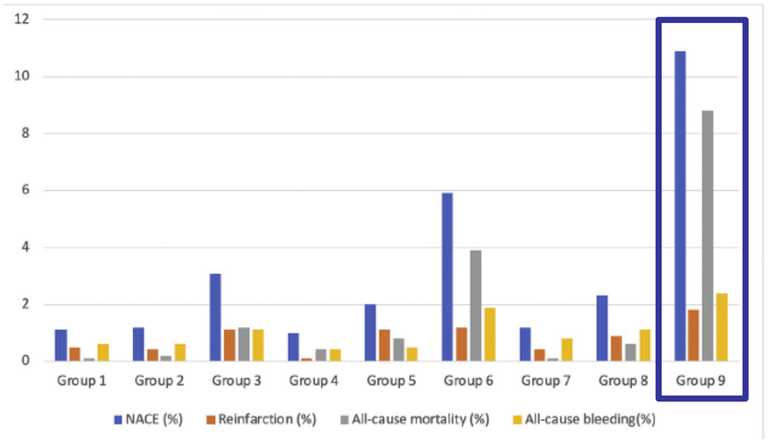
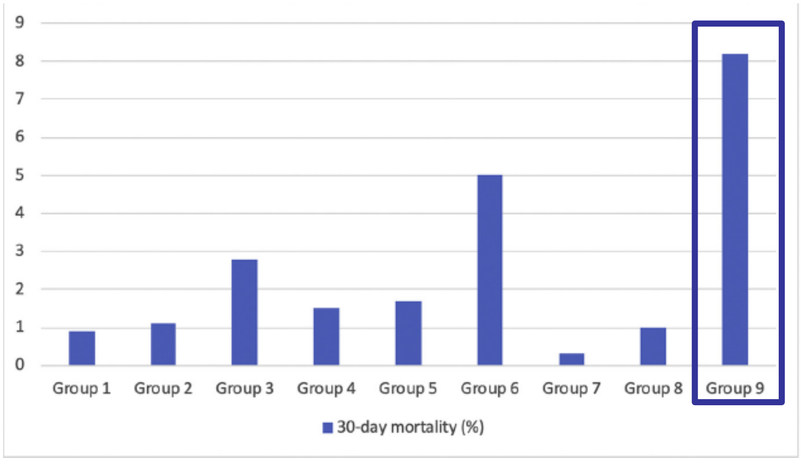
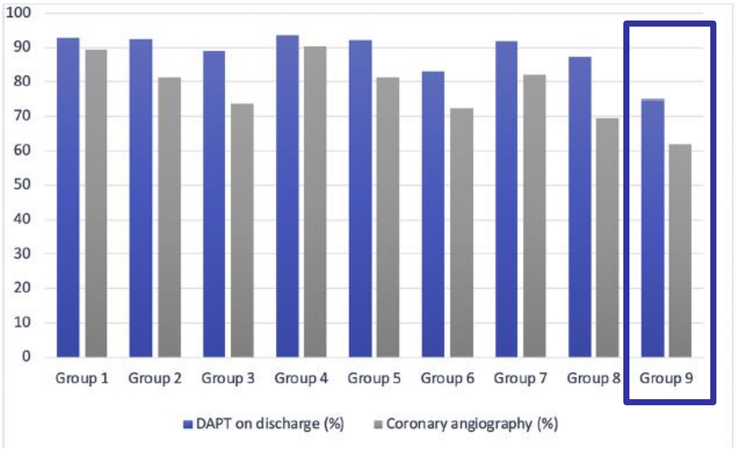
Functional versus Culprit-only Revascularization in Elderly Patients with Myocardial Infarction and Multivessel Disease: the FIRE Trial

Dual High-Risk Patients

- 32% of ACS patients are at Dual High-Risk
- Age is the main determinant of Dual High-Risk







Mohamed O, IJC 2019

Older adults with MI are at high risk of adverse outcome

- **Age and multivessel disease are the major determinants of ischemic events with consequent adverse prognosis**

CRUSADE 1-year outcome of NSTEMI elderly patients[1]

Age	Pts no	Death	MI
65-79	21586	13%	9%
80-84	7324	24%	12%
85-89	5007	34%	14%
>90	2794	46%	14%

Multivessel ACS elderly patients from the FRASER program[2]

Endpoint	Rate
Death	9%
Death/Rehospitalization	35%
PRECISE-DAPT	35±15
BARC 2-5	18%

Correlates of CV death, MI, ST in the LEADERS FREE trial[3]

