Vulnerable Plaque Research

TCT AP 2022

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Disclosure

- Allan and Gill Gray Professorship
- Allan Gray Fellowship Funds
- Abbott Fellowship Grant

Objectives

- Discuss the concept of “vulnerable plaque”
- Update on pathobiology of ACS
- “vulnerable plaque” clinical studies

“Einstein’s Definition of Insanity”

“Doing the same thing over and over again and expecting different results”

“Vulnerable Plaque Research and Einstein’s Definition of Insanity”

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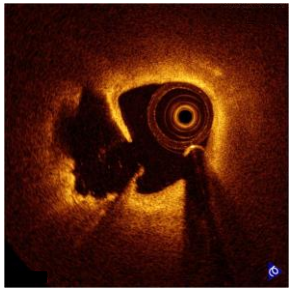
“It seems abundantly clear the entire concept of VP is fundamentally flawed and reflects an overly simplistic view of the pathophysiology of underlying coronary events”.

“To date, proponents of VP imaging have not conducted high-quality trials, and no imaging modality has demonstrated a meaningful clinical benefit.”

“After thousands of VP papers and more than 2 decades of research, we have little to show for these efforts.”

Nissen S. JACC 2020

The “Vulnerable Plaque” Preconception



- Most ACS are triggered by plaque rupture
- Most ruptures occur at thin-cap fibroatheromas (TCFA)

- Identifying TCFAs confers high risk of ACS
- Treating TCFA with stents prevents future ACS/SCD

Arbab-Zadeh A. Circulation 2012

The “Vulnerable Plaque” Facts

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- Atherosclerosis is a pan-vascular process.
- Plaque phenotype changes over time.
- Three quarters of plaques regress with medical therapy.
- Subclinical plaque disruption and healing contributes to plaque progression.
- Plaque erosion is responsible for 25-40% of ACS.

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Non-culprit plaque characteristics ACS vs. Non-ACS

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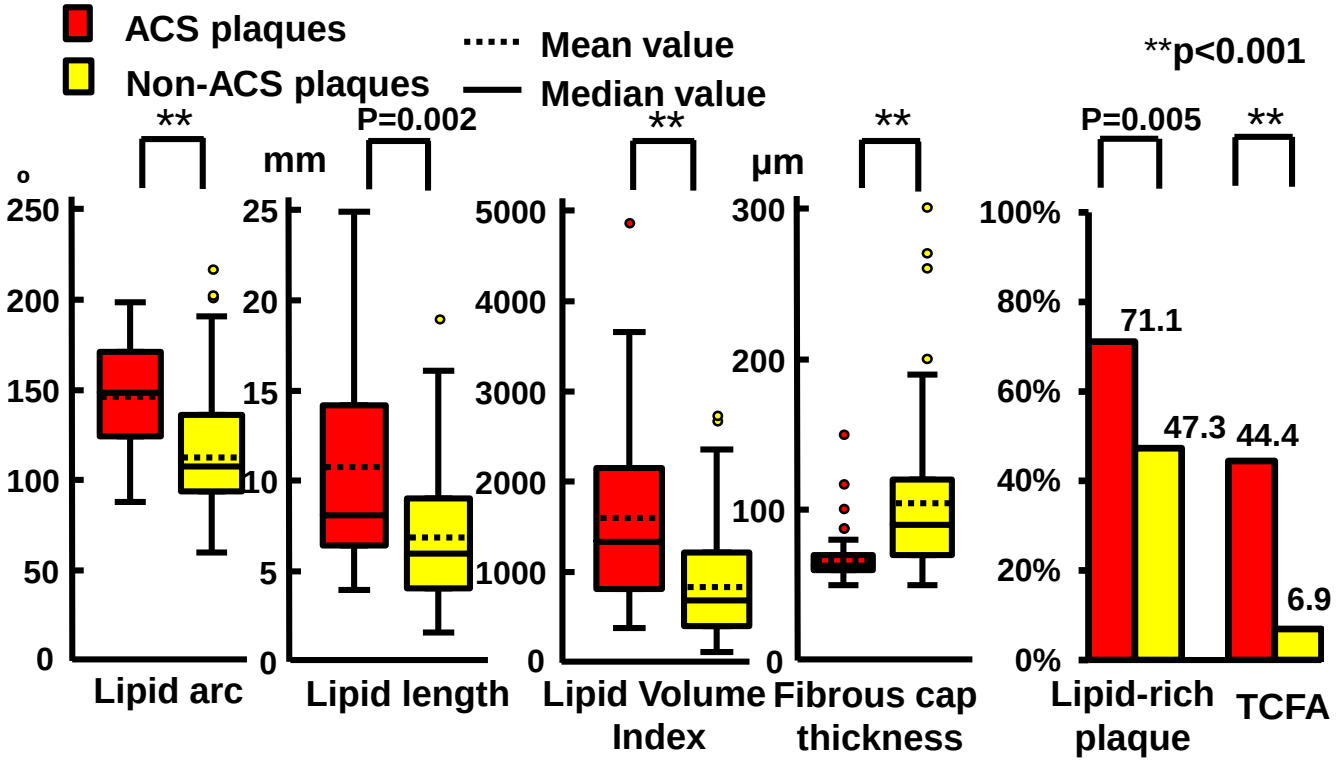

