ACTION Group
Academic Research Organization

AβYSS

La fin des bétabloquants dans l'IDM ?

AβYSS: Assessment of βeta blocker interruption one Year after an uncomplicated myocardial infarction on Safety and Symptomatic cardiac events requiring hospitalization

Background

- The historical benefit of treatment with β-blocker (βB) after a myocardial infarction (MI) is being questionned in our era of modern reperfusion strategies.

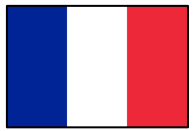
- The safety of the interruption of chronic βB treatment is unknown.

Hypothesis

- βB interruption among patients with a history of MI , preserved LVEF (≥40%), would be clinically safe and improve patients' quality of life (QoL).

Methods

- Academic, multicenter, open label, randomized, non-inferiority trial conducted at 49 sites in France.



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Funding

PHRC 2015 – French Ministry of Health & ACTION Group

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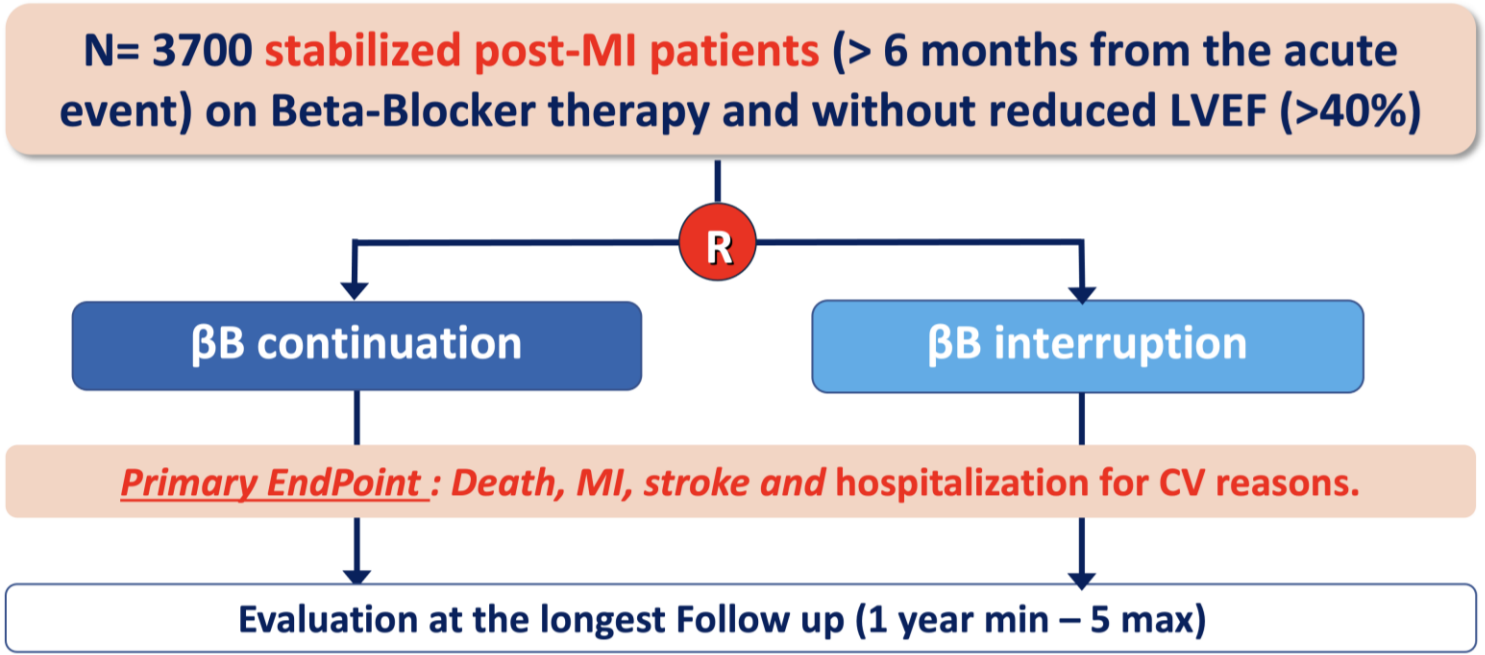
Study Design



NCT03498066 - EUDRACT No: 2017-003903-23

Inclusion Criteria

1. Patients ≥ 18 years of age
2. Current treatment with βB
3. Prior acute MI ≥ 6 months before randomization

Exclusion Criteria

1. Recent ACS (<6 months)
2. Altered LVEF <40%
3. Other primary indication for βB
- Uncontrolled high blood pressure (HBP)
- Prior episode of heart failure in the past 2 years
- Persistent angina or ischemia
- Prior episode of ventricular or supraventricular arrhythmia in the past year

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

Outcomes

Primary end point : Death, MI, stroke, or hospitalization for cardiovascular (CV) reasons

Main secondary end point : Change in QoL as measured by the European Quality of Life–5 Dimensions (EQ5D) questionnaire

Other secondary end points :

- Death, MI, stroke
- Death, MI, stroke, or hospitalization for heart failure
- Blood pressure and heart rate control

Clinical endpoints were evaluated at 6 months, 12 months and every year until the longest follow-up (minimum, 1 year).

