

# The Rationale for a Different Approach to Preventing Cardiovascular Disease

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## Abstract

**The Problem:** We have previously suggested that an alternative approach to preventing cardiovascular disease is necessary because atherosclerotic cardiovascular disease (ASCVD) has been increasing for the last 50 years and has now reached epidemic status. Since the year 2000, approximately 600,000 heart attacks and ASCVD related deaths have occurred annually in the United States. It is the most common cause of death in the U.S., more than all cancers combined. The financial costs are staggering, amounting to 555 billion dollars per year in direct and indirect costs. Outlook for an improvement in these statistics is not encouraging as the U.S. population continues to become more obese and to develop diabetes. **The Question:** Why is ASCVD continuing to be a major challenge to healthcare providers when the pathogenesis is known and inexpensive preventative treatment is available? The reasons are multiple and complex. First, present financial reimbursement policies of healthcare organizations reward treatment of a disease and its complications instead of preventing the disease. Second, professional guidelines and treatment goals are often too complex, subject to interpretation, and time-consuming to be useful in the clinical setting. Third, no specific follow-up of patients at risk for ASCVD is recommended when the risk assessment changes. Fourth, many expensive cardiovascular diagnostic tests are utilized without meeting appropriate guidelines for their use. Fifth, treatment of individuals without first proving the presence of disease results in poor adherence to therapy. **The Solution:** This article describes the rationale for a new approach to the prevention of ASCVD in asymptomatic individuals. It is based upon preventing ASCVD by identifying all asymptomatic individuals

with subclinical disease before an ASCVD event occurs. It recommends that all adults be screened for ASCVD on or before the age of 50 using a non-invasive atherosclerosis specific coronary artery calcium heart scan. Further recommendations include treating all calcium positive individuals to reverse their atherosclerotic coronary artery plaques with a combination of a low cholesterol diet, rosuvastatin 10 mg/day, and ezetimibe 10 mg/day. The therapeutic goal is a low-density lipoprotein cholesterol below 50 mg/dl to ensure regression of atherosclerosis. For individuals who have a zero calcium score, a repeat scan in 3 to 5 years is recommended. This new approach can easily be integrated into ongoing heart disease prevention programs to reduce the burden of ASCVD within the next five years. **Conclusion:** The mortality, morbidity, and cost of ASCVD have reached unacceptable levels. Reducing this disease to a rare condition will require the efforts of many individuals to organize, educate, and facilitate the goal of identifying all individuals with subclinical ASCVD. Once identified, aggressive therapy is required to reverse their atherosclerotic plaques in order to prevent heart attacks and atherosclerotic strokes. If successful, within 5 years the majority of the patients with asymptomatic ASCVD can be identified and if treated appropriately, reduce the prevalence and cost of ASCVD by 90%.

