**The Quantification of Total Coronary Atheroma Burden – A Major Step Forward**

Jean-Marc Foult[1], Shruthi Pranesh[2] and Matthew J. Budoff[3]

1. Department of Medicine, American Hospital of Paris, Paris, France
2. Division of Cardiology, Geisinger Holy Spirit Hospital, Camp Hill, PA, USA
3. Department of Medicine, Lundquist Institute, Torrance, CA, USA

**Corresponding Author:**

Matthew Budoff MD

1124 W Carson Street, Torrance CA 90502 USA

E: mbudoff@lundquist.org



**Abstract**

The extent of coronary artery disease has actually been shown to be an important indicator of prognosis. Cardiac CT has the ability to measure plaque, with both coronary artery calcium (CAC) scanning and computed tomographic angiography (CTA) to measure total atheroma burden. Beyond assessing stenosis and atherosclerosis, CT angiography can assess the high-risk plaque. These plaques are thought to be consistent with plaques that are vulnerable, more likely to rupture and cause acute coronary syndromes. However, the high-risk plaque concept suffers from poor reproducibility and poor positive predictive power. Total coronary artery burden has been shown to be a better predictor of coronary events than high risk plaques or stenosis. This paper reviews the literature in this regard and demonstrates total coronary atheroma burden to be the best predictor of future cardiovascular disease.

**Key Words**: Coronary atherosclerosis, CT angiography, plaque, outcomes, coronary artery disease, CT angiography

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More than half of acute coronary syndromes (ACS) occur in subjects with no significant coronary stenosis.[1] In view of the number of patients dying each year from a heart attack, the question of identifying these patients is of primary importance. A large body of evidence currently exists, indicating that total coronary atheroma burden (TOCAB) - the summed volume of all coronary plaques - is a major predictor of events, regardless of the presence or absence of a significant stenosis. TOCAB is derived by using quantitative software to sum the entire plaque volume in the coronary arteries. Quantitative analysis of the entire coronary tree is conducted for each patient. Vessel volume ($mm^3$) and plaque volume ($mm^3$) of all segments are obtained from the entire coronary tree and then added to generate vessel volume and plaque volume on the per-patient level (*Figure 1*).

That does not mean that the concept of significant stenosis is obsolete, since a fair number of ACS do occur in patients with stenosis beyond 70%; but it indicates that the extent of coronary atheroma is clearly a marker of risk, and should be taken into account in the management of patients with coronary disease.

The extent of coronary artery disease has actually been shown to be an important indicator of prognosis since quite a long time: the CASS (Coronary Artery Surgery Study) had provided evidence that patients with "triple vessel disease" were at higher risk than those with "double vessel disease", who themselves were at higher risk than patients with "single vessel disease". This, obviously, was about significant stenosis; but since 2005 and thanks to landmark studies about calcium scoring,[2] extremely strong evidence has been obtained in tens of thousands of patients, showing that the extent of calcified coronary plaques was highly predictive of events in the general asymptomatic population. In his early studies,

Agatston had established that calcium score – as calculated using his formulae – was highly correlated with total coronary atheroma burden.[3]

It is relatively simple to extract calcified plaques from a CT image obtained after a non-injected acquisition but performing the same operation with non-calcified plaques is a totally different story. Indeed, the contrast difference between a lipid-rich or a fibrous plaque and its neighbouring tissue is usually of little magnitude, making its extraction difficult, whether visual or mechanical. The progress of artificial intelligence and deep learning, however, permit such an analysis nowadays, and have led to an already significant number of publications demonstrating the clinical relevance of quantifying total coronary atheroma burden, with two targets: improving the identification of high-risk subjects, and monitoring the direct impact of treatments on coronary atheroma.

**Is there a "high-risk plaque"?**

The "high risk plaque" has been investigated by an impressive number of studies over the past 40 years, from pathological studies in the 70s, to studies based on invasive coronary angiography in the 80s, to current publications based on CTA images. Three major CTA criteria have been identified as putting a plaque at risk for the patient: 1. The presence of an hypodensity area (< 30HU), 2. Positive remodelling of the artery at the site of the lesion (> 10% of the vessel calibre), and 3. Micro-calcifications (<3mm). Several studies have established that the presence of such plaques was associated with a higher number of events.[4] The concept of "high risk plaque" however, suffers from several limitations. First, the 3 major criteria for identifying such plaques, although theoretically quantitative, remain essentially subjective, and their inter-observer reproducibility is low. Second, the sensibility

and specificity of these criteria for predicting ACS are low. For instance, in the study of Halon et al.,[5] 630 patients were followed-up for 9.2 years, with 3.5% of patients with high-risk plaques having an ACS, versus 0.6% in other patients, a statistically significant difference. In other words, 96.5% of patients with high-risk plaques never had an ACS, and only 3.5% of high-risk plaques led to ACS.

A third remark is that ACS usually results from a rapid progression of coronary atheroma, which proceeds in a non-linear and sometimes abrupt way.[6] Thus, the appearance of a coronary plaque 3 years before an ACS may not reflect its morphology in the minutes preceding the accident.

Finally, it is now well established that most ACS occur in a quite perturbed environment that affects the entire body, with signs of inflammation, often associated with haemostasis and neuro-hormonal disturbances.[7] One hypothesis is that the number of plaques – the extent of coronary atheroma – is a key factor in such an unstable situation: if a storm hits a village in the mountain, the odds for the thunder to destroy a chalet are higher if there are 500 chalets in the village, than if there are three.

