Global Coronary Flow Reserve Is Associated With Adverse Cardiovascular Events Independently of Luminal Angiographic Severity and Modifies the Effect of Early Revascularization

Increasing evidence suggests that global atherosclerotic disease burden and resultant ischemia, even absent obstructive epicardial lesions, are important contributors to overall cardiovascular risk, especially when functional outcomes such as cardiovascular death and heart failure are considered. Although luminal coronary angiography is a cornerstone of modern cardiovascular care, it is limited in its ability to identify diffuse atherosclerosis and small-vessel disease; this may help to explain why anatomically guided revascularization procedures have not resulted in improved outcomes in patients with stable ischemic heart disease in randomized, controlled trials comparing revascularization with guideline-directed medical therapy. Coronary flow reserve (CFR) is an integrated measure of focal, diffuse, and small-vessel coronary artery disease that assays the complex sequelae of ischemic insults in the heart and identifies patients at risk for cardiac death. This study demonstrated that (1) although global CFR is only modestly associated with the overall extent and severity of angiographic disease, both low CFR and high angiographic disease score are independently associated with adverse clinical events, and (2) global CFR modified the effect of revascularization, such that only patients with low CFR appeared to benefit from revascularization in this cohort, and only if the revascularization included coronary artery bypass grafting. As such, the present study raises the possibility that the type of revascularization for certain patients (ie, with preserved versus impaired CFR) may have profound implications for optimal management strategy. In addition, these findings identify diffuse atherosclerosis and microvascular dysfunction as potentially relevant targets for aggressive therapeutic intervention and global cardiovascular risk reduction. See p 19.

A Randomized Trial of Social Media From Circulation

Social media is commonly used by medical journals to distribute the findings of published articles. However, it is uncertain whether the use of social media in this way increases the dissemination of original published articles. To test this question, we performed a randomized trial of original articles published in Circulation. Articles were randomized to receive targeted social media exposure from Circulation, including postings on the journal’s Facebook and Twitter feeds as compared with control articles, which received no social media exposure from Circulation. Overall, 243 articles were randomized: 121 in the social media arm and 122 in the control arm. There was no difference in 30-day page views (409 [social media] versus 392 [control], P=0.80). No differences were observed by article type, whether an article had an editorial, or whether the corresponding author was from the United States. A social media strategy for a cardiovascular journal did not increase the number of times an article was viewed. Further research is necessary to understand the ways in which social media can increase the impact of published cardiovascular research. See p 28.

Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial

For the substantial proportion of patients with heart failure and preserved ejection fraction, no therapy has been shown to convincingly improve prognosis. In the randomized, placebo-controlled Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial, allocation to spironolactone did not significantly reduce the primary composite outcome of cardiovascular death, aborted cardiac arrest, or hospitalization for the management of heart failure. In a post hoc analysis, an unusually large difference in event rates was observed, with those enrolled from Russia and Georgia experiencing lower event rates than anticipated for patients with symptomatic heart failure, and 4-fold lower rates compared with those enrolled from the Americas (United States, Canada, Brazil, and Argentina). In this analysis, we report the patient characteristics between these regions, their prognosis, and their responses to spironolactone therapy. We describe profound differences in baseline characteristics and greater changes in potassium, creatinine, and blood pressure with spironolactone in the patients randomized in the Americas, and in this group, in which the event rates were more consistent with symptomatic heart failure, the primary outcomes of cardiovascular death and hospitalization for heart failure were reduced in the spironolactone group. Although post hoc analyses are fraught with hazard, in the absence of more robust data for the treatment of patients with heart failure with preserved ejection fraction, our findings of greater risk for hyperkalemia, increased creatinine, and associated potential benefits on cardiovascular death and hospitalization for heart failure are worthy of consideration. See p 34.

