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Mathematical modelling of the most effective goal of cholesterol-lowering treatment in primary prevention

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ABSTRACT

Objective To compare quantitatively different recommended goals for cholesterol-lowering treatment in the primary prevention of atherosclerotic cardiovascular disease (ASCVD).

Design Outcomes at pretreatment low-density lipoprotein (LDL) cholesterol concentrations from 2 to 5 mmol/L and 10-year ASCVD risk from 5% to 30% were modelled, using the decrease in risk ratio per mmol/L reduction in LDL cholesterol derived from randomised controlled trials (RCTs) of cholesterol-lowering medication.

Data source Summary statistics from 26 RCTs comparing treatment versus placebo or less versus more effective treatment and 12 RCTs in which statin was compared with a higher dose of the same statin or with a similar statin dose to which an adjunctive cholesterol-lowering drug was added.

Setting The different recommended goals are: (1) LDL cholesterol≤2.6 mmol/L (100 mg/dL); (2) LDL cholesterol≤1.8 mmol/L (70 mg/dL); (3) non-high density lipoprotein (HDL) cholesterol decrease of ≥40%; or (4) LDL cholesterol≤1.8 mmol/L (70 mg/dL) or decreased by ≥50% whichever is lower.

Participants RCT participants.

Interventions Statins alone or in combination with ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors.

Main outcome measures For each of the recommended therapeutic goals, our primary outcome was the number of events prevented per 100 people treated for 10 years (N_{100}) and the number of needed to treat (NNT) to prevent one event over 10 years.

Results At pretreatment LDL cholesterol 4–5 mmol/L, all four goals provided similar benefit with N_{100} 1.47–16.45 (NNT 6–68), depending on ASCVD risk and pretreatment LDL cholesterol. With initial LDL cholesterol in the range 2–3 mmol/L, the target of 2.6 mmol/L was the least effective with N_{100} between 0 and 2.84 (NNT 35–infinity). The goal of 1.8 mmol/L was little better. However, reductions in non-HDL cholesterol by ≥40% or of LDL cholesterol to 1.8 mmol/L and/or by 50%, whichever is lower, were more effective, delivering N_{100} of between 0.9 and 9.33 (NNT 11–111). Percentage decreases in LDL cholesterol or non-HDL cholesterol concentration are more effective targets than absolute change in concentration in people with initial values of <4 mmol/L.

Conclusions The LDL cholesterol target of 1.8 mmol/L is most effective when initial LDL cholesterol is >4 mmol/L. The time has probably come for the LDL cholesterol goal of <2.6 mmol/L to be abandoned.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We compared clinically relevant outcome (number needed to treat and atherosclerotic cardiovascular disease (ASCVD) events prevented per 100 people treated over 10 years) when different recommended therapeutic targets for cholesterol-lowering treatment were applied to people with commonly encountered low-density lipoprotein (LDL) cholesterol ranging from 2 to 5 mmol/L.
⇒ Our mathematical model is derived from ASCVD incidence and LDL cholesterol reduction in previously published meta-analyses of randomised controlled trial (RCT) results.
⇒ We applied our method to a spectrum of ASCVD risk expressed as number of events occurring in 100 people (%) over 10 years as recommended in clinical guidelines from 5% and above.
⇒ Guidelines are generalisations and individual therapeutic responses may in practice differ from those of participants in RCTs.
⇒ The effectiveness of treatment will be affected if adherence in clinical practice differs from that in RCTs.

INTRODUCTION

Statins consistently show a reduction in atherosclerotic cardiovascular disease (ASCVD) incidence in actively treated people relative to controls across a broad range of absolute ASCVD risk from <5% to >50% over 10 years.[1] This means that a proportion of people from middle age onwards will have sufficient ASCVD risk in order to benefit from statin treatment even though they have no current or previous clinical evidence of ASCVD (primary prevention). There is a reasonable consensus among those framing guidance for cholesterol-lowering treatment that in secondary prevention and particularly high-risk primary prevention, including people with familial hypercholesterolaemia, numerical goals for low-density lipoprotein (LDL) cholesterol, such as 1.8 mmol/L (70 mg/dL) or even lower, should be the target of treatment with statins with the addition of ezetimibe

and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition when necessary.[2 3] However, the majority of ASCVD events arise not from high-risk, high cholesterol individuals, but from people with not more than average risk and average LDL cholesterol levels, although at lower risk they are much more frequent.[4] Thus, in order to attain the greatest population impact, statins should be widely deployed. However, the question arises as to how best to direct statins to those who achieve benefit while, despite their safety,[5] avoiding prescribing them to those who may not. This has indeed proved to be a thorny issue.

