Statins – quo usque tandem?

Of Nutty Professors and Pristine Coronary Arteries

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"Professor Meier is nuts!"

This was the main complaint of a 64-year-old patient requesting a consultation. He had been on atorvastatin for two years, prescribed by his primary physician. Because of chest pain he recently underwent coronary angiography performed by Professor Meier. No coronary lesions were found; in fact, since his coronaries were in pristine shape, Professor Meier told the patient that he could stop the statin. "But", the patient indicated, "my LDL-C (low-density lipoprotein cholesterol) was above 150 mg/dl (3.9 mmol/l) before atorvastatin and now it has been well below 80 mg/dl (2.1 mmol/l). I never missed a dose and have zero side effects. I looked it up and guidelines clearly recommend a statin in cases like me. Also, I have hypertension and as is obvious, am a bit overweight".

My ever so slightly circumlocutory response went like this: "Look, I am not privy to Professor Meier's thought processes, but you may have a point. You had no adverse effects and there is little, if any, downside in taking a statin. Also, some professors came up with the bit-over-the-top rule that every hypertensive patient should be on a statin regardless of LDL-C levels. All things considered, I think you should continue your atorvastatin as before". The patient seemed greatly relieved, profoundly thanked me and left.

Braunwald-Horton Trajectory

At a closer look, the management of elevated LDL-C with pristine coronary arteries over the age of 65 (PCA65) is complex. Dr. Braunwald recently stated that "the atherosclerotic burden can be expressed in 'cholesterol-years' or 'LDL-C-years', analogous to pack-years of smoking" [1]. This burden will define the trajectory on which a person reaches the Atherosclerotic Cardiovascular Disease (ASCVD) threshold of seven LDL-C gram-years at a certain age [2]. Therefore, a patient whose LDL-C level averaged 100 mg/dl (2.6 mmol/l) would reach the ASCVD threshold at the age of 70. However, the Braunwald-Horton trajectory is amenable to lipid lowering therapy. If we were able to decrease LDL-C from 100 to 60 mg/dl beginning at the age of 30, the rate of ASCVD progression would be slowed down, to the effect that the LDL-C threshold would now be reached at the venerable age of 100 instead of 70 years.

PCA65 Patients

As clinicians, it is not uncommon to come across patients aged 65 years and more who, despite having elevated LDL-C levels, unexpectedly present with pristine coronary arteries documented by finding no anatomical reason for chest pain by coronary angiography or computed tomography (CT).

It is conceivable that these patients are relatively resistant to ASCVD since they present no visible coronary lesions despite a prolonged exposure to elevated LDL-C levels and other possible risk factors. The outright absence of ASCVD in patients aged 65 years or more, despite elevated LDL-C, indicates that the Braunwald-Horton trajectory is ascending much less steeply in those PCA65 patients. Their coronary clock is ticking very slowly, if at all. This means that, if the Braunwald-Horton trajectory for atherogenic effects remains linear, the prognosis for these patients should be excellent.

The Power of a Zero Calcium Score

A zero coronary artery calcium (CAC) score is not unusual in older patients. The estimates of prevalence range from7 to 35% among septuagenarians (MESA [3]). In a prospective follow-up of 9,715 individuals, Valenti et al. estimated the warranty period for asymptomatic individuals without CAC to be 15 years [4]. Mittal et al. reported that over a 13-year follow-up period, none of the 1,928 patients with a zero CAC score died of a coronary event, yielding a negative predictive value of 99.5% [5].

However, the prognostic power of a zero CAC score is not absolute, despite its high negative predictive value. A cohort study of

