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Has IMPROVE-IT improved cardiovascular outcome?

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SUMMARY

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a large double-blind, randomised controlled trial to investigate whether ezetimibe, an inhibitor of cholesterol absorption in the intestine, could further reduce cardiovascular events in addition to statins after acute coronary syndrome (ACS).[1] A total of 18,144 hospitalised patients within 10 days of ACS were randomised to receive simvastatin 40mg plus ezetimibe 10mg or simvastatin 40mg plus placebo. Inclusion criteria included an LDL-cholesterol concentration of 1.3–2.6 mmol/L in those already receiving lipid-lowering therapy or 1.3–3.2 mmol/L in those without lipid-lowering therapy at baseline. Patient characteristics were matched at baseline. Thirty-four percent of patients were on statins at the time of the index event. Mean LDL-cholesterol concentrations pre-trial were 2.4 mmol/L in both groups. The primary end-point was a composite of cardiovascular death, non-fatal myocardial infarction, unstable angina requiring rehospitalisation, coronary revascularisation, or non-fatal stroke. Median follow-up was 6 years.

Over the course of the entire trial, the median time-weighted average LDL-cholesterol concentration was 1.4 mmol/L in the simvastatin-ezetimibe group, compared to 1.8 mmol/L in the simvastatin monotherapy group (p <0.001). The absolute risk reduction (ARR) with simvastatin-ezetimibe for the primary end-point was 2% (Kaplan-Meier event rate 32.7% in the simvastatin-ezetimibe group vs 34.7% in the simvastatin monotherapy group, hazard ratio 0.936; 95% CI 0.89–0.99; p = 0.016). This translated into a number needed to treat of 50 over a 7-year period to prevent one primary end-point. Subgroup analysis suggested greater benefit in individuals with diabetes mellitus and those ≥ 75 years old. The absolute risk of any myocardial infarction was 1.7% lower in the simvastatin-ezetimibe group than with simvastatin alone (HR 0.87, p = 0.002) and the absolute risk of ischaemic stroke was 0.7% lower with combination therapy (HR 0.79, p = 0.008). No significant between-group differences were found in muscle, gallbladder, and hepatic adverse effects or cancer.

The authors concluded that ezetimibe in addition to simvastatin improved cardiovascular outcomes after ACS through lowering LDL-cholesterol. Prior to IMPROVE-IT, national guidelines have emphasised statin therapy as the preferred treatment for established cardiovascular disease.[2,3] This is based on the 'statin hypothesis' that statins have additional cardioprotective properties that cannot be fully explained by lowering LDL-cholesterol alone, e.g. antioxidant properties and improved endothelial function.[4] However, in IMPROVE-IT there was a 7.2% lower rate of major vascular events with a between-group difference in LDL-cholesterol of 0.33 mmol/L. This reduction in event-rate with addition of ezetimibe was the same as that predicted for a similar LDL-cholesterol reduction with statin therapy by the Cholesterol Treatment Trialists (CTT).[5] This suggests that LDL-cholesterol lowering per se is central to protecting against coronary heart disease, and provides for the first time clinical trial evidence that lowering LDL-cholesterol with a *non-statin* lipid-lowering agent can reduce cardiovascular disease risk.

OPINION

IMPROVE-IT has been hailed by many as a success, providing long-awaited evidence that a *non-statin* lipid lowering agent can translate into improved cardiovascular outcomes. This is in contrast to earlier studies such as ENHANCE which showed, in those with familial

hypercholesterolemia, combined therapy with ezetimibe and simvastatin did not result in a significant difference in carotid intima–media thickness compared with simvastatin alone, despite decreases in LDL cholesterol and C-reactive protein.[6]

However, distilling the numbers reveals some interesting reading. Combination therapy resulted in an overall ARR of 2% and relative risk reduction (RRR) of 6.4% in the primary *composite* end-point of cardiovascular death, non-fatal myocardial infarction, unstable angina requiring rehospitalisation, coronary revascularisation, or non-fatal stroke. However, there was no difference in cardiovascular mortality specifically (HR 1.00, p = 1.00). Subgroup analyses revealed only those aged 75 years or over, or with diabetes mellitus, appear to benefit (HR 0.797 [95% CI: 0.704–0.902] for those ≥75 years old; HR 0.856 [95% CI: 0.779–0.939] for those with diabetes mellitus), raising concerns about any benefit in the majority of patients without diabetes mellitus under 75 years of age.