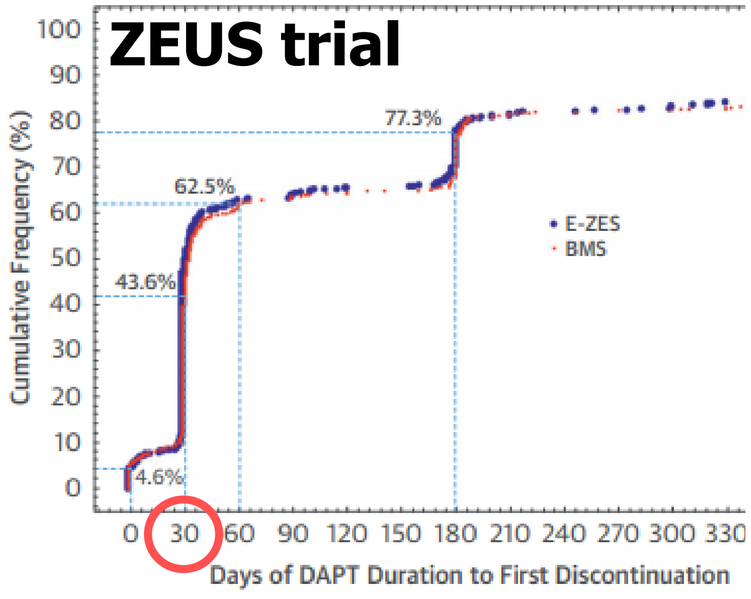
	HR (95%CI)	P value
Age >75	1.56 (1.23-1.97)	<0.001
Multivessel disease at baseline	1.66 (1.27-2.18)	<0.001
No. of implanted stent	1.13 (1.04-1.23)	0.005

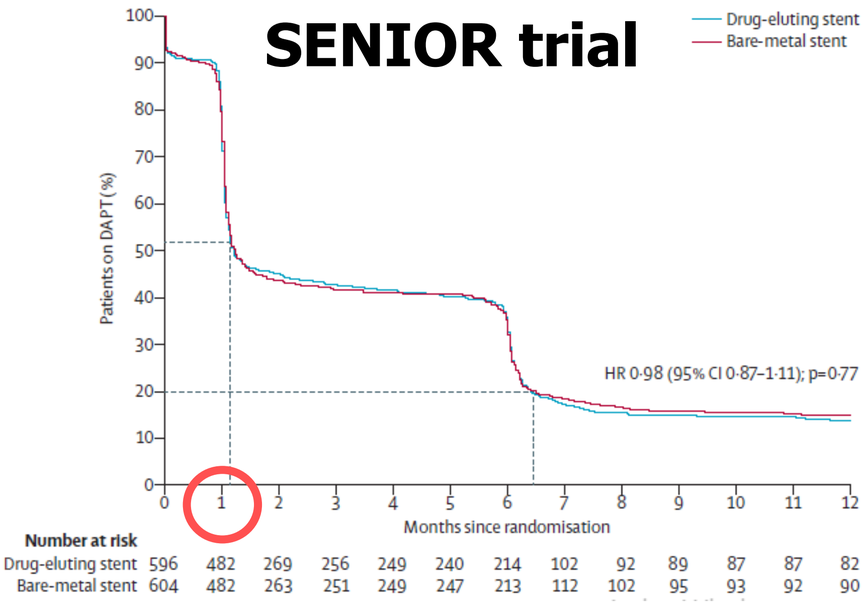
1. Madhavan MV, J Am Coll Cardiol. 2018;71:2015-2040. 2. Campo G, J Gerontol A Biol Sci Med Sci. 2019; In press. 3. Garot, P. et al. J Am Coll Cardiol. 2017;69:162–71.

FIRE TRIAL

What is the standard of care?

- Short DAPT





Valgimigli M, J Am Coll Cardiol. 2015;65:805-815.

Varenne O, Lancet. 2018;391:41-50

What is the standard of care?

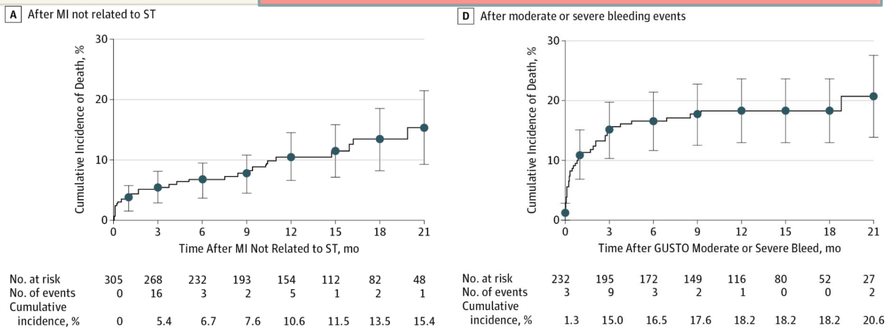
- Short DAPT

Table 1. Baseline Characteristics at Index Coronary Stenting by Ischemic and Bleeding Event Status[a]

