Editorial

Reducing exposure to cardiovascular risk factors: the legacy of prevention

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Over 50 years ago, the Framingham Heart Study investigators identified a range of common risk factors associated with atherosclerotic cardiovascular disease (ACVD) (1). Since then, several large-scale epidemiological studies conducted across all continents, such as the INTERHEART study, have linked ACVD risk factor exposure to cardiovascular outcomes (2). It is now commonly accepted that ACVD is mostly caused by measurable risk factors and the vast majority of these are modifiable, either via lifestyle modification, pharmacotherapy, or both. Of all ACVD risk factors, circulating cholesterol levels have perhaps received the most attention from not only the scientific and medical communities, but also by the media and the public alike. The association between cholesterol levels and ACVD has been studied for more than a century, with the cholesterol hypothesis having had its ups and downs [as recently summarized by Pedersen (3)]. Several lines of evidence [from experimental pre-clinical models, follow-up of patients with lipid disorders and more importantly randomized clinical trials (RCTs) of cholesterol lowering] now support the notion that the association between blood cholesterol levels and ACVD risk is likely causal. Furthermore, recent genetics association studies (also referred to as Mendelian randomization studies) performed in hundreds of thousands of patients have re-iterated the causality of blood cholesterol levels by showing that people harboring single-nucleotide polymorphisms (SNPs) that predispose them to lifelong low cholesterol levels have a substantially reduced ACVD risk (4). The same holds true for those with SNPs predisposing individuals to high cholesterol levels who subsequently are at higher ACVD risk (5). In both cases, the magnitude of the effect of the studied SNPs on blood cholesterol levels is directly proportional to their effect on ACVD risk (6), thereby providing another strong argument for cholesterol being causal in the aetiology of ACVD.

RCTs of cholesterol lowering with statins and ezetimibe have provided strong evidence for the benefits of targeting blood cholesterol levels for preventing ACVD (7,8). Depending on statin type, dose and population studied, RCTs have shown that compared with placebo, statin therapy typically reduces the relative risk of ACVD by 20–40%. Over the years, statin RCTs have been conducted in patients at high ACVD risk (for instance in patients with very high blood cholesterol levels, patients with ischemic heart disease, diabetic individuals) and in patients at lower ACVD risk, with comparable effects on relative risk reduction. In the most recent RCT involving cholesterol lowering (Heart Outcomes Prevention Evaluation; HOPE-3), patients without ACVD that had at least one cardiovascular risk factor benefited from a 24% relative ACVD risk reduction with rosuvastatin 10 mg compared with placebo (9). Because some trials have been conducted in patients at high cardiovascular risk and others have been conducted in patients at lower cardiovascular risk, for a given relative risk reduction, the absolute risk reduction of cardiovascular risk might be somewhat heterogeneous (only about 1% in the HOPE-3 trial), thereby questioning the widespread use of statin therapy as a result of a relatively large number of individuals requiring treatment to avert one clinical event.

In contemporary clinical settings, patients commencing statin therapy are typically advised to take their statin daily for the rest of their lives. However, the mean follow-up of most statin-based RCTs is typically around 5 years, which leaves an important knowledge gap of the long-term efficacy of statin therapy on cardiovascular outcomes. Fortunately, some of the early statin-based RCTs, despite a break in their randomization arms, have continued to follow study participants in these so-called "legacy trials", thus providing valuable information on the longer-term efficacy of statins (5–11 years following trial termination) (10-12). Recently, Ford *et al.* (13) extended the results of one of these landmark trials by publishing in *Circulation* the results of a 20-year follow-up of the West of Scotland Coronary Prevention Study (WOSCOPS). The WOSCOPS trial originally demonstrated in 1995 that pravastatin 40 mg daily in hypercholesterolemic men without established ACVD for an average of 4.9 years reduced the relative risk of ACVD by 31% and the absolute risk of ACVD by 2.4% (14). In their recently published follow-up investigation, the WOSCOPS investigators assessed the impact of their experiment on mortality, incident cancers, and cumulative number of admissions over 20 years or until death by examining electronic health records of all participants included in the original trial. After the 20-year follow-up, the authors found that all-cause mortality rates were 38.0% and 34.7% in the placebo and pravastatin groups respectively, yielding an absolute risk reduction of 3.3%. Cardiovascular mortality rates were 15.1% and 12.5% in the placebo and pravastatin groups respectively (an absolute risk reduction of 2.6%), thus providing some evidence that statin treatment for 5 years associates with a legacy benefit, further reiterating that lowering cholesterol levels could impart important longer-term benefits. Because post-trial statin therapy use was recorded for only 5 years following trial termination (and not for the last 10 years), it was not possible for the authors to estimate the extent of crossover therapy. Consequently, there is a possibility that the impact of cholesterol lowering with statins in this trial on cardiovascular outcomes might be underestimated. Because most guidelines of ACVD prevention worldwide recommend introducing statins in high-risk primary prevention populations, we may never know the true impact of lifelong statin therapy compared with placebo. As the mean age of participants in WOSCOPS at randomization was 55 years, and with the observation period being extended to when the mean age of study participants was approximately 75 years, this study might be as close as we can get to a real-world lifetime estimate of statin efficacy in men with hypercholesterolemia.

