Furthermore, BID dosing was associated with numerically higher bleeding rates compared with the same QD dose across the three total study doses (10 mg, 30 mg, 60 mg). Relative to placebo (3.1%), the increase in bleeding was statistically significant (p=0.002) for the darexaban 30-mg BID dose (11.3%). No cases of fatal bleeding or intracranial hemorrhage were reported in either study group. TIMI major bleeding rates were low in all groups; however, the rate for any TIMI bleeding followed the same dose-dependent increase as was seen for the primary endpoint. There was no difference in the composite efficacy endpoint of all-cause mortality, nonfatal MI, nonfatal stroke, and severe recurrent ischemia in any of the darexaban dose groups, individually or combined, when compared with placebo (p=NS).

Darexaban is a novel anti-Xa anticoagulant, similar to rivaroxaban and apixaban, which have already been evaluated in Phase 2 studies. While the Phase 3 APPRAISE-2 trial that evaluated apixaban in ACS was halted early due to excess bleeding risk, the ATLAS-2 trial (rivaroxaban in ACS) is ongoing. Insights from these Phase 3 trials will help clinicians understand whether there is a role for oral anticoagulant therapy in addition to antiplatelet therapy in patients with ACS and how to dose these new agents appropriately.

Additional reading: Steg G et al. *Eur Heart J* 2011.

EMPHASIS-HF: An Analysis of the High-Risk Groups

Written by Maria Vinall

Recent results from the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF) trial showed that eplerenone, compared with placebo, significantly reduced the risk of the composite of cardiovascular (CV) death and hospitalization for heart failure (HF) in patients with chronic systolic NYHA class II HF [NCT00232180; Zannad F et al. *N Engl J Med* 2011]. Subjects were randomized to eplerenone (up to 50 mg daily) or placebo, in addition to recommended background therapy. Enrollment in the trial, which randomized 2737 patients, was stopped prematurely after a median follow-up of 21 months, when an overwhelming benefit (HR, 0.63; p<0.001) with eplerenone on the primary endpoint of death from CV causes and hospitalization for HF was observed in the secondary interim analysis. After the trial was prematurely stopped for efficacy in May 2010, a subgroup of patients (58% of the patients who were randomized; n=1597) were followed for an additional 10 months on blinded therapy through March 2011, resulting in a mean follow-up of 25 months in the extended follow-up subgroup.

Bertram Pitt, MD, University of Michigan, Ann Arbor, Michigan, USA, presented three sets of new data from the trial: 1) safety and efficacy results of the extended follow-up of the EMPHASIS-HF study; 2) an exploratory analysis of recurrent hospitalization; and 3) analyses in five high-risk subgroups. The five subgroups of individuals who were considered to be at high risk were independently analyzed, including subjects with: age ≥75 years (n=184), left ventricular ejection fraction (LVEF) <30% (n=440), estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 (n=270), diabetes (n=240), and systolic blood pressure (SBP) <123 mm Hg (n=339).

Consistent with the main study, the primary composite endpoint of CV death or hospitalization for HF was reduced with eplerenone compared with placebo (HR, 0.66; 95% CI, 0.57 to 0.77; p<0.001) in the extended follow-up subgroup. An analysis of the cumulative number of hospitalization for HF (recurrent event analysis) also favored eplerenone (HR, 0.62; 95% CI, 0.53 to 0.72; p<0.001).

There were consistent reductions with eplerenone in the primary endpoint in each of the five individual high-risk groups (Table 1). Additionally, in each of the five subgroups, there were significant reductions with eplerenone in the secondary endpoints of all-cause hospitalization and in hospitalization for HF (p<0.01 for all comparisons).

Table 1. Rates of CV Death or HF Hospitalization During Study Extension.

	HR (95% CI)	p value
All Subjects	0.63 (0.54 to 0.74)	p<0.0001
≥75 years of age (n=184)	0.66 (0.49 to 0.88)	p=0.0044
LVEF <30% (n=440)	0.65 (0.54 to 0.78)	p<0.0001
eGFR<60 ml/min/1.73 m^2 (n=270)	0.62 (0.49 to 0.79)	p=0.0001
Diabetes mellitus (n=240)	0.54 (0.42 to 0.70)	p<0.0001
SBP <123 mm Hg (n=339)	0.63 (0.51 to 0.79)	p=0.0001

HR=hazard ratio; LVEF=left ventricular ejection fraction; eGFR=estimated Glomerular Filtration Rate; SBP=systolic blood pressure.

The safety endpoint of serum potassium greater than 5.5 mmol/L was more frequent with eplerenone overall and among each of the individual high-risk groups (p<0.05 for each comparison). There was no significant increase in serious hyperkalemia (K+ >6.0 mmol/L), hyperkalemia that led to drug discontinuation, hospitalization for hyperkalemia, or hospitalization for worsening renal function for eplerenone patients relative to placebo patients.

