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# Fibrous Cap Thickness and Lipid Core Size vs. Calcification in Plaque Risk

## Fibrous Cap and Lipid Core as Key Predictors of Rupture/Events

**Longitudinal imaging studies in both coronary and carotid arteries consistently show that plaques with a** thin fibrous cap **and a** large lipid-rich necrotic core **are the lesions most likely to rupture or lead to adverse cardiovascular events.** In coronary arteries, prospective trials have identified the "thin-cap fibroatheroma" (TCFA) phenotype – a large lipid core covered by a cap <65–75 μm – as a key high-risk feature. For example, the landmark PROSPECT study using intravascular ultrasound (IVUS) found that non-obstructive lesions which went on to cause future events had **large plaque burden, a substantial necrotic (lipid) core, and often met criteria for TCFA**, whereas calcification was not an independent predictor [1]. Similarly, an IVUS radiofrequency analysis showed plaques that caused 12-month events had ***more non-calcified (fibrofatty) content and*** **less* dense calcium** *compared to stable lesions* [2]*. In an OCT follow-up study of diabetics (COMBINE trial), lesions with OCT-detected TCFA had a fourfold higher 18-month event rate than those without TCFA (≈13.3% vs 3.1%) despite similar severity by angiography* [3]*. These findings underscore that cap thickness and lipid core size** are dominant determinants of plaque vulnerability in coronary disease.

In carotid arteries, high-resolution MRI studies echo the same theme. A 2017 MRI substudy of the AIM-HIGH trial found that **carotid plaques with large lipid cores and thin or ruptured fibrous caps were strongly associated with future cardiovascular events**, whereas calcified plaque volume was not [4]. In that study, each standard-deviation increase in lipid core volume raised risk by ~57%, and the presence of a thin/ruptured cap carried a **4-fold higher risk** of events, but higher calcium content showed no significant risk increase [4]. Likewise, other carotid imaging studies report that plaques with extensive lipid-rich necrotic cores or fibrous cap ulceration predict stroke risk, whereas calcium load alone has **little predictive value or even trends inversely** [5]. In short, across modalities and vascular beds, **plaque composition features like cap thickness and lipid core size emerge as much stronger predictors of rupture/clinical events than the degree of calcification**.

## Why Calcification Is Often Not Highlighted as a Major Risk Factor

Despite calcification being a hallmark of atherosclerosis, many longitudinal studies do **not** emphasize it as a major marker of plaque risk. One reason is that extensive calcification often correlates with plaque stability rather than vulnerability. **Heavily calcified plaques tend to be old, fibrotic lesions that cause stable angina (fixed stenosis) rather than acute rupture.** Autopsy and imaging data show that asymptomatic or stable patients often have **more calcified plaque burden** than those who present with acute symptoms [6]. By contrast, plaques that rupture in acute coronary syndromes frequently have large soft lipid cores and thin caps with only mild-to-moderate or "spotty" calcification. In clinical imaging studies, calcification measures have usually **failed to predict future events once plaque morphology is accounted for.** For instance, the OCT-based CLIMA study identified four high-risk features (minimal lumen area <3.5 $mm^2$, cap thickness <75 μm, lipid arc >180°, and macrophage infiltration) that together strongly predicted MI, but **calcification did not appear among these top predictors**. In a dedicated OCT analysis, the *pattern* of

calcifications in culprit lesions (number of deposits, size, depth) **did not differ** between plaques that had ruptured causing STEMI and those in stable angina patients [7] [8]. The authors concluded that OCT-visible calcium by itself "may not be a useful marker of local plaque vulnerability" [8]. Thus, many follow-up studies have found that while calcification indicates overall atherosclerotic burden, it **lacks specificity for identifying the plaques that will acutely rupture**, especially when compared to fibrous cap and lipid characteristics.

Another consideration is statistical and clinical overlap: calcification often coexists with other features, making its independent impact harder to discern. **Coronary calcium score (CAC)** is a strong *global* risk marker for CAD, but at the individual-plaque level a high CAC often means a patient has many stable calcified plaques *plus* some active plaques. It's the latter (active, lipid-rich lesions) that usually precipitate events. Indeed, coronary CT angiography studies have shown that the **volume of non-calcified (soft) plaque is far more predictive of acute coronary syndrome** than the volume of calcified plaque [1] [9]. In the CAPIRE cohort, for example, **high non-calcified plaque burden** was the strongest predictor of future ACS, whereas calcified plaque burden was not as prognostic [9]. In sum, calcification per se is often not highlighted as a risk factor because extensive calcium can mark quiescent, stable plaques, and its presence doesn't pinpoint *which* plaque is dangerous – unlike a thin-cap lipid-rich lesion.

