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doi:10.1016/j.ehj.2004.05.025

Long-term clopidogrel therapy in the drug-eluting stent era: beyond CREDO and PCI-CURE

We agree with the main thrust of the argument in the recent article by Eriksson¹ that long-term clopidogrel treatment (8 and 12 months) confers a small, or at most modest, advantage when compared to the standard 1-month treatment in patients undergoing percutaneous coronary intervention.

Eriksson should be commended for the critical analysis of the data from PCI-CURE and CREDO. In particular, for pointing out that the small absolute reductions in composite endpoints of death, myocardial infarction, revascularisation in the long-term clopidogrel treatment group compared to the standard 1-month treatment group, could easily be negated by the increased bleeding risk.

However, we wish to highlight that both trials were conducted before the era of drug-eluting stents. In fact, the main reason for prescribing clopidogrel beyond the standard 1-month period is not so much driven by the results of PCI-CURE or CREDO, but by the implantation of drug-eluting stents.

The theoretical concerns of delayed endothelialisation leading to stent thrombosis have not been borne out by trials comparing drug-eluting stents to bare metal stents. Nevertheless, all these trials of drug-eluting stents have used clopidogrel for beyond the standard 1-month period normally applied to bare metal stents.

In RAVEL,² where short coronary lesions (mean length 9.58 mm) were treated with a single sirolimus-eluting stent, clopidogrel was prescribed for 2 months. The SIRIUS³ and TAXUS IV trials involved treating longer lesion lengths (mean length 14.4 and 13.4 mm, respectively) and more complex disease (diabetes, multiple stents and small vessels). The duration of clopidogrel treatment for SIRIUS and TAXUS IV trials was therefore longer, at 3 and 6 months respectively. None of these trials showed an increased risk of stent thrombosis in the drug-eluting stent group when clopidogrel was prescribed for between 2 and 6 months.

In fact, two recent reports of stent thrombosis in drug-eluting stents⁵,⁶ in the literature demonstrate a strong link to the discontinuation of anti-platelet therapy within the first month. Lemos et al.,⁷ has shown that even in unselected “real world” patients outside the strict entry criteria of trials, patients with complex disease such as multi-vessel disease, bifurcation disease requiring multiple stenting can be treated with sirolimus-eluting stents effectively without an excess of stent thrombosis with clopidogrel treatment of 3–6 months duration.

Although the optimal duration of clopidogrel treatment after drug-eluting stent implantation is not known, empirical long-term treatment (3–6 months) is here to stay because of the fear of the dreaded complication of stent thrombosis and its serious consequences. Depending on lesion complexity and adverse patient characteristics such as diabetes, some authorities even recommend 6–12 months treatment with clopidogrel.⁸ This prolonged use of clopidogrel has economic consequences and should be considered in any cost analysis of the use of drug-eluting stents.

References


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doi:10.1016/j.ehj.2004.05.026

Long-term clopidogrel therapy in the drug eluting stent era: beyond CREDO and CURE-PCI: Reply

Sir

In the trials comparing drug-eluting stents with bare metal stents, clopidogrel (in addition to aspirin) had been administering for 2–6 months, and no increase in the incidence of stent thrombosis has been reported to date.¹ However, I share Dr. Koh’s and Dr. Kadr’s concerns about delayed endothelialisation with drug-eluting stents. Although the optimal period of clopidogrel therapy after drug-eluting stent implantation is not known, clopidogrel is prescribed for 6 months after the implantation of a drug-eluting stent in our institution, which probably provides a wide margin of safety. In contrast, anti-platelet therapy was discontinued after the procedure in four out of the seven patients with a stent thrombosis in the study of Jeremias et al.,² cited by Koh and Kadr. This is evidently not a strong argument for long-term clopidogrel therapy.

