Functional versus Culprit-only Revascularization in Elderly Patients with Myocardial Infarction and Multivessel Disease

The FIRE trial

on behalf of the FIRE trial Investigators

Background

- **The COMPLETE trial showed the benefit of complete revascularization in younger STEMI patients**
- **Older patients (75+) were poorly represented in RCTs investigating the benefit of complete revascularization**
- **The risk of periprocedural complications is higher and prognostically impactful in older patients**

Why FIRE was necessary ?!?

- STEMI
- Around 62 years old
- First event
- Low anatomic complexity
- NCL not on LAD

Patient at low risk, where a complete revascularization, which is safely performed, reduces long-term recurrence of MI and CV death

	COMPLETE N=4041	Compare-Acute N=885	CvLPRIT N=296	DANAMI-3-PRIMULTI N=627	Politi et al. N=214	PRAMI N=465
Pts.	2025/2016	590/295	146/150	313/314	84/130	234/231
Age, years	62±11	61±10	65±12	63±10	64±11	62±10
NCL (location) %						
LM	0.4	0	0	0	NA	NA
Proximal LAD	10.1	12.2	15.4	25.0	NA	26.2
Syntax score (baseline)	16.1	NA	NA	NA	NA	NA
Syntax score NCL	3.8	NA	NA	NA	NA	NA
1 year Mortality	1.7	1.5	2.8	4.5	11.2	13.6

Why FIRE was necessary ?!?

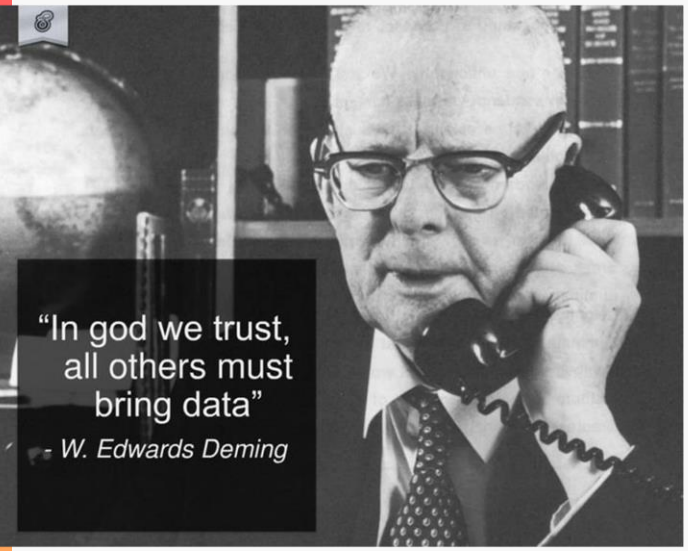

Table 1. Comparison of the COMPLETE Trial with Previous Trials of Complete Revascularization.*

Variable	PRAMI	CvLPRIT	DANAMI-3–PRIMULTI	Compare-Acute	COMPLETE
No. of patients	465	296	627	885	4041
Mean age — yr	62	65	63	61	62
Male sex — %	78	81	81	77	80
Myocardial infarction	20/231	4/146	16/313	28/590	160/2025
Revascularization	46/231	16/146	52/313	103/590	160/2025
Events with complete revascularization vs. treatment of culprit lesion only — hazard ratio (95% CI)					
Cardiovascular death or myocardial infarction	0.36 (0.18–0.73)	NA	0.80 (0.45–1.45)	NA	0.74 (0.60–0.91)
Death	NA	0.38 (0.12–1.20)	1.40 (0.63–3.00)	0.80 (0.25–2.56)	0.91 (0.69–1.20)

Should the results of the COMPLETE trial, in combination with the results of previous randomized trials, change the guidelines to support complete revascularization in all patients with STEMI and multivessel disease? Patients participating in trials are different from sicker patients seen in the clinical setting, and extrapolation of the results to patients with a greater risk of complications may not be safe.