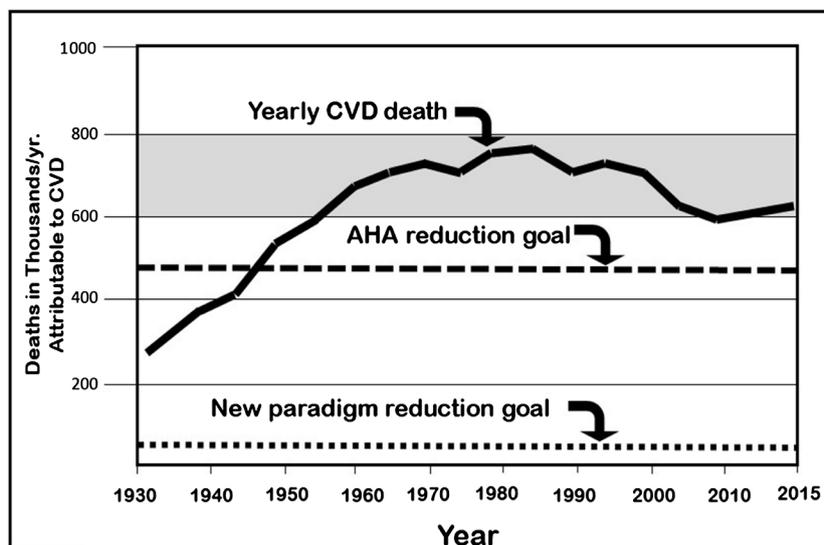
## Keywords

Cardiovascular Disease, Preventing, ASCVD

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## 1. Background

The statistics are staggering. Every minute at least one individual has a heart attack in the United States [1]. This equates to 600,000 persons per year, the size of a small city (Figure 1). This large number is more than all cancers combined. Furthermore, the prevalence of heart disease is increasing in spite of billions of dollars spent on treatment each year. The cost to society for each heart attack is \$94,000 (direct plus indirect costs) according to the American Heart Association [1]. The total cost in the United States of cardiovascular disease is 555 billion dollars per year and is projected to triple by 2039 [1]. Not included in these costs is the untold suffering and financial ruin experienced by innumerable families caring for heart attack victims. What is astounding is that cardiovascular disease is not a newly recognized disease entity, with an unknown cause and an unknown preventative treatment. In fact, its pathogenesis and effective prevention have been described in detail during the last 20 years, including the genetic determinants [2] [3] [4]. Half of acute coronary events occur in asymptomatic patients and nearly 70% of acute coronary events result from coronary lesions that are not obstructing flow prior to the event [5]. The purpose of this article is to begin the dialogue to change the current approach to cardiovascular disease to an alternative one that is effective, cost-saving, safe, and feasible.



**Figure 1.** Deaths attributable to diseases of the heart (data from [1]). Between 1960 and 2015, the death rate has remained between 600,000 and 800,000 individuals per year in the United States. The goals for reducing these deaths are 20% for the American Heart Association [8] and 90% for the new proposed paradigm.

The popular press often cites statistics showing that the death rate from cardiovascular disease is declining, and attributes this reduction to a decline in risk factors for ASCVD, especially smoking. Although this may be partially true for some risk factors, it is being counterbalanced by the increase in other risk factors such as obesity, diabetes, and insulin resistance [6]. Of particular importance is the fact that the overall prevalence of cardiovascular disease is increasing [7]. The burden of cardiovascular disease is increasing at an alarming rate due to the obesity epidemic, poor diet, high blood pressure, the aging population, and a dramatic rise in Type 2 diabetes—all major risk factors for heart disease and stroke. In 2015, the death rate from heart disease actually increased by 1 percent for the first time since 1969 [8]. In addition, ASCVD has become our nation's costliest chronic disease. In 2014, stroke and heart failure were the most expensive chronic conditions in the Medicare fee-for-service program. In 2011 the American Heart Association (AHA) predicted that by 2030, upwards of 40 percent of the U.S. population (more than 100 million Americans) would suffer from some form of ASCVD. Amazingly, that benchmark was reached in 2015—almost 15 years sooner than predicted [8].

Unfortunately, ASCVD and its associated risk factors exact a disproportionate toll on many racial and ethnic groups, accounting for almost 40 percent of the disparity in life expectancy between blacks and whites. Stroke and heart failure top the list of chronic conditions that account for the most spending in the Medicare fee-for-service program. This spending pattern reflects how the U.S. health care system often rewards efforts that treat disease and injury rather than those that prevent them. Cardiovascular disease is largely preventable, and prevention programs represent an enormous return on investment by reducing

some costs and promoting patient well-being, including length and quality of life [8].

## 2. The Critical Question

Why has this disease not been eliminated or at least reduced to a rare occurrence? The answer relates in part to the observation that, on average, it takes 17 years for medical advances to be applied to patient care [9]. The reasons for this delay are complex and not easily changed. When the public recognizes that an epidemic is a reality and demands a solution from the medical establishment, sufficient resources are then devoted to finding a rapid treatment or solution (e.g., the AIDS epidemic). In spite of the fact that many more individuals are dying of cardiovascular disease than AIDS, no public outcry about ASCVD has been forthcoming. People worry more about getting cancer than having a heart attack in spite of the fact that more individuals are likely to die of cardiovascular disease [8]. The stated 2018 goal of the AHA is to reduce cardiovascular disease by 20% [8]. Even in the unlikely event that this goal is achieved, it would still leave 480,000 individuals with heart attacks each year. Based on the AHA's own report, any reduction in cardiovascular disease is doubtful nor is a reduction in cardiovascular mortality likely [1]. For these reasons, a new paradigm for preventing cardiovascular disease is urgently needed.

## 3. The Current Approach

Before describing a new paradigm to prevent ASCVD, it may be useful to examine the limitations of the current medical approach to ASCVD.

**1) *Many asymptomatic individuals with no proven ASCVD are placed on preventive pharmacological therapy who would never experience cardiovascular disease in their lifetime* [10].**

This phenomenon is termed "overtreatment" and applies to several groups including smokers, patients with diabetes, and the elderly. Patients dislike being treated for a lifetime without knowing that the treatment is beneficial. The result is that compliance to preventative treatment is marginal. For example, only 50% of 75-year-old patients are still taking a prescribed statin six months after beginning "preventative" treatment [11]. Recent evidence suggests that patients do not want to take statin medications to prevent ASCVD, even if it would potentially add years to their lives [12] [13]. In addition, overtreatment exposes many individuals to unnecessary adverse effects and costs of the prescribed medications.

