

## Frequency of Acute Plaque Ruptures and Thin Cap Atheromas at Sites of Maximal Stenosis

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### Abstract

**Background:** There have been few autopsy studies relating sites of thin cap atheroma (TCFA) to sites of acute plaque rupture in culprit arteries, and sites of maximal narrowing in non-culprit arteries.

**Objectives:** We aimed to quantify and locate the frequency of TCFA related to the sites of maximal stenosis in atherosclerotic plaques.

**Methods:** We studied 88 hearts in victims of sudden death dying with coronary thrombus overlying acute plaque rupture. Thin cap atheromas were defined as fibrous cap < 65 microns overlying a necrotic core. Percent luminal narrowing was determined at the sites of plaque rupture and thin cap atheromas.

**Results:** There were 81 men and 7 women, mean age 50 years  $\pm$  9 SD. The plaque rupture was the site of maximal luminal narrowing in 47% of culprit arteries. TCFAs were present in 67 hearts (83%). Of these, 49 (73%) demonstrated TCFAs in the culprit artery; 17 (25%) in the culprit artery only, 32 (48%) in the culprit artery and in a non-culprit artery, and 18 (27%) only in a non-culprit artery. In non-culprit arteries, TCFAs represented the maximal site of stenosis in 44% of arteries. The acute rupture site is the site of maximal luminal narrowing in the involved vessel in 47% of hearts from patients dying with acute plaque rupture.

**Conclusions:** These data may suggest that luminal narrowing is not a reliable marker for TCFA. (Arq Bras Cardiol 2010;94(2): 143-149)

**Key Words:** Atherosclerosis; coronary artery disease; heart rupture; coronary stenosis.

### Introduction

Thin cap atheroma (TCFA) is considered to be the precursor lesion to acute plaque rupture, and has been defined as a fibroatheroma with a fibrous cap thinner than 65 microns<sup>1</sup>. The numbers of thin cap fibroatheromas have been described in a number of autopsy studies<sup>2-5</sup>. Imaging of TCFAs is not currently feasible by routine methods, due to lack of resolution capabilities, although a variety of investigational approaches are being studied to identify TCFAs in coronary arteries<sup>6-14</sup>.

The relationship between underlying plaque stenosis and areas of maximal luminal narrowing comparing rupture sites and TCFAs has not been fully studied at autopsy. Although maximal narrowing is frequently the site of plaque rupture or TCFA in a given artery, the frequency with which these lesions occupy the most severe lesion in terms of angiography is not known.

We studied a series of hearts with acute plaque rupture, in order to determine the frequency with which acute ruptures are the site of maximal luminal narrowing in a given artery

(culprit artery), and the frequency with which TCFA is the site of maximal luminal narrowing in non-culprit arteries.

### Methods

Hearts were seen in consultation from a Medical Examiner's office. Cases of sudden cardiac death were selected based on the presence of acute plaque rupture with luminal thrombus. Epicardial arteries were serially sectioned at 3 mm intervals and all arteries with grossly visible atherosclerosis embedded in paraffin after fixation. A mean of  $36 \pm 23$  segments were studied microscopically in each heart. Acute plaque rupture and thin cap atheroma were defined as previously described<sup>1</sup>. Specifically, thin cap atheroma denoted the presence of a necrotic core with an overlying fibrous cap, which measured  $\leq 65$  microns in thickness. Stenosis of the underlying plaque sites of rupture did not include the mural thrombus. Stenosis was determined by computed planimetry in most cases (SPOT® Insight Digital camera mounted on an Olympus BX41 microscope), after staining for elastic tissue outlining the internal elastic lamina by Movat pentachrome staining. Measurements included minimal thickness of the fibrous cap, internal elastic lamina area, and luminal area. In cases of thrombus, the thrombus area was excluded; in other words, only the underlying plaque was measured. Morphometry is

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performed using IPLab software (Scanalytics, Inc., Fairfax, VA). A segment devoid of necrotic core was required to consider a TCFA or acute rupture a distinct lesion and not a contiguous plaque type.

