See related editorial on pages 1425-7.

ISCHEMIC MITRAL REGURGITATION: REPAIR THE VALVE, RESHAPE THE VENTRICLE, OR BOTH?

To the Editor:

We read with interest the article by Kron and colleagues,¹ which addresses the complex issue of mitral repair durability in patients with ischemic mitral regurgitation (MR). The authors must be credited for reporting the particularly high rate of recurrence (ranging from 25.5% at 6 months up to 39% at 24 months) in the Cardiothoracic Surgery Network (CSTNet) trial. Interestingly, the authors claim that the mechanism for recurrence was largely mitral valve leaflet tethering, although no measures of tethering were retained in the model. Moreover, they identify basal aneurysm/dyskinesis as 1 of the more robust mechanisms of failure, and for this reason they advocate for more innovative repair techniques.

However, the desire for alternative repair techniques is not new. In 2002, Kron and colleagues² described the direct relocation of the posterior papillary muscle tip in a small group of patients with previous inferior myocardial infarction, but not severely dilated ventricles (<6 cm in end-systolic diameter). In patients with dilated left ventricles (>6 cm end-systolic diameter), the Dor procedure, that is, relocating the papillary muscle base, was advocated. Later, Levin and colleagues³ outlined the importance of anteroapical myocardial infarction causing MR despite the absence of inferobasal wall motion abnormalities. Recently, we⁴ addressed the differences between anterior and posterior remodeling in patients with previous myocardial infarction undergoing surgical ventricular reconstruction. In patients with previous inferior myocardial infarction, the remodeling can occur between the 2 papillary muscles or between the posteromedial papillary muscle and the posterior septum, which is usually deeply involved. Anyway, MR, if it occurs, is mainly related to localized inferobasal left ventricular (LV) remodeling causing lateral displacement of the posterolateral papillary muscle, increased internal diameter, and mitral valve

posterior leaflet tethering. Hence, MR occurs with less global LV remodeling and dysfunction, and especially without any involvement of the anteroseptal LV wall.

In patients with previous anterior myocardial infarction, MR occurs mainly in the setting of global LV dilatation and severe dysfunction, with tethering of both mitral valve leaflets due to apical displacement of papillary muscles. Accordingly, the surgical procedure to rebuild the LV cavity is different in the 2 groups,^{4,5} but the technique to repair the mitral valve, when indicated, is not. The result is a greater reduction of the internal diameter in the absence of a significant increase of the sphericity index in patients with posterior remodeling compared with patients with anterior remodeling.⁴ Accordingly, a lower rate of recurrence, as would be expected, could translate into better long-term survival. Therefore, we think that the problem is not how to repair the mitral valve, but the strategy with which the underlying ventricle is addressed, and surgical ventricular reconstruction plus mitral valve repair is a reasonable option for patients with previous inferior myocardial infarction and ischemic MR.

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OFF-PUMP VERSUS ON-PUMP CORONARY ARTERY BYPASS GRAFTING: WHO BENEFITS?

To the Editor:

We read with great interest the editorial commentary by Rubens¹ regarding our recently available meta-analysis² suggesting improved outcomes with off-pump coronary artery bypass grafting (CABG) relative to conventional on-pump CABG in high-risk patients. In brief, the analysis by including 100 randomized controlled trials (RCTs; N = 19,192 patients) comparing off-pump versus on-pump

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CABG demonstrated, apart from significant 28% reduction of the odds of 30-day cerebral stroke, that the benefits of off-pump CABG are more pronounced in patients at higher baseline risk. First of all, we are very grateful to Rubens¹ for the comments included in the editorial commentary; at the same time, we are glad that our research has become of interest to the international readership and may, in turn, contribute to the discussion on this timely topic.

First of all, Rubens¹ wonders whether the findings of the meta-analyses should, in general, inform the clinical practice, because as they are often driven by findings of small-sample trials, they do not reflect the findings of largest well-designed RCTs. To support this claim, he refers to a 2007 meta-analysis³ that demonstrated increased cardiovascular risk associated with rosiglitazone and eventually led the US Food and Drug Administration to withdraw the drug from the market. This study stood opposed to the large Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes trial, which in contrast showed similar risks of overall cardiovascular morbidity or mortality with rosiglitazone as compared with standard glucose-lowering drugs.⁴ Unlike the meta-analysis of Nissen and Wolski,³ however, which included by design heterogeneous studies on rosiglitazone (type 2 diabetes mellitus, impaired glucose tolerance or fasting glucose, chronic psoriasis and mild-to-moderate Alzheimer disease) with different glucose-lowering agents and placebo as control groups, our analysis focused on a single comparison on-pump versus off-pump CABG in patients with coronary artery disease. We noted no signs of heterogeneity, publication bias, and small-study effect for either of the outcomes analyzed. In addition, in the number of sensitivity analyses accounting for different statistical approaches, we demonstrated that the final estimates were not influenced by statistical model used, which indeed may have been the case in the meta-analysis on rosiglitazone.^{3,5}

Rubens¹ promptly points to the largest recent studies⁶⁻⁸ as source of high-quality evidence on the topic. These studies did indeed show no statistically significant difference with respect to 30-day incidence of stroke, probably because stroke is not a frequently seen entity after CABG, and studies were underpowered to detect any difference with respect to single end points. At closer look, however, one finds that the extent to which the rates of stroke were reduced in the German Off-Pump Coronary Artery Bypass Grafting in the Elderly trial,⁸ which exclusively enrolled older patients, was somewhat higher than that in the CABG Off or On Pump Revascularization study⁷ (mean age, 78.5 years; hazard ratio, 0.83; 95% confidence interval, 0.50-1.38 vs mean age, 67.5 years; 0.89; 0.51-1.54), thus suggesting that certain benefits might accrue with increasing risk (eg, advanced age).