**Coronary atheroma total burden is a powerful risk predictor**

As mentioned, the progression of coronary artery disease is a discontinuous process, which was initially studied from iterative invasive coronary angiography performed in the same patient.[8] These studies however, provided only a "luminal" information: invasive angiography shows a "cast" of the vessel lumen, but cannot assess the entire volume of plaques. More recent studies have been based on CTA and have therefore been capable to

measure Total Coronary Atheroma Burden (TOCAB), its evolution over time, and its value for predicting events.

In a 1,124 group of patients having 2 CTA performed with an interval of at least 2 years, TOCAB improved the predictive value of traditional risk factors, which in itself was low.[9]

In the 1,769 patients of the SCOT HEART trial,[10] followed up for a mean 4.7 years, low attenuation plaque burden was the strongest predictor of infarction, irrespective of cardiovascular risk score.

224 patients from the PARADIGM study were identified as "progressors": TOCAB was the most predictive item for progression, above the volume of calcified plaques, the presence of "plaques at risk", the presence of >50% stenosis, or traditional risk factors.[11] It should be noted that these patients were at low risk, since patients with events were not included in this analysis.

In another sub-group of the PARADIGM study which included 1,297 patients with no significant stenosis, TOCAB was the best predictor of an evolution toward a > 50% stenosis. "High-risk plaque" criteria were not predictive.[12]

In the CONFIRM study, 3547 patients with no significant stenosis were followed for 5.4 years. TOCAB was the best predictor for hard events, ahead of classical risk factors.[13]

In a quite original study,[14] 2,748 patients were followed for 5 years; 35 death from cardiac origin were recorded, 3 patients were eliminated from the study due to poor CTA image quality. The remaining 32 patients were matched with 32 patient control group. Average calcium score in the deceased group was 970 versus 283 in the control group ($p<0.02$), TOCAB was 303mm$^3$ versus 150mm$^3$ ($p<0.007$). 47% of the deceased patients had a >70% stenosis versus 22% in the control group ($p<0.03$). Contrast gradient – a new measure of the functional severity of a stenosis, calculated as the ratio of contrast density upstream versus downstream a stenosis – was 48% in the deceased group versus 26% in the control group ($p<0.004$). In this study, contrast gradient was the most powerful criteria associated with a fatal issue, followed by TOCAB, calcium score, and the presence of a >70% stenosis.

It appears therefore that TOCAB is a powerful tool for predicting both the progression of coronary atheroma, and the occurrence of serious adverse events. Calcium score and the presence of a >70% stenosis are also predictive of events, but their prognosis value is less than that of TOCAB.

**A technical issue – should TOCAB be normalized?**

Indeed, one may expect that a 3mm plaque might not have the same consequences in a 2mm or in a 4mm diameter vessel, hence addressing the question of a normalization of the data. In a subset of the PARADIGM study concerning 1479 patients,[15] a significant relationship was found between TOCAB, body surface area, and coronary arterial volume. When TOCAB was normalized to arterial volume, the influence of BSA no longer existed, suggesting that normalization of TOCAB could be of interest. It should be stressed that at the

current time, except for one study which was mentioned earlier in this review – no evidence exists that normalized TOCAB would provide superior information versus native data.

A common observation is that some patients have “small” coronary arteries, i.e., arteries whose diameter is reduced when compared to the size of their heart; 325 patients were followed 4.6 years,[16] with 11.1% cardiovascular events. Patients with a low arterial volume/myocardial mass ratio (<28mm3/g) had four times more events (17.2 versus 4.5, p<0.001), regardless of the presence of significant stenoses. Such a result supports the idea of a normalization of atheroma data to the volume of the coronary arterial tree.

**Assessing the direct impact of treatments on coronary atheroma**

A recent meta-analysis[17] including 12 studies indicates that statins, on the average, reduce the volume of plaques (-20mm$^3$), which increases in non-statin treated patients (+14mm$^3$). More specifically, it seems that statins induce a “healing” of plaques which tend to calcify, leading to a moderate rise of calcium score. At the same time, statins reduce the volume of non-calcified plaques. The impact of a series of other agents on coronary atheroma have been extensively analysed in a recent review.[18]

In conclusion, the management of risk factors is currently operated by monitoring the risk factor itself: blood pressure, glucose or cholesterol for instance. Recent studies, however, indicate that risk factors have a limited value for predicting the occurrence of serious adverse events, especially when compared to total coronary atheroma burden, whose predictive value is higher than that of calcium score, or even the presence of a significant stenosis. The quantitative evaluation of total coronary atheroma burden[19] can help identify

subjects at high risk, and can also be of value for directly assessing the efficiency of preventive actions, pharmacological as well as nonpharmacological, on the atherosclerotic plaques themselves. This important technological step can lead to a significant improvement in the prevention of cardiovascular accidents.

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**Figure 1:**

Plaque quantification software (QAngio CT, Medis Medical Imaging, Leiden, Netherlands) to quantify total plaque. Each vessel is traced and the software quantifies plaque burden (necrotic core, fibrousFatty, fibrous and calcific (Panel A). Lower right panel shows quantitation of lesion length, area stenosis, diameter stenosis and plaque volume.