Management of Asymptomatic Patients With Positive Coronary Artery Calcium Scans

Mark R. Burge,[1] R. Philip Eaton,[1] George Comerci,[2] Brendan Cavanaugh,[3] Barry Ramo,[3] and David S. Schade[1]

[1]Division of Endocrinology, DoIM, University of New Mexico School of Medicine, Albuquerque, New Mexico 87131; [2]Division of General Medicine, DoIM, University of New Mexico School of Medicine, Albuquerque, New Mexico 87131; and [3]New Mexico Heart Institute, Albuquerque, New Mexico 87102

Background: The widespread availability of the coronary artery calcium scan to diagnose coronary artery atheroma semiquantitatively and its prognostic significance has frequently resulted in a difficult therapeutic decision for physicians caring for asymptomatic patients.

Patients and Risk Factors: Of particular concern are patients over 40 years of age and young adults characterized by multiple cardiovascular risk factors. The correct prognostic interpretation of coronary artery calcium scores and the potential benefits and risks of various therapeutic modalities need to be understood.

Conclusion: This review describes the therapeutic choices available to endocrinologists and provides recommendations for various treatment options.

The coronary artery calcium (CAC) scan has become popular for individuals at risk for atherosclerotic cardiovascular disease. Indeed, CAC testing is increasingly being promoted to the public as a means of self-assessment of cardiovascular risk. There are several reasons for the widespread use of the coronary calcium scan, including its relatively low cost ($50 to $200 in most cities), its excellent predictive value for atherosclerotic cardiovascular disease (ASCVD) and mortality [1, 2], the noninvasive nature of the test, the low-dose radiation exposure (equivalent radiation to living in Denver for 3 months), and the fact that a physician's prescription is usually not required. The number of asymptomatic individuals in the high and intermediate risk categories in the United States is large and includes all diabetic patients and individuals with sufficient Framingham risk factors and/or genetic causes of hyperlipidemia. These individuals are often under the care of endocrinologists in concert with primary care physicians [3].

Decisions facing clinicians after the report of a positive coronary calcium scan in asymptomatic patients are (1) which medical therapy and lifestyle modifications to recommend, (2) how aggressively to reduce plasma low-density lipoprotein cholesterol (LDL-C), and (3) whether stress testing and/or referral to a cardiologist is indicated. This review discusses the pros and cons of these choices and makes recommendations based on the current medical literature. These recommendations apply only to asymptomatic patients without clinical evidence of heart disease and are primary prevention strategies. In asymptomatic patients

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Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; PCI, percutaneous coronary intervention.

with no report of angina but a positive calcium scan, one possibility is that the physician will order an exercise treadmill test. Excluding false-positive results (*e.g.*, induced by spasm of a coronary artery), a positive result indicates an obstruction of a coronary artery by at least 50%. What is the best next step? The choice is between coronary angiography with the intention to place a stent at the site of a constriction or to rapidly initiate aggressive medical therapy to reverse the atherosclerosis and the obstruction. During the reversal period, collateral channels may develop, increasing blood flow around the obstruction. Because long-term follow-up (>10 years) data from patients with stable angina demonstrate that intensive medical therapy is as beneficial as placement of a stent (which is more invasive and costly), there is minimal reason to order an initial stress test in patients with stable angina [4, 5].

