Strategies to alter the trajectory of atherosclerotic cardiovascular disease.

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Abstract

Purpose of the review: Cardiovascular disease prevention trials of lipid lowering with statins have shown unexpected long-term benefits after the formal randomized treatment stopped. This finding needs further exploration since it raises the possibility that the trajectory of the disease can be modified.

Recent findings: Extended follow up data are now available from further major primary prevention studies and from meta-analyses of the legacy effect of statin trials. New outcome studies have been proposed and launched to test the ability of early intervention to slow or regress atherosclerosis.

Summary: Legacy effects are apparent in trials of LDL lowering in hypercholesterolemic and hypertensive patient cohorts. Over follow up periods of decades, both cardiovascular mortality and all-cause mortality are reduced in individuals who received 3 to 5 years of statin therapy. The phenomenon is observed also in studies of intensive glycemic control suggesting that it is possible to impact plaque development with long-term beneficial consequences. Novel strategies for primary prevention are being devised that include the early use of both prolonged-moderate and short term-aggressive LDL lowering.

Key words: clinical trials, statin, primary prevention, fatty streak

Background

Current cardiovascular disease (CVD) intervention strategies are based on the understanding that atherosclerosis is a decades-long, silent process of pathological remodeling of the vessel wall that eventually manifests itself as an ischemic event. The age of clinical presentation, usually as acute coronary syndrome (ACS), peripheral artery disease, or ischemic stroke is in the sixth and seventh decade of life, and the medical response is to institute secondary prevention measures to reduce the risk of recurrent events (1,2). By the time a clinical event occurs the atherosclerotic plaque has developed into a complex lesion that has become enriched in macrophages, and has a thin, friable cap and necrotic, lipid-filled core. With aggressive risk factor control stabilization and regression of the lesion is possible (3,4), but even when LDL cholesterol (LDLc) levels are reduced profoundly (almost to zero) there remains considerable 'residual risk' of further events as seen in the PCSK9 (proprotein convertase subtilisin/kexin 9) inhibitor outcomes trials (5-7).

Primary CVD prevention is undertaken to a greater or lesser degree depending on the health care system and the enthusiasm of practitioners. In order to identify those asymptomatic individuals who most need active intervention, predictive tables are used such those based on SCORE in Europe (8), the Framingham risk model (9), or the Pooled Cohort equations as recommended by the latest USA guidelines (10,11). It is generally accepted that these risk tables over-emphasize age as a risk factor (12, 13**), and so even in the primary prevention setting current attention is focused on intervening late in the disease course. The shortcomings of these approaches (waiting for a clinical event to occur or using classical risk prediction methods) are now appreciated and there is an emerging consensus that our efforts should now be directed to altering the trajectory of atherogenesis much earlier in life (12-16). Available evidence, mostly from genetic studies (16,17,18*), indicates that even moderate LDLc lowering (and other avenues of risk factor control) initiated early will be highly effective in preventing events, and so residual risk may become a non-issue. Implementation of such a paradigm shift in prevention strategy will require further insight into the benefits and disadvantages of intervening at different stages of the disease process, and

novel approaches to identifying those at highest risk. As set out in this review, the observations that are moving many to consider an early intervention approach are (i) an appreciation of the long-term impact of therapy as revealed in the 'legacy effects' of statin treatment and intensive glucose lowering, (ii) recognition from animal model studies that complete regression of lesions may be possible but only at the early stages of plaque development, and (iii) the impact of genetic factors on CVD risk and response to treatment.

Legacy effects of cardiovascular disease intervention trials

With the increasing availability of extended follow-up information from cardiovascular outcome trials, it has become possible to evaluate if interventions designed to control major causal risk factors - raised LDL cholesterol, raised blood pressure, elevated glucose levels in diabetes – have a long-term benefit that continues after study treatment has stopped. This post-trial persistence in risk reduction has been termed the 'legacy' effect or 'carry-forward' benefit. Conceptually, it is predicated on the possibility that during the randomized trial the drug under investigation impacted on the pathological process in a way that altered the natural history of the disease, with the consequence that subjects in the active-treatment arm going forward experience a different trajectory of risk. The topic has been discussed with respect to statin studies in a previous article in this journal (19) and in other, more recent reviews (14,15, 20). One of the latest reports is that of the 16-year follow up of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) (21**). The original randomized trial in hypertensive patients evaluated the impact of amlodipine versus atenolol, and within a Lipid-Lowering Arm (LLA) of atorvastatin versus placebo on major coronary events (22). The long-term effects of these treatments are reported for the subset of subjects included in the ASCOT Legacy study; these were 8580 UK-based patients for whom mortality data was available. While there was no significant difference in all-cause mortality over 16 years, there were fewer stroke deaths in the amlodipine treated subjects (21). In the LLA subset, atorvastatin treatment for about 3 years (that is, during the formal double-blind phase of the trial) was associated with a 15% reduced risk of death from cardiovascular causes at 16

