ESC 2023
TRIALS' SUMMARY

Cardio_Cast

Presented by:

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Rosuvastatin vs. Atorvastatin Treatment in LODESTAR Trial

Randomized comparison of rosuvastatin vs. atorvastatin treatment in patients with coronary artery disease: a secondary analysis of the randomized LODESTAR trial

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on behalf of the LODESTAR trial investigators

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Background

- **Statins in coronary artery disease**
  - Intensive lowering of low-density lipoprotein (LDL) cholesterol levels is recommended in patients with coronary artery disease (CAD).
  - Among the various lipid-lowering drugs, statins are the cornerstone of therapy and high-intensity statins are generally used as the first-line therapy in patients with CAD.
  - Physicians make decisions for not only statin intensity but also statin type.

Mach F, et al. Eur Heart J 2020;41:111-188
Grundy SM, et al. J Am Coll Cardiol 2019;73:e285-350

  - However, few RCTs have directly compared the long-term clinical outcomes of the two most potent statins (rosuvastatin versus atorvastatin) in patients with CAD.

- **Aims**
  - To compare the long-term efficacy and safety between the rosuvastatin and atorvastatin treatment in patients with CAD

Study design

- LODESTAR :A randomised, open-label, multicenter trial (Hong SJ, et al. JAMA 2023;329:1078-1087)
- 2-by-2 factorial randomization (statin type and statin intensity strategy)
- Enrollment period: September 9, 2016 and November 27, 2019

- Key inclusion criteria
  - Patients ≥19 years old
  - Patients clinically diagnosed with coronary artery disease: stable angina, unstable angina, acute non-ST elevation myocardial infarction, and acute ST elevation myocardial infarction
  - Patients with signed informed consent

- Key exclusion criteria
  - Pregnant women or women with potential childbearing during the study period
  - Patients with severe adverse events or hypersensitive to statin
  - Patients receiving drug that interacts with statin (strong inhibitor of cytochrome p-450 3A4 or 2C9)
  - Patients with risk factors for myopathy, hereditary muscle disorder, hypothyroidism, alcohol use disorder, severe hepatic dysfunction (3 times the normal reference values), or rhabdomyolysis
  - Life expectancy <3 years
  - Patients who could not be followed for more than 1 year
  - Patients who could not understand the consent form

Study design

Patients with Coronary Artery Disease
N=4400

1:1 Randomization

Rosuvastatin treatment	**Atorvastatin treatment**
N=2204	**N=2196**

Clinical follow-up at 3 years
Composite of all-cause death, myocardial infarction, stroke, or any coronary revascularization

Trial Registration: Clinicaltrial.gov Identifier: NCT02579499

Statistical analysis

- The sample size estimation for the LODESTAR trial was performed on the basis of determining the primary objective of the study: to compare the treat-to-target strategy (target LDL cholesterol, 50-70mg/dL) with the high-intensity statin strategy in terms of 3-year occurrence of the primary outcome.

  Hong SJ, et al. *JAMA* 2023;329:1078-1087

- A 2-by-2 factorial randomization was prespecified, nevertheless, the sample size estimation was not performed for comparing the randomized statin types.

- Interaction between statin type and statin intensity strategy regarding the primary outcome was estimated, and there was no significant interaction.

- **This study focused on the randomized statin types in the LODESTAR trial**
  → 3-year clinical outcomes between the rosuvastatin and atorvastatin treatment in patients with CAD were evaluated

Study flow

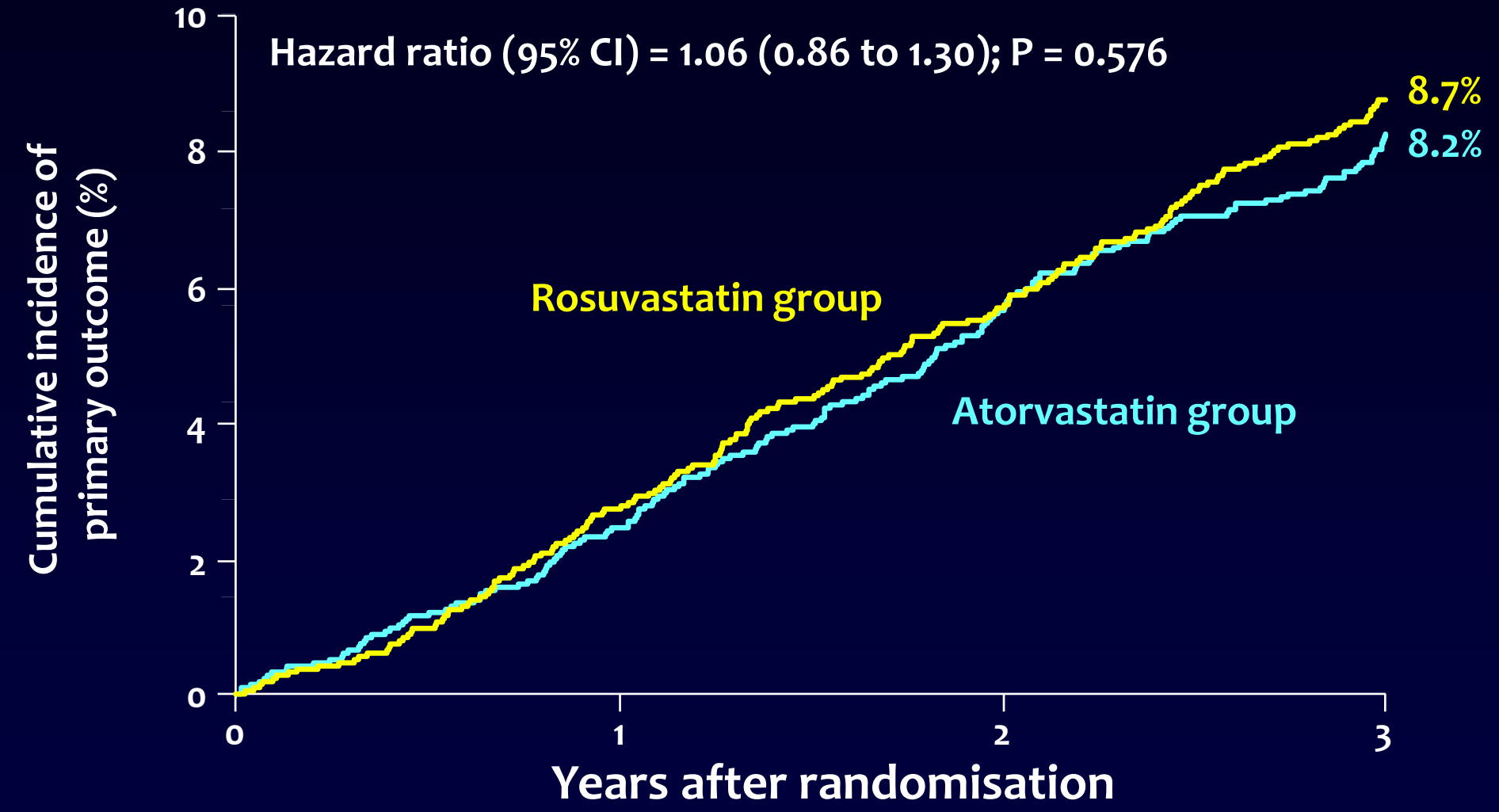
4400 underwent randomization

2204 Were assigned to receive rosuvastatin	**2196 Were assigned to receive atorvastatin**
1935 Received rosuvastatin as randomized	1898 Received atorvastatin as randomized
49 Did not complete statin therapy	46 Did not complete statin therapy
40 Due to adverse events	37 Due to adverse events
9 Due to poor compliance	9 Due to poor compliance
229 Did not receive rosuvastatin	252 Did not receive atorvastatin
21 Due to adverse events	30 Due to adverse events
18 Due to patients' request	16 Due to patients' request
5 Due to physicians' decision	11 Due to physicians' decision
170 Failure to comply with protocol	187 Failure to comply with protocol
6 Others	8 Others
16 Withdrew consent 13 Lost to follow-up 57 Died	14 Withdrew consent 12 Lost to follow-up 51 Died
2204 Included in the primary analysis	2196 Included in the primary analysis

Baseline clinical characteristics

	Rosuvastatin group (N=2204)	Atorvastatin group (N=2196)
Age, mean (SD), years	65 (10)	65 (10)
Female sex	602 (27)	626 (29)
Body-mass index, mean (SD), kg/m^2	24.8 (3.0)	24.7 (2.8)
Hypertension	1498 (68)	1439 (66)
Diabetes	725 (33)	743 (34)
Chronic kidney disease	149 (7)	170 (8)
Previous stroke	140 (6)	123 (6)
Previous PCI	1258 (57)	1199 (55)
Previous CABG	167 (8)	167 (8)
Clinical presentation at randomization		
Acute myocardial infarction within 1 year	175 (8)	163 (7)
Unstable angina or revascularization within 1 year	404 (18)	384 (18)
>1 year after myocardial infarction	322 (15)	353 (16)
>1 year after unstable angina or revascularization	906 (41)	878 (40)
Detection of CAD at screening without symptoms	397 (18)	418 (19)
Lipid lowering therapy before randomization		
Statin		
None	351 (16)	327 (15)
Low-intensity statin	43 (2)	50 (2)
Moderate-intensity statin	1277 (58)	1247 (57)
High-intensity statin	533 (24)	572 (26)
Ezetimibe	259 (12)	220 (10)
LDL cholesterol, mean (SD), mg/dL	86 (33)	87 (32)

Primary outcome



Rosuvastatin	2204	2126	2059	1984
Atorvastatin	2196	2124	2051	1990

Primary outcomes

	Rosuvastatin group (N=2204)	Atorvastatin group (N=2196)	Absolute difference (95% CI)	Hazard ratio (95% CI)	P Value
Primary outcome					
Death, myocardial infarction, stroke, or coronary revascularization	**189 (8.7)**	**178 (8.2)**	**0.5 (-1.2 to 2.1)**	**1.06 (0.86 to 1.30)**	**0.576**
Components of primary outcome					
Death	57 (2.6)	51 (2.3)	0.3 (-0.7 to 1.2)	1.12 (0.77 to 1.63)	0.570
Cardiac death	14	15			
Myocardial infarction	34 (1.5)	26 (1.2)	0.3 (-0.4 to 1.0)	1.27 (0.76 to 2.12)	0.366
Stroke	24 (1.1)	20 (0.9)	0.2 (-0.4 to 0.8)	1.20 (0.66 to 2.17)	0.549
Ischemic stroke	16	16			
Hemorrhagic stroke	8	4			
Coronary revascularization	115 (5.3)	111 (5.2)	0.2 (-1.2 to 1.5)	1.03 (0.80 to 1.34)	0.812

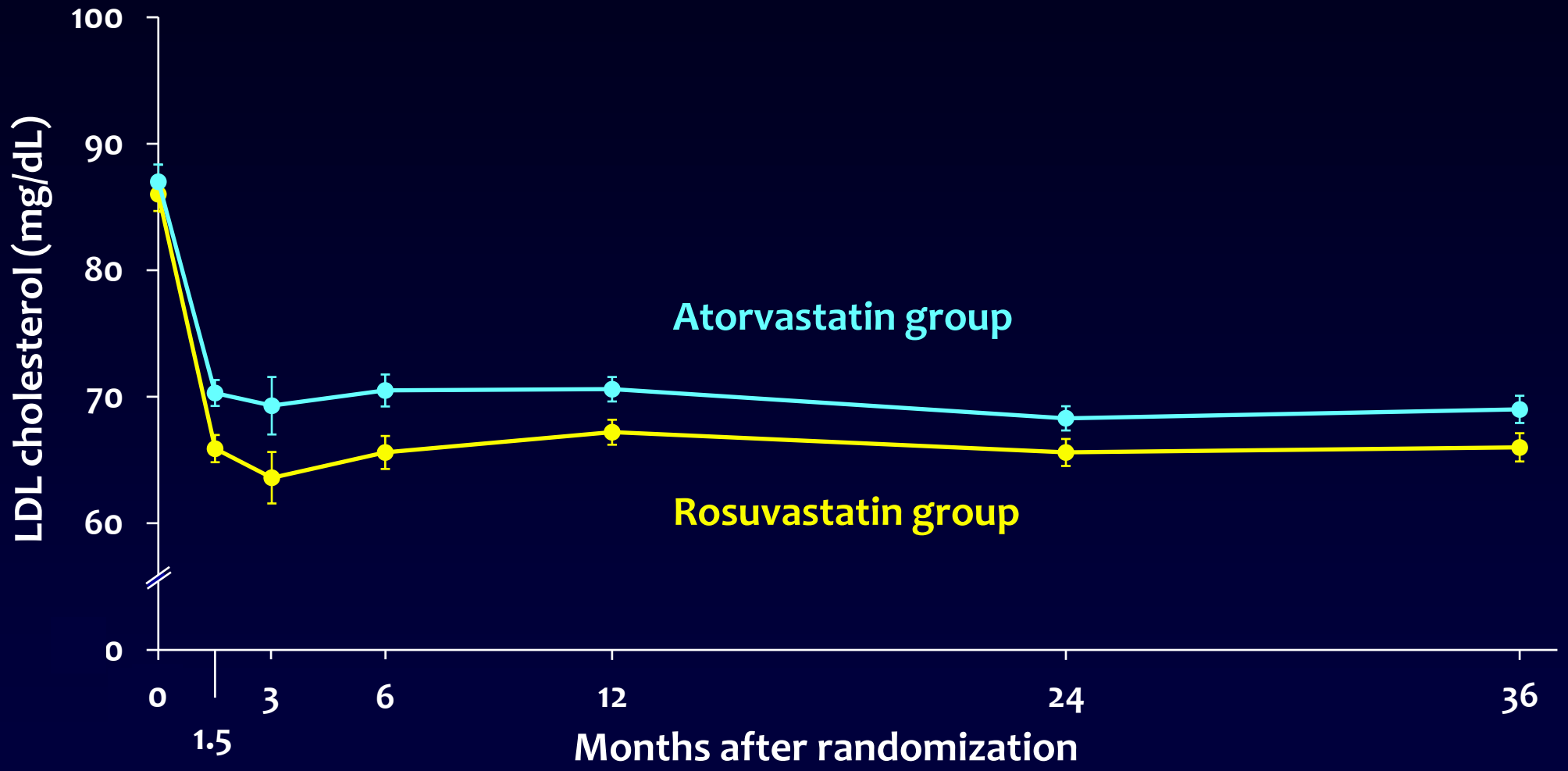
Secondary outcomes

	Rosuvastatin group (N=2204)	Atorvastatin group (N=2196)	Absolute difference (95% CI)	Hazard ratio (95% CI)	P Value
New-onset diabetes	**152 (7.1)**	**119 (5.5)**	**1.5 (0.1 to 3.0)**	**1.29 (1.01 to 1.63)**	**0.040**
New-onset diabetes among patients without diabetes at baseline	**152/1479 (10.4)**	**119/1453 (8.4)**	**2.1 (-0.0 to 4.2)**	**1.26 (0.99 to 1.60)**	**0.058**
Initiation of anti-diabetic medication among patients without diabetes at baseline	**104/1479 (7.2)**	**74/1453 (5.3)**	**2.0 (0.2 to 3.7)**	**1.39 (1.03 to 1.87)**	**0.031**
Hospitalization due to heart failure	12 (0.6)	8 (0.4)	0.2 (-0.2 to 0.6)	1.50 (0.61 to 3.66)	0.373
Deep vein thrombosis or pulmonary embolism	7 (0.3)	2 (0.1)	0.2 (-0.0 to 0.5)	3.50 (0.73 to 16.84)	0.096
Deep vein thrombosis	5	2			
Pulmonary embolism	3	0			
Peripheral artery revascularization	12 (0.5)	17 (0.8)	-0.3 (-0.8 to 0.2)	0.65 (0.30 to 1.38)	0.253
Aortic intervention or surgery	3 (0.1)	2 (0.1)	0.0 (-0.2 to 0.3)	1.50 (0.25 to 8.94)	0.658
Endovascular therapy	3	0			
Surgical therapy	0	2			
End-stage kidney disease	9 (0.4)	4 (0.2)	0.2 (-0.1 to 0.6)	2.25 (0.69 to 7.30)	0.166
Discontinuation of statin therapy	40 (1.8)	37 (1.7)	0.1 (-0.7 to 0.9)	1.08 (0.69 to 1.69)	0.741
Cataract operation	**53 (2.5)**	**32 (1.5)**	**1.0 (1.4 to 1.8)**	**1.66 (1.07 to 2.58)**	**0.022**
Composite of laboratory abnormalities	26 (1.2)	22 (1.0)	0.2 (-0.4 to 0.8)	1.24 (0.70 to 2.20)	0.466
Aminotransferase elevation	10	10			
Creatine kinase elevation	5	6			
Creatinine elevation	11	7			

Lipid-lowering therapy during the study period

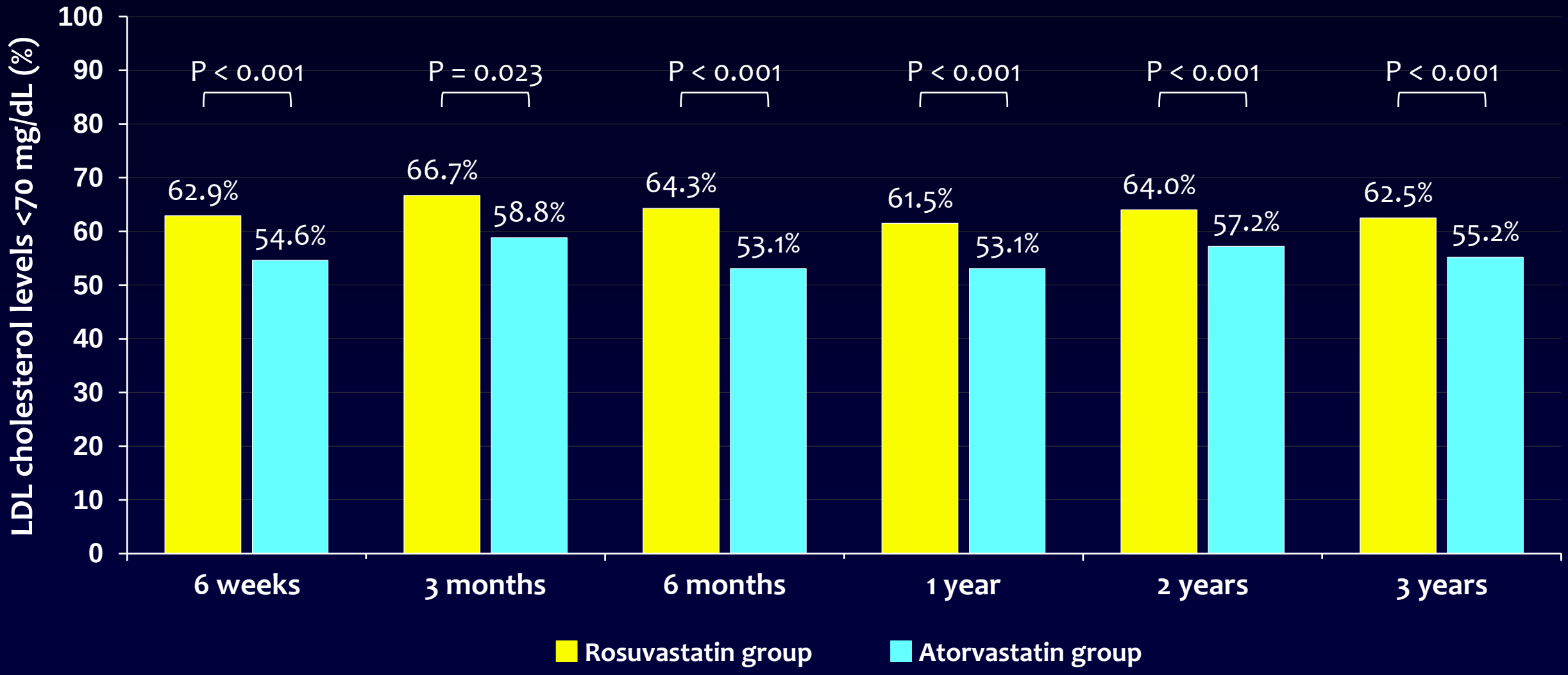
	Rosuvastatin group	Atorvastatin group	Absolute difference (95% CI)	P-value
High-intensity statins				
0 – 6 weeks	1602 / 2204 (72.7)	1596 / 2196 (72.7)	0.0 (-2.6 to 2.6)	1.000
6 week – 3 months	1599 / 2190 (73.0)	1616 / 2184 (74.0)	-1.0 (-3.6 to 1.6)	0.484
3 months – 6 months	1587 / 2189 (72.5)	1618 / 2177 (74.3)	-1.8 (-4.4 to 0.8)	0.184
6 months – 1 year	1569 / 2184 (71.8)	1611 / 2175 (74.1)	-2.2 (-4.9 to 0.4)	0.105
1 year – 2 years	1557 / 2167 (71.9)	1615 / 2163 (74.7)	-2.8 (-5.4 to -0.2)	0.040
2 years – 3 years	1517 / 2141 (70.9)	1580 / 2134 (74.0)	-3.2 (-5.9 to -0.5)	0.022
Ezetimibe				
0 – 6 weeks	18 / 2204 (0.8)	13 / 2196 (0.6)	0.2 (-0.3 to 0.7)	0.477
6 week – 3 months	97 / 2190 (4.4)	137 / 2184 (6.3)	-1.8 (-3.2 to -0.5)	0.008
3 months – 6 months	110 / 2189 (5.0)	148 / 2177 (6.8)	-1.8 (-3.2 to -0.4)	0.016
6 months – 1 year	150 / 2184 (6.9)	215 / 2175 (9.9)	-3.0 (-4.7 to -1.4)	<0.001
1 year – 2 years	200 / 2167 (9.2)	295 / 2163 (13.6)	-4.4 (-6.3 to -2.5)	<0.001
2 years – 3 years	252 / 2141 (11.8)	402 / 2134 (18.8)	-7.1 (-9.2 to -4.9)	<0.001

LDL cholesterol levels



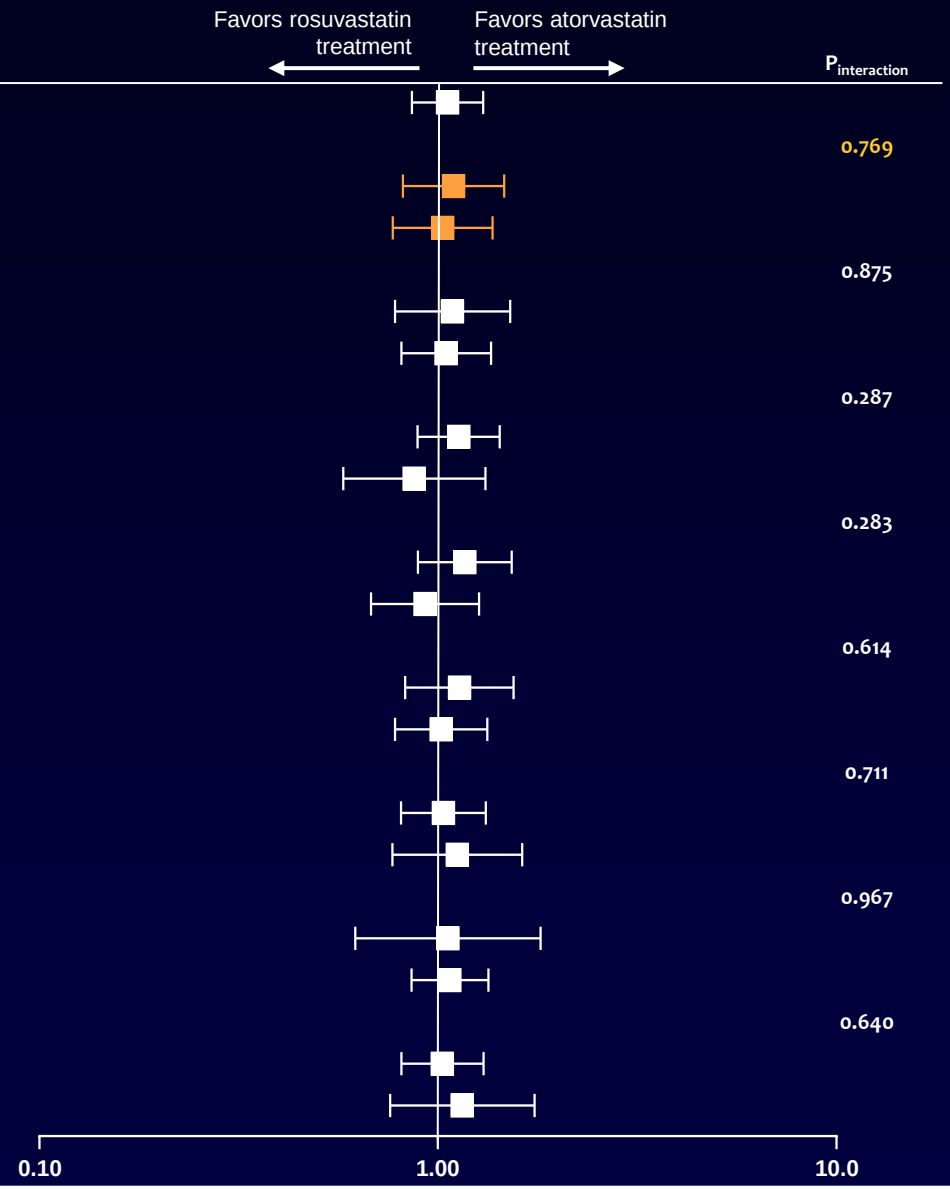
Rosuvastatin	2204	1570	447	1098	1875	1673	1582
Atorvastatin	2196	1629	391	1068	1841	1660	1532
Difference		-4.4	-5.7	-4.9	-3.4	-2.7	-3.0

LDL cholesterol levels below 70 mg/dL



Subgroup analyses for primary outcome

Subgroup	No. / Total (%) Rosuvastatin group	Atorvastatin group	HR (95% CI)	$P_{interaction}$
All patients	189/2204 (8.7)	178/2196 (8.2)	1.06 (0.86-1.30)	
Statin intensity strategy				0.769
Treat-to-target	92/1098 (8.5)	85/1102 (7.8)	1.09 (0.82-1.47)	
High-intensity statin	97/1106 (8.8)	93/1094 (8.6)	1.03 (0.77-1.37)	
Age, years				0.875
<65	73/1018 (7.2)	65/990 (6.6)	1.09 (0.78-1.52)	
≥65	116/1186 (9.9)	113/1206 (9.5)	1.05 (0.81-1.36)	
Sex				0.287
Male	148/1602 (9.3)	129/1570 (8.3)	1.13 (0.89-1.43)	
Female	41/602 (6.7)	49/626 (7.8)	0.87 (0.58-1.32)	
Body mass index, kg/m²				0.283
<25	112/1232 (9.2)	99/1266 (7.9)	1.17 (0.89-1.53)	
≥25	77/972 (8.0)	79/930 (8.6)	0.93 (0.68-1.27)	
Diabetes mellitus				0.614
Yes	82/725 (11.5)	75/743 (10.2)	1.13 (0.83-1.55)	
No	107/1479 (7.3)	103/1453 (7.2)	1.02 (0.78-1.33)	
Hypertension				0.711
Yes	133/1498 (9.0)	124/1439 (8.7)	1.03 (0.81-1.32)	
No	56/706 (8.0)	54/757 (7.2)	1.12 (0.77-1.63)	
Chronic kidney disease				0.967
Yes	26/149 (17.6)	28/170 (16.6)	1.06 (0.62-1.81)	
No	163/2055 (8.0)	150/2026 (7.5)	1.07 (0.86-1.34)	
Baseline LDL cholesterol, mg/dL				0.640
<100	144/1606 (9.0)	136/1555 (8.8)	1.03 (0.81-1.30)	
≥100	45/598 (7.7)	42/641 (6.7)	1.15 (0.76-1.75)	



Conclusion

- To our knowledge, this study is the first randomised trial comparing 3-year clinical outcomes of rosuvastatin treatment versus atorvastatin treatment in patients with CAD.

- The 3-year composite of all-cause death, MI, stroke, or any coronary revascularization did not differ between the rosuvastatin and atorvastatin treatment.

- Rosuvastatin treatment was associated with lower LDL cholesterol levels, but it also carried a higher risk of new-onset diabetes mellitus requiring anti-diabetic medication and cataract operation, compared with atorvastatin treatment.


Dreams will
come true

CLEAR OUTCOMES Analysis by Glycaemic Status

Professor Kausik K Ray FMedSci

On behalf of

Stephen J Nicholls, PhD, Na Li, PhD, Michael J Louie, MD, Danielle Brennan, MS,

A Michael Lincoff, MD, Steven E. Nissen, MD * CLEAR OUTCOMES Committees and Investigators

26 Aug 2023

ESC Congress 2023

Amsterdam & Online

Imperial College London

Study Sponsor:
Esperion Therapeutics, Inc.

Background

- In 2021, 529 million individuals were living with diabetes (DM) globally
- Diabetes doubles the risk of atherosclerotic cardiovascular disease
- LDL-C lowering with statins as first-line treatment reduces this risk in patients with DM (CARDS trial)
- Secondary prevention patients with DM derive greater absolute benefits when non-statin LLTs, such as ezetimibe and PCSK9 mAbs, are added to statins
- Many patients are unable to tolerate or maximize a statin leaving them at high residual risk of CVD

Background (cont)

- **Statins increase the risk of new-onset diabetes (NOD) in a dose dependent fashion**
  - Genetics suggest an on-target effect of HMGCoA inhibition
- **In trials with ezetimibe or PCSK9i added to statins there was no excess risk of NOD**
  - Genetics suggest that lower NPC1L1 or PCSK9 activity would increase risk of NOD
- **Genetic studies suggested that lower activity of ACLY, the target of Bempedoic Acid, would reduce CVD with no excess risk of NOD**

CLEAR Outcomes

Patients with, or at high risk for, CVD who are unable or unwilling to take guideline-recommended doses of statins

VISIT T1 (Day 1) (N=13970)

R

1:1

Bempedoic Acid 180 mg QD

End of Study Criteria

1. At least 1,620 adjudicated primary MACE-4
2. At least 810 adjudicated MACE-3
3. At least 24 months since the last patient was randomized

Placebo

Median Follow-Up: 40.6 months

Enrollment: December 2016 – August 2019

Time to Event Outcomes	Bempedoic Acid (N=6992)	Placebo (N=6978)	Bempedoic Acid vs Placebo	
	Events (n), %		HR (95% CI)	*P*-value
MACE-4	819 (11.7)	927 (13.3)	0.87 (0.79-0.96)	0.004
MACE-3	575 (8.2)	663 (9.5)	0.85 (0.76-0.96)	0.006

Prespecified DM Analysis - Endpoints

Efficacy Outcomes

- **MACE-4:** Cardiovascular death, non-fatal MI, non-fatal stroke, or coronary revascularization
- **MACE-3:** Cardiovascular death, non-fatal MI, or non-fatal stroke

Clinical Outcomes

- HbA1c*
- Fasting Glucose*
- New Onset Diabetes

***At 1 year (prespecified); At End of Study (post-hoc)**

Baseline Characteristics - balanced by randomization

Baseline Characteristics	Normoglycaemia (N=1801)		Prediabetes* (N=5796)		Diabetes** (N=6373)	
	Bempedoic Acid (n=937)	Placebo (n=864)	Bempedoic Acid (n=2911)	Placebo (n=2885)	Bempedoic Acid (n=3144)	Placebo (n=3229)
Age, years (SD)	63.7 (10.2)	64.1 (10.5)	65.0 (9.5)	64.8 (9.1)	66.5 (8.1)	66.5 (8.1)
Females, n (%)	475 (50.7%)	434 (50.2%)	1252 (43.0%)	1250 (43.3%)	1634 (52.0%)	1695 (52.5%)
Body mass index*, kg/m^2	27.6 (4.4)	28.0 (4.4)	29.2 (4.7)	29.1 (4.8)	31.2 (5.5)	31.2 (5.6)
Weight, kg (SD)	78.3 (15.0)	79.7 (15.4)	83.5 (16.1)	83.6 (16.2)	86.6 (18.0)	86.7 (18.2)
ASCVD Status Primary Prevention	194 (20.7%)	145 (16.8%)	537 (18.4%)	549 (19.0%)	1369 (43.5%)	1412 (43.7%)

Did not meet the criteria for either prediabetes or diabetes

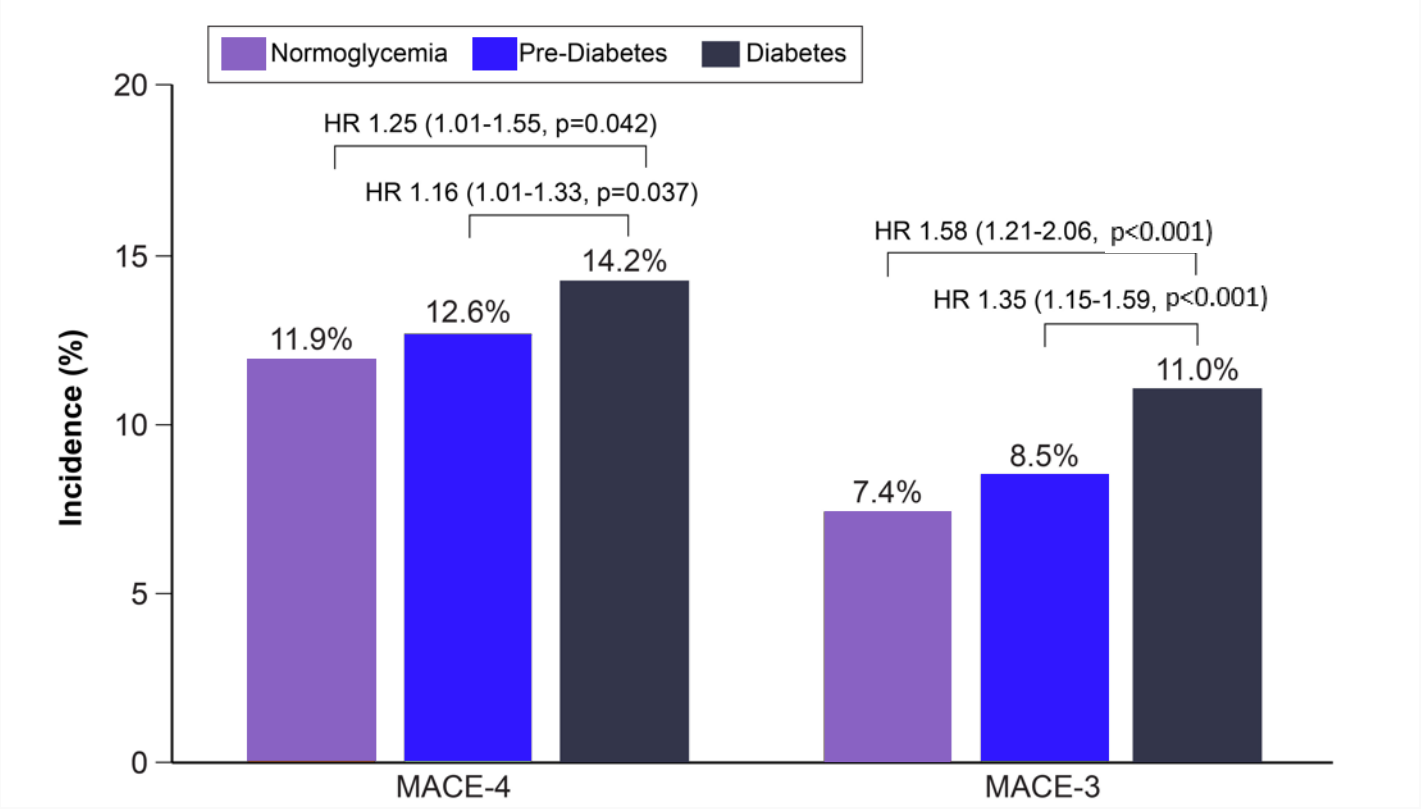
* HbA1c 5·7%-6·4% (39-48 mmol/mol), or ≥1 fasting serum glucose concentration of at least 5·6 mmol/L (100mg/dl), but with no more than one value of ≥7·0 mmol/L (126mg/dl)

** Medical history of diabetes; or use of glucose lowering medication; or HbA1c ≥6·5% (48 mmol/mol); or two or more fasting serum glucose concentration ≥7·0 mmol/L (126 mg/dL)

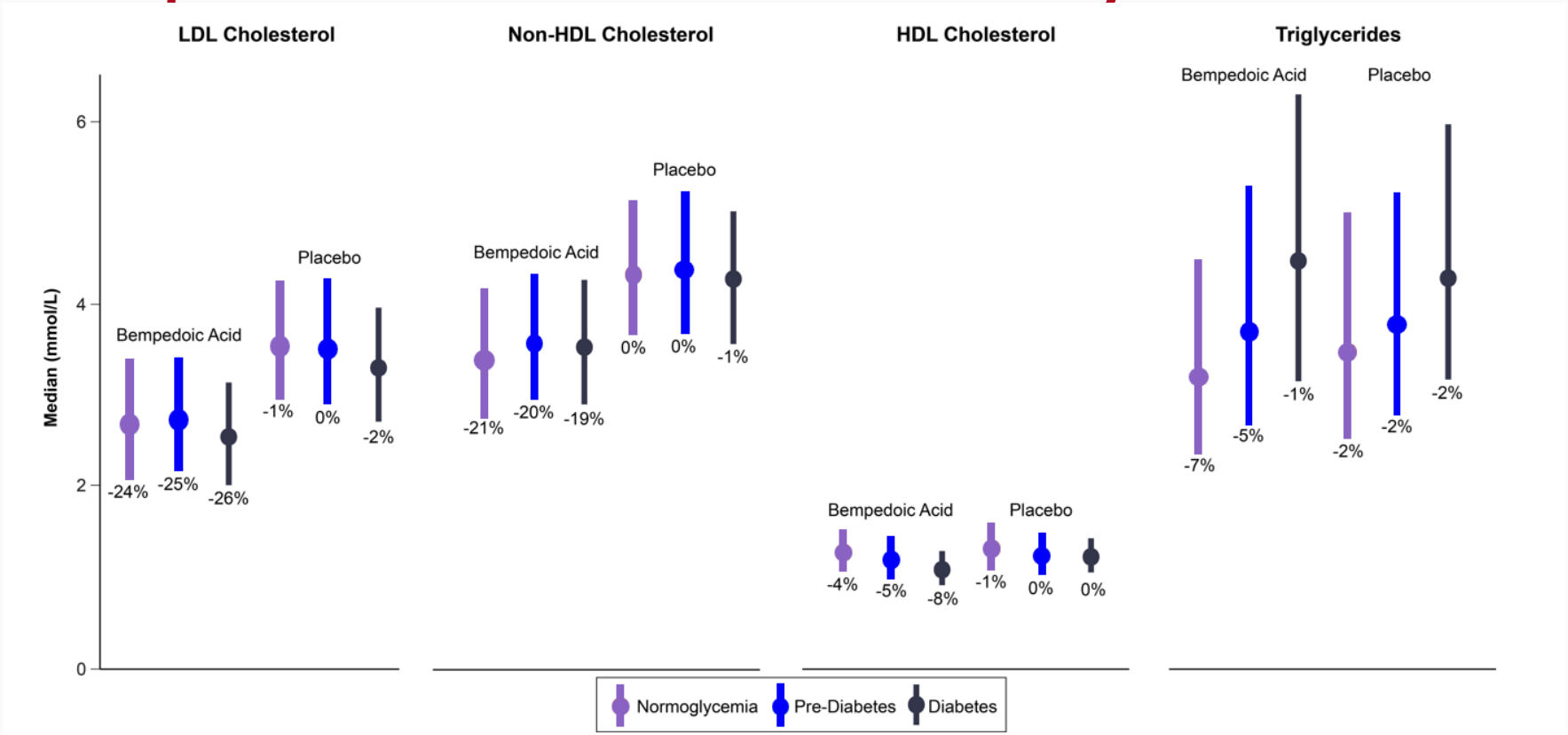
Baseline Characteristics (cont.) - balanced by randomization

Baseline Characteristics	Normoglycaemia (N=1801)		Prediabetes (N=5796)		Diabetes (N=6373)	
	Bempedoic Acid (n=937)	Placebo (n=864)	Bempedoic Acid (n=2911)	Placebo (n=2885)	Bempedoic Acid (n=3144)	Placebo (n=3229)
Duration of follow-up, months	43.0 (9.0)	42.7 (9.6)	42.1 (9.1)	42.0 (9.0)	40.4 (9.4)	40.7 (9.2)
Laboratory values at baseline						
LDL cholesterol, mmol/L	3.7 (0.9)	3.7 (1.0)	3.7 (0.9)	3.7 (0.9)	3.5 (0.8)	3.5 (0.9)
Non-HDL cholesterol, mmol/L	4.4 (1.0)	4.5 (1.1)	4.6 (1.1)	4.6 (1.1)	4.5 (1.0)	4.5 (1.0)
HDL cholesterol, mmol/L	1.4 (0.4)	1.4 (0.4)	1.3 (0.4)	1.3 (0.4)	1.2 (0.3)	1.2 (0.3)
Triglycerides, mmol/L	1.5 (1.1 – 2.1)	1.6 (1.2 – 2.1)	1.7 (1.3 – 2.3)	1.7 (1.3 – 2.3)	2.0 (1.5 – 2.7)	2.0 (1.5 – 2.6)
Haemoglobin A1c, %	5.3 (0.2)	5.3 (0.2)	5.7 (0.3)	5.7 (0.3)	7.0 (1.1)	7.0 (1.2)
Fasting glucose, mmol/L	5.0 (0.3)	5.0 (0.3)	5.8 (0.6)	5.8 (0.6)	7.8 (2.3)	7.8 (2.3)
Baseline Medications						
Statin	211 (22.5%)	192 (22.2%)	677 (23.3%)	661 (22.9%)	713 (22.7%)	720 (22.3%)
Ezetimibe	142 (15.2%)	116 (13.4%)	378 (13.0%)	397 (13.8%)	283 (9.0%)	296 (9.2%)

Incidence of Cardiovascular Events in the Placebo Group Increased Across Glycaemic Strata



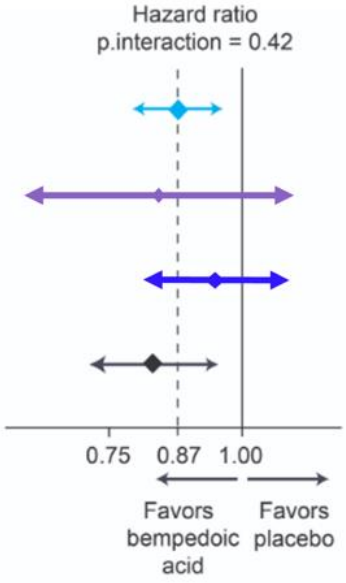
At 6 months LDL-C and non-HDL-C reductions with Bempedoic Acid were similar across Glycaemia Strata

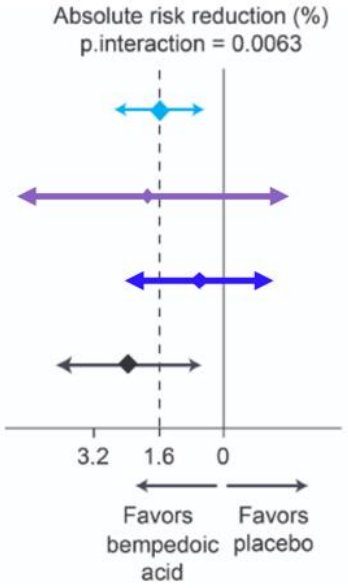


Error bars are IQRs. Median within-patient percentage changes from baseline are shown below each data point.

Bempedoic Acid provided similar relative but greater absolute benefits on MACE-4 in those with DM

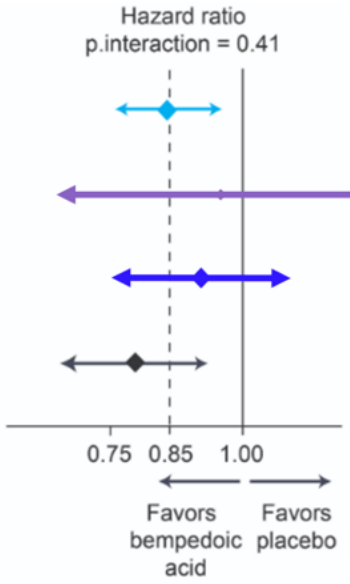
	Bempedoic Acid n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	Absolute Reduction (95% CI)
Overall	819/6992 (11.7%)	927/6978 (13.3%)	0.87 (0.79, 0.96)	1.6% (0.5%, 2.7%)
Normoglycemia	95/937 (10.1%)	103/864 (11.9%)	0.84 (0.63, 1.10)	1.9% (-1.12%, 4.8%)
Pre-Diabetes	350/2911 (12.0%)	364/2885 (12.6%)	0.94 (0.81, 1.09)	0.6% (-1.1%, 2.3%)
Diabetes	374/3144 (11.9%)	460/3229 (14.2%)	0.83 (0.72, 0.95)	2.4% (0.7%, 4.0%)

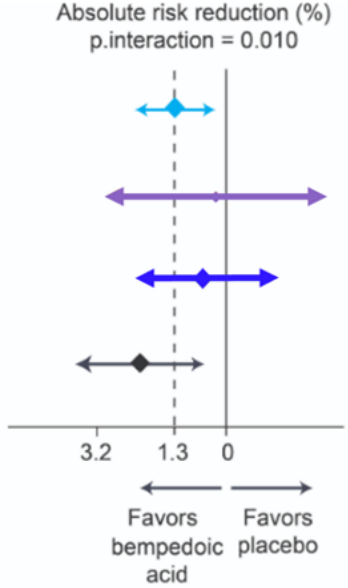




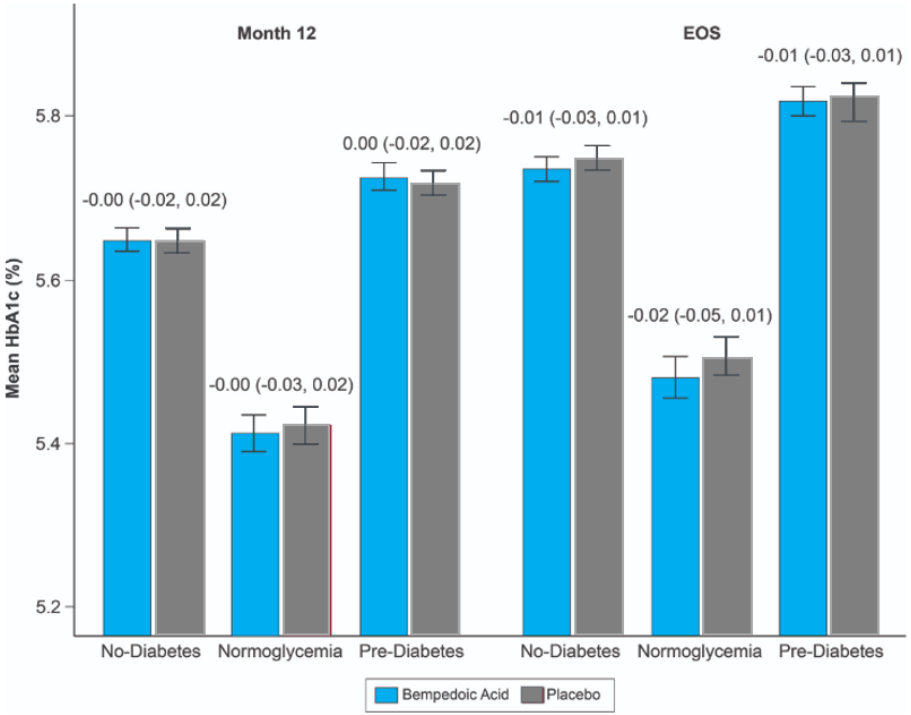
Bempedoic Acid provided similar relative but greater absolute benefits on MACE-3 in those with DM

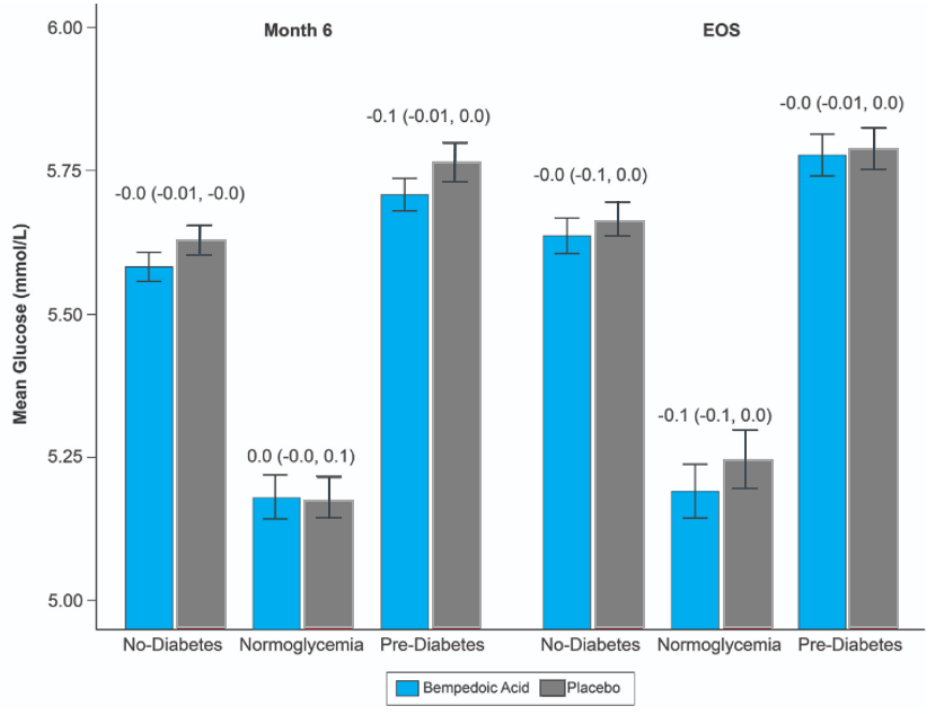
	Bempedoic Acid n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	Absolute Reduction (95% CI)
Overall	575/6992 (8.2%)	663/978 (9.5%)	0.85 (0.76, 0.96)	1.3% (0.3%, 2.2%)
Normoglycemia	67/937 (7.2%)	64/864 (7.4%)	0.96 (0.68, 1.35)	0.3% (-2.1%, 2.7%)
Pre-Diabetes	229/2911 (7.9%)	244/2885 (8.5%)	0.92 (0.77, 1.10)	0.6% (-0.8%, 2.0%)
Diabetes	279/3144 (8.9%)	355/3229 (11.0%)	0.80 (0.68, 0.93)	2.1% (0.7%, 3.6%)





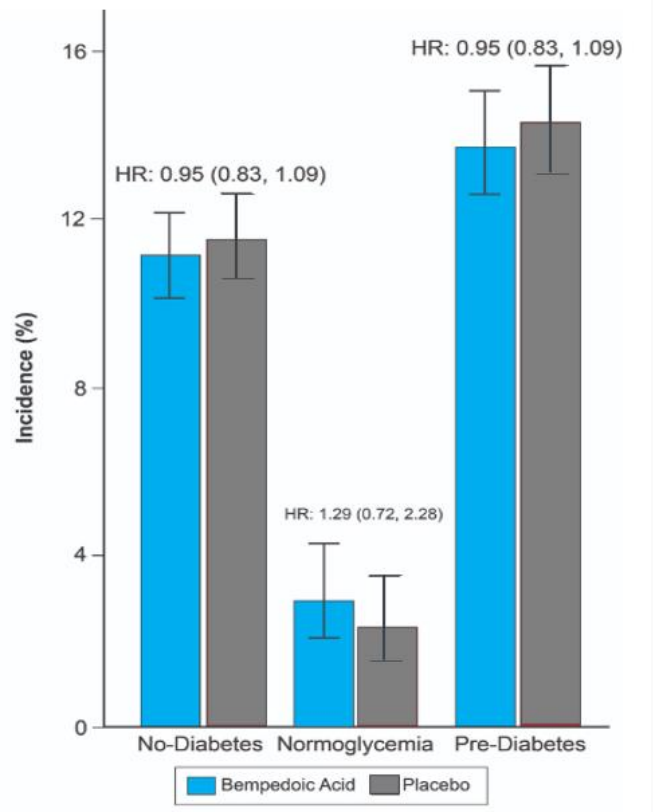
Bempedoic Acid did not worsen HbA1c or glucose levels in those without diabetes



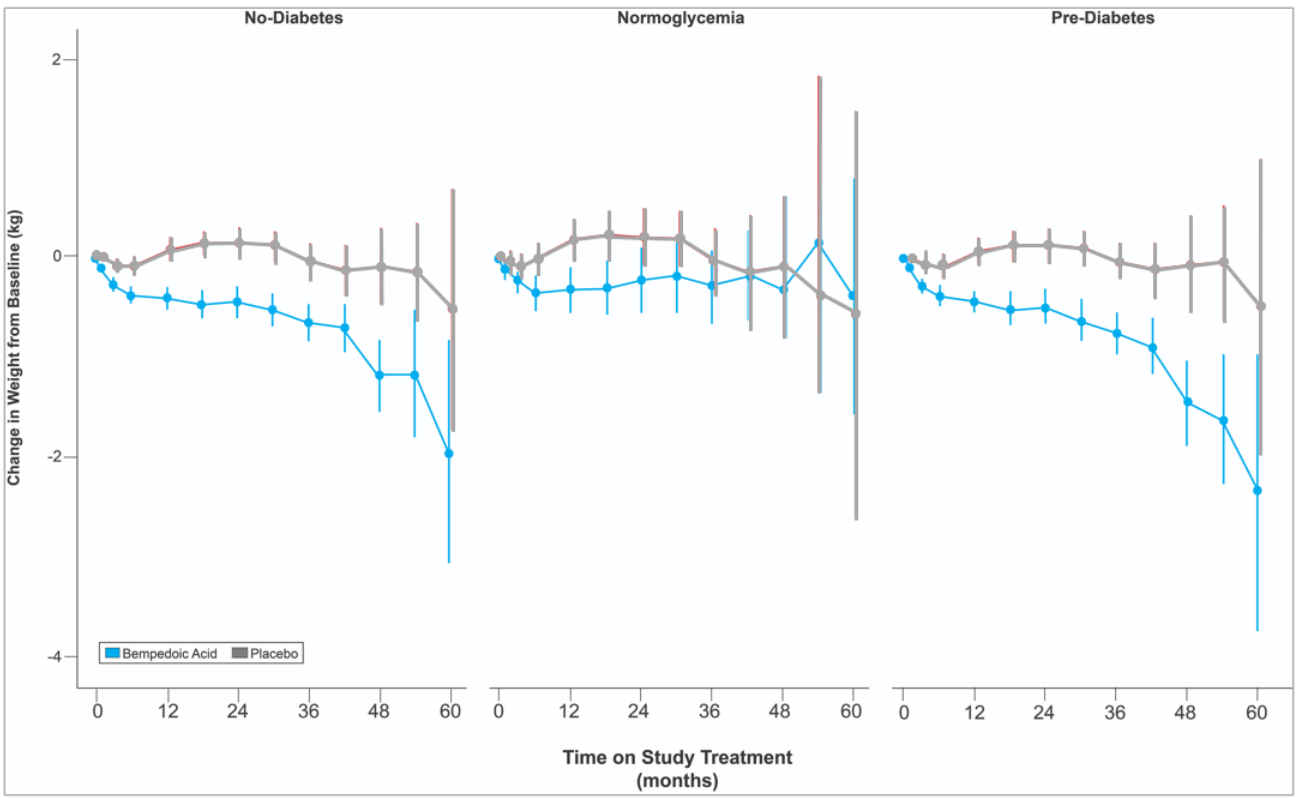


Bempedoic Acid did not increase the risk of New Onset Diabetes

- Individuals with normoglycaemia or prediabetes at baseline were considered to have NOD during the trial if one or more of the following criteria were met as defined in the ADA guidelines:
  - HbA_{1c} value of 6·5% or higher; or
  - Fasting serum glucose value of at least 7·0 mmol/L; or,
  - Two-hour post prandial glucose ≥11·1 mmol/L during an oral glucose tolerance test; or,
  - In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥ 11·1 mmol/L, or initiation of glucose lowering therapies.
  - In the absence of unequivocal hyperglycaemia, diagnosis required two abnormal test results from the same sample or in two separate test results.



Weight was lower in Bempedoic Acid treated patients compared to Placebo



Concordance of Mendelian Randomization and Pharmacotherapy RCTs

	Enhancing LDL Receptor Activity							
Pathway	**Cholesterol synthesis pathway**				**Cholesterol absorption**		**LDL receptor degradation**	
Target	**ACLY**		**HMGCoA**		**NPC1L-1**		**PCSK9**	
Mechanism of lowering	***Genetically Lower***	***Bempedoic Acid***	***Genetically lower***	***Statins***	***Genetically lower***	***Ezetimibe***	***Genetically lower***	***PCSK9i MAbs***
Efficacy								
LDL-C	Lower	Lower	Lower	Lower	Lower	Lower	Lower	Lower
CVD	Lower	Lower	Lower	Lower	Lower	Lower	Lower	Lower
Safety								
Weight or BMI	Lower	Lower	Higher	Higher	Unknown	Unknown	Unknown	Unknown
HbA1c/glucose	Neutral	Neutral	Higher	Higher	Higher	Neutral	Higher	Neutral
New Onset Diabetes	Neutral	Neutral	Higher	Higher	Higher	Neutral	Higher	Neutral

ACLY = ATP-citrate lyase; HMGCoA = 3-hydroxy-3-methylglutaryl coenzyme-A; NPC1L-1 = Niemann–Pick C1-like 1; PCSK9 = proprotein convertase subtilisin/kexin type 9; LDL = low density lipoprotein; LDL-C = low density lipoprotein cholesterol; CVD = cardiovascular disease; BMI = body mass index

Conclusion

- In patients with DM unwilling or unable to take guideline-recommended doses of statins, Bempedoic Acid significantly reduced cardiovascular risk with large absolute benefits as monotherapy
- In patients without DM at baseline, there were no adverse effects of Bempedoic Acid on measures of glycaemia or risk of New Onset Diabetes
- These data validate prior genetic data for ACLY inhibition for reducing LDL-C and risk of CV disease with no adverse effect on measures of glycaemia

RED-CVD trial

#ESCCongress

Improving early diagnosis of CVD in patients with type 2 diabetes and COPD

Conclusion

Active screening of patients with type 2 diabetes or chronic obstructive pulmonary disease (COPD) more than doubles new diagnoses of CVD compared with usual care.

Impact on clinical practice

A proactive diagnostic strategy identifies coronary artery disease (CAD), atrial fibrillation (AF) and heart failure (HF) in the community.

Study objectives

RED-CVD was a cluster randomised, pragmatic trial examining the ability of a stepwise diagnostic strategy to identify CAD, AF and HF in patients with COPD or type 2 diabetes using tools readily available in primary care.

Study population

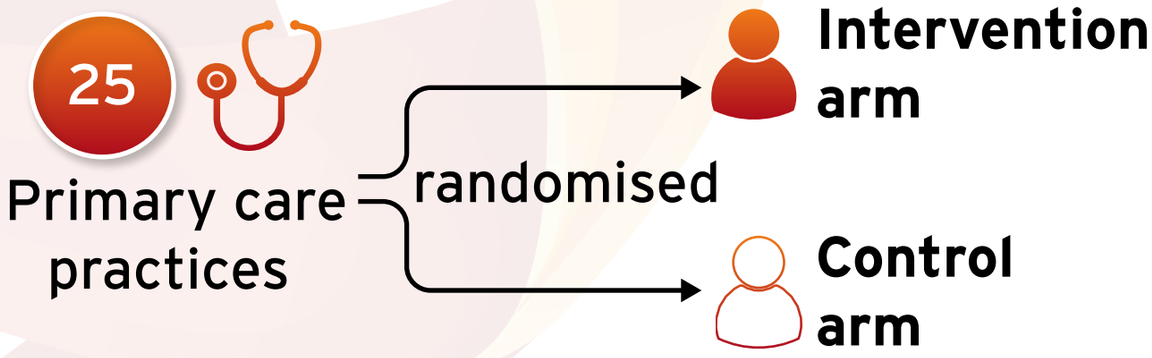
Primary care practices were the unit of randomisation.

Primary care practices across the Netherlands were eligible if they could add the early diagnosis strategy to their usual disease management programmes for type 2 diabetes and COPD.

Where?

the Netherlands

Who and what?



The intervention had 3 steps

Questionnaire on risk factors and symptoms, to be filled out at home prior to the next routine visit to a type 2 diabetes or COPD management programme;

For patients who scored above a prespecified threshold on the questionnaire: physical examination by the practice nurse focused on signs of HF, 12-lead electrocardiography and NT-proBNP measurements, to be performed during a routine visit;

Interpretation of the results of steps 1 and 2 by a GP and referral to a cardiologist or open access echocardiography if deemed necessary.

Primary endpoint

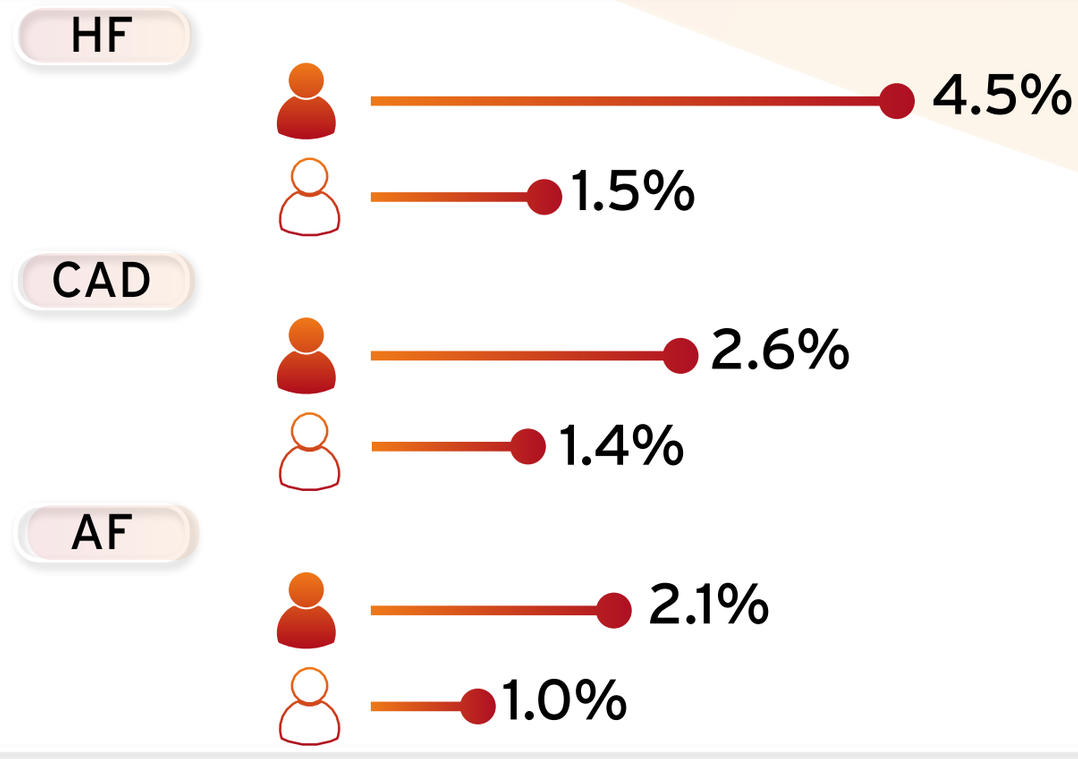
Composite of newly detected cases of HF, AF and CAD at 1 year after the baseline visit.

50 of 624 participants — 8.0%

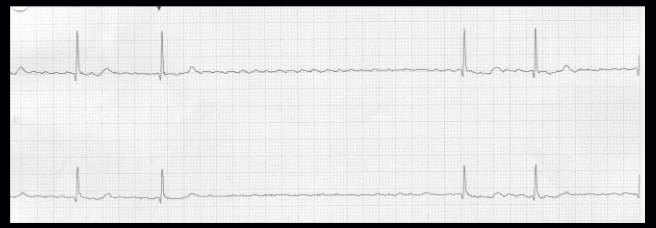
19 of 592 participants — 3.2%

- Newly diagnosed with at least one of HF, AF or CAD
- Adjusted odds ratio 2.83; 95% CI 1.62 to 4.95

Individual diagnoses



ESC



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Screening for heart failure and optimising pathways of care in people with pacemakers: The OPT-PACE randomised controlled trial

Klaus Witte

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NIHR | National Institute for Health Research

Disclosures

OPT-PACE was an independent investigator-initiated trial, funded through an NIHR Clinician Scientist Award to Klaus Witte (NIHR-CS-2012-032)

Background: Pacemakers for bradycardia

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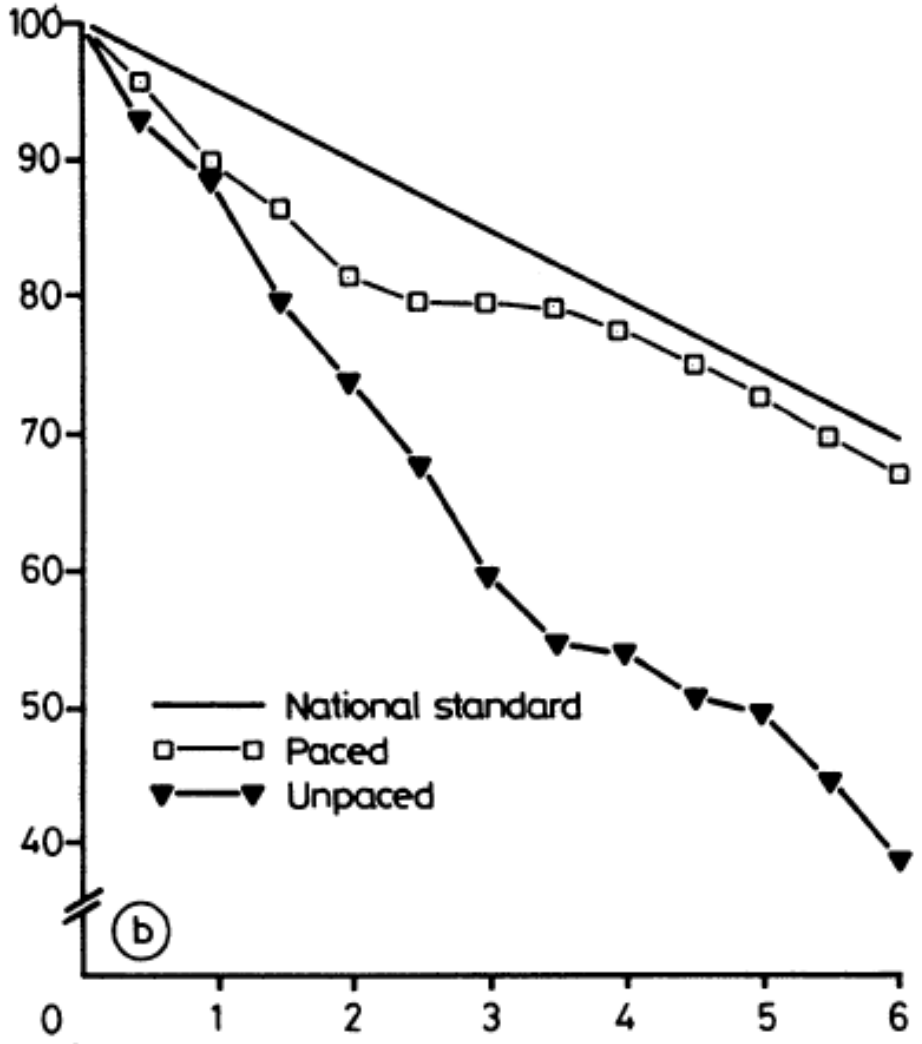
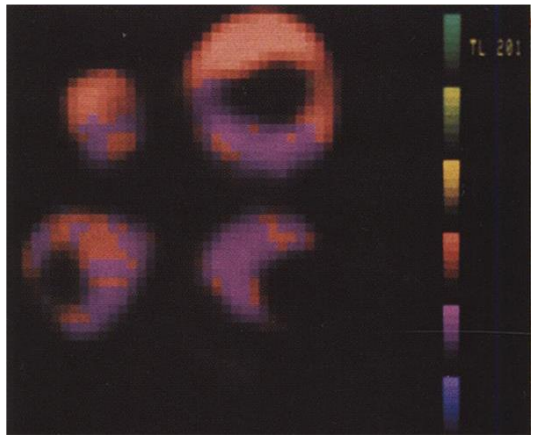
- ~1 million pacemaker implants per year worldwide
- Rates vary widely across Europe (median is ~600 per million per year)
- 80% are implanted in people >65 years of age
- Pacemaker therapy for AV block extends life
- But it comes at a cost…

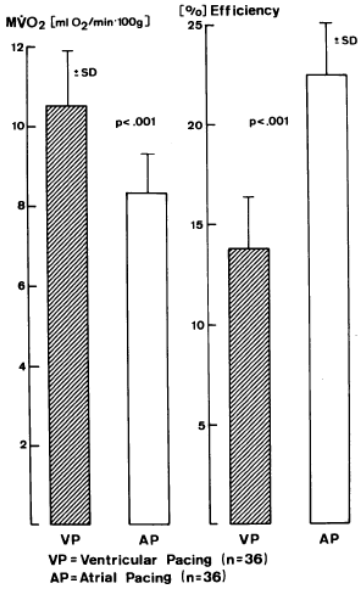


Timmis *et al*. *Eur Heart J* 2018
Mond *et al*. *PACE* 2011
Shaw *et al*. *Br Heart J* 1985

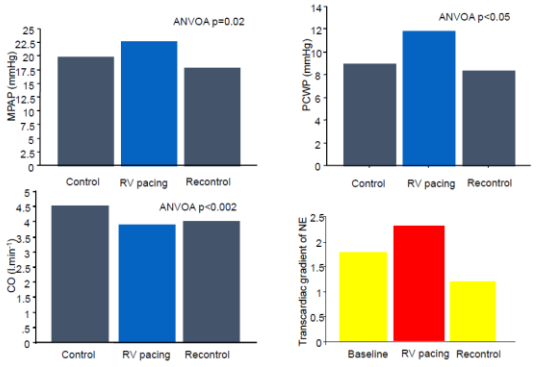
Complication: Heart Failure

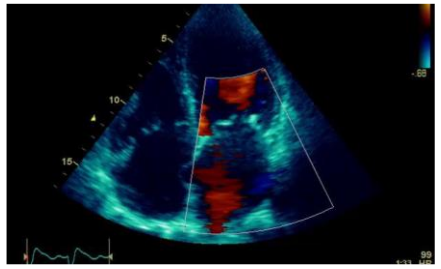


Lee et al *JACC* 1994

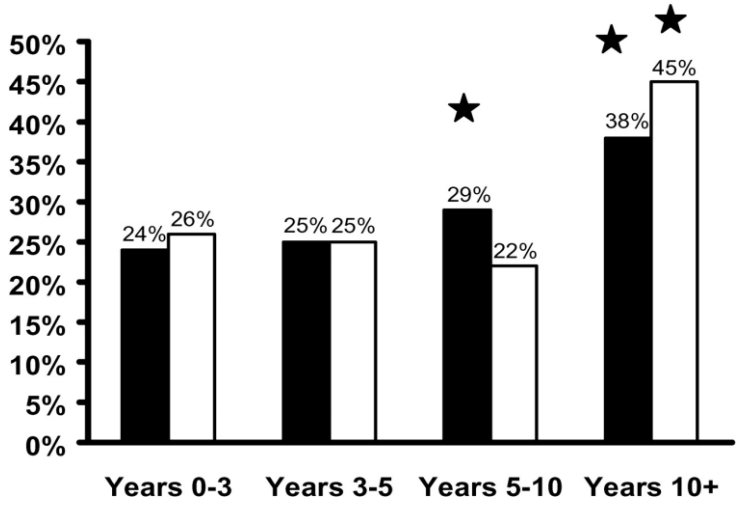


Baller et al *PACE*1988

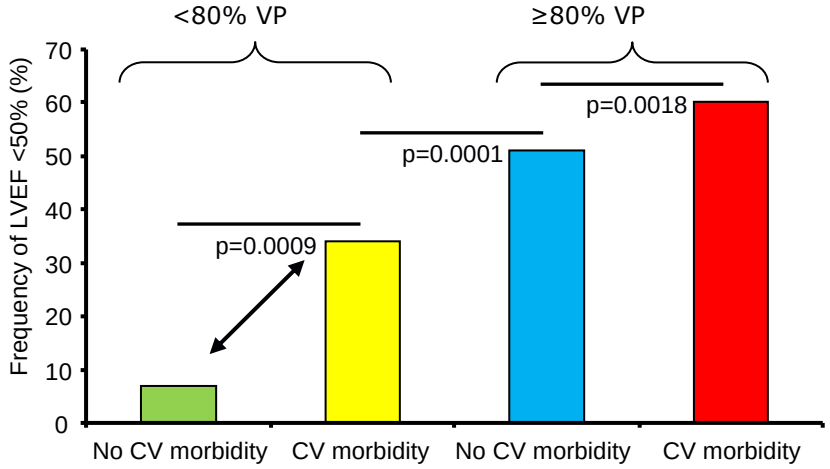




Witte *et al. Can J Cardiol 2006*



Thackray *et al Eur Heart J* 2003



Gierula et al *Clin Card 2013*

Therapeutic approaches for pacing-associated HF

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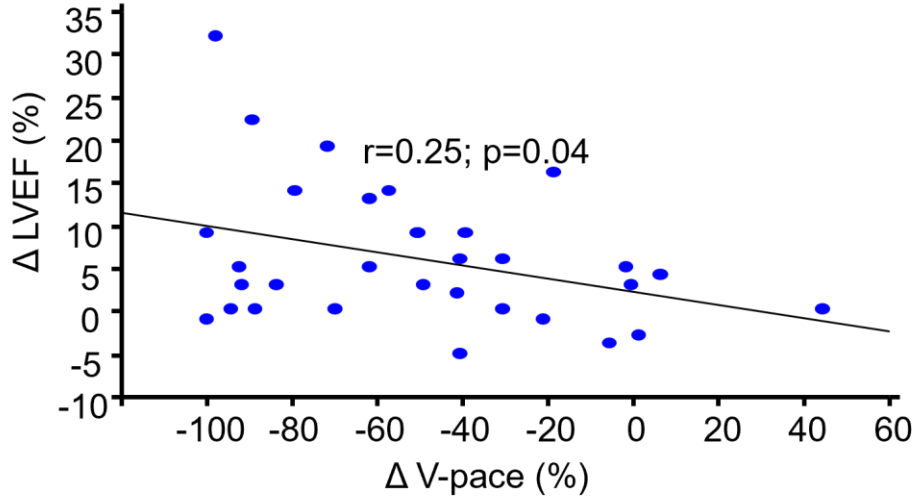
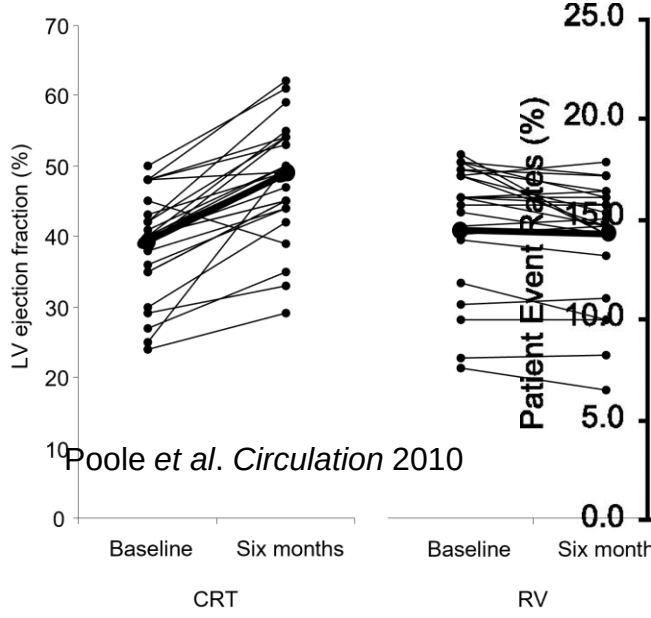
- Reprogramming: reduces RV pacing and improves LV function

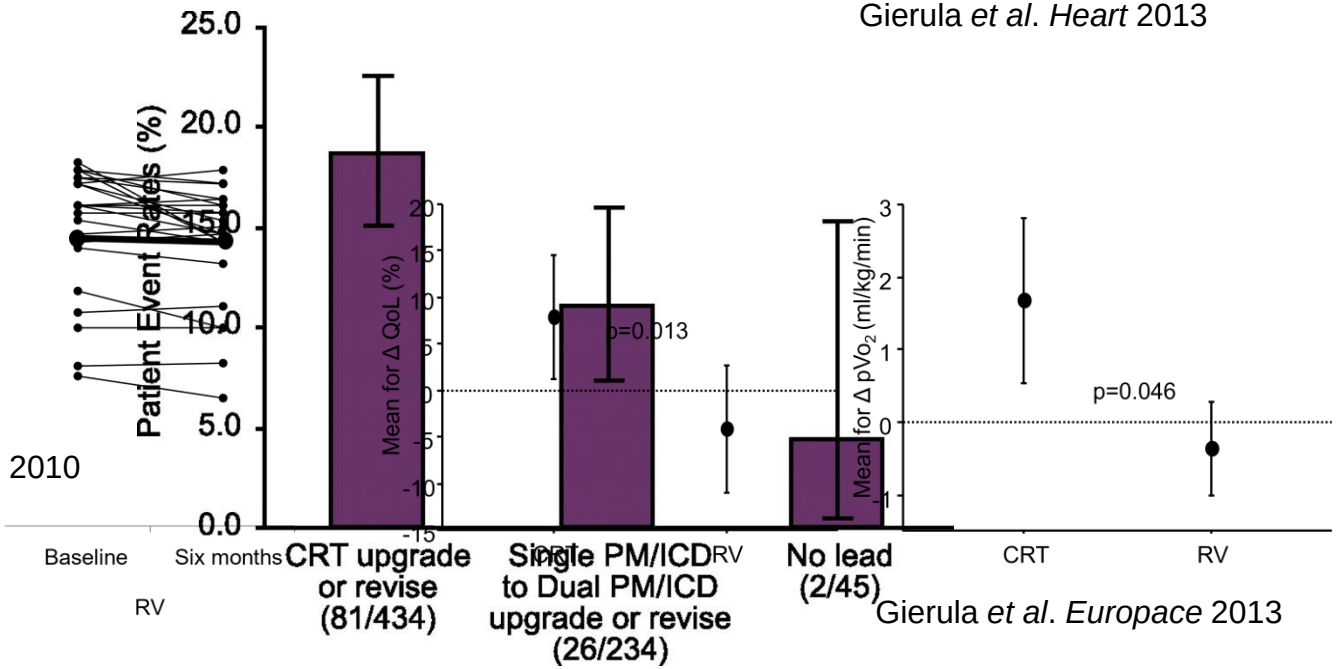
- Upgrade to CRT: improves LV function, quality of life and exercise capacity



Gierula *et al*. *Heart* 2013



Poole *et al*. *Circulation* 2010



Gierula *et al*. *Europace* 2013

Medical therapy for pacing-associated HF

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Check the guidelines

OPT-PACE: Aim

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To determine the benefit of screening for heart failure *and* optimising medical therapy in people with pacemakers

OPT-PACE: Trial design

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- Prospective, multicenter, randomised, controlled
- Academic trial without industry involvement
- Funding: National Institute for Health Research (UK) (NIHR-CS-2012-032)
- Sponsor: University of Leeds (Leeds Institute for Cardiovascular and Metabolic Medicine)
- Statistical management: Leeds Institute for Clinical Trials Research
- Participating centres:

  Leeds teaching Hospitals NHS Trust,

  Bradford Hospitals NHS Trust,

  Harrogate District Hospital NHS Trust
- Ethical approval: Health Research Authority (South Yorkshire Research Ethics Committee: 12/YH/0487)
- Clinical Trials registration: ClinicalTrials.gov (NCT01819662)

OPT-PACE: Participants

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Inclusion criteria:

- Standard pacemaker implanted for bradycardia for >12 months due to any indication in current clinical ESC guidelines.

Exclusion criteria:

- Existing implantable cardioverter defibrillator or cardiac resynchronisation device;
- <18 years old;
- Pregnant;
- Known HFrEF;
- Already under the care of HF services, awaiting heart transplantation;
- Life expectancy of <1 year due to co-morbidity;
- Significant cognitive impairment.

