Understanding IMPROVE-IT and the cardinal role of LDL-C lowering in CVD prevention

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Design and scientific rational

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT; ClinicalTrials.gov Identifier NCT00202878) randomized 18 000 patients who had an acute coronary syndrome event (STEMI, NSTEMI, unstable angina) within the previous 10 days to simvastatin 40/80 mg or to simvastatin 40 mg plus ezetimibe 10 mg (*Figure 1*). When the study was first designed (pre-2005),[1] a sample size of 10 000 patients was selected based on an anticipated event rate at 2 years of 23.5% in the control arm. This would have given statistical power to detect a 10% relative risk reduction. However, with the release of the CTT analyses in 2005[2] and 2010,[3] these assumptions were revised during the course of the study and a larger sample size of ∼18 000 patients was mandated in the third amendment. Trial termination is now event-driven and patients will be followed until at least 5250 subjects experience a primary end-point which consists of the first occurrence of cardiovascular death, nonfatal myocardial infarction, re-hospitalization for unstable angina, coronary revascularization, or stroke. The trial will provide definitive answers regarding the safety of the drug.[4]

IMPROVE-IT tests two hypotheses at the same time. One is that lower LDL-C is better even at very low LDL-C. The second is that adding another LDL-lowering drug to a statin reduces outcomes. Several aspects of the design are worth noting in light of recent similar trials. First, the comparison is statin plus placebo vs. statin plus ezetimibe, so the study will not provide information on the effects of ezetimibe monotherapy or on differences between statin-mediated compared with ezetimibe-mediated LDL lowering. Secondly, LDL-C was not titrated or matched in the two treatment arms (unlike AIM-HIGH) to similar levels in the statin vs. the statin + ezetimibe group. The LDL-C of the trial patients at baseline was 97 mg/dL.[1] If consecutive measures of in-trial LDL-C exceeded 79 mg/dL in the statin plus placebo group, the simvastatin daily dose was increased from 40 to 80 mg. It can be surmised, therefore, that LDL-C in the control group is likely to be <70 mg/dL and ezetimibe is being tested for its ability to generate an incremental clinical benefit in a well-treated population on statins with an already very low LDL-C. In interpreting this benefit, it is important to remember that the absolute risk reduction for the same relative LDL-C lowering diminishes for the same relative LDL-C lowering with lower baseline LDL-C (*Figure 2*). The 'IMPROVE-IT therapeutic scenario' is thus far removed from day-to-day clinical practice where ezetimibe is prescribed to patients with high LDL-C that cannot be controlled with statin monotherapy.

By 2010, the required number of subjects was randomized,[5,6] and the Data and Safety Monitoring Board (DSMB) announced in March 2013 that 88% of the 5250 events had occurred. It is predicted, therefore, the trial will complete in 2014. IMPROVE-IT when reported will be the largest and longest contemporary trial focusing specifically on LDL lowering. Controversy has surrounded the study for some time (e.g. see Califf *et al.*[4]) and results are anticipated eagerly not only to address the issue that many healthcare systems are spending a significant budget on ezetimibe despite the uncertainty regarding its impact on clinical outcomes, but also to answer questions posed concerning the efficacy of non-statin lipid-lowering drugs in the new US guidelines.[7]

What results can be expected?

The design paper postulated a 15 mg/dL difference in LDL-C between the two treatment arms and a reduction in cardiovascular events of 1% for every 1.6 mg/dL reduction in LDL-C,[1,8] giving an overall 9.375% hazard reduction[1,5] in an intention-to-treat analysis (*Figure 3*, scenario 1).

It is possible to refine the predicted outcome based on further consideration of the drug's effects and attendant risk reduction. The extent of LDL lowering by ezetimibe is usually taken as a relatively constant percentage (15–20%) of the starting level.[9] Thus, a better estimate of the LDL difference between the treatment arms in IMPROVE-IT is 12 mg/dL based on an 18% reduction on ezetimibe relative to the baseline LDL-C of 68 mg/dL in the control (statin