There were 5 types of plaques identified and measured in the 4 major arteries (left main, left anterior descending and diagonals, left circumflex and marginals, and right coronary artery): the acute rupture site; the site of maximal narrowing in the culprit artery (if not the rupture site); TCFAs proximal and distal to the rupture site in the culprit artery (maximum 2); TCFA with the most narrowing in non-culprit arteries (1 per artery, maximum 3 per heart); and maximal luminal narrowing in non-culprit arteries with TCFAs (maximum 3 per heart). All 88 hearts were considered in determining the frequency with which the rupture site was the site of maximal luminal narrowing in the culprit artery and comparing the % stenosis of the rupture site when maximal or not. TCFAs in the culprit artery were measured proximally and distally to the rupture site to determine the frequency of each group and how often the TCFA was the next most narrowed lesion after the rupture (Table 1). TCFAs in non-culprit arteries were similarly compared to sites of maximal narrowing (Table 2).

## Results

There were 81 men and 7 women. The mean age was 50 years (Table 3). The most frequent site of acute plaque rupture was the left anterior descending artery, followed by the right (Table 3). 67 of 88 hearts showed  $\geq 1$  TCFA; these hearts formed the basis for study.

Plaque ruptures were present in the left anterior descending artery and branches in 45 hearts, the right coronary and branches in 27 hearts, the left circumflex and marginals in 13 hearts, and the left main in 3. Figure 1 illustrates a classical example of an acute thrombus overlying plaque rupture. In 41 hearts, the underlying narrowing at the site of rupture was the maximal narrowing along the course of the culprit artery; in 47 hearts, it was not (Table 4). The mean difference in luminal area narrowing between the rupture site (excluding thrombus) and the other maximal narrowing site was 18% both for positive and negative delta (Table 4).

The maximal luminal narrowing was present in the culprit artery (that with the plaque rupture) in only 36% of hearts. The mean maximal narrowing in the non-culprit artery was

$81\% \pm 14$  vs.  $77\% \pm 14$  in the culprit artery ( $p = .06$  paired T test).

In 67 hearts with any TCFAs, 49 hearts had  $\geq$  TCFA in the culprit artery with acute rupture; of these, 17 had TCFAs in other arteries as well, and 18 hearts had TCFAs only in non-culprit arteries (Table 5). The mean number of TCFAs in the 67 hearts with  $\geq$  TCFA was  $1.8 \pm 1.6$  SD (Table 5). Figures 2 and 3 shows a TCFA and a thick fibrous cap fibroatheroma, respectively.

The most common location for TCFA was the LAD and diagonals (54), followed closely by the right and posterior descending (52). There were 4 TCFAs in the left main, and 32 in the circumflex distribution.

In the culprit artery (that with the acute rupture), 32 TCFAs were proximal, and 29 distal to the rupture site. There was no significant difference in luminal area narrowing (Table 1). In 34% of the cases, the TCFA was the site of maximal stenosis, with 43% the area of maximal stenosis if proximal to the rupture site (Table 2).

In non-culprit arteries (those without the acute rupture), 36 were the site of maximal luminal narrowing, 21 were proximal to a stable plaque with maximal narrowing, and 24 were distal (Table 2). The relationship among stenosis at the TCFA site, maximal narrowing in either culprit and non-culprit arteries or the rupture site (culprit) is shown in Table 6. The sites of maximal stenosis in both culprit and non-culprit arteries and the stenosis at the rupture site were significantly narrower than the mean of percentage luminal narrowing at the TCFA sites (Table 6).

## Discussion

The current study shows that less than 50% of acute ruptures occur at the site of maximal luminal narrowing, and that a similar proportion of TCFAs are present at sites of maximal stenosis in non-culprit arteries. These findings support angiographic studies that show that although segments narrowed  $>80\%$  are most likely to occlude by presumed rupture, the less obstructive plaques give rise to more occlusions because of their much greater number<sup>15</sup>. In the current study, the presence of TCFA in a large percentage of non-culprit arteries suggests that plaque burden may not be a reliable marker for predicting risk of sudden death, and that more than luminal narrowing, specific categorization of plaque

**Table 1 - Culprit artery TCFAS\***

	n	% total	N, site of maximal stenosis excluding rupture site (%)	Mean % narrowing $\pm$ SD	Artery involved
Proximal to rupture site	32	52	14 (43)	$62 \pm 20$	LAD 18 LCX 4 RCA 10
Distal to rupture site	29	48	7 (24)	$59 \pm 25$	LM 2 LAD 16 LCX 3 RCA 8
Total	61	100	21 (34)	$61 \pm 23$	

\*Only TCFA with greatest narrowing proximal or distal to rupture site included; TCFA - thin cap fibroatheroma; LAD - left anterior descending; LCX - left circumflex; RCA - right coronary artery.