Although randomized clinical trials evaluating the treatment of patients on the basis of their CAC score have not been done, extensive epidemiological and observational data are compelling and deserve serious consideration to guide physicians in making correct choices to recommend to their patients. Although the Multi-Ethnic Study of Atherosclerosis (MESA) clinical trial is the most well-described study [6], other investigators have also published their observations in populations that have received coronary calcium scores. For example, Arad *et al.* [7] studied 1177 high-risk, asymptomatic, middle-aged adult subjects for 3.6 years. The mean coronary artery calcium score was 764 among subjects with events, compared with a mean score of 135 among those without events. They conclude that "in asymptomatic adults, EBCT (coronary calcium) predicts coronary death and non-fatal MI." Alternatively, in a meta-analysis of five large population studies comprised of 6739 women at low cardiovascular risk, Kavousi *et al.* [8] reported that a positive calcium score was present in approximately one-third of individuals and was associated with an increased risk of cardiovascular events. Keelan *et al.* [9] performed CAC studies in 288 patients undergoing coronary angiography. After a follow-up period of 6.9 years, 22 patients experienced clinically important cardiovascular events. They conclude that "when a stepwise multivariable model was used, only age and CAC extent predicted hard events." Kuller *et al.* [10] studied 532 elderly individuals (age >80 years) in the Cardiovascular Health Study-Cognition Study. They concluded that "CAC, as a marker for atherosclerosis, is a determinant of mortality and risk of coronary heart disease and MI." In a study of the prevalence and severity of CAC in different racial groups, Lee *et al.* [11] studied 999 consecutive patients comprised of non-Hispanic white and non-Hispanic black racial groups. They conclude that "despite a worse cardiovascular profile, black Americans have significantly less CAC than white Americans." In a study of CAC and the occurrence of myocardial infarction in 1153 individuals with and without diabetes, Raggi *et al.* [12] concluded that diabetes causes an accelerated progression of atherosclerosis and that coronary calcium monitoring is an effective method to assess treatment efficacy. Rodrigues *et al.* [13] studied 621 patients with type 1 diabetes and concluded that overweight and obesity were independently associated with CAC and that only obesity was associated with CAC progression. Shaw *et al.* [14] studied 9715 asymptomatic individuals with a median follow-up of 14.6 years. They concluded that "the extent of CAC accurately predicts 15 year mortality in a large cohort of asymptomatic patients." Finally, in a very large cohort of 44,052 individuals, Tota-Maharaj *et al.* [2] studied the predictive value of calcium scoring in both young and elderly individuals. They conclude that "the value of CAC for predicting mortality extends to both elderly patients and those less than 45 years old. Elderly persons with no CAC have a lower mortality rate than younger persons with high CAC." The above studies are representative of many other studies that have examined the variables associated with CAC testing in asymptomatic individuals. This body of literature supports the conclusion that CAC testing is a major advance in noninvasive methodology to detect coronary artery disease and to predict future cardiovascular events and death.

1. Risk Factor Assessment and CAC Scoring

Prior to the availability of calcium scoring, combining cardiovascular risk factors was (and remains) a popular approach to determining an individual's overall risk of future

cardiovascular events. There are several approaches that combine several risk categories to attain an overall risk score for an individual patient (*e.g.*, Framingham, American Heart Association, Reynolds, and MESA). One of the most popular is the Framingham Risk Score, in which several risk categories are entered into an online risk calculator and a 10-year cardiovascular risk score is generated [15]. The main differences between the various risk scores available on the internet are the specific risk categories entered and the weights given to each category of risk. In addition, these risk scores have each undergone several revisions in attempts to improve their prognostic accuracy. The major difficulty of using all risk scores is the fact that the information entered into the risk score database reflects only one point in time, making it difficult to predict the risk in an individual whose cardiovascular risks may have changed in the past [16]. In addition, the model used to generate the risk predictions are usually based on one specific population. For example, the Framingham Risk Score is based on the white population in Framingham, MA, and may not be applicable to other racial groups.

The score assigned to a CAC scan summarizes the degree and extent of calcium contained in the four major coronary arteries and thus defines the magnitude of cardiac atherosclerosis present. The most commonly used scoring system is the Agatston score [17], which involves identifying "regions of interest" that contain calcium within coronary arteries and determining the area of all lesions >1 mm^2 in total area as well as the maximum calcific density for all lesions >130 Hounsfield Units. In spite of its limitations, the Agatston score has a long track record of proven utility in predicting new ASCVD events and remains the most widely used CAC scoring method for clinical application [18].

