



68° CONGRESSO NAZIONALE **SIGG**

Ritorno al futuro

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PALAZZO DEI CONGRESSI



**La Ranolazina si associa ad una ridotta
incidenza di Fibrillazione Atriale nei
pazienti con Sindrome Coronarica Cronica:
i risultati di un'analisi real-word su una
popolazione italiana**



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COS'E' LA RANOLAZINA?



Ranolazina, un derivato piperazinico, è un agente antianginoso che sembra ridurre l'ischemia miocardica attraverso l'inibizione della corrente tardiva del Na⁺ in entrata durante la ripolarizzazione cardiaca.



Nello scompenso cardiaco e nell'ischemia la corrente tardiva I_{Na} nei miociti del ventricolo è aumentata e ciò determina un aumento dell'ingresso di Na⁺.



L'accumulo di Na⁺ porta ad un aumento dello scambio Na⁺/Ca²⁺ in senso inverso e quindi ad un aumento della concentrazione di Ca²⁺ citosolico.



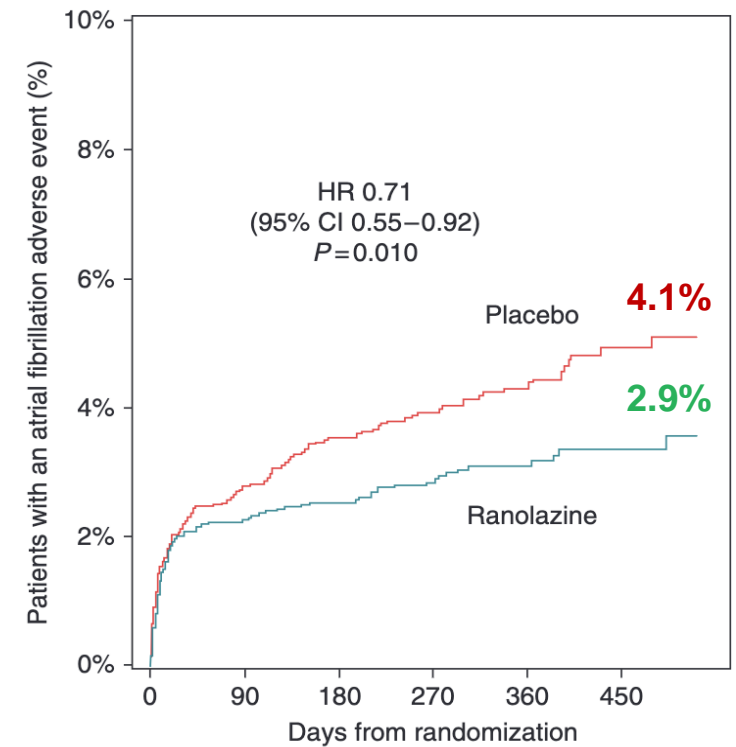
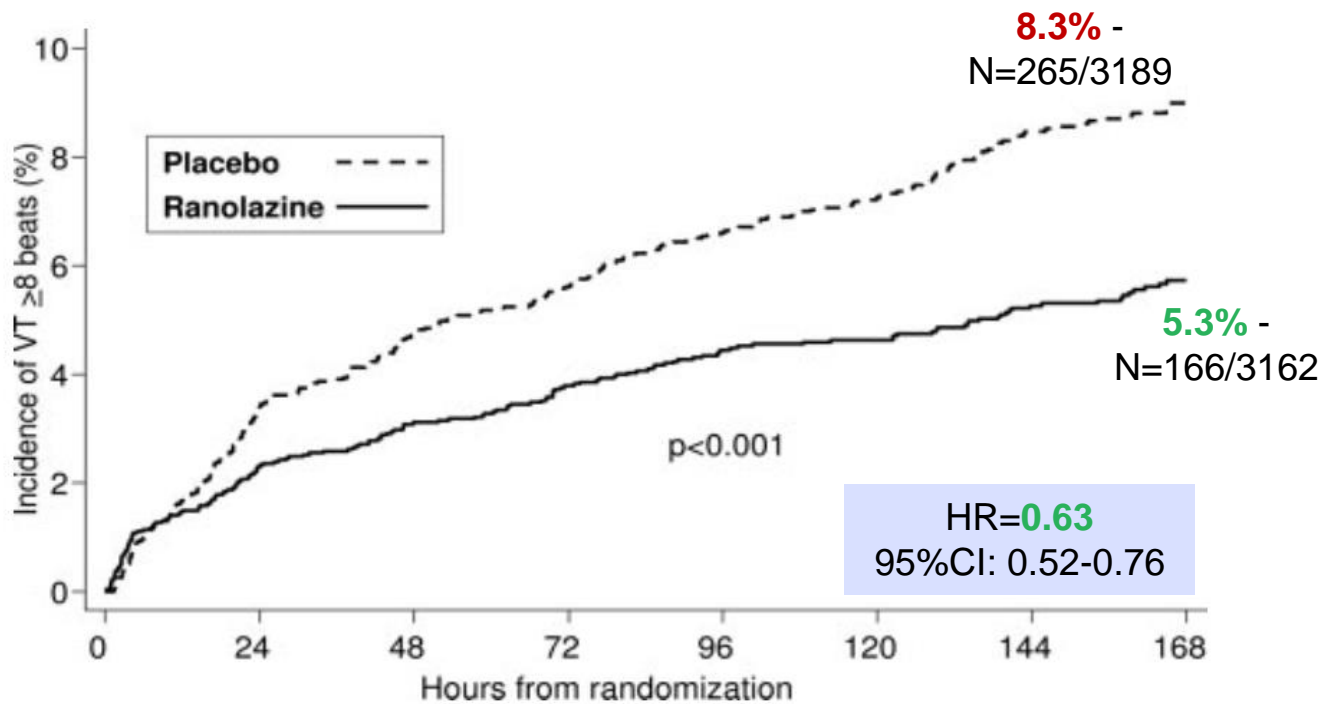
L'aumento del Ca²⁺ intracellulare nei miociti ventricolari può compromettere il rilassamento meccanico e promuovere l'instabilità elettrica prolungando il potenziale d'azione cardiaco e/o provocando il rilascio spontaneo di Ca²⁺ dal reticolo sarcoplasmatico.



