HMG-CoA Reductase Inhibitors for Dyslipidemia Treatment

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Dyslipidemia plays a fundamental role in the development and progression of atherosclerosis. Current guidelines for treating dyslipidemia focus on low-density lipoprotein–cholesterol (LDL-C). Despite advances in the pharmacotherapy of atherosclerosis, the most successful agents used to treat this disease—statins—remain insufficient in the primary or secondary prevention of acute myocardial infarction. Advancing therapy for hypercholesterolemia with emerging new drugs, either as monotherapy or in combination, is expected to improve cardiovascular outcomes.

dyslipidemias cholesterol statins gene therapy

1. Introduction

Dyslipidemia is one of the most important risk factors for atherosclerotic cardiovascular disease (ASCVD). In 2017, high non-HDL cholesterol was responsible for an estimated 3.9 million deaths worldwide [1]. Therefore, lipid-lowering therapies, especially statins, have been shown to be cost-effective or cost-saving, particularly in people with a high CV disease risk [2][3][4][5]. Although not the focus of this text, it is worth mentioning that effective community-based prevention strategies promoting lifestyle modification (e.g., dietary improvement and regular physical activity) are also needed to control dyslipidemia.

Cholesterol is a hydrophobic molecule, insoluble in plasma, with several vital functions in our body, such as the production of hormones and the formation of cell membranes. Since the discovery of cholesterol at the end of the 18th century, when it was isolated from gallstones, to its association with atherosclerosis, vast knowledge has been accumulated about the molecule, its metabolism, and its role in atherosclerosis.

Due to its insoluble nature, cholesterol is transported in plasma through lipoproteins, generally spherical structures made up internally of nonpolar lipids, such as cholesterol esters and triglycerides, and externally by polar lipids such as phospholipids, apolipoprotein, and free cholesterol [6]. On its surface, we observe the presence of apolipoproteins (apo), which are fundamental structures for the signaling, transport, and binding of lipoproteins to receptors. Due to their amphiphilic nature (membrane-forming molecules), they are crucial in the stability and function of lipoproteins.

Evidence from epidemiological and clinical studies supports a key role of circulating LDL-C and other apolipoprotein B (apoB)-containing lipoproteins in atherogenesis. Although the benefits of lipid lowering are well established in high-risk individuals, a number of trials show that the benefits extend to lower-risk individuals as well. Knowledge of cholesterol metabolism is essential for understanding dyslipidemia and the drugs used in its treatment.

Although statins remain the first line of pharmacotherapy, novel lipid-lowering therapies are currently available, such as PCSK9 inhibitors; gene therapy, including small interfering RNAs (inclisiran); ANGPTL3 inhibitors (evinacumab); CRISPR/Cas9, antisense Oligonucleotides (mipomersen); apoB and MTP Inhibitors; and, finally, vaccines against PCSK9 and targeted nanotherapy.

2. HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors, or statins, are the cornerstone of LDL-C-lowering therapy and are currently recommended as first-line therapy for the secondary prevention of atherosclerotic disease and for primary prevention in at-risk patients [7][8]. These drugs achieve LDL-C lowering by reducing cholesterol synthesis in the liver, ultimately leading to an increase in LDL receptors (LDLRs) in hepatocytes. The enhanced expression of LDLRs on the surface of hepatocytes results in an increased removal of LDL-C from circulation [7].

Statins have a relatively predictable effect on LDL-C. Low-intensity statins (simvastatin 10 mg, pravastatin 10–20 mg) reduce LDL-C by less than 30%, moderate-intensity statins (simvastatin 20–40 mg, atorvastatin 10–20 mg, rosuvastatin 5–10 mg, pravastatin 40–80 mg) reduce LDL-C by 30–50%, and high-intensity statins (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) reduce LDL-C by at least 50%. These values reflect population averages and may not be entirely applicable to individual patients [7][8].

Beyond LDL-C effects, statins also produce modest reductions in triglyceride levels and may lead to discrete increases in HDL-C, usually with a neutral effect on lipoprotein(a) [Lp(a)]. The classical “pleiotropic effects” of statins traditionally refer to the potential anti-inflammatory and antioxidant effects of the drug [7].