International Geographic Variation in Event Rates in Trials of Heart Failure With Preserved and Reduced Ejection Fraction

In this study we examined international geographical variations in event rates in 5 large clinical trials in heart failure. We compared the rates of hospitalization for heart failure, all-cause, and cardiovascular death in Eastern Europe/Russia, with Western Europe and the United States/Canada. In patients with heart failure and preserved ejection fraction (HF-PEF) we found higher rates of heart failure hospitalization in the United States/Canada compared with Eastern Europe/Russia, but less difference for patients with heart failure and reduced ejection fraction (HF-REF). The observed differences in event rates suggests international geographic variation in 1 or more of the following: the definition and diagnosis of HF-PEF, the risk profile of patients enrolled, the threshold for heart failure hospitalization, or some other factor. This finding has implications for the conduct of future global trials in HF-PEF. Greater standardization of entry criteria and the baseline risk profile of patients may reduce such variation. See p 43.

Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients With Heart Failure

The PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) trial compared the angiotensin receptor-neprilysin inhibitor LCZ696 (400 mg daily) with
the angiotensin-converting enzyme inhibitor enalapril (20 mg daily) in 8399 patients with heart failure and reduced ejection fraction in a double-blind trial. In a previous report, patients in the LCZ696 group had a 20% lower risk of cardiovascular death and a 16% lower risk of death for any reason (both \( P<0.0001 \)). This article reports on the effect of treatment on the clinical progression of heart failure in surviving patients. When compared with enalapril, fewer LCZ696-treated patients required intensified medical treatment for heart failure (\( P=0.003 \)) or an emergency department visit for worsening heart failure (\( P=0.001 \)). The patients in the LCZ696 group also had 23% fewer hospitalizations for worsening heart failure (\( P<0.001 \)) and were 18% less likely to require intensive care (\( P=0.005 \)), 31% less likely to receive intravenous positive inotropic agents (\( P<0.001 \)), and 22% less likely to have implantation of a heart failure device or cardiac transplantation (\( P=0.07 \)). The reduction in heart failure hospitalization with LCZ696 was evident within the first 30 days after randomization. Worsening symptoms of heart failure were consistently more common in the enalapril group. LCZ696 led to an early and sustained reduction in biomarkers of myocardial wall stress and injury (N-terminal pro-B-type natriuretic peptide and troponin) versus enalapril. These findings demonstrate that LCZ696 prevents the clinical progression of surviving patients more effectively than enalapril and provides further support for the use of this new approach to replace the current use of inhibitors of the renin-angiotensin system in chronic heart failure. See p 54.

**Prasugrel Plus Aspirin Beyond 12 Months Is Associated With Improved Outcomes After Taxus Liberté Paclitaxel-Eluting Coronary Stent Placement**

The complex issue of dual antiplatelet therapy duration after drug-eluting stents remains a hot topic, 8 years after initial concerns were voiced about late stent thrombosis. Despite intense study, the optimal duration of dual antiplatelet therapy remains undefined. In this article, we show that patients treated with TAXUS Liberté paclitaxel-eluting stents in combination with prasugrel plus aspirin benefit from 30 months therapy, rather than 12, chiefly because of lower myocardial infarction (MI) and stent thrombosis rates with longer therapy. After a year of treatment, an increase in MI was evident within 90 days of stopping prasugrel. Interestingly, a similar rise in MI was seen when prasugrel was stopped after 30 months, suggesting that risk of ischemic events persists beyond 30 months. Importantly, most MI were spontaneous (ie, not attributable to the paclitaxel-eluting stent); in fact, no stent-related MI occurred between 12 and 30 months in patients taking prasugrel. The increased risk of bleeding that came with prolonged therapy appeared to be acceptable. Although previous studies have suggested safety with ≤12-month dual antiplatelet therapy, our data suggest otherwise. Further study is needed to determine whether patient characteristics (eg, level of atherosclerotic disease activity, inflammation, genetic characteristics, concomitant therapies) can define those most likely to benefit from prolonged dual antiplatelet therapy after drug-eluting stents. See p 62.