Research Question

To investigate whether, in older patients (75+ years) with MI and multivessel disease, complete revascularization based on coronary physiology is superior to a culprit-only revascularization strategy

Organization

3 countries: Italy, Spain, Poland

34 centers

Study PI: Simone Biscaglia

Study Chair: Gianluca Campo

Executive Committee: Javier Escaned, Dariusz Dudek, Raul Moreno, Matteo Tebaldi, Emanuele Barbato

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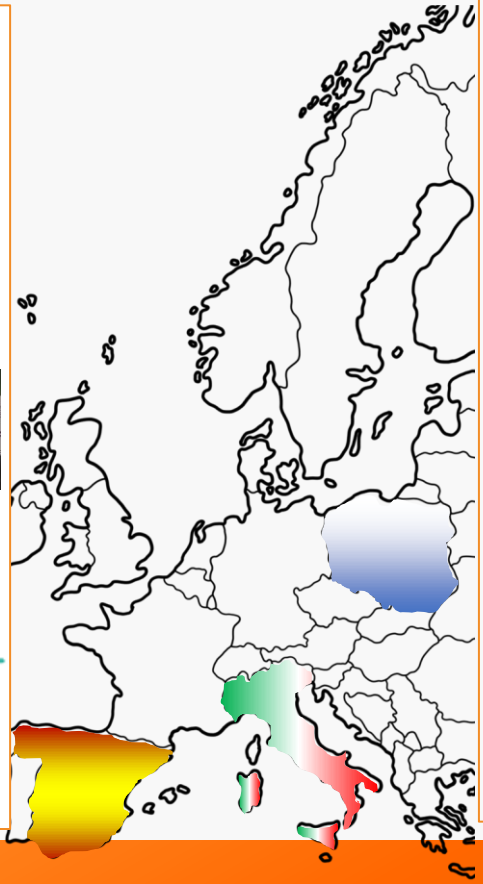


Investigator-driven trial

CFR Consorzio Futuro in Ricerca

Università degli Studi di Ferrara

Contributors

SMT

Medis Medical Imaging Systems

EUKON Future Healthcare Now

SIEMENS Healthineers

GE Healthcare

Insight Lifetech

AMGEN

Design

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

Pts ≥75 ys hospitalized for MI (STE or NSTE) with indication to invasive management

Multivessel disease at coronary artery angiography

Culprit lesion clearly identifiable and successfully treated

R

Physiology-guided Complete Revascularization

Culprit-only Revascularization

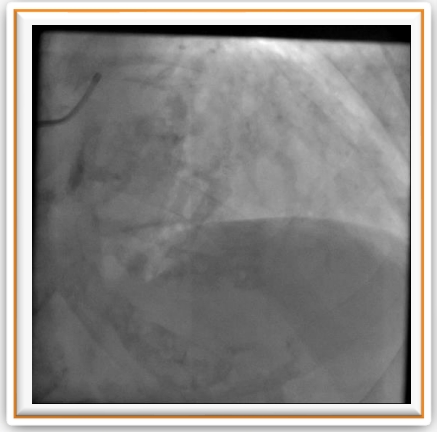
1-, 3-, and 5-year follow-up

Sample Size

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

Physiology & Stents

- **Non-culprit lesions were assessed with either wire-based FFR, resting index or angiography-derived FFR**
- **Flow-limiting lesions (FFR≤0.80, resting ≤0.89) had to be revascularized with biodegradable-polymer sirolimus ultra-thin stent(s)**



OR

Key role of Physiology

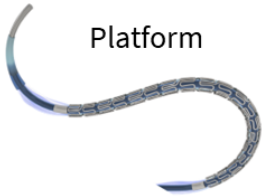
- **Gatekeeper for indicated procedures**
- **Less stents**
- **Less complications**
- **Maximal benefit in flow-limiting lesions**

Key role of Supraflez Cruz

- **Deliverability**
- **Safety with short DAPT regimen**
- **Few stent thrombosis**
- **Few instent restenosis**

Characteristics

Platform

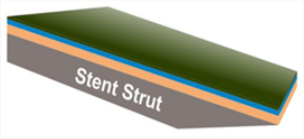


Stent Material: Co –Cr L605 with LDZ Connectors (Long Dual Z-Link) and unique design to improve deliverability

Strut Thickness: 60 µm across all stent diameters (2.00 to 4.50 mm)
Radial Strength: 1093 mmHg
Foreshortening: 0 % foreshortening (4mm Supraflex Cruz overexpanded to 5.5mm)[1]
Long Dual 'Z' Link" : Long connectors enhance the overall radial strength, Improves flexibility , Resists longitudinal compression

