Letters to the Editor

The Editor welcomes submissions for possible publication in the Letters to the Editor section that consist of commentary on an article published in the Journal or other relevant issues. Authors should:

- Include no more than 500 words of text, three authors, and five references
- Type with double-spacing
- See http://jtcs.ctsnetjournals.org/misc/ifora.shtml for detailed submission instructions.
- Submit the letter electronically via jtcvs.editorialmanager.com.

Letters commenting on an article published in the JTCVS will be considered if they are received within 6 weeks of the time the article was published. Authors of the article being commented on will be given an opportunity to offer a timely response (2 weeks) to the letter. Authors of letters will be notified that the letter has been received. Unpublished letters cannot be returned.

Reasons for inability of clopidogrel to inhibit platelet aggregation early after coronary artery bypass surgery

To the Editor:

Clopidogrel administration for platelet inhibition after coronary artery surgery and interventional cardiology is currently a topic of much-deserved attention and debate. I read with interest the recent article in the *Journal* by Lim and colleagues.[1] On the basis of the results of an interim analysis of their prospective, double-blind, randomized, controlled trial to compare the efficacy of clopidogrel and aspirin as antiplatelet agents, Lim and colleagues conclude that clopidogrel, unlike aspirin, did not inhibit platelet aggregation in the first 5 postoperative days and therefore should not be used as a sole antiplatelet agent early after coronary surgery. According to the authors, the ineffectiveness of clopidogrel was an "unexpected" finding. However, plenty of evidence is available from published studies to suggest a logical explanation for this unexpected finding.

Clopidogrel is a pro-drug, which is converted to an active, unstable drug by cytochrome P450 (CYP). The active drug irreversibly blocks 1 specific platelet: adenosine 5'-diphosphate receptor (P2Y12). It was recently suggested that the most abundant human CYP isoform, 3A4, activates clopidogrel.[2] Certain lipophilic statins (ie, simvastatin, atorvastatin, and lovastatin), which are substrates of the CYP3A4 isoform, competitively inhibit the metabolic activation of clopidogrel. As a result, the relative clopidogrel-induced platelet inhibition is diminished, especially if administered in a low dose.[3] Furthermore, clopidogrel administration results in interindividual variability in platelet inhibition. This variable platelet inhibition response to clopidogrel has been recognized by all who have tested clopidogrel efficacy by platelet aggregometry and correlates with CYP3A4 metabolic activity.[4] In addition, it is extremely important to remember that platelet inhibition by clopidogrel is dose-related up to a dose of 400 mg and that inhibition at a higher dose remains stable from 2 to 72 hours.[5]

A closer look at the study by Lim and colleagues[1] clearly reveals that all of these confounding factors are present and that they influence the results of their interim analysis. In my opinion, the conclusion of this study would be different if a larger dose of clopidogrel were used and nonresponders (≈10%) and low responders (≈20%), as well as those on statins, were excluded.

Shahzad G. Raja, MRCS
Department of Cardiac Surgery
Royal Hospital for Sick Children
Yorkhill NHS Trust
Glasgow G3 8SJ
United Kingdom

References

1. Lim E, Cornelissen J, Routledge T, Kirtland S, Charman SC, Bellm S, et al. Clopidogrel did not inhibit platelet function early after coronary bypass surgery: a prospective randomized trial. *J Thorac Cardiovasc Surg.* 2004;128:432-5.
2. Clarke TA, Waskell LA. Clopidogrel is metabolized by human cytochrome P450 3A and inhibited by atorvastatin. *Drug Metab Dispos.* 2003;31:53-9.
3. Neubauer H, Gunesdogan B, Hanefeld C, Spiecker M, Mugge A. Lipophilic statins interfere with the inhibitory effects of clopidogrel on platelet function—a flow cytometry study. *Eur Heart J.* 2003;24:1744-9.
4. Lau WC, Gurbel PA, Watkins PB, Neer CJ, Hopp AS, Carville DG, et al. Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. *Circulation.* 2004;109:166-71.
5. Thebault JJ, Kieffer G, Cariou R. Single-dose pharmacodynamics of clopidogrel. *Semin Thromb Hemost.* 1999;25(Suppl 2):3-8.

doi:10.1016/j.jtcvs.2004.09.027

Reply to the Editor:

The opinion on the interaction between statins and clopidogrel is still subject to fierce debate.[1,2] However, excluding sub-

jects from the analysis because they are on statins effectively excludes the majority of patients undergoing coronary surgery. We report that clopidogrel, unlike aspirin, did not inhibit platelet aggregation in the first 5 postoperative days, a result that is applicable to the wider population of patients irrespective of the eventual outcome of the drug interaction debate.