Although coronary angiography has often been considered the "gold standard" approach to defining the severity of atherosclerosis, recent studies have shown that CAC scores are better predictors of future cardiovascular events in asymptomatic individuals [19–22]. For example, in the MESA study, 6722 men and women were followed for a median of 3.8 years (Fig. 1) [23]. As shown in Fig. 2, when combined with traditional risk factors, the baseline CAC score predicted future cardiovascular events with improved accuracy. When the Framingham Risk score and the CAC score are combined, an improved prognostic outcome can be calculated [1]. Easy access to this improved, validated tool for cardiovascular event prediction is available at https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx [24]. The presence of calcium in coronary arteries is very strong evidence of the presence of atherosclerotic plaque [19]. The calcium should be considered a sign of atheroma presence and not necessarily a threat for future cardiovascular events. In fact,
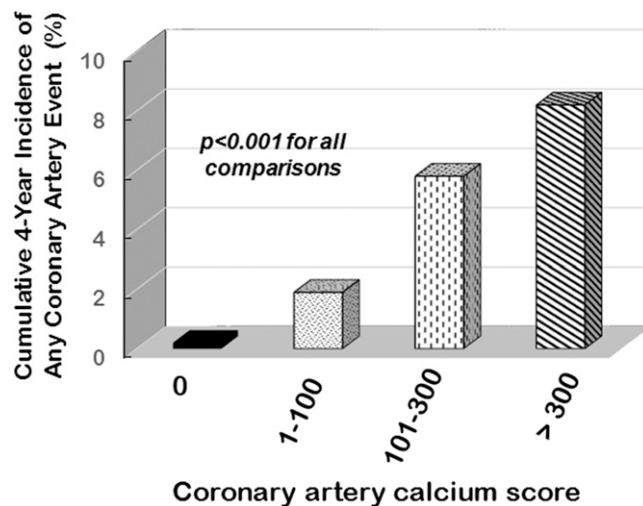
Figure 1. Cumulative incidence of any coronary event over 4 to 5 years of follow-up after receiving a CAC score evaluation among 6722 multiethnic men and women without preexisting cardiovascular disease in the MESA study. Adapted from Detrano *et al.* [23].
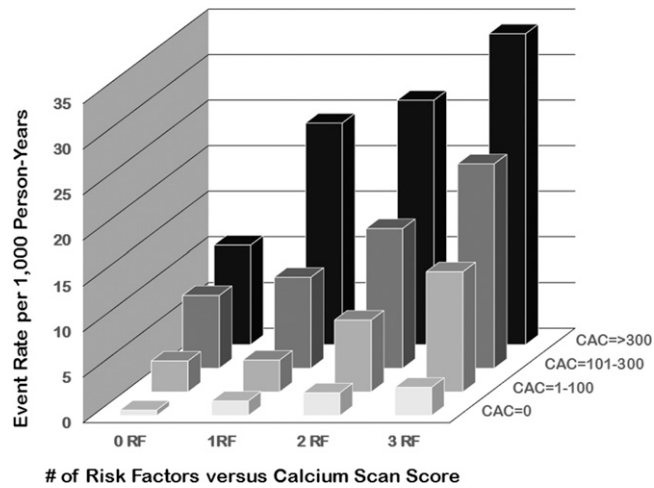
Figure 2. The importance of both the calcium score and the number of risk factors in determining the prognosis of individuals. The composite scores may be easily obtained by using the MESA risk calculator as described in the text. Adapted from Silverman *et al*. [25]. The risk factors considered to construct the bar graphs were: current smoking, hypertension, diabetes, and a family history of coronary heart disease. Definitions of these risk factors are provided in Silverman *et al*. [25].

the majority of infarction-associated arterial thromboses are due to rupture of non-calcified, nonobstructive plaques [26].

2. Stress Testing

Stress testing is often recommended to exclude potentially dangerous coronary artery disease. This approach involves stressing the cardiovascular system either with standardized exercise or stimulating the cardiovascular system with medication. The primary purpose is to identify coronary artery obstructive lesions with greater than 50% luminal obstruction. However, stress testing in asymptomatic individuals has low sensitivity and specificity (45% to 60%) [27]. The cost of the test can range between $300 and $700 depending on the institution and whether radioactive isotopes are used. Of note is that the risk to benefit ratio for adverse events increases in low-risk individuals [27].

In many locations, stress testing is performed after referring the asymptomatic patient to a cardiologist. After a positive stress test, the next step is usually coronary angiography to identify obstructive lesions. A recent review of coronary angiography recommends caution in the use of this test because (1) the resolution of coronary angiography is low; (2) the obtained images are two dimensional, making it difficult to define the shape of the vessel; and (3) the assessment of obstruction does not include the presence of previously developed collateral vessels, which may provide adequate blood flow past the obstruction [28]. According to the US Preventive Services Task Force: "The primary tangible harm of screening exercise tolerance testing is the potential for medical complications related to cardiac catheterization done to further evaluate a positive result. Coronary angiography is generally considered a safe procedure. Of all persons undergoing outpatient coronary angiography, however, an estimated 0.08% will die as a result of the procedure and 1.8% will experience a complication. Complications of coronary angiography include myocardial infarction, stroke, arrhythmia, dissection of the aorta and coronary artery, retroperitoneal bleeding, femoral artery aneurysm, renal dysfunction, and systemic infection" [29]. In addition, the charges for this test are between $5000 and $10,000 at most locations, and the patient's copay for the procedure may approach 50% [30].