The clinical value of long-term therapy with clopidogrel in addition to aspirin has recently been called in question.³,⁴ Now the Management of ATherothrombosis with Clopidogrel in High-Risk Patients with
Recent Transient Ischemic Attack or Ischemic Stroke (MATCH) trial also raises serious concerns about the safety of combining aspirin and clopidogrel long-term. In MATCH, clopidogrel and aspirin (n = 3797) were compared with clopidogrel alone (n = 3802) after an ischemic stroke or transient ischemic attack. There was a non-significant 0.73% absolute risk reduction in the composite of cardiovascular death, myocardial infarction or ischemic stroke during 18 months of follow-up in patients receiving both aspirin and clopidogrel, compared with those receiving clopidogrel only. However, the absolute risk of life-threatening or major bleedings increased by 2.62% in patients who were given both aspirin and clopidogrel (p < 0.001). Accordingly, the number needed to harm was only around 38.

Obviously, further study is needed to determine the risks and benefits of combining aspirin and clopidogrel for more than a few months in patients with atherothrombotic disease, including those receiving a drug-eluting stent. Remember Voltaire’s bright reflection: “The best may be the enemy of the good”.

References

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Cardiovascular disease, periodontitis, and the monocyte relationship

To the Editor

One investigative approach to linking periodontal disease to atherosclerotic cardiovascular disorders is demonstrating a shared risk factor with the potential for actually mediating cardiovascular disease. In this regard, the Buhlin et al.,1 report comparing cardiovascular risk factors between patients with severe periodontal disease (without known history of cardiovascular disorders) and healthy individuals suggests discovery of an important relationship. Their meticulous and innovative investigation discloses that a unique haematological index, the peripheral blood monocyte count, associates strongly with severe periodontal disease. Yet the investigators dismiss any potential for clinical relevance of this finding on the stated ground that the monocyte levels were within the “normal” range, and consequently they excluded this variable from their reported multivariable models and analyses.

The discovery of novel risk factors in exploratory studies like the Buhlin study requires entertaining scenarios beyond the entrenched paradigms. Moreover, several bases do exist to support an inference that peripheral blood monocyte indices, within today’s reference range, may in fact operate to confer substantial cardiovascular disease risk. The true healthy range for peripheral blood monocyte levels vis-à-vis cardiovascular disease is not known. This conundrum persists because an appropriate reference population cannot be constituted. Present day technology does not enable physicians to validate the absence of underlying atherosclerosis. Therefore the statistical approach used today to define the reference range, for example, as two standard deviations above and below the mean is problematic in that it relies on a group of apparently healthy individuals. However a more meaningful approach, defining abnormal values as those associated with adverse physiological or clinical consequences, is feasible. Several initial developments in this direction are reported. First, the available longitudinal epidemiological studies indicate that minor increments in monocyte counts and proportions (that fall well within their reference ranges) do convey long-range predictive value for clinical cardiovascular disease and mortality.2–4 Second, the available longitudinal clinical imaging studies show that minor incremental differences in monocyte counts or proportions within today’s reference range associate with near-term augmentation in rates of atherosclerotic vascular lesion progressions. The putative atherogenic effect of circulating monocytes manifests at native lesions in non-manipulated arteries as well as at intravenously triggered lesions such as restenosis after angioplasty or endovascular stent placement.5–7

In summary, this cumulative evidence enables the conclusion that it is both valid scientifically and clinically relevant for investigators to pursue evaluating monocyte levels in future risk factor analyses of cardiovascular disease. This logic is germane to the aim of the Buhlin study seeking to identify independent risk factors for periodontal disease that might be shared with cardiovascular diseases. Therefore the inclusion of peripheral blood monocyte indices (absolute count and relative proportion) as variables into their multivariable models is warranted. This more comprehensive modelling might also serve to illuminate interactions between circulating monocytes and the inflammatory mediators and biomarkers discussed (e.g., C-reactive protein, TNF-α receptor 1, IL-6), where such physiological relationships in vivo have yet to be articulated.

References

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