ALBATROSS and REMINDER trials update

Pooled Patient-level Analysis From the ALBATROSS and REMINDER Randomized Trials

Authors

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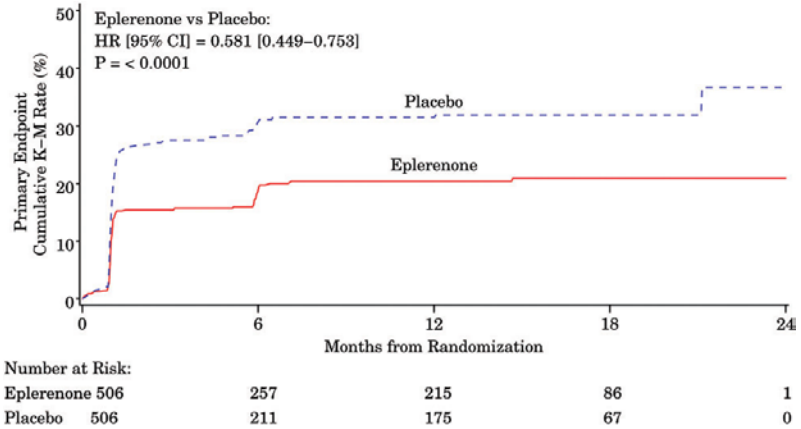
Declaration of Interest

- Funding:
  - ALBATROSS: French Ministry of Health and the Institute of Cardiometabolism And Nutrition (ICAN)
  - REMINDER: PFIZER
- F Beygui:
  - Institutional research grants and/or honoraria
    - ASTRAZENECA, MEDTRONIC, BIOSENSOR, BOSTON SCIENTIFIC, ACIST
  - None with respect to the present presentation

Background 1

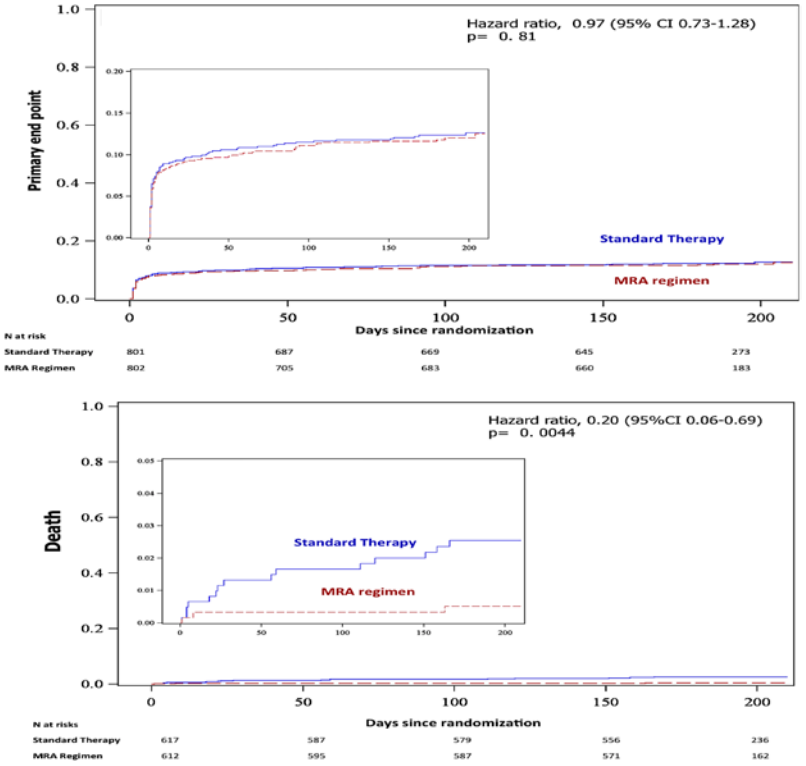
- High aldosterone plasma levels early after STEMI are associated with mortality
- Early administration of MRA after myocardial infarction in preclinical models improves myocardial healing and both electrical and structural remodeling
- MRAs reduce mortality in severely and mildly symptomatic chronic heart failure and post-MI heart failure