years (Table 1). This relative risk reduction in CVD mortality was virtually identical in magnitude to that seen at the end of the in-trial period (22). In addition, all-cause and coronary heart disease mortality showed trends to long-term benefit in the atorvastatin treated subjects (21). These findings are in line with the results from the West of Scotland Coronary Prevention Study (WOSCOPS) in which we observed a significant 21% reduction in CVD risk (based on non-fatal and fatal events) over 20 years of extended follow up and a 13% decrease in total mortality (23). The concordance between the two trials is shown in Table 1. The lipid lowering arm of ALLHAT-LLT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Therapy), the third major primary prevention trial for which extended follow up data are available, showed non-significant results over the long term even for cardiovascular mortality (Table 1). This weaker effect is usually attributed to the relatively small difference in LDLc between the two treatment arms in this trial (24). Of note also is the observation that while cardiovascular deaths were reduced in both WOSCOPS and ASCOT-LLA and there was a trend in ALLHAT-LLT, over the whole observation period stroke deaths were not impacted by statin-associated legacy effects.

In an attempt to clarify further the legacy phenomenon, a meta-analysis of key statin studies was undertaken by Nayak et al (25*) who examined mortality rates in major primary and secondary prevention statin trials for which long-term follow-up was available. They paid particular attention to the post-trial period rather than total follow-up (which includes the trial itself as shown in Table 1) arguing that a legacy effect should be evidenced by a risk reduction once active treatment had stopped. A difference was noted between the five secondary prevention studies where no mortality benefit was found post-trial - relative risk (RR) 0.99 (95% confidence limits (CI) 0.94 - 1.05) - and the three primary prevention trials (WOSCOPS, ASCOT and ALLHAT (21,23,24)) which on aggregate showed a significant decrease in risk of cardiovascular mortality – RR 0.91 (CI 0.84-0.98)- and all-cause mortality, RR 0.92 (CI 0.88-0.96). The main shortcoming of this analysis, as recognized by the investigators, is that event rate comparisons between treatment groups post-trial may be confounded by differential treatment effects during the formal trial. However, the concordance across studies indicates

that early intervention in asymptomatic individuals with elevated risk factors (the trials were conducted in hypercholesterolemic or hypertensive cohorts) may provide added benefit as the treatment impacts on the atherosclerotic plaque and its development (see 19 for a more detailed discuss on possible mechanisms). In this context, it is interesting to note that additional analysis of another primary prevention trial, HOPE (Heart Outcomes Prevention Evaluation)-3, showed that year on year during the main study there was appreciable diminution of the LDLc difference between the two treatment arms of the trial (due to drop-in and drop-out) but the cumulative event curves continued to show ever greater separation between those on placebo and rosuvastatin (26). This was interpreted as evidence for a within-study legacy effect that will be investigated further with post-trial follow-up.

Long-term follow up also provides important insights into safety of drugs where there is a perceived issue over tolerability or adverse events. WOSCOPS documented no difference in non-cardiovascular mortality or incident cancers over 20 years (23). The ASCOT investigators took advantage of the trial design to compare reported rates of adverse events on statin versus placebo during the 3-year blinded phase and the subsequent 2-year follow-up during which monitoring continued. They reported that when doctor and patient were unaware of treatment allocation there was no difference in muscle-related side effects but during the open phase more patients on statin reported musculoskeletal symptoms (27).

Statin therapy is not the only intervention in the cardiovascular field to report a legacy effect. Persistent, post-trial risk reductions in micro-vascular and macro-vascular disease were found in subjects randomized to intensive glycemic control versus 'usual care' in the DCCT/EDIC study in type 1 diabetics (28*) and in the UKPDS trial in type 2 diabetics (29), but this has not been a universal observation (30). The phenomenon was explored further in a recent meta-analysis which reported that there was no evidence overall for a legacy effect in patients with type 2 diabetes who had suffered a coronary event or were at very high risk (31), but subjects who were newly diagnosed type 2 diabetics without established CHD

exhibited a post-trial benefit from better glycemic control (31). Presumably again the stage of development of the atherosclerotic plaque was a major determinant of the potential for a legacy effect to occur. In terms of mechanism, the post-trial risk reduction may not be attributable entirely to chronically improved glucose control since the difference in HbA1c in UKPDS between treated groups disappeared within the first year of the study (29, but see also findings in 30). Other potential mechanisms including protein glycation, metabolic memory of target cells, and epigenetic changes have been explored but as yet no clear front runner has emerged (28, 32). In a direct comparison within a single study, the UKPDS investigators reported that better blood pressure control was not associated with a post-trial risk reduction in cardiovascular outcomes (33). However, other studies have suggested that a legacy effect can be seen for this risk factor as well (15, 20), although it may be smaller than that observed for LDL lowering (20).

