Controversies and Advances in the
Treatment of Cardiovascular Disease
The Twentieth in the Series

December 2-3, 2021 ♦ The Maybourne Beverly Hills

Evaluating Coronary Anatomy Is the Best Way to Improve Outcomes

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BHF Duke of Edinburgh Chair of Cardiology

Conflicts of interest

Grants, consultancy or clinical trial contracts with:

- Abbott, Amgen, AstraZeneca, Autoplaque, BMS, Boehringer Ingleheim, Cleerly, Elly Lilly, GE, GSK, Jansen, MSD, Novartis, Pfizer, Phillips, Roche, Sanofi, Siemens, Toshiba, UCB, Wyeth, Zealand.

Publishing:

- BMJ Group, Elsevier

Research funding:

- British Heart Foundation, Medical Research Council, Wellcome Trust, Chief Scientist Office, Chest Heart Stroke Scotland

Chief Investigator of the SCOT-HEART trial

Evaluating Coronary Anatomy
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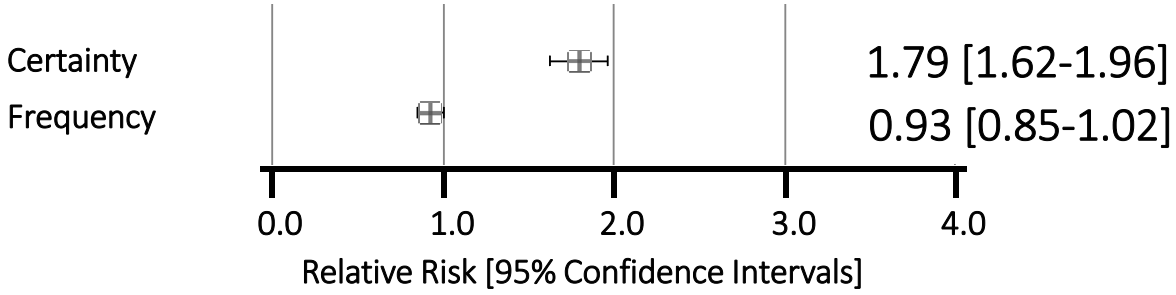
- Diagnosis
- Prognosis
- Management
- Clinical Outcomes

Diagnosis: Anatomical Testing with CT

Lancet 2015;385:2383-2391

Attending Clinician: Diagnosis of Coronary Heart Disease

Attending Clinician: Diagnosis of Angina due to CHD



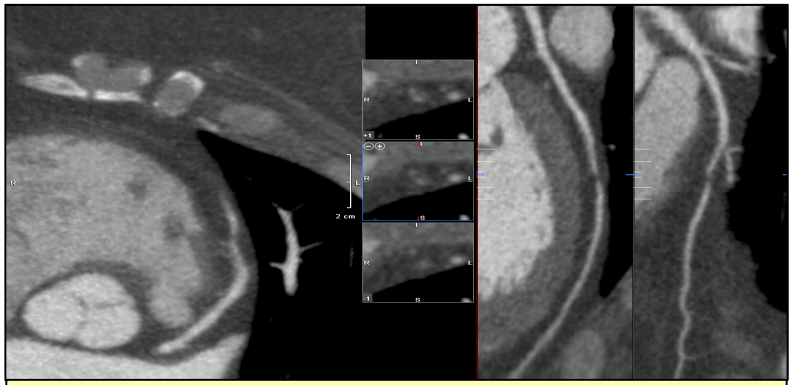
Overall Changes in Diagnosis: 25% versus 1%, P<0.001

Anatomical Testing with CT

Avoid Unnecessary Invasive Angiography, More Actionable Disease

Reduced likelihood of demonstrating normal coronary arteries
(P<0.001)

Hazards Ratio 0.392
(95% CI, 0.227-0.676)

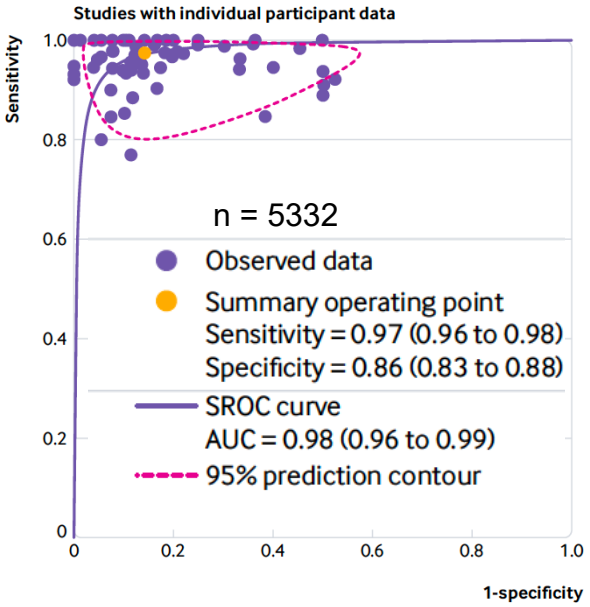


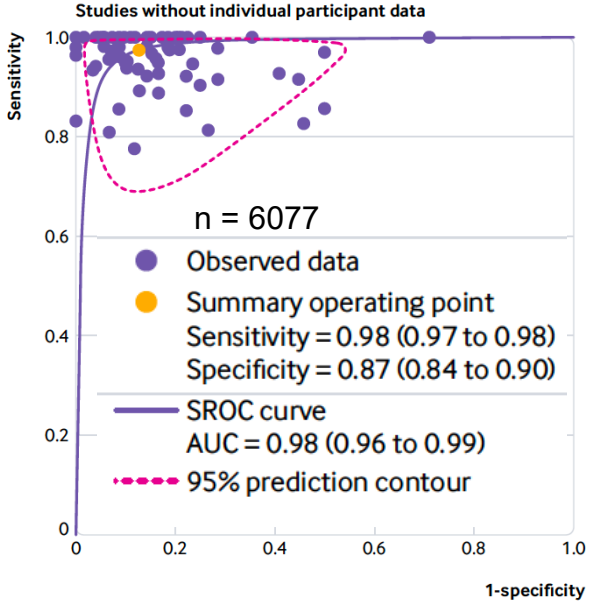
Increased likelihood of identifying obstructive coronary artery disease
(P=0.005)

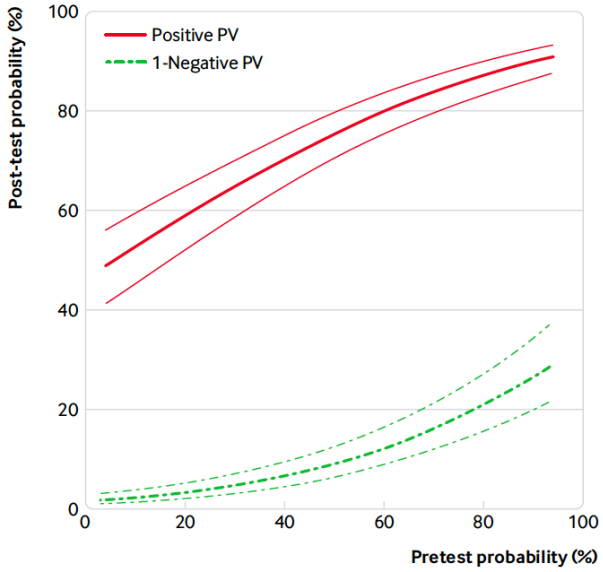
Hazards Ratio 1.293
(95% CI, 1.081-1.548)

Williams et al. *J Am Coll Cardiol.* 2016;67:1759-1768

Diagnosis of obstructive coronary artery disease using computed tomography angiography in patients with stable chest pain depending on clinical probability and in clinically important subgroups: meta-analysis of individual patient data