OPT-PACE: Pathways of care

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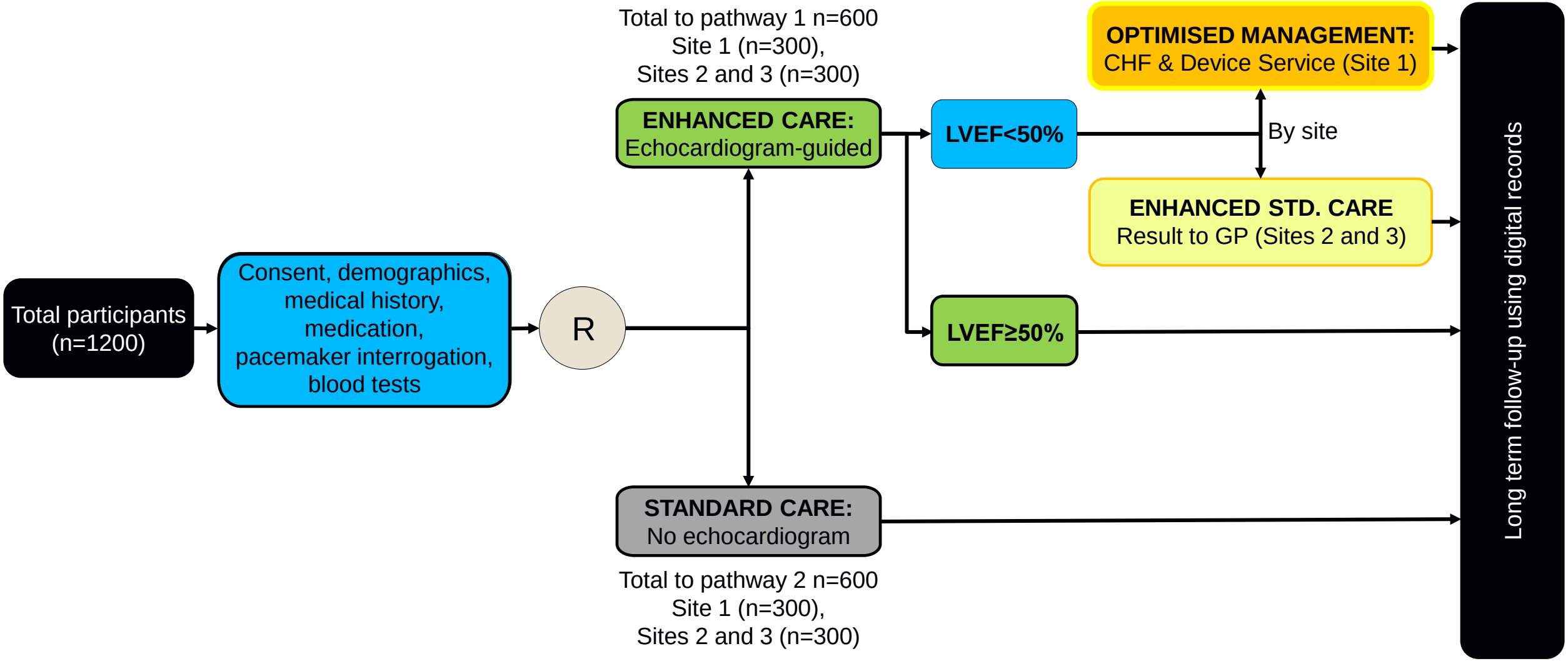

OPT-PACE: Endpoints

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Primary:
Time to first event of all-cause mortality or heart failure hospitalisation between randomised groups (echocardiogram *versus* no echocardiogram).

Prespecified subgroup analysis of pathways of care in the echocardiogram group (primary care driven management versus chronic heart failure and device service)

Secondary:
Effect on medical therapy of optimised management of a population with a pacemaker

Effect of medical therapy on quality of life

OPT-PACE: Statistical considerations

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Background Data: 491 patients, 40% prevalence of CHF, but **15% p.a. hosp for HF/death**

Primary endpoint: Effect of enhanced investigation and optimised management on total mortality, HFH

Power calculation: 15% HFH/death rate reduced to 9% by CHAD Service based upon reduction of event rates with combined optimal medical therapy and a power of 0.90 with overall two-sided type 1 error rate 0.05) required 146 events in 1020 participants in each group (uplifted to 1200 to account for ~10% drop-out

Recruitment target: 200 patients with LVSD

Randomised: Echocardiogram pathway and then treatment allocated by centre

OPT-PACE: Flow diagram of inclusions

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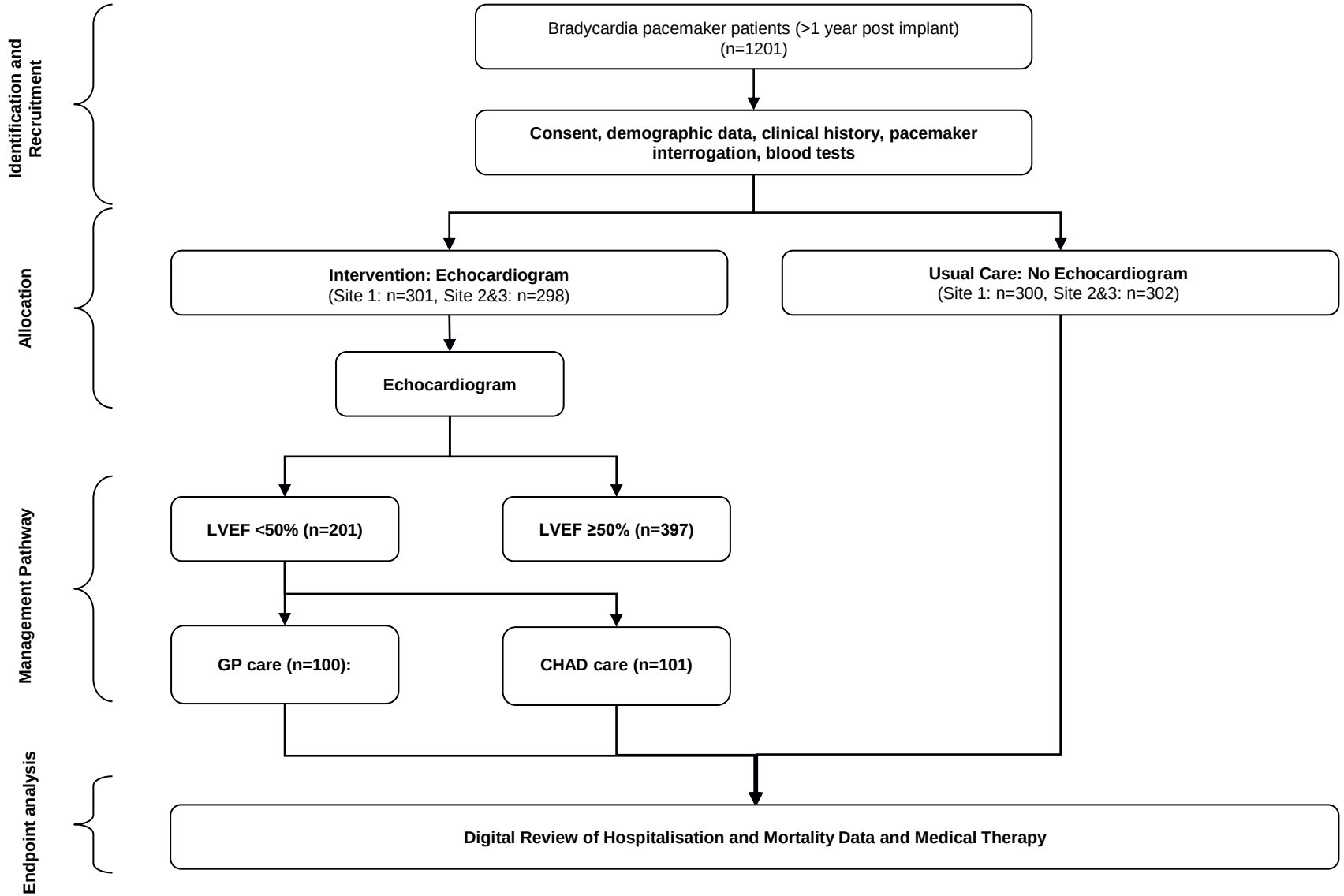

OPT-PACE: Baseline characteristics

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	Total (n=1201)	Echocardiogram (n=599)	No echocardiogram (n=602)
Site 1	601 (50%)	301 (50%(	300 (50%)
Site 2	300 (25%)	148 (25%)	152 (25%)
Site 3	300 (25%)	150 (25%)	150 (25%)
Patient Demographics			
Age (years)	75.2 (12.0)	74.9 (12.2)	75.5 (11.9)
Height (cm)	167 (14)	167 (13)	166 (14)
Weight (kg)	78 (17)	78 (16)	77 (17)
Clinical History			
Myocardial Infarction [n](%)	215 (18%)	105 (18%)	110 (18%)
Diabetes Mellitus [n] (%)	253 (21%)	122 (20%)	131 (21%)
CABG [n](%)	105 (9%)	48 (8%)	57 (9%)
PCI [n](%)	107 (9%)	57 (10%)	50 (8%)
CVA [n](%)	190 (16%)	100 (17%)	90 (15%)
Haemodynamic and ECG data			
Resting Heart Rate (bpm)	69 (12)	69 (12)	69 (12)
Resting Systolic BP(mmHg)	138 (23)	138 (22)	138 (24)
Atrial Rhythm			
Atrial Fibrillation [n] (%)	356 (30%)	194 (32%)	162 (27%)
Paced [n] (%)	108 (9%)	46 (8 %)	62 (10%)
Sinus Rhythm [n] (%)	737 (61%)	359 (60%)	62.79 (63%)
Pacemaker data			
Indication			
Atrioventricular block [n] (%)	419 (34.9%)	213 (35.6%)	206 (34.3%)
Sinus Node Disease [n] (%)	643 (53.5%)	323 (53.7%)	320 (53.1%)
Other [n] (%)	139 (11.6%)	63 (10.7%)	76 (12.6%)
Duration of pacing (years)	7.2 (6.2)	7.2 (6.0)	7.2 (6.4)
Atrial Fibrillation burden (%)	29 (44)	30 (45)	28 (43)
Atrial Pacing burden (%)	32 (35)	32 (35)	33 (35)
Ventricular Pacing burden (%)	40 (42)	41 (43)	38 42)
Base Rate (bpm)	56 (7)	56 (8)	56 (8)
Echocardiographic Data			
LVEF (%)			
LVEDD (mm)			
LVSD (LVEF<50%) [n] (%)			

Continuous data are expressed as mean (SD) or categorical data as [n] (%) as indicated.

CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention, CVA; cerebrovascular attack, BP; blood pressure, LVEF; left ventricular ejection fraction, LVEDD; left ventricular end diastolic diameter.

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UNIVERSITY OF LEEDS

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Base Rate (bpm)	56 (7)	56 (8)	56 (8)
Echocardiographic Data			
LVEF (%)		53 (9)	
LVEDD (mm)		47 (7)	
LVSD (LVEF<50%) [n] (%)		201 (34%)	

Continuous data are expressed as mean (SD) or categorical data as [n] (%) as indicated.

CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention, CVA; cerebrovascular attack, BP; blood pressure, LVEF; left ventricular ejection fraction, LVEDD; left ventricular end diastolic diameter.

OPT-PACE: Follow-up

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Participants were followed for a median of 31 (inter-quartile range 30, 40) months

OPT-PACE: Follow-up and primary outcome

UNIVERSITY OF LEEDS

Participants were followed for a median of 31 (inter-quartile range 30, 40) months

Primary outcome occurred in 106 of 600 (18%) people randomised to receive TTE-guided care and 115 of 601 (19%) participants in the usual care group (HR 0.89; 95% CI 0.69, 1.17; p=0.41)

Driven by 59 (27%) first HFHs and 162 (73%) deaths.

Estimated treatment effect adjusted by statistically significant predictors did not alter results ($HR_{adjusted}$ 0.95; 95% CI 0.72, 1.24; p=0.70)

OPT-PACE: Follow-up and primary outcome

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A pre-specified subgroup analysis of the TTE-guided care group only was carried out comparing TTE with and without CHF & Device (CHAD) clinic

OPT-PACE: Follow-up and primary outcome

UNIVERSITY OF LEEDS

A pre-specified subgroup analysis of the TTE-guided care group only was carried out comparing TTE with and without CHF & Device (CHAD) clinic

Primary outcome was significantly lower in those receiving CHAD care, compared to those receiving echocardiographic-guided primary care physician management or usual care

(12% vs 24% vs 19% respectively; HR 0.67, 95%CI 0.46, 0.98; p=0.050)

OPT-PACE: Primary outcome & prespecificed analysis

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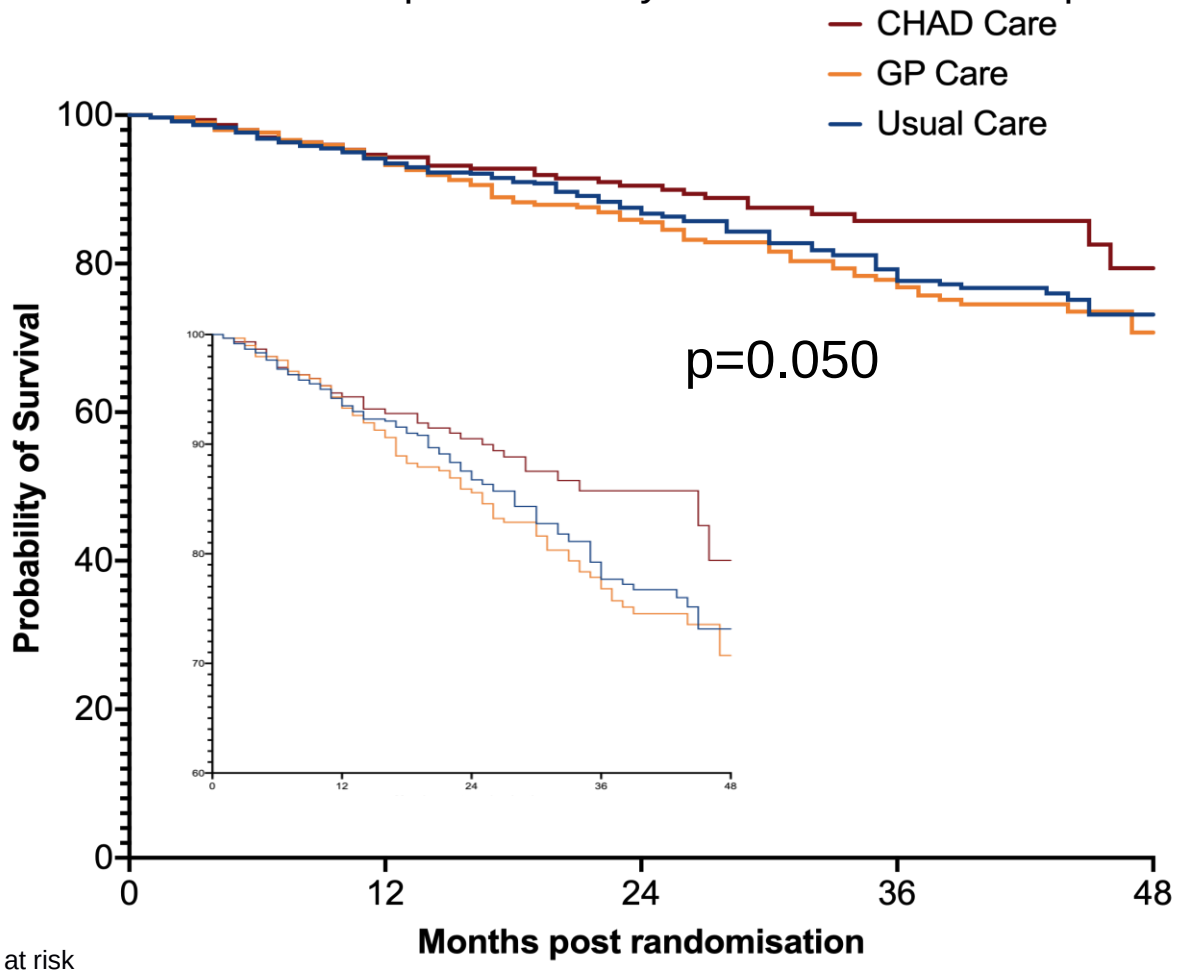
Time Free of All-Cause Mortality or Heart Failure Hospitalisation by Randomisation Group



Number at risk					
CHAD Care	301	271	170	73	18
GP Care	298	279	256	143	11
Usual Care	602	550	430	189	27

OPT-PACE: Secondary outcome

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Achievement of optimally tolerated medical therapy

Medical Therapy	HF Clinic (n=83)	Standard care (n=73)	Odds Ratio (95% CI)
Beta blocker	67	43	2.92 (1.43, 5.99)
ACEi or ARB	58	40	1.86 (0.96, 3.59)
Loop Diuretic	31	23	1.27 (0.65, 2.47)
MRA	15	5	2.95 (1.01, 8.61)
Statin	46	37	1.19 (0.62, 2.22)
Calcium Antagonist	7	7	0.84 (0.28, 2.53)
Anti-platelet	27	19	1.34 (0.67, 2.70)
Amiodarone	2	2	0.86 (0.12, 6.30)
Warfarin	35	34	0.85 (0.45, 1.61)
Digoxin	8	5	1.42 (0.44, 4.52)
Anti-Diabetic	13	16	0.65 (0.28, 1.44)

Continuous variables are expressed as mean (95% Confidence Interval)

ACEi; Angiotensin-converting-enzyme inhibitor,
ARB; Angiotensin II receptor blocker,
MRA; mineralocorticoid receptor antagonist.

OPT-PACE: Limitations

UNIVERSITY OF LEEDS

- Trial recruited in three hospitals in Yorkshire in the UK
  - (2 secondary care and 1 teaching hospital);
- No SGLT2i (likely to contribute to greater effect in the ‘intervention’ arm);
- Excluded people with known LVSD (likely to contribute to greater effect in the ‘intervention’ arm);
- Regionally held digital data for hospitalisation endpoints (unlikely hospitalisation elsewhere, and likely balanced across groups) – national data for mortality updated daily;
- Delay to the effects of optimal medical therapy;
- OPT-pace was study of medical optimisation, and not of the benefits of CRT upgrade.

OPT-PACE: Conclusions

UNIVERSITY OF LEEDS

Screening for LV dysfunction in patients with pacemakers will identify a large proportion of people with HFrEF

Screening and identification alone does not lead to improved outcomes

Optimal therapy for these patients associated with lower hospitalisation and mortality rates

Medical optimisation in patients with HF and a pacemaker should be delivered in a combined CHF&Devices clinic

Future outcomes studies of device for bradycardia need to include optimal medical therapy in both groups.

‘It’s not just about the data, it’s also how you use them’

OPT-PACE: Acknowledgements

UNIVERSITY OF LEEDS

Dr Maria Paton (NIHR Post-doc)

Dr. Maria Paton PhD

Leeds General Infirmary

Leeds Institute for CV and Metabolic Medicine

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NIHR | National Institute for Health Research

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ctru University of Leeds

Prof. Deb Stocken, (LICTR)

Mentorship and friendship Prof. Mark Kearney (Faculty Dean)

Prof. Mark Kearney
Dean Leeds Medical School and BHF Chair

My previous and current PhD Fellows

Dr. John Gierula PhD

Dr. Haqeel Jamil MD, PhD

Dr. Jack Garnham PhD

Dr. Sam Straw MB, PhD

Dr. Judith Lowry PhD

Mrs. Charlotte Cole MSc

BUDAPEST CRT Upgrade trial

#ESCCongress

CRT upgrade in HF with RV pacing

Conclusion

Upgrade to cardiac resynchronisation therapy with a defibrillator (CRT-D) reduces morbidity and mortality and improves left ventricular reverse remodelling in select patients with heart failure and reduced ejection fraction (HFrEF) and intermittent or permanent right ventricular (RV) pacing.

Impact on clinical practice

HFrEF patients with a pacemaker or ICD should be strictly followed in clinical practice and in those with intermittent or permanent RV pacing, a CRT upgrade should be performed immediately without deferring the procedure to a later date (e.g. battery replacement).

Study objectives

BUDAPEST CRT Upgrade was the first trial to compare the efficacy and safety of a CRT upgrade, compared to ICD alone, in HFrEF patients with a pacemaker or ICD and intermittent or permanent RV pacing.

Study population

HFrEF patients

- with ejection fraction ≤35%
- had received a pacemaker or ICD >6 months previously
- had HF symptoms
- had a wide paced QRS complex
- had a high burden of RV pacing
- treated with guideline-directed medical therapy

Patients were excluded if they were eligible for CRT according to current guidelines

Where?

7 countries

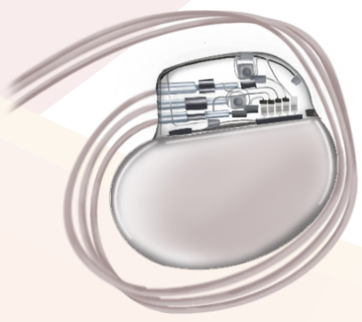
17 sites

Who and what?

360 patients

randomised 3:2

CRT-D upgrade



ICD

Median follow-up ▶ 12.4 months

Primary endpoint

Composite of HF hospitalisation, all-cause mortality, or <15% reduction of left ventricular end-systolic volume

Rate%

32.4%

78.9%

Adjusted odds ratio 0.11
95% CI 0.06–0.19; p<0.001

Secondary endpoint

Composite of HF hospitalisation and all-cause mortality reduced with

vs

Adjusted hazard ratio 0.28
95% CI 0.17–0.46; p<0.001

ESC

NOAH-AFNET 6 trial #ESCCongress

Oral anticoagulation in patients with atrial high-rate episodes

Conclusion

Blood thinners (anticoagulants) cause bleeding without preventing stroke in patients with atrial high-rate episodes (AHRE), but without electrocardiogram (ECG)-diagnosed atrial fibrillation.

Impact on clinical practice

The results clearly suggest to demand ECG documentation of atrial fibrillation prior to initiation of oral anticoagulation.

Study objectives

NOAH-AFNET 6 was the first trial to investigate the efficacy and safety of oral anticoagulation in patients with AHRE, but without ECG-documented atrial fibrillation.

Study population

Patients ≥65 years with

- AHRE episodes ≥6 minutes detected by implantable devices
- ≥1 additional stroke risk factor
  - heart failure
  - hypertension
  - diabetes
  - prior stroke or transient ischaemic attack
  - vascular disease
  - age ≥75 years

Where?

18 European countries

206 sites

Who and what?

2,536* patients

randomised 1:1

anticoagulation (edoxaban)

no anticoagulation (placebo with no active compound or aspirin 100 mg once daily in patients with an indication for antiplatelet therapy)

**the primary, modified intention-to-treat analysis population who received ≥1 dose of study drug*

The trial was stopped early due to safety signals and a trend towards futility for efficacy after enrolment of all planned patients.

Primary endpoint

Composite of stroke, systemic embolism, or cardiovascular death

Rate%		Hazard ratio
3.2%/year	4.0%/year	0.81 (95% CI 0.6–1.1; p=0.15)

Safety outcome

Composite of major bleeding and all-cause death

Rate%		Hazard ratio
5.9%/year	4.5%/year	1.3 (95% CI 1.0–1.7; p=0.03)

The difference in safety outcomes was driven by an expected increase in major bleeding with

vs.

Hazard ratio 2.10
95% CI 1.30–3.38; p=0.002

ESC

Posterior wall isolation improves outcomes for persistent atrial fibrillation with rapid posterior wall activity

Peter Kistler MBBS, PhD, FHRS

on behalf of the CAPLA investigators

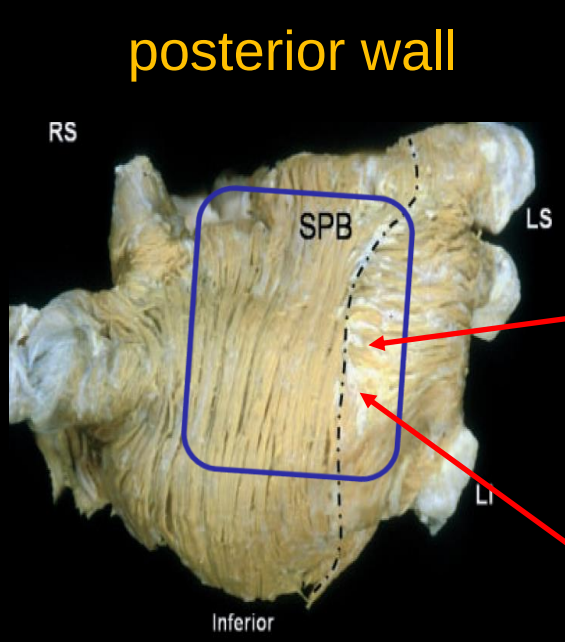
Professor University of Melbourne

Head Clinical Electrophysiology Research

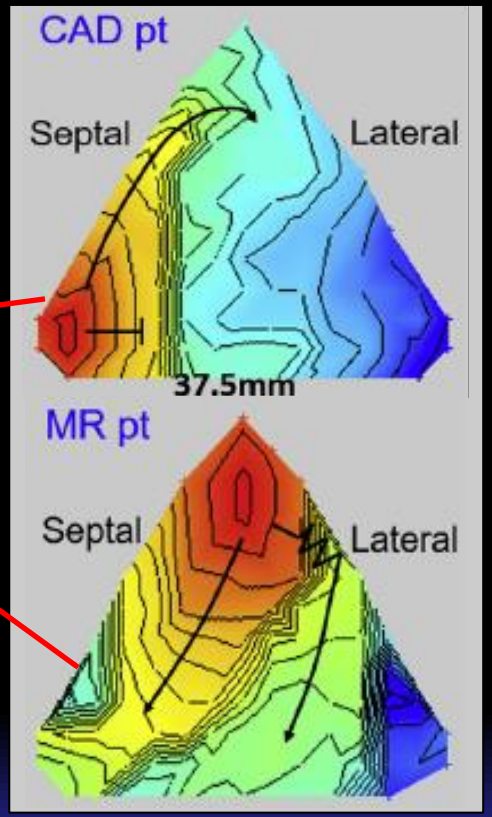
The Alfred Hospital, Melbourne, Australia

Left atrial posterior wall: role in AF

- Common embryologic origin to PVs
- Source of non PV AF triggers
- Parasympathetic ganglia
- Site of proximal rotational activity or AF drivers
- “belt and braces” approach to posterior PVI
- Debulking: ↓critical atrial mass



Ho SY et al JCE 1999;10:1525-33.

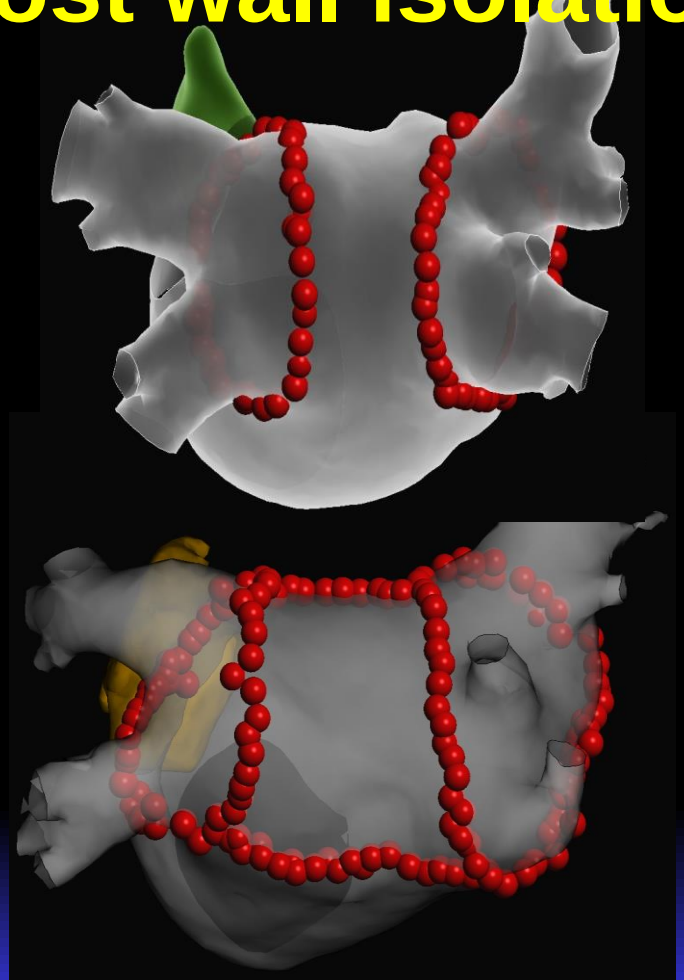


Roberts-Thomson K et al JACC 2008;51: 856-62

RCT of PVI vs PVI + post wall isolation

338 patients with perAF from 11 centres across 3 countries (Australia, Canada and UK)

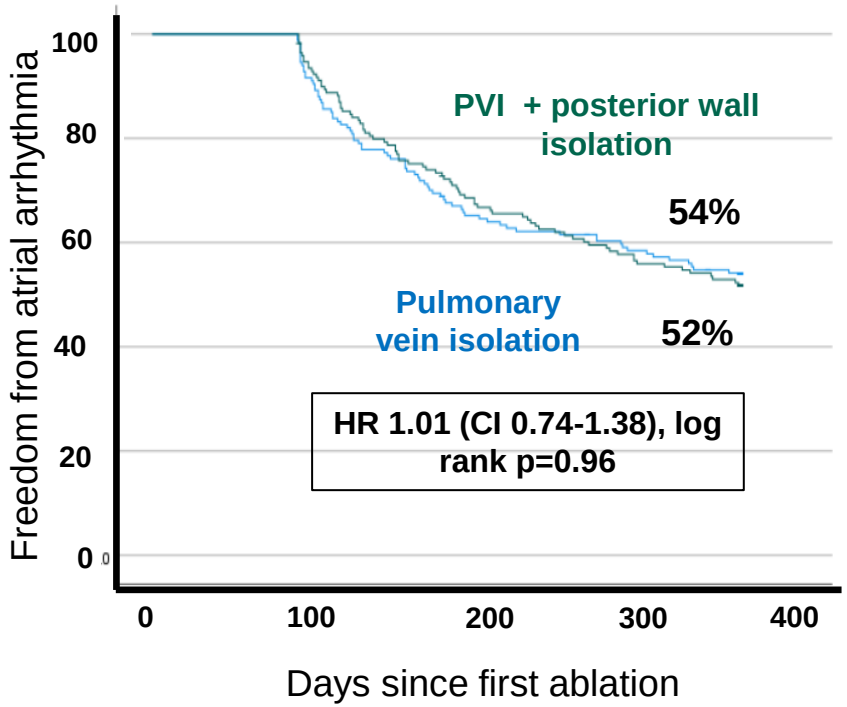
GA, imaging guided transseptal
Cardioversion to sinus rhythm if in AF
Force sensing irrigated RF 40-50W target LSI or AI
Esophageal temp monitor
Additional ablation ONLY for Atc
Follow Up 12mths

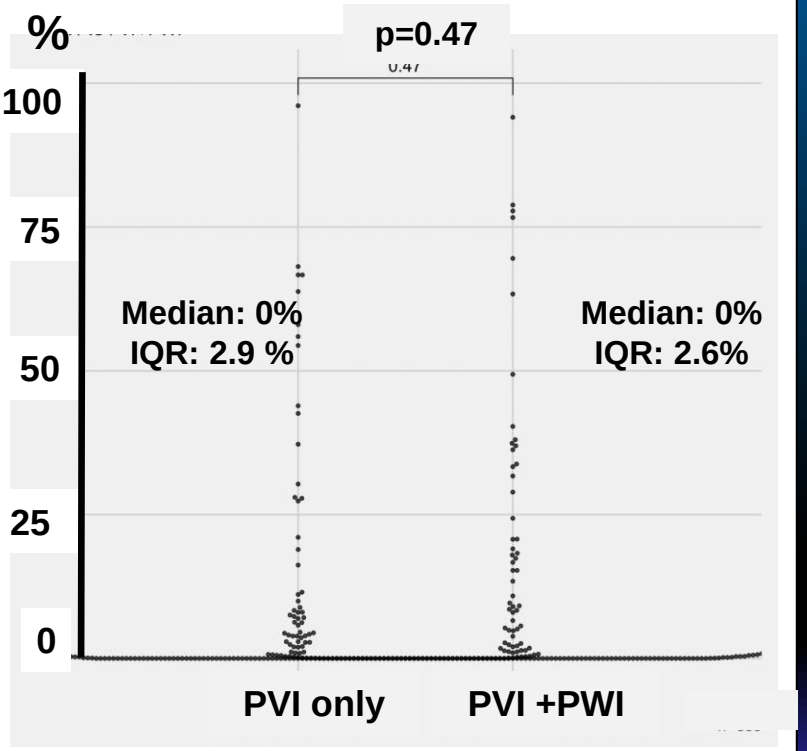


JAMA 2023 May 23;329(20):1794-1795

1 endpoint: Freedom from AF/AT off AADs at 12months

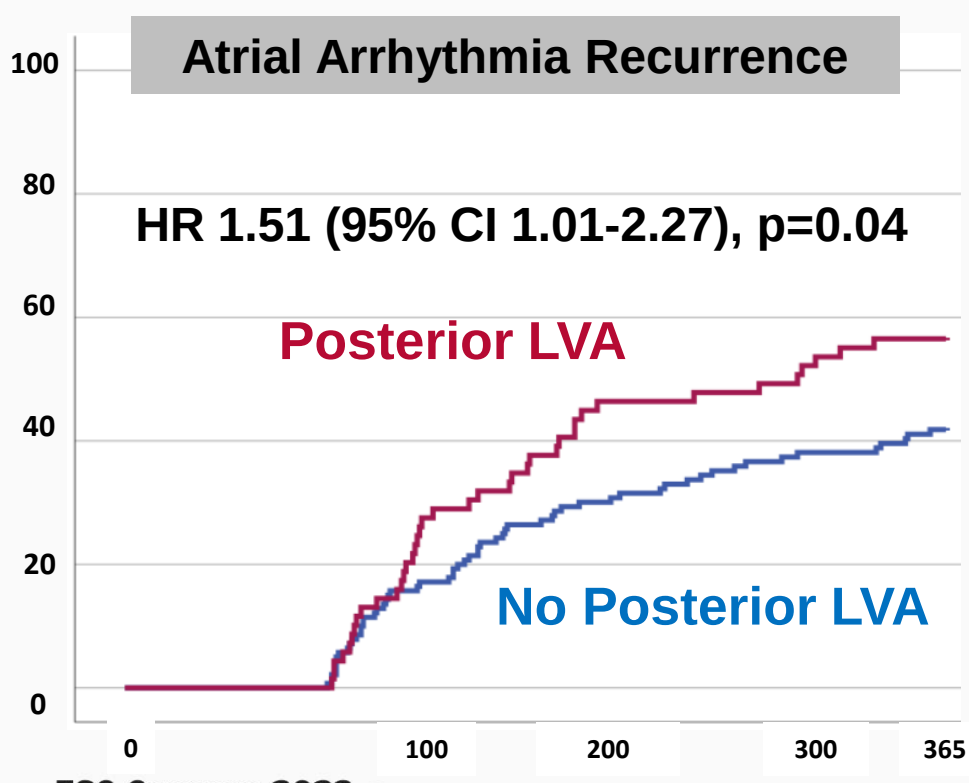
AF Burden

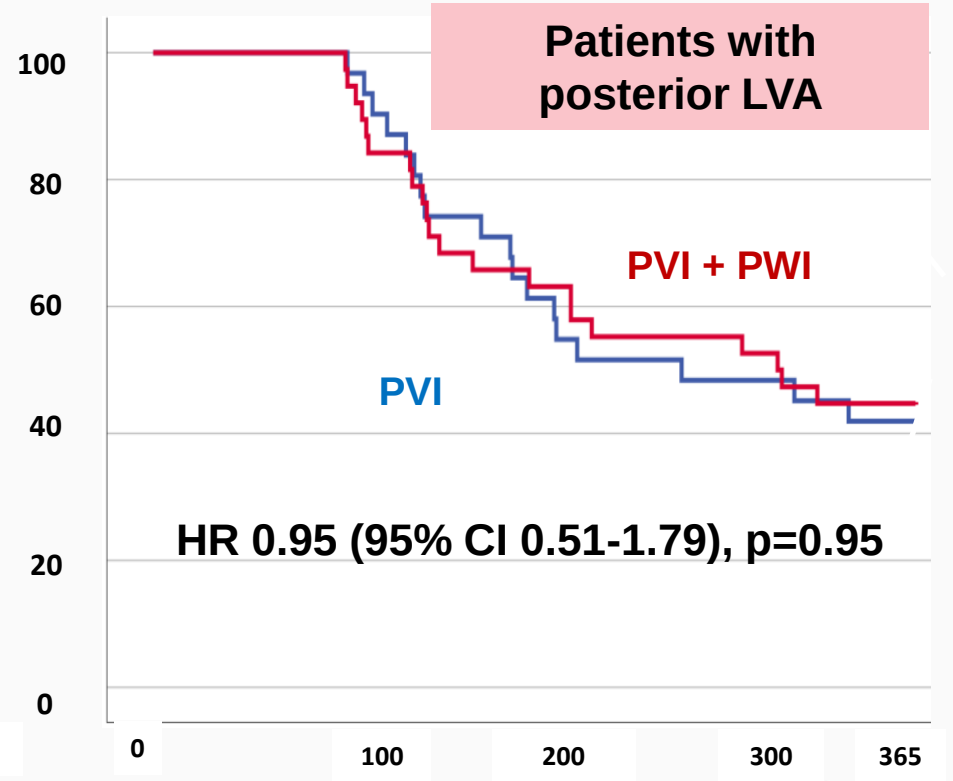




JAMA 2023 May 23;329(20):1794-1795

Impact of low posterior left atrial wall voltage on outcomes of catheter ablation for persistent AF



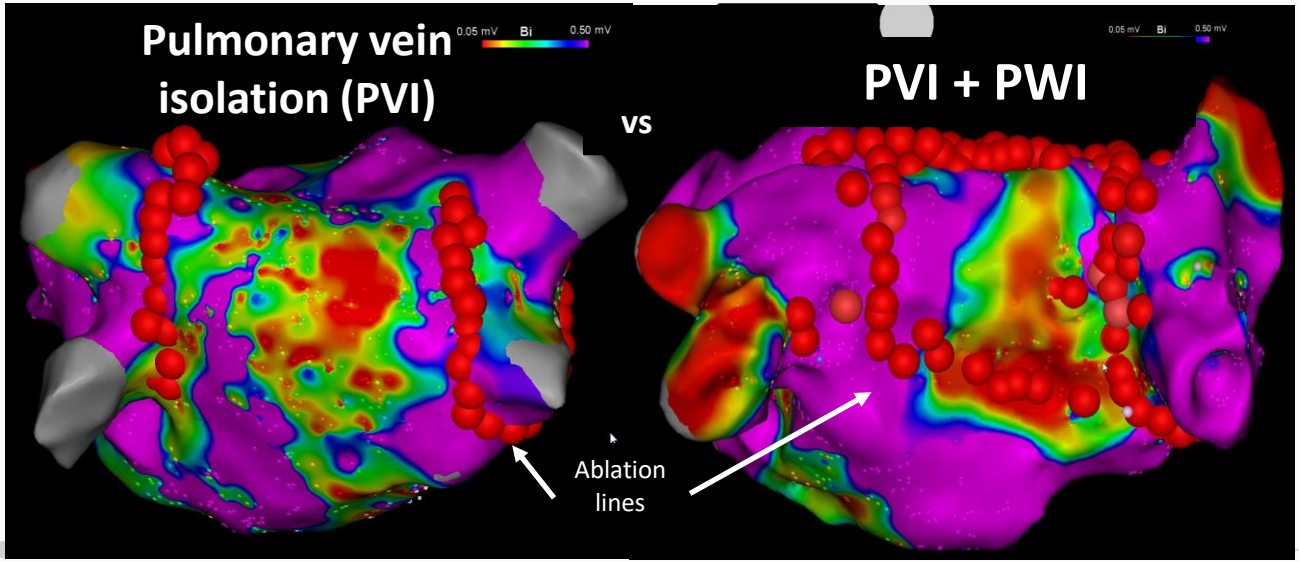


ESC Congress 2023
Amsterdam & Online

Chieng D et al JACC EP in press 2023

Impact of low posterior left atrial wall voltage on outcomes of catheter ablation for persistent AF

	Additional LA segment(s) with LVA	P value
Posterior wall LVA	**51/56 (91.7%)**	P<0.01
No posterior wall LVA	56/98 (57.1%)	

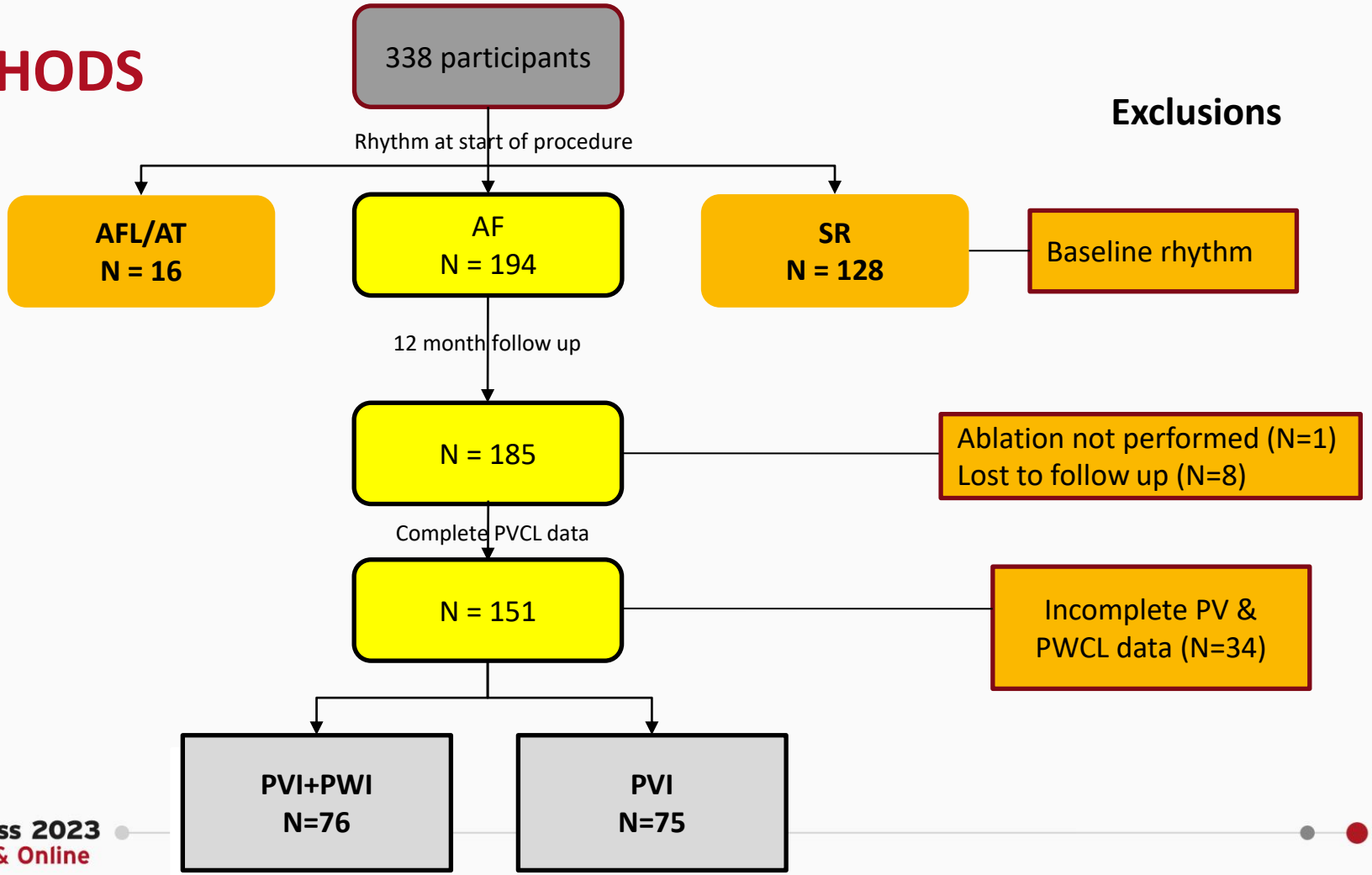


Chieng D et al JACC EP in press 2023

Objective

- **To determine the impact of PV and PW electrical characteristics on AF ablation outcomes in the CAPLA randomised study.**

METHODS



Exclusions

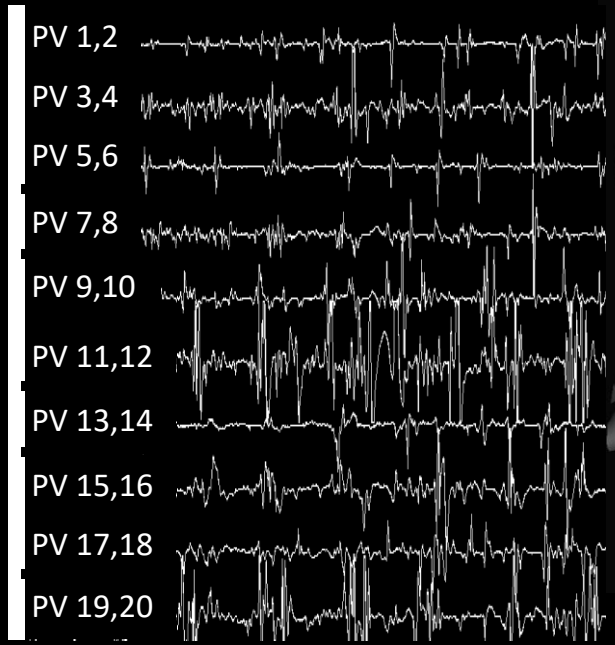
Baseline characteristics

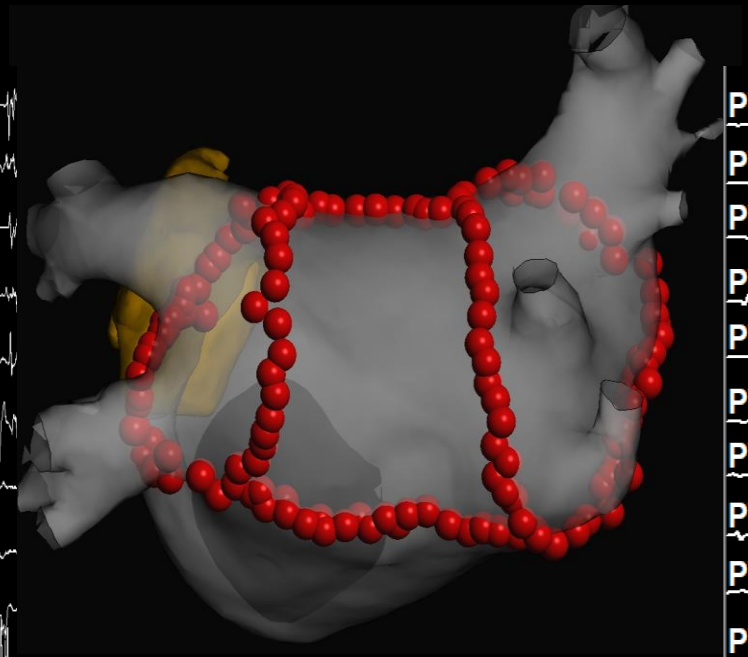
	PVI N=75	PVI+PWI N=76	P value
Demographics			
Age (years), mean±SD	65±10	65±9	0.773
Female, n (%)	22 (29.3)	18 (23.7)	0.465
BMI, kg/m^2, mean±SD	30.3±6.1	30.6±5.7	0.745
Long standing PerAF n (%)	14 (18.7)	13 (17.1)	0.775
Comorbidities			
Hypertension, n (%)	34 (45.3)	40 (52.6)	0.420
Stroke, n (%)	5 (6.7)	3 (3.9)	0.491
Heart failure, n (%)	35 (46.7)	33 (43.4)	0.743
CHADS2VASc, mean±SD	2.0±1.1	2.1±1.2	0.635
Echocardiographic parameters			
LVEF, %, mean±SD	51±14	52±13	0.749
LAVI, ml/m^2, mean±SD	49±14	54±17	0.120

Cycle length EGM characteristics

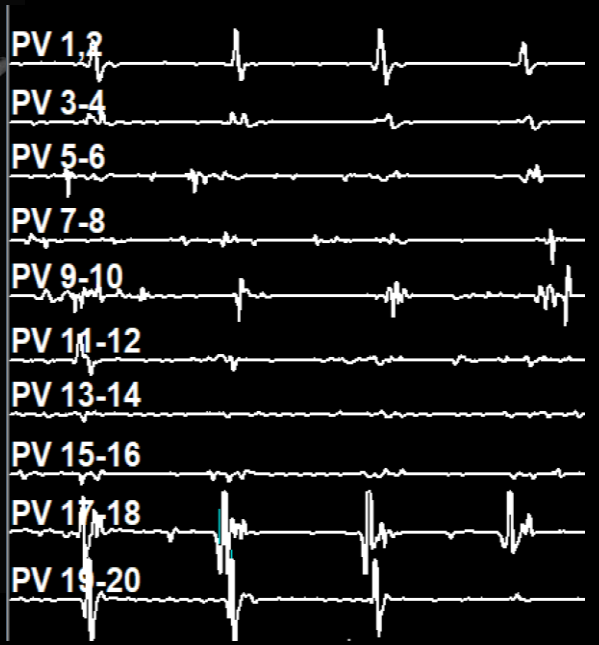
Cycle length parameters	PVI N=75	PVI+PWI N=76	P value
Average PVCL (ms)	183±22	176±21	0.084
Fastest PVCL	127±23	120±25	0.080
Average PWCL (ms)	179±19	173±19	0.114
Fastest PWCL	142±16	138±18	0.104
LAA CL (ms)	175±23	171±20	0.218
Posterior wall voltage (mV)	1.4±0.6	1.4±0.7	0.889
Posterior low voltage (<0.5mV)	25 (33%)	35 (46%)	0.110

Faster posterior wall activity

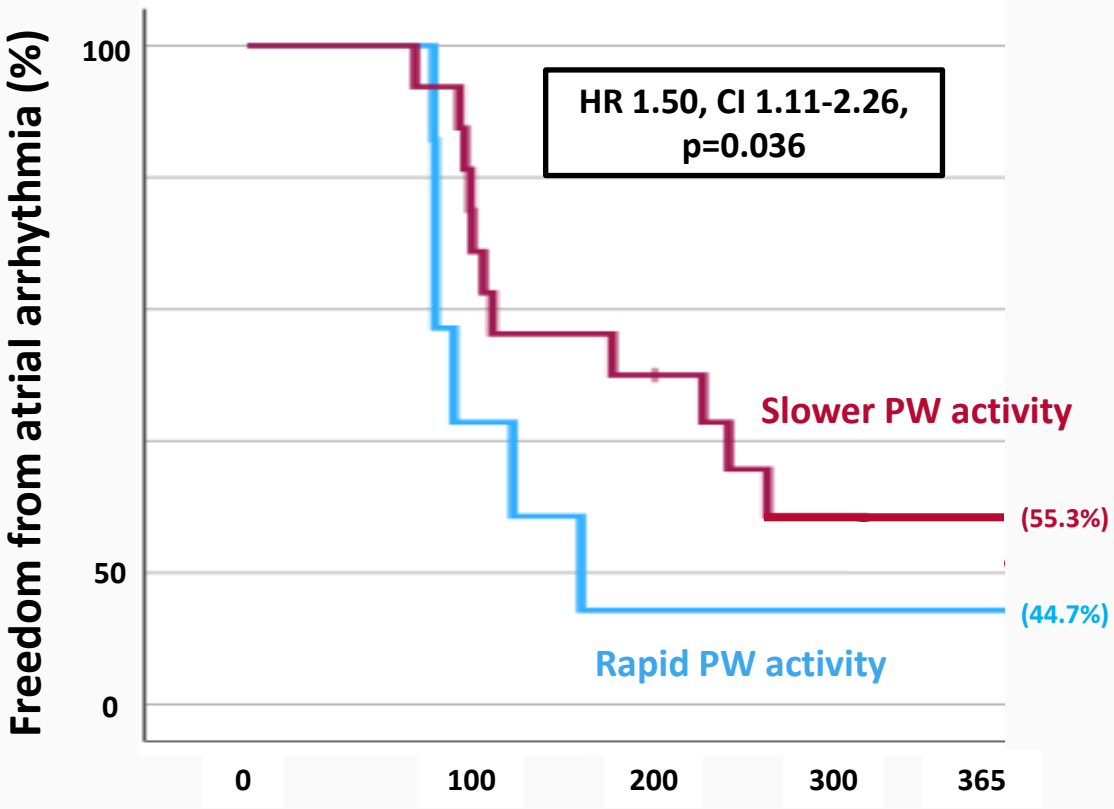


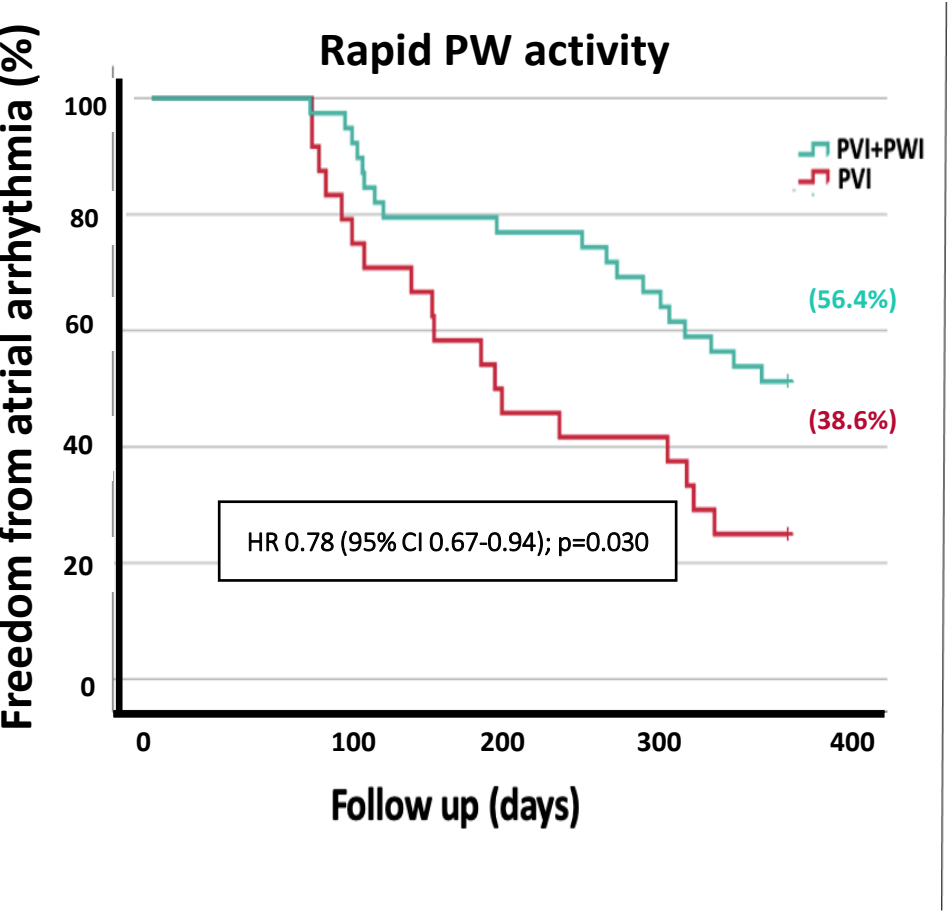


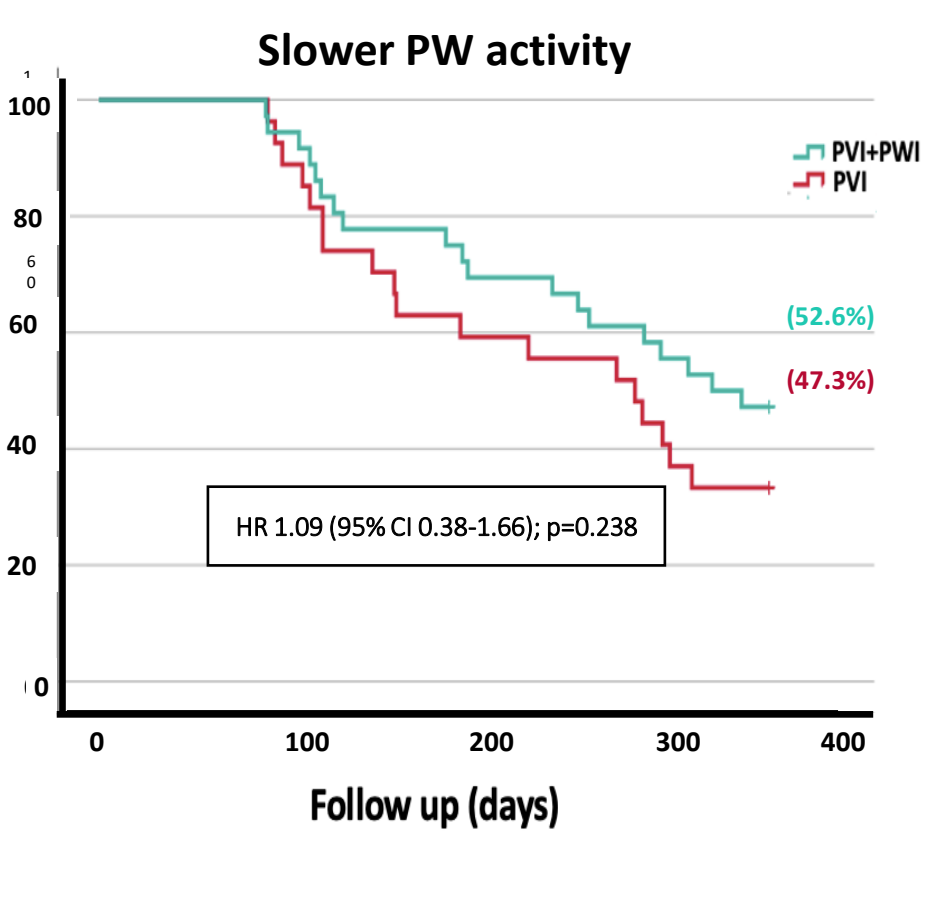
Slower posterior wall activity

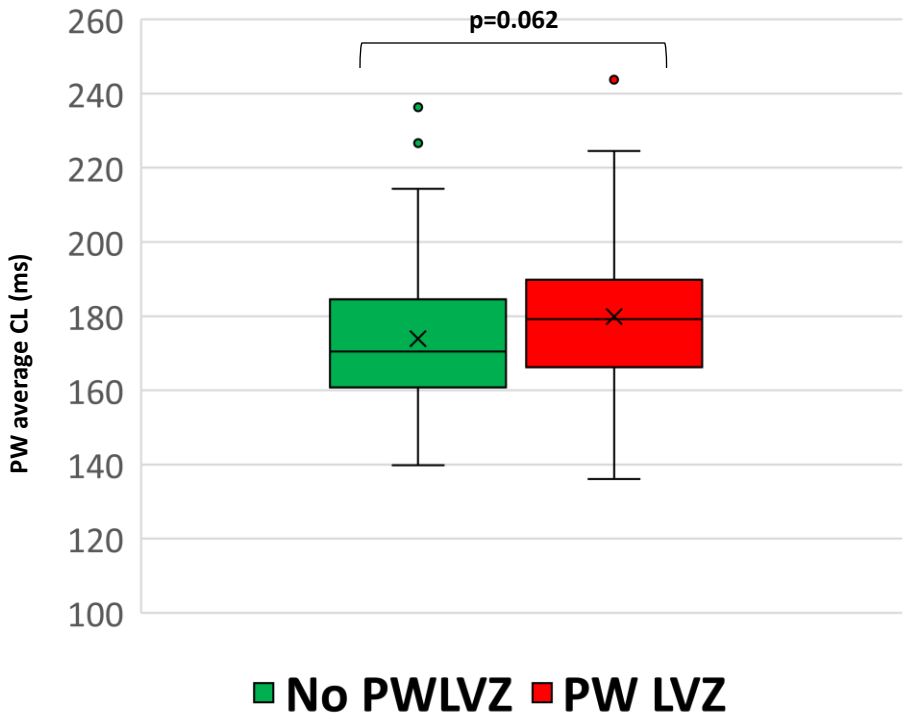


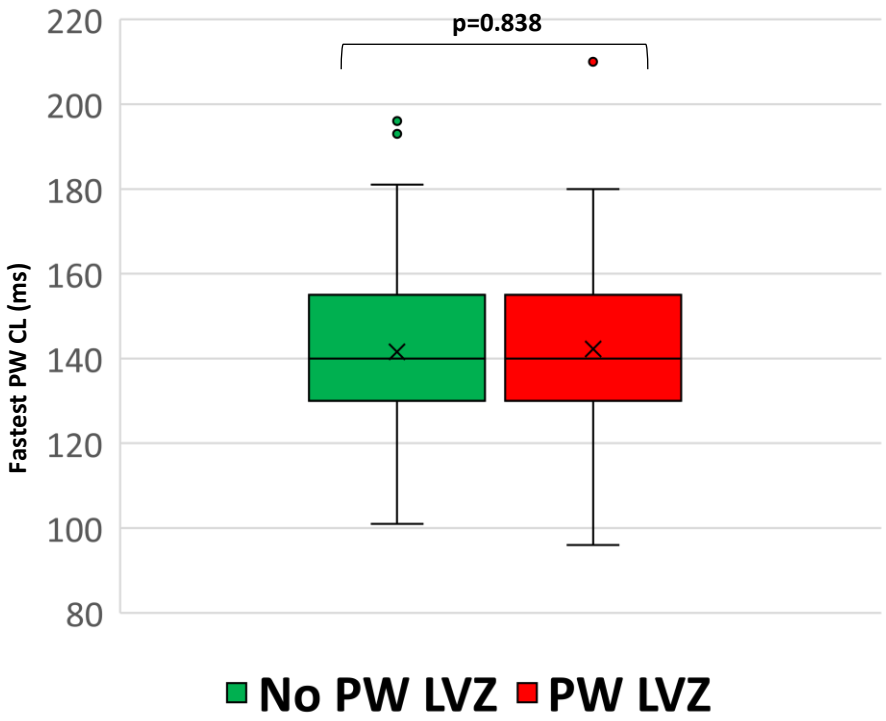
Arrhythmia free survival in those undergoing PVI only stratified by Post Wall activity




Rapid PW activity
Freedom from atrial arrhythmia (%)
100
80
60
40
20
0
PVI+PWI
PVI
(56.4%)
(38.6%)
HR 0.78 (95% CI 0.67-0.94); p=0.030
0
100
200
300
400
Follow up (days)


Slower PW activity
100
80
60
40
20
0
PVI+PWI
PVI
(52.6%)
(47.3%)
HR 1.09 (95% CI 0.38-1.66); p=0.238
0
100
200
300
400
Follow up (days)





PW CL according to PW voltage status. There was no significant difference between those with or without low voltage with respect to average PW cycle length (left) or fastest PW cycle length (right).

Conclusions

- Rapid posterior wall activity is associated with an ↑risk of AF recurrence post catheter ablation.
- The addition of PWI in this subgroup was associated with a significant improvement in freedom from AF compared to PVI alone.
- The presence of rapid PW activity may identify patients with persistent AF likely to benefit from PWI.

Study investigators

- Peter M Kistler (PI), David Chieng*
- Hariharan Sugumar, Liang-Han Ling, Sandeep Prabhu, Aleksandr Voskoboinik
- Ahmed Al-Kaisey, Ramanathan Parameswaran, Robert D Anderson, Joshua Hawson, Louise Segan, Sue Finch
- Geoffrey Wong, Joseph B Morton, Bhupesh Pathik, Alex J McLellan, Geoffrey Lee,
- Michael Wong, Rajeev K Pathak, Deep Chandh Raja,
- Laurence Sterns, Matthew Ginks, Christopher M Reid,
- Prashanthan Sanders and Jonathan M Kalman.

Atrial Fibrillation Progression After Cryoablation vs. Radiofrequency Catheter Ablation

Dr. Jason Andrade MD FRCPC FESC FEHRA for the CIRCA-DOSE Investigators
Vancouver General Hospital, Centre for Cardiovascular Innovation

August 25 2023

Disclosures

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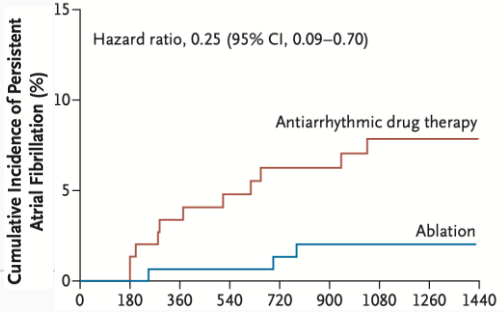
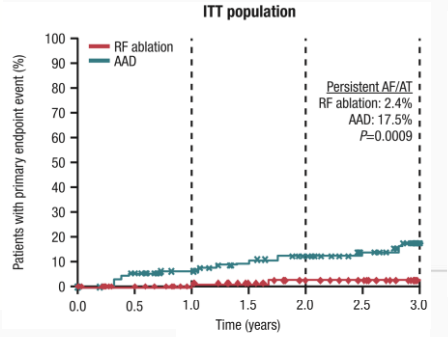
- Heart and Stroke Foundation of Canada (CIRCA-DOSE)
- Michael Smith Foundation for Health Research
- Medtronic, Inc (CIRCA-DOSE)
- Baylis Medical; Bayer HealthCare; BMS/Pfizer Alliance; Servier

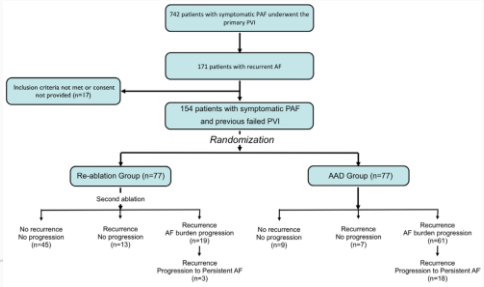
- **Mitigation:**
  - No external party was involved in the design and preparation of this presentation.

Studies of Ablation and AF Progression

	Andrade et al. EARLY-AF/PROGRESSIVE-AF	Kuck et al. ATTEST-AF	Pokushalov et al.
Number of Participants	303	255	154
Population	Paroxysmal AF	Paroxysmal AF	Paroxysmal AF
• Previous Interventions	**Treatment Naive**	**Previous AAD Failure**	**Previous AAD failure & Previous Ablation failure**
• Progression to Persistent AF	**1.9% Cryo-ABL vs. 7.4% AAD** **HR 0.25** (95%CI 0.07-0.70) NNT 18	**2.4% RF-ABL vs. 17.5% AAD** **HR 0.11** (95%CI 0.02-0.47) NNT 8	**4% RF-ABL vs. 23% AAD** **RR 0.17** (95%CI 0.05-0.54) NNT 5







Atrial Fibrillation Progression After Cryoablation vs. Radiofrequency Catheter Ablation

Circulation

ORIGINAL RESEARCH ARTICLE

Cryoballoon or Radiofrequency Ablation for Atrial Fibrillation Assessed by Continuous Monitoring

A Randomized Clinical Trial

Editorial, see p 1789

Jason G. Andrade, MD
Jean Champagne, MD
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Anthony S.L. Tang, MD
Paul Khairy, MD, PhD
For the CIRCA-DOSE Study Investigators*

BACKGROUND: Advanced generation ablation technologies have been developed to achieve more effective pulmonary vein isolation (PVI) and minimize arrhythmia recurrence after atrial fibrillation (AF) ablation.

METHODS: We randomly assigned 346 patients with drug-refractory paroxysmal AF to contact force–guided radiofrequency ablation (CF-RF; n=115), 4-minute cryoballoon ablation (Cryo-4; n=115), or 2-minute cryoballoon ablation (Cryo-2; n=116). Follow-up was 12 months. The primary outcome was time to first documented recurrence of symptomatic or asymptomatic atrial tachyarrhythmia (AF, atrial flutter, or atrial tachycardia) between days 91 and 365 after ablation or a repeat ablation procedure at any time. Secondary end points included freedom from symptomatic arrhythmia and AF burden. All patients received an implantable loop recorder.

RESULTS: One-year freedom from atrial tachyarrhythmia defined by continuous rhythm monitoring was 53.9%, 52.2%, and 51.7% with CF-RF, Cryo-4, and Cryo-2, respectively (P=0.87). One-year freedom from symptomatic atrial tachyarrhythmia defined by continuous rhythm monitoring was 79.1%, 78.2%, and 73.3% with CF-RF, Cryo-4, and Cryo-2, respectively (P=0.26). Compared with the monitoring period before ablation, AF burden was reduced by a median of 99.3% (interquartile range, 67.8%–100.0%) with CF-RF, 99.9% (interquartile range, 65.3%–100.0%) with Cryo-4, and 98.4% (interquartile range, 56.2%–100.0%) with Cryo-2 (P=0.36). Serious adverse events occurred in 3 patients (2.6%) in the CF-RF group, 6 patients (5.3%) in the Cryo-4 group, and 7 patients (6.0%) in the Cryo-2 group, with no significant difference between groups (P=0.24). The CF-RF group had a significantly longer procedure duration but significantly shorter fluoroscopy exposure (P<0.001 vs cryoballoon groups).

*Additional CIRCA-DOSE Study Investigators are listed in the Appendix

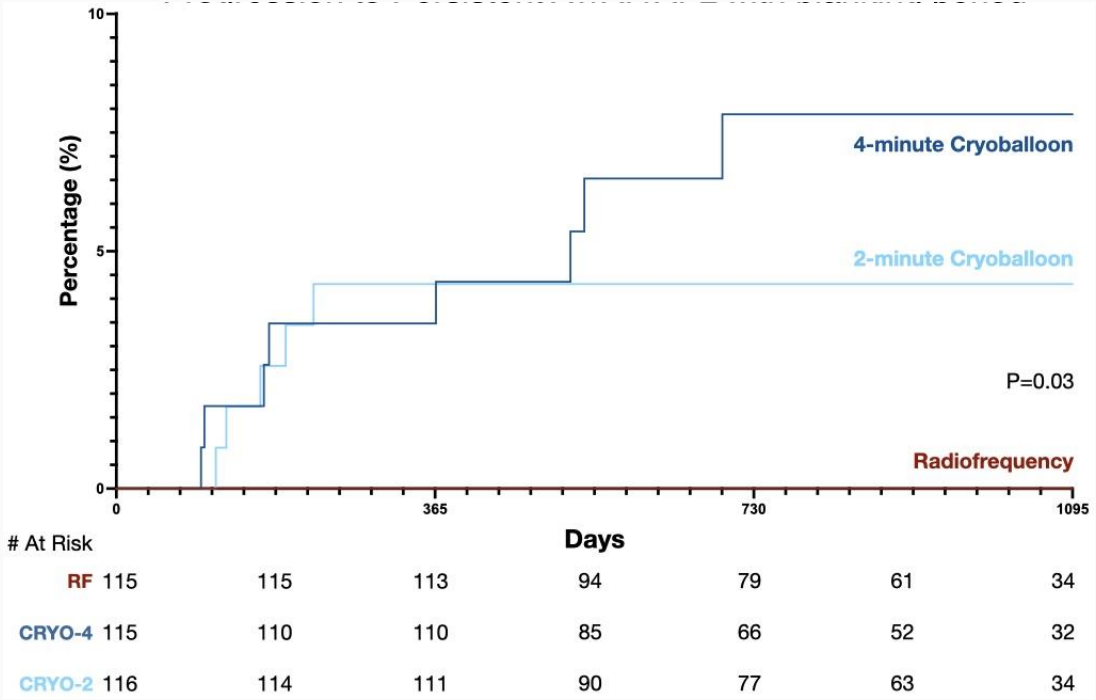
- **CIRCA** - Cryoballoon vs. Contact-force Irrigated Radiofrequency Catheter Ablation for AF
- **DOSE** - DOuble Short (2-minute) vs. Standard (4-minute) cryoapplication Exposure
- **Continuous cardiac monitoring**

Atrial Fibrillation Progression After Cryoablation vs. Radiofrequency Catheter Ablation

- **346 patients with drug-refractory paroxysmal AF**
- **Randomized to:**
  - Contact-force guided RF ablation (CF-RF, 115)
  - 4-minute cryoballoon ablation (CRYO-4, 115)
  - 2-minute cryoballoon ablation (CRYO-2, 116)
- **Followed for:**
  - Median 944.0 days (interquartile range [IQR], 612.5 to 1104)
- **Endpoints:**
  - Progression to Persistent AF (AF episode lasting 7 days, as detected by ILR)
  - Recurrence of Atrial Tachyarrhythmia (AT/AF/AFL) > 30s
  - AF Burden (percent time in AF)

Atrial Fibrillation Progression After Cryoablation vs. Radiofrequency Catheter Ablation

- **Progression to Persistent Atrial Tachyarrhythmia**



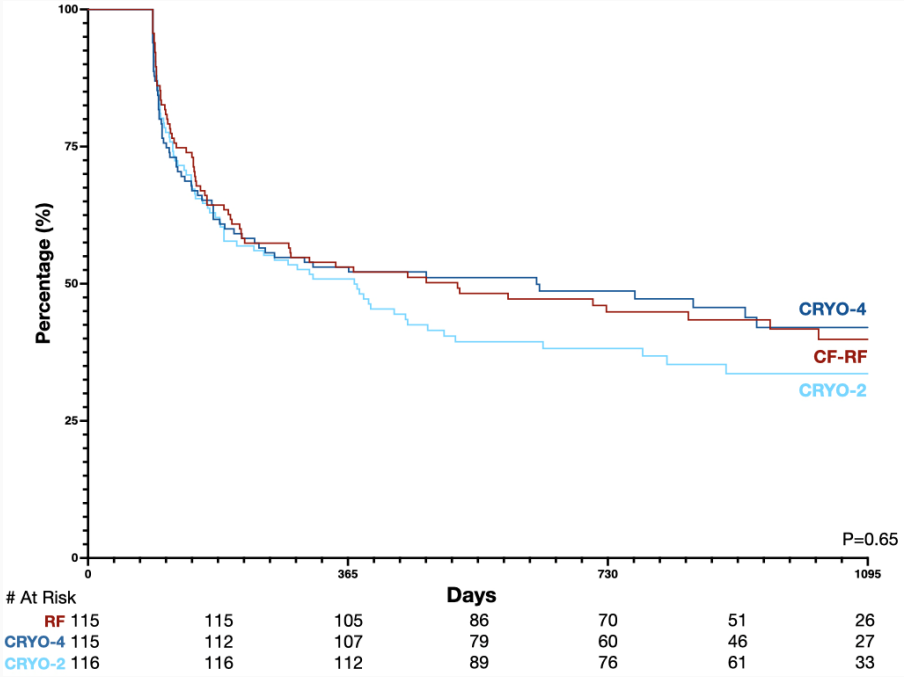
	HR (95%CI)	P
CRYO-4 vs. CF-RF	17.73* (2.21, 2293.41)	0.003
	7.737# (1.934-30.96)	0.004
CRYO-2 vs. CF-RF	11.06* (1.25, 1452.01)	0.027
	7.455# (1.291-43.04)	0.025

*Proportional Hazards with Firth correction

#Mantel Haenszel approach

Atrial Fibrillation Progression After Cryoablation vs. Radiofrequency Catheter Ablation

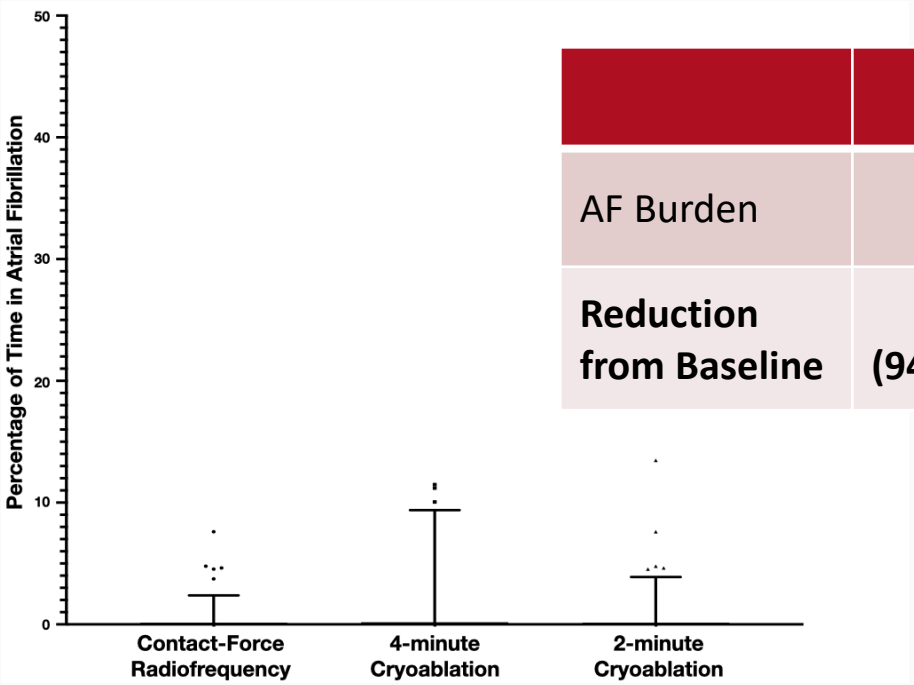
- **Atrial Tachyarrhythmia Recurrence (AT/AF/AFL)**



	HR (95%CI)	P
CRYO-4 vs. CF-RF	1.02 (0.72, 1.44)	0.9
CRYO-2 vs. CF-RF	1.22 (0.88, 1.70)	0.24

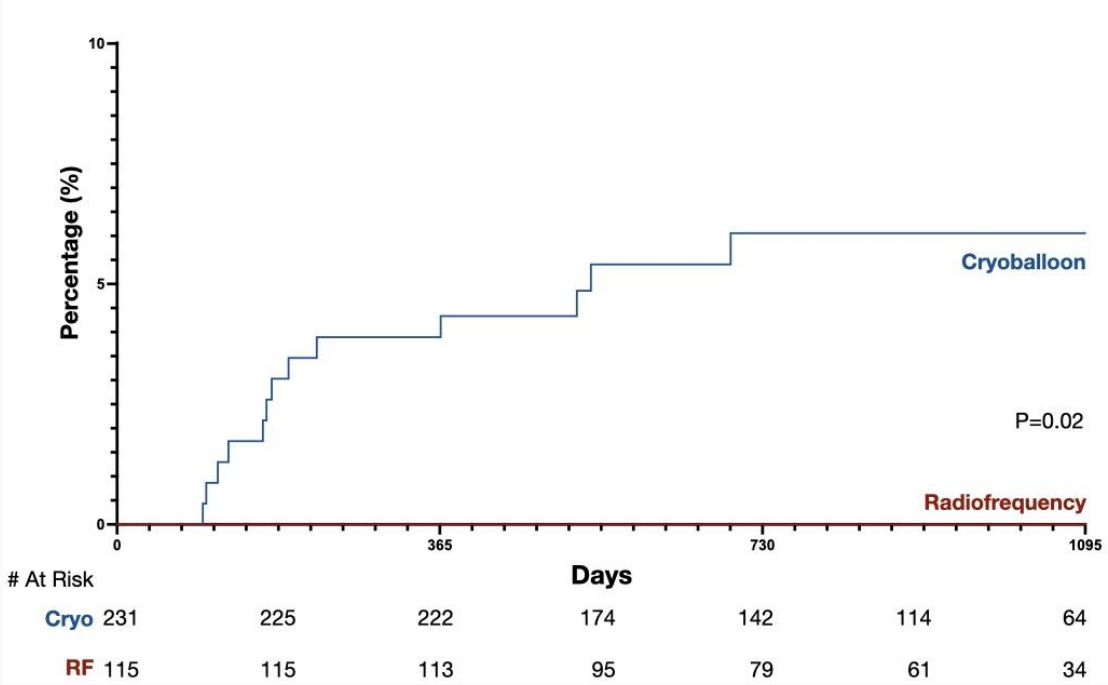
Atrial Fibrillation Progression After Cryoablation vs. Radiofrequency Catheter Ablation

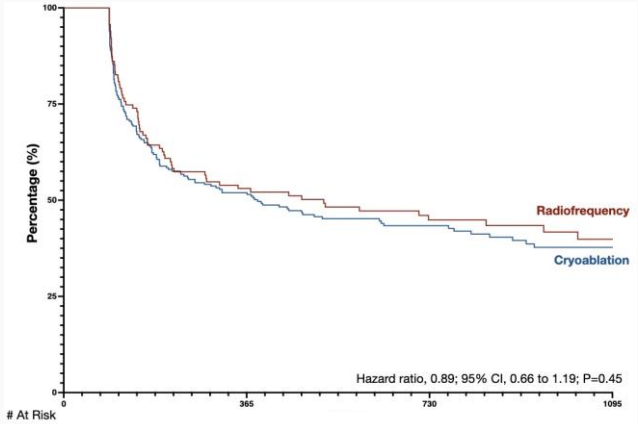
- **Atrial Tachyarrhythmia Burden (% Time in AF)**

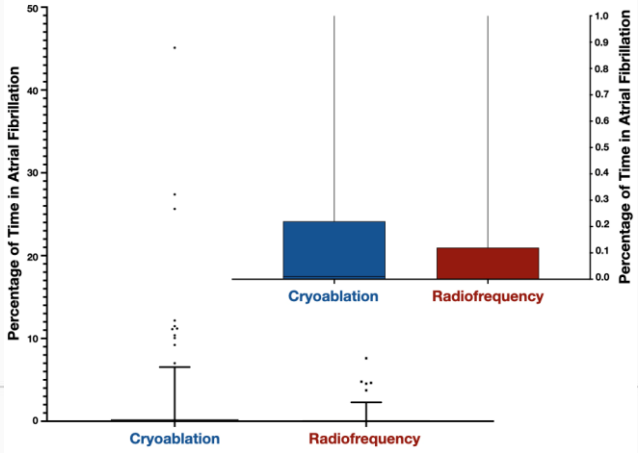


	CF-RF	CRYO-4	CRYO-2
AF Burden	0.00 (0.00, 0.12)	0.00 (0.00, 0.19)	0.00 (0.00, 0.12)
Reduction from Baseline	**99.5% (94.0%, 100.0%)**	**99.9% (93.3%, 100.0%)**	**99.1% (87.0%, 100.0%)**

Atrial Fibrillation Progression After Cryoablation vs. Radiofrequency Catheter Ablation





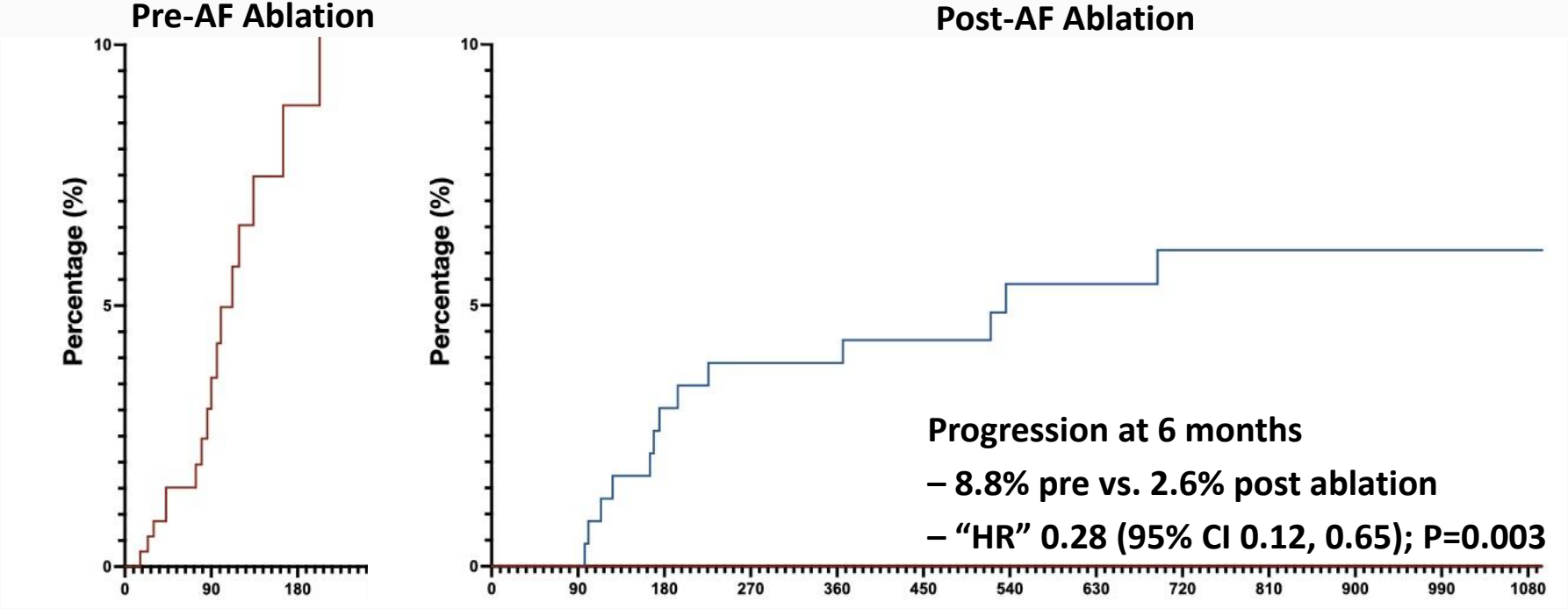


HR 13.82 (95% CI 1.84, 1768.12)*

HR 4.54 (95% CI 1.44, 14.32)#

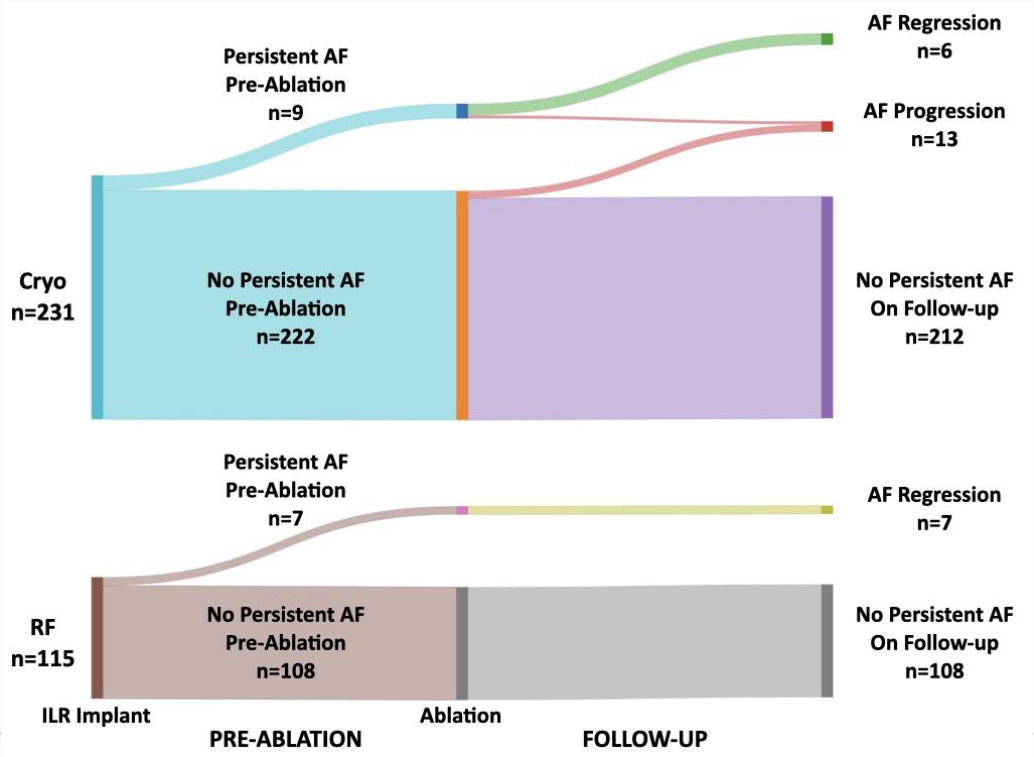
Atrial Fibrillation Progression After Cryoablation vs. Radiofrequency Catheter Ablation

- **Atrial Fibrillation Progression Pre-Post Ablation**



Atrial Fibrillation Progression After Cryoablation vs. Radiofrequency Catheter Ablation

- **Atrial Fibrillation Regression**



Atrial Fibrillation Progression After Cryoablation vs. Radiofrequency Catheter Ablation

a. Cryoballoon ablation and contact-force guided radiofrequency ablation are equally efficacious in:

a. Preventing AF recurrence on prolonged follow-up.

b. Reducing the long-term burden of AF as assessed by continuous cardiac monitoring.

b. Atrial fibrillation progression was observed less frequently after radiofrequency ablation compared to cryoballoon ablation.

c. A significant number of patients who progressed to persistent AF while awaiting ablation experienced “regression” post ablation

DANPACE II

Minimized atrial pacing and risk of atrial fibrillation in sinus node dysfunction

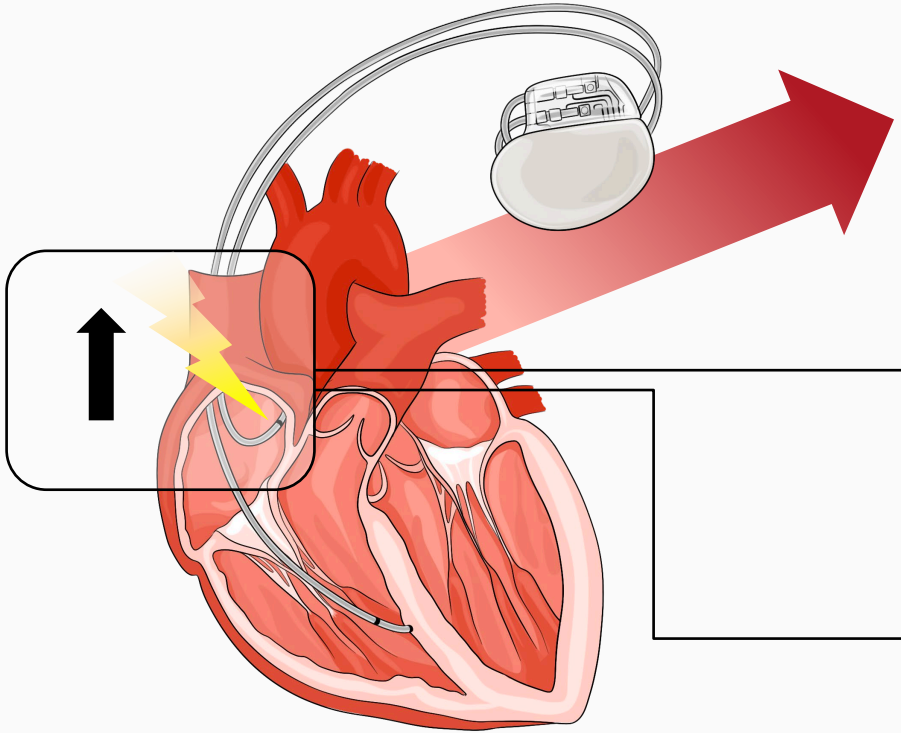
Assoc. Prof. Mads Brix Kronborg, MD PhD DMSc
On behalf of the DANPACE II investigators

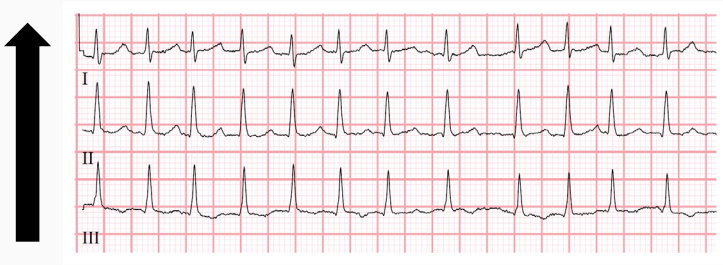
08.28.2023

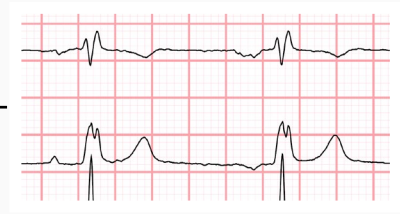
AARHUS UNIVERSITY HOSPITAL
AARHUS UNIVERSITY

Background

Does minimized atrial pacing in patients with sinus node dysfunction reduce the risk of atrial fibrillation?