LDZ link to zip through complex lesion

Drug Carrier(Polymers)

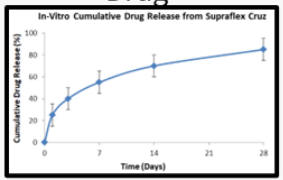


Biodegradable Polymer Matrix: Poly-L Lactide (PLLA), Poly L-Lactide-co-Caprolactone (PLCL), Polyvinylpyrrolidone (PVP). A top protective layer (Without Drug). Middle layer (Drug + Polymers) Base layer (Drug + Polymers) .

Coating: **Circumferential, Average thickness: 4 to 6 µm**

Alternate **LDZ link** orientation to handle any curve or tortuosity

Drug



Sirolimus: 1.4 µg/mm²
Release Profile :

- About 80% of the drug is released at 4 weeks in biological media while 100% drug is released at a slow rate within 3 months.
- The initial moderate level of Sirolimus drug release from middle layer coating helps to inhibit early phase of neointimal hyperplasia.
- Controlled drug release kinetics from base layer coating is beneficial to maintain the effective amount of drug level in the arterial tissues which are required to prevent smooth muscle cell proliferation.

In phase design to provide agility

Endpoints

Primary

Death, any MI, any stroke, or ID-revascularization

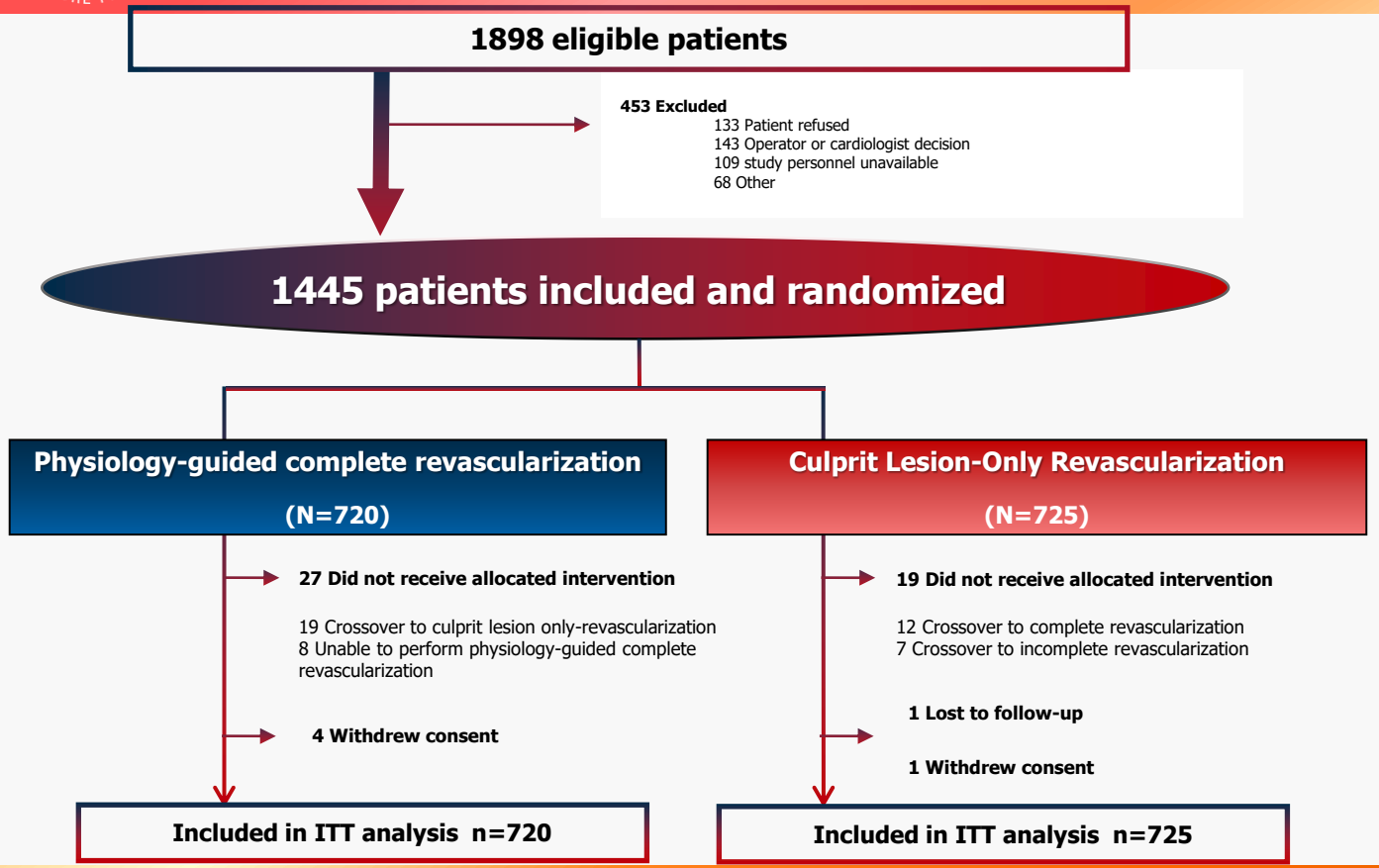
Key secondary

Cardiovascular death or MI

Safety

CA-AKI, stroke, or BARC type 3-5 bleeding

Flow-Chart



- **76%** of eligible patients enrolled
- **2.6%** crossover from culprit-only
- Follow-up complete in **99.9%** of patients

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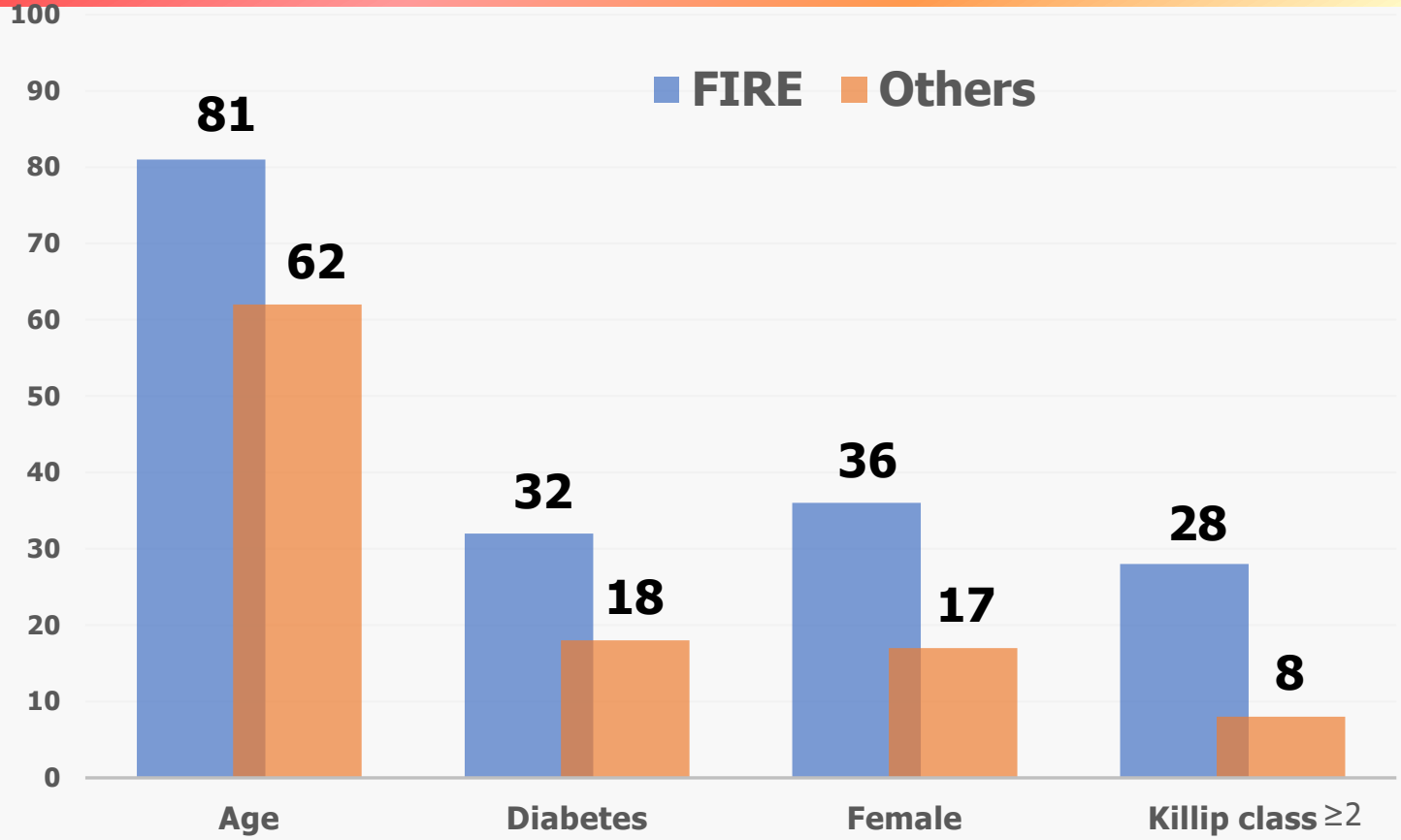
Baseline Characteristics