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;258:168-176

Key Baseline Characteristics

	βB INTERRUPTION N = 1846	βB CONTINUATION N = 1852
Age — yr	63.5 ± 11.2	63.5 ± 10.9
Male sex — no. (%)	1530 (82.9)	1531 (82.6)
Hypertension — no. (%)	786 (42.6)	805 (43.4)
Diabetes — no. (%)	372 (20.1)	375 (20.2)
Past medical history		
ST-segment elevation MI — no. (%)	1168 (63.3)	1162 (62.7%)
Median duration between MI and randomization (IQR)— yr	2.9 (1.2—6.2)	2.8 (1.1—6.6)
Revascularization for the MI event — no. (%)	1755 (95.1)	1757 (94.8)
Health status at baseline		
Median LVEF at randomization (IQR) — %	60 (52—60)	60 (52—60)
Patients with LVEF between 40 to 50% — no. (%)	430 (23.3)	435 (23.5)
Residual angina — no. (%)	21 (1.1)	30 (1.6)
Median Heart Rate (IQR)— BPM	63 (57—71)	63 (57—71)
Median systolic blood pressure (IQR)— mm Hg	132 (121—144)	131 (121—144)
Median diastolic blood pressure (IQR) — mm Hg	77 (70—83)	77 (70—83)
LDL cholesterol - Median (IQR) - mg/dl	70 (56—91)	73 (56—95)

Follow up

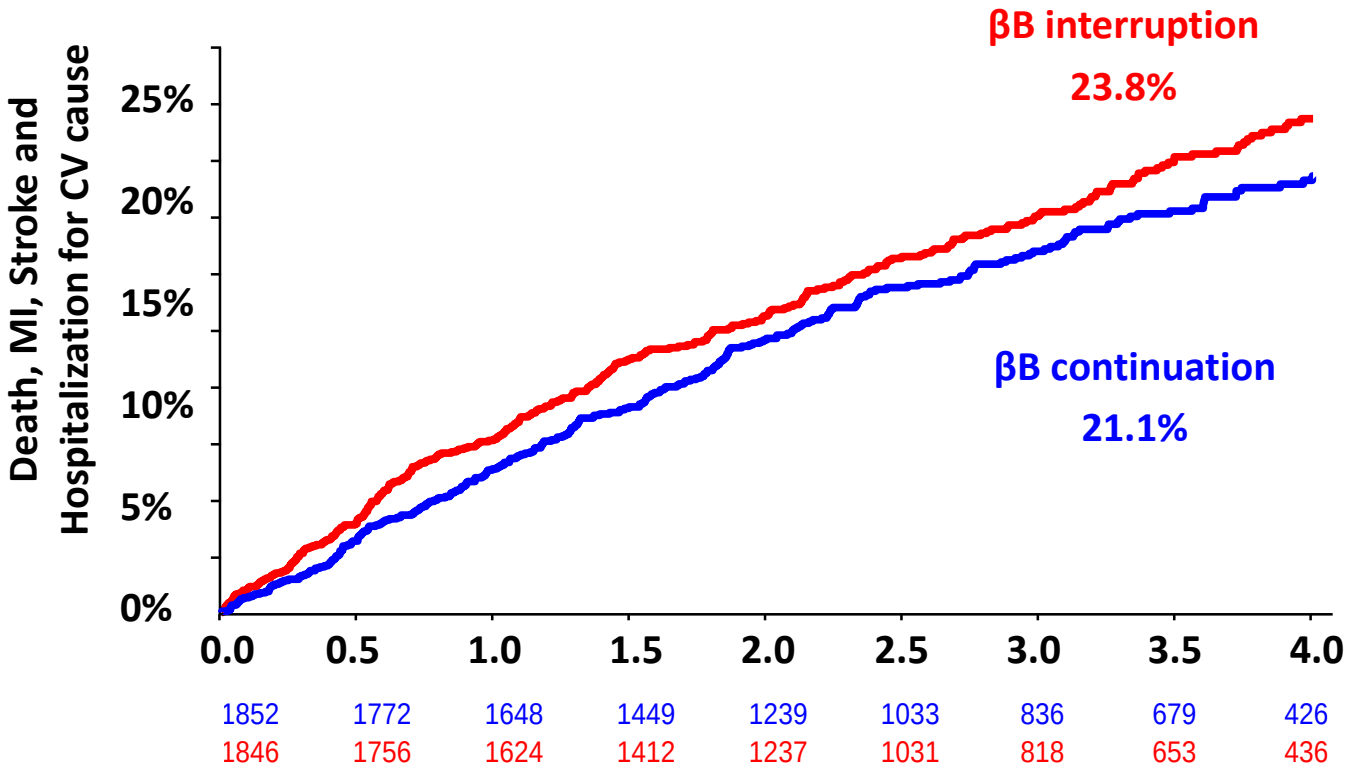
- Randomization between **August 28, 2018**, and **September 12, 2022**; scheduled recruitment continued during the coronavirus disease 2019 pandemic and lockdown in France.

- Patients were followed for a **median of 3.0 years** (interquartile range, 2.0 to 4.0) up to 5 years (minimum one year).

