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New metrics needed to visualize the long-term impact of early LDL-C lowering on the cardiovascular disease trajectory

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Abstract

Short-term absolute cardiovascular event rates in young/middle-aged people are low even if they have risk factors, and parameters such as number-needed-to-treat over 5 years are inadequate to visualize and to communicate the lifelong benefit of interventions such as statin therapy to individuals and to healthcare providers. To understand more fully the impact of risk factors, and lifestyle and pharmacological interventions, there is a need to focus on disease trajectory over a lifetime and to develop new metrics of success. A shift to primordial ('true') prevention of the formation of atherosclerotic lesions will require new tools and approaches in the interaction between physicians and patients as individuals or populations.

Keywords

Risk; Cardiovascular; Disease trajectory; NNT; LDL-C; Metrics

1. Introduction

Atherogenesis is initiated, and progresses, by the life-long, multiplicative action of intrinsic predisposing traits (e.g., genetic variants, gender) and extrinsic risk factors acting on the arterial endothelium and underlying vessel wall. In exploring the genesis of a disease and the potential for intervention, the view of a medical field can be narrowed inadvertently by adopting constructs that limit critical thinking around the scope and ambition of treatment and prevention strategies. In a paradigm that can trace its origins back to the LRC Cholestyramine Trial we have become used to talking about 'relative risk reduction' (larger the better), LDL goals, secondary and primary prevention (a simplistic dichotomy discordant with the underlying disease process), and 'residual risk' (with the wrong implication that the residuum can be eliminated). While these have been helpful concepts to visualize the results of pivotal clinical trials and establish the evidence base, arguably it is time to develop a

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framework that better reflects the lifelong pathogenesis of atherosclerotic disease, and the possibilities for more effective intervention. History tells us that we should be ambitious since vascular disease is largely preventable as evidenced by the epidemiological transition in CVD mortality which from its peak in 1967 has declined 70%.

2. Disease trajectory and lifetime risk

Atherosclerosis is a decade-long disease process [1]. Fatty lesions are present in the coronary vasculature of young people, and with time these become more numerous, complex and fragile (Fig. 1). Thus, in most adults a variety of lesions is present with more advanced plaques undergoing rupture, repair and remodelling in a clinically silent process. Originally, we were dependent mainly on autopsy information to understand the nature of the condition in man but in recent years improved techniques for vascular imaging have enhanced our understanding of atherogenesis, revealing the underlying pathology even in asymptomatic individuals. We are now at a stage where advanced imaging of arterial beds holds the promise of developing individualized assessments of vascular disease trajectories [8,9].

As plaques develop and age their reversibility decreases. The clinical horizon is reached when cap rupture exposes a large pro-thrombotic surface and the clotting potential in blood is chronically or episodically high. It follows that all are on a CVD trajectory where the probability of a clinical event is determined by non-modifiable (age, sex, genes) and modifiable risk factors (smoking, diet, physical activity, blood pressure, lipids). The concept of lifetime risk usefully moves the focus away from short term, age-dominated risk estimation and associated treatment strategies towards lifelong goals for intervention [2,10,11]. Establishing early the lowest possible trajectory for a given non-modifiable background is the epitome of effective prevention. In this paradigm, the best results come from ‘primordial prevention’ [3,12] aimed at avoiding fatty streak formation or converting nascent lesions to stable structures.

Communicating this preventive strategy, in which health benefits are earned after decades, to symptom-free young adults warrants the development of better metrics of success, a better assessment of the impact of intervention, and a targeted approach to treatment. Genetic studies can help greatly in this discussion. Inheritance of gene variants that lead to lower than average circulating levels of LDL is associated with reduced risk of CVD. Further, the relation between genetically determined LDL-C concentration and CV risk is linear and steeper than that seen in intervention trials (that is the decrement in CVD risk per unit drop in LDL is much greater in Mendelian randomisation studies than in statin based clinical trials). This emerging evidence is dramatic proof of the “dose-dependent” effect of life-long exposure to LDL-C, and a strong signal that the earlier the intervention, the better the result [4,13].

3. Metrics – lifetime benefit/gain in event-free years

While formal analysis of trials is based on the first major event, a patient’s vascular journey encompasses subsequent outcomes including, potentially, heart failure, dementia, or sudden cardiac death. The importance of considering *lifetime benefit* is highlighted by the recent

WOSCOPS 15 year health economic analysis [5,14]. Here it was seen that while 5 years of within-trial statin treatment led to a 30% reduction in CVD risk, over the next 10 years there was a significant decrease in stroke and a 45% fall in the rate of heart failure. Clearly if we judge the impact of therapy solely on relative/absolute risk reduction of the first event, we underestimate substantially the lifetime benefit that accrues from LDL lowering therapy (and other forms of risk factor control).