Little consideration has been given to the suggestion of excluding nonresponders and low responders from the analysis. If we did that for any arm of any trial only the favorable responders would be left, giving the false impression of treatment efficacy. It is plausible that increasing the dose of clopidogrel may increase antiplatelet effects in similar conditions (but this should not be assumed). However, the current recommended dose is 75 mg per day, and a loading dose of clopidogrel is only indicated in unstable angina (300 mg single loading dose).[3] This information is consistent with the product information sheet issued by Sanofi-Synthelabo (New York, NY).

Our aim was to report the results of an intention-to-treat randomized clinical trial, using approved drug doses, with findings that can be generalized to the wide population undergoing coronary surgery, not to manipulate analyses to favor any particular arm.

Eric Lim
Papworth Hospital
Cambridge
United Kingdom

References

1. Saw J, Steinhubl SR, Berger PB, Kereiakes DJ, Serebruany VL, Brennan D, et al. Lack of adverse clopidogrel-atorvastatin clinical interaction from secondary analysis of a randomized, placebo-controlled clopidogrel trial. *Circulation.* 2003;108:921-4.
2. Mitsios JV, Papathanasiou AI, Rodis FI, Elisaf M, Goudevenos JA, Tselepis AD. Atorvastatin does not affect the antiplatelet potency of clopidogrel when it is administered concomitantly for 5 weeks in patients with acute coronary syndromes. *Circulation.* 2004;109:1335-8.
3. British National Formulary. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain; 2003.

doi:10.1016/j.jtcvs.2004.09.028

Clinical efficacy of retrograde coronary sinus perfusion in off-pump surgery

To the Editor:

I read with great interest the article by Castella and Buckberg[1] on retrograde coronary sinus perfusion in off-pump surgery. My colleagues and I have been constantly stimulated by the pioneering work of Dr Buckberg on myocardial preservation. It is indeed very gratifying and encouraging to know that the technique we[2] have been using regularly since September 1997 to perform off-pump coronary artery bypass grafting (OPCABG) with no ischemia during periods of construction of the distal anastomosis has been proven by the very elegant work of Castella and Buckberg[1] to be effective in reducing systolic and diastolic dysfunction during periods of coronary occlusion. In our technique, after midsternotomy a retrograde coronary sinus catheter is inserted and connected to an antegrade cannula in the ascending aorta.[2] Perfusion is now allowed through this route from the aorta to the coronary sinus, onward through the capillaries to the myocardium, and out through the arterioles at the site of ischemia. There is ample proof that ischemia is relieved as evidenced by the following facts: (1) reversion of electrocardiographic changes of ischemia, (2) vigorous backbleeding of dark blood on temporary release of the distal snare after arteriotomy, and (3) a good oxygen extraction ratio across the myocardium calculated by sampling blood from the antegrade cannula and from the arteriotomy.[3]

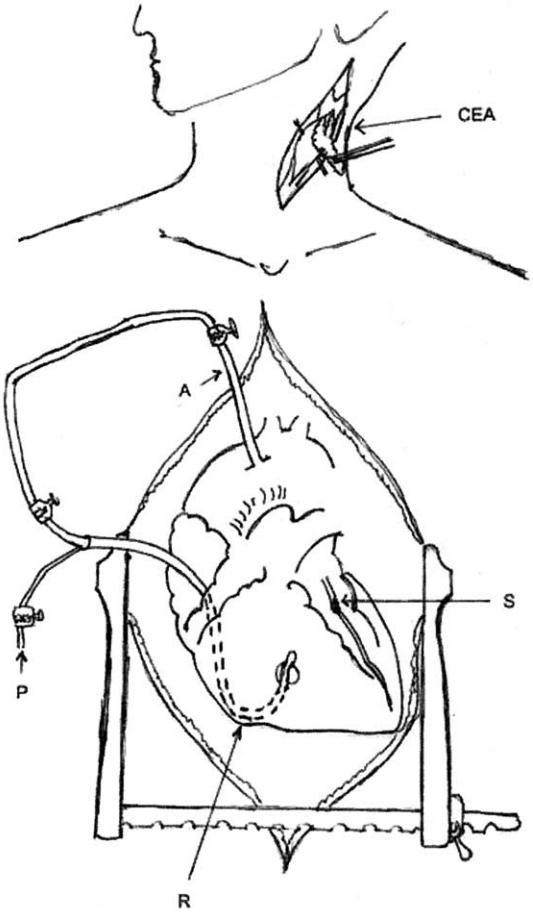

Figure 1. Technique of retrograde perfusion during combined carotid endarterectomy and coronary artery bypass grafting. *A,* Antegrade cardioplegia cannula; *R,* retrograde coronary sinus cannula; *S,* stenosed coronary artery; *CEA,* carotid endarterectomy in progress; *P,* pressure monitoring line.