Indian Heart Journal 72 (2020) 221–224

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Editorial

Statins in primary prevention: is the enthusiasm justified?

Keywords:
Primary prevention
Statins

1. Introduction

On the basis of multiple lines of evidence (clinical and experimental), LDL-cholesterol (LDL-C) and other Apo-B containing lipoproteins {(VLDL remnants, Lp(a)} are believed to be causal for atherosclerotic cardiovascular disease (ASCVD).[1,2] Statins occupy a central position in the optimized medical therapy of subjects with established ASCVD and those deemed to be at high risk (predicted 10-year ASCVD risk >20%).[3,4] Owing to the reported benefits of lowering LDL-cholesterol (LDL-C), the last two iterations of the lipid guidelines of the American Heart Association (AHA) / American College of Cardiology (ACC) lowered the bar for initiating statin therapy for primary prevention, recommending them for all adults with LDL-C > 190 mg/dl, practically all subjects with type 2 Diabetes (T2D), and adults over 40 with predicted 10-year ASCVD Risk ≥ 7.5%.[3] The 2018 update went further, recommending consideration of statins for people with borderline risk (predicted 10-year ASCVD risk 5–7.5%) in the presence of other risk enhancing factors, and additional therapy (ezetimibe and / or PCSK9 inhibitors) in very high risk ASCVD patients or familial hypercholesterolemia (FH) if the LDL-C goals remained unmet (70 mg/dl for the former and 100 mg/dl in the latter).[3,4]

We aim to address some pertinent questions in low (10-year ASCVD risk <5%), borderline (5–7.5%) and intermediate-risk (7.5-<20%) individuals, especially the two lower risk populations.

2. How robust is the data for primary prevention?

Trends for benefits were reported from most studies, but only three of the 7 largest primary prevention trials had statistical significant reduction in mortality.[5] WOSCOPS[6] included a high-risk population enrolling only men with average LDL-C 192 mg/dl, patients with angina, previous strokes and claudication (previous myocardial infarction (MI) was an exclusion criteria), and reported significant reduction in CV death ($p = 0.033$), however total mortality reduction was borderline significant (22% reduction, $p = 0.051$). On the other hand, MEGA[7] was a study in a low-risk Japanese population with a 98.3% survival at 5 years in the placebo group, so its applicability to higher-risk Caucasian or South Asian populations is limited. JUPITER,[8] the largest study, was prematurely terminated at 1.9 years (planned duration up to 5 years), with 0.56% absolute risk reduction (ARR) of composite primary endpoint (numbers needed to treat-NNT of 31 at 4 years). For a trial that was reportedly terminated due to an "unequivocal reduction in CV mortality",[9] the study surprisingly doesn't mention the number of CV deaths specifically,[8,10] (a later reply by the authors[11] revealed no significant difference in CV mortality as the numbers of confirmed deaths from cardiovascular causes were 35 in the rosuvastatin group and 43 in the placebo group. Curiously, fatal MI and stroke were merely 12 in both arms, the rest were supposedly other CV causes like aneurysm ruptures).[8,10,11]

At least 18 systematic reviews (SR) evaluating primary prevention reported consistent reduction in major vascular events (MVE); whereas mortality reduction was noted in some (Cochrane Collaboration meta-analysis[12] of 18 trials in 2013, Cholesterol Treatment Trialists' (CTT) Collaboration,[13,14] Brugts et al[15]), but not all.[16–18] The Cochrane review reported a 14% reduction in total mortality (ARR of 0.7%, NNT 96 for 5 years). However, the trials included, were not strictly primary prevention trials and the investigators gave disproportionate weightage to two trials -WOSCOPS and JUPITER).[5,12] This had tilted the balance in favor of statins; notably, these were not low-risk subjects as the predicted ASCVD risk was 9.2% in WOSCOPS. In this Cochrane review the diabetic subset of Heart Protection Study (HPS)[19] was also included.[5,12]

