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J. Am. Coll. Cardiol. 2003;42;772
doi:10.1016/S0735-1097(03)00793-9

This information is current as of November 10, 2009

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<http://content.onlinejacc.org/cgi/content/full/42/4/772>

JACC

JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY



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doi:10.1016/S0735-1097(03)00791-5

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Clopidogrel Versus Ticlopidine After the Placement of Coronary Artery Stents

In a study published recently in *JACC*, Mueller et al. (1) compared treatment with clopidogrel and aspirin to ticlopidine and aspirin in patients undergoing coronary stent placement. Both drugs were started after the procedure and continued for four weeks. Ticlopidine was given as a 500-mg loading dose followed by 250 mg twice daily thereafter; however, clopidogrel was given without loading: 75 mg daily. The results suggested that clopidogrel was inferior to ticlopidine in terms of cardiovascular mortality. In other studies involving clopidogrel, a loading dose of 300 mg was given initially followed by 75 mg daily thereafter (2,3). A loading dose of 300 mg of clopidogrel is needed in order to achieve timely platelet inhibitory effect (4). The lack of clopidogrel loading clearly delays the effect of clopidogrel and, therefore, may cause a higher thrombotic stent occlusion (TSO) rate (the TSO rate was not reported by Mueller et al.). Use of a clopidogrel loading dose in this instance may show clopidogrel not to be inferior to ticlopidine (3).

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doi:10.1016/S0735-1097(03)00793-9

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REPLY

We fully agree with Dr. Rott that the lack of a loading dose of clopidogrel is an important issue in interpreting our data. After completion of our study, two major clinical trials, Clopidogrel for the Reduction of Events During Observation (CREDO) (1) and ISAR-REACT (2), were reported that highlight the need for a loading dose of clopidogrel. In CREDO, the best clinical outcome was seen in those patients who achieved the full antiplatelet effect of clopidogrel at the time of intervention, which was 6 h after a loading dose of 300 mg. Based on clinical observations (3) and *ex vivo* analysis of platelet function (4), the ISAR-REACT trial used an even higher loading dose of clopidogrel, 600 mg, which enables the full antiplatelet effect of clopidogrel within 2 h (4). With this loading scheme, the antithrombotic efficacy in patients undergoing elective interventions could not be further improved even with abciximab, as shown by the composite 30-day end point of death, myocardial infarction, and urgent revascularization (2).

In light of these new findings, we cannot exclude that the results of our trial, as well as those of other trials suggesting inferiority of clopidogrel compared with ticlopidine (5), would have been different had an appropriate loading dose been used. Notably, a high loading dose may overcome the other potential explanation of our findings, which is the interference of statins. Although the issue has not been completely settled, preliminary reports indicate that attenuation of the antiplatelet effect by statins is not detectable after a 600-mg loading dose (6).

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doi:10.1016/S0735-1097(03)00794-0

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This information is current as of November 10, 2009

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