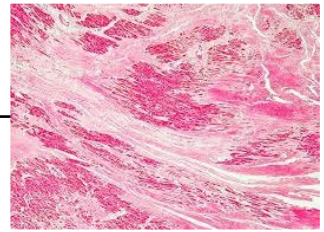






Prolongation and abnormal propagation?

OR



Progressive atrial disease?

Elkayam et al., Pacing Clin Electrophysiol 2011 , Fontenla et al. Pacing Clin Electrophysiol 2016 , Bukari et al. J Interv Card Electrophysiol 2018

Methods

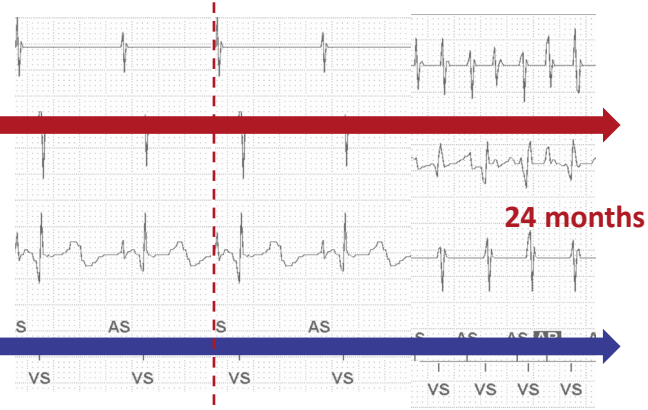
Remote monitoring

SND

1:1

DDD-40

DDDR-60



Primary endpoint

AF >6 minutes

Secondary endpoints

- AF >6 hours or >24 hours
- Persistent AF
- Stroke, TCI or embolism
- All-cause mortality
- QoL & 6-minute walk test
- Time to crossover

Safety endpoint

Syncope or presyncope

Permanent/persistent AF

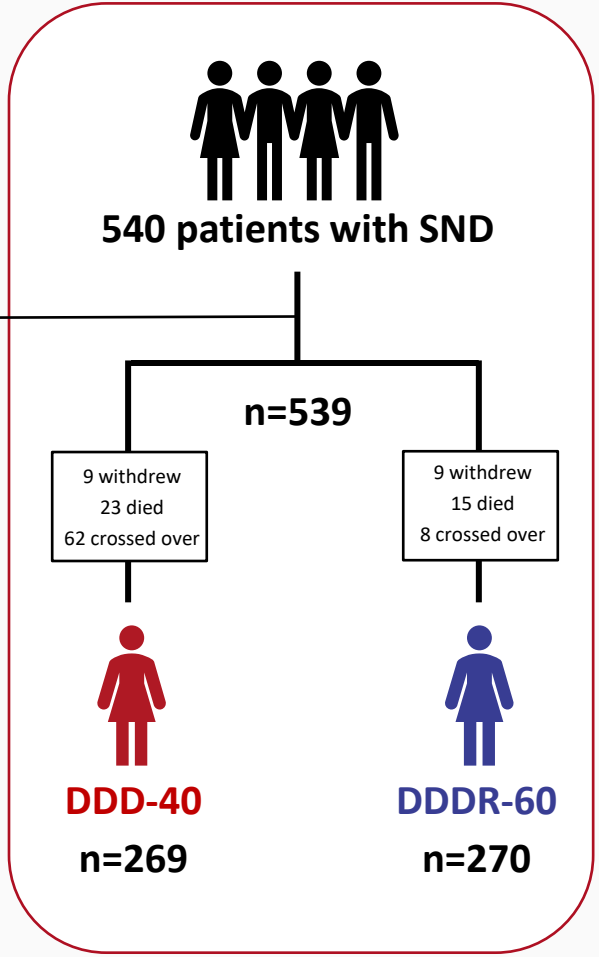
Bradycardia/chronotropic incompetence ≠DDD 40

6-min

SF-36

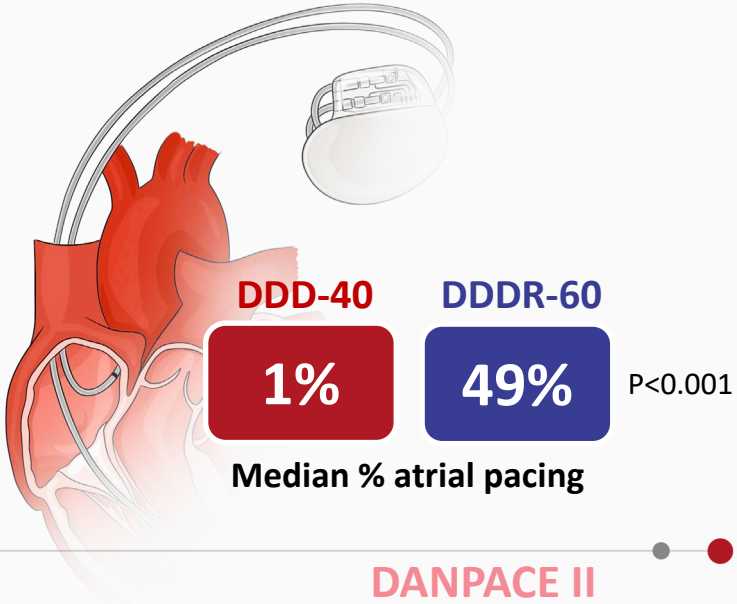
12 months

Results

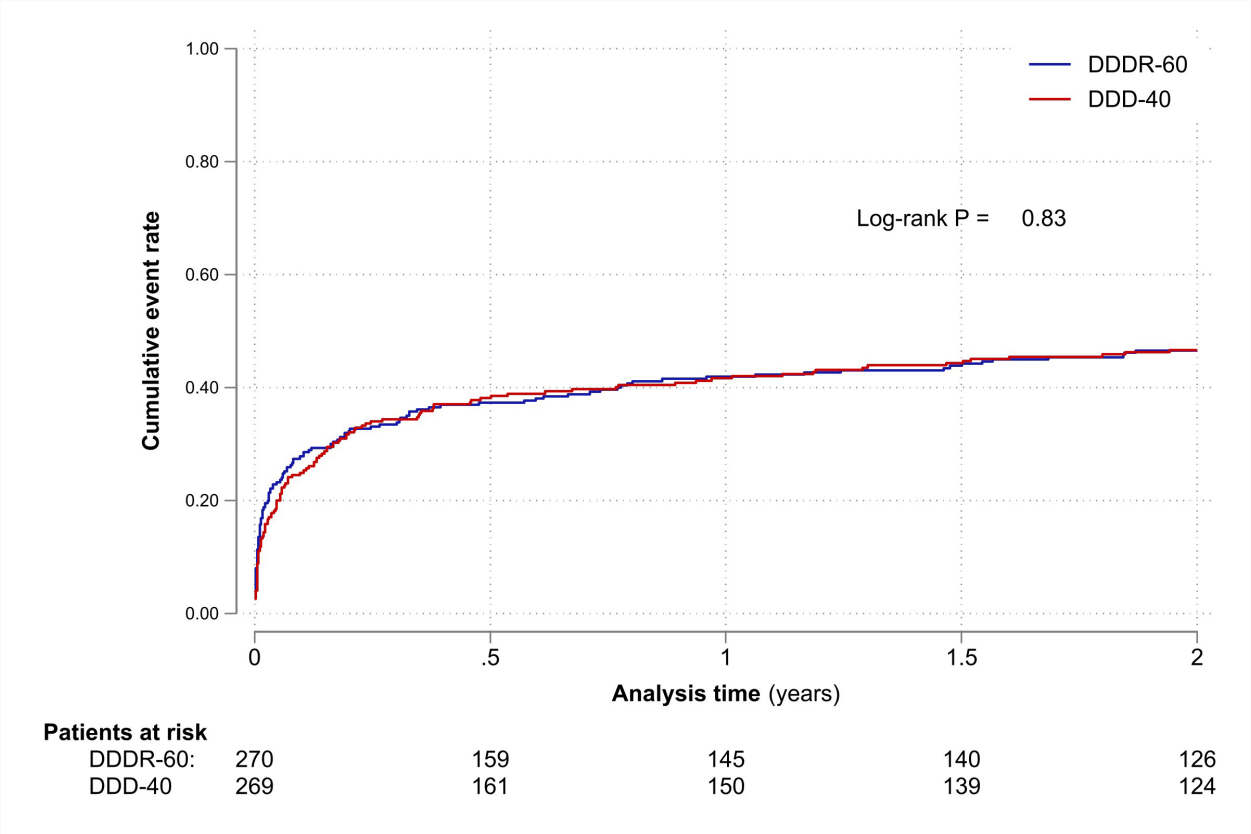


ITT analysis

	DDDR-60 (n=270)	DDD-40 (n=269)
Women, n (%)	130 (48)	140 (52)
Age in years, median (IQR)	73 (67-79)	74(67-80)
History of AF, n (%)	115 (43)	121 (45)



Atrial fibrillation >6 minutes



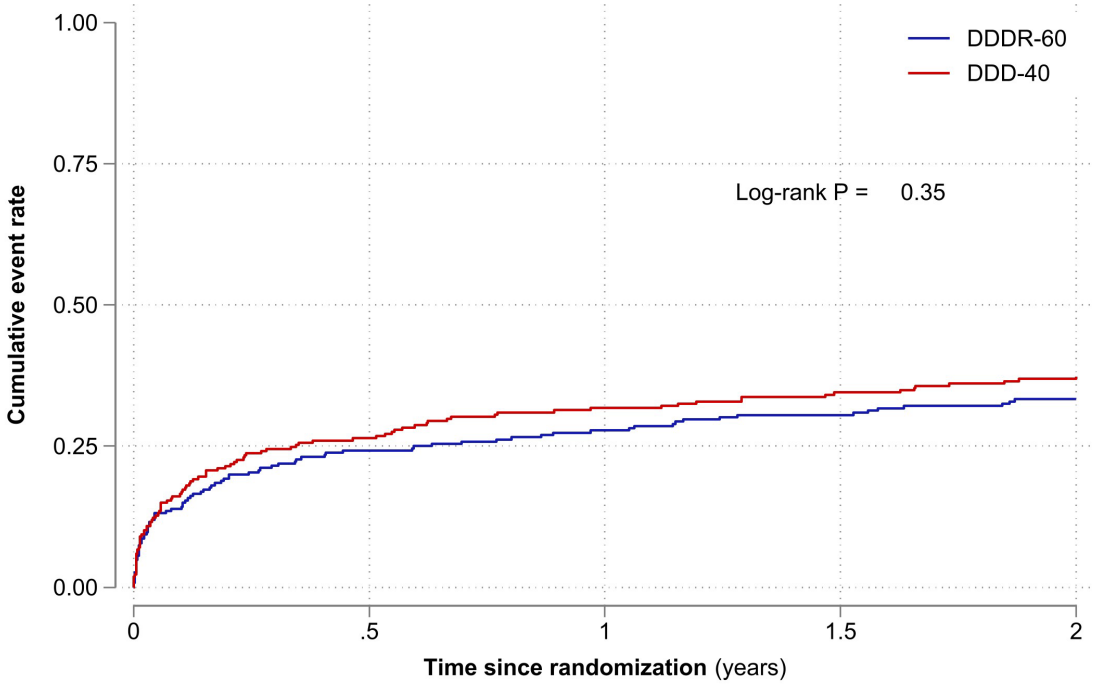
DDDR-60

124 (46%)

DDD-40

124 (46%)

Atrial fibrillation >6 hours



Patients at risk

Control:	270	195	183	176	159
Intervention:	269	193	177	166	150

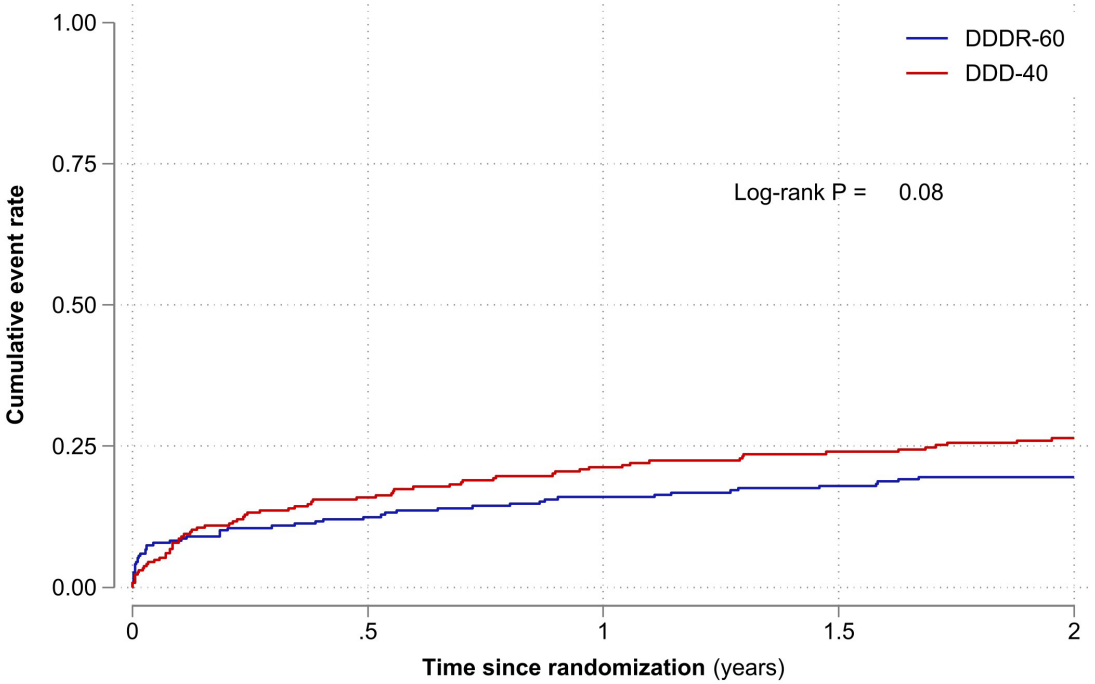
DDDR-60

87 (32%)

DDD-40

98 (36%)

Atrial fibrillation >24 hours



Patients at risk

Control:	270	225	213	208	193
Intervention:	269	220	204	192	175

DDDR-60

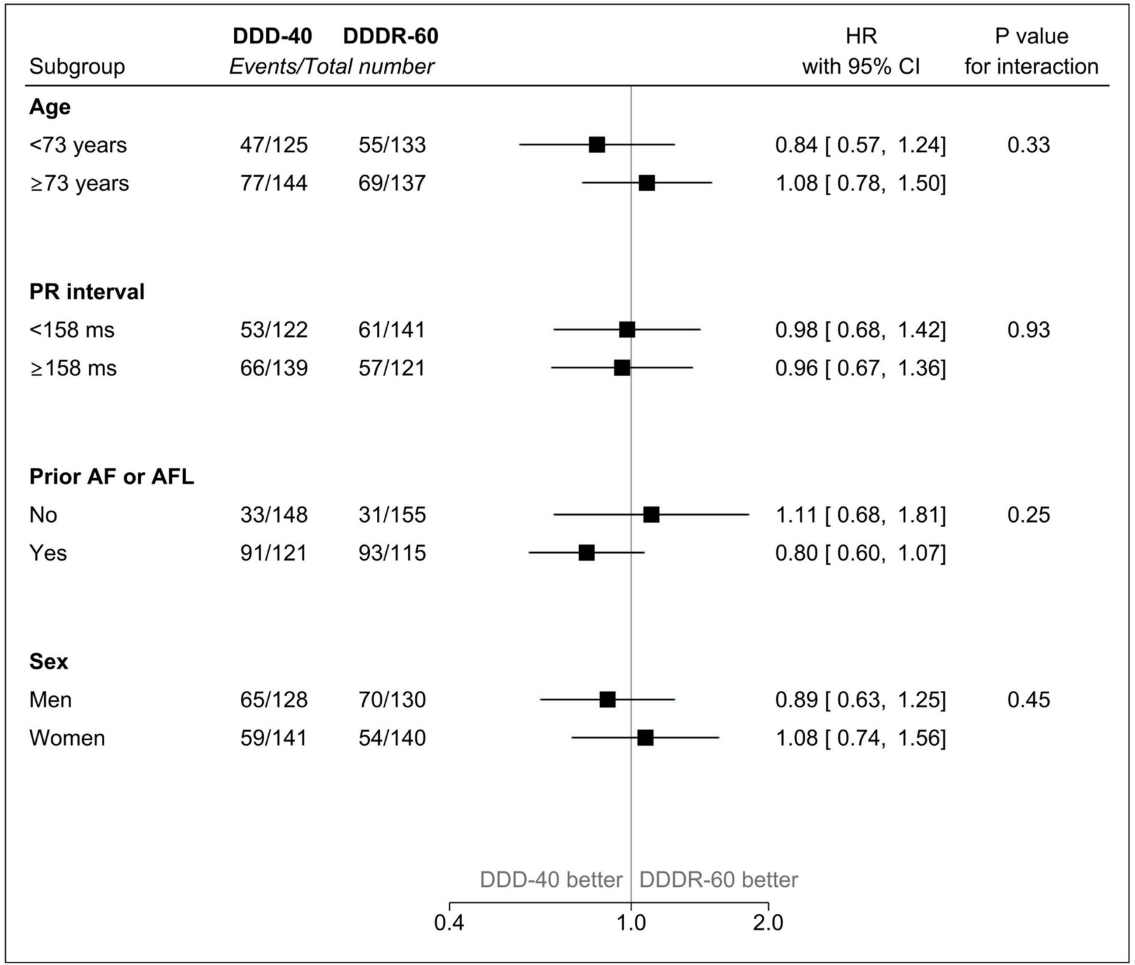
51 (21%)

DDD-40

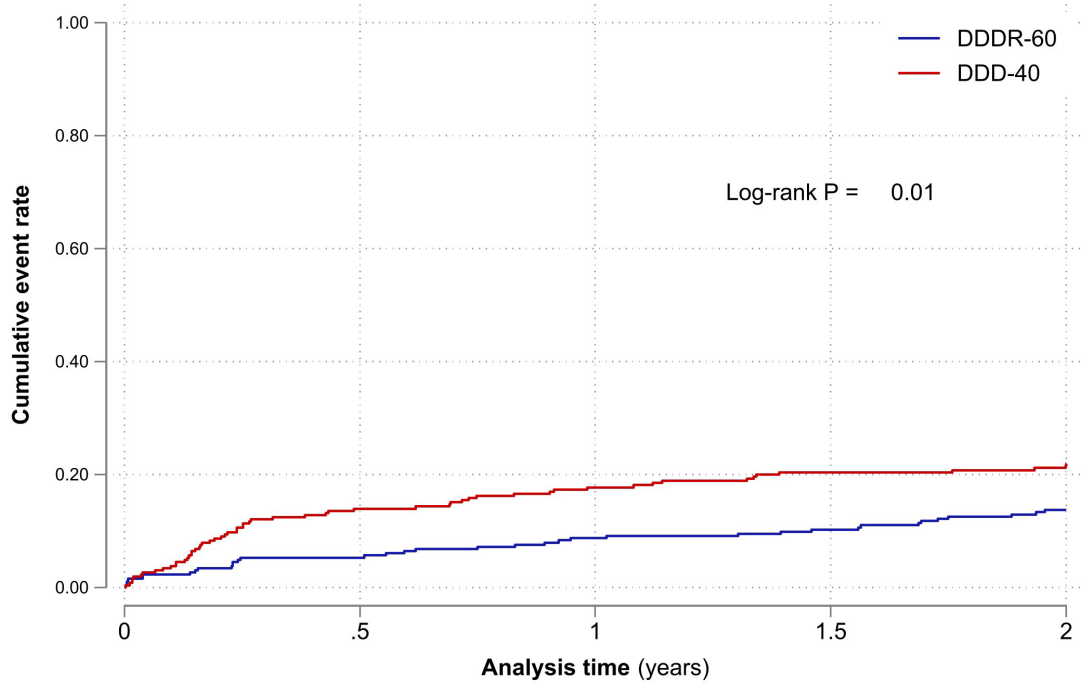
69 (26%)

Atrial fibrillation >6 minutes

Subgroups



Syncope or presyncope



Patients at risk

DDDR-60:	270	243	231	226	204
DDD-40	269	225	212	200	186

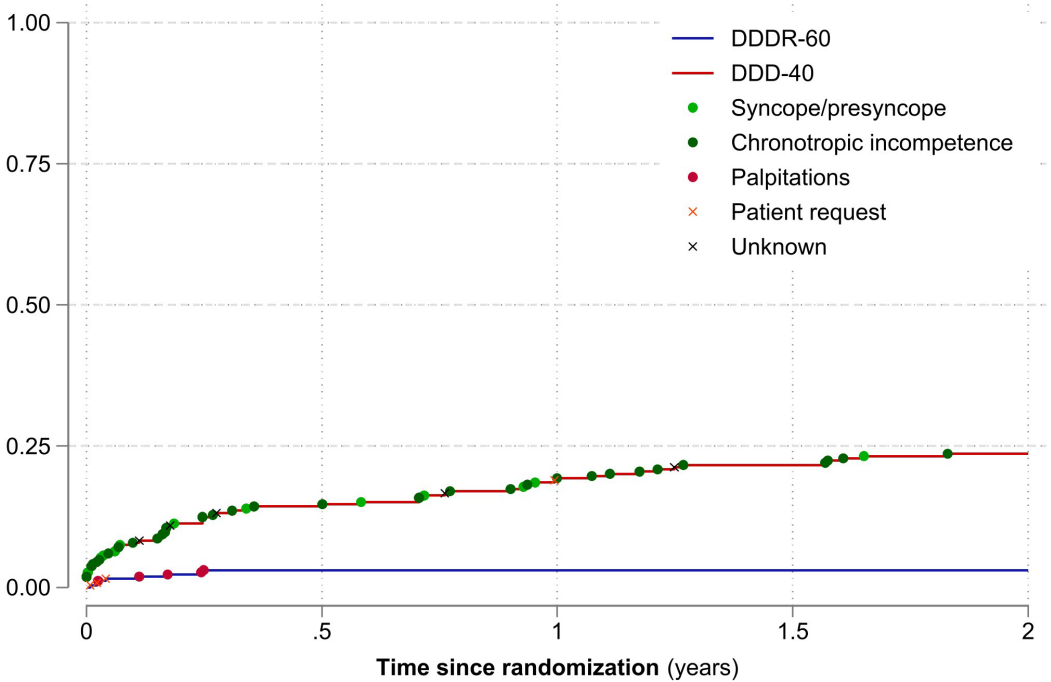
DDDR-60

36 (13%)

DDD-40

58 (22%)

Crossovers



Patients at risk

DDDR-60:	270	249	246	245	232
DDD-40:	269	224	210	198	183

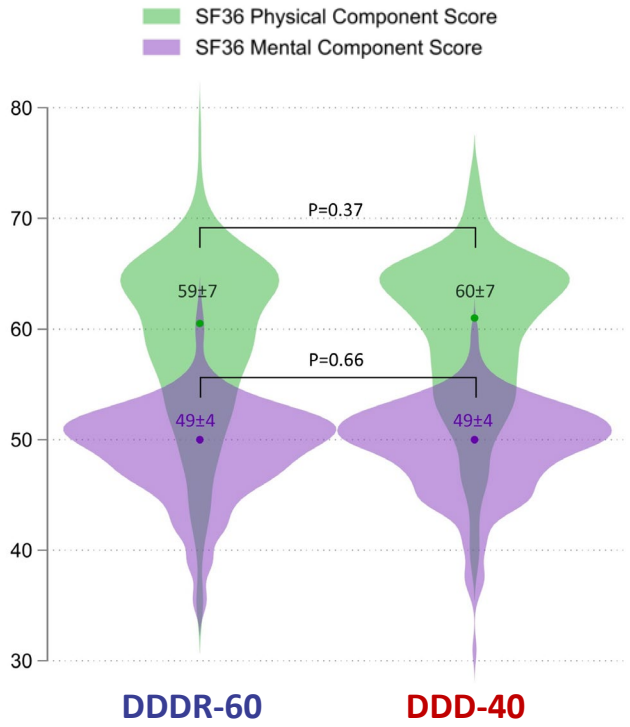
DDDR-60

8 (3%)

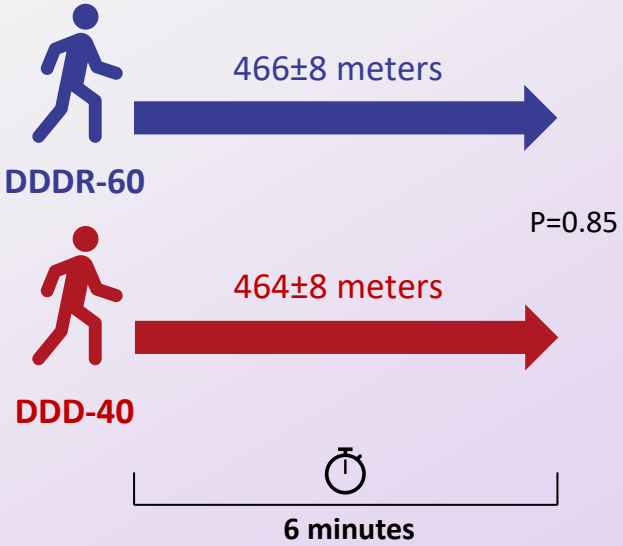
DDD-40

62 (23%)

Quality of life



6-minute walk test



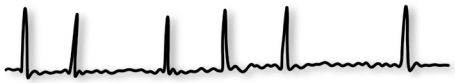
DANPACE II

539 patients with SND

DDD-40
n=269

DDDR-60
n=270

24 months



AF >6 minutes

Summary & Conclusion

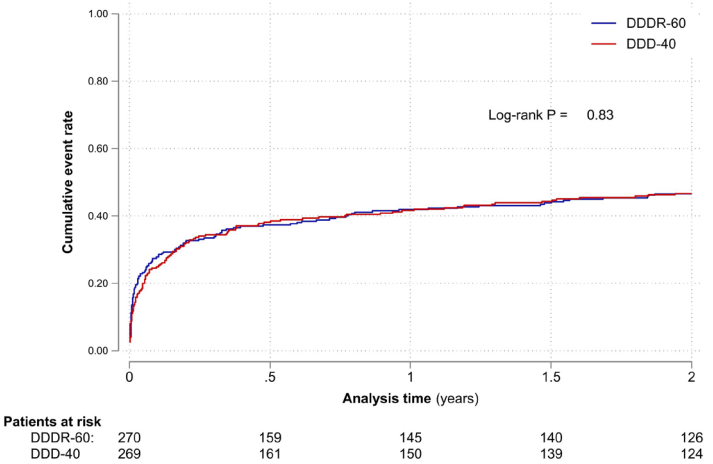
Median % atrial pacing

DDD-40
1%

DDDR-60
49%

P<0.001

Atrial fibrillation >6 minutes



Reduced atrial pacing did not reduce the incidence of AF

DDD-40 ↑ Syncope/presyncope ↑ Crossovers → Quality of Life → Exercise capacity

Acknowledgements

Investigators

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Trial Coordinating Centre

Henriette Holmberg,
Rita Moehl,
Lotte Bording Lindskow.

DPIR
DANISH PACEMAKER AND ICD REGISTER

DICTATE-AHF

Efficacy and Safety of Dapagliflozin in Acute Heart Failure

NCT04298229

Zachary Cox, PharmD

Professor, Lipscomb University College of Pharmacy, USA

Department of Pharmacy, Vanderbilt University Medical Center

On behalf of DICTATE-AHF Investigators

August 28, 2023

Background

Two Goals for Acute Heart Failure

1) Decongestion

2) GDMT Optimization

→ Improve Post-DC Outcomes

Loop + Acetazolamide	✓	⊘	No Improvement
Loop + Thiazide	✓	⊘	No Improvement
Loop + SGLT2i	?	✓	Improved Outcomes

Background

- **Concerns of early in-hospital SGLT2 inhibitor SAFETY:**
  - Hypoglycemia
  - Ketoacidosis
  - Worsening renal function
  - Genitourinary infections
  - Questionable magnitude of diuretic and natriuretic benefit

Early addition of Dapagliflozin is a potential strategy to improve achievement of both primary AHF therapeutic goals, but **efficacy and safety** are unknown

DICTATE-AHF Design

- Investigator-initiated, multicenter, prospective, randomized, open-label study funded by AstraZeneca

  Objective efficacy outcomes and blinded assessment of safety outcomes

- 240 Patients hospitalized with hypervolemic AHF randomized within 24 hours of presentation
  - Regardless of LVEF
  - Beginning April 2020, only patients with Type 2 diabetes mellitus were included
    - September 2021 - protocol amended to include:
      - With or without type 2 diabetes mellitus
      - eGFR $\geq$ 25 mL/min/1.73m^2

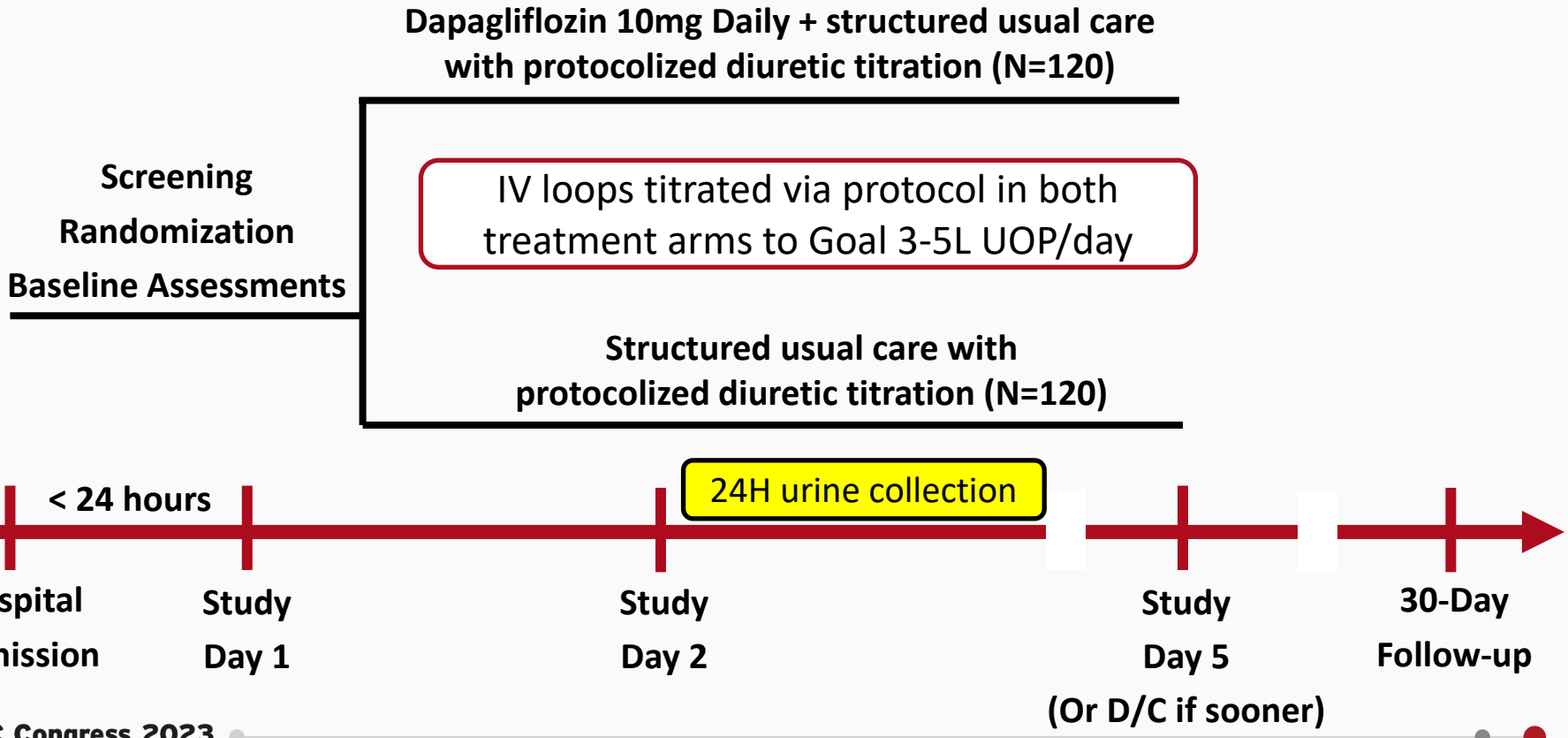
Key Inclusion Criteria

- Age of 18 years or older
- Randomized within 24 hours of presentation hypervolemic AHF:
  - ≥2 objective measures of hypervolemia
- Planned or current use of IV loop diuretic therapy
- eGFR ≥ 25 mL/min/1.73m^2

Key Exclusion Criteria

- Type 1 diabetes
- Serum glucose < 80mg/dL
- Systolic blood pressure < 90mmHg
- IV inotropic therapy
- History of diabetic ketoacidosis
- Inability to perform standing weights or measure urine output accurately

DICTATE-AHF


Dapagliflozin 10mg Daily + structured usual care with protocolized diuretic titration (N=120)
Screening
Randomization
Baseline Assessments
IV loops titrated via protocol in both treatment arms to Goal 3-5L UOP/day
Structured usual care with protocolized diuretic titration (N=120)
< 24 hours
24H urine collection
Hospital Admission
Study Day 1
Study Day 2
Study Day 5 (Or D/C if sooner)
30-Day Follow-up

Study Outcomes

Primary Outcome

$$\text{Diuretic Efficiency} = \frac{\text{Cumulative weight change (kg)}}{\text{Cumulative loop diuretic dose (mg)}}$$

- Calculated until Day-5 or hospital discharge if sooner
- Expressed as *kg/40mg IV Furosemide equivalents*
- Compared across treatment assignment using a proportional odds regression model adjusting for baseline weight

Study Outcomes

Secondary Outcomes adjudicated by blinded committee

- Incidence of worsening HF during hospital stay
- HF-related or diabetes-related 30-day readmissions

Safety Outcomes adjudicated by blinded committee

- Incidence of diabetic ketoacidosis
- Prolonged hospitalization for hypotension
- Prolonged hospitalization for hypoglycemia
- Change in eGFR from baseline to end-of-study

Select Exploratory Outcomes

- Measures of natriuresis and diuresis
- Hospital length of stay

Baseline Characteristics

Characteristic	Total Population (N=238)	Usual Care (N=119)	Dapagliflozin (N=119)
Age (yrs)	65 (56 – 73)	64 (55 – 74)	65 (56 – 73)
Male Sex	61%	56%	66%
White Race	68%	71%	66%
T2DM	71%	71%	71%
LVEF $\leq$ 40%	52%	55%	48%
SBP (mmHg)	121 (110 – 136)	120 (110 – 136)	121 (112 – 136)
eGFR (mL/min/1.73m^2)	53 (42 – 70)	54 (40 – 71)	51 (43 – 68)
IV furosemide dose prior to randomization (mg)	80 (40 – 140)	80 (80 – 120)	80 (40 - 160)

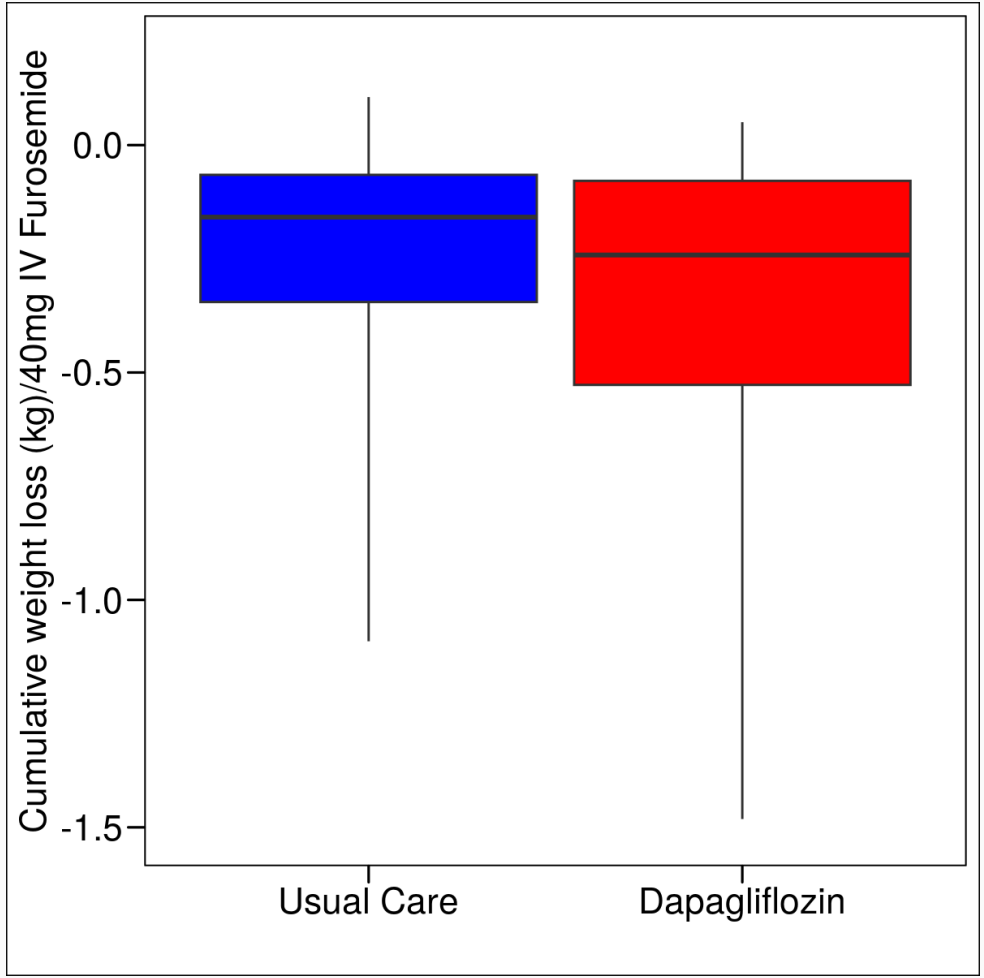
Primary Outcome

Adjusted Odds Ratio 0.65

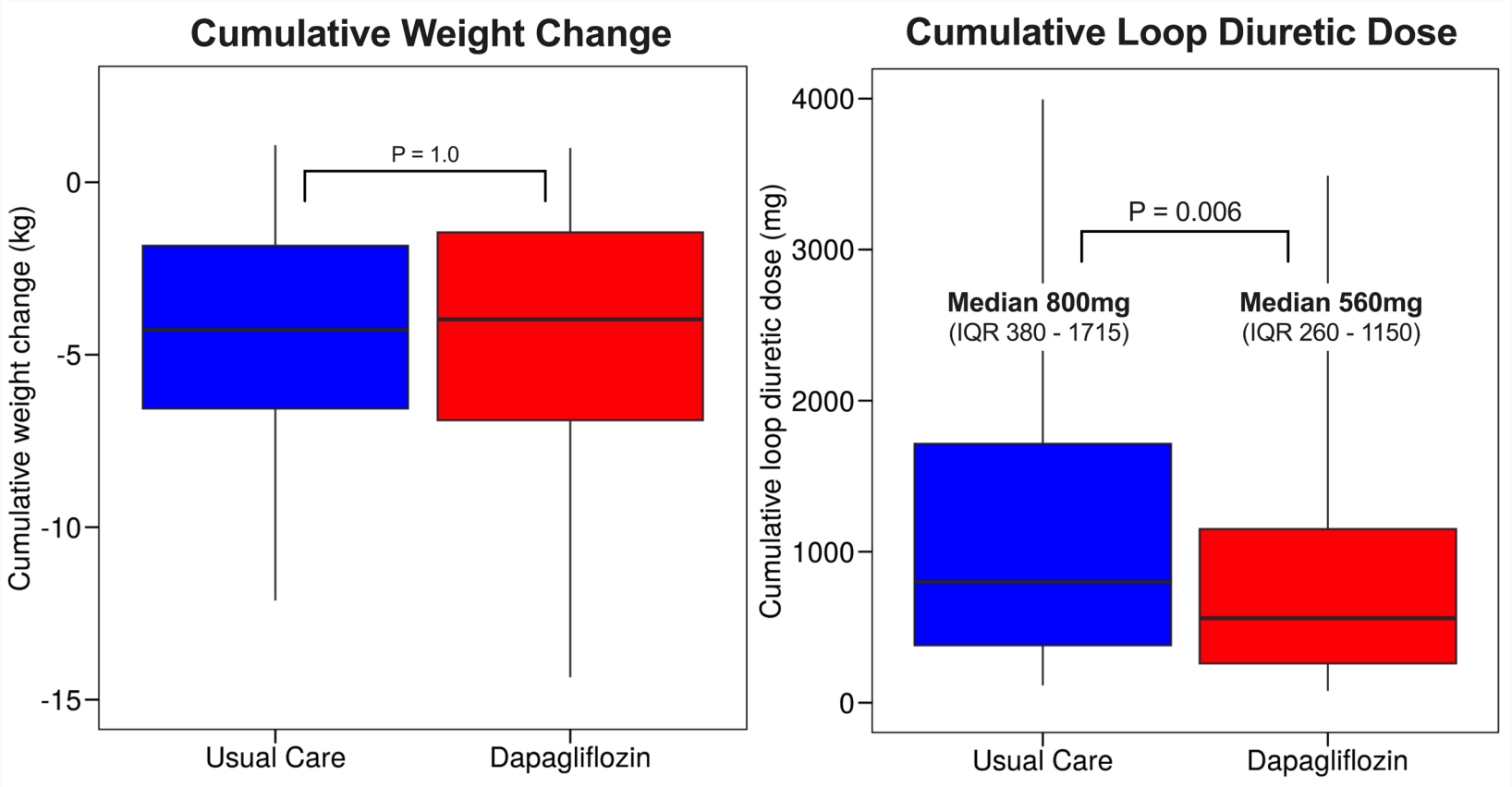
(95% CI 0.41 – 1.01); P=0.06

Unadjusted Odds Ratio 0.64

(95% CI 0.41 – 1.00)

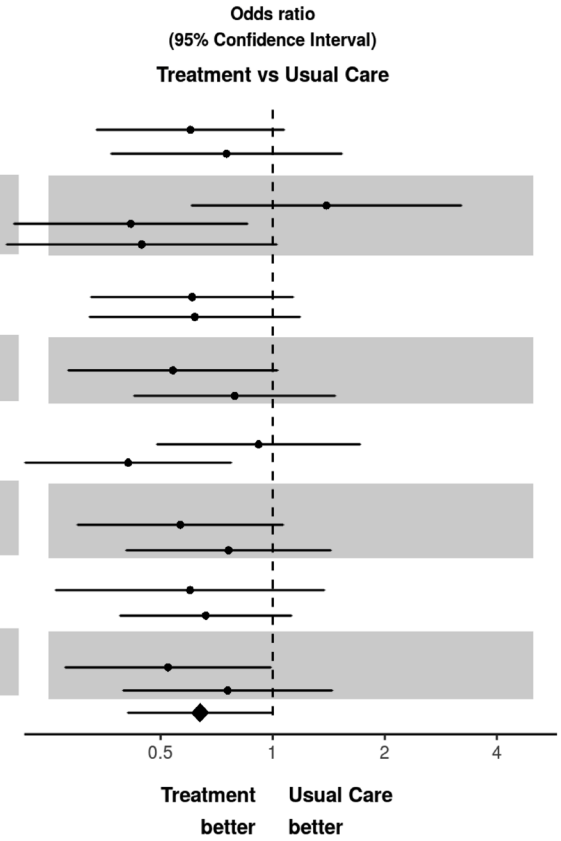


Primary Outcome Components

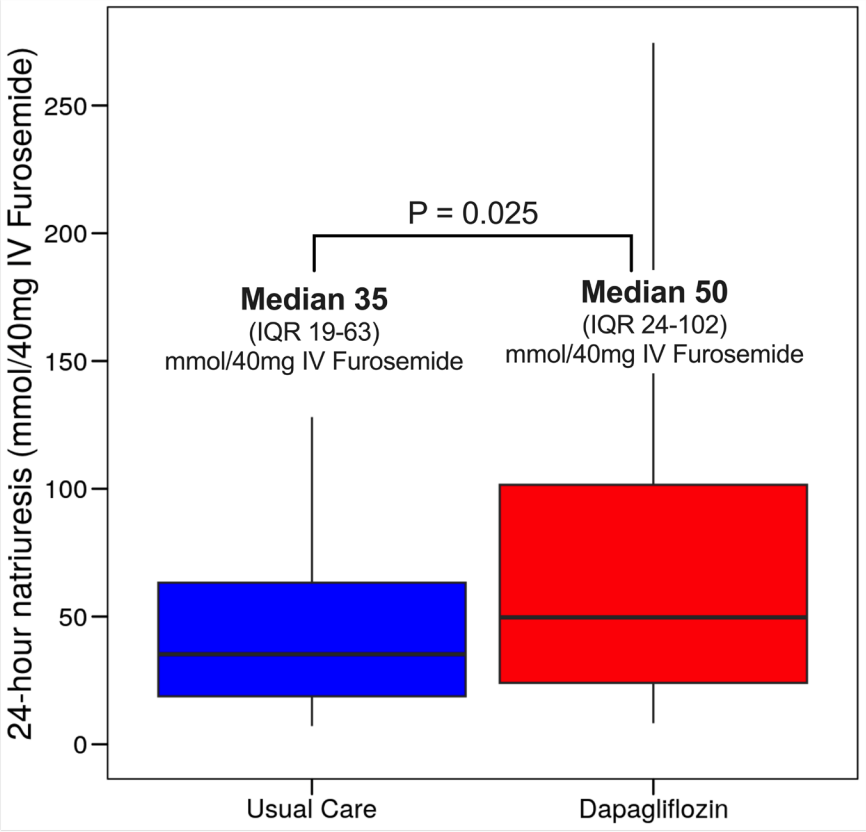


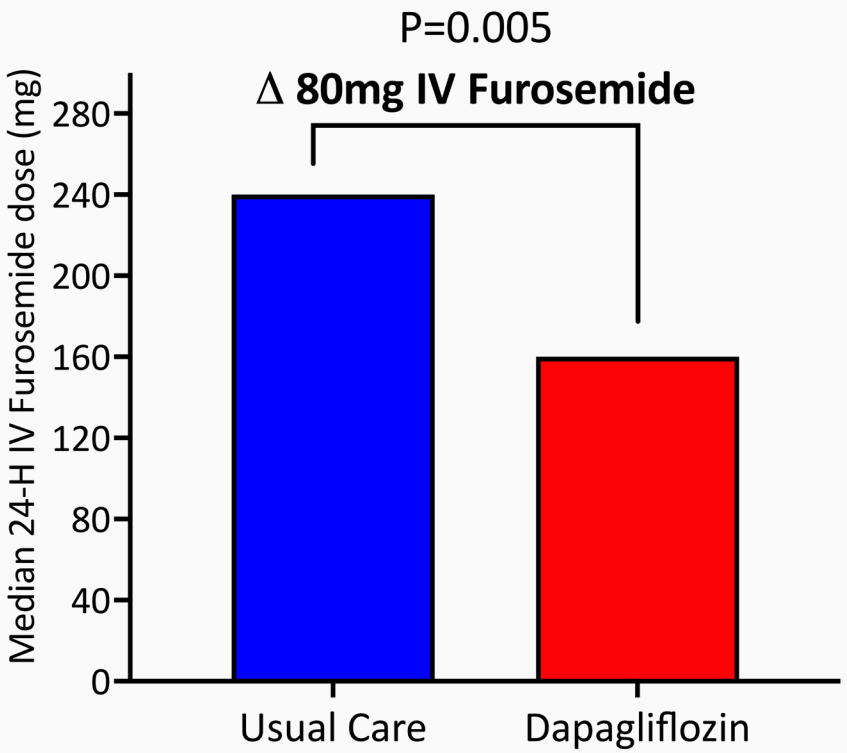
Heterogeneity of Treatment Effect

Subgroup	No. of Patients	Treatment	Usual Care
		Estimated mean weight change per 40mg Furosemide-equivalents (95% CI)	
Sex			
Male	145	-0.45 (-0.57, -0.33)	-0.32 (-0.43, -0.22)
Female	93	-0.36 (-0.50, -0.22)	-0.29 (-0.40, -0.19)
Edema score			
No/Mild	68	-0.27 (-0.39, -0.15)	-0.34 (-0.49, -0.19)
Moderate	92	-0.51 (-0.67, -0.34)	-0.29 (-0.40, -0.19)
Severe	65	-0.50 (-0.68, -0.33)	-0.29 (-0.42, -0.16)
NT-proBNP			
Below median	115	-0.36 (-0.48, -0.25)	-0.25 (-0.35, -0.15)
At/above median	115	-0.49 (-0.64, -0.34)	-0.36 (-0.48, -0.25)
BMI			
Below median	121	-0.50 (-0.64, -0.36)	-0.34 (-0.46, -0.22)
At/above median	117	-0.33 (-0.45, -0.22)	-0.28 (-0.38, -0.19)
eGFR			
Below median	120	-0.30 (-0.40, -0.20)	-0.28 (-0.38, -0.18)
At/above median	118	-0.57 (-0.72, -0.41)	-0.32 (-0.43, -0.22)
Weight			
Below median	123	-0.47 (-0.60, -0.34)	-0.32 (-0.44, -0.21)
At/above median	115	-0.36 (-0.48, -0.24)	-0.30 (-0.39, -0.20)
Type 2 Diabetes			
No	69	-0.48 (-0.66, -0.30)	-0.35 (-0.49, -0.20)
Yes	169	-0.39 (-0.50, -0.29)	-0.30 (-0.38, -0.21)
Ejection Fraction			
<= 40	115	-0.49 (-0.64, -0.35)	-0.33 (-0.43, -0.22)
> 40	108	-0.35 (-0.46, -0.24)	-0.29 (-0.39, -0.18)
Overall	***238***	***-0.42 (-0.52, -0.32)***	***-0.31 (-0.39, -0.23)***

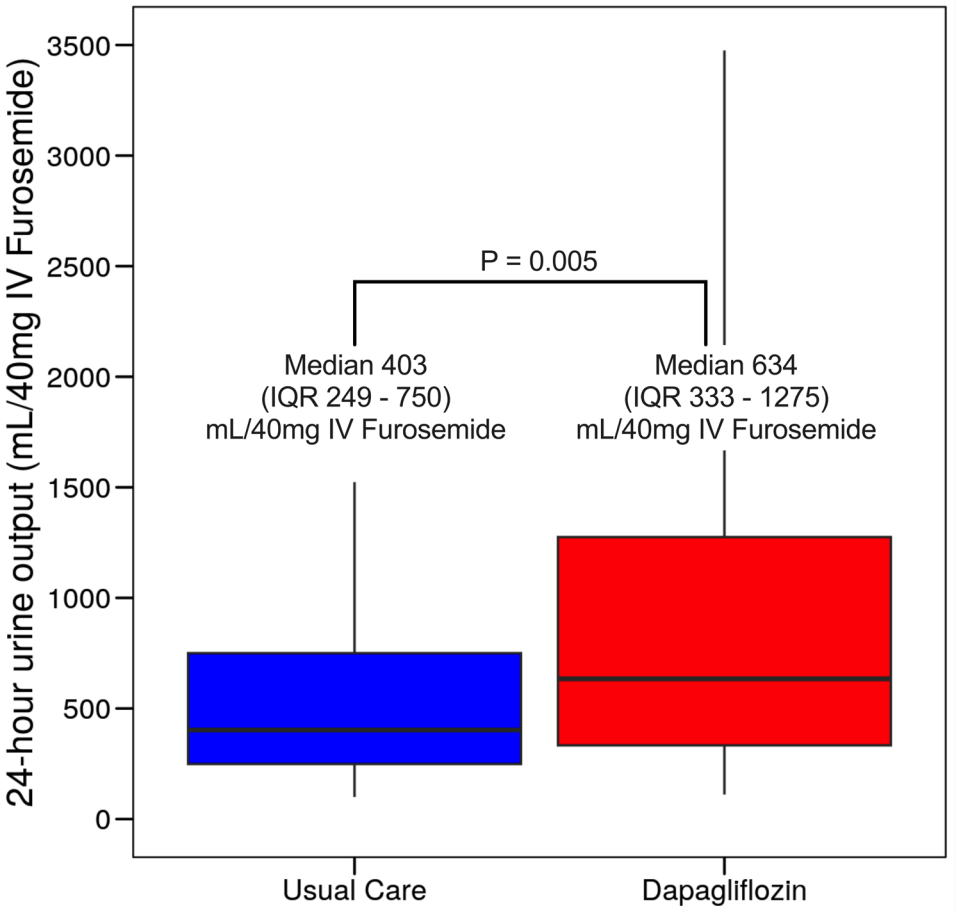


Improved 24-Hour Natriuresis with Dapagliflozin

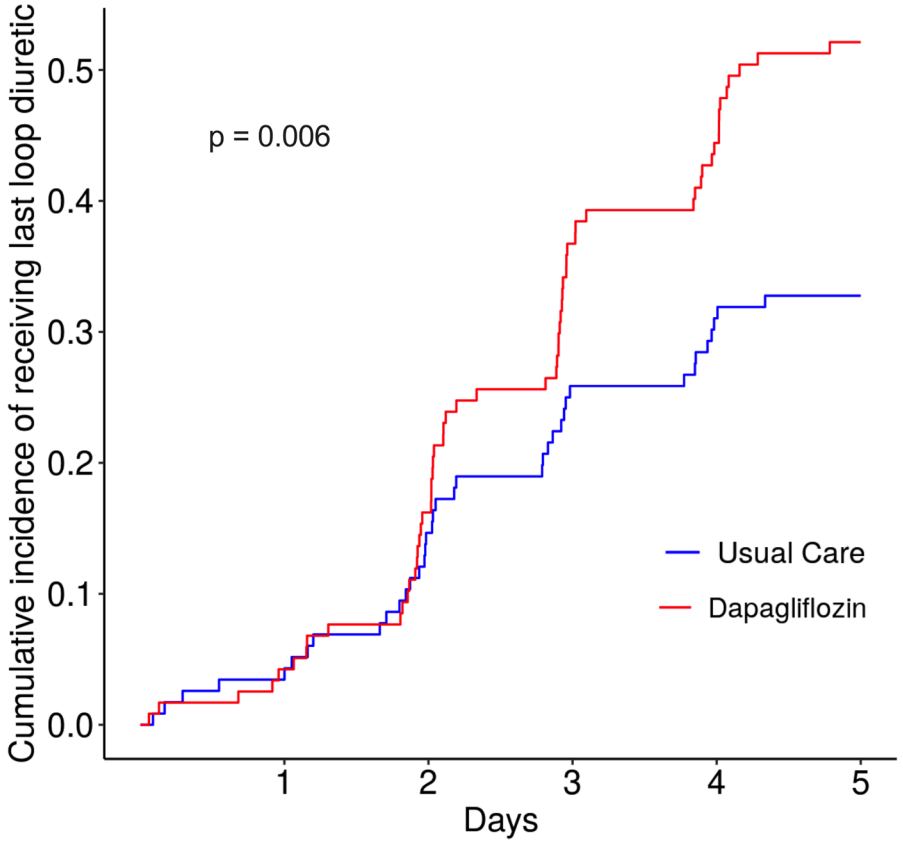


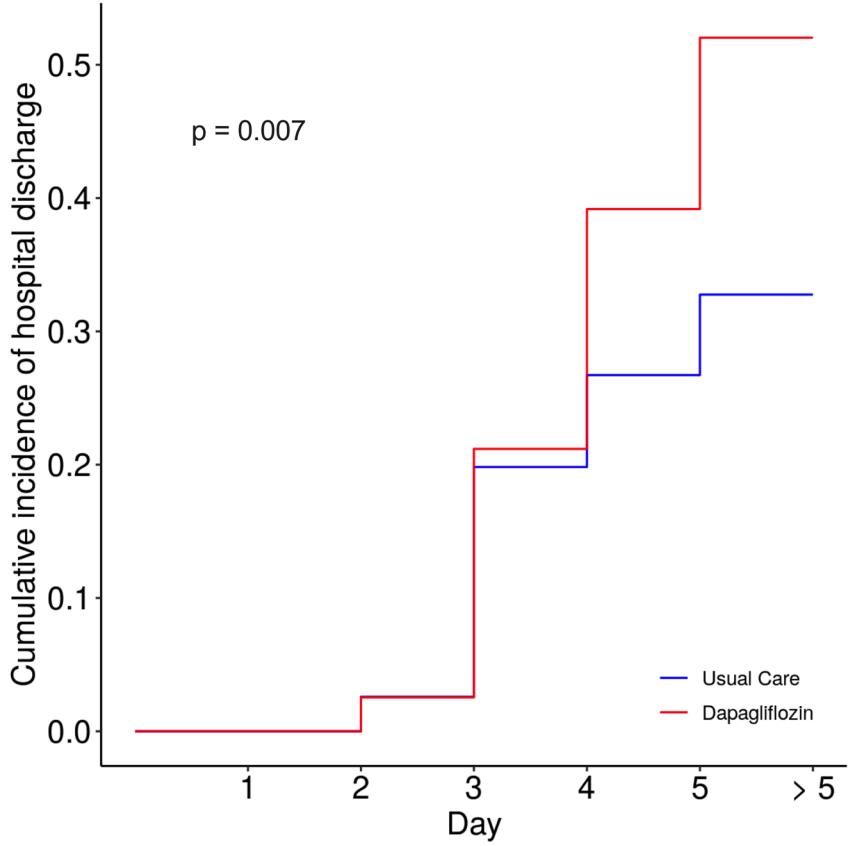


Improved 24-Hour Diuresis with Dapagliflozin



Faster Time to Oral Diuretic Transition and Discharge





Secondary Outcomes

Secondary Outcomes, N	Usual Care	Dapagliflozin
Worsening heart failure	3	4
30-day hospital readmission for ADHF or diabetes-related reasons	8	7
ADHF-related readmission	8	6
Diabetes-related readmission	0	1

Safety Outcomes and Adverse Events

Safety Outcomes	Usual Care	Dapagliflozin
Ketoacidosis	0	0
Symptomatic hypotension	4	2
Prolonged hospitalization for hypotension	1	1
Hypoglycemia	9	7
Prolonged hospitalization for hypoglycemia	0	0
Genitourinary tract infections	1	0
Change in eGFR (mL/min/1.73m^2)	-3.0 (-9 to 2)	-2.0 (-10 to 4)

Conclusions

1. Dapagliflozin had a strong signal to improve diuretic efficiency supported by:
   - Increased natriuresis and diuresis per 40mg of IV furosemide
   - Decreased total dose and duration of loop diuretics required
   - Decreased time to hospital discharge
2. Early dapagliflozin initiation was safe across all diabetic and cardiorenal outcomes

Totality of DICTATE-AHF data supports the early initiation of dapagliflozin in AHF to safely facilitate decongestion and GDMT optimization

DICTATE-AHF Study Team

Principal Investigator: JoAnn Lindenfeld
Co- PI: Zachary Cox
Co- Investigator: Sean Collins

Site Investigators:
Zachary Cox, Pharm.D. – Vanderbilt University
Gabriel Hernandez, M.D. – University of Mississippi
Kirkwood Adams, M.D. – University of North Carolina
A. Tom McRae, M.D. – Centennial Hospital
Mark Aaron, M.D. - St Thomas Hospital System
Luke Cunningham, M.D. – Integris Medical Center

Clinical Coordinating Center:
Sean Collins, Christy Kampe, Karen Miller

Data Coordinating Center:
Chris Lindsell, Frank Harrell, Cathy Jenkins

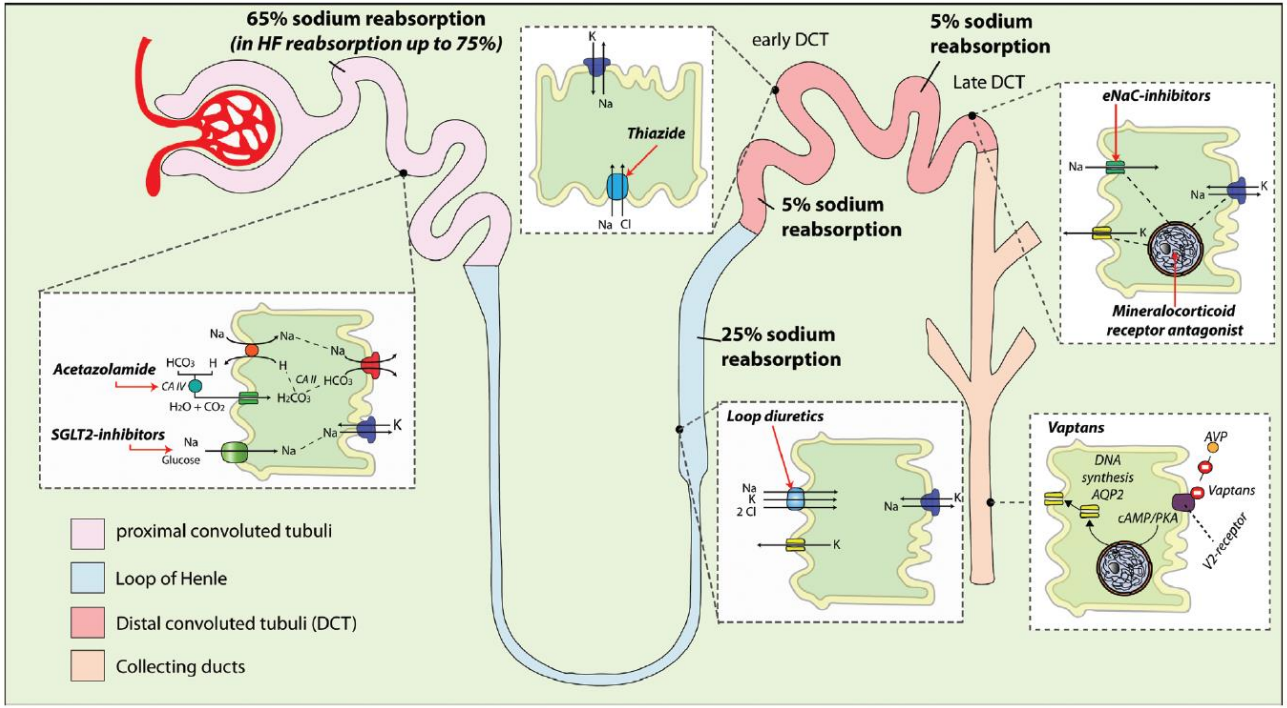
The ADVOR trial: update on renal interactions

Jeroen Dauw*, Evelyne Meekers*, Pieter Martens, Sebastiaan Dhont, Frederik H. Verbrugge, Petra Nijst, Jozine M. ter Maaten, Kevin Damman, Alexandre Mebazaa, Gerasimos Filippatos, Frank Ruschitzka, W.H. Wilson Tang, Matthias Dupont, Wilfried Mullens

Friday 25 August 2023

@JeroenDauw

Background



Acetazolamide blocks sodium reabsorption in the proximal tubule where the majority of sodium is reabsorbed

Mullens W et al. Eur J Heart Fail. 2019; 21:137-155

The NEW ENGLAND JOURNAL of MEDICINE

ADVOR

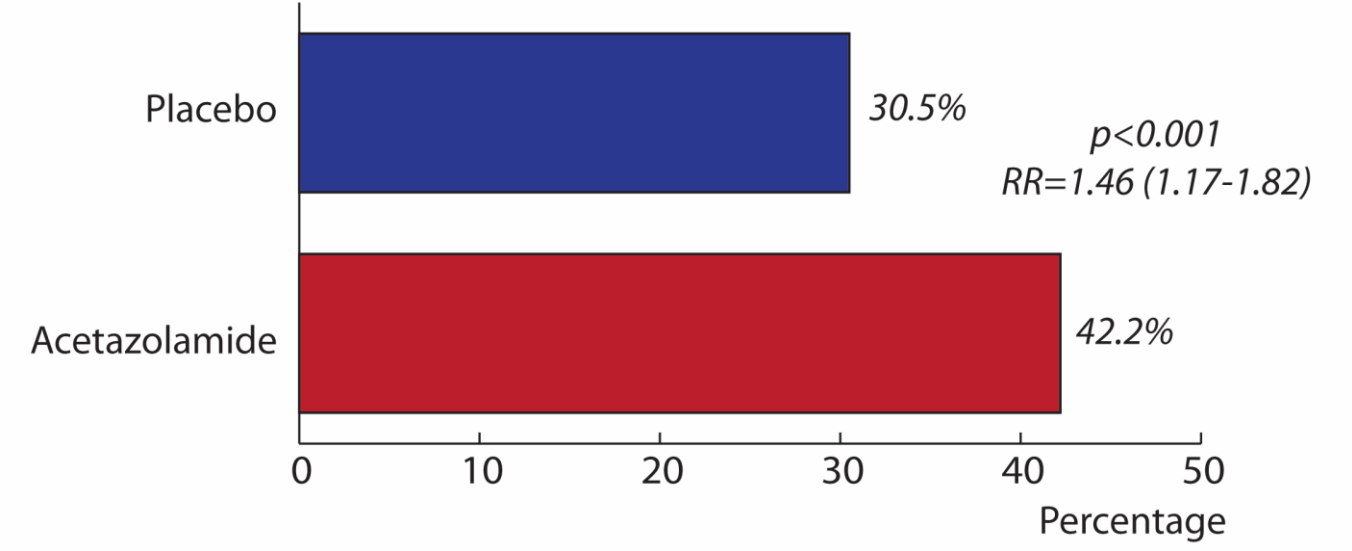
ORIGINAL ARTICLE

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

W. Mullens, J. Dauw, P. Martens, F.H. Verbrugge, P. Nijst, E. Meekers, K. Tartaglia, F. Chenot, S. Moubayed, R. Dierckx, P. Blouard, P. Troisfontaines, D. Derthoo, W. Smolders, L. Bruckers, W. Droogne, J.M. Ter Maaten, K. Damman, J. Lassus, A. Mebazaa, G. Filippatos, F. Ruschitzka, and M. Dupont, for the ADVOR Study Group*

Mullens W, Dauw J et al. N Engl J Med. 2022;387:1185-1195

Background



Acetazolamide + loop diuretics vs. loop diuretics alone associated with more successfull decongestion after 3 days

Mullens W, Dauw J et al. N Engl J Med. 2022;387:1185-1195

Aims

1. To evaluate the treatment effect of acetazolamide according to baseline renal function

2. To evaluate the effect of acetazolamide on renal function and its relation with outcomes

Methods

ADVOR
A multicenter, randomized, double-blind, placebo-controlled, trial

519 acute decompensated heart failure patients

500 mg acetazolamide IV + loop diuretics IV (*oral home dose bid*)
vs.
placebo + loop diuretics IV (*oral home dose bid*)

Primary endpoint: successful decongestion after 3 days without need for diuretic therapy escalation

Mullens W, Dauw J et al. N Engl J Med. 2022;387:1185-1195

Methods: patient selection

Main inclusion criteria

- Admitted with ADHF
- At least 1 sign of volume overload (edema, pleural effusion*, ascites°)

  To be confirmed with radiography or ultrasonography of the chest or ultrasonography of the abdomen°*
- At least 1 month maintenance dose of oral loop diuretics (≥ 40 mg furosemide)
- NT-proBNP > 1000 pg/ml or BNP > 250 pg/ml

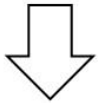
Main exclusion criteria

- Acetazolamide maintenance therapy
- Treatment with SGLT2i
- Systolic blood pressure < 90 mmHg
- eGFR < 20 ml/min

Mullens W, Dauw J et al. N Engl J Med. 2022;387:1185-1195

Methods: congestion score

EDEMA	No edema (score 0)	Trace edema (pitting disappear immediately) (score 1)	Clear pitting edema (score 2)	Visual deformation above ankle (score 3)	Visual deformation above knee (score 4)
PLEURAL EFFUSION (to be confirmed by chest X-ray or ultrasound on admission if suspected)	No pleural effusion (score 0)	Minor (non-amenable for punction) pleural effusion (score 2)		Major (amenable for punction) pleural effusion (score 3)	
ASCITES (to be confirmed by ultrasound on admission if suspected)	No ascites (score 0)	Minor ascites, only detected by echography (score 2)		Significant ascites (score 3)	



