UNIVERSITÀ DEGLI STUDI FIRENZE
DIPARTIMENTO DI MEDICINA SPERIMENTALE E CLINICA

Meet the Expert

L'APPROCCIO TERAPEUTICO AL PAZIENTE ANZIANO CON CARDIOPATIA ISCHEMICA CRONICA

TERAPIA MEDICA OTTIMIZZATA E ANGIOPLASTICA CORONARICA

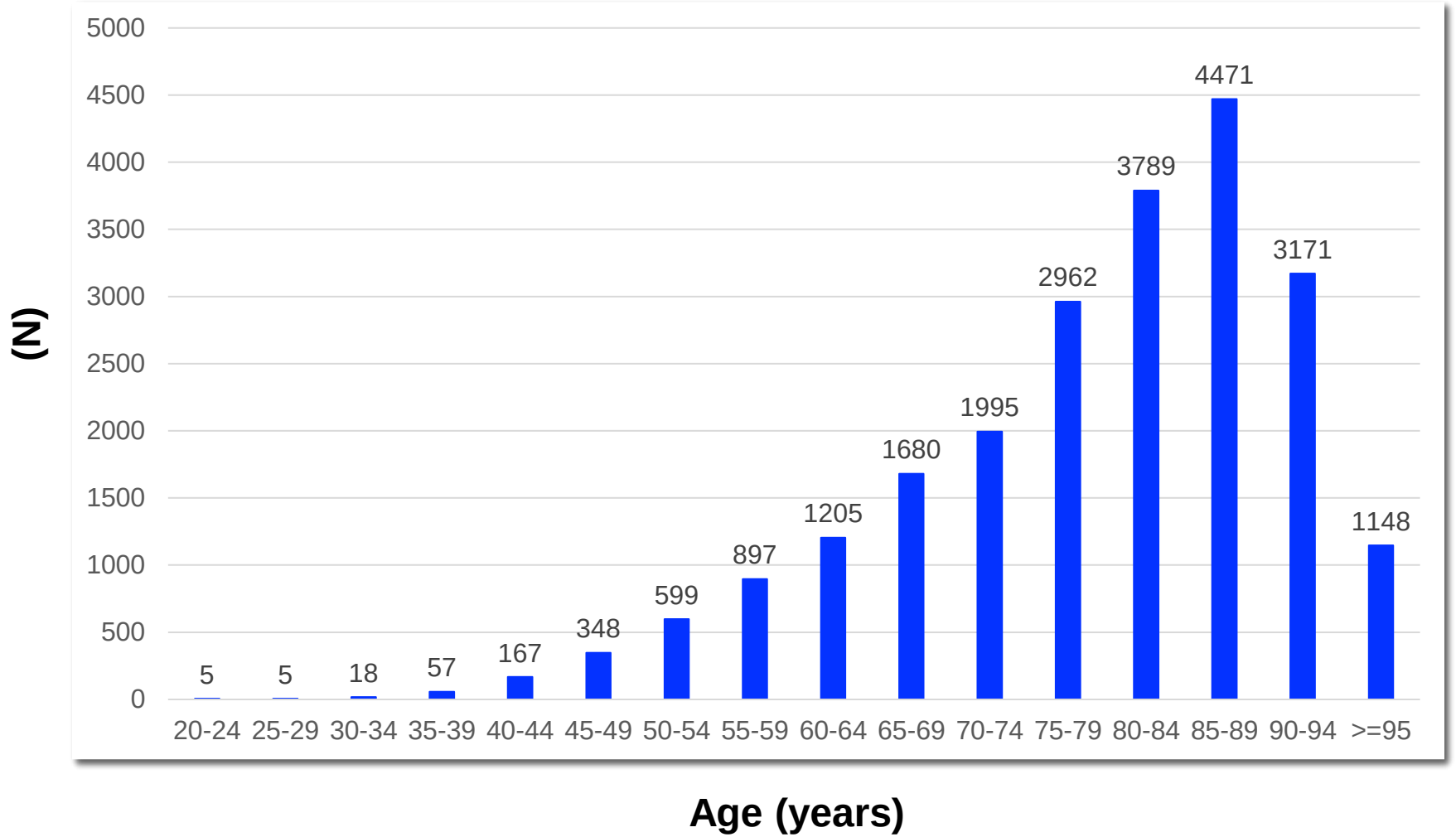
Stefano Fumagalli

Unità di Terapia Intensiva Geriatrica e Unità di Aritmologia Geriatrica, Università di Firenze e AOU Careggi

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

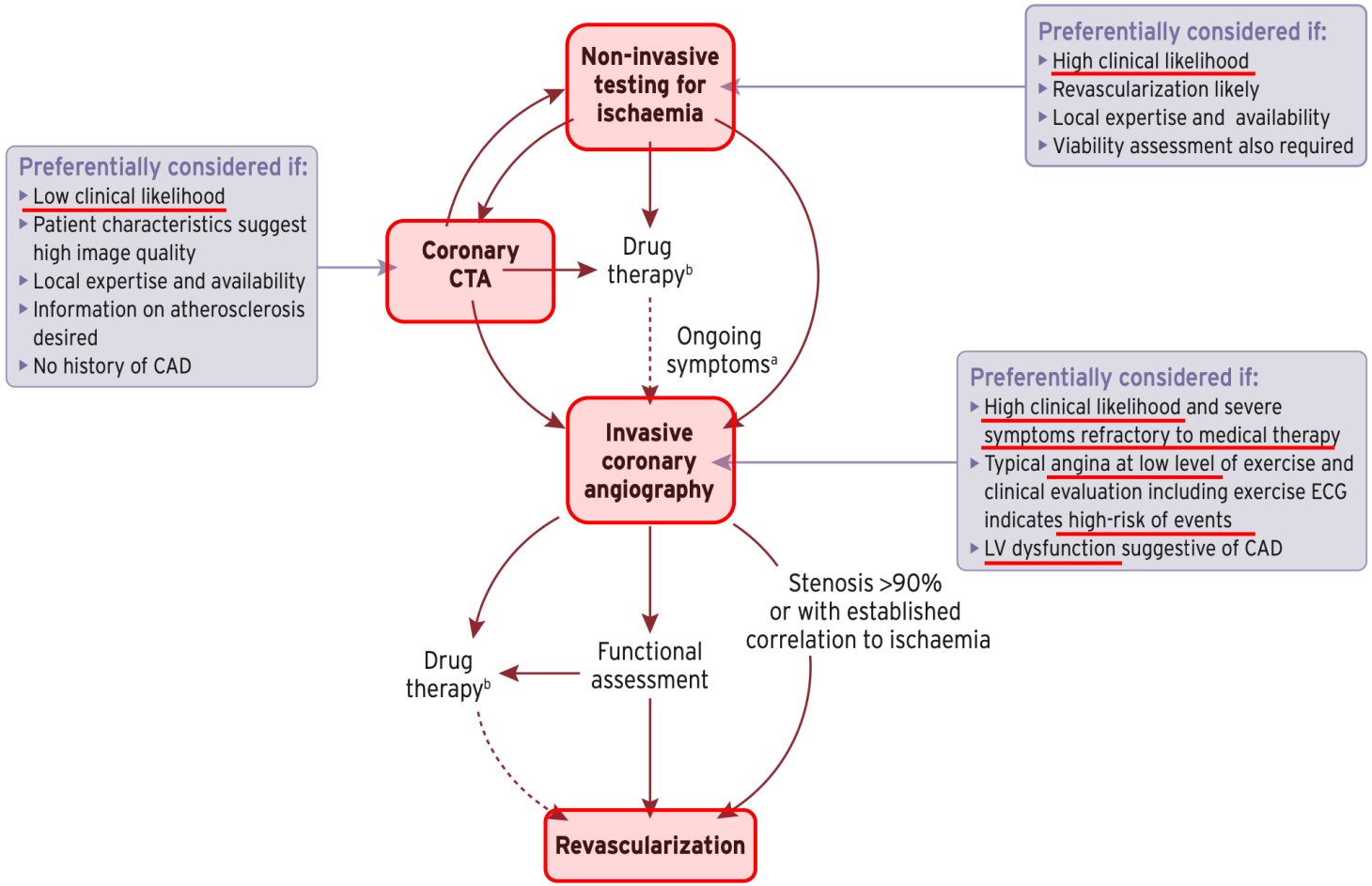
The epidemiology of myocardial infarction mortality in Italy

Mortality by age, in 2017 (Web accessed from: I.Stat - http://dati.istat.it/#)



2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

Diagnostic pathways in symptomatic patients with suspected CCS



8.2.4 Elderly

Recommendations for elderly patients with chronic coronary syndromes

Recommendations	Class[a]	Level[b]
It is recommended that particular attention is paid to side effects of drugs, intolerance, and overdosing in elderly patients.	I	C
The use of DES is recommended in elderly patients.[508,509]	I	A
Radial access is recommended in elderly patients to reduce access-site bleeding complications.[506,507]	I	B
It is recommended that diagnostic and revascularization decisions are based on symptoms, the extent of ischaemia, frailty, life expectancy, and comorbidities.	I	C

Knuuti J, Eur Heart J 2020

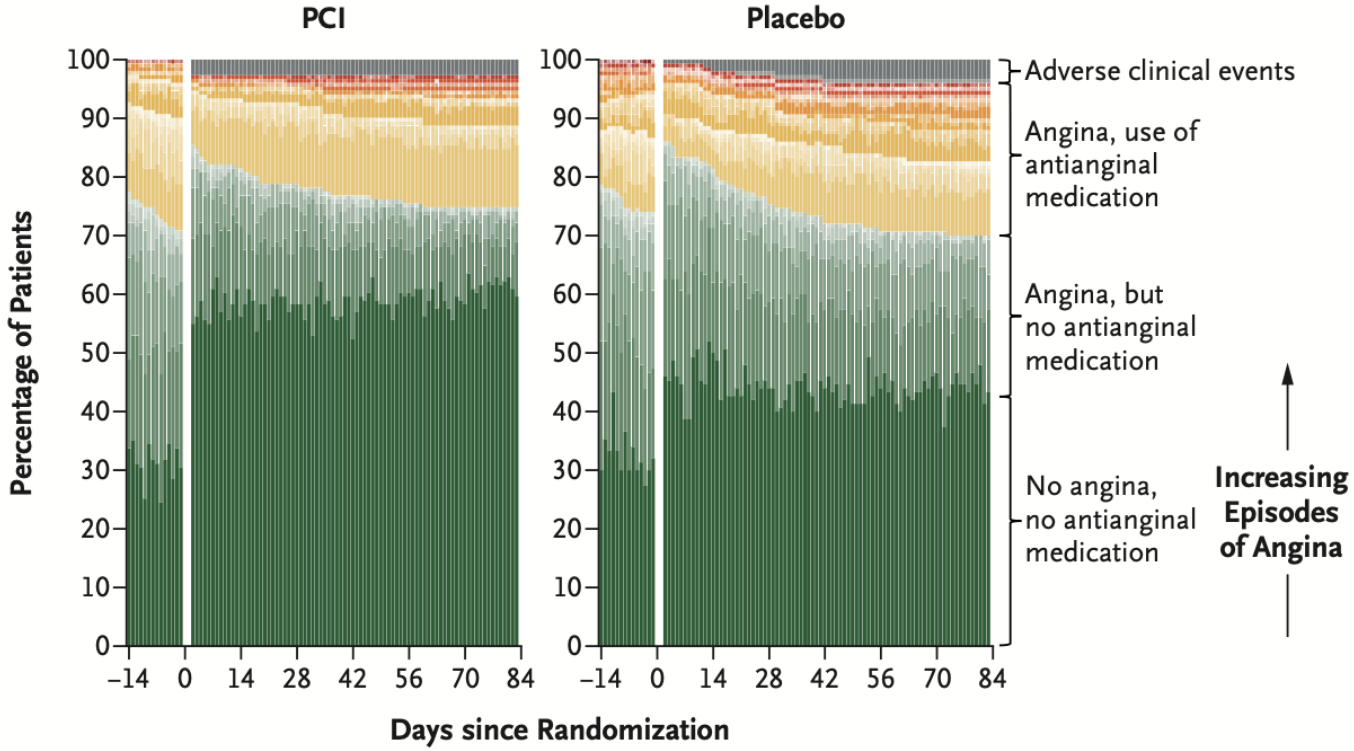
A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina

Rajkumar CA,
N Engl J Med 2023

Angina Symptom Score and Daily Angina Episodes in the ORBITA-2 trial (Age: 64 years; Men: 79%; Ischemic areas - 1/2/3: 80/17/2%; PCI/Placebo – N=150/151; 2018-23; FU: 12 weeks)

