REDUCE-AMI, AβYSS: faut-il instaurer ou continuer les béta bloquants en post infarctus ?

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PG.Steg – liens d'intérêt

- Bourses de recherche: **Amarin, AstraZeneca, Sanofi**

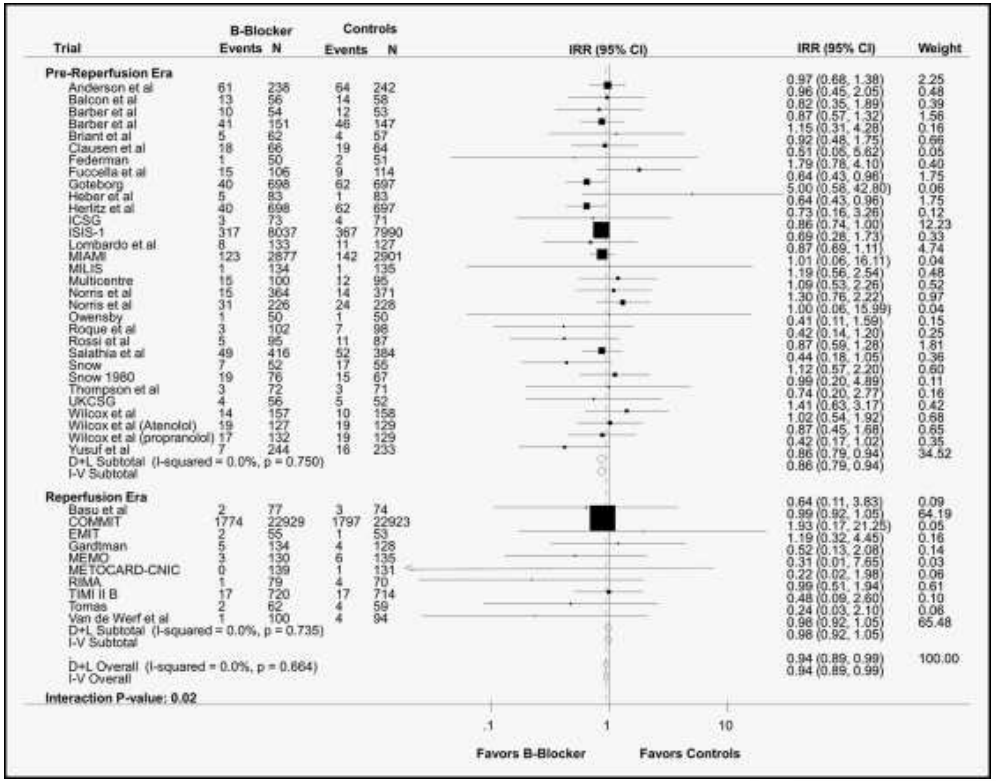
- Essais cliniques, consulting, orateur: **Amarin, Amgen, AstraZeneca, Bayer, BMS, Idorsia, Janssen, Merck, Novartis, Novo-Nordisk, PhaseBio, Pfizer, Sanofi**

- "Senior Associate Editor" de ***Circulation***

- "Chief Medical Officer", **Bioquantis**

Meta-analysis of RCTs testing BBs in AMI : All-cause mortality

Analysis stratified by reperfusion status.



Pre-reperfusion era
IRR: 0.86 (0.79,0.94)

Reperfusion era
IRR: 0.98 (0.92, 1.05)