Regarding clinical applications for statins, this text is divided into primary prevention, secondary prevention, and special groups, such as heart failure (HF) and chronic kidney disease (CKD) patients. The main trials in these categories are summarized in **Table 1**, **Table 2** and **Table 3**.

2.1. Primary Prevention

In a primary prevention setting, any intervention aimed at reducing challenging outcomes such as mortality or myocardial infarction (MI) must involve large and/or long trials with sufficient power to detect differences in the inherently low event rate when compared to secondary prevention trials. Furthermore, the highest degree of scrutiny and critical reasoning is necessary before recommending an intervention to asymptomatic individuals,

since its benefits tend to manifest in the long term, while unaccounted adverse effects may arise from any kind of intervention.

One of the first and most relevant trials that rose to this challenge was the West of Scotland Coronary Prevention Study Group (WOSCOPS) trial [9]. In this study, pravastatin 40 mg was tested against placebo in patients with elevated LDL-C levels and no documented coronary artery disease (CAD). Over the 4.9 years of follow-up, LDL-C levels were reduced by an average of 26%, and patients in the pravastatin group had lower rates of MI and coronary-heart-disease-related death.

Subsequently, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) evaluated the effect of cholesterol lowering with lovastatin in patients with moderately elevated lipid levels without clinically evident ASCVD [10]. Lovastatin reduced the risk of the primary outcome of MI, unstable angina (UA), or sudden cardiac death (SCD). However, due to the low cardiovascular (CV) risk of the enrolled patients, the absolute risk reduction (ARR) of 0.2% per year was much smaller than demonstrated in previous trials (number needed to treat [NNT] of 86). Furthermore, the study was stopped early for efficacy. Statistical simulations, however, suggest that truncated studies overestimate the magnitude of benefit of the treatment being evaluated by up to 29% [11].

Two other important studies that showed the CV benefits of statins in patients without documented ASCVD were ASCOT-LLA and MEGA.

The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA) trial showed that, among patients with hypertension and relatively low cholesterol, treatment with atorvastatin was associated with a reduction in the primary endpoint of MI or coronary death at a 3-year follow-up [12].

The Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) trial showed that treatment with pravastatin in addition to diet modification was associated with a reduction in coronary heart disease events compared with diet modification alone at a mean 5.3-year follow-up [13].

Despite the evidence provided by the WOSCOPS study, concerns have arisen regarding patients with lower LDL-C levels but with an estimated risk of ASCVD. Thus, markers capable of detecting patients who may benefit from statin therapy for primary prevention have been investigated. The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial compared rosuvastatin vs. placebo in patients with LDL-C < 130 mg/dL, no known ASCVD and high-sensitivity C-reactive protein (hsCRP) levels of 2.0 mg per liter or higher [14]. The study showed a reduction in the primary composite endpoint (MI, stroke, arterial revascularization, hospitalization for UA, or CV death) [HR 0.56, 95% CI 0.46 to 0.69, ARR of 0.59% per year for the primary endpoint, NNT 169]. For coronary events, including fatal or non-fatal myocardial infarction, 500 persons need to be treated for one year to prevent one event.

Finally, the Heart Outcomes Prevention Evaluation (HOPE)-3 trial showed that, in patients with intermediate risk (estimated annual rate of major adverse cardiovascular events [MACEs] ~1%), rosuvastatin resulted a reduction in

the composite coprimary endpoint of CV death, MI, or stroke compared to placebo (HR 0.76, 95% CI 0.64 to 0.91, NNT of 91) [15].

Despite the cardiovascular benefits suggested by the aforementioned trials, it is important to not overlook clinical reasoning and to recognize the magnitude of the findings. Due to the inherently low incidence of events in the primary prevention population, it is important to acknowledge that the clinical benefit is marginal during the follow-up period of the trials, resulting in high NNTs. Additionally, older patients comprise the majority of these study populations. The long-term benefits are likely greater than those found in the aforementioned trials, and lifelong LDL-C-lowering therapies might have a more significant impact when considering younger patients with high LDL-C levels or higher than average CV risk factors.