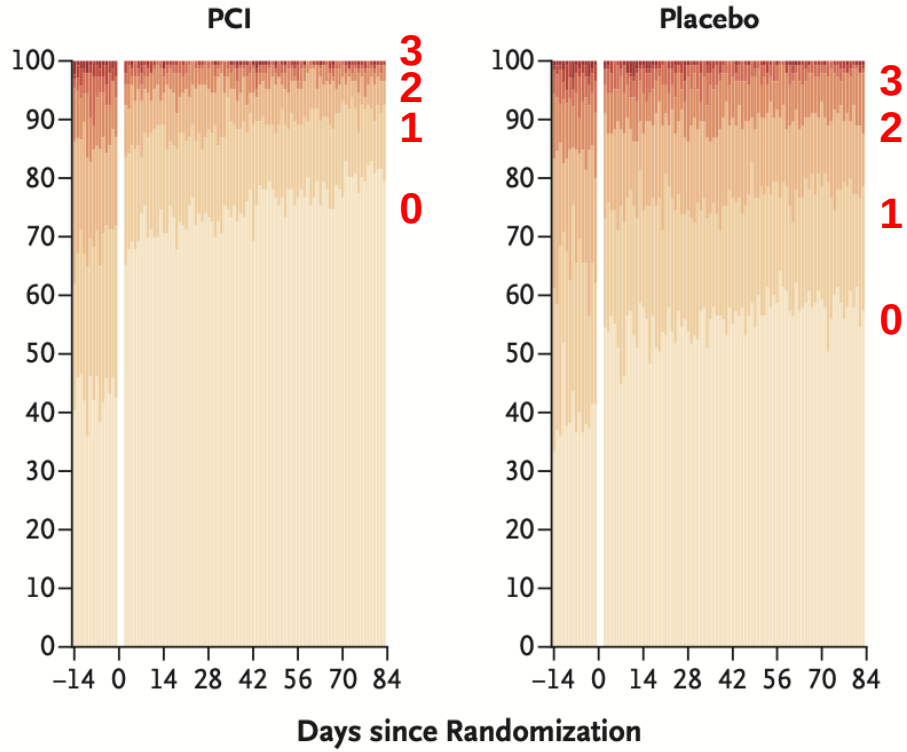
Angina symptom score

PCI – **2.9** vs. Placebo –**5.6**
OR=**2.21**, 95%CI: 1.41-3.47



Daily angina episodes

PCI – N=**0.3** vs. Placebo – N=**0.7**
OR=**3.44**, 95%CI: 2.00-5.91

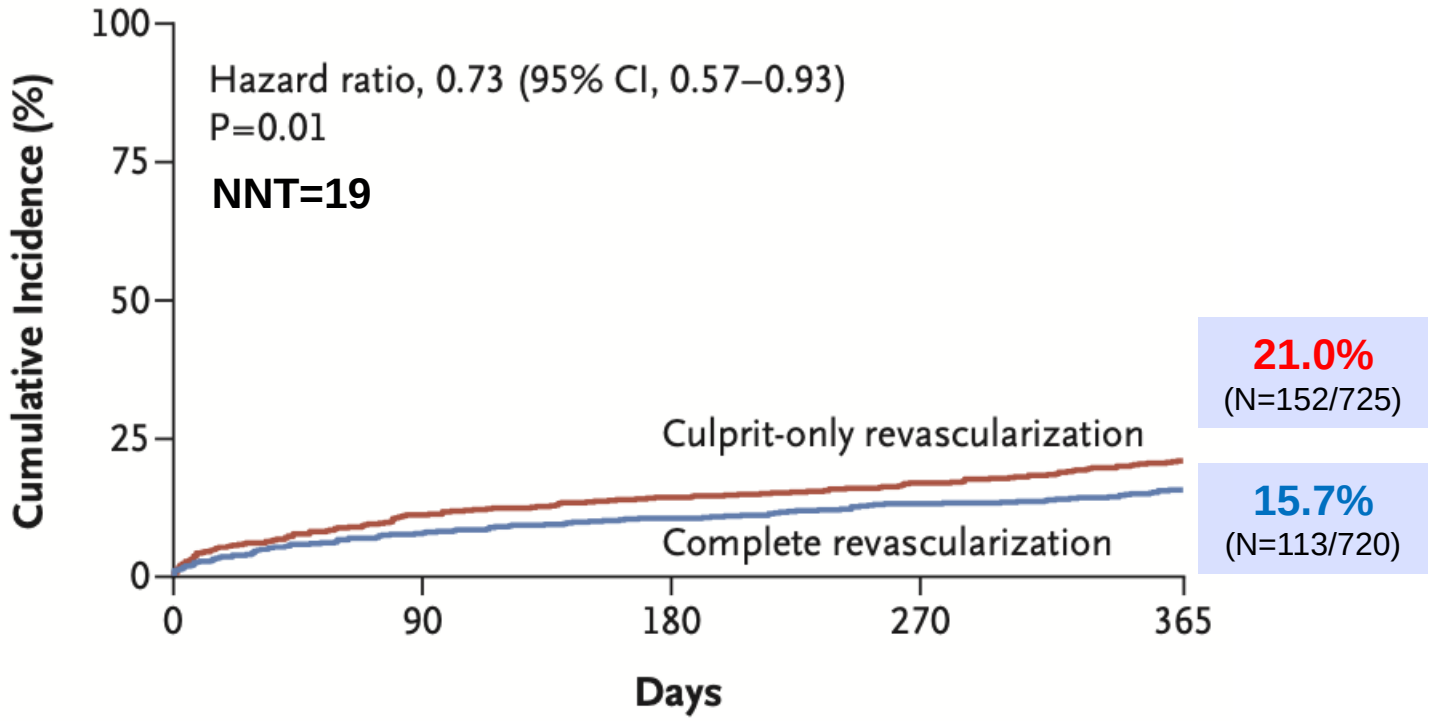


Complete or Culprit-Only PCI in Older Patients with Myocardial Infarction

1-year incidence of the Primary Outcome in the FIRE - Functional Assessment in Elderly MI Patients with Multivessel Disease – Trial (Culprit/Complete Rev. - N=725/720; Age: 80 years; Women: 36.5%; STEMI: 35.2%; 2019-21)

Primary Outcome
Death
Myocardial infarction
Stroke
Ischemia-driven revascularization

Non-culprit vessels
N=948
1 – 69.9%
≥2 – 30.1%
Treated – N=431 (**45.5%**)



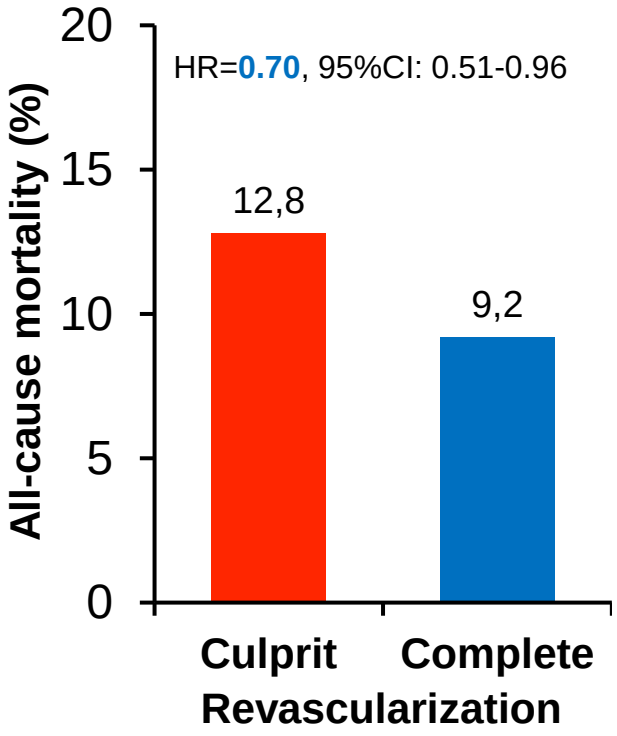
21.0%
(N=152/725)

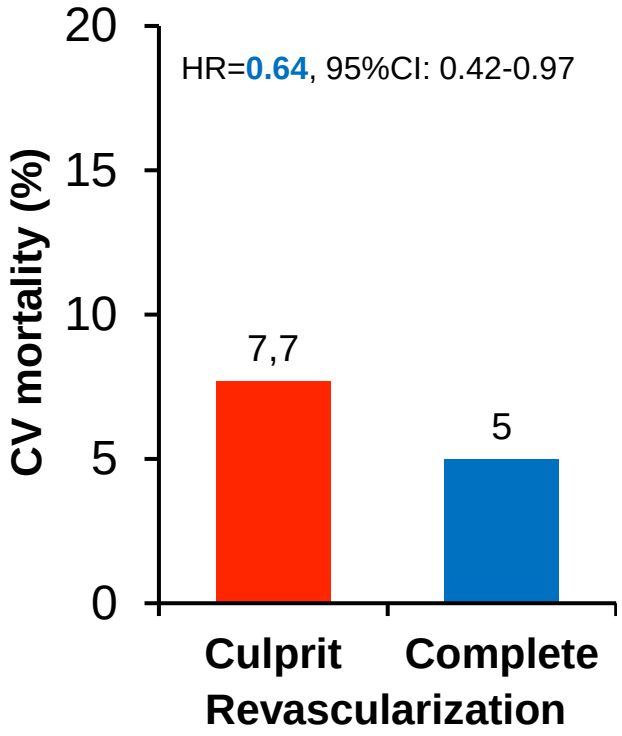
15.7%
(N=113/720)

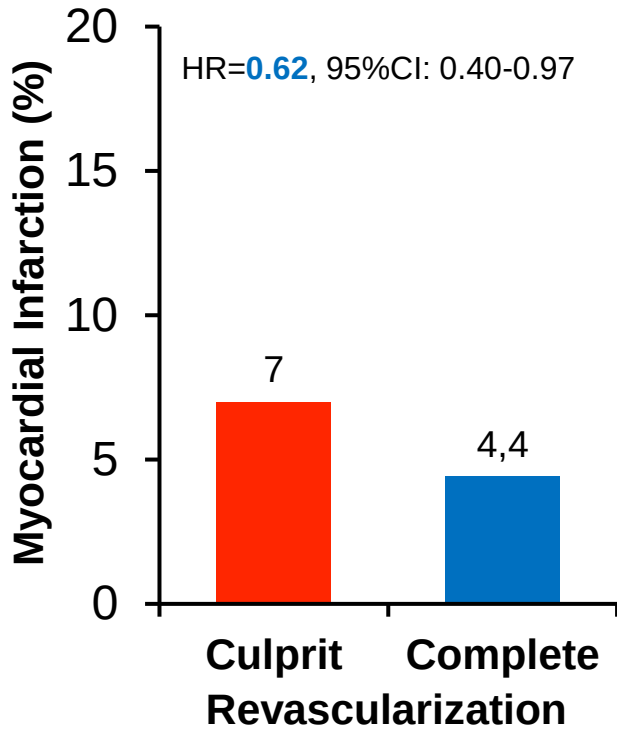
Biscaglia S,
NEJM 2023

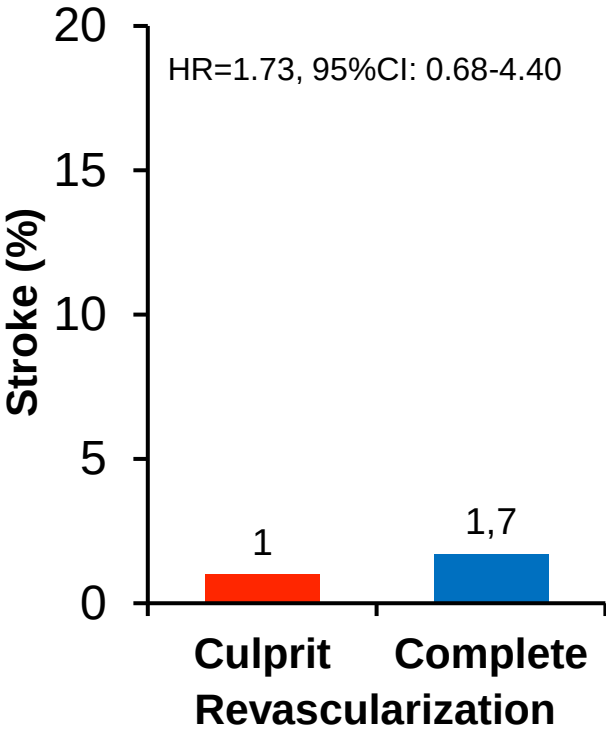
Complete or Culprit-Only PCI in Older Patients with Myocardial Infarction

1-year Efficacy Outcomes in the FIRE Trial





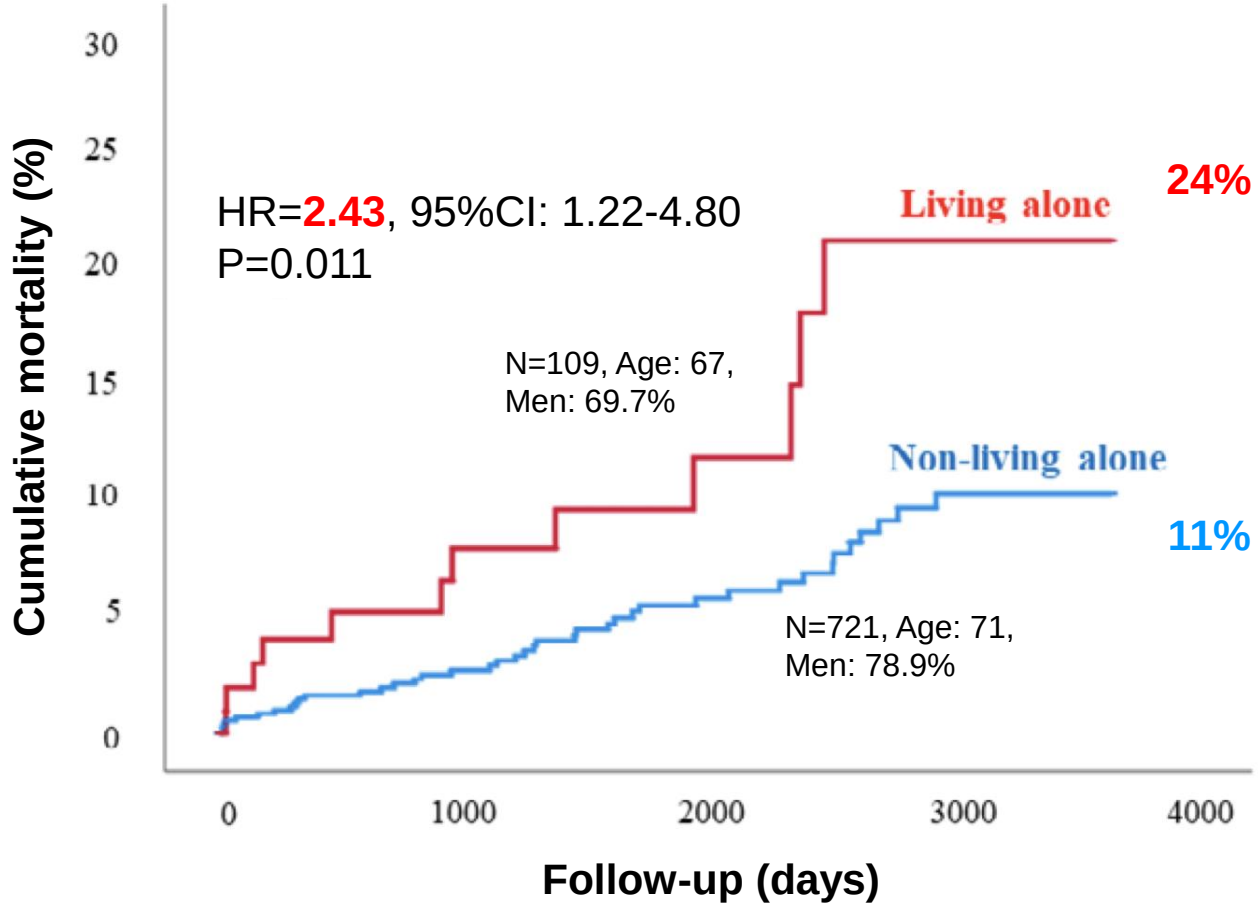




Biscaglia S,
NEJM 2023

The Prognostic Implications of Living Alone on Long-Term Mortality in Patients with Chronic Coronary Syndrome after Percutaneous Coronary Intervention

Cardiac death according to whether the patients lived alone (Fukushima Medical University Hospital; 2010-20; Follow-up: 1622 days)

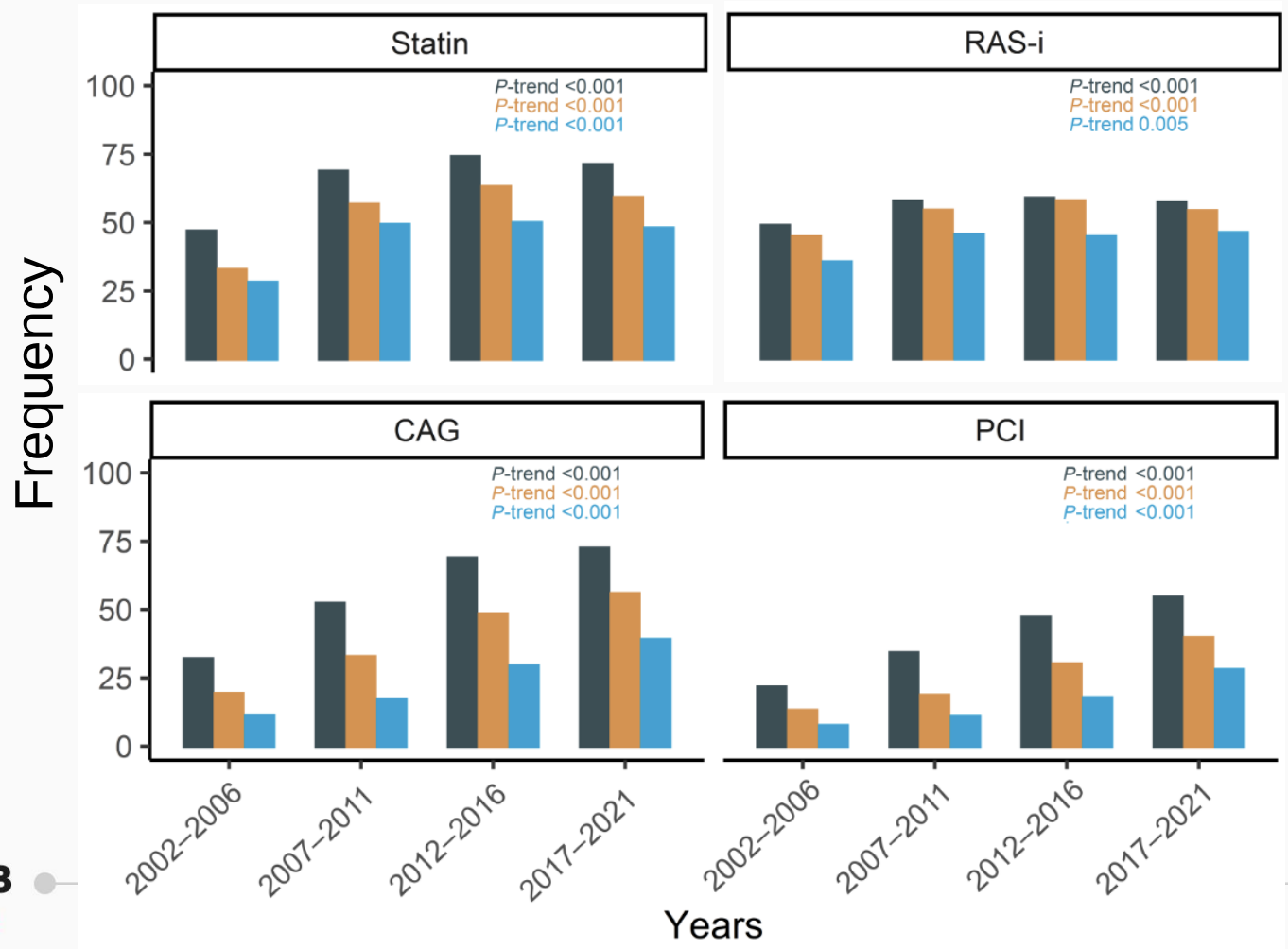


Isomatsu D,
Int Heart J 2023

Frailty, Treatments, and Outcomes in Older Patients With Myocardial Infarction: A Nationwide Registry-Based Study

Guideline-recommended management by period and frailty

Gaps in evidence
At which degree of frailty, treatment of specific risk factors should be less aggressive.