Background 2



REMINDER trial

G. Montalescot et al.Eur Heart J 2014;35:2295–2302



ALBATROSS trial

F Beygui et al. J Am Coll Cardiol 2016;67:1917–1927

Purpose

To assess the benefit of MRA regimens on mortality in low risk STEMI using an individual patient-level data analysis of pooled STEMI populations of ALBATROSS and REMINDER trials

	ALBATROSS	REMINDER
Patient population	STEMI (n=1229) or NSTEMI (n=369) Randomization ≤72 hours after symptom onset	STEMI (n=1012) patients. Randomization ≤24 hours after symptom onset
Design	Randomized, open-labeled, blinded endpoint	Randomized, double blinded, placebo-controlled
Treatment	IV potassium canrenoate (200mg), PO spironolactone(25mg OD)	PO eplerenone (25 to 50 mg OD)
Comparator	Standard treatment	Placebo
Key exclusion criteria	• Known hyperkaliemia (>5.5 mmol/l) • eGFR <30 ml/min • Plasma creatinine level > 220 µmol/l • > 10 minutes cardiac arrest	• LVEF <40% • History of heart failure • eGFRe ≤30 mL per minute per 1.73 m2 • serum creatinine ≥220 mmol/L
Primary outcomes	Death, resuscitated cardiac arrest, significant ventricular arrhythmia, class IA indication for implantable defibrillator, new or worsening heart failure	Cardiovascular mortality, re-hospitalization for HF or sustained VT or VF, left ventricular ejection fraction ≤ 40% ≥1 month post- ®, high BNP/NT-proBNP after 1 month

Methods: statistical analysis

- Individual patient-level data analysis of pooled populations (pre-planned by the steering committees)
- Efficacy endpoints:
  - Primary outcome: Death of any cause
  - Secondary key outcome: Death or resuscitated sudden death
  - Analyzed as time-to-event outcomes using Cox models systematically stratified on the study identifier and as binary outcomes using a Mantel-Haenszel test stratified on the study
- Safety endpoints: Analyzed as binary variables with a Mantel-Haenszel test stratified on the study
- *Post hoc* sensitivity analyses: Cox models adjusted on variables unequally distributed between the treatment arms ($p < 0.20$)
- Inter-study heterogeneity: Breslow-Day test, interaction between the study identifier and the treatment arm, the I^2 statistics (Sidik-Jonkman)
- Consistency: Subgroup interaction analysis