**Long-Term Efficacy and Safety of Biodegradable-Polymer Biolimus-Eluting Stents: Main Results of the Basel Stent Kosten-Effektivitäts Trial–PROspective Validation Examination II (BASKET-PROVE II), A Randomized, Controlled Noninferiority 2-Year Outcome Trial**

There is an ongoing controversy over the potential association of the durable polymer of durable-polymer drug-eluting stents (DP-DES) with very late stent thrombosis (VLST) and related myocardial infarction or death beyond 1 year after implantation. To overcome this perceived deficiency of durable polymers, DES with biodegradable polymers (BP-DES) were introduced. BP-DES have been shown to be noninferior compared with DP-DES during the initial year after implantation and superior to first-generation DP-DES thereafter, but no comparison of early efficacy and late safety of BP-DES to second-generation best-in-class everolimus-eluting DP-DES (Xience Prime) and to newest-generation thin-strut bare-metal stents (Prokinetik) within 1 trial have been performed. BASEl Stent Kosten-Effektivitäts Trial–PROspective Validation Examination II (BASKET-PROVE II) filled this gap, evaluating the biolimus-eluting BP-DES (Nobori) in 2291 patients with a follow-up of 2 years. The BP-DES proved to be as effective and noninferior by intention-to-treat to the DP-DES to prevent restenosis. In fact, both DES were superior to the bare-metal stents regarding this primary end point, particularly by reducing target-vessel revascularization. However, BP-DES did not further reduce the rate of VLST, myocardial infarction, or cardiac death beyond 1 year. Overall, stent thrombosis rates were very low in BASKET-PROVE II with all 3 stents, possibly because of the prasugrel-based dual antiplatelet therapy in this study. The lack of an improved late safety (ie, the lack of a reduction of VLST with BP-DES compared with best-in-class DP-DES observed here) seems to question the concept that durable polymers are key in late stent thrombosis formation; however, only a mega-trial may provide a definite proof for this. See p 74.

**Edoxaban Effects on Bleeding Following Punch Biopsy and Reversal by a 4-Factor Prothrombin Complex Concentrate**

The oral factor Xa inhibitor edoxaban has demonstrated safety and efficacy in stroke prevention in patients with atrial fibrillation and treatment and secondary prevention of venous thromboembolism. Reversal of anticoagulant effects of non–vitamin K oral anticoagulants, including edoxaban, is important in the event of clinically relevant bleeding, or when emergency intervention is called for in patients receiving a non–vitamin K oral anticoagulant. In this phase 1, double-blind, randomized, placebo-controlled, 2-way crossover single-site study, the reversal of edoxaban’s effects on bleeding duration and bleeding volume following punch biopsy were investigated by using descending doses of a 4-factor prothrombin complex concentrate (4F-PCC). Intravenous administration of 4F-PCC 50, 25, or 10 IU/kg following edoxaban 60 mg dose-dependently reversed edoxaban’s effects on bleeding duration and endogenous thrombin potential, with complete reversal at 50 IU/kg. A similar trend was seen for bleeding volume. The effects on prothrombin time were partially reversed at 50 IU/kg. The 4F-PCC dose-dependently reversed the effects of edoxaban (60 mg), with complete reversal of bleeding duration and endogenous thrombin potential and partial reversal of prothrombin time following 50 IU/kg. Punch biopsy was shown to have acceptable sensitivity and variability to assess the reversal of edoxaban’s effects. Further, these results suggest that 4F-PCC represents a readily available, widely marketed option in cases where rapid reversal of edoxaban anticoagulation is essential. A 4F-PCC 50 IU/kg dose appears to be appropriate for reversal of the effects of a therapeutic dose of edoxaban in the case of clinically relevant bleeding or an urgent need for surgery. See p 82.
Circulation: Clinical Summaries: Original Research Put Into Perspective for the Practicing Clinician

Circulation. 2015;131:2-3
doi: 10.1161/CIR.0000000000000153
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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