Haase *et al. BMJ* 2019;365:l1945

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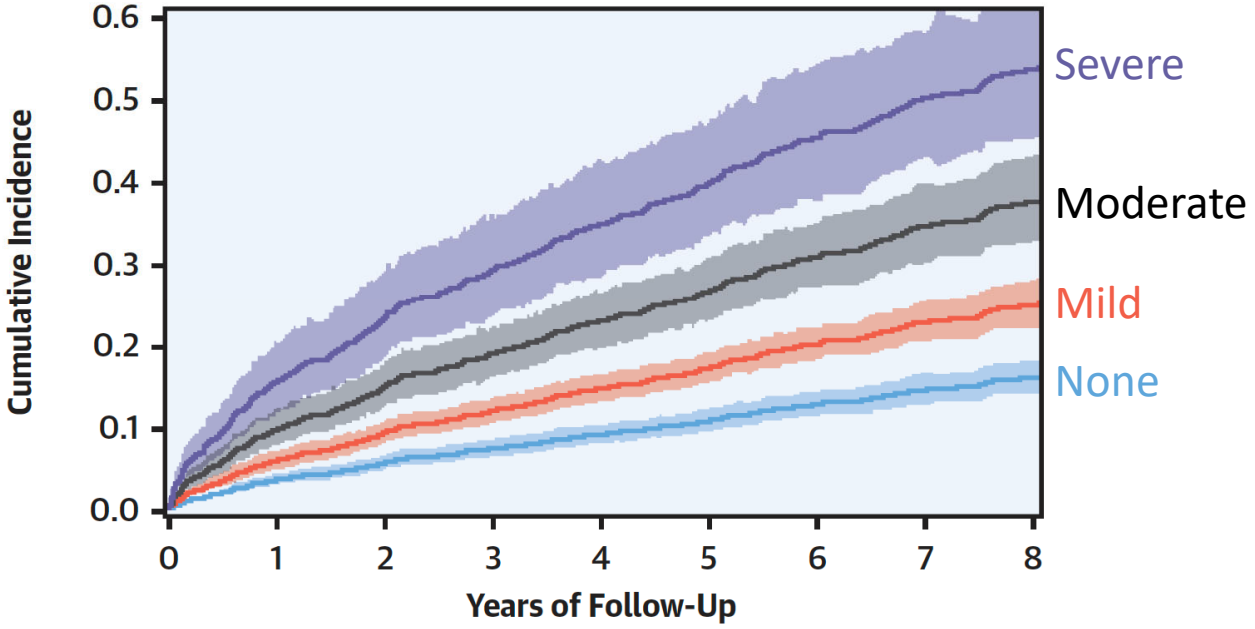
Strength of Ischaemia Testing is Risk Prediction

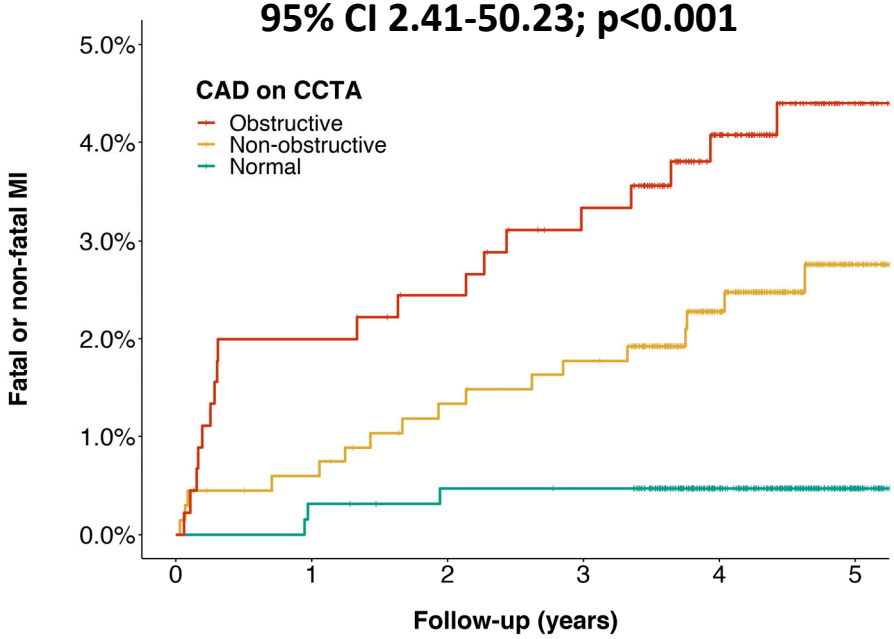


Kwong *et al. J Am Coll Cardiol* 2019;74:1741-1755

Future Risk of Myocardial Infarction

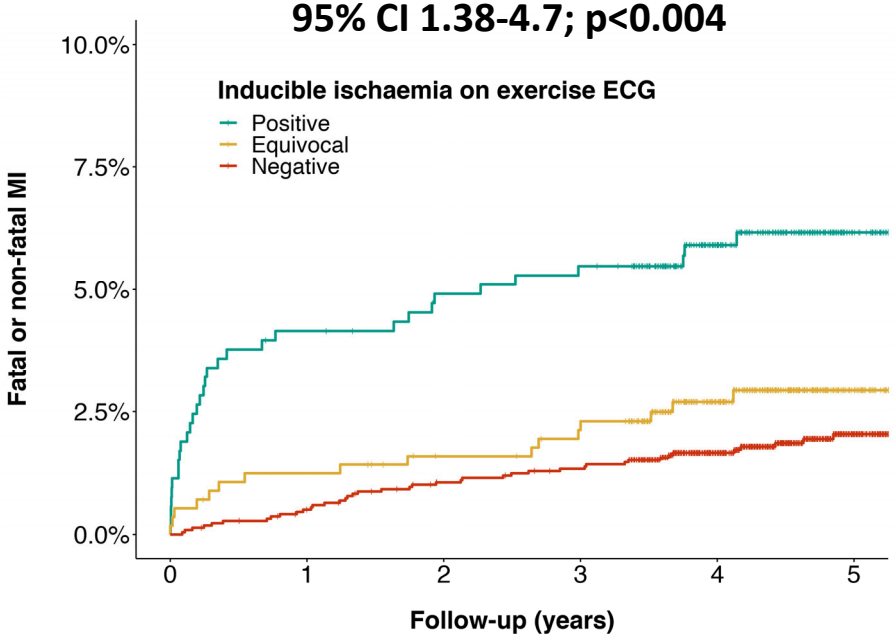
Anatomical Versus Functional

Hazard Ratio 11.0
95% CI 2.41-50.23; p<0.001



Half of MIs had no obstructive disease

Hazard Ratio 2.52
95% CI 1.38-4.7; p<0.004



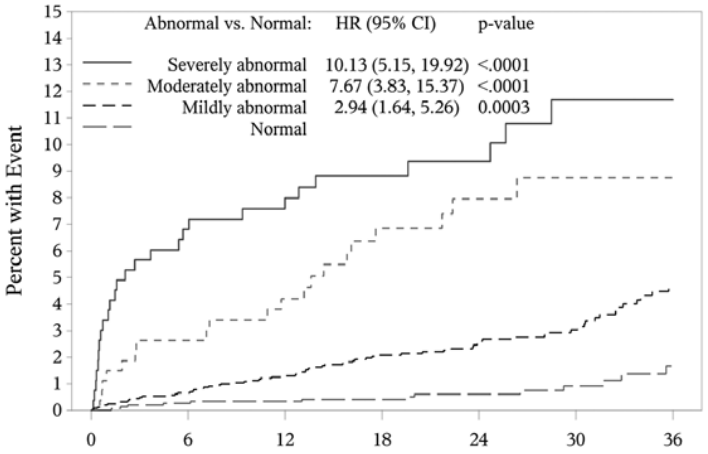
Only third of MIs had abnormal exercise test

