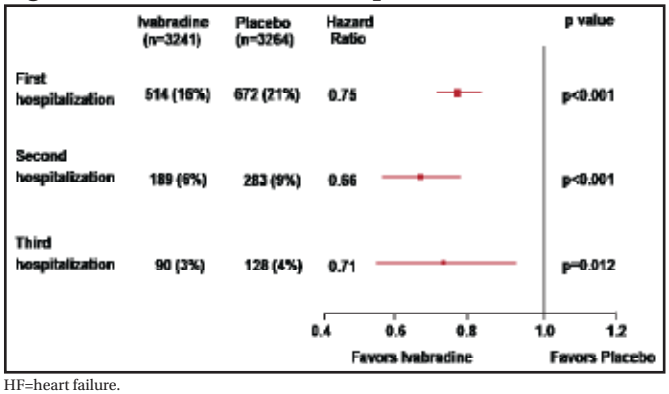
recurrent hospitalizations for worsening HF throughout the entire duration of SHIFT [Borer JS et al. *Eur Heart J* 2012]. The endpoints were the effect of ivabradine on total heart failure hospitalizations (incidence rate ratio [IRR] vs placebo) and repeated HF hospitalizations (total-time approach: 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

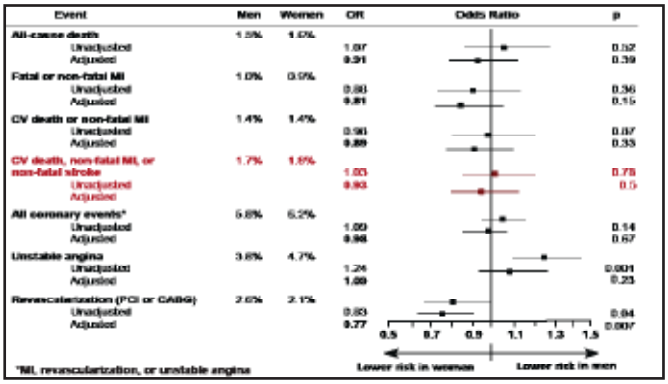
Despite substantial differences in the risk profiles of men and women with stable coronary artery disease (CAD), outcomes at 1 year appear to be similar, according to an analysis of data from the international Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease [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).

The risk profile differed substantially by gender, with women more likely to have hypertension or diabetes (Table 1). Women were also more likely to have angina but were less likely to have had diagnostic non-invasive testing or coronary angiography, to have received evidence-based pharmacologic treatments, or to have had revascularization (Table 1).

Figure 1. Major CV Outcomes at 1 Year.



CABG=coronary artery bypass grafting; CV=cardiovascular; MI=myocardial infarction; PCI=percutaneous coronary intervention.

Table 1. Gender Differences in Stable CAD in CLARIFY.

Characteristics	Men (%)	Women (%)	p value
Risk Factors			
Family history of premature CAD	28	31	<0.0001
Treated hypertension	69	78	<0.0001
Diabetes	28	33	<0.0001
Medical History			
Angina	21	29	<0.0001
Coronary angiography	86	80	<0.0001
Noninvasive test for MI	63	58	<0.0001
MI	62	51	<0.0001
Peripheral artery disease	10	8	<0.0001
Stroke	4	4	0.24
TIA	3	4	0.0033
PCI	59	55	<0.0001
CABG	25	17	<0.0001
Pharmacologic Treatments			
Lipid-lowering drugs	93	90	<0.0001
Aspirin	88	87	0.048
ACE inhibitor and/or ARB	76	76	
β-blocker	75	75	

ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; CABG=coronary artery bypass grafting; CAD=coronary artery disease; MI=myocardial infarction; PCI=percutaneous coronary intervention; TIA=transient ischemic attack.

Prof. Steg noted several limitations to the study. The primary limitation was the relatively low number of women, which he noted may have been related to the inclusion criteria required by the study. In addition, the cohort sample may not be representative of a population-based sample, as physician and patient participation in the CLARIFY registry is voluntary. Also, despite adjustments for potential confounders, residual confounding cannot be excluded.

HPS2-THRIVE Results

Written by Lori Alexander

Approximately two thirds of patients can tolerate extended-release (ER) niacin when combined with laropiprant, according to a prespecified interim safety and tolerability analysis of the Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events [HPS2-THRIVE; NCT00461630] study. The addition of niacin/laropiprant to statin therapy offers a dual goal of decreasing low-density lipoprotein-cholesterol (LDL-C) and increasing high-density lipoprotein-cholesterol (HDL-C).

Niacin, the first lipid-modifying drug, is one of the most effective agents for increasing HDL-C levels. However, its use has been limited by its side effects, particularly flushing. Coadministration of laropiprant, a selective prostaglandin D antagonist, has been shown to reduce flushing. However, the drug may not reduce this side effect in all patients, as flushing can occur through other pathways.

HPS2-THRIVE includes more than 25,000 patients in Europe and China who have cardiovascular disease (CVD) and are at high risk for recurrent vascular events. The patients were randomly assigned to ER niacin 2 g/laropiprant or to placebo. All patients also received LDL-C reducing therapy with simvastatin 40 mg, with or without ezetimibe 10 mg. The study is the largest one to date to evaluate the CV benefits of increasing HDL-C levels. Jane Armitage, MD, Oxford Clinical Trial Service, Oxford, United Kingdom, reported on the safety and tolerability of the combination drug.

Patients were treated with ER niacin/laropiprant or placebo during an 8-week run-in phase prior to randomization. During this phase, 25.4% of patients in the ER niacin/laropiprant group withdrew from therapy for any medical reason; the primary reasons were cutaneous effects (primarily flushing, 11.3%) and gastrointestinal symptoms (5.5%). An additional 8.7% of patients in this group withdrew during the randomized treatment phase, again primarily because of cutaneous effects (5.1%) and gastrointestinal symptoms (3.6%). Among patients in the placebo group, 1.2% withdrew during the treatment phase because of cutaneous effects and 1.6% because of gastrointestinal symptoms.