Characteristic	Culprit-Only (N=725)	Physiology-Guided Complete (N=720)
Age (IQR) – yr	80 (77-84)	81 (77-84)
Female sex	265 (36.6)	263 (36.5)
Comorbidities		
Hypertension	592 (81.7)	593 (82.4)
Diabetes	233 (32.1)	230 (31.9)
Prior MI	116 (16)	104 (14.4)
eGFR <60 ml/min	332 (45.8)	330 (45.8)
PAD	127 (17.5)	122 (16.9)
Clinical presentation		
STEMI	256 (35.3)	253 (35.1)
NSTEMI	469 (64.7)	467 (64.9)

Characteristic	Culprit-Only (N=725)	Physiology-Guided Complete (N=720)
Killip class ≥2	208 (28.7)	204 (28.3)
Hospital LOS	5 (3-7)	6 (4-8)
Medication at discharge		
Aspirin	683 (94.2)	692 (96.1)
Clopidogrel	358 (49.4)	371 (51.5)
Ticagrelor	337 (46.5)	326 (45.3)
Prasugrel	16 (2.2)	16 (2.2)
Vitamin K antagonist	36 (5)	27 (3.8)
NOAC	129 (17.8)	137 (19)
ACEi or ARB	552 (76.1)	556 (77.2)
Statin	661 (91.2)	680 (94.4)

Baseline Characteristics



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Procedural Characteristics

Characteristic	Culprit-Only (n=725)	Physiology-Guided Complete (N=720)
Procedures		
Total number	725	961
Days from index to staged procedures	-	3 (2-4)
Radial access	672 (92.7)	911 (94.8)
Number of non-culprit vessels per patient		
One	510 (70.3)	503 (69.9)
Two or more	215 (29.7)	217 (30.1)
Location of non-culprit vessels		
LAD	291 (30.6)	296 (31.2)
LCX	319 (33.5)	308 (32.5)
RCA	320 (33.6)	310 (32.7)
RI	21 (2.2)	34 (3.6)

Characteristic	Culprit-Only (n=725)	Physiology-Guided Complete (N=720)
RVD	3.0 (2.5-3.0)	3.0 (2.5-3.0)
Diameter stenosis	70 (60-80)	70 (60-80)
Percent diameter stenosis		
50-69%	401 (42.2)	390 (41.1)
70-89%	378 (39.7)	380 (40.1)
90-99%	172 (18.1)	178 (18.8)
Type of physiological assessment		
Wire-based hyperemic	-	451 (49.6)
Wire-based non hyperemic	-	138 (15.2)
Angiography-based index	-	320 (35.2)
Functionally significant NCL	-	425 (44.8)

