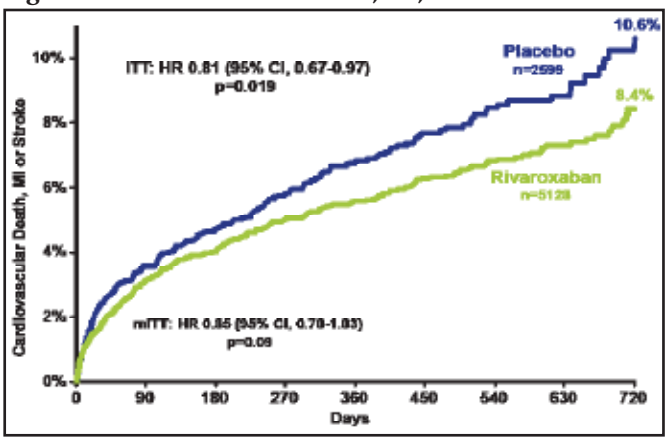
of the prespecified subgroup in 7187 patients with STEMI in that trial. Effective long-term anticoagulant therapy has been of particular interest in this subpopulation because of prior studies that demonstrated an increase in thrombin production that lasted several months after STEMI.

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).

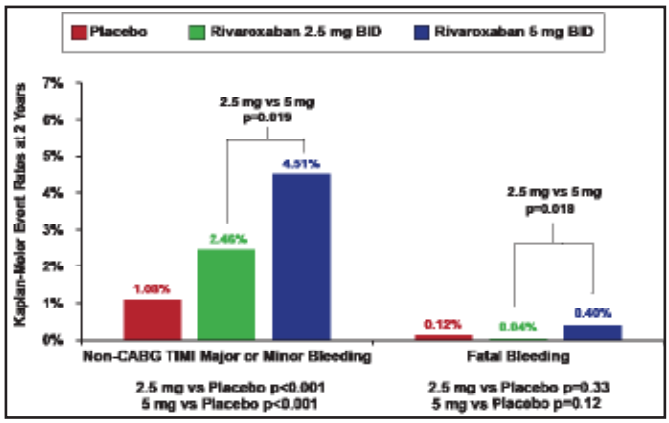
Figure 1. Cardiovascular Death, MI, or Stroke.



ITT=intention to treat; MI=myocardial infarction; mITT=modified ITT.
Reproduced with permission from J. Mega, MD, MPH.

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).

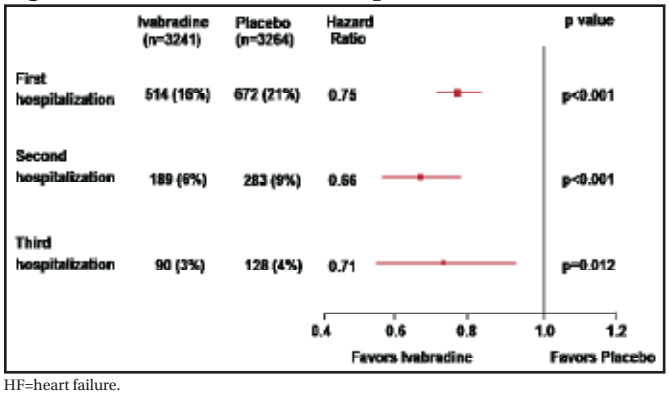
Since a significant proportion of healthcare resource and economic burden is attributable to recurrent hospitalization in patients with HF, the aim of the current analysis presented by Jeffrey S. Borer, MD, State University of New York Downstate Medical Center, Brooklyn and New York, New York, USA, was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

recurrent hospitalizations for worsening HF throughout the entire duration of SHIFT [Borer JS et al. *Eur Heart J* 2012]. The endpoints were the effect of ivabradine on total heart failure hospitalizations (incidence rate ratio [IRR] vs placebo) and repeated HF hospitalizations (total-time approach: time from randomization to first, second, and third hospitalizations), as well as total CV hospitalizations and total hospitalizations for any cause. The analyses, which were post hoc, were adjusted for protocol-specified prognostic factors present prior to randomization, including β-blocker intake, New York Heart Association (NYHA) class, ischemic cause of HF, LVEF, age, systolic blood pressure (BP), heart rate, and creatinine clearance.

