Commentary

Identification and treatment of those most at risk for premature atherosclerotic cardiovascular disease: We just cannot seem to get it right

ARTICLE INFO

Keywords
Atherosclerosis
Coronary artery calcium
Diabetes mellitus
Low-density lipoprotein cholesterol
Premature coronary artery disease
Risk estimation

1. Introduction

With the exception of age, sex, and genetic background, the most important clinical factors that determine risk for developing atherosclerotic cardiovascular disease (ASCVD) are modifiable: dyslipidemia, hypertension, insulin resistance/diabetes mellitus, obesity, smoking, and inactivity [1]. The impact of modifiable risk factors on risk for ASCVD can readily be attenuated through pharmacologic intervention and lifestyle modification. Evidence-based guidelines for managing dyslipidemia, hypertension, obesity, and diabetes are crafted with extreme care and updated on a regular basis in an effort to reflect the most recent findings from important clinical trials [2–4]. Despite all that we have learned, recommendations from guidelines tend to be poorly followed as reflected by multiple decades worth of data showing poor goal attainment rates for specific risk factors and appropriate medications being under-utilized, under-titrated, or not used at all even when they are clearly clinically indicated [5–8].

When considered over the lifetime of an individual with an “average” background of risk factors, the arterial vasculature is subjected to considerable physiological abuse from toxic lipids, variations in hydrostatic pressure, inflammatory mediators, increased oxidative tone, and a plethora of interactions between endothelial cells and such blood components as platelets and leukocytes, among other deleterious influences. Arterial injury accrues progressively over time, initiating a variety of maladaptive, pathophysiological responses promoting atherogenesis. It is clear that there is nothing “essential” about hypertension, when it comes to cholesterol lower is better, and even modestly elevated serum glucose levels can induce endothelial dysfunction and drive atherogenesis. There is generally a fine line between normal function and the initiation of nuclear transcription and cytosolic biochemical signaling pathways that precipitate the constellation of responses giving rise to cardiovascular disease. We have the means to intercept much of this at an early stage, yet so often appropriate intervention is not taken (due to inertia on the part of both patients and clinicians) and patients go on to develop ASCVD and its sequelae, including myocardial infarction (MI), stroke, need for coronary and peripheral revascularization, and death. A variety of risk calculators are available [9,10], but most clinicians do not take the time to use them or it is felt they either over-estimate or under-estimate risk in certain groups [11,12], thereby discouraging their application. True primordial prevention intercepts pathogenic mechanisms before disease assumes a foothold. It is likely that the majority of patients we consider to be in the primary prevention setting already have some degree of ASCVD. This is a suboptimal approach to ASCVD prevention.

2. Low-density lipoprotein cholesterol

LDL-C is the end product apo B-containing lipoproteins. It is an endovascular toxin with a dose-response relationship to risk for ASCVD. There is no evidence to substantiate the widely held view that there is some minimal level of this lipoprotein in blood that is necessary to sustain life or that if its serum level is reduced below this “threshold,” risk for adverse events somehow increase. The log-linear relationship between LDL-C and the hazard ratio for an acute cardiovascular event is unity at an LDL-C of approximately 40 mg/dL [13], which also closely approximates the LDL-C on average of infants and hunter-gatherer populations [14]. This should be considered to be physiologically “normal.” Clearly, the LDL-C levels characterizing populations around the world exceed levels that are physiologically safe; this conclusion is unequivocally supported by the fact that ASCVD remains the leading cause of death and disability in most nations. Epidemiologic observational studies as well as genome-wide association and mendelian randomization studies clearly support the conclusion that when it comes to polymorphisms that lead to lifelong reductions in LDL-C, risk is reduced in
proportion to the magnitude of LDL-C reduction [15,16]. Risk reduction from congenitally reduced LDL-C exceeds that observed in clinical trials with lipid-lowering agents because the reduction is incurred from the moment of conception, thereby reducing the total duration of exposure (area under the curve) to toxic levels of this lipoprotein [17]. Risk reduction in this context is proportional to both the magnitude of reduction in LDL-C and the duration of time over which this reduction is sustained. In an elegant trajectory analysis of the Framingham Offspring Study spanning 35 years, it was shown that persons with lifelong “borderline” LDL-C levels (115–120 mg/dL) have a 2.9-fold higher incidence of ASCVD compared to persons with “optimal” LDL-C defined as lifelong 80–90 mg/dL [18].