Singh *et al. JAMA Cardiol* 2020;5:1-10

Future Risk of Myocardial Infarction

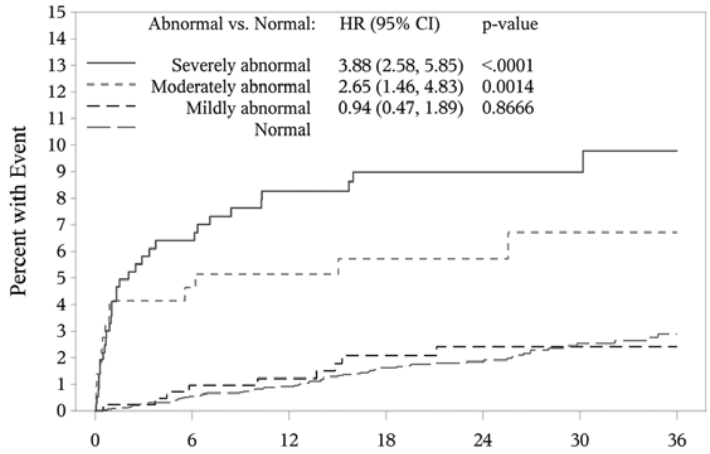
Anatomical Versus Functional Testing

Anatomic Testing



>50% of MIs had non-obstructive disease

Functional Testing



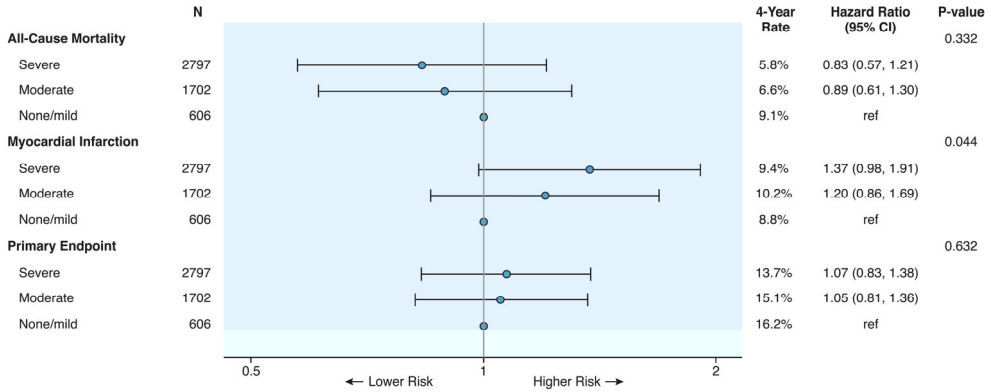
>50% of MIs had a normal functional test

Hoffmann *et al. Circulation* 2017;135:2320-2332

ISCHEMIA Trial Outcomes
Functional Versus Anatomical

Degree of Ischaemia

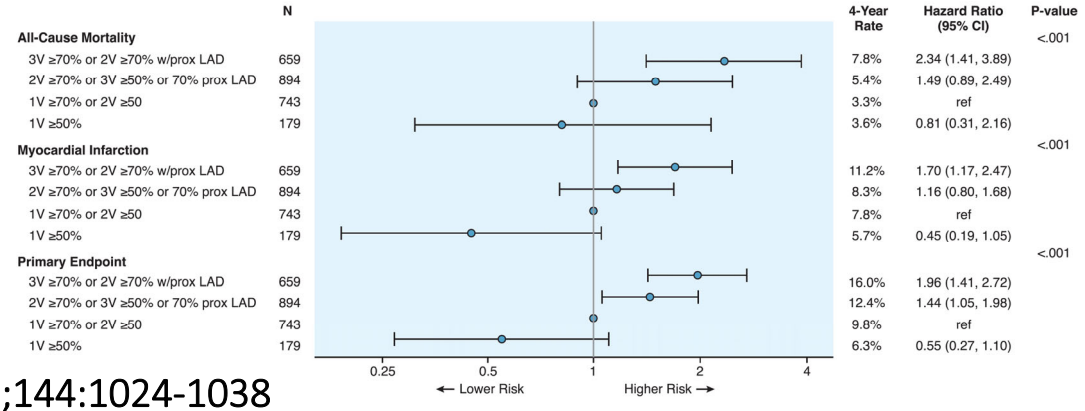
n=5179



	N	4-Year Rate	Hazard Ratio (95% CI)	P-value
All-Cause Mortality				0.332
Severe	2797	5.8%	0.83 (0.57, 1.21)	
Moderate	1702	6.6%	0.89 (0.61, 1.30)	
None/mild	606	9.1%	ref	
Myocardial Infarction				0.044
Severe	2797	9.4%	1.37 (0.98, 1.91)	
Moderate	1702	10.2%	1.20 (0.86, 1.69)	
None/mild	606	8.8%	ref	
Primary Endpoint				0.632
Severe	2797	13.7%	1.07 (0.83, 1.38)	
Moderate	1702	15.1%	1.05 (0.81, 1.36)	
None/mild	606	16.2%	ref	

Severity of
Coronary Artery Disease

n=2475



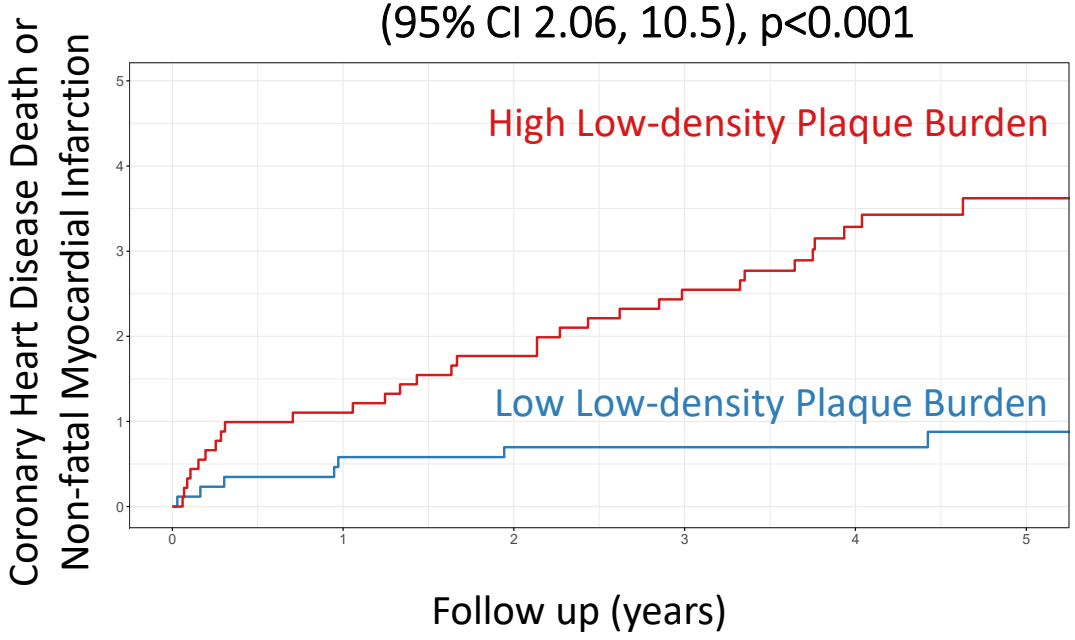
	N	4-Year Rate	Hazard Ratio (95% CI)	P-value
All-Cause Mortality				<.001
3V ≥70% or 2V ≥70% w/prox LAD	659	7.8%	2.34 (1.41, 3.89)	
2V ≥70% or 3V ≥50% or 70% prox LAD	894	5.4%	1.49 (0.89, 2.49)	
1V ≥70% or 2V ≥50	743	3.3%	ref	
1V ≥50%	179	3.6%	0.81 (0.31, 2.16)	
Myocardial Infarction				<.001
3V ≥70% or 2V ≥70% w/prox LAD	659	11.2%	1.70 (1.17, 2.47)	
2V ≥70% or 3V ≥50% or 70% prox LAD	894	8.3%	1.16 (0.80, 1.68)	
1V ≥70% or 2V ≥50	743	7.8%	ref	
1V ≥50%	179	5.7%	0.45 (0.19, 1.05)	
Primary Endpoint				<.001
3V ≥70% or 2V ≥70% w/prox LAD	659	16.0%	1.96 (1.41, 2.72)	
2V ≥70% or 3V ≥50% or 70% prox LAD	894	12.4%	1.44 (1.05, 1.98)	
1V ≥70% or 2V ≥50	743	9.8%	ref	
1V ≥50%	179	6.3%	0.55 (0.27, 1.10)	