The appearance of legacy effects lasting decades in individuals with less advanced atherosclerotic disease does not mean that we should provide a relatively brief period of risk factor control to alter the trajectory of the pathological process and then relax treatment regimens. Rather, our focus should be on identifying those at highest risk in early adult life and instituting moderate improvements in LDLc and blood pressure, and in diabetics achieve better glycemic control, and by maintaining these interventions over the long term achieve a better than expected outcome. Variations on this strategy, as described below, suggest the use of more aggressive regimens to 'cure' atherosclerosis through profound LDL lowering (34).

Novel LDL lowering intervention strategies

If the objective of LDLc lowering is to slow, halt or reverse development of the atherosclerotic plaque, then the question arises as to what can be achieved at various stages of atherogenesis as discussed at the recent European Society of Cardiology roundtable (13). The earliest lesions seen in young adults take the form of fatty streaks (35-37) which over years progress into multicellular complex lesions with a thin, fragile cap which is prone to rupture, leading to an atherothrombotic event. Intervention to lower LDLc in people with established

disease – usually, as noted above, aged 50-60 years and above - leads to slowed progression and where very low LDL levels are achieved, regression of plaque. The clearest example of this phenomenon in humans was observed in the GLAGOV (Global Assessment of Plaque Regression With a PCSK9
Antibody as Measured By Intravascular Ultrasound) study (3) in which a PCSK9 inhibitor was used to profoundly reduce LDLc and the majority of subjects exhibited reduction in lesion size. However, contrary to expectation the reduction in size was not accompanied by a selective decrease in lipid content or the necrotic core (38*). Clearly, regression of advanced lesions leaves a residual plaque which may be the basis for the residual risk. From animal and human studies, it is increasingly clear that our attention must turn to earlier lesions – the fatty streak- if intervention is to lead not only to plaque regression but complete resolution and restoration of fully functional vessel wall (12,13,34).

A number of investigators have proposed intervention strategies which have the goal of dramatically altering cardiovascular disease trajectory as depicted in Figure 1. The Eliminate Coronary Artery Disease (ECAD) trial (39) was launched to investigate in subjects with one risk factor (smoking, truncal obesity, hypertension, family history of CHD, South Asian ancestry) the potential for moderate LDLc lowering (20mg/ day atorvastatin) to impact CVD risk in mid-life (age 35 to 50 years for men, 45 to 59 for women). The rationale is based on the observations that aboriginal populations that maintain a low LDL throughout life exhibit little cardiovascular disease (40), and that in Western countries those with inherited lower LDLc (as in PCSK9 loss-of-function variants (18, 41)) have a substantially decreased risk of major coronary events. The age range chosen is thought to be young enough so that there are few complex atherosclerotic lesions present but old enough to give sufficient events over a 10 -year follow-up. Recruitment is ongoing with an anticipated trial end in 2023 (see NCT 02245087), although termination is event driven. It is anticipated that in the active treatment arm in ECAD lesion formation will be minimized since LDLc levels are maintained in the range seen in CVD-free populations ('stasis' as depicted in Figure 1), and what plaque is present is unlikely to progress. The greatest challenge in such a long trial in asymptomatic individuals is to maintain adherence to the study

medication. There is likely to be significant 'drop-in' if a non-endpoint ACS event occurs, or the subject decides to take up cholesterol control measures as they get older. 'Drop-out' is probably the bigger problem due to loss of interest or perceived side effects. In WOSCOPS we experienced 28% non-compliance to the study drug regimen over a 5-year period of followup (42) despite a pro-active program of recruit retention. Continued education and frequent communication with volunteers reinforcing the aims of the study will help minimize non-compliance but the statistical power of the trial will be weakened if it is significant.

In an alternative, more aggressive, approach, Robinson et al (43*) have outlined a potential clinical trial in which young to early mid-life adults with a significant burden of uncalcified atherosclerotic plaque are subject to profound LDLc lowering with target levels in the range 0.5-1.0 mmol/l (20 to 40 mg/dl - the 'regression' range in Figure 1) for a short – 3-year – intervention period. The objective of 'CURE-Athero' is to 'eradicate' disease by regressing and resolving existing lesions, mainly fatty streaks. Animal studies support the concept that with aggressive lowering of apolipoprotein B -containing lipoproteins, lesions of this type can be removed and normal vessel wall regained (37, 44). The planned age range is 25-55 years and subjects would be recruited on the basis of the PDAY risk score (45) and evidence of lesions on computed tomography angiography imaging. The proposed end-point is change in plaque volume (43). (Note CURE-Athero is not yet launched). If this approach were to prove successful then there would need to be an evaluation of the cost effectiveness of using what is an expensive drug in this context. The benefits would need to persist over a long period to balance the costs of screening and treatment. Once, the 'eradication' phase was complete then inexpensive statin therapy could be used to maintain the benefits over the long term, as suggested below.