- **Low rate of cross over (5.7%)** from one strategy to the other (209 patients) and was more frequent in the interruption group (158 patients [**8.6%**]) than in the continuation group (51 patients [**2.8%**]).

Primary Results

Primary Outcome

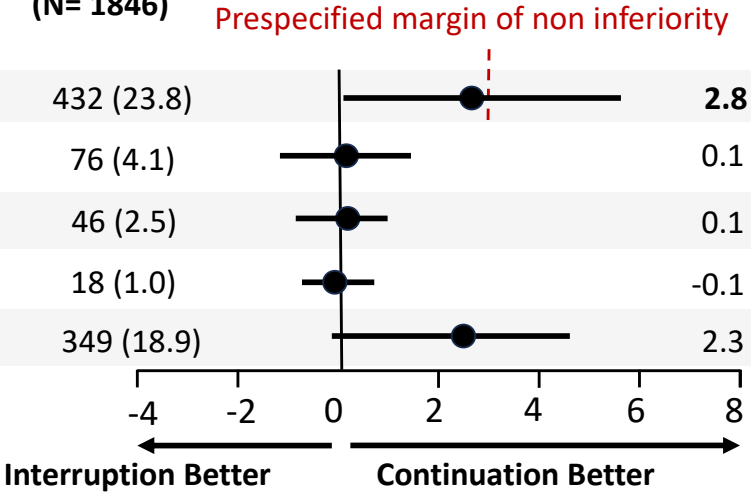


ITT
HR 1.16
(95% CI) 1.01 to 1.33
p = 0.44 for non-inferiority

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

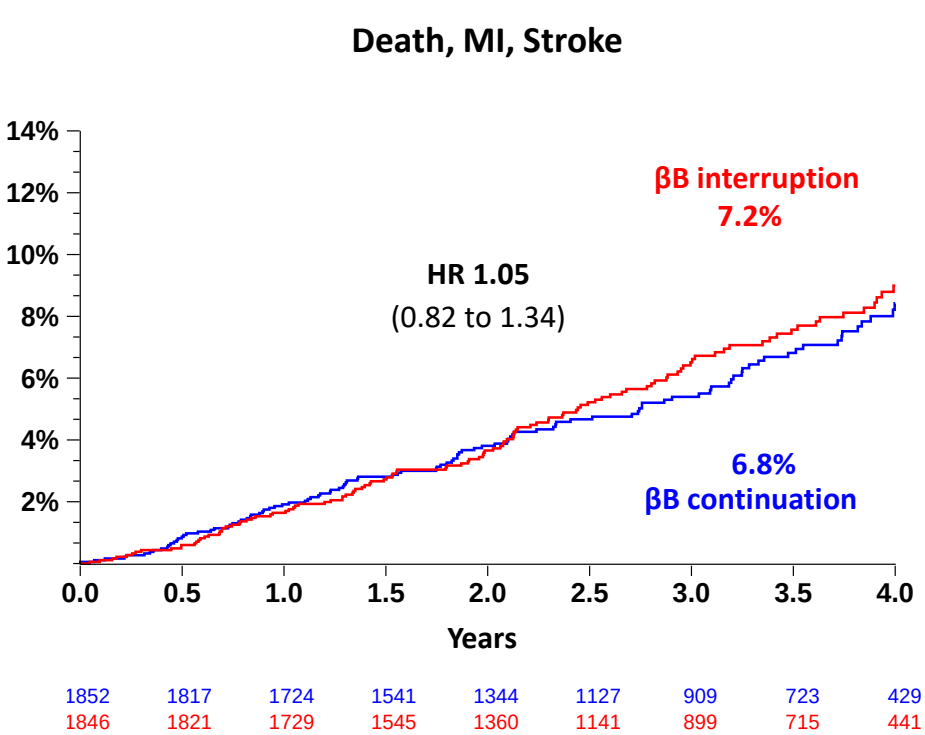
Primary Outcome Components

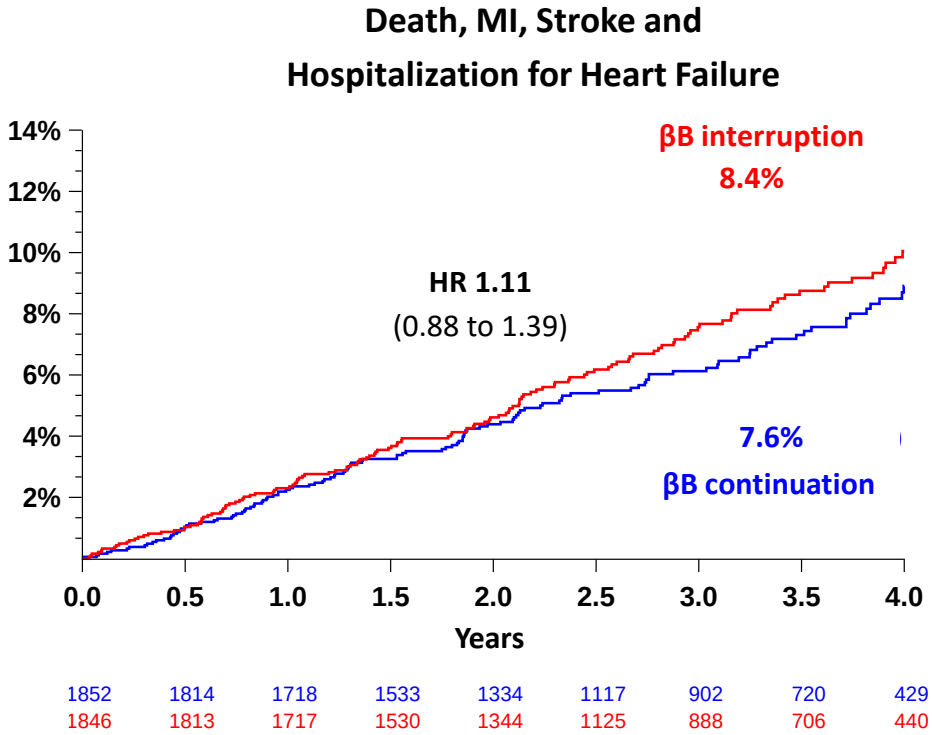
End Points	Beta-Blocker Continuation (N=1852)	Beta-Blocker Interruption (N= 1846)	Risk Difference (95% CI) (percentage points)