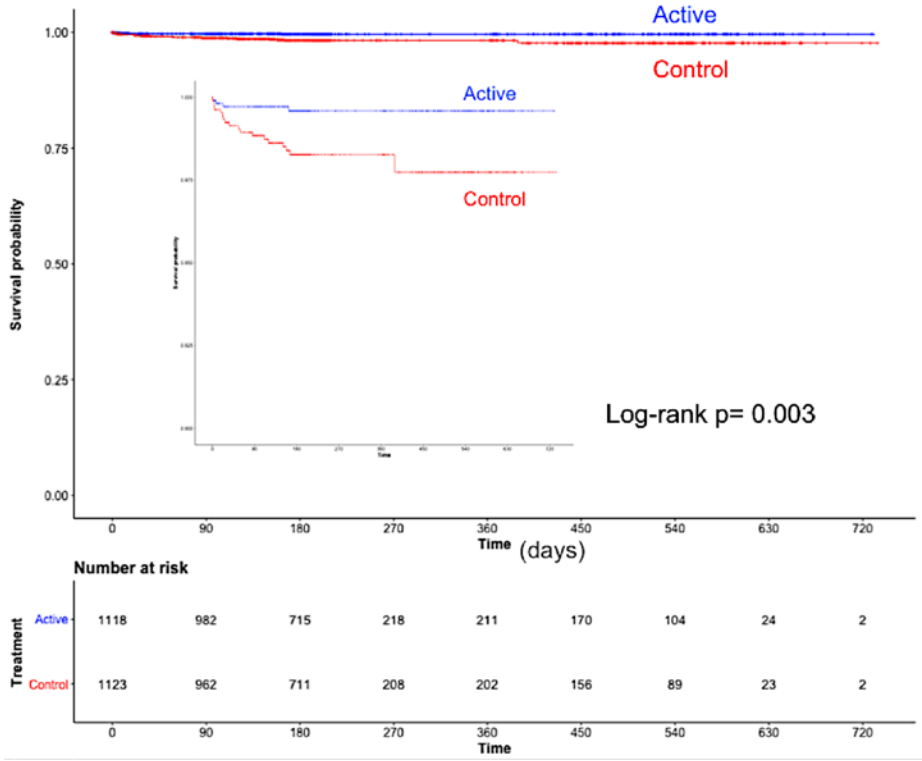
Results 1: Baseline characteristics

	Active n=1118	Control n=1123	p
Age (years)	58±11	58±12	0.8
Gender (Female)	178(15.9)	199(17.7)	0.3
Body mass index (Kg/m^2)	27±5	27±5	0.12
Heart rate (per minute)	73±15	74±15	0.02
SBP(mmHg)	123±21	125±21	0.02
Killip class ≥ 2	29(2.6)	53(4.7)	0.007
eGFR (mL/min)	102±35	105±37	0.14
GRACE score	140±22	140±24	0.6
Systemic hypertension	464(41.5)	500(44.5)	0.15
Diabetes mellitus	145(13.0)	153(13.6)	0.7
Hypercholesterolemia	450(40.3)	433(38.6)	0.4
Active smoker	375(33.5)	397(35.4)	0.4
Prior myocardial infarction	71(6.4)	65(5.8)	0.6
Prior stroke	28(2.5)	16(1.4)	0.09

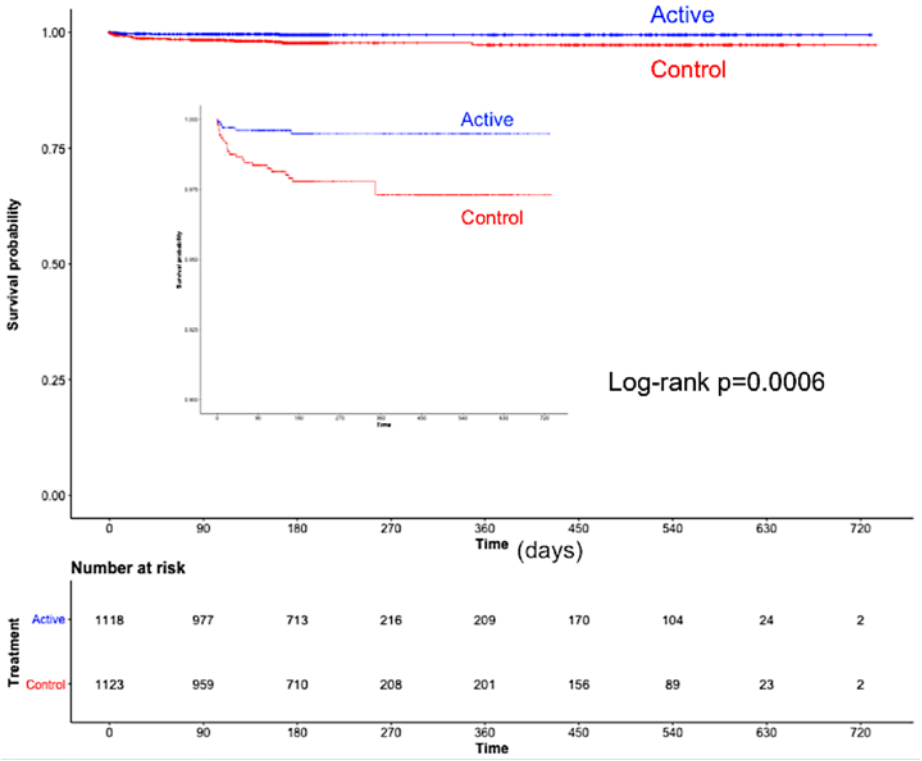
Results 2: Initial/in-hospital management

	Active n=1118	Control n=1123	p
Primary PCI	971(86.9)	983(87.5)	0.7
Any PCI	1028(91.9)	1032(91.9)	0.96
Coronary Bypass surgery	23(2.1)	18(1.6)	0.5
Fibrinolysis	96(8.6)	93(8.3)	0.8
Aspirin	1096(98.0)	1105(98.4)	0.6
Clopidogrel	734(65.7)	711(63.3)	0.3
Prasugrel	619(55.4)	654(58.2)	0.2
Ticagrelor	13(1.2)	15(1.3)	0.9
Any p2y12 inhibitor	1110(99.3)	1115(99.3)	1.0
ACEi or ATA	975(87.2)	989(88.1)	0.6
Beta-blockers	1037(92.8)	1040(92.6)	0.95
Statins	1076(96.2)	1095(97.5)	0.11
LVEF	53±9	53±9	0.2
Follow-up duration (days)	244±165	241±163	0.7