These findings are only relevant to a secondary prevention cohort. Of note, 35% of patients were already treated with lipid-lowering agents and 42% with aspirin. Mean LDL-cholesterol was 2.43 mmol/L at baseline. Some argue ezetimibe was being tested in an already well-treated population.[7] It is perhaps not surprising the ARR was only 2% as patients had a lower baseline LDL-cholesterol and so the same RRR will produce less absolute cardiovascular disease risk reduction. If entry criteria included individuals with higher LDL-cholesterol at baseline, the ARR and RRR may have been more pronounced.

The authors state the results endorse that 'lower is better' and that reducing LDL-cholesterol further below 1.8 mmol/L can provide additional clinical benefit. Further, the event rate reduction with ezetimibe was similar to that predicted by the CTT for statins, supporting the view that it is primarily LDL-cholesterol lowering causing improved outcome with statins rather than other 'pleiotropic effects'.[8]

So how does this relate to current guidelines and clinical practice? IMPROVE-IT focused on a secondary prevention cohort, already well-treated with low initial LDL-cholesterol and receiving a low potency statin. However, those at greatest risk are those with intractably high LDL-cholesterol. The use of a low potency statin is in contrast to the UK population where national guidelines recommend the use of 80mg atorvastatin following ACS.[3] A more relevant study would be to include a third arm comparing with high potency statin therapy.

There are still several questions left unanswered. We have no information on the use of combination therapy in primary prevention. With the modest benefits seen in a secondary prevention cohort, will any such benefit be significant enough to translate into primary prevention? In a population at greater risk, e.g. with high LDL-cholesterol or familial hypercholesterolaemia, will we see greater benefit? Regarding the management of statin-intolerant individuals with high cardiovascular risk, does ezetimibe monotherapy offer similar cardiovascular benefits?

Should we incorporate ezetimibe more in national guidelines and if so, for whom? Currently, ezetimibe is advised as a possible treatment for adults with primary (heterozygous-familial and non-familial) hypercholesterolaemia either as monotherapy in those intolerant of statins or in combination with a tolerable statin dose.[3] SIGN guidelines, currently being updated, recommend combination therapy of standard dose statin and ezetimibe in those intolerant of higher-dose statin therapy.[2] IMPROVE-IT provides for the first time, albeit modest, clinical outcome data to support this. Combination therapy will be of greatest benefit to those at greatest risk, i.e. in secondary prevention individuals with high LDL-cholesterol or familial hypercholesterolaemia intolerant to high-dose statins.

Of note, 42% of patients discontinued the study medication in both groups over the trial period, equating to 7% per year.[1] The authors state this is similar to previous studies. There was no statistically significant difference between the two groups in any of the pre-specified safety endpoints or rate of discontinuation of study medication due to side effects. However, the high overall discontinuation rate emphasises the more pressing point of poor long-term adherence with medication. Perhaps rather than focusing on driving down LDL-cholesterol even lower with an expensive drug for modest further benefit, we should focus on ensuring patients are taking existing therapy.

So, does combination therapy with simvastatin-ezetimibe lead to improved cardiovascular outcomes in secondary prevention? The overall 6.4% RRR is modest and questions are raised over the significance of this finding in those < 75 years old and without diabetes mellitus. Specifically, there was no difference in chronic heart disease mortality between groups. The 42% discontinuation rate of study medication provides the take home message that, instead of striving to lower LDL-cholesterol even further with additional medication, we should focus on ensuring adherence to existing therapies. However, in those at significant risk and intolerant of high dose statin therapy, IMPROVE-IT provides evidence, albeit modest, that lowering LDL-cholesterol through the alternative combination of modest dose simvastatin with ezetimibe may be beneficial.

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