Questi eventi forniscono sia il substrato, la dispersione della ripolarizzazione trans-miocardica, sia i fattori scatenanti, la ripolarizzazione precoce e tardiva, per sviluppare potenziali aritmie ventricolari.



Effect of ranolazine on atrial fibrillation in patients with non-ST elevation acute coronary syndromes: observations from the MERLIN-TIMI 36 trial



remains important. The possible anti-arrhythmic effects of ranolazine warrant additional investigation.

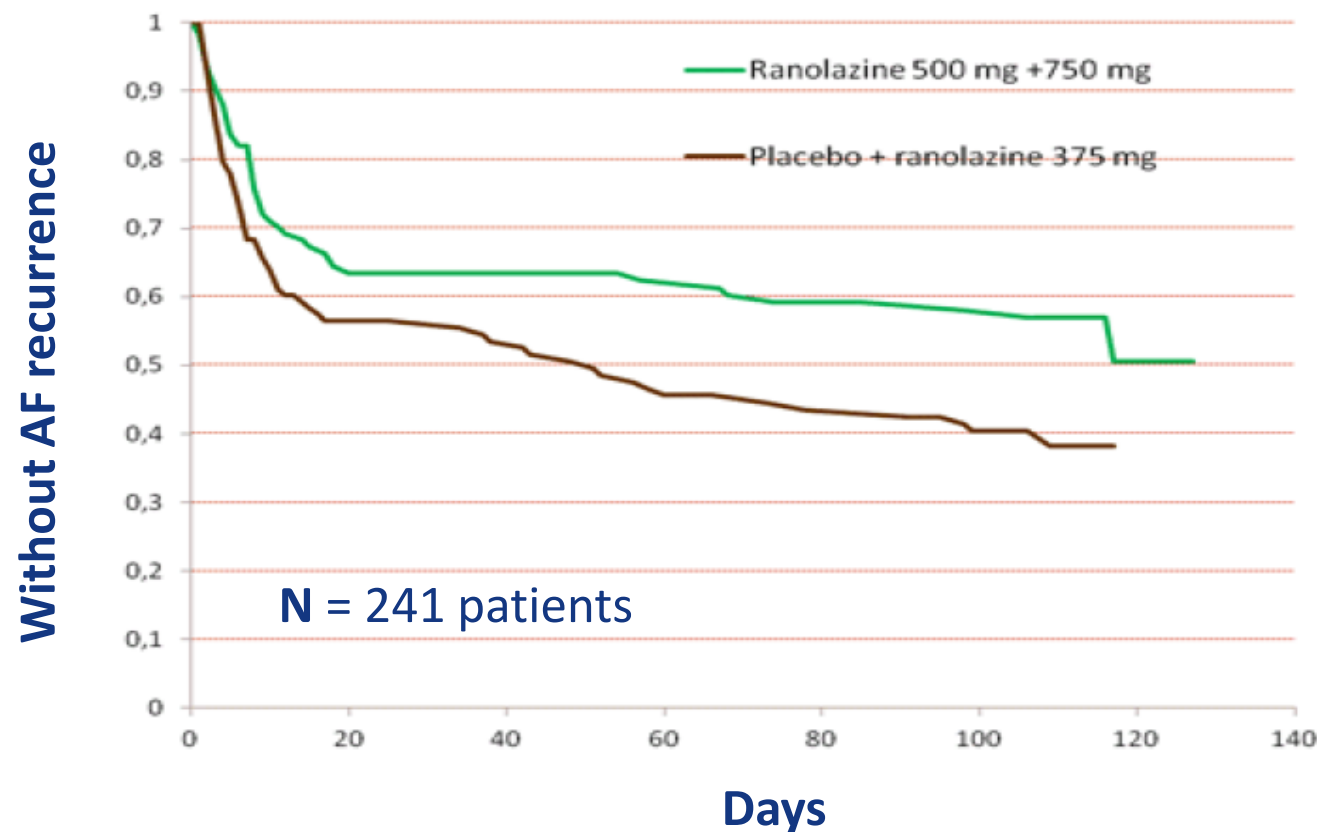


Ranolazine in the treatment of atrial fibrillation: Results of the dose-ranging RAFFAELLO (Ranolazine in Atrial Fibrillation Following An Electrical Cardioversion) study

Recidive tardive (>14 gg)

RR=0.51,
95%CI (0.25-1.00), p=0.03

I bloccanti della corrente tardiva del Na⁺, riducendo i *trigger*, potrebbero rappresentare un **nuovo strumento** contro la fibrillazione atriale.