Primary Endpoint	384 (21.1)	432 (23.8)	**2.8 (<1 to 5.5)**
Death	74 (4.0)	76 (4.1)	0.1 (-1.2 to 1.4)
Myocardial Infarction	44 (2.4)	46 (2.5)	0.1 (-0.9 to 1.1)
Stroke	19 (1.0)	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)



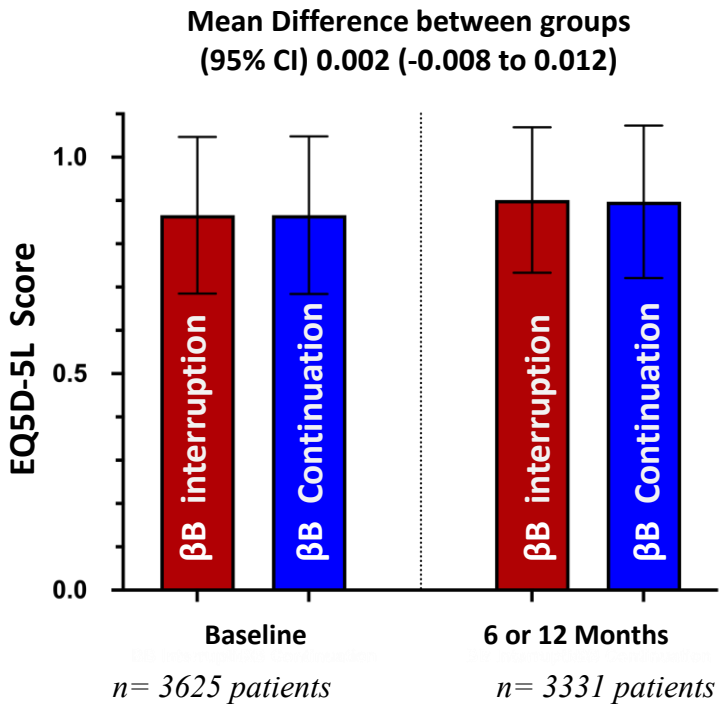
Interruption of βB treatment was **NOT non-inferior** to a strategy of βB continuation

Secondary Outcomes





Quality of Life



No improvement of Quality of Life

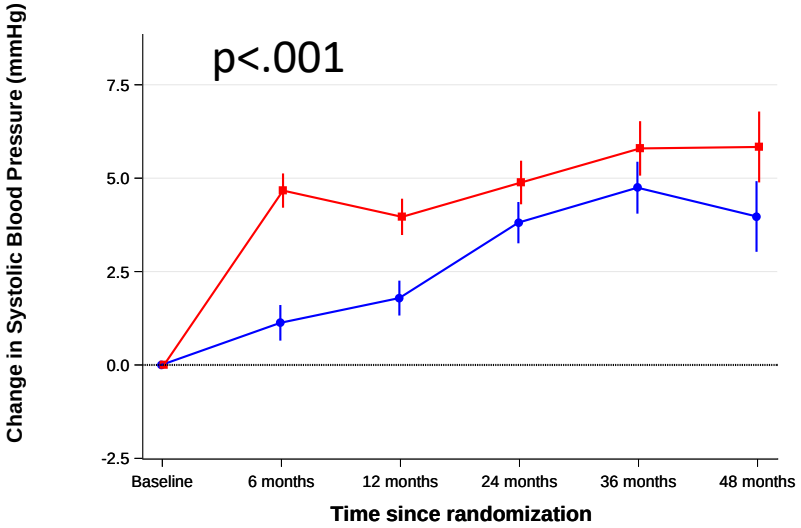
Hospitalization

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)