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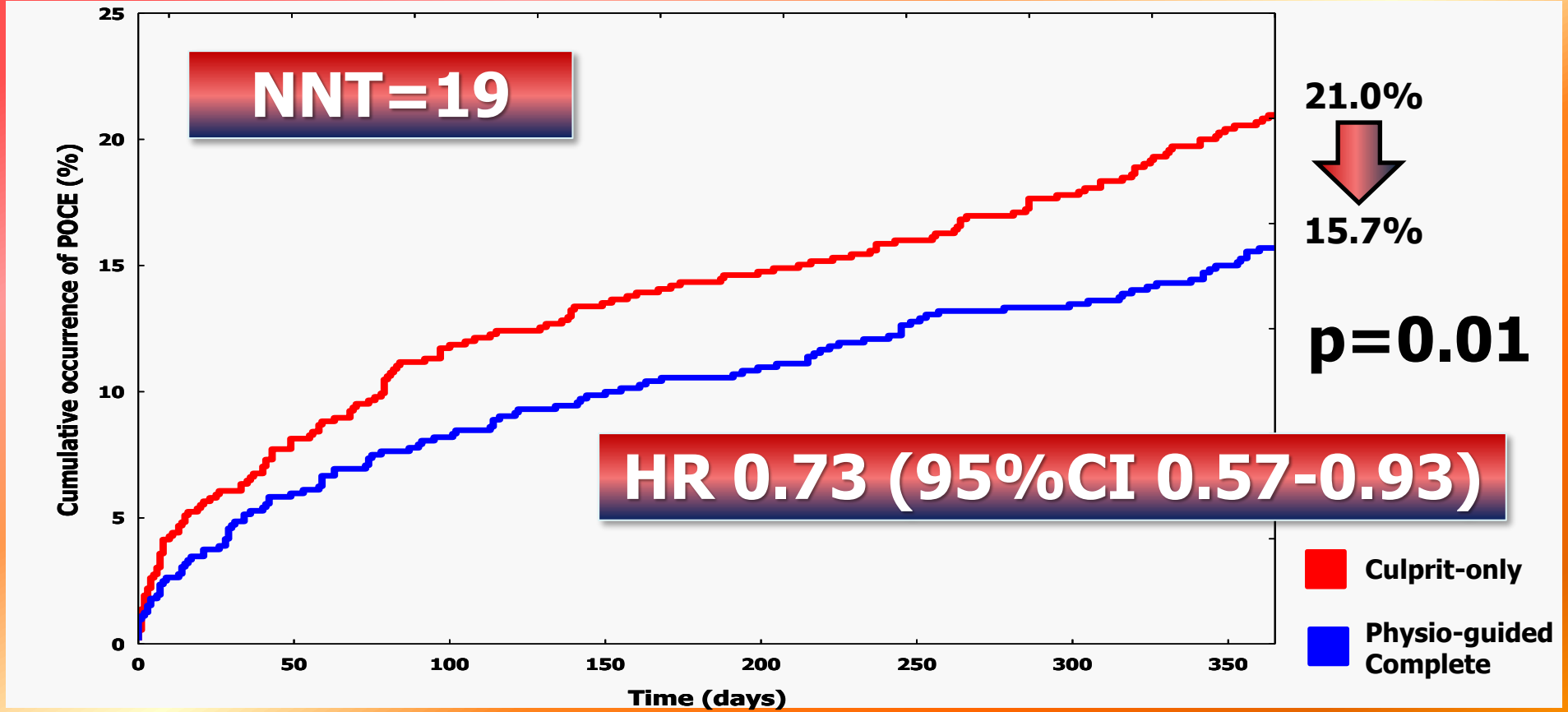
Primary Endpoint