Variants to the design of ECAD and CURE-Athero might involve using biomarkers or genetics to address the issue of how best to select individuals for early intervention LDL lowering, and how to follow progress in regressing atheroma (Figure 1). Cardiac specific biomarkers such as high-sensitivity troponin- I or T

and NT-proBNP (N-terminal proB-type natriuretic peptide) show promise in the general population as predictors of risk many years before an ischemic coronary event (46,47) and change in their circulating concentration may provide an index of reduction in plaque burden for those on statin therapy as suggested by the findings from WOSCOPS (46). Combining the approaches of the trials described above into a workable life-long prevention strategy might conceptually involve identification of a high-risk cohort of the population in early mid-life (age 30 to 50 y) through risk factor assessment, genetic profiling, and measurement of biomarker levels and plaque burden. Aggressive LDL lowering (LDLc <1 mmol/l) can then be initiated for 3 to 5 years to resolve plaque and then a maintenance phase begun where moderate dose statin is used to keep LDLc below 2.6 mmol/l. If monitoring shows a rise in biomarkers then a further phase of aggressive treatment could be considered. This proposed strategy is termed 'biomarker - guided phased prevention' in the figure.

Use of genetics in CVD primary prevention strategies

In addressing the issue of subject selection for intervention to alter the trajectory of atherosclerosis, it is worth considering the role of genetic predisposition to increased CVD risk. Familial hypercholesterolemia is the prime example of an inherited trait that leads to premature CHD (Figure 1) and identification of carriers of the causative gene mutations and early treatment is considered essential (48). It is now recognized that people with a combination of genetic variants that give rise to increased LDL levels are also an appropriate target for more aggressive intervention (49, 50). As in the case of FH it is likely that such individuals will have had higher LDLc levels from a young age and therefore the exposure – 'LDLc x years' – will be greater than in people with no genetic predisposition. Use of global genetic risk scores or LDL-specific scores may be a readily applicable means of selection for intervention. Further, recent studies have suggested that those with an increased genetic component to risk exhibit a greater relative risk reduction when given LDLc lowering therapy (49,51*). In a meta-analysis combining three primary prevention studies (JUPITER [Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin], ASCOT and WOSCOPS) it was reported that, despite a similar degree of LDLc

lowering, the relative risk reduction for subjects with a high gene score was 46% compared to 26% for those with a low gene score (P=0.05 for heterogeneity in response) (51). The agreement between trials was remarkable. Further, Natarjan et al (51) observed a strong association between sub-clinical atherosclerosis (coronary artery calcification burden) and gene score in a cohort of young adults, suggesting that the use of imaging as proposed in CURE-Athero (43) may also yield a population that responds particularly well to LDL lowering. Biomarkers such as C-reactive protein are strongly associated with risk of cardiovascular disease but their use for subject selection in the context of early intervention may not identify a subset of individuals who show an enhanced response to statins; in the JUPITER trial the relative risk reduction was the same regardless of baseline level of this inflammation marker (52).

Conclusions

Observations from extended follow-up of clinical trials have revealed unanticipated benefits from therapy in that during the post-trial period there is continued decrease in cardiovascular risk. The current concept is that reduction in causal risk factors, particularly LDLC lowering or intensive glycemic control, alters the trajectory of the disease by inducing changes in the nature of the plaque or laying down a 'metabolic memory' that leads to more benign conditions going forward. This advantageous outcome seems to be available if individuals are treated early in the course of the disease, and for this reason and following other key observations of atherosclerosis reversibility there is an emerging consensus that our collective attention should now focus developing better strategies in primary prevention aimed at identifying the subset of the population at highest risk and intervening to reduce dramatically or eliminate the potential for clinical events to occur. Implementation of this concept will be challenging but trials are on-gong that will demonstrate its worth.

Key points

- Primary prevention trials of statin therapy in both hypertensive (ASCOT) and hypercholesterolemic (WOSCOPS) patients show evidence of legacy effects where a risk reduction in cardiovascular disease outcomes is present years after the end of the formal trial.
- LDL lowering and intensive glycemic control studies demonstrate a long-term benefit that indicates the merits of early intervention in individuals who have not yet developed complex atherosclerotic lesions.
- Novel primary prevention strategies have been proposed, and some are being tested to identify those most at risk before any clinical disease is apparent and to slow or reverse the atherogenic process.

Acknowledgements

Financial support – None

Conflict of Interest – The author has received grants and honoraria from commercial companies in the area of lipid lowering drugs (Merck, Sharpe & Dohme, Amgen, Sanofi-Regeneron, Daiichi-Sankyo, Roche).