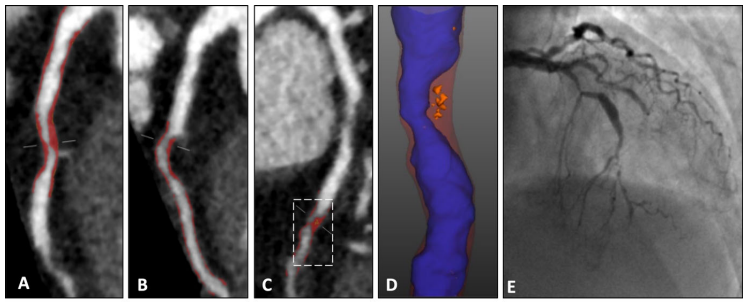
Reynolds *et al. Circulation* 2021;144:1024-1038

Advanced Anatomical Assessment

Quantitative Plaque Characteristics and Outcome

Hazard Ratio 4.65
(95% CI 2.06, 10.5), p<0.001





Independent of cardiovascular risk score, coronary artery calcium score, stenosis severity

Williams *et al. Circulation* 2020;141:1452-1462

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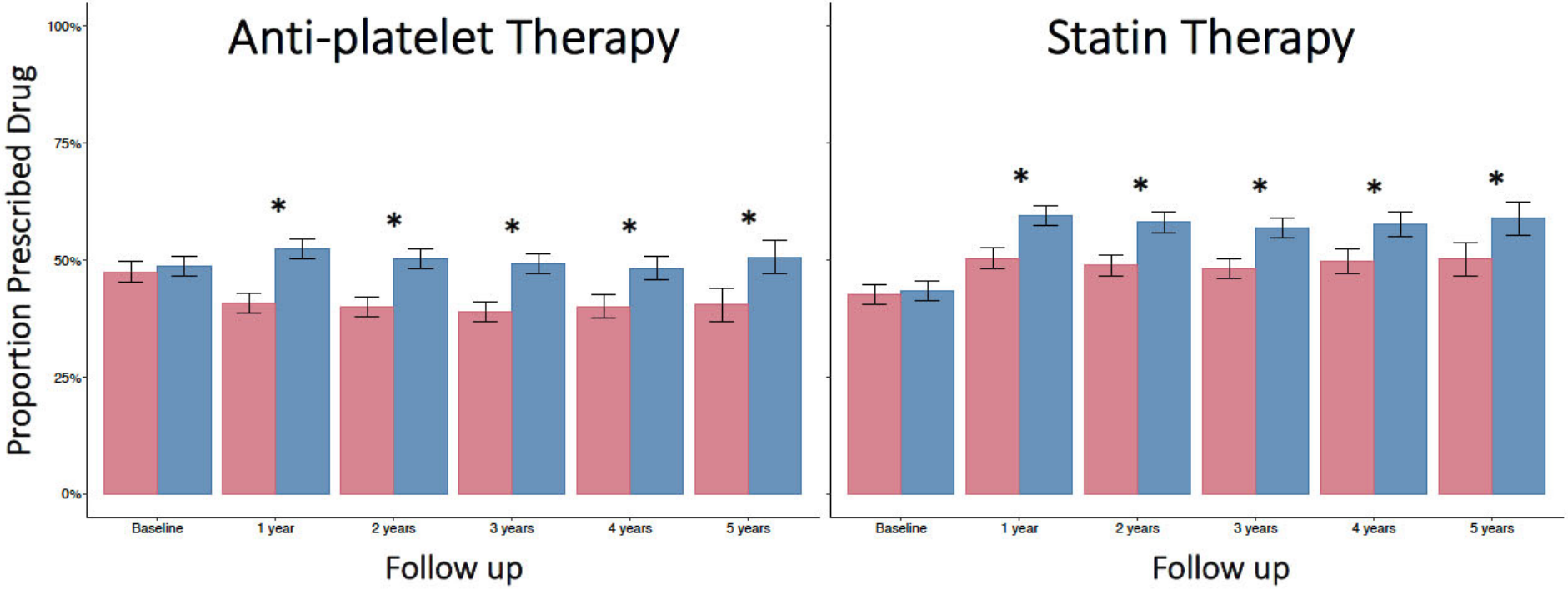
CT Coronary Angiography

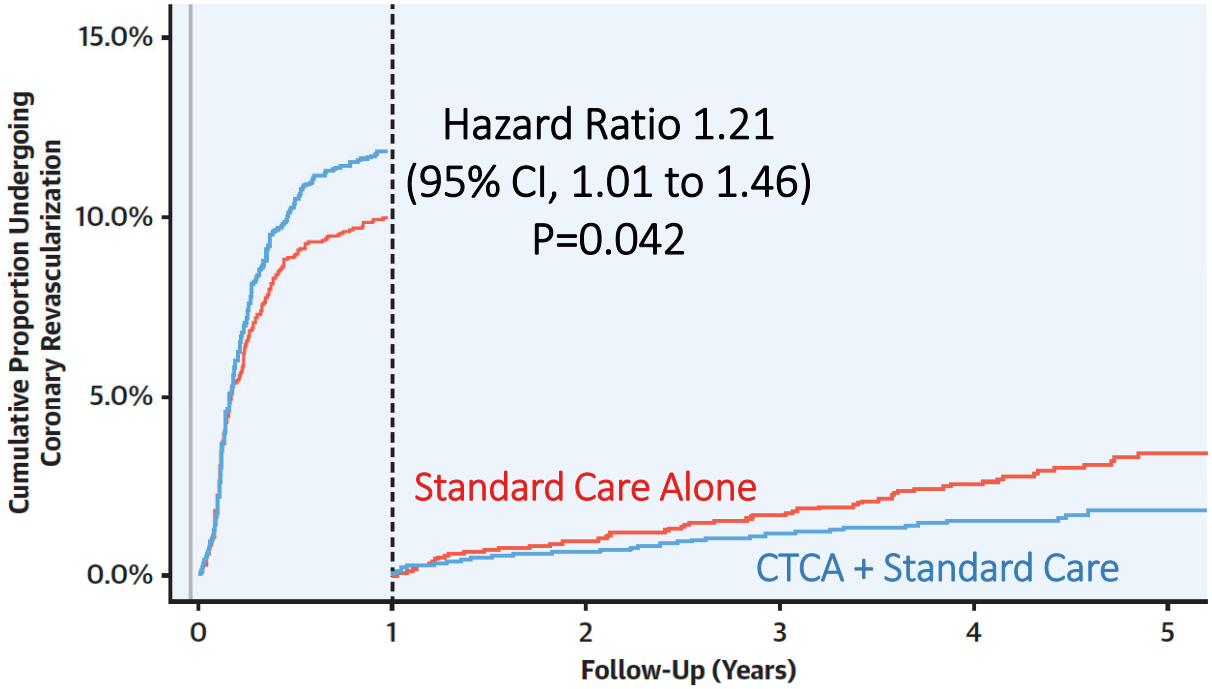
More Preventative Therapies



N Engl J Med 2018;379:924-933

CT Coronary Angiography

Better Targeted Angiography and Revascularisation



Hazard Ratio 0.59
(95% CI, 0.38 to 0.90)
P=0.015

No. at Risk						
Standard Care	2,073	1,865	1,847	1,834	1,450	794
CTCA	2,073	1,827	1,815	1,806	1,426	771

