(3) Our patient level analysis of both trial and audit data suggests that diabetes per se is not an independent risk factor for revascularization, but may be merely a convenient aggregate marker for other causal factors. It is important to distinguish between those variables which reflect the long-term risk of incident or progressive arterial disease (of which diabetes is clearly a primary member), and those variables which relate to the short-term risk of restenosis in individual lesions. The former are essentially systemic, whereas the latter are more likely to be localised and related to anatomy. Our forthcoming economic analysis includes results suggesting that the latter may be the more important.

In conclusion, our own research would suggest that small vessels and anatomical complexity are more influential in predicting restenosis than simply diabetes. These findings could be confirmed by analyses of individual patient data from the existing and ongoing trials of DES. This would remove the need for further specific but expensive studies of DES in diabetics, as called for by Scheen and colleagues.

References

benefit awaits the results of the CHARISMA trial.

References


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Long-term clopidogrel following PCI: marginal antithrombotic effects are offset by increased bleeding risks — Reply

Dear Sir,

Dr. Steinhubl and Dr. Topol, authors of CREDO, disagree with my analysis of long-term clopidogrel therapy after percutaneous coronary intervention (PCI) in the PCI–CURE and CREDO trials. However, their arguments seem biased and misleading.

The CREDO trial showed a minor absolute reduction of 1.1% (p = 0.009) in the composite of death, myocardial infarction or stroke from one month to the end of follow-up (mean nine months) in patients receiving clopidogrel in addition to aspirin, compared with aspirin alone. However, the number of ischaemic events was nearly identical in the clopidogrel and placebo groups after the first three months. In fact, among patients given 101–199 mg aspirin per day in CURE, clopidogrel did not contribute to any further reduction in ischaemic events. If 1000 patients in CURE received clopidogrel instead of placebo for nine months, 15 myocardial infarctions would be avoided (12 of which during the first three months) at the price of an extra 10 major and 27 minor bleedings. No life would be saved, no stroke prevented, and the costs of clopidogrel to accomplish this would be around 500 000 EUR. This is clearly an injudicious way to utilize healthcare resources.

In the PCI–CURE substudy of CURE, clopidogrel between 30 days following PCI and the end of follow-up did not result in a significant reduction of cardiovascular death or myocardial infarction. Thus, neither CURE, nor PCI–CURE support clopidogrel long-term.

The CREDO trial showed a small absolute reduction in the composite of death, myocardial infarction or stroke (1.9%, p = 0.04) between day 29 and 1 year following PCI in patients on long-term clopidogrel. However, there was no difference in the composite of death, myocardial infarction, stroke or major bleeding between day 29 and 1 year post-PCI in CREDO: clopidogrel, 88/1053 (8.4%) versus placebo, 95/1063 (8.9%). Besides, PCI–CURE and CREDO demonstrated conflicting results regarding the incidence of myocardial infarction and the need for repeat revascularization from one month to end of follow-up.

Steinhubl and Topol ignore the other side of the picture. In CREDO there was a 2.1% (p = 0.07) absolute increase in severe bleedings, in CURE 1.0% (p = 0.001), and in MATCH 2.6% (p < 0.001) in patients given both clopidogrel and aspirin. In particular, the MATCH trial highlights the hazards of prescribing clopidogrel with aspirin for longer periods of time. The combination actually carries a risk that is larger than the potential benefit, at least in subsets of patients with atherothrombotic disease. The increased risk of severe bleedings also overthrows Steinhubl’s and Topol’s comparison of long-term clopidogrel with some other long-term preventative therapies with a far less risk of severe adverse events.

In summary, clopidogrel long-term (in addition to aspirin) following PCI does not reduce mortality and has a marginal influence on ischaemic events. An increase in severe bleedings may further offset any possible benefit. Consequently, there is no evidence at present to support the routine continuation of clopidogrel for more than a few months after PCI. Let us await the results of the CHARISMA trial with open minds.

Table 1 Reduction in death, myocardial infarction and stroke with long-term preventative therapies

<table>
<thead>
<tr>
<th></th>
<th>Relative risk reduction (%)</th>
<th>Absolute risk reduction (%)</th>
<th>Mean duration of treatment (years)</th>
<th>Number of events prevented in 1000 patients per year of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (previous MI patients)</td>
<td>25</td>
<td>3.5</td>
<td>2.25</td>
<td>15.5</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>22</td>
<td>3.8</td>
<td>5</td>
<td>7.6</td>
</tr>
<tr>
<td>Statins</td>
<td>31</td>
<td>2.2</td>
<td>3.9</td>
<td>4.4</td>
</tr>
</tbody>
</table>

*Data in the Lescol Intervention Prevention Study (LIPS) is for cardiac death and myocardial infarction only.