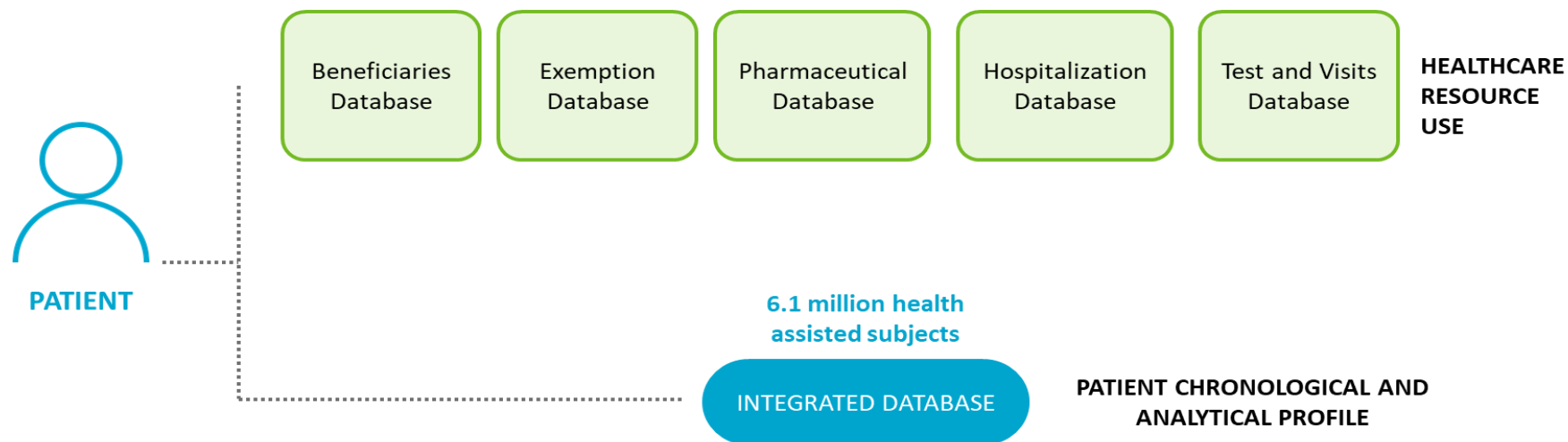
OBIETTIVI DELL'ANALISI



Valutare se i pazienti con angina trattati con ranolazina hanno un rischio ridotto si sviluppare eventi clinici (fibrillazione atriale, diabete mellito, eventi e procedure cardiovascolari, scompenso cardiaco, morte) in un contesto real-world.

DATA SOURCE

ADMINISTRATIVE DATABASES





METHODS

GEOGRAPHICAL DISTRIBUTION OF PATIENTS



About **6 million** of health-assisted individuals were screened:

- **14%** from Northern Italy
- **42%** from Center Italy
- **48%** from Southern Italy

For the current analysis, Italian Entities databases were selected **by their geographical distribution** (Northern / Center / Southern Italy), **by data completeness**, and **by the duration period of data availability**



METHODS

STUDY DESIGN AND STUDY POPULATION



HEALTH-ASSISTED
INDIVIDUALS
N= 6.1 M

INCLUSION CRITERIA FOR ANGINA PATIENTS

Patients with **chronic coronary syndrome** were identified by the hospitalization discharge diagnosis ICD-9-CM codes 413-414 during all available period *before the first prescription of medications*

Patients were assigned to one of the two mutually exclusive cohorts



RANOLAZINE COHORT

Patients with at least one prescription of **RANOLAZINE** (ATC code: C01EB18) during study period (**2010-2020**)



OTHER TREATMENT COHORT

Patients with at least one prescription of **OTHER MEDICATIONS** indicated: **Beta blocking agents** (ATC code: C07), **Calcium channel blockers** (ATC code: C08), **Nitrates** (ATC code: C01DA), **Acetylsalicylic acid** (low-dose, ATC code: B01AC06), **Nicorandil** (ATC code: C01DX16), **Ivabradine** (ATC code: C01EB17)

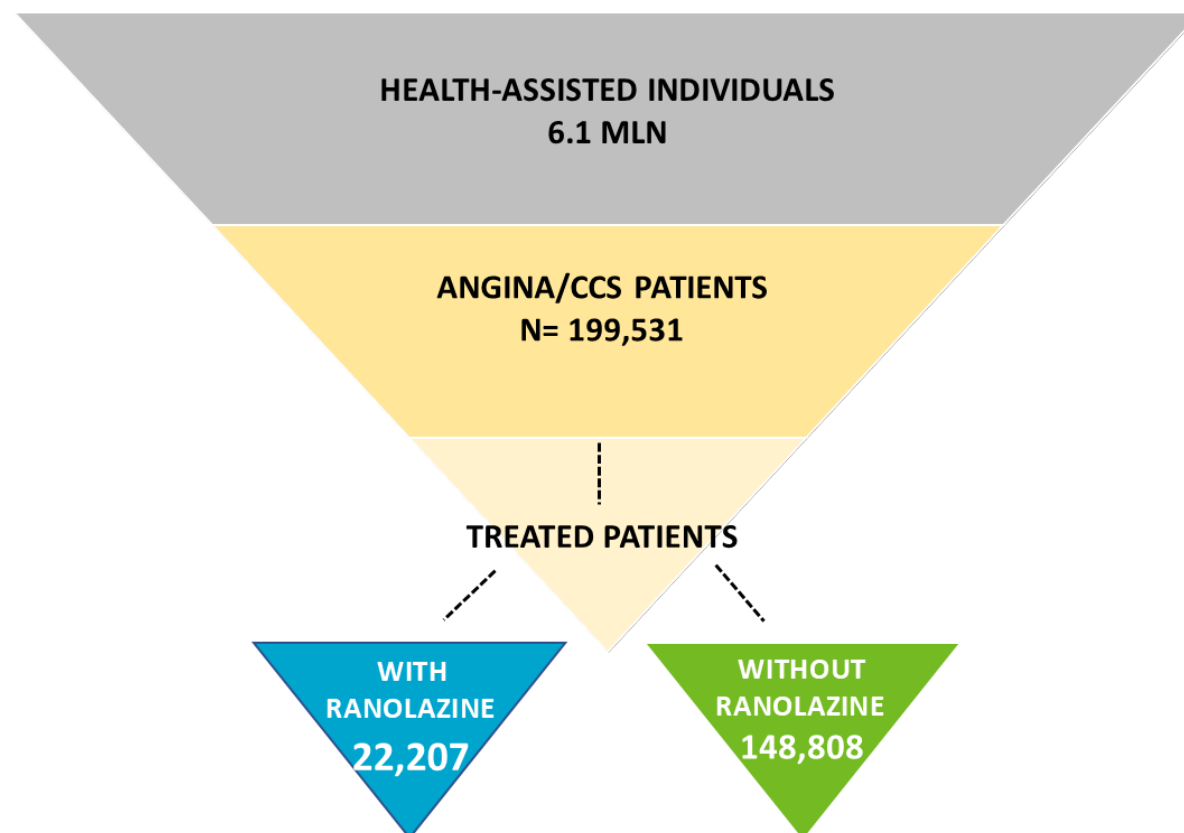
Index-date: date of first prescription of RANOLAZINE or OTHER TREATMENT during **inclusion period (Jan 2011-Dec 2020)**