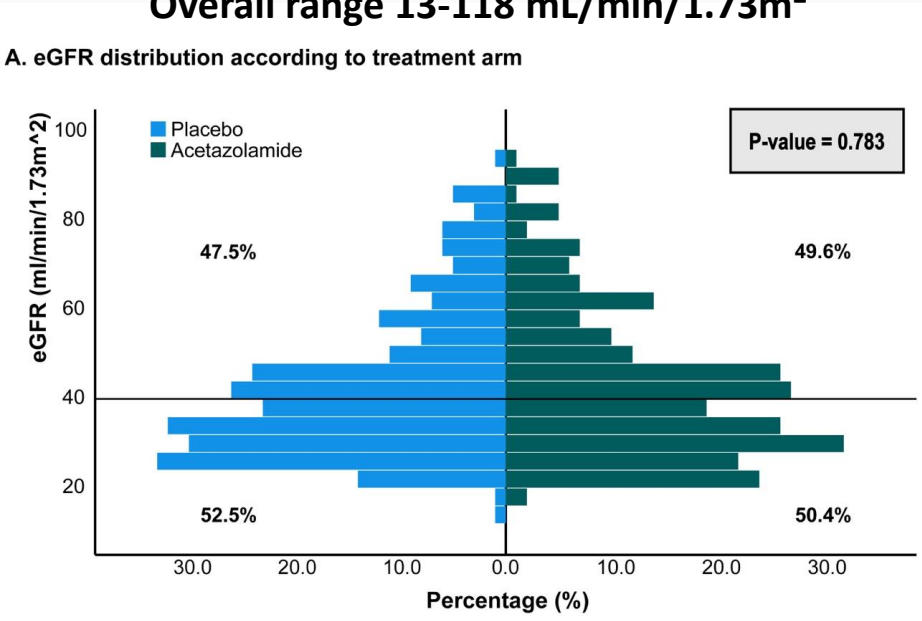
Successful decongestion

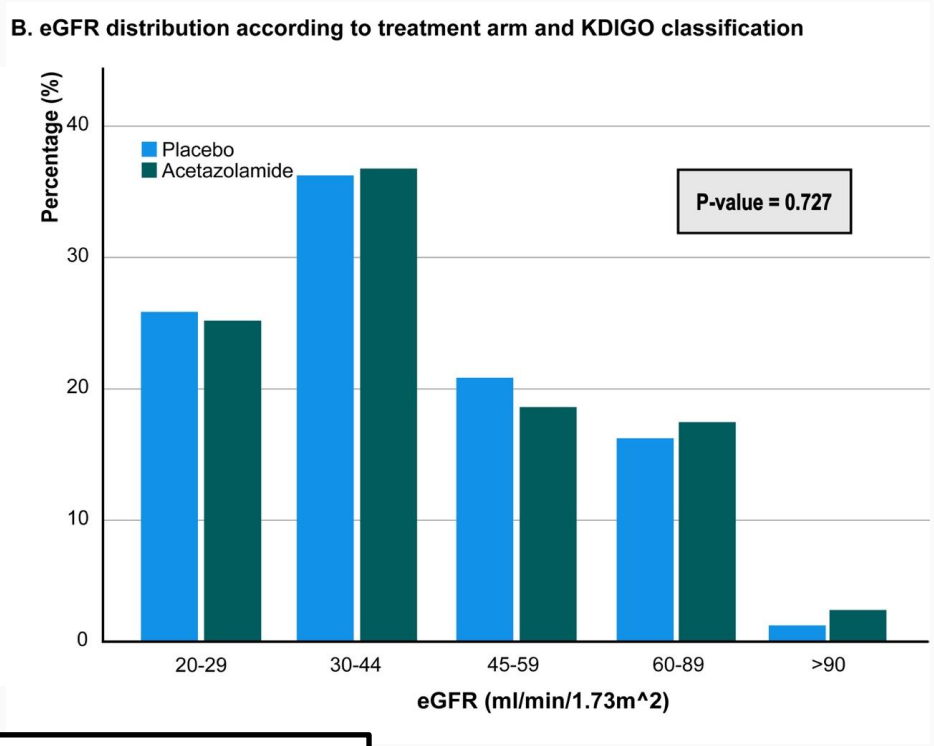
Continue IV diuretic therapy

Mullens W, Dauw J et al. N Engl J Med. 2022;387:1185-1195

Results: eGFR distribution

Overall range 13-118 mL/min/1.73m²





eGFR culculated with CKD-EPI

Results: baseline characteristics according to eGFR

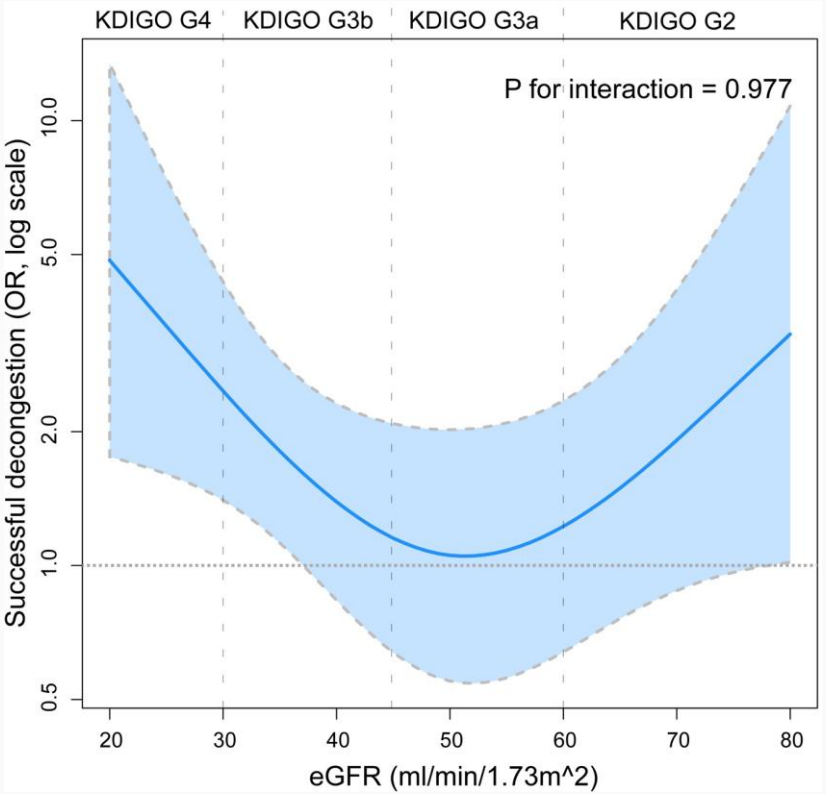
All analyses were adjusted for baseline differences

	eGFR ≤ 40 ml/min/1.73m² (n=265)	eGFR > 40 ml/min/1.73m² (n=254)	P-value
Acetazolamide	129 (48.7%)	130 (51.2%)	0.599
Age (years)	80 ± 8	77 ± 10	<0.001
Female	109 (41.1%)	85 (33.5%)	0.085
Congestion score	4 (3-6)	4 (3-6)	0.630
Home maintenance dose of furosemide (mg)	80 (40-132.2)	40 (40-100)	<0.001
LVEF (%)	42 ± 17	44 ±15	0.129
NT-proBNP (pg/mL)	7386 (3883-14417)	4435 (2517-8907)	<0.001
Ischemic cause	123 (46.4%)	109 (42.9%)	0.428
Hemoglobin (g/dL)	11.7 ± 1.9	12.1 ± 2.1	0.015
Sodium (mmol/L)	139.7 ± 4.0	139.2 ± 4.6	0.265
Serum creatinine (mg/dL)	1.92 (1.64-2.215)	1.17 (1.00-1.40)	<0.001
eGFR (mL/min/1.73m²)	30 (25-34)	54 (45-67)	<0.001
Treatment			
ACEi/ARB/ARNI	136 (51.3%)	133 (52.4%)	0.861
Beta blocker	221 (83.4%)	198 (78.0%)	0.121
MRA	115 (43.4%)	101 (39.8%)	0.423

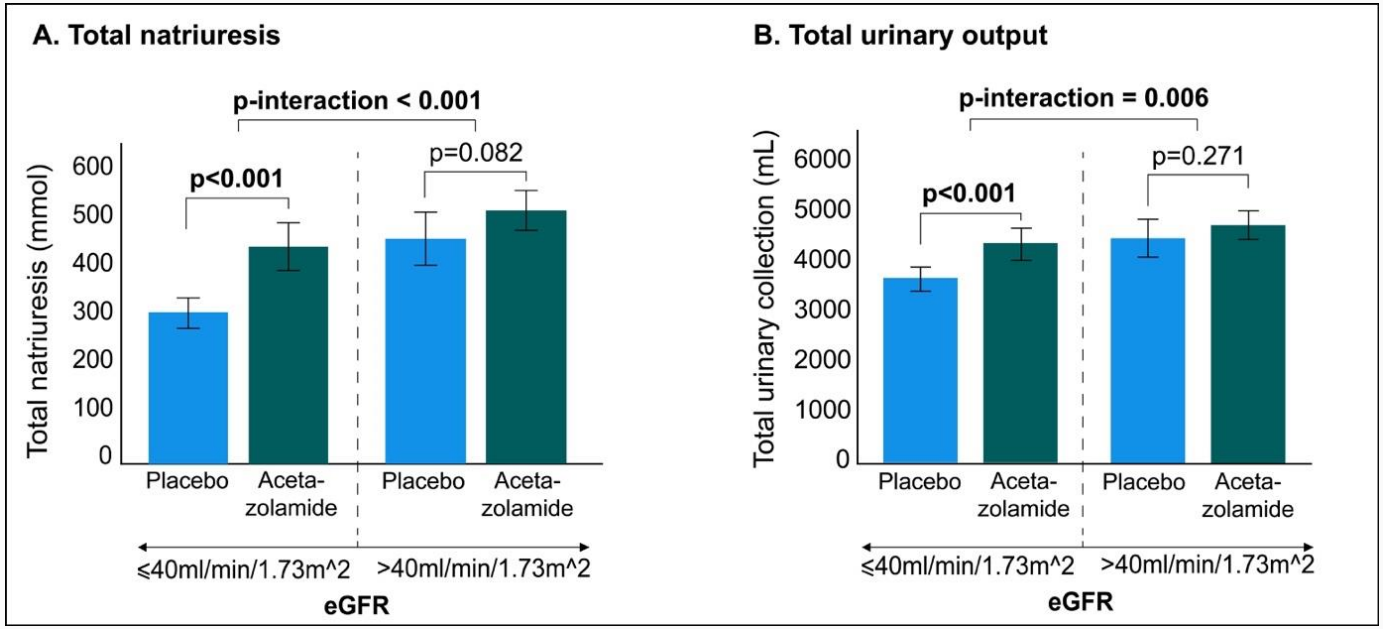
Results: acetazolamide treatment effect according to median eGFR

Parameter	Placebo	Acetazolamide	Adjusted OR/HR	P-value	*P-interaction
Primary endpoint (OR)					
Overall	79/259 (30.5%)	108/256 (42.2%)	1.97 (1.29-3.02)	0.002	
eGFR ≤40 ml/min/1.73m^2	34/136 (25.0%)	54/129 (41.9%)	2.32 (1.27-4.24)		0.672
eGFR >40 ml/min/1.73m^2	45/123 (36.6%)	54/127 (42.5%)	1.79 (0.97-3.30)		
Complete decongestion at discharge (OR)					
Overall	145/250 (58.0%)	190/252 (75.4%)	2.37 (1.54-3.65)	<0.001	
eGFR ≤40 ml/min/1.73m^2	77/132 (58.3%)	91/127 (71.7%)	1.88 (1.02-3.45)		0.467
eGFR > 40 ml/min/1.73m^2	68/118 (57.6%)	99/125 (79.2%)	3.00 (1.56-5.77)		
All-cause mortality and heart failure hospitalization (HR)					
Overall	72/259 (27.8%)	76/256 (29.7%)	1.09 (0.78-1.54)	0.618	
eGFR ≤40 ml/min/1.73m^2	43/136 (31.6%)	47/129 (36.4%)	1.17 (0.75-1.83)		0.636
eGFR >40 ml/min/1.73m^2	29/123 (23.6%)	29/127 (22.8%)	0.99 (0.96-1.02)		

Results: acetazolamide treatment effect across eGFR range

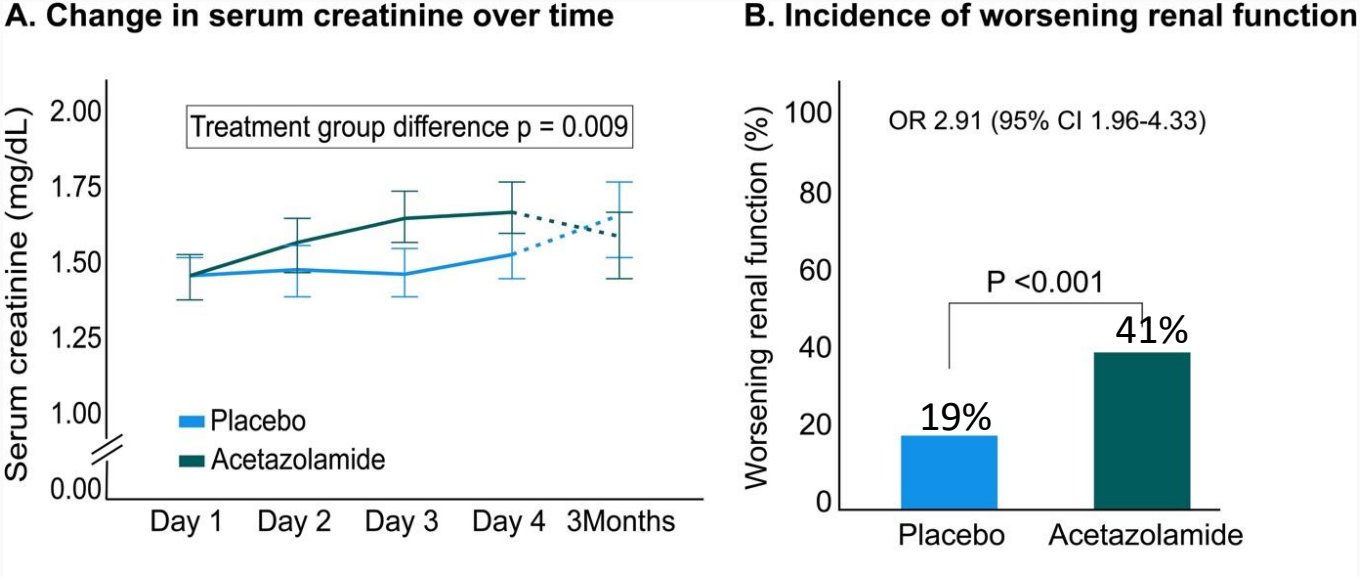


Results: renal function and diuretic response

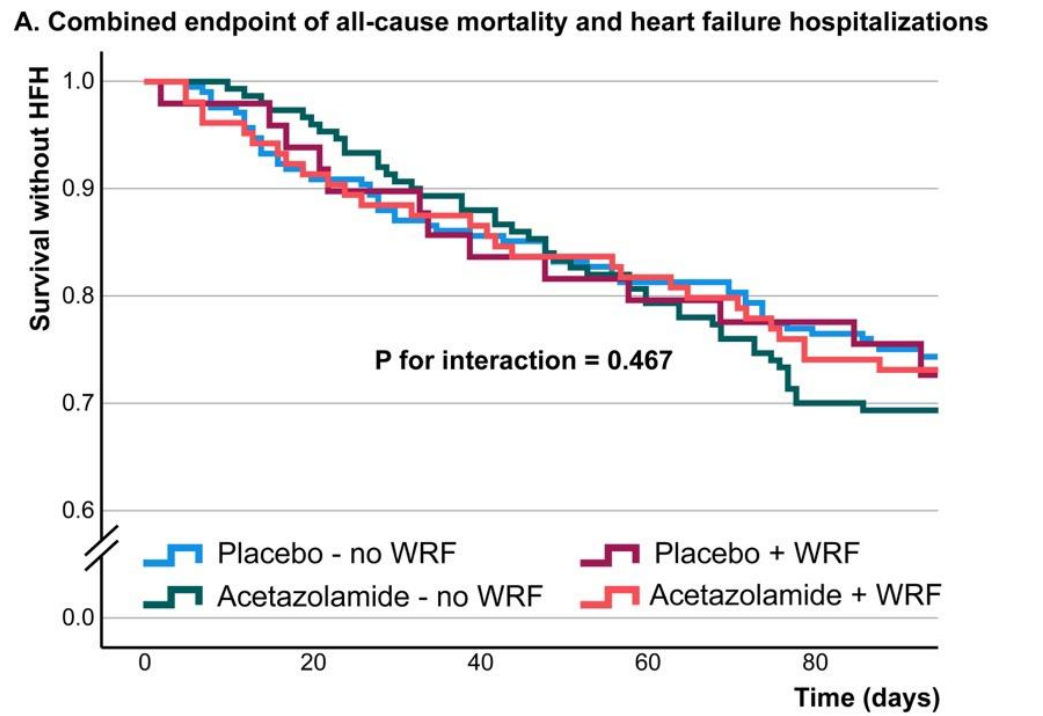


Results: worsening renal function

Worsening renal function = creatinine increase ≥ 0.3 mg/dL

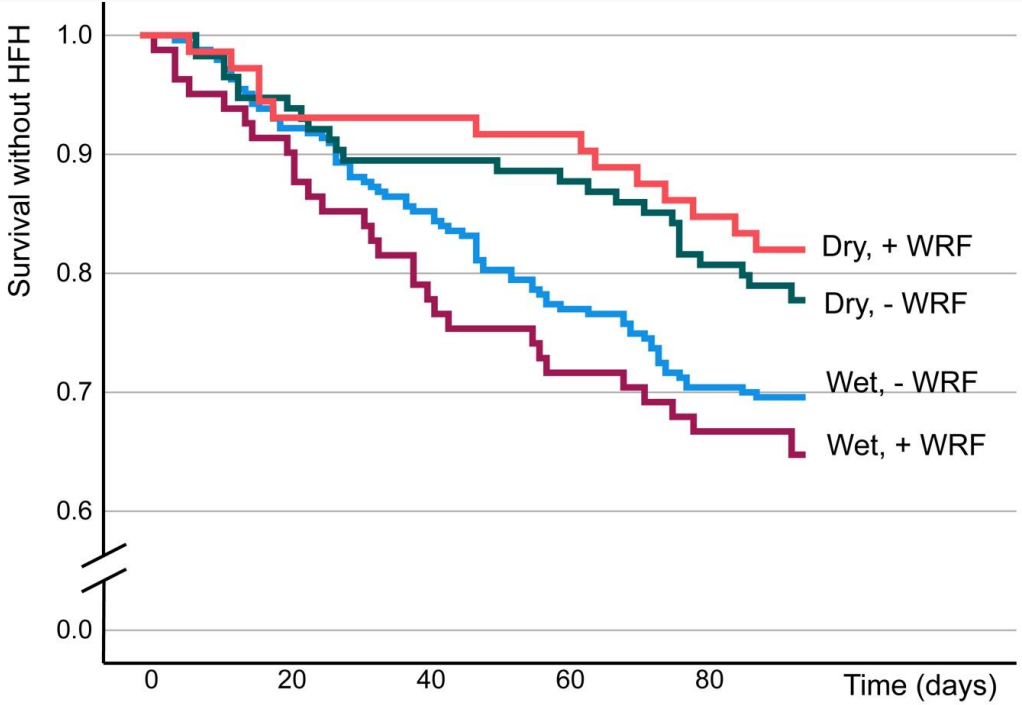


Results: occurrence of WRF and outcomes



No interaction between treatment effect and WRF on outomes

Results: succesful decongestion and outcomes



WRF +

HR 0.51

95% CI [0.27-0.94]

p=0.032

WRF -

HR 0.51

95% CI [0.27-0.94]

p=0.032

P for interaction 0.805

Conclusion

- The addition of acetazolamide to standardized loop diuretics in patients with acute decompensated heart failure is associated with a higher incidence of successful decongestion **across the full (≥20) eGFR range**
- All acetazolamide treated patients had higher natriuresis and diuresis, but the effect was even higher in patients with lower eGFR
- Acetazolamide was associated with more worsening renal function, but no difference in serum creatinine after 3 months
- No benefit on combined endpoint heart failure hospitalization or mortality
- Worsening renal function was only associated with worse outcomes in patients with persistent congestion

Simultaneously published

Renal Function and Decongestion With Acetazolamide in Acute Decompensated Heart Failure: The ADVOR Trial

ESC European Society of Cardiology

European Heart Journal

Renal Outcomes in PARAGLIDE-HF and PARAGON-HF

Muthiah Vaduganathan, MD MPH
Brigham and Women's Hospital
Harvard Medical School

on behalf of
Robert J. Mentz, Brian L. Claggett, Ian J. Kulac, Jonathan H. Ward, Adrian F. Hernandez, David A. Morrow, Randall C. Starling, Eric J. Velazquez, Kristin M. Williamson, Akshay S. Desai, Shelley Zieroth, Martin Lefkowitz, John J.V. McMurray, Eugene Braunwald, Scott D. Solomon

Pooled Analysis Registration: PROSPERO CRD42023410574

Disclosures

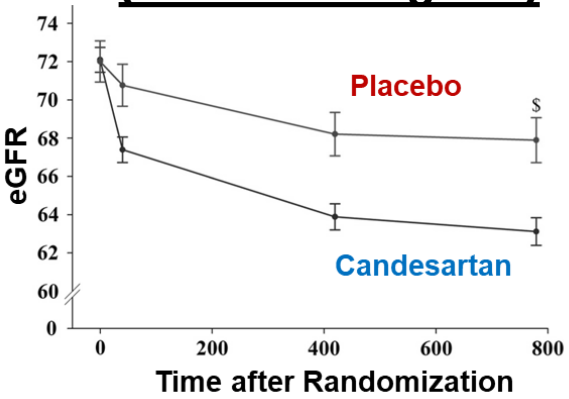
- **Presenter Disclosures:** Dr. Vaduganathan has received research grant support, served on advisory boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Chiesi, Cytokinetics, Lexicon Pharmaceuticals, Merck, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health, and participates on clinical trial committees for studies sponsored by AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics.

- **Funding:** PARAGLIDE-HF and PARAGON-HF were funded by Novartis Pharmaceuticals Corporation.

- **Data Analysis:** Individual-participant level data access for both trials were obtained and pooled data were analyzed independently at Brigham and Women’s Hospital.

No Previous HF Medical Therapy Has Definitively Demonstrated Benefit on Renal Outcomes in HF and LVEF>40%

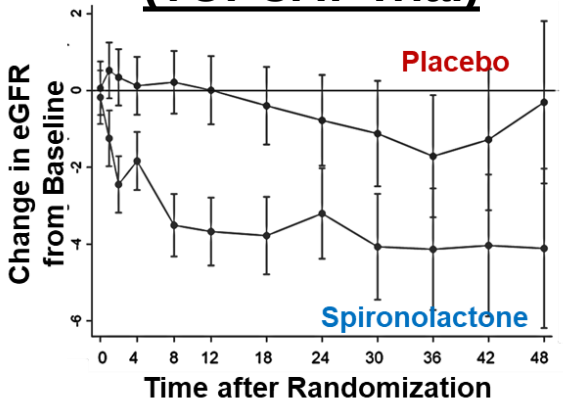
ARB (CHARM Program)



Damman K et al. EJHF 2016

Potentially higher risk of renal events

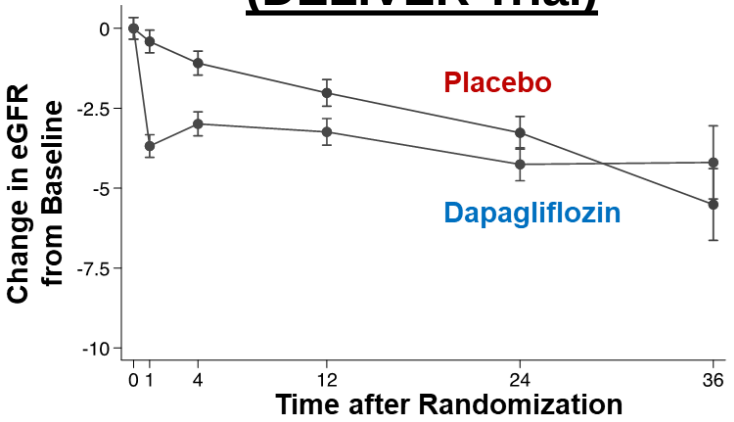
MRA (TOPCAT Trial)



Vaduganathan M et al. EJHF 2022

Potentially higher risk of renal events

SGLT2i (DELIVER Trial)



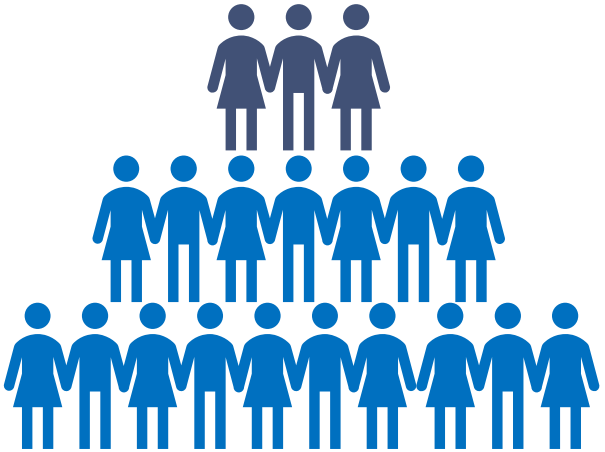
Mc Causland F et al. JAMA Cardiology 2023

Slowing of decline in chronic eGFR, but no definitive reduction in renal events

Pre-Specified Participant-Level Pooled Analyses

PARAGLIDEHF

PARAGONHF



Renal Outcome Assessment in Pooled Analysis of All 5,262 Participants

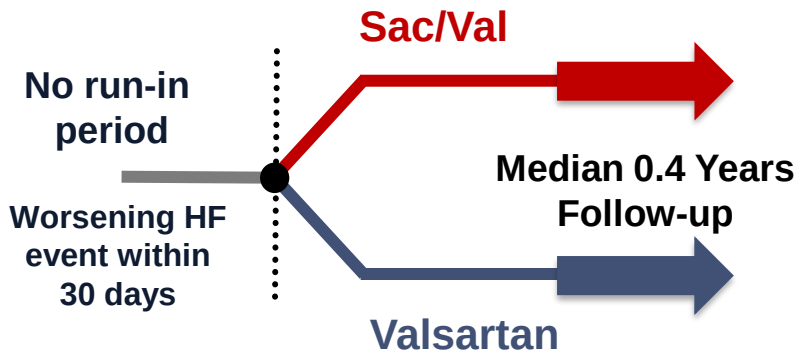
- **Renal composite outcome:** Time to first ≥50% decline in eGFR from baseline, ESRD, or renal death
- **Total slope of serial eGFR measurements**

Vaduganathan M *et al.* EHJ 2023

Entry criteria	Study design

PARAGLIDE-HF (n=466)

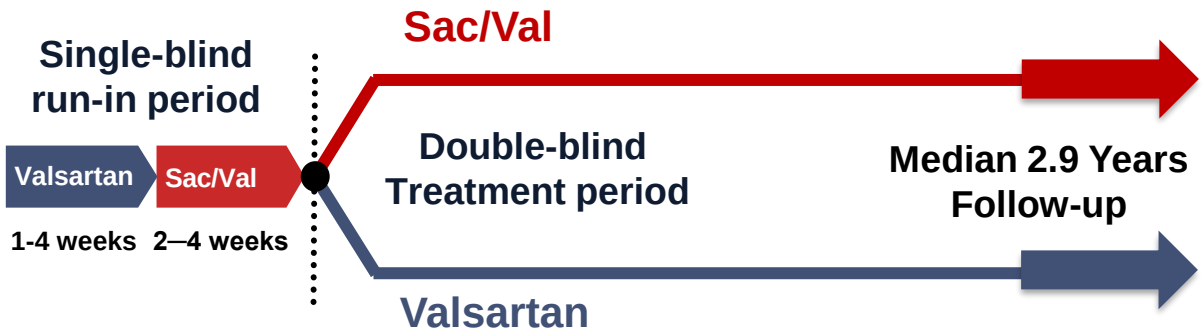
- Age ≥18 years
- HF with LVEF >40%
- Current or recent worsening HF event
- Elevated natriuretic peptides
- **eGFR ≥20mL/min/1.73 m²**



Mentz RJ, *et al. J Card Fail* 2023

PARAGON-HF (n=4,796)

- Age ≥50 years
- HF with LVEF ≥45%
- NYHA class II-IV
- Elevated natriuretic peptides
- Structural heart disease
- **eGFR ≥25mL/min/1.73 m²***



Solomon SD, *et al. JACC HF* 2017

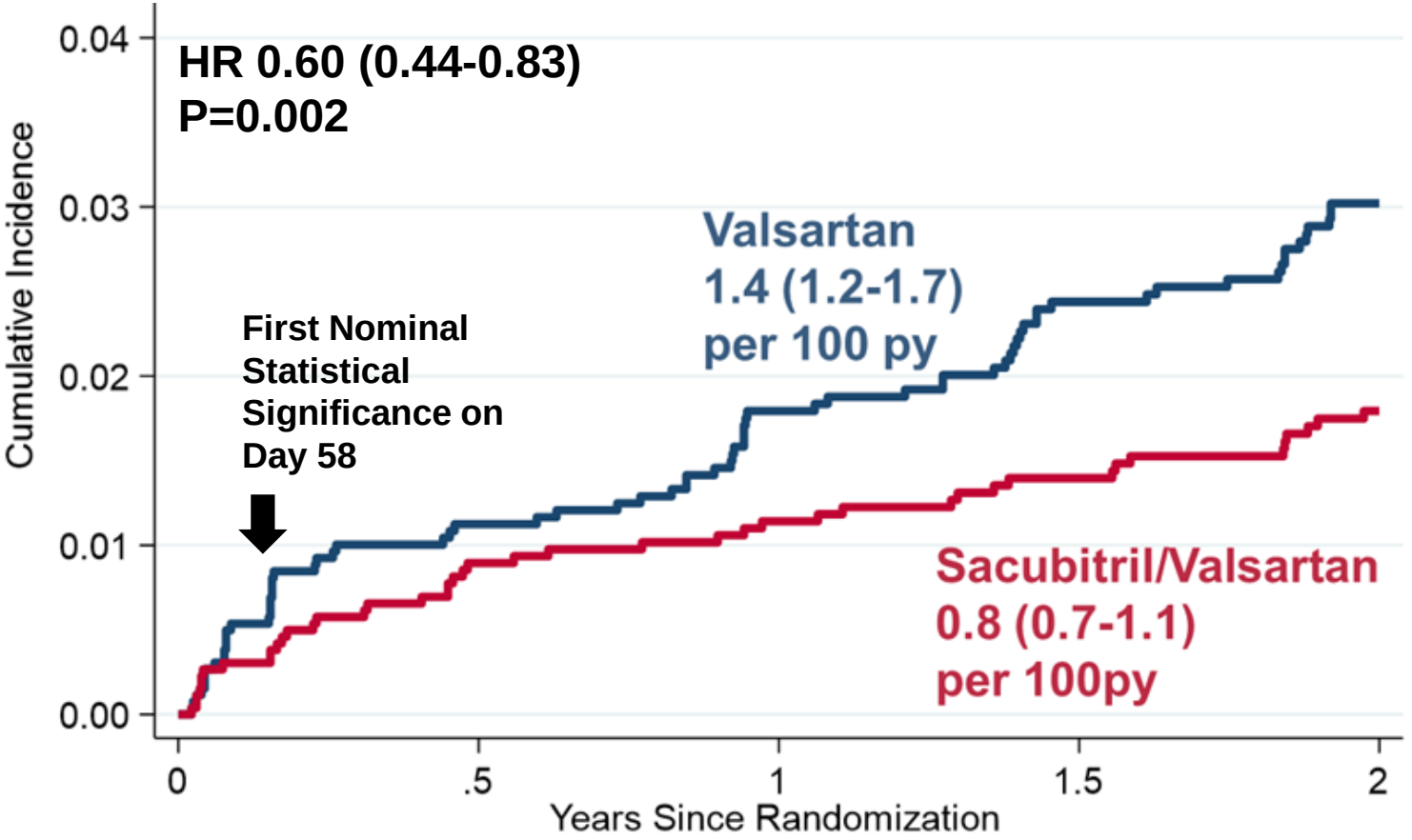
* ≥30 mL/min/1.73 m² at screening and ≥25 mL/min/1.73 m² at randomization and without greater than a 35% reduction in eGFR during either run-in period

Baseline Characteristics

	Sac/Val (n=2,640)	Val (n=2,622)
Age (years)	72 ± 9	73 ± 9
Men	48%	48%
Black race	4%	4%
LVEF (%)	57 ± 8	57 ± 8
Hypertension	96%	95%
Atrial fibrillation or flutter	53%	54%
Systolic blood pressure (mmHg)	131 ± 16	131 ± 16
Body mass index (kg/m^2)	31 ± 6	31 ± 6
eGFR (mL/min/1.73m^2)	62 ± 19	62 ± 19
Serum potassium (mmol/L)	4.5 ± 0.5	4.5 ± 0.5
NT-proBNP (pg/mL)	945 [490, 1700]	947 [461, 1714]
ACEi or ARB	85%	86%
MRA	25%	27%
β-blocker	80%	79%
SGLT2i	2%	2%

Renal Composite: Nominal Significance within 2 months

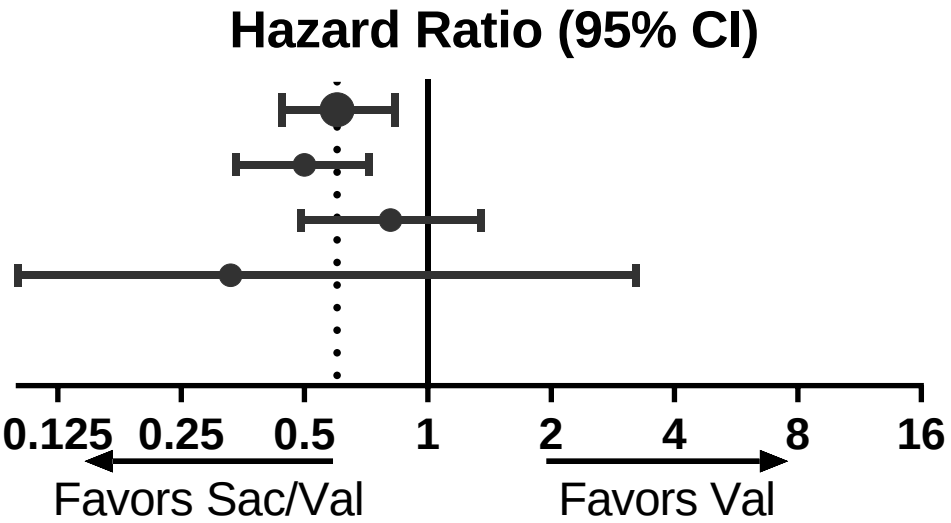
Time to first ≥50% decline in eGFR from baseline, ESRD, or renal death



Renal Composite: Contribution of Each Component to Benefit

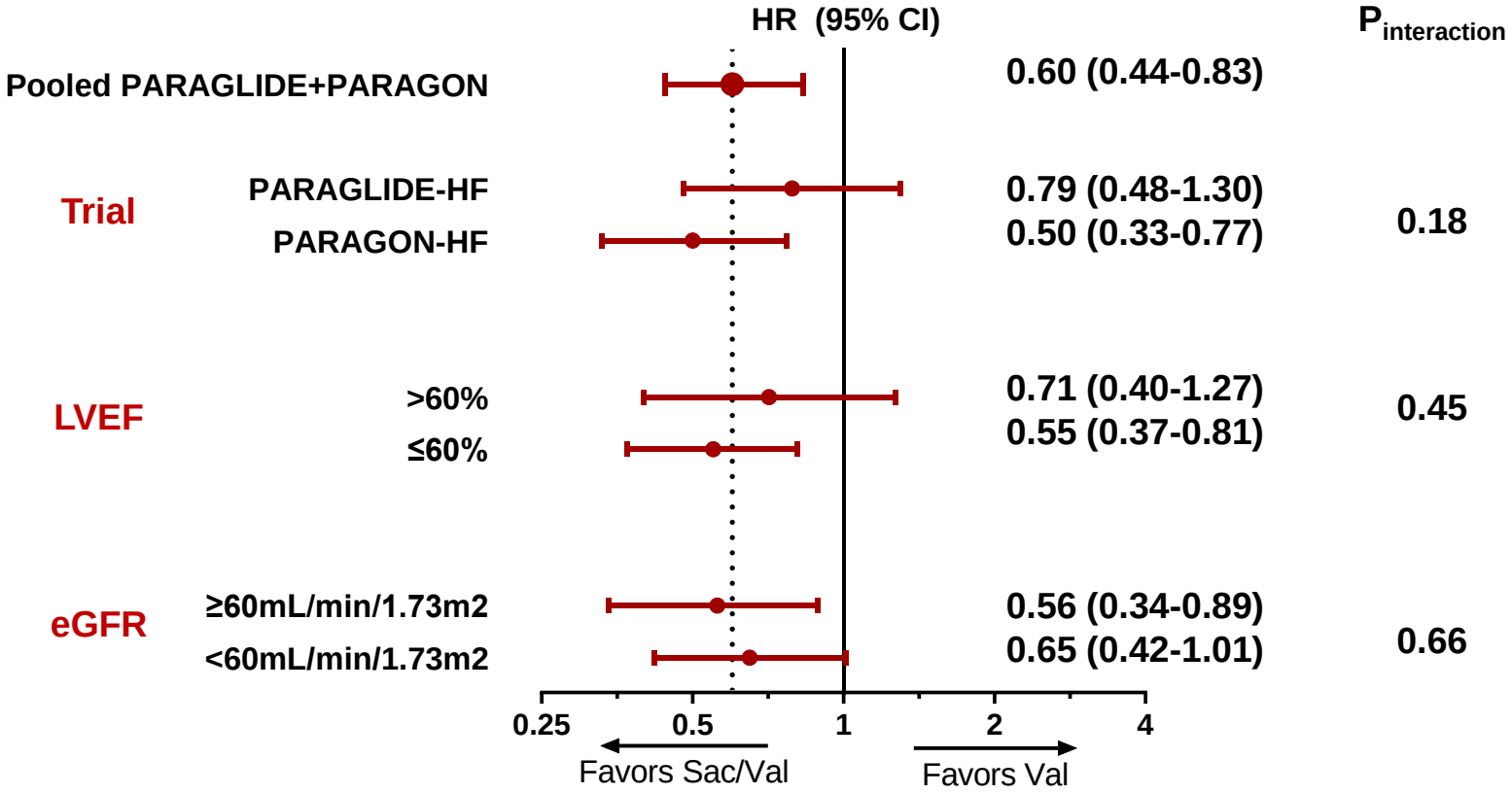
Time to first ≥50% decline in eGFR from baseline, ESRD, or renal death

	# of Events Sac/Val	# of Events Val
Renal Composite Endpoint	60	99
≥50% decline in eGFR	41	82
ESRD	27	34
Renal Death	1	3



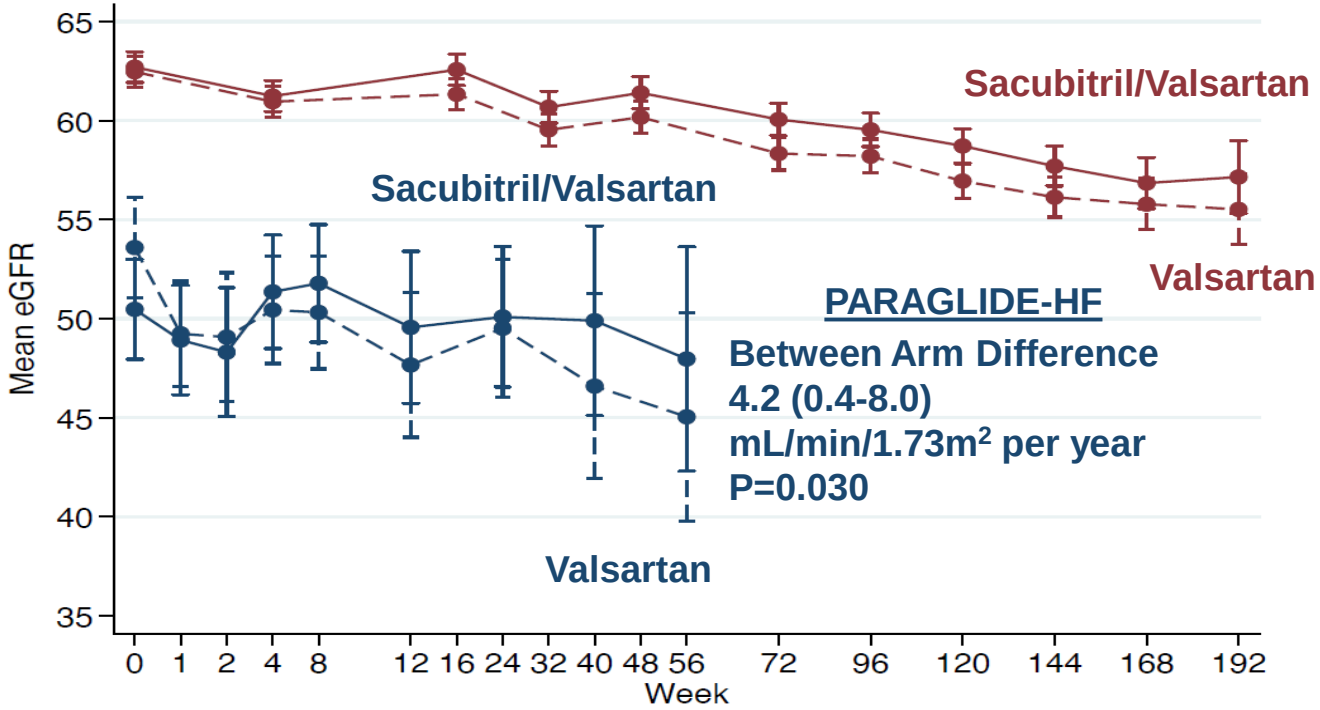
The sum of the individual component events exceed the number of events of the renal composite endpoint as more than one component may meet the endpoint definition at the same timepoint

Renal Composite: Consistent Across Key Subgroups



Treatment effects on the renal composite endpoint were consistent across key demographics, clinical characteristics, and background medications

Sacubitril/Valsartan Slows Decline in eGFR over Time Compared with Valsartan



PARAGON-HF

Between Arm Difference
0.6 (0.3-0.8)
mL/min/1.73m^2 per year
P<0.001

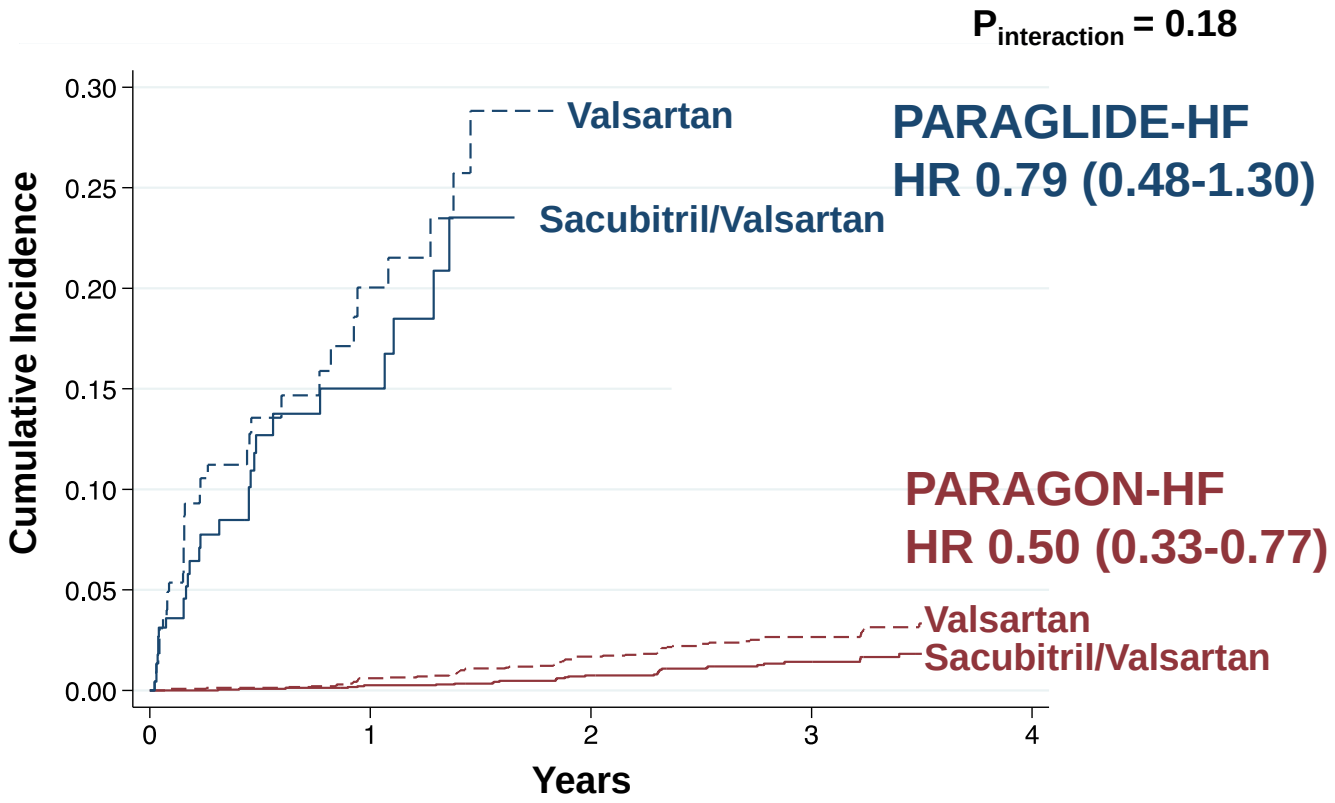
Summary: Pooled Analyses of PARAGLIDE-HF & PARAGON-HF

- Sacubitril/valsartan reduced clinically relevant renal events in both high-risk patients hospitalized for acute HF and those in ambulatory care
- These renal benefits were observed rapidly with statistically significant reductions in renal events first observed within months of treatment initiation and extended across all key subgroups
- Sacubitril/valsartan slowed decline in eGFR over time compared with valsartan

Among both hospitalized and ambulatory patients with HF with mildly reduced or preserved ejection fraction, sacubitril/valsartan reduced risks of renal events and slowed decline in eGFR over time compared with valsartan.

Renal Composite: Consistent Between Trials

Time to first ≥50% decline in eGFR from baseline, ESRD, or renal death



PUSH-AHF trial

#ESCCongress

Natriuresis guided therapy in acute heart failure

Conclusion

A pragmatic natriuresis guided diuretic approach in patients with acute heart failure (AHF) significantly increases 24-hour natriuresis without impacting all-cause mortality or HF rehospitalisation.

Impact on clinical practice

Clinicians should consider natriuresis guided diuretic therapy as a first step to a personalised treatment approach in patients with AHF to improve decongestion.

Study objectives

The PUSH-AHF trial investigated the effectiveness of natriuresis guided diuretic therapy on natriuresis and clinical outcomes in patients with AHF.

Study population

Patients

- AHF requiring treatment with intravenous (IV) loop diuretics

The inclusion and exclusion criteria were intentionally broad to enrol a contemporary, representative, all-comer AHF population.

Where?

University Medical Centre Groningen, the Netherlands

Primary endpoints: p<0.025 for each was considered statistically significant

24-hour natriuresis

409 ± 178 mmol

345 ± 202 mmol

p=0.0061

Combined endpoint of time to all-cause mortality or HF rehospitalisation at 180 days

46 patients (31%)

50 patients (31%)

Hazard ratio 0.92; 95% CI 0.62 to 1.38; p=0.6980

Who and what?

310 patients

randomised 1:1

Natriuresis guided diuretic therapy

Twice daily IV diuretic therapy

Spot urinary sodium determined at 2, 6, 12, 18, 24 and 36 hours after starting IV loop diuretics

Therapy intensified using a prespecified stepwise approach if response insufficient:

- spot urinary sodium <70 mmol
- and/or diuresis <150 ml/hour

Standard of care

Twice daily IV diuretic therapy

Physicians blinded to urinary sodium levels

STEP-HFpEF trial

#ESCCongress

Once-weekly semaglutide in people with HFpEF and obesity

Conclusion

Semaglutide improves heart failure-related symptoms and physical function and results in greater weight loss compared with placebo in patients with heart failure with preserved ejection fraction (HFpEF) and obesity.

Impact on clinical practice

The results indicate that obesity is not simply a comorbidity in patients with HFpEF but a root cause and a target for therapeutic intervention.

Study objectives

The STEP-HFpEF trial tested the hypothesis that treatment with semaglutide can significantly improve symptoms, physical limitations and exercise function, in addition to weight loss, in patients with HFpEF and obesity.

Study population

HFpEF patients

- left ventricular ejection fraction ≥45%
- body mass index ≥30 kg/m2
- HF symptoms
- functional limitations (New York Heart Association functional class II–IV and Kansas City Cardiomyopathy Questionnaire Clinical Summary Score [KCCQ-CSS] <90 points)

Where?

13 countries in Asia, Europe, North America and South America

96 sites

Who and what?

529 patients

randomised 1:1

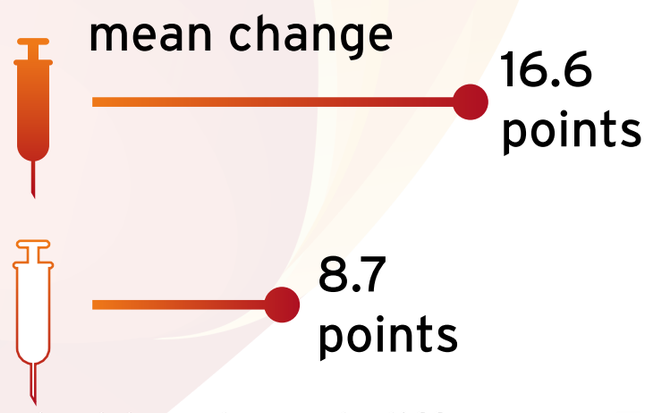
once-weekly for 52 weeks

semaglutide 2.4 mg

placebo

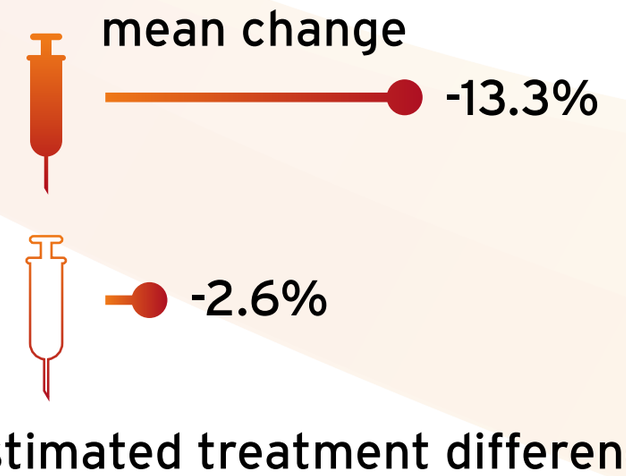
Primary endpoints

change from baseline to week 52 in KCCQ-CSS



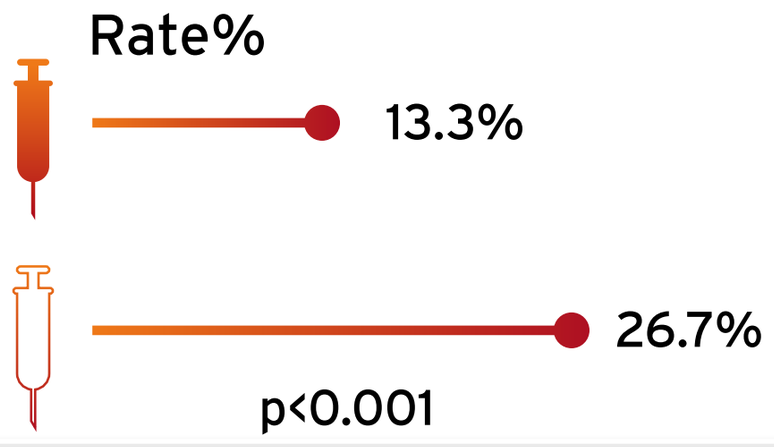
estimated treatment difference 7.8 points
95% CI 4.8 to 10.9
p<0.001

change from baseline to week 52 in body weight



estimated treatment difference -10.7%
95% CI -11.9% to -9.4%
p<0.001

Serious adverse events



p<0.001

ESC

CASTLE-HTx trial

#ESCCongress

Catheter ablation versus medical therapy to treat atrial fibrillation in end-stage heart failure

Conclusion

Atrial fibrillation (AF) ablation is associated with lower rates of death, urgent heart transplantation or left ventricular assist device (LVAD) implantation compared with medical therapy in patients with end-stage heart failure (HF).

Impact on clinical practice

Patients with end-stage HF eligible for heart transplantation have been excluded from major trials, leaving them with no recommendations or evidence for the optimal treatment of AF and advanced HF. The trial showed that AF ablation improves outcomes in this group.

Study objectives

The CASTLE-HTx trial tested whether AF ablation is superior to medical therapy concerning mortality and need for urgent transplantation or LVAD implantation.

Study population

Patients

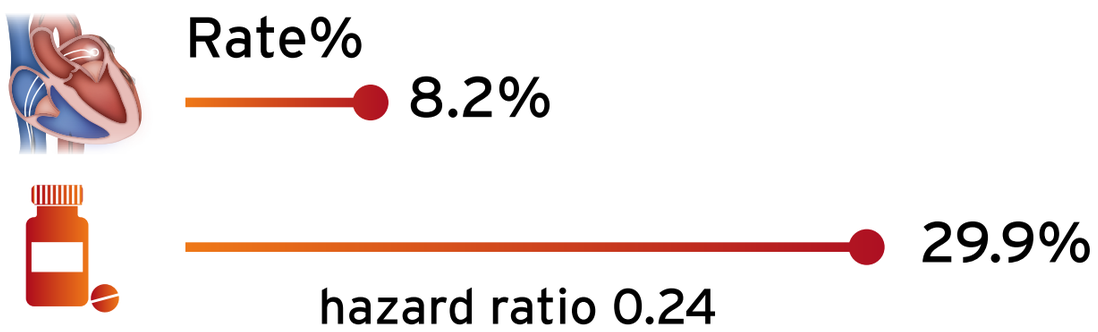
- with symptomatic AF
- with end-stage HF eligible for heart transplantation
- in New York Heart Association functional class II, III, or IV
- had left ventricular ejection fraction (LVEF) ≤35%
- were fitted with a cardiac device for continuous monitoring

Where?

Heart and Diabetes Center North Rhine-Westphalia, Bad Oeynhausen, Germany

Primary endpoint

Composite of all-cause mortality, worsening HF requiring urgent heart transplantation, or implantation of LVAD.



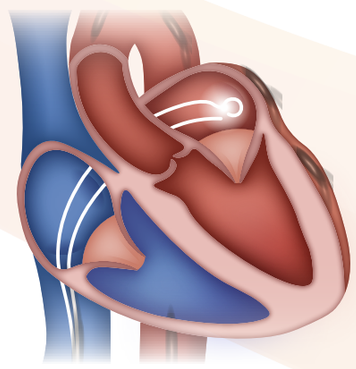
Who and what?

194 patients

randomised 1:1

First-time catheter ablation of AF

Medical therapy for AF



Both groups received guideline-directed HF therapy.

The study was stopped for efficacy by the Data Safety Monitoring Board 1 year after randomisation was completed.

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AMERICAN COLLEGE of CARDIOLOGY®

HEART-FID

Efficacy and Safety of Ferric Carboxymaltose as Treatment For HF With Iron Deficiency

Double-Blind, Multicenter, Placebo-Controlled, Industry Sponsored, Randomized Trial

OBJECTIVE: To assess the effect of Ferric Carboxymaltose (FCM) administration on safety and outcomes in patients with heart failure (HF).

3,065 PATIENTS

INCLUSION CRITERIA:

- Patients Iron Deficiency (Ferritin <100 ng/ml or 100-300 ng/ml with TSAT <20%)
- HFrEF (<40%) on maximally tolerated GDMT
- HF hospitalization within the last 12 months or Nt-proBNP > 600pg/mL (>1000 pg/mL if in atrial fibrillation)

1,532 PATIENTS GIVEN WEIGHT-BASED INFUSIONS OF FCM

VS.

1,533 PATIENTS GIVEN INFUSIONS OF SALINE

PRIMARY ENDPOINT

THE HIERARCHICAL COMPOSITE OF MORTALITY, HF HOSPITALIZATION AND CHANGE IN 6-MINUTE WALK DISTANCE FAVORED THE TREATMENT ARM (P=0.019).

SECONDARY ENDPOINTS

ALL-CAUSE MORTALITY WAS REDUCED (8.6% VS. 10.3%)

HYPERSENSITIVITY/ANAPHYLACTOID REACTIONS WERE INCREASED WITH FCM (7 VS. 1)

CONCLUSION

In patients with iron deficiency and HFrEF, treatment with FCM was safe and resulted in improvement in the hierarchical endpoint of mortality, HF hospitalization and 6-minute walk.

Mentz, R. Ferric Carboxymaltose in Heart Failure with Iron Deficiency. *New England Journal of Medicine* 2023;Aug 26:[Epublished]

Developed and reviewed by Kent Brummel, MD

ILUMIEN IV trial

#ESCCongress

OCT versus angiography

Conclusion

Optical coherence tomography (OCT)-guided percutaneous coronary intervention (PCI) leads to a larger minimum stent area but does not reduce the 2-year rate of target vessel failure compared with angiography-guided PCI.

Impact on clinical practice

OCT-guided PCI led to a larger minimum stent area, enhanced the safety of the PCI procedure and resulted in nearly a two-thirds reduction in stent thrombosis during 2-year follow-up. However, OCT guidance did not reduce the 2-year rate of target vessel failure compared with angiography-guided PCI.

Study objectives

The ILUMIEN IV trial investigated whether OCT-guided PCI is superior to angiography-guided PCI for minimum stent area and target vessel failure in complex patients and lesions.

Study population

Patients with medication-treated diabetes and/or complex lesions.

Where?

18 countries

80 sites

Who and what?

2,487 patients randomised 1:1

- OCT-guided PCI
- Angiography-guided PCI

Co-primary endpoints

post-PCI minimum stent area assessed by OCT

OCT-guided PCI	5.72 mm²	difference 0.36 mm² 95% CI 0.21 to 0.51 p<0.001
Angiography-guided PCI	5.36 mm²	

2-year rate of target vessel failure (composite of cardiac death, target vessel myocardial infarction, or ischaemia-driven target vessel revascularisation)

OCT-guided PCI	Kaplan-Meier estimated rate 7.4%	hazard ratio 0.90 95% CI 0.67 to 1.19 p=0.45
Angiography-guided PCI	8.2%	

Secondary endpoint

Stent thrombosis within 2 years

OCT-guided PCI	Rate 0.5%	hazard ratio 0.36 95% CI 0.14 to 0.91
Angiography-guided PCI	1.4%	

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ValorHCM

Myosin Inhibition in Patients with Obstructive HCM Referred for Septal Reduction Therapy

Week 56 results of the VALOR-HCM Trial

Milind Y Desai MD MBA

Haslam Family Endowed Chair in Cardiovascular Medicine
Professor of Medicine, CCLCM
Vice-Chair, Heart, Vascular & Thoracic Institute
Director, Hypertrophic Cardiomyopathy Center

Cleveland Clinic

On behalf of the VALOR-HCM investigators

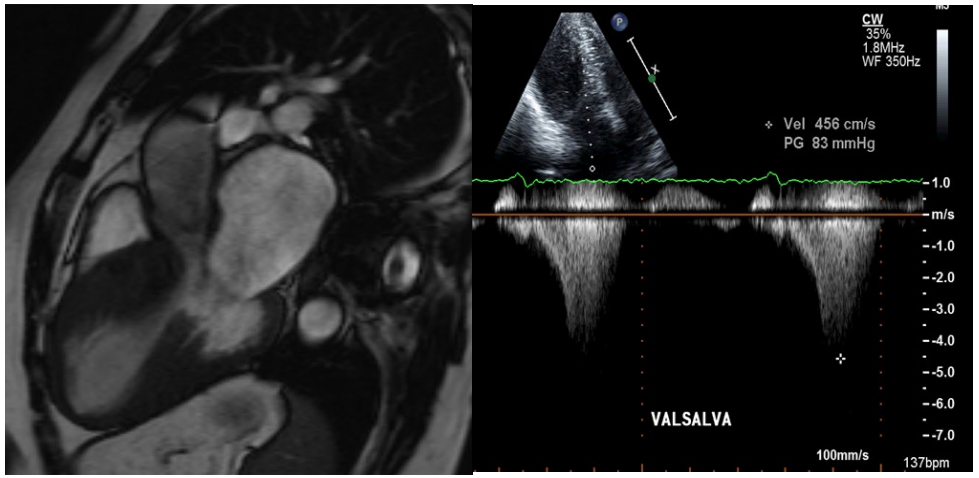
C5Research
Cleveland Clinic Coordinating Center for Clinical Research

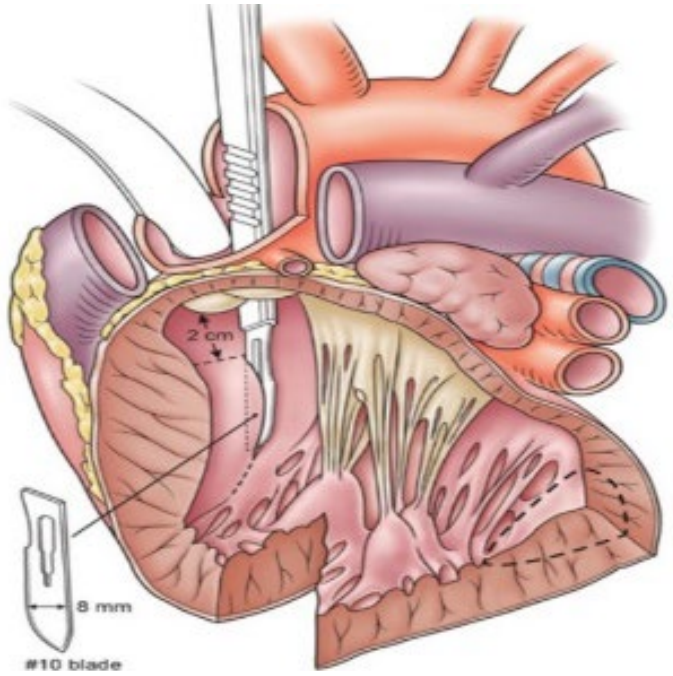
ESC Congress 2023 Amsterdam

Disclosures: Dr. Desai is a consultant for Bristol Myers Squibb, Cytokinetics, Tenaya and Medtronic
The VALOR-HCM study was funded by Bristol Myers Squibb, Princeton, NJ

Obstructive Hypertrophic Cardiomyopathy

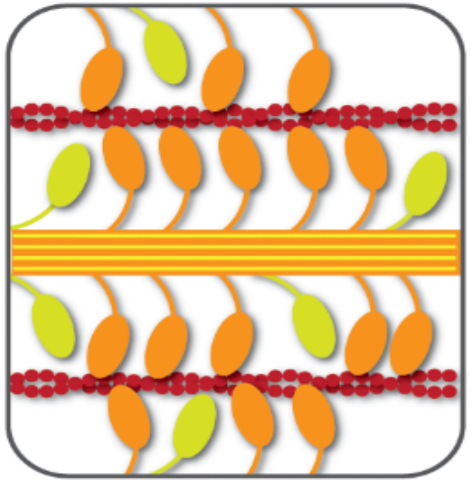
- Hypertrophic cardiomyopathy (HCM) is a myocardial disorder characterized by primary left ventricular (LV) hypertrophy
  - Two-thirds of patients have obstructive HCM
  - Current guideline-recommended medical therapies not developed specifically for HCM
- Septal reduction therapies (SRT), either surgical septal myectomy or alcohol ablation, recommended for intractable symptoms despite maximal medical therapy
  - Although SRT improves long-term survival, symptoms and quality of life, optimal results require specialized care not widely available
  - Unmet need for medical alternatives to SRT





Ommen S, Mital S et al. J Am Coll Cardiol. 2020 Dec 22;76(25):e159-e240, Maron B, Desai M et al. J Am Coll Cardiol. 2022 Feb 1;79(4):390-414, Desai M Smedira N et al. Circulation. 2013 Jul 16;128(3):209, Desai M, Smedira N et al. JAMA Network Open 2022, Olivotto et al. Lancet. 2020 Sep 12;396(10253):759-769 Desai MY et al. J Am Coll Cardiol. 2022 Jul 12;80(2):95-108

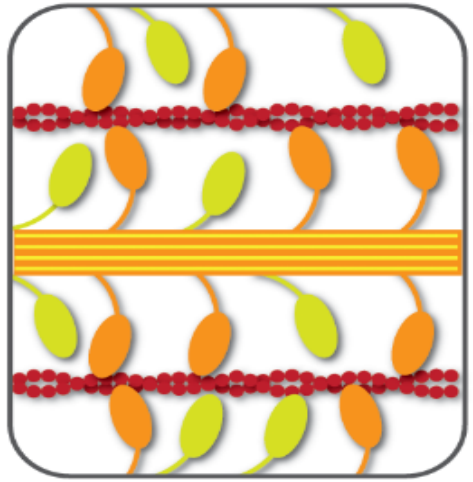
Mavacamten: First in Class Cardiac Myosin Inhibitor



HCM Sarcomere

- Hyper contractility
- Impaired relaxation
- Altered myocardial energetics

Mavacamten



HCM Sarcomere with Mavacamten

- Reduces myosin-actin cross bridges
- Attenuates hypercontractility and improve compliance and energetics

In Phase III RCTs of symptomatic obstructive HCM patients (EXPLORER-HCM and VALOR-HCM), mavacamten reduces need for SRT, improves LVOT gradient, QOL and physical functioning

Currently, clinically approved in 5 continents for use in adult symptomatic obstructive HCM patients

EXPLORER-HCM (Clinicaltrials.gov NCT03470545) and VALOR-HCM (Clinicaltrials.gov NCT04349072)

Desai MY et al. J Am Coll Cardiol. 2022 Jul 12;80(2):95-108, Desai MY et al. Circulation 2023 Mar 14;147(11):850-863, Olivotto et al. Lancet. 2020 Sep 12;396(10253):759-769, Spertus J et al. Lancet. 2021 Jun 26;397(10293):2467-2475

VALOR-HCM

Phase III placebo-controlled RCT (for 16 weeks) with placebo to mavacamten cross over starting Week 16

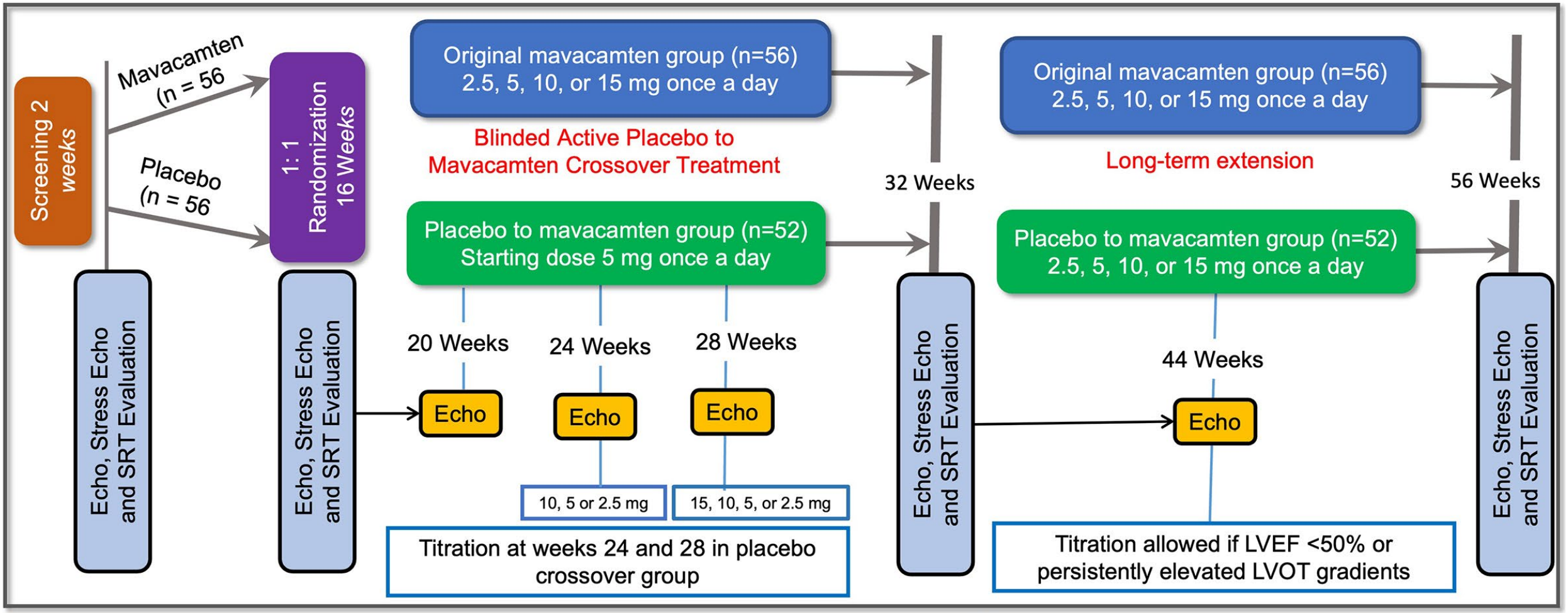
Sought to determine if addition of mavacamten to maximally-tolerated medical therapy would allow severely symptomatic oHCM patients to improve sufficiently that they no longer met guideline criteria for SRT or chose not to undergo SRT

Principal Objective of Week 56 VALOR-HCM

Report the safety and efficacy results through 56 weeks of dose-blinded treatment in patients initially randomized to mavacamten (Day 1 to Week 56) and patients initially randomized to placebo who crossed over to mavacamten for 40 weeks exposure (Week 16 to Week 56)

Desai MY et al. J Am Coll Cardiol. 2022 Jul 12;80(2):95-108
Desai MY et al. Circulation 2023 Mar 14;147(11):850-863

Study Design



Mavacamten titrated using core-lab measured ECHO LVEF and LVOT gradient at rest and Valsalva provocation

Mavacamten titrated using site measured ECHO LVEF and LVOT gradient at rest and Valsalva provocation

Key inclusion criteria

- Age ≥18 years
- Documented HCM with maximum septal wall thickness ≥15 mm or ≥13 mm with family history of HCM (determined by a core echo laboratory)
- Severe symptoms despite maximally-tolerated medical therapy
  - NYHA functional Class III/IV or Class II with exertional syncope or near syncope
  - Maximal medical HCM therapy could include disopyramide and/or combination therapy
- Dynamic LVOT gradient at rest or with provocation (Valsalva maneuver or exercise) ≥50 mmHg
- Documented LV ejection fraction ≥60%
- Must have been referred within the past 12 months for SRT and actively considering scheduling the procedure
  - Patients could elect to proceed to SRT at any time following randomization

Desai M et al. 2021 Sep;239:80-89
Desai MY et al. J Am Coll Cardiol. 2022 Jul 12;80(2):95-108.

Efficacy and Safety Endpoints

ValorHCM

- Composite principal endpoint
  - Patient decision to proceed with SRT
  - Eligibility for SRT according to the 2011 AHA/ACC guidelines
  - SRT status non-evaluable
- Change from baseline in clinical, laboratory and echocardiographic endpoints
  - Resting and provokable LVOT gradient
  - NYHA functional class
  - Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score (KCCQ-23 CCS)
  - N-terminal pro brain natriuretic peptide (NT-proBNP) and Cardiac troponin I
  - LV mass index, Left atrial volume index and Septal E/e'
- Safety endpoints
  - Death, LV ejection fraction <50%, hospitalization for heart failure, and atrial fibrillation or ventricular tachyarrhythmia

Gersh et al. HCM Guidelines. J Am Coll Cardiol. 2011 Dec 13;58(25):e212-60

Results: Baseline Characteristics

	Original Mavacamten Group (n=56)	Placebo to Mavacamten Crossover Group (n=52)
Age, mean(SD)	59.8 (14.2) years	60.9 (10.4) years
Female sex	27 (48.2%)	27 (51.9%)
Family history of HCM	17 (30.4%)	15 (28.9%)
NYHA Class III or higher	52 (92.9%)	50 (96.2%)
Type of SRT recommended Myectomy Alcohol septal ablation	 48 (85.7%) 8 (14.3%)	 47 (90.4%) 5 (9.6%)
Medical therapy n(%) Beta Blocker monotherapy Nondihydropyridine CCB monotherapy Combination therapy	 26 (46.43%) 7 (12.50%) 20 (35.7%)	 23 (44.2%) 10 (19.2%) 17 (32.7%)
Resting LVOT Gradient, mean(SD)	51.2 (31.4) mmHg	46.6 (29.1) mmHg
Post-exercise Gradient, mean(SD)	82.5 (34.7) mmHg	82.9 (36.7) mmHg
LV ejection fraction, %, mean(SD)	67.9 (3.7)	68.7 (3.1)
KCCQ-23 CSS -points, mean (SD)	69.5 (16.3)	67.6 (18.7)
NT-proBNP – ng/L, median (IQR)	724 (291, 1913)	706 (372, 1318)
Cardiac troponin I, ng/L , median (IQR)	17.3 (7.0, 31.6)	13.2 (6.6, 27.4)

22 (20%) were on disopyramide (mono or combination therapy)

Composite SRT endpoint at Week 56

	Patients initially treated with mavacamten (56 weeks exposure) N=56	Patients crossed over to mavacamten (40 weeks exposure) N=52
Principal SRT composite outcome – no. (%)	5 (8.9)	10 (19.2)
Patient decision to proceed with SRT	3 (5.4)	3 (5.08)
SRT-eligible based on guideline criteria	1 (1.8)	4 (7.7)
SRT status not evaluable (imputed as meeting SRT criteria or mavacamten failure)*	1 (1.8)	3 (5.8)

Between Week 32 and 56, a NET INCREASE of 3 patients in the placebo group and a NET DECREASE of 1 patient in the original mavacamten group meeting the composite SRT outcome

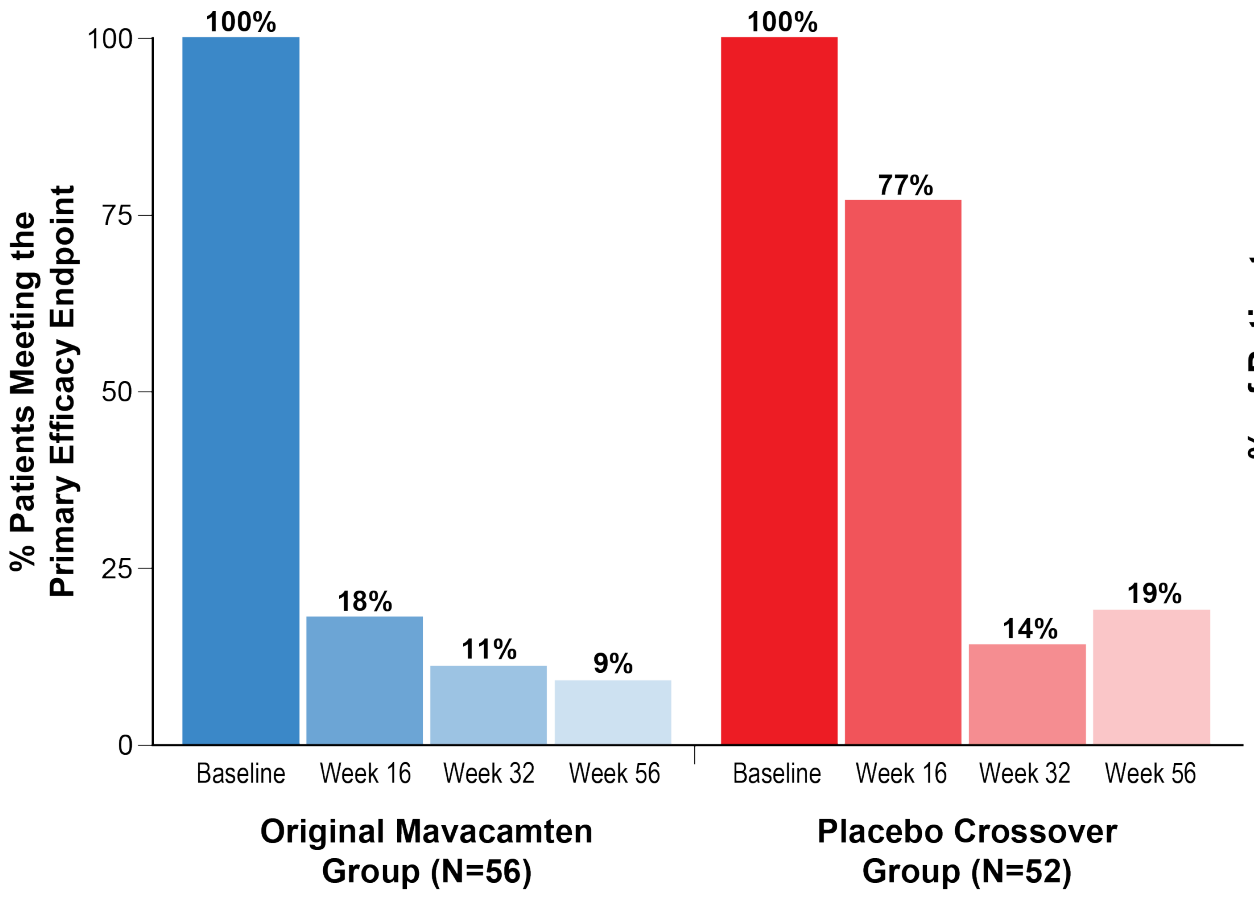
96/108 (89%) have continued in the long-term extension of this ongoing study without SRT

*2 withdrew consent, 1 withdrawn by PI due to noncompliance and 1 unable to complete week 56 exercise echo, so provoked LVOT gradient not assessed

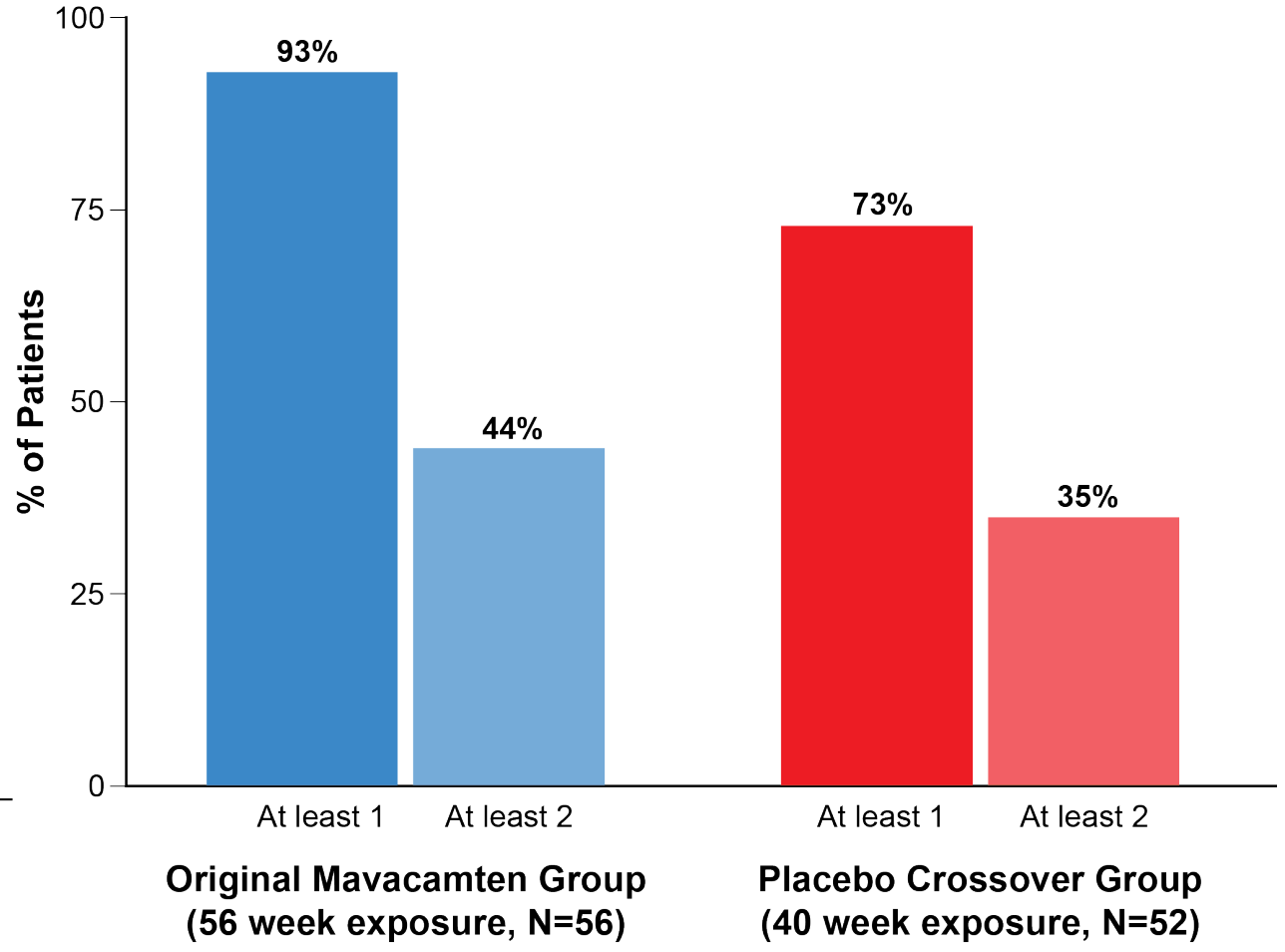
Gersh et al. HCM Guidelines. J Am Coll Cardiol. 2011 Dec 13;58(25):e212-60

Sustained Improvement in Principal Endpoint and NYHA Class

Principal Composite Endpoint



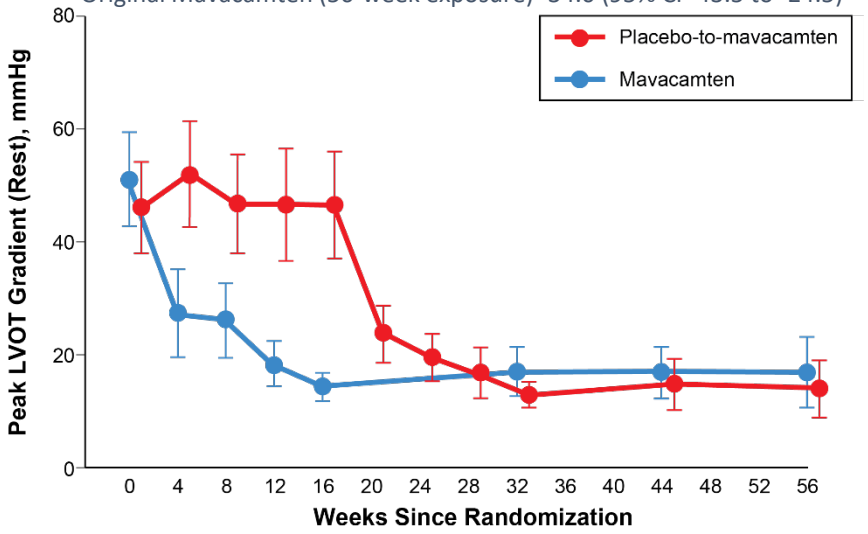
NYHA Class Improvement At Week 56



Sustained Improvement in Efficacy Endpoints

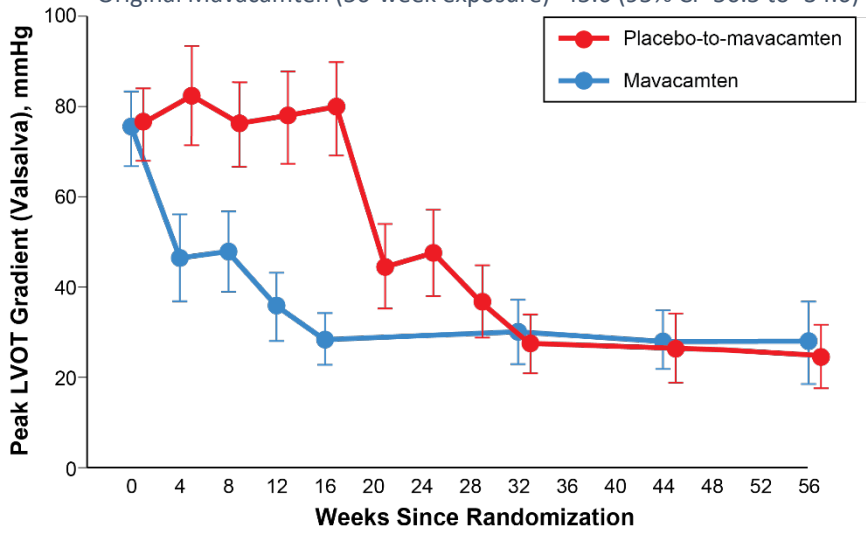
Resting LVOT Gradient

Original Placebo (40-week exposure) -33.2 (95% CI -41.9 to -24.5)
Original Mavacamten (56-week exposure) -34.0 (95% CI -43.5 to -24.5)