Prior to randomization, patients with ≥3 hospitalizations were older, had a higher heart rate, lower systolic BP, diastolic BP, and LVEF, higher NYHA class, longer duration of HF, higher incidence of diabetes, and more were taking mineralocorticoid receptor antagonists, diuretics, and digitalis, though fewer were able to tolerate β-blockers, compared with patients with <3 hospitalizations.

At 30 months, the cumulative incidence of HF hospitalizations was 25% lower in the ivabradine group (n=3241) versus the placebo group (n=3264). Patients in the ivabradine group versus the placebo group had significantly fewer total hospitalizations for HF (902 vs 1211; IRR, 0.75; 95% CI, 0.65% to 0.87%; p=0.0002), hospitalizations for any cause (2661 vs 3110; IRR, 0.85; 95% CI, 0.78% to 0.94%; p=0.001), and CV hospitalizations (1909 vs 2272; IRR, 0.84; 95% CI, 0.76% to 0.94%; p=0.002). Using the total-time approach, during the total follow-up interval, significantly fewer ivabradine patients versus placebo patients had a second hospitalization (6% vs 9%; HR, 0.66; 95% CI, 0.55% to 0.79%; p<0.001) and third hospitalization (3% vs 4%; HR, 0.71; 95% CI, 0.54% to 0.93%; p=0.012; Figure 1).

Figure 1. Recurrence of HF Hospitalization.



HF=heart failure.
Reproduced with permission from JS Borer, MD.

Heart rate reduction with ivabradine in patients with chronic HF in sinus rhythm with a heart rate ≥70 bpm and already receiving guideline-suggested therapies substantially decreased the risk of clinical deterioration as reflected by the reduction in total hospitalizations for worsening HF, reduction in the incidence of recurrent HF hospitalizations, and increase in time to first and subsequent hospitalizations. This benefit reduces the total burden of HF for the patient and can be expected to substantially reduce healthcare costs. These findings are consistent with the 2012 European Society of Cardiolgy heart failure guidelines that recommend ivabradine for the reduction of HF hospitalization in patients who meet the SHIFT trial's eligibility criteria, and who are treated with maximal HF therapy, including an ACEI or ARB, maximized β-blockade, and mineralocorticoid receptor antagonist.

CLARIFY: Similar 1-Year Outcomes for Men and Women with Stable CAD

Written by Lori Alexander

Despite substantial differences in the risk profiles of men and women with stable coronary artery disease (CAD), outcomes at 1 year appear to be similar, according to an analysis of data from the international Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease [CLARIFY; Steg PG et al. *Eur Heart J* 2012] registry. The study adds new insights into gender differences in stable CAD, as relatively few studies have compared outcomes in this patient population. However, results should be interpreted in the context of an observational registry data set.

The study included data for 30,977 outpatients with stable CAD, defined as prior myocardial infarction (MI), angiographic coronary disease (>50% lesion), ischemic symptoms and a positive stress test, or prior coronary revascularization from 45 countries; 23,975 (77.4%) of the patients were men. The main outcome was a composite of cardiovascular (CV) death, MI, or stroke. Analyses were time to first event, and comparisons by gender were adjusted for differences in patient baseline characteristics.

At 1 year, the rate of the primary outcome was similar for men and women (adjusted rates, 1.7% vs 1.8%, respectively; OR, 0.93; 95% CI, 0.75 to 1.15; p=0.5), reported Philippe Gabriel Steg, MD, Hôpital Bichat, Paris, France, who presented the findings of the study. Women were at similar risk as men for major CV outcomes (Figure 1). Prof. Steg added that there was an interaction between gender and age, with younger women having slightly better outcomes than younger men; however, the same was not true for middle-aged or older women (p-interaction=0.0077).