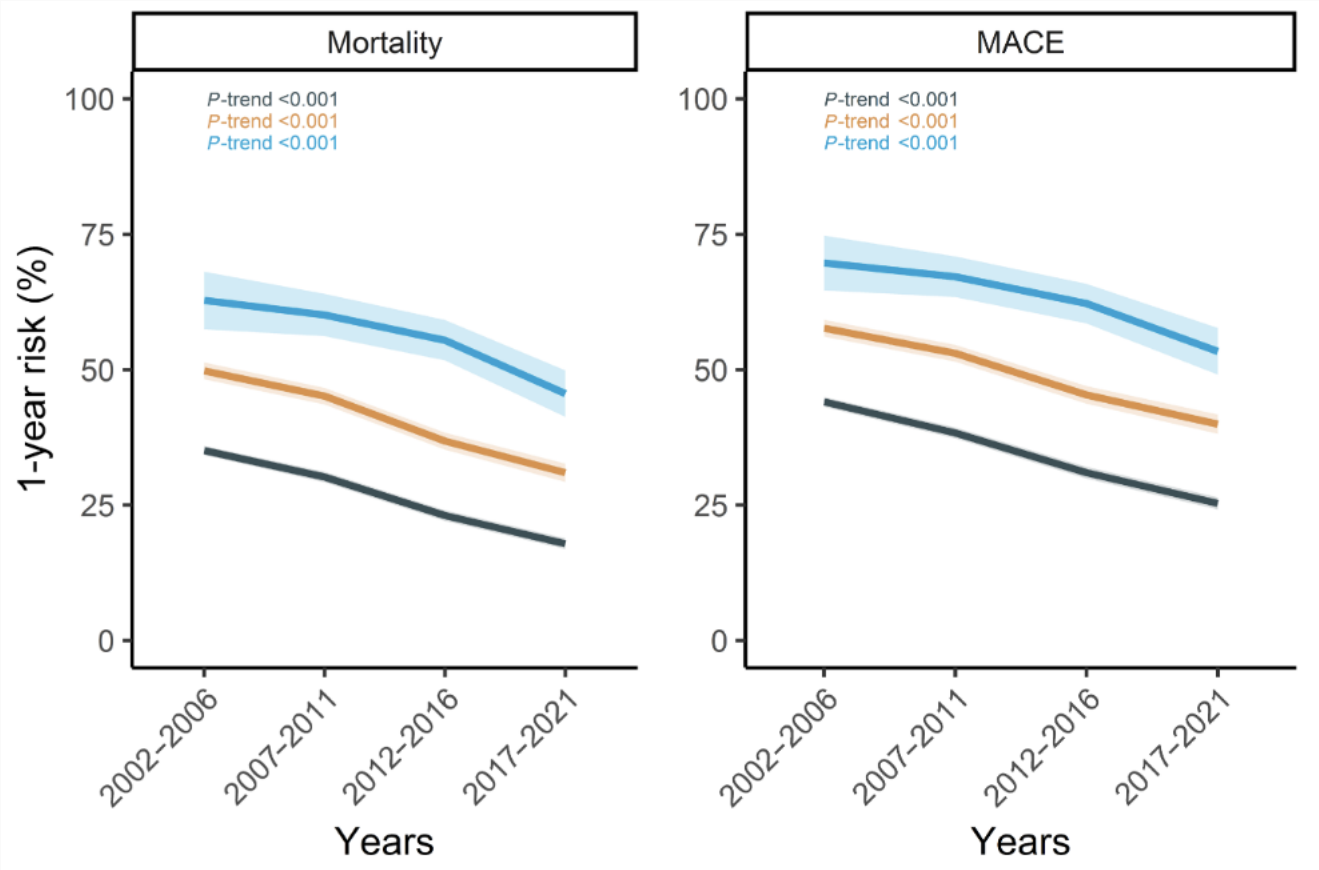
Frailty
Low N=34049
Intermediate N=14821
High N=2152

Age: 82 years
Women: 50.2%

Christensen DM, JAHA 2023

Frailty, Treatments, and Outcomes in Older Patients With Myocardial Infarction: A Nationwide Registry-Based Study

Absolute 1-year risk of death and MACE by frailty



Christensen DM, JAHA 2023

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

Suggested stepwise strategy for long term anti-ischaemic drug therapy in patients with CCS and specific baseline characteristics

	Standard therapy	High heart rate (e.g. >80 bpm)	Low heart rate (e.g. <50 bpm)	LV dysfunction or heart failure	Low blood pressure
1st step	BB or CCB[a]	BB or non-DHP-CCB	DHP-CCB	BB	Low-dose BB or low-dose non-DHP-CCB[c]
2nd step	BB + DHP-CCB	BB + CCB[b]	Switch to LAN	BB + LAN or BB + ivabradine	Switch to ivabradine[d], ranolazine or trimetazidine[e]
3rd step	Add 2nd line drug	BB + ivabradine[d]	DHP-CCB + LAN	Add another 2nd line drug	Combine two 2nd line drugs
4th step			Add nicorandil, ranolazine or trimetazidine		

2nd line drugs
Long-acting nitrates
Nicorandil
Ranolazine
Ivabradine
Trimetazidine

Knuuti J, Eur Heart J 2020

RESULTS-STUDY POPULATION
DATABASE, OUTCOMES AND PATIENTS

The importance of «Big Data»

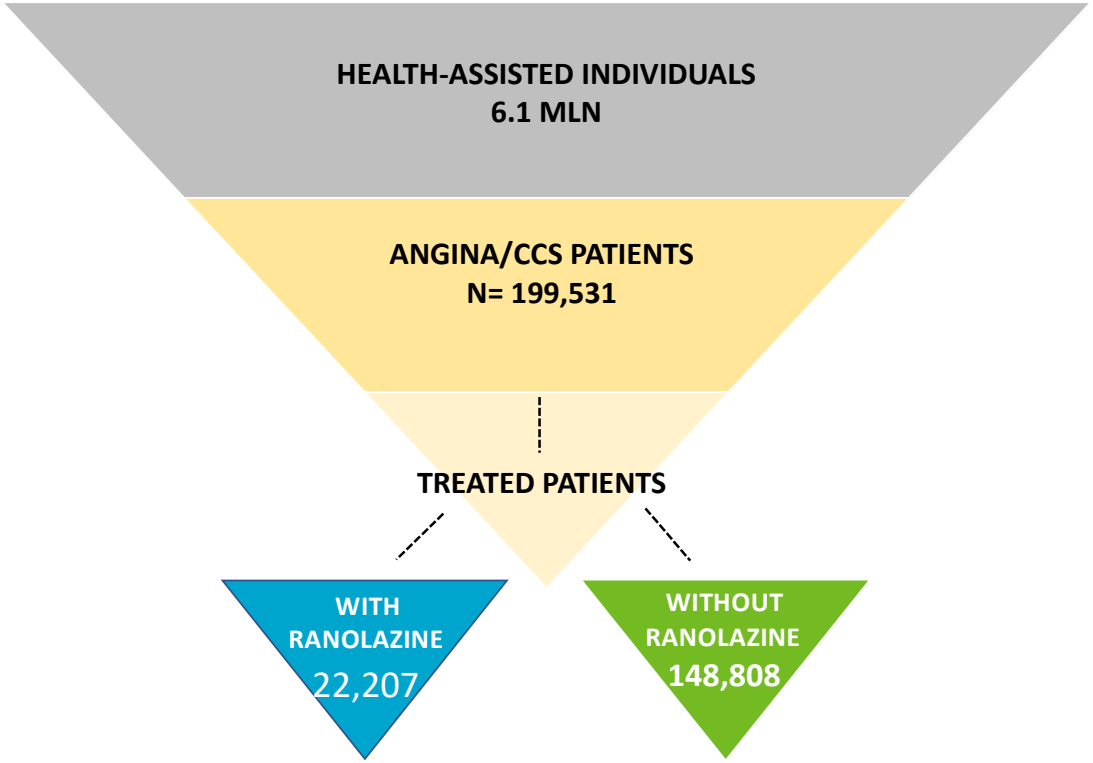
To evaluate whether **ANGINA PATIENTS TREATED WITH RANOLAZINE HAVE A REDUCED RISK FOR THE OCCURRENCE OF CLINICAL OUTCOMES** (Atrial Fibrillation, Diabetes Mellitus, Cardiovascular events and procedures, Heart Failure, Death) in a real-world setting

Ranolazine is a piperazine derivative, acting as an inhibitor of the late inward Na^+ current during cardiac repolarization

In ischemia and HF, late I_{Na} in ventricular myocytes is augmented, which increases Na^+ entry and, through the reverse-mode Na^+-Ca^{2+} exchange, the cytosolic Ca^{2+} concentration

The increased intracellular Ca^{2+} can impair mechanical relaxation and promote electric instability

These events provide both the substrate and the triggers to precipitate cardiac arrhythmias



RESULTS –BASELINE CHARACTERISTICS

BASELINE CHARACTERISTICS BY RANOLAZINE THERAPY, AFTER PSM

	Ranolazine	Other Drugs	SMD
n	**6,384**	**25,536**	
Male (n, %)	**5,188 (68.5)**	**17,772 (69.6)**	**0.008**
Age (mean, SD)	**70.7 (10.8)**	**70.3 (11.8)**	**0.030**
- Age 18-49 (n, %)	200 (3.1)	1,262 (4.9)	
- Age 50-59 (n, %)	849 (13.3)	3,720 (14.6)	
- Age 60-64 (n, %)	731 (11.5)	2,841 (11.1)	
- Age 65-69 (n, %)	991 (15.5)	3,502 (13.7)	
- Age 70-74 (n, %)	1,106 (17.3)	3,891 (15.2)	
- Age 75-79 (n, %)	1,074 (16.8)	4,030 (15.8)	
- Age 80-84 (n, %)	835 (13.1)	3,458 (13.5)	
- Age 85-89 (n, %)	442 (6.9)	2,062 (8.1)	
- Age 90+ (n, %)	156 (2.4)	770 (3.0)	
Charlson index (mean, SD)	**0.7 (1.0)**	**0.7 (1.0)**	**0.004**
Charlson 0 (n, %)	3,221 (50.5)	13,357 (52.3)	
Charlson 1 (n, %)	2,236 (35.0)	8,102 (31.7)	
Charlson 2 (n, %)	638 (10.0)	2,782 (10.9)	
Charlson 3+ (n, %)	289 (4.5)	1,295 (5.1)	

≥70 years
Ranolazine: 56.5%
Other drugs: 55.6%

Mean follow-up
Ran: *4.7 (2.5) years*
Other Drugs: *5.5 (3.2) years*
Overall population: *5.3 (3.1)*

STANDARDIZED MEAN DIFFERENCE - SMD - VALUES BELOW 0.2 INDICATE THAT THE TWO SUB-GROPS ARE NOT SIGNIFICANTLY DIFFERENT

RESULTS –BASELINE CHARACTERISTICS

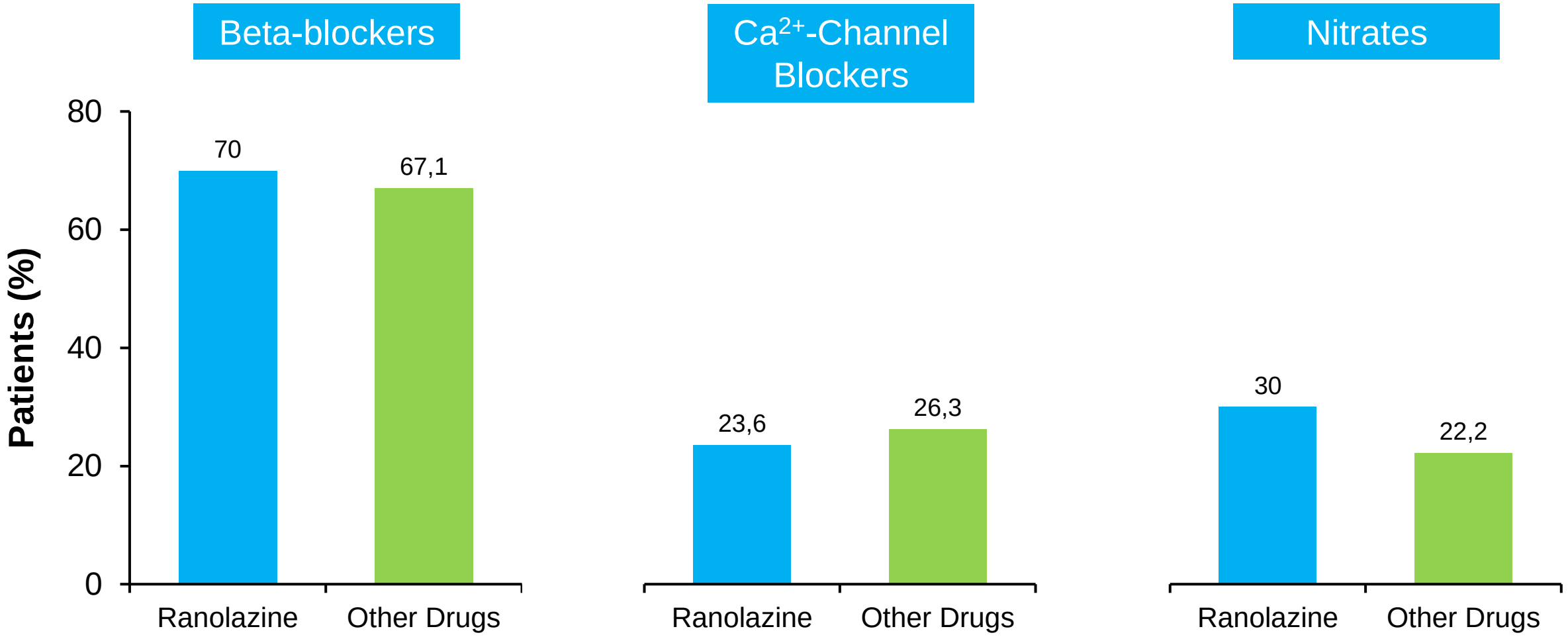
CLINICAL CHARACTERISTICS AMONG THE SUB-GROUPS, AFTER PSM

	Ranolazine	Other Drugs	SMD
n	**6,384**	**25,536**	
Dyslipidemia (n, %)	5,745 (90.0)	22,629 (88.6)	0.044
Diabetes (n, %)	185 (2.9)	924 (3.6)	0.041
Atrial fibrillation (n, %)	652 (10.2)	2,511 (9.8)	0.013
Heart failure (n, %)	812 (12.7)	3,296 (12.9)	0.006
AMI (n, %)	2,251 (35.3)	8,467 (33.2)	0.044
PAD (n, %)	9 (0.1)	33 (0.1)	0.003
Stroke (n, %)	851 (13.3)	3,350 (13.1)	0.006
Renal failure (n, %)	472 (7.4)	1,901 (7.4)	0.002
COPD (n, %)	1,775 (27.8)	6,825 (26.7)	0.024
Tumors (n, %)	432 (6.8)	1,661 (6.5)	0.011
Cardiovascular procedures (n, %)	3,524 (55.2)	13,701 (53.7)	0.031
Antihypertensive (n, %)	6,190 (97.0)	24,700 (96.7)	0.013
Ivabradine (n, %)	383 (6.0)	1,382 (5.4)	0.025
ASA (n, %)	3,816 (59.8)	15,636 (61.2)	0.030
Beta blockers (n, %)	4,453 (69.8)	18,041 (70.7)	0.020
Calcium antagonists (n, %)	1,373 (21.5)	5,624 (22.0)	0.013
Nitrates (n, %)	1,754 (27.5)	6,511 (25.5)	0.045