**2) *High doses of statins are often prescribed before alternative medications (such as ezetimibe) are employed* [14].**

This occurs in spite of the fact that the side effects of statins (myalgias and diabetes) are dose related and Robert's rule states that the doubling of a statin dose only increases its low density lipoprotein cholesterol (LDLc) lowering capacity by 7% [15]. One reason for this observation is the increase in proprotein convertase subtilisin-kexin type 9 (PCSK9) induced by statins that reduces their ef-

fectiveness [16]. In contrast, ezetimibe reduces LDLc concentration 20% with similar side effects to placebo treatment [17]. When used with a high potency statin, the LDLc lowering effects are additive and the side effects are the same as using the statin alone [18].

**3) *The goals of statin therapy for most intermediate risk individuals is 70 mg/dl in spite of extensive data demonstrating that the lower the LDLc cholesterol, the lower the ASCVD event rate [19].***

Since reversal of atherosclerosis has been shown to occur at approximately 70 mg/dl or below, many individuals will still be producing atherosclerotic plaques at 70 mg/dl (they are on the wrong side of the reversal, bell shaped curve.) [14]. Furthermore, LDLc levels significantly below 70 mg/dl have been shown to be safe and attainable [20].

**4) *The cost of health care has continued to increase during the last ten years.***

A large part of this cost is due to ASCVD and the increasing array of invasive procedures, poly pharmacy, and hospitalizations necessary to maintain individuals suffering from an ASCVD event. The current expenditure for ASCVD care approximates \$1,000 year for every man, women, and child in the US. This cost is projected to triple by year 2035 [1]. These costs have a detrimental effect on the quality of medical care, which preferentially affect the poor and unemployed individuals.

**5) *Testing a patient for heart disease can be very expensive.***

In addition to the cost of multiple physician visits, a myriad of testing procedures is available. For example, a stress test costs \$500 or more depending on whether pharmacological stimulation or radioactive isotopes are also employed. The main limitation of a stress test is that it does not identify the site of obstruction, even if one exists. It has been estimated that more than 56,000 unnecessary stress tests are done each year in the United States [21]. Coronary angiography costs between \$5000 and \$10,000 and frequently follows a stress test. This test is often done in spite of the limited information it provides [22] and the fact that it does not predict the arterial location of a future heart attack [23]. When a coronary artery constriction is identified on angiography, one or more stents may be placed in the artery to reduce perceived angina, in spite of a randomized controlled trial demonstrating that placing a stent in non-acutely ill patients is not superior to aggressive medical therapy except for limited pain relief [24]. The benefits of medical therapy in preference to coronary revascularization for suppression of ischemia have been demonstrated in stable patients after acute myocardial ischemia [25]. Furthermore, the total cost of stent placement approaches \$40,000.

**6) *The physician attempting to follow the most current recommendations for preventing ASCVD faces a bewildering task.***

There are at least 21 professional organizations that publish recommendations for treating ASCVD [26]. Not surprisingly, there is little agreement among or-

organizations' recommendations [26]. In addition, most recommendations are too complex to be useful to caregivers trying to take care of individual patients [27]. This is one of several reasons that physicians do not follow clinical practice guidelines [28]. Organizations tend to rely on results of randomized controlled trials in spite of the fact that most of these trials have poor external validity (*i.e.*, application to patients seen in the clinic) [29]. In addition, the major organizations have not increased the number of randomized clinical trials since 2004 upon which their recommendations are based [30]. This complexity and poor applicability are frequently recognized and result in short abbreviated synopses in medical journals [31]. Whether these summaries are actually useful to practicing physicians is unknown.

**7) *A major deficiency in current recommendations to prevent cardiovascular disease is the lack of planned follow-up.***

For example, what should the physician do if the patient improves his lifestyle (by getting adequate exercise, achieving normal body weight, and following a low cholesterol diet) or alternatively, gains significant weight and develops pre-diabetes? Even if the patient does not change his lifestyle, his risk for cardiovascular disease will increase as he ages, since advancing age is the most significant risk factor for ASCVD [32] [33]. Furthermore, the degree of risk is often different when a ten year risk assessment is compared to a 30 year assessment [34]. No guidance is provided to the practitioner by current recommendations on how often or how he should reassess his patient or change his therapeutic approach.