Of note, although never shown in a single RCT for the reasons mentioned previously, the significant reduction in

the incidence of stroke after off-pump CABG relative to on-pump CABG is not novel and has been demonstrated in both observational data^{9,10} and in previous meta-analyses of RCTs.¹¹⁻¹³ Our meta-analysis, by incorporating data from most recent large RCTs, not accounted for in the previous reports, only confirms and corroborates these findings, showing a significant 28% reduction in the odds of cerebral stroke (odds ratio, 0.72; 95% confidence interval, 0.56-0.92; $P = .009$; $I^2 = 0\%$).

The main focus of the current meta-analysis,² however, was to identify patients who might benefit from off-pump CABG. An important finding of our analysis is the significant, negative relationship between patient risk profile and benefits of off-pump CABG with respect to the single end points all-cause mortality, myocardial infarction, and stroke. Therefore, patients who are more likely to die or have myocardial infarction or cerebral stroke occur within first 30 days after revascularization, yield higher protection against these endpoints when operated on off pump, and off-pump CABG should strongly be considered for these patients.

Rubens¹ asks whether we have confidence that the results of this meta-analysis in particular should influence practice such that we should routinely advocate for an off-pump strategy. Current guidelines state that “both procedures usually result in excellent outcomes and that neither technique should be considered superior to the other.”¹⁴ On the other hand, they point to advantages of off-pump CABG when performed in high-risk patients at high-volume off-pump centers.^{11,15-17} From our own clinical perspective (more than 98% CABG procedures performed off pump), the answer is yes; patients at high risk for complications after cardiopulmonary bypass and crossclamping of the aorta are the subgroup that will benefit most from cardiopulmonary bypass avoidance. In addition, these patients may be provided with equivalent, complete coronary revascularization.

We cannot agree more with Rubens¹ with regard to the indisputable value of multiple arterial grafts, long-term survival, repeat revascularization, angina-free survival, and completeness of revascularization indices. These are, however, achievable to a similar extent with both on-pump and off-pump CABG performed in high-volume centers by experienced surgeons.

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OFF-PUMP ON-PUMP DEBATE: CAVEAT EMPTOR

Reply to the Editor:

The eye sees only what the mind is prepared to comprehend.

—Robertson Davies

The meta-analysis is a useful tool for the clinician to distill and condense trial information to facilitate evidence-based medical practice. The reader must come to the table, however, with the eye of a cynic, with a full understanding of the steps that have been taken to avoid bias in the presentation as subtle changes and manipulations of the complex statistics can dramatically sway the outcomes and thus the interpretation. It is apparent that Kowalewski and colleagues¹ have taken steps to bolster our confidence that the heterogeneity of the trials and the trial size were not factors in the single positive outcome. As raised in the accompanying editorial, however, do small trials of low quality still impact the overall answer?

The problem of trial quality is a major concern in systematic reviews. A Cochrane Collaborative study demonstrated the implications of more than 70 meta-analyses in the literature by replicating the data analysis. This study found that more than two-thirds of the conclusions that favored one of the interventions were no longer supported if trials with inadequate concealment of allocation were excluded.²

It is interesting to note that the question of off-pump versus on-pump coronary artery bypass grafting has been simultaneously addressed in a publication in a sister journal.³ One could criticize the study of Deppe and colleagues³ as less diligent in terms of the literature search as it did not, for eg, include congress proceedings. On the other hand, I believe that a more robust assessment of the quality of the trials was completed, with 3 scoring systems including the Jadad score.⁴ When all trials were considered, Deppe and colleagues³ did identify similar findings in terms of perioperative stroke and off-pump surgery. Publication bias was evident with regard to the stroke outcome, as demonstrated by the funnel plot analysis, but this may have been explained by their less diligent search relative to that of Kowalewski and colleagues.¹ When the assessment was limited to the 13 identified trials of “high quality,” however, there was no longer a stroke benefit associated with off-pump surgery (off-pump, 1.5%; on-pump, 1.8%; odds ratio, 0.86; 95% confidence interval 0.65-1.13; $P = .3146$).

Kowalewski and colleagues¹ have disclosed their passion for and belief in off-pump surgery by the declaration of their personal experience with 98% of patients treated. But does this zealotry inspire confidence in the reader that subtle unintentional bias has not been imposed with the complex statistical approaches used? Did Kowalewski and colleagues¹ set out to answer a question, or to prove a point? Further,