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STATIN THERAPY AND LIPID GOAL ATTAINMENT IN PATIENTS WITH CORONARY ARTERY DISEASE

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Abstract

Statins reduce cardiovascular events in people with coronary artery disease in proportion to the fall in LDL cholesterol, and guidelines now recommend progressively lower targets. This narrative review summarises published work on how often those targets are reached in practice; it reports no new patient data. It covers the trial evidence for lower targets, the shifting goals set by American and European guidelines, registry findings on attainment, and barriers such as poor adherence, statin-associated symptoms, measurement error and clinical inertia. Registries consistently show that most patients receive a statin but only a minority reach goal. Evidence on interventions to close the gap is thinner than the evidence for the drugs themselves.

1. INTRODUCTION

Coronary artery disease is still the commonest single cause of death in most high- and middle-income countries, and lowering low-density lipoprotein cholesterol (LDL-C) remains one of the best-established ways of reducing the risk of a further event. The causal role of LDL particles in atherosclerosis rests on genetic, epidemiological and trial evidence that point in the same direction [1]. Statins were the first drugs to prove the case in practice. The Scandinavian Simvastatin Survival Study showed in the mid-1990s that lowering cholesterol in people with established coronary disease reduced mortality [2], and large pooled analyses since then have confirmed a consistent proportional benefit for every unit of LDL-C removed [3, 4, 5].

The difficulty is not a lack of efficacy. It is the distance between what a statin can do in a

trial and what it does in an ordinary clinic. Registries of coronary patients repeatedly find that most are prescribed a statin, yet only a minority reach the LDL-C level their guidelines recommend [6, 7]. This review looks at that gap. It describes the evidence on which LDL-C goals are based, how guideline goals have shifted, what registries report about goal attainment, why patients and prescribers fall short, and what strategies might close the gap. It is a narrative synthesis of published work, and it reports no new patient data.

Goal attainment is a moving target in more than one sense. Each major guideline revision has altered either the number to be reached or the philosophy of reaching it, so a figure quoted for the proportion of patients at goal in one decade cannot be compared directly with a figure from another [8, 9, 10, 11]. The measurement of LDL-C itself introduces further variation, because laboratories estimate it in different ways and the results are affected by fasting state, triglyceride level and timing relative to a recent event [12, 13]. Readers should keep these points in mind when comparing the percentages cited in the sections that follow.

A note on terms helps. In this article statin intensity follows the convention used in the American guidelines, in which high-intensity treatment is expected to lower LDL-C by roughly half or more, moderate intensity by about a third to a half, and low intensity by less than that [9, 10]. Atorvastatin at 40 to 80 mg and rosuvastatin at 20 to 40 mg are the usual high-intensity choices. Goal attainment means reaching the numerical LDL-C threshold set by the guideline in force, not merely being on a statin of a certain dose [8, 9].

2. EVIDENCE FOR LOWER LDL-C TARGETS

The first large trials compared a statin with placebo. In 4S, simvastatin lowered LDL-C by about a third in patients with angina or previous infarction and reduced both coronary events and all-cause mortality over five years [2]. Subsequent meta-analyses by the Cholesterol Treatment Trialists' Collaboration drew the trials together. The 2005 prospective meta-analysis of 14 trials found that each 1 mmol/L reduction in LDL-C reduced the risk of major vascular events by about a fifth, whatever the baseline level [5]. The later individual-patient analysis confirmed a proportional reduction of roughly 22% per mmol/L, and that more intensive regimens produced a further reduction of around 15% over less intensive ones [3].

Head-to-head trials of high- versus moderate-intensity therapy gave the clearest support for treating to lower levels. In PROVE IT, patients hospitalised with an acute coronary syndrome who received atorvastatin 80 mg reached a median on-treatment LDL-C of about 62 mg/dL, compared with 95 mg/dL on pravastatin 40 mg, and had fewer major events within two years [14]. TNT randomised people with stable coronary disease to atorvastatin 80 mg or 10 mg, with mean LDL-C values near 77 and 101 mg/dL, and the higher dose produced a relative reduction of about a fifth in major cardiovascular events [15]. IDEAL used a different comparator, and its primary endpoint missed statistical significance, though several secondary outcomes favoured the high dose [16].