Kato K. Circ Img 2013

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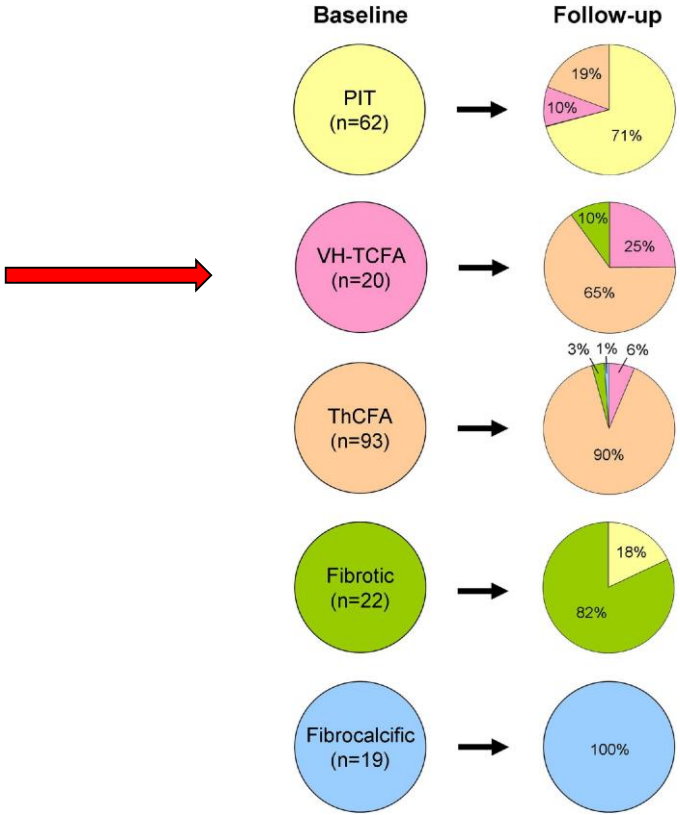
Dynamic Nature of Coronary Plaque Phenotype



