Treat-to-Target or High-Intensity Statins in Patients with Coronary Artery Disease[1]

LODESTAR Trial Summary

SUMMARY

- When prescribing statins for secondary prevention, a strategy of starting with a moderate-intensity statin and treating to LDL target (1.3-1.8 mmol/L) was non-inferior to starting with a high-intensity statin (defined as rosuvastatin 20mg or atorvastatin 40mg) in terms of primary (1°) outcome benefit (death, MI, stroke, revascularization).
- Adverse events were similar overall; numerically: some were fewer, some were greater, in the treat-to-target group.

Bottom Line:

- There is debate as to which approach to statins is better; a fixed-dose, high-intensity "fire and forget" approach (avoiding ongoing lab tests and dose titration), versus a "treat-to-target" approach. Those who lean towards a **"high-intensity fixed-dose" approach** will value the avoidance of unnecessary lab tests, dose titration. Those who lean towards a **"treat-to-target" approach** will value the potential for some patients to have lower statin dosing, along with the hope of better tolerability/safety. Such tolerability/safety was not statistically significant in this RCT; however there is a potential for a trivial or small advantage. From an overall outcomes point of view, no important difference was seen! Non-inferiority of treat-to-target supported. This RCT in 2 prevention supports either approach noting that treat-to-target is "non-inferior" to fixed-dose, high-intensity.

BACKGROUND

- Statin guidelines vary in terms of two approaches to initiating statin therapy in patients with coronary artery disease (CAD). Specifically, how does a treat-to-target LDL approach compare to a high-intensity approach for initiating statins?
- Prior evidence lay with fixed-dose high- and moderate-intensity approaches; treat-to-target was not previously specifically studied.
- Statins lower risk of CV events in secondary prevention. Benefits of high-intensity statins have been greater than low-intensity statins. Use of high-intensity statins from the get-go is simple, matches the trials done, and offers a simple approach that does not require further LDL monitoring and dosage adjustment. However, initiation with a moderate-intensity statin followed by dosage titration according to an LDL target, may result in similar benefit along with tailored dosing and improved adherence.
- Given the growing interest in "time needed to treat" (time/resources for clinicians to assess, monitor, follow-up with patient, etc.), the trial has been looked at from the alternative vantagepoint; specifically, does monitoring/titrating statin intensity according to LDL targets offer any additional benefit over a "fire and forget" strategy to offset the time/resources required by clinician/patient?

LODESTAR TRIAL DESIGN AND POPULATION (SEE ORIGINAL ARTICLE/SUPPLEMENT FOR FULL CRITERIA)

DESIGN:

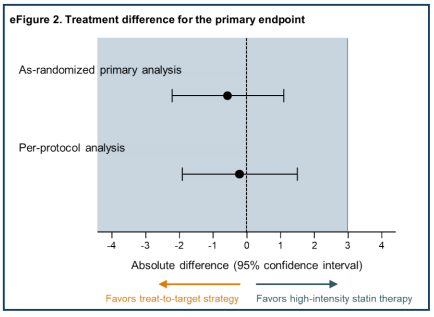
- randomized, open-label, non-inferiority, active comparator trial; allocation concealed; additional randomized stratification was done for a) baseline LDL, b) presence of diabetes, c) acute coronary syndrome, d) use of atorvastatin or rosuvastatin; multicenter at 12 centers in South Korea; clinical follow-up for 36 months; funding provided by Sam Jin Pharmaceutical and Chong Kun Dang
- the independent clinical end point committee was blinded to therapy assignment when categorizing each clinical event

POPULATION:

- **INCLUSION:** age 19+ with coronary artery disease (stable angina, unstable angina, acute non-ST elevation MI, and acute ST elevation MI)
- **EXCLUSIONS included:** women who were pregnant or with childbearing potential; hx of severe adverse event or hypersensitivity to statin; concomitant drug interaction with statin (strong inhibitor of 3A4 or 2C9); life expectancy of <3 years; severe hepatic dysfunction (LFTs 3x normal)
- **POPULATION at baseline (recruitment Sept 2016-Nov 2019; well balanced):**
  - **n=4400 enrolled**; mean age 65 yrs, ~72% male, presumably Asian based on geography (**South Korea**), BMI mean ~24.7
  - Clinical presentation: 74% were beyond 1 year of their initial diagnosis or revascularization procedure
    - AMI hx: <1yr since, ~7%; >1yr since, ~15%
    - Unstable angina or revascularization <1yr since ~18%; >1yr since ~40%
    - Detection of CAD at screening without symptoms ~18%
  - Med Hx: 67% hypertension, 57% previous PCI, 33% diabetes;
  - Statin intensity before randomization: ~25% high, 57% moderate, 2% low, 16% none;
  - Ezetimibe ~11%
  - Lipid levels, mean at baseline: LDL ~2.2mmol/L, HDL ~1.2mmol/L, TC ~4.0mmol/L; TG ~1.55mmol/L

INTERVENTION/COMPARISON:

- **Treat-to-target (moderate-intensity statin therapy guided by LDL)** vs **high-intensity statin** as control (1:1 stratification)
  - **moderate**: rosuvastatin 10mg or atorvastatin 20mg once daily; **high**: rosuvastatin 20mg or atorvastatin 40mg
    - Note: previous high-dose atorvastatin trials have used 80mg (e.g. 80mg vs 10mg [TNT]) rather than 40mg
  - Treat-to-target LDL: 1.3 - 1.8mmol/L; (dosage: up-titrated if >1.8; down-titrated if <1.3); 17% required up-titration; 9% required down-titration; and 73% were maintained
  - For treat-to-target patients already on a statin at initiation, an equivalent intensity was maintained at entry if LDL <1.8mmol/L
  - Physicians had discretion to adjust dose (detailed report of reason was required)



OUTCOMES – evaluated over 36 months:

- **Primary:** Composite of death, MI, stroke, coronary revascularization
- **Secondary, select**: new onset diabetes, discontinuation of statin, lab abnormalities, ESRD; post-hoc safety composite; monitoring: glucose, AST, ALT, creatinine, CK, A1c {the post-hoc outcome introduces significant bias as unblinded, and selective in adverse events Included (left out negative or neutral ones such as hosp for HF, cataract, etc.)}