The greatest objection to stress testing and coronary angiography is the fact that the identification of an obstructive lesion does not usually identify future causative sites of

myocardial infarctions. Because myocardial infarctions almost always result from unstable atherosclerotic plaques that rupture into the coronary artery lumen, coronary angiography identification of an obstructive lesion does not usually identify alternative causative sites of future myocardial infarctions [26]. Unstable plaques may be far removed from the lumen-narrowing lesions observed during coronary angiography. Thus, in asymptomatic individuals who have no anginal symptoms during their normal daily activities, the benefit from ordering stress testing or coronary angiography is questionable. For the above reasons, stress testing in asymptomatic individuals has not been shown to reduce future cardio-vascular events [29]. Stress testing guidelines generally discourage using this approach in asymptomatic individuals.

3. Reversibility of Atherosclerosis

New information concerning the pathogenesis of atherosclerosis has become available during the last decade [31]. Both hyperlipidemia and inflammation play critical roles with other cardiovascular risk factors, such as hypertension and diabetes, increasing cardiovascular risk [32]. Risk factors damage the arterial endothelium, which then permits increased trans-migration of LDL particles. Oxidized LDL particles attract increased numbers of inflam-matory cells, which promote atherosclerotic plaque formation [33].

On the positive side, there is also ample evidence that atherosclerosis is a reversible disease. Several controlled trials have demonstrated that reversibility occurs at an LDL-C of approximately 65 mg/dL, assuming other risk factors are also addressed [34–39]. Statins, which are the mainstay of antiatherosclerosis therapy, have both LDL-C lowering and anti-inflammatory activity [40]. These beneficial effects of statin therapy on atherosclerotic plaque composition can be observed within 1 month of starting statin therapy and are consistent with converting an unstable plaque to a stable plaque [41]. These observations provide a strong impetus for physicians to aggressively address risk factors, contributing to an initial positive calcium score.

4. Aggressive Medical Therapy

Most major professional organizations recommend an LDL-C <70 mg/dL for patients at increased ASCVD risk. The LDL-C principle, which was recently reviewed [42], states that the lower the LDL-C concentration, the lower the incidence of a cardiovascular atherosclerotic events (there is no lower threshold for a beneficial effect). This principle suggests that LDL-C level <70 mg/dL should be the goal for everyone with an elevated risk for cardiovascular disease and that an even lower LDL-C level should be the goal for individuals with multiple risk factors [42].

Achieving an LDL-C goal of <70 mg/dL is possible in almost all individuals without a genetic cause of severe hyperlipidemia. Moreover, no unexpected side effects have been observed at LDL-C levels <50 mg/dL [43]. Because most individuals were born with an LDL-C of between 50 and 70 mg/dL, these levels should not be considered abnormal [44]. In addition, the normal LDL-C range is 50 to 70 mg/dL for native hunter-gatherers, free-living primates, and other wild mammals (none of which develop atherosclerosis) [45]. Because all cells in the body have the capacity to synthesize cholesterol, additional cholesterol from circulating LDL-C is not required in adults for health, and the recent availability of high-potency statins, ezetimibe, and PCSK9 inhibitors make the goal of <70 mg/dL practical [46, 47].

5. Medical Therapy vs Percutaneous Intervention

A clinical trial comparing medical therapy alone vs percutaneous coronary intervention (PCI) alone in asymptomatic individuals with a positive calcium scan score would provide im-portant information concerning the relative value of each therapy. Unfortunately, there are no published clinical trials addressing this issue. Alternatively, clinical trials are available

that compare medical therapy vs PCI plus medical therapy in individuals with stable angina. These individuals usually do not have symptoms of angina at rest, although they may have angina with exercise. The conclusion of a meta-analysis examining these studies concluded no benefit of PCI beyond that achieved with optimal medical treatment except relief of angina, particularly for single-vessel disease [4, 48, 49]. In addition, the longest observational study available (15 years) demonstrated no difference in mortality between PCI and medical therapy in these patients [5]. Furthermore, what formerly was considered "optimal medical therapy" no longer meets current treatment guidelines because improved medications to treat atherosclerosis are now available [42].