Bangalore S et al. ***Am J Med*** 2014;127:939-53

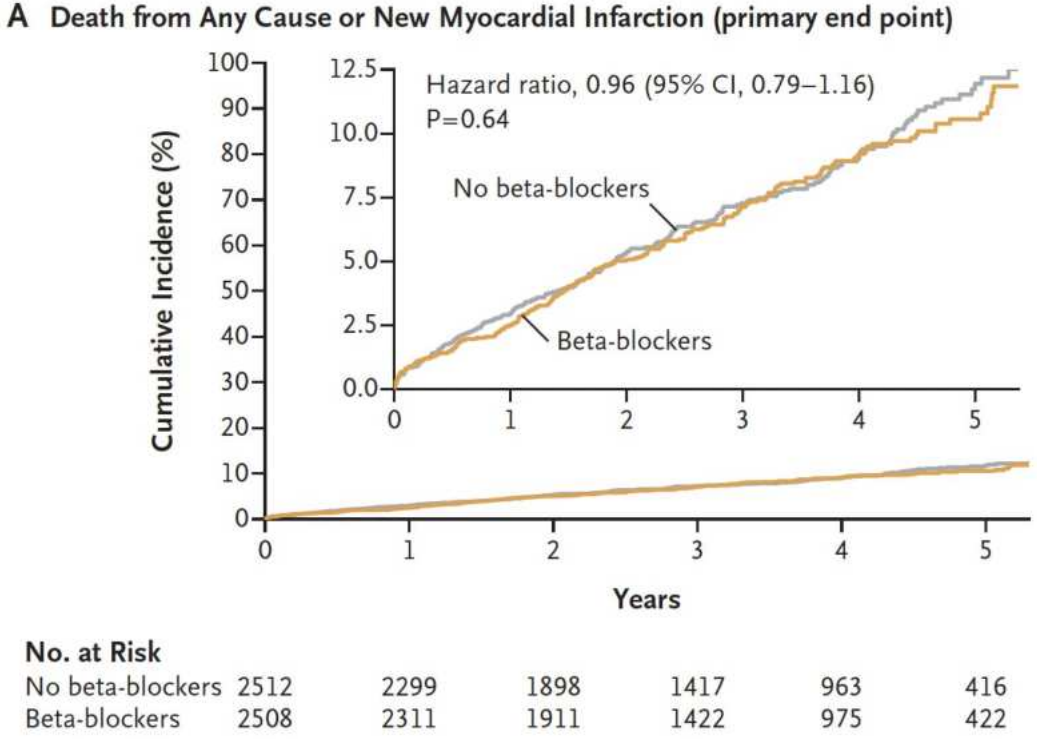
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Beta-Blockers after Myocardial Infarction and Preserved Ejection Fraction

T. Yndigegn, B. Lindahl, K. Mars, J. Alfredsson, J. Benatar, L. Brandin, D. Erlinge, O. Hallen, C. Held, P. Hjalmarsson, P. Johansson, P. Karlström, T. Kellerth, T. Marandi, A. Ravn-Fischer, J. Sundström, O. Östlund, R. Hofmann, and T. Jernberg, for the REDUCE-AMI Investigators*

The REDUCE AMI trial



Yndigegn T et al. ***NEJM*** 2024

Limites de l'essai

- Doses faibles
- Essai en ouvert
- Crossovers fréquents (18% vs 14%)
- Bénéfice « potentiel » de 21% des BB

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REDUCE AMI secondary endpoints

End Point	Beta-Blockers (N=2508)	No Beta-Blockers (N=2512)	Hazard Ratio (95% CI)†	P Value
	number (percent)			
Primary end point				
Death from any cause or myocardial infarction	199 (7.9)	208 (8.3)	0.96 (0.79 to 1.16)	0.64
Secondary end points				
Death from any cause	97 (3.9)	103 (4.1)	0.94 (0.71 to 1.24)	
Death from cardiovascular causes	38 (1.5)	33 (1.3)	1.15 (0.72 to 1.84)	
Myocardial infarction	112 (4.5)	117 (4.7)	0.96 (0.74 to 1.24)	
Hospitalization for atrial fibrillation	27 (1.1)	34 (1.4)	0.79 (0.48 to 1.31)	
Hospitalization for heart failure	20 (0.8)	22 (0.9)	0.91 (0.50 to 1.66)	
Safety end points				
Hospitalization for bradycardia, second- or third-degree atrioventricular block, hypotension, syncope, or implantation of a pacemaker	86 (3.4)	80 (3.2)	1.08 (0.79 to 1.46)	
Hospitalization for asthma or COPD	15 (0.6)	16 (0.6)	0.94 (0.46 to 1.89)	
Hospitalization for stroke	36 (1.4)	46 (1.8)	6.80 (−7.11 to 20.72)†	