Adamson *et al. J Am Coll Cardiol.* 2019;74:2058-2070

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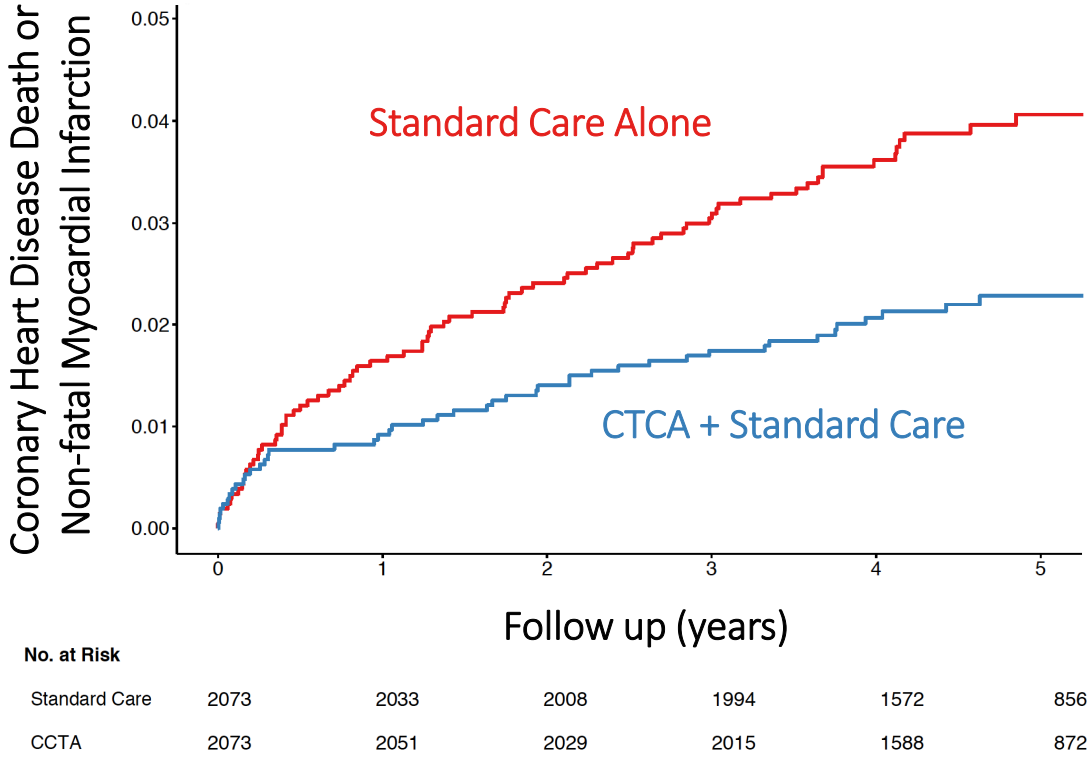
Anatomical Testing

The SCOT-HEART Trial



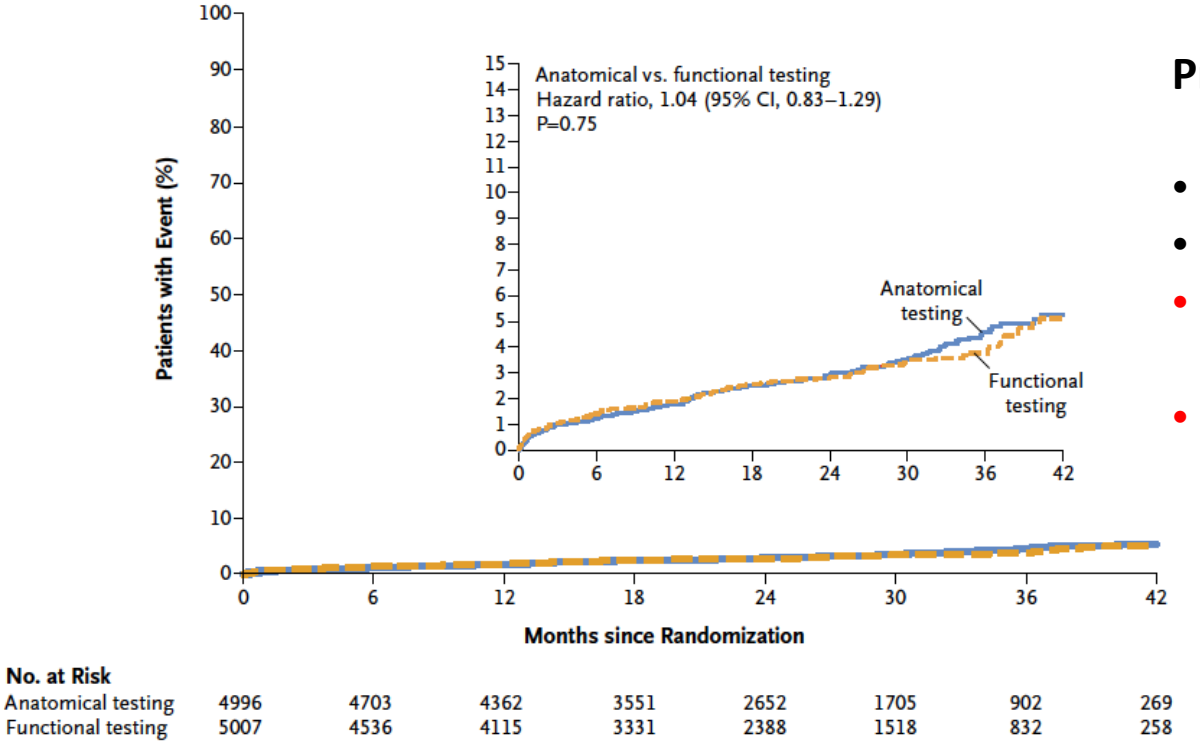
No. at Risk

Standard Care	2073	2033	2008	1994	1572	856
CCTA	2073	2051	2029	2015	1588	872

Hazard Ratio 0.59
(95% CI, 0.41 to 0.84)
P=0.004

N Engl J Med 2018;379:924-933

The PROMISE Trial



No. at Risk								
Anatomical testing	4996	4703	4362	3551	2652	1705	902	269
Functional testing	5007	4536	4115	3331	2388	1518	832	258

Primary Endpoint:

- **All-cause death**
- **Myocardial infarction**
- **Hospitalization for unstable angina**
- **Major complication of cardiovascular procedures or diagnostic testing (stroke, major bleeding, renal failure or anaphylaxis)**

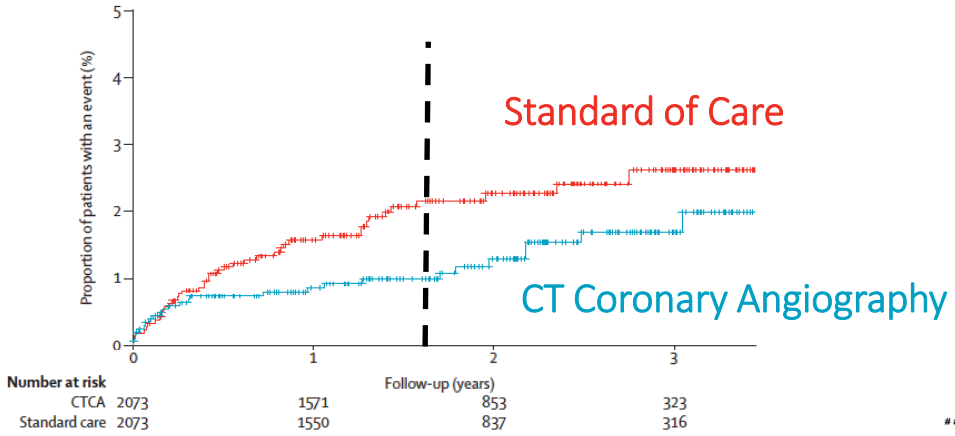
Douglas et al. N Engl J Med 2015;372:1291-1300

Short-term Effects of CTCA

Clinical Outcomes

The SCOT-HEART Trial

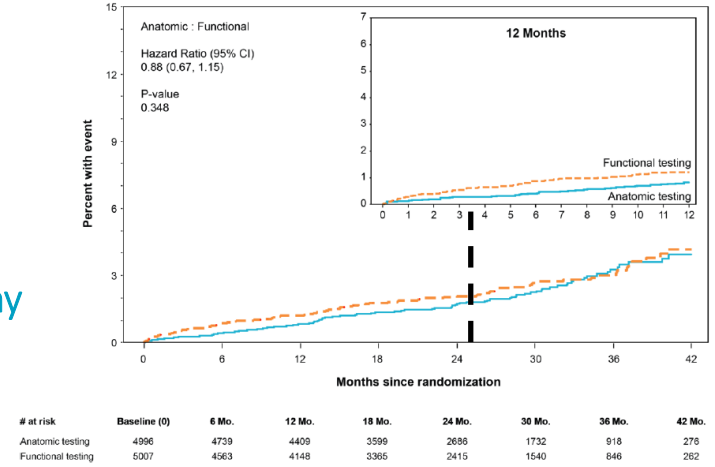
CHD death or non-fatal myocardial infarction
HR 0.62 (95% CI, 0.38-1.01), P=0.053