Imaging studies add a biological rationale. In ASTEROID, treatment with rosuvastatin 40 mg lowered LDL-C to around 60 mg/dL and was accompanied by regression of coronary atheroma on intravascular ultrasound, the first time that a statin alone had been shown to do this on average across a group [17]. GLAGOV later tested a PCSK9 antibody in people already on statins, taking mean LDL-C down to about 37 mg/dL and producing further regression in plaque volume compared with placebo [18]. Imaging cannot replace outcomes, but together these trials suggest that plaques respond to lipid lowering in a graded manner, with little sign of a floor within the range tested [17, 18].

Outcome trials of non-statin drugs allowed the lower-is-better hypothesis to be tested at levels that statins alone seldom reach. IMPROVE-IT added ezetimibe to simvastatin after an acute coronary syndrome, lowered median LDL-C from 70 to 54 mg/dL, and produced a small but significant reduction in events [19]. FOURIER gave evolocumab on

top of statin treatment and achieved a median LDL-C near 30 mg/dL, with about a 15% relative reduction in its primary composite endpoint [20]. ODYSSEY OUTCOMES gave alirocumab after acute coronary syndrome with a similar relative effect, and a larger absolute gain among those whose baseline LDL-C was highest [21]. The earlier alirocumab programme had already shown a large reduction in LDL-C on top of maximum tolerated statin [22].

Questions about very low LDL-C have not materialised as safety problems in the trials so far. A meta-analysis that grouped patients by baseline LDL-C found that lower achieved levels were associated with lower mortality, without an obvious increase in harm at the bottom of the range [23]. The Cholesterol Treatment Trialists reported no excess of adverse events with more intensive regimens beyond the small known increase in diabetes diagnosis and rare myopathy [3, 24, 25]. Another analysis showed that, among statin-treated patients, apolipoprotein B and non-HDL cholesterol discriminated risk better than LDL-C when the measures disagreed [26]. This is relevant to goal-setting, though guidelines have mostly kept LDL-C as the main target [8, 9].

Who benefits is another question the pooled data can answer. The 2015 individual-patient analysis found that the proportional reduction in major vascular events per unit of LDL-C lowering was similar in women and men, although women have often been prescribed lower-intensity regimens in practice and were fewer in the trials [4]. Older participants gained as well, and the relative effect did not fall away at the upper end of the age range studied, which matters in a disease that is concentrated in people over 65 [3, 4]. Participants at lower baseline risk in the meta-analysis of low-risk groups showed the same proportional effect and no increase in non-vascular mortality, though the absolute gain was smaller [25].

Absolute benefit does not rise uniformly with intensity. People at lower baseline risk gain little in absolute terms from additional lowering, and a statin may even be unnecessary for those with a low probability of an event [25]. For secondary prevention the calculation is different, because annual event rates are high enough that a relative reduction of 15 to 20 per cent translates into a large number of events avoided. The same analysis that justified lowering LDL-C in low-risk groups also showed that the proportional effect was similar across subgroups, which supports the logic of setting goals by risk category rather than by LDL-C level alone [23, 25].

3. EVOLUTION OF GUIDELINE GOALS

Guideline bodies have not agreed on how to apply this evidence. The 2013 American guideline dropped numerical targets altogether and recommended fixed-intensity statin therapy for defined groups, on the grounds that the major trials had tested doses and not targets [10]. European guidance kept targets, and the 2016 ESC/EAS document recommended an LDL-C below 70 mg/dL, or at least a 50% reduction from baseline when that level could not be reached, for patients at very high risk, a category that includes established coronary disease [11]. The two approaches differ most in what happens after the statin is started. One stops; the other asks for a measurement and a decision.

Later documents have narrowed the gap. The 2016 ACC decision pathway introduced LDL-C thresholds that, if exceeded on maximally tolerated statin, should prompt the addition of ezetimibe or a PCSK9 inhibitor [27]. The 2018 AHA/ACC multisociety guideline kept a statin-first approach but set an LDL-C threshold of 70 mg/dL in very-high-risk patients for considering ezetimibe, followed by a PCSK9 inhibitor [9]. The 2019 ESC/EAS guideline went further and recommended both a 50% reduction and an absolute goal below 55 mg/dL for very-high-risk patients, with an even lower figure of 40 mg/dL proposed for those who have a second vascular event within two years [8].