**8) *The use of the global risk calculator misclassifies the degree of risk in many individuals [35].***

Current guidelines suggest using one of the several available internet risk score calculators to assess risk of an individual patient [27]. By their very nature, these risk scores do not include several ASCVD risk factors because of their complexity, lack of availability, and inability to be measured accurately (e.g., genetic predisposition to ASCVD or protection from ASCVD, which can only be measured indirectly from family history). They also do not quantitate well individuals who have changed their risk categories such as gaining weight, stopping and starting smoking, developing diabetes, etc. Since these risk scores may be used to decide whether to treat patients with medications, both under treatment and over treatment of ASCVD is inevitable. However, combining risk scores with coronary artery calcium (CAC) scores provides an improved risk prediction [36].

**Because of these multiple problems with current ASCVD recommendations, a new approach is warranted. These new recommendations should meet the following criteria:**

**1) *Only treat individuals with proven cardiovascular disease.***

Since ASCVD is not a contagious disease, accomplishing herd immunity by treating all patients at some prespecified level of risk affords no protection to unaffected individuals. Therefore, the current recommendations of prescribing pharmacological therapy to individuals who have no proven coronary atheros-

clerosis and who would never get ASCVD, only expose them to the medication's cost and adverse effects [37]. In contrast, the proposed approach of treating only individuals with proven cardiac lesions focuses treatment that patients and caregivers can understand as preventing future catastrophic cardiovascular events. A positive coronary artery calcium CAC score provides a strong incentive for adherence to therapy and results in a significant reduction in both medication compliance and ASCVD risk factors [38].

**2) *When asymptomatic ASCVD is diagnosed, treat aggressively with inexpensive and minimal side effect medications.***

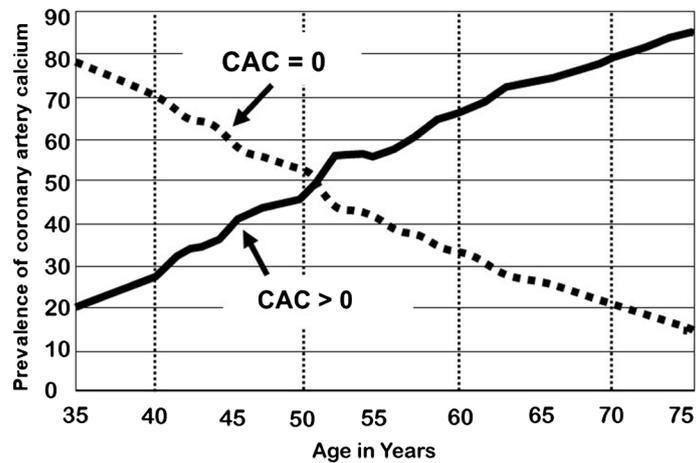
The goal of therapy should be to reverse and eliminate ASCVD, not just to reduce the non-specific risk calculation to a lower level. An LDLc goal of <50 mg/dl is achievable in almost all individuals who do not have a severe genetic defect in apolipoprotein B or the LDLc hepatic receptor. An LDLc goal of <50 mg/dl is safe (normally present at birth) and below the average LDLc of 70 mg/dl, the level at which atherosclerotic plaques start to be reversed in patients with proven disease [39].

**3) *A low cholesterol diet is preferable to a weight loss diet.***

Although achieving normal body weight and exercise is healthful [40], it should not necessarily be the goal of ASCVD preventive therapy. Instead, the recommendation should emphasize "eating smart," which involves avoiding foods that increases circulating LDLc (such as egg yolks and saturated fats) [41] [42]. Eating smart is readily achievable because it does not require weight loss or excluding desirable foods. It involves eating and preparing specific foods in moderation and with foresight to reduce LDLc.

**4) *Diagnosing ASCVD should be done non-invasively and at a very modest cost.***

The coronary artery calcium scan meets both of these requirements. It not only establishes the presence of coronary plaques and predicts future risk better than currently employed cardiovascular testing methods [43], but it also provides an assessment of overall atherosclerotic burden [44]. At autopsy, increasing coronary calcium areas are associated with increasing advanced atherosclerotic lesions, regardless of patient gender [45]. The prevalence of a positive CAC score at different ages has been described (Figure 2) [46]. The CAC score is not a perfect test. It does not identify non-calcified plaques that can erupt and cause a coronary occlusion. For this reason, it is not as sensitive or as specific as intracoronary ultrasound or coronary angiography [47]. However, both of these tests are invasive, expensive and not amenable to general use in asymptomatic individuals. Of importance is the observation that Individuals with a zero calcium score have a minimum number of non-calcified plaques [48]. For this reason, the prognosis of individuals with a zero CAC score is excellent. For example, in the Multi-ethnic Study of Atherosclerosis (MESA) database of 6,698 adults followed for seven years, individuals with no major risk factors had a CHD event rate of only 2.1 per 1,000 years [35]. Even with risk factors, the CAC score of