RESULTS — follow up over 3 yrs

Clinical Endpoints	Treat-to-Target n=2200 (randomized) n=2108 (per-protocol)	High-Intensity n=2200 (randomized) n=2106 (per-protocol)	ARR/ARI P value	NNT/NNH /3yrs	Comments
PRIMARY ENDPOINT (Composite) - (ITT data from Table 2; per protocol data from eTable 9)					**Primary and Secondary Outcomes:**
Death, MI, stroke, coronary revascularization (ITT)	8.05% (n=177)	8.6% (n=190)	↓0.6% p<0.001 non-inferiority*	No difference	**Per-protocol analysis:** often preferred for non-inferiority & safety analyses
Death, MI, stroke, coronary revascularization (per-protocol)	8.3%	8.5%	↓0.2% p<0.001 non-inferiority*	No difference	**Subgroup analysis**: -fairly homogeneous; all subgroup 95% CI overlap with "all patients" -in the subgroup "<1yr since acute MI", there is some indication that high-intensity cohort may have done better (statistically non-significant; consistent with previous evidence for high-dose in acute MI)
PRIMARY ENDPOINT – Components of the Composite (ITT)					
-All cause death	2.5%	2.5%	↔ p=0.99		
-MI	1.6%	1.2%	↑0.4% p=0.23		
-Stroke	0.8%	1.3%	↓0.5% p=0.13		
-Coronary revascularization	5.2%	5.3%	↓0.1% p=0.89		
Safety/Other Outcomes – Select (per protocol data from eTable 9 used preferentially for safety endpoints)					**Safety/AEs/Other/Subgroups**
Discontinuation ~ poor compliance	0.59%	0.22%	-		**Overall rates** of AE, SAE: not reported
Did not up-titrate or maintain high-intensity per protocol	3.6%	4.0%	-		**LDL-C levels** differed only in the first 6 weeks (higher in the treat-to-target group)
Any adverse event	Not reported	Not reported	-		**Top 3 reasons for discontinuing statin:** -general weakness, GI symptoms, muscle symptoms
Serious adverse event (**SAE**)	Not reported	Not reported	-		**Rosuvastatin vs Atorvastatin Pre-specified Subgroup Analysis[2]:** -rosuvastatin mean daily dose: 17mg -atorvastatin mean daily dose: 36mg -rosuvastatin cohort had lower LDL levels (1.8mmol/L vs 1.9mmol/L p<0.001), but higher risk of new-onset diabetes (7.2% vs 5.3% p=0.03) and cataract surgery (2.5% vs 1.5% p=0.02); primary outcome was similar (8.7vs 8.2% p=0.58). Other safety endpoints did not differ.
New onset diabetes **, ***	5.6%	7.0%	-1.3% p=0.07		
Cataract operation **	2.0%	2.0%	-		
Discontinuation of statin **	1.5%	2.3%	-0.7% p=0.09		
Composite of lab abnormalities **	0.8%	1.1%	-0.2% p=0.43		
Hosp due to HF **	0.6%	0.2%	0.4% p=0.06		
End-stage renal disease **	0.1%	0.3%	-0.2% p=0.21		
?? Post-hoc: composite of ↑ new-diabetes, ALT or CK ↑, or ESRD **	6.1%	8.0%	?? -1.9% p=0.015; post-hoc, selective in endpoints chosen (e.g. left out Hosp for HF)		**Patients WITH vs WITHOUT diabetes** Prespecified Subgroup Analysis[3]: -no significant difference
% with LDL <1.8mmol/L @3 mo	59.2%	67.3%	p=0.02		
% with LDL <1.8mmol/L @3 yrs	58.2%	59.7%	p=0.41		
LDL, mean in overall study period	1.79 mmol/L	1.77 mmol/L	p=0.21		
On high intensity statin at 3 yrs	56%	89%			
Ezetimibe use at 3 yrs	20%	11%			

*= CI, p-value for non-inferiority endpoints (primary endpoint) calculated for upper boundary $_{97.5\%}$ only (1-sided) **= a 2° safety endpoint, therefore per protocol population used (as per supplement); *** note that RCTs regarding statins in general, and RCTs in high-CV risk patients with diabetes have positive CV outcomes despite seemingly adverse effects on glucose or incidence of diabetes

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- The first RCT to actually study a target LDL range.
- Reasonable time period, patient-risk, choice of therapies; although not blinded, did blind assessors & safety monitor; well differentiated cohorts.
- Well balanced groups; included patient important outcomes for primary endpoint.

LIMITATIONS

- Other lipid lowering (e.g. ezetimibe), while not recommended, was allowed; and as open-label design, would introduce bias
- Only ~60% achieved the LDL target in the treat-to-target group; how would non-statin add-on therapy affect outcomes (surrogate and clinical)?
- High-intensity doses were lower than other high-intensity RCTs (half-dose of what could have been chosen; atorvastatin 40mg, rosuvastatin 20mg); (80mg atorvastatin was the high-intensity studied in TNT, SPARCL, PROVE-IT; 40mg rosuvastatin was the high-intensity dose studied in ASTRONOMER, SATURN). As a result, the difference in intensity between cohorts was diminished, biasing towards less difference in outcomes. (Of interest, more patients in the treat to target cohort ended up on 80mg atorvastatin compared to the high-intensity cohort.)
- Most patient (84%) previously on a statin and thus population skewed to those more likely to tolerate and be adherent to therapy.

