PLACE
PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

CONSENSUS CONFERENCE IMPLANTABLE CARDIAC MONITOR: LE NUOVE APPLICAZIONI

Stratificazione del rischio post-IMA: il ruolo del monitoraggio alla luce del BIOGUARD

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Sudden death in patients with MI, LV dysfunction, and HF

The VALIANT Trial

- The overall risk of sudden death increases with a decreasing LVEF.
- It is greatest among patients with the lowest LVEF (≤ 30%), but even patients with a high LVEF (> 40%) are at substantially increased risk in the post-infarction period.

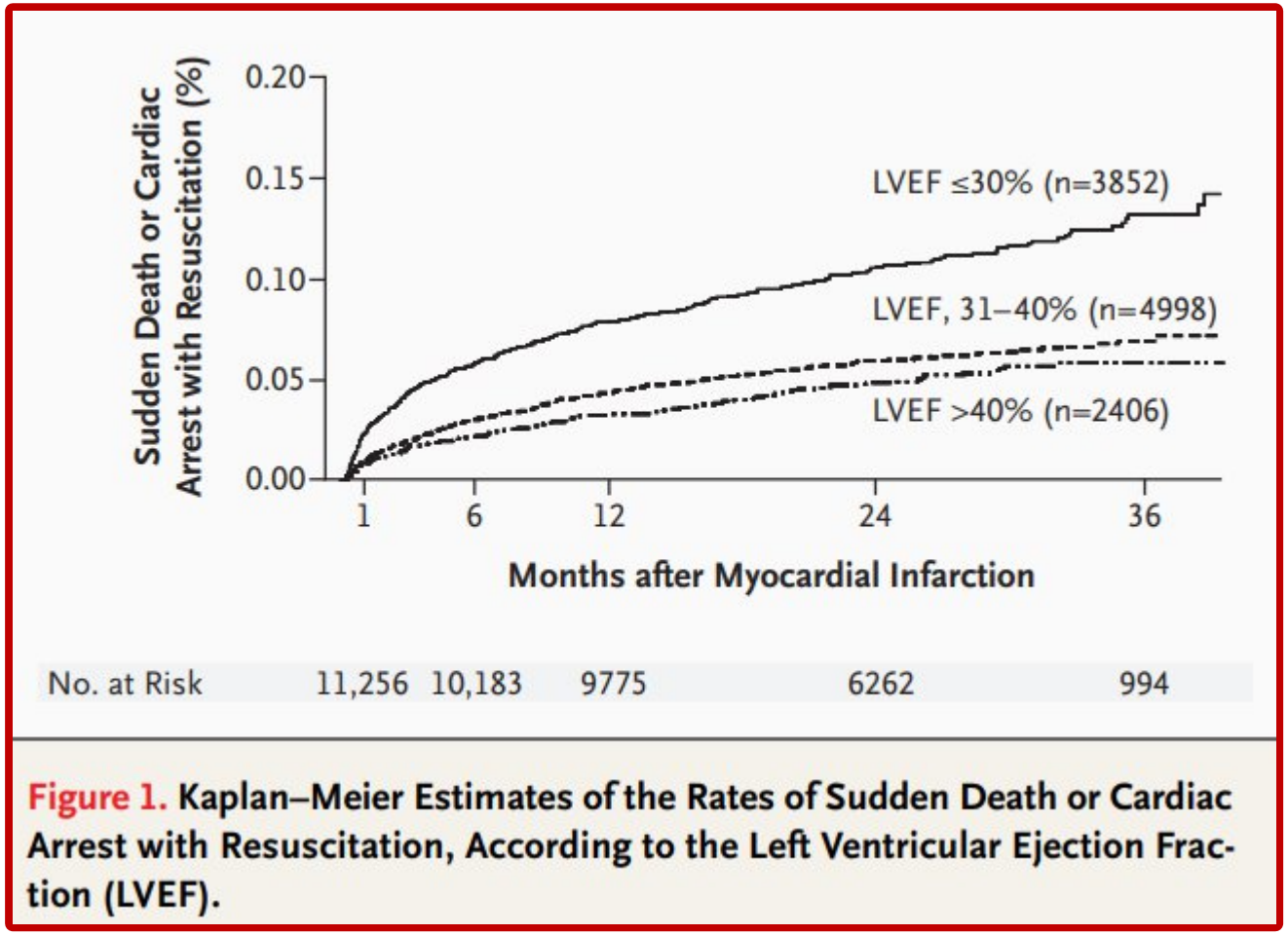


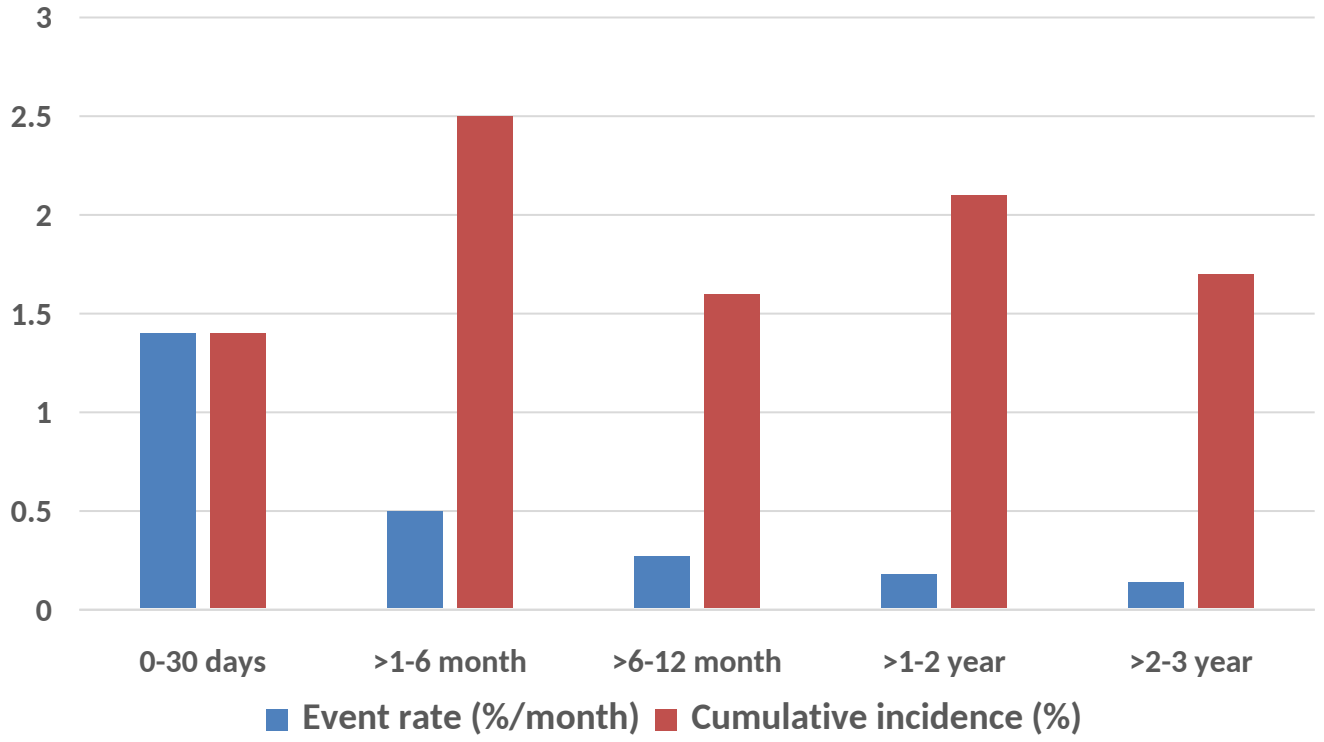
Figure 1. Kaplan–Meier Estimates of the Rates of Sudden Death or Cardiac Arrest with Resuscitation, According to the Left Ventricular Ejection Fraction (LVEF).

1. Solomon SD, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. N Engl J Med. 2005 Jun 23;352(25):2581-8.

Sudden death in patients with MI, LV dysfunction, and HF

The VALIANT Trial

The absolute risk is greatest in the early period after myocardial infarction and declines significantly over time, but cumulative incidence remains high up to 3 years of follow-up.