The CTT Collaboration (in 2012[13] and 2015[14]) reported a uniform significant 22% reduction in MVEs with 9% reduction in all-cause mortality in 174,000 patients from 27 trials, having divided the population into 5 categories of *baseline 5-year ASCVD risk* (<5%, 5-<10%, 10-<20%, 20-<30%, ≥30% predicted risk). Of 27 trials, only 3 were primary prevention trials and five compared low vs. high dose statins in known ASCVD. Overall approximately 60% individuals had ASCVD with net predicted **5-year risk** of 13.7% in the placebo vs. statin trials and 20.8% in the low vs. high dose statin trials. Furthermore, the baseline risk was not pre-specified in the individual trials.[5,13,22] The group with *ASCVD risk* <10%, had 0.3% ARR for MVEs (0.2% in females) after 5 years of statin use. Notably, the total mortality in the lowest-risk group was similar with statins or placebo (195 vs. 193) due to higher non-vascular mortality with statins (116 vs. 101). Vascular mortality was reduced with statins only in the two high-risk subgroups (20-<30% and ≥30% risk)[13,14,20] and not in the <20% risk categories. Thus, who is benefitted needs consideration, **as the <10% 5-year risk category cannot be easily converted into 5–7.5% or <5% 10-year risk.**[13,14] Another analysis of this data did not find mortality benefits in lower-risk subjects (<5% and 5–10% predicted risk), even including subjects with

https://doi.org/10.1016/j.ihj.2020.07.021

established ASCVD, and reported survival benefits only in the >20% risk groups.[21]

Other meta-analyses[16–18] found similar lowering of MVEs without significant mortality reduction. Of note, at least 44 cholesterol-lowering RCTs reported no survival benefit (26 of them are statin trials), seven non-statin trials with significant reductions in LDL-C reported substantial clinical harms, including the cholesterol ester transfer protein-CETP inhibitor trials[22,23]

Women, young adults and the elderly are typically underrepresented in RCTs: a meta-analysis of over 65,000 subjects including 35% women was published without gender specific results.[16] Among individual studies, JUPITER showed no mortality reduction in females <65 years.[8,10] Of four meta-analyses[14,18,24,25] specifically evaluating women given statins for primary or secondary prevention, two found no survival benefits in females,[18,24] while the other two reported similar risk reduction as in males.[14,25] However, the total events and mortality in women on placebo were almost consistently lower than in men on statins,[25] whereas adverse effects (AE) were higher in women, who were more likely to develop muscle pains, hepatic dysfunction and diabetes.[8,14,18,22,24–26]

The increased mortality reported in elderly individuals with lower cholesterol levels needs further evaluation. One SR reported an inverse relationship between LDL-C and total mortality,[27] apparently due to higher non-cardiovascular mortality associated with gastro-intestinal and respiratory illnesses,[28] sepsis[29] and cancers,[30] both in untreated subjects as well as those taking cholesterol lowering drugs. Three large RCTs with statins (CARE,[31] PROSPER[32] and SEAS[33]) and combined data from 4S and HPS reported significantly more cancers in the treatment arm.[30] Following this, statin trials excluded non-melanoma skin cancers from the adverse events.[27,30] PROSPER was designed to evaluate individuals aged 70–82 years given pravastatin for 3 years and reported lower CVD but similar all-cause mortality owing to higher cancer deaths.[32]

Finally, most trials enrolled men > 40 years of age and women > 50–60 years age, hence the recommendation to initiate statins in adults > 20 years of age also appears to be without adequate evidence, except in FH.[1–8,12–18,22,24,25] **In sum, the data for primary prevention is consistent for reduction of events, not total mortality, and that too only in middle-aged males.**

3. Is lower always better for cholesterol?

This paradigm is based on the demonstration of greater reduction in CVD events with increasing reduction in LDL-C, a conclusion derived by drawing a regression line through endpoints in statin and placebo groups in different trials.[1,13,34,35] Warren[34] demonstrated that if mean placebo endpoints are compared with the mean active drug, the placebo line is steeper, a finding that is hardly plausible. Thus, the slope of the Ballantyne plot[35] reflects the natural association of LDL-C with atherosclerosis in addition to statin effect.[34] Their real impact is demonstrable by *lines joining the placebo points with the respective treatment points for each trial*: these are shallower and suggest that *the lower the baseline cholesterol, the lesser the benefit of statins.*[34] The concept of proportional event reduction with LDL-C reduction is therefore weaker than hitherto suggested, with part of the benefit also being attributable to pleiotropic effects of statins.[22,34]

Trials have evaluated higher dose statins and statin combinations with other lipid lowering agents (ezetimibe, niacin, fibrates, CETP inhibitors and recently PCSK9 inhibitors) in ASCVD, demonstrating extra reduction in cumulative CVD events without survival benefit. Disturbingly, there was numerically higher mortality in the aggressive arm in at least 5 of 11 reported trials, with only IDEAL,[36] PROVE-IT[37] and REVEAL[38] reporting non-significantly better survival.[22,34,36–45]