These results showed a consistent benefit in the reduction of CV death or hospitalization for HF over continued follow-up and among individual high-risk subgroups. Important reductions were also seen in the secondary endpoints of all-cause hospitalization and in hospitalization for HF. While these results show compelling evidence for efficacy that is consistent with guideline recommendations for this class of medications, there were higher rates of hyperkalemia, and the study protocol required careful monitoring with visits every 4 months. This should be considered when applying these results with eplerenone in clinical practice.

The PRODIGY Trial – More Information about DAPT after DES Implantation

Written by Rita Buckley

Two years of dual antiplatelet therapy (DAPT) after drug-eluting stent (DES) implantation is no better than 6 months of DAPT in preventing adverse cardiac events, according to the Prolonging dual antiplatelet treatment after Grading Stent-Induced Intima Hyperplasia Study [PRODIGY; NCT000611286]. Marco Valgimigli, MD, PhD, University of Ferrara, Ferrara, Italy, reported the main results of the PRODIGY trial.

PRODIGY was an open-label, three-center, randomized, factorial assignment clinical trial to assess the efficacy and safety of prolonged DAPT (up to 2 years) with aspirin and clopidogrel after coronary stenting compared with currently recommended DAPT regimens (a minimum of 1 month after bare-metal stent [BMS] or 6 months after DES).

Inclusion criteria included males and females aged ≥18 years with coronary artery disease with low-, intermediate-, or high-risk coronary anatomy who were considered suitable for percutaneous coronary intervention with stent placement. The primary outcome was the composite endpoint of death, myocardial infarction (MI), or stroke, occurring from 31 days up to 24 months after intervention. The primary safety outcome was Bleeding Academic Research Consortium (BARC) type 2, 3, and 5 bleeding (Table 1) [Mehran R et al. *Circulation* 2011].

Patients (n=1970) who were scheduled for elective, urgent, or emergency coronary angioplasties were initially randomized in a 1:1:1:1 fashion to one of four stent types: everolimus-eluting stent, paclitaxel-eluting stent, zotarolimus-eluting stent, or third-generation thin-strut BMS. At 30 days, patients in each stent group were then further randomized to either 6 or 24 months of DAPT to ensure that the length of DAPT was equally distributed within each of the four stent groups.

Table 1. BARC Definitions.

Type 0: No bleeding
Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance studies, hospitalization, or other treatment by a health care professional
Type 2: Any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5, but does meet at least one of the following criteria: 1. requiring non-surgical medical intervention by a health care professional 2. leading to hospitalization or increased level of care 3. prompting evaluation

Type 3
• Type 3a
  • Overt bleeding plus hemoglobin (Hb) drop of 3 to 5 g/dL* (provided Hgb drop is related to bleed)
  • Any transfusion with overt bleeding
• Type 3b
  • Overt bleeding plus Hgb drop of ≥5 g/dL* (provided Hb drop is related to bleed)
  • Cardiac tamponade
  • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
  • Bleeding requiring intravenous vasoactive drugs
• Type 3c
  • Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal)
  • Subcategories; confirmed by autopsy or imaging
  • Intra-ocular bleed compromising vision

Type 4: CABG-related bleeding • Perioperative intracranial bleeding within 48-hours • Reoperation following closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 units of whole blood or packed red blood cells (PRBC) within a 48 hour period** • Chest tube output of ≥2 L within a 24-hour period • If a CABG-related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as a "not a bleeding event"

Type 5: Fatal bleeding
• Type 5a
  • Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious
• Type 5b
  • Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Obvious platelet transfusions should be recorded and reported but are not included in these definitions until information is obtained about the relationship to outcomes; *Corrected for transfusion (1 unit PRBC or 1 unit whole blood=1 g/dL Hgb); **Only allogeneic transfusions are considered transfusions for BARC Type 4 bleeding; Cell saver products will not be counted.

Results showed that the cumulative risk of the primary outcome at 2 years was 10.1% with the 24-month treatment and 10.0% with the 6-month treatment (HR, 0.98; 95% CI, 0.74 to 1.29; p=0.91). The individual risks of death, MI, cerebrovascular accident, or stent thrombosis did not differ between the two groups.

Patients who received long-term DAPT had a roughly 2-fold greater risk of BARC (2, 3, or 5) bleeding events (HR, 2.17; 95% CI, 1.44 to 3.22; p=0.00018). The risks of TIMI-defined major bleeding (p=0.04) and red blood cell transfusion (p=0.04) were also increased in the 24-month clopidogrel group.