Atherosclerosis begins at an early age and its clinical manifestations generally become apparent in the 6th or 7th decade of life. Risk factor burden early in life predicts risk of ASCVD in adulthood. In the Muscatine study, the presence of ASCVD risk factors at age 15 years was predictive of coronary artery calcification (CAC) in early adulthood in both men and women [19]. The Cardiovascular Risk in Young Finns study demonstrated that LDL-C levels measured in childhood were highly predictive of common carotid artery intima media thickness (CIMT) after 21 years of follow-up [20]. The Bogalusa Heart Study similarly found that baseline LDL-C levels of children were highly predictive of CAC in adulthood (age 25–37 years); there was a statistically significant trend for increasing CIMT across quartiles [21]. In the Coronary Artery Risk Development in Young Adults (CARDIA study, the baseline Pathobiological Determinants of Atherosclerosis in Youth (PDAY) risk score measured at age 18–30 years was highly predictive of CAC and abdominal aortic calcium deposition after 25 years of follow-up [22]. Among unfortunate young men (mean age 22 years) killed in the Korean [23] and Vietnam [24] Wars, 77% and 45%, respectively, already had anatomically evident coronary artery disease. In another study of men killed in Vietnam (mean age 20 years), 19% already atherosclerotic lesions >50% obstructive [25]. A sample of young men and women (mean age 25.6 years) killed from noncardiac trauma revealed that 75.8% had established atherosclerotic plaques and 21% had lesions >50% obstructive [26].

3. Premature coronary artery disease

Generally, premature CAD is defined as the presence of coronary atherosclerosis in men <55 years and <65 years in women, though definitions vary study to study. CAD in young adults occurs at age <45 years. A family history of premature CAD escalates risk for ASCVD substantially. Obstructive sleep apnea, even after adjustment for other risk covariates, correlates with a 2.1-fold higher risk of familial premature CAD mortality [27]. Premature CAD is an agressive form of ASCVD, progression can be fulminant, and correlates highly with dyslipidemia, male sex, smoking, inflammatory disease, hypertension and, understandably, family history of premature CAD [28,29]. Hence, many of the principal risk factors for premature CAD are modifiable. If inadequately treated, long-term prognosis for these patients is generally poor, mandating very aggressive risk factor identification and control [30]. Risk factors for progression of CAD and first recurrent event in patients with premature CAD include continue smoking, inadequate control of diabetes and hypertension, persistent inflammatory disease, and sub-Saharan African race [29]. Although risk scoring algorithms frequently underestimate risk in patients who develop premature CAD, CAC measurement substantially increases our ability to identify these patients [31]. In the Dallas Heart Study, among the young (men aged <45 years and women <55 years), a family history of premature CAD was an independent predictor of CAC, particularly among those participants with two or more ASCVD risk factors [32]. Among 3514 participants aged 40–54 years in the Progression of Early Subclinical Atherosclerosis (PESA) study, not unexpectedly, dyslipidemia, smoking, family history of premature CAD, and hypertension all correlated with progression of atherosclerotic disease. Of these risk factors, dyslipidemia was the strongest modifiable risk factor [33]. The PESA study also demonstrated that 61.8% of these apparently healthy participants already had subclinical atherosclerosis and 40% experienced some degree of progression over 3 years of follow-up in either the coronary or peripheral vascular territories.

Among men and women aged <55 years, from 1979 to 1989 there was a significant reduction in CV mortality. However, during the next 20 years, this age group did not experience further improvements in CV mortality [34]. In contrast, older age groups continued to experience improvements in CV mortality. This is quite puzzling given the fact that the years proceeding forward from 1990 were associated with the introduction of statins, β-blockers and angiotensin converting enzyme inhibitors, and antiplatelet agents as standard of care for patients with CAD. This attests to the challenges intrinsic to the treatment of the younger age group with CAD. Despite all we know about risk factors and their management, the incidence of premature CAD (men < 50 years, women < 55 years) was stable for both men and women between 2000 and 2016 [35]. This incidence was 46–53 vs 18–23 per 100,000 for men and women, respectively. Between 2007 and 2016, a period of time when approaches to ASCVD prevention and treatment were well defined, mortality rates for these groups remained unchanged. Among women <45 years, mortality was higher than for men. In totality, these data suggest that identification of patients with premature CAD is poor and their management leaves many of these patients vulnerable to acute CV events due to inadequate intensity of intervention with pharmacologic agents and lifestyle modification.

