The MI subgroup included 17,779 patients who had a qualifying spontaneous MI; 8898 were randomly assigned to vorapaxar and 8881 to placebo. A low–bleeding-risk cohort was identified (n=14,909). The primary efficacy endpoint was CV death, MI, or stroke analyzed by intention to treat. The principal safety endpoint was Global Use of Strategies to Open Occluded coronary arteries (GUSTO) moderate or severe bleeding. Most (98%) patients were on aspirin and 78% were on a thienopyridine. The median follow-up was 30 months, and the results were presented as 3-year Kaplan-Meier estimates.

Dr. Scirica reported that vorapaxar significantly reduced the rate of the primary endpoint compared with placebo (8.1% vs 9.7%; HR, 0.80; 95% CI, 0.72 to 0.89; p<0.0001). Vorapaxar reduced the rate of the primary endpoint both early (Day 0 to 360; p=0.003) and late (Day 360 to 1080; p=0.004; Figure 1).

Figure 1. Early and Late Efficacy of Vorapaxar Among the Subgroup of Patients with a Prior MI Cohort.
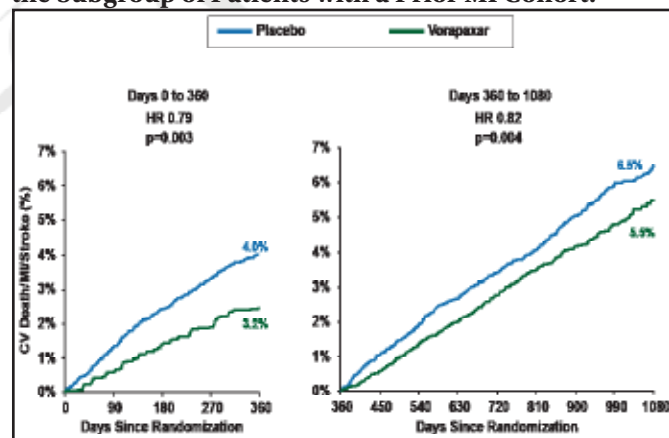

Reproduced with permission from The *Lancet;* Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: A prespecified subgroup analysis of the TRA 2°P-TIMI 50 trial. Scirica BM et al. 2012;doi:10.1016/S0140-6736(12)61269-0.

Based on prior studies, a cohort of patients (n=14,909; 84% of the MI cohort) who were age <75 years, had no history of TIA or stroke, and were ≥60 kg were selected as having the best potential for net clinical benefit [Wiviott SD et al. *N Engl J Med* 2007]. In this group, CV death, MI, or stroke was less common in the vorapaxar group compared with those in the placebo group (6.8% vs 8.6%; HR, 0.75; 95% CI, 0.66 to 0.85; p<0.0001), as was CV death (1.5% vs 2.0%; HR, 0.73; 95% CI, 0.56 to 0.95; p=0.020).

Consistent with the overall trial safety results, vorapaxar increased GUSTO moderate or severe bleeding (3.4% vs 2.1%; p<0.0001), as well as TIMI clinically significant bleeding (15.1% vs 10.4%; p<0.0001); TIMI major bleeding not associated with coronary artery bypass grafting (2.2% vs 1.6%; p=0.033; Figure 2). Rates of intracranial hemorrhage (0.6% vs 0.4%) and fatal bleeding (0.2%

vs 0.1%) were not numerically higher but significantly different (p=0.076 and p=0.30, respectively).

