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.

In patients who received first- or second-generation DES, outcomes failed to show a benefit of DAPT treatment for 24 months. According to Prof. Valgimigli, "While we cannot rule out the possibility that a smaller-than-previously anticipated benefit may exist, the clear increase in bleeding, transfusion, and net adverse clinical events suggests that current recommendations may have overemphasized the benefit over the risk of long-term treatment with aspirin and clopidogrel."

These findings question the validity of current guideline recommendations, which were based on registry data. According to Prof. Valgimigli, if the risk of morbidity due to bleeding outweighs the anticipated benefit that is afforded by thienopyridine therapy, earlier discontinuation should be considered [Duke Heart Registry; *JAMA* 2007].

PURE: CV Drugs Underused for Secondary Prevention in Poor and Rural Populations

Written by Anne Jacobson

Despite proven efficacy and relatively low cost, key secondary prevention medications are widely underused in populations with prevalent cardiovascular disease (CVD), particularly in poor countries and rural areas, according to findings from the Prospective Urban Rural Epidemiological (PURE) study.

PURE is the first prospective study to evaluate the use of cardiovascular (CV) drugs for secondary prevention across countries with differing levels of economic development. Salim Yusuf, MD, McMaster University, Hamilton, Ontario, Canada, presented results from the PURE study.

From 2003 to 2009, the PURE study enrolled 153,996 adults from 628 urban and rural communities in 17 countries, with a subset of 5650 patients who reported a prior coronary heart disease (CHD) event and 2292 who reported a prior stroke. Participating countries were classified as high-income (Canada, Sweden, and United Arab Emirates), upper-middle-income (Argentina, Brazil, Chile, Malaysia, Poland, South Africa, and Turkey), lower-middle-income (China, Colombia, and Iran), and low-income (Bangladesh, India, Pakistan, and Zimbabwe), based on World Bank criteria at the beginning of the study. Medical history and use of key secondary preventive medications were assessed with a combination of telephone interviews, home visits, and clinic visits.

Across all countries, only a minority of patients aged 35 to 70 years with a history of CHD or stroke reported taking key secondary preventive drugs, including antiplatelet drugs, aspirin (25.3%), angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs; 19.5%), β-blockers (17.4%), or statins (14.6%).

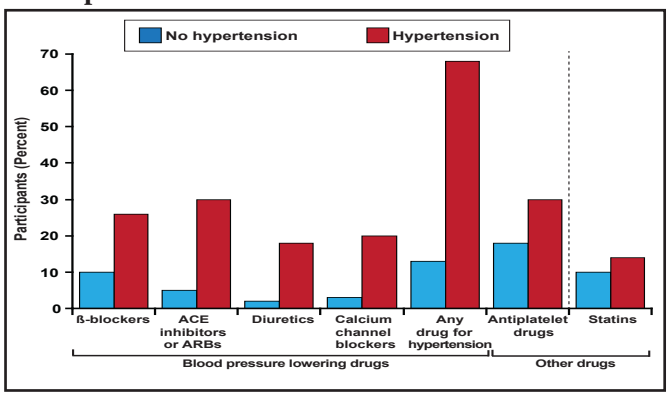
Between-country variations in medication use were twice as large as patient-level variability due to age, sex, education, smoking, obesity, hypertension, and diabetes, suggesting that national policies and health system structures have a predominant role in secondary prevention.

Medication use was highest in high-income countries and decreased with country income (p-trend <0.0001 for every drug type). Gaps between low-income and high-income countries were approximately 7-fold for aspirin and 20-fold for statins. Although 88.8% of patients in high-income countries took at least 1 drug for secondary prevention, far fewer patients received any medication in upper-middle-income countries (54.9%), lower-middle-income countries (30.7%), and low-income countries (19.8%).

There were also differences that were observed between types of communities, with patients in urban areas more likely than those in rural communities to take antiplatelet drugs (28.7% vs 21.3%), β-blockers (23.5% vs 15.6%), ACE inhibitors or ARBs (22.8% vs 15.5%), and statins (19.9% vs 11.6%), regardless of the economic status of the country (p<0.0001 for all drugs). However, gaps between urban and rural medication use were widest in the poorest counties (p interaction<0.0001).

Among patient-level factors, patients with CVD and hypertension were more likely than those with CVD alone to receive drugs that also lowered blood pressure, including β-blockers (28% vs 10%) and ACE inhibitors or ARBs (30% vs 5%; Figure 1). Conversely, younger patients; women; smokers; and those who were less educated, nonobese, or nondiabetic were less likely to use drugs for secondary prevention.

Figure 1. Drug Use by History of Hypertension in Participants with CVD.



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