

IMPROVE-IT

To add, or not to add ezetimibe **EZETROL** to moderate dose statin?

What we already knew?

- Statins... have consistently demonstrated efficacy in lowering not only LDL, but risk of cardiovascular (CV) events +/- mortality in those with high CV risk. ¹
- Ezetimibe...²
 - has **no evidence as monotherapy** for lowering CV/mortality risk
 - has had very limited, disappointing surrogate outcome evidence, e.g. no ↓ in intima - media thickness ^{ENHANCE}
 - failed to lower CV/mortality risk in combination with a statin when compared to a placebo in mild - to - moderate, asymptomatic aortic stenosis patients ^{SEAS}
 - when combined with a proven statin therapy (e.g. simvastatin 20mg daily) in chronic kidney disease & dialysis patients (stage 3 - 4 CKD patients), was associated with a benefit. However, given the placebo-controlled trial design, the benefit could have been due to the statin alone. ^{SHARP}

What IMPROVE-IT may add?

- Ezetimibe may modestly lower CV event risk when added to a moderate dose statin (simvastatin 40mg).

IMPROVE-IT ^{3,4} n=18,144; stable-recent ACS, normal LDL median 2.46 → 1.4 vs 1.8mmol/L	Ezetimibe _{10mg} + Simvastatin _{40mg}	Simvastatin 40mg	NNT	P	Comment
Composite of CV death, MI, unstable angina requiring hospitalization, revascularization or stroke (1° Endpoint)	32.7%	34.7%	50/7yrs [350/yr]	0.016	♦ relative risk ↓ = 6.4% ♦ most benefit in ↓ MI
Death, all-cause	15.4%	15.3%	N/A	0.78	♦ lack of benefit of concern to some given trial size/duration

So, where does ezetimibe now fit in CV risk reduction therapy options?

IN FAVOUR of a more prominent role for ezetimibe	AGAINST a more prominent role for ezetimibe
<ul style="list-style-type: none"> ♦ its addition to moderate dose statin therapy lowers CV event risk in very high risk patients ♦ avoiding high dose statins may provide a tolerability advantage in those prone to statin intolerance ♦ seems to support the "lower is better" approach to LDL in CV risk reduction. (However, does <u>not</u> compare to high-dose statin, give insight on how low may be too low, nor how to address patients with high LDL who were excluded from trial.) 	<ul style="list-style-type: none"> ♦ benefit was modest (NNT 50 patients over 7 years to prevent 1 CV – broad composite - event) ♦ higher dose statins, have previously been proven to lower risk in very high risk patients, and in a shorter time frame (gold standard comparison) ♦ after several disappointing trials, they finally studied enough high risk patients for a long enough time, & looked at a very broad composite outcome. ♦ questionable value from cost-benefit point of view ♦ protocol continuously modified & questionable statistics

Questions Still Remaining

- Whether a similar "benefit" would be seen with adding ezetimibe to any other statin?
- How would addition of ezetimibe compare to higher-dose statin (atorvastatin 80mg or rosuvastatin 20-40mg)?
{For comparison, **PROVE-IT**: similar ≤10days after ACS patient group; atorvastatin 80mg vs pravastatin 40mg: ↓ death/ MI/angina/ stroke by 3.9% /2yrs, NNT=26/2yrs [~52/year]; ↓ all-cause death part of the driver (this is a stronger benefit in a much shorter time period compared to **IMPROVE-IT**)
TNT: atorvastatin 80mg vs 10mg in patients with CHD & revascularization hx; ↓ 1st CHD event by 2.2%/5yrs, NNT=46 [~230/year]}[†]

Contextualization & Individualization of Therapy

- What other CV risk reduction measures are being implemented? (Don't forget **lifestyle** factors!)
- Is patient young enough, & **high-enough risk** to warrant a combination regimen or high-dose statin?
- Is **statin intolerance** a barrier to higher-dose statin therapy in this patient? If not, a "risk-matched" statin regimen may offer more benefit sooner and avoids need for an additional drug.²
- What are the relative **patient preferences** in terms of a) wanting more medications, b) perceived value for the additional medication options? c) consideration for non-drug risk reduction options?, d) cost factor (atorvastatin 80mg/day = **\$300/yr**; and simvastatin 40mg + ezetimibe 10mg = **\$600/yr**)^{SK}, and e) the needed ~ **7-year time-to-benefit**.

An RxFiles Preliminary Trial Summary was published with the preliminary data released prior to full trial publication. Nothing has changed in terms of primary results. With the full trial publication now available (June 2015), the following is of note:

- Treatment group may have a bit more baseline CV risk than control group (slightly increased previous MI, beta-blocker, thienopyridine use)
- Kaplan-Meier Curves for primary end point appear to divide after 4 years, but difference marginal
- Canadians made up only 6% (n=1107) of the study population (North America ~38%).
- Superiority trial design with intention-to-treat analysis for both efficacy & safety (no modified-ITT or per-protocol), however almost half of the patients discontinued the study early:
 - Simvastatin: 45.9% (4163/9077) (never received study drug n=222, did not complete final visit n=1,249, completed final visit but was not taking study drug n=2,692)
 - Ezetimibe + simvastatin: 44.5% (4025/9067) (never received study drug n=216, did not complete final visit n=1,235, completed final visit but was not taking study drug n=2,574)
 - Per-protocol analysis provides a better assessment of overall safety as it only includes patients who followed study protocol (e.g. took study medications).
- Subgroups:
 - most of the benefit in age ≥ 75 yr HR = 0.797; 95% CI 0.704-0.902; interaction p=0.005;
 - also benefit for age ≥ 65 , but non-significant for interaction HR = 0.890; 95% CI 0.824-0.961; interaction p=0.098
 - also most benefit in patients with **diabetes** HR = 0.856; 95% CI 0.779-0.939; interaction p=0.023
- FDA Briefing Document Dec 2015:
 - FDA statistical reviewers seriously questioned the validity of the statistical analysis.
 - Primary endpoint data (whether did or did not have a 1⁰ endpoint) was missing in 11% of patients
 - Protocol for the trial was continuously modified

Trial Supplement - & noted by FDA Advisory Meeting Dec 2015)

CAUTIONS: 1) benefit modest; 2) lack of *high-dose statin* as the gold standard comparison; 3) death outcome disappointing; 3) results/contextualization controversial which may explain publication delay; 4) select population: e.g. *inclusion*: LDL normal 1.3-3.2_{mmol/L} (1.3-2.6_{mmol/L} if already on tx), age 50+; *excluded* if CrCl <30, previous high-dose statin, etc.³

¹ MAJOR STATIN TRIALS: All-Cause Mortality Outcomes <http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-lipid%20agents-major%20trials.pdf>

² Statin Intolerance - Management Considerations. RxFiles Q&A Summary, June 2013. Accessed Dec 8, 2014. <http://www.rxfiles.ca/rxfiles/uploads/documents/Lipid-Statins-Intolerance.pdf>

³ Trial Summary IMPROVE-IT. CardioSource ACC. Accessed Dec 8, 2014. http://www.cardiosource.org/science-and-quality/clinical-trials/i/improve-it.aspx?w_nav=RI

⁴ Cannon CP, Blazing MA, Giugliano RP, et al; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015 Jun 18;372(25):2387-97. Murphy SA, Cannon CP, Blazing MA, et al. Reduction in Total Cardiovascular Events With Ezetimibe/Simvastatin Post-Acute Coronary Syndrome: The IMPROVE-IT Trial. J Am Coll Cardiol. 2016 Feb 2;67(4):353-61.

⁵ FDA Briefing Document Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) December 14, 2015

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM476505.pdf>