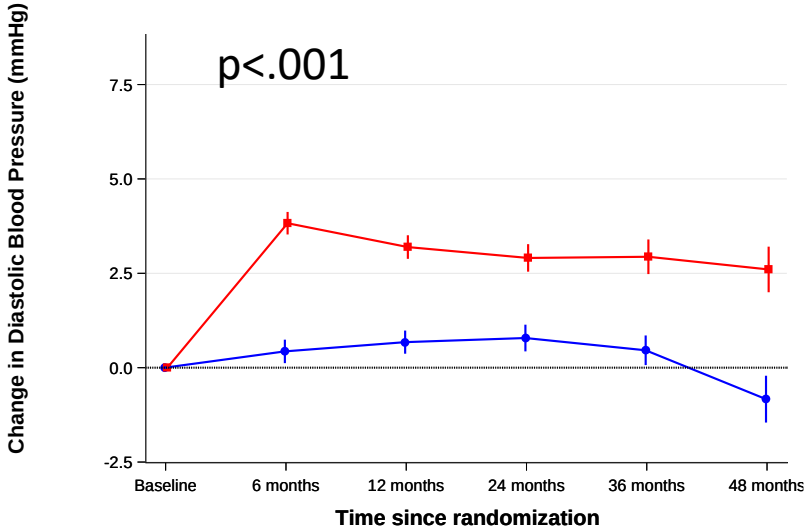
Higher rate of coronary-related reasons

Secondary Results

Effect of βB 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



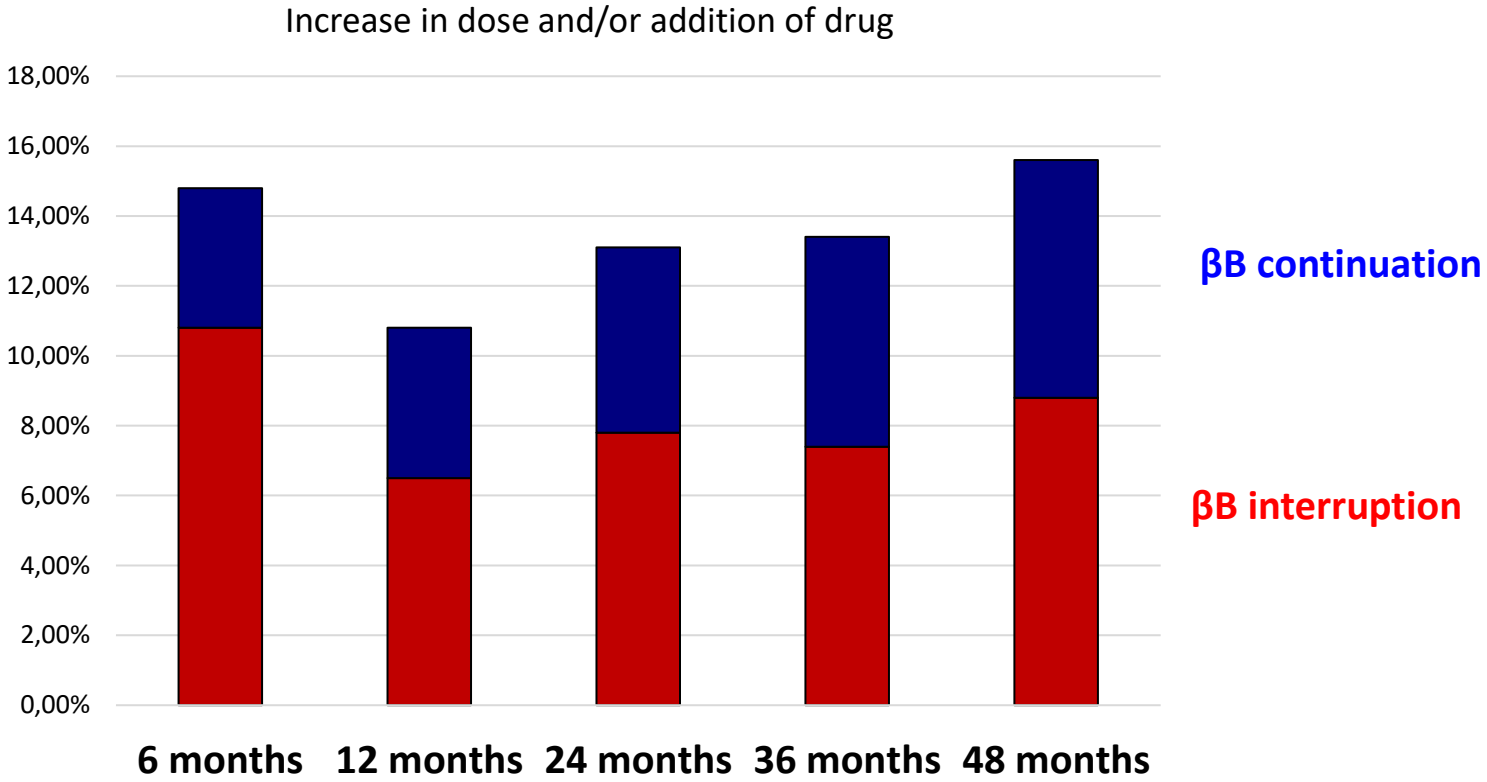
No. with Data						
ß-blocker continuation	1814	1321	1413	1072	726	412
ß-blocker interruption	1810	1413	1440	1068	719	408