STANDARDIZED MEAN DIFFERENCE - SMD - VALUES BELOW 0.2 INDICATE THAT THE TWO SUB-GROPS ARE NOT SIGNIFICANTLY DIFFERENT

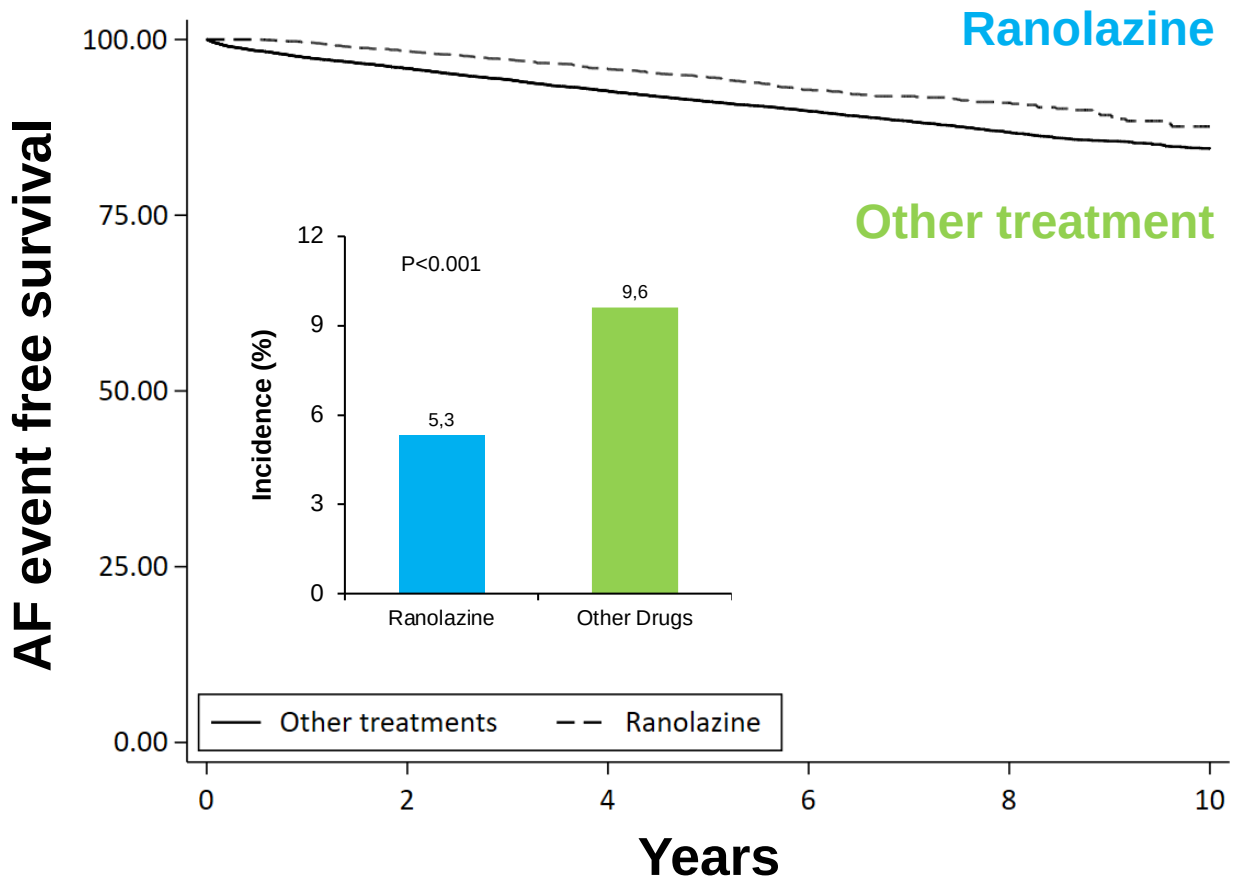
RESULTS

USE OF OTHER ANTIANGINAL DRUGS AT BASELINE BY GROUP



RESULTS

Kaplan-Meier Rates of Atrial Fibrillation Occurrence by Ranolazine Therapy



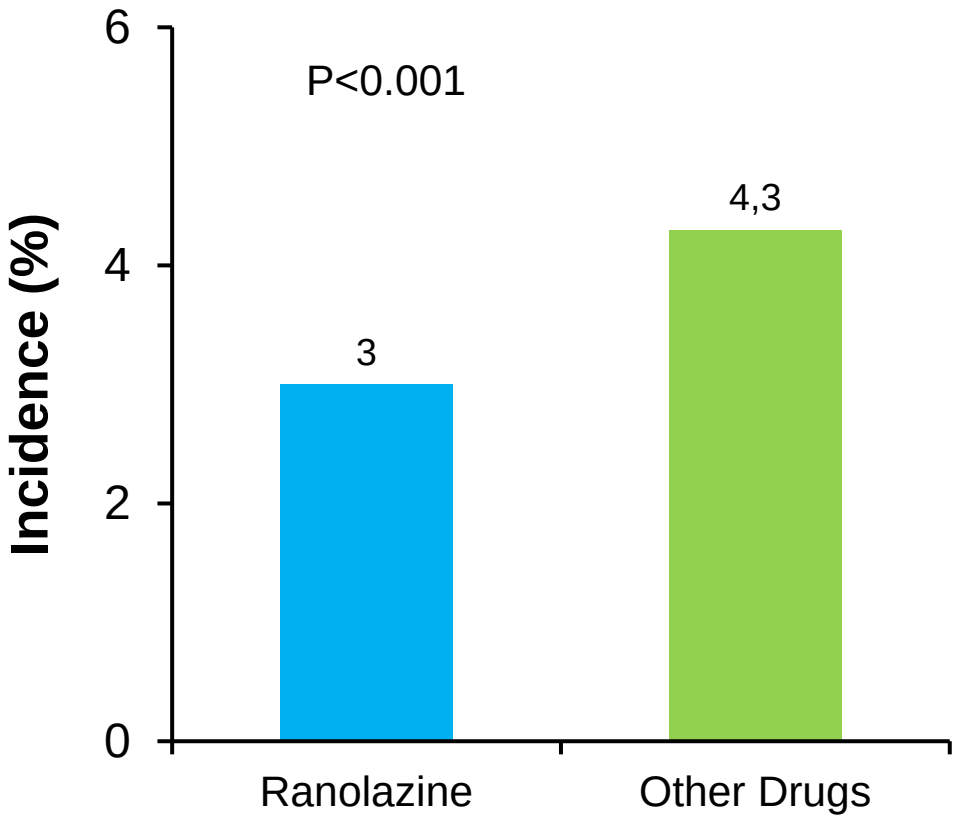
Adjusted **HR**=0.59,
95% CI=0.53-0.67

P<0.001

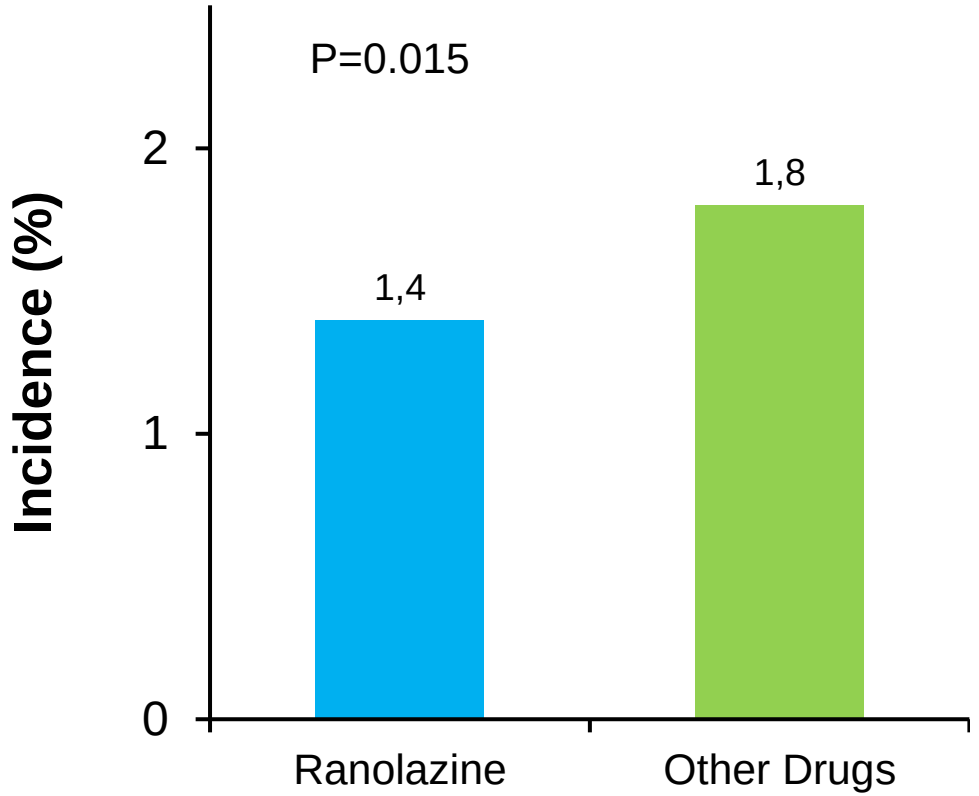
RESULTS – SAFETY OUTCOMES

INCIDENCE OF BRADY- & TACHYARRHYTHMIAS BY RANOLAZINE THERAPY

Bradyarrhythmias – ALL CASES



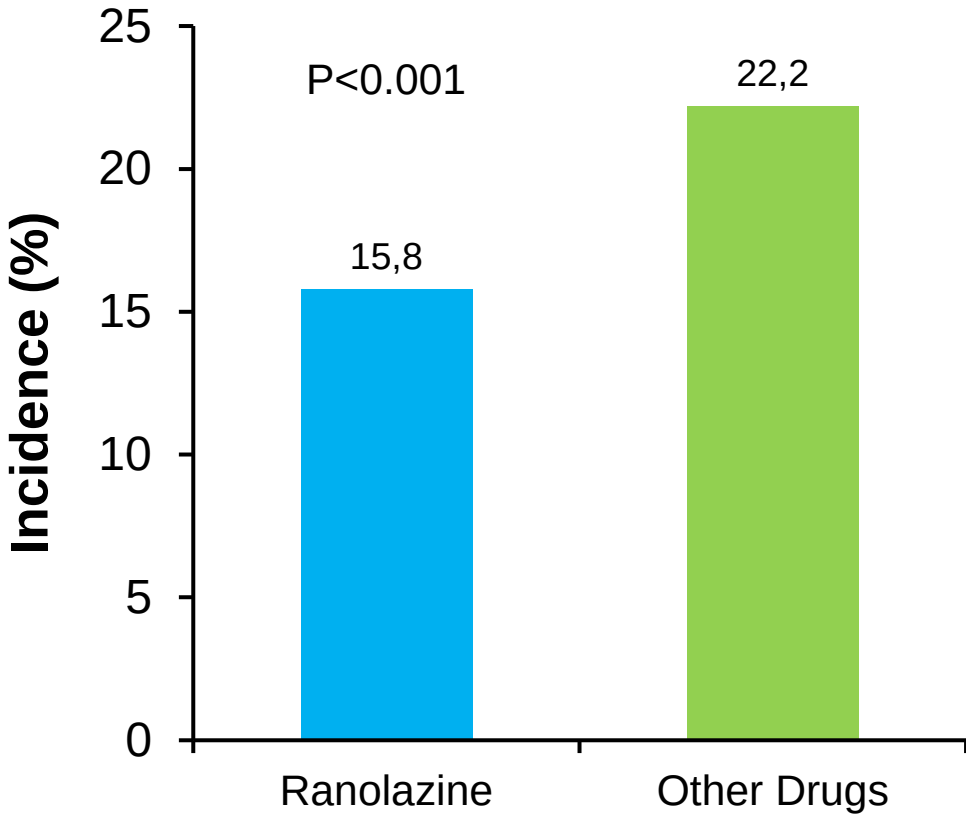
Ventricular arrhythmias



ICD 9 CM codes:
427.1: Paroxysmal VT
427.4: VF / V. Flutter

RESULTS – PRIMARY OUTCOME
NEW OCCURRENCE OF A CARDIOVASCULAR PROCEDURE, POST PSM

CV Procedures – ALL CASES



CV procedures: Pacemaker / ICD, angioplasty, CABG, other procedures on heart, cardiac valves, arteries and veins

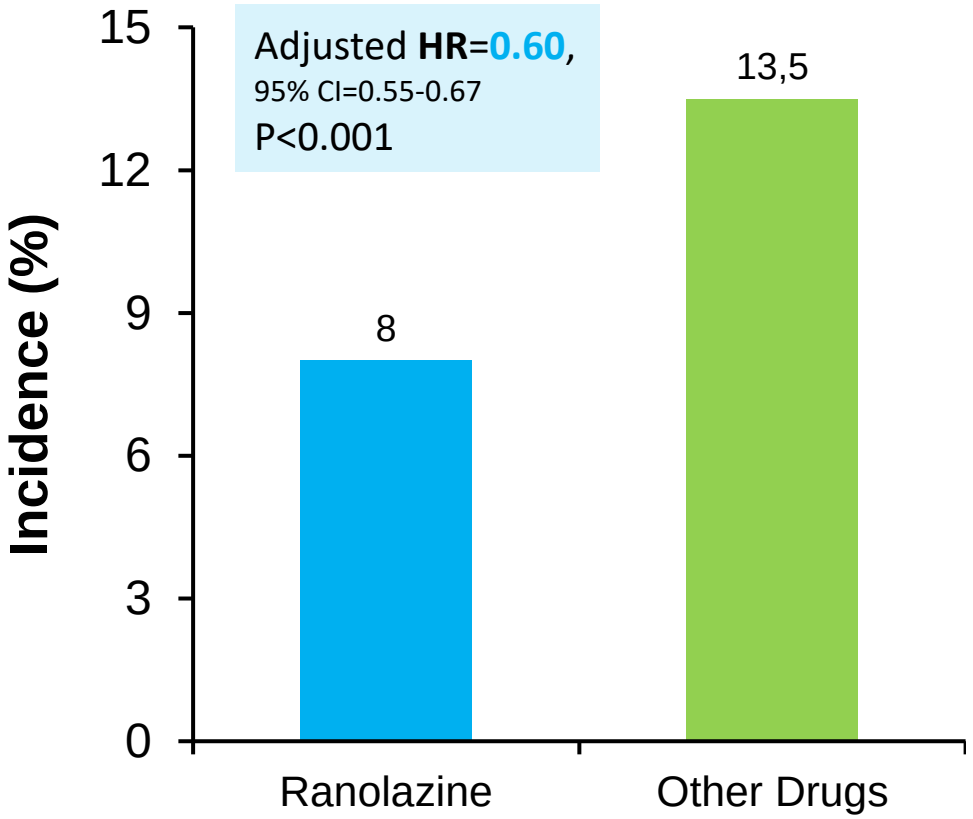
	HR	95% CI		p
Ranolazine cohort	**0.70**	**0.64**	**0.78**	**<0.001**
Men	**1.79**	**1.65**	**1.94**	**<0.001**
Age	**1.00**	**1.00**	**1.01**	**0.045**
Charlson index	**1.07**	**1.01**	**1.13**	**0.021**
Dyslipidemia	**1.27**	**1.13**	**1.42**	**<0.001**
Diabetes	1.16	0.96	1.39	0.117
Atrial fibrillation	**1.27**	**1.12**	**1.43**	**<0.001**
AMI	**1.34**	**1.24**	**1.45**	**<0.001**
Hypertension	0.98	0.80	1.19	0.823
Stroke	**0.83**	**0.74**	**0.94**	**0.003**
Renal failure	**1.24**	**1.09**	**1.41**	**0.001**
COPD	0.93	0.85	1.02	0.132
Tumors	0.92	0.78	1.08	0.308
Ivabradine	**1.30**	**1.12**	**1.52**	**0.001**
ASA	1.05	0.98	1.13	0.175
Beta blockers	**1.22**	**1.12**	**1.32**	**<0.001**
Calcium antagonists	**1.19**	**1.10**	**1.29**	**<0.001**
Nitrates	**1.33**	**1.23**	**1.43**	**<0.001**