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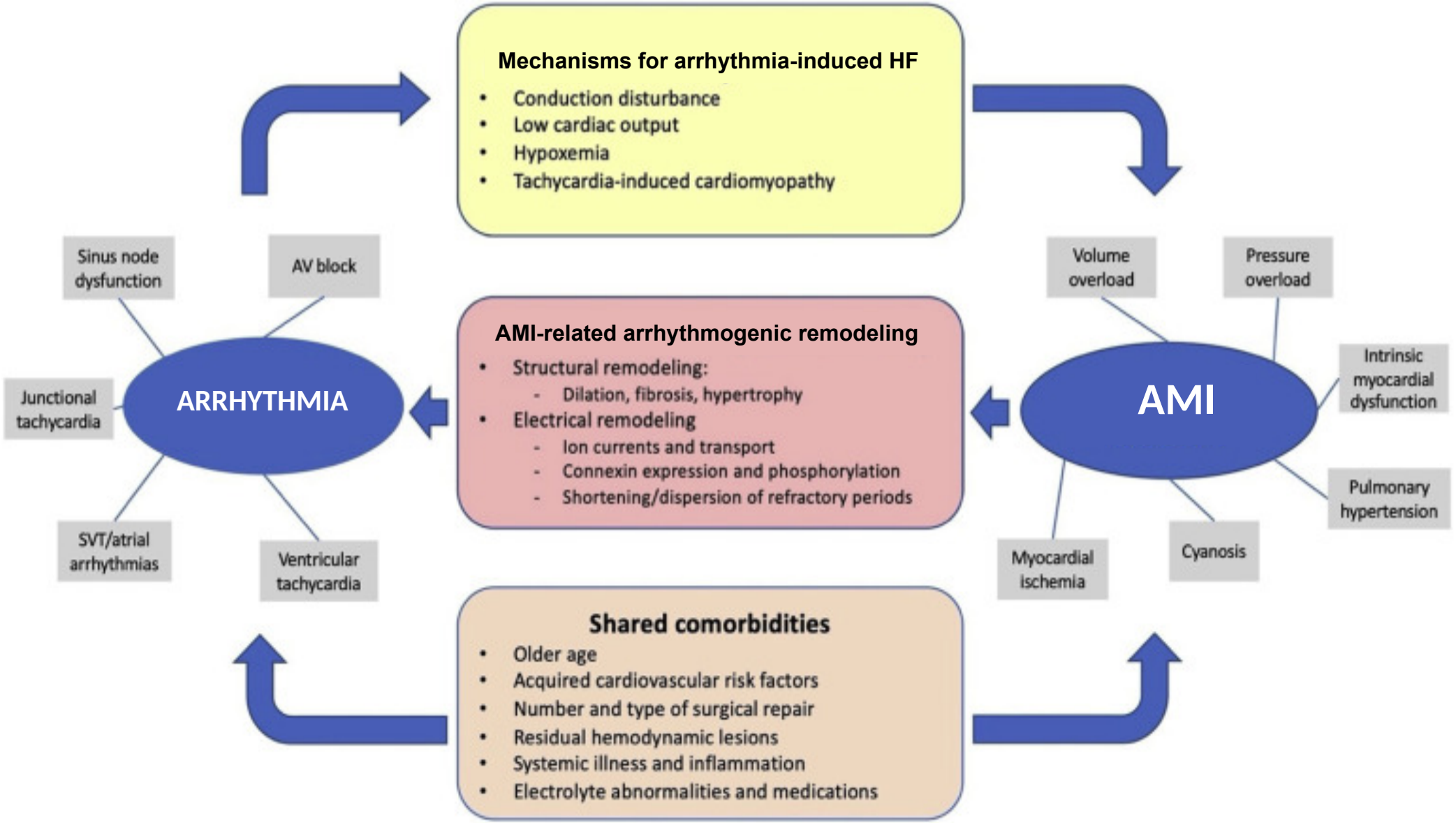
Cardiac arrhythmias after AMI



Cardiac arrhythmias after AMI

- Cardiac arrhythmias might be asymptomatic and clinical detection is usually based upon randomly performed 24- or 48-hour ECG Holter with large temporal gaps among them. For this reason, these intermittent ECG monitoring techniques have been shown to underdiagnose cardiac arrhythmias.
- Implantable cardiac monitoring (ICM), by allowing a continuous cardiac rhythm monitoring, can overcome these limitations and allows to reliably identify cardiac arrhythmias, up to 4 years after AMI.
- Miniaturization and simplification of the implant procedure have significantly increased the adoption of ICM in clinical practice.

Long-Term Recording of Cardiac Arrhythmias With an Implantable Cardiac Monitor in Patients With Reduced Ejection Fraction After Acute Myocardial Infarction

The Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) Study

Objective:

- To study the incidence and prognostic significance of arrhythmias documented by ar implantable cardiac monitor among patients with AMI and LVEF ≤40%.

Methods:

- Observational study.
- 297 patients in the acute phase (3 to 21 days) of an AMI and ≤ 40%
- ICM implanted 11±5 days after AMI
- Mean follow-up: 1.9±0.5 years.

Endpoint:

- Cardiac death and all-cause mortality.

Table 2. Characteristics of Study Patients by Outcome

	No Cardiac Death	Cardiac Death
n (%)	270 (91)	27 (9)
Age, y	63.6±10.9	68.2±11.9*
Male gender, n (%)	208 (77)	21 (78)
Prior MI, n (%)	93 (34)	17 (63)*
Prior CHF, n (%)	23 (9)	9 (33)*
Diabetes mellitus, n (%)	49 (18)	10 (37)*
Hypertension, n (%)	118 (44)	11 (41)
QRS ≥120 ms	32 (12)	11 (42)*
NYHA class III–IV	32 (12)	8 (31)*
LVEF		
LVEF <30% at enrollment, n	51 (23)	6 (32)
3–7 d after index MI, %	31.4±6.4	29.1±6.3
6 wk after index MI, %	35.8±10.3	31.4±7.9
Characteristics of AMI, n (%)		
Q-wave AMI	168 (63)	10 (39)*
Anterior location	157 (58)	12 (44)
β-blocker, n (%)		
At discharge	259 (96)	27 (100)
At 6 wk after AMI (n=289)	250 (95)	21 (100)
ACE inhibitor/AT blocker, n (%)		
At discharge	246 (91)	22 (82)
At 6 wk after AMI (n=289)	235 (90)	17 (81)
Statin, n (%)		
At discharge	224 (83	21 (78)
At 6 wk after AMI (n=289)	218 (83)	16 (76)
Antiplatelet agent, n (%)		
At discharge	243 (90)	26 (96)
At 6 wk after AMI (n=289)	232 (86)	19 (70)
History of AF at enrollment, n (%)	21 (8)	5 (19)

Bloch Thomsen PE, et al. Long-term recording of cardiac arrhythmias with an implantable cardiac monitor in patients with reduced ejection fraction after acute myocardial infarction: the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study. Circulation. 2010 Sep 28;122(13):1258-64.

The Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) Study

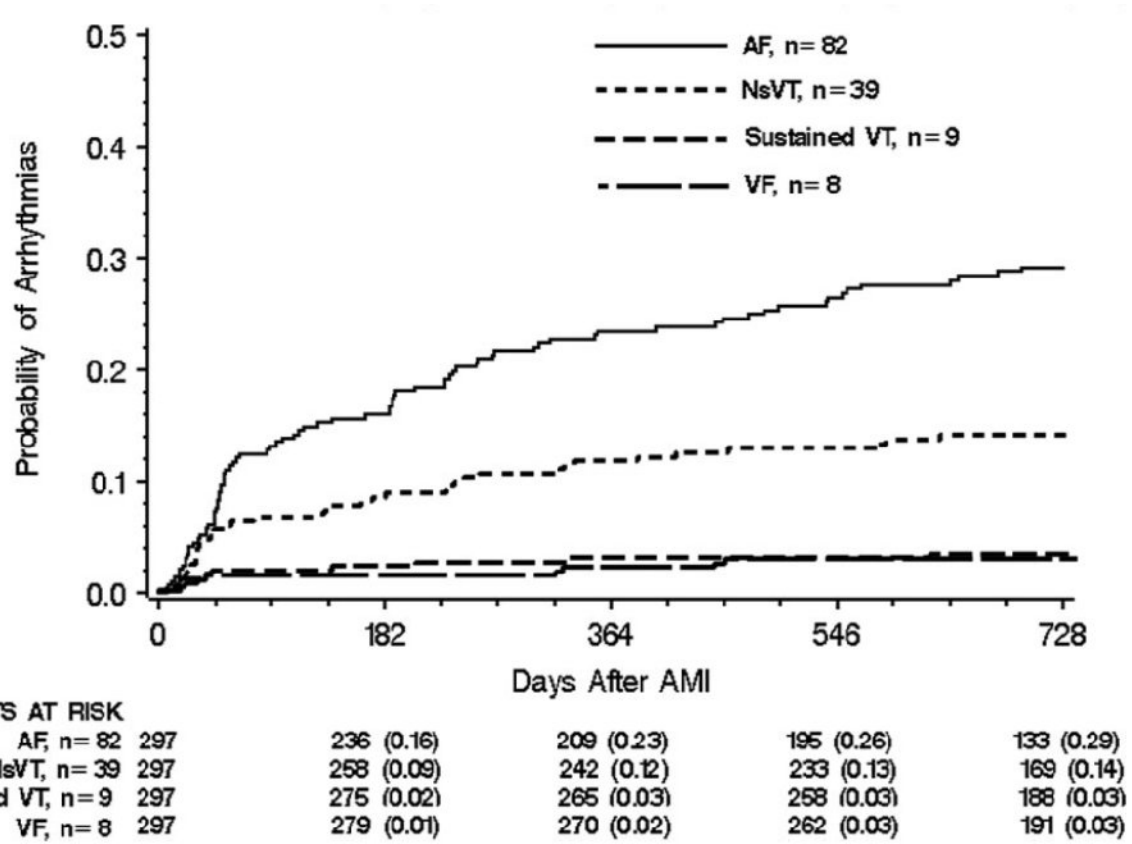
Results:

46% at least one arrhythmia (86% asymptomatic)

Arrhythmia	Patients, n (Incidence, %)	Events, n
Sinus bradycardia (≤30 bpm, ≥8 beats)	20 (6.7)	111
Sinus arrest (≥5 s)	16 (5.4)	23
New-onset AF (≥125 bpm, ≥16 beats)	82 (27.6)	538
High-degree AV block (second to third degree; ≤30 bpm, ≥8 beats)	29 (9.8)	124
Nonsustained VT (≥125 bpm, ≥16 beats, <30 s)	39 (13.1)	64
Sustained VT (≥125 bpm, ≥30 s)	9 (3.0)	20
VF (≥125 bpm, ≥16 beats)	8 (2.7)	19
Any arrhythmia	137 (46.1)	885

Events adjudicated according to the following: sinus bradycardia ≤30 bpm for ≥8 seconds, sinus arrest with pauses ≥5 seconds, and high-degree (second to third degree) AV block ≤30 bpm lasting ≥8 seconds. Tachycardia: ≥125 bpm for ≥16 beats. Sustained VT: ≥30 seconds at ≥125 bpm. This table includes all documented arrhythmias.

Cumulative incidence of arrhythmias increases over time



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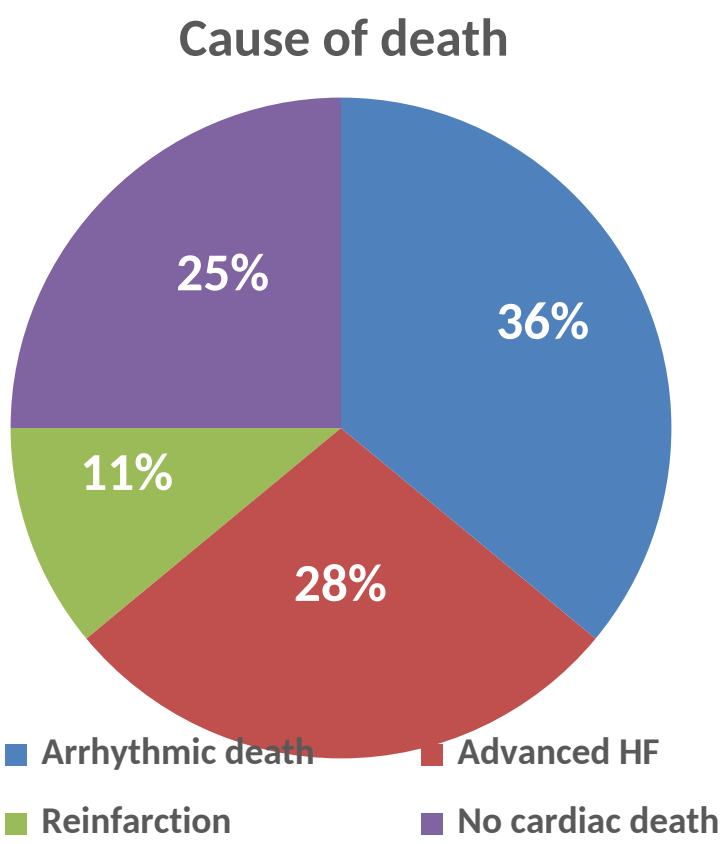
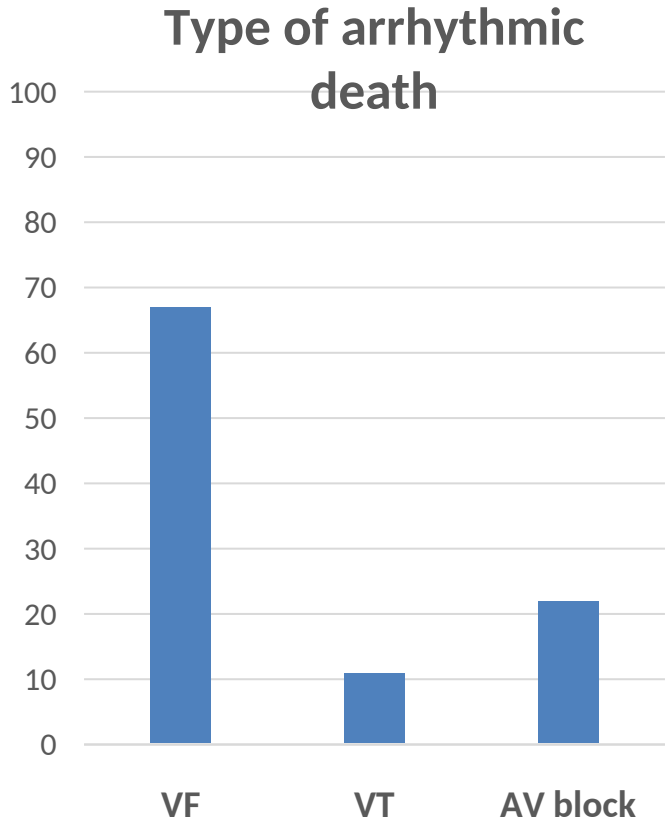
The Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) Study

Results:

36 (12%) patients died during follow-up





	Cardiac Death			All-Cause Mortality		
Arrhythmia	HR	*P*	95% CI	HR	*P*	95% CI
High degree AV block on ICM	6.75	<0.001	2.565–17.84	4.97	<0.001	2.09–11.83
Sinus bradycardia on ICM	4.15	0.012	1.37–12.62	2.60	0.07	0.92–7.28
Sinus arrest on ICM	1.33	0.79	0.16–11.08	1.01	1.00	0.13–7.93
Nonsustained VT on ICM	1.98	0.17	0.74–5.24	1.33	0.54	0.53–3.36
New-onset AF on ICM*	1.03	0.96	0.36–2.91	1.10	0.84	0.45–2.67
Sustained VT on ICM	3.61	0.12	0.71–18.26	2.83	0.19	0.60–13.41

Results from Cox regression analysis treating ICM-documented arrhythmias occurring until 1 day before the end point as time-dependent covariates and adjusting for prespecified baseline variables: age >70 years, previous MI, and QRS >120 milliseconds.

*Model adjusted for AF at enrollment.

Bloch Thomsen PE, et al. Long-term recording of cardiac arrhythmias with an implantable cardiac monitor in patients with reduced ejection fraction after acute myocardial infarction: the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study. Circulation. 2010 Sep 28;122(13):1258-64.

Telemedical cardiac risk assessment by implantable cardiac monitors in patients after myocardial infarction with autonomic dysfunction (SMART-MI-DZHK9): a prospective investigator-initiated, randomised, multicentre, open-label, diagnostic trial

Objective:

- Telemedical monitoring using ICM is effective for early detection of subclinical severe arrhythmias in patients with previous AMI, cardiac autonomic dysfunction, and only moderately reduced LVEF.

Methods:

- Randomized 1:1, multicenter, open-label, diagnostic trial → ICM monitoring vs. conventional care
- 400 patients (201 ICM group vs. 199 control group)
- AMI with PCI ≤ 39 days, LVEF 36-50%, cardiac autonomic dysfunction*
- Median follow-up 21 months

Endpoint:

- Time to detection of serious arrhythmic events (AF ≥6 min, high-degree AV block, fast NSVT, SVT/VF).