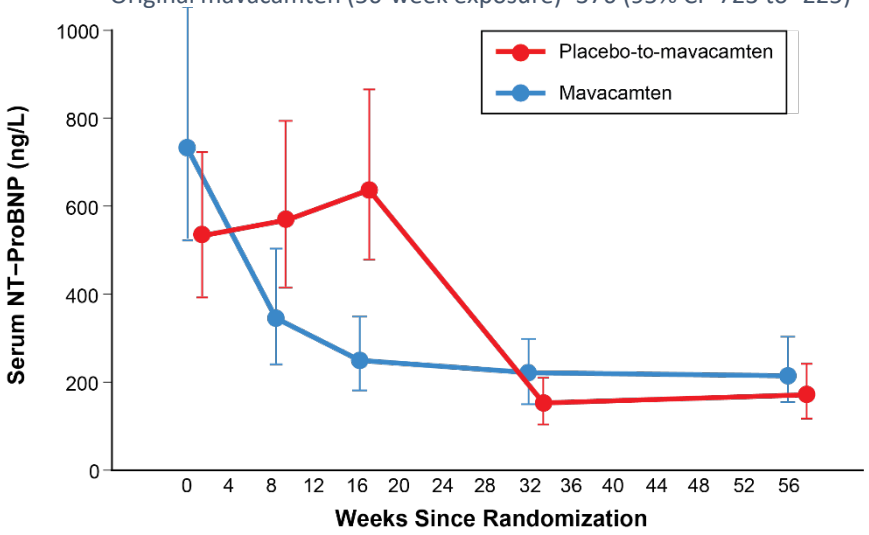
Valsalva LVOT Gradient

Original Placebo (40-week exposure) -54.6 (95% CI -66.0 to -43.3)
Original Mavacamten (56-week exposure) -45.6 (95% CI -56.5 to -34.6)



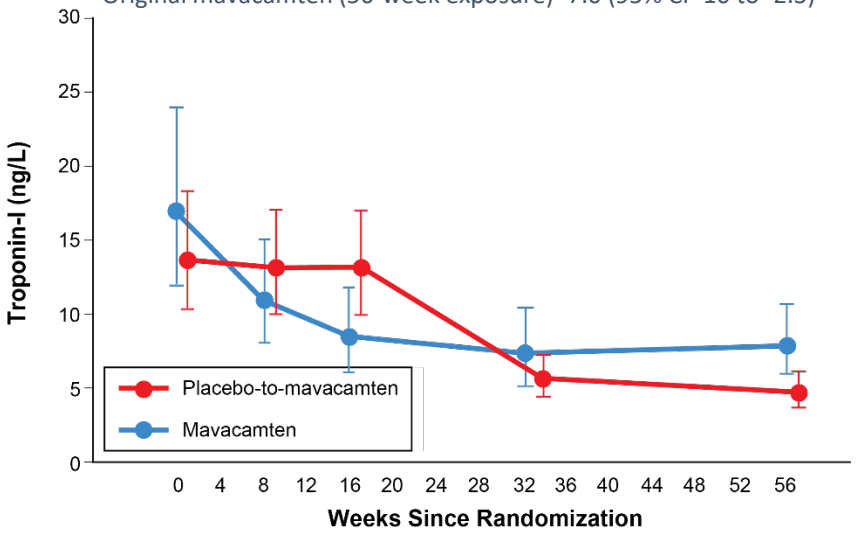
NT-ProBNP

Original placebo (40-week exposure) -423 (95% CI -624 to -252)
Original mavacamten (56-week exposure) -376 (95% CI -723 to -225)



Troponin I

Original placebo (40-week exposure) -6.2 (95% CI -11.5 to -3.3)
Original mavacamten (56-week exposure) -7.0 (95% CI -10 to -2.3)

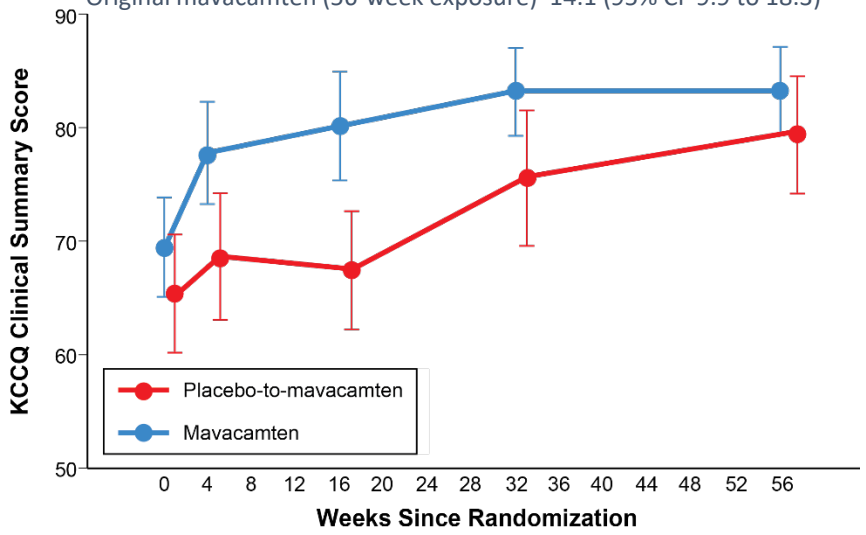


Sustained Improvement in QOL and Favorable Cardiac Remodeling

Valor HCM

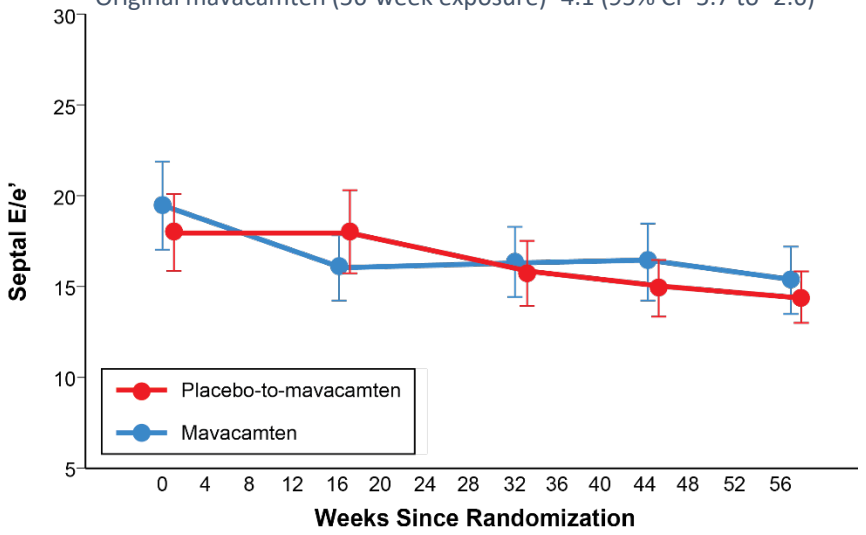
KCCQ Score

Original placebo (40-week exposure) 11.7 (95% CI 6.9 to 16.4)
Original mavacamten (56-week exposure) 14.1 (95% CI 9.9 to 18.3)



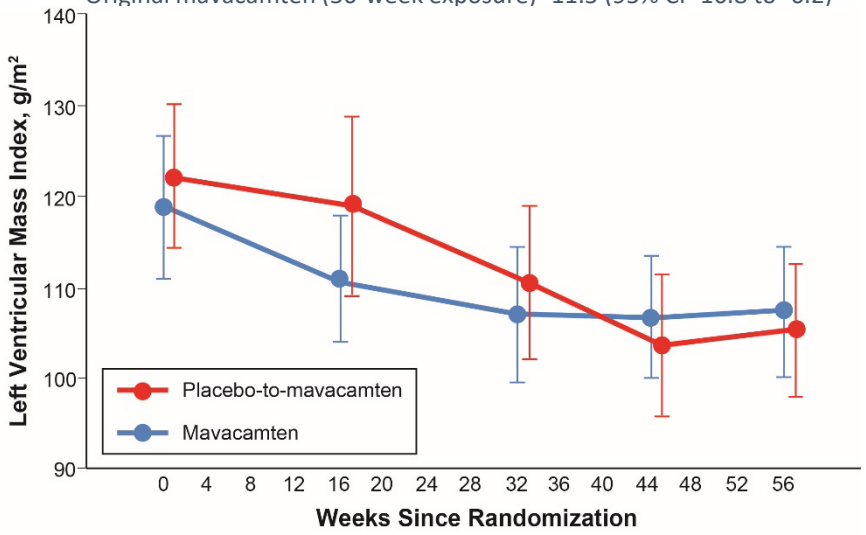
Septal E/e'

Original placebo (40-week exposure) -3.6 (95% CI -5.8 to -1.5)
Original mavacamten (56-week exposure) -4.1 (95% CI -5.7 to -2.6)



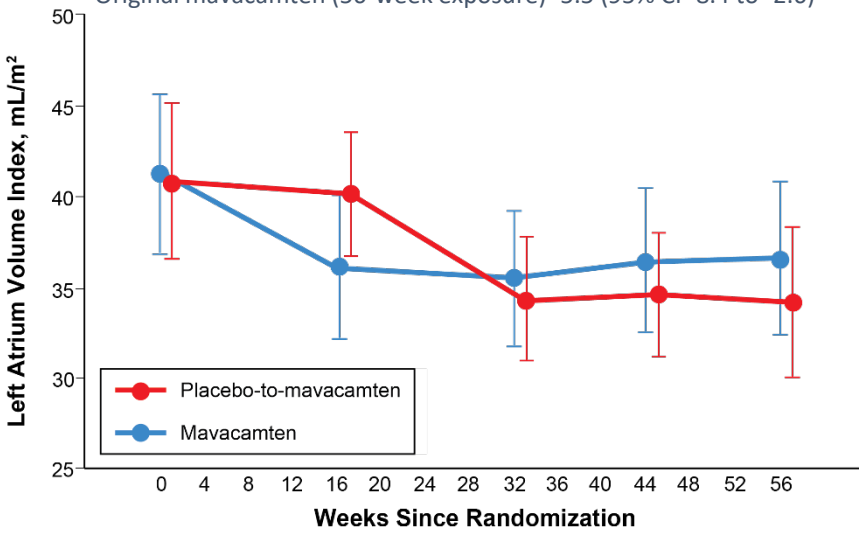
LV-Mass Index

Original placebo (40-week exposure) -14.5 (95% CI -20.8 to -8.3)
Original mavacamten (56-week exposure) -11.5 (95% CI -16.8 to -6.2)



LA Volume Index

Original placebo (40-week exposure) -5.3 (95% CI -7.6 to -2.9)
Original mavacamten (56-week exposure) -5.5 (95% CI -8.4 to -2.6)



Key efficacy findings, separated by sex

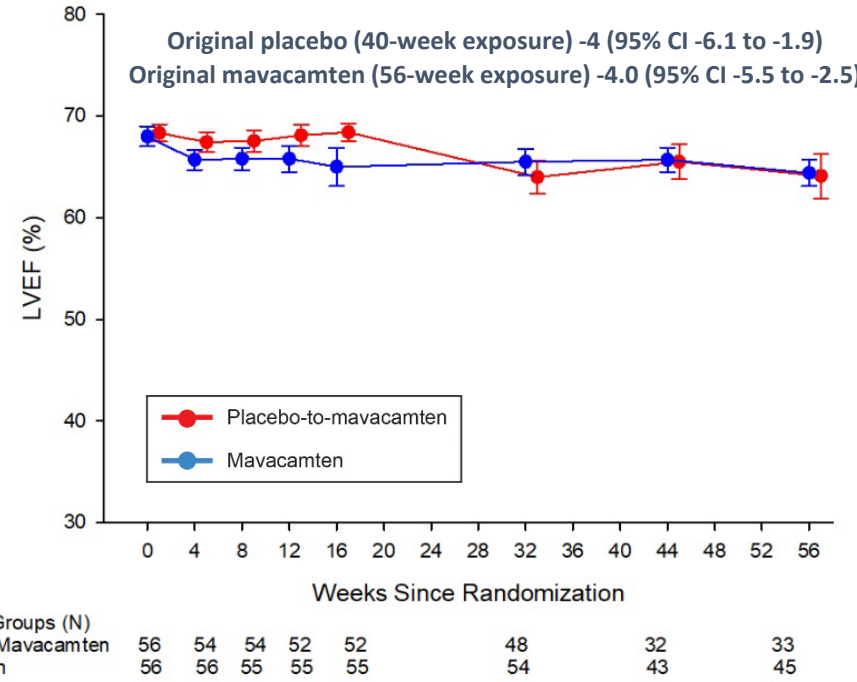
	Mavacamten exposure			
	Original Placebo (40 weeks)		Original Mavacamten (56 weeks)	
	Men (N=25)	Women (N=27)	Men (N=29)	Women (N=27)
Principal endpoint	4 (16.0)	6 (22.2)	2 (6.9)	3 (11.1)
At least 1 class of NYHA improvement	20 (80.0)	17 (65.4)	25 (89.3)	26 (96.3)
At least 2 class of NYHA improvement	9 (36.0)	9 (34.6)	14 (50.0)	10 (37.0)
Change in KCCQ-23-CSS, mean (95% CI)	10.2 (4.4 to 16.1)	13.0 (5.1 to 20.9)	12.1 (5.0 to 19.2)	16.2 (11.3 to 21.1)
Change in resting LVOT gradient (mmHg)	-35.2 (-47.4 to -23.0)	-31.2 (-44.3 to -18.0)	-29.8 (-40.9 to -18.8)	-38.7 (-55.2 to -22.2)
Change in Valsalva LVOT gradient (mmHg)	-58.1 (-74.6 to -41.5)	-51.1 (-67.8 to -34.5)	-34.8 (-50.5 to -19.1)	-57.7 (-72.4 to -42.9)
Change in NT-proBNP – ng/L, median (95% CI)	-442 (-815 to -175)	-423 (-659 to -154)	-196 (-413 to -109)	-723 (-1427 to -273)
Change in cardiac troponin I – ng/L, median (95% CI)	-10 (-17.7 to -3.1)	-4.2 (-10.0 to -2.8)	-6.4 (-14.2 to 0.3)	-7.4 (-15.9 to -2.8)
Change in LV filling pressures (E/'e' ratio)	-5.7 (-9.9 to -1.6)	-1.7 (-3.3 to -0.06)	-3.4 (-5.7 to -1.1)	-5.0 (-7.3 to -2.7)
Change in left atrial volume index – ml/m^2	-3.4 (-6.2 to -0.6)	-7.0 (-10.7 to -3.2)	-4.8 (-9.7 to 0.09)	-6.2 (-9.6 to -2.8)

Similar efficacy across both sexes

Selected safety endpoints at Week 56

Characteristic	Placebo-to-mavacamten (40 weeks exposure) N=52	Original mavacamten (56 weeks exposure) N=56	Total mavacamten N=108
Safety endpoints			
Permanent study drug discontinuation a) LVEF <30% b) Two consecutive LVEF measurements of < 50% despite dose reduction to 2.5 mg	 2 (3.8) 1 (1.9)	 0 0	3 (2.8)
One Temporary Interruption for LVEF (>30% to <50%)	2 (3.8)	7 (12.5)	9 (8.3)
Total with ANY LV EF (<50%)	5 (9.6)	7 (12.5)	12 (11.1)
Cardiac death	1 (1.9)*	0	
Heart failure hospitalization	1 (1.9)¥	0	
Selected serious treatment-emergent adverse events			
At least one serious treatment-emergent adverse event	6 (11.5)	4 (7.1)	10 (9.3)
Atrial fibrillation	0	3 (5.4)	3 (2.8)
Congestive heart failure	1 (1.9)	0	1 (0.9)
Ventricular arrhythmia	1 (1.9)	0	1 (0.9)
Drug administration site reaction	2 (3.8)	0	2 (1.9)
COVID-19	0	1 (1.8)	1 (0.9)

LV Ejection fraction



9/12 (75%) patients with LVEF < 50% were asymptomatic and able to resume mavacamten at a lower dose, after temporary interruption

* This patient had a site-reported LV ejection fraction of 30% and mavacamten was discontinued.

¥ This patient was admitted for congestive heart failure with concomitant atrial fibrillation and had a core-lab reported LV ejection fraction < 30%. Mavacamten was permanently discontinued.

Strengths and Limitations

- Composite efficacy endpoint driven by reduction in guideline eligibility for SRT
  - At Week 56, 9 out of 10 patients chose to remain on medical therapy vs. going for SRT
  - Efficacy findings similar in both sexes
  - Echo evidence of sustained disease modification
- Drug efficacy and safety monitored by echo-based LVEF and LVOT gradients, not drug concentrations
  - Successful utilization of site-based echo measurements (after Week 44)
- Need to ascertain long-term safety
  - Effect of mavacamten on long-term arrhythmias and sudden death not assessed
- Current study included predominantly white patients treated at high-volume HCM centers with established SRT programs

Conclusions

Valor HCM

- In obstructive HCM patients with intractable symptoms, referred for SRT, administration of mavacamten, titrated using echocardiography:
  - Significantly reduced eligibility for invasive SRT at 56 weeks
  - Showed treatment benefits for all efficacy endpoints
    - Resting and provoked LVOT gradient, NYHA Class, KCCQ-CSS
    - Reduction in biomarkers (NT ProBNP and troponin I) and significant improvement in echo indices (LV mass index, LA volume index, E/e')
- Given the potential for LV systolic dysfunction, safety and efficacy require continued monitoring

Provides an alternative for medically refractory patients with obstructive HCM, which may obviate the need for SRT in many patients

Longer-term studies evaluating the effect of mavacamten on outcomes are needed

Simultaneous publication in JAMA Cardiology

Research

JAMA Cardiology | Original Investigation

Mavacamten in Patients With Hypertrophic Cardiomyopathy Referred for Septal Reduction

Week 56 Results from the VALOR-HCM Randomized Clinical Trial

Milind Y. Desai, MD, MBA; Anjali Owens, MD; Kathy Wolski, MPH; Jeffrey B. Geske, MD; Sara Saberi, MD, MS; Andrew Wang, MD; Mark Sherrid, MD; Paul C. Cremer, MD, MS; Neal K. Lakdawala, MD; Albree Tower-Rader, MD; David Fermin, MD; Srihari S. Naidu, MD; Nicholas G. Smedira, MD, MBA; Hartzell Schaff, MD; Ellen McErlean, RN, MSN; Christina Sewell, RN; Lana Mudarris, PharmD; Zhiqun Gong, MS; Kathy Lampl, MD; Amy J. Sehnert, MD; Steven E. Nissen, MD

IMPORTANCE There is an unmet need for novel medical therapies before recommending invasive therapies for patients with severely symptomatic obstructive hypertrophic

Editor's Note

Supplemental content

Acknowledgements

Our sincere thanks to all the patients who participated in the trial

- **VALOR HCM Trial Leadership**
  - **Cleveland Clinic Coordinating Center for Clinical Research (C5Research):** Steven E. Nissen MD (Executive Committee Chairman), Milind Y. Desai MD (Study Principal Investigator), Kathy Wolski MPH (Lead Statistician), Christina Sewell BSN (Lead Project Manager), Ellen McErlean MSN (Manager, Project and Site Management), , Tammy Gamble (Project Specialist)
  - **Executive Committee:** Steven E. Nissen MD (Chairman) Cleveland Clinic, Milind Desai MD (Study Principal Investigator) Cleveland Clinic, Srihari Naidu MD Westchester Medical Center, Nick Smedira MD Cleveland Clinic, Hartzell Schaff MD Mayo Clinic, Anjali Owens MD University of Pennsylvania, Jeffrey Geske MD Mayo Clinic, Amy Sehnert MD (non-voting) BMS.
  - **Independent Data Monitoring Committee:** Jean Rouleau MD (Chairman) Montreal Heart, Gary S. Francis MD University of Minnesota, Kenneth Mahaffey MD Stanford University, A.A. Afifi Ph.D. (statistician) UCLA School of Public Health. Axio, a Cytel Company: David Kerr MS (SDAC Biostatistician).

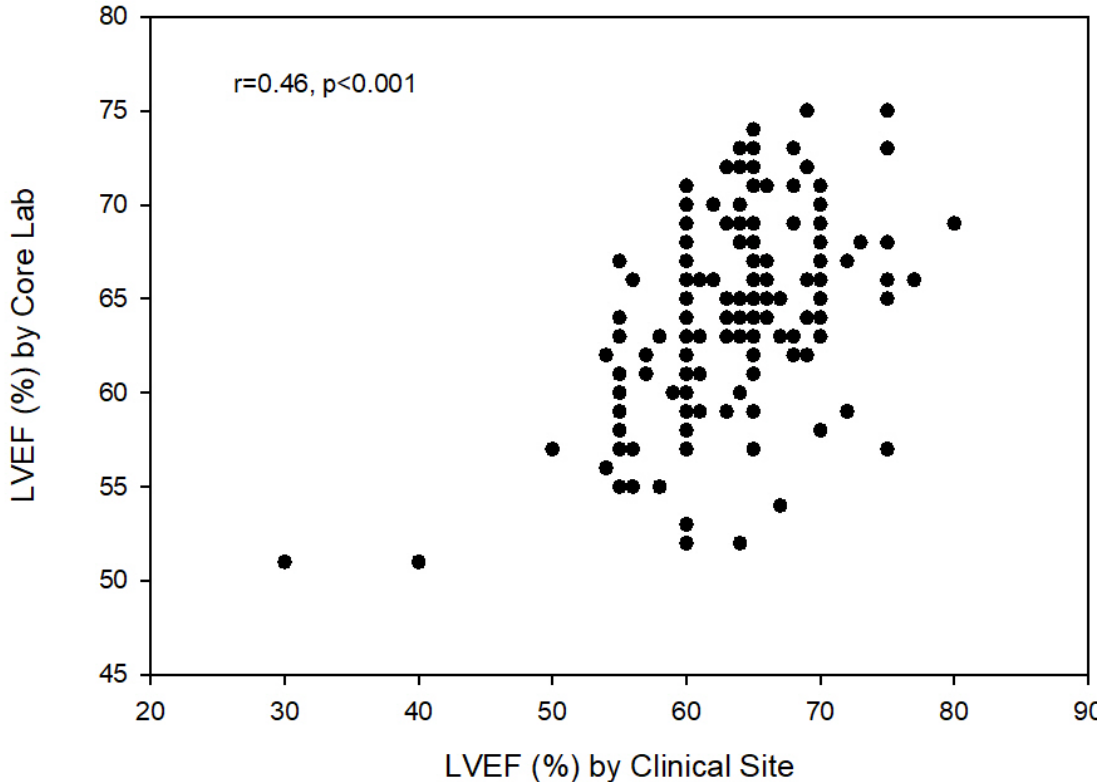
- **VALOR HCM Site Investigators**
  - M. Desai (Cleveland Clinic), J. Geske (Mayo Clinic-Rochester), M. Sherrid (New York University Langone Medical Center), A.T. Owens (University of Pennsylvania-Heart and Vascular Center), S. Saberi (University of Michigan Cardiovascular Center), A. Wang (Duke University School of Medicine), A Tower-Rader (Massachusetts General Hospital), D. Fermin (Corewell Health), N. Lakdawala (Brigham and Women's Hospital), A. Masri (Oregon Health & Science University), M. Zenker (Saint Thomas West Hospital), J. Stendahl(Yale University School of Medicine), M. Wheeler (Stanford University Medical Center), R. Bach (Washington University School of Medicine), J. Orford (Intermountain Medical Center), S. Naidu (Westchester Medical Center), F. Rader (Cedars-Sinai Medical Center), P. Bajona (Allegheny General Hospital), M. Desai (Cleveland Clinic Florida-Weston)

- **Acknowledgments**
  - **C5Research Imaging Core Lab:** Paul Cremer MD, Wael A. Jaber MD, Serge C. Harb MD, Annitta Flinn RDCS, Allen Borowski RDCS, Jeanne Drinko RDCS, Amy Kanta RDCS, Maureen Martin RDCS, Margaret Park RDCS, Jill Odabashian RDCS, Cathy McDowell, Michelle Baksar, Eva Balazs.
  - **C5Research Stats:** Kathy Wolski MPH (Lead Statistician), Qiuqing Wang (statistician), Craig Balog (statistical programming support).
  - **Medpace Contract Research Organization:** Dr. Richard Lee (Medical Monitor), James Creager (Clinical Trial Manager), Brian Knauf(Data Manager)
  - **Additional acknowledgements:** Dr. Desai acknowledges the contribution of Barbara Bittel, RN BSN and Susan Ospina MSN, CNP in the conduct of the trial.

Back-up slides

Correlation between site-read and core-lab read echocardiograms

	Core laboratory read echo	Site-read echo	Correlation, r	p-value
LV ejection fraction	64.8 ± 4.9	64.0 ± 6.1	0.46	<0.001
Valsalva LVOT gradient, mmHg	26.1 ± 26.6	24.3 ± 29.7	0.86	<0.001
Resting LVOT gradient, mmHg	15.2 ± 16.9	12.5 ± 17.7	0.90	<0.001



Data on 8 patients undergoing SRT

ValorHCM

Subject	Original treatment arm	Age	Sex	Mavacamten dose before SRT	LV ejection fraction at end of treatment prior to SRT	SRT type	End of treatment	Valsalva LVOT gradient (mm Hg) at end of treatment (pre-SRT)	Valsalva LVOT gradient (mm Hg) 24 weeks post-SRT	NYHA Class at 24 weeks post-SRT	Complications
1	Placebo*	55	male	0	70%	Myectomy	Week 8	75	13	I	None
2	Placebo*	45	male	0	68%	ASA	Week 8	10	8	I	None
3	Placebo to mavacamten crossover	57	male	5 mg	70%	ASA	Week 20	43	49	III	Needed a 2nd ASA
4	Placebo to mavacamten crossover	36	Female	15 mg	72%	Myectomy	Week 32	53	24	I	Wound cellulitis
5	Placebo to mavacamten crossover	62	Female	10 mg	67%	Myectomy	Week 56	102	8	I	Post-operative hypotension, thrombocytopenia, pneumothorax, hallucinations
6	Mavacamten	22	male	5 mg	68%	Myectomy	Week 28	73	18	I	None
7	Mavacamten	66	female	15 mg	71%	Myectomy	Week 16	46	12	II	Postoperative respiratory failure(COVID-19) and atrial fibrillation
8	Mavacamten	41	Female	5 mg	60%	Myectomy	Week 4	51	71	II	None

Final drug dosing

Final Dosing	Original mavacamten group N=56	Placebo crossover group N=52
Final dosing at Week 56		
2.5 mg	11 (19.6%)	6 (11.5%)
5 mg	17 (30.4%)	14 (26.9%)
10 mg	16 (28.6%)	23 (44.2%)
15 mg	12 (21.4%)	9 (17.3%)

Background therapy reduction table

	Placebo-to-mavacamten N=52	Original mavacamten N=56	Total N=108
Beta blocker (n=83 at baseline)			
Increased dose	3 (5.8)	2 (3.6)	5 (4.6)
Decreased dose	3 (5.8)	10 (17.9)	13 (12.0)
Maintained dose	32 (61.5)	33 (58.9)	65 (60.2)
Calcium channel blocker (n=38 at baseline)			
Increased dose	1 (1.9)	0	1 (0.9)
Decreased dose	2 (3.8)	3 (5.4)	5 (4.6)
Maintained dose	19 (36.5)	13 (23.2)	32 (29.6)
Disopyramide (n=19 at baseline)			
Increased dose	1 (1.9)	0	1 (0.9)
Decreased dose	0	2 (3.6)	2 (1.9)
Maintained dose	7 (13.5)	9 (16.1)	16 (14.8)

20 background HCM therapy dose reductions

OCTOBER trial

#ESCCongress

OCT-guided or angiography-guided PCI in complex bifurcation lesions

Conclusion

In patients with complex bifurcation lesions, optical coherence tomography (OCT)-guided percutaneous coronary intervention (PCI) is associated with better outcomes after 2 years than angiography-guided PCI.

Impact on clinical practice

The results suggest that routine use of structured OCT guidance during PCI of complex bifurcation lesions should be considered to improve prognosis.

Study objectives

OCTOBER was the first adequately powered clinical trial to examine whether routine use of OCT during PCI of complex bifurcation lesions improves clinical outcomes compared to standard practice with angiographic guidance and optional use of intravascular ultrasound (IVUS) in left main bifurcations.

Study population

Patients with complex bifurcation lesions requiring PCI

Where?

13 European countries

38 heart centres

Who and what?

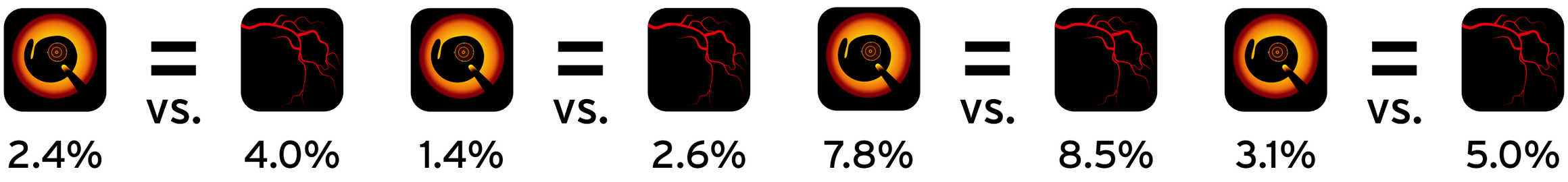
Primary endpoint

Major adverse cardiac events (MACE), defined as a composite of cardiac death, target lesion myocardial infarction, and ischaemia-driven target lesion revascularisation, after 2 years

Kaplan-Meier estimated hazard ratio 0.70
95% CI 0.50–0.98
p=0.035

Secondary endpoints

Differences in secondary clinical endpoints after 2 years did not reach statistical significance, but the trial was not powered for these endpoints



ESC

Late-Breaking Science

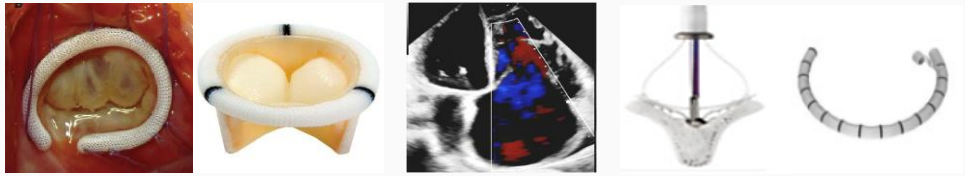
Registries on valvular heart disease

Friday 25th August, 2023

Timing of Intervention in Patients with Severe Tricuspid Regurgitation

Julien DREYFUS and David MESSIKA-ZEITOUN

On behalf of the TRIGISTRY investigators



Disclosure

Julien DREYFUS, MD, PhD

Proctor: Abbott

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BACKGROUND

- **Tricuspid regurgitation (TR) = Public health problem**
  - **Highly prevalent in the general population**
  - **Associated with an increased mortality and morbidity**

- **Isolated tricuspid valve surgery**
  - **Rarely performed and most patients conservatively managed**
  - **Associated with a high post-operative mortality**
  - **Strong evidence regarding benefit of TR correction is still lacking**

- **Transcatheter intervention**
  - **Represent a less invasive alternative to surgery**
  - **Dominant mode of TR correction in several countries**
  - **TRILUMINATE did not to show any improvement on mortality or heart failure admissions at one year**

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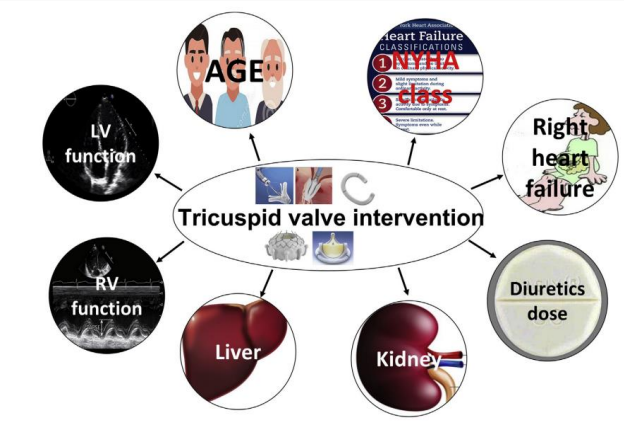
BACKGROUND

- **Clinical presentation**
  - Main driver of the post-operative outcome
  - Intervention performed late in the course of the disease → high in-hospital mortality rate / poor outcome
- **TRI-SCORE**
  - Predict in-hospital mortality after isolated tricuspid valve surgery at the individual level
  - Ideally suited to stage TR populations

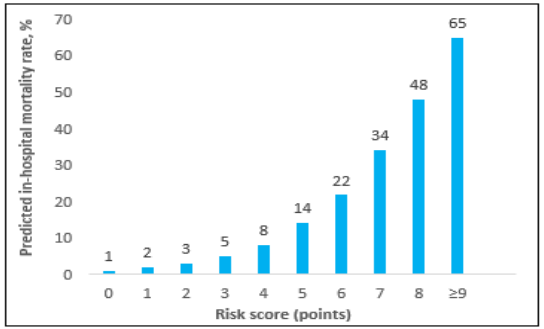


TRI-SCORE

Risk factors and scoring system for in-hospital mortality after isolated tricuspid valve surgery

Risk factors (final model from multivariate analysis)	Scoring
Age ≥ 70 years	1
NYHA functional class III-IV	1
Right-sided heart failure signs	2
Daily dose of furosemide ≥ 125mg	2
Glomerular filtration rate < 30 ml/min	2
Elevated total bilirubin	2
Left ventricular ejection fraction < 60%	1
Moderate/severe right ventricular dysfunction	1
Total	12

Predicted in-hospital mortality rate according to the final risk score model



Messika-Zeitoun D et al. JACC Intv 2022; Dreyfus J et al. EHJ 2021; Dreyfus J et al. EHJ 2023

AIM

To evaluate whether the benefit of an intervention and its modality vary according to TR disease stage as assessed using the TRI-SCORE

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TRIGISTRY

- **Multicenter international registry**
  - **Adult patients with severe functional TR on native valve**
  - **Isolated TR (< moderate concomitant left-sided valvular heart disease, no aortic or mitral valve intervention (either surgical or transcatheter) within 3 months)**
  - **TRI-SCORE available (8 mandatory parameters)**
  - **> 30 centers, 10 countries**

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TRIGISTRY PARTICIPATING CENTERS

AUSTRIA:
- Medical University of Vienna, VIENNA

CANADA:
- University of Ottawa Heart Institute, OTTAWA
- Quebec Heart and Lung Institute, QUEBEC CITY
- Toronto Heart Center, St. Michael's Hospital, TORONTO
- St. Paul Hospital, VANCOUVER

FRANCE :
- Amiens University Hospital, AMIENS
- Bichat Hospital, Université de Paris, PARIS
- Louis Pradel Cardiovascular Hospital, BRON
- Henri Mondor Hospital, CRÉTEIL
- CHU Lille, LILLE
- APHM, La Timone Hospital, MARSEILLE
- CHU Nancy-Brabois, NANCY
- Université de Nantes, CHU de Nantes, NANTES
- CHU de Rennes, RENNES
- CHU Charles Nicolle, ROUEN
- Centre Cardiologique du Nord, SAINT-DENIS
- Toulouse University Hospital, TOULOUSE

GERMANY:
- University Hospital of the Ruhr University Bochum, BAD OEYNHAUSEN
- Heart Center University Hospital, BONN
- Faculty of Medicine and University Hospital Cologne, COLOGNE
- Helios Klinikum Erfurt, ERFURT
- CardioVascular Center Frankfurt, FRANKFURT AM MAIN
- Albertinen Heart Center, HAMBURG
- Asklepios Klinik Sankt Georg, HAMBURG
- University Heart and Vascular Center, HAMBURG
- Heart Center Leipzig at University of Leipzig, LEIPZIG
- University Medical Center, MAINZ
- University Hospital of Munich, MUNICH

ISRAEL:
- Tel Aviv Medical Center, Sackler Faculty of Medicine, TEL AVIV

ITALY:
- Istituto Auxologico Italiano, IRCCS, MILAN
- Vita-Salute San Raffaele University, IRCCS San Raffaele Hospital, MILAN

SPAIN:
- Hospital Clínico San Carlos, MADRID
- Hospital 12 de Octubre, MADRID
- Hospital Universitario Ramón y Cajal, MADRID
- University Hospital Alvaro Cunqueiro, VIGO

SWITZERLAND:
- Inselspital, University of Bern, BERN
- Cardiocentro Ticino Institute, EOC, LUGANO
- Zurich University Hospital, ZURICH

THE NETHERLANDS:
- Leiden University Medical Center, LEIDEN

USA:
- Montefiore Medical Center, NEW YORK
- Mount Sinai Health System, NEW YORK
- New-York-Presbyterian/Columbia University Medical Center, NEW YORK
- Mayo Clinic, ROCHESTER

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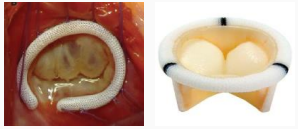
METHODS – THE THREE TREATMENT MODALITIES

- **Medical therapy**: no surgical or transcatheter intervention

- **Surgery**: isolated tricuspid valve surgery (repair or replacement) (no concomitant intervention: mitral or aortic valve, coronary artery bypass graft…)



- **Transcatheter valve repair**: multiple repair techniques (no transcatheter valve replacement)

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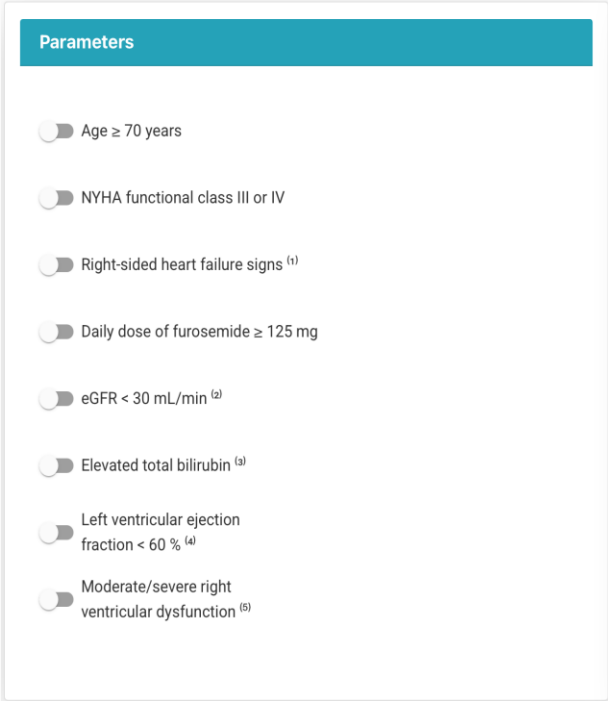
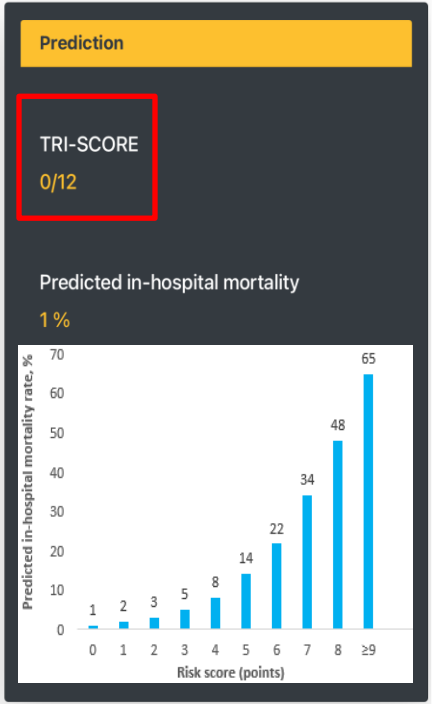
METHODS – TRI-SCORE CATEGORIES

Clinical stage as assessed using the TRI-SCORE:

- Low risk: TRI-SCORE ≤ 3
- Intermediate risk: TRI-SCORE 4-5
- High risk: TRI-SCORE ≥ 6

www.tri-score.com





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Survival rate at 2 years

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RESULTS

2413 patients

with severe isolated functional tricuspid regurgitation on native valve

1217 patients

MEDICAL THERAPY

551 patients

ISOLATED TRICUSPID VALVE SURGERY

645 patients

TRANSCATHETER VALVE REPAIR

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RESULTS – BASELINE CHARACTERISTICS

Characteristics	Overall (N=2413)
Age – years	72±12
Female sex – no. (%)	1270 (53)
New York Heart Association functional class III-IV – no. (%) *	1562 (65)
Right-sided heart failure signs – no. (%) *	1431 (59)
Atrial fibrillation – no./total no. (%)	1532/2317 (66)
Glomerular filtration rate <30ml/min – no. (%) *	266 (11)
Elevated total bilirubin – no. (%) *	688 (29)
Left Ventricle ejection fraction – %	51±14
Moderate/severe right ventricular dysfunction – no. (%) *	1001 (41)
TRI-SCORE	5 [3-6]
≤3 – no. (%)	764 (32)
4-5 – no. (%)	800 (33)
≥6 – no. (%)	849 (35)

Values are number of patients (percentage), mean ± standard deviation or median [inter-quartiles].
* Parameters included in the TRI-SCORE

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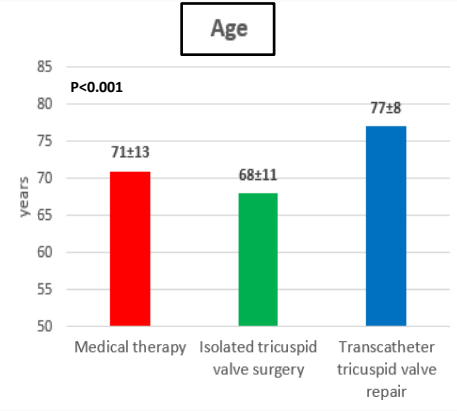
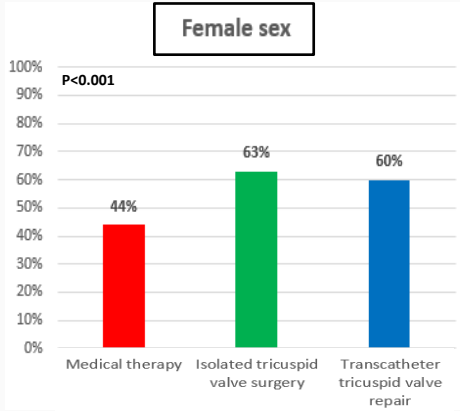
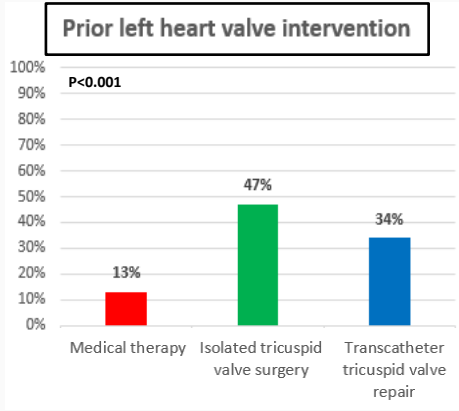
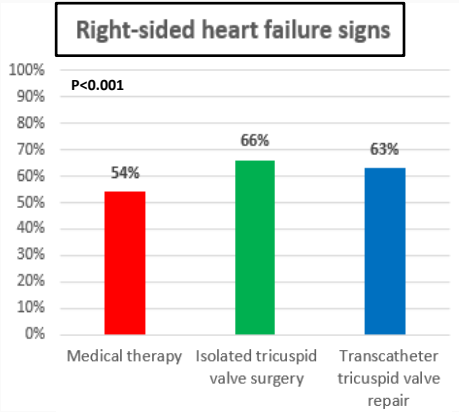
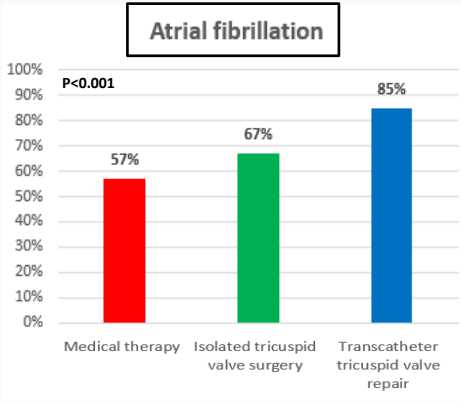
RESULTS – BASELINE CHARACTERISTICS

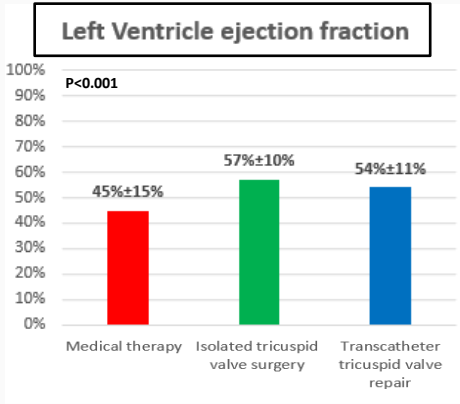


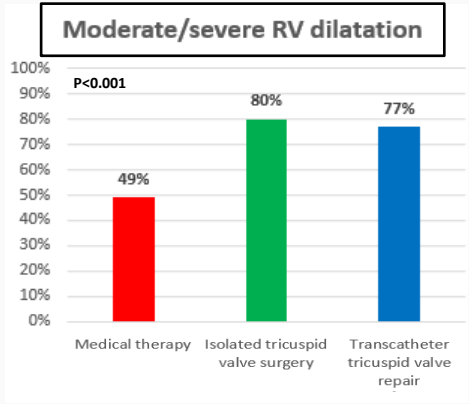


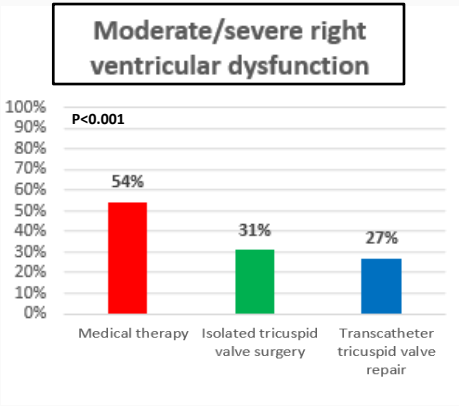












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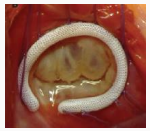
RESULTS

INTERVENTION

551 patients

ISOLATED TRICUSPID VALVE SURGERY

- **200 patients (36%)** — **REPAIR**
- **351 patients (64%)** — **REPLACEMENT**
  - BIOPROSTHESIS: 319 patients (91%)
  - MECHANICAL VALVE: 32 patients (9%)



645 patients

TRANSCATHETER VALVE REPAIR

- **509 patients (76%)** — **EDGE-TO-EDGE REPAIR**
  - MITRACLIP: 231 patients (45%)
  - TRICLIP: 109 patients (22%)
  - PASCAL: 169 patients (33%)
- **136 patients (24%)** — **ANNULOPLASTY**
  - CARDIOBAND: 125 patients (90%)
  - Others: 11 patients (8%)

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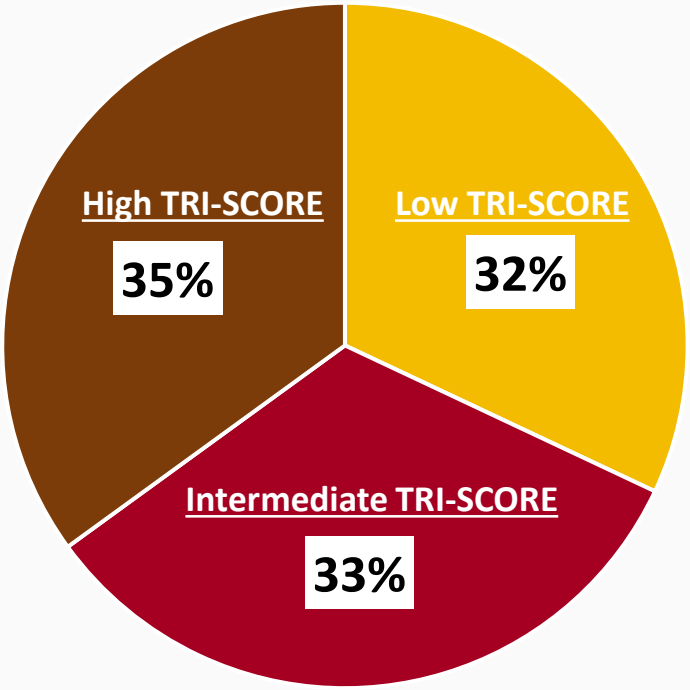
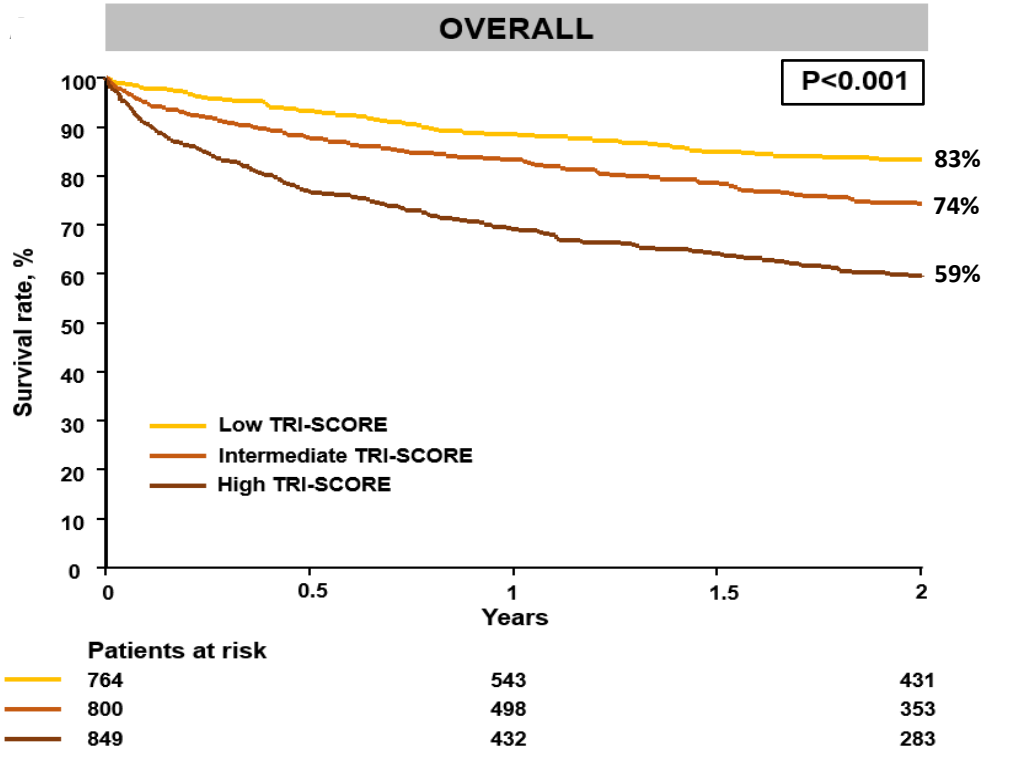
RESULTS - IMPACT OF TRI-SCORE





Result remained unchanged after adjustment for age, sex, atrial fibrillation and comorbidities* (P<0.001)

*diabetes, chronic lung disease, coronary artery disease, and prior left heart valve intervention

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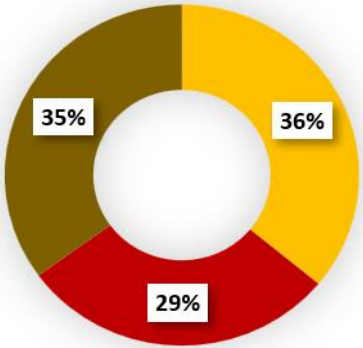
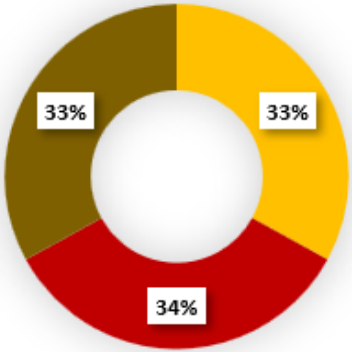
RESULTS - IMPACT OF TRI-SCORE

TRI-SCORE

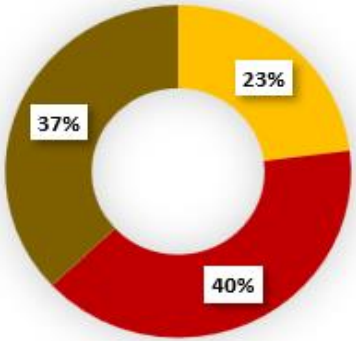
Medical therapy



Isolated tricuspid valve surgery



Transcatheter tricuspid valve repair



- Low TRI-SCORE
- Intermediate TRI-SCORE
- High TRI-SCORE

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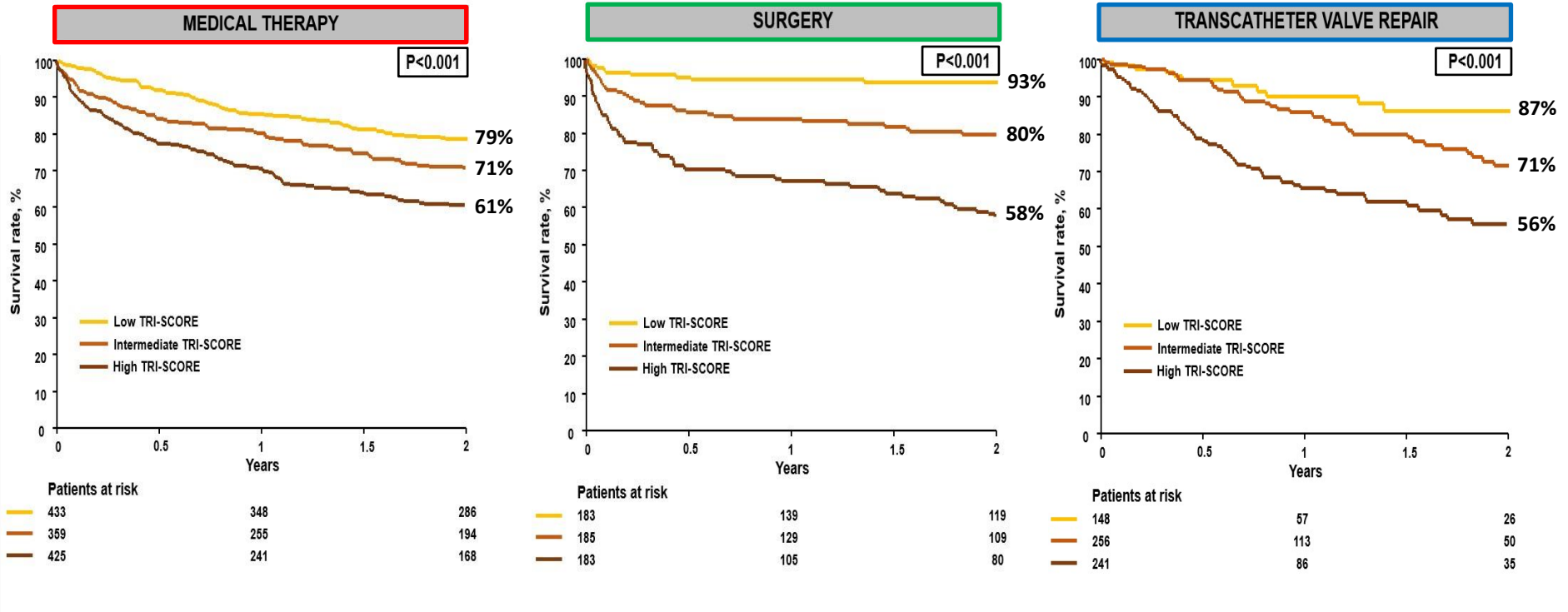
RESULTS - IMPACT OF TRI-SCORE



Results remained unchanged after adjustment for age, sex, atrial fibrillation and comorbidities* (all P<0.001)

*diabetes, chronic lung disease, coronary artery disease, and prior left heart valve intervention

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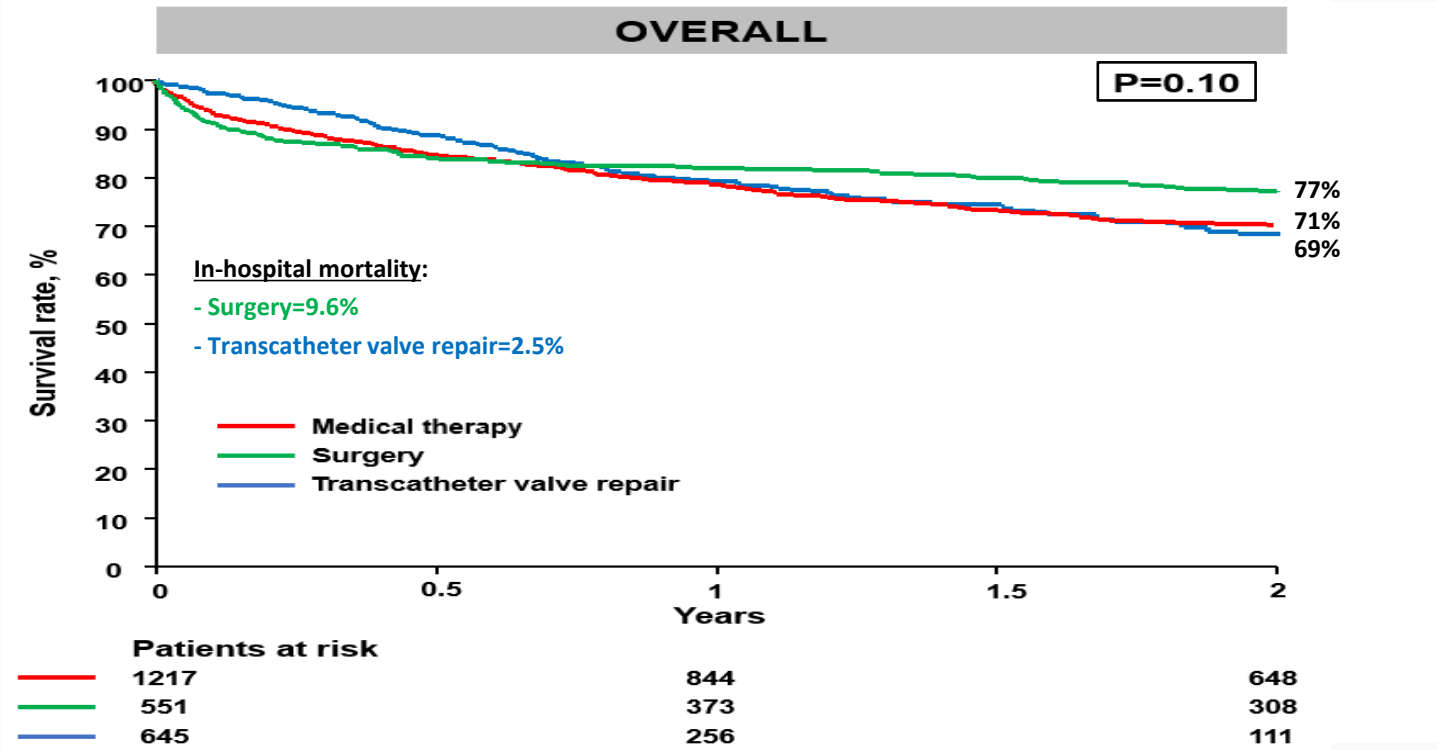
RESULTS – IMPACT OF TREATMENT MODALITY



Result remained unchanged after adjustment for age, sex, atrial fibrillation and comorbidities (P=0.23)

* diabetes, chronic lung disease, coronary artery disease, and prior left heart valve intervention

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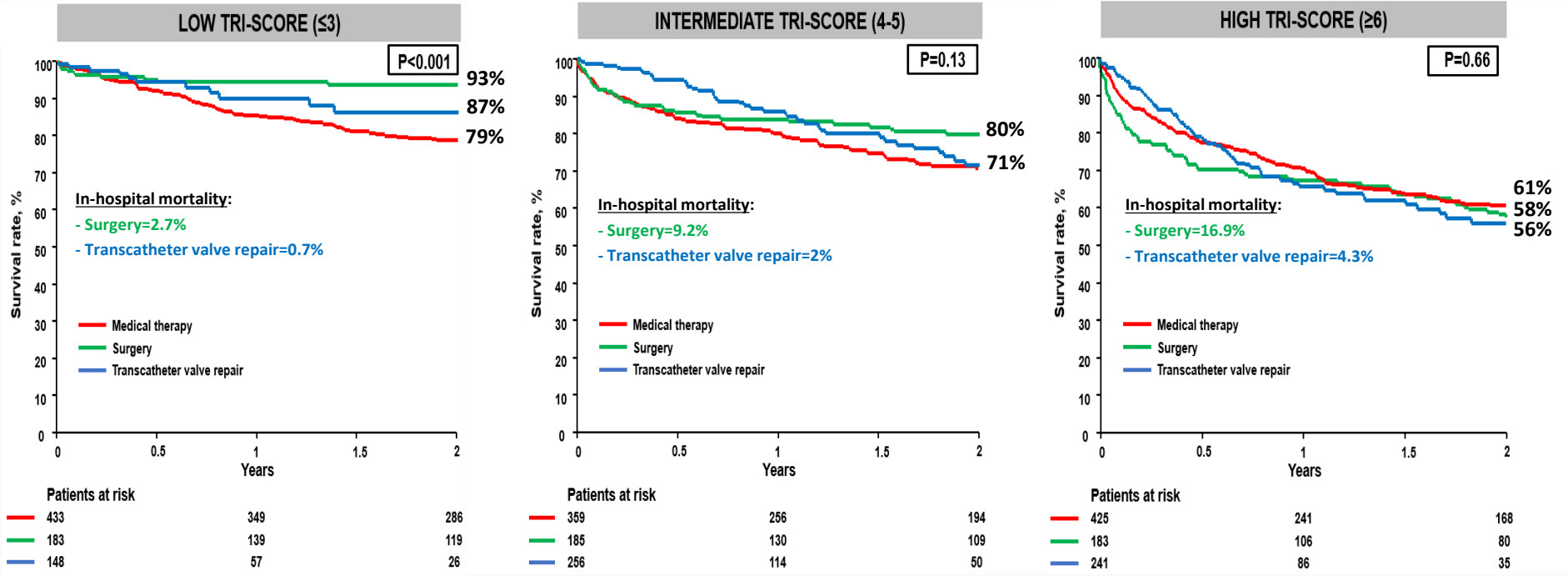
RESULTS - IMPACT OF TREATMENT MODALITY



Results remained unchanged after adjustment for age, sex, atrial fibrillation and comorbidities*

P=0.006 for low TRI-SCORE

P=0.15 for intermediate TRI-SCORE

P=0.48 for high TRI-SCORE

*diabetes, chronic lung disease, coronary artery disease, and prior left heart valve intervention

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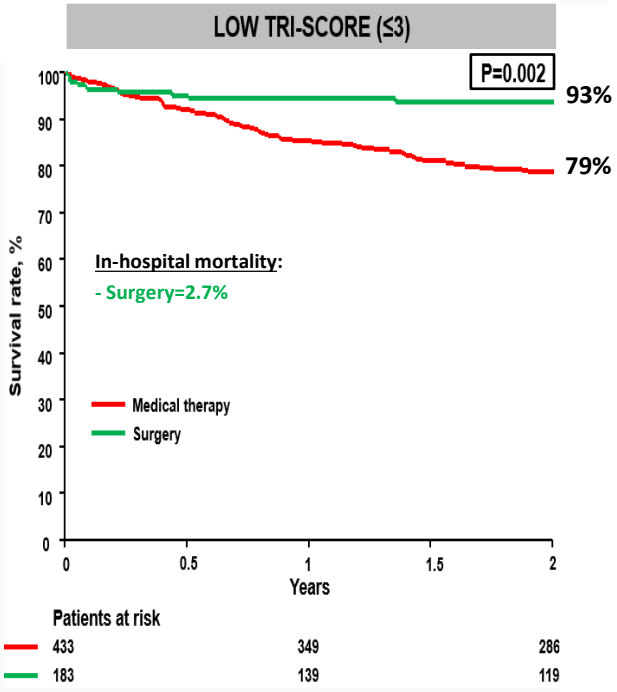
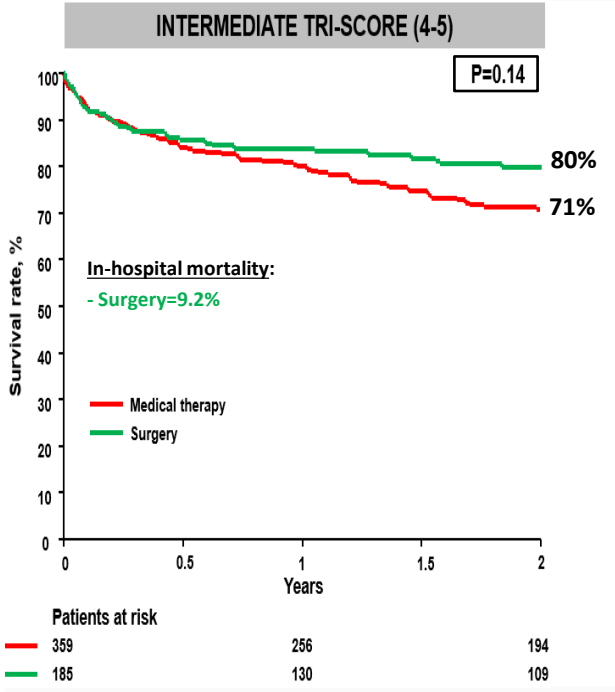
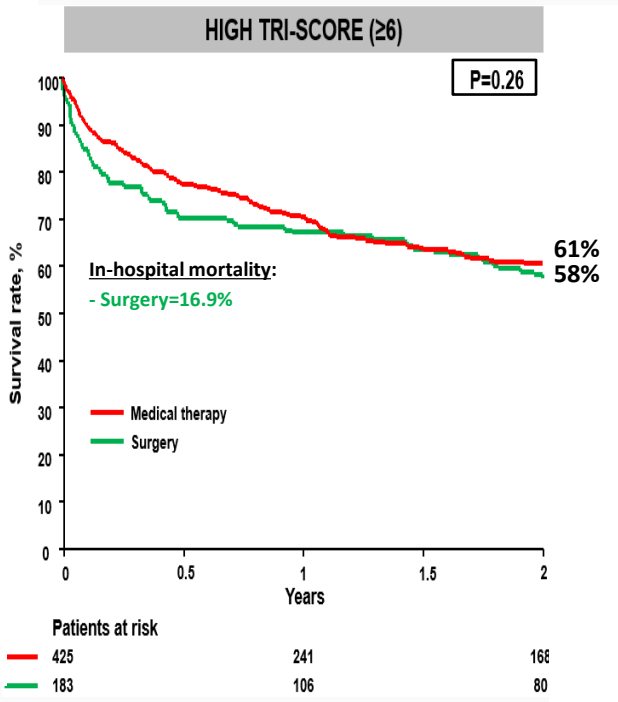
RESULTS - IMPACT OF TREATMENT MODALITY

- **Surgery vs medical therapy**







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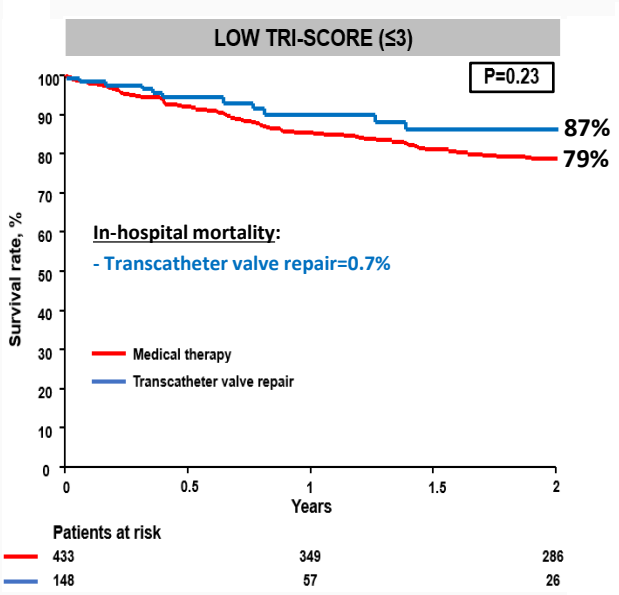
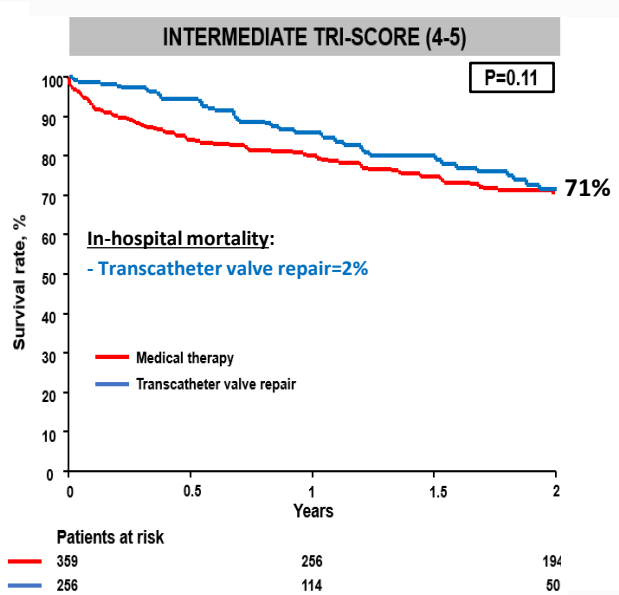
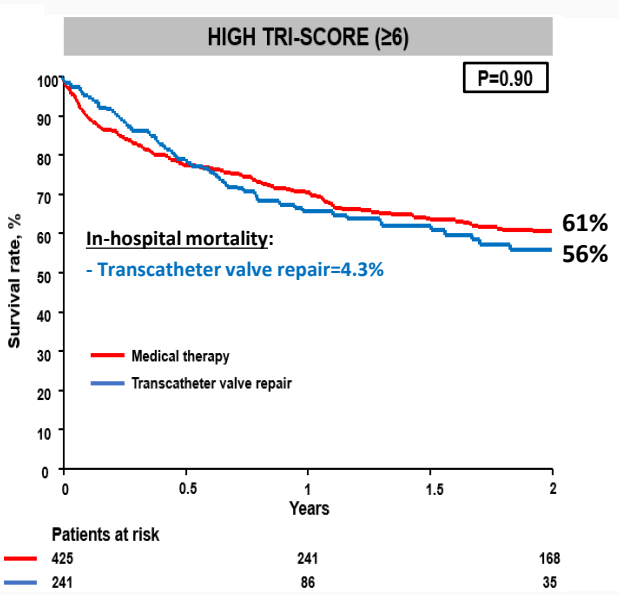
RESULTS - IMPACT OF TREATMENT MODALITY

Transcatheter valve repair vs medical therapy







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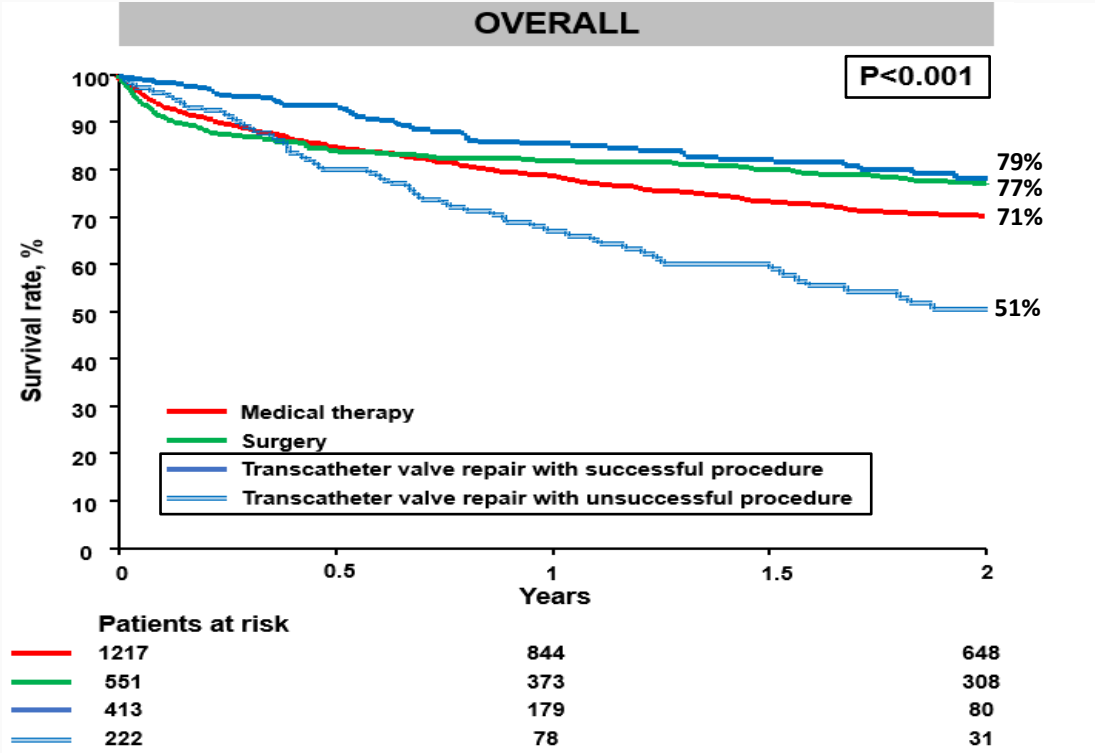
RESULTS – IMPACT OF RESIDUAL TR

<u>Procedural success</u>: TR ≤ mild to moderate (2+) at discharge (after surgery or transcatheter intervention)

- **Surgery = 97%**

- **Transcatheter = 65%**



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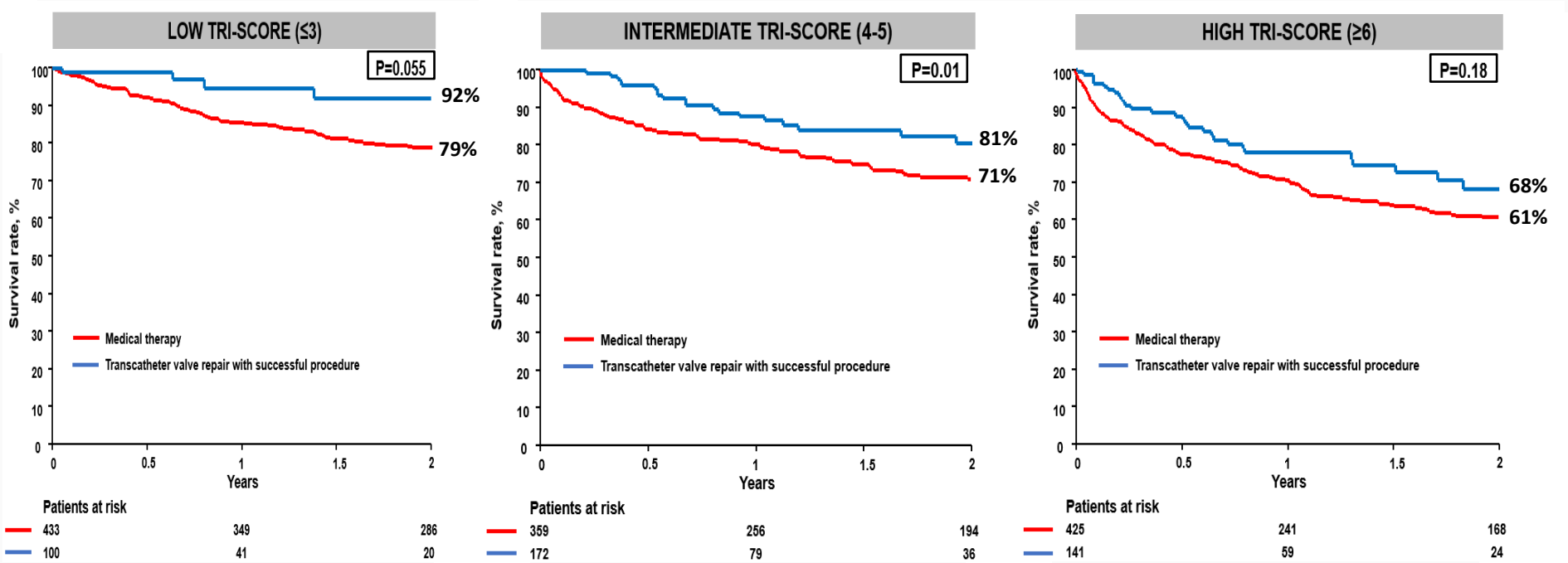
RESULTS – IMPACT OF RESIDUAL TR

➢ Transcatheter valve repair with successful procedure vs medical therapy



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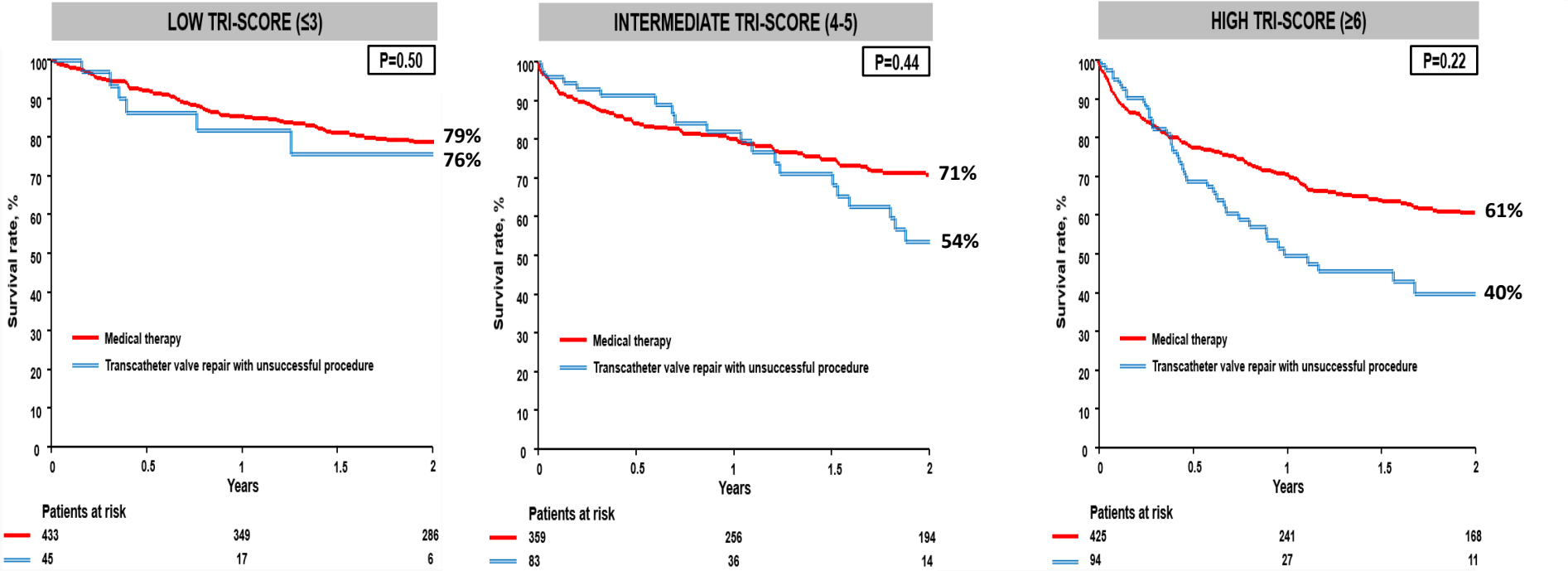
RESULTS – IMPACT OF RESIDUAL TR

- **Transcatheter valve repair with unsuccessful procedure vs medical therapy**



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CONCLUSIONS

1. TRIGISTRY confirms and extends the predictive value of the TRI-SCORE irrespectively of treatment modality at 2 years

2. A tricuspid valve intervention was associated with better survival rates than medical therapy at 2 years in the low and, to a lower extent, intermediate TRI-SCORE categories while survival was similar across groups in the high TRI-SCORE category

3. TRIGISTRY highlighted the prognostic importance of optimal TR correction

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PERSPECTIVES

- Our results suggest that, in patients with severe TR, a curative intervention should be considered at an early stage of the disease as assessed by the TRI-SCORE

- TRIGISTRY will guide the design of future randomized controlled trials aiming to formally demonstrate the benefit of tricuspid valve interventions

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WINDECKER Stephan
ZAMORANO Jose Luis

OCTIVUS trial

OCT- vs. IVUS-Guided PCI

#ESCCongress

Conclusion

Optical coherence tomography (OCT) is non-inferior to intravascular ultrasound (IVUS) for guiding percutaneous coronary intervention (PCI) in patients with diverse coronary artery lesions.