NOTE: Patients with previous cardiovascular proceures were excluded

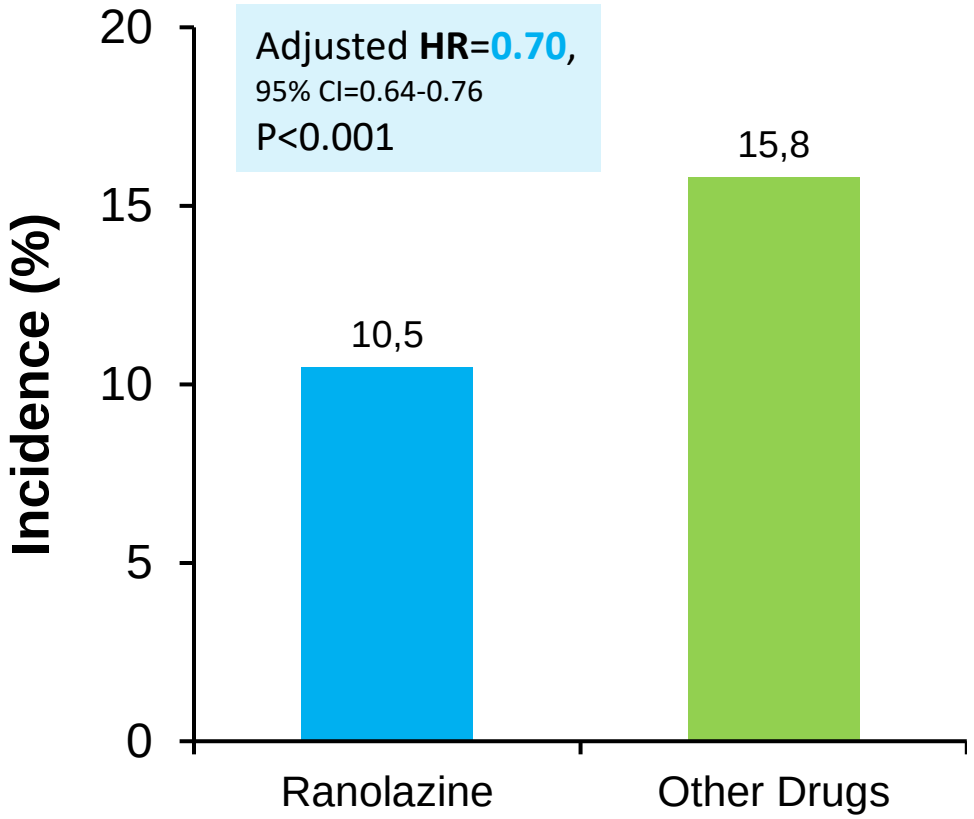
RESULTS – PRIMARY OUTCOME

INCIDENCE OF HEART FAILURE AND NEW ONSET DIABETES, BY RANOLAZINE THERAPY

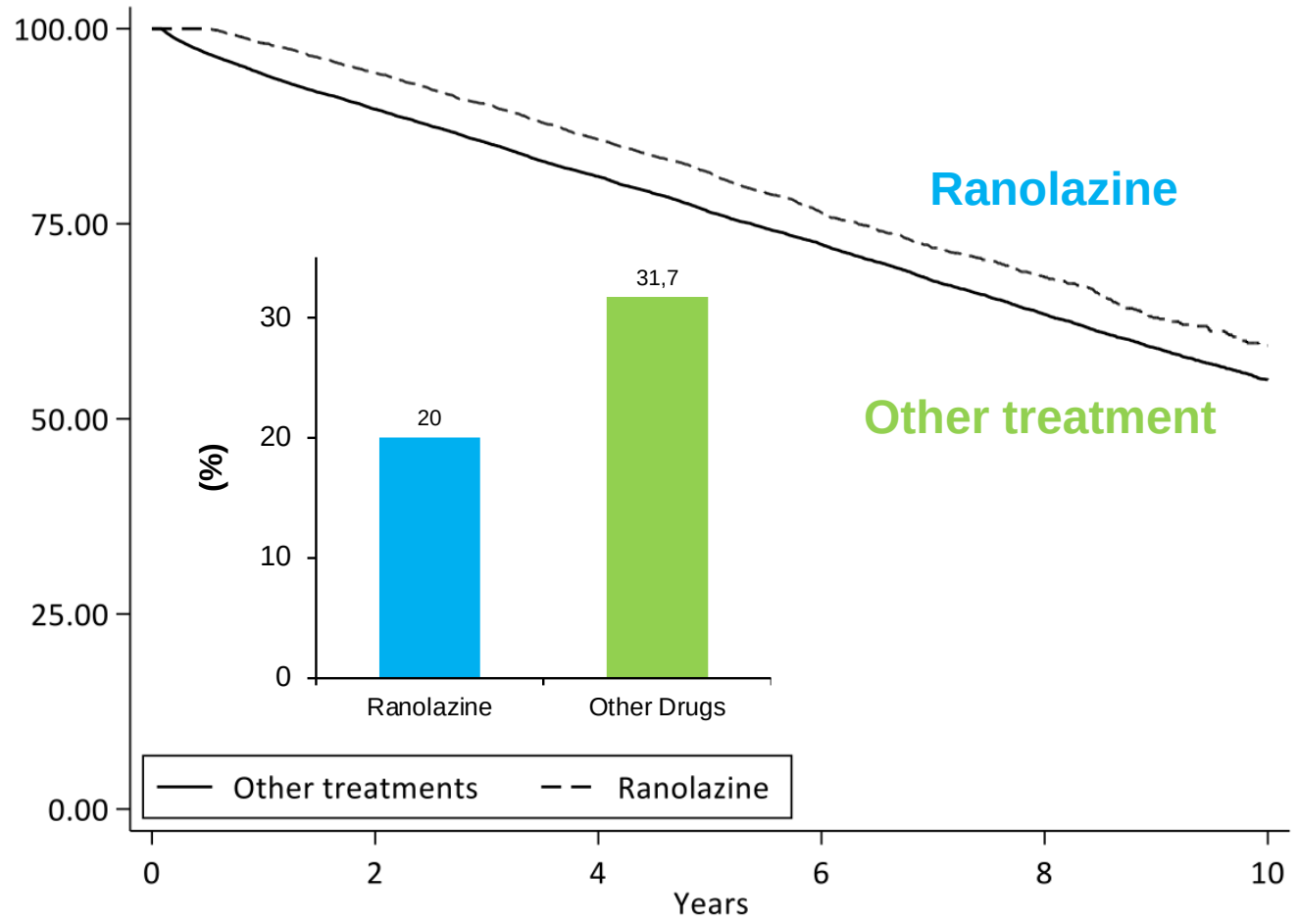
Heart Failure – ALL CASES



Diabetes – ALL CASES



RESULTS – PRIMARY OUTCOME
ALL-CAUSE MORTALITY BY RANOLAZINE THERAPY



Adjusted **HR**=**0.74**,
95% CI=0.70-0.79

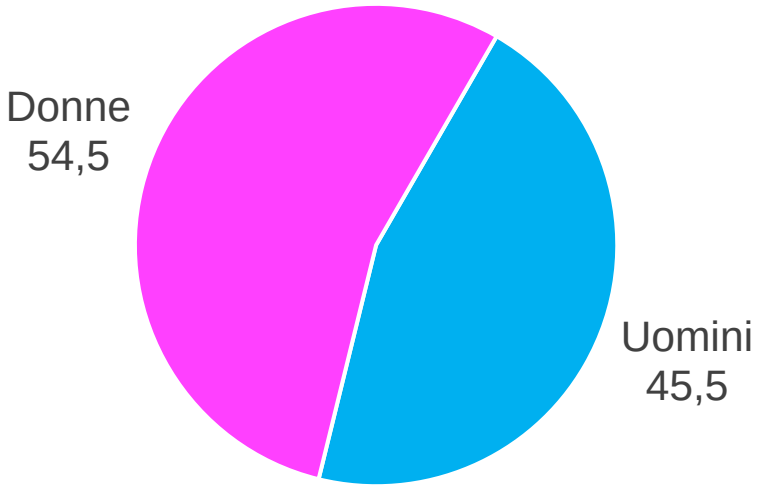
P<0.001

Conclusioni

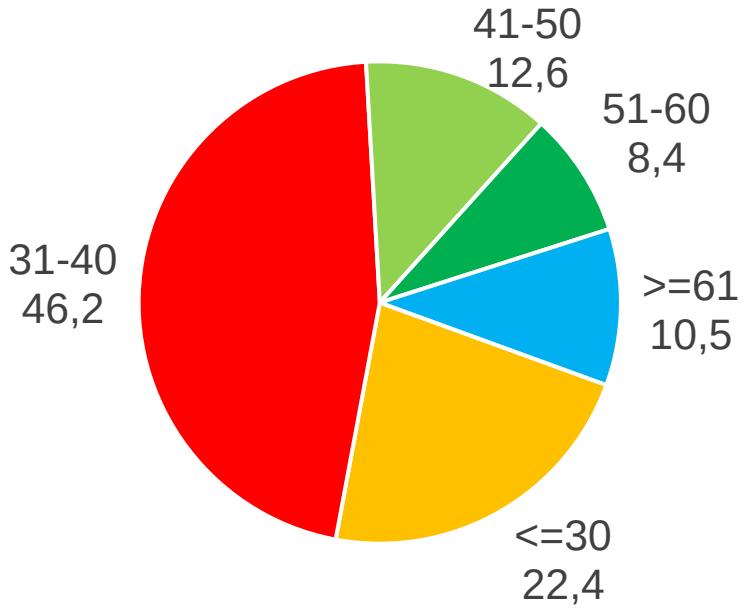
- Le procedure di rivascolarizzazione miocardica sono sicure ed efficaci anche in pazienti di età avanzata
- Il risultato di un'angioplastica può essere influenzato da variabili non soltanto cliniche. La VMD rappresenta uno strumento utile per migliorare ulteriormente i benefici della procedura
- Età e genere femminile possono correlarsi a «sotto-trattamento»
- La ranolazina, con la sua azione farmacologica, non limitata alla sola corrente tardiva del Na^+, si associa a importanti effetti terapeutici nel paziente con SCC
- Le terapie farmacologica e interventistica hanno ridotto la mortalità e migliorato gli «outcome» clinici anche nel paziente fragile con SCC

La gestione dei pazienti anziani con SCC - I risultati "On Going" della Survey SIGG
(I) I PARTECIPANTI

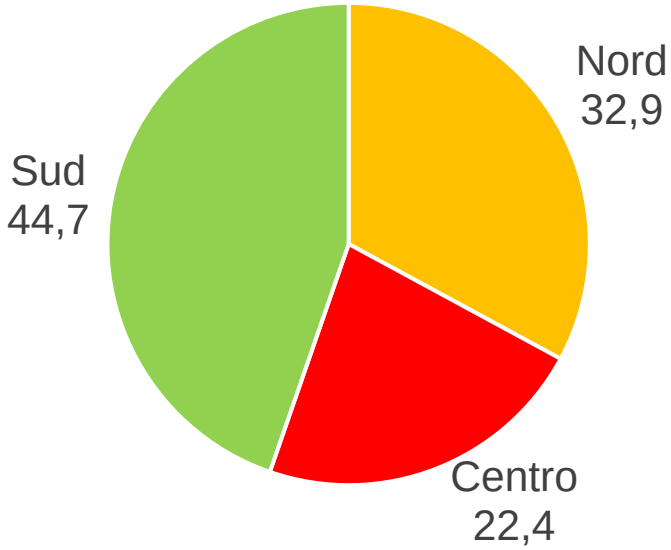
Sesso



Gruppi di età

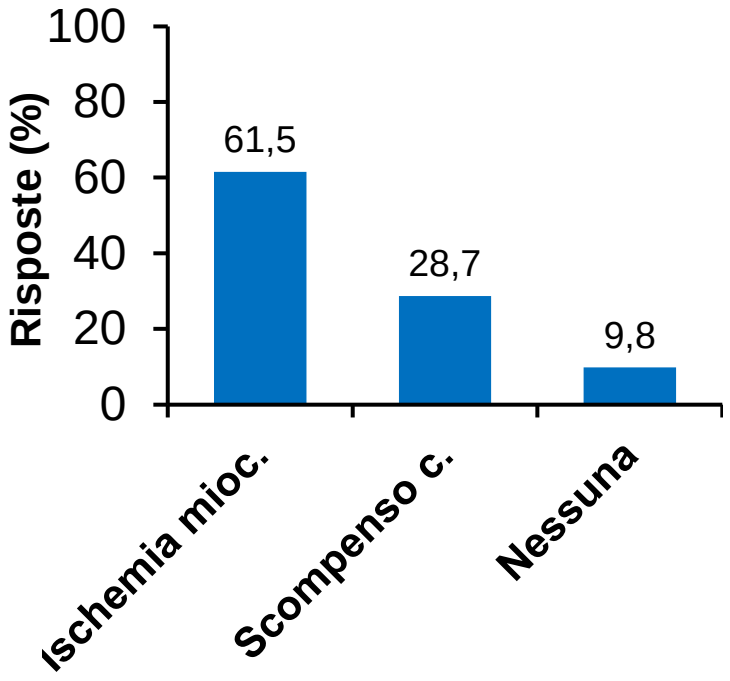


Area geografica

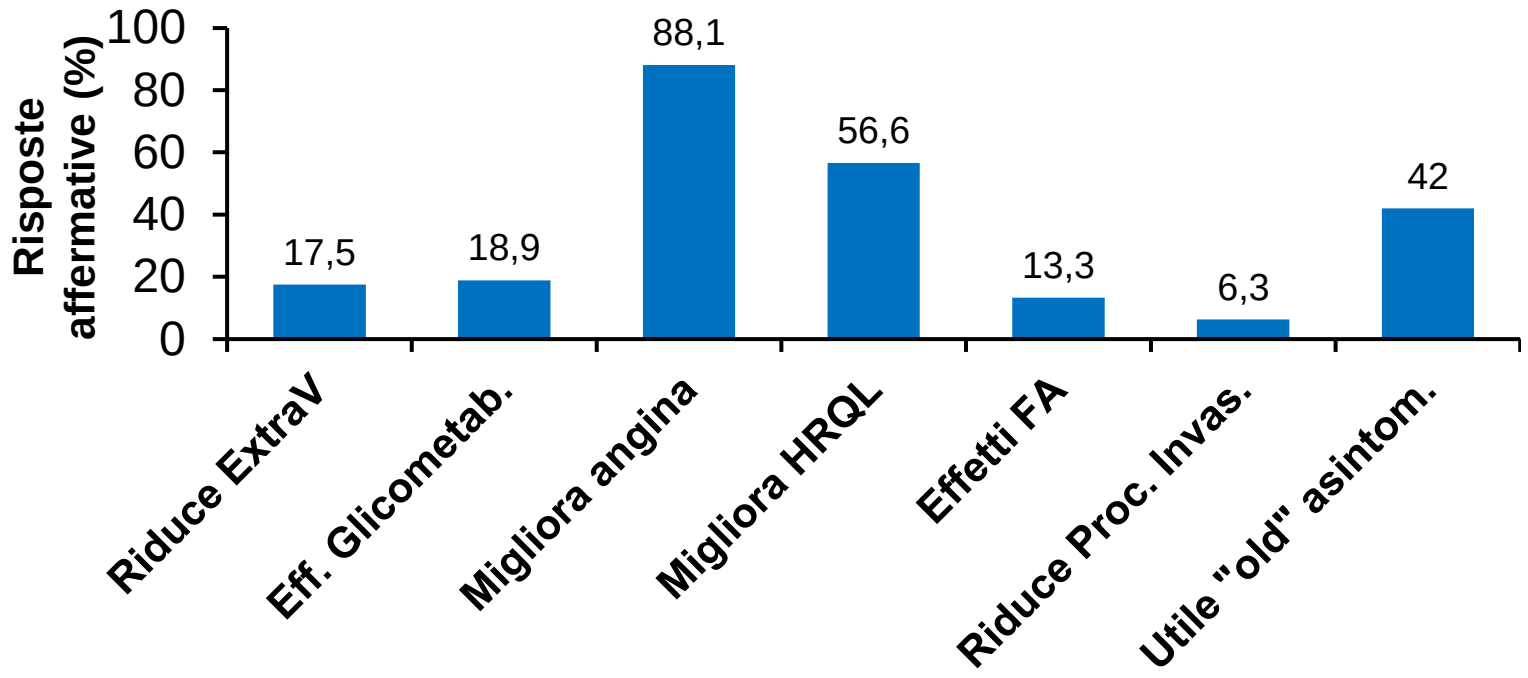


N=143

La gestione dei pazienti anziani con SCC - I risultati "On Going" della Survey SIGG
(II) GLI EFFETTI DI RANOLAZINA