Results 3: Primary and key secondary outcomes



Death



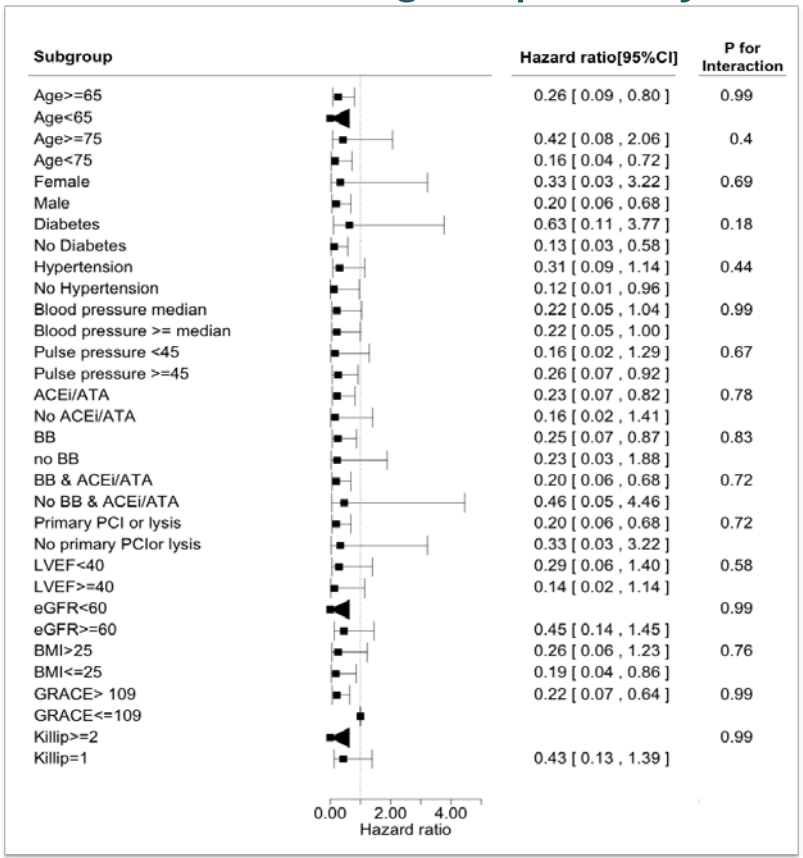
Death or resuscitated sudden death

Results 4: Outcomes and inter-study heterogeneity

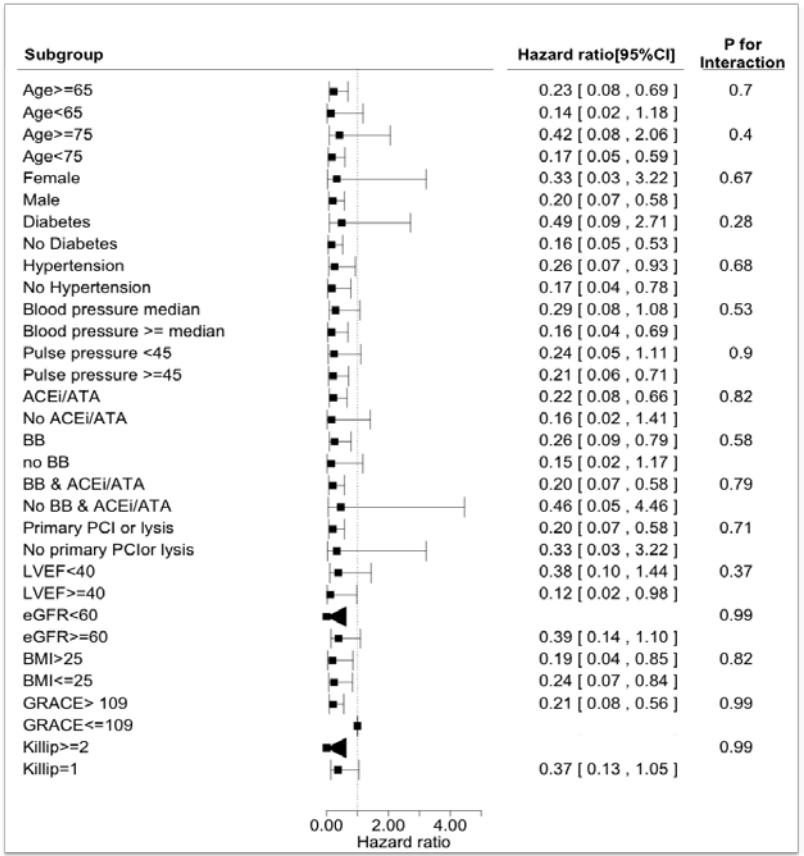
	n (%)		Active versus control				Inter-study heterogeneity		
	Active n=1118	Control n=1123	HR (95% CI)	p	Adj-HR (95% CI)	p	B-D p	Cox p	I^2 (%)
Death	**4 (0.4)**	**18 (1.6)**	**0.23 (0.08-0.67)**	**0.003**	**0.24 (0.08-0.72)**	**0.01**	0.7	0.7	0
Death/resuscitated sudden death	**5 (0.4)**	**23 (2)**	**0.22 (0.08-0.57)**	**0.0006**	**0.21 (0.08-0.57)**	**0.002**	0.8	0.8	0
Sudden cardiac death	2 (0.2)	3 (0.3)	0.2 (0.02-1.7)	0.1	0.54 (0.08-3.83)	0.5	**0.2**	**0.99**	**17**
Cardiovascular death	**4 (0.4)**	**14 (1.2)**	**0.28 (0.09-0.86)**	**0.02**	**0.28 (0.09-0.88)**	**0.03**	0.6	0.6	0
Resuscitated sudden death	1 (0.1)	5 (0.4)	0.20 (0.02-1.70)	0.1	0.21 (0.02-1.84)	0.2	0.3	0.99	0
Ventricular fibrillation	**1 (0.1)**	**6 (0.5)**	**0.18 (0.02-1.54)**	**0.08**	**0.19 (0.02-1.56)**	**0.1**	0.3	0.99	0
Ventricular tachycardia	42 (3.8)	43 (3.8)	1.24 (0.81-1.91)	0.3	1.29 (0.84-1.99)	0.3	0.3	0.99	0
Heart failure	43 (3.8)	48 (4.3)	1.06 (0.7-1.6)	0.8	0.90 (0.59-1.38)	0.6	0.3	0.2	0
Recurrent myocardial infarction	11 (1.0)	12 (1.1)	0.98 (0.43-2.23)	0.96	1.04 (0.46-2.38)	0.92	**0.1**	**0.2**	**58**
Safety outcomes			**OR (95% CI)**	**p**					
Acute renal failure	24 (2.1)	15 (1.3)	1.62 (0.84-3.11)	0.3	-	-	0.4	-	0