	Implantable cardiac monitor group (n=201)	Control group (n=199)
Age, years	64 (57–73)	65 (57–73)
Sex		
Male	152/201 (76%)	170/199 (85%)
Female	49/201 (24%)	29/199 (15%)
Caucasian	201/201 (100%)	199/199 (100%)
Cardiovascular risk factors		
Diabetes	60/200 (30%)	59/198 (30%)
Use of insulin for diabetes	25/199 (13%)	22/199 (11%)
Current smoker	64/198 (32%)	62/195 (32%)
Arterial hypertension	139/199 (70%)	147/198 (74%)
Hypercholesterinaemia	103/196 (53%)	95/195 (49%)
CHA_2DS_2-VASc score	3 (2–4)	3 (2–4)
CHA_2DS_2-VASc score 3 or higher	131/201 (65%)	120/199 (60%)
Medical history		
History of previous myocardial infarction	27/199 (14%)	35/199 (18%)
Renal dysfunction	21/200 (10%)	22/199 (11%)
Peripheral artery disease	9/201 (4%)	12/197 (6%)
History of stroke	8/201 (4%)	12/198 (6%)
Chronic obstructive pulmonary disease	16/199 (8%)	13/199 (7%)
Heart rate, beats per min	74 (68–81)	73 (64–84)
Body-mass index, kg/m²	28·4 (25·5–31·0)	27·2 (24·4–29·9)
Creatinine, mg/dL	1·00 (0·87–1·20)	1·00 (0·87–1·19)
Index myocardial infarction		
Non-ST segment elevation myocardial infarction	79/201 (39%)	85/199 (43%)
ST segment elevation myocardial infarction	122/201 (61%)	114/199 (57%)

Cardiac autonomic dysfunction: periodic repolarization dynamics and deceleration capacity of heart rate.

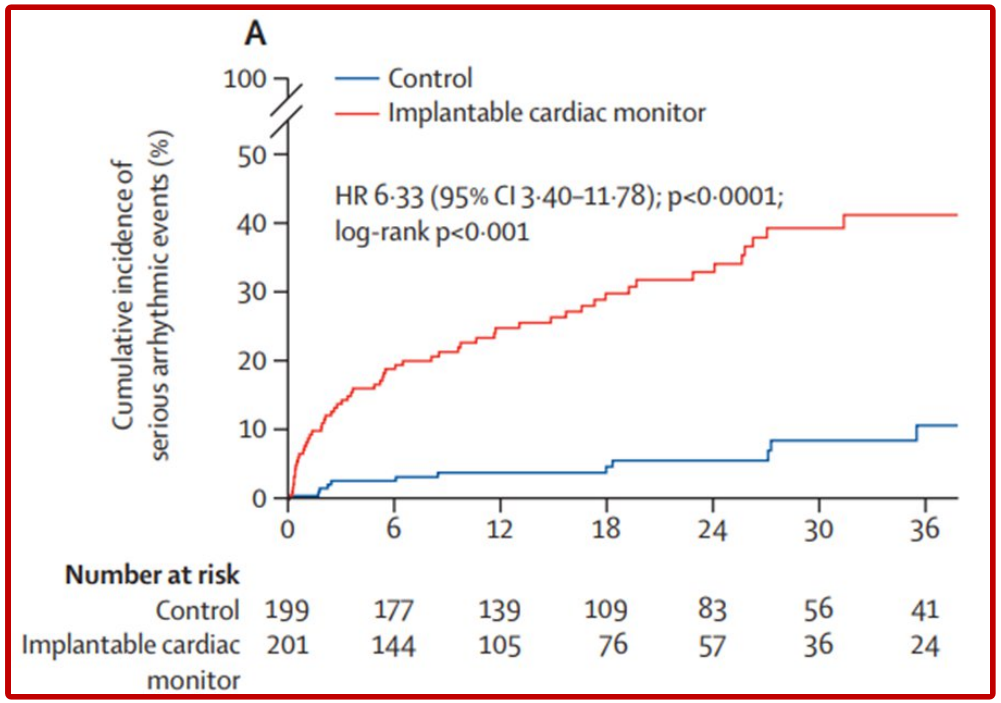
Bauer A, et al. The Lancet Digital Health. 2022;4:e105-e116

Telemedical cardiac risk assessment by ICM in patients after AMI with autonomic dysfunction: The **SMART-MI** Trial

Results:

- Serious arrhythmic events detected in 60 (30%) patients in ICM group vs. 12 (6%) in control group (HR 6.33, 95% CI 3.40-11.78, p<0.001).
- AF ≥ 6 min (23%) was the most commonly encountered arrhythmia.

	Implantable cardiac monitor group (n=201)	Control group (n=199)	Hazard ratio (95% CI)	p value
Primary endpoint: serious arrhythmic events	60 (30%)	12 (6%)	6·33 (3·40–11·78)	<0·0001
Secondary endpoints				
Single components of serious arrhythmic events				
Atrial fibrillation ≥6 min	47 (23%)	11 (6%)	5·24 (2·71–10·14)	<0·0001
Atrioventricular block >IIb	14 (7%)	0	..	<0·0001*
Fast non-sustained ventricular tachycardia	6 (3%)	0	..	0·013*
Sustained ventricular tachycardia or ventricular fibrillation	6 (3%)	2 (1%)	2·94 (0·59–14·55)	0·19
Composite of fast non-sustained ventricular tachycardia and sustained ventricular tachycardia or ventricular fibrillation	9 (4%)	2 (1%)	4·51 (0·97–20·93)	0·054



Bauer A, et al. The Lancet Digital Health. 2022;4:e105-e116

Telemedical cardiac risk assessment by ICM in patients after AMI with autonomic dysfunction: The **SMART-MI** Trial

Results:

- Throughout the study, more diagnostic and therapeutic interventions were initiated in the ICM group than in the control group:

- *ICD implantation (13 pts vs. 5 pts, p=0. 056)*
- *PM implantations (6 vs. 9, p=0.041)*
- *EPS (12 vs. 3, p=0.019)*
- *CA (10 vs. 3, p=0.051)*
- *OAC initiation due to AF (37 vs. 11, p<0.001).*

In both the interventional group and the control group, detection of serious arrhythmic events significantly predicted subsequent MACE.

	Implantable cardiac monitor group (n=201)		Control group (n=199)	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Death	3·28 (1·02–10·61)	0·047	..*	..*
Cardiovascular death	3·89 (0·86–17·63)	0·078	..*	..*
Death, stroke, thromboembolic complications, or hospitalisation due to acute decompensated heart failure	6·12 (2·64–14·21)	<0·0001	6·99 (2·24–21·79)	0·0008
Cardiovascular death, stroke, thromboembolic complications, hospitalisation due to acute decompensated heart failure (major adverse cardiac and cardiovascular events)	6·82 (2·86–16·22)	<0·0001	7·30 (2·37–22·82)	0·0006

*No deaths occurred in patients experiencing serious arrhythmic events in the control group.

Bauer A, et al. The Lancet Digital Health. 2022;4:e105-e116

CARISMA Study and **SMART-MI** Trial

Conclusions:

- Both trials investigated the incidence and prognostic significance of long-term arrhythmias in patients surviving AMI, with reduced or only moderately reduced LVEF, with/without cardiac autonomic dysfunction.
- Through ICM monitoring, severe arrhythmias are observed in 30 to 46% of these patients, and are frequently asymptomatic (86%).
- Severe arrhythmias, by increasing the risk of all-cause mortality and cardiac death, have a significant prognostic impact.

Can early diagnosis and treatment of ICM-detected cardiac arrhythmias improve prognosis?

Biomonitoring in Patients with Preserved Left Ventricular Function after Diagnosed Myocardial Infarction: **BIO|GUARD-MI Study**