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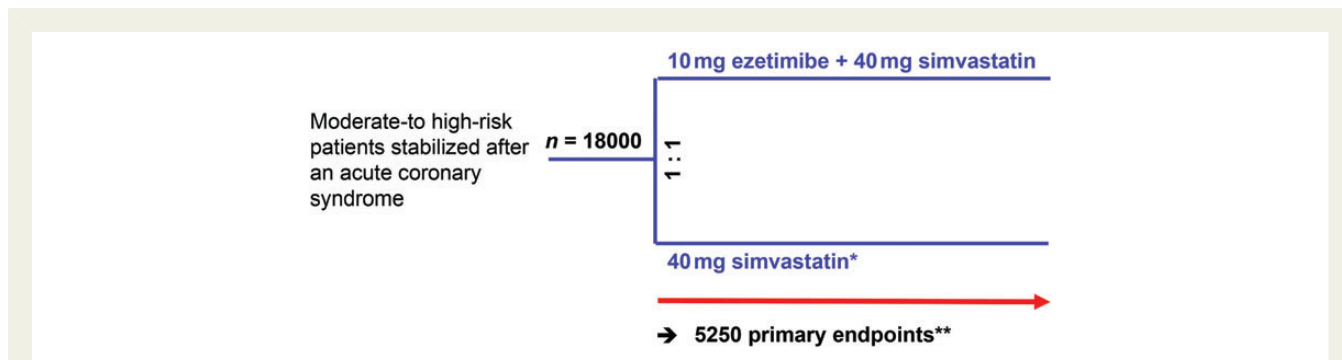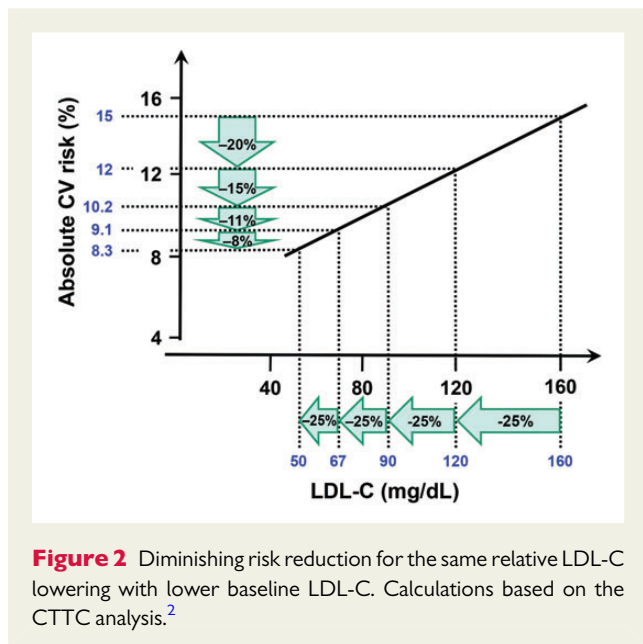
Figure 1 Design of the IMProved Reduction of Outcomes: VYTORIN Efficacy International Trail (IMPROVE-IT). *if consecutive in-trial measures of LDL-C are >79 mg/dL, simvastatin dose will be increased to 80 mg. **primary end-point is the first occurrence of cardiovascular death, non-fatal myocardial infarction, rehospitalization for unstable angina, coronary revascularization (occurring at least 30 days after randomization), or stroke.

Figure 2 Diminishing risk reduction for the same relative LDL-C lowering with lower baseline LDL-C. Calculations based on the CTTC analysis.[2]

plus placebo) group. Furthermore, the Cholesterol Treatment Trialists Collaboration (CTTC) investigators report a slightly more conservative 22% relative risk reduction (RRR) per 1.0 mmol/L drop in LDL-C (i.e. a 1% RRR for every 1.8 mg/dL LDL lowering).[3] These refined estimates result in a predicted RRR of 6.98% (*Figure 3*, scenario 2).

Observed LDL differences when ezetimibe is given on top of high dose statin may be less than the 'headline' amount noted above. In a recent meta-analysis Guyton and co-workers[10] reported an 11.1% decrement in LDL-C when ezetimibe was added to statin. In the context of IMPROVE-IT, this decreases the anticipated RRR to 4.3% (*Figure 3*, scenario 3). Taking into account dropouts and crossover, the predicted LDL-C difference may fall to 8% (5.4 mg/dL) and the RRR would shrink to 3.1% (*Figure 3*, scenario 4).

The last two scenarios are likely to reduce substantially the power of the study to report a statistically significant result for efficacy. However, even the first two, more optimistic, settings depend on at least three additional factors being in play: (i) that further LDL-C lowering in statin-treated patients with already very low LDL-C gives additional benefit and (ii) the number of patients that dropout or are lost to follow-up does not compromise the final outcome unduly (iii) that the extent of event reduction per unit LDL decrease is the same for ezetimibe compared with statins.