Current guidelines generally recommend statins to be considered when ASCVD risk is between 5% and 10% over the next 10 years, taking into account a range of other factors.[2 3 6] Often, it is not made clear that statin effectiveness is determined not only by the pretreatment absolute ASCVD risk but also by the pretreatment LDL cholesterol concentration, which is a determinant of the extent to which reduction is possible.[7 8] The reduction in relative ASCVD risk per mmol/L decrease in LDL cholesterol of 22% is similar regardless of its pretreatment value.[1 8] However, the absolute benefit in terms of reduction in ASCVD incidence varies widely with absolute risk and the extent to LDL cholesterol reduction (in term of mmol/L rather than percentage decrease) is achieved.[7 8] To a large extent, the latter will depend not only on the initial LDL cholesterol concentration but also on the level at which treatment is aimed. Although crucial, therapeutic goals differ considerably between guidelines.[2 3 6] Some set a higher target for people at lower risk than for those at higher risk. Both in Europe and the USA, the goal for many people with average risk and average LDL cholesterol is 2.6 mmol/L (100 mg/dL).[2 3] For similar people, the National Institute for Healthcare and Clinical Excellence (NICE) guidelines recommend fixed-dose statin treatment that is usually atorvastatin 20 mg daily (typically producing a 43% decrease in LDL cholesterol[6]) or an equivalent dose of another statin.[6] There is the rider that treatment may be intensified in compliant patients achieving <40% decrease in non-HDL cholesterol. The effect of statins on very LDL (VLDL) cholesterol is smaller in percentage terms than that on LDL and furthermore prevailing VLDL cholesterol concentrations are low unless substantial hypertriglyceridaemia is present.[9] So essentially the target for LDL cholesterol lowering set by NICE is a decrease by ≥40%. The European[2] and the USA[3] guidance provides additional LDL cholesterol targets of ≤1.8 mmol/L (100 mg/dL) in higher-risk patients and the former also sets a goal for LDL cholesterol reduction of ≥50%. Thus, if this is interpreted as a target of 1.8 mmol/L or 50% reduction, whichever is the lower, yet another potential therapeutic aim is created.

We have assessed the likely outcome of the various therapeutic targets in terms of the number of ASCVD events prevented per 100 people receiving cholesterol-lowering treatment (N_{100}) and the number needed to receive treatment to prevent one event (NNT).[5]

METHODS

For a full description of the equations to calculate N_{100} and NNT see our earlier publications.[5 7 8] The equation we have used is

N_{100}=ASCVD risk×(1−[$0.78^{\text{LDL cholesterol decrease}}$]), when LDL cholesterol is in mmol/L. Where 0.78 is a constant which derived from meta-analysis of randomised trials of statins[1] and applies equally to LDL cholesterol reduction with ezetimibe and PCSK9 inhibition.[8] N_{100} is the number of ASCVD events prevented in the next 10 years per 100 people treated and ASCVD risk is fatal and non-fatal ASCVD events per 100 people over the next 10 years without cholesterol-lowering treatment (the metric estimated in risk engines recommended in the USA[3] and NICE[6] recommendations). In the current European recommendations, only fatal events are predicted which are 3–4 times fewer.[2] The term $0.78^{\text{LDL cholesterol reduction}}$ is the change in the ratio of ASCVD events due to the reduction in LDL cholesterol in mmol/L[7 10] (or $0.9936^{\text{LDL cholesterol reduction}}$ in mg/dL[11]) in statin-treated people to those not receiving statin. The term $1–0.78^{\text{LDL cholesterol reduction}}$ is thus the proportionate decrease in ASCVD incidence in statin-treated people for the reduction in LDL cholesterol. For example, when no decrease occurs ASCVD risk is unchanged (0.78^0=1). If, however, LDL cholesterol is decreased by 1.5 mmol/L, the risk of ASCVD declines by $1–078^{1.5}$=1–0.69=0.31 or 31%. When absolute ASCVD risk in the next 10 years is 10% (10 events per 100 people), risk is reduced by 10×0.31=3.1 per 100 people treated. This is N_{100}. The NNT is $100/N_{100}$. In this case 100/3.1=32. Thus, 32 such people achieving a decrease of 1.5 mmol/L in LDL cholesterol must be treated for 10 years to prevent one ASCVD event.