**Figure 2.** Changes in the prevalence of coronary artery calcium (CAC) with increasing age in 44,052 asymptomatic individuals referred for risk stratification. At 40 years of age, ~30% of adults have a positive score; at 50 years ~50% are positive; at 60 years ~65% are positive; and at 70 years ~80% are positive. If all adults are screened with a CAC study by age 50, approximately half of them will have subclinical ASCVD. (Data derived from [46]).

zero was predictive of lower risk [49]. This is true even in Type 2 diabetes, at least in the short term [50] [51]. In the largest meta-analysis published including 29,312 asymptomatic individuals, a zero CAC scan resulted in only 154 ASCVD events (0.43%) during an observation period of 4.3 years [52]. In contrast, individuals with even a low score (<10) are at increased risk for an ASCVD event compared to individuals with a zero score [53]. Since atherosclerosis is a progressive disease and CAC scores almost always progress [54], all individuals with a positive CAC score should be treated. The only exception to this recommendation is individuals with a score between one and ten. There is a small variability between different types of scanners and even between the initial and a repeat CAC score in an individual [55]. Therefore, the recommendation for treatment of an individual with a score of 1 to 10 should be left to a discussion between the primary care physician and the patient. If the decision is not to treat, then the CAC score should be repeated within 5 years.

The CAC test has been criticized by the United States Public Service Task Force because there are no randomized clinical trials demonstrating that its use results in a reduction of ASCVD events [56]. However, the problem with this conclusion is that it presupposes that a “test” by itself should result in a favorable outcome. It has been estimated that to do a randomized clinical outcomes trial comparing CAC testing with no testing would require between 50,000 and 100,000 participants and at least ten years of observation [5]. This study is not only impractical, but probably not feasible as new anti-atherosclerotic therapies may become available during the clinical trial. It is more reasonable to base the merits of the CAC test on its ability to detect ASCVD and to predict future ASCVD events. There are several excellent reviews available describing the strengths and weaknesses of CAC testing [57] [58] [59].

**5) In patients with no identifiable ASCVD, periodic reassessment is crit-**

***ical to identifying individuals who later develop asymptomatic ASCVD.***

Similar to other preventative testing (e.g., mammography for breast cancer and colonoscopy for colon cancer), repeat coronary artery calcium scanning should be repeated at specified intervals. A reasonable interval is every four years for individuals with any significant risk factors and every five years for individuals with no risk factors. Yearly serial CAC scanning has demonstrated that in individuals with an initial zero CAC score, follow-up at 4 years results in 12% of individuals becoming CAC positive and 25% at five years [60]. Use of one of the several total risk scores may be useful in identifying asymptomatic individuals at particularly high risk for ASCVD [36].

**6) *Treatment algorithms must be simple and effective.***

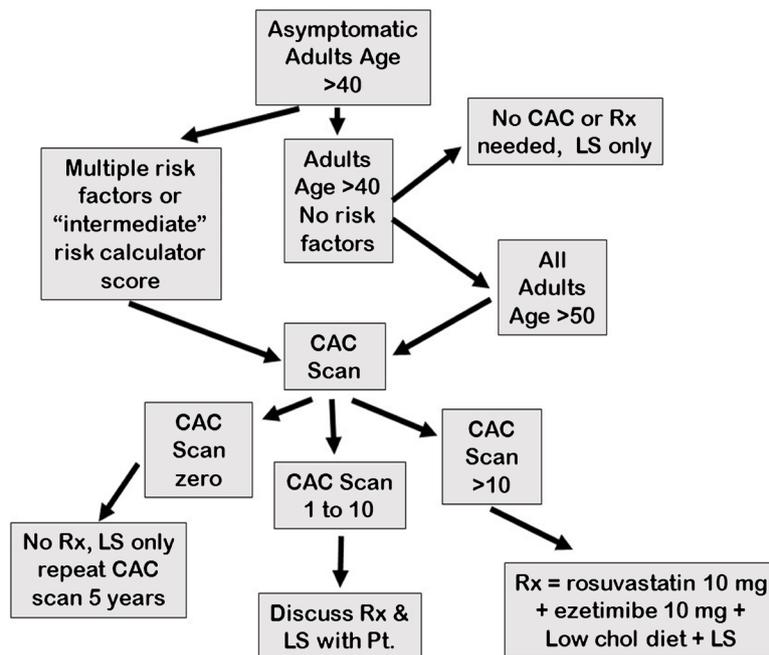
Defining goals of therapy is important to both caregivers and patients. Meeting the criteria of an LDLc of <50 mg/dl for all individuals with proven ASCVD is simple, safe, and effective. The preferred treatment approach is to use a low dose of rosuvastatin (10 mg) plus ezetimibe (10 mg); the latter will lower the LDLc an additional 20% [61]. In concert with a low cholesterol diet, this combination will reduce almost all individuals with an initial LDLc <150 mg/dl to an LDLc <50 mg/dl at a cost of approximately 60 cents/day [62]. Many medical insurance companies now provide these medications at minimal or no charge.