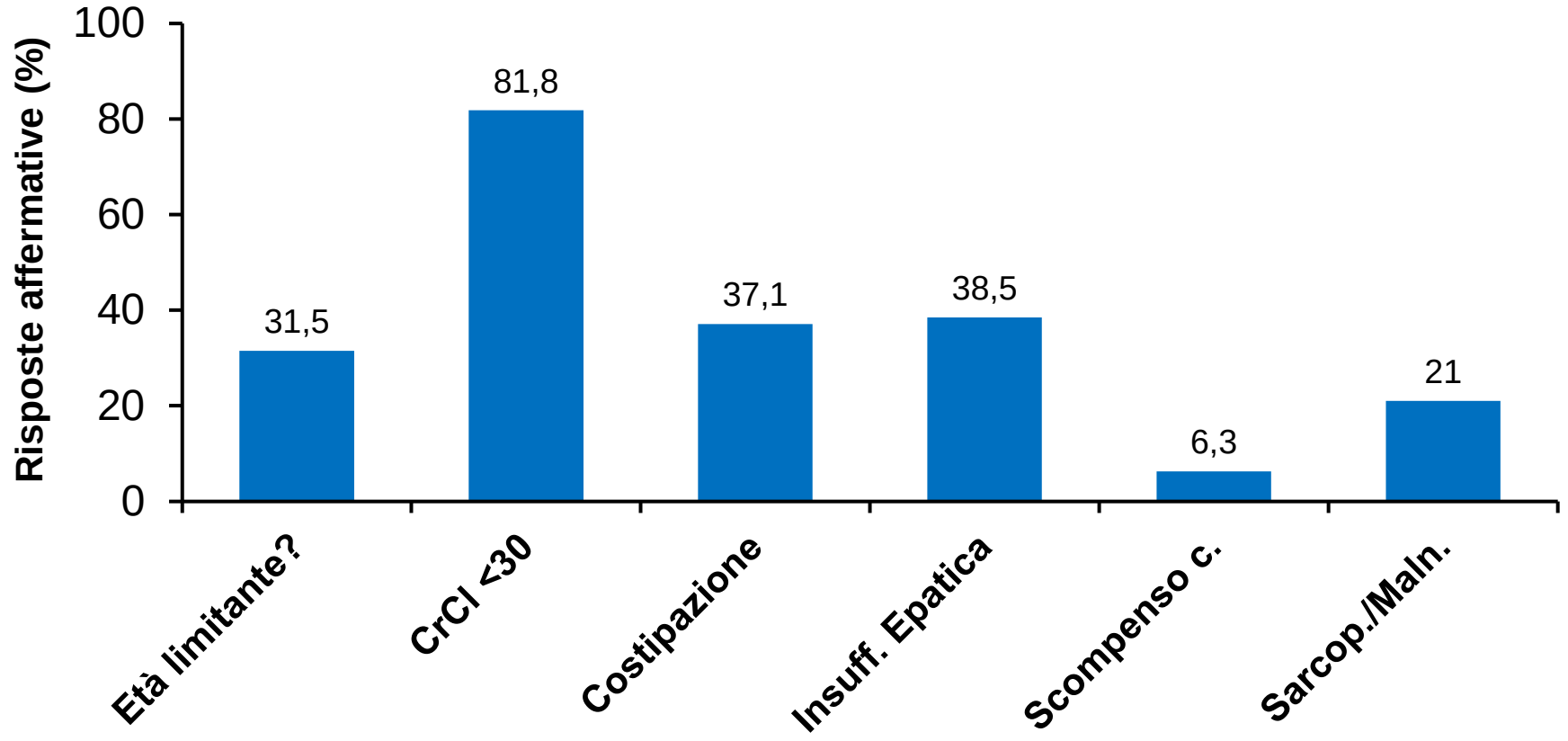


In quali situazioni la corrente tardiva del sodio ha attività aumentata?



Quali sono i benefici di Ranolazina nel paziente anziano con SCC?

La gestione dei pazienti anziani con SCC - I risultati "On Going" della Survey SIGG
(III) QUALI LIMITI PER RANOLAZINA?



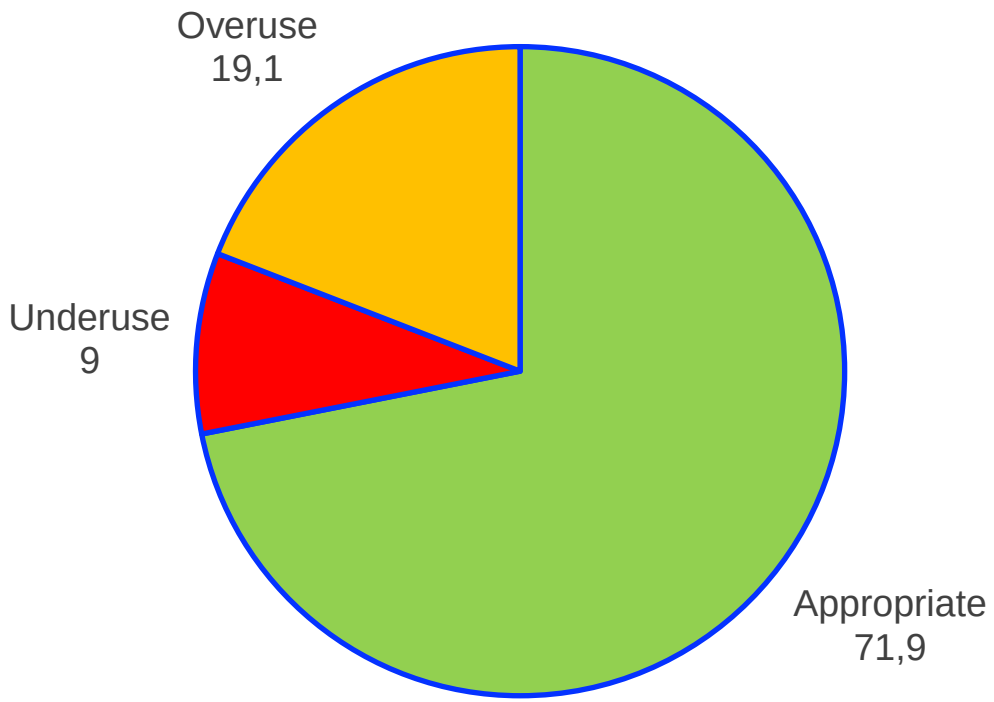
Ritieni che l'età avanzata sia limitante?

Quali patologie associate sono fattore limitante all'uso di ranolazina nel paziente anziano con SCC?

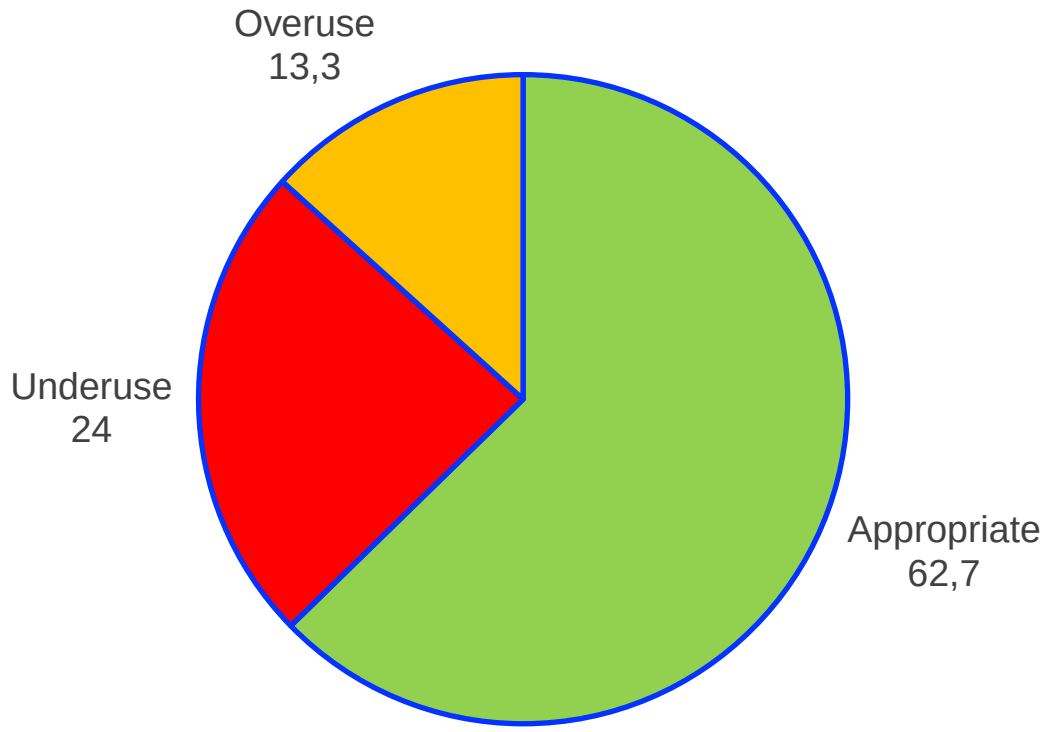
Statin therapy in multimorbid older patients with polypharmacy- a cross-sectional analysis of the Swiss OPERAM trial population

Appropriateness of statin prescribing in the Swiss OPERAM trial population (N=715; Age: 80 years; Men: 60%)

Primary prevention (N=278)



Secondary prevention (N=437)

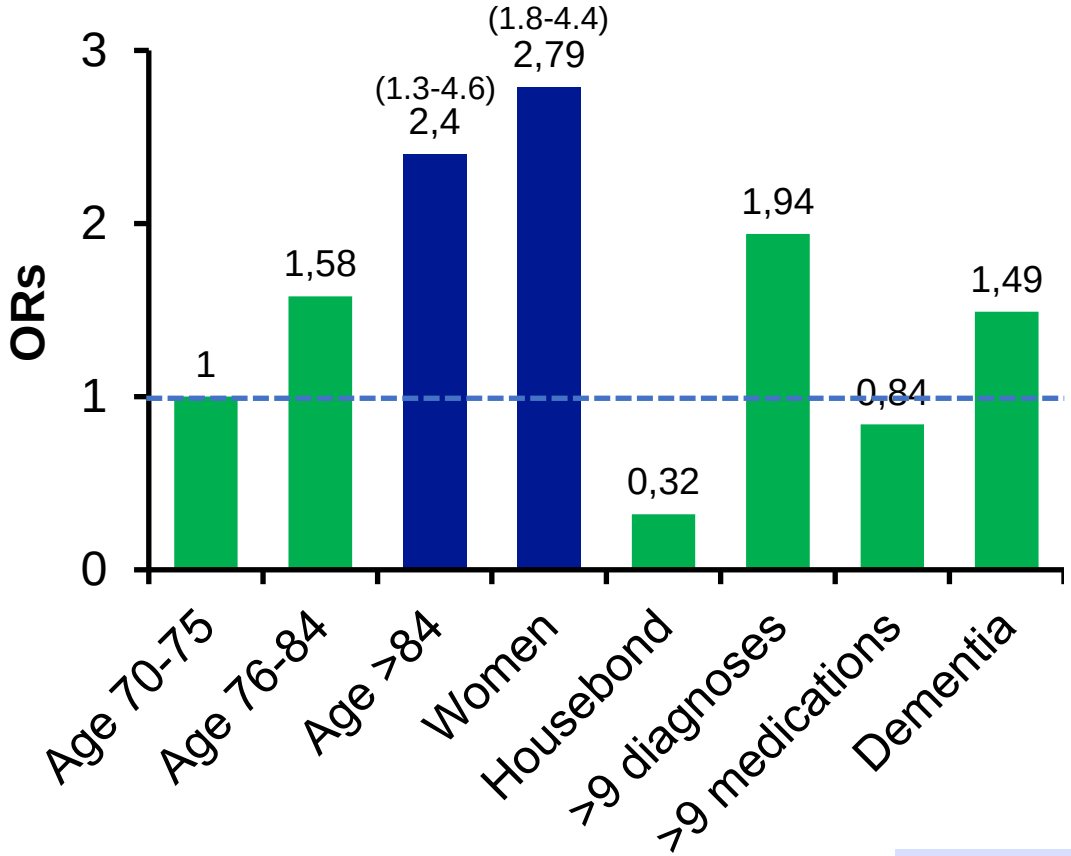


Adam L, Front Cardiovasc Med 2023

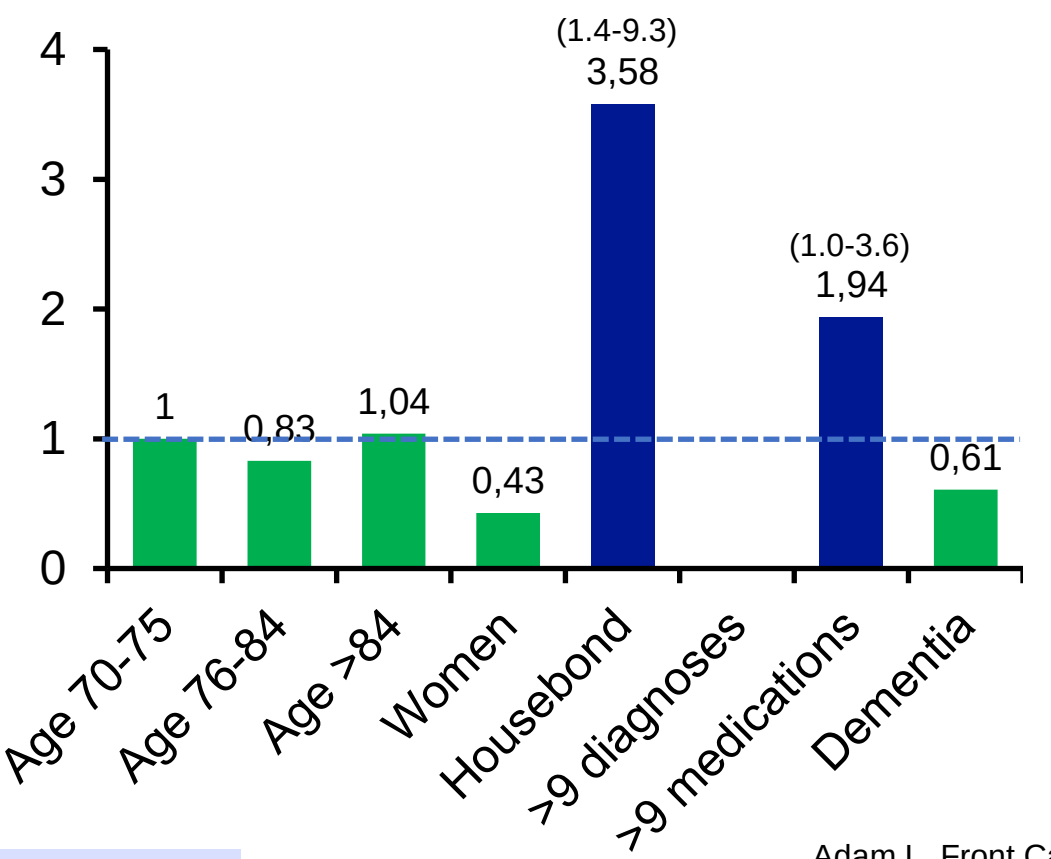
Statin therapy in multimorbid older patients with polypharmacy- a cross-sectional analysis of the Swiss OPERAM trial population