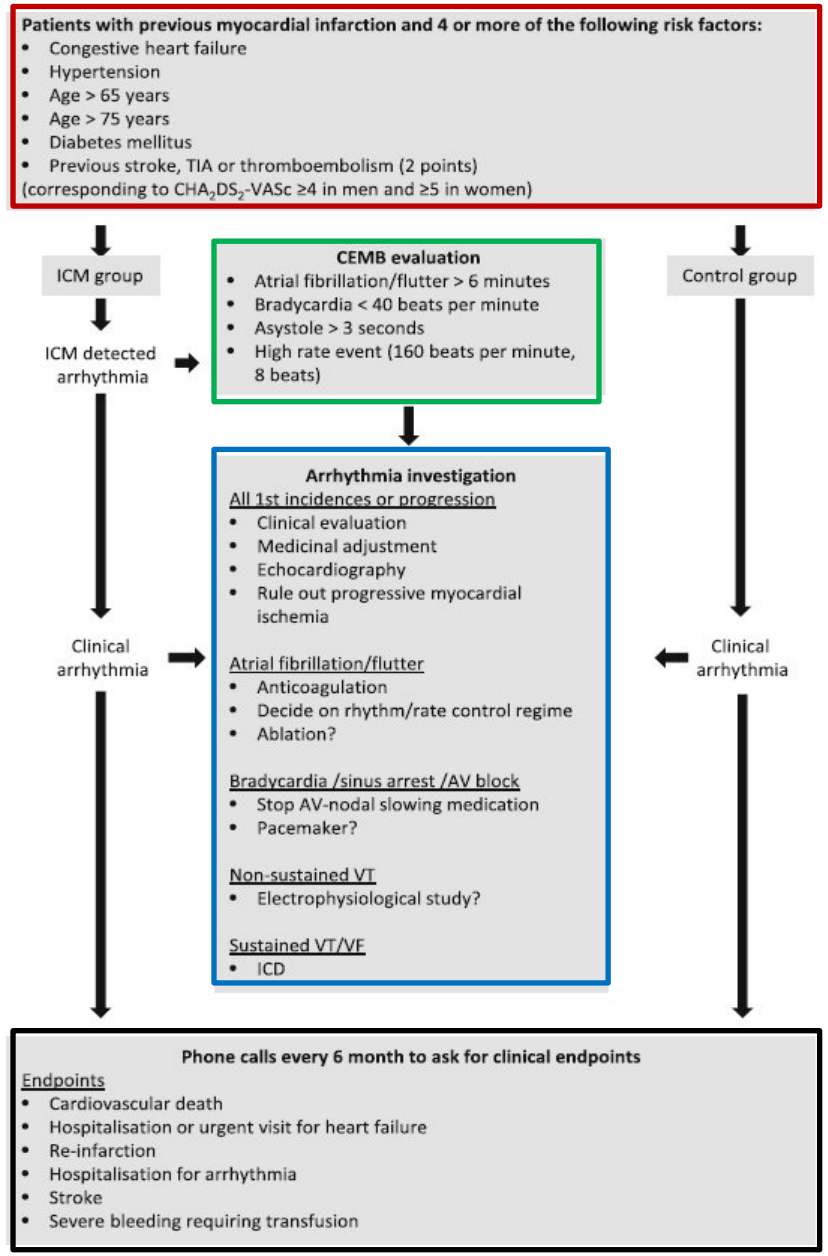
The BIO|GUARD-MI study is the first trial to investigate whether early treatment after ICM-documented arrhythmias in high-risk post-MI patients improves outcome.

High-risk patients
(high CHA2DS2-VASc score)

ICM-detected or clinically-detected arrhythmias

Guidelines-guided arrhythmia management

Primary endpoint: time to MACE



Jons C, et al. Trials. 2019 Sep 11;20(1):563.

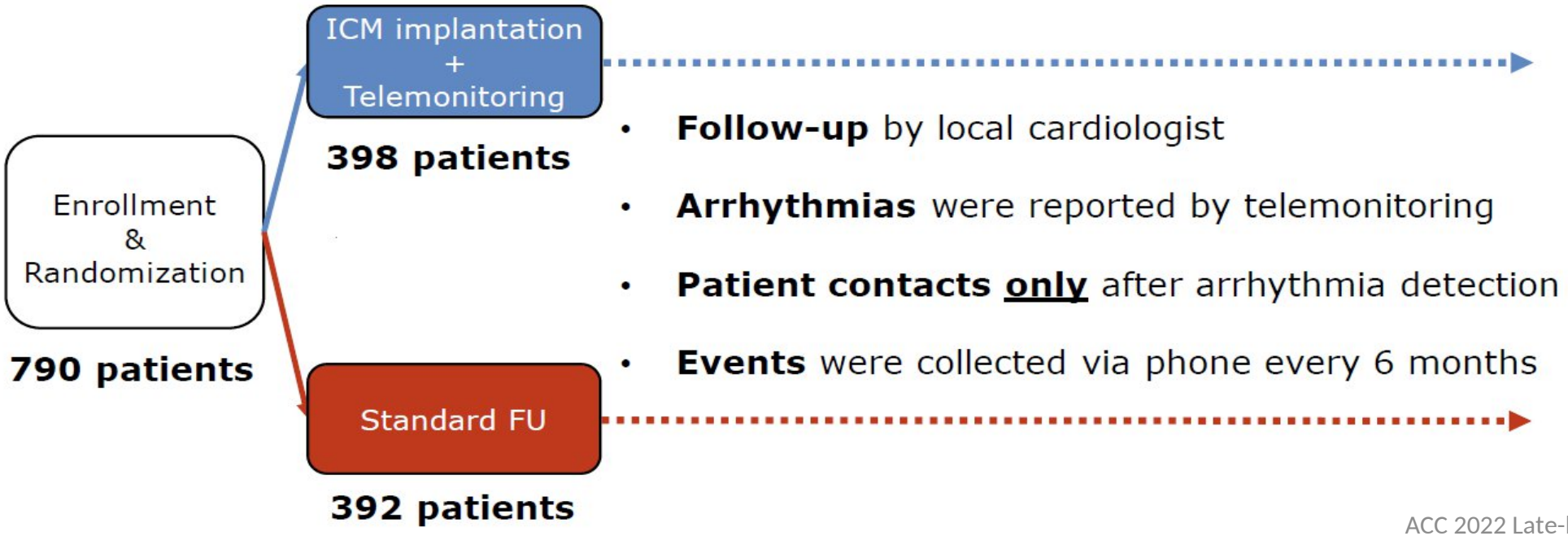
Biomonitoring in Patients with Preserved Left Ventricular Function after Diagnosed Myocardial Infarction: **BIO|GUARD-MI Study**

Objective:

- To investigate whether the early diagnosis of cardiac arrhythmias, provided by the BIOMONITOR with Home Monitoring, and the consequent treatment of the patient will decrease the risk to experience a MACE in patients after MI, with LVEF >35% and CHA2DS2-VASc score ≥4 (M) or ≥5 (F)

Methods:

- Randomized, controlled, parallel-group, open, prospective, multi-center, international study
- Median follow-up 2.5 years after randomization



Biomonitoring in Patients with Preserved Left Ventricular Function after Diagnosed Myocardial Infarction: **BIO|GUARD-MI Study**

Results:

- Characteristics of study population

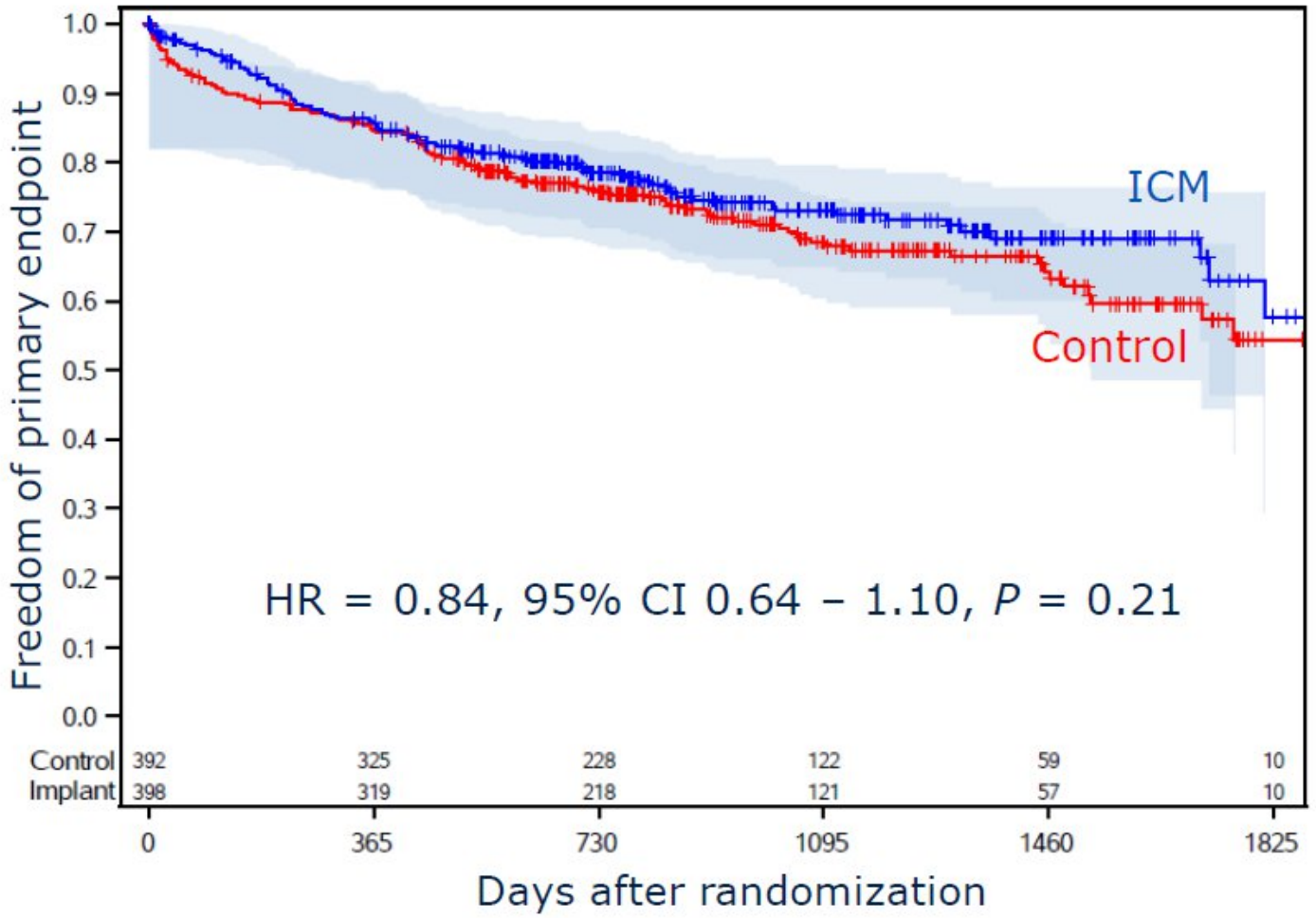
	ICM (n=398)	Control (n=392)
	N (%) / mean ± SD	N (%) / mean ± SD
Age – years	**72 ± 8**	**71 ± 9**
Male gender	291 (73)	277 (71)
More than one myocardial infarction	66 (17)	70 (18)
PCI at index event	314 (79)	321 (82)
Acute MI (less than 40 days ago)	**137 (35)**	**141 (36)**
NSTEMI	**205 (52)**	**198 (51)**
Left ventricular ejection fraction	53 ± 9	53 ± 8
CHA_2DS_2-VASc	**4.8 ± 0.9**	**5.0 ± 1.0**
Heart failure	135 (34)	136 (35)
Diabetes	240 (60)	244 (62)
Stroke, TIA or TE event	88 (22)	109 (28)
ACEi/ARB	323 (82)	301 (77)
Beta blocker	334 (84)	318 (81)
Statin	359 (90)	347 (89)
Platelet aggregation inhibitor	369 (93)	361 (92)