Variable	No./Total No. (%)					
	By Ischemic Event Status			By Bleeding Event Status		
	Ischemic Event (n = 478)	No Ischemic Event (n = 11 170)	*P* Value	Bleeding Event (n = 232)	No Bleeding Event (n = 11 416)	*P* Value
Age, mean (SD), y	62.2 (10.4)	61.3 (10.3)	.05	66.6 (10.3)	61.2 (10.3)	<.01

Table 3. Risk of Mortality After Ischemic and Bleeding Events During the 21-Month Postrandomization Period

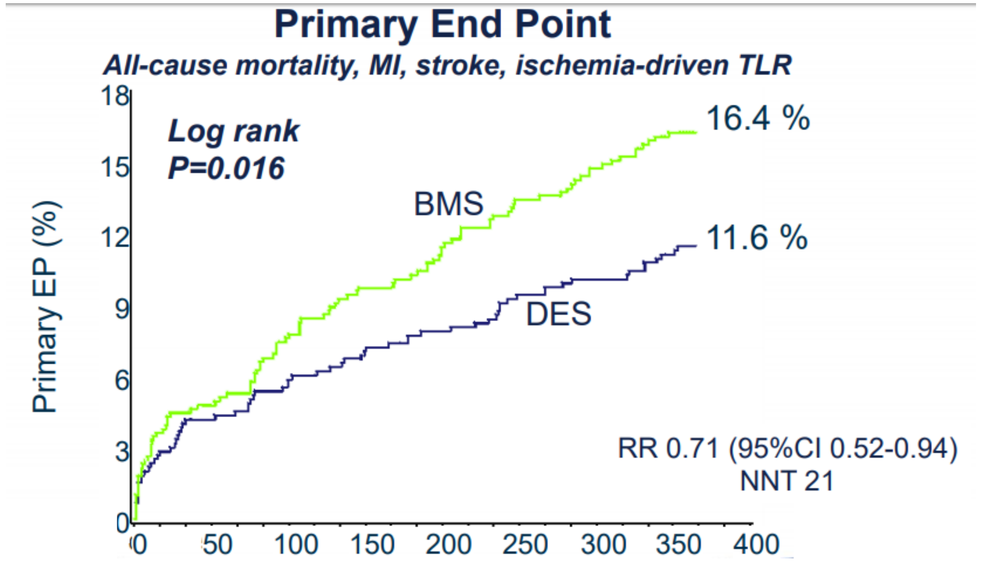
Variable	Adjusted HR (95% CI) for Mortality[a]
Bleeding events	
GUSTO moderate bleed	8.0 (4.7-13.7)
GUSTO severe bleed	36.3 (23.3-56.6)
GUSTO moderate or severe bleed	18.1 (12.6-26.0)
BARC 2, 3, or 5 bleed	9.3 (6.6-13.1)
BARC 2 or 3 bleed	5.7 (3.8-8.4)
BARC 3 or 5 bleed	16.2 (11.2-23.5)
BARC 2 bleed	3.4 (1.9-6.1)
BARC 3 bleed	8.6 (5.5-13.4)

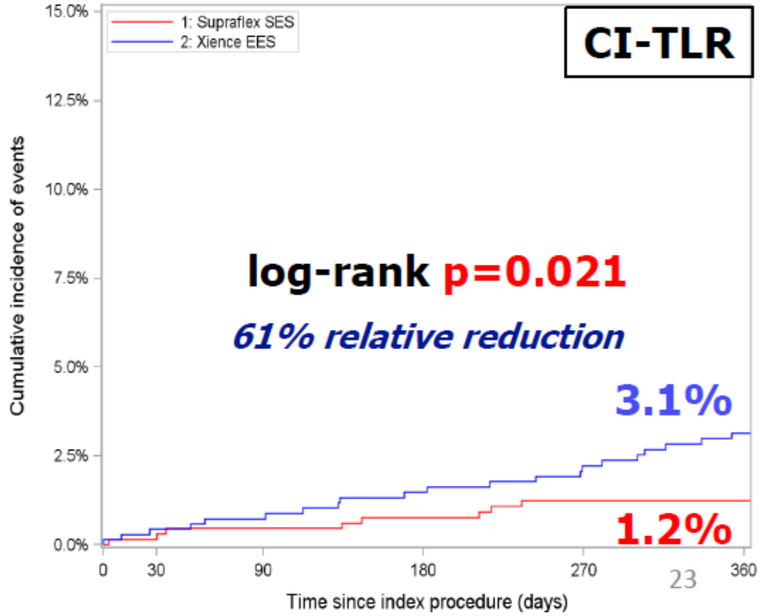


Secemsky EA, JAMA Cardiol. 2017;2:478-487.

What is the standard of care?