Kubo T. JACC 2010

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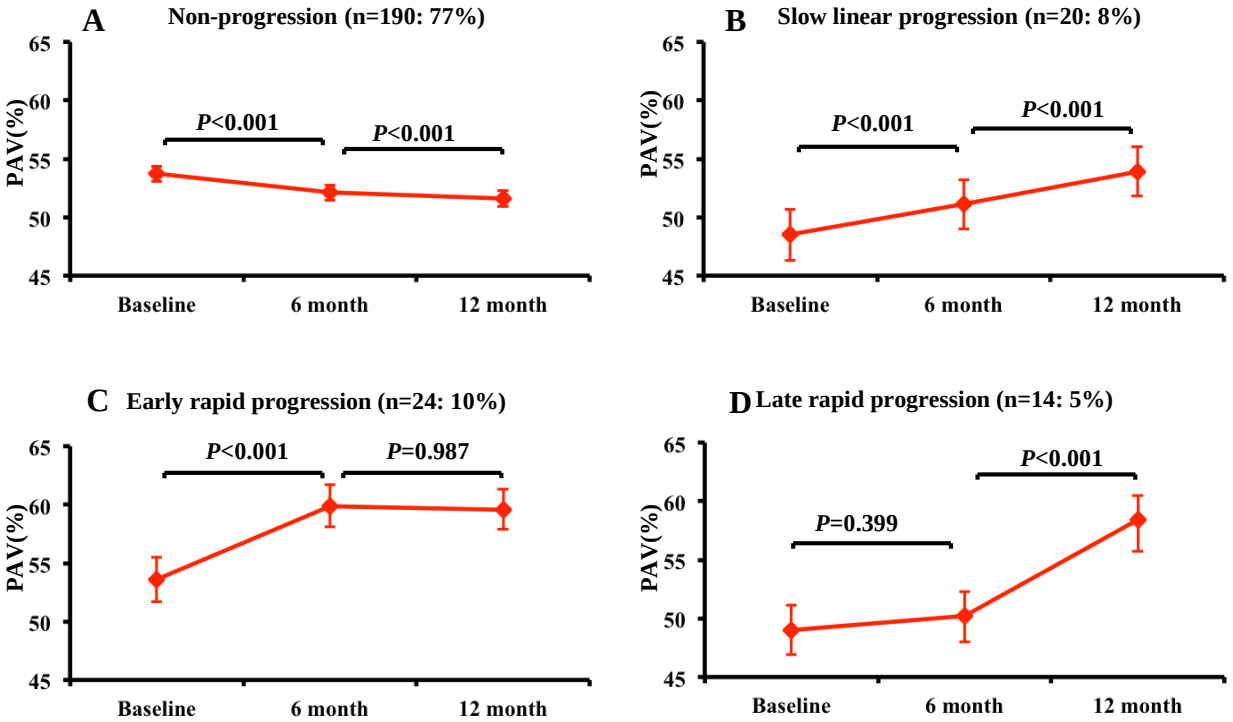
Patterns of Plaque Progression



Jang IK EHJ 2019

Stabilization of Fibrous Cap Thickness (FCT)

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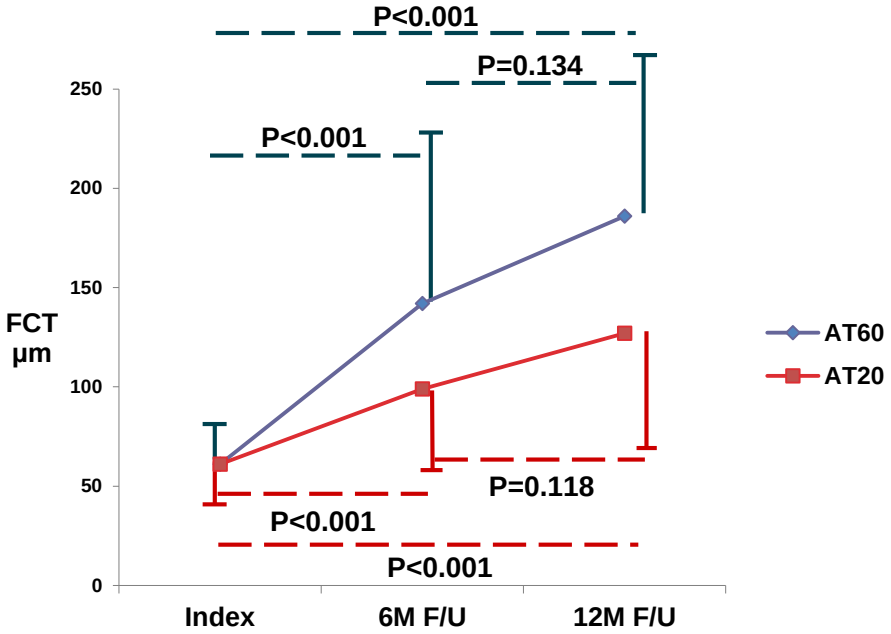

AT 60 mg (n = 36)	61±21	142±91	186±85
AT 20 mg (n = 30)	61±18	99±49	127±68
P AT60 vs. AT20	0.963	0.022	0.004

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Natural History of Atherosclerosis