**7) *The new paradigm must be capable of being integrated with the current approach to ASCVD prevention.***

It is important to continue the current efforts at improving lifestyle and treating proven ASCVD with modern technics, medications, and procedures. Moreover, as the new paradigm is gradually incorporated into a community, the incidence of new onset ASCVD will decrease substantially. At this point, the major expenses of providing ongoing cardiac care will decrease. At some point, the usefulness of coronary artery stents, coronary bypass procedures, and cardiac assist devices will be minimal.

**4. A Simplified Approach—The Goal of Prevention Is to Identify Subclinical ASCVD in All Adults before an ASCVD Event Occurs**

This approach requires testing asymptomatic individuals for heart disease before they have a heart attack or stroke [63] (Figure 3). In reality, this dictates testing everyone by the age of 50 years and individuals after the age of 40 who are at intermediate risk or greater. Figure 2 demonstrates that a significant number of individuals at these ages will have a positive calcium score. Once a positive CAC scan is identified, the goal of therapy is an LDLc <50 mg/dl [64]. This is readily achieved with a low cholesterol diet, rosuvastatin 10 mg/day and ezetimibe 10 mg/d. At these low medication dosages, adverse effects are minimal and the benefits of reducing ASCVD are great. For individuals with zero score CAC scans, a repeat CAC scan in five years is recommended and earlier at four years if major risk factors are present [60].



**Figure 3.** A stepwise algorithm to identify adults who need therapy to reverse their ASCVD. By age 50, all adults should have been screened for ASCVD or be on ASCVD reversal therapy. If the initial coronary artery calcium (CAC) score is zero, a repeat CAC scan should be done within 5 years. Only individuals with proven ASCVD receive therapy. LS = lifestyle improvement; Rx = Treatment; Pt = Patient.

### 1) Why the recommendation of a < 50 mg/dl goal for LDLc?

All studies that have examined the relationship between LDLc and ASCVD events have demonstrated that the lower the LDLc, the fewer the ASCVD events [65]. However, there are very little long-term data demonstrating that very low LDLc is safe (*i.e.*, <30 mg/dl). To date, the only time that circulating LDLc has been shown to be necessary for hormonal synthesis is in the fetus, whose adrenal gland utilizes it for steroidogenesis [66] [67]. This occurs because at that time other hormone producing glands, especially the placenta, are not mature enough to synthesize sufficient cholesterol for hormonal requirements. The long-term data that very low levels of circulating LDLc are safe comes from patients with genetically induced hypobetalipoproteinemia. In these individuals with approximately 25% of circulating apoB lipoprotein, no hormonal abnormalities have been reported [68]. Short-term data (three years or less) that low levels of LDLc are safe come from two sources. First, the LDLc at birth ranges between 50 and 70 mg/dl [69]. Second, in randomized clinical trials in which patients were treated with both a maximally tolerated statin and a PCSK9 inhibitor, the mean LDLc of the interventional group was 30 mg/dl [70] [71]. In this group, no adverse events were observed compared with the placebo group with a mean LDLc of 70 mg/dl. Finally, it may not be necessary in an asymptomatic primary prevention group to obtain an LDLc much below 50 mg/dl to reverse atherosclerotic plaques [39]. Therefore, it seems prudent to choose an LDLc goal of <50 mg/dl as a realistic, attainable goal that is clinically effective in stabilizing and

reversing atherosclerotic plaques within 30 days [72].

The arguments for using one LDLc goal for all individuals at increased risks have previously been made [64]. Briefly, recommending one goal has the attributes of simplicity, safety, effectiveness, and achievability in almost all individuals. Furthermore, there are no convincing data that recommending high dose statins for high risk individuals and a moderate dose statin for intermediate risk individuals has any benefits. Rosuvastatin at 10 mg/day is approximately equal in LDLc lowering capability to 40 mg/day of atorvastatin [73]. In asymptomatic individuals at intermediate risk, rosuvastatin at 10 mg/d demonstrated a significant reduction in ASCVD [74]. Since rosuvastatin is 90% excreted unchanged, its interference with the metabolism of other concurrent medications is minimal. When combined with ezetimibe 10 mg, at least 60% reduction in circulating LDLc may be expected [75]. When that pharmaceutical combination is employed with a low cholesterol diet, almost all individuals will achieve a circulating LDLc below 50 mg/dl [64].

