Clopidoogrel and mortality

Several readers challenged our presentation and interpretation of the CHARISMA and CLARITY-TIMI trials. Prescrire justifies its assessment.

Once again your presentation of clinical trial results in issue 273 of la revue Prescrire (translated in Prescrire International n°85 page 194) adopts a negative (“the glass is half-empty”) point of view. With respect to the Clarity TIMI 28 study, you stated that there was no significant effect on mortality at one month, on the basis of an endpoint combining recurrent myocardial infarction, stroke and cardiovascular death. You could just as well have pointed out (“the glass is half-full”) that, at one month, study data also show a 20% reduction in an endpoint combining cardiovascular death, myocardial infarction, recurrent ischaemia necessitating revascularisation (p=0.026; confidence interval (CI) 0.65–0.97), or alternatively that at one month there was a statistically significant reduction in an endpoint combining cardiovascular death, myocardial infarction, stroke and recurrent ischaemia necessitating revascularisation (1).

Similarly, you provide details on a subgroup of high-risk patients with no documented cardiovascular events in the Charisma study, and correctly conclude that, in this population, the clopidogrel-aspirin combination is no better than aspirin alone. But then you fail to provide corresponding data for the subgroup of patients who had already had cardiovascular events and who benefited from the two-drug combination compared with aspirin alone, even though the difference was only statistically significant (p=0.046; CI 0.77–0.998) (2).

If you want to maintain the integrity and quality of your journal, as well as the accuracy of the articles you publish, you should provide your readers, especially non-specialists, with all the available data from a study and not just selected results. (Drug companies tend to do the same thing, but in reverse), it is just as serious (or perhaps even more serious for strict methodologists). The Charisma study compared aspirin + clopidogrel with aspirin + placebo in patients at high risk of atherothrombotic disease (2,3). The primary outcome measure was a composite score combining myocardial infarction, stroke, and death due to cardiovascular causes. These events occurred in 6.8% of patients receiving aspirin + clopidogrel and in 7.3% of patients receiving aspirin + placebo, the confidence interval ranged from 0.83 to 1.05 and the difference was not statistically significant. This means there is no point adding clopidogrel to aspirin in this setting. This much at least is perfectly clear.

Three-quarters of at-risk patients had already had a symptomatic vascular disorder (coronary heart disease, stroke, lower-limb artery disease), and one-quarter of patients had multiple and/or cardiovascular risk factors. When the editors of the Charisma article (or the sponsors) state that there was a significant difference in favour of clopidogrel in patients with symptomatic atherosomatic arterial disease, they base their claim on a subgroup analysis that has no clinical relevance. Moreover, the patients were not stratified for this inclusion criterion before randomisation, and this retrospective comparison cannot provide reliable evidence. At best, it might warrant a new clinical trial only focusing on this type of patient.

When Prescrire makes exactly the same mistake (but in reverse), it is just as serious (or perhaps even more serious for strict methodologists). The title of your article “Patients at high cardiovascular risk: excess mortality of about 1.6% on aspirin + clopidogrel” (la revue Prescrire issue 273, Prescrire International n°85), was the study population receiving primary or secondary prevention? Your article is not very clear on this point, nor is the summary of the original publication (2,3). If the patients were receiving dual-agent antiplatelet therapy as primary prevention, the negative results are hardly surprising.

I am just a “simple” vascular physician with no shares in Sanofi Aventis. I have the following question: in the first half of the article entitled “Patients at high cardiovascular risk: excess mortality of about 1.6% on aspirin + clopidogrel” (la revue Prescrire issue 273, Prescrire International n°85), was the study population receiving primary or secondary prevention? Your article is not very clear on this point, nor is the summary of the original publication (2,3). If the patients were receiving dual-agent antiplatelet therapy as primary prevention, the negative results are hardly surprising.

I hope these suggestions will contribute to tempering the systematically negative tone you adopt when examining new studies.

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subgroup” in which even a difference with a p value of 0.04 has no clinical significance and no statistical reality, given the authors’ use of multiple comparisons.

To speak of excess mortality in a particular subgroup is just as illogical as to speak of reduced mortality in another subgroup. The trial results are negative, and that’s all: there’s no point risking specious analyses of any sort. When will you publish a critique of one of your own articles?

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The Clarity-Timi 28 and COMMIT trials focused on secondary prevention: the patients had a history of myocardial infarction at enrolment in these trials (1). The Charisma trial combines two different situations. The patients either had a history of cardiovascular disease (coronary or non coronary) and received secondary prevention, or they had risk factors (arterial hypertension, smoking, etc.) and received primary prevention (2,3).

Overall mortality: not just another factor in combined endpoints.

For several years now, designers of protocols for “large trials” have tended to use a combination of criteria as the “primary outcome measure”.

These combinations often include the number of deaths, the number of cardiovascular events, the number of hospitalisations, and sometimes the number of particular interventions (revascularisation for example). These combined outcome measures generally have a certain pathophysiological coherence and tend to increase the statistical power of comparative trials. On the downside, they lend the same statistical weight to very different clinical events such as death and hospitalisation.

Beyond the numbers and mathematical abstractions dear to some clinical trial designers, the death of a patient does not have the same significance or the same consequences as a hospitalisation. The Prescrire editorial staff therefore analyses the results of clinical trials by first examining the possible impact of the treatment on overall mortality.

We do not adopt “the glass is half-empty” viewpoint: we mentioned the “positive” short-term effect of clopidogrel on mortality in the acute phase of myocardial infarction (1), but we focus first and foremost on questions that arise in daily practice, rather than on arbitrarily defined “treatment responses”.

Overall mortality: first rule out a harmful effect.

The overall mortality rate is also the best criterion for confirming whether or not a given treatment has a harmful overall effect despite a possible benefit on a specific criterion. Examples of totally unforeseen excess mortality abound: take, for instance, the CAST trial of antiarrhythmic drugs and the WHO trial of clofibrate (4.5).

In the Charisma trial, according to the Endpoints and Subgroup Analysis sections of the published article, the comparison of mortality rates in the overall population of patients at high cardiovascular risk was planned from the outset (3). This comparison gave a p value of 0.04.

True, in comparative trials designed to show the superiority of one treatment over another, a p value of 0.01 is usually required to show the statistical significance of a difference in a secondary endpoint (6).

But here we are dealing with a serious adverse event, and the potential for harm must be taken very seriously. After all, patients’ well-being is more important than details of statistical methodology. With respect to the possible increase in overall mortality in primary prevention, a p value of 0.04 is sufficient to support a recommendation against using the treatment in question, without waiting for the results of other trials.

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1- Prescrire Editorial Staff “Acute myocardial infarction: aspirin + clopidogrel reduce mortality by about 0.5% ” Prescrire Int 2006; 15 (85): 194.
2- Prescrire Editorial Staff “Patients at high cardiovascular risk: excess mortality of about 1.6% on aspirin + clopidogrel ” Prescrire Int 2006; 15 (85): 194.
5- Prescrire Editorial Staff “Cholesterol-lowering drugs” Prescrire Int 1999; 8 (42): 116-120.