6. Antihyperlipidemic Therapy

Assuming the LDL-C goal for asymptomatic individuals with a positive calcium score is <70 mg/dL, how should this be achieved? Most outcome trials include a statin, preferably a high-potency statin. Both atorvastatin and rosuvastatin are now generic, and one of these medications should be prescribed first. Because side effects of statins are dose related, the lowest possible dose should be used. This is particularly true because the lowest usual dose of a potent statin (10 mg) achieves the greatest percentage reduction in LDL-C (~75%) of the total response. Doubling the 10-mg dose usually results in only a 6% reduction in LDL concentration [50]. The reason for this reduced effect is that statins increase PCSK9 protein as the statin dose increases, which impairs their ability to progressively lower LDL-C [51]. Statins also indirectly increase the intestinal absorption of cholesterol by reducing the intrahepatic content of cholesterol [52]. For this reason, ezetimibe works well with statins by blocking cholesterol absorption from the gut with minimal side effects [53]. Based on these data, our initial treatment recommendation is to prescribe 10 mg of ezetimibe and 10 mg of either atorvastatin or rosuvastatin. This combination is well tolerated by almost all patients and results in a very major reduction (~50%) of LDL-c within 6 weeks [54].

Unfortunately, some patients are intolerant of statins or do not achieve LDL-C goals despite the addition of ezetimibe to the statin. Such patients may be ideal candidates for a PCSK9 inhibitor, but this will likely require preauthorization and a higher-tier copay level. In patients with a genetic cause of hypercholesterolemia, the combination of all three classes of drugs will usually succeed in dramatically reducing the LDL-C concentration.

7. American College of Cardiology/American Heart Association Guidelines

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines have given CAC testing a class IIB rating, which means that there are no randomized control studies addressing CAC scoring and that conclusions may be based on one nonrandomized controlled study. In evaluating this rating, several issues should be considered. First, CAC testing was also discussed in the 2010 ACC/AHA guidelines, and these recommendations state that "measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year risk)" [55]. Second, the one cited study involved 6814 white, black, Hispanic, and Chinese men and women aged 45 to 84 years with no clinical cardiovascular disease who participated in the MESA [56]. This multicenter landmark study, from which many additional publications were generated, provides convincing data on the importance of calcium scoring to assess future cardiovascular risk [1, 57, 58]. Third, many additional studies have been published since the 2013 guidelines were published, validating the use of CAC testing in different populations (see specific studies cited above). Fourth, a randomized controlled study comparing CAC testing with placebo will never be successfully completed because of prohibitive ethical issues, the expense and long duration required (>10 years), and the necessity to maintain individuals at risk in an untreated state. Other frequently used tests that provide insight into the cardiovascular condition of an individual (*e.g.*, the electrocardiogram, cardiac stress testing, ankle-brachial index, and coronary angiography) have also never been validated with a

randomized controlled trial [59]. Fifth, a recent review of 19 different professional organizations that have also issued treatment guidelines for cardiovascular disease demonstrates very little agreement on diagnostic testing and treatment [60]. Guidelines published by the SHAPE (Screening for Heart Attack Prevention and Education) organization are in agreement with the recommendations in this article [61].

8. Recommendations

Considering the above cited data, our recommendations for asymptomatic individuals at rest with a positive CAC score are to immediately initiate lifestyle plus aggressive LDL-lowering therapy. Reassessment of the LDL concentration within 3 months with adjustment of the medication is critical to reversing atherosclerosis (Fig. 3). Referral for stress testing and cardiology consultation should be delayed until evidence of unstable angina exists. No immediate or long-term benefit to such individuals from either stress testing or coronary angiography has been documented in the literature. In addition, cardiac catheterization entails a major increase in cost to the insuring entity and to the patient as well as an increased risk for adverse events. Appropriate exercise, diet, and medications should be considered lifelong strategies to counteract the previous lifetime exposure to atherosclerotic risk factors [62].