- Degrabable Polymer DES





Supraflex Cruz
Sirolimus Eluting Cobalt Chromium Coronary Stent System

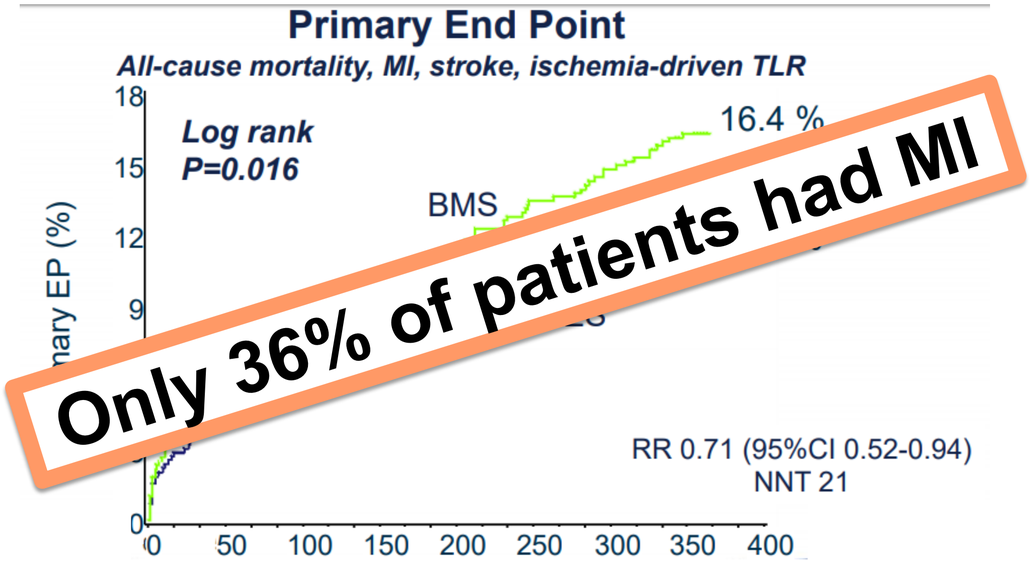
Varenne, TCT 2017

Serruys, TCT 2018

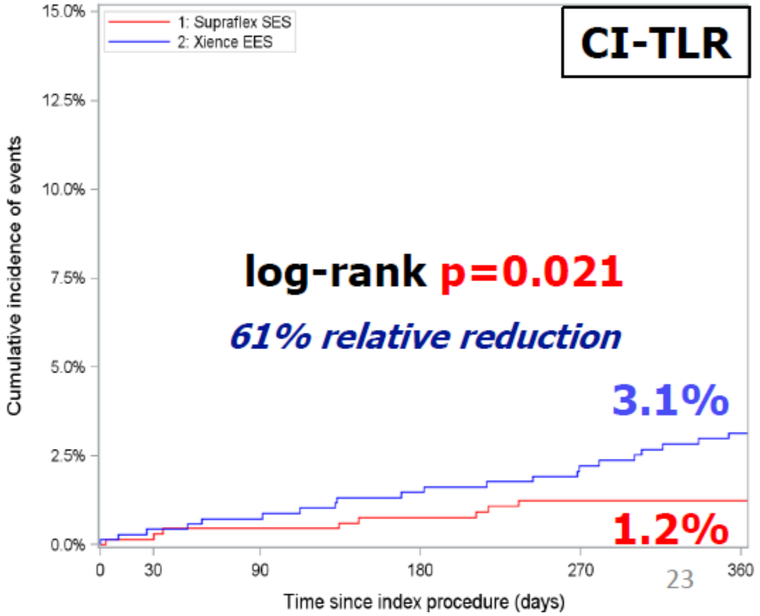
FIRE TRIAL

What is the standard of care?

- Degrabable Polymer DES



Only 36% of patients had MI



Supraflex Cruz

Sirolimus Eluting Cobalt Chromium Coronary Stent System

FIRE TRIAL

Varenne, TCT 2017

Serruys, TCT 2018

What is the standard of care?

- Culprit only strategy

However, HBR patients continue to suffer a high incidence of adverse events beyond the first year, most likely due to advanced age, major comorbidities, and possibly because of only partial revascularization in some patients (multivessel disease was reported in 62% of patients, but multivessel index revascularization was done in only 22%) (1).

Garot, P. et al. J Am Coll Cardiol. 2017;69(2):162–71

FIRE TRIAL

What is the standard of care?