The TNT trial[39] gave proof of concept as CVD events were reduced by 1.5% with a 17% extra reduction in LDL-C, but with a 6-fold increase in deranged liver function tests (LFT), 0.2% vs. 1.2%; the mortality was non-significantly higher in the high-dose atorvastatin group. The IMPROVE-IT trial[40] recorded an impressive 24% extra reduction in LDL-C with additional ezetimibe, but only a 2% ARR in the combined end point after 6 years (HR 0.936, 95% CI 0.89–0.99); despite significantly lesser MI (13.1 vs. 14.8%), total deaths were non-significantly higher in the ezetimibe arm. The earlier ENHANCE trial[41] with ezetimibe, and the large AIM-HIGH[42] and HPS2-THRIVE[43] studies with niacin were also disappointing in their failure to provide any incremental benefit when added to statins.[34] PCSK9 inhibitors lower LDL-C to the supposedly ideal median of 30–40 mg/dl, but failed to show mortality reduction in the huge FOURIER trial[44] despite significant reduction in the risk of MI (468 vs. 639), stroke and revascularization: the active arm recorded a non-significantly higher CV (251 vs. 240) and total mortality (444 vs. 426).[34,44]

Finally, the sizeable HPS[19] and the only "pure primary prevention" meta-analysis[16] reported lack of correlation between baseline LDL levels or the mean reduction in LDL-C levels and outcomes. **Improved survival with lower cholesterol thus remains unproven in primary prevention.** Of note, the ED_{50} for atorvastatin (the dose that lowers LDL-C by 50% of maximum effect, i.e., 80 mg) is 3 mg; 20 mg is nearly at the top of the dose–response curve and is likely to be a reasonable dose for lower risk subjects. The benefits continue to accrue with time, being 3 times higher at 5 years compared to one: atorvastatin 10 mg reduces LDL-C by about 37% and reduces MVEs by 40% at 3 years.[46]

4. Risk-benefit ratio with statins

Serious AE of statins include rhabdomyolysis (about 1:10,000), new onset T2D (0.5–1.1%) and derangement of LFT (0.2–1.2%).[13,47] Musculoskeletal pain is the commonest "benign" AE; an analysis using NHANES data estimated that of 22% individuals on statins who reported musculoskeletal pain, about 25% of any pain and 45% of lower extremity pain could be ascribed to statin use: a staggering number, considering the hundreds of millions of statin users globally.[48,49] The unacknowledged myalgias are probably the most critical factor for poor adherence to statins, especially in primary prevention. A Canadian cohort with over 140,000 individuals reported dropout rates of over 50% at 1 year and 75% at two.[50]

JUPITER reported 25% increased new-onset T2D within 1.9 years (50% increased risk in females),[8] Women's Health Initiative (WHI) 48% higher risk,[51] and two other reviews reported 18% increase in diabetes.[12,52] A retrospective cohort study designed to examine this association reported 14% new-onset diabetes over a mean follow-up of 5.5 years; T2D (OR 1.87, 95% CI 1.67–2.01) and T2D with complications (OR 2.5, 95% CI 1.88–3.32). The risk was still higher with high-intensity statin therapy.[53] Other notable AEs include derangements of liver function (OR 3.73, 95% CI 2.11–6.58), renal function (OR 1.30, 95% CI 1.14–1.48)[5] and polyneuropathy (HR of 14.2).[54] The reassuring results of CTT: 5 new cases of myopathy, 50–100 new diabetes and 5–10 hemorrhagic strokes in treating 10,000 subjects for 5 years, are thus discordant with the considerably higher AEs reported in observational cohorts (e.g., 530 cases of musculoskeletal pain in NHANES data or 14% new-onset T2D reported in a propensity score-matched analysis).[13,14,48,53] Observational studies tend to overreport AEs, whereas RCTs underestimate them, as vulnerable individuals get excluded in the pretrial run-in period (36% in HPS, 35% in TNT).[19,39,47]

In comparison to robust ARR in mortality ranging from 0.43 to 3.33% (median 1.75%) in five major secondary prevention trials, all-cause mortality reduction in primary prevention is borderline