Lancet 2015;385:2383-2391

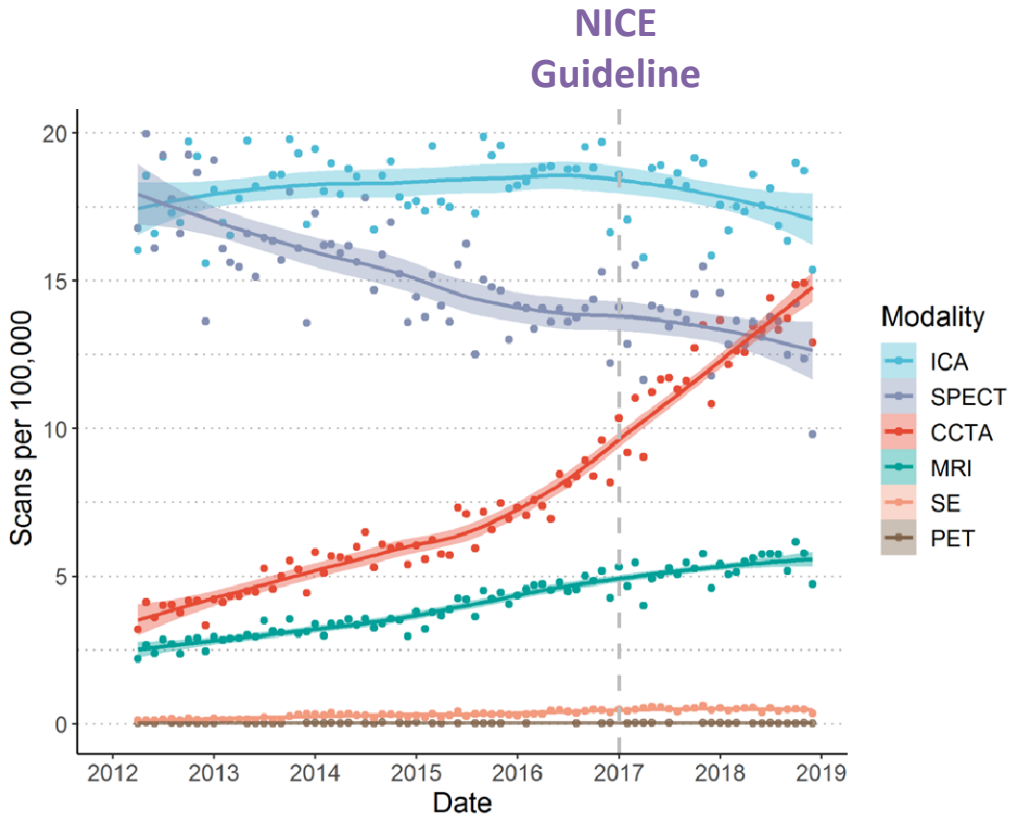
The promise Trial

Death or non-fatal myocardial infarction
HR 0.66 (95% CI, 0.44-1.00), P=0.049



N Engl J Med 2015;372:1291-1300

Impact of NICE Recommendation on Clinical Practice in England



Since NICE Guidance 2016

Year-on-year average annual growth:

- **CT Coronary Angiograms 53±79 versus 2±53 tests/100,000/yr (p<0.001)**

Year-on-year average annual decline:

- **Invasive Coronary Angiography -13±48 versus +5±36 tests/100,000/yr (p=0.03).**

Unpublished

Regions with the Highest Growth in CTCA Have Better Outcomes

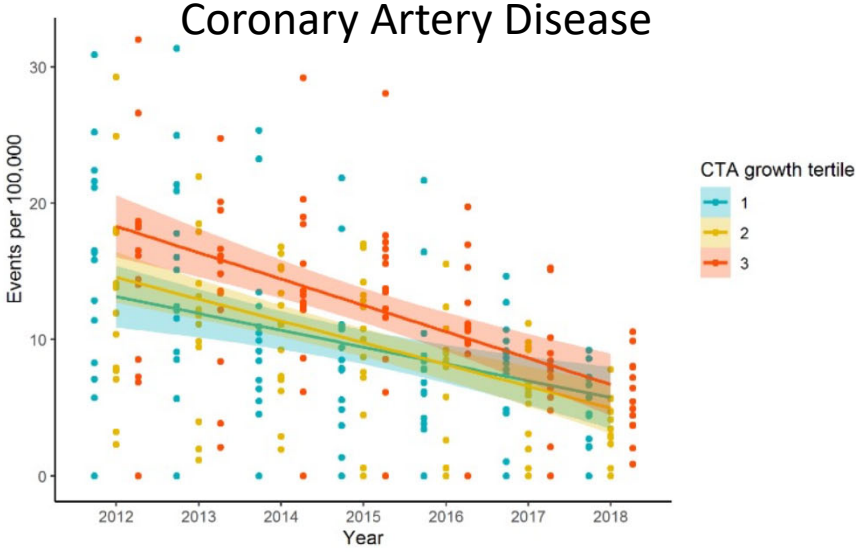
Hospitalisations for Myocardial Infarction

Lowest Growth: +1.8 (95% CI 0.9 to 2.7)

Highest Growth: -0.7 (95% CI -0.8 to 1.7)

myocardial infarctions per 100,000 population/year

Deaths from Coronary Artery Disease



Lowest Growth: -2.32 (95% CI -2.82 to -2.10)

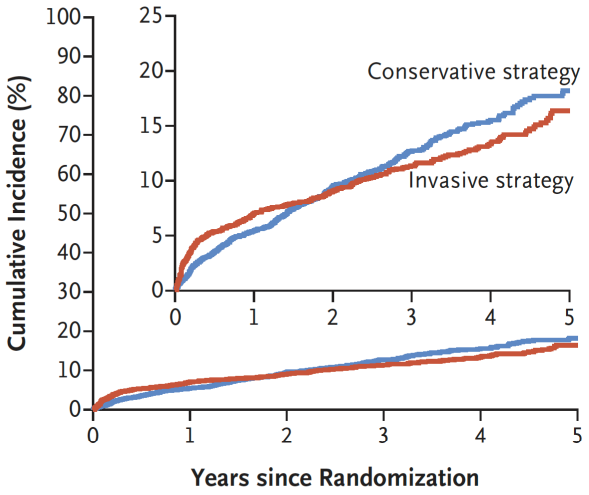
Highest Growth: -3.29 (95% CI -3.60 to -2.95)

deaths per 100,000 population/year

McCall-Weir *et al. Unpublished*

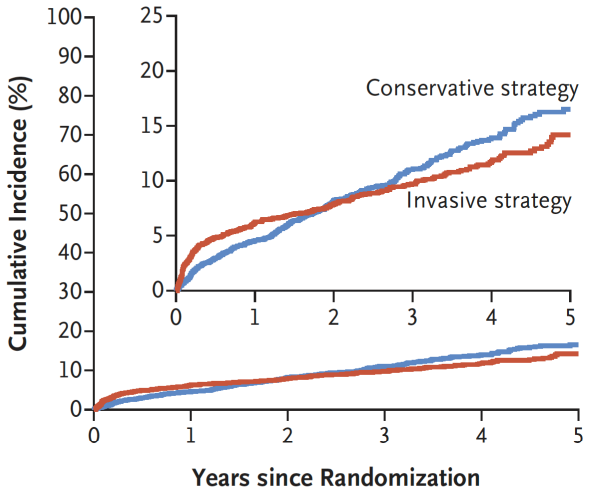
ISCHEMIA Trial

A **Primary Composite Outcome**



No. at Risk						
Conservative strategy	2591	2431	1907	1300	733	293
Invasive strategy	2588	2364	1908	1291	730	271