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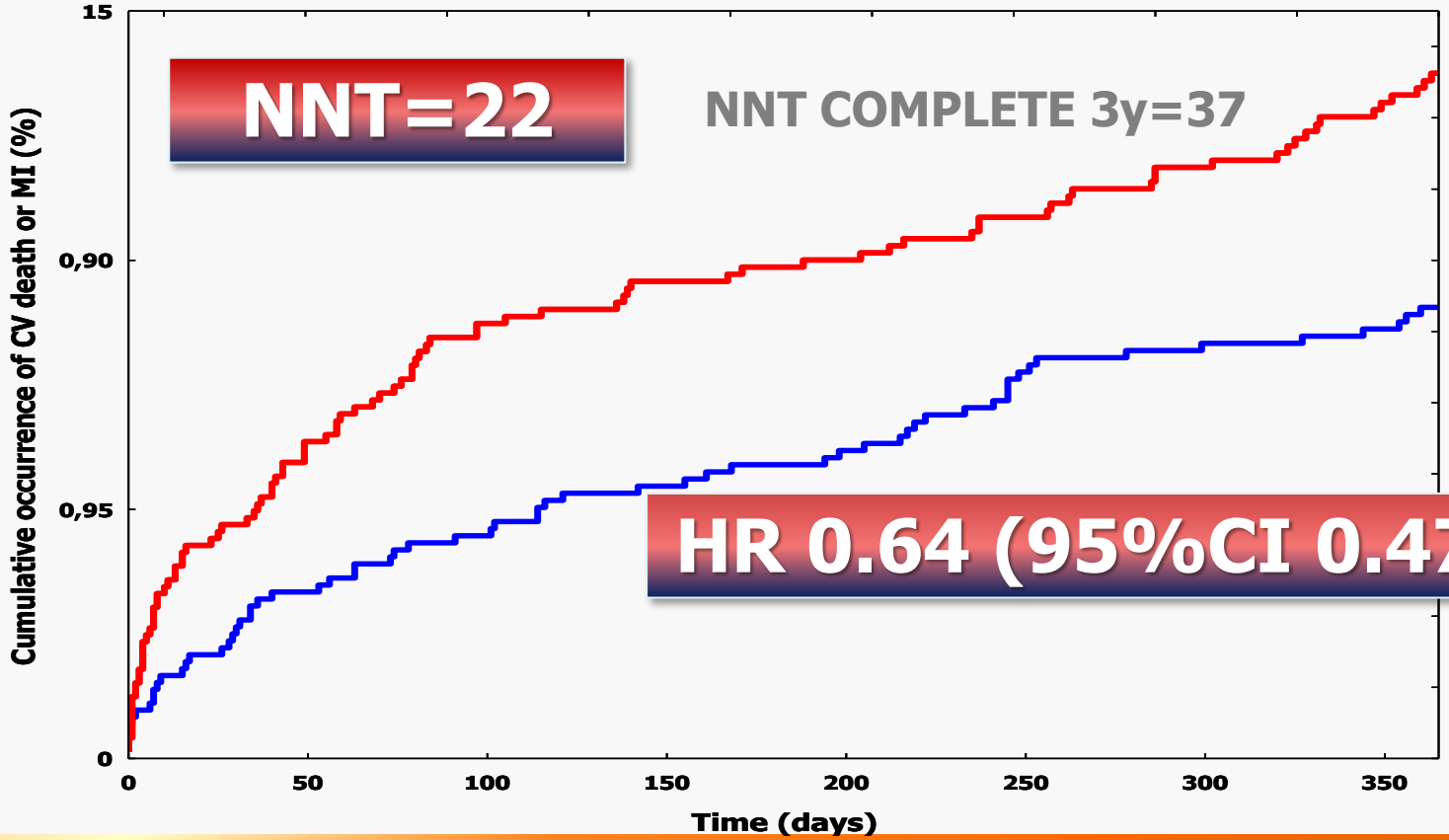
Key Secondary Endpoint



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Safety and Secondary Endpoint

Outcome	Culprit-Only (n=725) no. (%)	Complete (n=720) no. (%)	Hazard Risk (95% CI)	P
Death	93 (12.8)	66 (9.2)	**0.70 (0.51-0.96)**	**0.027**
Cardiovascular death	56 (7.7)	36 (5)	**0.64 (0.42-0.97)**	**0.034**
Non-cardiovascular death	37 (5.1)	30 (4.2)	0.82 (0.50-1.32)	0.40
Stroke	7 (1.0)	12 (1.7)	1.73 (0.68-4.40)	0.25
Myocardial infarction	51 (7.0)	32 (4.4)	**0.62 (0.40-0.97)**	**0.035**
ID-revascularization	49 (6.8)	31 (4.3)	**0.63 (0.40-0.98)**	**0.041**
Safety endpoint*	148 (20.4)	162 (22.5)	1.11 (0.89-1.37)	0.37

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Limitations

- Open label study
- Our results may not apply to:
  - Complete revascularization outside index hospitalization
  - Complete revascularization guided by conventional angiography
  - Patients not treated with biodegradable-polymer sirolimus eluting stent

Conclusions

Among patients aged 75 years or older with MI and multivessel disease, physiology-guided complete revascularization, as compared to a culprit-only revascularization strategy, reduced

- **Composite of death, MI, stroke, or ID-revascularization**
- **Cardiovascular death or MI**