UNCERTAINTIES

- This RCT studied secondary prevention in patients with CAD; how might outcomes in a primary prevention population differ?
- What effect would higher high-intensity starting doses (ie rosuvastatin 40mg; atorvastatin 80mg) have on the overall benefit, harm or tolerability?
- How would the "treat-to-target" strategy results be affected by greater allowance of non-statin, add-on therapies?
- How would tolerability and safety be different in a cohort who had not been previously on a statin?
- How would the net risk/benefit progress over a longer period of time (ie. >3 years)?
- Is the risk of new onset diabetes and/or cataracts more specific to rosuvastatin? (Increased risk of diabetes was seen in the Subgroup study for LODESTAR, and was 1st observed with rosuvastatin the JUPITER RCT; however, this may also be due to potency differences.)

Other notes of interest:

Costs: atorvastatin 20mg ~17/month, 40mg ~17/month; rosuvastatin 10mg ~14/month, 20mg ~15/month (Saskatchewan/NIHB: full coverage)

RxFILES RELATED LINKS

- Landmark Lipid Trials: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-lipid%20agents-major%20trials.pdf
- Lipid Lowering Therapy – Drug Comparison Chart: https://www.rxfiles.ca/RxFiles/uploads/documents/members/CHT-lipid%20agents.pdf

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References:

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2) Lee YJ, Hong SJ, Kang WC, Hong BK, Lee JY, Lee JB, Cho HJ, Yoon J, Lee SJ, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, Jang Y, Hong MK; LODESTAR investigators. **Rosuvastatin versus atorvastatin** treatment in adults with coronary artery disease: secondary analysis of the randomised LODESTAR trial. BMJ. 2023 Oct 18;383:e075837. Online access.

3) Lee SJ, Kang WC, Lee JY, Lee JB, Yang TH, Yoon J, Lee YJ, Hong SJ, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, Hong BK, Jang Y, Hong MK; LODESTAR Investigators. Treat-to-target versus high-intensity statin treatment in patients **with or without diabetes mellitus**: a pre-specified analysis from the LODESTAR trial. EClinicalMedicine. 2023 Sep 20;64:102227. Online access.

AE=adverse event **ALT**=alanine aminotransferase **ARI**=absolute risk increase **ARR**=absolute risk reduction **AST**=aspartate aminotransferase **CAD**=coronary artery disease **CI**=confidence interval CK=creatine kinase **CV**=cardiovascular **CVD**=cardiovascular disease **d**=day **DM**=diabetes mellitus **HDL**=high density lipoprotein cholesterol **hx**=history **ITT**=intention to treat **LDL**=low density lipoprotein cholesterol **MI**=myocardial infarction **n**=number **NNH**=number needed to harm **NNT**=number needed to treat **PCI**=percutaneous coronary intervention **PP**=per protocol **RCT**=randomized controlled trial **TG**=triglyceride

LDL: to Target or Not to Target…; Some Reflections in Understanding the Two Paradigms

1) Theoretical Pathophysiology and Mechanisms of Action – these are distinct from outcome evidence

a. LDL has been, and is, a main component of both CV risk estimation, and CV lowering, hypothesis
b. Lowering LDL with a statin, and some other drugs, lowers CV risk
   i. With statins, this possibly supports, but does not prove, an LDL hypothesis
   ii. If lowering LDL had a 100% batting record for lowering CV risk, that would be somewhat compelling evidence. However, we do have examples of lowering LDL, raising HDL, but not reducing risk (e.g. **torcetrapib** ↑CV events & mortality)
c. One of the things EBM focuses on is *patient outcomes* as important. *Surrogate markers/theoretical MOAs* are interesting but potentially incorrect/incomplete. Thus, when looking at the dyslipidemia and CV risk evidence, one may question, "is it totally related to LDL, or are other things going on (e.g. pleiomorphic, anti-inflammatory effects)?"
d. When it comes to statins, and some other interventions, there is good correlation for LDL lowering and CV risk lowering.
e. The "…for every 1mmol/L …" analysis is observational from RCTs and provides support for cholesterol/LDL as a potential key mechanism, BUT, the case of torcetrapib Link reminds us that the association/benefit holds for some treatments/patient cohorts, but not all. In the end, ***patient important outcomes*** **are what matter**.