Impact on clinical practice

The results add compelling evidence on the relative efficacy and safety of an OCT-guided strategy compared with an IVUS-guided strategy for PCI.

Study objectives

The OCTIVUS trial was a head-to-head comparison of OCT- and IVUS-guided PCI with regards to clinical outcomes in patients with a broad range of coronary artery lesions.

Study population

Patients

- aged ≥19 years
- undergoing PCI with contemporary drug-eluting stents or drug-coated balloons (only for in-stent restenosis) for significant coronary artery lesions

Where?

South Korea — 9 sites

Who and what?

2,008 patients

randomised 1:1

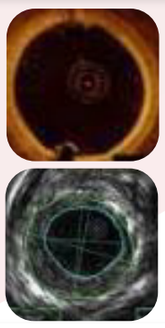
OCT-guided PCI

IVUS-guided PCI

after diagnostic coronary angiography

Primary endpoint

Composite of death from cardiac causes, target vessel myocardial infarction or ischaemia-driven target vessel revascularisation at 1 year, which was powered for noninferiority of the OCT group as compared with the IVUS group (noninferiority margin, 3.1 percentage points)



Rate%

2.5%

3.1%

risk difference, −0.6 percentage points
upper boundary of the one-sided
97.5% CI 0.97; p<0.001 for noninferiority

Safety endpoints

Incidence of contrast-induced nephropathy was similar

 = 

1.4% 1.5%

Incidence of major procedural complications was lower with

 vs.  p=0.048

2.2% 3.7%

ESC

FFR- versus Angiography-Guided Multivessel Revascularization in ST-Elevation Myocardial Infarction Patients

The FLOWER MI trial : 3-year outcomes

Nicolas DANCHIN, MD, on behalf of Etienne PUYMIRAT and the FLOWER-MI investigators

27 August 2023

Disclosures – Nicolas Danchin, MD

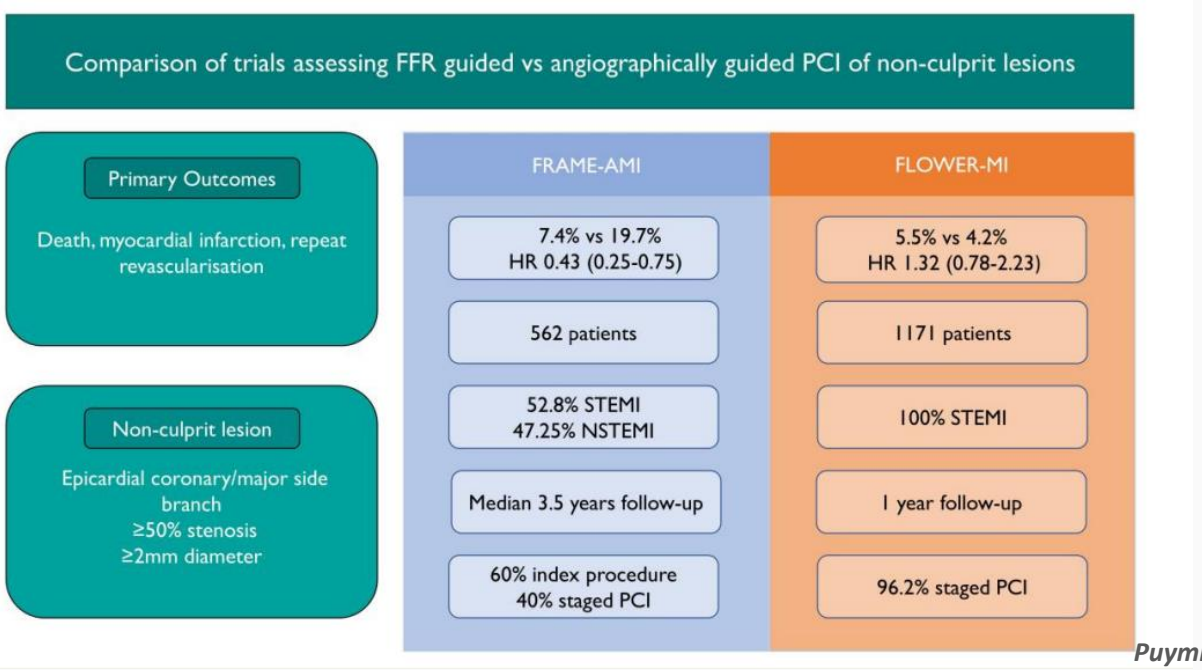
Within the 36 past months, I has/had a financial interest/arrangement or affiliation with the organization(s) listed below.

Financial Relationship	Company
• Research Support	None
• Lecture and/or Consulting Fees	Amgen, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Maincare, MSD, Pfizer, Sanofi, Servier, Socar, UCB

FLOWER-MI is an academic study, funded by a grant from the "Programme Hospitalier de Recherche Clinique» (PHRC) issued by the French Ministry of Health. The study was sponsored by Assistance Publique-Hôpitaux de Paris, with an unrestricted grant from Abbott which provided the coronary pressure guidewire (Radi Medical Systems)

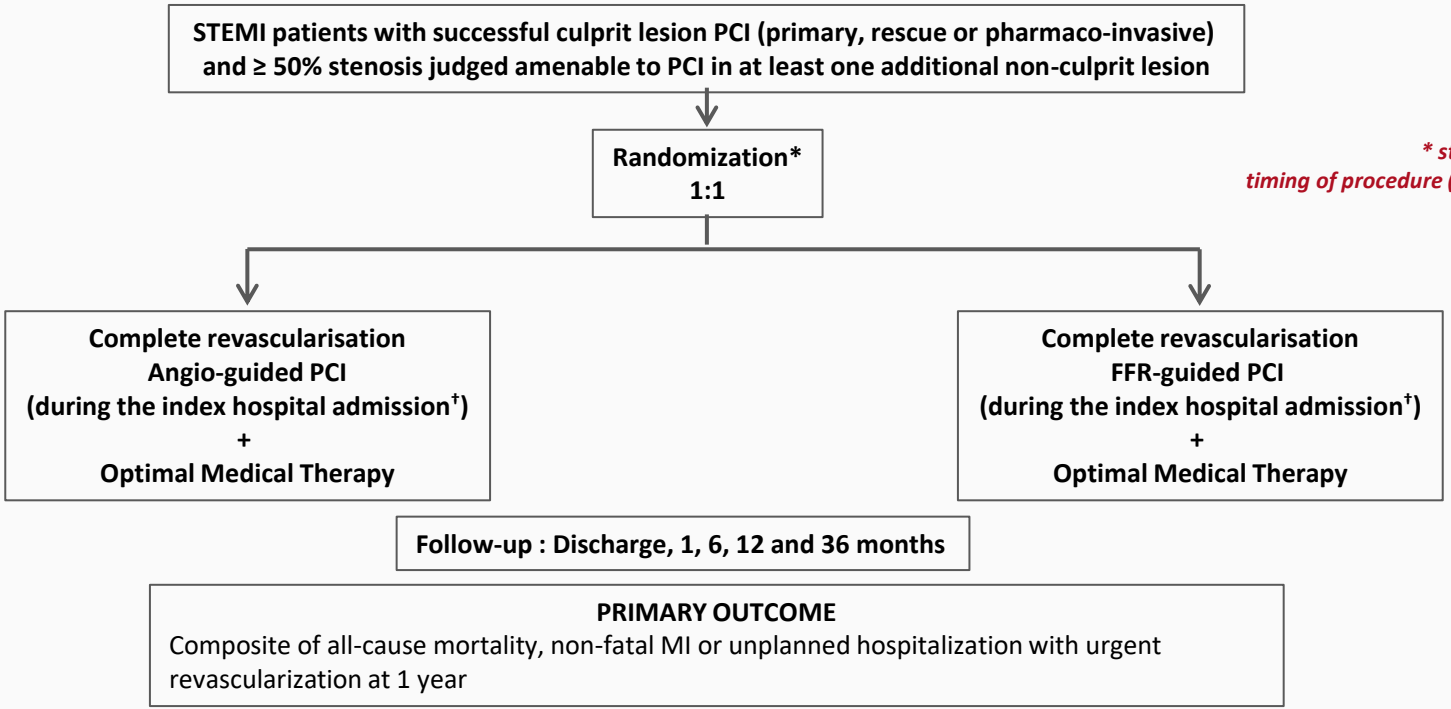
Background

- The value of a fractional flow reserve (FFR)-guided strategy for non-culprit lesions in AMI patients is controversial



Mehta SR et al. EHJ 2023
Lee JM et al. EHJ 2023
Puymirat E et al. N Engl J Med 2021

FLOWER MI Study Design



Anticipated rate of primary EP at one year 9.5% vs 15%

Puymirat E et al. Am Heart J 2020

Patient selection

INCLUSION CRITERIA

STEMI patients

Age ≥18 y

Successful culprit lesion PCI (primary, rescue or pharmaco-invasive) and ≥50% stenosis judged amenable to PCI in at least one additional non-culprit lesion

Willing and able to provide informed, written consent

EXCLUSION CRITERIA

Cardiogenic shock

Previous coronary bypass surgery

Extremely tortuous, calcified coronary vessels or CTO

Patients with single-VD

MVD patients referred to surgery

Hypersensitivity to adenosine

Life expectancy <2 years

Pregnancy

Participation in another study

Participant not affiliated to the French social security

Baseline characteristics

Characteristics	FFR-Guided PCI (n=586)	Angio-Guided PCI (n=577)
Age (year)	62.5 ± 11.0	61.9 ± 11.4
BMI (kg/m²)	26.7 (24.2-29.1)	26.6 (24.4-29.7)
Male	85.0	81.1
Hypertension	43.2	45.4
Diabetes mellitus	18.3	14.2
Hypercholesterolemia	39.6	41.1
Current smoker	40.1	36.4
Previous MI	7.7	5.4
Previous PCI	10.1	7.6
Previous stroke	2.7	3.0
Peripheral-vessel disease	2.7	4.0
Chronic renal insufficiency	1.9	12.1

Clinical presentation	FFR-Guided PCI (n=586)	Angio-Guided PCI (n=577)
Location of infarction		
• Anterior	29.8	34.6
Arteries with stenosis		
• 2	72.4	77.5
• 3	25.8	19.9
Killip class ≥ 2	6.7	5.3
LVEF (%)	50 (45-60)	50 (45-58.3)

Procedural Data

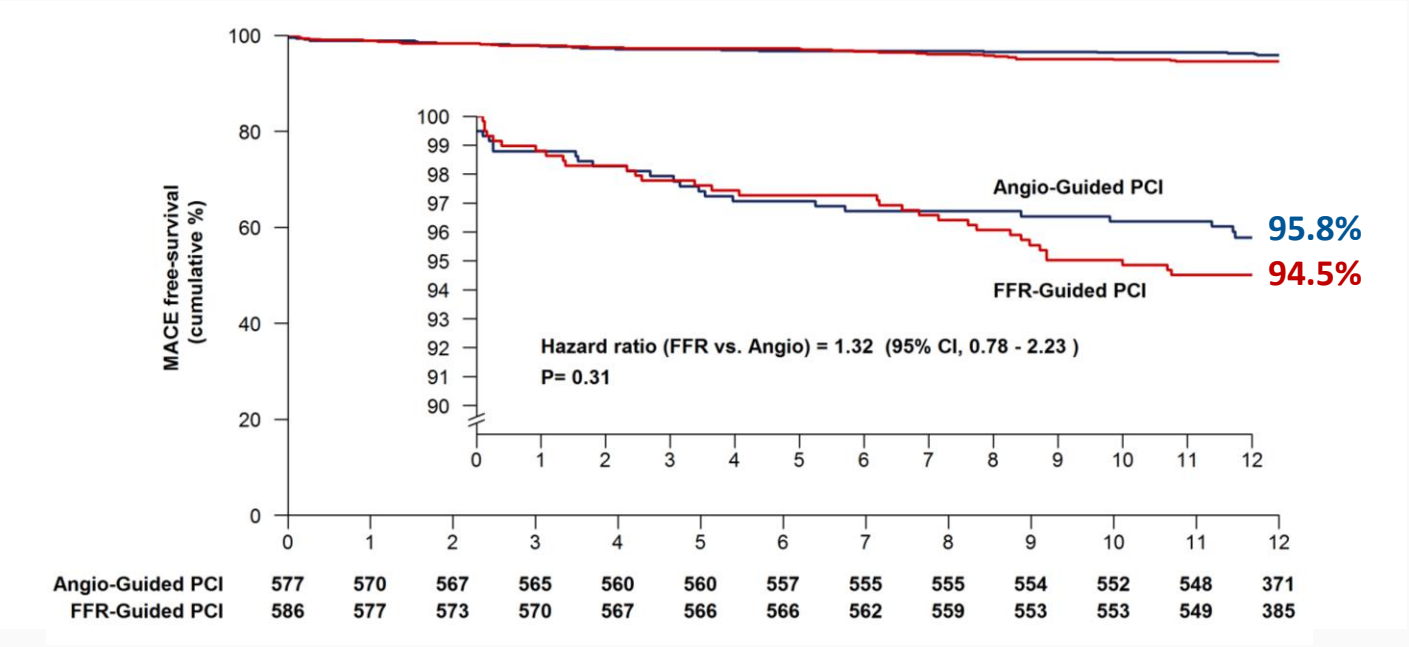
Characteristics of lesions	FFR-Guided PCI (n=586)	Angio-Guided PCI (n=577)
Location of CL ‡		
• LMCA	3/718 (0.4)	4/706 (0.6)
• LAD	222/718 (30.9)	241/706 (34.1)
• LCX	135/718 (18.8)	144/706 (20.4)
• RCA	358/718 (49.9)	317/706 (44.9)
Location of non-CL ‡		
• LMCA	7/980 (0.7)	9/891 (1.0)
• LAD	458/980 (46.7)	402/891 (45.1)
• LCX	303/980 (30.9)	262/891 (29.4)
• RCA	212/980 (21.6)	218/891 (24.5)
Diameter of non-CL (mm)	2.86 ± 0.48	2.97 ± 0.53

PCI of non-culprit lesion	FFR-Guided PCI (n=586)	Angio-Guided PCI (n=577)
Staged procedure of non-CL	96.6	95.8
FFR procedure attempted†	95.7	NA
Mean FFR value		
• FFR before PCI	0.79 ± 0.11	NA
• FFR post PCI	0.90 ± 0.06	NA
Lesions with FFR ≤0.80	55.7	NA
PCI (≥1) per patient	**66.2**	**97.1***
Mean no. of stents used†	**1.01 ± 0.99**	**1.50 ± 0.86***
Type of stent used		
• Zotarolimus eluting	16.1	13.5
• Sirolimus eluting	17.9	20.0
• Everolimus eluting	51.9	52.8
• Others drug-eluting	13.2	12.9
• Bare-metal stent	0.8	0.7

‡ no./total no. of lesions (%); † per patient
** < 0,01*
CL, culprit lesion

Primary outcome at 1 Year

FFR-guided strategy was not superior to an angiography-guided strategy for reducing the risk of the composite of death from any cause, non-fatal MI, and unplanned hospitalization leading to urgent revascularization at 1-year



Low event rates of MACE at 1 year: 4.2% / 5.5%

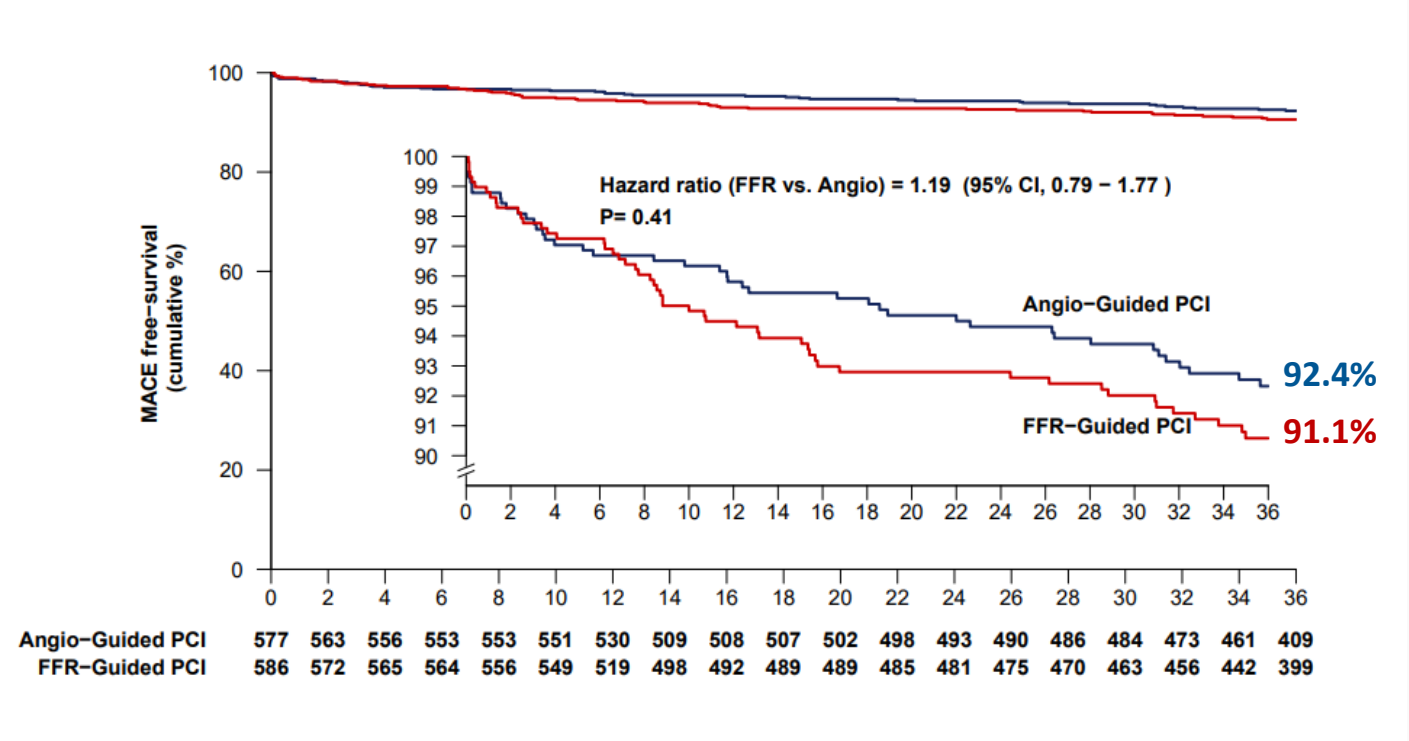
** Major Adverse Cardiac Events (MACE) denotes the composite of all-cause mortality, nonfatal MI, and unplanned hospitalization leading to urgent revascularization*

Puymirat E et al. N Engl J Med 2021

Purpose

- The pre-specified extension phase of the FLOWER MI trial was designed to determine whether a difference in outcomes would be observed beyond the initial one-year follow-up

Primary outcome at 3 Years



Low event rates of MACE at 3 years: 7.6% / 8.9%

** Major Adverse Cardiac Events (MACE) denotes the composite of all-cause mortality, nonfatal MI, and unplanned hospitalization leading to urgent revascularization*

Primary and secondary outcomes at three years

Primary outcome at 3 years	FFR-Guided PCI (n=586)	Angio-Guided PCI (n=577)	HR (95% CI)	P Value
MACE*	8.9 (n=52)	7.6 (n=44)	1.19 (0.79-1.77)	0.41
Death from any cause	3.8 (n=22)	4.0 (n=23)	0.96 (0.53-1.71)	-
Myocardial infarction	3.9 (n=23)	2.4 (n=14)	1.63 (0.84-3.16)	-
Unplanned hospitalization leading to urgent revascularization	3.6 (n=21)	3.1 (n=18)	1.15 (0.61-2.16)	-

** Major Adverse Cardiac Events (MACE) denotes the composite of all-cause mortality, nonfatal MI, and unplanned hospitalization leading to urgent revascularization*

Prespecified clinical outcomes at 3 Years

Secondary outcomes at 3 years	FFR-Guided PCI (n=586)	Angio-Guided PCI (n=577)	HR (95% CI)
Stent thrombosis (%)	0.7	1.2	0.56 (0.16-1.91)
Any revascularization (%)	9.0	7.1	1.30 (0.86-1.95)
Hospitalization for heart failure (%)	1.7	2.6	0.66 (0.29-1.48)
Hospitalization for recurrent ischemia (%)	7.5	5.0	1.54 (0.96-2.46)
Any hospitalization in Cardiology (%)	15.7	12.1	1.34 (0.98-1.83)

Functional status at 3 years	FFR-Guided PCI (n=586)	Angio-Guided PCI (n=577)	HR (95% CI)
Number of anti-anginal medications used *	0.88 ± 0.5	0.9 ± 0.5	0.98 (0.86-1.12)
QALY based on EQ-5D score	0.88 ± 0.14	0.87 ± 0.23	-0.01 (-0.03-0.02)

** Antianginal medications included beta-blockers, calcium antagonists, and nitrates. Rate of means estimated by a negative binomial model*

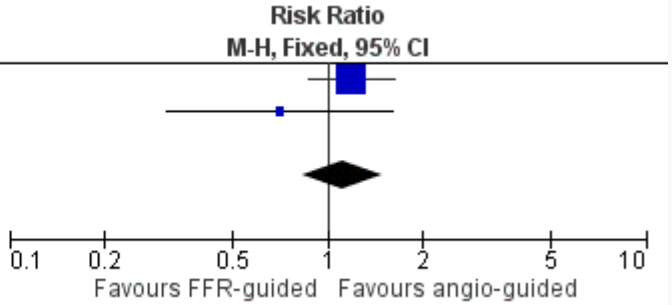
Analysis of FFR-guided versus angio-guided PCI in STEMI patients with multivessel disease: a pooled analysis of the FRAME-AMI and FLOWER-MI trials

Composite outcomes (death, re-MI or any repeat revascularization) in the FRAME-AMI and FLOWER-MI trials

Study or Subgroup	FFR-guided Events	FFR-guided Total	Angio-guided Events	Angio-guided Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FLOWER-MI 2023	76	577	65	586	83.4%	1.19 [0.87, 1.62]
FRAME-AMI 2023	9	131	13	134	16.6%	0.71 [0.31, 1.60]
Total (95% CI)		**708**		**720**	**100.0%**	**1.11 [0.83, 1.48]**
Total events	85		78			

Heterogeneity: Chi² = 1.35, df = 1 (P = 0.25); I² = 26%

Test for overall effect: Z = 0.69 (P = 0.49)



Conclusions

- **In patients presenting with STEMI and MVD treated with multivessel revascularization during the index hospitalization:**
  - Event rates up to 3 years are low
  - FFR-guided PCI of non-infarct-related lesions does not reduce the risk of a composite outcome of death, re-infarction or urgent revascularization at 3-years, as compared with an angiography-guided strategy
  - A pooled analysis using data from the FLOWER-MI and FRAME-AMI trials confirms the lack of benefit of an FFR-guided versus angio-guided strategy in STEMI patients with multivessel disease

Acknowledgements

Steering committee:
Chair: E. Puymirat
Scientific Coordinator: N. Danchin, B. De Bruyne
Members: B. De Bruyne; G. Cayla; G. Chatelier; N. Danchin; G. Montalescot, T. Simon, P.G. Steg

Clinical events committee: D. Blanchard (chair), M.A. Isorni, D. Foissier
Medico-economic analysis: I. Durand-Zaleski, A. Le Bras (Clinical Research Unit Eco Ile de France, Hôpital Hôtel Dieu, Assistance Publique - Hôpitaux de Paris (AP-HP), Paris, France)
Biostatistics / Methodology: G. Chatelier, A. Charles Nelson (Clinical Research Unit, Hôpital européen Georges-Pompidou, AP-HP, Paris, France)
Administration sponsorship and coordination : AP-HP, Paris, France; J. Djadi-Prat (project leader); H. Manseur
Methodology / Academic Research Organization (ARO): French Alliance for Cardiovascular Clinical Trials (FACT) /French Clinical Research Infrastructure Network (FRCIN): N. Danchin, T. Simon, P.G. Steg

The authors are deeply indebted to all patients who accepted to participate in the surveys, and to the physicians who took care of the patients at the participating institutions.

Meta-analysis of iFR-SWEDEHEART and DEFINE-FLAIR

Five-year major cardiovascular events are increased when coronary revascularization is guided by instantaneous wave-free ratio compared to fractional flow reserve: a pooled analysis of iFR-SWEDEHEART and DEFINE-FLAIR trials

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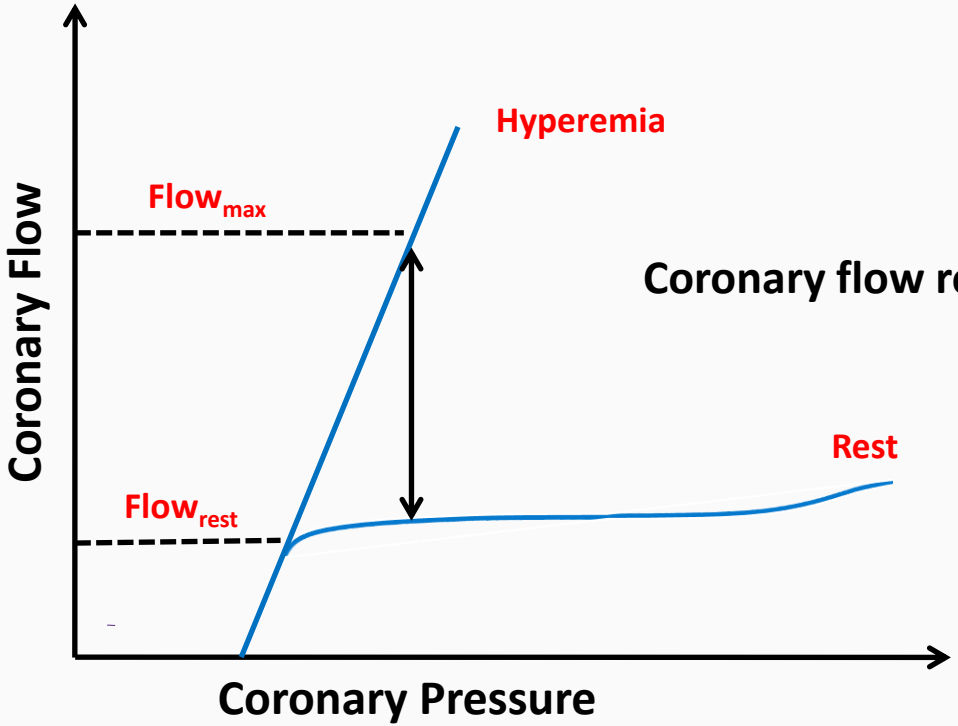
Jelmer Westra
Niels Thue Olesen
Niels Henrik Bruun
Lisette Okkels Jensen
Thomas Engstrøm
Evald Høj Christiansen

August 27th, 2023

Conflicts of interests

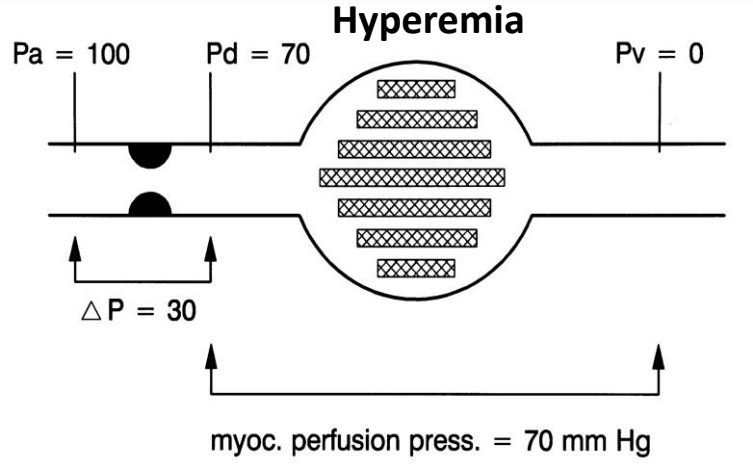
- I do not have any potential conflict of interest to declare

Coronary Flow and Pressure

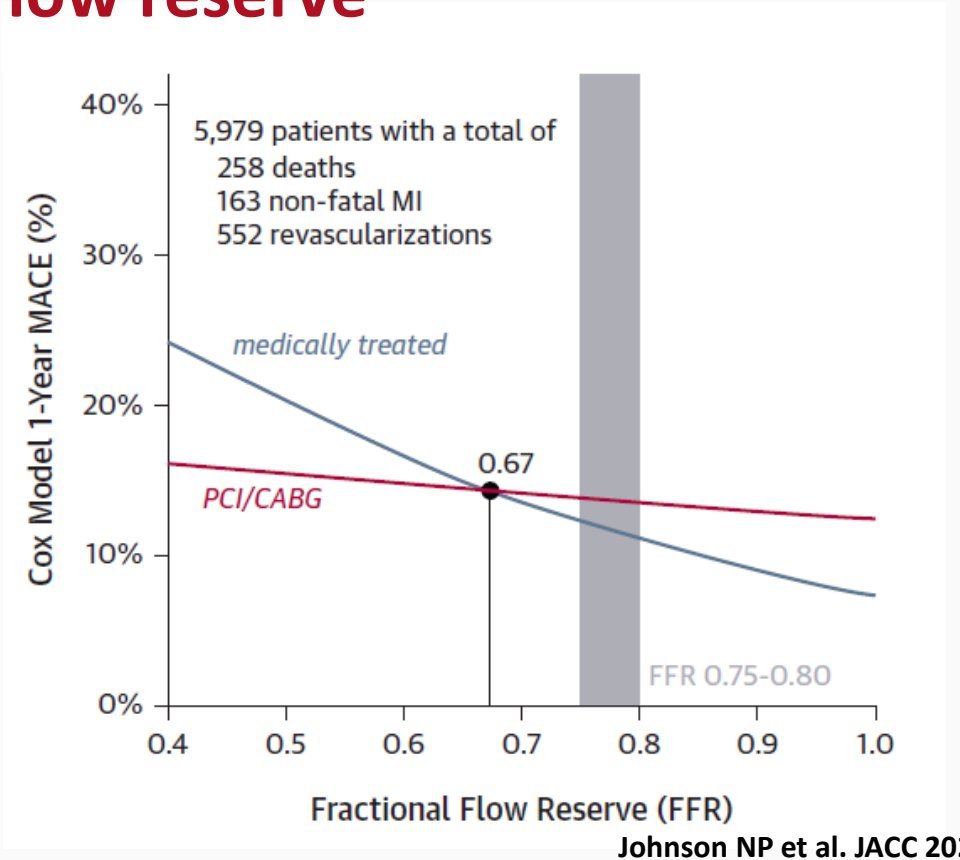


$$\text{Coronary flow reserve} = \frac{Flow_{max}}{Flow_{rest}}$$

Fractional flow reserve



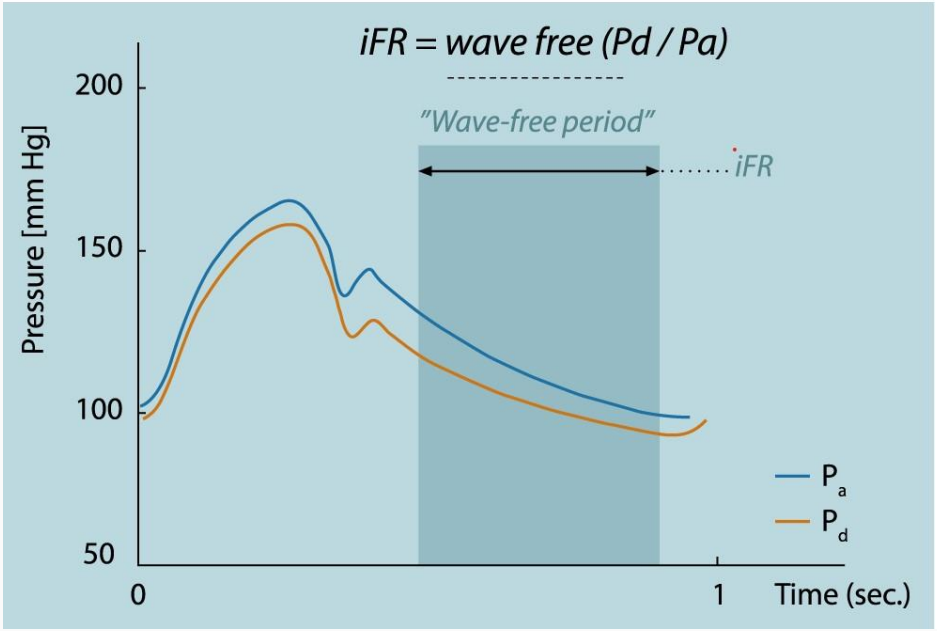
$$FFR = \frac{70\ mmHg}{100\ mmHG} = 0.70$$



Pijls N. et al. Circulation 1995

Johnson NP et al. JACC 2021

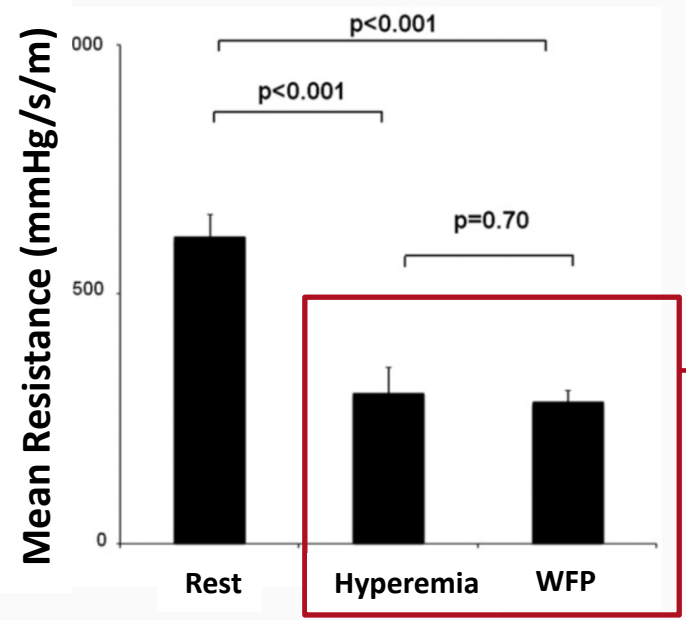
Instantaneous wave-free ratio (iFR)



Minimum resistance during wave free period

$$\text{iFR} = \frac{Pd_{wave\_free}}{Pa_{wave\ free}}$$

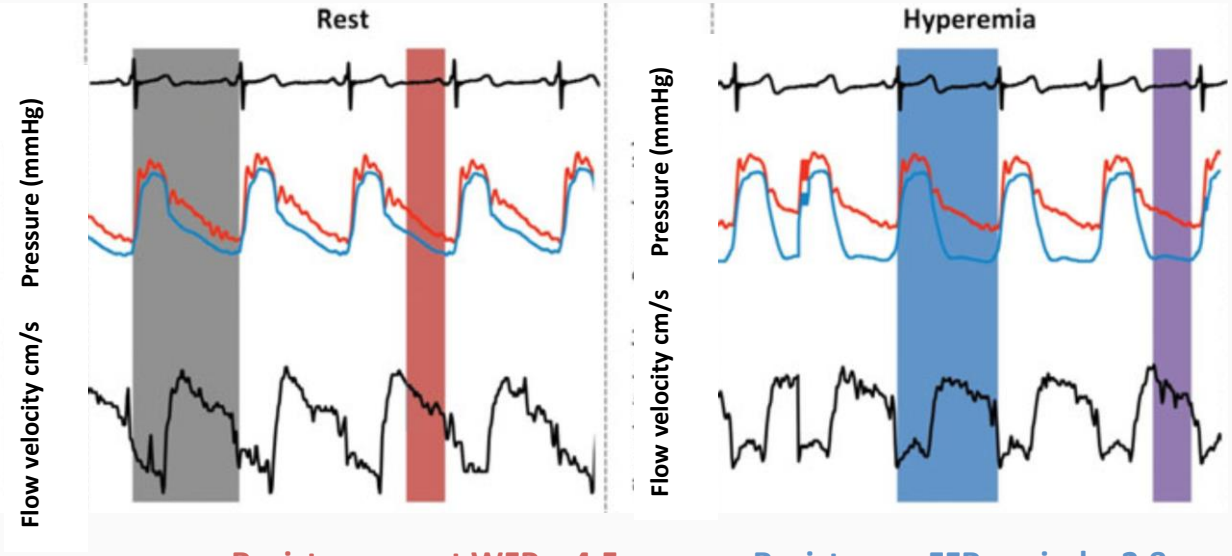
Resistance during the wave-free period (WFP)



”In the first part of this study, we identified the existence of a diastolic interval in which intracoronary resistance rest is equivalent to time-averaged resistance during FFR measurements.”

Sen S, *JACC*. 2012 Apr 10;59(15):1392-402. (Figure 5A and Methods text with *emphasis*)

Resistance in WFP higher than hyperemic resistance



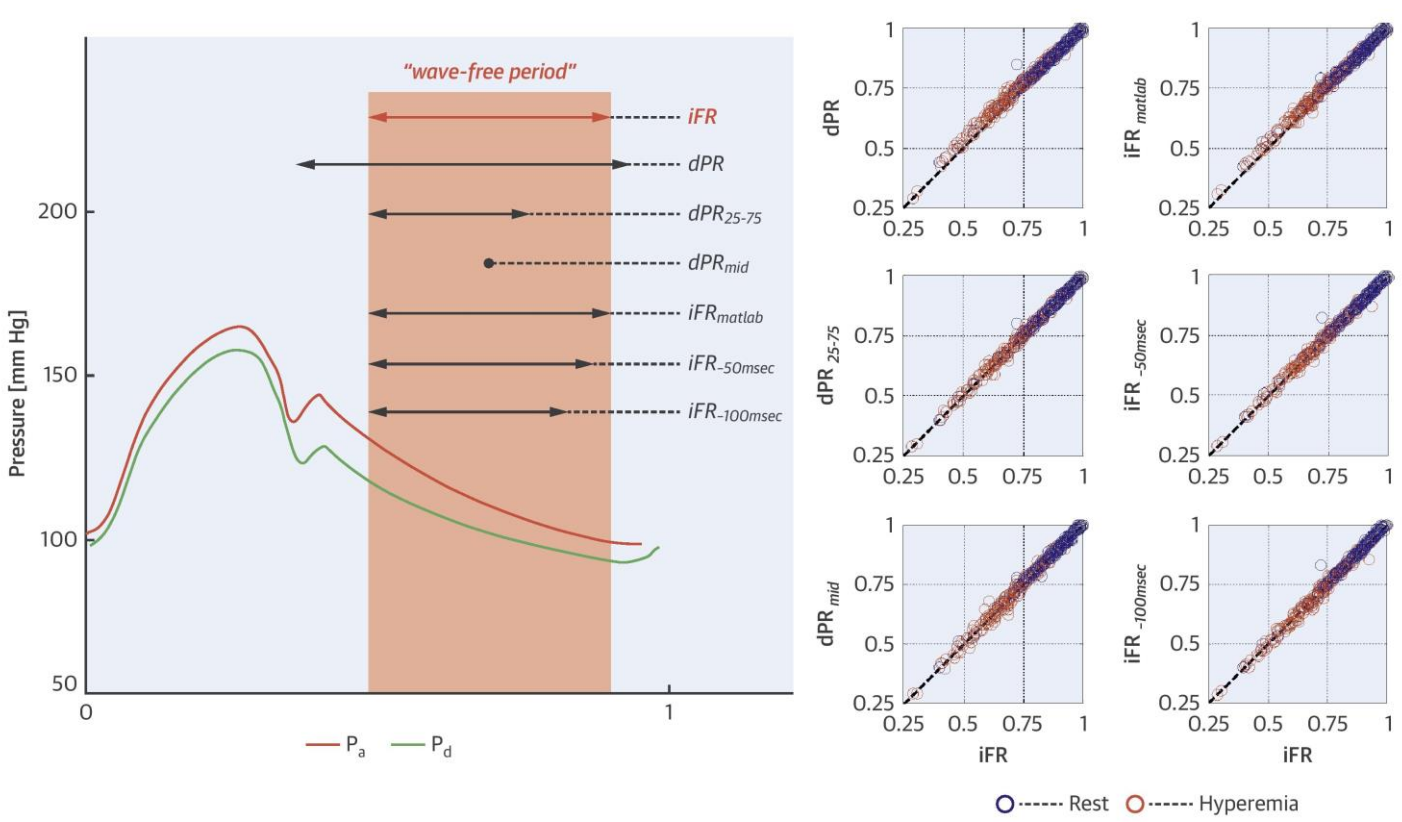
Resistance: rest WFP = 4.5

Resistance: FFR period = 2.8

"A *natural incremental hierarchy exists* between the physiological states assessed: resting whole cycle, *resting wave-free period*, *hyperaemic whole cycle* and hyperaemic wave-free period physiology."

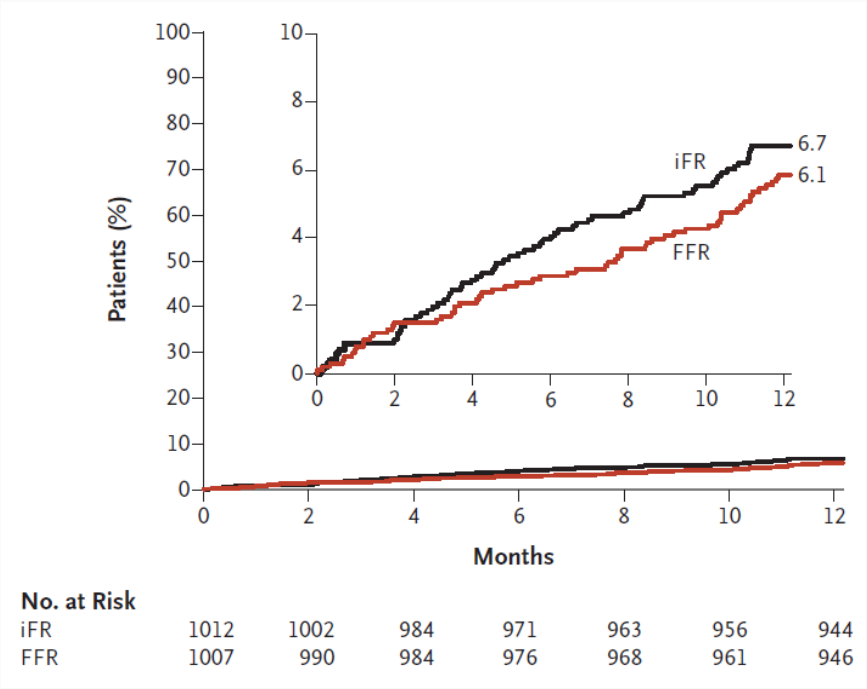
Nijjer SS, *EHJ*. 2016 Jul 7;37(26):2069-80. (Figure 1 portion, p-value and quote from results with *emphasis*)

CENTRAL ILLUSTRATION: Correlations and AUC Values >0.99 for All Resting Pd/Pa Ratios Over Different Periods in Diastole Compared With iFR as the Reference Standard

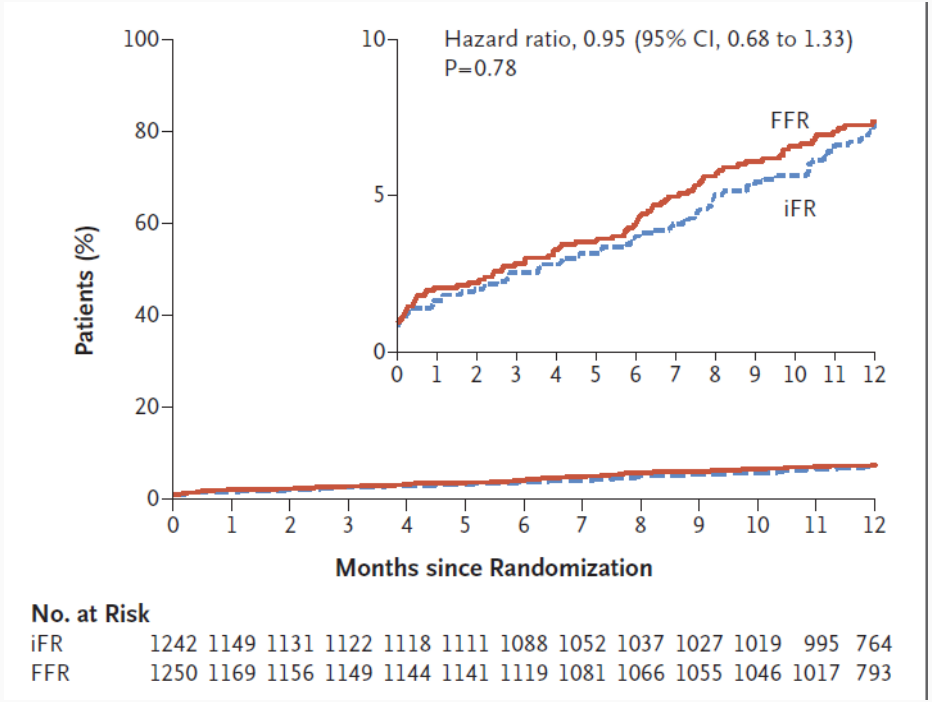


van't Veer, M. et al. J Am Coll Cardiol. 2017;70(25):3088-96.

DEFINE-FLAIR and iFR-SWEDEHEART – MACE 12 months

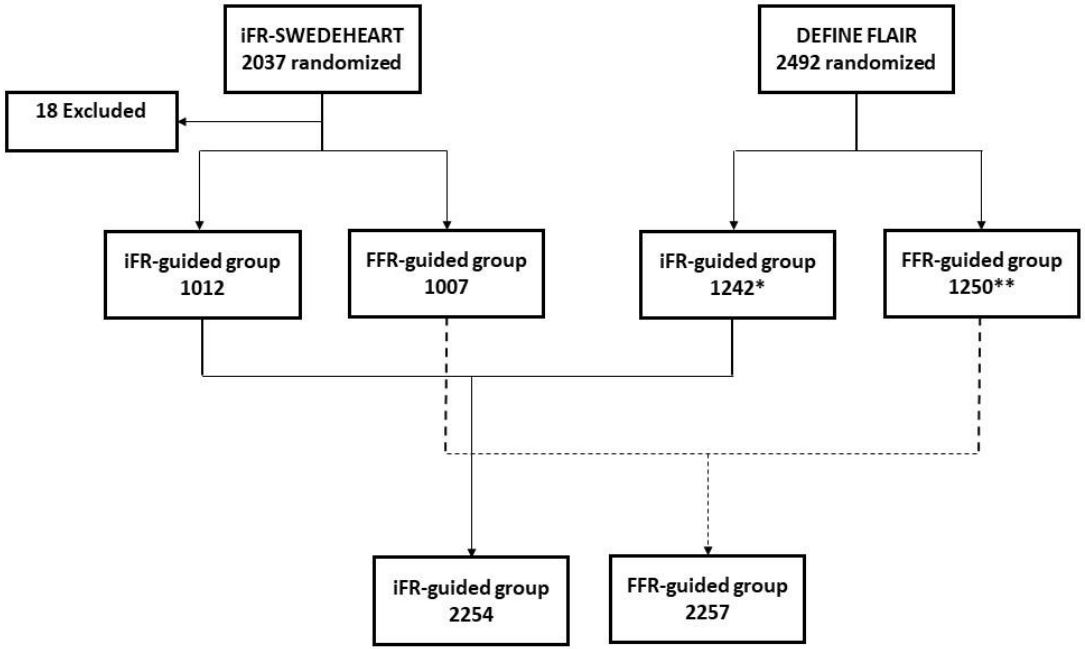


Götberg M. et al. N Engl Med. 2017 May 11;376:1813-1823



Davies J. et al. N Engl Med. 2017 May 11376:1824-1834

Pooling of 5-year outcome data from iFR-SWEDEHEART and DEFINE-FLAIR



Digitalizing 5-year KM-curves
(Wei and Royston, Stata J 2017)

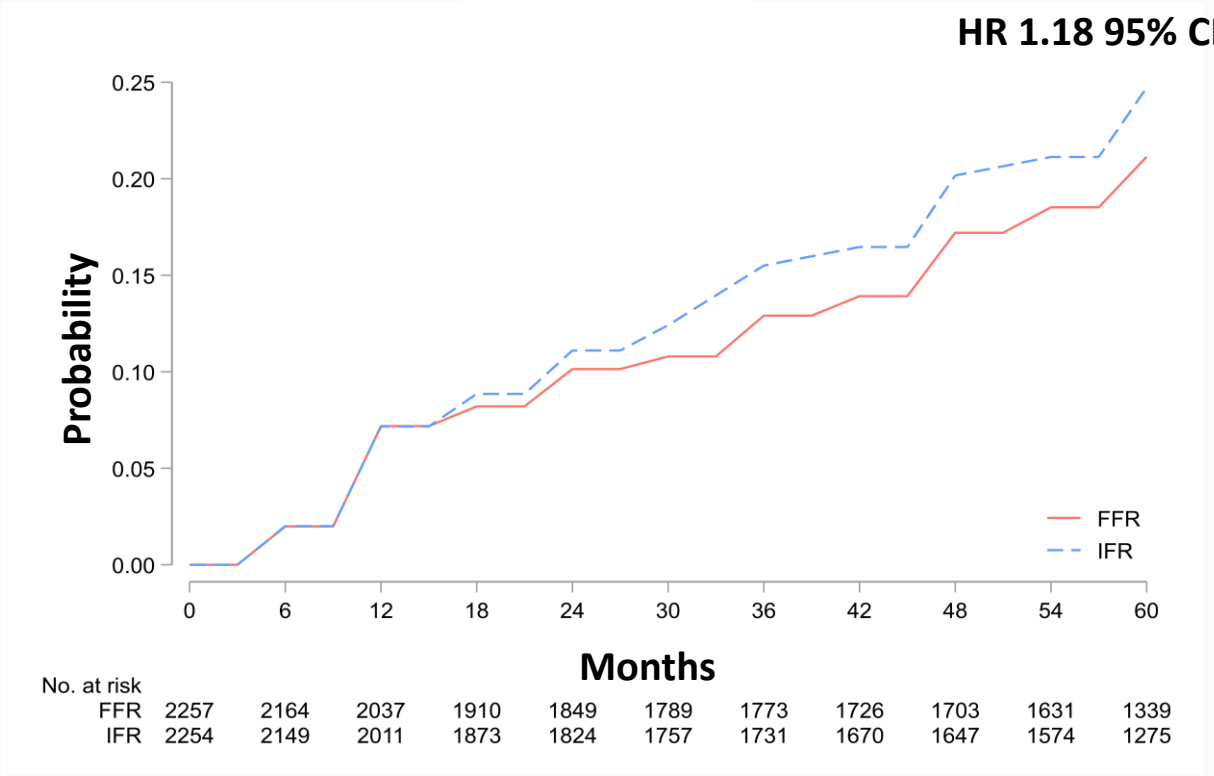
Eftekhari A et al. Eur Heart J. 2023, in press

	iFR Group N = 2254	FFR Group N = 2257
Age	67.1±10	66.2±10
Male gender	1718 (76)	1695 (75)
Acute coronary syndrome	622 (28)	612 (27)
Chronic coronary syndrome	1618 (72)	1644 (73)
CCS class		
I	500 (22)	426 (19)
II	729 (32)	713 (32)
III	176 (8)	228 (10)
IV	81 (4)	75 (3)
Multivessel disease	869 (39)	887 (39)
Diabetes	614 (27)	589 (26)
Hypertension	1603 (71)	1594 (71)
Previous PCI	1008 (45)	1081 (48)
Previous MI	695 (31)	711 (32)

Eftekhari A et al. Eur Heart J. 2023, in press

MACE

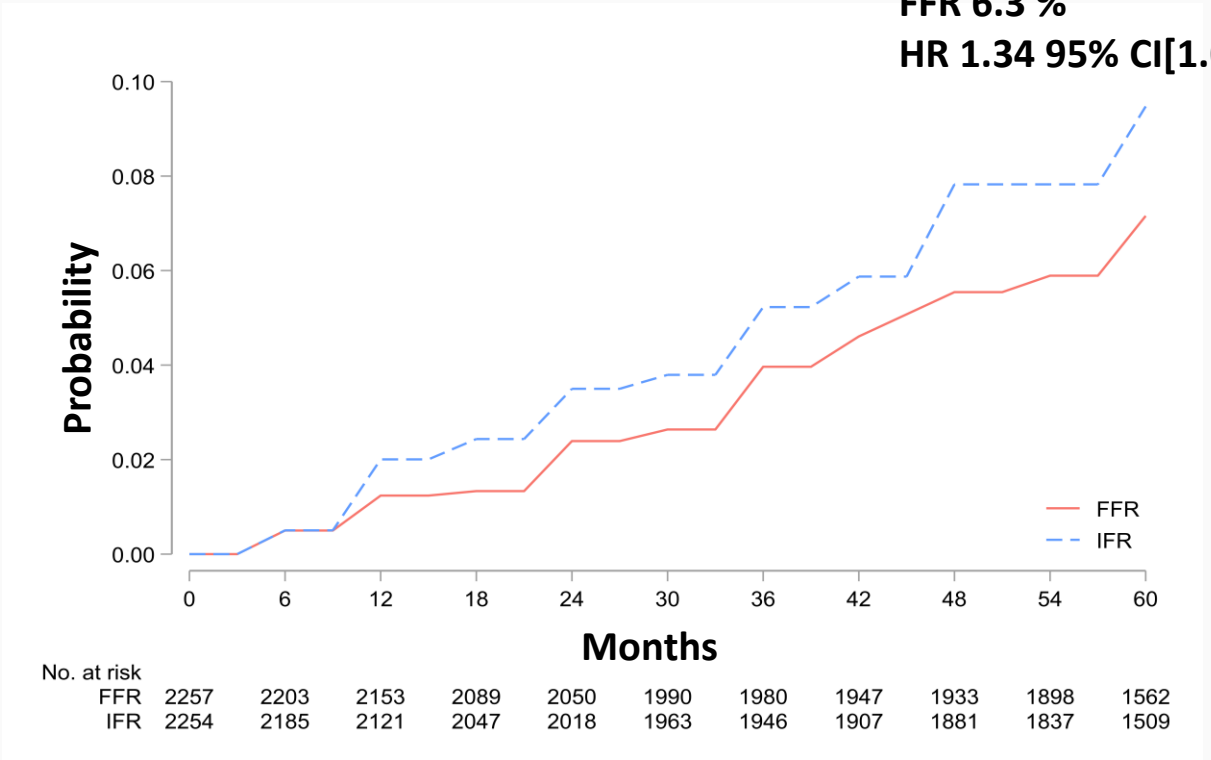
iFR 21.5 %
FFR 18.6 %
HR 1.18 95% CI[1.04; 1.34]



Eftekhari A et al. Eur Heart J. 2023, in press

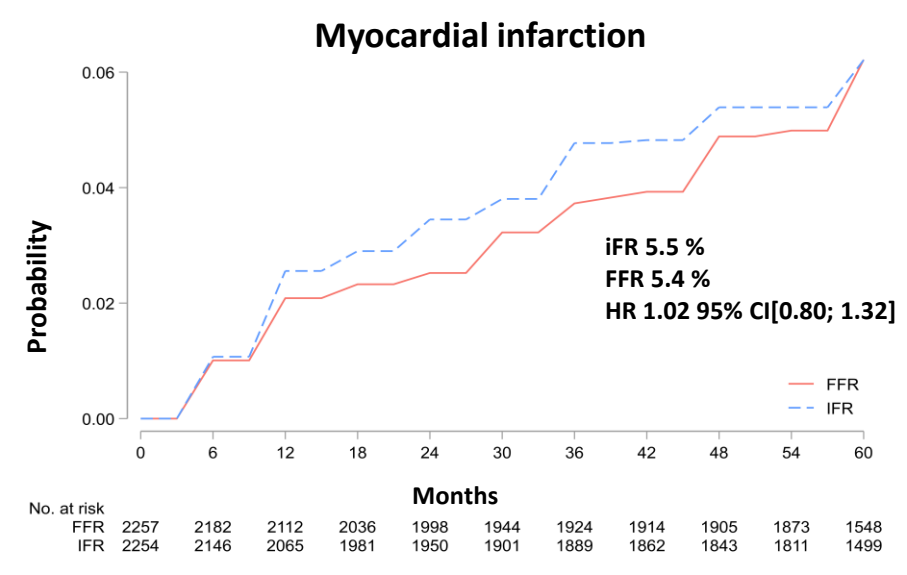
All-cause mortality

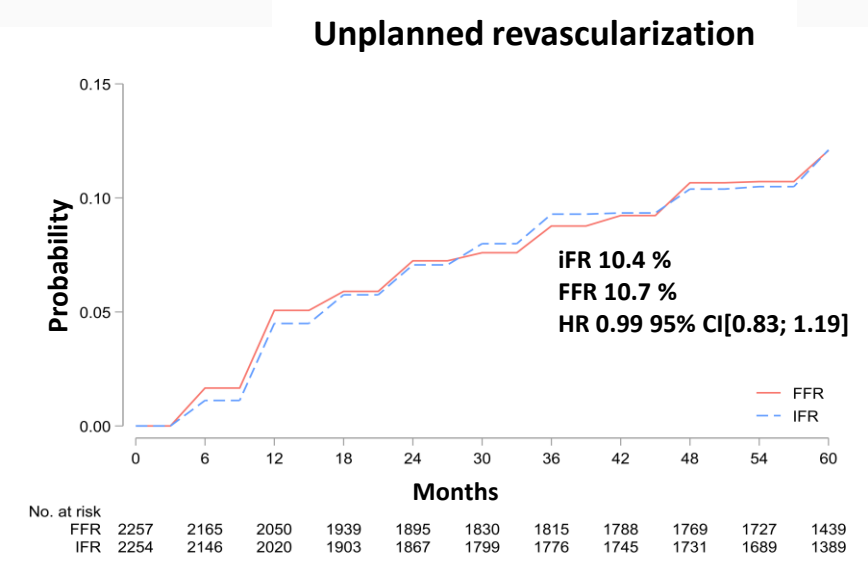
iFR 8.3 %
FFR 6.3 %
HR 1.34 95% CI[1.08; 1.67]



Eftekhari A et al. Eur Heart J. 2023, in press

Myocardial infarction and unplanned revascularization





Eftekhari A et al. Eur Heart J. 2023, in press

Procedural data

	iFR Group N = 2254	FFR Group N = 2257	RR 95% [CI]
Mean FFR	NA	0.83±0.1	
Maen iFR	0.91±0.1	NA	
Revascularization	1126 (50)	1236 (55)	0.91 [0.86; 0.96]
PCI	1008 (45)	1081 (48)	0.94 [0.75; 0.99]
Total stents	1520	1693	0.90 [0.84; 0.96]
CABG	118 (5)	155 (7)	0.86 [0.75; 0.99]

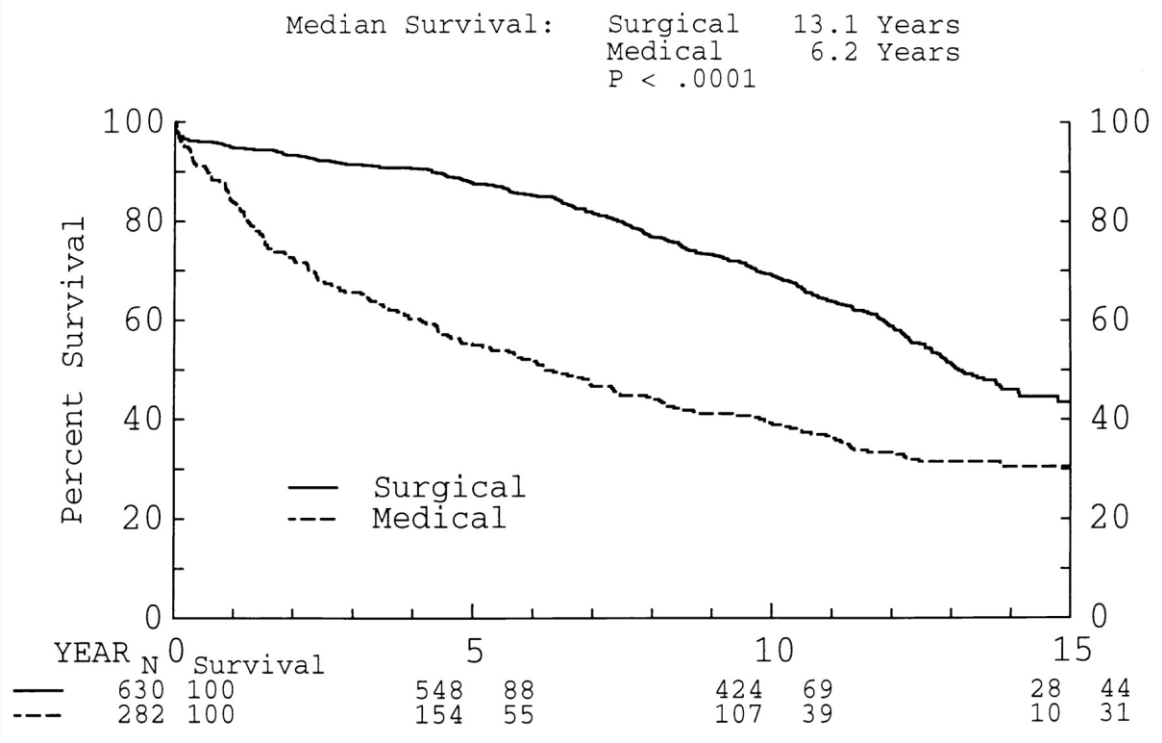
Eftekhari A et al. Eur Heart J. 2023, in press

Angio vs. physiology guided stragtey

	Physiology-guided strategy	Angio-guided strategy	Total treated vessels/patients
iFR-SWEDEHEART (vessels)	958 (50.6)	937 (49.4)	1895 (100)
DEFINE-FLAIR (patients)	912 (72.6)	345 (27.4)	1257 (100)

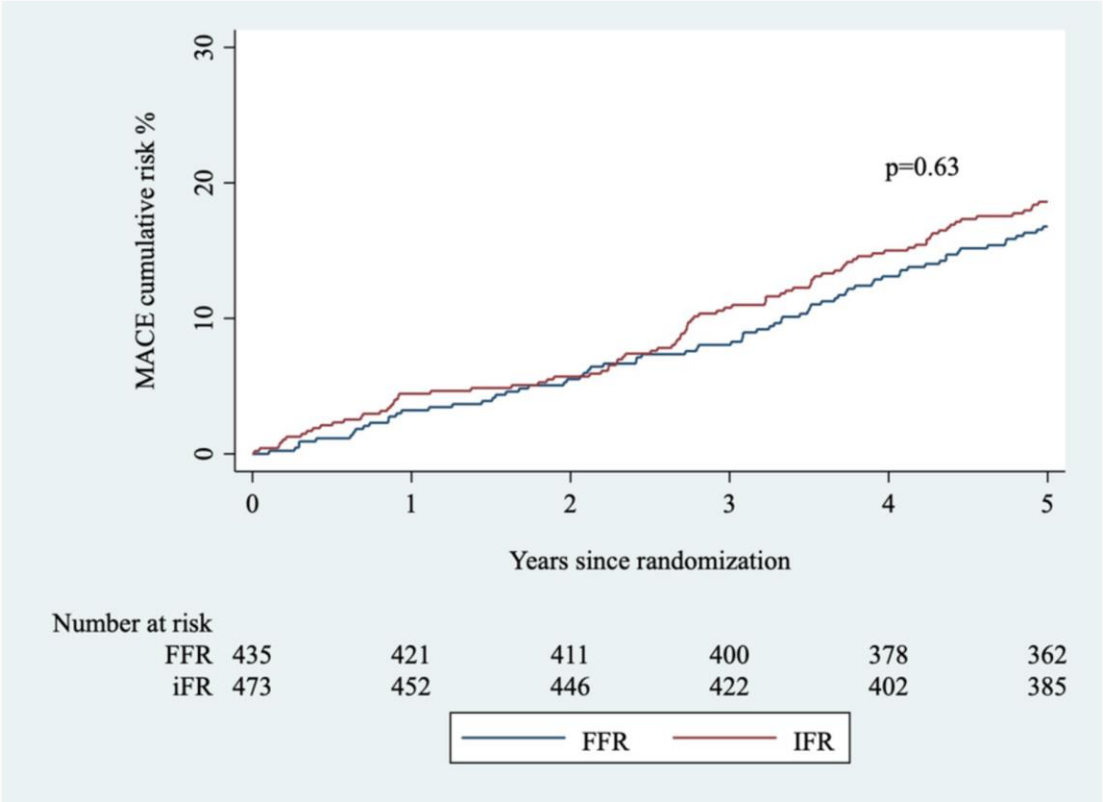
Eftekhari A et al. Eur Heart J. 2023, in press

Prognostic value of LM/LAD-lesions



Caracciolo EA. et al. Circulation 1995 May 1;91:2325-34

Deferred cases – iFR-SWEDEHEART



Berntop K. et al. J Am Heart Assoc. 2023 Feb 7;12:028423

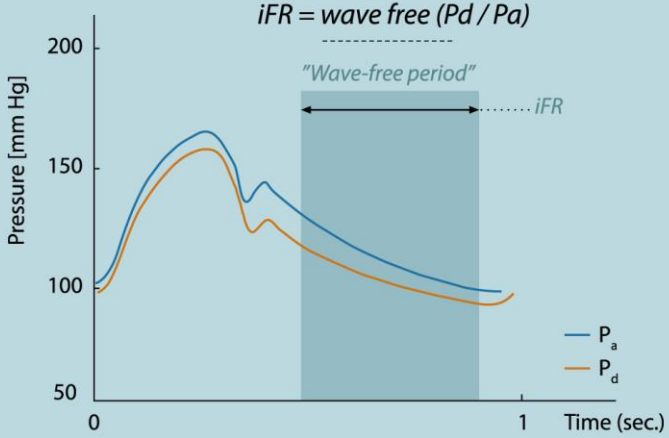
Summary and conclusion

PURPOSE Evaluate clinical outcome of iFR vs. FFR guided PCI

Theoretical calculation of FFR and iFR

FFR = hyperemic (Pd / Pa)

iFR = wave free (Pd / Pa)

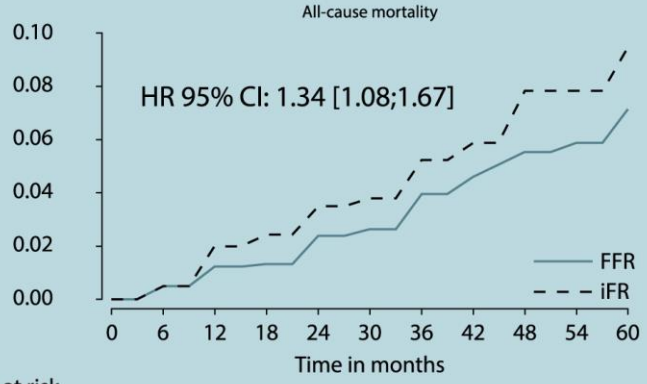


METHODS Study-level meta-analysis of DEFINE FLAIR and iFR SWEEDEHEART at 5-years

FINDINGS

FFR	iFR
N = 2257	N = 2254

Increased all-cause mortality in iFR-arm



No. at risk											
FFR	2257	2203	2153	2089	2050	1990	1980	1947	1933	1898	1562
iFR	2254	2185	2121	2047	2018	1963	1946	1907	1881	1837	1509

Eftekhari A et al. Eur Heart J. 2023, in press

Functional versus Culprit-only Revascularization in Elderly Patients with Myocardial Infarction and Multivessel Disease

The FIRE trial

Simone Biscaglia, MD

University Hospital of Ferrara (Italy)

on behalf of the FIRE trial Investigators

Background

- Older patients (75+) are poorly represented in conventional randomized controlled trials
- The risk of periprocedural complications is higher and prognostically impactful older patients[1]
- The benefit of complete revascularization in this subset of patients has been recently questioned[2]

1. Biscaglia S, Am Heart J. 2020;229:100-109. 2. Joshi FR, Catheter Cardiovasc Interv. 2021;97:E467-E474.

Research question

To investigate whether, in older patients (75+ years) with MI and multivessel disease, complete revascularization based on coronary physiology is superior to a culprit-only revascularization strategy

Study Organization

3 countries: Italy, Spain, Poland

34 centers

Study PI: Simone Biscaglia

Study Chair: Gianluca Campo

Executive Committee: Javier Escaned, Dariusz Dudek, Raul Moreno, Matteo Tebaldi, Emanuele Barbato

CEC: Rita Pavasini, Paolo Cimaglia

CRC: Veronica Lodolini, Martina Viola

Stats: Elisa Maietti, Anna Zanetti, Nicola Pesenti

CROs: AdvicePharma, Impulsae Consulting, KCRI

Sponsor:

CFR Consorzio Futuro in Ricerca

Università degli Studi di Ferrara

Grant Suppliers:

SMT

Medis Medical Imaging Systems

EUKON Future Healthcare Now

SIEMENS Healthineers

GE Healthcare

Inclusion & Exclusion Criteria

Inclusion

- 75+ years old
- MI (STEMI or NSTEMI)
- Multivessel disease
- Successful PCI of culprit lesion

Exclusion

- Non culprit lesion on left main
- Unclear culprit lesion
- Life expectancy <1 year
- Prior CABG
- Planned surgical revasc

Study Design

All comers, prospective, randomized, multicenter, open-label trial with blinded adjudicated evaluation of outcomes (PROBE).

Pts ≥75 ys hospitalized for MI (STE or NSTE) with indication to invasive management

Multivessel disease at coronary artery angiography

Culprit lesion clearly identifiable and successfully treated

R

Physiology-guided Complete Revascularization

Culprit-only Revascularization

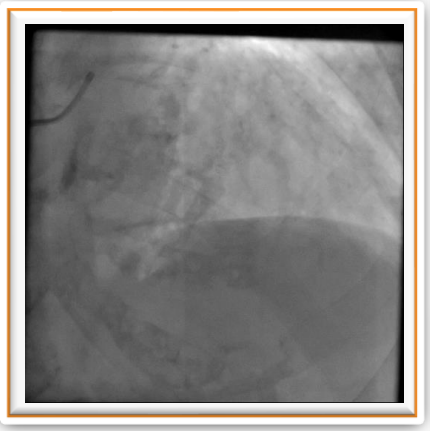
1-, 3-, and 5-year follow-up

Sample Size

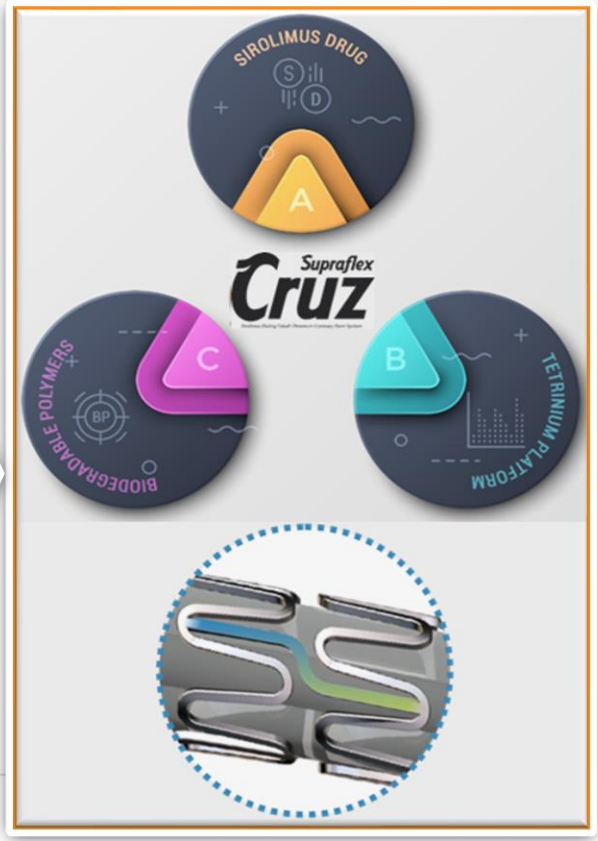
We estimated a conservative 15% rate of the primary endpoint at 1 year in the culprit-only strategy group. Considering that functional assessment should reduce the primary endpoint of at least 30%, 1368 patients are required to have a 80% chance of detecting, as significant at the 5% level, a 30% difference in the primary outcome between the two groups

Coronary Physiology & Stents

- **Non-culprit lesions were assessed with either wire-based FFR, resting index or angiography-derived FFR**
- **Flow-limiting lesions (FFR≤0.80, resting ≤0.89) had to be revascularized with biodegradable-polymer sirolimus ultra-thin stent(s)**



OR



Study Endpoints

Primary endpoint

1-year death, any MI, any stroke, or id-revascularization

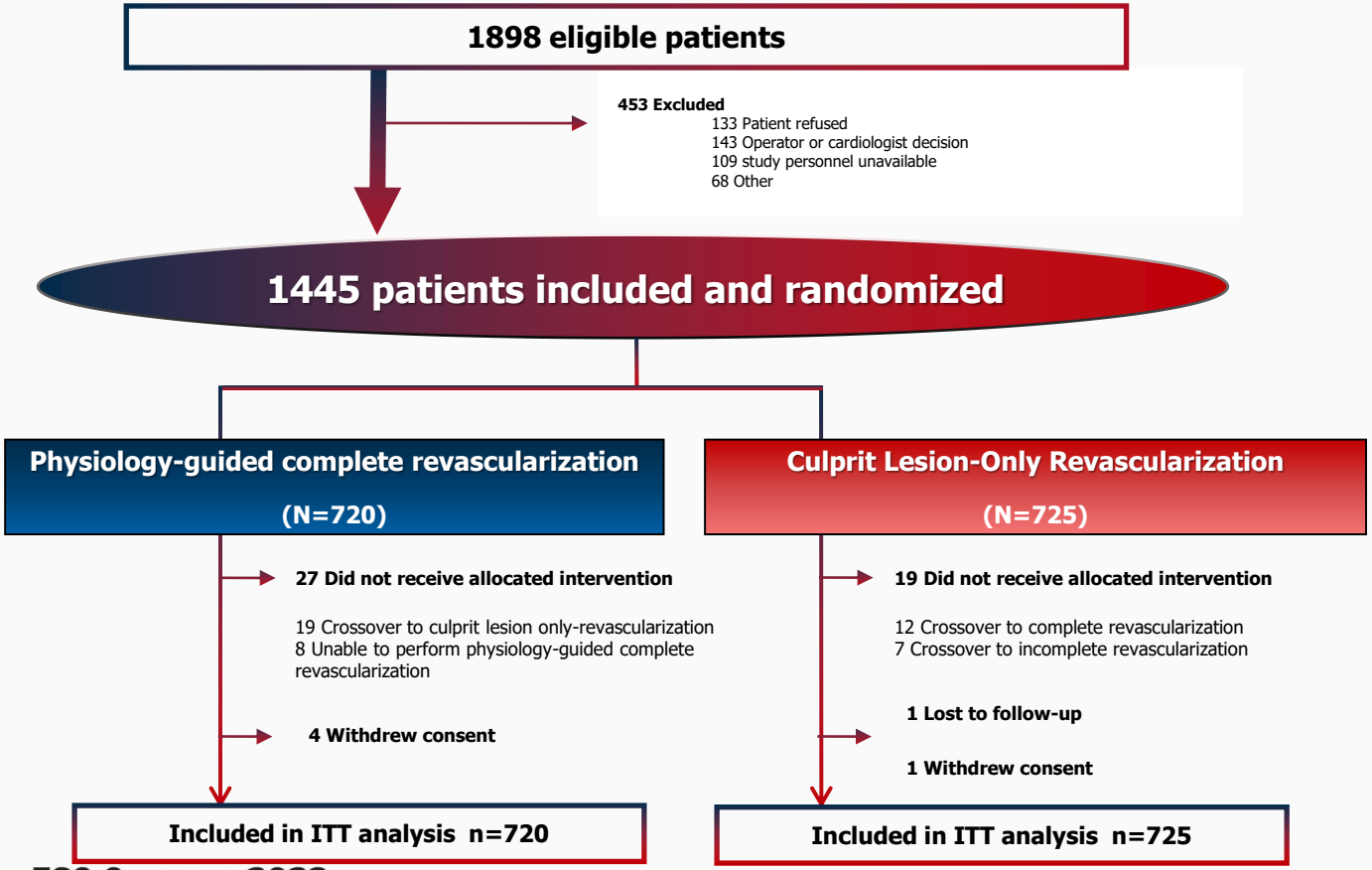
Key secondary endpoint

1-year cardiovascular death or MI

Safety endpoint

1-year CA-AKI, stroke, or BARC type 3-5 bleeding

Study flow-chart



- **76%** of eligible patients enrolled
- **2.6%** crossover from culprit-only
- Follow-up complete in **99.9%** of patients

Baseline Characteristics

Characteristic	Culprit-Only (N=725)	Physiology-Guided Complete (N=720)
Age (IQR) – yr	80 (77-84)	81 (77-84)
Female sex	265 (36.6)	263 (36.5)
Comorbidities		
Hypertension	592 (81.7)	593 (82.4)
Diabetes	233 (32.1)	230 (31.9)
Prior MI	116 (16)	104 (14.4)
eGFR <60 ml/min	332 (45.8)	330 (45.8)
PAD	127 (17.5)	122 (16.9)
Clinical presentation		
STEMI	256 (35.3)	253 (35.1)
NSTEMI	469 (64.7)	467 (64.9)

Characteristic	Culprit-Only (N=725)	Physiology-Guided Complete (N=720)
Killip class ≥2	208 (28.7)	204 (28.3)
Hospital LOS	5 (3-7)	6 (4-8)
Medication at discharge		
Aspirin	683 (94.2)	692 (96.1)
Clopidogrel	358 (49.4)	371 (51.5)
Ticagrelor	337 (46.5)	326 (45.3)
Prasugrel	16 (2.2)	16 (2.2)
Vitamin K antagonist	36 (5)	27 (3.8)
NOAC	129 (17.8)	137 (19)
ACEi or ARB	552 (76.1)	556 (77.2)
Statin	661 (91.2)	680 (94.4)

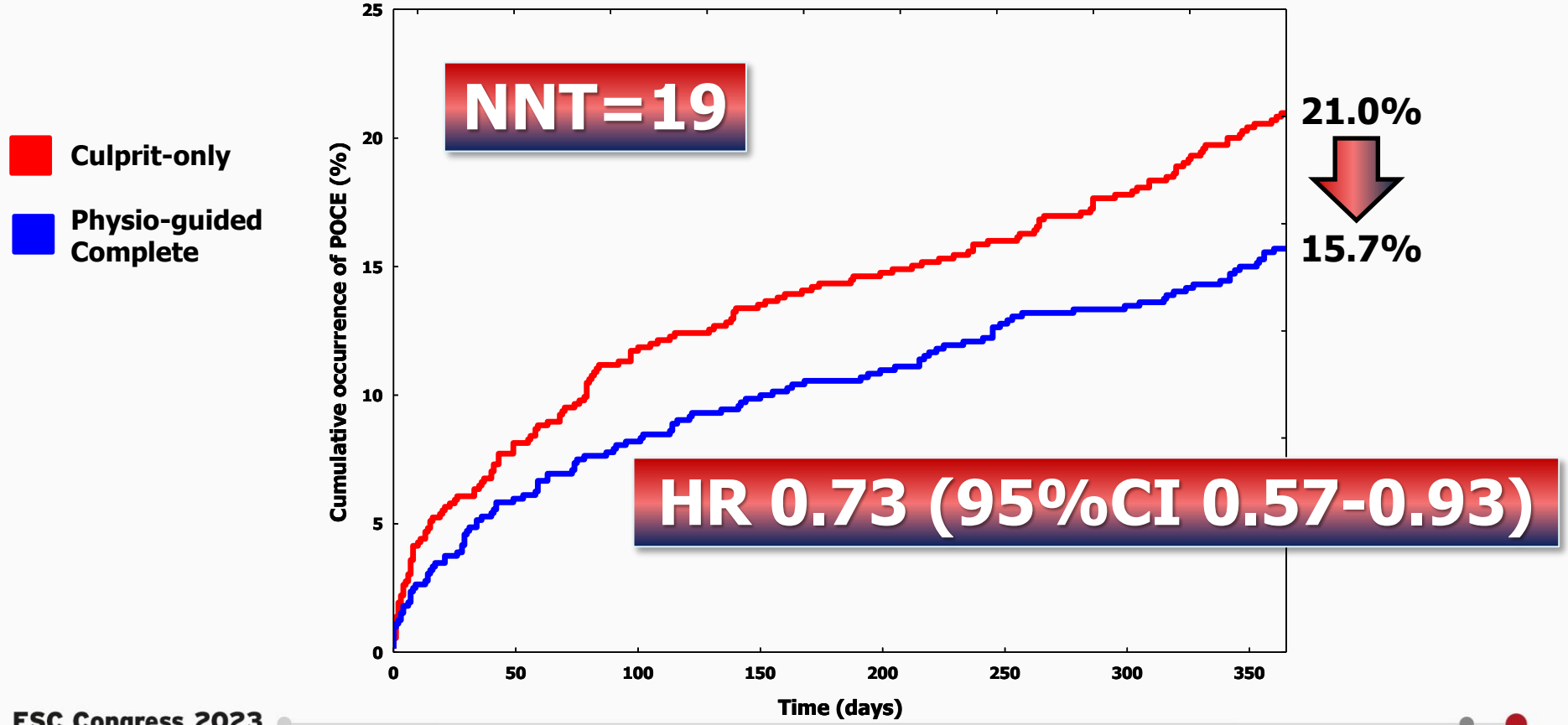
Procedural Characteristics

Characteristic	Culprit-Only (n=725)	Physiology-Guided Complete (N=720)
Procedures		
Total number	725	961
Days from index to staged procedures	-	3 (2-4)
Radial access	672 (92.7)	911 (94.8)
Number of non-culprit vessels per patient		
One	510 (70.3)	503 (69.9)
Two or more	215 (29.7)	217 (30.1)
Location of non-culprit vessels		
LAD	291 (30.6)	296 (31.2)
Circumflex artery	319 (33.5)	308 (32.5)
Right coronary artery	320 (33.6)	310 (32.7)
Ramus intermedius artery	21 (2.2)	34 (3.6)

Characteristic	Culprit-Only (n=725)	Physiology-Guided Complete (N=720)
RVD	3.0 (2.5-3.0)	3.0 (2.5-3.0)
Diameter stenosis	70 (60-80)	70 (60-80)
Percent diameter stenosis		
50-69%	401 (42.2)	390 (41.1)
70-89%	378 (39.7)	380 (40.1)
90-99%	172 (18.1)	178 (18.8)
Type of physiological assessment		
Wire-based hyperemic	-	451 (49.6)
Wire-based non hyperemic	-	138 (15.2)
Angiography-based index	-	320 (35.2)
Functionally significant non-culprit vessel	-	425 (44.8)

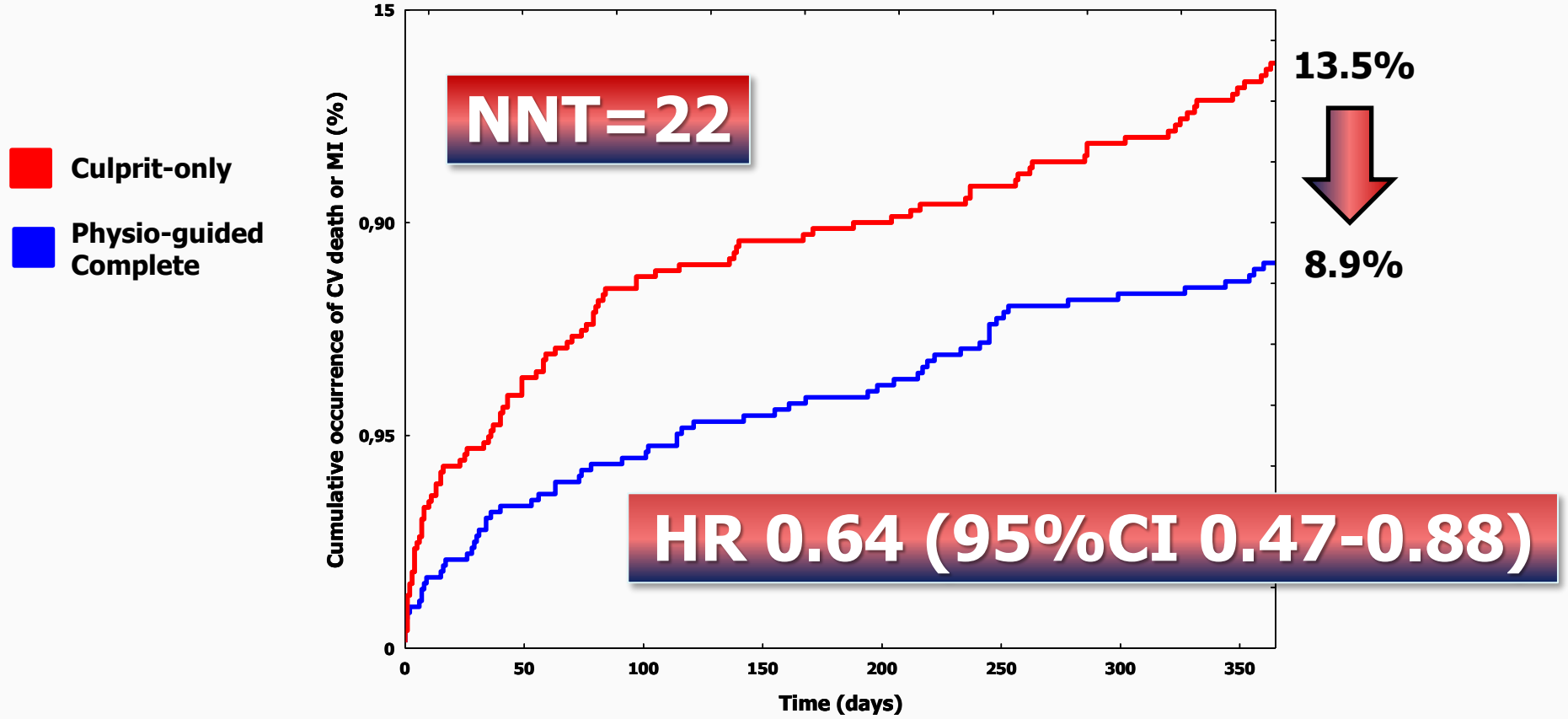
Primary endpoint

All-cause death, any MI, stroke, or id-revascularization



Key secondary endpoint

CV death or MI



Safety and Secondary Endpoints

Outcome	Culprit-Only (n=725) no. (%)	Complete (n=720) no. (%)	Hazard Risk (95% CI)
Death	93 (12.8)	66 (9.2)	**0.70 (0.51-0.96)**
Cardiovascular death	56 (7.7)	36 (5)	**0.64 (0.42-0.97)**
Non-cardiovascular death	37 (5.1)	30 (4.2)	**0.82 (0.50-1.32)**
Stroke	7 (1.0)	12 (1.7)	1.73 (0.68-4.40)
Myocardial infarction	51 (7.0)	32 (4.4)	**0.62 (0.40-0.97)**
Ischemia-driven revascularization	49 (6.8)	31 (4.3)	**0.63 (0.40-0.98)**
Safety endpoint*	148 (20.4)	162 (22.5)	1.11 (0.89-1.37)

*Composite of contrast-associated acute kidney injury, stroke, or BARC type 3, 4, or 5 bleeding

Study limitations

- Open label study
- Our results may not apply to:
  - Complete revascularization outside index hospitalization
  - Complete revascularization guided by conventional angiography
  - Patients not treated with biodegradable-polymer sirolimus eluting stent

Conclusions

Among patients aged 75 years or older with MI and multivessel disease, physiology-guided complete revascularization, as compared to a culprit-only revascularization strategy, reduced

- **Composite of death, MI, stroke, or ischemia-driven revasc**
- **Cardiovascular death or MI**

The NEW ENGLAND JOURNAL of MEDICINE

FIRE TRIAL

Extremely grateful to all the FIRE investigators:

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MULTISTARS AMI trial #ESCCongress

Multivessel immediate versus staged revascularisation in STEMI

Conclusion

Immediate multivessel percutaneous coronary intervention (PCI) is non-inferior to staged multivessel PCI for reducing death and ischaemic events in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel coronary artery disease.

