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Mortality risk with dual antiplatelet therapy?

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The Dual Antiplatelet Therapy (DAPT) Study identified significant reduction in ischemic cardiovascular events with prolonged thienopyridine use on a background of aspirin therapy. An unexpectedly higher mortality rate was seen among randomized drug-eluting stent (DES)-treated subjects treated with continued thienopyridine compared with placebo (2.0% vs. 1.5%, $p=0.05$).¹ Given the critical role that these medications play in the treatment of cardiovascular disease, these findings have prompted appropriate attention. Palmerini and colleagues now report increased risk of mortality with continued therapy based on meta-analysis of 10 randomized trials, largely driven by results from the DAPT Study.²

Concurrently with the publication of the DAPT Study, we published a meta-analysis of 14 randomized trials of dual antiplatelet therapy duration in patients with cardiac, vascular or cerebrovascular disease ($N=69,644$ patients).³ We found no significant association whether or not data from the DAPT Study were included, or after restricting the analysis to 42,616 subjects with coronary artery disease. The results are unchanged after updating this analysis with two additional randomized trials completed since the publication of our study. (Figure)

In examining the relationship of dual antiplatelet therapy and mortality among only trials of DES-treated patients, Palmerini *et al.* essentially present a subgroup of our meta-analysis, resulting in the DAPT Study contributing nearly 1/3 of the subjects. This selective strategy excluded 6 high quality blinded, randomized trials of nearly 30,000 subjects with at least 2 years average follow-up, the majority of whom had coronary artery disease – the putative disease of interest in the Palmerini study.

If a true association exists between thienopyridine therapy and mortality, the most plausible mechanism would be via bleeding, a risk present regardless of the patient population. Within the DAPT Study, fatal bleeding was rare (0.15% for continued thienopyridine vs 0.09% for placebo, $p=0.38$) and a blinded independent adjudication committee found that difference in death between arms was not principally accounted for by deaths related to bleeding.¹ Given that the death differences in the DAPT Study were not driven by a plausible biological mechanism and were inconsistent with comprehensive meta-analysis, the subgroup analysis offered by Palmerini et al. should not prompt inappropriate discontinuation of a therapy with proven benefits in patients with cardiovascular disease.

References

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Updated comprehensive meta-analysis of trials evaluating extended duration dual antiplatelet therapy in cardiovascular and cerebrovascular disease, showing no significant association between extended therapy and all-cause mortality. The meta-analysis by Palmerini et al. excludes 6 randomized clinical trials (*), resulting in the DAPT Study representing one-third of included patients, and accounting for more than 40% of the difference in death events between the compared groups.