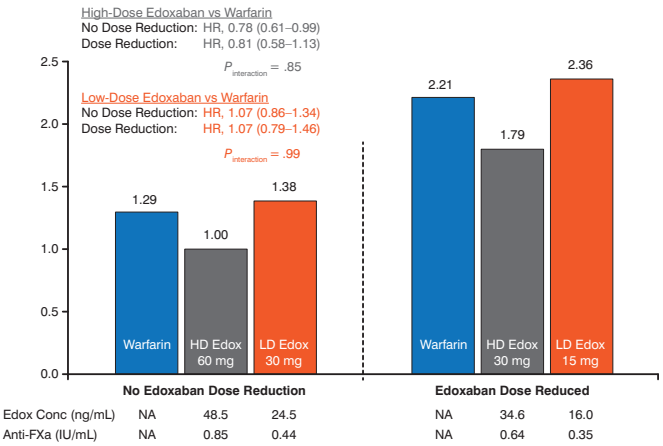
The mean trough concentrations of edoxaban were 48.5 ± 45.8 and 24.5 ± 22.7 ng/mL with the 60- and 30-mg doses in the NDR group and 34.6 ± 30.9 and 16.0 ± 14.5 ng/mL in the DR groupo, respectively.

Mean trough anti–factor Xa activity was 0.85 ± 0.76 and 0.44 ± 0.37 IU/mL in the NDR group with the 60- and 30-mg doses and 0.64 ± 0.54 and 0.35 ± 0.28 IU/mL in the DR group, respectively. There was a good correlation between the trough edoxaban concentration and trough anti–factor Xa activity, irrespective of the edoxaban dose or DR ($r = 0.96$, $P < .0001$).

For the primary outcome, the efficacy of edoxaban (60 and 30 mg) versus warfarin was similar irrespective of a DR. Edoxaban 15 mg was associated with a nonsignificant increased risk versus warfarin and edoxaban 30 mg (Figure 1).

The risk for major bleeding was lower with both doses of edoxaban versus warfarin. For both doses, there was a significantly lower risk for major bleeding in the DR group versus the NDR group ($P_{Interaction} = .02$ for edoxaban 60 mg, $P_{Interaction} = .002$ for edoxaban 30 mg; Figure 2). A similar finding was evident for the annual risk for intracranial hemorrhage, with a significant reduction in the DR group versus the NDR group in the edoxaban 30 mg arm (Figure 3).

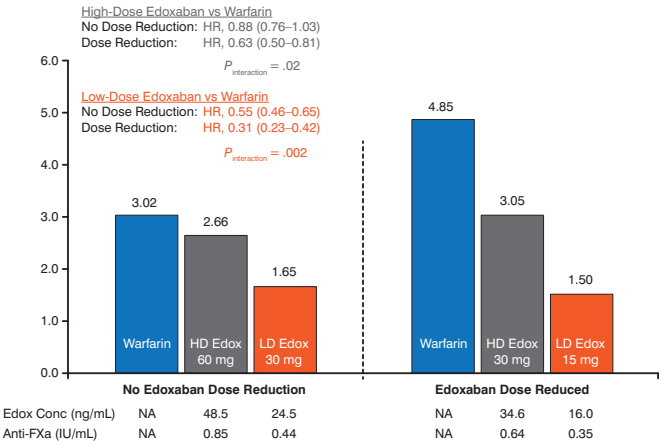
Figure 1. Primary Outcome With Maintained or Lowered High- and Low-Dose Edoxaban



Edox, edoxaban; FXa, factor Xa; HD, high-dose; LD, low-dose; NA, not applicable; SEE, systemic embolic event.

Reproduced with permission from C Ruff, MD, MPH.

Figure 2. Annual Risk for Major Bleeding



Edox, edoxaban; FXa, factor Xa; HD, high-dose; LD, low-dose; NA, not applicable; SEE, systemic embolic event.

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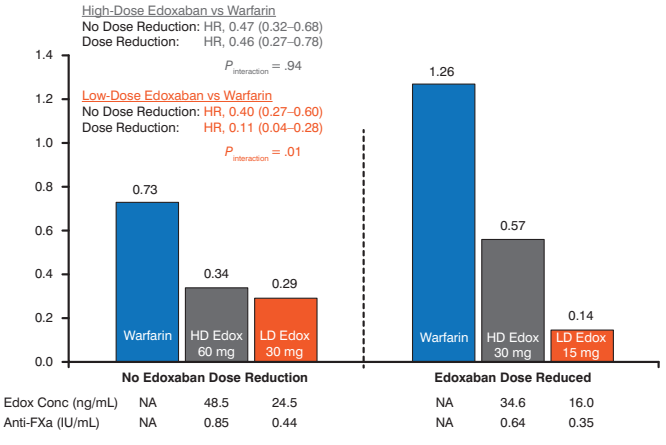
Figure 3. Annual Risk for Intracranial Hemorrhage



Edox, edoxaban; FXa, factor Xa; HD, high-dose; LD, low-dose; NA, not applicable; SEE, systemic embolic event.

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The therapeutic window of edoxaban showed that the dose-response curve was steepest for major bleeding, shallower for stroke and SEEs, and nearly flat for intracranial hemorrhage.

The mean edoxaban exposure and anti–factor Xa activity was reduced by 29% to 35% and 20% to 25%, respectively, in the DR and NDR groups. These data validate the strategy of tailoring the dose of NOACs on the basis of clinical factors alone to achieve the dual goal of preventing excess drug levels and optimizing an individual patient's risk for ischemic and bleeding events and demonstrate that the therapeutic window for edoxaban

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).

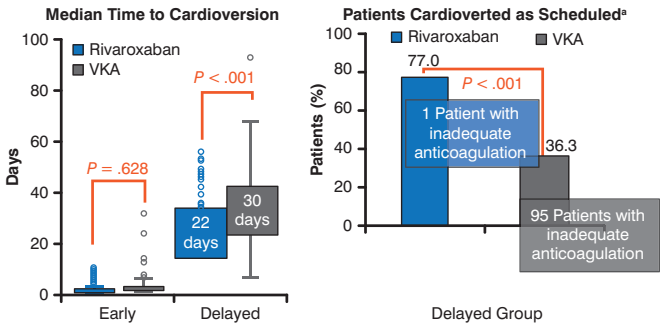
According to Prof Cappato, although cardioversion is commonly performed worldwide to restore normal rhythm in patients with AF [Hernández-Madrid A et al. *Europace* 2013], without appropriate anticoagulation therapy, the periprocedural risk of thromboembolism for this procedure is 5% to 7% [Stellbrink 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