References

(1) Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM, De Backer G, Roffi M, Aboyans V, Bachl N, Bueno H, Carerj S, Cho L, Cox J, De Sutter J, Egidi G, Fisher M, Fitzsimons D, Franco OH, Guenoun M, Jennings C, Jug B, Kirchhof P, Kotseva K, Lip GY, Mach F, Mancia G, Bermudo FM, Mezzani A, Niessner A, Ponikowski P, Rauch B, Ryden L, Stauder A, Turc G, Wiklund O, Windecker S, Zamorano JL. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol 2016;23:Np1-np96.

(2) Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1082-e1143. doi: 10.1161/CIR.0000000000000625.

(3) Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, Koenig W, Somaratne R, Kassahun H, Yang J, Wasserman SM, Scott R, Ungi I, Podolec J, Ophuis AO, Cornel JH, Borgman M, Brennan DM, Nissen SE. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. JAMA. 2016;316:2373-2384.

(4) Stegman B, Shao M, Nicholls SJ, Elshazly M, Cho L, King P, Kapadia S, Tuzcu M, Nissen SE, Puri R. Coronary atheroma progression rates in men and women following high-intensity statin therapy: A pooled analysis of REVERSAL, ASTEROID and SATURN. Atherosclerosis. 2016;254:78-84.

(5) Sabatine MS, De Ferrari GM, Giugliano RP, Huber K, Lewis BS, Ferreira J, Kuder JF, Murphy SA, Wiviott SD, Kurtz CE, Honarpour N, Keech AC, Sever PS, Pedersen TR. Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease. Circulation. 2018;138:756-766.

(6) Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376:1713-1722.

(7) Jukema JW, Szarek M, Zijlstra LE, de Silva HA, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Karpov Y, Moryusef A, Pordy R, Prieto JC, Roe MT, White HD, Zeiher AM, Schwartz GG, Steg PG; ODYSSEY OUTCOMES Committees and Investigators. Patients with Recent Acute Coronary Syndrome and Polyvascular Disease Derive Large Absolute Benefit from Alirocumab: ODYSSEY OUTCOMES Trial. J Am Coll Cardiol. 2019. pii: S0735-1097(19)33921-X. doi: 10.1016/j.jacc.2019.03.013.

(8) Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24:987-1003.

(9) Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837–47.

(10) Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S1–45

(11) Damen JA, Pajouheshnia R, Heus P, Moons KGM, Reitsma JB, Scholten RJPM, Hooft L, Debray TPA. Performance of the Framingham risk models and pooled cohort equations for predicting 10-year risk of cardiovascular disease: a systematic review and meta-analysis. Damen JA, Pajouheshnia R, Heus P, Moons KGM, Reitsma JB, Scholten RJPM, Hooft L, Debray TPA. BMC Med. 2019;17:109. doi: 10.1186/s12916-019-1340-7.

(12) Robinson JG, Ray K. Moving toward the next paradigm for cardiovascular prevention. Circulation 2016;133:1533–1536.

(13) ** Graham I, Shear C, De Graeff P, Boulton C, Catapano AL, Stough WG, Carlsson SC, De Backer G, Emmerich J, Greenfeder S, Kim AM, Lautsch D, Nguyen T, Nissen SE, Prasad K, Ray KK, Robinson JG, Sasiela WJ, Bruins Slot K, Stroes E, Thuren T, Van der Schueren B, Velkovski-Rouyer M, Wasserman SM, Wiklund O, Zouridakis E; European Society of Cardiology Cardiovascular Roundtable. New strategies for the development of lipid-lowering therapies to reduce cardiovascular risk. Eur Heart J Cardiovasc Pharmacother. 2018;4:119-127.
A valuable summary of where we are in CVD prevention in both primary and secondary settings, and where we might usefully go.

(14) Takata K, Psaltis PJ, Nicholls SJ. Investigating the long-term legacy of statin therapy. J Thorac Dis. 2017;9:936-939.

(15) Khunti K, Kosiborod M, Ray KK. Legacy benefits of blood glucose, blood pressure and lipid control in individuals with diabetes and cardiovascular disease: Time to overcome multifactorial therapeutic inertia? Diabetes Obes Metab. 2018;20:1337-1341.

(16) Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Borén J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgözoglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38:2459-2472

(17) Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, Kahn J, Afonso L, Williams KA Sr, Flack JM Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol. 2012;60:2631-9

(18) *Benn M, Tybjærg-Hansen A, Nordestgaard BG. Low LDL Cholesterol by PCSK9 Variation Reduces Cardiovascular Mortality. J Am Coll Cardiol. 2019;73:3102-3114.
An important addition to the argument that moderate LDL lowering over a long period can be highly beneficial.

(19) Packard CJ, Ford I. Long-term follow-up of lipid-lowering trials. Curr Opin Lipidol. 2015;26:572-9.