Yndigegn T et al. ***NEJM*** 2024

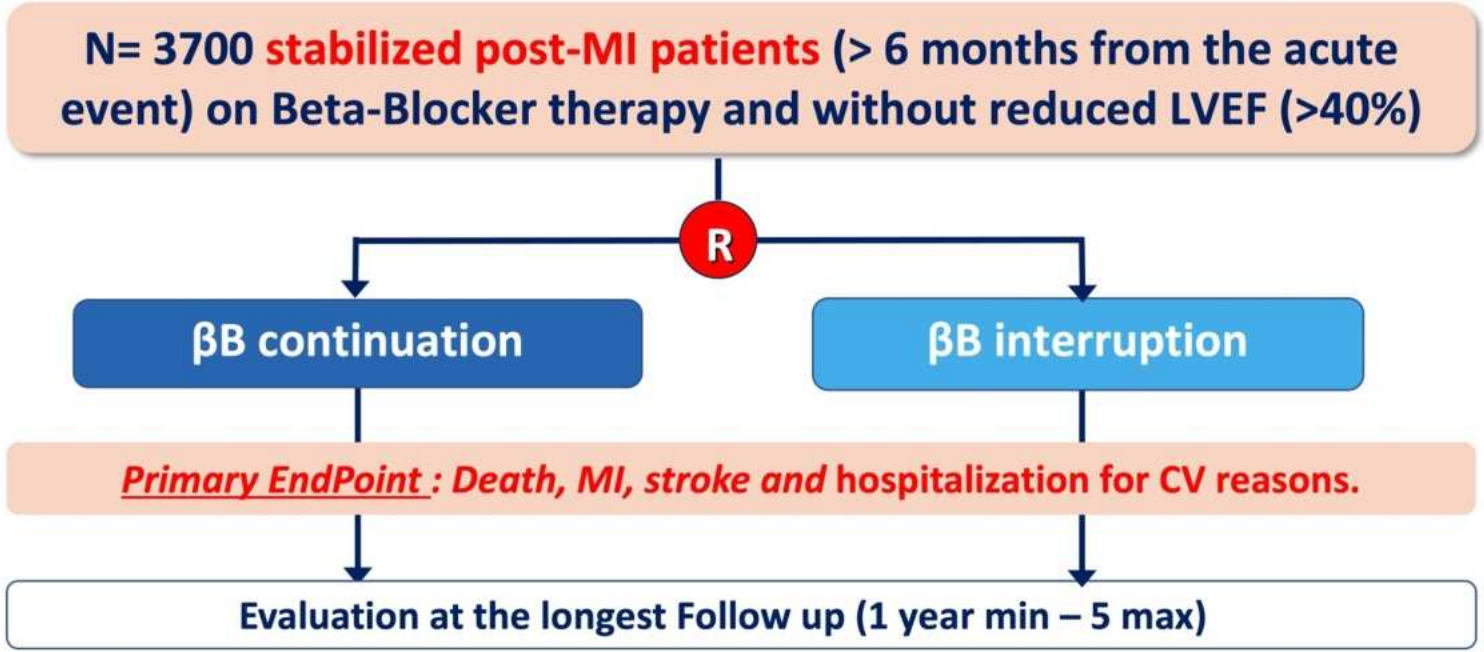
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Beta-Blocker Interruption or Continuation after Myocardial Infarction

J. Silvain, G. Cayla, E. Ferrari, G. Range, E. Puymirat, N. Delarche, P. Guedeney, T. Cuisset, F. Ivanes, T. Lhermusier, T. Petroni, G. Lemesle, F. Bresoles, J.-N. Labeque, T. Pommier, J.-G. Dillinger, F. Leclercq, F. Boccara, P. Lim, T. Besseyre des Horts, T. Fourme, F. Jourda, A. Furber, B. Lattuca, N. Redjimi, C. Thuaire, P. Deharo, N. Procopi, R. Dumaine, M. Slama, L. Payot, M. El Kasty, K. Aacha, A. Diallo, E. Vicaut, and G. Montalescot, for the ABYSS Investigators of the ACTION Study Group*

AβYSS trial design



NCT03498066 - EUDRACT No: 2017-003903-23

Silvain J. et al. ***Am Heart J***. 2023;258:168-176

Analysis Plan and Power

- 80% power to test the non-inferiority hypothesis for a prespecified margin of **3% in absolute risk difference** assuming overall event rate of 12%