Impact on clinical practice

Immediate PCI of non-culprit lesions is as effective and safe as a staged procedure. The results were generally consistent across prespecified key subgroups, particularly among women and men, young and older patients, and patients with or without diabetes.

Study objectives

The MULTISTARS AMI trial investigated whether immediate complete revascularisation at the time of primary PCI was non-inferior to staged (within 19 to 45 days) multivessel PCI among haemodynamically stable patients with STEMI and multivessel coronary artery disease.

Study population

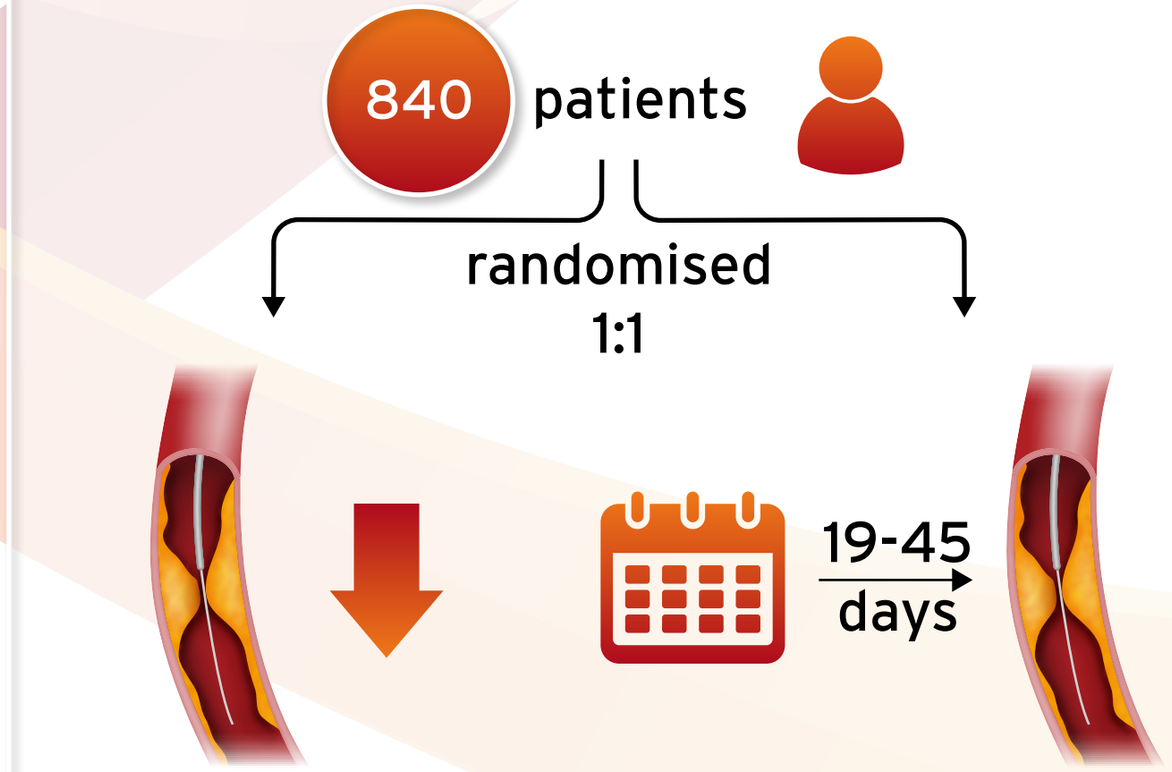
Patients with acute STEMI (presenting within 24 hours of symptom onset) and multivessel coronary artery disease (defined as ≥1 coronary lesion with ≥70% diameter stenosis on coronary angiography based on visual estimation in a non-culprit coronary artery of ≥2.25 mm and ≤5.75 mm in diameter), who were haemodynamically stable after successful primary PCI of the infarct-related coronary artery.

Where?

Europe

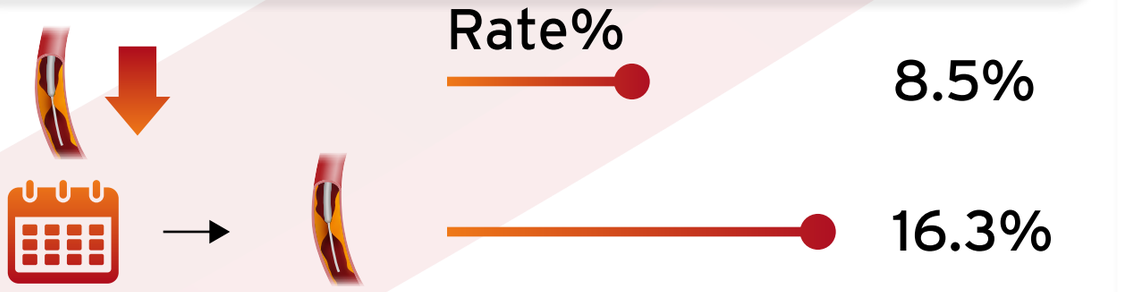
37 sites

Who and what?



Primary endpoint

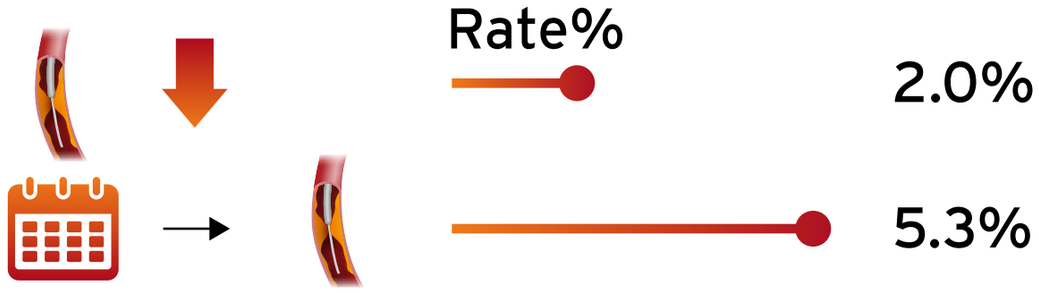
Composite of all-cause death, non-fatal myocardial infarction, stroke, unplanned ischaemia-driven revascularisation, or hospitalisation for heart failure within 1 year after randomisation.



risk ratio 0.52; 95% CI 0.38 to 0.72
p<0.001 for non-inferiority; p<0.001 for superiority

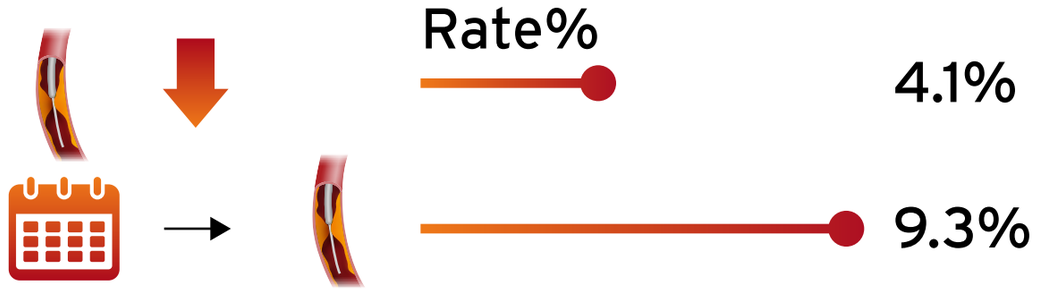
Secondary endpoints

non-fatal myocardial infarction



hazard ratio HR 0.36; 95% CI 0.16 to 0.80

unplanned ischaemia-driven revascularisation



hazard ratio 0.42; 95% CI 0.24 to 0.74

ESC

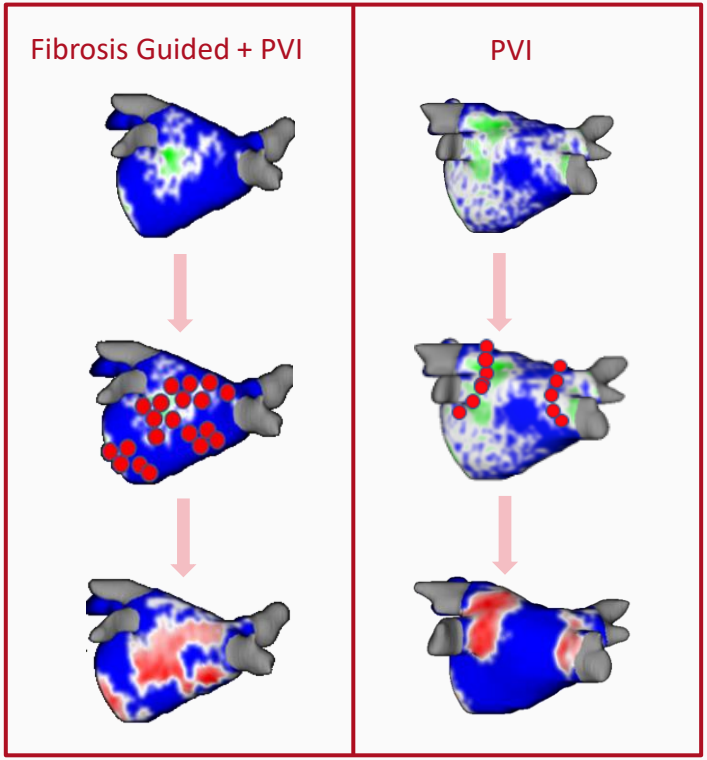
Fibrosis Guided Ablation Superior to Pulmonary Vein Isolation in Younger Persistent Atrial Fibrillation Patients

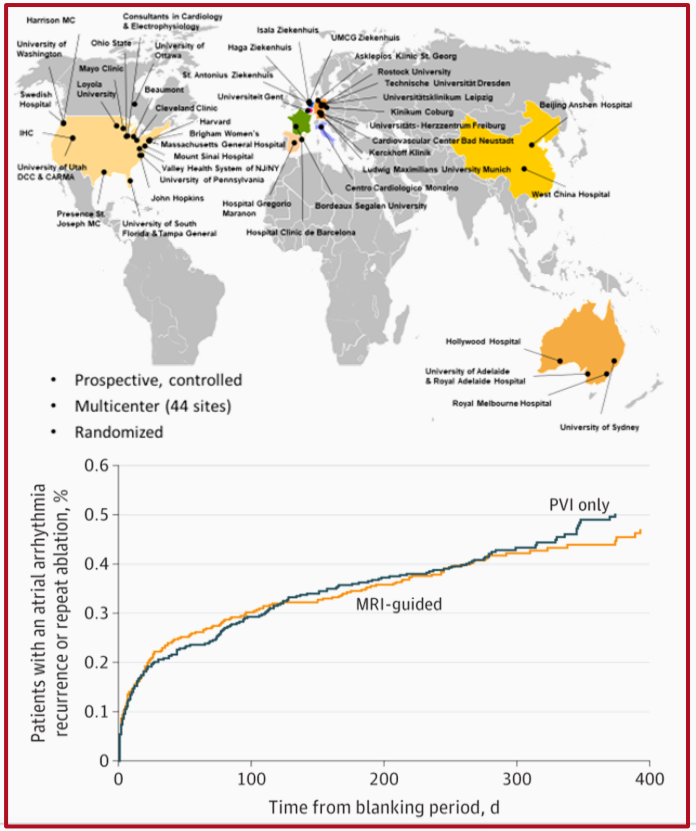
An Artificial Intelligence Driven DECAAF II Sub analysis

Nassir Marrouche, MD, FHRS, FACC

August 25th,2023

DECAAF II: Intention to Treat Analysis Showed that Fibrosis-Guided Ablation is Not Superior to PVI

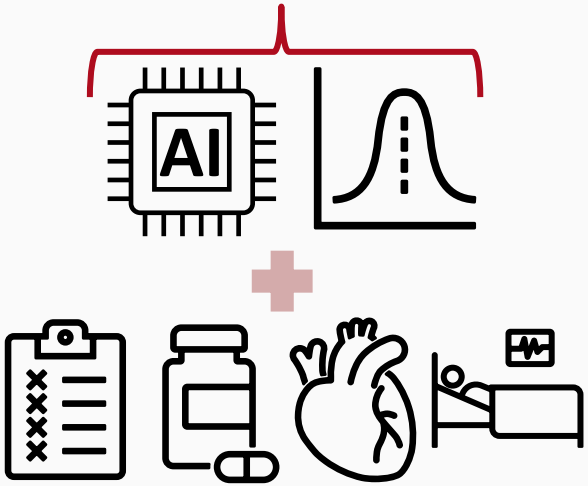


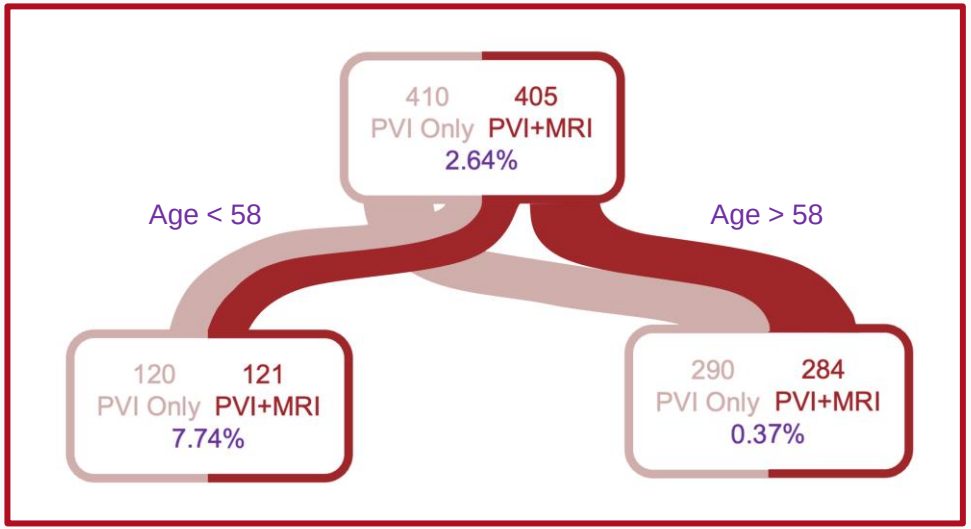


Marrouche et al, JAMA 2022

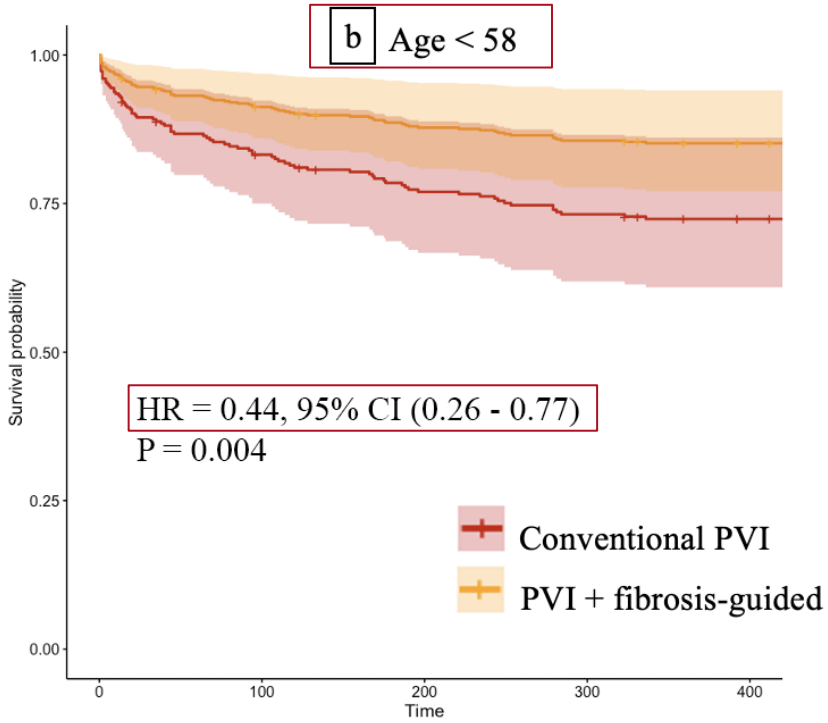
DECAAF II: AI-Based Causal Tree Learning

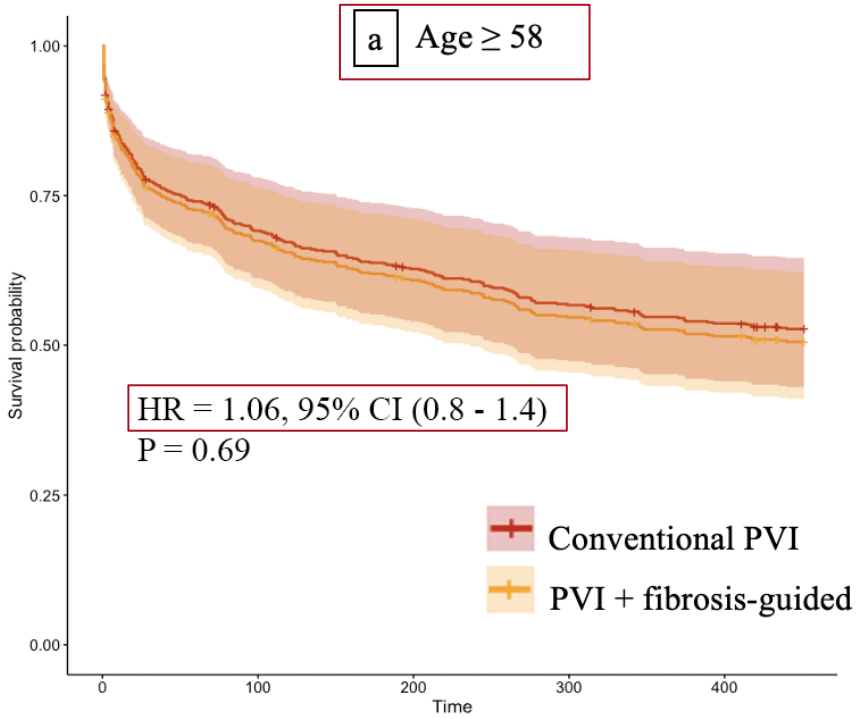
Causal Tree Learning





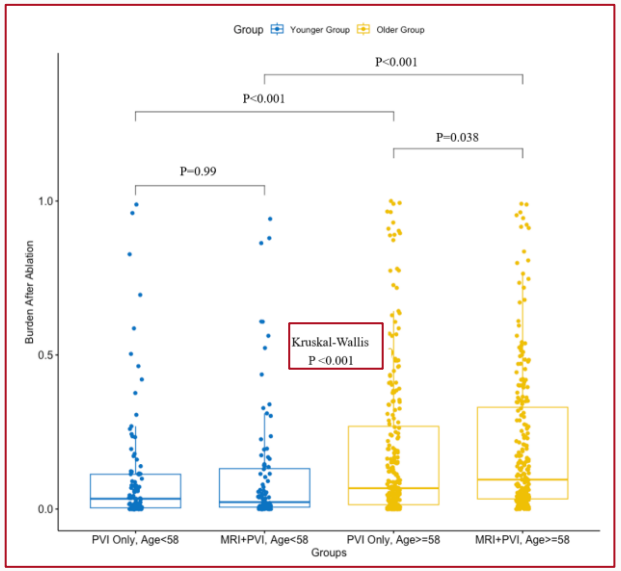
Artificial Intelligence Detected that Fibrosis-Guided Ablation Significantly Decreases AF Recurrence in Young Patients



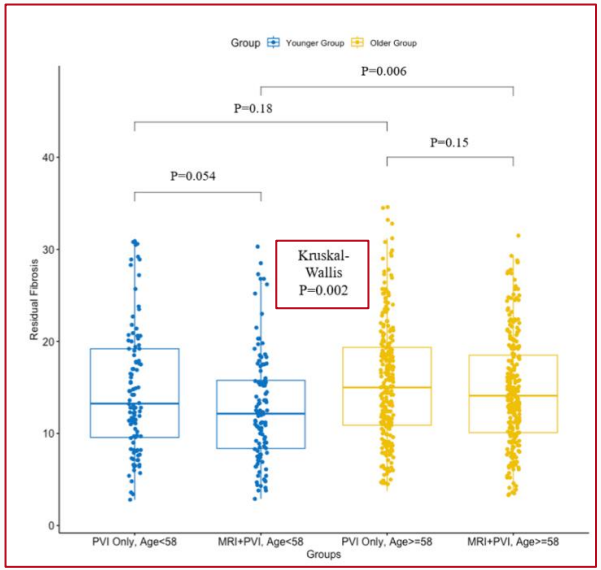


Ablation in Young Patients leads to less AF Burden and Residual Fibrosis, and Improved Quality of Life

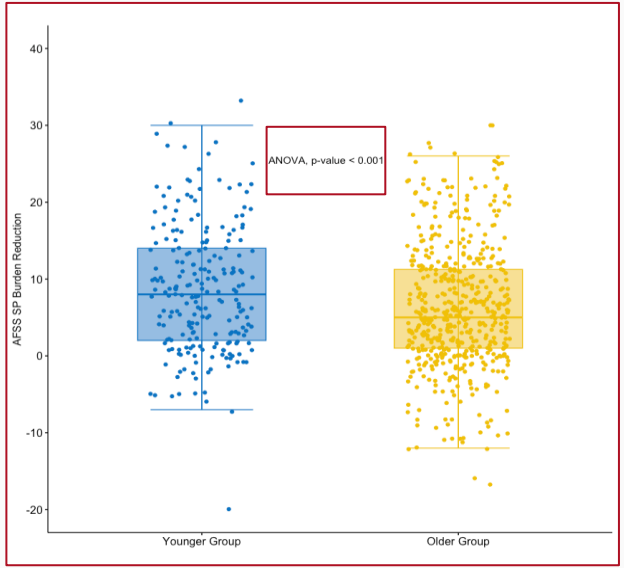
Lower AF Burden



Lower Residual Fibrosis

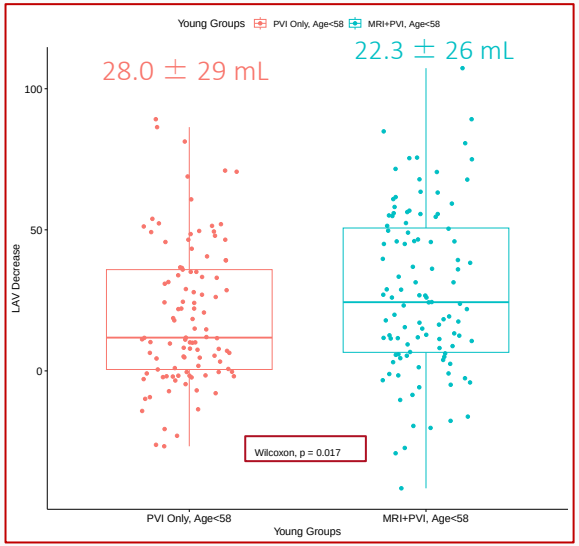


Improved Quality of Life

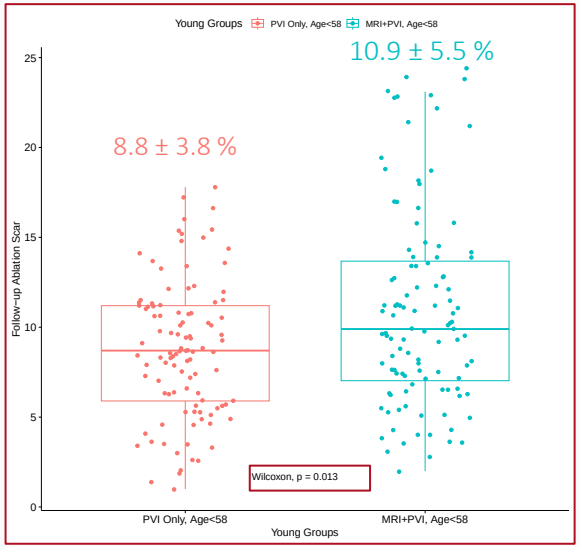


Fibrosis-Guided Ablation leads to better Remodeling in Young Patients

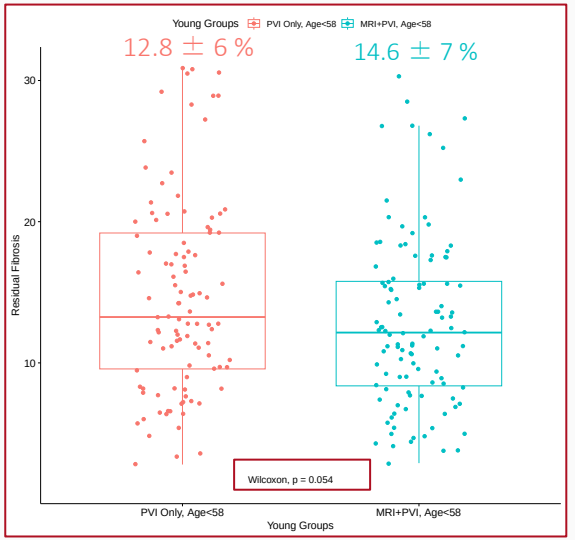
More Left Atrial Volume Change



Better Scar Formation



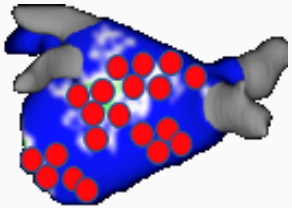
Possible Decreased Residual Fibrosis



Take Home Message

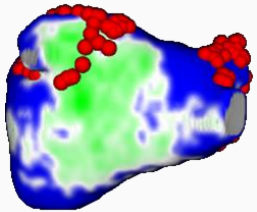
Treatment Strategy

Age < 58



Fibrosis-guided ablation

Age > 58



PVI

The ARAMIS trial

Anakinra versus Placebo, a Double Blind Randomized Controlled Trial for the Treatment of Acute Myocarditis

Mathieu Kerneis, MD, PhD; Fleur Cohen, MD, PhD; Alain Combes, MD, PhD; Eric Vicaut MD, PhD; Gilles Montalescot, MD, PhD

on behalf of the ARAMIS investigators

Declaration of interest

Dr Mathieu Kerneis reports :

- consulting/lectures fees from Kiniksa, Eligo, Sanofi, Bayer.
- Research grants from Federation Francaise de Cardiologie and French Health Ministry
- Patent for the use of Abatacept in ICI induced myocarditis

All Disclosures are available on www.action-group.org

Study Organization

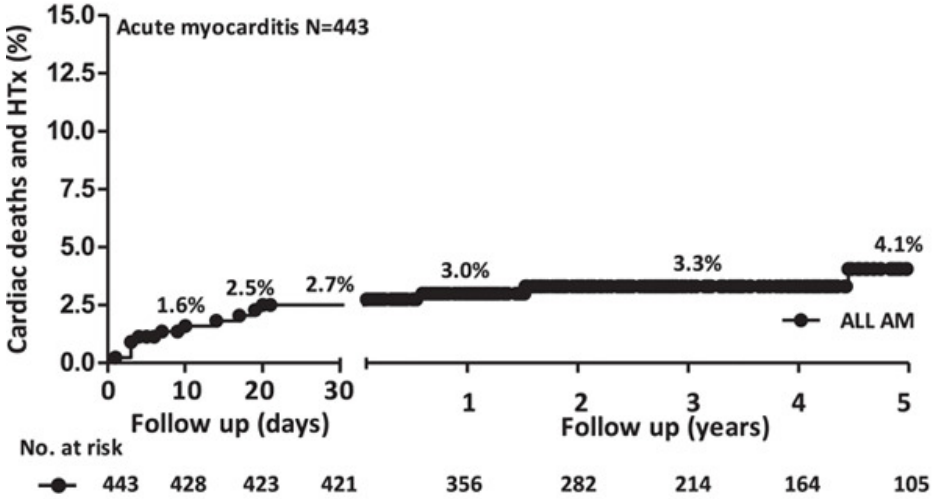
ARAMIS = Independent Academic Trial

- **Academic coordinating center :** Institute of Cardiology – ACTION Group – Pitié Salpétrière Hospital
- **Academic Sponsor :** Assistance Publique-Hopitaux de Paris
- **Academic Global Trial Operations :** URC Lariboisiere, ACTION Group, Paris
- **Academic Funding :** French Ministry of Health (PHRC)
- **Investigation Sites :** 6 academic centers in France
- All analyses were performed by an **independent academic statistician**

Background

Acute Myocarditis

Acute myocarditis (AM) is an **inflammation** of the myocardium that can cause **life-threatening events**



Ammirati et al. Circ 2018

Treatment of Acute Myocarditis

There is no evidence that a treatment targeting inflammation can improve outcome in « virus-negative » myocarditis patients[1]

A strategy of immunomodulation has not been evaluated in acute myocarditis patients with unknown viral replication (without EMB)[2]

Experimental studies and case reports suggest that blockade of the IL1-β pathway could be effective in AM [3,4]

Anakinra, an IL1-R antagonist, used in inflammatory diseases, has an acceptable **safety profile**[5]

[1] Frustaci, *et al.* EHJ 2009 - *TIMIC Trial*

[2] Tschöpe, *et al.* Nat Rev Cardiol 2021

[3] Lim BK, et al. Circ, 2002; [4] Cavalli G et al. Crit Care Med, 2016

[5] Brucato A et al., JAMA, 2016

Goal

To perform a pragmatic trial evaluating the inhibition of the IL-1β immune innate pathway with anakinra, to reduce the risk of clinical events in acute myocarditis patients

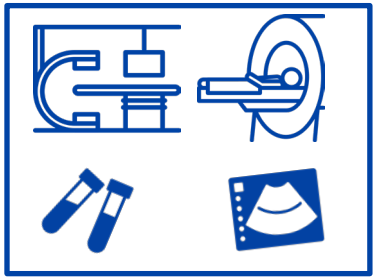
Study design

Study Design of the ARAMIS Trial

Randomized, Double Blind, Multicenter, Phase IIb trial

AM patients

Diagnosis



Within 72 hours

Treatment

R

- Placebo + Standard Therapy
- Anakinra 100mg sc o.d. + Standard Therapy

Follow-up

Number of days alive free of any myocarditis complications

28 days

- **Admission For a Suspected AM**
- **Confirmation of diagnosis and randomization**
- **Hospital Discharge**
- **Primary Endpoint**

Number of days considered for the Primary Endpoint

Inclusion/Exclusion Criteria

Inclusion

Myocarditis was defined as follows :

- Chest Pain
- **AND** modification of the ECG *or* elevated Troponin (at least 1.5 X ULN)
- **AND** CMR Lake Louise Criteria

AND Normal Coronary angiography or CTA in > 40 y/o *or* with CV risk factors

Exclusion

- < 18 y/o or > 65 y/o
- LV assistance
- Mechanical Ventilation
- **Any clinical suspicion of autoimmune, giant cell, eosinophilic, or sarcoidosis related myocarditis**
- Renal Failure
- Anti-TNF, CTC/NSAID use
- Malignancy

Endpoints

Primary Efficacy endpoint :
Number of days alive free of any myocarditis complications

HF requiring hospitalization
Chest Pain requiring medication
LVEF < 50% in TTE
Ventricular arrhythmia, VT or VF

within 28 days post hospitalization

Primary Safety endpoint :
Number of SAEs, including those potentially related to the drug :

Severe infection
ALT/AST > 10x ULN
Neutropenia < 1. 109/L
Renal failure (↑ 50% creat),
Thrombopenia < 50 000 mm3,
BARC> 3, Anaphylactic reaction
100% ↑ of LDL Cholesterol

Sample Size

Superiority trial

anakinra at the approved dosage of 100mg o.d + SOC (betablocker + ACE inhibitor)

vs placebo + SOC

↑ of the number of days free of myocarditis complications

> 1.5 day = clinically meaningful

SD of the 1°EP = 2.3

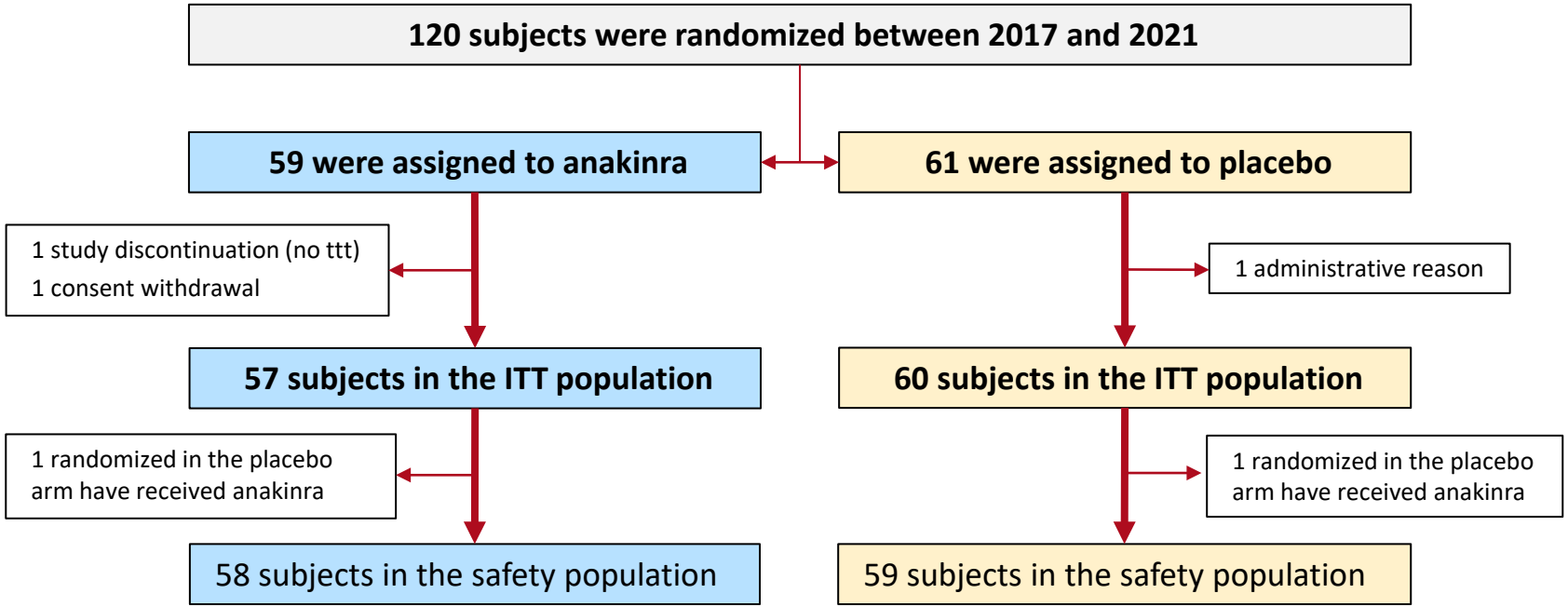
based on the AMPHIBIA registry (NCT04844151)

60 patients in each group

⇒ 80% power to demonstrate a 1.5 day difference

⇒ 5% two-sided significance level

Flow Chart


120 subjects were randomized between 2017 and 2021
59 were assigned to anakinra
61 were assigned to placebo
1 study discontinuation (no ttt)
1 consent withdrawal
1 administrative reason
57 subjects in the ITT population
60 subjects in the ITT population
1 randomized in the placebo arm have received anakinra
1 randomized in the placebo arm have received anakinra
58 subjects in the safety population
59 subjects in the safety population

Patient characteristics

Clinical Presentation (1/2)

	Anakinra N=57	Placebo N=60
Median Age, (Q1;Q3), yrs	28.0 (22.8 ; 38.1)	29.0 (23.2 ; 34.0)
Male — no of patients (%)	52 (91.2%)	50 (83.3%)
Current smoker — no. (%)	30 (52.6%)	30 (50.0%)
Past Medical History		
Prior myocarditis — no. (%)	1 (1.8%)	3 (5.0%)
Recent Bacterial infection— no. (%)	9 (15.8%)	6 (10.0%)
Recent Viral infection — no. (%)	25 (43.9%)	27 (45.0%)
Chest Pain — no.(%)	57 (100%)	60 (100%)
Dyspnea — no. (%)	4 (7.0%)	9 (15.0%)
Cardiogenic shock — no. (%)	1 (1.8%)	0 (0.0%)
Ventricular fibrillation — no. (%)	1 (1.8%)	0 (0.0%)
Conduction disorders — no. (%)	0 (0.0%)	1 (1.7%)
Clinical infectious syndrome — no. (%)	16 (28.1%)	18 (30.0%)

Clinical Presentation (2/2)

	Anakinra N=57	Placebo N=60
Troponin in fold increase of the ULN - Median (Q1;Q3)	**98 (33 ;194)**	**75 (22;217)**
CRP, mg/L - Median (Q1;Q3)	**37 (16;68)**	**23 (14;52)**
(NTpro)BNP, in fold increase of the ULN - Median (Q1;Q3)	0.9 (0.4;1.9)	0.5 (0.3;1.0)

Right or Left BB block — no. (%)	5 (8.8%)	4 (6.7%)
ST-segment elevation — no. (%)	**37 (64.9%)**	**39 (65.0%)**
ST segment depression — no. (%)	5 (8.8%)	7 (11.7%)

Coronary Imaging — no. (%)	48 (84.2%)	47 (78.3)

0 patient with EMB

Non Invasive Imaging

	Anakinra N=57	Placebo N=60
Left ventricular ejection fraction (TTE), %		
Median (Q1;Q3)	60 (50;61)	60 (50;60)
Min, Max	40, 73	35, 66
Ventricular dysfunction with TTE (LVEF<50%) — no. (%)	7 (12.3%)	5 (8.3%)
Regional wall motion abnormalities (TTE) — no. (%)	18 (31.6%)	16 (26.7%)
Left ventricular ejection fraction (MRI), %		
Median (Q1;Q3)	54 (50;60)	55 (52;60)
Min, Max	36, 72	38, 70
Ventricular dysfunction with MRI (LVEF<50%) — no. (%)	13 (22.8%)	10 (16.7%)

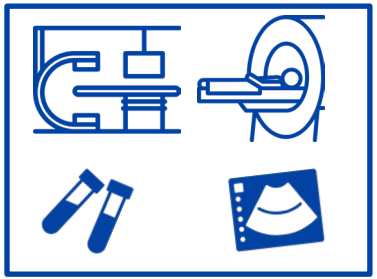
Absence of pericardial effusion — no. (%)	48 (85.7%)	47 (78.3%)

Results

Study course

AM patients

Diagnosis



R

Treatment

Follow-up

Composite Outcome 13.7%

2 days (1;3)

Min – Max = 0 - 4

2 days (1;3)

Min – Max = 1 - 6

28 days

CCU Admission For a Suspected AM

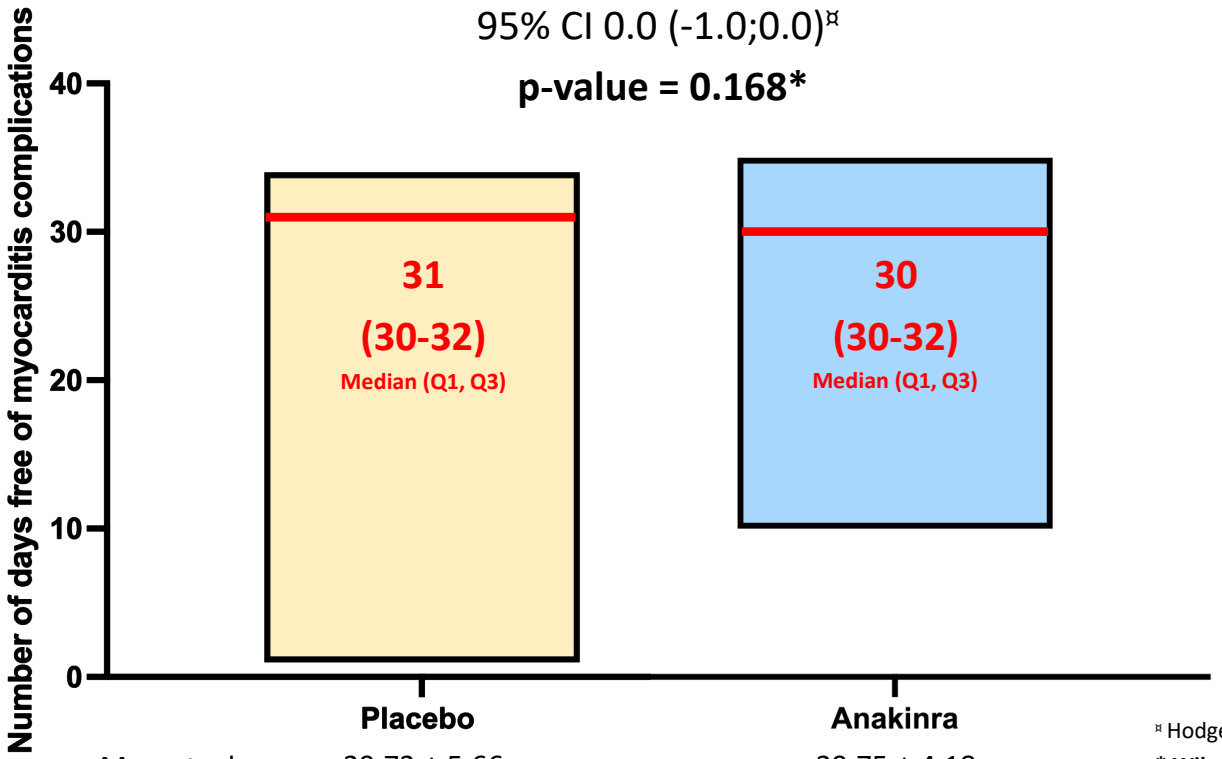
Confirmation of diagnosis and randomization

Hospital Discharge

Primary Endpoint

Number of days considered for the Primary Endpoint

Primary Endpoint : Number of days free of complications



Red Line = Median

Box = Min-Max

¤ Hodges-Lehmann's median difference

*** Wilcoxon-Mann Whitney test**

Non parametric Ancova p-value = 0.192

Components of the Primary endpoint

	Anakinra N=57	Placebo N=60	Odds Ratio (95% CI)
Composite outcome* — no. (%)	**6 (10.5%)**	**10 (16.7%)**	**0.59 (0.19; 1.78)**
Ventricular arrhythmia at 28 days post discharge — no. (%)	1 (1.8%)	1 (1.7%)	
Chest pain requiring medication at 28 days post discharge — no. (%)	**2 (3.5%)**	**6 (10.0%)**	**0.33 (0.06; 1.76)**
Ventricular dysfunction (LVEF<50%) at 28 days post discharge — no. (%)	4 (8.5%)	4 (7.4%)	1.16 (0.27; 5.09)

***ventricular arrhythmia, HF, chest pain requiring medication or LVEF<50% at 28 days post discharge — no. (%)**

Safety Endpoints

	Anakinra N=58	Placebo N=59	Odds Ratio* (95% CI)	Odds Ratio** (95% CI)
Serious Adverse Event — no. of patients (%)	7 (12.1%)	6 (10.2%)	1.21 (0.37; 3.94)	1.20 (0.35; 4.07)

	Anakinra	Placebo
Serious Adverse Event*. — no. of events *One patient can present several events*	10/10	6/6
Serious Adverse Event potentially related to the drug . ***(Hepatic cytolysis, n=1)***	1	0
Severe Infection	0	0

* Unadjusted Odds Ratio. **Adjusted Odds Ratio for Age and baseline LVEF

Conclusions

ARAMIS, the largest RCT in acute myocarditis, enrolled for the first time an all-comer **acute** myocarditis population diagnosed on **CMR**, mostly at **low risk of events.**

A short administration of anakinra did **not increase the number of days free of myocarditis complications**

There was no safety issue with anakinra administered during the acute phase of myocarditis diagnosed without EMB (**no proof of absence of viral replication**)

Further RCT studies are needed to explore the potential benefit of the anti-inflammatory strategy in acute myocarditis patients at **higher risk of events**

Larger studies are needed to evaluate **prolonged anti inflammatory strategies** in acute myocarditis patients at « low-to-moderate risk » (16% of events at M1)

Thank You to the ARAMIS Team

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Dr Mathieu KERNEIS
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Steering Commitee : Dr Mathieu Kerneis, Pr Fleur Cohen, Pr Alain Combes, Pr Eric Vicaut, Pr Gilles Montalescot

Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy

Results of the ATTRibute-CM Trial

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27 Aug 2023

ESC Congress 2023
Amsterdam & Online

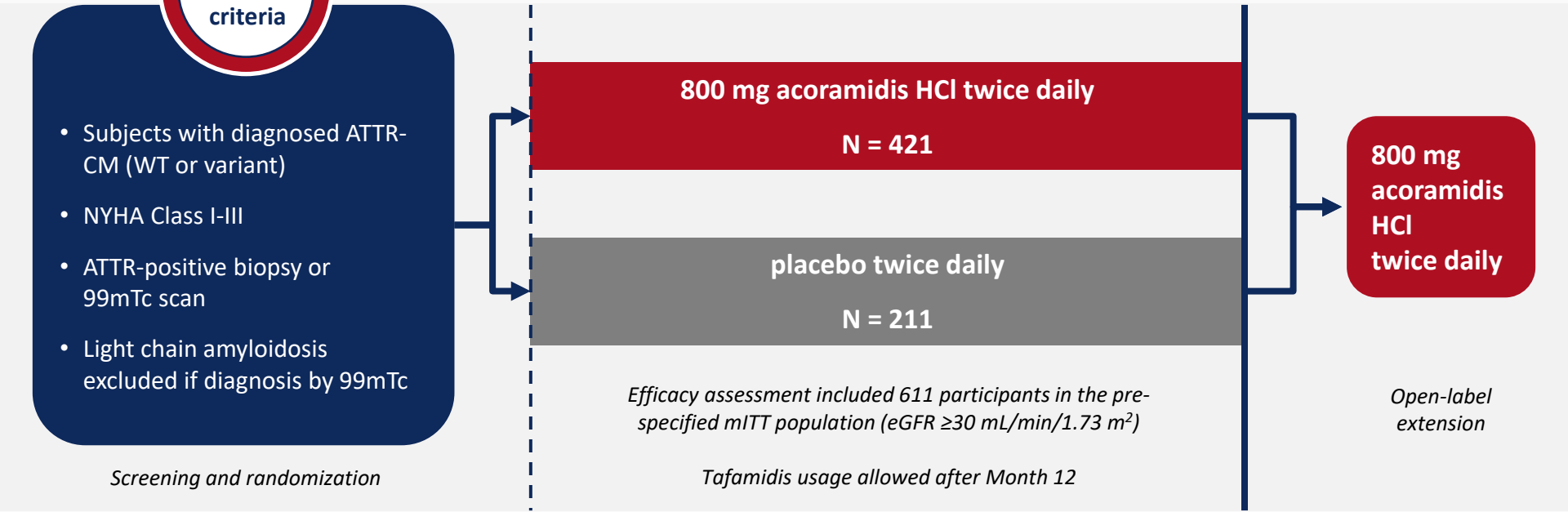
Disclosures

Advisor/consultant for BridgeBio, Alnylam, Ionis, AstraZeneca, Intellia, Pfizer, ATTRalus, Lycia

Acoramidis is an investigational molecule. The safety and efficacy have not been fully evaluated by regulatory authorities.

ATTRibute-CM: Study Design

30-month primary endpoint:
Hierarchical analysis consisting of all-cause mortality, cumulative frequency of CVH, change from baseline in NT-proBNP, and change from baseline in 6MWD



6MWD = Six-minute walk distance; NYHA = New York heart association; 99mTc = Technetium labeled pyrophosphate (PYP) or bisphosphonate (e.g., DPD); mITT = Modified intent-to-treat. eGFR = Estimated glomerular filtration rate. ClinicalTrials.gov identifier: NCT03860935.

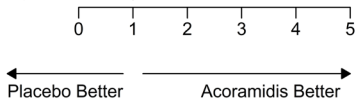
ATTRibute-CM: Baseline Demographic Characteristics

Characteristic	Acoramidis (N=421)	Placebo (N=211)
Age (years), mean (SD)	77.4 (6.5)	77.1 (6.8)
Male sex, n (%)	384 (91.2)	186 (88.2)
ATTRwt-CM, n(%)	380 (90.3)	191 (90.5)
NT-proBNP (pg/mL), median (IQR)	2326 (1332, 4019)	2306 (1128, 3754)
eGFR (mL/min/1.73m^2), mean (SD)	60.9 (18.2)	61.0 (18.7)
TTR (mg/dL), mean (SD)	23.2 (5.6)	23.6 (6.1)
KCCQ-OS, mean (SD)	71.5 (19.4)	70.3 (20.5)
6MWD (m), mean (SD)	361.2 (103.7)	348.4 (93.6)
Concomitant tafamidis use, n (%)*	61 (14.5)	46 (21.8)

ATTRwt-CM = Transthyretin amyloidosis wild-type cardiomyopathy; NT-proBNP = N-terminal pro-B-type natriuretic peptide; IQR = interquartile range; TTR = transthyretin; KCCQ-OS = Kansas City cardiomyopathy questionnaire overall summary score.
*Tafamidis usage allowed after Month 12.

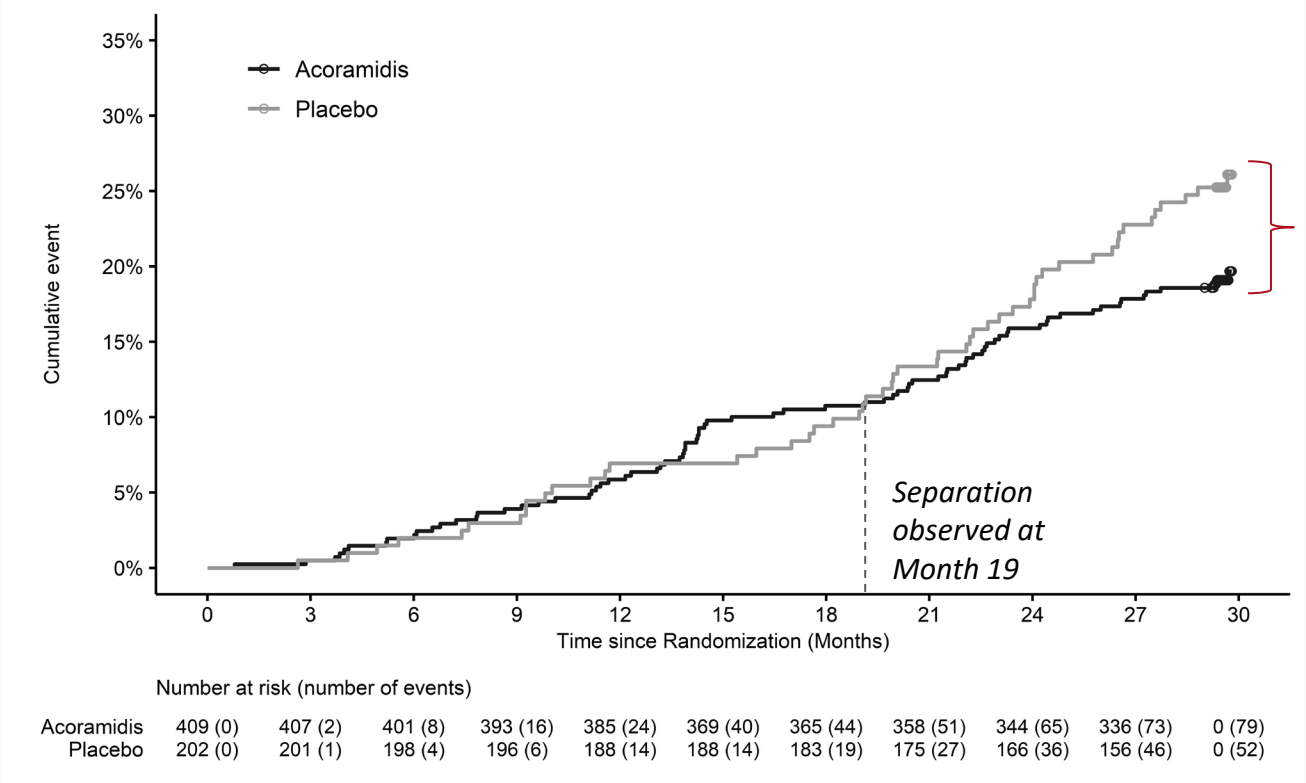
ATTRibute-CM: Primary Outcome Overall and by Subgroups

Subgroup	No. of Patients	Win Ratio [95% CI]	FS test P-value
Overall	611(100.0)	1.772 [1.417, 2.217]	<0.0001
ATTR-CM Genotype			
ATTRm-CM	59(9.7)	2.529 [1.303, 4.911]	0.0061
ATTRwt-CM	552(90.3)	1.756 [1.396, 2.208]	<0.0001
NT-proBNP (pg/mL)			
<= 3000	401(65.6)	1.787 [1.373, 2.325]	<0.0001
> 3000	210(34.4)	1.678 [1.160, 2.426]	0.0060
eGFR (mL/min/1.73m2)			
< 45	94(15.4)	1.410 [0.849, 2.341]	0.1841
>= 45	517(84.6)	1.797 [1.452, 2.226]	<0.0001
Age (years)			
< 78	299(48.9)	2.052 [1.489, 2.829]	<0.0001
>= 78	312(51.1)	1.499 [1.098, 2.045]	0.0107
NYHA Class			
I, II	512(83.8)	1.892 [1.479, 2.419]	<0.0001
III	99(16.2)	1.150 [0.652, 2.030]	0.6292



FS = Finkelstein-Schoenfeld; CI = Confidence interval.

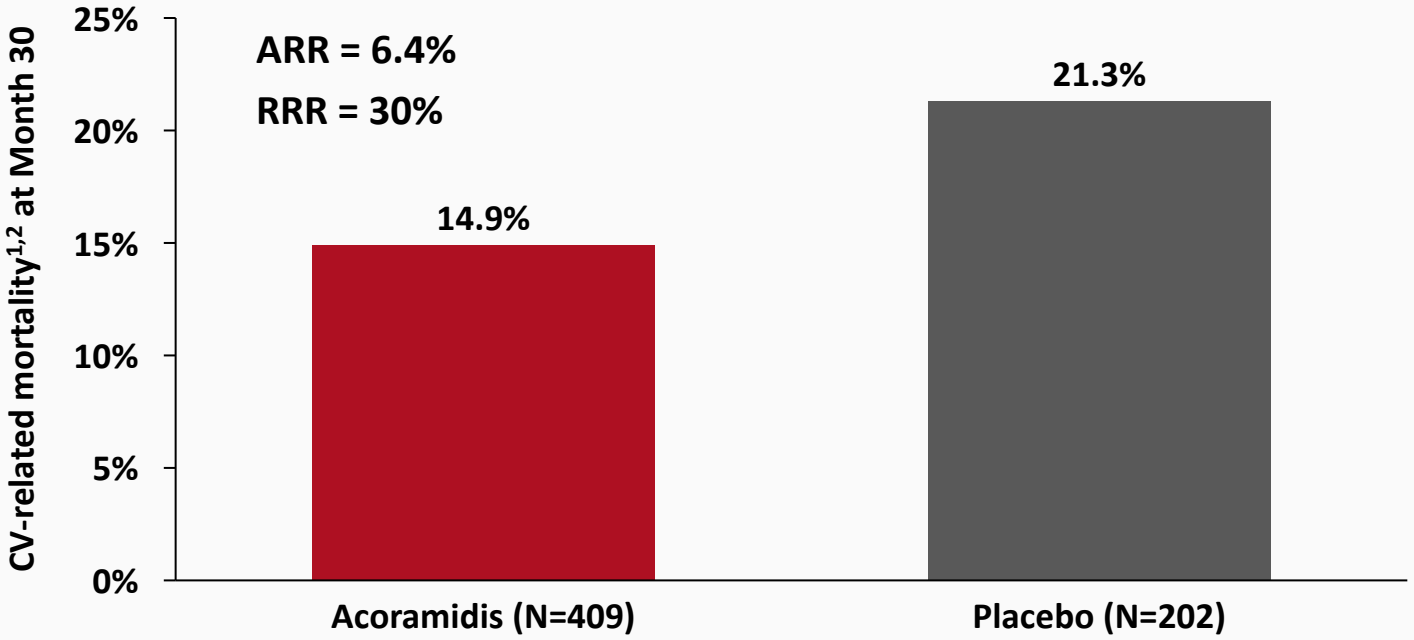
ATTRibute-CM: All-Cause Mortality



ARR = Absolute risk reduction; RRR = Relative risk reduction.

All-cause mortality includes heart transplant, implantation of cardiac mechanical assist device, and all-cause death.

ATTRibute-CM: Cardiovascular-Related Mortality



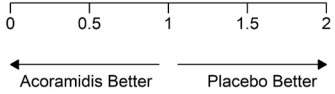
CV-related: Cardiovascular-related.

[1]Heart transplant and implantation of cardiac mechanical assistance device (CMAD) were treated as death for this analysis. N =1 heart transplant & N = 1 CMAD implantation in placebo group.

[2]CV-related mortality includes all adjudicated CV-related and undetermined cause of death.

ATTRibute-CM: Frequency of CVH; P<0.0001 on overall analysis

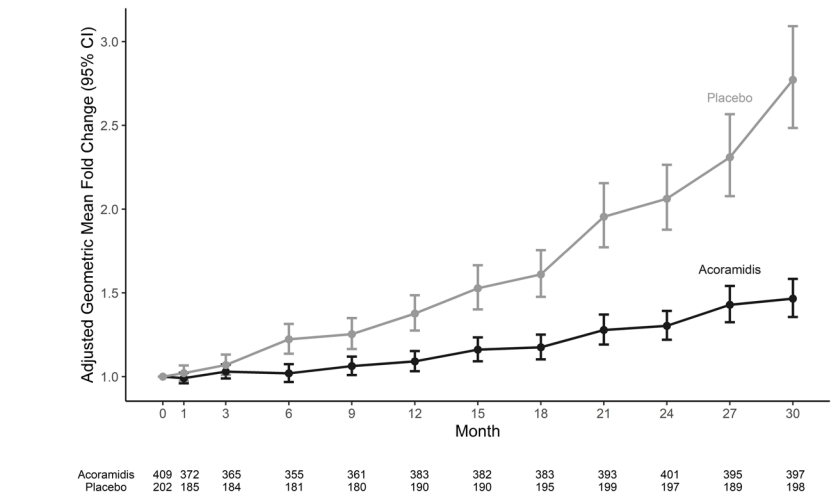
Subgroup	No. of Patients	Relative Risk [95% CI]
Overall	611(100.0)	0.496 [0.355, 0.695]
ATTR-CM Genotype		
ATTRm-CM	59(9.7)	0.377 [0.139, 1.027]
ATTRwt-CM	552(90.3)	0.514 [0.360, 0.734]
NT-proBNP (pg/mL)		
<= 3000	401(65.6)	0.456 [0.299, 0.695]
> 3000	210(34.4)	0.576 [0.330, 1.003]
eGFR (mL/min/1.73m2)		
< 45	94(15.4)	0.594 [0.250, 1.415]
>= 45	517(84.6)	0.481 [0.334, 0.692]
Age (years)		
< 78	299(48.9)	0.437 [0.275, 0.696]
>= 78	312(51.1)	0.576 [0.353, 0.940]
NYHA Class		
I, II	512(83.8)	0.447 [0.310, 0.645]
III	99(16.2)	0.721 [0.313, 1.660]



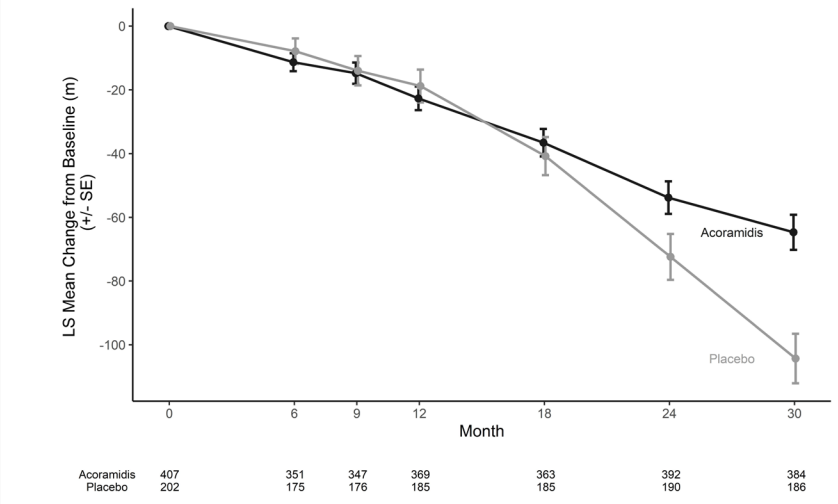
Negative binomial regression with treatment group, stratification factors, and subgroup of interest was used to analyze the cumulative frequency of adjudicated CV-related hospitalization.

ATTRibute-CM: Change from Baseline in NT-proBNP & 6MWD

Change from Baseline in NT-proBNP[1]



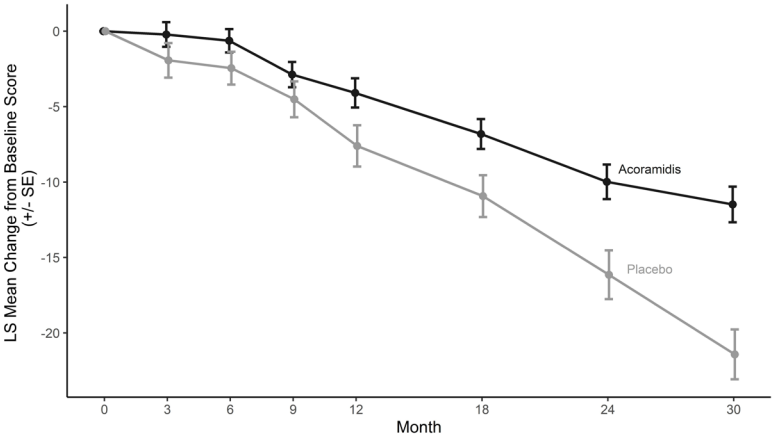
Change from Baseline in 6MWD[1]



[1]Analyzed using mixed effects model with repeated measures. Missing measurements due to early discontinuation imputed using the Jump to Reference method. Missing measurements due to death performed by sampling with replacement from bottom 5% of observed values.

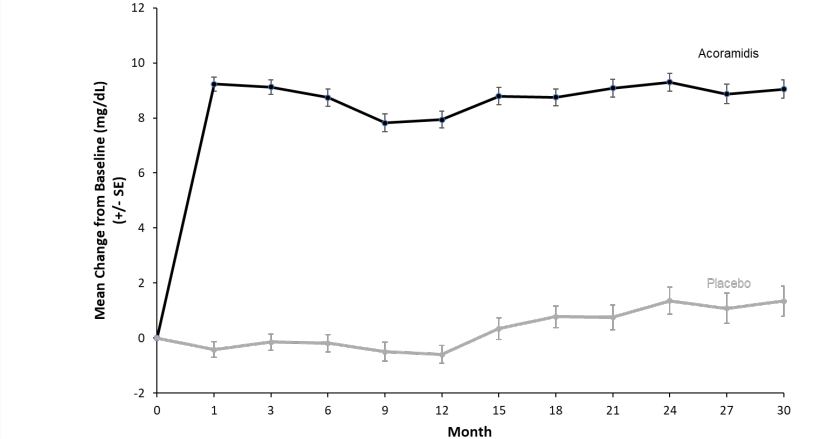
ATTRibute-CM: Change from Baseline in KCCQ-OS & Serum TTR

Change from Baseline in KCCQ-OS[1]



Acoramidis	408	263	389	390	397	404	407	405
Placebo	202	134	192	194	196	199	201	201

Change from Baseline in Serum TTR[2]

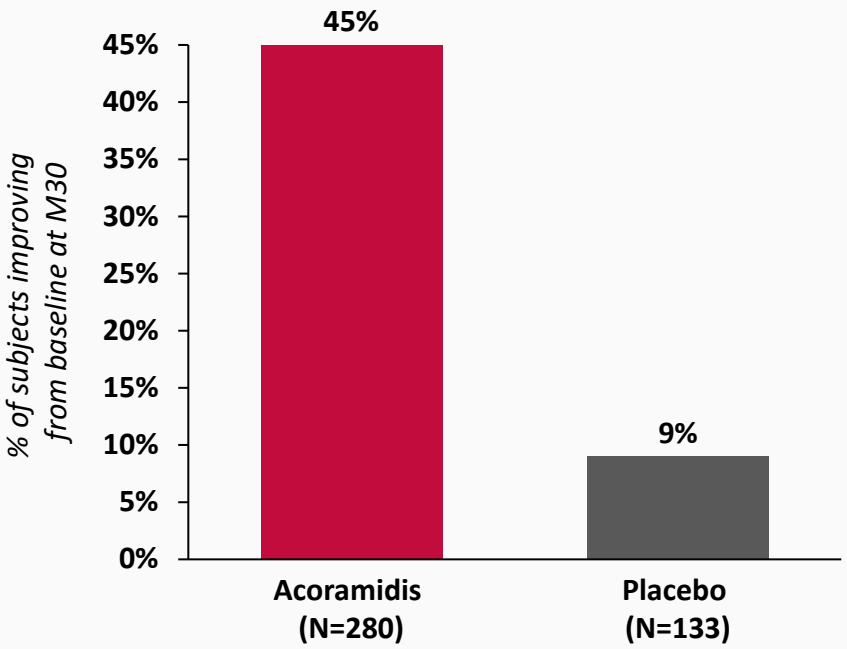


Acoramidis	406	363	348	324	319	328	307	300	294	297	280	283
Placebo	199	178	175	165	162	168	160	160	154	142	128	135

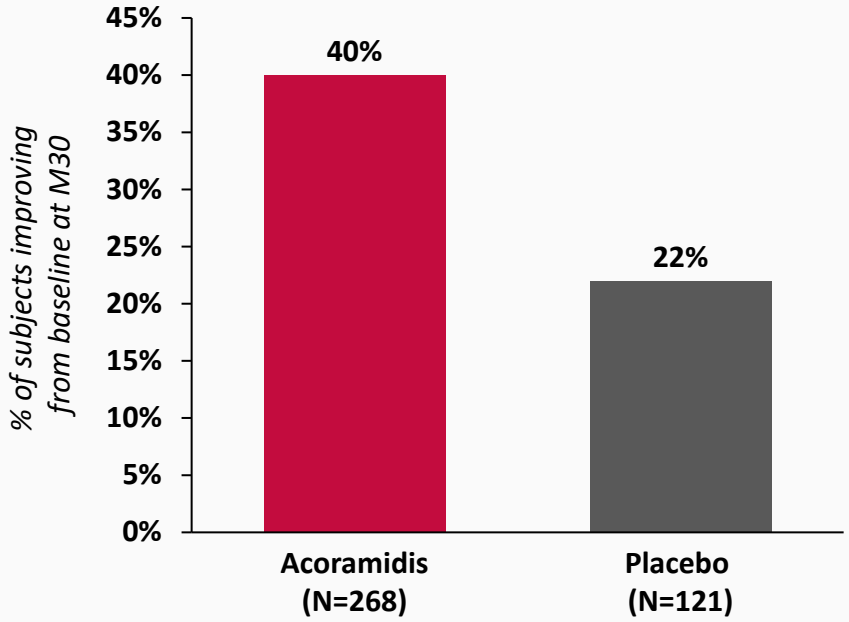
[1]Analyzed using mixed effects model with repeated measures. Missing measurements due to early discontinuation imputed using the Jump to Reference method. Missing measurements due to death performed by sampling with replacement from bottom 5% of observed values. [2]Observed measurements without any imputation. No adjustment was made for early discontinuation for any reason, including death.

ATTRibute-CM: Improvements in Disease Measures

Improvement from baseline in NT-proBNP



Improvement from baseline in 6MWD



mITT population. Improvement is defined as <0 pg/mL change from baseline to month 30 for NT-proBNP; >0 meter change from baseline to month 30 for 6MWD. In both cases, among subjects with both baseline and month 30 values.

ATTRibute-CM: Patient Safety

Subjects with one or more event(s)	Acoramidis N=421 N (%)	Placebo N=211 N (%)
Any treatment-emergent adverse events (TEAEs)	413 (98.1%)	206 (97.6%)
TEAE with fatal outcome	60 (14.3%)	36 (17.1%)
TEAE leading to hospitalization	212 (50.4%)	128 (60.7%)
TEAE leading to study drug discontinuation	39 (9.3%)	18 (8.5%)
Any treatment-emergent serious adverse events (SAEs)	230 (54.6%)	137 (64.9%)
Treatment-emergent SAEs leading to study drug discontinuation	21 (5.0%)	15 (7.1%)
Severe TEAEs[1]	157 (37.3%)	96 (45.5%)

Acoramidis was generally well-tolerated with no findings of potential clinical concern

All Adverse Events (AEs) occurring during the treatment period are considered treatment-emergent adverse events (TEAEs). Serious Adverse Event (SAE) meets seriousness criteria.
[1]Severity as assessed by the investigator.

ATTRibute-CM: Conclusions

- **Primary endpoint analysis (Finkelstein-Schoenfeld hierarchy of ACM, CVH, NT-proBNP, 6MWD) highly statistically significant**
  - Win ratio 1.8; p<0.0001; 58% of win ratio ties broken by ACM + CVH
- **Consistent treatment effect across secondary endpoints**
  - Better preservation of functional capacity (6MWD) and QoL (KCCQ-OS)
  - Reduced progressive increase in NT-proBNP; 45% of patients improved
- **81% survival rate on acoramidis approaches survival rate in age-matched US database (~85%)[1,2]**
- **0.29 mean annual CVH frequency on acoramidis approaches annual hospitalization rate observed in broader US Medicare population (~0.26)[3]**
- **Reassuring safety profile**

[1]ssa.gov. [2]Miller et al., Am J Card 2021 [3]US Department of Health & Human Services, Jan 2018.

ATTRibute-CM: Acknowledgements

- Patients, caregivers
- Investigators, research staff
- Steering Committee, Data Monitoring Committee, Clinical Events Committee, Data Reporting Center
- Patient advocacy organizations
- BridgeBio scientists and supporting employees

Bioflow-DAPT

Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk

A randomized, open-label clinical trial to assess the safety of HBR patients undergoing PCI with implantation of a drug-eluting stent and treated with DAPT for 1 month

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25 August 2023

Declaration conflict of interest

- Grants and/or personal fees from Astra Zeneca, Terumo, Alvimedica/CID, Abbott Vascular, Daiichi Sankyo, Bayer, CoreFLOW, Idorsia Pharmaceuticals-Ltd, Universität Basel Department Klinische Forschung, Vifor, Bristol-Myers-Squib SA, Biotronik, Boston scientific, Medtronic, Vesalio, Novartis, Chiesi, PhaseBio.

Background

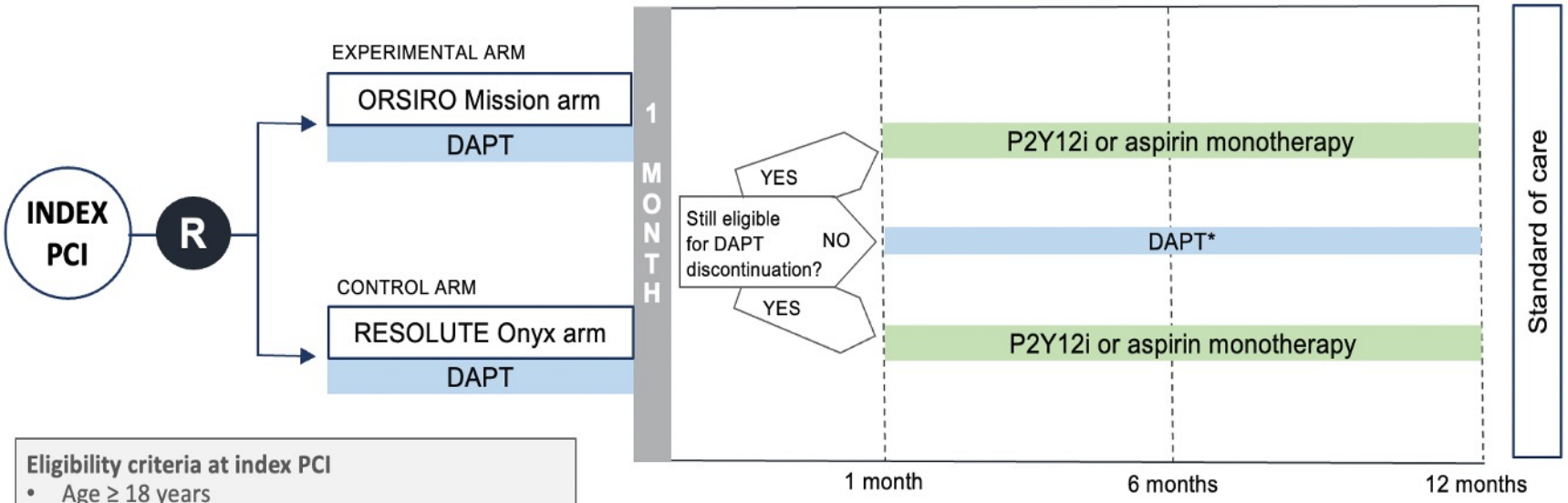
- Randomized and non-randomized studies have shown that 1-month DAPT after PCI reduces bleeding without compromising safety compared with more prolonged treatment durations in patients at high bleeding risk (HBR).[1,2]

- However, there is limited information on the comparative efficacy and safety of different stent platforms in HBR patients undergoing an abbreviated DAPT duration after PCI.

- Onyx ONE compared 2 drug-eluting stent platforms in patients at high bleeding risk undergoing 1 month of DAPT and showed that durable-polymer zotarolimus-coated stents were associated with non-inferior outcomes to polymer-free umirolimus-coated stents.[3]

1. Valgimigli M et al. N Engl J Med. 2021;385:1643-1655. 2. Mehran R et al. JACC Cardiovasc Interv. 2021;14:1870-1883.
3. Windecker S et al *N Engl J Med*. 2020;382:1208-1218

Study Design



Eligibility criteria at index PCI

- Age ≥ 18 years
- Acceptable candidate for treatment with DES
- Patient at HBR
- Able to comply with all protocol and follow-up requirements
- Eligible for 1-month DAPT

12-month primary endpoint
The composite of cardiac death, myocardial infarction and definite or probable ST

* Subjects will not be excluded from the study but will be assessed at each follow-up visit through 12 months.