9. Conclusions

Physicians will be faced with increasing numbers of asymptomatic individuals who have had CAC testing [3, 63, 64]. When this score is positive, patients are often concerned about their risk of having a cardiovascular event. In general, the higher the Agatston score, the greater the risk. Combining CAC scores with the Framingham risk score will further refine risk predictions. Once risk is defined, physicians should emphasize to patients that atherosclerosis is a reversible disease, provided that aggressive risk factor management is undertaken. Physicians should review the lifestyle of patients and the various cardiovascular risk factors that are amenable to change. Smoking, hypertension, and hyperglycemia should all be aggressively treated if not at goal. Based on the LDL-C principle, we recommend an LDL-C goal of <70 mg/dL, with a goal of <50 mg/dL for individuals with a high CAC score (>400). These goals are achievable in almost all individuals with the availability of high-potency statins, ezetimibe, and PCSK9 inhibitors. Inflammation, if present, should be addressed by statin and
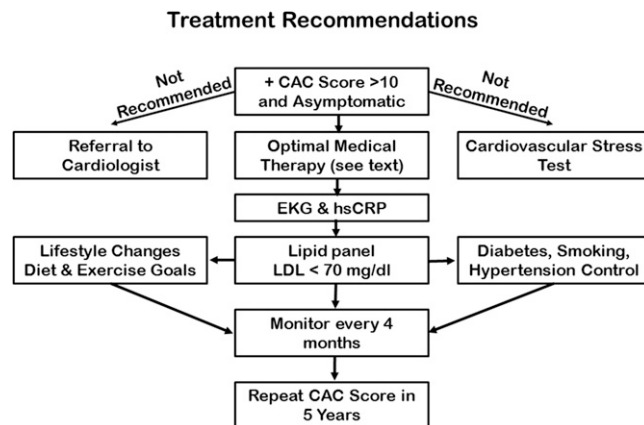
Figure 3. Treatment recommendations for an asymptomatic patient presenting with a positive calcium scan. The algorithm is based on aggressively addressing the four main cardiovascular risk factors, including abnormal lipids, hypertension, diabetes, and smoking through lifestyle improvement and medication prescription and adherence. EKG, electrocardiogram; hsCRP, high-sensitivity C-reactive protein.

Table 1. Frequently Asked Questions for Treatment of an Asymptomatic (No Ischemic Symptoms) Individual With a Positive Coronary Artery Calcium Scan

Question	Answer	Reference
What CAC score is considered positive?	Traditionally a score >10, but recent data suggest that a score of 1–10 indicates increased risk.	17, 66
What is the earliest age at which a CAC scan should be recommended?	With no major risk factors: 50 y of age for female patients, 40 y of age for male patients. With risk factors (e.g., diabetes), a decade earlier for preventive treatment.	42, 67
Do higher scores indicate greater CVD risk?	Yes. Scores (risk) are usually divided 10–100, 101–200, 201–300, >300.	23
Is cardiac stress testing recommended?	No. Cardiac stress testing offers no direct patient benefit in the asymptomatic patient.	29
Is a cardiology consult recommended?	No. Cardiology consult offers no direct patient benefit of invasive procedures in the asymptomatic patient.	28, 29
What medical treatment is recommended?	Aggressive lifestyle modifications, multiple risk factor control, and Rx to decrease LDL-C.	42
What is the best risk factor outcomes predictor?	CAC score combined with Framingham risk factor assessment.	1
Where can I obtain this risk factor calculator at no cost?	https://www.mesa-hlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx	1
Is coronary calcium beneficial or detrimental?	Beneficial. It is only a marker for atherosclerosis; it may stabilize plaques.	31
What medications work well with statin therapy?	Ezetimibe is complementary and works at different cellular sites than statins.	53, 68
What dose of a statin is most effective with the fewest side effects?	The lowest dose (10 mg) achieves ~75% of the maximal therapeutic effect with minimal side effects.	50
What should be the optimal LDL goal?	Less than 70 mg/dL; preferably 50 mg/dL if any risk factors still exist.	42
Is there a proportional LDL-lowering dose response with higher statin doses?	No. Statins increase PCSK9 protein, which negates the benefits of statins on LDL by decreasing hepatic LDL receptors.	51
What are the benefits of obtaining/using a CAC score?	(1) Improved prognostic score, (2) improved adherence to therapy, (3) prevention of unnecessary medical (statin) therapy.	19, 21
What are the drawbacks of coronary angiography?	Cost = $5000–$10,000; death = 0.08%; complications = 1.8%	29

ezetimibe therapy with the goal of a high-sensitivity C-reactive protein of <2.0 mg/L. A healthy diet with reduced saturated fat will provide further support for reducing LDL-C [65]. A list of the most common frequently asked questions by physicians and/or patients with short answers and cited literature is provided in Table 1.

Acknowledgments

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