## **2) *Why utilize the CAC scan to diagnose ASCVD?***

There have been over 2000 articles describing the usefulness of the CAC scan to diagnose ASCVD. This test has been particularly useful for predicting future ASCVD events in various populations, including referral populations and multiethnic screening populations [76]. When compared to either treadmill-ECG or technetium-stress testing in patients evaluated for chest pain, CAC has a higher diagnostic ability for detection of obstructive angiographic CAD [77]. The great advantage of the CAC scan is its low cost (\$50 to \$150), its non-invasiveness, its lack of adverse events (the radiation dose is less than 1 mSv—similar to living in Denver for 3 months), its simplicity (requires 10 minutes), and its broad applicability (can be performed by any modern CT scanner). Most importantly, a positive CAC scan is specific for the presence of atherosclerotic disease, not just the risk of disease [59]. It can be used to diagnose atherosclerotic disease in all adult age groups and has even been shown to be positive (albeit at a very low value) in obese adolescents [78]. The fact that it does not identify non-calcified plaques is only a minimal drawback as long as individuals with any CAC score are treated. We acknowledge that the decision to treat a CAC score between 1 and 10 is controversial because of the very low ten year ASCVD event rate in this range of CAC [52] [79]. However as recently reviewed, individuals with CAC scores between 1 and 10 have three times the ASCVD event rate as individuals with a zero score [53]. This information should be considered by the primary caregiver and discussed with the patient before treatment decisions are made.

There is currently an active debate as to whether the CAC scan can be used to exclude obstructive coronary artery disease [80]. There are both strong advocates and negators depending upon the patient selection, the definition of obstructive disease, and the “gold standard” that is used to confirm the diagnosis [81] [82] [83]. However, these studies are examining CAC testing in symptomatic patients either presenting to an emergency room or being referred to coronary angiography [84]. This population is not the focus of the current propos-

al, which provides recommendations for asymptomatic individuals with varying numbers of ASCVD risk factors.

Scanning a general population with varying numbers of risk factors will result in different percentages of positive scores, depending upon their degree of risk. Insight into the percentage of positivity for different risk categories is available from the MESA clinical trial database in which 6814 healthy adults (free of cardiovascular disease) ages 45 to 84 yrs. were recruited from six diverse communities. In this large group that underwent calcium scanning close to enrollment, the percentage of calcium scan positive individuals were as follows: for very low ten year risk individuals (<5% ten year ASCVD risk), 21% were positive; for low risk individuals (5% to 7.5% ten year ASCVD risk), 43% were positive; for intermediate risk individuals (>7.5% to 20%), 55% were positive; and for high risk individuals (>20% ten year ASCVD risk), 74% were positive [12]. Therefore, when screening a large population of healthy individuals, a significant number of persons will have identifiable cardiovascular disease, irrespective of their risk.

### **3) Sensitivity and specificity of CAC**

Several authors have calculated the sensitivity and specificity of the CAC scan in different populations at various follow-up intervals [85] [86]. However, this calculation is dependent upon the end point that is chosen. For the approach to ASCVD prevention suggested in this article, the CAC endpoint is “to identify all individuals with a true positive CAC score.” The reason for this endpoint is that these are the individuals who are recommended for therapy to reverse their atherosclerotic plaques. Individuals with a zero score will not be treated but rescanned in three to five years, the shortest interval for individuals with multiple major ASCVD risk factors [32] [87]. In this context, the sensitivity of CAC testing is extremely high (>95%). The only false negatives will be individuals having a very low calcium score that was not identified because of calcification between radiographic cardiac slices or inherent differences between scanning equipment or techniques at different locations [88]. Similarly, specificity will also be close to 100% because false positive CAC scans are extremely rare [59]. Individuals with only non-calcified plaques will not be identified by this approach since they will have a zero calcium score. However, these individuals have very few non-calcified plaques and therefore they are at a very low risk for an ASCVD event and will qualify for rescanning in three to five years [53]. Compared with coronary angiography, CAC is superior for quantifying plaque burden and predicting future ASCVD events [89] [90].