- Culprit only strategy
  - No randomized trials
  - 76% of patients not receiving CAA ≥75 years[1]
  - 75% receive culprit only revascularization[1,2]
  - Two main determinants of mortality:[1]
    - CAA avoidance
    - Multivessel disease

1. Feldman L, Eur Heart J Acute Cardiovasc Care. 2017;6:262-271; 2. Wang TY, Am Heart J. 2016;172:9-18.

FIRE TRIAL

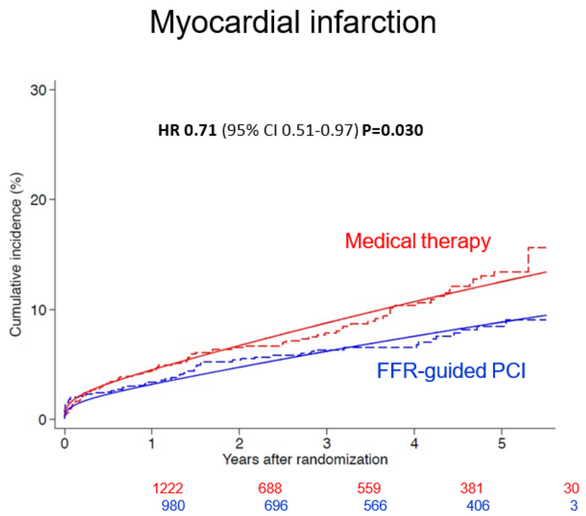
What is missing?

- Is complete revascularization able to improve prognosis in this subset of patients?

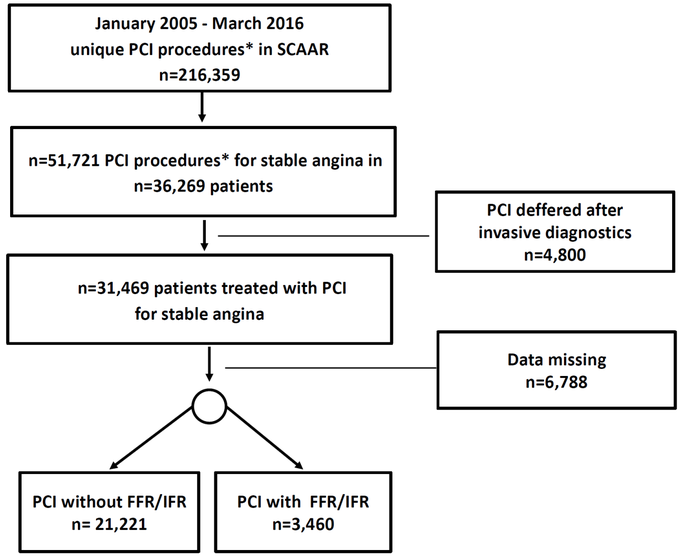
What is missing?

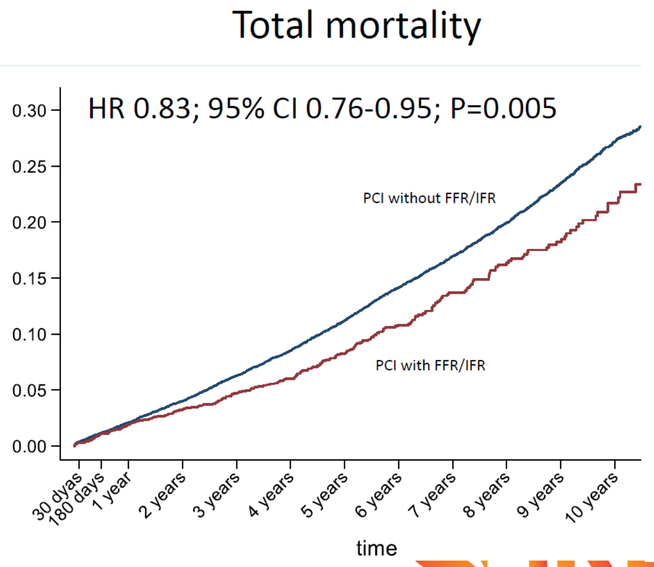
- What is complete revascularization in 2019?

FAME-II, DANAMI-3
PRIMULTI, Compare-Acute



SCAAR 10 years





Age, MI and functional assessment

- Age of MI patients is constantly increasing[1]
- Trials on strategy in MI patients as well as those on functional assessment included younger patients (mean age 60-65 years)
- Functional assessment has not been validated in NSTEACS

Age in contemporary trials on revascularization strategy in STEMI and/or functional assessment

Trial	Groups	Mean Age
PRAMI	angio-complete vs culprit only	62
CvLPRIT	angio-complete vs culprit only	65
DANAMI-3 PRIMULTI	FFR complete vs culprit only	63
COMPARE-ACUTE	FFR complete vs culprit only	61
DEFINE-FLAIR	iFR vs FFR	65
IFR-SWEDEHEART	iFR vs FFR	67

1. Yeh RW, N Engl J Med. 2010 Jun 10;362(23):2155-65.

FIRE TRIAL

FIRE trial rationale:

A complete revascularization Functionally-driven with degradable polymer DES (Supraflex Cruz) in older adults (≥75 yo) with MI (STE or NSTE) and multivessel disease may improve prognosis compared to the actual standard of care in these patients, namely culprit only revascularization.