Biomonitoring in Patients with Preserved Left Ventricular Function after Diagnosed Myocardial Infarction: **BIO|GUARD-MI Study**

Results:

- <u>Primary endpoint (MACE)</u>

A trend towards MACE reduction in the ICM group was observed but did not reach statistical significance (HR=0.84, p=0.21).



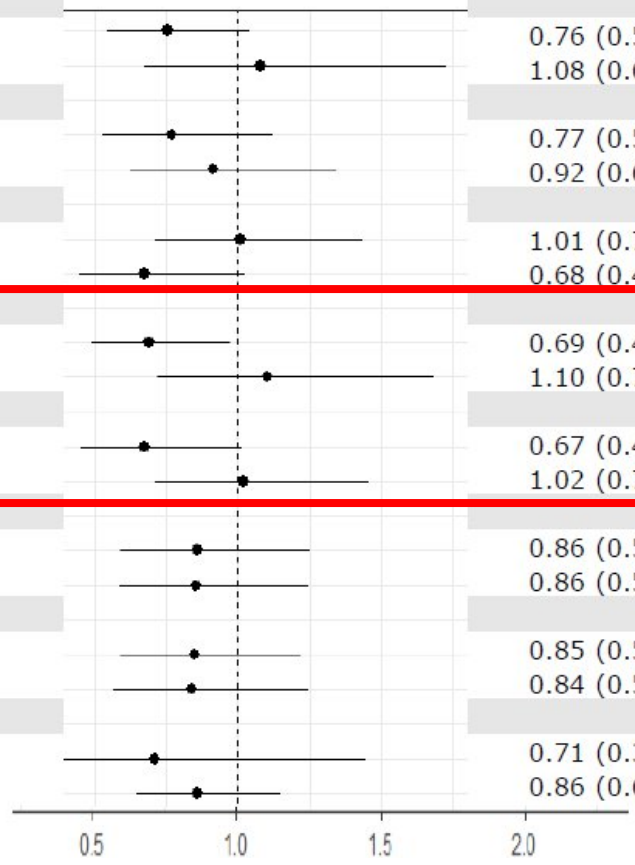
Biomonitoring in Patients with Preserved Left Ventricular Function after Diagnosed Myocardial Infarction: **BIO|GUARD-MI Study**

Results:

- Primary endpoint (MACE): subgroup analysis

Sub-group analysis shows a significant MACE reduction with ICM in NSTEMI vs. STEMI.

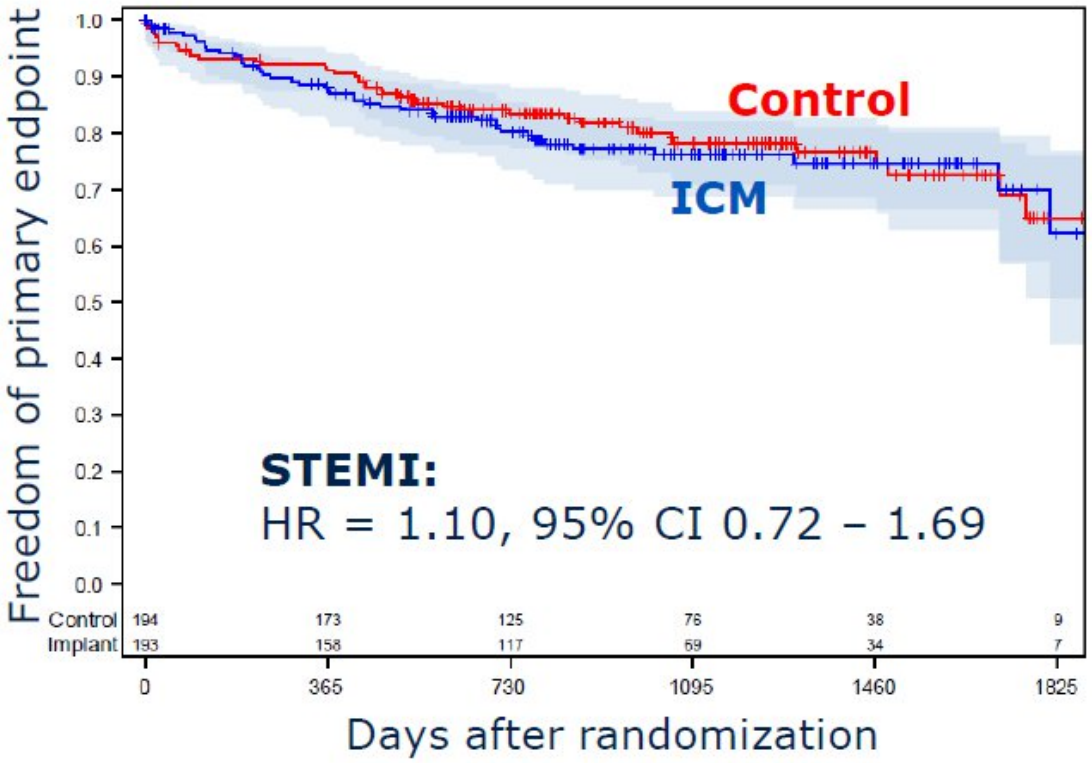
	Number of patients		Number of events		HR (95% CI)	P_{int}
	ICM	Contr	ICM	Contr		
Gender						
Men	291	277	65	83	0.76 (0.55 – 1.05)	0.21
Women	107	115	34	36	1.08 (0.67 – 1.73)	
Age						
< 72 years	188	203	47	65	0.77 (0.53 – 1.12)	0.51
≥ 72 years	210	189	52	54	0.92 (0.63 – 1.34)	
Body mass index						
< 30	242	233	61	62	1.01 (0.71 – 1.44)	0.14
≥ 30	153	158	37	56	0.68 (0.45 – 1.02)	
Type of infarction						
NSTEMI	205	198	56	77	0.69 (0.49 – 0.98)	0.09
STEMI	193	194	43	42	1.10 (0.72 – 1.69)	
Acute (< 40 d) or prior infarction						
Acute	137	141	38	60	0.67 (0.45 – 1.01)	0.13
Prior	258	247	61	59	1.02 (0.71 – 1.46)	
CHA_2DS_2-VASc						
≤ 4	232	209	52	56	0.86 (0.59 – 1.25)	0.98
≥ 5	166	183	47	63	0.86 (0.59 – 1.25)	
LV ejection fraction						
< 54%	195	197	52	66	0.85 (0.59 – 1.22)	0.99
≥ 54%	203	195	47	53	0.84 (0.57 – 1.25)	
Renal disease						
Yes	49	40	14	17	0.71 (0.35 – 1.45)	0.61
No	338	346	83	101	0.86 (0.64 – 1.15)	