Table 1. Primary prevention trials. Legend: CAD: coronary artery disease; CV: cardiovascular; hsCRP: high sensitivity C-reactive protein; MI: myocardial infarction; UA: unstable angina; TC: total cholesterol.

Study	Sample Size	Characteristics of Patients	Comparison Groups	Follow-Up	LDL-C Reduction	CV Effects
WOSCOPS (1995) [9]	6595	TC > 252 mg/dL	Pravastatin 40 mg vs. placebo	4.9 years	26%	Reduction in MI or coronary death (HR 0.69, 95% CI 0.57 to 0.83, NNT 111)
AFCAPS/TexCAPS (1998) [10]	6605	LDL-C 130–180 mg/dL	Lovastatin 20–40 mg vs. placebo	5.3 years	25%	Reduction in coronary events (HR 0.63, 95% CI 0.50 to 0.79, NNT 86)
ASCOT-LLA (2003) [12]	10,305	Hypertension and CV risk factors	Atorvastatin 10 mg vs. placebo	3.3 years	35%	Reduction in MI or coronary death (HR 0.64, 95% CI 0.50 to 0.83, NNT 83)
MEGA (2006) [13]	7832	TC 220–270 mg/dL	Pravastatin 10 mg vs. placebo	5.3 years	18%	Reduction in CAD (HR 0.67, 95% CI 0.49 to 0.91, NNT 119)
JUPITER (2008) [14]	17,802	LDL-C < 130 mg/dL + hsCRP ≥ 2 mg/L	Rosuvastatin 20 mg vs. placebo	1.9 years	50%	Reduction in CV death, MI, stroke, arterial revascularization, or UA hospitalization (HR 0.56, 95% CI 0.46 to 0.69, NNT 169)
HOPE-3 (2016) [15]	12,705	Intermediate CV risk (CV	Rosuvastatin 10 mg vs.	5.6 years	26.5%	Reduction in CV death, MI, or stroke

Study	Sample Size	Characteristics of Patients	Comparison Groups	Follow-Up	LDL-C Reduction	CV Effects
		event rate 1%/year)	placebo			(HR 0.76, 95% CI 0.64 to 91, NNT 91)

n use and a lower incidence of events. However, the clinical significance of such reduction will depend on the absolute rate of events, with more evident benefit observed in patients at the highest risk of MACEs. This is evident in secondary prevention clinical studies.

The Scandinavian Simvastatin Survival Study (4S) trial randomized 4444 patients with coronary artery disease (CAD), defined by prior MI or angina, to simvastatin or placebo [16]. The trial was stopped early due to an ARR of 3.3% in all-cause mortality with simvastatin (11.5% vs. 8.2%; p = 0.0003; NNT 30). In addition to being a truncated study, the low rate of aspirin use among the 4S trial population (~37%) draws attention. Possibly, the magnitude of the benefit would be attenuated with widespread aspirin use.

The Cholesterol and Recurrent Events (CARE) trial confirmed a reduction in coronary events in patients with previous MI, even in a group with lower total cholesterol levels (<240 mg/dL, mean LDL-C of 139) [17] Similarly, the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial showed a reduction in coronary death in patients with previous MI or hospitalization for UA (NNT of 53) [18]. The Heart Protection Study (HPS) showed a reduction in all-cause mortality, driven by vascular causes (7.6% vs. 9.1%, HR 0.83, 95% CI 0.75 to 0.91, NNT 67) in high-risk patients—65% with previous CAD [19]. On the other hand, the Fluvastatin On Risk Diminishing after Acute Myocardial Infarction (FLORIDA) trial showed that fluvastatin did not reduce coronary events in post-MI patients [20]. However, the trial was underpowered, and a post hoc analysis revealed a trend towards a reduction in the primary endpoint in patients with pronounced ischemia at the trial onset [21].

So far, the relationship between intervention and outcome seems to be established, with greater benefits naturally seen in patients at a higher baseline risk. However, a new question has arisen: What is the best statin regimen for reducing cardiovascular outcomes?

The Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial tested different intensity regimens in patients in the acute phase of an MI [22]. Among those up to 10 days after an acute event, atorvastatin 80 mg reduced a composite of death from any cause, MI, documented UA requiring rehospitalization, and revascularization after 30 days of randomization or stroke when compared to pravastatin 40 mg (22.4% vs. 26.3%, HR 0.84, 95% CI 0.74 to 0.95). However, it is important to note that this endpoint is very broad and includes more fragile outcomes such as unstable angina and need for revascularization. Moreover, reductions in LDL-C levels in the pravastatin group were strikingly low (baseline LDL-C 106 mg/dL and LDL-C achieved at follow-up 95 mg/dL), which surely favors the atorvastatin group, which achieved LDL-C of 62 mg/dL on follow-up (41% reduction).

The Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial tested atorvastatin 80 mg vs. simvastatin 20 mg and found no difference in the primary endpoint of coronary death, non-fatal MI, or cardiac arrest with resuscitation (HR 0.89, 95% CI 0.78 to 1.01) [23]. One limitation of this trial was the smaller than

expected reductions in LDL-C levels, which were around 34% with atorvastatin 80 mg and 17.7% in the simvastatin 20 mg group, possibly blunting an eventual difference in effects, but this is merely speculatory.

The Treating to New Targets (TNT) trial tested different regimens of atorvastatin (80 mg vs. 10 mg, a high- vs. a moderate-intensity regimen) in patients with stable CAD [24]. This trial found a reduction in coronary death, nonfatal non-procedural MI, and resuscitation after cardiac arrest or stroke (8.7% vs. 10.9%, NNT of 46). The primary endpoint was mainly driven by MI and stroke.

Finally, the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial tested different simvastatin doses (20 mg vs. 80 mg) and found no difference in efficacy outcomes yet with a higher incidence of myopathy [25]. Thus, simvastatin 80 mg should not be used.

Based on findings from randomized clinical trials (RCTs), it appears that high-intensity regimens lead to a modest benefit in patients with CAD, even with “normal” LDL-C levels. This benefit is mainly driven by a reduction in cardiac events, although clear mortality benefits are not evident.

Table 2. Secondary prevention trials. * Included both primary and secondary prevention patients. Legend: ACS: acute coronary syndrome; CA: cardiac arrest; CAD: coronary artery disease; DM: diabetes mellitus; HTN: hypertension; MI: myocardial infarction; TC: total cholesterol; UA: unstable angina.

Study	Sample Size	Characteristics of Patients	Comparison Groups	Follow-Up	LDL-C Reduction	CV Effects
4S (1994) [16]	4444	Angina or previous MI	Simvastatin 20–40 mg vs. placebo	5.4 years	35%	Reduction in death (HR 0.70, 95% CI 0.58 to 0.85, NNT 30)
CARE (1996) [17]	4159	Previous MI TC < 240 mg/dL LDL-C 115–174 mg/dL	Pravastatin 40 mg vs. placebo	5 years	28%	Reduction in coronary death or MI (10.2% vs. 13.2%, NNT 34)
LIPID (1998) [18]	9014	Previous MI or UA TC 155–271 mg/dL	Pravastatin 40 mg vs. placebo	6.1 years	25%	Reduction in coronary death (6.4% vs. 8.3%, NNT 53)
FLORIDA (2000) [20]	540	MI	Fluvastatin 80 mg vs. placebo	1 year	21%	No significant differences in major coronary event
HPS * (2002) [19]	20,536	TC > 135 mg/dL + CAD or other arterial disease or DM or >65 years male w/HTN	Simvastatin 40 mg vs. placebo	5 years	35%	Reduction in all-cause mortality (12.9% vs. 14.7%, NNT 56)