## Calcification's Non-Linear, Context-Dependent Role in Vulnerability

**The effect of calcification on plaque stability appears to be non-linear and highly context-dependent.** Recent evidence suggests a **"biphasic" relationship** [10]**:** *microcalcifications* or small, spotty calcium deposits can *increase* vulnerability, whereas large, confluent calcifications may actually *stabilize* plaques [10]. In other words, a little bit of calcium in the wrong place can be dangerous, but a lot of calcium may signify a more inert plaque. Mechanistically, tiny calcium deposits (on the order of tens of microns) embedded in the fibrous cap create interfaces of different stiffness that **concentrate mechanical stress**, facilitating cap rupture under pressure [11]. Biomechanical modeling indicates that microcalcifications (5–65 μm) in a fibrous cap can markedly intensify local stress and promote rupture [11]. These microcalcifications often accompany active inflammation; indeed, *"spotty" calcification on CT* – defined as multiple small calcium spots within a plaque – is recognized as one feature of high-risk plaques (alongside positive remodeling and low attenuation suggesting lipid) [12]. Spotty calcifications reflect an **"active" calcification stage associated with inflammation** [6], and their presence in a noncalcified lipid plaque is thought to indicate ongoing plaque instability. Imaging studies support this: plaques that have ruptured tend to show **more numerous small calcium deposits**, whereas **stable plaques show fewer but larger calcium masses** [10]. Consistently, one IVUS study noted that plaques causing events had **less overall calcified mass** than those that remained stable, implying that heavy calcification might have a stabilizing effect [2].

On the other hand, **large, thick calcifications can act like a "cast" on the plaque**, potentially reducing deformability and sealing off the lipid core. Extensive calcification is also accompanied by less active inflammation (macrophage infiltration is inversely related to calcification extent) [6]. This may explain why heavily calcified plaques are often clinically stable. However, even large calcification can contribute to risk if it is **surface-breaking**. *Superficial calcified nodules* – where calcific material protrudes into the lumen with an overlying disrupted cap – are a recognized but uncommon cause of thrombosis in acute coronary syndromes [13]. These typically occur in arteries with long-standing calcific disease and are estimated to cause a minority of ACS (on the order of 5%) [13]. Thus, context matters: **calcification's impact depends on its *amount, size, and location within the plaque*** [10]. Recent high-resolution modalities reinforce this nuanced view. For example, ^18F-NaF PET imaging can highlight active microcalcification that is not yet

visible on CT, often flagging vulnerable plaques that CT calcium scoring misses [14] [15]. Meanwhile, standard CT calcium scoring primarily detects large, established calcifications, which show minimal NaF uptake and are less linked to near-term events [16].

In contrast to calcification, **fibrous cap thickness and lipid core size have a more linear relationship with plaque risk** – thinner caps and larger necrotic cores consistently mean higher vulnerability. Intravascular OCT can directly measure fibrous cap thickness, and both research and clinical practice recognize a cap thickness threshold (≈65 μm) below which plaques are at high risk of rupture [17] [10]. Lipid-rich cores appear as low-attenuation areas on CT or as signal-poor regions on IVUS/OCT, and a larger lipid pool means more potential thrombotic material if the cap gives way. These features do not depend on complex biomechanical context as much as calcification does – they are intrinsically dangerous because they indicate a plaque loaded with thrombotic debris and insufficient fibrous support.

## Imaging Studies' Interpretation of Calcification vs. Cap/Lipid

**Modern imaging studies interpret calcification in light of this complexity.** In coronary CT angiography, radiologists look for *"spotty calcifications"* in otherwise soft plaques as a red flag, but a plaque that is densely calcified throughout is often deemed more stable unless there are accompanying high-risk signs (like a napkin-ring sign of necrotic core) [12]. Intravascular ultrasound and OCT reports focus more on plaque burden, lumen area, cap status, and lipid arc; calcium is noted (especially if it may complicate stenting), but it's usually *not* the deciding factor for vulnerability. For instance, the presence of a thin fibrous cap on OCT is a strong predictor of events, whereas calcium arc or calcium length by OCT has not shown a clear correlation with outcomes in prospective studies [8]. Some OCT analyses even found no significant difference in calcium patterns between ruptured and stable plaques, reinforcing that **calcium alone is a poor discriminator of risk** [8]. High-risk carotid MRI features likewise center on lipid core size, fibrous cap integrity, and intraplaque hemorrhage, with calcification burden showing **little influence on predicting stroke** [5].

Overall, **calcification is often de-emphasized as a primary risk factor because its role in plaque instability is dual and context-dependent**. Small, early calcifications can contribute to vulnerability (and are considered alongside cap and core features in advanced imaging), but large calcifications frequently signal a more quiescent plaque. Long-term clinical studies in the past decade — in top journals like *JACC*, *Circulation*, and *NEJM* — repeatedly conclude that it is the **thin fibrous cap and large lipid-necrotic core** that most strongly predict plaque rupture or adverse events [4] [1]. Calcification tends not to be highlighted because, unless it occurs in a certain "risky" form (spotty or superficial), it does not independently confer high risk and may even denote stability [10]. In summary, contemporary imaging research portrays calcification as a **"friend or foe" depending on its pattern** – a factor that must be interpreted in context – whereas a thin cap over a big lipid core is an unequivocal foe when it comes to plaque vulnerability and future cardiovascular events.

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