Characterization period: all available period **before the index-date** (at least 12 months)

Follow-up period: all available period after the index-date (**at least 12 months**)



RESULTS-STUDY POPULATION FLOW-CHART FOR PATIENTS IDENTIFICATION





RESULTS –BASELINE CHARACTERISTICS

BASELINE CHARACTERISTICS AMONG THE SUB-GROUPS

	Overall	Ranolazine	Other Drugs	SMD
n	171,015	22,207	148,808	
Follow-up, year (mean, SD)	4.9 (3.1)	4.4 (2.6)	5.0 (3.2)	
Men (n, %)	112,813 (66.0)	15,007 (67.6)	97,806 (65.7)	0.033
Age (mean, SD)	72.0 (11.5)	71.5 (10.4)	72.1 (11.6)	0.058
- Age 18-49 (n, %)	6,197 (3.6)	580 (2.6)	5,617 (3.8)	
- Age 50-59 (n, %)	19,182 (11.2)	2,474 (11.1)	16,708 (11.2)	
- Age 60-64 (n, %)	17,274 (10.1)	2,404 (10.8)	14,870 (10.0)	
- Age 65-69 (n, %)	23,256 (13.6)	3,457 (15.6)	19,799 (13.3)	
- Age 70-74 (n, %)	27,314 (16.0)	3,963 (17.8)	23,351 (15.7)	
- Age 75-79 (n, %)	29,190 (17.1)	4,030 (18.1)	25,160 (16.9)	
- Age 80-84 (n, %)	25,610 (15.0)	3,166 (14.3)	22,444 (15.1)	
- Age 85-89 (n, %)	15,944 (9.3)	1,636 (7.4)	14,308 (9.6)	
- Age 90+ (n, %)	7,048 (4.1)	497 (2.2)	6,551 (4.4)	
Charlson index (mean, SD)	1.3 (1.4)	1.2 (1.2)	1.3 (1.4)	0.044
Charlson 0 (n, %)	56,612 (33.1)	6,844 (30.8)	49,768 (33.4)	
Charlson 1 (n, %)	57,318 (33.5)	8,166 (36.8)	49,152 (33.0)	
Charlson 2 (n, %)	31,968 (18.7)	4,429 (19.9)	27,539 (18.5)	
Charlson 3+ (n, %)	25,117 (14.7)	2,768 (12.5)	22,349 (15.0)	

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



RESULTS –BASELINE CHARACTERISTICS CLINICAL CHARACTERISTICS AMONG THE SUB-GROUPS

	Overall	Ranolazine	Other Drugs	SMD
n	171,015	22,207	148,808	
Dyslipidemia (n, %)	121,208 (70.9)	19,884 (89.5)	101,324 (68.1)	0.544
Diabetes (n, %)	52,290 (30.6)	8,583 (38.6)	43,707 (29.4)	0.197
Atrial fibrillation (n, %)	25,046 (14.6)	2,519 (11.3)	22,527 (15.1)	0.112
Heart failure (n, %)	30,847 (18.0)	3,929 (17.7)	26,918 (18.1)	0.010
AMI (n, %)	38,549 (22.5)	8,083 (36.4)	30,466 (20.5)	0.359
PAD (n, %)	234 (0.1)	44 (0.2)	190 (0.1)	0.017
Stroke (n, %)	30,660 (17.9)	3,747 (16.9)	26,913 (18.1)	0.032
Renal failure (n, %)	19,715 (11.5)	2,606 (11.7)	17,109 (11.5)	0.007
COPD (n, %)	47,336 (27.7)	6,870 (30.9)	40,466 (27.2)	0.083
Tumors (n, %)	14,438 (8.4)	1,695 (7.6)	12,743 (8.6)	0.034
Total cardiovascular procedures (n, %)	77,809 (45.5)	12,450 (56.1)	65,359 (43.9)	0.245
<i>Myocardial revascularization (n, %)</i>	<i>57,068 (33.4)</i>	<i>10,018 (45.1)</i>	<i>47,050 (31.6)</i>	
<i>Other cardiovascular procedures (n, %)</i>	<i>65,049 (38.0)</i>	<i>10,388 (46.8)</i>	<i>54,661 (36.7)</i>	
Antihypertensives (n, %)	162,003 (94.7)	21,585 (97.2)	140,418 (94.4)	0.141
Ivabradine (n, %)	7,693 (4.5)	1,713 (7.7)	5,980 (4.0)	0.158
ASA (n, %)	109,204 (63.9)	12,947 (58.3)	96,257 (64.7)	0.131
Beta blockers (n, %)	115,365 (67.5)	15,546 (70.0)	99,819 (67.1)	0.063
Calcium antagonists (n, %)	44,403 (26.0)	5,250 (23.6)	39,153 (26.3)	0.062
Nitrates (n, %)	39,752 (23.2)	6,653 (30.0)	33,099 (22.2)	0.176