The first patient in the WOSCOPS trial was enrolled on February 1, 1989 and study recruitment was completed by September 1, 1991. Therefore, extrapolating the results of WOSCOPS to contemporary ACVD risk prevention settings warrants caution as patient enrolment in this trial occurred about 25 years ago. Towards the end of the 1980s, it was not uncommon to observe patients with isolated high cholesterol levels in the absence of other CVD risk factors (except smoking, whereby the prevalence was also approximately twice as high compared with contemporary trends). Over the past few decades, the reduction of blood cholesterol levels and of the prevalence of smoking has provided important reductions in ACVD risk across the population, although the slope of the reduction of ACVD risk has plateaued during the past 10 years (15). In parallel, other ACVD risk factors are currently on the rise. For instance, a recent study has shown that the worldwide prevalence of diabetes mellitus has almost doubled over the past three decades. During this period, we have turned into a society wherein the consumption of processed foods with poor nutritional value and sugar-sweetened beverages is nowadays the norm rather than the exception. Hence, elevated blood cholesterol level nowadays is rarely found in isolation, most frequently observed within a constellation of other risk factors such as abdominal obesity, insulin resistance and systemic inflammation. Additionally, although low-density lipoprotein (LDL) cholesterol levels may not be higher in these patients, individuals with abdominal obesity and insulin resistance are often hypertriglyceridemic, characterized by a greater proportion of small, dense LDL particles with a higher atherogenic potential compared with patients with larger and more buoyant LDL particles (16). Therefore, consideration should be given to apolipoprotein B (an estimate of the number of circulating LDL particles) levels or non-high-density lipoprotein cholesterol levels as these are stronger predictors of cardiovascular events compared to LDL cholesterol levels, even in patients treated with statins (17).

The joint epidemics of obesity and type 2 diabetes have been on the radar screen of public health organizations for a number of years. Therefore, in their strategy to reduce the burden of ACVD by 2020, the American Heart Association (AHA) has suggested to focus on seven risk factors for optimally managing ACVD risk: high cholesterol levels, high blood pressure, diabetes, an elevated body mass index, smoking, unhealthy eating and physical inactivity. Although

a handful of studies have shown that meeting all seven AHA criteria for a healthy heart can be associated with a 80–90% CVD risk reduction in classical epidemiological studies (18-20), no RCTs have tested the hypothesis that reducing cholesterol in the context of the management of other clinical and lifestyle-related risk factors could improve cardiovascular outcomes over time. Interestingly, the Finnish Diabetes Prevention Study provided evidence that a legacy benefit can be observed with lifestyle modification therapy aimed at improving dietary quality and physical activity levels for the prevention of type 2 diabetes in overweight individuals with pre-diabetes, 13 years following the initiation of a 4-year trial (21). Other legacy trials have been conducted in the context of preventing micro and macrovascular complications in diabetic patients. For instance, results of the UKPDS follow-up study suggest that the sustained, early intensive control of blood glucose levels eventually translates into a significant benefit upon the development of ACVD many years down the track (22). Although the biological mechanisms pertaining to this 'legacy' effect are currently unknown, the legacy effect trials provide evidence supporting the initiation of anti-atherosclerotic therapies. Even if long-term compliance to such therapies may be compromised for various reasons, longer-term benefits akin to 'vascular memory' could be observed. Investigators of ongoing or future trials conducted across different population subsets should consider conducting similar investigations to either extend or refute these findings with other anti-atherosclerotic compounds, and identify the underlying biological mechanisms that could thus explain these legacy effects.