(ARR varied from −0.09 to 0.89%, median 0.49% in the 7 major trials).[5] Hence, nearly 200 intermediate-risk patients need treatment with statins for 2–5 years to save one life, meaning 199 individuals will be potentially at risk of AEs without significant benefit. And even this benefit is not seen in lower risk patients with <7.5% ASCVD risk.[5] A meta-analysis in 2015 calculated the average prolongation of survival during the duration of primary prevention trials to be a paltry 3.1 days (4.2 days in secondary prevention trials), though it is hard to extrapolate these results to individual patients.[55]

4.1. Synthesis and the way ahead

Statins (and select other LDL-lowering therapies like ezetimibe and PCSK-9 inhibitors) reduce MVEs and usually CHD mortality in individuals with established ASCVD with modest effects on total mortality. The major benefits in primary prevention accrue to high-risk individuals, with limited evidence for clear survival advantage, especially in females (<50 years age), elderly > 75 years and young individuals who don't have FH.[1,5–8,12–19,22,24–30,32–34] As no primary prevention trial has tested "lower is better", justification is lacking for recommending high-dose statins or combinations using LDL-C as a surrogate for mortality benefits.[5,34,36–45] There is a vast gulf between AEs reported in RCTs and observational studies, suggesting that the favorable risk-benefit ratio in high-risk subjects becomes suspect in lower risk individuals, especially as they are more likely to get AEs (owing to the longer duration of use), whereas benefits remain proportionately lower due to lesser baseline risk.[13,14,47–54] Thus, it appears inappropriate to use the weak survival benefit in combined statin trials and extrapolate these to a low-risk population (a study found nearly equal benefits in reducing MI from eating "an apple a day" as a daily statin).[56] PREDIMED[57] and Lyon study[58] reported major benefits despite not changing cholesterol levels significantly; a Cochrane SR in 2008 reported the salutary effects of exercise and diet for preventing T2D in individuals with prediabetes or metabolic syndrome.[59] Lifestyle modification with diet and exercise have measurable advantages, and need to be reinforced prior to, if not parallel to drug therapy.[56–59]

Finally, the ASCVD score[3] was developed in 2013 using data from cohorts that were several decades old; an evaluation reported that its performance was *"worse than almost any previously published cardiovascular model.*[60] An evaluation of ASCVD, three older Framingham based scores-FRS-CHD, ATPIII-FRS-CHD, FRS-CVD and the Reynold's Risk Score (RRS) with events in the MESA study[61] concluded that the first four scores overestimated ASCVD risk by 37–154% in males and 8–67% in females. Actual event rate was 3% in men and 5.1% in women in risk group 7.5–10%, suggesting that nearly half the subjects advised statins may have a true 10-year risk of well below 7.5%.[61,62] The lack of correlation of reduction in CHD mortality with the over 3 times increase in statin utilization from 2000 to 2012 in 12 Western European countries also begs consideration as about 2/3 of the people are currently on statins for primary prevention.[17,63,64] There is thus an urgent need for dedicated studies in lower risk subjects before recommending statins in low and borderline-risk individuals for primary prevention.

4.2. List of quoted trials

AIM-HIGH: Atherothrombosis Intervention in Metabolic Syndrome with low HDL/HIGH
Triglycerides Trial
CARE: Cholesterol And Recurrent Events Trial
CTT: Cholesterol Treatment Trialists' Collaboration
ENHANCE: Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis
Regression Trial
FOURIER: Further Cardiovascular Outcomes Reasearch with PCSK9 Inhibition in Subjects with
Elevated Risk
HPS: Heart Protection Study
HPS2-THRIVE: Treatment of HDL to Reduce the Incidence of Vascular Events
IDEAL: incremental Decrease in Endpoints Through Aggressive Lipid Lowering
IMPROVE-IT trial: IMProved Reduction of Outcomes: Vytorin Efficacy International Trial
JUPITER: Justification for the Use of Statins in Primary Prevention
MEGA: Management of Elevated cholesterol in the primary prevention Group of Adult
Japanese
NHANES: National Health and Nutrition Examination Survey
PREDIMED: Primary Prevention of Cardiovascular Disease with a Mediterranean Diet
PROVE-IT/ TIMI-22: Pravastatin or Atorvastatin Evaluation and Infection Therapy trial
PROSPER: PROspective Study of Pravastatin in the Elderly at Risk
REVEAL: Randomized EValuation of the Effects of Enacetrapib through Lipid-modification
SEAS: Simvastatin and Ezetimibe in Aortic Stenosis study
TNT: Treating to New Targets
WOSCOPS: West of Scotland Coronary Prevention Study

Conflicts of interest

None declared.

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