PAD: Peripheral artery disease (code 443.9)
Antihypertensives: ATC codes C02, C03, C07, C08, C09

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



RESULTS –BASELINE CHARACTERISTICS

BASELINE CHARACTERISTICS AMONG THE SUB-GROUPS, 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)	

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-GROUPS 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

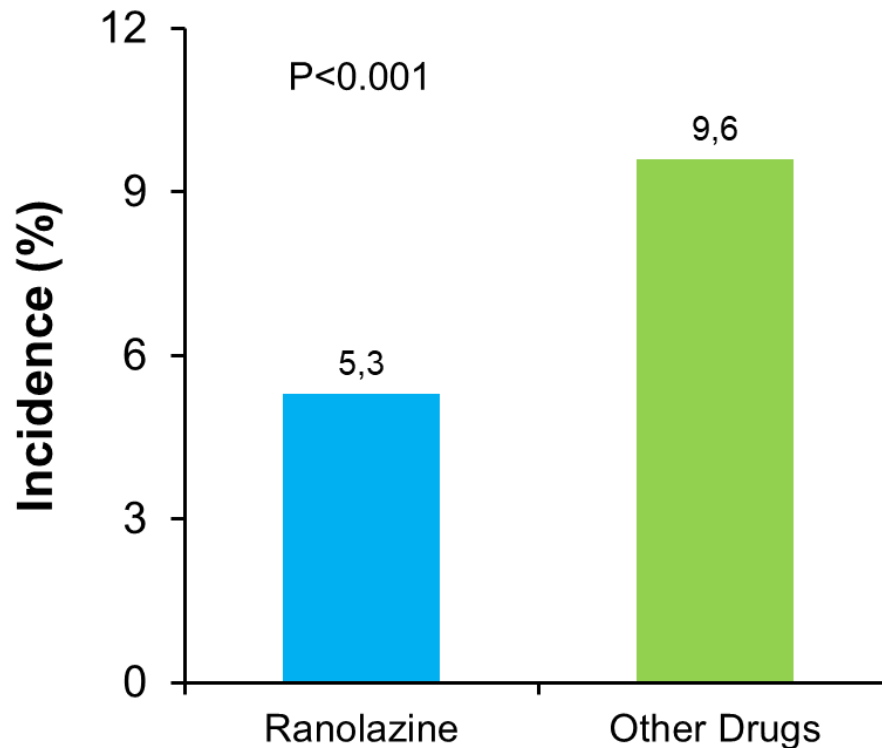
STANDARDIZED MEAN DIFFERENCE - SMD - VALUES BELOW 0.2 INDICATE THAT THE TWO SUB-GROUPS ARE NOT SIGNIFICANTLY DIFFERENT