Table 2 - TCFAs in non-culprit arteries\*

	n	% total	Mean % narrowing	Artery involved
Proximal to maximal stenosis	21	26	59 ± 19	LAD 6 LCX 6 RCA 9
Distal to maximal stenosis	24	30	52 ± 21	LAD 4 LCX 8 RCA 12
Site of maximal stenosis	36	44	75 ± 17	LM 1 LAD 11 LCX 11 RCA 13
Total	81	100	64 ± 21	

\*Only TCFA with greatest narrowing proximal per artery included; TCFA - thin cap fibroatheroma; LAD - left anterior descending; LCX - left circumflex; RCA - right coronary artery; LM - left main.

morphology need to be assessed by imaging methods. Our findings that TCFA is present in areas of less than maximum stenosis is similar to angiographic and necropsy studies that

Table 3 - Demographic data of all patients by culprit artery and frequency of thin-cap fibroatheroma

Culprit artery	N	M:F	Age ± SD
LM	3	3:0	45 ± 5
LAD/LD	44	41:3	49 ± 9
LCX/OM	13	12:1	52 ± 12
RCA/PDA	27	24:3	52 ± 11
Multiple*	1	1:0	55
Any TCFAS	67	61:6	50 ± 10
No TCFAS	21	20:1	49 ± 7
Total	88	81:7	50 ± 9

\*An occlusive thrombus in the PLAD was used for subsequent data analysis; there was also a non-occlusive thrombus in the right coronary; LM = left main; LAD/LD = left anterior descending or left diagonal; LCX/OM = left circumflex or obtuse marginal; RCA/PDA = right coronary artery or posterior descending artery; TCFA = thin cap fibroatheroma.

have shown that the risk of plaque rupture correlates only weakly with the degree of luminal narrowing<sup>16</sup>.

TCFAs are distributed, in our study, fairly uniformly throughout the coronary arteries, and only 18 of 67 hearts showed TCFAs only in non-culprit arteries, but that 50 of 67 showed some TCFAs in non-culprit arteries. We also demonstrate that the numbers of TCFAs proximal and distal to the culprit lesion was similar. Furthermore, only 44% of TCFAs in non-culprit arteries represented the sites of maximal narrowing, and those TCFAs that were not at sites of maximal narrowing were evenly distributed proximally and distally. These data suggest that by percent stenosis, it would be difficult to locate TCFAs angiographically, due to their random distribution throughout the coronary circulation.

The majority of coronary thrombi are associated with plaque rupture, of which TCFA is generally considered the precursor lesion<sup>16</sup>. Although TCFA is synonymous with the concept of a "vulnerable plaque" in angiographic and autopsy studies, the plaque progression mechanism is complex, and may involve both local and systemic factors<sup>17,18</sup>. Although most, if not all plaque ruptures originate from TCFAs, plaque rupture is not the only mechanism of coronary thrombosis. Plaque erosion accounts for a minority of acute coronary thrombi, and are especially frequent in young patients. Because erosions may occur in plaques that may not possess necrotic cores, and are not caused by cap disruption, the precursor lesion of plaque erosion is unknown<sup>19-21</sup>.

Table 4 - Plaque ruptures, relationship of underlying luminal narrowing with maximal stenosis in culprit artery