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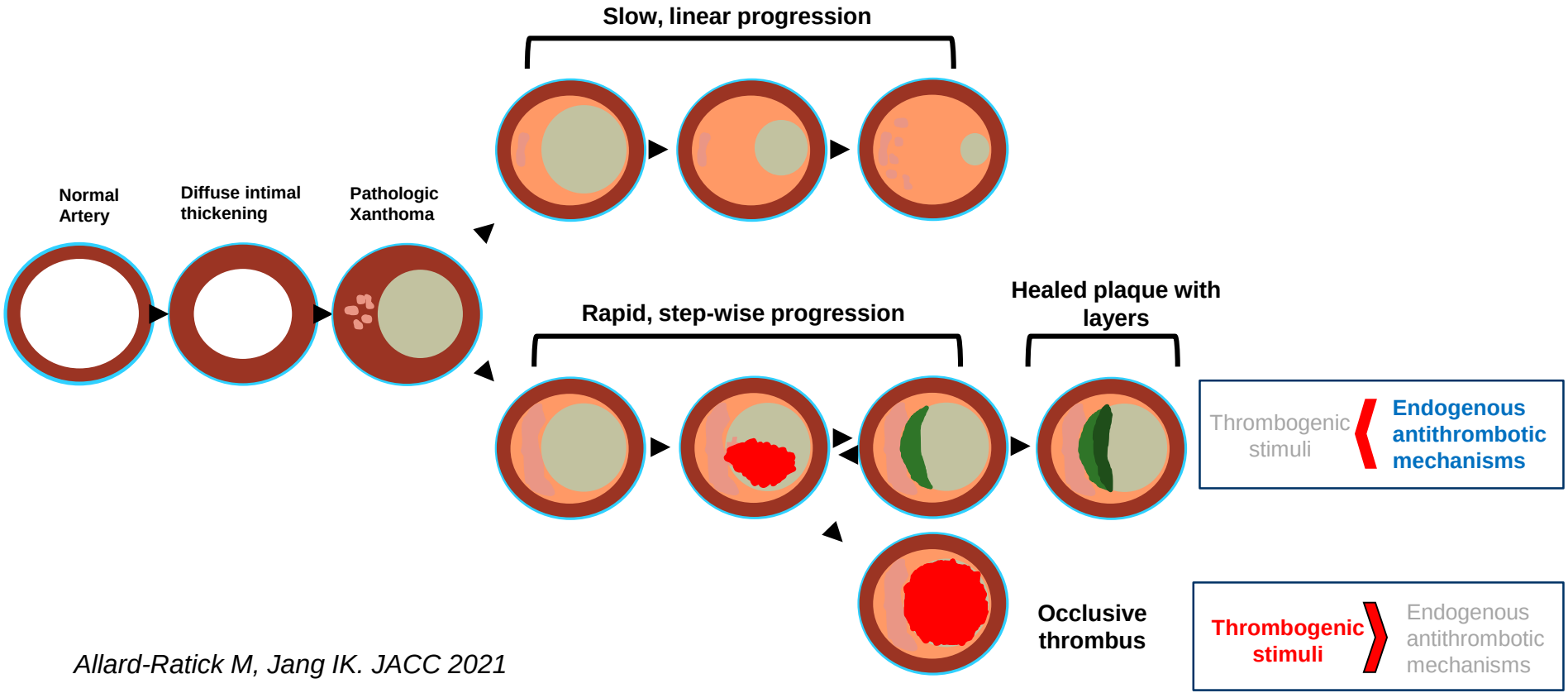
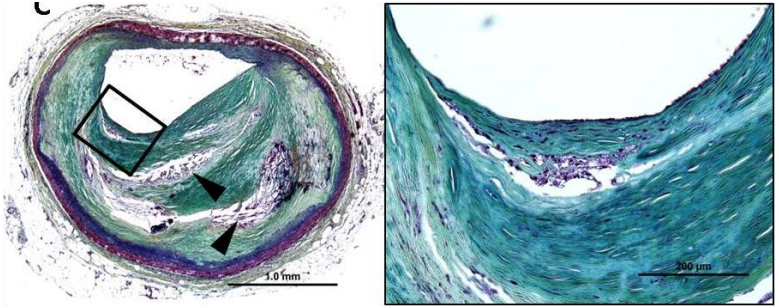
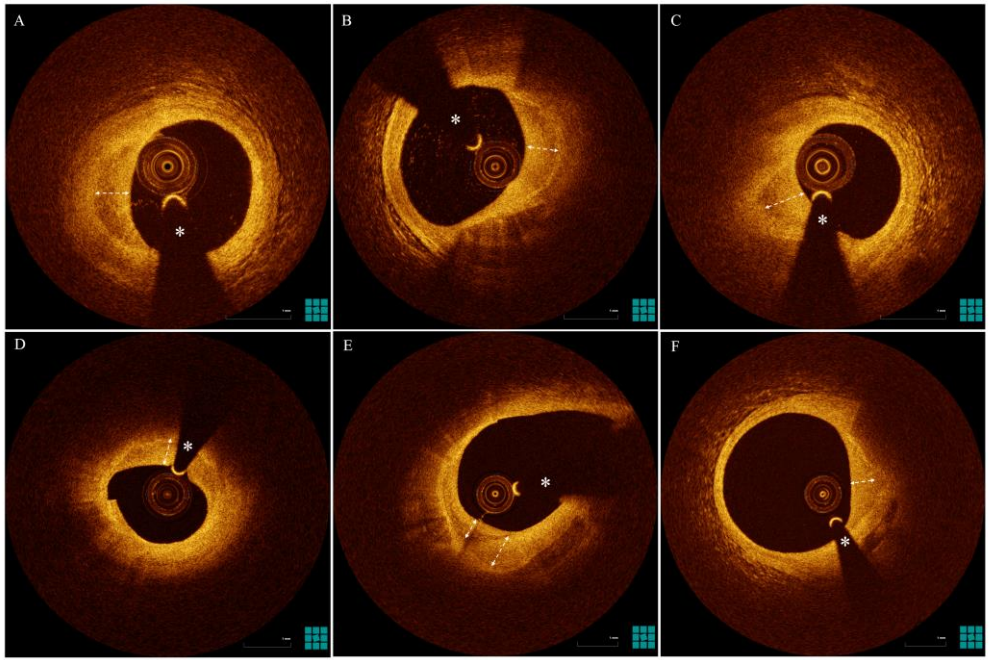