Statement of patient or public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Number of ASCVD events prevented per 100 people treated for 10 years (N_{100})

There are substantial differences in N_{100} (tables 1–4). The LDL cholesterol goal of 2.6 mmol/L (table 1) is the least effective when pretreatment LDL cholesterol is <4 mmol/L. Aiming for 1.8 mmol/L produces some improvement in the N_{100} at LDL cholesterol<4 mmol/L (table 2). Decreasing the non-HDL cholesterol by 40% leads to a further improvement with initial LDL cholesterol<4 mmol/L, but is least effective at higher levels (table 3). Overall, the doctrine of decreasing LDL

Table 1 ASCVD events prevented per 100 people (N_{100}). Goal: LDL cholesterol reduced to 2.6 mmol/l

	Pre-treatment LDL cholesterol (reduction) mmol/l			
ASCVD risk	2 (0)	3 (0.4)	4 (1.4)	5 (2.4)
5.00%	0	0.47	1.47	2.25
7.50%	0	0.71	2.2	3.37
10.00%	0	0.95	2.94	4.49
15.00%	0	1.42	4.4	6.74
20.00%	0	1.89	5.87	8.98
30.00%	0	2.84	8.81	13.47

ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein.

Table 3 ASCVD events prevented per 100 people (N_{100}). Goal: non-HDL cholesterol reduced by 40%

	Pre-treatment LDL cholesterol (reduction) mmol/l			
ASCVD risk	2 (0.8)	3 (1.2)	4 (1.6)	5 (2.0)
5%	0.9	1.29	1.64	1.96
7.50%	1.35	1.93	2.46	2.94
10%	1.8	2.58	3.28	3.92
15%	2.7	3.87	4.92	5.87
20%	3.61	5.16	6.56	7.83
30%	5.41	7.73	9.84	11.75

ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein.

cholesterol to either 1.8 mmol/L or by 50%, whichever is lower, provides the most effective outcome (table 4).

Number needed to treat for 10 years to prevent one ASCVD event (NNT)

Figure 1A–C shows the NNTs for pretreatment LDL cholesterol from 2 to 5 mmol/L for three representative degrees of 10-year ASCVD risk, 7.5%, 15% and 30% for four LDL cholesterol treatment goals (data presented in online supplemental table 1A–C). At all three degrees of ASCVD risk, the curves shift downwards on the NNT axis and to the left on the pretreatment LDL cholesterol axis to indicate an improvement (decrease) in NNTs as pretreatment LDL cholesterol and ASCVD risk increase. NNTs for a target LDL of 2.6 mmol/L are highest with values of <30 being achieved with an ASCVD risk of >7.5% over 10 years only when initial LDL cholesterol is ≥5 mmol/L (figure 1A). The LDL cholesterol concentration goal of 1.8 mmol/L, but with ASCVD risk 7.5%, does not reach NNT<30 until pretreatment LDL cholesterol levels exceed 4 mmol/L and only when ASCVD risk reaches 30% is NNT of <30 achieved at initial LDL cholesterol levels exceeding 2.5 mmol/L. Decreasing LDL cholesterol by 40% is, however, more effective in terms of reducing NNTs at lower pretreatment LDL cholesterol concentrations and aiming to lower LDL cholesterol to 1.8 mmol/L or by 50% whichever is lower is even more so. At higher initial LDL cholesterol levels of 4–5 mmol/L, the four therapeutic LDL cholesterol targets tested were similarly effective in each category of risk, but it should not be concluded that percentage targets continue to be as effective as is lowering LDL cholesterol to 1.8 mmol/L or less at even higher LDL cholesterol concentrations (see the Discussion section).

Table 2 ASCVD events prevented per 100 people (N_{100}). Goal: LDL cholesterol reduced to 1.8 mmol/l

	Pre-treatment LDL cholesterol (reduction) mmol/l			
ASCVD risk	2 (0.2)	3 (1.2)	4 (2.2)	5 (3.2)
5%	0.24	1.29	2.11	2.74
7.50%	0.36	1.93	3.16	4.11
10%	0.48	2.58	4.21	5.48
15%	0.73	3.87	6.32	8.23
20%	0.97	5.16	8.42	10.97
30%	1.45	7.73	12.63	16.45

ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein.

DISCUSSION

Our most important conclusion is that cholesterol lowering to fixed LDL cholesterol targets is clinically ineffective in people whose initial LDL cholesterol is <4 mmol/L, particularly when they are at low ASCDV risk, and should no longer be practised. It does not produce a worthwhile return in terms of ASCVD prevention. This is important because the majority of people destined to experience an ASCVD event will have LDL cholesterol concentrations in the range 3–4 mmol/L, close to the average for the population in Europe and the USA.[4 12–15]

Table 4 ASCVD events prevented per 100 people (N_{100}). Goal: LDL cholesterol reduced to 1.8 mmol/l or by 50%, whichever is lower

	Pre-treatment LDL cholesterol (reduction) mmol/l			
ASCVD risk	2 (1.0)	3 (1.5)	4 (2.2)	5 (3.2)
5%	1.1	1.56	2.11	2.74
7.50%	1.65	2.33	3.16	4.11
10%	2.2	3.11	4.21	5.48
15%	3.3	4.67	6.32	8.23
20%	4.4	6.22	8.42	10.97
30%	6.6	9.33	12.63	16.45

ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein.