The WOSCOPS investigators have provided convincing evidence to reinforce the notion that cholesterol lowering with statins can lead to clinically significant cardiovascular benefits across almost the entire lifespan in patients with hypercholesterolemia, supporting the concept that a more widespread use of statins in at-risk patients could reduce cardiovascular mortality and morbidity. Although widespread statin use has contributed to the observed decrease in cardiovascular mortality during the past few decades (23), cardiovascular mortality rates have stopped declining, possibly as a consequence of counterproductive adverse lifestyle-related diseases such as obesity and type 2 diabetes. Managing cholesterol levels with statins in high-risk primary prevention cohorts therefore needs to be supplemented by lifestyle changes that target dietary quality and physical activity levels if we want to be successful at further reducing the global burden of ACVD.

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References

1. Tsao CW, Vasan RS. Cohort Profile: The Framingham Heart Study (FHS): overview of milestones in cardiovascular epidemiology. Int J Epidemiol 2015;44:1800-13.
2. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937-52.
3. Pedersen TR. The Success Story of LDL Cholesterol Lowering. Circ Res 2016;118:721-31.
4. Cohen JC, Boerwinkle E, Mosley TH Jr, et al. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264-72.
5. Helgadottir A, Gretarsdottir S, Thorleifsson G, et al. Variants with large effects on blood lipids and the role of cholesterol and triglycerides in coronary disease. Nat Genet 2016;48:634-9.
6. Ference BA, Yoo W, Alesh I, et al. 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.
7. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.
8. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe

Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015;372:2387-97.
9. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med 2016;374:2021-31.
10. Pedersen TR, Wilhelmsen L, Faergeman O, et al. Follow-up study of patients randomized in the Scandinavian simvastatin survival study (4S) of cholesterol lowering. Am J Cardiol 2000;86:257-62.
11. Heart Protection Study Collaborative Group, Bulbulia R, Bowman L, et al. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. Lancet 2011;378:2013-20.
12. Sever PS, Chang CL, Gupta AK, et al. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the U.K. Eur Heart J 2011;32:2525-32.
13. Ford I, Murray H, McCowan C, et al. 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;133:1073-80.
14. 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.
15. Ma J, Ward EM, Siegel RL, et al. Temporal Trends in Mortality in the United States, 1969-2013. JAMA 2015;314:1731-9.
16. Arsenault BJ, Lemieux I, Després JP, et al. Cholesterol levels in small LDL particles predict the risk of coronary heart disease in the EPIC-Norfolk prospective population study. Eur Heart J 2007;28:2770-7.
17. Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. JAMA 2012;307:1302-9.
18. Folsom AR, Yatsuya H, Nettleton JA, et al. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. J Am Coll Cardiol 2011;57:1690-6.
19. Lachman S, Peters RJ, Lentjes MA, et al. Ideal cardiovascular health and risk of cardiovascular events in the EPIC-Norfolk prospective population study. Eur J Prev Cardiol 2016;23:986-94.
20. Akesson A, Larsson SC, Discacciati A, et al. Low-risk diet and lifestyle habits in the primary prevention of myocardial infarction in men: a population-based prospective cohort study. J Am Coll Cardiol 2014;64:1299-306.
21. Lindström J, Peltonen M, Eriksson JG, et al. Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS). Diabetologia 2013;56:284-93.
22. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
23. Young F, Capewell S, Ford ES, et al. Coronary mortality declines in the U.S. between 1980 and 2000 quantifying the contributions from primary and secondary prevention. Am J Prev Med 2010;39:228-34.

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