Allard-Ratick M, Jang IK. JACC 2021

Healed (Layered) Plaque





Evidence of previous plaque disruption was present in up to 73% in autopsy cases

Fracassi F. JACC 2019, Vergallo R. JAMA Card 2019, Russo M. ATVB 2020

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In Vivo Prevalence of Plaque Erosion

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Study/Year	Ref.	Presentation	n*	Plaque Rupture	Plaque Erosion
Jia et al. 2013	8	ACS	126	55 (44%)	39 (31%)
Hu et al. 2014	25	STEMI	23	11 (48%)	8 (35%)
Higuma et al. 2015	26	STEMI	112	72 (64%)	30 (27%)
Saia et al. 2015	27	STEMI	97	63 (65%)	32 (33%)
Niccoli et al. 2015	28	ACS	139	82 (59%)	57 (41%)
Yonetsu et al. 2016	29	ACS	318	141 (44%)	131 (41%)
Kajander et al. 2016	30	STEMI	93	34 (49%)	31 (44%)
Kwon et al. 2016	31	ACS	133	90 (68%)	43 (32%)
Hu et al. 2017	32	ACS	141	79 (56%)	62 (44%)
Dai et al. 2018	33	STEMI	822	564 (69%)	209 (25%)
Yamamoto et al. 2019	34	ACS	1,241	607 (49%)	477 (38%)
Total			3245	1798 (**55.1%**)	1119 (**34.5%**)

Kolte D, Jang IK. JAMA 2021, Fahed A, Jang IK. Nature Rev Card 2021

VP Clinical Studies

VP Clinical Studies

- First VP study
- The PROSPECT trial
- MGH Registry study

First Study on Vulnerable Plaque

Professor Yasumi Uchida

In 157 patients with stable angina, yellow plaque on coronary angioscopy had a higher incidence of ACS (28.2% vs. 3.4%, p=0.00021) at 1 year.