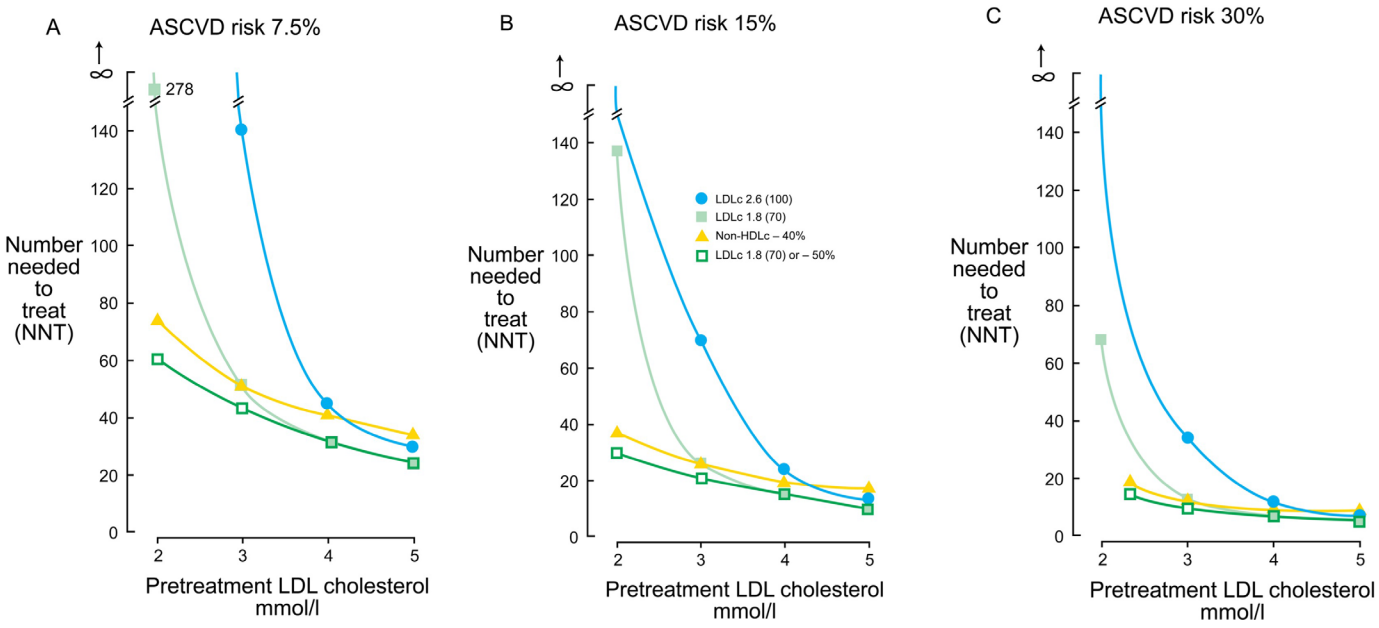

Figure 1 The number needed to treat for 10 years to prevent one ASCVD event over the next 10 years as a function of the pretreatment LDL cholesterol concentration with different recommended treatment goals (A) when pretreatment ASCVD risk is 7.5%, (B) when pretreatment ASCVD risk is 15% and (C) when pretreatment ASCVD risk is 30%. The therapeutic targets are LDL cholesterol 2.6 mmol/L (100 mg/dL, blue), LDL cholesterol 1.8 mmol/L (70 mg/dL, grey), non-HDL cholesterol decreased by 40% (yellow) and LDL cholesterol 1.8 mmol/L (70 mg/dL) or decreased by 50%, whichever is lower (green). ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein.

In people with LDL cholesterol<4 mmol/L, a percentage reduction is a much more effective therapeutic goal. An important rider to this is that at higher initial LDL cholesterol levels, we have previously shown that a target for LDL cholesterol lowering couched in terms of percentage reduction is less effective than aiming for 1.8 mmol/L or in secondary prevention even lower levels.[8 16] This is almost self-evident once it is realised that the extent to which absolute ASCVD incidence is reduced is related to the magnitude of the decrease in LDL cholesterol concentration.[7 8] At LDL cholesterol levels above 3.6 mmol/L, for example, a 50% decrease will achieve a smaller lowering of LDL cholesterol than aiming for 1.8 mmol/L. Thus, our findings strongly advocate a percentage reduction in LDL cholesterol for pretreatment levels<4 mmol/L and a concentration target for higher levels; in other words, 50% reduction or to 1.8 mmol/L whichever is lower.