Figure 2. Bleeding Endpoints.
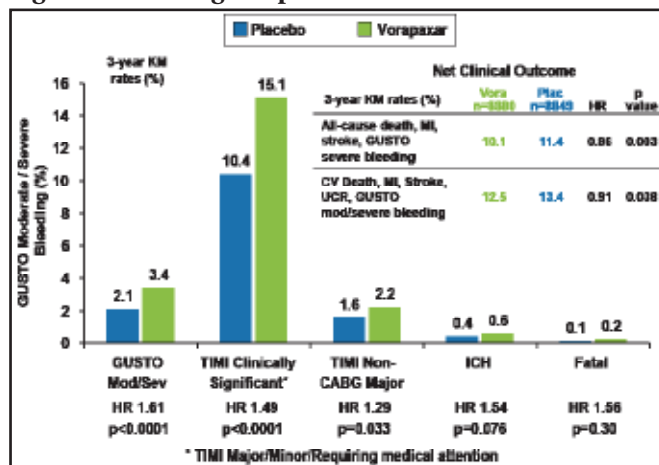
CV=cardiovascular; GUSTO=Global Use of Strategies to Open Occluded coronary arteries; ICH-intracranial hemorrhage; KM=Kaplan-Meier; TIMI=Thrombolysis in Myocardial Infarction; UCR-urgent coronary revascularization.
Reproduced with permission from BM Scirica, MD.

The net clinical benefit in the MI cohort with vorapaxar was significant, with a lower rate of all-cause death, MI, stroke, and GUSTO severe bleeding (10.1% vs 11.4%; HR, 0.86; p=0.003) and a lower rate of CV death, MI, stroke, urgent revascularization, and GUSTO moderate/severe bleeding (12.5% vs 13.4%; HR, 0.91; p=0.038). Dr. Scirica noted that the benefit of vorapaxar was consistent, offering an advantage regardless of the timing of MI, at early and late time periods, and with or without use of a thienopyridine in addition to aspirin.

Rivaroxaban of Benefit in STEMI: ATLAS ACS 2-TIMI 51

Written by Lori Alexander

Treatment with a low dose of rivaroxaban, an oral factor Xa inhibitor, has been shown to reduce recurrent cardiovascular (CV) events and offer a survival benefit without a significant increase in fatal bleeding for patients who have had an ST-segment elevation myocardial infarction (STEMI).

Rivaroxaban reduced recurrent CV events across the spectrum of acute coronary syndrome in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 [ATLAS ACS 2-TIMI 51; J Mega et al. *N Engl J Med* 2012] trial. Jessica L. Mega, MD, MPH, Brigham and Women's Hospital, Boston, Massachusetts, USA, reported the findings from an analysis

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of the prespecified subgroup in 7187 patients with STEMI in that trial. Effective long-term anticoagulant therapy has been of particular interest in this subpopulation because of prior studies that demonstrated an increase in thrombin production that lasted several months after STEMI.

The patients were randomly assigned to treatment with rivaroxaban at 2.5 mg BID (n=2601) or 5 mg BID (n=2584) or to placebo (n=2632). The patients received thienopyridine at the physician's discretion, as well as aspirin at a dose of 75 to 100 mg QD. The primary efficacy endpoint was a composite of CV death, MI, or stroke, and the primary safety endpoint was TIMI major bleeding not associated with coronary artery bypass grafting.

The primary efficacy endpoint occurred in significantly fewer patients in both rivaroxaban groups (Figure 1). The benefit of rivaroxaban was apparent as early as 30 days—1.7% in the combined rivaroxaban groups compared with 2.3% in the placebo group (HR, 0.71; 95% CI, 0.51 to 0.99; p=0.042 for the intention to treat group). When each rivaroxaban group was compared with placebo, both were associated with a lower rate of the primary efficacy endpoint: 10.6% for placebo versus 8.7% for the 2.5 mg group (p=0.047) versus 8.2% for the 5 mg group (p=0.051). However, only the lower dose was associated with a significantly lower rate of CV death: 4.2% for placebo versus 2.5% for the 2.5 mg group (p=0.006) versus 4.0% for the 5 mg group (p=0.64).