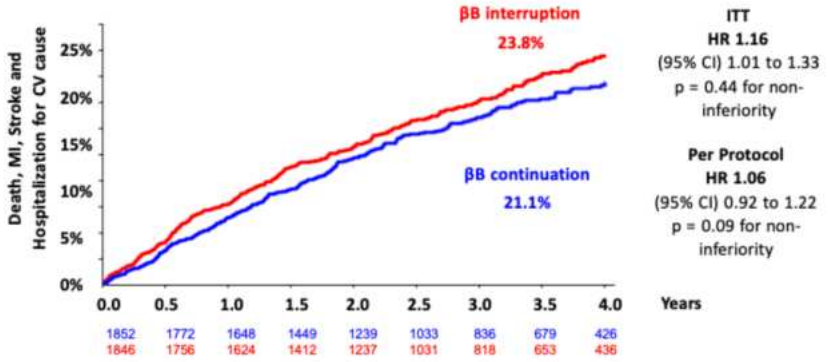
- Sample size: 3700 participants

- **Non-inferiority study** based on concordance of conclusions made in both ITT and PP populations，two-sided test with alpha=0.05, log-binomial regression model using multiple imputation

Silvain J. et al. ***Am Heart J***. 2023 epub Jan 20

AβYSS trial

Primary Outcome

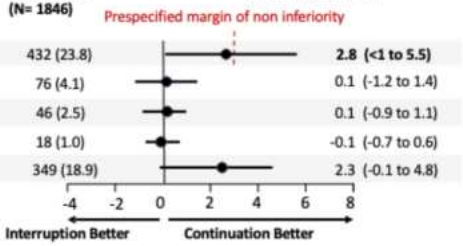


ITT
HR 1.16
(95% CI) 1.01 to 1.33
p = 0.44 for non-inferiority

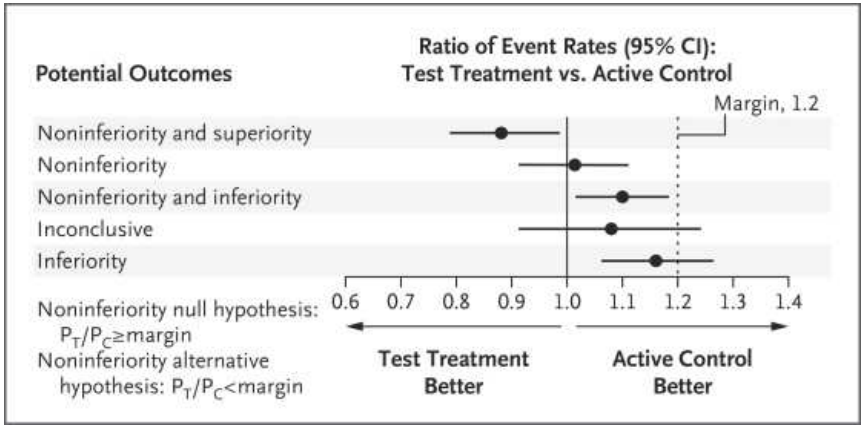
Per Protocol
HR 1.06
(95% CI) 0.92 to 1.22
p = 0.09 for non-inferiority

Primary Outcome Components

End Points	Beta-Blocker Continuation (N=1852)	Beta-Blocker Interruption (N= 1846)	Risk Difference (95% CI) (percentage points)
Primary Endpoint	384 (21.1)	432 (23.8)	**2.8 (<1 to 5.5)**
Death	74 (4.0)	76 (4.1)	0.1 (-1.2 to 1.4)
Myocardial Infarction	44 (2.4)	46 (2.5)	0.1 (-0.9 to 1.1)
Stroke	19 (1.0)	18 (1.0)	-0.1 (-0.7 to 0.6)
Hospitalisation for cardiovascular reason	307 (16.6)	349 (18.9)	2.3 (-0.1 to 4.8)



Interruption of βB treatment was **NOT non-inferior** to a strategy of βB continuation