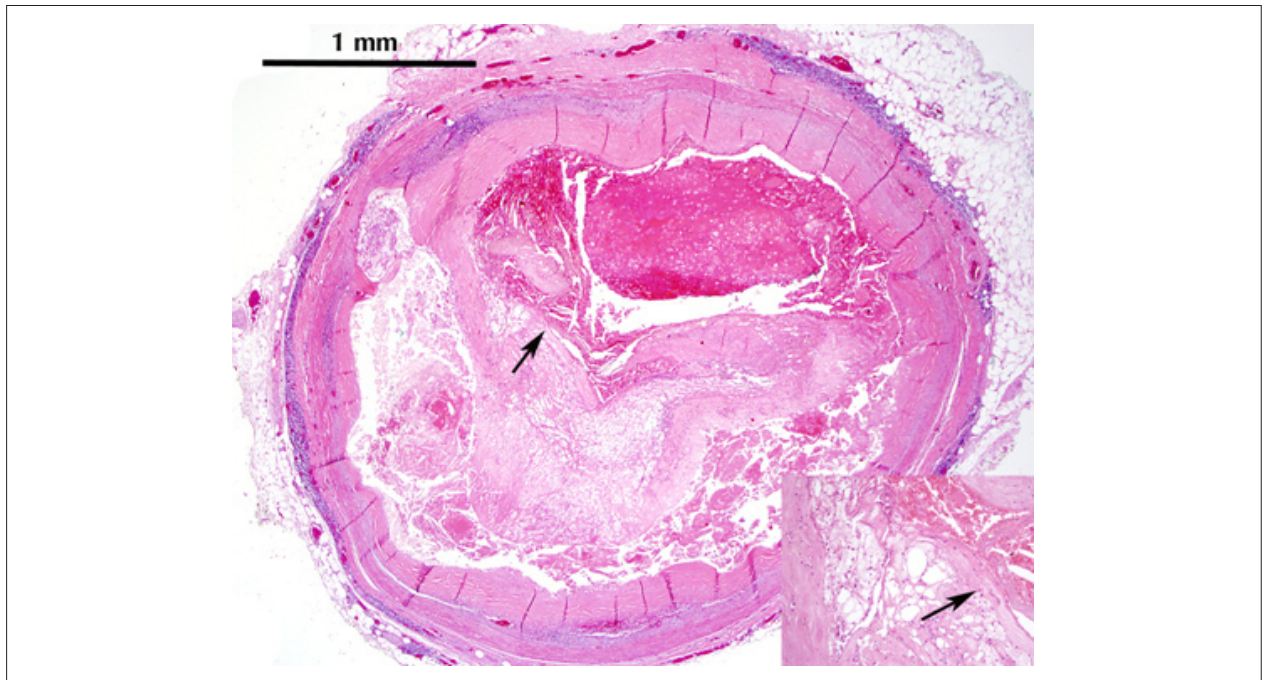
	n	% of total	% narrowing, underlying rupture site	% narrowing, underlying rupture site	Arteries
Rupture max. narrowing (underlying plaque)	41	47	81 ± 14	81 ± 14	LAD 17 RCA 14 LCX 9 LM 3
Rupture not maximal narrowing	47	53	65 ± 14	65 ± 14	LAD 28 RCA 13 LCX 4

LAD - left anterior descending and diagonals; RCA - right coronary artery and posterior descending; LCX - left circumflex and marginal branches; LM - left main.

**Table 5 - Frequency and location of TCFA in hearts with any TCFA**

	n	Mean TCFA, same artery	Mean TCFA, other arteries	Mean TCFA, total
Culprit artery only	17	1.3 ± 0.6	0	1.3 ± 0.6
Different artery only	18	0	1.2 ± 0.6	1.2 ± 0.6
Culprit and different	32	1.5 ± 0.7	2.0 ± 1.0	3.5 ± 1.4
All	67	0.8 ± 0.9	1.0 ± 1.1	1.8 ± 1.6

TCFA - thin cap fibroatheroma.



**Figure 1 - Acute plaque rupture, left anterior descending coronary artery.** Low magnification showing acute occlusive thrombus overlying atheroma with rupture on shoulder (arrow, main figure and inset) and communication of the thrombus with atheroma core. Hematoxylin and eosin, original magnification 20x.

The definition of thin cap is derived from previous findings that determined that >95% of ruptured plaques had areas of cap thinning to at least 65 microns<sup>1</sup>. The necrotic core of TCFA is usually large, and the thinned cap is densely infiltrated by macrophages<sup>5</sup>. Vulnerable plaques are generally characterized as those having a thin inflamed fibrous cap over a very large lipid core. However, only a small percentage of such plaques get ruptured, and the identifying characteristics of TCFA that progress to rupture are unknown<sup>22</sup>. The current study corroborates previous findings that plaques that may be prone to rupture occur proximally and in a similar distribution as acute plaque rupture<sup>3,4,23,24</sup>. The coronary distribution of fibrous-cap atheromas has been shown similar to those of TCFA and plaque ruptures<sup>3</sup>.

The current study shows that TCFA are located close to rupture sites (either proximally or distally in similar proportions) in culprit coronaries, but in a significant number of cases, they were also located in other non-culprit coronary segments. This study corroborates findings of location and distribution of TCFA in the coronary tree. Kolodgie et al<sup>3</sup> also found that

the majority of TCFA, ruptures and healed ruptures occur in the proximal LAD.

The number of TCFA found in our study represents only a small percentage of area and length when the whole coronary tree is used as denominator. Another whole heart autopsy study also identified that ruptures and TCFA accounted only for 1.6% and 1.2%, respectively, of the total length of the coronary tree in a population dying of cardiovascular causes<sup>2</sup>. These represent a smaller portion than those identified the current study, but a difference in population selection is noted, since our study included only sudden unexpected deaths. Furthermore, the frequency of acute ruptures and TCFA in sudden coronary death varies with risk factors, age and gender<sup>25</sup>. Our study had an intrinsic male bias, precluding gender comparison, but there was no age difference among patients with TCFA and those without.