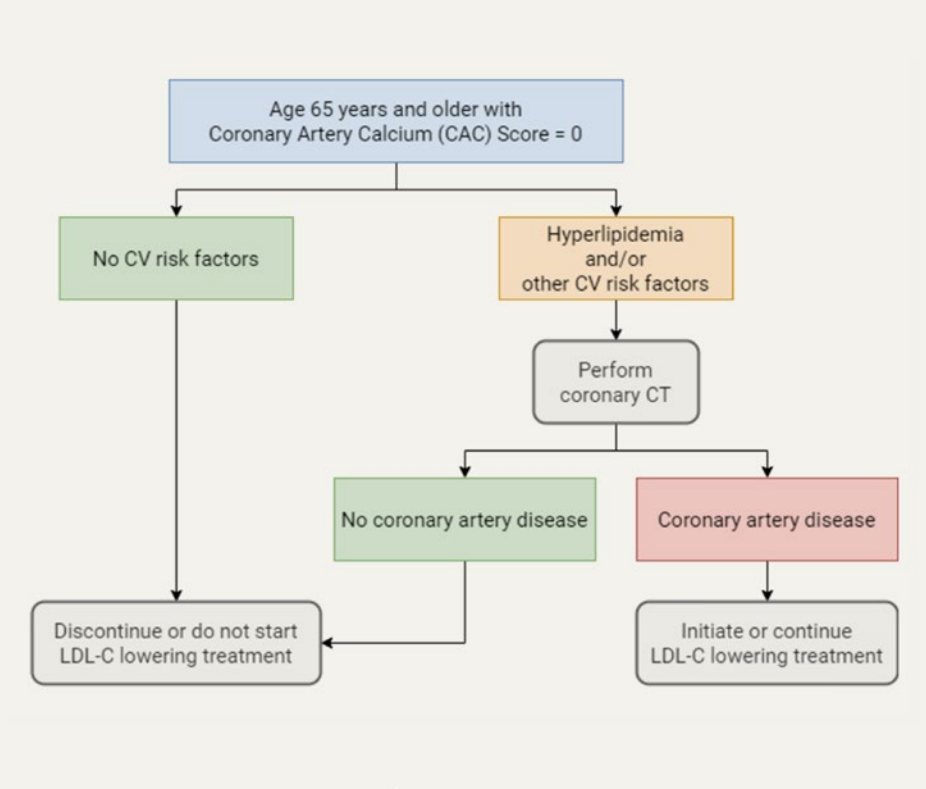

Figure 1: Strategy for management of older patients with zero CAC.
CV: cardiovascular; CT: computed tomography; LDL-C: low-density lipoprotein cholesterol.

23,759 symptomatic patients documented that the incremental diagnostic value of a CAC score of zero to rule out obstructive coronary artery disease (CAD) was highly dependent on age. A CAC score of zero was associated with a substantial reduction in the likelihood of obstructive CAD in patients older than 70 years, whereas the diagnostic value of a zero CAC score was much smaller in younger patients [6].

Bigler and Gräni have discussed, that regardless of age, CAC may miss the early phase of CAD and the most vulnerable plaques, namely the formation of non-calcified plaques (also known as "low-attenuation" or "soft" plaques) [7]. Finally, as for any diagnostic procedure, interpretation of CAC is prone to errors [8].

To Treat or Not to Treat

For now, the evidence for primary preventive lipid lowering therapy remains inconclusive for older adults. However, PCA65 patients (documented by either angiogram [preferred] or CT) are and will likely remain impervious to ASCVD. They may not live long enough to develop a de novo ASCVD of clinical significance. However, this verdict only holds true if their Braunwald-Horton trajectory will progress linearly at the same pace as before, and they do not acquire new risk factors. As recently documented by Mortensen et al., in zero CAC patients, diabetes, current smoking, and low high-density lipoprotein cholesterol levels were still associated with future ASCVD events, whereas LDL-C levels no longer had an effect [9]. Thus, even among patients with elevated LDL-C levels, a careful clinical evaluation could allow to identify elderly patients with such a low ASCVD risk that statins and other preventive measures could be safely avoided [4].

Outlook

Clearly, the 65+ patient with cardiovascular risk factors and/or subclinical atherosclerosis remains challenging. The ongoing STREAM Trial [10] is designed to determine whether the outcome of cardiovascular events and all-cause mortality differs after statin discontinuation compared to statin continuation in patients aged 70 years or more without clinical cardiovascular disease. A nested study will determine whether the treatment effect is modified by presence of subclinical atherosclerosis as measured by CAC.

Notwithstanding Robert Walser's dictum of "Who is of lively spirit, simply goes nuts every now and then" ("Wer lebhaften Geistes ist, spinnt eben ab und zu mal." [11]), if there are any nutty professors in this story, Professor Meier was certainly not among them.

Conflict of Interest Statement

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