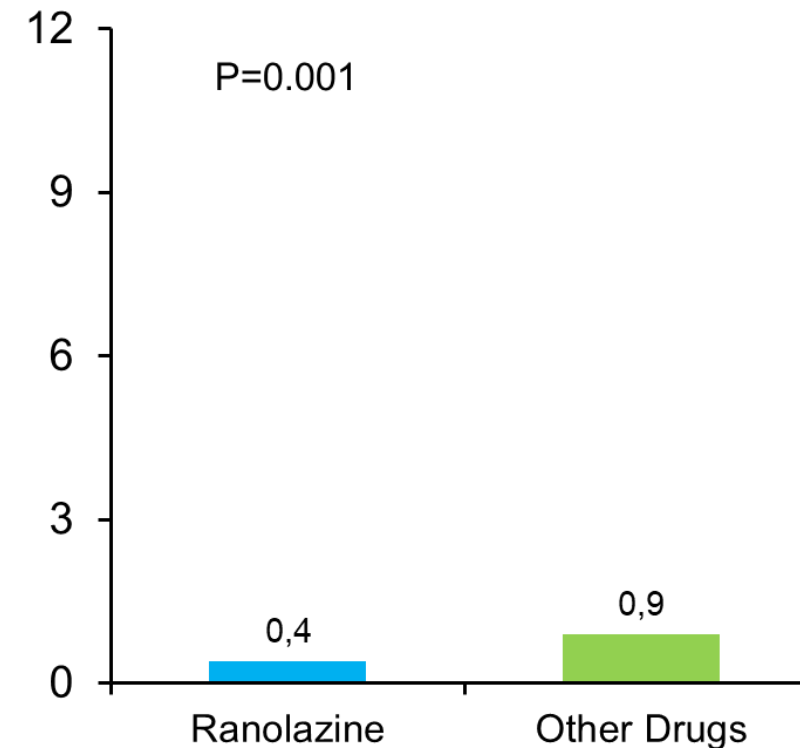
RESULTS

INCIDENCE OF ATRIAL FIBRILLATION BY RANOLAZINE THERAPY

Atrial Fibrillation – ALL CASES



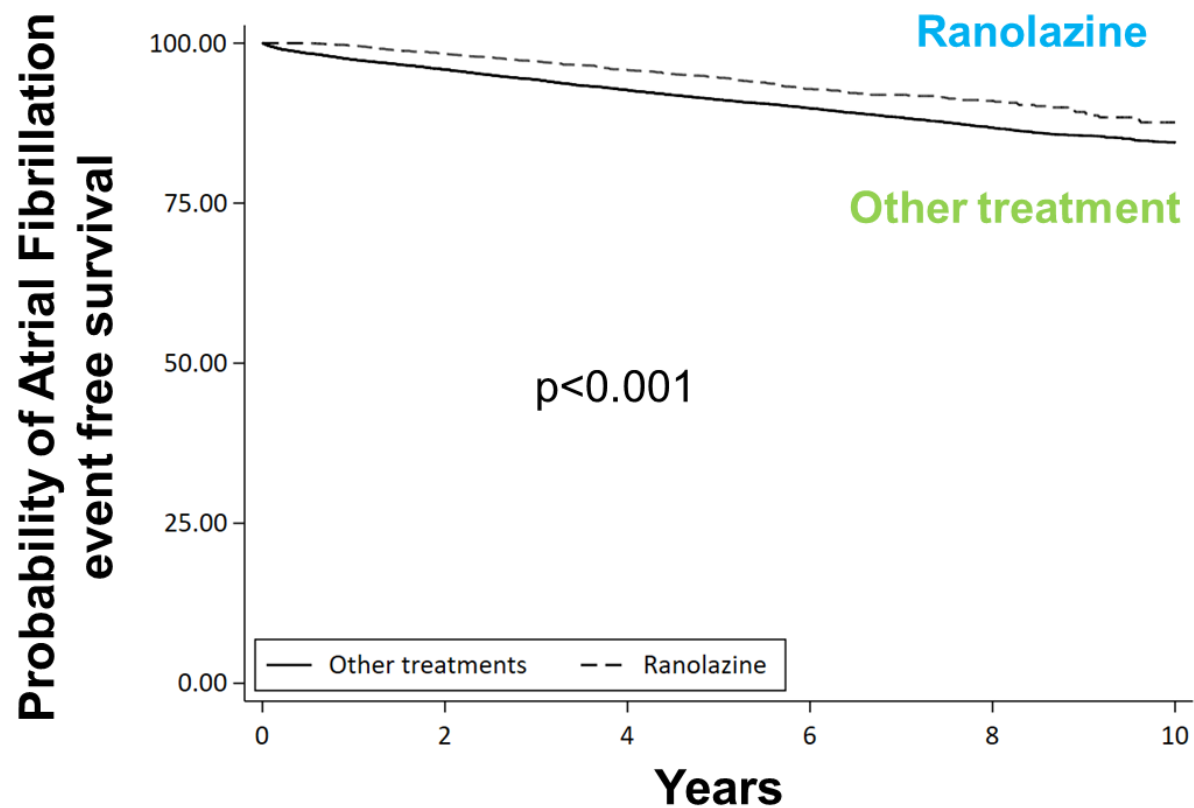
Atrial Fibrillation – CASES ASSOCIATED WITH DEATH