Study	Sample Size	Characteristics of Patients	Comparison Groups	Follow-Up	LDL-C Reduction	CV Effects
PROVE-IT (2004) [22]	4162	ACS < 10 days	Atorvastatin 80 mg vs. pravastatin 40 mg	24 months	31%	Reduction in all-cause mortality, MI, UA hospitalization, revascularization in 30 days, or stroke (HR 0.84, 95% CI 0.74 to 0.95, NNT 53)
IDEAL (2005) [23]	8888	Previous MI	Atorvastatin 80 mg vs. simvastatin 20 mg	4.8 years	20%	No significant differences in major coronary event
TNT (2005) [24]	10,001	CAD	Atorvastatin 80 mg vs. atorvastatin 10 mg	4.9 years	24%	Reduction in CV death, MI, CA, or stroke (HR 0.78, 95% CI 0.69 to 0.89, NNT 45)
SEARCH (2010) [25]	12,064	Previous MI LDL-C > 135 mg/dL (statin use) or LDL-C > 193 mg/dL (no statin)	Simvastatin 20 mg vs. simvastatin 80 mg	6.7 years	14%	No significant differences in CV events

has been raised that specific groups could have clinical benefits from statins.

The Collaborative Atorvastatin Diabetes Study (CARDS) trial tested atorvastatin 10 mg vs. placebo for primary prevention in patients with diabetes and at least one additional risk factor (retinopathy, albuminuria, current smoking, or hypertension), with LDL-C < 160 mg/dL [26]. Although truncated (terminated 2 years earlier due to prespecified efficacy criteria), this trial showed a reduction in CV events (9.0% vs. 3.2%, NNT 32).

The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) trial randomized patients with diabetes in primary (79%) and secondary prevention (21%) to receive atorvastatin 10 mg or placebo [27]. The trial found no difference in the primary endpoint of CV death, MI, stroke, revascularization, worsening UA requiring hospitalization, or resuscitated cardiac arrest. These results can be explained by significant steering disturbances during the trial. Widespread recognition of the importance of CV prevention in diabetes patients led to a recommendation to stop the study medications and allocate all secondary prevention patients and previously primary prevention patients who now met an endpoint to receive usual care. This resulted in a very low completion rate, with only 67% of the intervention group and 58% of the placebo group receiving the study medication at the end of the double-blind follow-up. This reduction in the number of participants reduces the power to detect differences and hinders the evaluation of the results; caution should be taken when using these findings.

Sub-analyses of the HPS and ASCOT-LLA trials with diabetic patients showed that statin reduces CV events [28][29].

Three clinical trials have evaluated the cardiovascular effects of statins in patients with chronic kidney disease [30][31][32]. None of them showed CV benefits of statins in this patient population.

On the other hand, the Study of Heart and Renal Protection (SHARP) showed that ezetimibe/simvastatin, compared to placebo, reduces LDL-C and atherosclerotic and major vascular events in patients with CAD but no overt CAD (11.3% vs. 13.4%, HR 0.83, 95% CI 0.74 to 0.94) [33].

Therefore, CKD patients who are not on dialysis might benefit from statins, with a modest impact, while CKD patients on dialysis do not appear to derive benefits from this therapy.

Patients with HF have often been excluded from statin trials. However, two clinical trials have evaluated the effects of rosuvastatin in patients with chronic symptomatic HF [34][35]. Both trials did not show a reduction in CV events in this population.

An elderly population was exclusively studied in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial [36]. This study showed a reduction in the composite primary outcome of coronary death, MI, and stroke (14.1% vs. 16.2%, HR 0.85, 95% CI 0.74 to 0.97, NNT 48) in the statin group.

People with HIV infection, a group with an increased CV risk, were also analyzed in a recent phase 3 trial. In the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study, 7769 participants with HIV infection were randomized to daily pitavastatin at a dose of 4 mg or placebo. After a median follow-up of 5.1 years, the study was interrupted due to efficacy. The rate of MACEs was 4.81 and 7.32 per 1000 person years in the pitavastatin and placebo groups, respectively (HR 0.65, 95% CI 0.48 to 0.90, p = 0.002). Muscle-related symptoms and incident diabetes were more common in the pitavastatin group [37].