2) The long list of RCTs lowering LDL supports, but does not prove, the LDL hypothesis

a. Important to remember that the benefit, in evidence terms, was tied to a drug (usually a statin), a dose intensity, and an at-risk patient cohort. LDL was observed off to the side, or sometimes used to prompt increasing dose intensity. Link
b. Is LDL responsible for the whole effect, part of the effect, or is it just along for the ride? Is LDL all about benefit, or is there some **net benefit/harm** that may vary **depending on** patient type, concomitant treatments, etc.?

3) The role of *fire-and-forget* (it's more about the drug and dose intensity) vs *treat-to-target* (it's all about the LDL) approaches has been debated for years

a. Some who value a high quality, direct, and *PICO approach* to evidence may favour *fire and forget*. Those who believe, and focus in on the LDL model, and are welcoming of less-direct evidence, may favour *treat to target*. Some may value the best of either approach.
b. If only we had an RCT that would test the two approaches head-to-head…
   i. Welcome LODESTAR – not perfect, but finally some definitive insights…, or possibly more questions 😊

4) LODESTAR - Finally an RCT to test the two paradigms Link to LODESTAR Trial Summary (for critical appraisal and observations)

a. Interestingly, although many would think the LDL target has the better history of evidence, LODESTAR acknowledges that they are finally testing an LDL *treat to target approach* against the previous RCT standard of *drug & dose intensity* (with a tiny bit of LDL level observing/dabbling off the side) – essentially, a *fire-and-forget* approach.
b. What **LODESTAR** finds: {a **2° prevention RCT** in Korean patients comparing a treat-to-target approach with fire-and-forget}
   i. Efficacy wise: in high-risk patients, LDL **treat-to-target is non-inferior to high-intensity statin (ie. atorvastatin 40mg, or rosuvastatin 20mg) from the get go** (within the range of LDL levels and patient types treated, over 3 years)
      1. **Note: efficacy wise, one can do the extra work/lab follow-up (7 lipid levels/3yrs), and precisely titrate doses, to achieve …. the same outcome as those who just go high-intensity from the get-go.**
   ii. BUT, LODESTAR leaves room for some deliberation and nuance regarding which is better.
      1. Numerically, though not statistically significant, efficacy favours the *treat-to-target* approach, trivially.
      2. On the side of safety/tolerability, there are hints that *treat-to-target* looks marginally better (e.g. ALT, CK; discontinuations, ± new diabetes; but not HF); however the open-label design, and a selective post-hoc composite, leads to bias, limiting certainty. Tolerability strategies may be a useful consideration for some.
      3. All-cause death rates exactly the same in both groups, statistically and numerically.
      4. Although the control group, aka *fire-and-forget,* started with high-intensity statin, this was only 40mg atorvastatin; as tolerated, it could have been bumped up to 80mg to match the high-intensity statin evidence from PROVE-IT, TNT and IDEAL (and maybe even the other arm of LODESTAR). Not doing this was a small disadvantage for efficacy, but perhaps also a small advantage for tolerability.
c. **Regardless of which approach one takes, *the results are likely to be more similar than different***
   i. This allows for some nuance in application to patient care.
      1. **If no difference seen** here in 2° prevention, is there even less to differentiate in 1° prevention?
      2. Which approach will serve **the patient in front of me** best? (E.g. impact on patient quality of life, of needing to go for more vs less testing, appointments, visits to pharmacy, etc.)
      3. Which approach serves the **societal** primary care effort to provide best value healthcare for as many **patients** as possible, while allowing for simplicity and a better work-life balance for **clinicians**?
      4. Which approach allows for **individualized considerations** regarding the patient or specialists involved? e.g. one could take one approach in less complicated patients, and "ramp up" those who are, or become, complicated (e.g. 2° prevention, or familial hypercholesterolemia)
      5. Which approach is likely to **best serve/compliment the additional interventions** (e.g. PCSK9s) that high-risk patients may be on? Safety may be tied to the lab reference criteria used in the RCTs.

5) The biggest impact on the world of CV risk reduction is offering higher-risk patients a statin; from there, proceed with care!