These revisions have a straightforward consequence for attainment figures. When the goal moves from 70 to 55 mg/dL, a patient who was at goal last year may be above it this year without any change in treatment. A Swedish simulation using national data on patients with a recent myocardial infarction

suggested that, under the 2019 European goals, a large majority would need treatment beyond a statin and that even optimal use of ezetimibe would leave many above threshold [28]. This is not a reason to avoid stricter goals. It does mean that the share of patients at goal is partly a product of the guideline in force, and that proportions must be read alongside the target being used [8, 28].

Whether goals are a sound principle at all has been argued for a decade. Supporters note that individual responses to the same dose vary widely, so a fixed dose can leave one patient at 50 mg/dL and another at 100, and that a target gives a reason to intensify treatment [11, 26]. Critics note that the large statin trials randomised to doses and not to targets, so the benefit of aiming at a number is inferred and not demonstrated directly [10]. On-treatment analyses suggest that risk follows the achieved level closely, which favours measurement, and apolipoprotein B or non-HDL cholesterol may capture residual risk better than LDL-C alone [26]. The debate is unresolved, and both positions find some support in the data [10, 11, 26].

4. GOAL ATTAINMENT IN PRACTICE

Registry data from clinics tell a consistent story, even if the percentages differ. The fifth EUROASPIRE survey, which examined patients with coronary disease in 27 European countries, found that most were taking a statin but that fewer than a third had an LDL-C below 70 mg/dL, the target in the guidelines of the time [6]. The DA VINCI study analysed lipid-modifying therapy and LDL-C values across several European countries and found that only a minority of very-high-risk patients met the 2016 goals, with attainment lower again under the stricter 2019 goals [7]. Selected findings are summarised in table 1, and the entries are grouped by theme in fig. 1.

American data show a comparable pattern. The GOULD registry followed patients with established atherosclerotic disease over two years and reported that the use of high-intensity statins was far from universal, that add-on non-statin therapy was prescribed to only a small share of those above their LDL-C threshold, and that LDL-C changed little over follow-up for most patients [29]. Treatment intensity at discharge after a coronary event is therefore a decisive moment, and intensity tends to fall rather than rise afterwards. Both the European and the American registries suggest that the first prescription is largely what the patient is left with [6, 29].

Table 1: Selected published evidence relevant to LDL-C goal attainment in coronary artery disease

Study or source	Main finding	Ref.
4S simvastatin, prior CHD	First large secondary-prevention trial to show lower mortality with a statin in coronary disease	[2]
CTT meta-analyses 26 and 27 trials	About one-fifth fewer major vascular events per 1 mmol/L LDL-C reduction, with more intensive regimens adding benefit	[3, 4]
PROVE IT and TNT atorvastatin 80 mg	Lower on-treatment LDL-C and fewer events than with moderate-intensity therapy	[14, 15]
IMPROVE-IT ezetimibe added	Further LDL-C lowering and a modest reduction in events after acute coronary syndrome	[19]
FOURIER and ODYSSEY OUTCOMES	PCSK9 antibodies cut LDL-C sharply and reduced events in statin-treated patients	[20, 21]
CLEAR Outcomes bempedoic acid	Modest reduction in major events in statin-intolerant patients	[30]
ACC/AHA 2013 and ESC/EAS 2016	Fixed-intensity statin approach versus explicit LDL-C targets for very-high-risk patients	[10, 11]
ESC/EAS 2019	Goal below 55 mg/dL plus at least 50% reduction in very-high-risk patients	[8]
EUROASPIRE V 27 countries	Most coronary patients took statins, yet fewer than a third had LDL-C below 70 mg/dL	[6]
DA VINCI European registry	Minority met 2016 goals; attainment lower again with the stricter 2019 targets	[7]
Adherence meta-analysis	About half of secondary-prevention patients take medicines as prescribed; poor adherence linked to more events	[31]