4. Study to avoid cardiovascular events in British Columbia (save BC)

In this issue of the AJPC, Vikulova and coworkers leverage the SAVE BC [36] cohort of 417 patients (72% male) with premature CAD (males ≤ 50 years and females ≤ 55 years) to compare the capacity of the US [37], Canadian [38], and European [39] guidelines to correctly estimate ASCVD risk and identify patients likely to benefit from risk reduction with statins, quantify statin usage and LDL-C target attainment, and evaluate risk factors that increase the likelihood of statin treatment. Participants had a luminal stenosis of ≥50% on angiography in at least one epicardial artery after presenting with a first acute coronary syndrome (ST-segment and non-ST-segment elevating MIs, stable or unstable angina pectoris, or referral for elective coronary angiography). The findings of these investigators are discouraging and show that current approaches to identifying and treating patients with premature CAD continue to be remarkably inadequate.

Median ages for study participants were 45.9 and 50.7 years for men and women, respectively. Participants had major CV risk factors at baseline: 94.3% had at least one, and 26.9%, 25.2%, and 23.5% had two, three, or four or more major risk factors, respectively. The prevalence of dyslipidemia, family history of premature CAD, hypertension, current smoking, obesity, and diabetes were 68.6%, 41%, 47%, 41%, 27%, respectively. More than 18% of female participants had a history of gestational diabetes, 10.3% met criteria for familial hypercholesterolemia (FH), and 23% had diabetes and met criteria for statin therapy. Of these participants, only 41.7%, 61.4%, and 34.3% would qualify for statin therapy according to the US, Canadian, and European guidelines, respectively. Only 11.0% of participants attained their guideline-stipulated LDL-C goal before presentation and, of particular importance, only 17% of the total number of patients were prescribed statins prior to their diagnosis of CAD. Of particular note are the observations that 29% of patients with FH and 31% with diabetes were treated with statins. Of greater concern is the fact that only 3.4% and 14.3% attained their lipid targets on therapy, a family history of premature onset CAD was not associated with treatment, and cigarette smoking was inversely associated with treatment.

These findings are cause for grave concern and highlight a number of issues. First, none of the risk calculators are particularly good at...
identifying persons at high risk for premature CAD. Second, the low rates of treatment for persons with FH, diabetes, family history of premature CAD, and multiple CV risk factors is alarming. Lipid target attainment rates for patients with FH and diabetes are also remarkably low given that they, too, confer marked elevation in ASCVD risk. Third, smoking was inversely associated with the prescription for statins, despite the fact that it is well known that smokers also benefit substantially from statin therapy in both the primary and secondary prevention settings [40,41].

Given all that we know about atherogenesis and CAD prevention, it is extraordinary that a family history of premature CAD and cigarette smoking did not prompt the initiation of statin therapy. Both are highly established major CV risk factors.

The reticence for treating patients, including young patients, with statins needs to end. The inclination to treat patients at risk with inappropriately low doses of statins and the inertia in titrating statins so as to facilitate lipid target attainment is also a global problem. The reduction of CV risk with statins is one of the most highly investigated issues in the entire history of medicine. Much work has been done to date on characterizing barriers to the initiation and sustained usage of statins. Yet, progress in this area is extraordinarily difficult to achieve. Given the dramatic impact CAD of premature onset has on the lives of those affected, effort needs to be made to augment earlier and more accurate identification of these patients. In addition, it is clear that lipid guidelines are still not appropriately applied in everyday patient care. This suggests that they are either too complicated for the average health care provider to understand and institute, or the perceived risks of statin therapy remain heavily exaggerated and their broad spectrum of benefits remain heavily exaggerated and their broad spectrum of benefits.

Declaration of competing interestCOI

The reticence for treating patients, including young patients, with statins needs to end. The inclination to treat patients at risk with inappropriately low doses of statins and the inertia in titrating statins so as to facilitate lipid target attainment is also a global problem. The reduction of CV risk with statins is one of the most highly investigated issues in the entire history of medicine. Much work has been done to date on characterizing barriers to the initiation and sustained usage of statins. Yet, progress in this area is extraordinarily difficult to achieve. Given the dramatic impact CAD of premature onset has on the lives of those affected, effort needs to be made to augment earlier and more accurate identification of these patients. In addition, it is clear that lipid guidelines are still not appropriately applied in everyday patient care. This suggests that they are either too complicated for the average health care provider to understand and institute, or the perceived risks of statin therapy remain heavily exaggerated and their broad spectrum of benefits remain heavily exaggerated and their broad spectrum of benefits.

Declaration of competing interestCOI

The reticence for treating patients, including young patients, with statins needs to end. The inclination to treat patients at risk with inappropriately low doses of statins and the inertia in titrating statins so as to facilitate lipid target attainment is also a global problem. The reduction of CV risk with statins is one of the most highly investigated issues in the entire history of medicine. Much work has been done to date on characterizing barriers to the initiation and sustained usage of statins. Yet, progress in this area is extraordinarily difficult to achieve. Given the dramatic impact CAD of premature onset has on the lives of those affected, effort needs to be made to augment earlier and more accurate identification of these patients. In addition, it is clear that lipid guidelines are still not appropriately applied in everyday patient care. This suggests that they are either too complicated for the average health care provider to understand and institute, or the perceived risks of statin therapy remain heavily exaggerated and their broad spectrum of benefits remain heavily exaggerated and their broad spectrum of benefits.