Effects in a statin-treated population

There has been, and still is, debate on whether statins exert beneficial effects on vascular function and inflammation in addition to LDL lowering, i.e. cholesterol independent 'pleiotropic' actions and these may not be replicated with ezetimibe therapy.[11,12] Since the two treatment arms of IMPROVE-IT will have different achieved LDL-C levels the question of whether the two drug classes exert a further, differential impact on vascular disease per mg/dL LDL lowering will not be answered. The vascular/clinical effect could be less, equal or theoretically enhanced. Retrospective analyses of ENHANCE and SHARP suggest that the clinical benefits of ezetimibe therapy fall on the statin-LDL regression line, and therefore most likely are equal to statin-mediated LDL lowering.[13,14]

The clinical impact of further LDL reduction in a population with a starting LDL-C <70 mg/dL is unknown. The epidemiological association of cholesterol with risk is not linear but flattens in the lower range,[15,16] and the absolute risk reduction with statins depends not only on mg/dL reduction but importantly on the initial LDL-C concentrations (*Figure 2*) with sharply diminishing returns in the lower regions (for review, see Shepherd[17]). In addition, the relative importance of LDL-C for CV risk appears to be significantly lower in statin-treated compared with statin-naive patients, especially when LDL-C concentrations are <100 mg/dL.[18–20] The LDL-attributable risk diminishes in patients on statin treatment and with very low LDL-C concentrations. Thus the use the CTT regression line based on the effects in statin-naive patients to calculate the power of adjunct lipid-lowering drugs on-top of statins may be potentially misleading.[21]

Scenario 1 — Cannon et al. (5250 primary endpoints; expectation of 1.6-mg/dL LDL-C change translating into a 1% clinical benefit, expected 15 mg/dL difference in LDL-C)
Statin control: 7.25 events per 100 patients per year
Statin + ezetimibe: 6.57 events per 100 patients per year
RRR: 9.375%; ARR 0.68%

Scenario 2 — Risk reduction according to CTT-Analysis (22%RRR per 1 mM/L), ezetimibe effect on LDL-C 18%, LDL-C in statin control group 68 mg/dl
Statin control: 7.25 events per 100 patients per year
Statin + ezetimibe: 6.74 events per 100 patients per year
RRR 6.98 %; ARR 0.51%

Scenario 3 — Risk reduction according to CTT-Analysis (22%RRR per 1 mM/L), ezetimibe effect on LDL-C 11.1% (according to meta-analysis by Guyton et al.)
Statin control: 7.25 events per 100 patients per year
Statin + ezetimibe: 6.94 events per 100 patients per year
RRR 4.30 %; ARR 0.31%

Scenario 4 — Rrisk reduction according to CTT-Analysis, ezetimibe effect on LDL-C 8% (due to drop-out and cross-over)
Statin control: 7.25 events per 100 patients per year
Statin + ezetimibe: 7.02 events per 100 patients per year
RRR 3.10 %; ARR 0.23%

Figure 3 Hypothetical scenarios for the outcome of IMPROVE-IT. CTTC, Cholesterol Treatment Trialists Collaboration.

Scenario	Event rate in placebo group	Event rate in active treatment group	RRR	*P*-value
No dropout, No loss to follow-up	20%	15%	25%	$P=0.004$
Scenario 1: 20% dropout, but no loss to follow-up	20% Observed event rate 20% among adherent subjects, 20% among non-adherent subjects	16% Observed event rate 15% among adherent subjects, 20% among non-adherent subjects	20%	$P=0.02$
Scenario 2: 2% loss to follow-up, worst case analysis	19.6% Observed event rate 20% in 98% of subjects, assumed event rate 0% in 2% of subjects	16.7% Observed event rate 15% in 98% of subjects, assumed event rate 100% in 2% of subjects	14.8%	$P=0.10$

Figure 4 Importance of 'DropOut' and 'Loss to Follow-Up'. Quantitative example in a trial randomizing 2000 patients to placebo vs. an active treatment with a relative risk reduction of 25%.

Dropout and loss to follow-up

'Dropout' and 'loss to follow-up' patients impact significantly on a trial designed to be evaluated on the basis of an 'intention-to-treat' approach; a statistical analysis that considers a worst-case scenario is depicted in *Figure 4*. Extensive measures are taken by those who conduct trials to minimize the number of patients who stop taking trial drug or whose endpoint status cannot be determined. There have been notable successes in recent very large trials testing the new oral anticoagulants where loss to follow-up was typically well <1%.[22,23] IMPROVE-IT faces two substantial problems that made it difficult for the study centres to keep referring physicians and patients motivated. The first and most important cause of dropout is the very long duration of the study. The second relates to the external and negative pressure due to the critical discussion and media attention focused on ezetimibe in the context of ENHANCE and SEAS that have questioned the efficacy and safety.[13,24] Furthermore, more efficacious statins (atorvastatin and rosuvastatin) have

become more widely available during the course of the trial which may further dilute the LDL-lowering effect. Taken together, it seems likely that the rates of incomplete follow-up will be a significant issue that impacts any treatment-attributable difference in primary and secondary endpoints between the two arms, making the data very difficult to interpret. Therefore an on-treatment analysis may provide more appropriate clinical information than the traditional intention-to-treat analysis.