B **Death from Cardiovascular Causes or Myocardial Infarction**



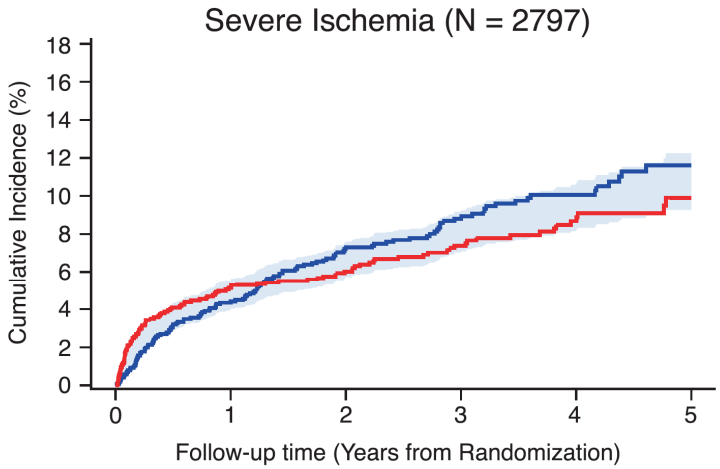
No. at Risk						
Conservative strategy	2591	2453	1933	1325	746	298
Invasive strategy	2588	2383	1933	1314	742	282

Maron *et al*. *N Engl J Med* 2020;382:1395-1407

ISCHEMIA Trial

Rates of Myocardial Infarction

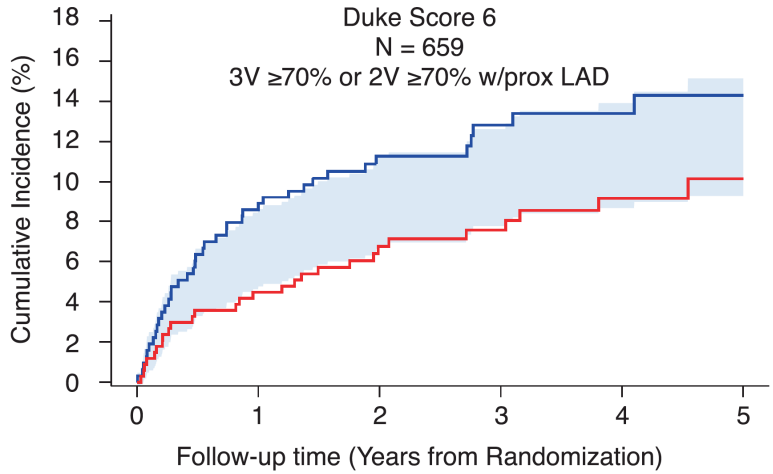
Severe Ischaemia



Subjects at Risk

CON	1415	1328	1049	728	443	170
INV	1382	1264	1025	701	420	153

Severe Coronary Artery Disease



Subjects at Risk

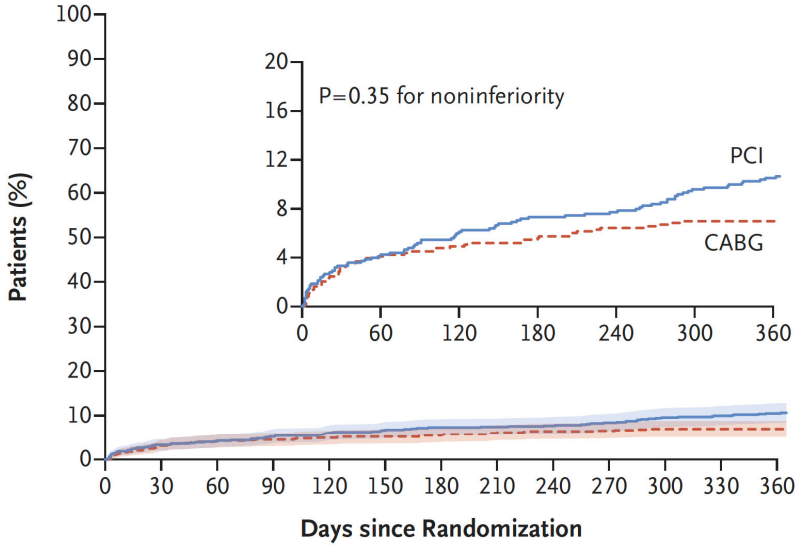
CON	316	284	222	150	98	31
INV	343	312	252	188	120	50

Reynolds *et al*. *Circulation* 2021;144:1024-1038

FAME 3 Trial

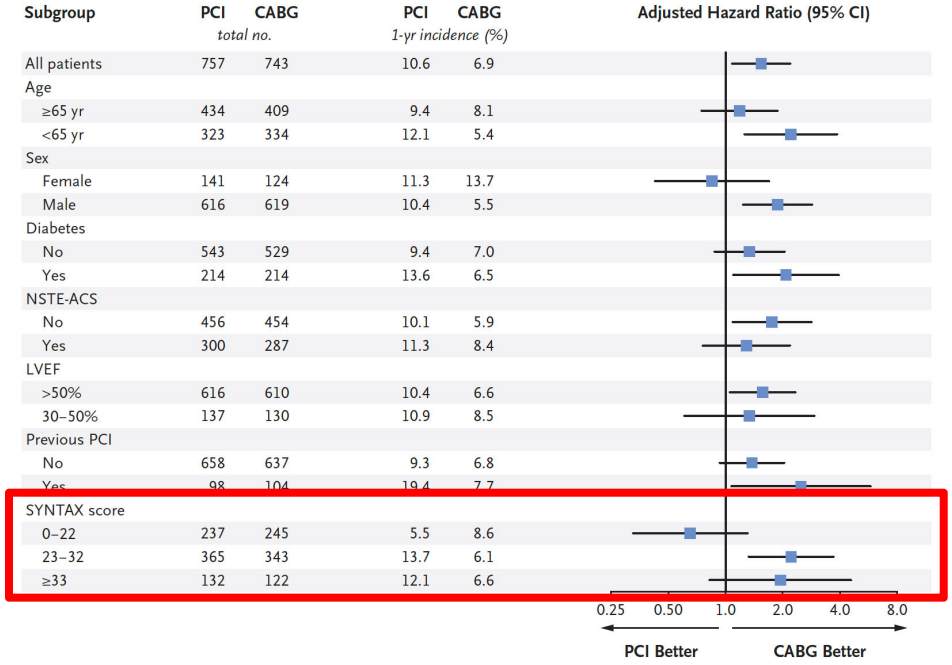
Its all about plaque bypass

Hazard Ratio 1.5 (95% CI 1.1 to 2.2)