(20) Hirakawa Y, Arima H, Rodgers A, Woodward M, Chalmers J. Cumulative in-trial and post-trial effects of blood pressure and lipid lowering: systematic review and meta-analysis. J Hypertens. 2017;35:905-913.

(21) **Gupta A, Mackay J, Whitehouse A, Godec T, Collier T, Pocock S, Poulter N, Sever P. Long-term mortality after blood pressure-lowering and lipid-lowering treatment in patients with hypertension in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Legacy study: 16-year follow-up results of a randomised factorial trial. Lancet. 2018;392:1127-1137.
This is the latest 16-year report from the ASCOT-LLA sub-study which uses mortality data to document the legacy effects in that trial. There is the promise also of a future paper which will include morbidity outcomes to clarify further the potential long-term benefits of statin use.

(22) Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003;361:1149-58.

(23) Ford I, Murray H, McCowan C, Packard CJ. Long-term safety and efficacy of lowering low-density lipoprotein cholesterol with statin therapy: 20-year follow-up of West of Scotland Coronary Prevention Study. Circulation 2016;133:1073-1080.

(24) Margolis KL, Davis BR, Baimbridge C et al for the ALLHAT Collaborative Research Group. Long-term follow up of moderately hypercholesterolemic hypertensive patients following randomization to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). J Clin Hypertens. 2013;15(8):542-54.

(25) *Nayak A, Hayen A, Zhu L, McGeechan K, Glasziou P, Irwig L, Doust J, Gregory G, Bell K. Legacy effects of statins on cardiovascular and all-cause mortality: a meta-analysis. BMJ Open. 2018;8(9):e020584. doi: 10.1136/bmjopen-2017-020584.
This analysis focussed specifically on the post-trial findings in major primary and secondary prevention trials and documented a discordancy between the two settings in that the former but not the latter were most likely to exhibit a legacy effect of statin therapy.

(26) Howard TM, Bavishi AA, Stone NJ. A New HOPE? Lessons from Heart Outcomes Prevention Evaluation-3. Am J Med. 2018;131:134-140.

(27) Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, Collins R, Sever P; ASCOT Investigators. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. Lancet. 2017;389:2473-2481.

(28) *Riddle MC, Gerstein HC The Cardiovascular Legacy of Good Glycemic Control: Clues About Mediators From the DCCT/EDIC Study. Diabetes Care. 2019;42:1159-1161.
An excellent overview of the concept of legacy effects from the standpoint of glucose control and its impact on cardiovascular disease.

(29) Holman RR[1], Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577-89.

(30) Reaven PD, Emanuele NV, Wiitala WL, Bahn GD, Reda DJ, McCarren M, Duckworth WC, Hayward RA; VADT Investigators. Intensive Glucose Control in Patients with Type 2 Diabetes - 15-Year Follow-up. N Engl J Med. 2019;380:2215-2224.

(31) Zhang X, Liu Y, Zhang F, Li J, Tong N. Legacy Effect of Intensive Blood Glucose Control on Cardiovascular Outcomes in Patients With Type 2 Diabetes and Very High Risk or Secondary Prevention of Cardiovascular Disease: A Meta-analysis of Randomized Controlled Trials. Clin Ther. 2018;40:776-788.

(32) Murray P[1], Chune GW, Raghavan VA. Legacy effects from DCCT and UKPDS: what they mean and implications for future diabetes trials. Curr Atheroscler Rep. 2010;12:432-9.

(33) Holman RR[1], Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med. 2008;359:1565-76.

(34) Robinson JG, Davidson MH. Can We Cure Atherosclerosis. Rev Cardiovasc Med. 2018;19(S1):S20-S24

(35) Wissler RW, Strong JP. PDAY Research Group: Risk factors and progression of atherosclerosis in youth. Am J Pathol 1998;153:1023-1033.

(36) McGill HC Jr[1], Herderick EE, McMahan CA, Zieske AW, Malcolm GT, Tracy RE, Strong JP. Atherosclerosis in youth. Minerva Pediatr. 2002;54:437-47.

(37) Fisher EA. Regression of Atherosclerosis: The Journey From the Liver to the Plaque and Back. Arterioscler Thromb Vasc Biol. 2016;36:226-35

(38) *Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJP, Koenig W, Somaratne R, Kassahun H, Yang J, Wasserman SM, Honda S, Shishikura D, Scherer DJ, Borgman M, Brennan DM, Wolski K, Nissen SE. Effect of Evolocumab on Coronary Plaque Composition. J Am Coll Cardiol. 2018;72:2012-2021.
Despite profound reduction in LDL on PCSK9 inhibitor, this paper reports that there was no selective decrease in plaque elements associated with cholesterol deposition (lipid content, necrotic core size).