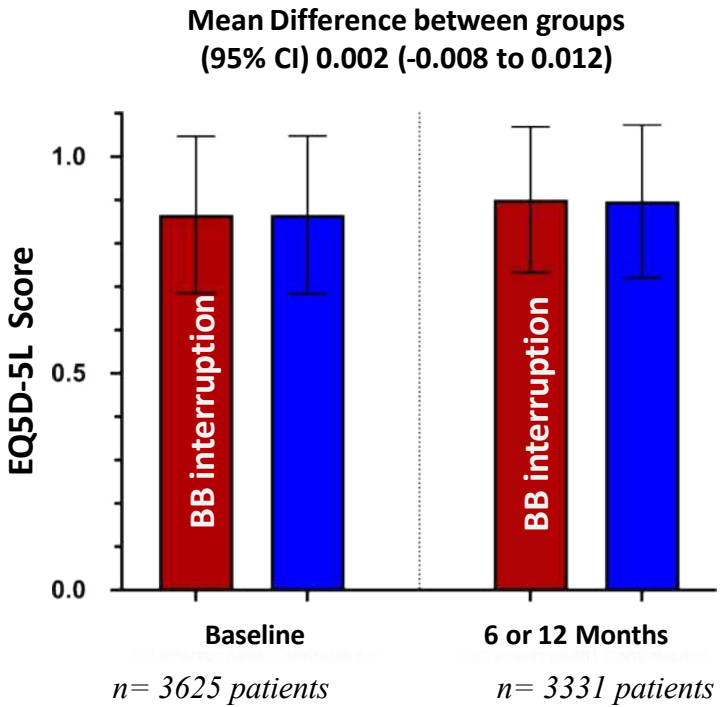
Mauri L et al. ***NEJM*** 2017

Silvain J et al. ***NEJM*** 2024

No improvement of Quality of Life

More coronary-related hospitalizations

Quality of Life



Hospitalization

End points — no. (%)	βB interruption N = 1846	βB continuation N = 1852
Hospitalization for cardiovascular reason	**349 (18.9%)**	**=307 (16.6%)**
Coronary-related reasons	**263 (14.2)**	**221 (11.9)**
Angina/ischemia	67 (3.6)	55 (3.0)
Angiography	146 (7.9)	117 (6.3)
Percutaneous coronary intervention	90 (4.9)	84 (4.5)
Coronary artery bypass graft surgery	4 (0.2)	4 (0.2)

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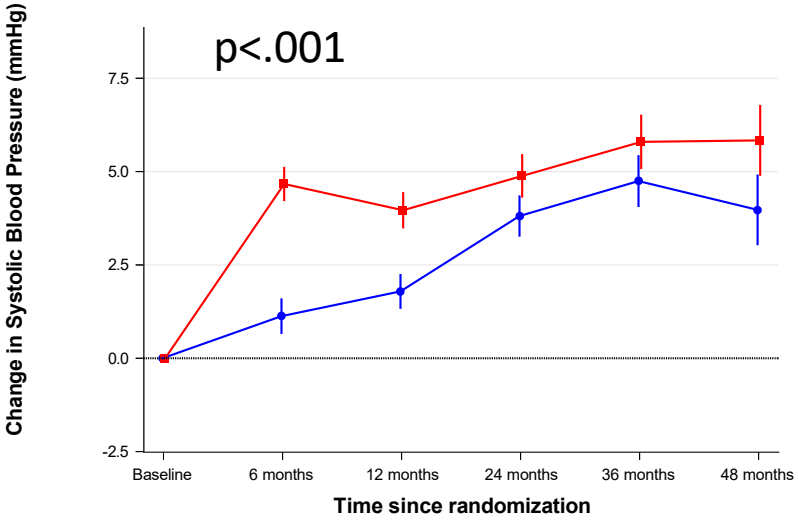
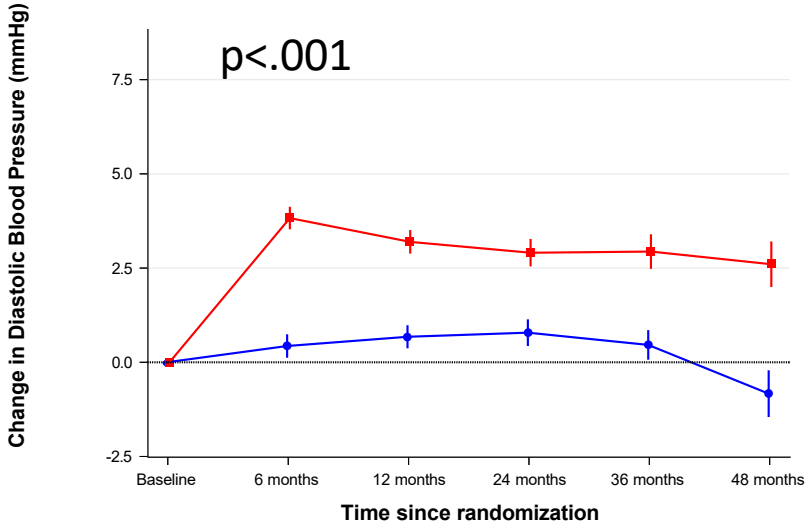
Effect of BB interruption on Blood Pressure