Uchida Y. Am Heart J 1995

The PROSPECT Study

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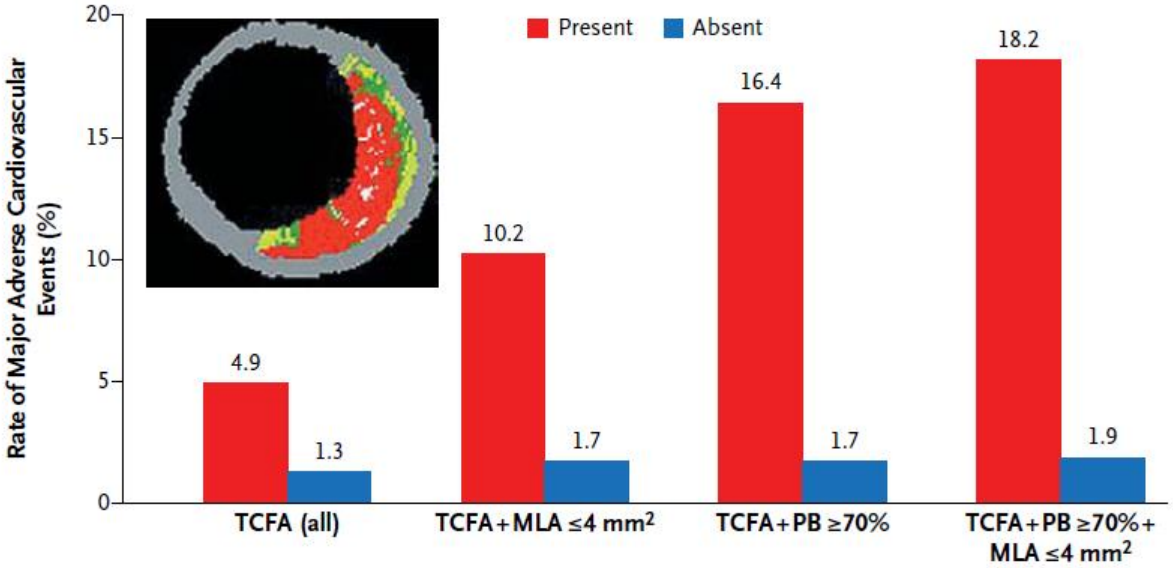

Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

Stone GW et al. NEJM 2011;364:226-35

The PROSPECT Study

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Type of Events	Events due to Nonculprit Lesions
Death from cardiac causes	
Myocardial infarction	
Rehospitalization for angina	
Total MACE	11.6% (75 patients)

PROSPECT: Multivariable Correlates of Non-Culprit Lesion Related Events

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Independent predictors of lesion level events by Cox Proportional Hazards regression

Variable	HR [95% CI]	P value
PB ≥ 70%	5.03 [2.51, 10.11]	<0.0001
VH-TCFA	3.35 [1.77, 6.36]	0.0002
MLA ≤ 4.0 mm2	3.21 [1.61, 6.42]	0.001

VH-TCFA: Plaque burden (PB) > 40% + absence of visible fibrous cap

The PROSPECT Study

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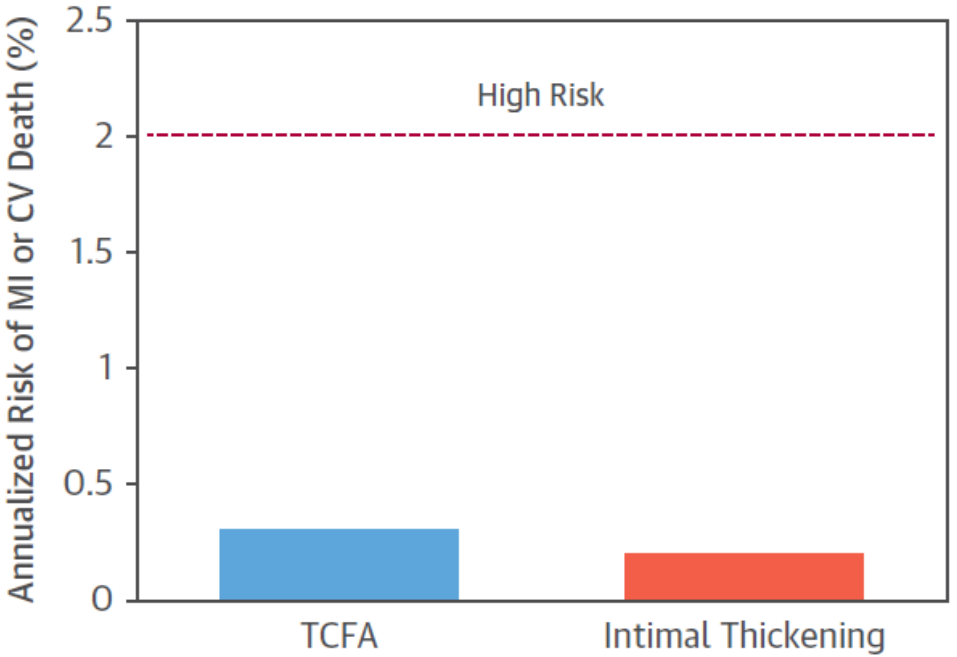
FIGURE 1 Risk of MI or Death Associated With Individual Plaques in the PROSPECT Study



Arbab-Zadeh A and Fuster V. JACC 2015

PROSPECT: Take home message

- Potential risk of MI (STEMI + NSTEMI) from VH-TCFA is 1%, which is similar to that from intimal thickening.
- Plaque burden (vs.plaque phenotype) is an important factor for development of recurrent ischemic events.
- Risk of 3 vessel imaging is 1.6%.