(39) Domanski MJ, Fuster V, Diaz-Mitoma F, Grundy S, Lloyd-Jones D, Mamdani M, Roberts R, Thorpe K, Hall J, Udell JA, Farkouh ME. Next Steps in Primary Prevention of Coronary Heart Disease: Rationale for and Design of the ECAD Trial. J Am Coll Cardiol. 2015;66:1828-1836.

(40) Chen Z, Peto R, Collins R, et al. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. BMJ 1991;303:276–82.

(41) Cohen JC[1], Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006;354:1264-72.

(42) Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333:1301–7.

(43) *Robinson JG, Williams KJ, Gidding S, Borén J, Tabas I, Fisher EA, Packard C, Pencina M, Fayad ZA, Mani V, Rye KA, Nordestgaard BG, Tybjærg-Hansen A, Douglas PS, Nicholls SJ, Pagidipati N, Sniderman A. Eradicating the Burden of Atherosclerotic Cardiovascular Disease by Lowering Apolipoprotein B Lipoproteins Earlier in Life. J Am Heart Assoc. 2018;7:e009778. doi: 10.1161/JAHA.118.009778.
This paper is a useful review of the concept of early intervention to reverse atherosclerosis and 'cure' the disease. It covers animal model and clinical findings and outlines a potential trial to explore this approach.

(44) Björkegren JL[1], Hägg S[2], Talukdar HA[3], Foroughi Asl H[3], Jain RK[4], Cedergren C[3], Shang MM[3], Rossignoli A[3], Takolander R[5], Melander O[6], Hamsten A[7], Michoel T[8], Skogsberg J[3]. Plasma cholesterol-induced lesion networks activated before regression of early, mature, and advanced atherosclerosis. PLoS Genet. 2014;10:e1004201. doi: 10.1371/journal.pgen.1004201.

(45) McMahan CA, Gidding SS, Fayad ZA, Zieske AW, Malcom GT, Tracy RE, Strong JP, McGill HC Jr; for the Pathobiological Determinants of Atherosclerosis in Youth Research Group. Risk scores predict atherosclerotic lesions in young people. Arch Intern Med. 2005;165:883–890.

(46) Ford I, Shah AS, Zhang R, McAllister DA, Strachan FE, Caslake M, Newby DE, Packard CJ, Mills NL. High-Sensitivity Cardiac Troponin, Statin Therapy, and Risk of Coronary Heart Disease. J Am Coll Cardiol. 2016;68:2719-2728

(47) Natriuretic Peptides Studies Collaboration. Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant data meta-analysis. Lancet Diabetes & Endocrinology 2016; 4:840-9.

(48) Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averna M, Borén J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjærg-Hansen A; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Consensus Statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478-3490.

(49) Mega JL, Stitziel NO, Smith JG, Chasman DI, Caulfield M, Devlin JJ, Nordio F, Hyde C, Cannon CP, Sacks F, Poulter N, Sever P, Ridker PM, Braunwald E, Melander O, Kathiresan S, Sabatine MS Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. Lancet. 2015;385:2264-2271

(50) Beaney K, Drenos F, Humphries SE. How close are we to implementing a genetic risk score for coronary heart disease? Expert Rev Mol Diagn. 2017;17:905-915.

(51) *Natarajan P, Young R, Stitziel NO, Padmanabhan S, Baber U, Mehran R, Sartori S, Fuster V, Reilly DF, Butterworth A, Rader DJ, Ford I, Sattar N, Kathiresan S. Polygenic Risk Score Identifies Subgroup With Higher Burden of Atherosclerosis and Greater Relative Benefit From Statin Therapy in the Primary Prevention Setting. Circulation. 2017;135:2091-2101.
This report explored the concept that people with a strong genetic predisposition to develop CVD (high gene score) were candidates for early intervention, and it was found that these individuals also had a greater risk

reduction for a given LDL decrease compared to subjects without a high gene score.

(52) Ridker PM, MacFadyen J, Libby P, Glynn RJ Relation of baseline high-sensitivity C-reactive protein level to cardiovascular outcomes with rosuvastatin in the Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). Am J Cardiol. 2010;106:204-9.

(53) ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998–3007.