RESULTS

Kaplan-Meier Rates of Atrial Fibrillation Occurrence by Ranolazine Therapy

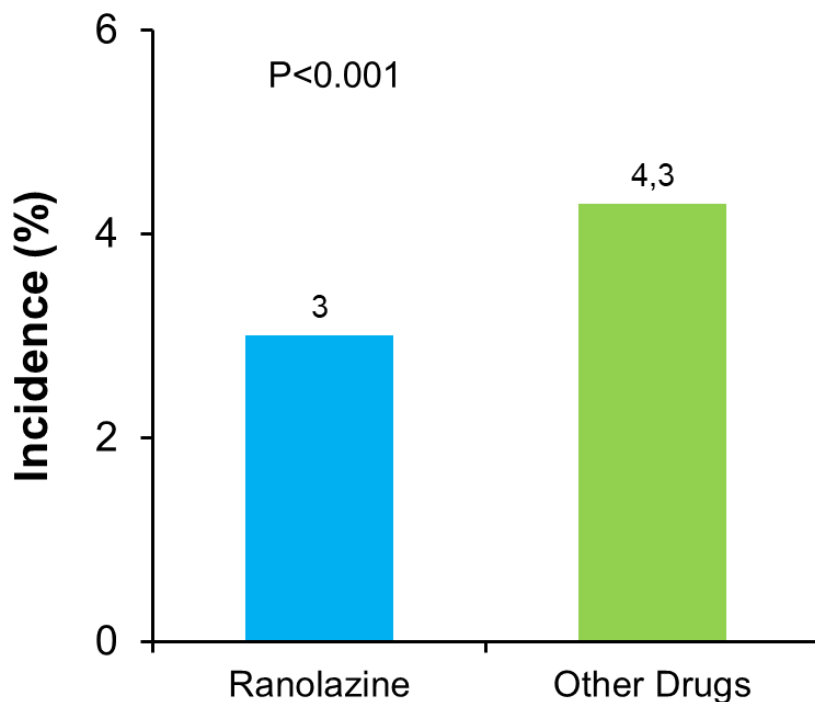




RESULTS – SAFETY OUTCOMES

INCIDENCE OF BRADYARRHYTHMIAS BY RANOLAZINE THERAPY

Bradyarrhythmias – ALL CASES

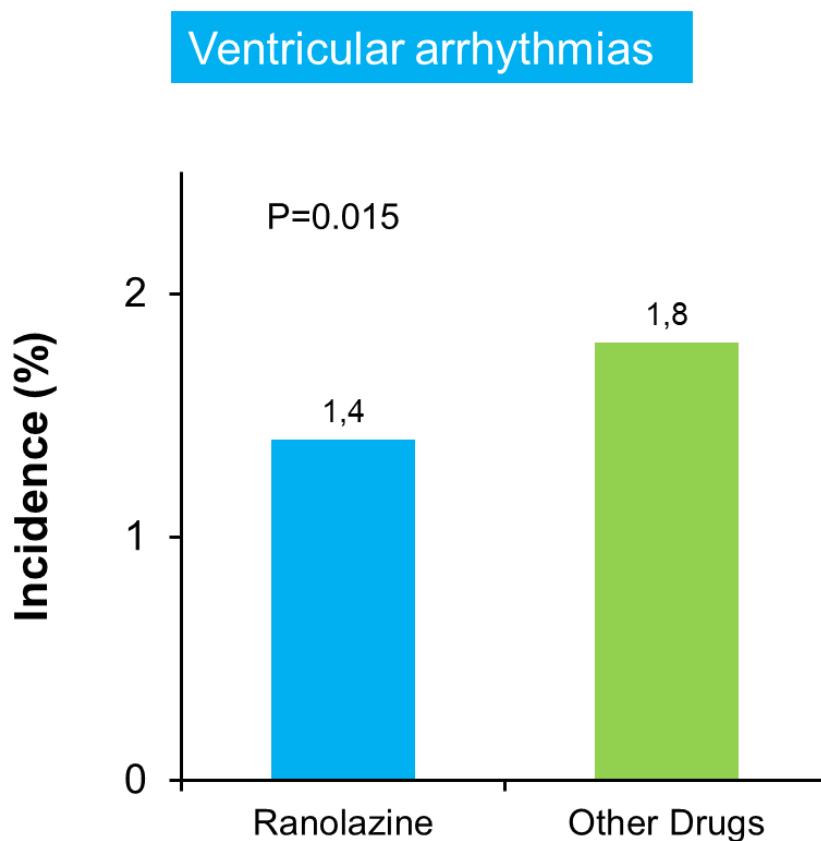


	HR	95% CI		p
Ranolazine cohort	0.76	0.65	0.88	<0.001
Men	1.56	1.37	1.77	<0.001
Age	1.04	1.03	1.04	<0.001
Charlson index	1.09	1.01	1.18	0.035
Dyslipidemia	0.93	0.79	1.11	0.425
Diabetes	1.12	0.84	1.49	0.449
Atrial fibrillation	1.16	0.98	1.38	0.094
Heart failure	2.06	1.79	2.38	<0.001
AMI	1.05	0.93	1.19	0.410
Hypertension	1.09	0.79	1.50	0.597
Stroke	1.01	0.85	1.20	0.894
Renal failure	0.92	0.75	1.14	0.461
COPD	1.00	0.87	1.15	0.978
Tumors	0.85	0.66	1.09	0.194
Cardiovascular procedures	0.89	0.79	1.00	0.052
Ivabradine	1.26	1.01	1.57	0.045
ASA	0.99	0.88	1.12	0.927
Beta blockers	0.97	0.85	1.10	0.589
Calcium antagonists	1.00	0.88	1.15	0.943
Nitrates	1.12	0.99	1.26	0.073



RESULTS – SAFETY OUTCOMES

INCIDENCE OF VENTRICULAR ARRHYTHMIAS BY RANOLAZINE THERAPY



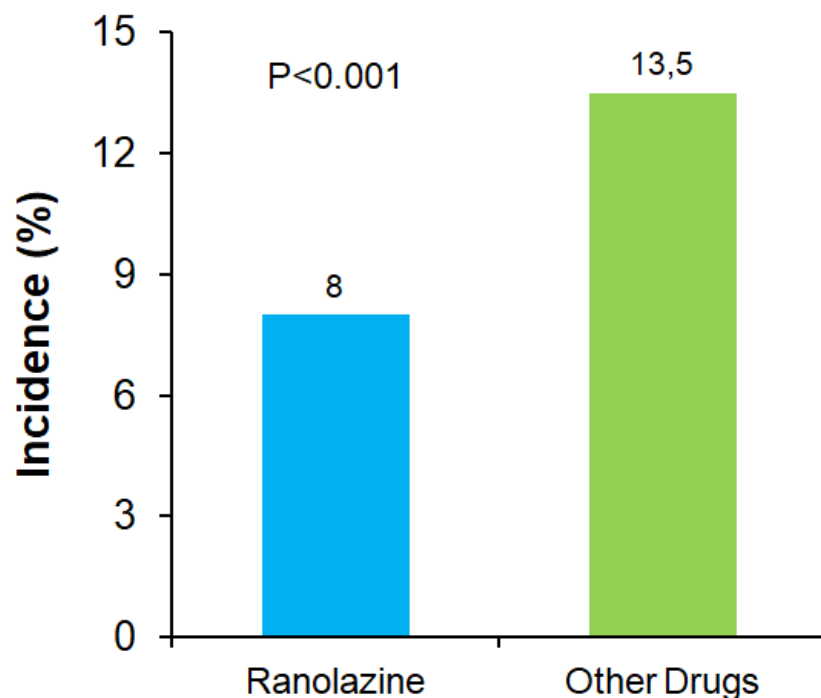
ICD 9 CM codes:
427.1: Paroxysmal VT
427.4: VF / V. Flutter