Further, relative and absolute risk reduction, number-needed-to-treat and other yardsticks that we traditionally use are not easy to explain to general physicians and to patients. Other areas of medicine talk about ‘increased survival’ and ‘% event free’, and we in the cardiovascular community could usefully adopt similar terminology that will be more readily understood and helpful in setting out the benefits of early intervention; examples are ‘*gain in event free years*’ or ‘*vascular age*’ (Fig. 1). Quantifying these metrics that describe an altered disease trajectory is a challenge which requires prolonged follow-up, but this is increasingly achievable with the advent of electronic health records [5,14].

4. Impact – prevention versus postponement

The goal in asymptomatic ‘low-risk’ patients and those with established CVD is to reduce modifiable risk (Fig. 1) but in later life there is probably a limit to the extent to which complex plaques can regress, and the most likely outcome is remodelling to generate a more stable lesion and postponement of future events [1]. Meta-analysis of statin trials has revealed that a 1.0 mmol/l (38.7 mg/dl) decrease in LDLc leads to a 22% relative risk reduction [6,15]. However, recent genomic studies of loci regulating LDL [4,13] suggest that clinical trials in middle aged/older individuals have underestimated the impact of therapy and that a drop in LDL of this magnitude if lifelong is associated with a 40 to 50% decrement in CVD. These observations support the concept that early prevention of lesion formation rather than plaque stabilisation later may deliver a quantitatively greater benefit.

5. Stratified medicine

Recent genomic studies and trial evidence have re-focussed our attention on a single target – LDL. This lipoprotein, low in teenagers, increases about 50% by 40 years of age. If its low level in the young could be maintained in those with the greatest propensity to develop CVD then primordial prevention becomes possible. Identification of genes [4,13,16] that regulate LDL opens the way to using genetic screening in the population, or in families at risk, especially with familial hypercholesterolemia, to select those that may need early pharmacologic therapy while the general population receives broad lifestyle advice. A targeted approach to statin use helps optimise the benefit to risk ratio [7], and a similar, appropriate early use of other therapies as they are developed will also substantially contribute to minimizing risk.

In conclusion, there is arguably a pressing need for a multidisciplinary effort to build a better conceptual framework and communication tools based on understanding of the disease trajectory of CVD to aid both doctors and patients in grasping lifetime risk, the lifelong goals of therapy and the potentially large benefits of early intervention.

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Disease trajectories in CHD prevention

Fig. 1.

Disease trajectories in CHD prevention. Atherosclerosis starts in most people in early adult life. Fatty streaks appear that graduate to more complex lesions in a decades-long process of cholesterol accumulation, thickening of the artery wall, formation of focal lesions and increased cellularity. Lesions with a high content of macrophages and a thin cap are considered unstable and likely to rupture; those rich in smooth muscle cells and collagen are more stable. The diagram shows idealized, age-based disease trajectories. A significant part of the total risk of a vascular event is non-modifiable by current strategies (i.e., it is due to factors such as sex and variation in key predisposing genes). Age-related changes take place in the vasculature and atherosclerosis progresses even in people with apparently '*optimal risk factor status*' (non-smokers, lean, normal blood pressure etc.) as indicated by the blue-shaded area and green line. Individuals with single or multiple lifestyle or environmental risk factors (high LDL, raised blood pressure, obesity) have a steeper trajectory as shown by the red line and clinical events may occur in middle age. These risk factors can be modified through prudent lifestyle, exercise and drug use, and if their effects on the artery wall could be eliminated completely then this gives a measure of the '*total modifiable risk*' (subjects would move from the red to green trajectory). Intervention with drugs such as statins lowers LDL and as a result stabilises lesions. However, we know from clinical trials in mid to late life that this first-line treatment strategy reduces only part of the modifiable risk and there remains a '*residual modifiable risk*' (as depicted by the dotted blue line) that can be addressed by more intensive treatment with higher statin doses or with adjunct drugs or more aggressive lifestyle change. In later life, given the existence and complexity of atherosclerotic lesions it is likely that the residual risk cannot be eliminated entirely even if

all risk factors are treated and the trajectory will remain above that considered optimal (solid blue line). There is an increasing appreciation that a strategy of primordial, possibly stratified, prevention will yield the best outcome for people at risk. In this approach intervention starts early in life on order to prevent the formation of lesions. The individual may then indeed follow the optimum trajectory. These concepts can be explained better using new metrics of CVD prevention such as *gain in event free years*, *vascular age* and *life-years* gained.