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

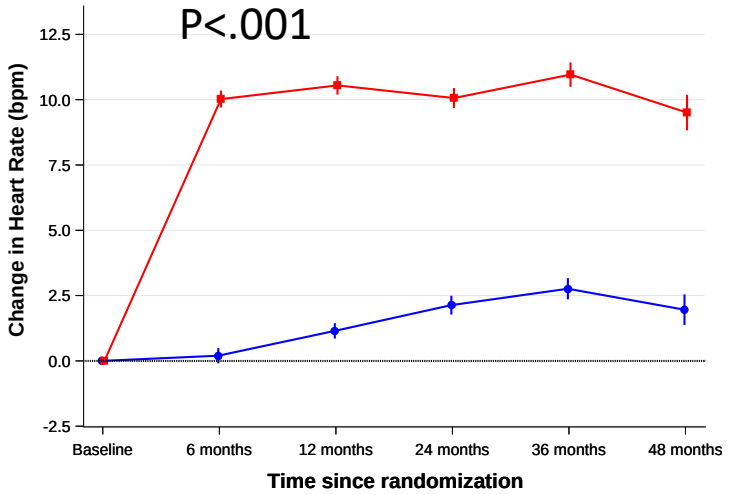
+ 3.7 mmHg Systolic Blood Pressure [2.6, 4.8 mmHg]; p<.001

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

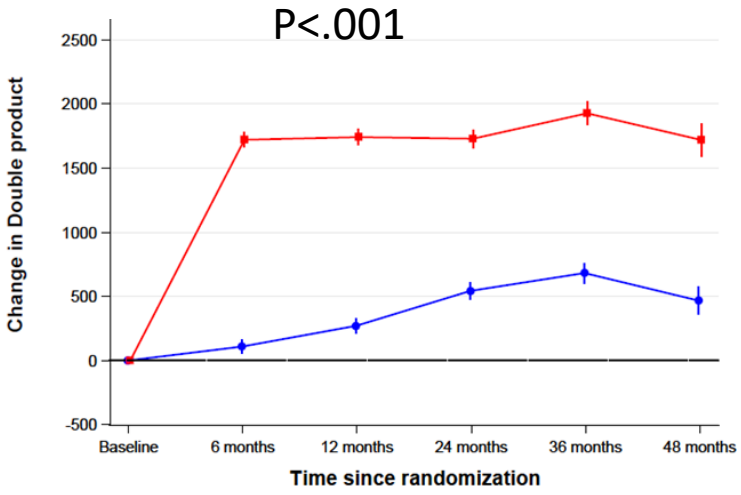
Any increase of antihypertensive therapy



Effect of βB interruption on Heart Rate control



No. with Data						
ß-blocker continuation	1815	1312	1402	1040	708	394
ß-blocker interruption	1808	1409	1415	1046	679	394



No. with Data						
ß-blocker continuation	1789	1280	1369	1019	689	387
ß-blocker interruption	1791	1379	1391	1026	673	382

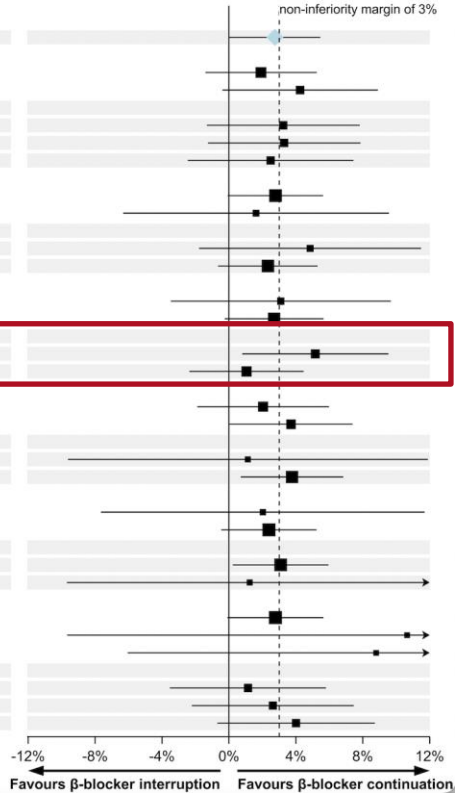
βB interruption group at 6 months resulted in an increase of :