FIRE TRIAL

FIRE trial population:

Inclusion criteria

- ☑ Patients ≥ 75 years AND
- ☑ MI (STE or NSTE-MI) with indication to invasive management AND
- ☑ MVD: at least 1 coronary artery non-culprit lesion at least 2.5 mm 50-99% amenable to PCI AND
- ☑ Successful treatment of culprit lesion with biodegradable polymer DES

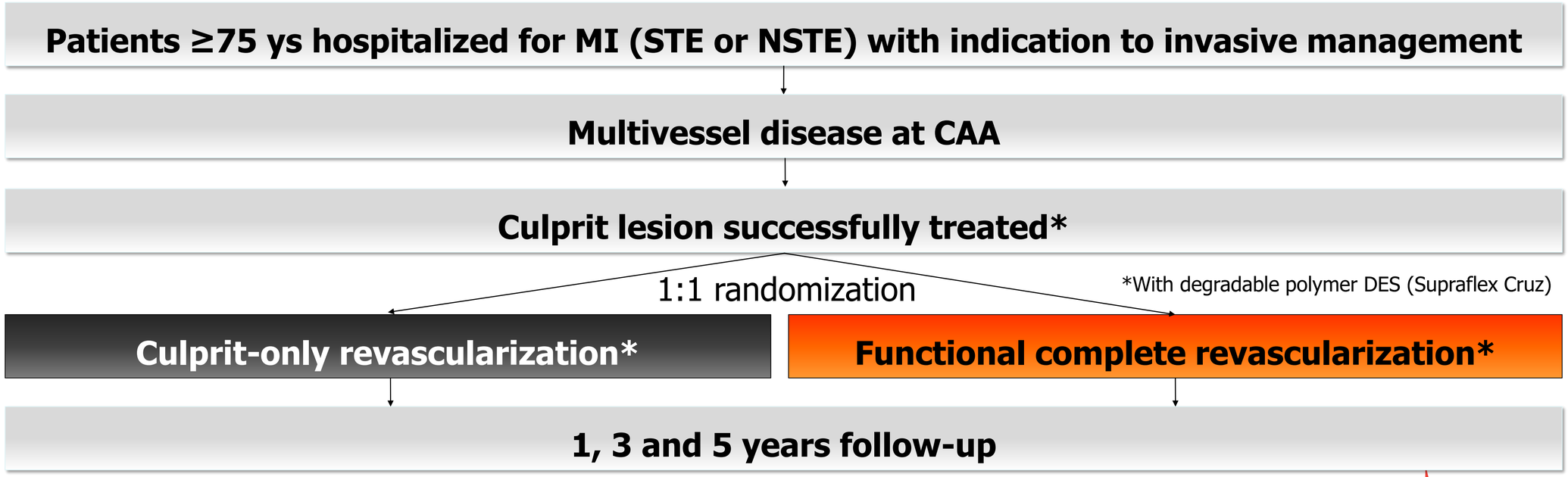
Exclusion criteria

- ☒ Planned surgical revascularization
- ☒ Inability to identify a clear culprit lesion
- ☒ Left Main lesion as non-culprit
- ☒ Non-cardiovascular co-morbidity reducing life expectancy to < 1 year
- ☒ Any factor precluding 1-year follow-up
- ☒ Prior CABG Surgery

FIRE TRIAL

Study Design and Flow Chart

All comers, prospective, randomized, multicenter, open-label trial with blinded adjudicated evaluation of outcomes (PROBE).



1400 patients

Primary endpoint: all-cause death, any MI, stroke, revascularization at 1 year

FIRE TRIAL

FIRE trial Endpoints

Primary endpoint

- POCE (all-cause death, any MI, any stroke, any revascularization) at 1 year

Secondary endpoints

- POCE at 3 and 5 years
- DOCE (CV death, MI or non-culprit TVR) at 1 and 3 years
- CV death or MI, Death or MI at 1, 3 and 5 years
- EQ-5D quality of life scale, SPBB, SAQ Frequency scale at 1 year
- Rate of ischemic adverse events in very HBR patients with 1 month DAPT
- AFI/QFR vs culprit only
- AFI/QFR vs hyperemic indices

Sample size calculation

Ischemic outcome at 1 year in patients with ACS treated with culprit-only revascularization

Study	MI	Repeat revascularization	MACE
COMPARE-ACUTE	4.7%	17.5%	20.5%
CVLPRIT	2.7%	8.2%	21.2%
PRAMI	8.6%	19.9%	22.9%
DANAMI-3-PRIMULTI	5%	9%	22%
TRANSLATE-ACS	7%	17%	22%

Primary endpoint reduction with functional guided revascularization in ACS setting