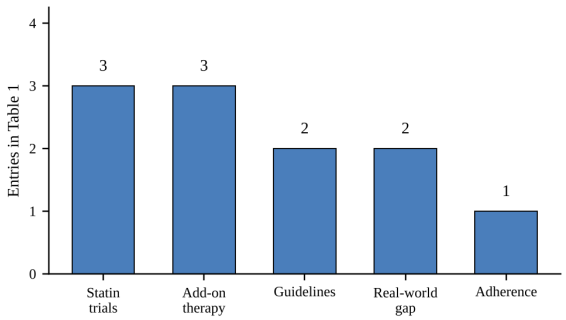


Fig. 1: Number of entries in table 1 by evidence theme

Outcomes data show that the gap matters. In a Swedish nationwide cohort of patients after myocardial infarction, those who reached lower LDL-C values, and those treated with high-intensity statins, had fewer major adverse cardiovascular events during follow-up, and the association was graded [32]. This is observational evidence, so confounding by adherence and health status is possible, yet it agrees with the randomised data [3, 14, 15]. The finding also gives pharmacists and clinicians a practical reason to ask what the actual measured LDL-C is, rather than whether a statin is on the medication list [32].

Several features of study design explain why quoted attainment rates are so different. Registries enrol different populations, from recent infarction to long-standing stable disease, and the time since the event affects both the prescribed regimen and the measured LDL-C. They define goals differently and use different laboratory methods, with some calculating LDL-C and others measuring it directly [12, 13]. Some use a single value, others the lowest or latest value on record. Participation bias is also likely, because centres that join a registry may manage lipids better than average [6, 7, 29]. For these reasons the figures should be read as a range of plausible values, not as national estimates.

Registry populations differ from trial populations in ways that matter here. Trials of intensive therapy generally enrol patients who are willing to attend frequent visits and who tolerate a run-in period on the study drug, and their adherence is monitored. Registry patients include people who are older, frail, on many other drugs or lost to follow-up after discharge. When a registry shows lower attainment than a trial, part of the difference reflects who is included and how closely they are watched, not only a failure of care, and the registries themselves note this limitation [6, 7, 29].

5. BARRIERS TO REACHING GOAL

Adherence is the largest single barrier. A meta-analysis of studies in cardiovascular prevention found that only around half of patients in secondary prevention took their medicines as prescribed, and that poor adherence was associated with a higher risk of cardiovascular events [31]. In a large study of patients with established atherosclerotic disease, those with better statin adherence had lower mortality than those who took the drug irregularly, with a dose-response pattern [33]. Non-adherence also inflates the apparent failure of a drug. A patient who takes atorvastatin on four days out of seven will have an LDL-C that looks like resistance to treatment, when it is actually missed doses [31, 33].

Tolerability is the second theme, and it is complicated by the nocebo effect. Statin-associated muscle symptoms are the commonest reason given for stopping, yet blinded trials report similar rates of muscle complaints in statin and placebo groups, and the Cholesterol Treatment Trialists concluded that most of the symptoms attributed to statins in routine care are not due to the drug [24]. A cohort study of statin discontinuation in routine care found that a considerable share of patients stopped because of a perceived adverse event, and many of those who were rechallenged could tolerate a statin again [34]. The European Atherosclerosis Society has published a structured approach to assessment, rechallenge with a different statin or dose, and alternative regimens [35].

Patients' own accounts are informative. A large internet-based survey of current and former statin users in the United States found that many of those who had stopped did so without a clinician's advice, and that worries about side effects and about taking long-term medicines were common among them [36]. Many respondents also believed that lifestyle changes alone would be enough or that they could take a break from the treatment. These

beliefs are open to change, but only if someone asks about them. A short conversation at the pharmacy counter or in a clinic about why the statin matters after a coronary event may be more effective than another prescription [33, 36].

Genetic and pharmacokinetic factors play a smaller but real role. A genome-wide study identified a common variant in the SLCO1B1 gene, which codes for a hepatic uptake transporter, that strongly increases the risk of myopathy with high-dose simvastatin [37]. The finding explains why high-dose simvastatin has been largely replaced by atorvastatin and rosuvastatin in secondary prevention. Drug interactions that raise statin exposure, such as those with certain macrolides, azole antifungals and some calcium-channel blockers, also contribute, as does the older age and renal impairment of many coronary patients. Awareness of these factors helps prescribers to select a regimen that the patient is more likely to continue [35, 37].

Lifestyle and associated conditions complicate lipid control. The EUROASPIRE V survey found high rates of obesity, persistent smoking and poorly controlled blood pressure or glycaemia in coronary patients, alongside the shortfall in LDL-C control, and relatively few had attended a prevention or rehabilitation programme [6]. Diet, weight and physical activity change LDL-C modestly, but they matter for overall risk and for triglycerides, which in turn affect how LDL-C is estimated [6, 12]. Patients juggling several new medicines after an infarction may also give priority to antiplatelet and blood pressure tablets, and the statin can slip down their list unless it is reinforced at each contact [6, 31].