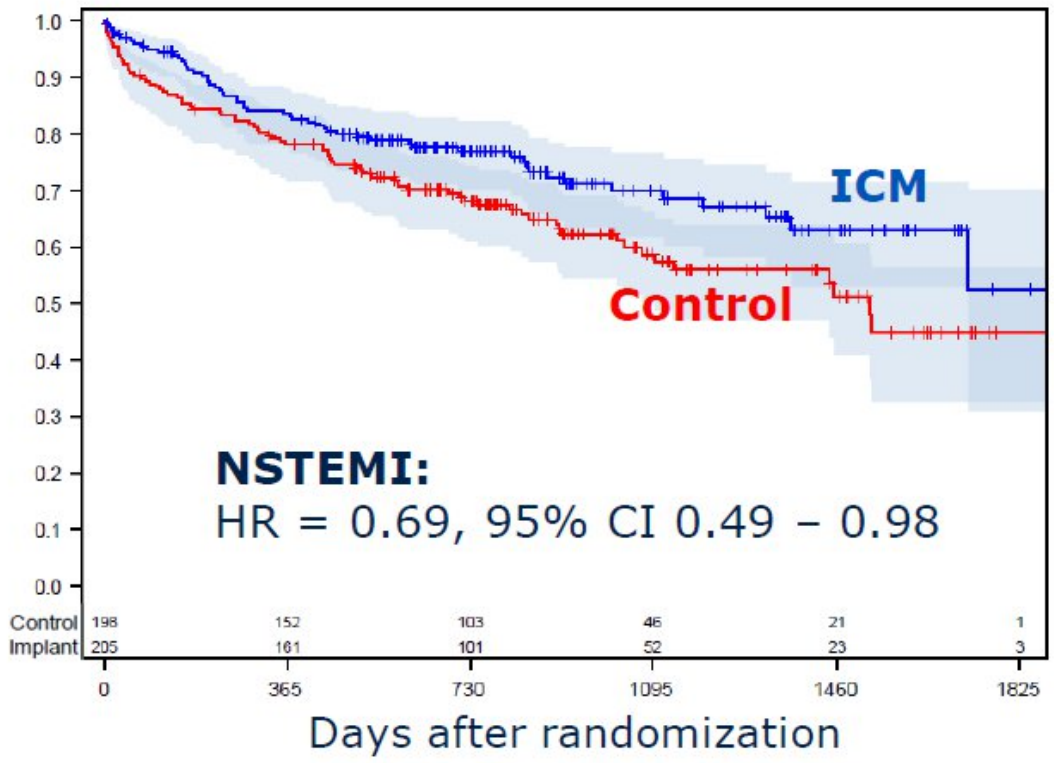


Biomonitoring in Patients with Preserved Left Ventricular Function after Diagnosed Myocardial Infarction: **BIO|GUARD-MI Study**

Results:

- Primary endpoint (MACE): subgroup analysis
- NSTEMI vs. STEMI patients → 31% MACE reduction with ICM in NSTEMI patients.



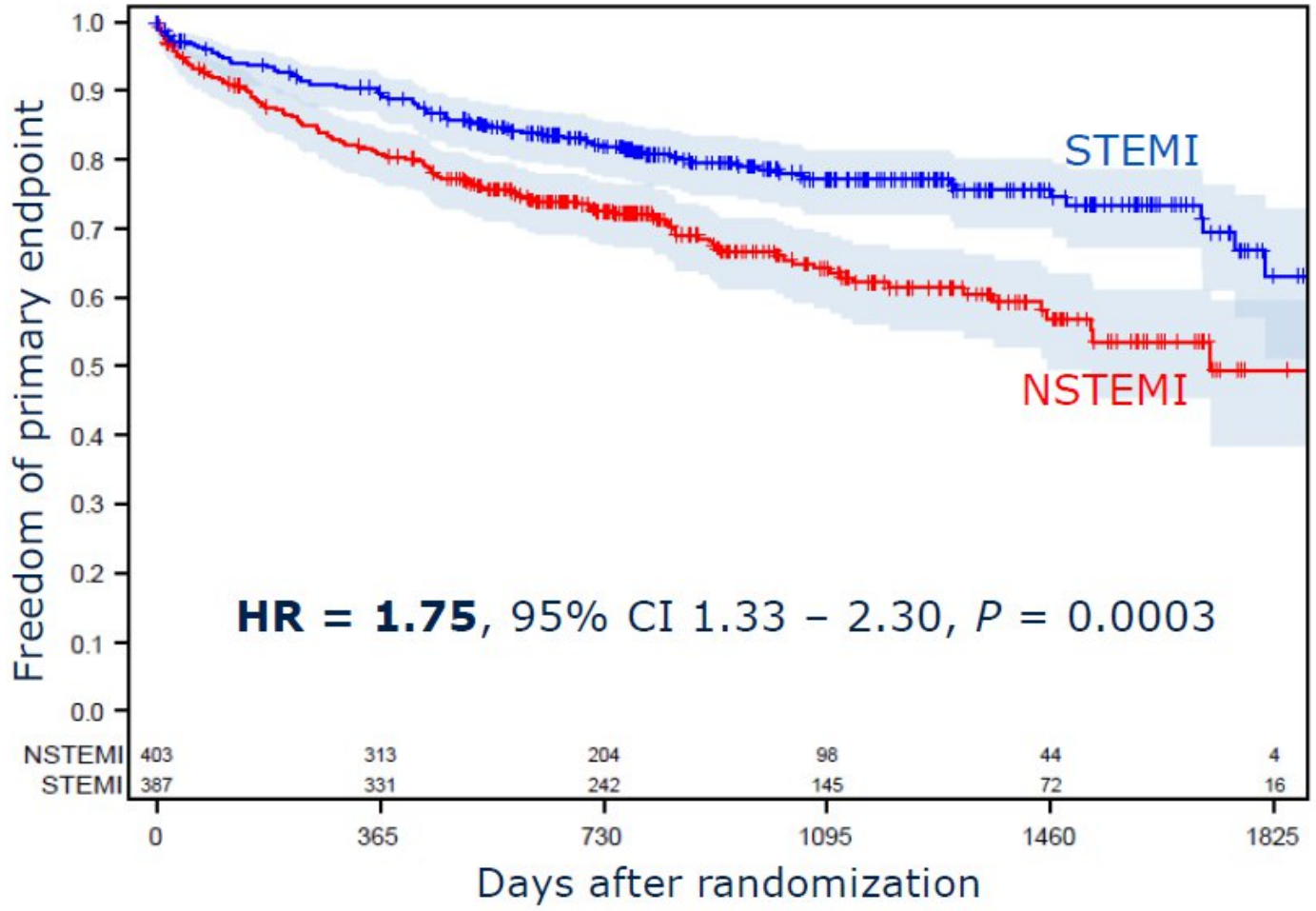


Biomonitoring in Patients with Preserved Left Ventricular Function after Diagnosed Myocardial Infarction: **BIO|GUARD-MI Study**

Results:

- Primary endpoint (MACE): higher risk of MACE for NSTEMI patients.