+ 9.8 bpm Resting Heart Rate [9.1, 10.6 bpm] , P<.001

+1616 Double Product (SBP x HR)[1484, 1749], P<.001

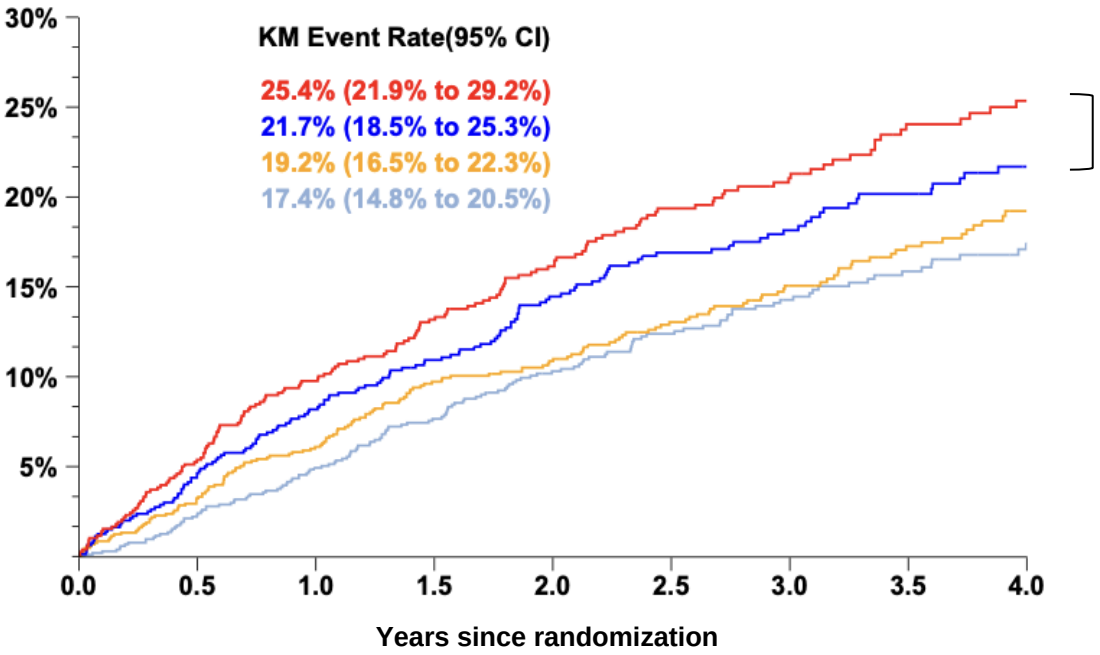
Prespecified Subgroup

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 with hypertension at baseline

Primary Endpoint in Hypertensive (HBP) patients



adjHR 1.18
95%CI 1.01 to 1.36
P=0.03

adjHR 1.05
95%CI 0.86 to 1.28
P=.64

No. at Risk

No HBP β-blocker continuation	1047	1013	947	837	711	591	482	388	235
No HBP β-blocker interruption	1060	1019	948	831	725	604	491	392	243
HBP β-blocker continuation	805	759	701	612	528	442	354	291	191
HBP β-blocker interruption	786	737	676	581	512	427	327	261	193

A study of the ACTION Group
www.action-groupe.org

Limitations of the trial

- **Prospective randomized open blinded end-point (PROBE)** study design

  => all events were adjudicated in a blinded fashion.

- **Hospitalization for Cardio-Vascular reason** is a soft endpoint but important in the life of patients.

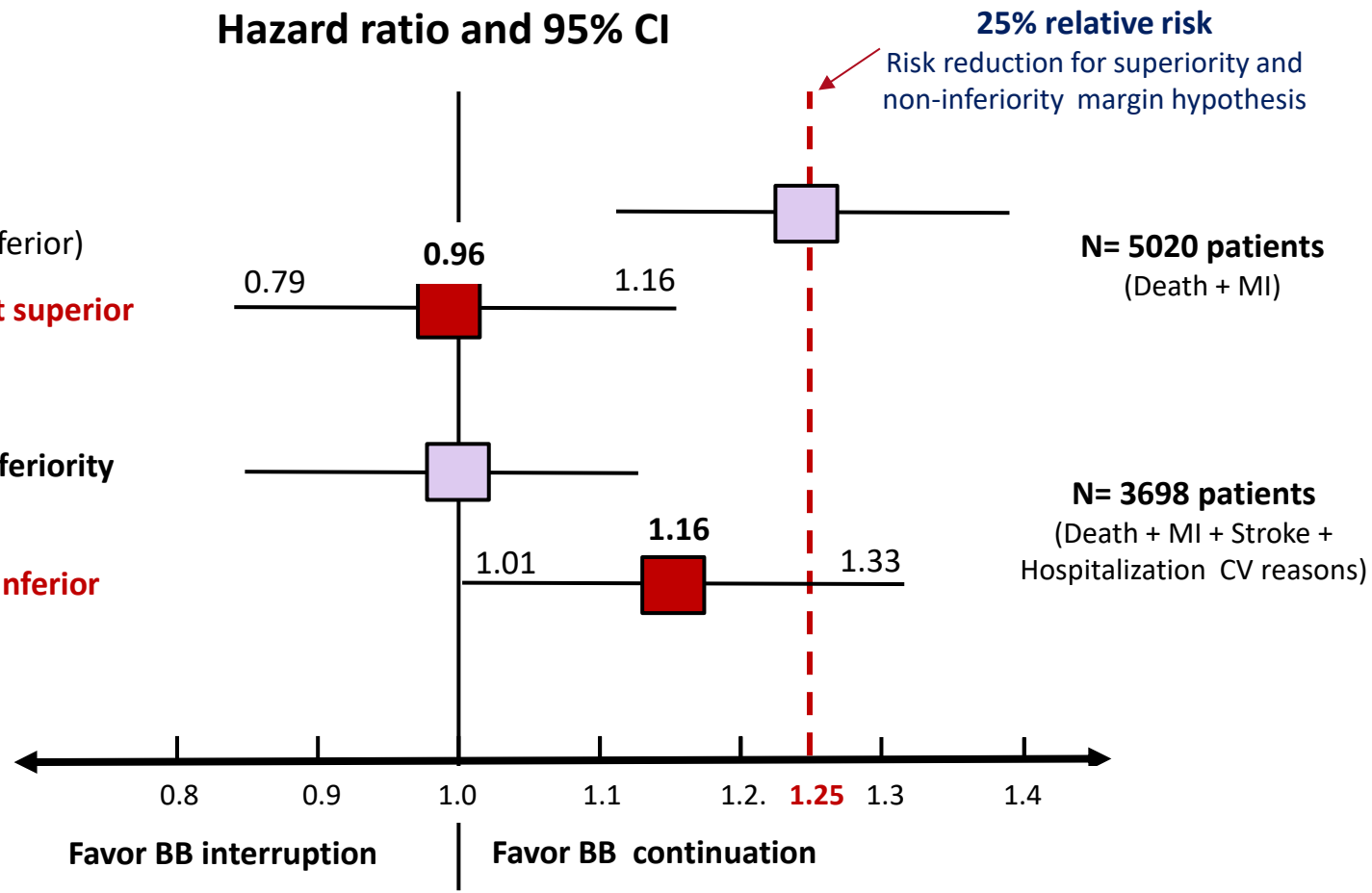
- **The 3% absolute risk margin of non-inferiority** can be discussed