Study	Primary endpoint	HR
COMPARE ACUTE	MACCE	0.35 [0.22-0.55]
DANAMI-3-PRIMULTI	Death, MI, or IDR	0.56 [0.38-0.83]

FIRE TRIAL

Sample size calculation

We estimated a conservative 15% rate of the primary endpoint at 1 year in the culprit-only strategy group. Considering that functional assessment should reduce the primary endpoint of at least 30%, 1368 patients are required to have a 80% chance of detecting, as significant at the 5% level, a 30% difference in the primary outcome between the two groups considering a 15% rate of the primary endpoint in the control group. Considering a 2% attrition rate final sample size is inflated to 1400 patients

FIRE TRIAL

Study Organization

PI: **Simone Biscaglia**
University of Ferrara

Executive Committee:
Matteo Tebaldi
University of Ferrara

CFR
CONSORZIO FUTURO IN RICERCA

Sponsor: **Consorzio Futuro in Ricerca**

Study Chair: **Gianluca Campo**
University of Ferrara

Executive Committee:
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Hospital La Paz Madrid

With Unconditioned Support from:

SMT

Medis
Medical Imaging Systems

EUKON
medical

Spain National Coordinator:
Javier Escaned
Hospital Clinico San Carlos Madrid

Executive Committee:
Emanuele Barbato
Federico II University, Naples

FIRE TRIAL

FIRE trial program

- We will generate data on several topics
- Investigators will have the opportunity to propose and conduct substudies