Declaration of competing interestCOI

The reticence for treating patients, including young patients, with statins needs to end. The inclination to treat patients at risk with inappropriately low doses of statins and the inertia in titrating statins so as to facilitate lipid target attainment is also a global problem. The reduction of CV risk with statins is one of the most highly investigated issues in the entire history of medicine. Much work has been done to date on characterizing barriers to the initiation and sustained usage of statins. Yet, progress in this area is extraordinarily difficult to achieve. Given the dramatic impact CAD of premature onset has on the lives of those affected, effort needs to be made to augment earlier and more accurate identification of these patients. In addition, it is clear that lipid guidelines are still not appropriately applied in everyday patient care. This suggests that they are either too complicated for the average health care provider to understand and institute, or the perceived risks of statin therapy remain heavily exaggerated and their broad spectrum of benefits remain heavily exaggerated and their broad spectrum of benefits.

Declaration of competing interestCOI

The reticence for treating patients, including young patients, with statins needs to end. The inclination to treat patients at risk with inappropriately low doses of statins and the inertia in titrating statins so as to facilitate lipid target attainment is also a global problem. The reduction of CV risk with statins is one of the most highly investigated issues in the entire history of medicine. Much work has been done to date on characterizing barriers to the initiation and sustained usage of statins. Yet, progress in this area is extraordinarily difficult to achieve. Given the dramatic impact CAD of premature onset has on the lives of those affected, effort needs to be made to augment earlier and more accurate identification of these patients. In addition, it is clear that lipid guidelines are still not appropriately applied in everyday patient care. This suggests that they are either too complicated for the average health care provider to understand and institute, or the perceived risks of statin therapy remain heavily exaggerated and their broad spectrum of benefits remain heavily exaggerated and their broad spectrum of benefits.

Declaration of competing interestCOI

The reticence for treating patients, including young patients, with statins needs to end. The inclination to treat patients at risk with inappropriately low doses of statins and the inertia in titrating statins so as to facilitate lipid target attainment is also a global problem. The reduction of CV risk with statins is one of the most highly investigated issues in the entire history of medicine. Much work has been done to date on characterizing barriers to the initiation and sustained usage of statins. Yet, progress in this area is extraordinarily difficult to achieve. Given the dramatic impact CAD of premature onset has on the lives of those affected, effort needs to be made to augment earlier and more accurate identification of these patients. In addition, it is clear that lipid guidelines are still not appropriately applied in everyday patient care. This suggests that they are either too complicated for the average health care provider to understand and institute, or the perceived risks of statin therapy remain heavily exaggerated and their broad spectrum of benefits remain heavily exaggerated and their broad spectrum of benefits.

Declaration of competing interestCOI

The reticence for treating patients, including young patients, with statins needs to end. The inclination to treat patients at risk with inappropriately low doses of statins and the inertia in titrating statins so as to facilitate lipid target attainment is also a global problem. The reduction of CV risk with statins is one of the most highly investigated issues in the entire history of medicine. Much work has been done to date on characterizing barriers to the initiation and sustained usage of statins. Yet, progress in this area is extraordinarily difficult to achieve. Given the dramatic impact CAD of premature onset has on the lives of those affected, effort needs to be made to augment earlier and more accurate identification of these patients. In addition, it is clear that lipid guidelines are still not appropriately applied in everyday patient care. This suggests that they are either too complicated for the average health care provider to understand and institute, or the perceived risks of statin therapy remain heavily exaggerated and their broad spectrum of benefits remain heavily exaggerated and their broad spectrum of benefits.

Declaration of competing interestCOI

The reticence for treating patients, including young patients, with statins needs to end. The inclination to treat patients at risk with inappropriately low doses of statins and the inertia in titrating statins so as to facilitate lipid target attainment is also a global problem. The reduction of CV risk with statins is one of the most highly investigated issues in the entire history of medicine. Much work has been done to date on characterizing barriers to the initiation and sustained usage of statins. Yet, progress in this area is extraordinarily difficult to achieve. Given the dramatic impact CAD of premature onset has on the lives of those affected, effort needs to be made to augment earlier and more accurate identification of these patients. In addition, it is clear that lipid guidelines are still not appropriately applied in everyday patient care. This suggests that they are either too complicated for the average health care provider to understand and institute, or the perceived risks of statin therapy remain heavily exaggerated and their broad spectrum of benefits remain heavily exaggerated and their broad spectrum of benefits.