### **4) Feasibility**

Is this new approach to preventing ASCVD feasible? Recent studies suggest that it is [91]. Both rosuvastatin and ezetimibe are generic medications and have minimal side effects, specifically at the low dose of 10 mg/day [92]. Since all modern CT scanners are able to perform CAC scans, CT scanning is available throughout the United States. As of 2017, there were approximately 43 CT scanners in the US per one million populations. Assuming that 50% of this pop-

ulation would be over 40 and scan eligible, there would be 43 scanners per 500,000 individuals. By scanning this population over 5 years, there would be 43 scanners for every 100,000 population per year. Thus, each CT scanner would do 2325 scans per year or approximately 6 scans per day. A CAC scan takes 10 minutes to complete, requires minimal preparation, and can be scheduled at the convenience of the CT facility and patient. If CAC scanning is introduced over a five year time frame, this resource will be available in almost all major communities. Even more attractive is the fact that introducing these new guidelines does not negate current guidelines. Gradual replacement will occur as more CAC scans are performed. Eventually, as ASCVD is reduced, not only will huge savings be realized, but many lives will be saved.

### **5) Cost Assessment**

If one assumes that half of the populations are adults over the age of 40 years, then approximately 165 million individuals would be eligible for a CAC scan (excluding symptomatic individuals). If this program is introduced over five years, then at any given year, 33 million individuals would need to be scanned. Therefore  $33 \text{ million} \times \$150/\text{scan}$  is 5 billion dollars/year. If it is assumed that half of these scans are positive (Figure 2), then 17 million/yr. individuals need pharmacological treatment. The cost for these generic medications is 56 cents/day or 204 dollars/year/individual. Therefore,  $\$204 \times 17 \text{ million}$  individuals equals 3.47 billion dollars/yr. Since these individuals would need treatment for their lifetime, the maximum number of individuals under therapy at five years would be 85 million. Since the U.S is spending 333 billion dollars/yr. on ASCVD (direct costs), the cost of this new program would be less than one twentieth of the current expenditures [1].

### **6) The suggested approach is similar to other accepted health maintenance guidelines.**

For example, the American Cancer Society currently recommends colonoscopy to exclude colon cancer beginning at age 45 [93].

Colonoscopy detects the growth of polyps and early cancer which are harbingers of future invasive colon cancers [94]. It also recommends repeat testing at various intervals depending of the patient's degree of risk [95]. It is not a perfect test as some cancers may be overlooked. However, this approach has been shown to be cost effective and lifesaving [93]. The suggested approach in this article is similar in many respects to recommendations for colonoscopy except that colonoscopy is much more expensive, invasive, and uncomfortable for patients. Atherosclerotic disease is treated aggressively when identified with a positive coronary calcium scan. If negative, then a rescan in five years is warranted. Similar to colonoscopy in saving lives from cancer deaths, CAC scanning can save many more lives resulting from an atherosclerotic death [64].

## **5. Challenges to a New Approach**

Change is difficult, particularly in the medical field, which includes both finan-

cial and traditional institutions that do not necessarily benefit from alternative approaches to established diseases. Prevention and treatment of many diseases have continued long after the futility of traditional medical therapy has been demonstrated. For example, “blood-letting” to remove “bad humors” was continued for over 200 years and was even applied to Abraham Lincoln on his deathbed after being shot in the head in Ford’s theatre [96]. Since 1955, more than 600,000 individuals have died every year from cardiovascular disease in spite of the availability new medications and procedures to protect the heart (Figure 1). These data by themselves should alert the medical community that a new approach is needed.

As with any new program, organizational issues will arise that present specific challenges. For example, caregivers will need to be trained in the assessment of both CAC scanning and aggressive medical therapy. Availability of computed tomography (CT) scanning in rural America will be challenging and appropriate transportation of patients to CT centers will need to be arranged. CT centers that currently do not provide CAC scanning will need to be convinced of the importance of this service. Finally, patient oriented health care organizations will need to embrace and support a new approach to ASCVD prevention. As difficult as these changes may be, they are not insurmountable. Many other major diseases in the past have presented similar challenges and positive solutions have been identified.

## 6. Summary

More than one half million heart attacks occur in the United States per year. Furthermore, the increasing costs of ASCVD medical care in the United States make the current approach to ASCVD unsustainable without negatively affecting other urgent medical needs. Current recommendations for preventing ASCVD have not been effective in reducing the epidemic in this country. The suggested new approach of aggressively identifying and treating asymptomatic patients with proven heart disease would correct many of the ineffective approaches in the past. Effective preventive therapy would save billions of dollars and millions of lives. The suggested approach could be readily integrated into the current healthcare system within five years.

## Conflicts of Interest

The authors have no conflicts of interests relevant to this manuscript. The authors have nothing to disclose.

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## Abbreviation List

- 1) ASCVD = atherosclerotic cardiovascular disease
- 2) LDLc = low density lipoprotein cholesterol
- 3) AHA = American Heart Association
- 4) PCSK9 = proprotein convertase subtilisin-kexin type 9
- 5) CAC = coronary artery calcium
- 6) MESA = multi-ethnic study of atherosclerosis
- 7) CT = computed tomography