No. at Risk

PCI	757	728	721	713	707	702	697	696	693	687	678	674	670
CABG	743	709	701	698	695	693	691	686	683	682	679	679	679

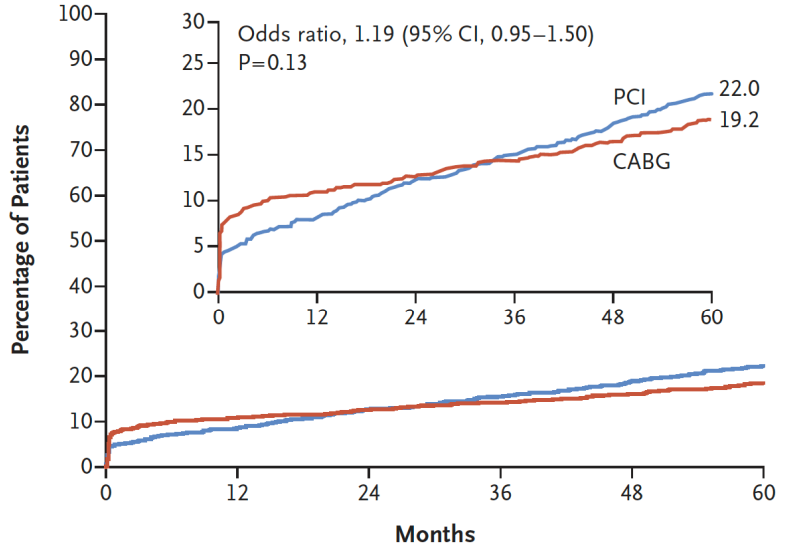


Fearon *et al. N Engl J Med* 2021; in press

EXCEL and ISCHEMIA Trials

Its all about plaque bypass

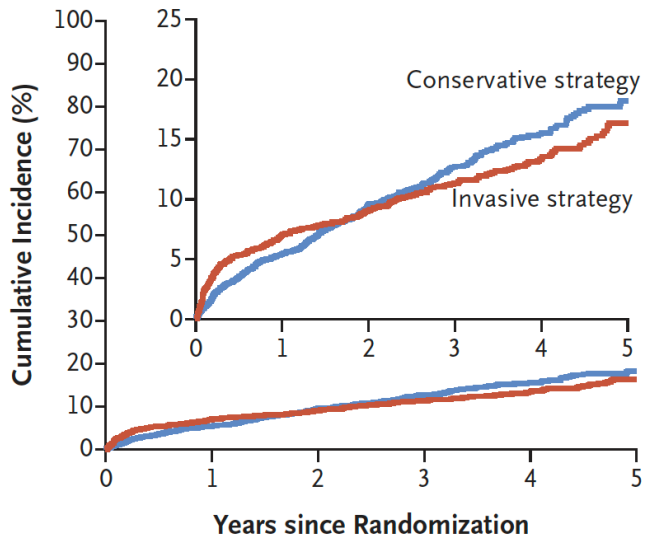
A Death, Stroke, or Myocardial Infarction



No. at Risk						
PCI	948	854	809	778	738	486
CABG	957	818	789	763	734	532

Stone *et al. N Engl J Med* 2019;381:1820-1830

A Primary Composite Outcome



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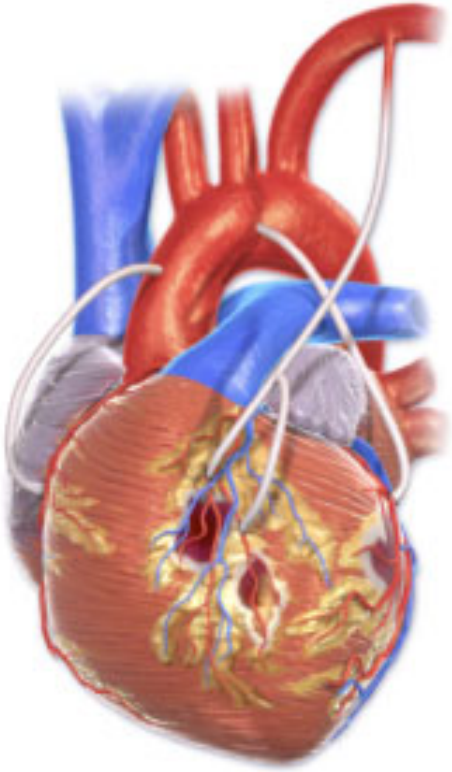
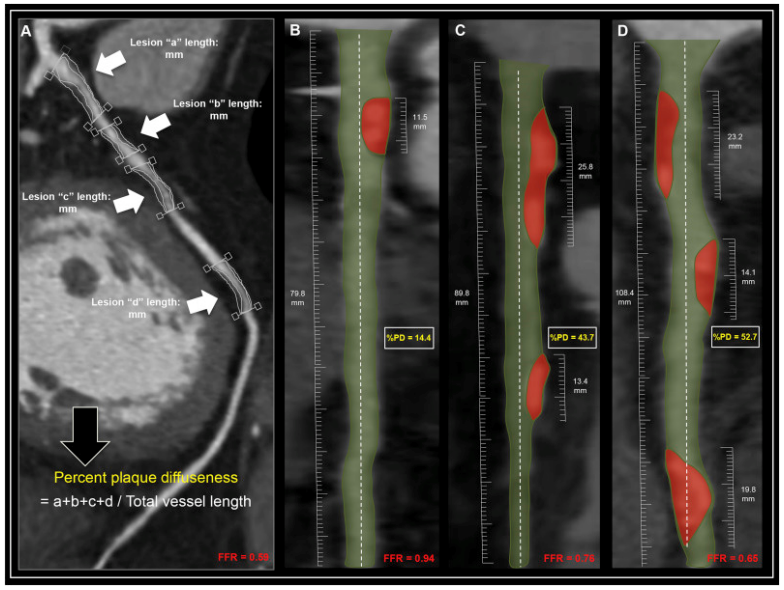
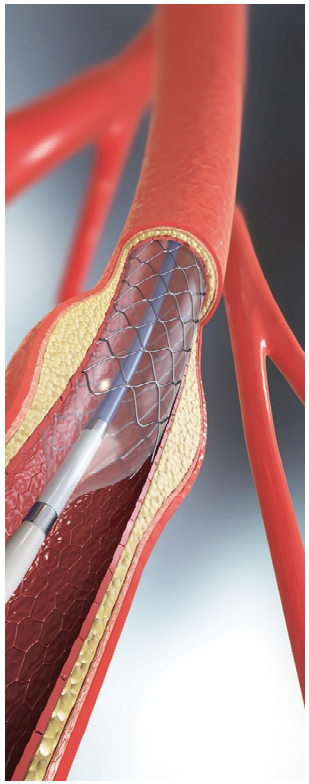
Maron *et al. N Engl J Med* 2020;382:1395-1407

‘Plaque Bypass’ Reduces Events







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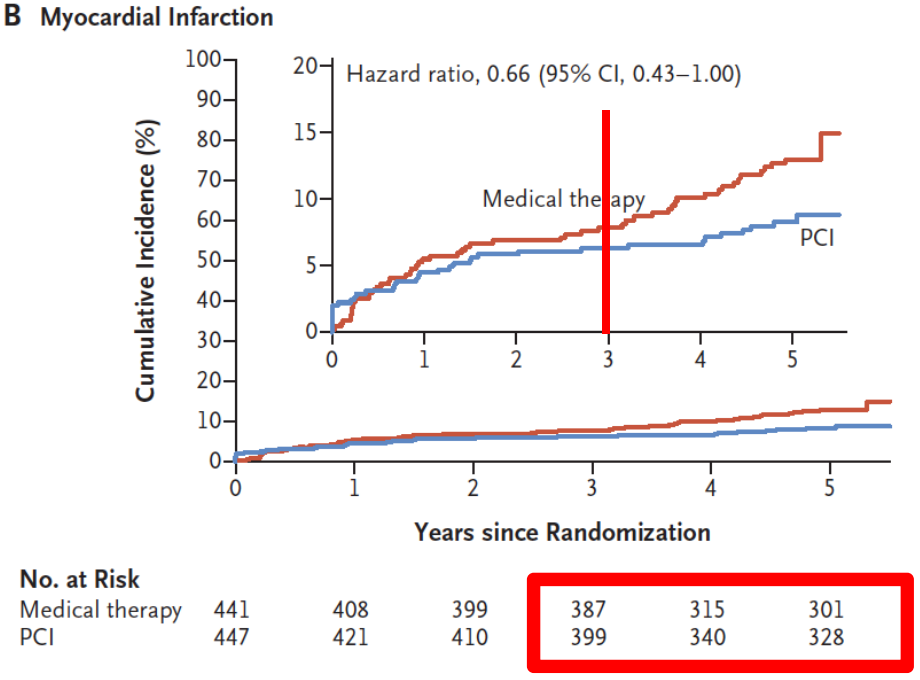
Buachaille Etive Mòr

ORIGINAL ARTICLE

Five-Year Outcomes with PCI Guided by Fractional Flow Reserve

In November 2014, the sponsor decided to close out the trial once all the included patients had completed their 3-year visit. The reason indicated by the sponsor was that results were unlikely to change substantially with longer patient follow-up

Case-ascertainment Bias?
Plausibility?



Xaplanteris *et al*. *N Engl J Med* 2018;379:250-259