Associations with statin underuse or overuse in secondary prevention

Underuse All patients with CV disease if not taking a statin



Overuse Statin without a formal indication or with a life-limiting disease

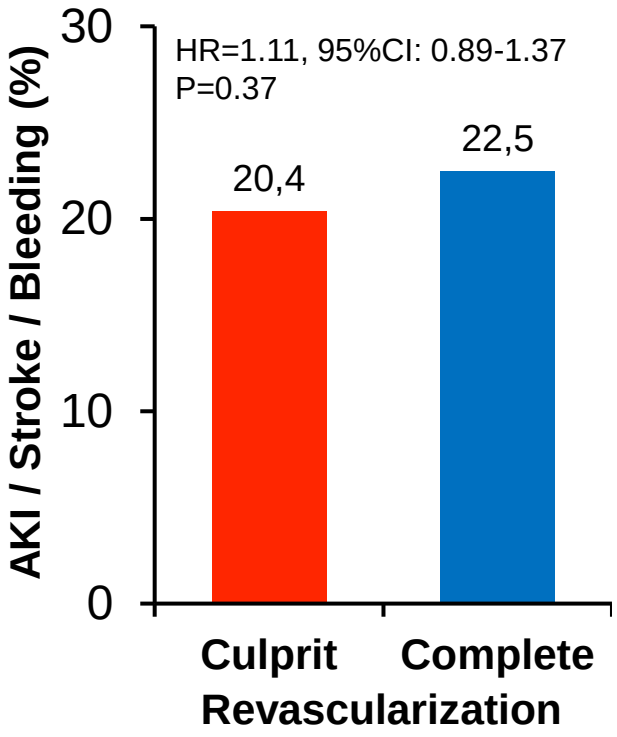


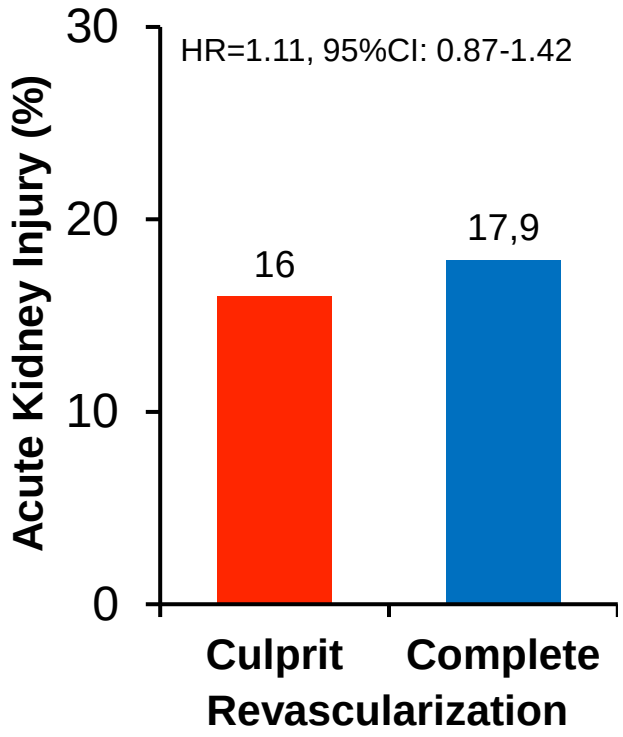
Blue bars indicate statistical significance

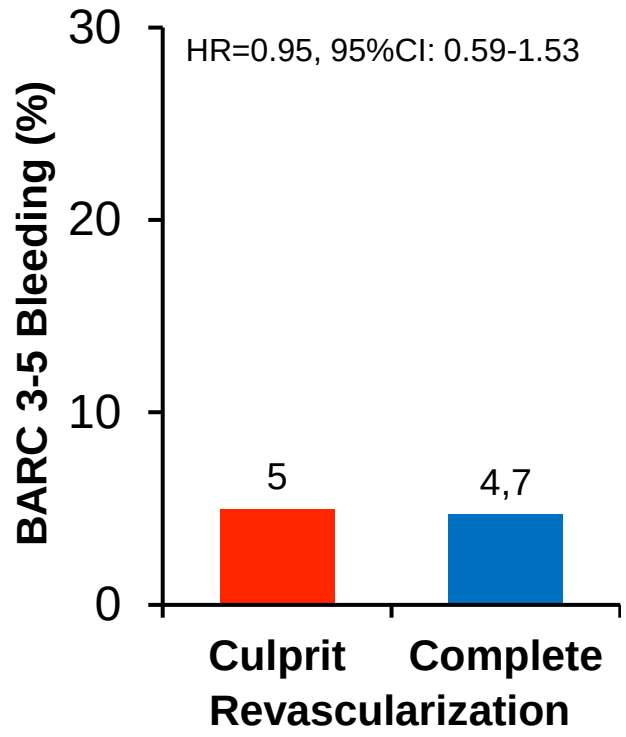
Adam L, Front Cardiovasc Med 2023

Complete or Culprit-Only PCI in Older Patients with Myocardial Infarction

1-year Safety Outcomes in the FIRE Trial







AKI - contrast-associated acute kidney injury

Bleeding - BARC type 3, 4, or 5 bleeding

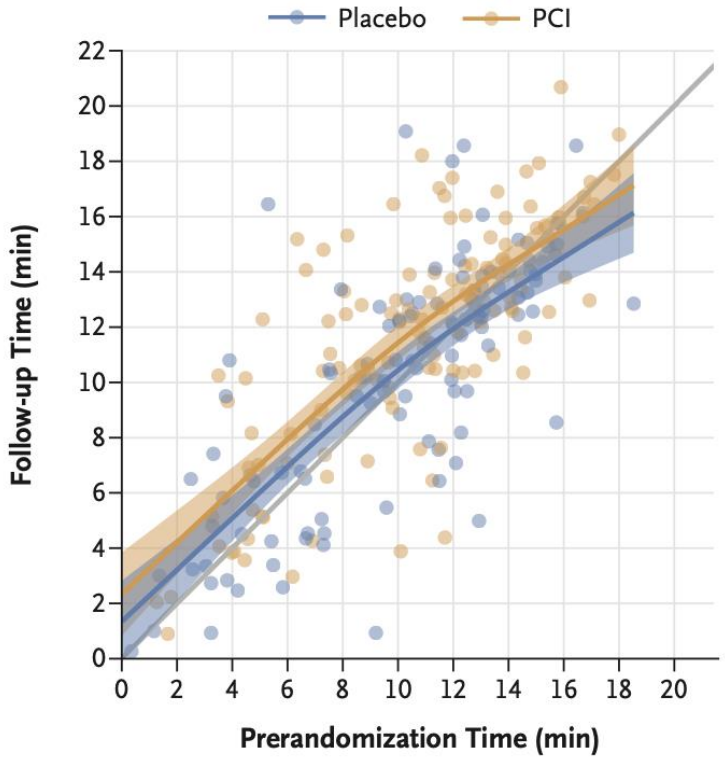
Biscaglia S, NEJM 2023

A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina

Secondary End-Points of the ORBITA-2 trial

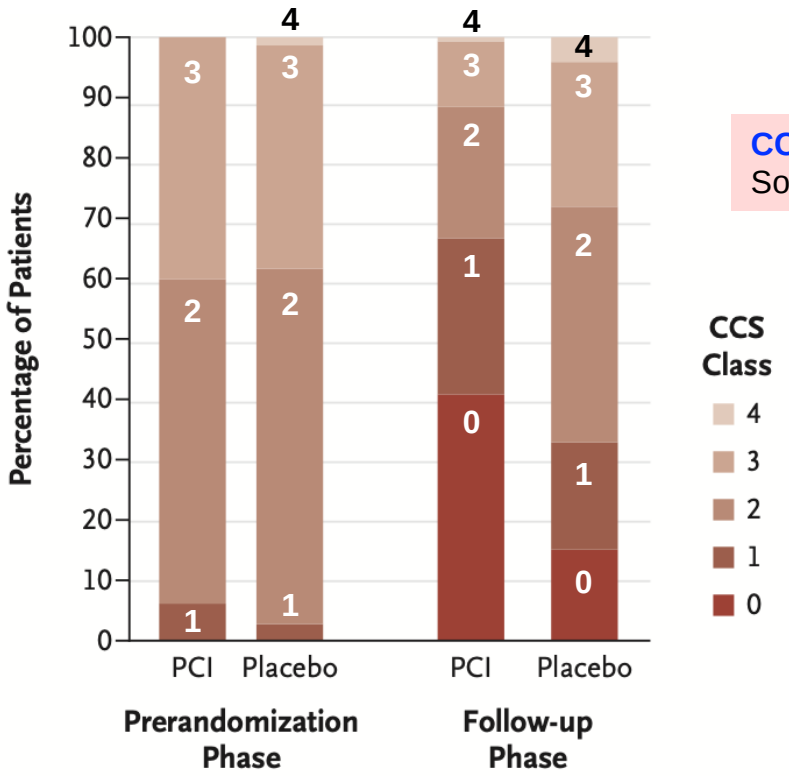
Treadmill Exercise Time

PCI –**701 s** vs. Placebo – **641 s**
Δ=**59**, 95%CI: 16-103



CCS Angina Severity Class

PCI – **0.9** vs. Placebo – N=**1.7**
OR=**3.76**, 95%CI: 2.43-5.82



CCS: Canadian Cardiovascular Society

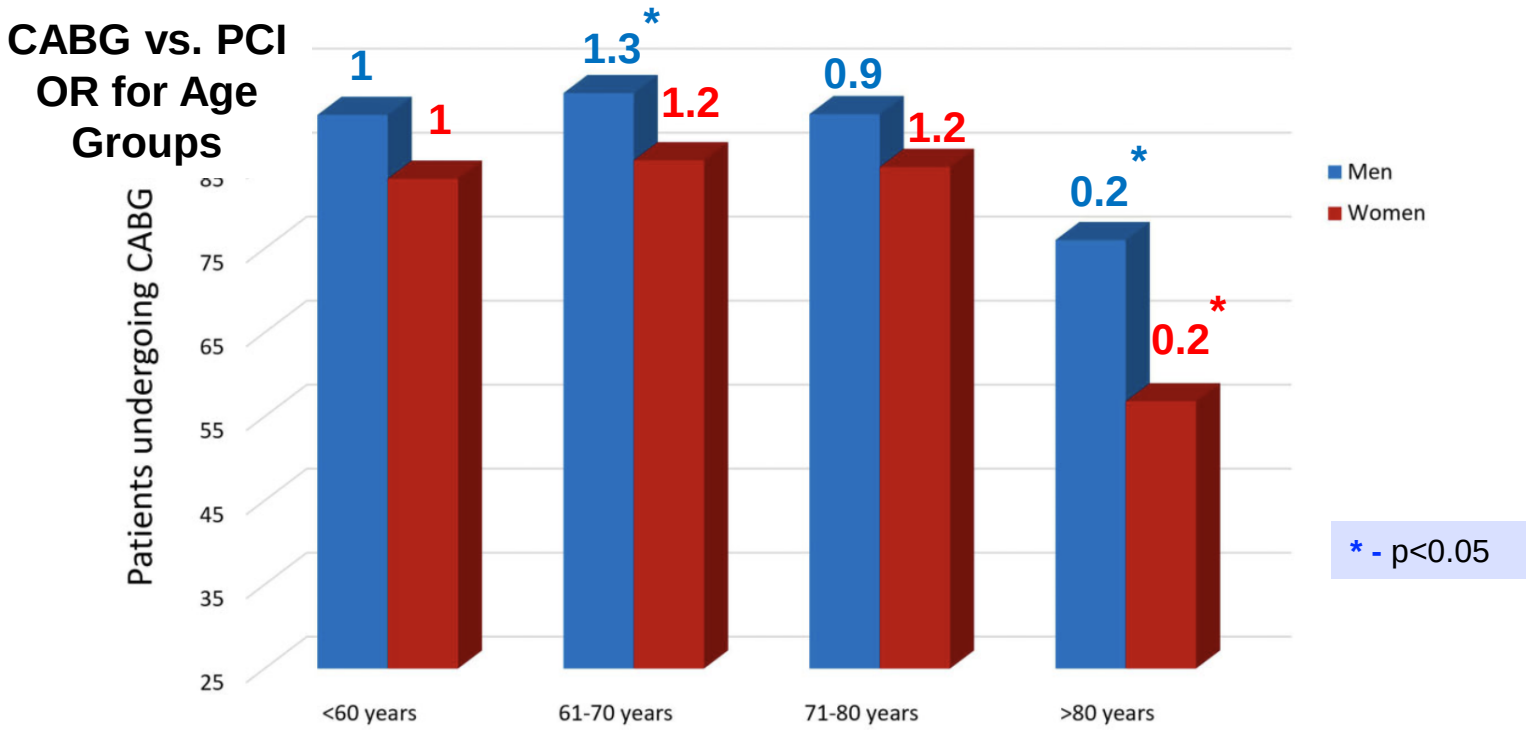
Rajkumar CA,
N Engl J Med 2023

Revascularization strategies for multivessel coronary artery disease based on sex and age

CABG vs. PCI in CCS (the National Inpatient Sample; N=121150; Age: 67; Women: 21.7%; CCS: 60.8%; 2019-20)

CABG vs. PCI - OR for Sex

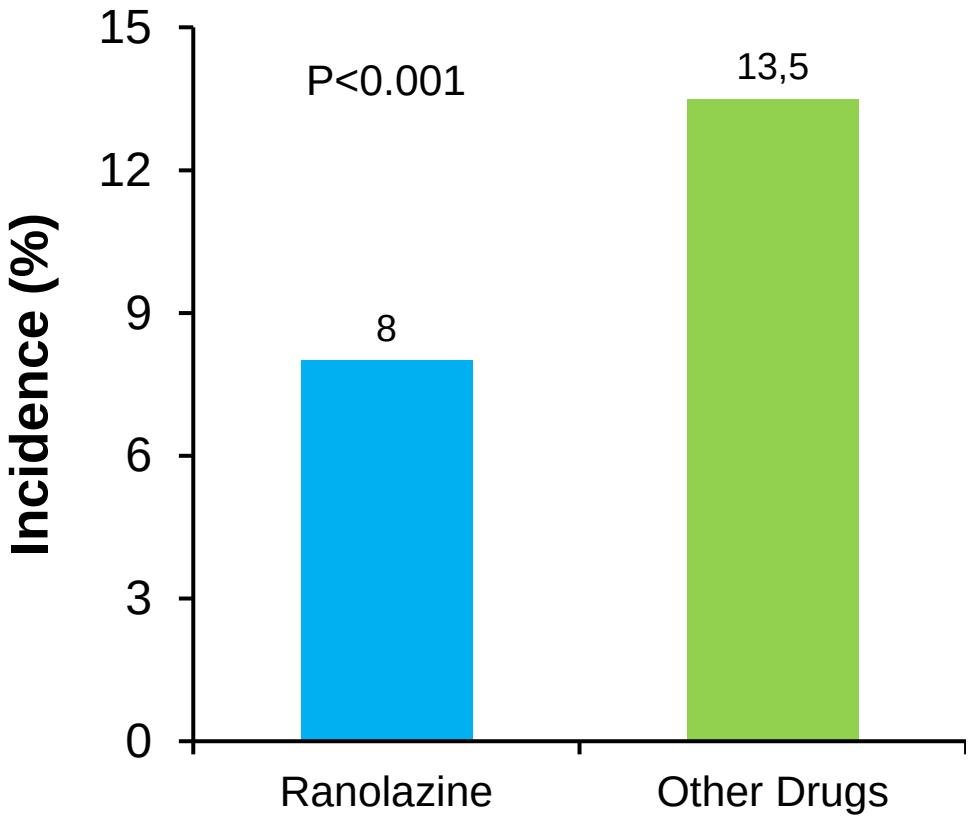
OR=**0.4** 95%CI: 0.3-0.6 | OR=**0.4** 95%CI: 0.3-0.5 | OR=**0.6** 95%CI: 0.4-0.8 | OR=**0.2** 95%CI: 0.1-0.4