Key Messages

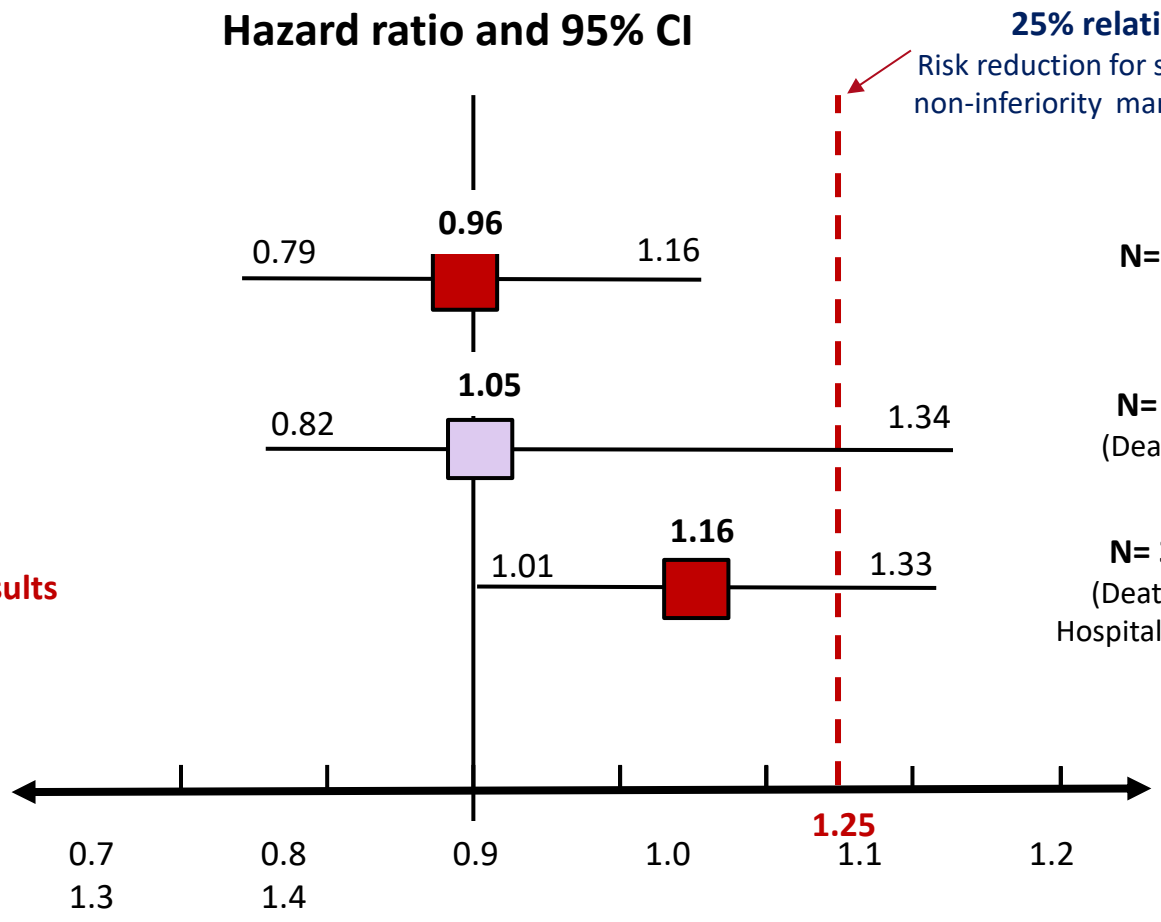
- ABYSS did not demonstrate the safety of **βB interruption in MI patients with preserved LVEF ,** a strategy that led to a higher rate of hospitalizations especially in hypertensive patients.

- **βB interruption** did not improve patient's quality of life and **increased Blood Pressure, resting Heart Rate**

ABYSS and REDUCE-MI



ABYSS and REDUCE-MI



Thanks to all 259 investigators !

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