Therapeutic inertia sits on the prescriber's side of the problem. A clinician who sees an LDL-C of 80 mg/dL in a patient on a moderate statin may consider it acceptable, particularly when the previous value was well above 100, and the next appointment may be months away. The registries suggest that dose titration and add-on therapy are used less often than the guidelines imply, even in patients far above threshold [7, 29]. Some of this is reasonable clinical judgement, because multimorbidity, frailty and polypharmacy are common. Some is the product of systems in which nobody is responsible for the lipid result after discharge, a problem that is organisational more than clinical [6, 7].

Cost and access limit the use of newer agents. PCSK9 antibodies are effective but expensive and require injections, and in many countries their use is restricted to patients with very high LDL-C despite maximum oral therapy, with prior authorisation that adds to delay [7, 20, 21]. Ezetimibe is inexpensive and available as a generic, yet registries show that it is added less often than guidelines would predict [7, 29]. In such settings the cheapest route to improved attainment is often to maximise the statin and add ezetimibe early, before considering injectables [8, 27]. Where an injectable is unavoidable, support with self-injection technique and refill reminders matters, since adherence to a fortnightly or monthly injection is also imperfect [20, 21, 31].

6. MEASURING AND MONITORING LDL-C

Attainment can only be judged as accurately as LDL-C is measured. Most laboratories still estimate LDL-C from total cholesterol, HDL cholesterol and triglycerides with the Friedewald equation, which assumes a fixed ratio of triglyceride to very-low-density lipoprotein cholesterol [12]. The assumption fails at high triglyceride levels and tends to underestimate LDL-C when the true value is low, which is exactly the range that matters for current goals. A later method that uses an adjustable factor derived from a very large laboratory database agreed better with direct measurement at low LDL-C and high triglycerides [13]. Choosing the method therefore affects whether a given patient appears to be at goal.

Monitoring has its own conventions. Guidelines advise repeating the lipid profile some four to twelve weeks after starting or changing treatment, and then every year or so if the patient is stable [8, 9]. A non-fasting sample is generally acceptable, and apolipoprotein B or non-HDL cholesterol can supplement the report in patients with raised triglycerides, diabetes or very low LDL-C [8,

26]. In practice the first check is often missed, which delays recognition that a patient is above threshold. Because values fluctuate from one visit to the next, a single reading just above or below a threshold should be interpreted with care [8, 9, 12].

Biological and analytical variation may be modest compared with the gap between treatment intensity and need, but it creates apparent responders and non-responders. A patient whose LDL-C was 72 mg/dL last time and 68 mg/dL this time has not necessarily improved, and regression to the mean makes patients selected for a high value look better at the next measurement even without any change [12, 13]. For this reason the focus in practice should be on sustained patterns, treatment decisions at each visit and the ratio of change from baseline, as recommended by European guidance [8, 11]. Recording the baseline value before treatment starts is surprisingly often neglected, and without it a percentage reduction cannot be calculated at all [8, 11].

7. STRATEGIES TO CLOSE THE GAP

The first strategy is to start strongly. Following an acute coronary syndrome, a high-intensity statin should be given early and in full dose, not titrated upwards over months, since the trial evidence for early intensive treatment is strong and the discharge prescription tends to persist [9, 14, 32]. Lipid-lowering plans documented in discharge letters, with a named person responsible for the first follow-up check, are an obvious operational step. Atorvastatin and rosuvastatin remain the usual first choices, and switching rather than stopping is a sensible first response to side effects [35, 37].

The second strategy is early combination therapy. Because the LDL-C reduction from adding ezetimibe to a maximal statin is about a fifth, and that from a PCSK9 antibody is more than half, simple arithmetic shows that many very-high-risk patients cannot reach 55 mg/dL on a statin alone [19, 20, 22, 28]. Guidance has accordingly moved towards stepwise addition of ezetimibe and then a PCSK9 inhibitor when the threshold is not reached [8, 9, 27]. Some experts advocate starting combination treatment at the outset in patients whose baseline LDL-C is far above goal, but randomised trials comparing early with sequential combination are still needed [8, 28].