	HR	95% CI		p
Ranolazine cohort	0.79	0.63	0.99	0.042
Men	3.16	2.45	4.07	<0.001
Age	1.00	1.00	1.01	0.277
Charlson index	0.95	0.83	1.09	0.457
Dyslipidemia	0.88	0.67	1.16	0.363
Diabetes	0.65	0.36	1.18	0.155
Atrial fibrillation	1.38	1.07	1.77	0.013
Heart failure	3.52	2.90	4.27	<0.001
AMI	1.39	1.17	1.66	<0.001
Hypertension	1.21	0.71	2.06	0.478
Stroke	0.73	0.54	1.00	0.051
Renal failure	1.29	0.95	1.76	0.108
COPD	1.15	0.92	1.44	0.225
Tumors	0.77	0.50	1.19	0.236
Cardiovascular procedures	0.99	0.82	1.18	0.872
Ivabradine	1.75	1.32	2.33	<0.001
ASA	0.85	0.71	1.01	0.069
Beta blockers	1.15	0.93	1.41	0.199
Calcium antagonists	0.84	0.67	1.05	0.122
Nitrates	1.29	1.07	1.55	0.008



RESULTS – PRIMARY OUTCOME
INCIDENCE OF HEART FAILURE BY RANOLAZINE THERAPY

Heart Failure – ALL CASES

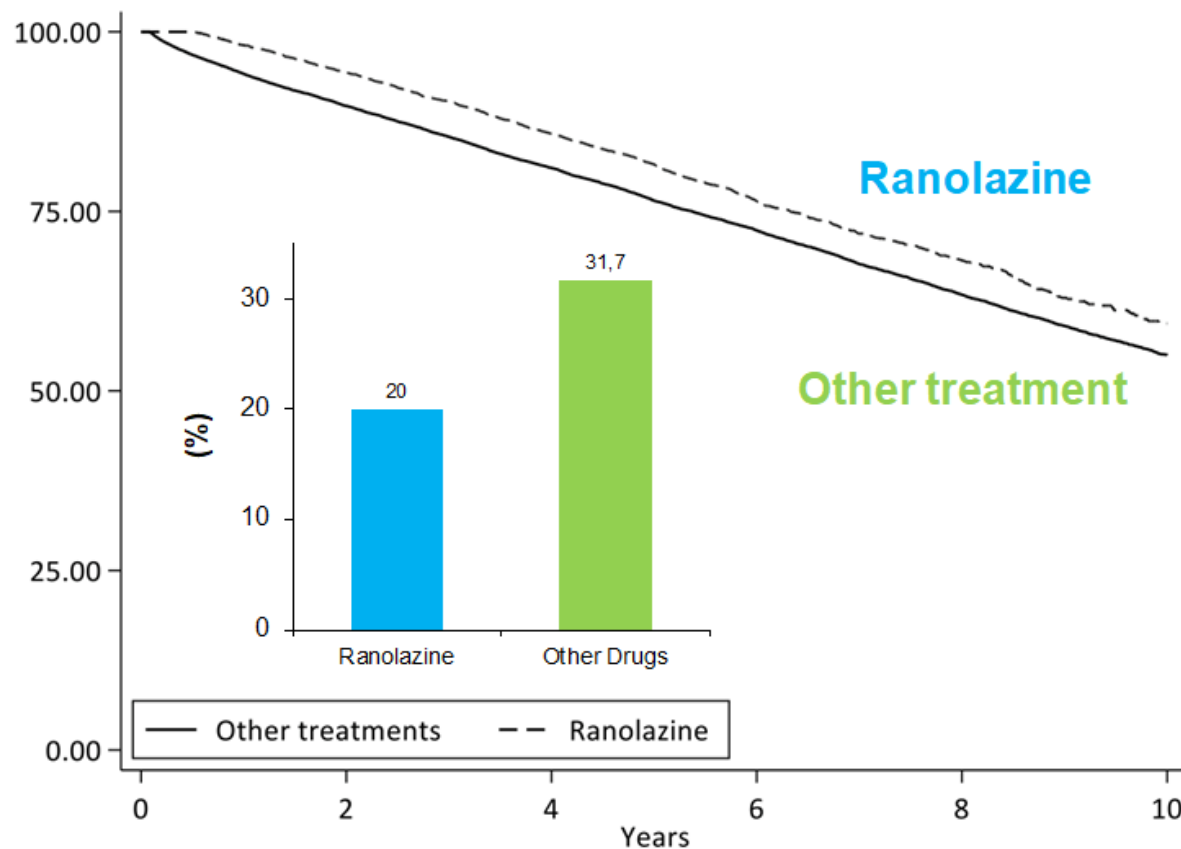


	HR	95% CI		p
Ranolazine cohort	0.60	0.55	0.67	<0.001
Men	1.18	1.10	1.27	<0.001
Age	1.06	1.06	1.06	<0.001
Charlson index	1.05	1.00	1.11	0.037
Dyslipidemia	0.86	0.78	0.95	0.004
Diabetes	1.45	1.23	1.70	<0.001
Atrial fibrillation	1.78	1.61	1.96	<0.001
AMI	1.37	1.28	1.48	<0.001
Hypertension	1.21	0.99	1.48	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 ALL-CAUSE MORTALITY BY RANOLAZINE THERAPY



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

P<0.001



CONCLUSIONI



La presente analisi suggerisce che la Ranolazina possa ridurre significativamente il rischio di sviluppo di fibrillazione atriale in pazienti affetti da sindrome coronarica cronica seguiti in un *follow-up* a lungo termine



L'impiego del farmaco non è stato associato ad una maggiore incidenza di bradiaritmie o di aritmie ventricolari maggiori.



Anche l'incidenza di scompenso cardiaco e la mortalità per tutte le cause sembrano ridotte nei pazienti che trattati con la Ranolazina.



Questi risultati potrebbero rappresentare la base per nuovi studi clinici specifici volti a confermare le proprietà antiaritmiche del farmaco anche in una popolazione non affetta da sindrome coronarica cronica.