In addition, the long duration of the trial will lead to large numbers of different vascular events that occur after the first event. To evaluate whether additional LDL lowering by ezetimibe reduces the 'atherosclerosis burden' and its subsequent clinical complications, it is of relevance to analyse the repeated occurrence of events. Such an analysis performed for the IDEAL trial revealed that intensive statin therapy continued to be more effective compared with the standard statin therapy beyond the first event.[25]

Lifetime benefit and disease trajectory

Formalism in the statistical analysis of clinical outcome trials counts the first occurrence of a pre-specified endpoint event, e.g. a myocardial infarction or stroke but not subsequent clinical incidents. This provides a rigorous assessment of the treatment effect in terms of a relative or absolute risk reduction but does not capture the full clinical impact of the therapy. Cost-effectiveness assessments also are hampered by the lack of long-term follow-up data that stretch beyond the end of the trial. Given that vascular disease has a decades long pathogenesis and the fact that the first clinical manifestation of the underlying atherosclerotic process is but part of a disease trajectory, it makes sense to understand also the lifetime benefit of an intervention such as LDL-lowering therapy. Some of the key statin trials have published the results of prolonged follow-up that take into account events that occurred in-trial and those that happened during a period of extending surveillance either by reviewing patient records or through electronic record linkage.[26] Fifteen years of electronic health record linkage in the case of WOSCOPS revealed that benefit from trial therapy in terms of risk reductions for heart failure (43%) and stroke (18%) occurred beyond the end of the 5-year-study period. Further, cost-effectiveness was much greater than first appreciated when a longer view was taken.[27] By extrapolation, therefore, a full picture of the impact of ezetimibe in IMPROVE-IT, assuming that there is a small treatment effect on the primary endpoint, may only emerge when the entire disease trajectory is established for those in the two treatment arms.

Conclusions that are NOT supported by IMPROVE-IT

We have explained above why the problems of the design and the duration of the study make it unlikely that IMPROVE-IT will show a substantial absolute risk reduction in the ezetimibe arm. 'Drug failure' has to be differentiated from 'design failure'. It, therefore, seems to be important to address ahead of time three areas of potential misconception:

(1) A negative or equivocal result caused by the specific problems in the study does not demote LDL-C as a causative risk factor, or LDL lowering as the primary treatment strategy.

(2) It will be important to analyse—ideally prior to publication of the study—whether the results are consistent with the LDL-C/event regression line observed in statin meta-analyses such as CTTC. If the results are consistent with the effect expected from LDL-C lowering, one can extrapolate with comfort from a quantitatively small absolute risk reduction by ezetimibe in patients with very low baseline LDL-C to a substantially larger event reduction in individuals with high baseline LDL-C. Clinicians, currently, use ezetimibe for patients that do not achieve sufficient LDL lowering on statins, e.g. because of high baseline levels, statin intolerance or myalgia. Clinicians do NOT use ezetimibe for patients that reach an LDL-C <70 mg/dL on statins alone. It should be borne in mind that the design of the IMPROVE-IT was driven mainly by scientific questions of the study group and by the sponsor rather than clinical relevance. A study design testing ezetimibe vs. placebo in moderate risk patients vs. placebo similar to JUPITOR but with higher entry LDL-C, or with ezetimibe added to any statin in stable CVD patients statin with LDL-C >100 mg/dL would be more appropriate to address the clinical effectiveness of ezetimibe. The significant problems of the IMPROVE-IT design should not lead to a situation where well-tolerated medications are potentially withdrawn and made unavailable for patients with progressive atherosclerotic diseases and uncontrolled LDL-C.

(3) Impact on the development of future drugs: a neutral IMPROVE-IT clearly should not discourage ongoing studies, e.g. using PCSK9-inhibitors nor lead to stopping the search for novel LDL-C lowering targets.[28] Residual risk on statin treatment is high and atherosclerotic diseases remain the major killer worldwide. However, a simple lesson for clinical trials may come out of IMPROVE-IT: LDL-C lowering should be tested in patients with high LDL-C but not in patients with low LDL-C.

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