Declaration of competing interestCOI

The reticence for treating patients, including young patients, with statins needs to end. The inclination to treat patients at risk with inappropriately low doses of statins and the inertia in titrating statins so as to facilitate lipid target attainment is also a global problem. The reduction of CV risk with statins is one of the most highly investigated issues in the entire history of medicine. Much work has been done to date on characterizing barriers to the initiation and sustained usage of statins. Yet, progress in this area is extraordinarily difficult to achieve. Given the dramatic impact CAD of premature onset has on the lives of those affected, effort needs to be made to augment earlier and more accurate identification of these patients. In addition, it is clear that lipid guidelines are still not appropriately applied in everyday patient care. This suggests that they are either too complicated for the average health care provider to understand and institute, or the perceived risks of statin therapy remain heavily exaggerated and their broad spectrum of benefits remain heavily exaggerated and their broad spectrum of benefits.

Declaration of competing interestCOI

The reticence for treating patients, including young patients, with statins needs to end. The inclination to treat patients at risk with inappropriately low doses of statins and the inertia in titrating statins so as to facilitate lipid target attainment is also a global problem. The reduction of CV risk with statins is one of the most highly investigated issues in the entire history of medicine. Much work has been done to date on characterizing barriers to the initiation and sustained usage of statins. Yet, progress in this area is extraordinarily difficult to achieve. Given the dramatic impact CAD of premature onset has on the lives of those affected, effort needs to be made to augment earlier and more accurate identification of these patients. In addition, it is clear that lipid guidelines are still not appropriately applied in everyday patient care. This suggests that they are either too complicated for the average health care provider to understand and institute, or the perceived risks of statin therapy remain heavily exaggerated and their broad spectrum of benefits remain heavily exaggerated and their broad spectrum of benefits.

Declaration of competing interestCOI

The reticence for treating patients, including young patients, with statins needs to end. The inclination to treat patients at risk with inappropriately low doses of statins and the inertia in titrating statins so as to facilitate lipid target attainment is also a global problem. The reduction of CV risk with statins is one of the most highly investigated issues in the entire history of medicine. Much work has been done to date on characterizing barriers to the initiation and sustained usage of statins. Yet, progress in this area is extraordinarily difficult to achieve. Given the dramatic impact CAD of premature onset has on the lives of those affected, effort needs to be made to augment earlier and more accurate identification of these patients. In addition, it is clear that lipid guidelines are still not appropriately applied in everyday patient care. This suggests that they are either too complicated for the average health care provider to understand and institute, or the perceived risks of statin therapy remain heavily exaggerated and their broad spectrum of benefits remain heavily exaggerated and their broad spectrum of benefits.
progression of multiterritorial subclinical atherosclerosis. J Am Coll Cardiol 2020; 75(14):1617–27.

[34] Wilmot KA, O’Raherty M, Capewell S, Ford ES, Vaccarino V. Coronary heart disease mortality declines in the United States from 1979 through 2011: evidence for stagnation in young adults, especially women. Circulation 2015;132(11):997–1002.

[35] Vikulova DN, Grubisic M, Zhao Y, Lynch K, Humphries KH, Pimstone SN, Brunham LR. Premature atherosclerotic cardiovascular disease: trends in incidence, risk factors, and sex-related differences, 2000 to 2016. J Am Heart Assoc 2019; 8(14):e012178.

[36] Brunham LR, Lynch K, English A, Sutherland R, Weng J, Cho R, Wong CC, Anis AH, Francis GA, Khan NA, et al. The design and rationale of SAVE BC: the study to avoid CardioVascular events in British Columbia. Clin Cardiol 2018;41(7):888–95.

[37] Grundy SM, Stone NJ, Bailey AL, Beam C, Bircher KK, Blumenthal RS, Braun LT, Ferrari Sd, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/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(25):e1082–143.

[38] Anderson TJ, Grégoire J, Pearson GJ, Barry AR, Couture P, Dawes M, Francis GA, Genest Jr J, Grover S, Gupta M, et al. 2016 Canadian cardiovascular society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2016;32(11):1263–82.

[39] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(1):111–88.

[40] Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344(8934): 1383–9.

[41] Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333(20):1301–8.

Peter P. Toth∗
CGH Medical Center, Sterling, IL, USA
Cicarrone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, MD, USA

∗ Rock Falls Medical Center, 1315 Dixon Avenue, Rock Falls, IL, 61071, USA.

E-mail address: peter.toth@cghmccom.