No. with Data						
ß-blocker continuation	1813	1323	1414	1072	727	413
ß-blocker interruption	1810	1413	1441	1067	719	408



No. with Data						
ß-blocker continuation	1814	1321	1413	1072	726	412
ß-blocker interruption	1810	1413	1440	1068	719	408

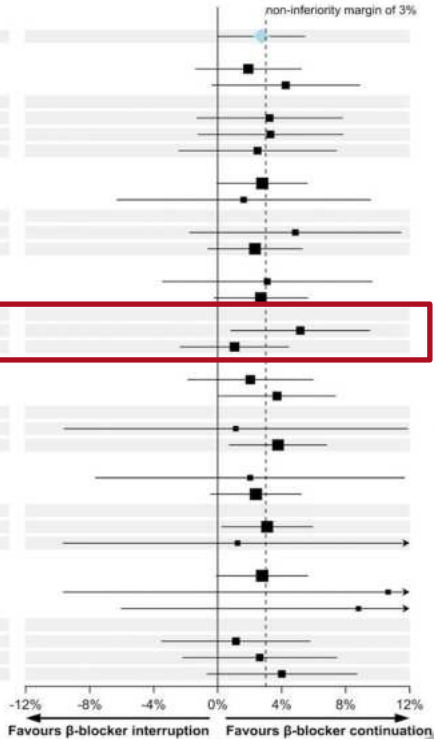
βB interruption group at 6 months resulted in an increase of :

+ 3.7 mmHg Systolic Blood Pressure [2.6, 4.8 mmHg]; p<.001

+ 3.9 mmHg Diastolic Blood Pressure [3.0, 4.0 mmHg]; p<.001

Prespecified Subgroup Analysis

Subgroup	β-blocker interruption events/total (%)	β-blocker continuation events/total (%)	Risk difference (95% CI)
Overall	432/1812 (23.8)	384/1821 (21.1)	2.8 (0.0 to 5.5)
Last MI before randomization			
STEMI	250/1148 (21.8)	227/1143 (19.9)	1.9 (-1.4 to 5.2)
NSTEMI	182/664 (27.4)	157/678 (23.2)	4.3 (-0.4 to 8.9)
Time between last MI and randomization, tertiles			
T1, <1.6 years	131/588 (22.3)	118/620 (19.0)	3.2 (-1.3 to 7.8)
T2, 1.6 to <4.9 years	140/630 (22.2)	109/576 (18.9)	3.3 (-1.3 to 7.9)
T3, ≥4.9 years	160/589 (27.2)	152/616 (24.7)	2.5 (-2.5 to 7.4)
Age group			
<75 years	337/1532 (22.0)	300/1561 (19.2)	2.8 (-0.1 to 5.6)
≥75 years	95/280 (33.9)	84/260 (32.3)	1.6 (-6.3 to 9.6)
Sex			
Female	79/307 (25.7)	66/316 (20.9)	4.8 (-1.8 to 11.5)
Male	353/1505 (23.5)	318/1505 (21.1)	2.3 (-0.6 to 5.3)
Diabetes mellitus			
Yes	110/361 (30.5)	101/369 (27.4)	3.1 (-3.5 to 9.7)
No	322/1451 (22.2)	283/1452 (19.5)	2.7 (-0.3 to 5.7)
Hypertension			
Yes	223/770 (29.0)	188/790 (23.8)	5.2 (0.8 to 9.5)
No	209/1042 (20.1)	196/1031 (19.0)	1.0 (-2.4 to 4.5)
Multivessel Disease			
Yes	253/941 (26.9)	240/966 (24.8)	2.0 (-1.9 to 6.0)
No	179/871 (20.6)	144/855 (16.8)	3.7 (0.0 to 7.4)
Renal Insufficiency			
Yes	22/105 (21.0)	22/111 (19.8)	1.1 (-9.6 to 11.9)
No	365/1450 (25.2)	314/1467 (21.4)	3.8 (0.7 to 6.8)
Ejection Fraction			
FE <50 %	51/170 (30.0)	47/168 (28.0)	2.0 (-7.7 to 11.7)
FE ≥50 %	367/1603 (22.9)	331/1614 (20.5)	2.4 (-0.5 to 5.2)
Revascularization type			
Complete	361/1572 (23.0)	316/1590 (19.9)	3.1 (0.2 to 5.9)
Incomplete	50/150 (33.3)	43/134 (32.1)	1.2 (-9.7 to 12.2)
Revascularization			
PCI	383/1631 (23.5)	329/1589 (20.7)	2.8 (-0.1 to 5.6)
Fibrinolysis	7/26 (26.9)	7/43 (16.3)	10.6 (-9.7 to 31.0)
CABG	20/62 (32.3)	19/81 (23.5)	8.8 (-6.1 to 23.7)
Heart rate, tertiles			
T1, <60 beats/min	137/612 (22.4)	126/593 (21.2)	1.1 (-3.5 to 5.8)
T2, 60 to <68 beats/min	129/551 (23.4)	121/582 (20.8)	2.6 (-2.2 to 7.5)
T3, ≥68 beats/min	153/613 (25.0)	128/611 (20.9)	4.0 (-0.7 to 8.7)