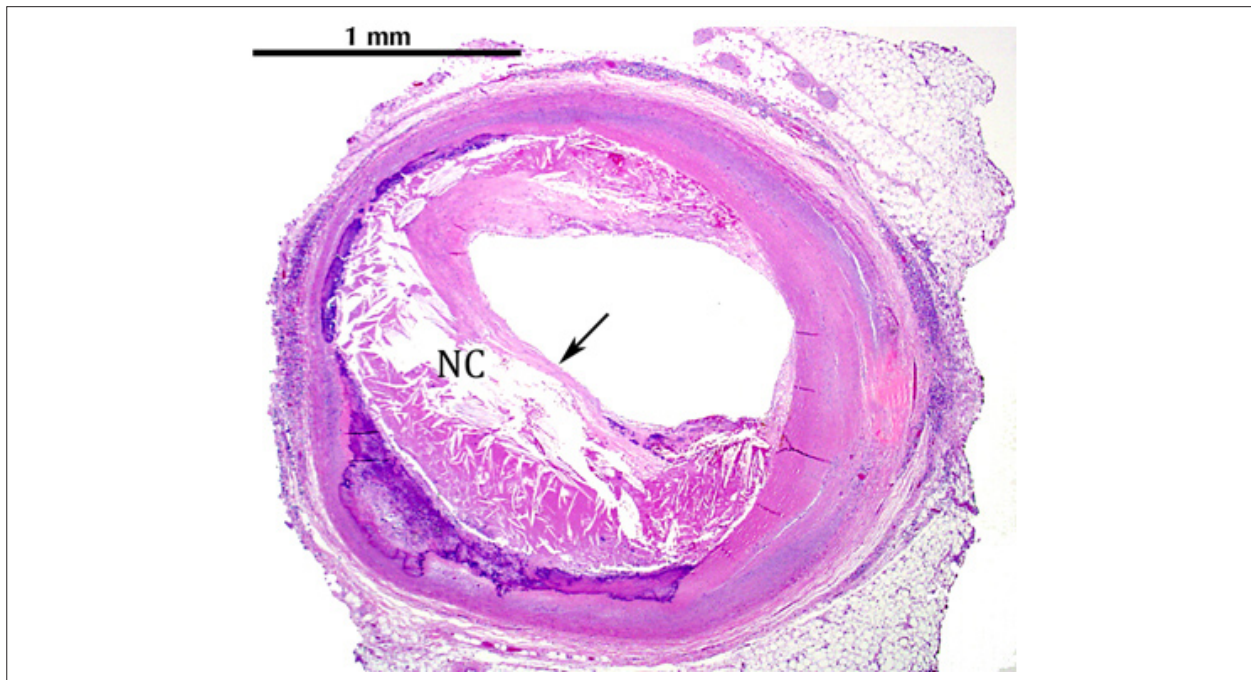
The goal of newer imaging studies is to image not only the lumen but the characteristics of the plaque in order to identify those prone to rupture<sup>25</sup>. Intravascular ultrasound (IVUS) can visualize atherosclerotic plaque and bring information on the