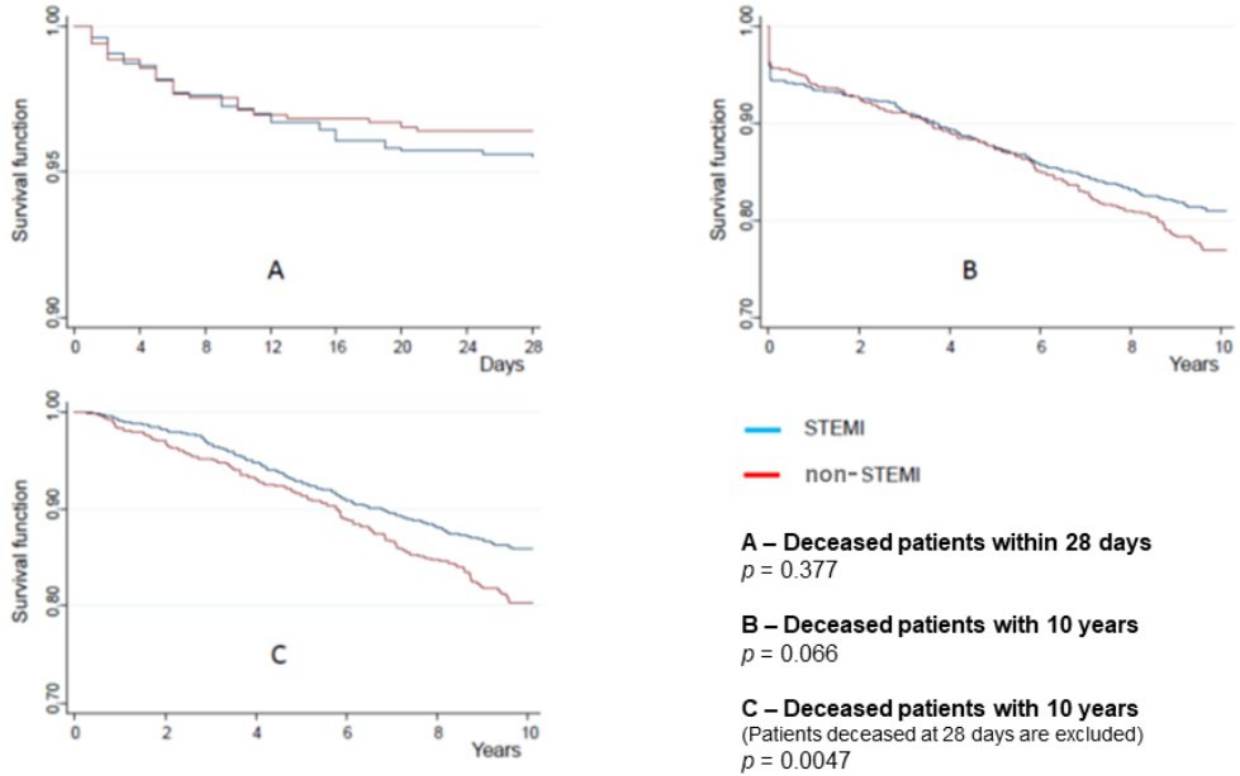
The benefit of ICM-guided treatment in NSTEMI patients appears to be connected to their higher risk for primary endpoint events (75% increased risk of MACE in NSTEMI patients).



NSTEMI vs STEMI

- I pazienti STEMI ricevono terapie primarie e secondarie di prevenzioni più aggressive rispetto ai pazienti NSTEMI[1].
- Dopo i primi 30 giorni dall'evento, la mortalità a lungo termine sembra essere maggiore nei pazienti NSTEMI vs STEMI[2].

- Questo potrebbe essere in parte spiegato da terapie e follow-up meno aggressive nei pazienti NSTEMI e potrebbe spiegare il beneficio osservato nel BIOGUARD-MI nel gruppo NSTEMI.



1 Montalescot G, et al. STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry). Eur Heart J. 2007 Jun;28(12):1409-17.
2 Bouisset F, et al. Comparison of Short- and Long-Term Prognosis between ST-Elevation and Non-ST-Elevation Myocardial Infarction. J Clin Med. 2021 Jan 7;10(2):180.

Biomonitoring in Patients with Preserved Left Ventricular Function after Diagnosed Myocardial Infarction: **BIO|GUARD-MI Study**

Results:

- Time to first arrhythmia

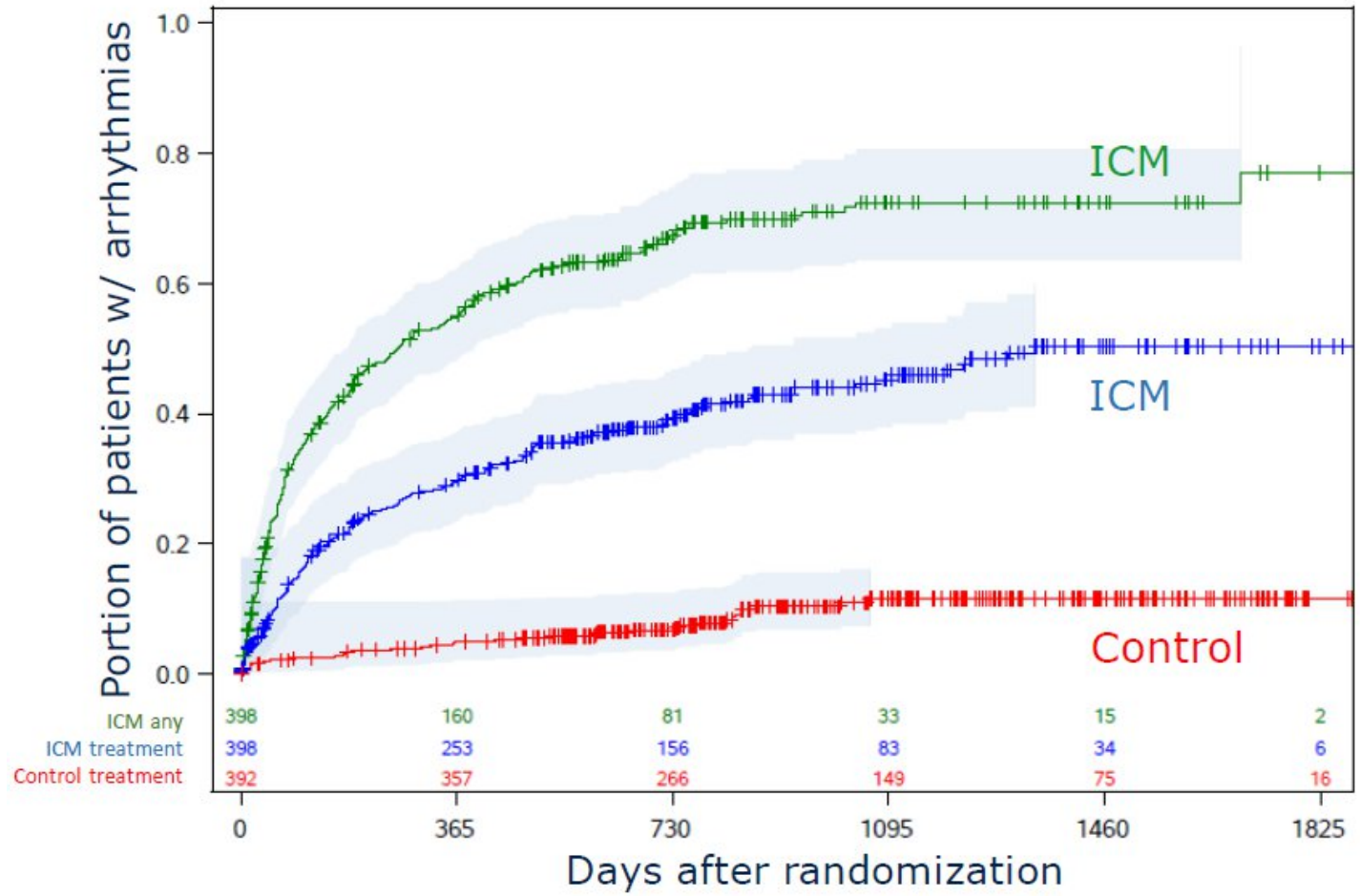
- Continuous arrhythmia monitoring in post-MI patients identifies a large arrhythmia burden, and many of the arrhythmias require guideline recommended therapies (39% vs. 6.7%, HR 5.9, p< 0.001).

- Most commonly therapy started:

✓ OAC initiation (40%)

✓ PM implant (20%)

✓ Beta-blocking tailoring (18%)



Biomonitoring in Patients with Preserved Left Ventricular Function after Diagnosed Myocardial Infarction: **BIO|GUARD-MI Study**

BIO|GUARD-MI

Conclusions:

- Arrhythmias are connected to poor outcomes after MI.
- BIO|GUARD-MI is the first trial to investigate the impact of continuous arrhythmia monitoring with ICMs on clinical outcomes in post-MI patients.
- Compared to conventional care, ICM-based continuous monitoring allowed to detect arrhythmias in a substantial proportion of high-risk patients with previous MI (67%), often leading to significant therapy change.
- Early treatment of high-risk NSTEMI patients guided by continuous arrhythmia monitoring with BIOMONITOR and Home Monitoring may reduce MACE.

Stratificazione del rischio post-IMA: il ruolo del monitoraggio alla luce del BIOGUARD

Take home massages

- Severe arrhythmias are frequently observed in high-risk patients with previous MI and lead to an increased risk of all-cause mortality and cardiac death.
- CARISMA, SMART-MI, and BIOGUARD-MI studies have all confirmed the superiority of ICM in detecting cardiac arrhythmias, compared to conventional ECG Holter monitoring techniques.
- The randomized BIO|GUARD-MI study showed for the first time that early treatment after ICM-documented arrhythmias could improve outcomes, particularly in the subset of high risk patients with previous NSTEMI. Further trials are required to confirmed this observation.
- Considering the evidence accumulated so far, there is no indication to routinely implant an ICM in patients with previous AMI and severely/moderately reduced LVEF. A better risk stratification of this wide and heterogeneous cohort of patients is strongly needed.