A third group of options is directed at the statin-intolerant patient. Bempedoic acid, an oral inhibitor of ATP citrate lyase, lowered LDL-C by about a fifth beyond background therapy in high-risk patients who were taking maximally tolerated statins [38], and an outcome trial in statin-intolerant patients later reported a modest reduction in major cardiovascular events [30]. PCSK9 antibodies are an alternative when oral drugs are insufficient [20, 21]. These agents expand the choices for people who cannot take standard doses, though the sample sizes and follow-up periods of these trials remain smaller than those of the long-running statin programmes [30, 38].

Even good control leaves a residual risk, and this should be explained to patients and clinicians alike. In the PCSK9 outcome trials, participants who reached very low LDL-C still had a substantial rate of further events over the follow-up period, and the absolute benefit was greatest in those with the highest baseline risk, such as recent myocardial infarction, multivessel disease or diabetes [20, 21]. This is the argument for targeting resources at the highest-risk patients first. It is also a reminder that LDL-C lowering is one component of secondary prevention, which also includes antithrombotic treatment, blood pressure control, smoking cessation and rehabilitation [6, 9].

System-level interventions are widely proposed, but their evidence is less direct. Pharmacist-led lipid clinics, nurse-run follow-up after myocardial infarction, automated reminders linked to laboratory results and shared decision-making tools all aim at the adherence and inertia problems identified earlier [7, 31, 33]. They are plausible and relatively cheap. Their effects on LDL-C and outcomes have been reported with differing levels of rigour, so claims should be treated with caution until larger and better-designed evaluations are available. Pharmacy teams are well placed to repeat the key message that LDL-C, once above goal, is a treatable risk factor [31, 36].

8. LIMITATIONS AND FUTURE DIRECTIONS

This review has several limitations. It is narrative, so the selection of studies reflects the authors' judgement and may favour well-known trials. The registries cited differ in countries, years, methods and definitions, and their results cannot be pooled. Most of the attainment data predate the 2019 goals or reflect only the early period of their adoption [6, 7, 8]. The observational outcome data on LDL-C reduction are subject to confounding [32]. Newer agents are described with data from trials whose follow-up is still limited, and some real-world uptake data come from health systems that may not match those of the reader [29, 30, 38].

Several questions deserve research. Randomised trials of strategy, such as a treat-to-target approach versus fixed-dose therapy, or early versus stepwise combination therapy, would answer questions that guidelines now settle by consensus [8, 10, 28]. Implementation studies that test the effect of pharmacist or nurse follow-up on LDL-C and event rates are needed, as are better data on women, older adults and people with multimorbidity, who are under-represented in trials [4, 6]. Finally, standardised reporting of attainment in registries, with the threshold, assay and time since event stated, would allow fairer comparison between countries and years [7, 12, 13].

9. CONCLUSION

The case for lowering LDL-C in coronary artery disease is as firm as any in cardiovascular medicine. Trials of statins, ezetimibe and PCSK9 antibodies agree that lower on-treatment levels bring fewer events, with no clear safety signal at the levels reached so far [3, 19, 20, 23]. Guidelines have responded by moving towards stricter and more explicit goals, though American and European documents still differ in method [8, 9, 10, 11]. Registries from several countries show that these goals are met by only a minority of patients [6, 7, 29].

Closing the gap will need action on several fronts at once. High-intensity statin treatment should begin early, adherence and symptoms deserve systematic attention, and combination therapy should be added without delay when the threshold is missed [9, 27, 31, 35]. Measurement should be reliable and the target reported alongside any attainment figure [12, 13]. For pharmacists and clinicians the practical message is simple: ask for the latest LDL-C value, compare it with the goal that applies to that patient, and act on the difference [8, 32].

10. ABBREVIATIONS

LDL-C-Low-density lipoprotein cholesterol, PCSK9-Proprotein convertase subtilisin/kexin type 9, ESC-European Society of Cardiology, EAS-European Atherosclerosis Society, AHA-American Heart Association, ACC-American College of Cardiology, HDL-High-density lipoprotein, ATP-Adenosine triphosphate, CTT-Cholesterol Treatment Trialists' Collaboration

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12. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

13. CONFLICT OF INTERESTS

Declared none

14. REFERENCES

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