Figure 1. Cardiovascular Death, MI, or Stroke.
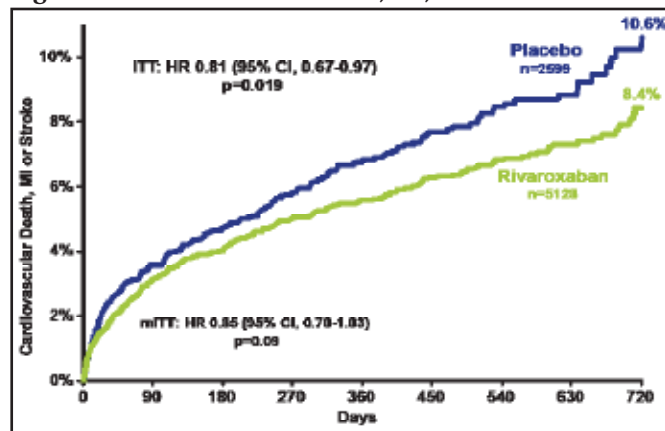
ITT=intention to treat; MI=myocardial infarction; mITT=modified ITT.
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The primary safety endpoint was significantly increased in both rivaroxaban groups, with rates of 1.7% (2.5 mg group), 2.7% (5 mg group), and 0.6% (placebo; p<0.001 for comparison of either dose with placebo; Figure 2). However, fatal bleeding was not significantly increased with rivaroxaban: 0.12% (placebo) versus 0.04% (2.5 mg rivaroxaban; p=0.33) versus 0.40% (5 mg rivaroxaban; p=0.12).

Figure 2. Other Safety Endpoints.
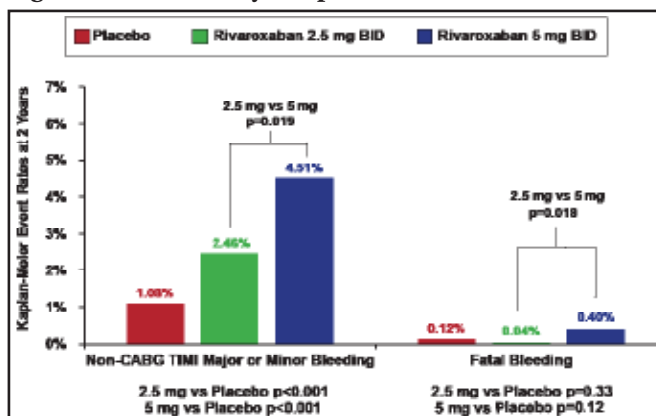
CABG=coronary artery bypass graft; TIMI=thrombolysis in myocardial infarction.
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Dr. Mega and colleagues concluded that treatment with rivaroxaban 2.5 mg BID offers an effective strategy to reduce thrombotic events in patients following STEMI.

Ivabradine Effect on Recurrent Hospitalization for HF

Written by Lori Alexander

The Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial [SHIFT] was a randomized, double-blind, placebo-controlled trial in 6505 patients with moderate to severe chronic heart failure (HF), which tested whether isolated heart rate reduction with the I_f inhibitor ivabradine improves cardiovascular (CV) outcomes [Swedberg K et al. *Lancet* 2010]. Inclusion criteria included hospitalization for worsening HF within 12 months prior to randomization, left ventricular ejection fraction (LVEF) ≤35%, sinus rhythm and heart rate ≥70 beats per minute (bpm), and current treatment with guidelines-based background HF therapy, including maximized β-blockade. Ivabradine was significantly better than placebo for the primary endpoint of CV death or hospitalization for worsening HF, with an 18% reduction in the cumulative frequency of events (HR, 0.82; 95% CI, 0.75 to 0.90; p<0.0001). Ivabradine versus placebo also reduced the rate of hospitalization for HF by 26% (HR, 0.74; 95% CI, 0.66 to 0.83; p<0.0001).

Since a significant proportion of healthcare resource and economic burden is attributable to recurrent hospitalization in patients with HF, the aim of the current analysis presented by Jeffrey S. Borer, MD, State University of New York Downstate Medical Center, Brooklyn and New York, New York, USA, was to assess the effect of treatment with ivabradine on