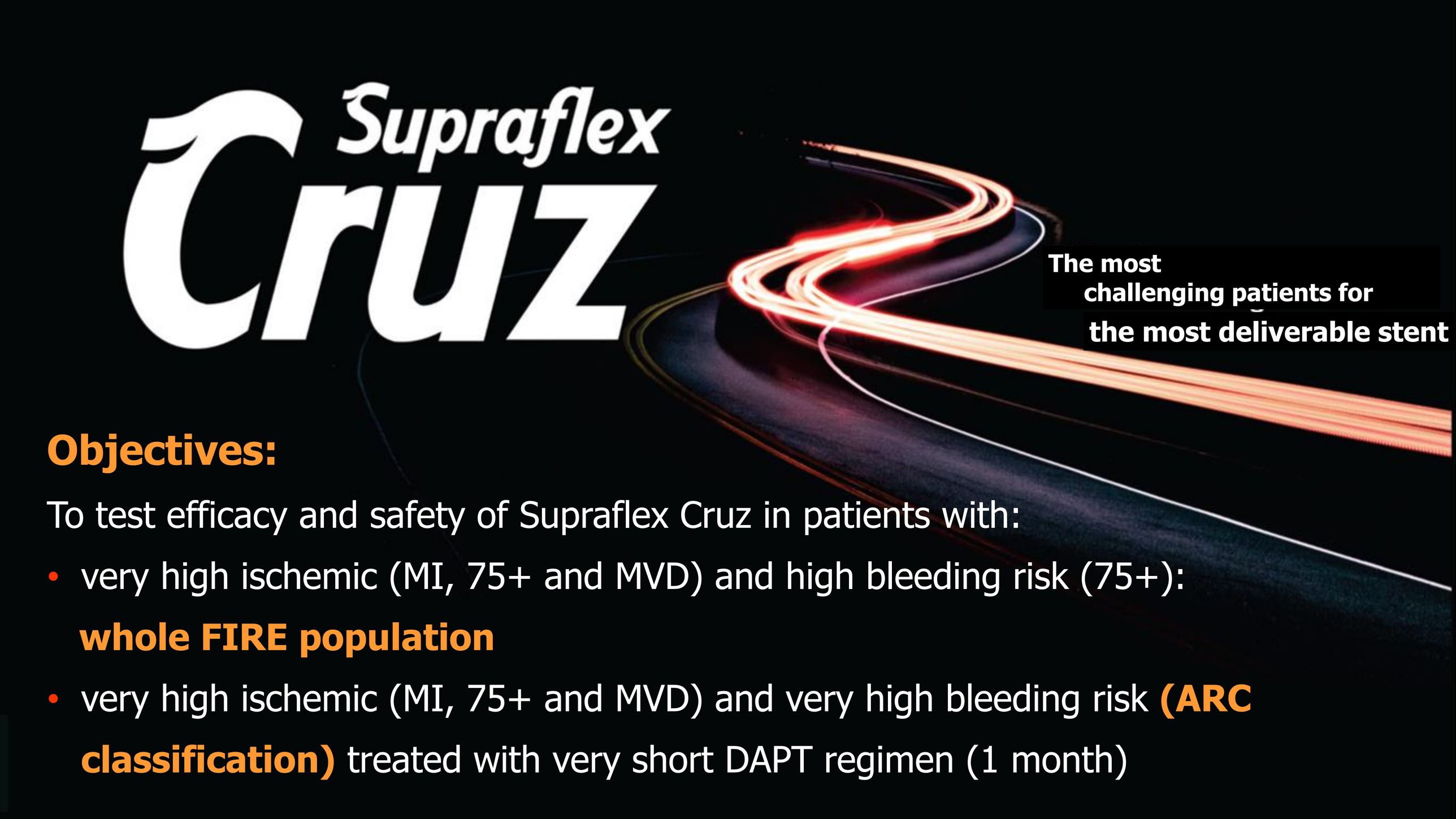
FIRE trial program

SUPER-FIRE

prespecified analysis regarding efficacy and safety of Supraflex stent in patients with Myocardial Infarction and High Bleeding Risk

FIRE TRIAL

Supraflex Cruz



The most challenging patients for the most deliverable stent

Objectives:

To test efficacy and safety of Supraflex Cruz in patients with:

- very high ischemic (MI, 75+ and MVD) and high bleeding risk (75+): **whole FIRE population**
- very high ischemic (MI, 75+ and MVD) and very high bleeding risk **(ARC classification)** treated with very short DAPT regimen (1 month)

FIRE trial program

QFiRe

prespecified analysis regarding efficacy and safety of Quantitative Flow Ratio (QFR) assessment of non-culprit lesion/s in patients with Myocardial Infarction

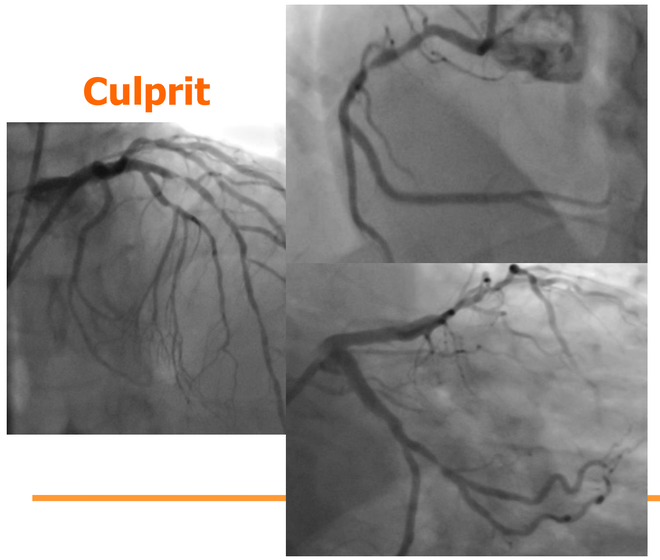
QFiRe - Objectives

- To test efficacy and safety of QFR in patients the **whole FIRE population**
- To test efficacy and safety of QFR in **NSTEMI patients**
- To test efficacy and safety of QFR in **STEMI patients**

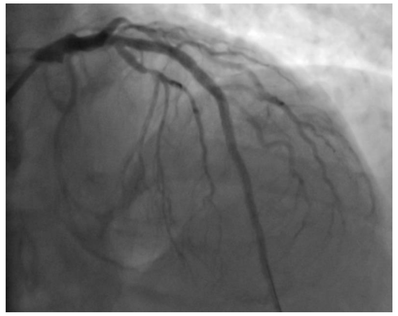
Step 1 Angio

Non-culprit

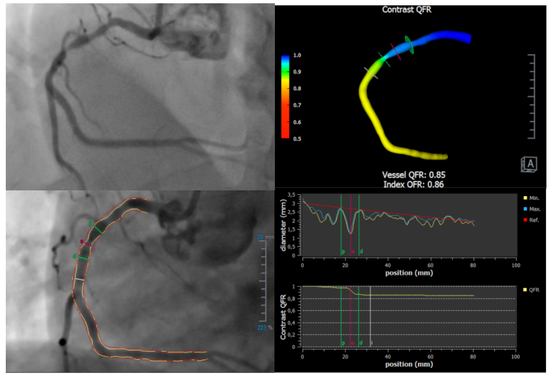
Culprit

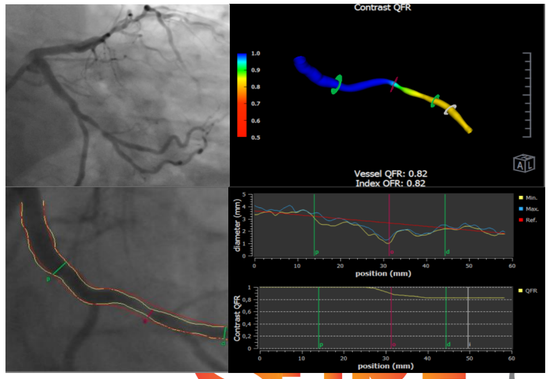


Step 2 Culprit PCI



Step 3 Non-Culprit QFR





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