We have assumed that the advice to reduce non-HDL cholesterol by 40%[6] will affect mainly LDL cholesterol and have based our calculation of the outcome of NICE guidance on a 40% decrease in LDL cholesterol. Our calculations have been based on LDL cholesterol rather than non-HDL cholesterol, because the body of evidence relating changes in LDL cholesterol to changes in ASCVD incidence is vast[1 10]: the only meta-analysis of randomised clinical trials of cholesterol-lowering medication relating outcome to non-HDL cholesterol used a single factor to convert LDL to non-HDL cholesterol which applies only to a narrow range and essentially relied on the between-trial variation in LDL cholesterol.[17] We accept that VLDL cholesterol predicts ASCVD, although less strongly than LDL,[18] and that VLDL cholesterol is decreased by statin medication, in percentage terms by about half as much LDL cholesterol and with a flatter dose–response curve.[9] None the less, in the majority of people VLDL contributes little to non-HDL cholesterol compared with LDL. For example, when LDL cholesterol is 4 mmol/L and triglycerides are 1.5 mmol/L, VLDL cholesterol is approximately 0.68 mmol/L[19] and the non-HDL cholesterol will be 4.68 mmol/L. The VLDL cholesterol response say to atorvastatin is about half that of LDL cholesterol.[20] Therefore, a 40% decrease in non-HDL cholesterol in this example then represents a 43% decrease in LDL cholesterol combined with a 21% decrease in VLDL cholesterol. Thus, we concede that the decrease may in some patients be slightly higher than 40% (and in others with raised triglycerides slightly lower), but this would make no difference to our conclusions, because we have also examined another percentage reduction in LDL cholesterol, namely 50%, with almost identical conclusions.

It might be thought that to apply a single value for the risk ratio between no treatment and the receipt of different statins, ezetimibe and PCSK9 inhibitors would be questionable. However, there is remarkable consistency in finding that ASCVD risk is decreased by 22% for each 1 mmol/L decrease in LDL cholesterol in the randomised controlled trial (RCTs) of these medications.[1 5 10] That this applies to more recently introduced treatments must, of course, be checked before applying the same principles to their use. Our study has the usual limitations which apply to translation of RCT results into clinical practice, particularly patient adherence when

treatment is for a longer term and in the case of statins, there is a public perception that side effects such as myalgia are commonly treatment related.[5]

CONCLUSION

We conclude that in primary prevention, the optimal treatment goal for cholesterol-lowering treatment is LDL cholesterol<1.8 mmol/L or decreased by 50% whichever is lower. This should apply regardless of the pretreatment LDL cholesterol concentration. It is an easily communicated mantra which can be readily applied in clinical practice.

Contributors HS: Conceptualisation and review and editing of tables and figures. SA and ZI: Software validation and review and editing. PD: Conceptualisation, formal analysis, data curation, writing the first draft and guarantor.

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Competing interests HS and PND have served as cosultants to pharmaceutical companies marketing lipid lowering drugs, and have received travel expenses, payment for speaking at meetings and funding for other research from some of these companies. SA received honoraria from companies marketing lipid lowering drugs.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Supplementary tables 1a-c

a.Data for figure 1a (ASCVD risk 7.5% 10^{-1} years)

Target	NNT			
	Pre-treatment LDL cholesterol (mmol/l)			
	2	3	4	5
LDLc 2.6 (100)	∞	141	45	30
LDLc 1.8 (70)	278	52	32	24
Non-HDLc -40%	74	52	41	34
LDLc 1.8 (70) or -50%	61	43	32	24

b. Data for figure 1b (ASCVD risk 15% 10^{-1} years)

Target	NNT			
	Pre-treatment LDL cholesterol (mmol/l)			
	2	**3**	**4**	**5**
LDLc 2.6 (100)	∞	70	23	15
LDLc 1.8 (70)	137	26	16	12
Non-HDLc -40%	37	26	20	17
LDLc 1.8 (70) or -50%	30	21	16	12

c. Data for figure 1c (ASCVD risk 30% 10^{-1} years)

Target	NNT			
	Pre-treatment LDL cholesterol (mmol/l)			
	2	**3**	**4**	**5**
LDLc 2.6 (100)	∞	35	11	7
LDLc 1.8 (70)	69	13	8	6
Non-HDLc -40%	18	13	10	9
LDLc 1.8 (70) or -50%	15	11	8	6