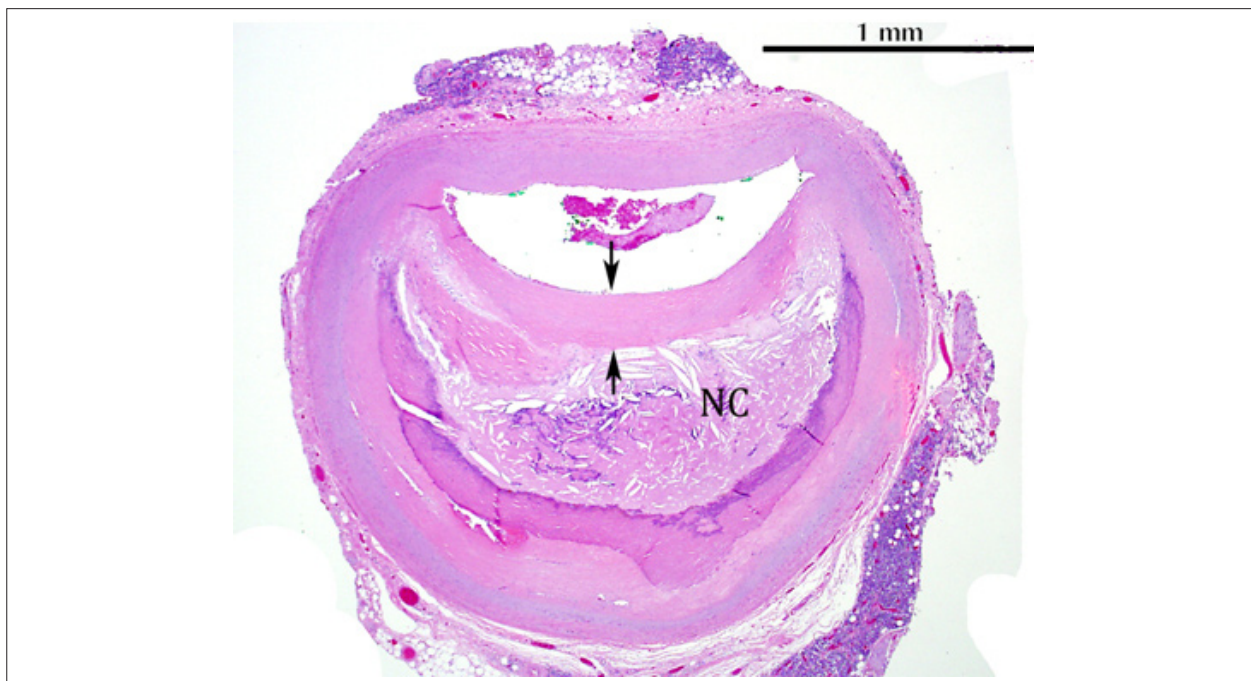
**Table 6 - Relationship between stenosis at TCFA site vs. maximal narrowing and rupture site narrowing Percent luminal narrowing, mean  $\pm$  S.D.**

Site	Culprit artery	Non-culprit arteries
TCFA with maximal stenosis	61.0 $\pm$ 22.6	63.6 $\pm$ 20.9
Maximal stenosis, any plaque type	74.3 $\pm$ 17.4*	71.7 $\pm$ 17.2**
Rupture site	70.0 $\pm$ 15.1***	N/A

\*  $p = .0007$  vs TCFA; \*\*  $p = .002$  vs TCFA; \*\*\*  $p = .006$  vs TCFA; N/A - not applicable. TCFA - thin-cap fibroatheroma. SD - standard deviation.



**Figure 2 - Thin cap fibroatheroma (TCFA) left anterior descending artery. Note thread like fibrous cap separating necrotic core (NC) from coronary lumen. (arrow).**



**Figure 3 - Atheroma. Thick fibrous cap (arrows) over necrotic core (NC). Compare thickness of cap with previous picture.**

presence of calcification and amount of fibrous tissue, but it fails to provide quantification of specific plaque composition<sup>26,27</sup>. A more recent approach called virtual histology IVUS (VH-IVUS) has been used in the attempt to characterize plaques in vivo. Nakamura et al<sup>28</sup> studied non-culprit segments in patients with stable angina and acute coronary syndrome and found, similar to our study, a large number of presumed TCFA in non-culprit segments of patients with acute coronary syndrome. IVUS cannot, however, identify specific plaque components, which can be assessed by near infrared spectroscopy<sup>7</sup>. Moreno et al<sup>29</sup> reported a sensitivity and specificity of 77 and 93% for TCFA when compared to histological assessment in post-mortem coronary segments of patients with acute coronary events. Lastly, computed tomography-based techniques such as multidetector-row CT and optical coherence tomography are promising new methods of evaluating atherosclerotic plaque and its composition<sup>13,30</sup>. Similar to our results, an autopsy study using optical coherence tomography found that 64% patients with acute coronary syndrome had 1 or more TCFAs. The authors concluded that TCFAs, clustering in the proximal segments of the 3 major epicardial coronary arteries, are a common finding in unselected autopsy subjects<sup>10</sup>.

In conclusion, a large number of TCFAs occur in regions proximal and distal to culprit plaques (ruptures) and at sites away from these lesions. These TCFAs occur at sites of maximum luminal narrowing at a similar rate to ruptures, namely between 40 and 50%. Therefore, luminal narrowing cannot be taken as a reliable angiographic marker for assessment of patient's risk, and further autopsy and angiographic studies are needed in order to establish the subset of TCFAs that are "vulnerable".

#### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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#### Study Association

This study is not associated with any post-graduation program.

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## Original Article

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