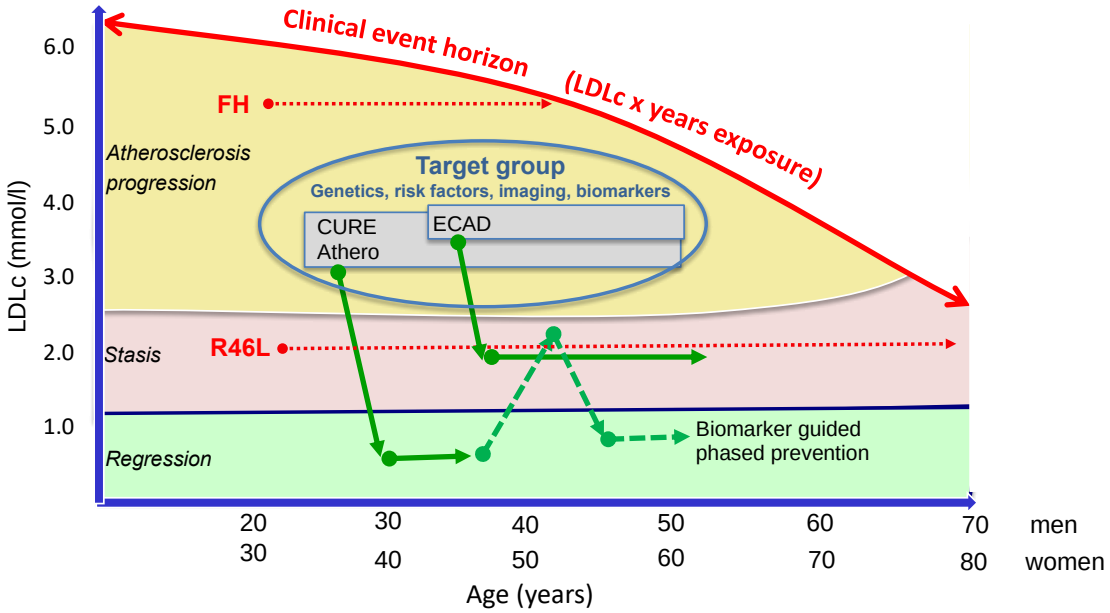
Figure legend

Figure 1. This schematic depicts novel strategies in primary prevention focused on early intervention to slow, halt or reverse atherogenesis before the occurrence of a clinical event. Based on the prevailing LDL cholesterol concentration (LDLc), the ability to form atherosclerotic plaque is divided into three broad states, *progression* - where fatty streaks will eventually become complex lesions vulnerable to rupture, *stasis* - where lesion progression is unlikely, and *regression* – where any fatty streaks present will tend to shrink in size and eventually resolve. The decreasing horizon with age represents the cumulative exposure to raised LDL in LDLc x years, and is the point at which an ACS event is likely to occur. Inherited conditions such as familial hypercholesterolemia (FH) and PCSK9 loss-of-function variants (R46L) provide examples of accelerated and slow atherogenesis (18,41,48). A potential target group for early intervention is shown. Individuals are identified as being at high risk on the basis of gene score, classical risk factors, biomarker measurement or coronary artery imaging. Intervention options are as in the ECAD trial (39) where subjects are given a moderate dose of statin to lower LDLc into the *stasis* range (as a target), or as in the proposed CURE-Athero study where aggressive LDLc lowering into the *regression* range is used to resolve any early lesions present (43). The putative 'biomarker-guided phased prevention' strategy envisages episodes of aggressive and then maintenance LDLc lowering depending on the level of cardiac biomarkers and/or lesions on imaging.

.**Table 1.** Comparison of legacy effects in placebo-controlled statin trials in cardiovascular disease primary prevention.

Endpoint	Study (overall follow up)	Hazard ratio (CI)	P
Cardiovascular mortality	WOSCOPS (20 y)[a]	0.79 (0.69-0.90)	0.0004
	ASCOT-LLA (16 y)[b]	0.85 (0.72-0.99)	0.0395
	ALLHAT-LLT (8.8 y)[c]	0.93 (0.84-1.04)	0.19
Stroke death	WOSCOPS	1.15 (0.86-1.53)	0.35
	ASCOT-LLA	1.02 (0.67-1.55)	0.92
	ALLHAT-LLT	1.02 (0.78-1.33)	0.89
Total mortality	WOSCOPS	0.87 (0.80-0.94)	0.0007
	ASCOT-LLA	0.92 (0.84-1.02)	0.091
	ALLHAT-LLT	0.96 (0.89-1.03)	0.24

Notes: Data from references [a](23), [b](21), and [c](24). The hazard ratios and 95th percent confidence limits (CI) refer to the entire length of follow up (in-trial plus post-trial events). The rates for ALLHAT-LLT are per 10 years. The drug used in ALLHAT and WOSCOPS was pravastatin, and in ASCOT was atorvastatin. In-trial LDL difference between statin versus placebo arms was 1.3 mmol/l for WOSCOPS, 1.2 mmol/l for ASCOT-LLA and 0.6 mmol/l for ALLHAT-LLT (from 22,42, 53).


Clinical event horizon
(LDLc x years exposure)
FH
Atherosclerosis progression
Target group
Genetics, risk factors, imaging, biomarkers
CURE Athero
ECAD
R46L
Stasis
Regression
Biomarker guided phased prevention
LDLc (mmol/l)
6.0
5.0
4.0
3.0
2.0
1.0
20 30 40 50 60 70 men
30 40 50 60 70 80 women
Age (years)