K+> 5.5 mmol/L	**37 (3.3)**	**20 (1.8)**	**1.89 (1.09-3.29)**	**0.03**	-	-	0.8	-	0
K+> 6 mmol/L	11 (1.0)	4 (0.4)	2.77 (0.88-8.74)	0.1	-	-	**0.2**	-	**29**

Results 5:Subgroup analysis

death



Death/Resuscitated sudden death



Limitations

- Limitations inherent to the pooling data from different studies with different designs and different active treatments.
  - A class effect is very likely between the drugs
  - The stratified and adjusted analyses minimize bias
  - Absence of inter-study heterogeneity
- Definitions were different for ventricular tachycardia and heart failure between studies
- Event rates were low, lack of power to detect differences
- The subgroup analysis should be considered with consideration of the risk of multiple testing with low event rates.

Conclusions

- Our analysis based on pooled patient-level data from two randomized trials suggests a significant reduction of death associated with MRA regimens given early after low risk STEMI
- Such regimens are associated with higher rates of moderate hyperkalemia (>5.5 mmol/L) but not with higher rates of acute renal failure or severe hyperkalemia (>6 mmo/L)
- Although our study seems robust with respect to its primary outcome, the low event rates should be considered and lead to adequately sized and specifically designed RCT to confirm the potentially major clinical benefit associated with low-cost treatments.