→ Intracoronary imaging is not justified even in ACS patients.

MGH Registry: Plaque-based Analysis

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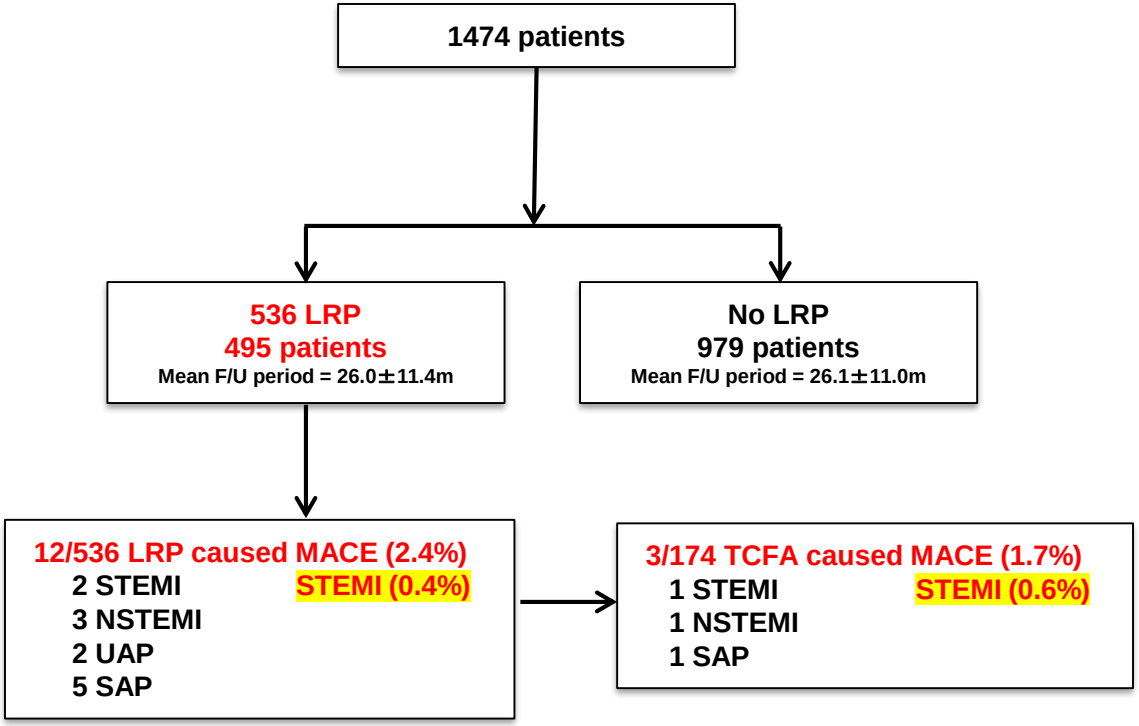

Jang IK. EHJ 2019

MGH Registry Study: Summary

- LRP was found in non-culprit regions of target vessel in 1/3 of patients.
- Presence of LRP in the non-culprit regions of the target vessel predicts increased risk for future NC-MACE.
- However, MACE was primarily driven by revascularization and not by AMI or SCD.
- Only 0.4% of LRP and 0.6% of TCFA identified by OCT in the culprit vessel caused STEMI during 4-year F/U.

Conclusion

- The concept of “vulnerable plaque” needs to be re-visited.
- Atherosclerosis is a pan-vascular process with repetitive plaque disruption and healing.
- Over 75% of atherosclerotic plaques stabilize with contemporary medical therapy.
- Plaque erosion is responsible for 25-40% of ACS.

Take home message

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"The absence of natural history studies, the invasive nature of the current diagnostic modalities, effective contemporary medical therapy, and erosion contributing to a significant portion of patients with ACS make vulnerable plaque research a major challenge."

Jang IK. Eur Heart J 2019

Thank you

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