Finally, a meta-analysis of data from 170,000 patients evaluated statin vs. placebo and different statin regimens and reported a 10% reduction in all-cause mortality per 38 mg/dL LDL-C reduction (HR 0.90, 95% CI 0.87 to 0.93) [38]. In an unweighted analysis of the 21 placebo-controlled trials included, any major vascular event occurred in 3.6% in the placebo groups vs. 2.8% in the statin groups, translating into a 0.8% ARR and a 22% RRR. Regarding higher- vs. lower-intensity regimens, higher-intensity regimens led to reductions in major vascular events (RRR 15%, 95% CI 11 to 18), especially when weighted for LDL-C reductions (RRR per 1 mmol/L reduction in LDL-C), suggesting that greater reductions in LDL-C accompany greater reductions in MACEs.

The evidence presented so far establishes the relationship between intervention and effect, and statins reduce CV events. The magnitude of benefits should, however, always permeate clinical reasoning, and NNTs ranging from 30 to much higher numbers have been found. The higher the baseline risk, the greater benefit that should be expected from statins. There is a logical chain binding CV risk factors, CV disease, and death. Treating one will probably affect the other but with progressively smaller magnitude. On the other hand, benefits in the discussed trials above seem to increase over time, which is expected since risk factors may be lifelong cumulative. Trials tend to follow patients over the course of a few years, and potential long-term benefits should be taken into account. The

concepts proven with the studies above should be used as tools to individualize decision making for each particular patient.

Table 3. Statins in special groups. Legend: ACS: acute coronary syndrome; CHD: coronary heart disease; CKD: chronic kidney disease; CV: cardiovascular; DM: diabetes mellitus; LVEF: left ventricular ejection fraction; HIV: human immunodeficiency virus; MACEs: major cardiovascular events; MI: myocardial infarction; NYHA: New York Heart Association; TGs: triglycerides.

Study	Sample Size	Characteristics of Patients	Comparison Groups	Follow-Up	LDL-C Reduction	CV Effects
CARDS (2004) [26]	2838	DM (40–75 years) + LDL-C < 160 mg/dL + TGs < 600 mg/dL + additional risk factor	Atorvastatin 10 mg vs. placebo	3.9 years	40%	Reduction in ACS, revascularization, or stroke (HR 0.63, 95% CI 0.48 to 0.83, NNT 31)
ASPEN (2006) [27]	2410	Diabetes (40–75 years) + LDL < 160 mg/dL or < 140 mg/dL (prior MI or revascularization)	Atorvastatin 10 mg vs. placebo	4 years	29%	No significant differences in CV events
ALERT (2003) [30]	2102	Renal or combined renal and pancreas transplants > 6 months	Fluvastatin 40 mg vs. placebo	5.1 years	25%	No significant differences in CV events
4D (2005) [31]	1255	Diabetes + CKD on dialysis	Atorvastatin 20 mg vs. placebo	4 years	42%	No significant differences in CV events
AURORA (2009) [32]	2773	CKD on dialysis	Rosuvastatin 10 mg vs. placebo	3.8 years	43%	No significant differences in CV events
SHARP (2011) [33]	9270	CKD	Simvastatin 20 mg + ezetimibe 10 mg vs. placebo	4.9 years	31%	Reduction in coronary death, MI, stroke, or revascularization (HR 0.83, 95% CI 0.74 to 0.94, NNT 53)
CORONA (2007) [34]	5011	LVEF < 40% + NYHA II–IV	Rosuvastatin 10 mg vs. placebo	2.7 years	45%	No significant differences in CV events
GISSI-HF (2008) [35]	6975	Heart failure NYHA II–IV	Rosuvastatin 10 mg vs. placebo	3.9 years	16%	No significant differences in CV events

Study	Sample Size	Characteristics of Patients	Comparison Groups	Follow-Up	LDL-C Reduction	CV Effects
PROSPER (2002) [36]	5804	Elderly (70–82 years) + high CV risk	Pravastatin 40 mg vs. placebo	3.2 years	34%	Reduction in coronary death, MI, or stroke (HR 0.85, 95% CI 0.74 to 0.97, NNT 48)
REPRIEVE (2023) [37]	7769	HIV	Pitavastatin 4 mg vs. placebo	5.1 years	30%	Reduction in MACEs (HR 0.65, 95% CI 0.48 to 0.90)

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