Sulaiman S,
Eur J Cardiothorac Surg
2023

RESULTS – PRIMARY OUTCOME
INCIDENCE OF HEART FAILURE BY RANOLAZINE THERAPY

Heart Failure – ALL CASES

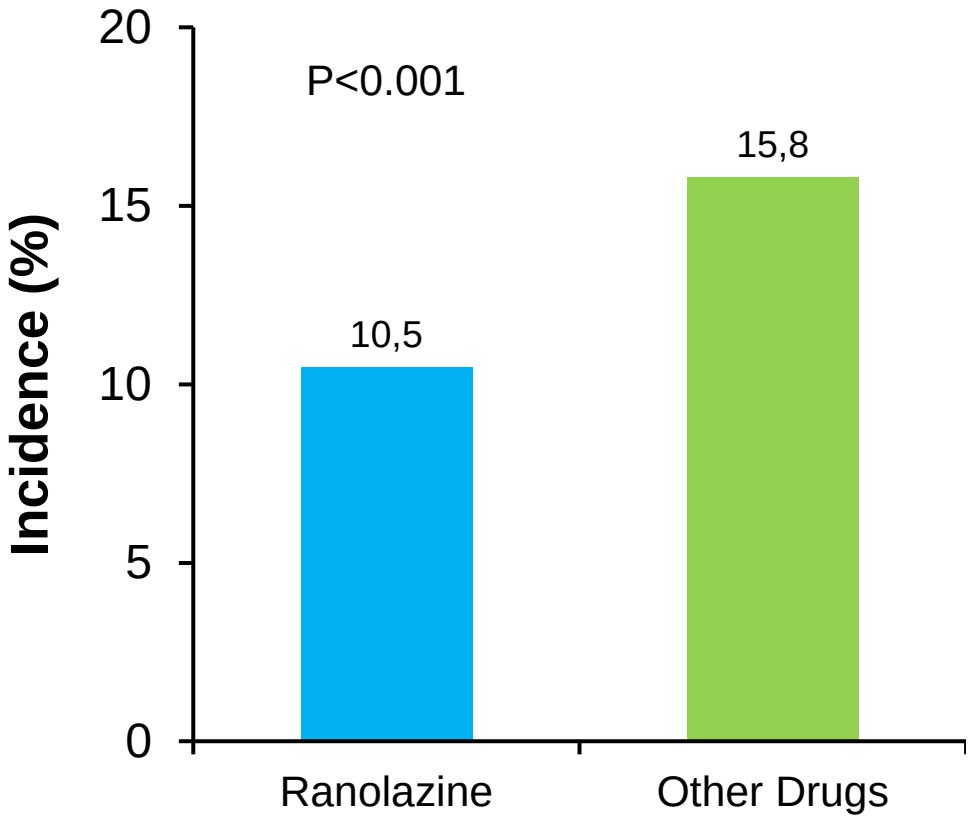


	HR	95% CI		p
Ranolazine cohort	**0.60**	**0.55**	**0.67**	**<0.001**
Men	**1.18**	**1.10**	**1.27**	**<0.001**
Age	**1.06**	**1.06**	**1.06**	**<0.001**
Charlson index	**1.05**	**1.00**	**1.11**	**0.037**
Dyslipidemia	**0.86**	**0.78**	**0.95**	**0.004**
Diabetes	**1.45**	**1.23**	**1.70**	**<0.001**
Atrial fibrillation	**1.78**	**1.61**	**1.96**	**<0.001**
AMI	**1.37**	**1.28**	**1.48**	**<0.001**
Hypertension	1.21	0.99	1.48	0.064
Stroke	0.97	0.87	1.07	0.542
Renal failure	**1.54**	**1.37**	**1.73**	**<0.001**
COPD	**1.32**	**1.21**	**1.43**	**<0.001**
Tumors	1.07	0.93	1.22	0.369
Cardiovascular procedures	**0.89**	**0.83**	**0.96**	**0.001**
Ivabradine	**1.80**	**1.58**	**2.05**	**<0.001**
ASA	0.99	0.92	1.06	0.799
Beta blockers	**1.16**	**1.08**	**1.26**	**<0.001**
Calcium antagonists	0.94	0.87	1.02	0.115
Nitrates	**1.27**	**1.18**	**1.37**	**<0.001**

NOTE: Patients with previous heart failure were excluded

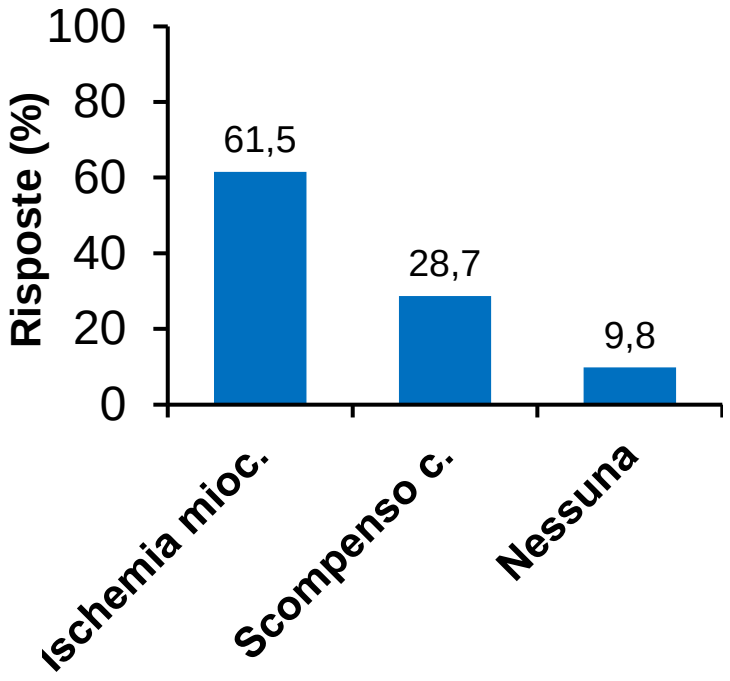
RESULTS – PRIMARY OUTCOME
NEW OCCURRENCE OF DIABETES BY RANOLAZINE THERAPY

Diabetes – ALL CASES

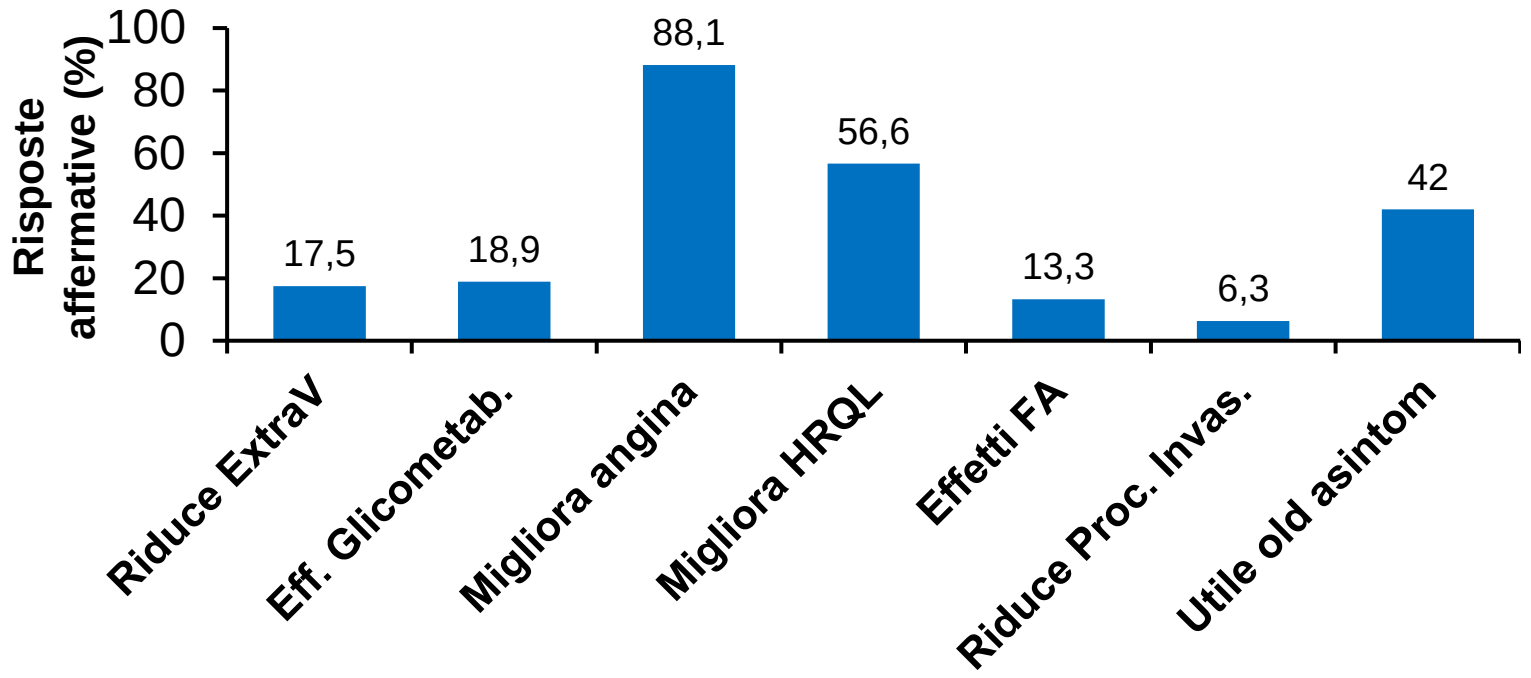


	HR	95% CI		p
Ranolazine cohort	**0.70**	**0.64**	**0.76**	**<0.001**
Men	1.05	0.98	1.12	0.156
Age	**0.99**	**0.99**	**1.00**	**<0.001**
Charlson index	**1.08**	**1.04**	**1.13**	**0.001**
Dyslipidemia	0.95	0.86	1.05	0.302
Atrial Fibrillation	0.97	0.87	1.08	0.584
Heart Failure	**1.23**	**1.12**	**1.35**	**<0.001**
AMI	**1.10**	**1.03**	**1.17**	**0.003**
Hypertension	0.89	0.76	1.05	0.163
Stroke	**1.14**	**1.04**	**1.25**	**0.007**
Renal failure	0.99	0.87	1.12	0.866
COPD	1.01	0.94	1.10	0.720
Tumors	0.91	0.79	1.05	0.185
Cardiovascular procedures	1.03	0.97	1.10	0.305
Ivabradine	**1.14**	**1.01**	**1.29**	**0.039**
ASA	0.99	0.93	1.06	0.859
Beta blockers	1.05	0.98	1.13	0.136
Calcium antagonists	**1.23**	**1.15**	**1.32**	**<0.001**
Nitrates	**1.26**	**1.18**	**1.35**	**<0.001**

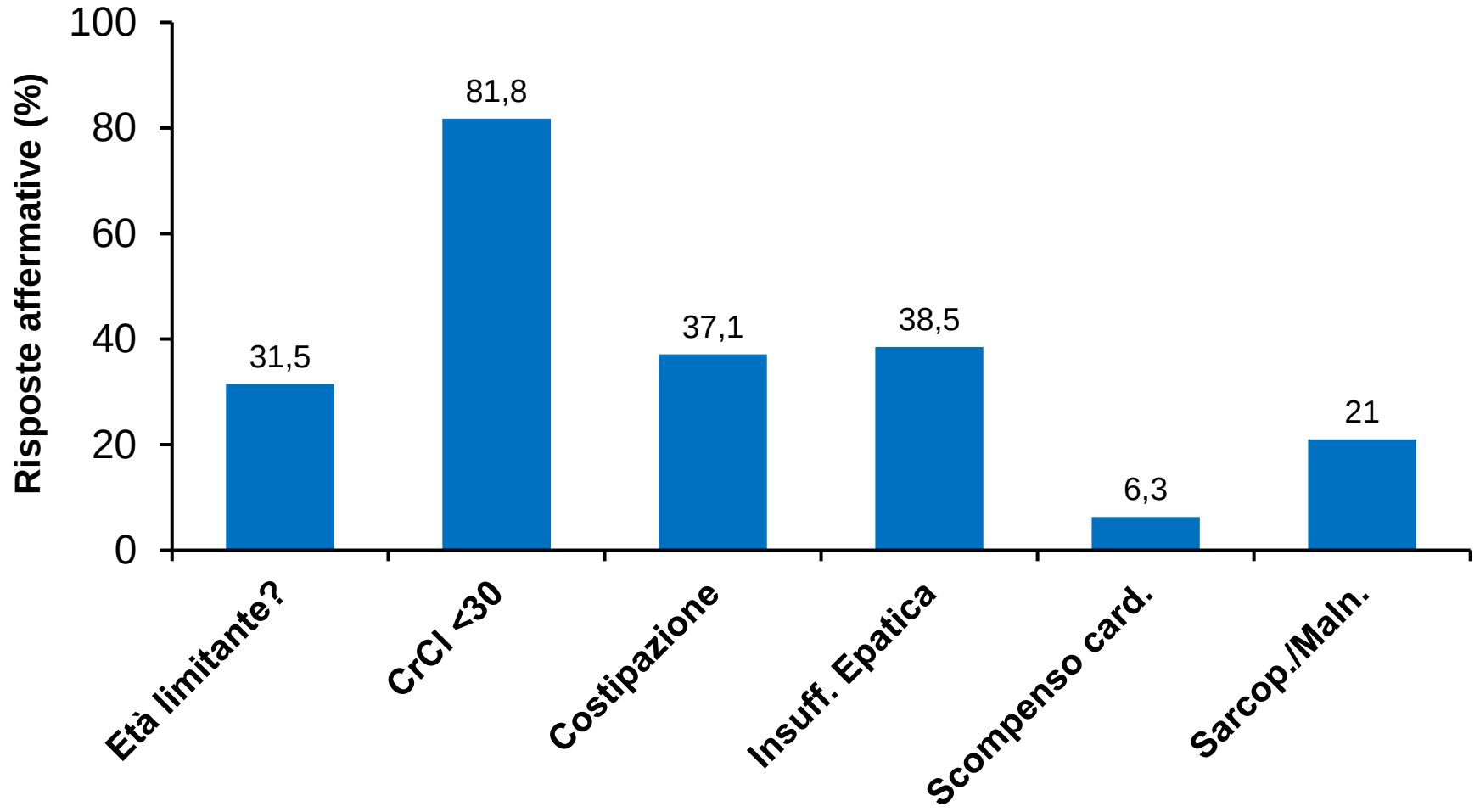
NOTE: Patients with previous diagnosis of diabetes were excluded



In quali situazioni la corrente tardiva del sodio ha attività aumentata?



Quali sono i benefici di Ranolazina nel paziente anziano con SCC?



Ritieni che l'età avanzata sia limitante?

Quali patologie associate sono fattore limitante all'uso di ranolazina nel paziente anziano con SCC?