43% of the population had hypertension at baseline

Table 1. Current Trials of Beta-Blockers in Patients with Myocardial Infarction or Chronic Coronary Syndrome without Heart Failure.*

Acronym†	ClinicalTrials.gov No.	No. of Patients	Trial Location	Patients' Condition	Question	Primary End Point	Expected Completion
REDUCE-AMI[8]	NCT03278509	5000	Sweden, Estonia, and New Zealand	Acute MI with LVEF >50% and receipt of angiography	Beta-blocker vs. no beta-blocker	Death from any cause or new MI	Completed
DANBLOCK	NCT03778554	2760	Denmark	≤2 wk after MI and LVEF >40%	Beta-blocker vs. no beta-blocker	Death from any cause, recurrent MI, revascularization with PCI or CABG, ischemic stroke, incident heart failure, malignant ventricular arrhythmia, or resuscitated cardiac arrest	2024
BETAMI	NCT03646357	2900	Norway	Type 1 MI treated with PCI or lysis	Beta-blocker vs. no beta-blocker	Death from any cause, recurrent MI, heart failure, coronary revascularization, ischemic stroke, malignant ventricular arrhythmia, or resuscitated cardiac arrest	2024
REBOOT	NCT03596385	8468	Spain and Italy	MI without heart failure and with LVEF >40%	Beta-blocker vs. no beta-blocker	MACE‡	2024
SMART DECISION	NCT04769362	2540	South Korea	Receiving beta-blockers for ≥1 yr after MI	Continuation of beta-blocker vs. discontinuation	MACE‡	2025
AβYSS	NCT03498066	3700	France	STEMI or NSTEMI treated with beta-blocker, without heart failure or LVEF <40%	Continuation of beta-blocker vs. discontinuation at >6 mo after MI	Death from any cause, MI, stroke, or hospitalization for cardiovascular causes	2024
ABBREVIATE	NCT05081999	8500	Canada	Stable ischemic heart disease, without left ventricular dysfunction or heart failure	Continuation of beta-blocker vs. discontinuation	Death from any cause, nonfatal MI, hospitalization for resuscitated cardiac arrest, unstable angina leading to urgent revascularization, or heart failure	2026

* CABG denotes coronary-artery bypass grafting, LVEF left ventricular ejection fraction, MACE major adverse cardiac events, MI myocardial infarction, NSTEMI, non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

† ABBREVIATE denotes De-Adoption of Beta-Blockers in Patients with Stable Ischemic Heart Disease, AβYSS Beta-Blocker Interruption after Uncomplicated Myocardial Infarction, BETAMI Beta-Blocker Treatment after Acute Myocardial Infarction in Patients without Reduced Left Ventricular Systolic Function, DANBLOCK Danish Trial of Beta-Blocker Treatment after Myocardial Infarction without Reduced Ejection Fraction, REBOOT Treatment with Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction, REDUCE-AMI Randomized Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction, and SMART DECISION Long-term Beta-Blocker Therapy after Acute Myocardial Infarction.

‡ MACE was defined as death from any cause, MI, or hospitalization for heart failure.

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Conclusion

- A l'ère moderne, il n'est pas certain que l'instauration systématique d'un tt bétabloqueur en post infarctus soit utile si la fonction VG est préservée et qu'il n'y a ni insuffisance cardiaque ni arythmie
- A distance de l'infarctus, si on arrête les béta-bloquants, ne pas oublier que cela élève la pression artérielle chez les hypertendus
- Plusieurs grands essais randomisés sont en cours et leurs résultats attendus prochainement