High Bleeding Risk Definition (1 or more criteria)

a. ≥ 75 years of age

b. Moderate or severe chronic kidney disease or failure

c. Advanced liver disease

d. Cancer diagnosed or treated within the previous 12 months or actively treated

e. Anemia with hemoglobin < 11.0 g/dL or requiring transfusion within 4 weeks before randomization

f. Baseline thrombocytopenia

g. History of stroke, previous intracerebral hemorrhage (ICH) or presence of a brain arteriovenous malformation

h. History of hospitalization for bleeding within previous 12 months

i. Chronic clinically significant bleeding diathesis

j. Clinical indication for chronic or lifelong oral anticoagulation (OAC)

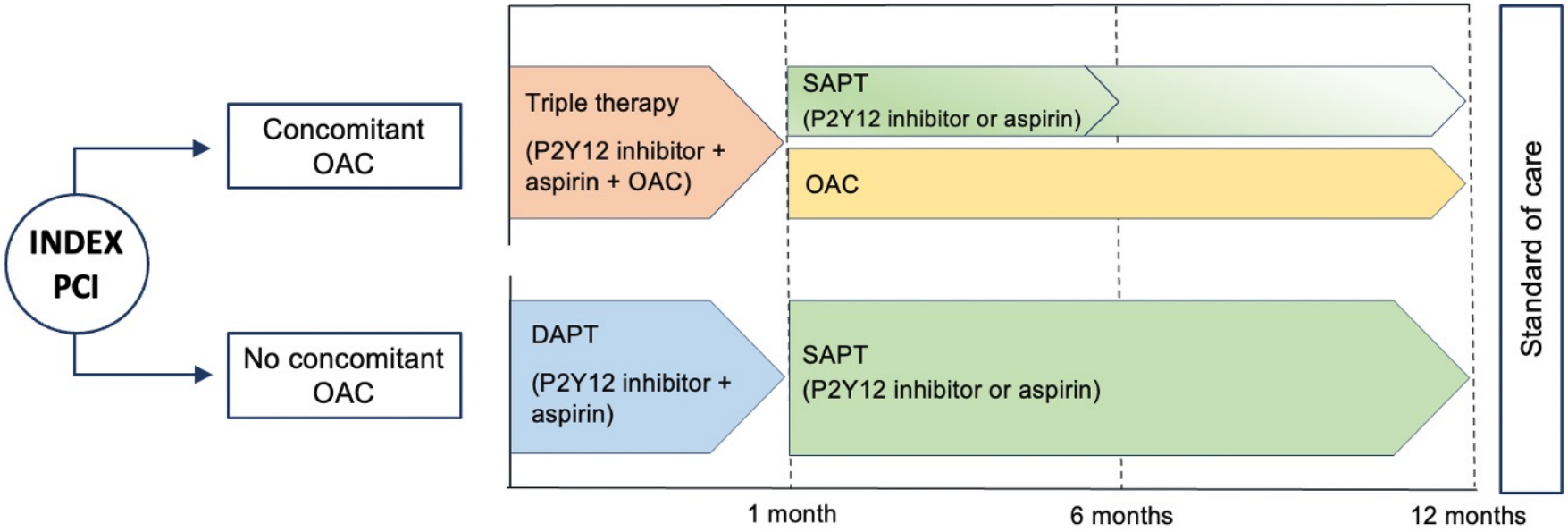
k. Clinical indication for chronic steroid or oral non-steroidal anti-inflammatory drug(s) other than aspirin

l. Non-deferrable major surgery on DAPT

m. Recent major surgery or major trauma within 30 days before PCI

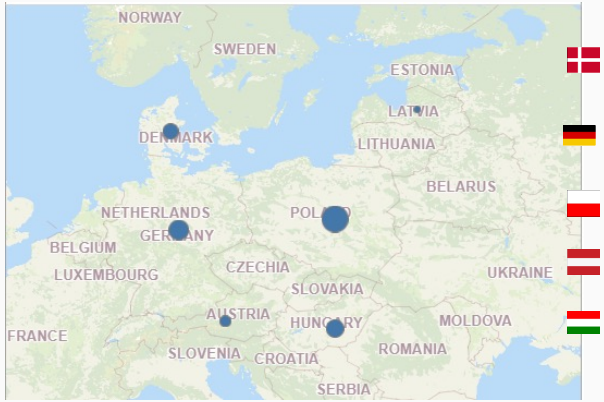
n. PRECISE DAPT score ≥ 25

Medication Chart



Landi A et al. 2023. J Cardiovasc Transl Res. doi: 10.1007/s12265-023-10400-x

52 Enrolling Sites in 18 Countries



A.Erglis, A. Kalnins

H. Kelbæk, N.T. Olsen

R. Tölg, M. Haude, T. Schmitz, M. Sherif, J. Wöhrle

A. Wlodarczak, J. Legutko

G. Toth- Gayor, M-C Brandt

B. Merkely, A. Vorobcsuk, I. Horvath

A. Yung, B. Yan

W. Kehasukcharoen, S. Nakarin

S. Azmi

D. Khoo Zhi Lin

N. Collins, I. Shiekh, W. Van Gaal,

J. Somaratne

DSMB/ CEC

- R. Birkemeyer
- L. Buellesfeld
- B. Witzenbichler
- S. Schneider

S. Somi

F. Stammen, B. Ferdinande, J. Kefer, P. Coussement

M. Moccetti,P. L. Dietrich, S. Fournier, J. Iglesias, V. Rubimbura

J.M. De La Torre; A. Torres Bosco, J. Sanchis Fores

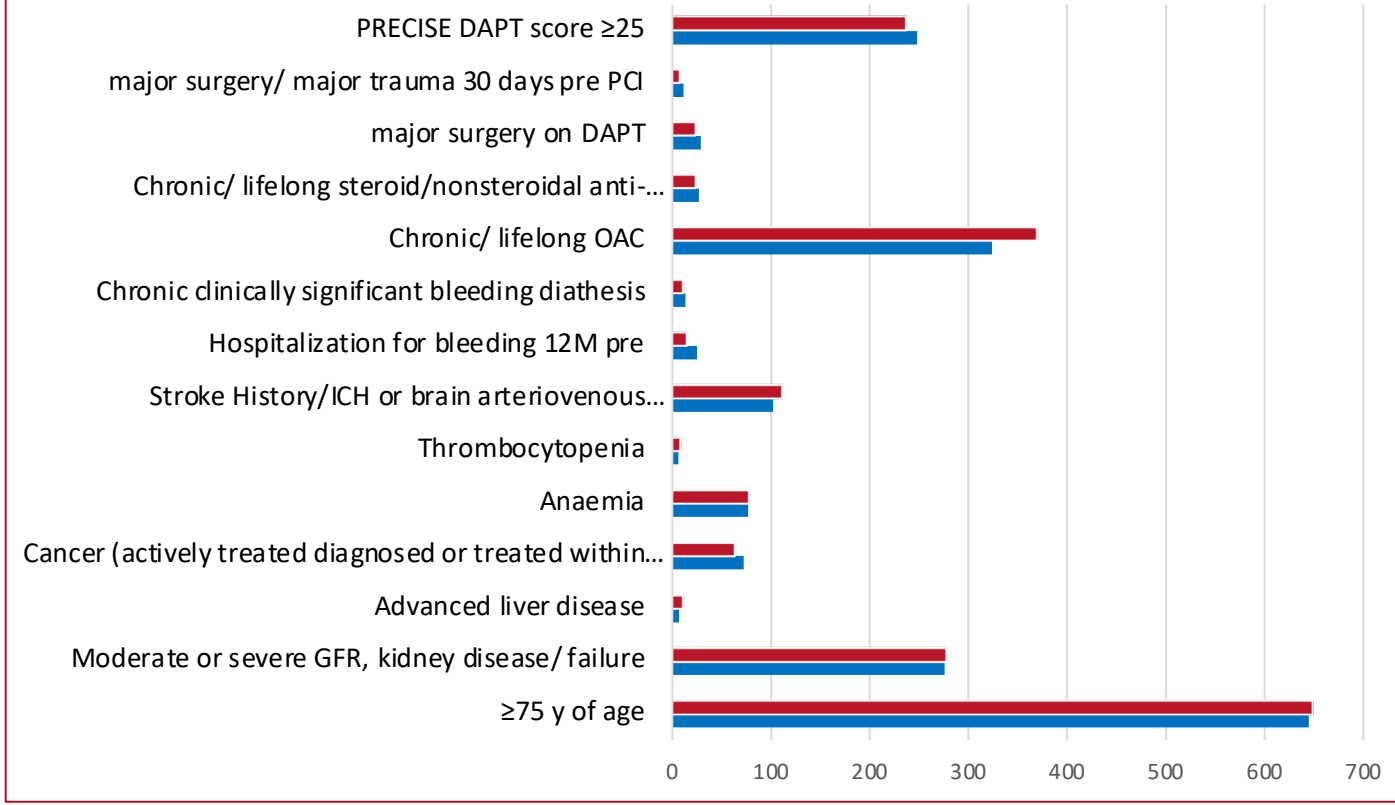
G. Cayla, M. Godin, T. Lhermusier, B. Honton, F. Sanguineti, J. Silvain, E. Puymirat, G. Lemesle, D. Romain

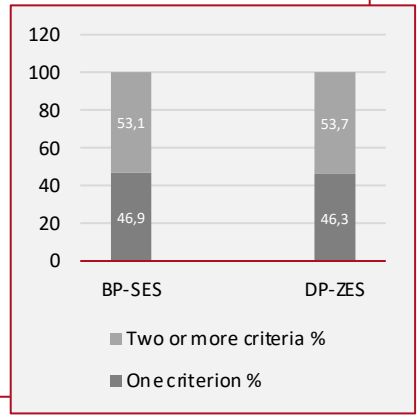
S. Galli, D. Capodanno, M. Ferlini, E. Nicolini

Patient Characteristics (N=1948 pts)

Characteristic	BP-SES (n=969 Patients)	DP-ZES (n=979 Patients)
Age [years] Mean ± SD	76.0 ± 8.5	75.6 ± 8.2
Male	658 (67.9)	679 (69.4)
Renal disease	321 (33.1)	323 (33.0)
Hepatic disease	30 (3.1)	32 (3.3)
Respiratory disease	142 (14.7)	136 (13.9)
Hypertension	787 (81.2)	804 (82.1)
Hypercholesterolemia	659 (68.0)	678 (69.3)
Diabetes	301 (31.1)	311 (31.8)
Smoking History		
Ex-smoker	317 (32.7)	324 (33.1)
Current smoker	131 (13.5)	120 (12.3)
Congestive heart failure	215 (22.2)	202 (20.6)
Oral anticoagulant	324 (33.4)	369 (37.8)
Stable angina	477 (49.6)	495 (50.9)
Silent ischemia	190 (19.8)	197 (20.3)
Non–ST-elevation myocardial infarction	182 (19.0)	180 (18.5)
ST-elevation myocardial infarction	16 (1.7)	17 (1.7)

High-Bleeding Risk Criteria





Procedural Characteristics at Patient Level (1)

Characteristic	Biodegradable-Polymer Stent (n=969 Patients)	Zotarolimus-Eluting Stent (n=979 Patients)
Access[b], no. (%)		
Radial	815 (84.1)	834 (85.2)
Femoral	137 (14.1)	130 (13.3)
Brachial	10 (1.0)	9 (0.9)
Lesion location[c], no. (%) (at least 1 lesion)		
Left main	45 (3.7)	38 (3.9)
Left anterior descending	529 (55.2)	541 (55.6)
Left circumflex	270 (28.2)	264 (27.1)
Right coronary artery	310 (32.3)	299 (30.7)
Bypass graft	16 (1.7)	15 (1.5)
At least one B2/C lesion class[c], no. (%)	583 (60.9)	614 (63.5)
At least one lesion with moderate or severe calcification‡, no. (%)	339 (35.3)	335 (34.5)
At least one lesion with bifurcation[c], no. (%)	290 (30.2)	308 (31.7)

a Plus–minus values are means±SD.

b Unknown for 7 patients in biodegradable-polymer stent group and 6 patients in the zotarolimus-eluting stent group.

c Unknown for 10 patients in biodegradable-polymer stent group and 6 patients in the zotarolimus-eluting stent group (percentages were calculated using a total of 959 patients in the biodegradable-polymer stent group and 973 patients in the zotarolimus-eluting stent group).

Procedural Characteristics at Patient Level (2)

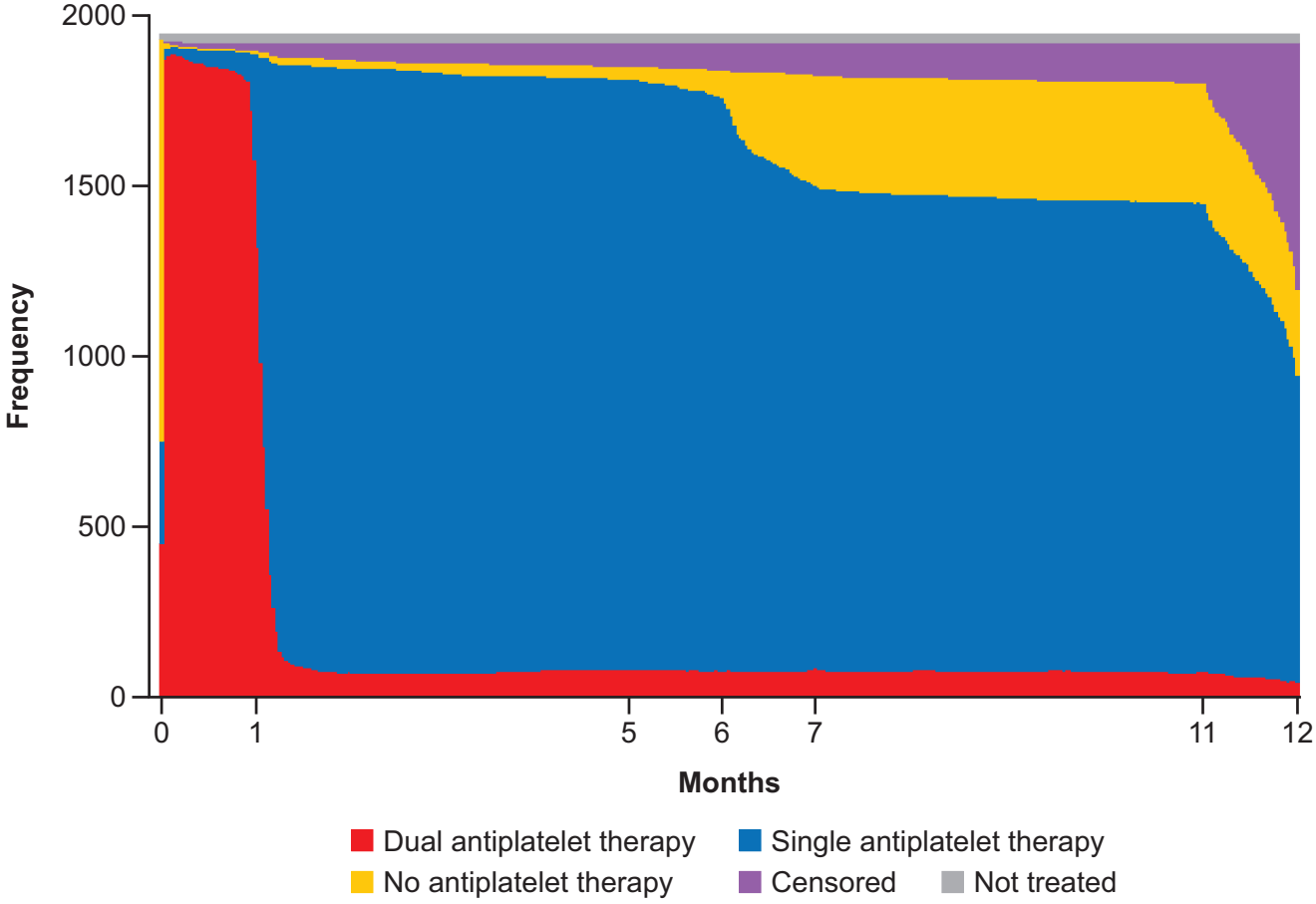
Characteristic	Biodegradable-Polymer Stent (n=969 Patients)	Zotarolimus-Eluting Stent (n=979 Patients)
≥ 1 lesion with chronic total occlusion[c], no. (%)	24 (2.5)	22 (2.3)
≥ 1 lesion with in-stent restenosis[c], no. (%)	47 (4.9)	50 (5.1)
Mean reference vessel diameter per subject[c], mm	3.1 ± 0.5	3.1 ± 0.5
Mean diameter stenosis per subject[c], %	82.0 ± 11.8	82.2 ± 13.0
Mean lesion length per subject[c], mm	20.8 ± 11.1	21.3 ± 12.2
Multivessel intervention, no. (%)	210 (21.9)	181 (18.6)
Number of vessels treated per patient[d], no. (%)		
One	738 (77.0)	779 (80.1)
Two	173 (18.0)	150 (15.4)
Three	33 (3.4)	24 (2.5)
Number of stents per patient	1.7 ± 1.0	1.7 ± 1.0
Total stent length per patient	37.2 ± 25.4	36.7 ± 24.4
Any overlapping stenting, no. (%)	174 (18.0)	212 (21.7)

a Plus–minus values are means±SD.

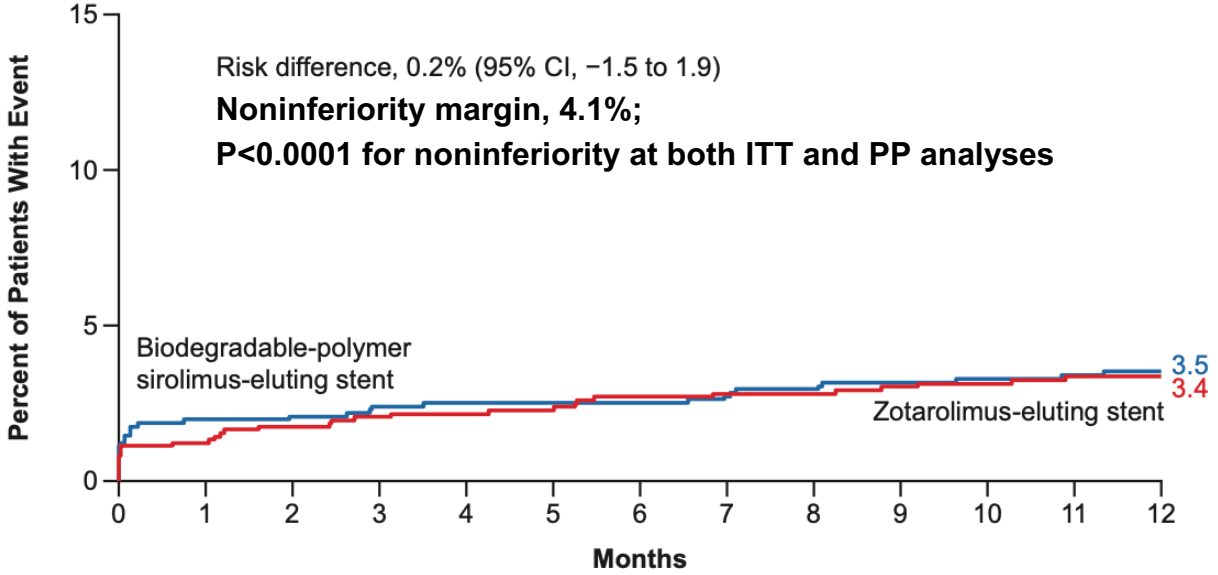
c Unknown for 10 patients in biodegradable-polymer stent group and 6 patients in the zotarolimus-eluting stent group (percentages were calculated using a total of 959 patients in the biodegradable-polymer stent group and 973 patients in the zotarolimus-eluting stent group).

d Four patients in the biodegradable-polymer stent group and 6 in the zotarolimus-eluting stent group had 4 treated vessels; 1 patient in the zotarolimus-eluting stent group had 5 treated vessels and 11 patient in biodegradable-polymer stent group and 13 in the zotarolimus-eluting stent group had only coronary artery bypass graft treatment.

Adherence to Antiplatelet Therapy after PCI



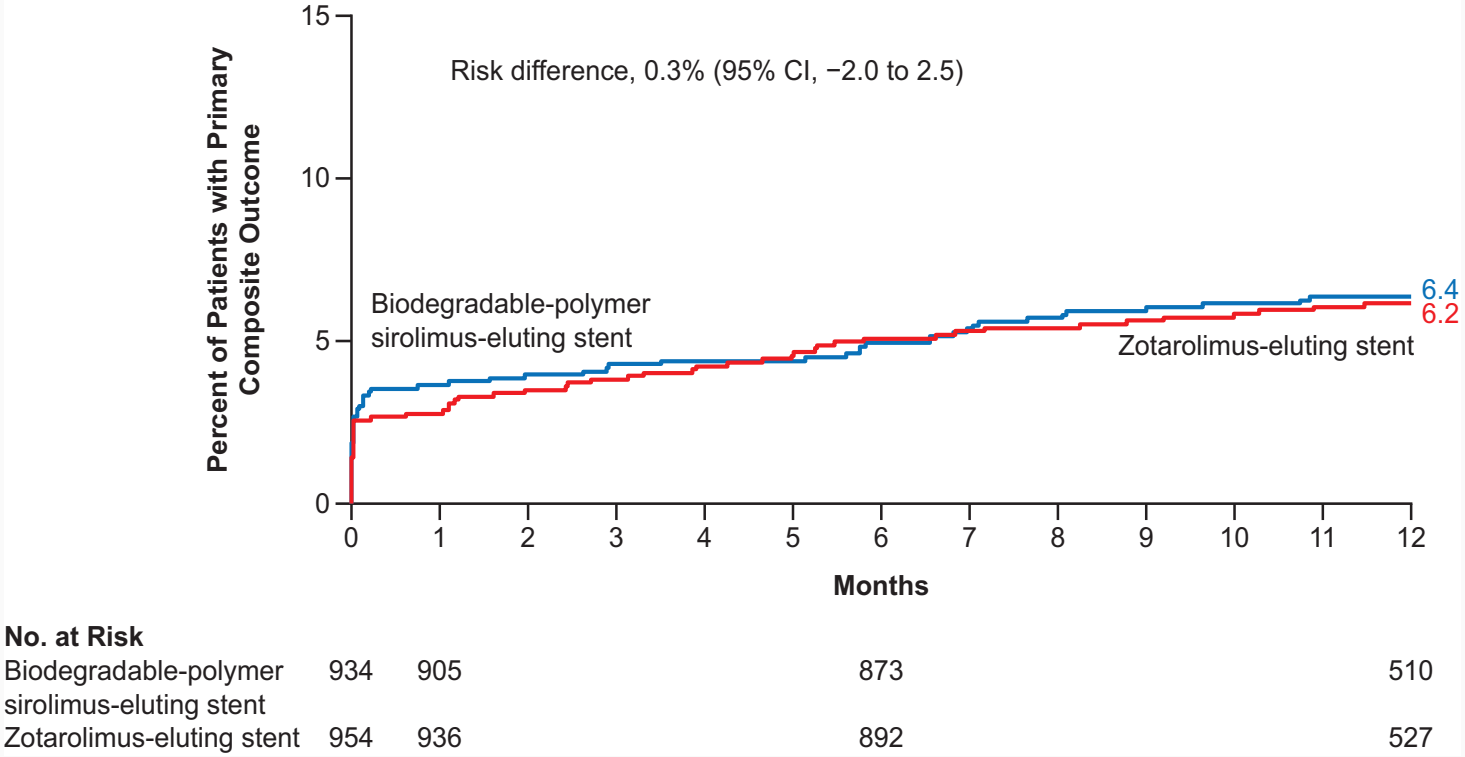
Primary Outcome: Cardiac Death, Myocardial Infarction*, or Stent Thrombosis



No. at Risk				
Biodegradable-polymer sirolimus-eluting stent	941	921	896	526
Zotarolimus-eluting stent	960	950	913	537

*ARC-2 definition

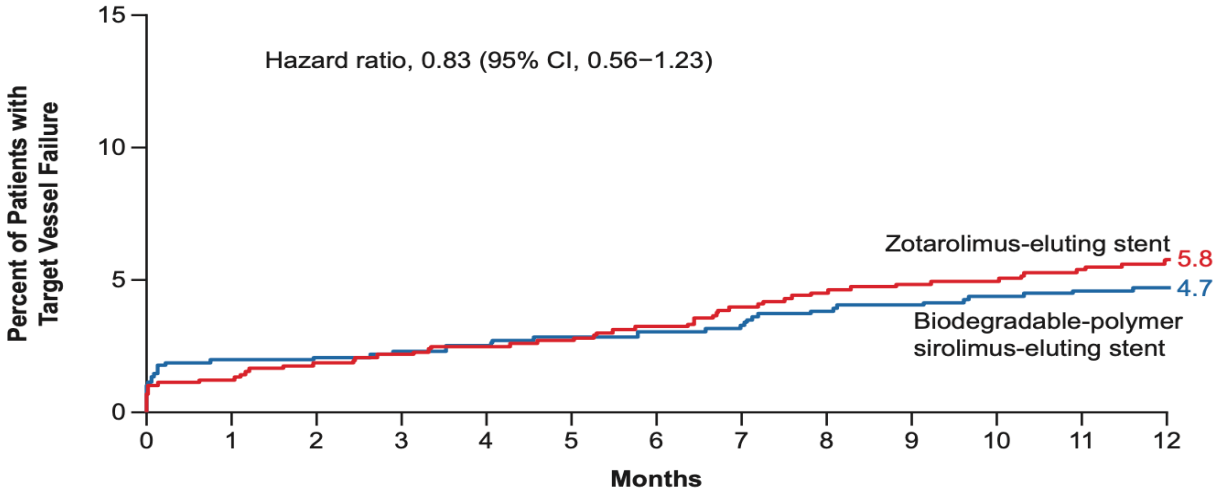
Prespecified EP: Cardiac Death, Myocardial Infarction*, or Stent Thrombosis



No. at Risk				
Biodegradable-polymer sirolimus-eluting stent	934	905	873	510
Zotarolimus-eluting stent	954	936	892	527

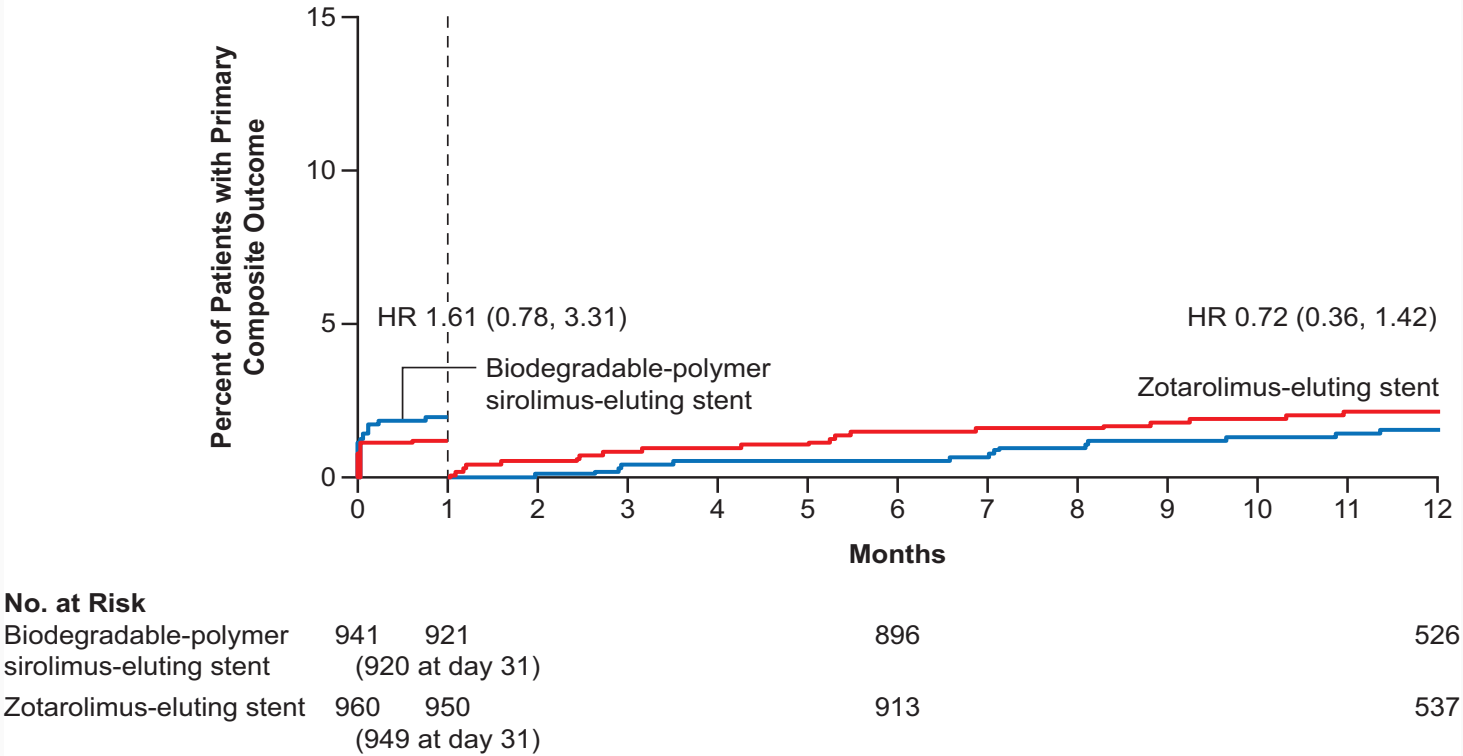
*Third Universal MI definition

Target Vessel Revascularization



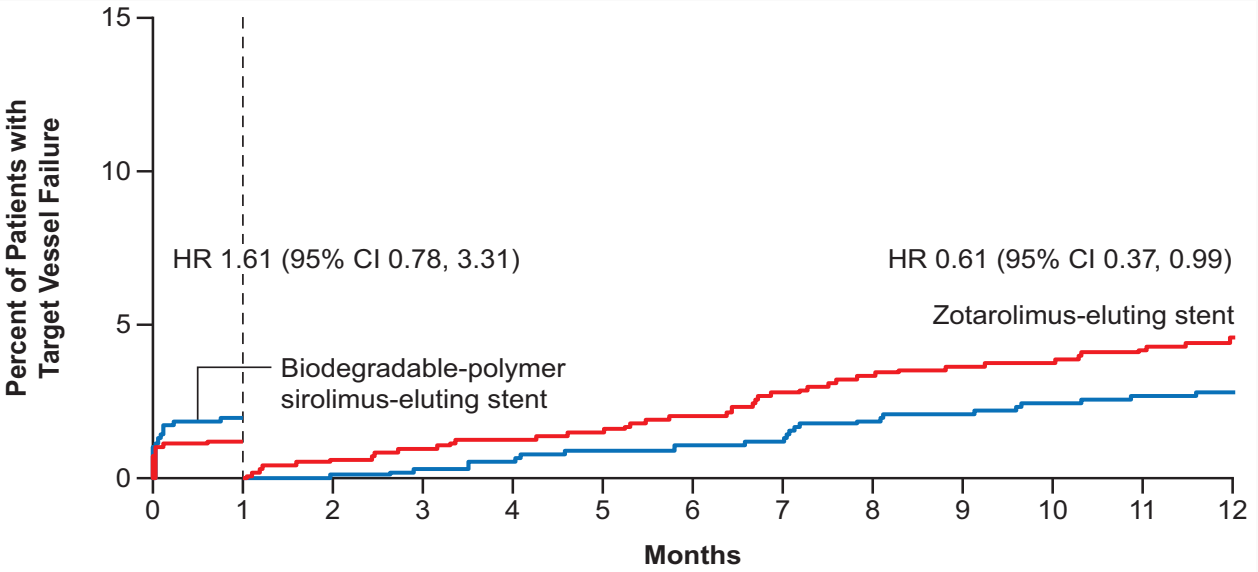
No. at Risk				
Biodegradable-polymer sirolimus-eluting stent	942	921	891	518
Zotarolimus-eluting stent	961	950	909	527

Prespecified Landmark Analysis at 30 days: Primary Endpoint*



*: ARC-2 definition

Prespecified Landmark Analysis at 30 days: Target Vessel Failure



No. at Risk

Biodegradable-polymer sirolimus-eluting stent	942	921 (920 at day 31)	891	518
Zotarolimus-eluting stent	961	950 (949 at day 31)	909	527

Limitations

- Incidences of outcome events at 1 year were lower than expected
- Treatments were open label
- Decision to continue aspirin or a $P2Y_{12}$ inhibitor was at the discretion of the physicians (Rx was stratified accordingly)
- Complete SDV was implemented in a random cohort of 28.2% of the patients
- Angiograms were not assessed by an independent core-laboratory

Conclusion

In patients at high risk for bleeding, a strategy of PCI with BP-SES (Orsiro) followed by 30 days of DAPT therapy was non-inferior to DP-ZES (Onyx) with respect to the incidence of death from cardiac causes, myocardial infarction, or stent thrombosis

Circulation

CIRCULATION. 2023; [PUBLISHED ONLINE AHEAD OF PRINT]. DOI: 10.1161/CIRCULATIONAHA.123.065448

BIODEGRADABLE-POLYMER OR DURABLE-POLYMER STENTS IN PATIENTS AT HIGH BLEEDING RISK. A RANDOMIZED, OPEN-LABEL CLINICAL TRIAL

ARCO VALGIMIGLI, MD, PHD; ADRIAN WLODARCZAK, MD; RALPH TÖLG, MD; BÉLA MERKELY, MD, PHD; HENNING KELBÆK, MD; JACEK LEGUTKO, MD, PHD; STEFANO GALLI, MD; MATTHIEU GODIN, MD; GABOR G. TOTH, MD, PHD; THIBAULT LHERMUSIER, MD; BENJAMIN HONTON, MD; PETER LAURENZ DIETRICH, MD; FRANCIS STAMMEN, MD; BERT FERDINANDE, MD; JOHANNE SILVAIN, MD, PHD; DAVIDE CAPODANNO, MD, PHD; GUILLAUME CAYLA, MD, PHD; FOR THE BIOFLOW-DAPT INVESTIGATORS

CIRCULATION

HTTPS://WWW.AHAJOURNALS.ORG/DOI/10.1161/CIRCULATIONAHA.123.065448

CAMAREC

FIRST-LINE CMR FOR SYSTOLIC DYSFUNCTION

Evaluate **CMR** for **Predicting CAD** In Unexplained **LV Dysfunction**

Dr Louis-Marie Desroche – 27 August 2023

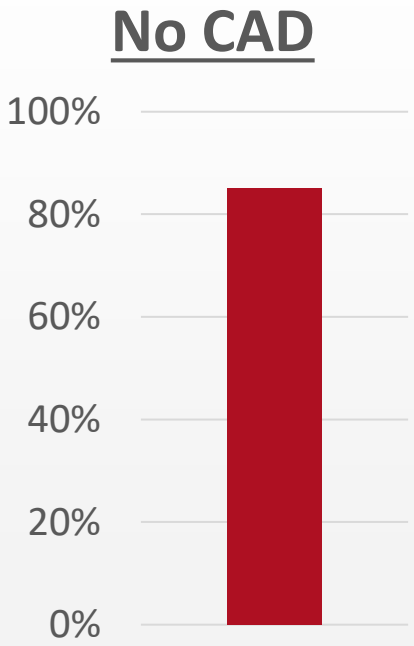
MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ

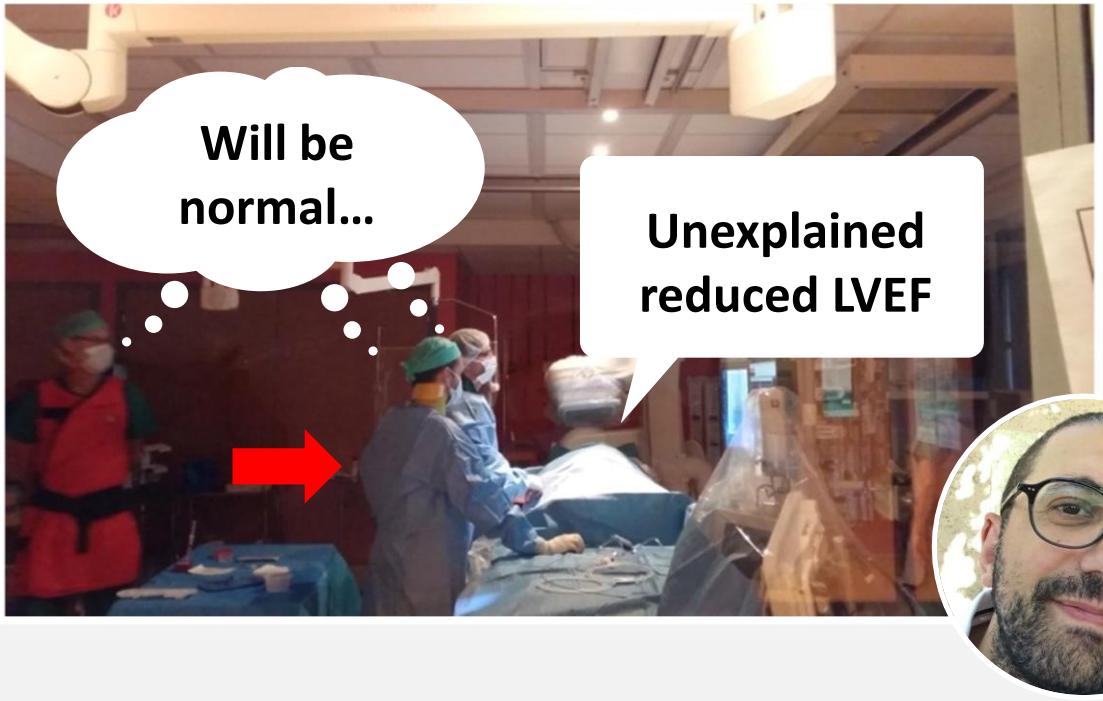
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

ENC ÉCOLE NUMÉRIQUE DE CARDIOLOGIE

CHU CENTRE HOSPITALIER UNIVERSITAIRE LA RÉUNION

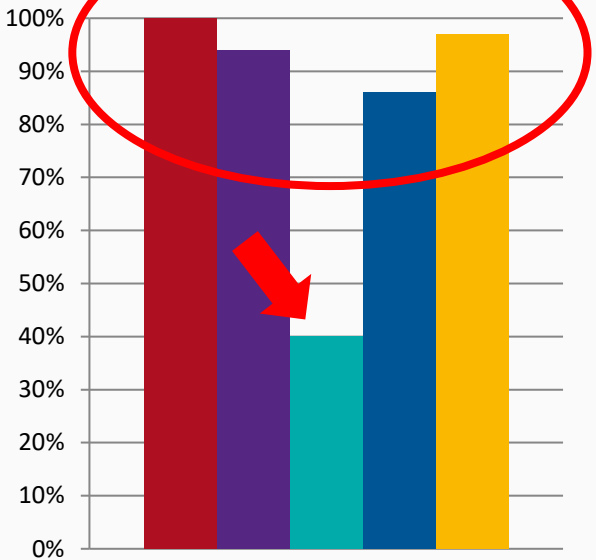
Frustration : the beginning of the journey

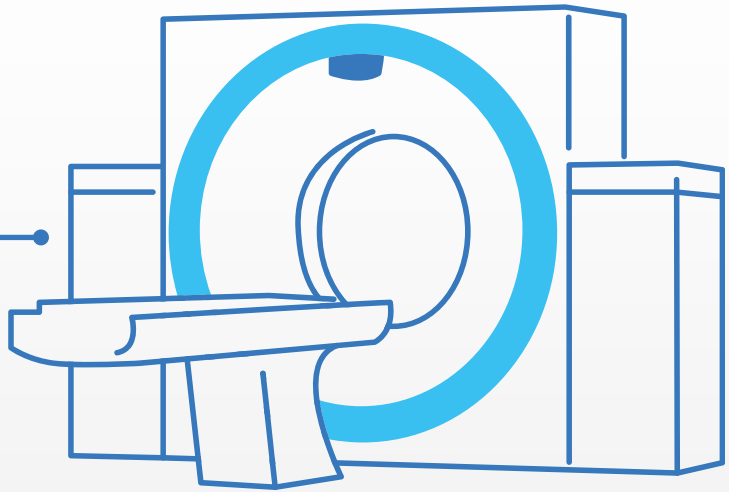




A New Hope: CMR

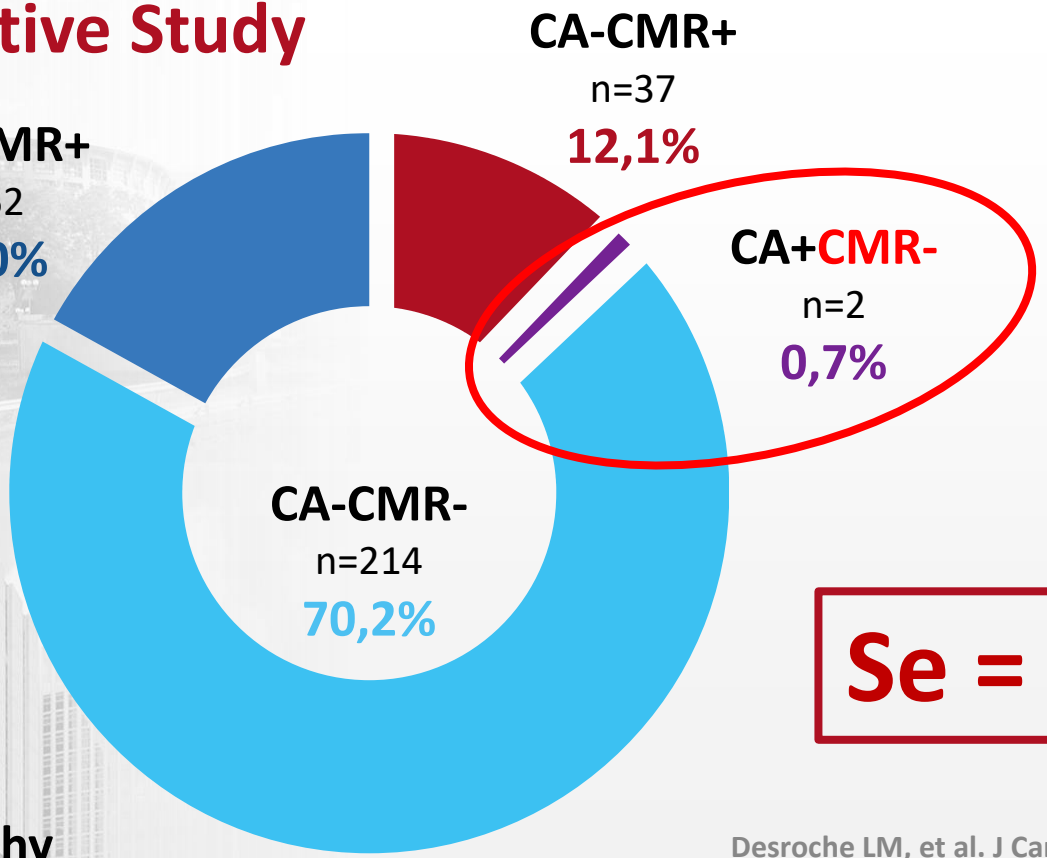
CMR sensitivity to predict s-CAD in reduced LVEF





- McCrohon et al., Circulation, 2003.
- Soriano et al., Int J Cardiol, 2007.
- Schietinger et al., Int J Cardiovasc Imaging, 2007.
- Valle-Muñoz et al., Eur J Echocardiogr, 2009.
- Assomull et al., Circulation, 2011.

A Pilot Retrospective Study



Se = 96%

CA : Coronary Angiography

Desroche LM, et al. J Card Fail. 2020 Dec

The CAMAREC Study

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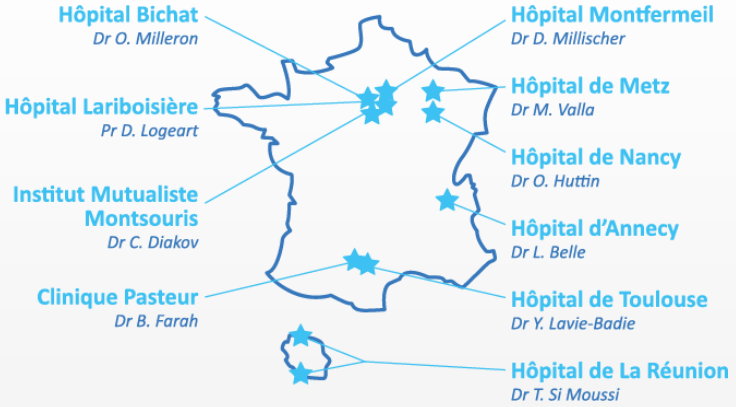
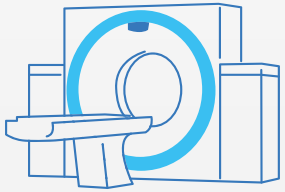
MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ
Liberté
Égalité
Fraternité

CAMAREC
FIRST-LINE CMR FOR SYSTOLIC DYSFUNCTION



ESC

American Heart Association.



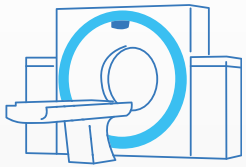
« capable of identifying heart failure caused by CAD »

Donal et al., Eur Heart J Card. Imag., 2019 Aug
Glikson et al., Eur Heart J, 2021 Sep
Heidenreich et al., Circulation, 2022 May

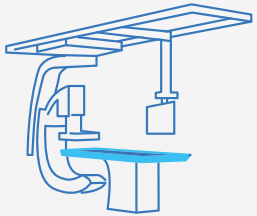
The CAMAREC design

Unexplained LVEF ≤ 45%

Cardiac-MRI
(first)



Coronary Angiography
(second)



CMR reading committee

CA reading committee

Felker's criteria

CMR's performance to predict CA+ ?

CMR-first strategy

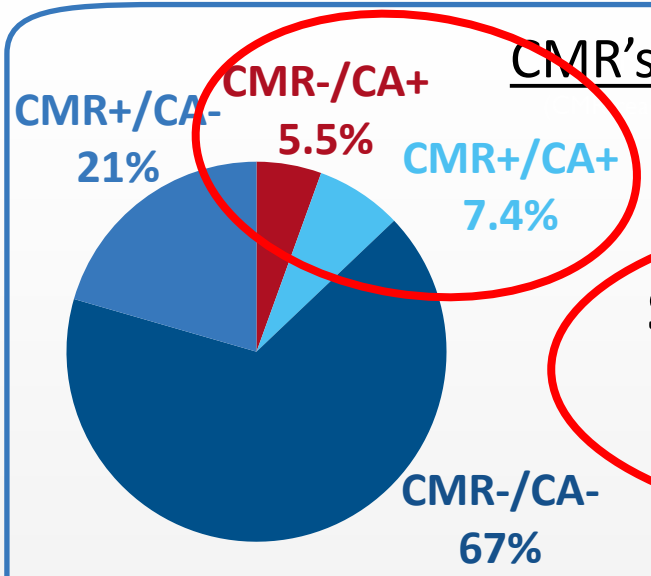
€ saved ? CA+ missed ?

Results : characteristics

	Overall N = 380
Age, median [IQR], years	63 [52-71]
Male sex, n (%)	259 (68)
Body Mass Index, median [IQR]	26 [22-30]
Hypertension, n (%)	158 (42%)
Dyslipidaemia, n (%)	73 (19%)
Smoking History, n (%)	197 (53%)
Diabetes, n (%)	85 (22%)
Left Ventricular Ejection Fraction, median [IQR], %	28 [20-35]
Presence of Significant Coronary Artery Disease, n (%)	49 (13%)

= CA+

Main Results



CMR's performance to predict CA+ :

Se = 57% [CI: 43-71]

Sp = 76% [CI: 72-81]

PPV = 26% [CI: 18-35]

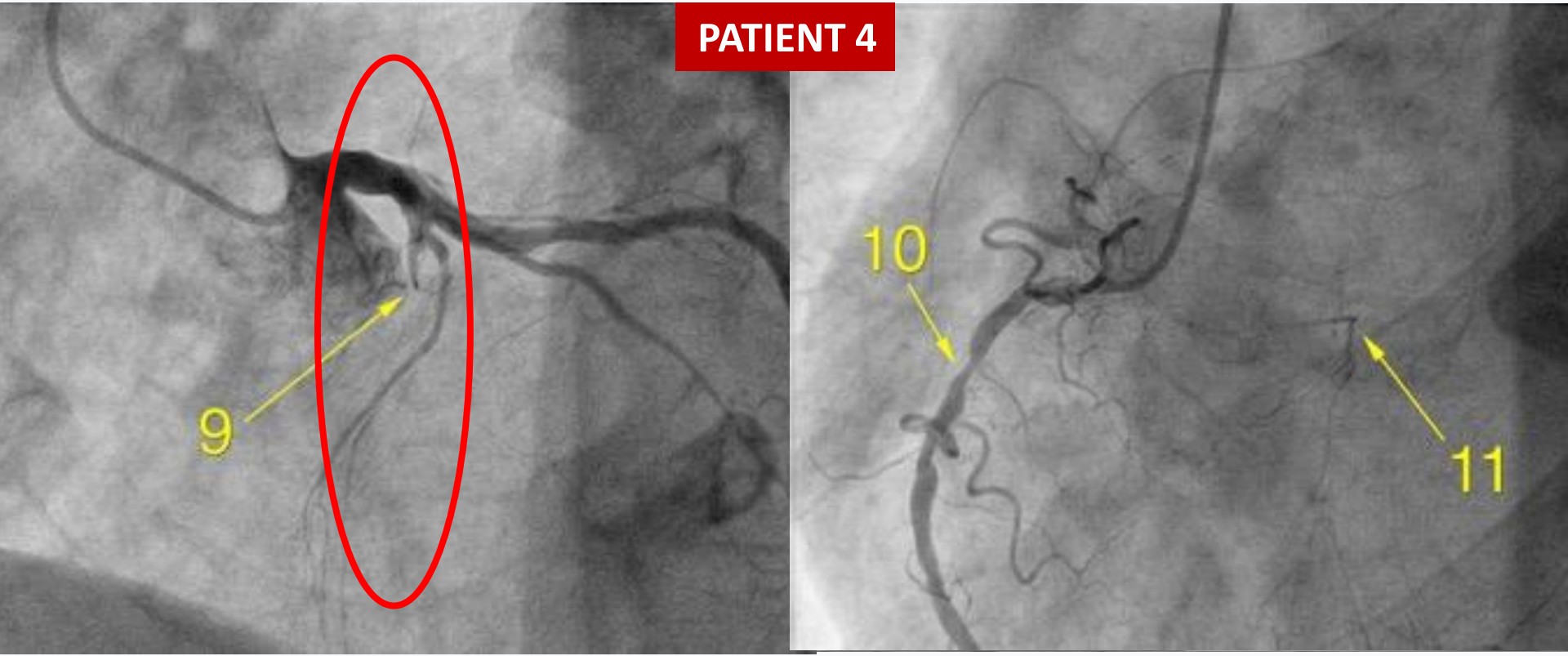
NPV = 92% [CI: 89-95]

CMR-first strategy :

- 72% pts : CA not performed
- 392 € saved /patient

- 6% pts : CA+ not recognised
- 5% pts : revascularizat° not performed

Illustration of some of the 21 CMR-CA+ patients



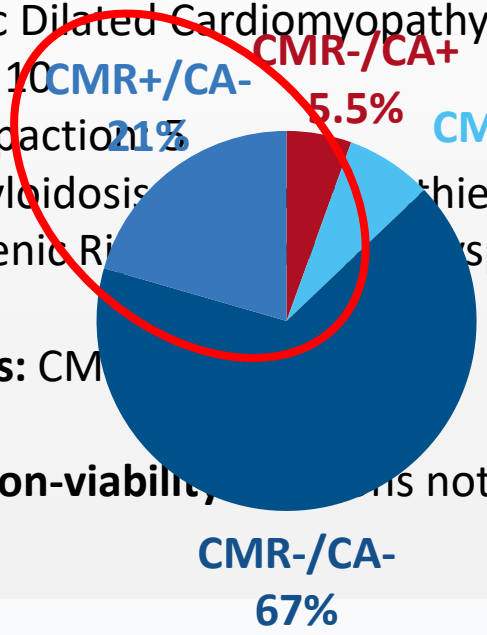
Results - Key CMR Contributions

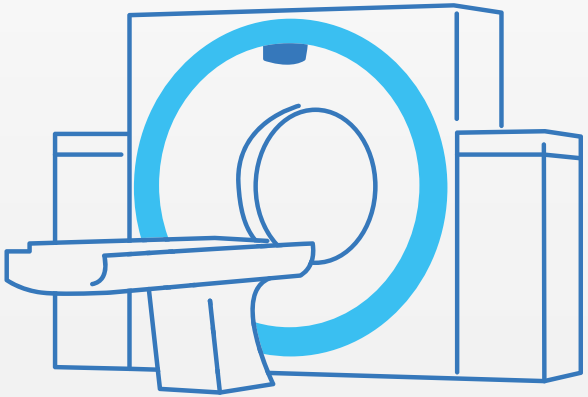
Cardiomyopathies:

- **Potential MINOCA:** 78 (21%)
- Hypertrophic Dilated Cardiomyopathy: 38
- Myocarditis: 10
- LV Non-Compaction: 5
- Others : Amyloidosis [illegible] thies: 1; Sarcoidosis: 1; Arrhythmogenic Ri[illegible]splasia: 1

Intra-LV Thrombus: CM[illegible]

CMR-confirmed non-viability[illegible] is not revascularized.



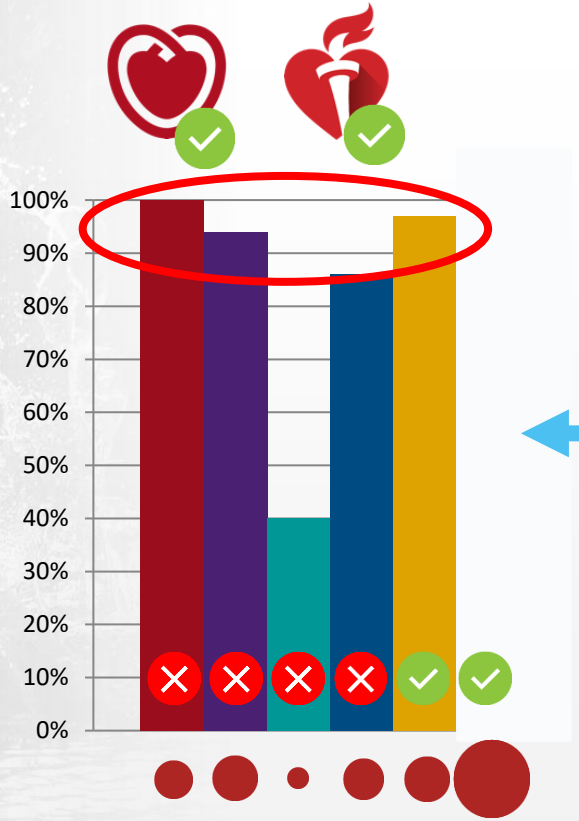


Stone in calm waters

: 2 reading committees

: Not 2 committees

: No. of patients



- McCrohon et al., Circulation, 2003.
- Soriano et al., Int J Cardiol, 2007.
- Schietinger et al., Int J Cardiov Imag, 2007.
- Valle-Muñoz et al., Eur J Echocard, 2009.
- Assomull et al., Circulation, 2011.

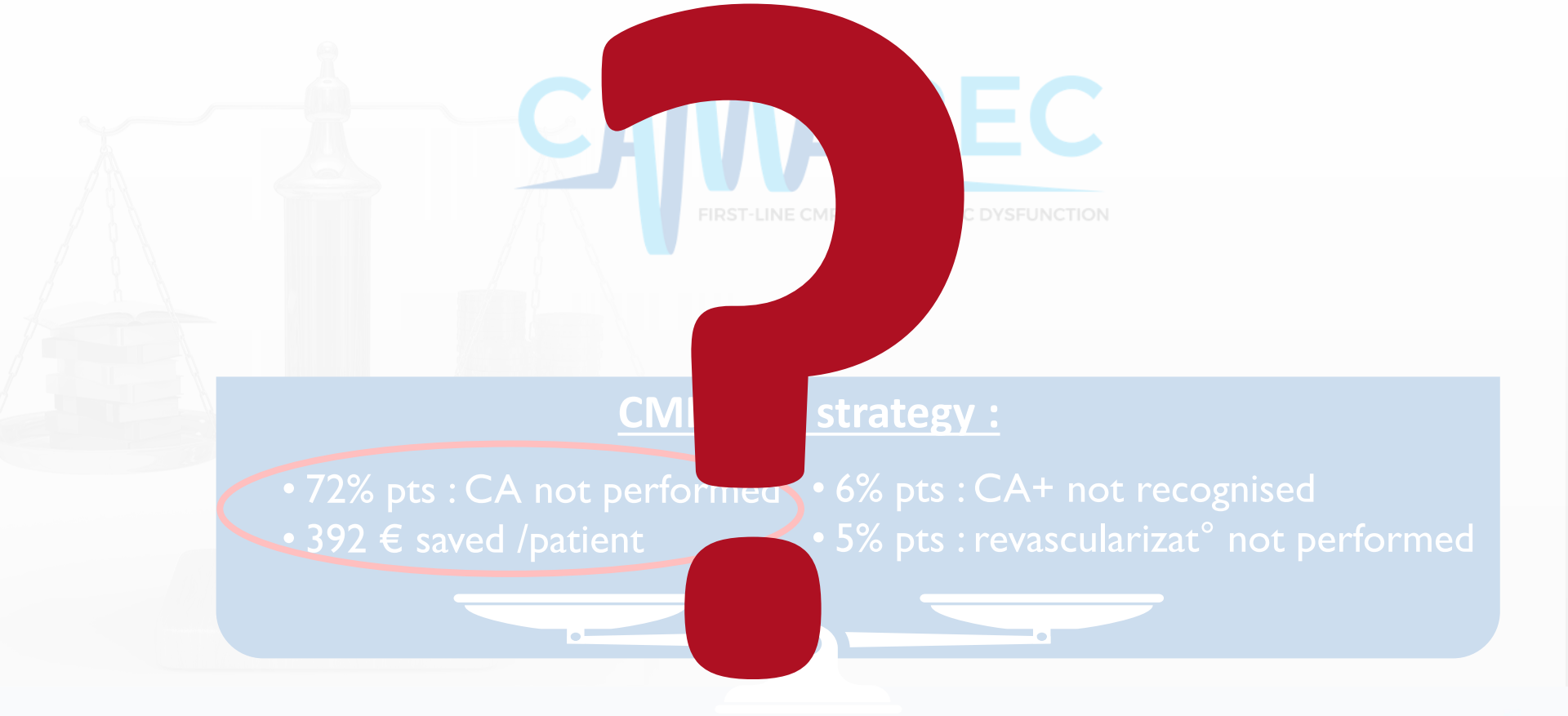
CMAREC
FIRST-LINE CMR FOR SYSTOLIC DYSFUNCTION

Se = 57% [CI: 43-71]

If similar CA+ criteria used…

CMR sensitivity to predict CAD in reduced LVEF

An unexpected choice

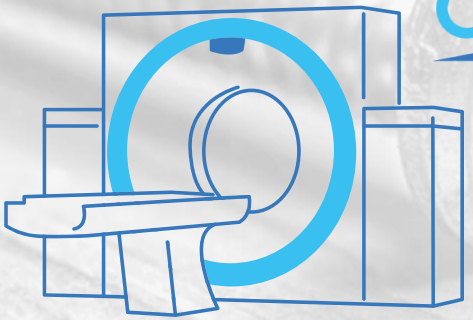


CMR strategy :

- 72% pts : CA not performed
- 392 € saved /patient
- 6% pts : CA+ not recognised
- 5% pts : revascularizat° not performed

The Right Tool for the Right Problem

Predicting s-CAD in LV dysfunction



CAMAREC
FIRST-LINE CMR FOR SYSTOLIC DYSFUNCTION

Se = 57%

- Coronary CT ?
- PET ?
- Stress CMR ?
- High-field MRI ?

+/- AI

➔ or Both Myocardial & Coronary Analysis ?

Conclusion

CAMAREC
FIRST-LINE CMR FOR SYSTOLIC DYSFUNCTION

CMR for

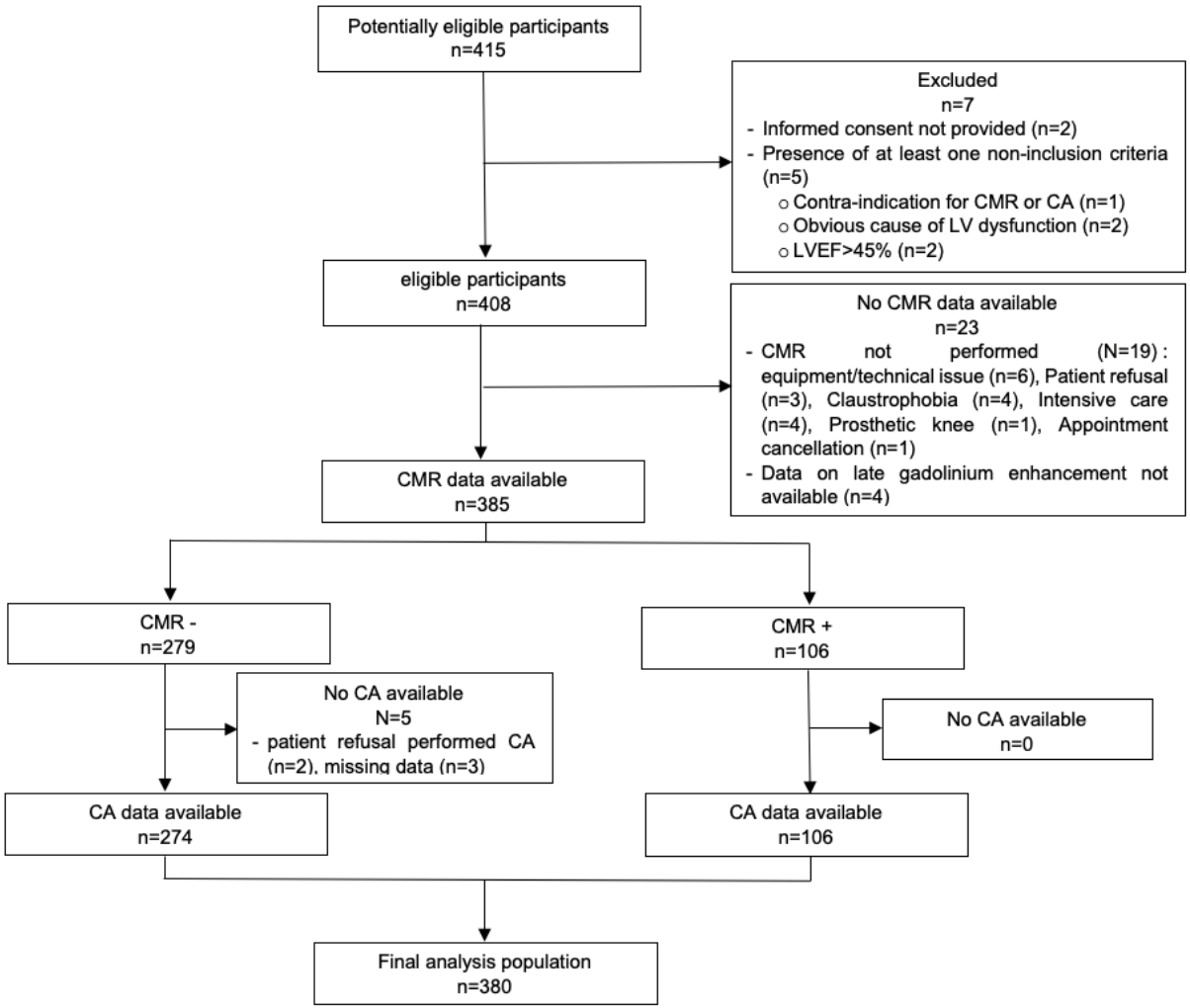
Predicting s-CAD

In Unexplained LV Dysfunction

392 € saved /patient

Se = 57%

Flowchart


Potentially eligible participants
n=415
Excluded
n=7
- Informed consent not provided (n=2)
- Presence of at least one non-inclusion criteria (n=5)
o Contra-indication for CMR or CA (n=1)
o Obvious cause of LV dysfunction (n=2)
o LVEF>45% (n=2)
eligible participants
n=408
No CMR data available
n=23
- CMR not performed (N=19) : equipment/technical issue (n=6), Patient refusal (n=3), Claustrophobia (n=4), Intensive care (n=4), Prosthetic knee (n=1), Appointment cancellation (n=1)
- Data on late gadolinium enhancement not available (n=4)
CMR data available
n=385
CMR -
n=279
CMR +
n=106
No CA available
N=5
- patient refusal performed CA (n=2), missing data (n=3)
No CA available
n=0
CA data available
n=274
CA data available
n=106
Final analysis population
n=380

Inclusion and exclusion criteria

Inclusion Criteria	Non-Inclusion criteria
(1) aged 18 years or older; (2) LVEF ≤ 45% on transthoracic echocardiography; (3) provided informed consent; (4) underwent a preliminary clinical examination to exclude obvious etiologies	(1) known significant coronary artery stenosis (history of myocardial infarction or coronary artery stenosis); (2) formal indication for CA other than LV dysfunction (typical angina, acute coronary syndrome, etc.); (3) obvious etiology for LV dysfunction (valvular, rhythmic, etc.); (4) pregnancy, desire for pregnancy, breastfeeding, woman of reproductive age without effective contraception or negative pregnancy test; (5) other contraindication for cardiac magnetic resonance (CMR) (known severe allergy to gadolinium) or coronary artery angiography; (6) first diagnosis of LVEF dysfunction > 8 weeks; (7) patient not covered by social security or the CMU; (8) patients under guardianship or unable to give consent; (9) patients already included in another study at the same time; (10) individuals specifically protected by French law (e.g., those deprived of liberty by administrative or judicial decision, hospitalized without consent, admitted to health and social institution for purposes other than research, minors, and adults who are protected or unable to express their consent).

International guidelines and consensus

ESC

« Best resolution to differentiate between ischemic and non-ischemic cardiomyopathy »

EACVI

« CMR can be employed to exclude the ischemic component of LV dysfunctions »

American Heart Association.

« LGE is capable of identifying heart failure caused by CAD »

Supplemental Table 1.				
Costs (€)	Base case value	Low estimate	High estimate	Source
Cost of cardiac magnetic resonance imaging				
Cost of the act	€69	€69	€69	Health insurance
Cost of technical charge	€124	€120	€139	Health insurance
Cost of coronary angiography				
Cost of the act	€259	€259	€259	Health insurance
Hospital stay		no stay	severity level 3	
	€3,995	€0	€77,609	National hospital information agency

Extracorporeal life support for acute myocardial infarction complicated by cardiogenic shock

ECLS-SHOCK

Holger Thiele on behalf of the ECLS-SHOCK Investigators

26th of August 2023

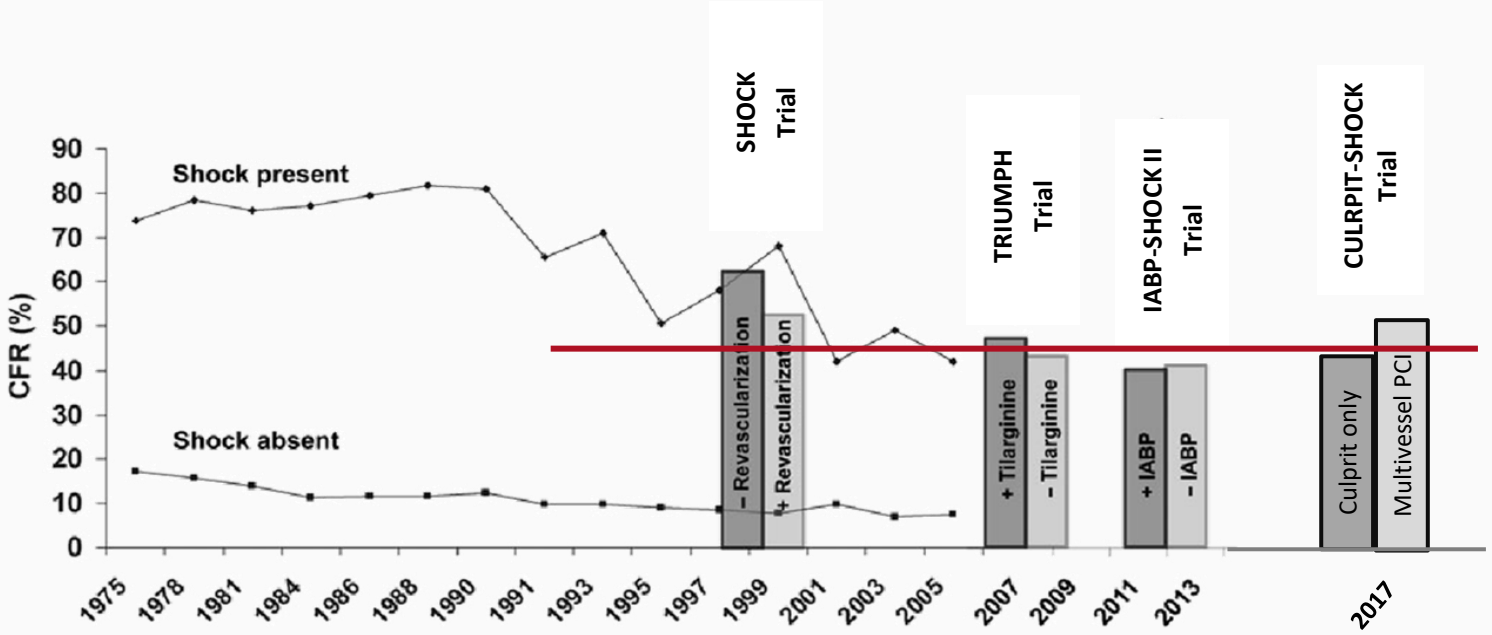
Conflict of Interest Statement

Funding:
German Research Foundation
German Heart Research Foundation
German Cardiac Society
European Union
Else-Kröner-Fresenius-Foundation
Schwiete-Foundation
Boston Scientific

Consulting:
None

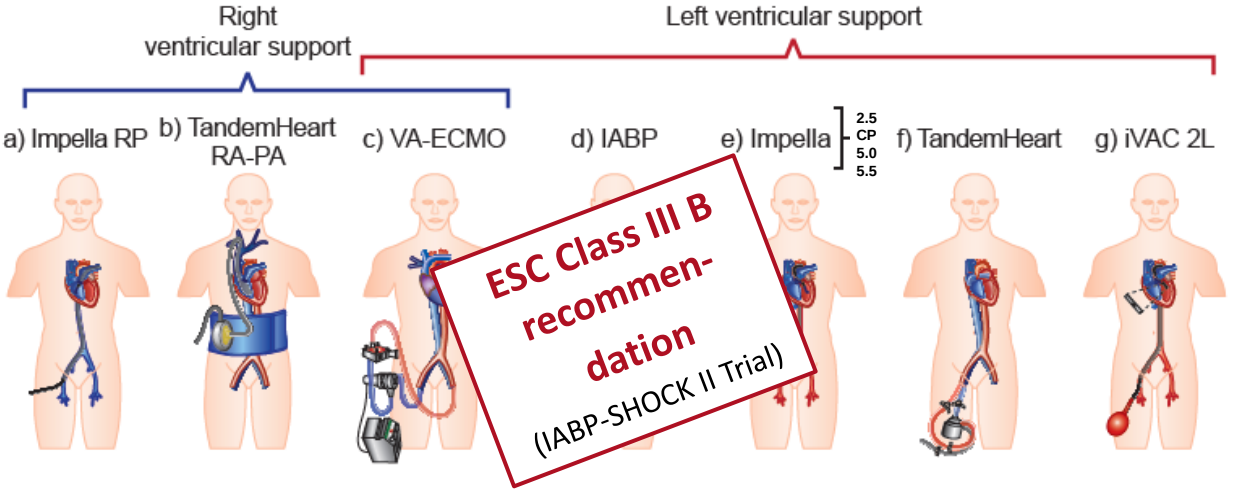
Speaker Honoraria:
None

Cardiogenic Shock - Mortality over Time



Adapted from Werdan et al. Eur Heart J 2014;35:156-167

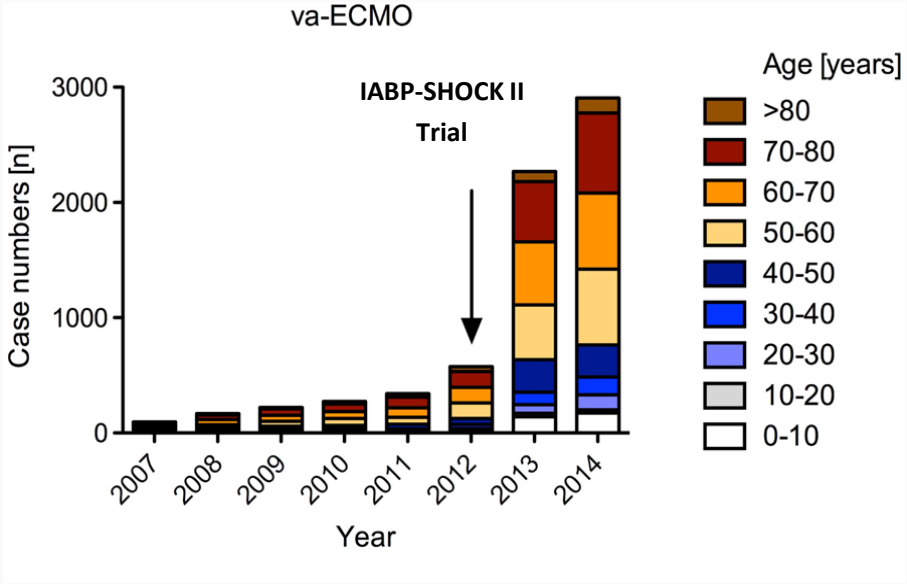
Currently Available MCS

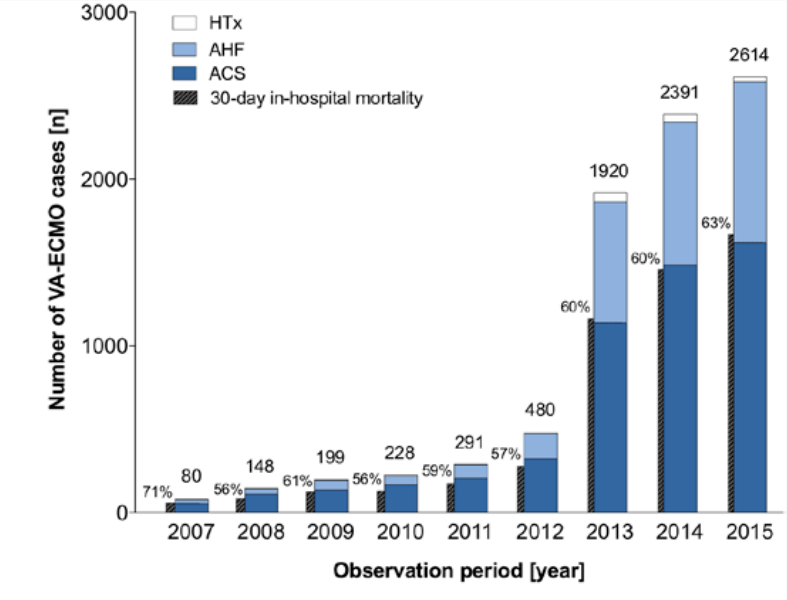


	a) Impella RP	b) TandemHeart RA-PA	c) VA-ECMO	d) IABP	e) Impella 2.5 CP 5.0 5.5	f) TandemHeart	g) iVAC 2L
Flow:	max. 4.0 L	max. 4.0 L	max. 7.0 L		2.5-5.5 L	max. 4.0 L	max. 2.8 L
Pump speed:	33.000 rpm	max. 7.500 rpm	max. 5000 rpm		max. 51.000 rpm	max. 7.500 rpm	40 ml/beat
Cannula size:	22 F	29 F	14-19 F arterial 17-21F venous	7-8 F	12-14 F	12-19 F arterial 21F venous	17 F
Insertion/ Placement	Femoral vein	Internal jugular vein	Femoral artery Femoral vein	Femoral artery	Femoral artery	Femoral artery Femoral vein for LA access	Femoral artery
LV Unloading	-	-	-	(+)	+ - ++	++	+
RV Unloading	+	+	++	-	-	-	-

Thiele et al. Eur Heart J 2019:40:2671-2683
Byrne/Ibanez et al. Eur Heart J 2023;epub

Increase in VA-ECMO (ECLS) Over Time





Karagiannidis et al. Intensive Care Med.2016;42:889–896
Becher et al. Circulation 2018;138:2298-2300

Endpoints/Statistical Methodology

ECLS-SHOCK

Primary endpoint

30-day all-cause mortality

Secondary endpoints

- Time to hemodynamic stabilization
- Duration of catecholamine therapy
- Serial creatinine-level and creatinine-clearance until hemodynamic stabilization
- Mean and area under the curve of arterial lactate during 48 hours after PCI
- Peak release of myocardial enzymes
- Serial SAPS II
- Length of mechanical ventilation
- Length of ICU stay
- Length of hospital stay
- Acute renal failure requiring renal replacement therapy within 30 days
- Recurrent myocardial infarction within 30 days
- Need for repeat revascularization (PCI and/or CABG) within 30-days
- Rehospitalization for heart failure within 30 days
- Cerebral performance category (CPC) at 30 days

Sample size

- **Estimated event rate** for primary endpoint**:**
  - **49%** in **control group** versus
  - **35%** in **ECLS group**
- 1 interim analysis (50% of patients)
- 2-sided Chi^2-test; power: 80%, alpha=0.048 for final analysis → **390 patients**
- To compensate for losses in follow-up → **420 patients**

Thiele et al. Am Heart J 2021;234: 1-1

In- and Exclusion Criteria

ECLS-SHOCK

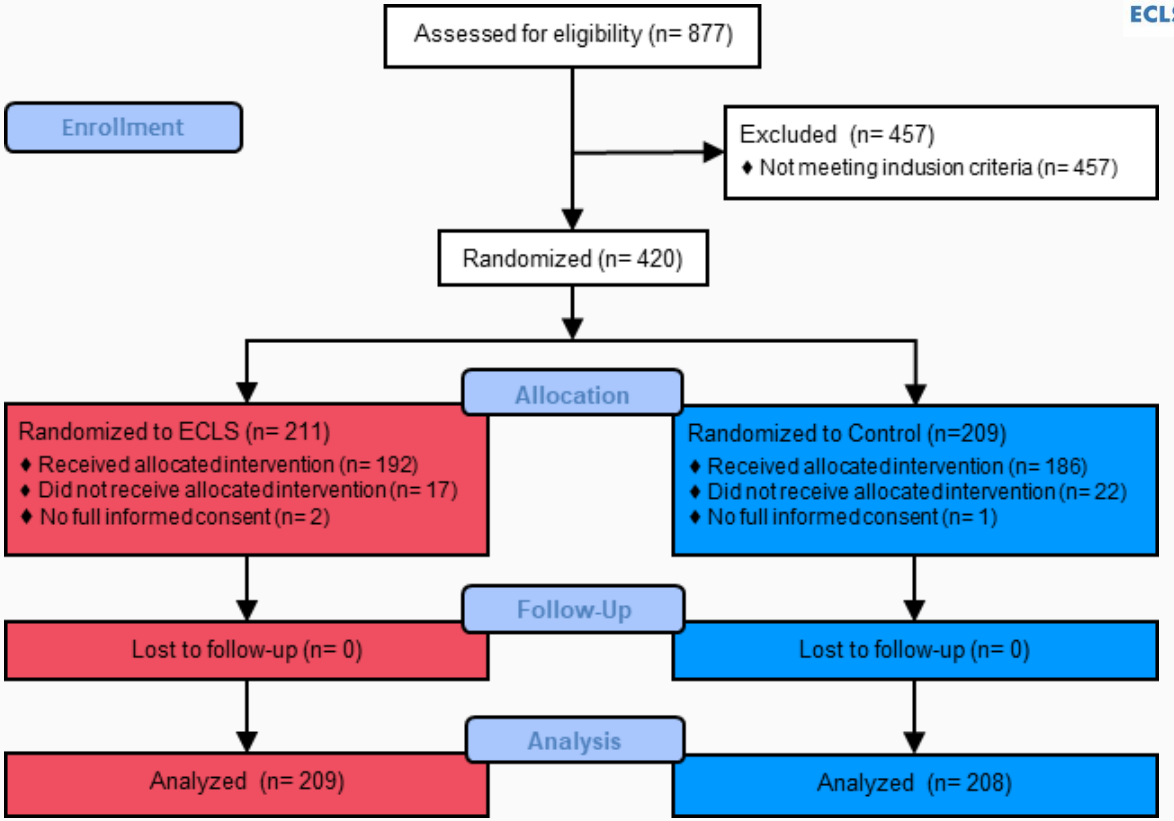
Inclusion Criteria	Exclusion Criteria
• Cardiogenic shock complicating AMI (STEMI or NSTEMI) plus obligatory: 1. Planned revascularization 2. SBP <90 mmHg >30 min or catecholamines required to maintain SBP >90 mmHg 3. Signs of impaired organ perfusion with at least one of the following criteria: ➢ Altered mental status ➢ Cold, clammy skin and extremities ➢ Oliguria with urine output <30 ml/h 4. Arterial lactate >3 mmol/l • Informed consent	• Resuscitation >45 minutes • Mechanical cause of cardiogenic shock • Onset of shock >12 h • Severe peripheral artery disease with impossibility to insert ECLS cannulae • Age <18 years or >80 years • Shock of other cause (bradycardia, sepsis, hypovolemia, etc.) • Other severe concomitant disease with limited life expectancy <6 months • Pregnancy • Participation in another trial

Thiele et al. Am Heart J 2021;234: 1-1

Trial Flow

ECLS-SHOCK

44 study sites



Thiele et al. Am Heart J 2021;234: 1-1

Baseline Characteristics

ECLS-SHOCK

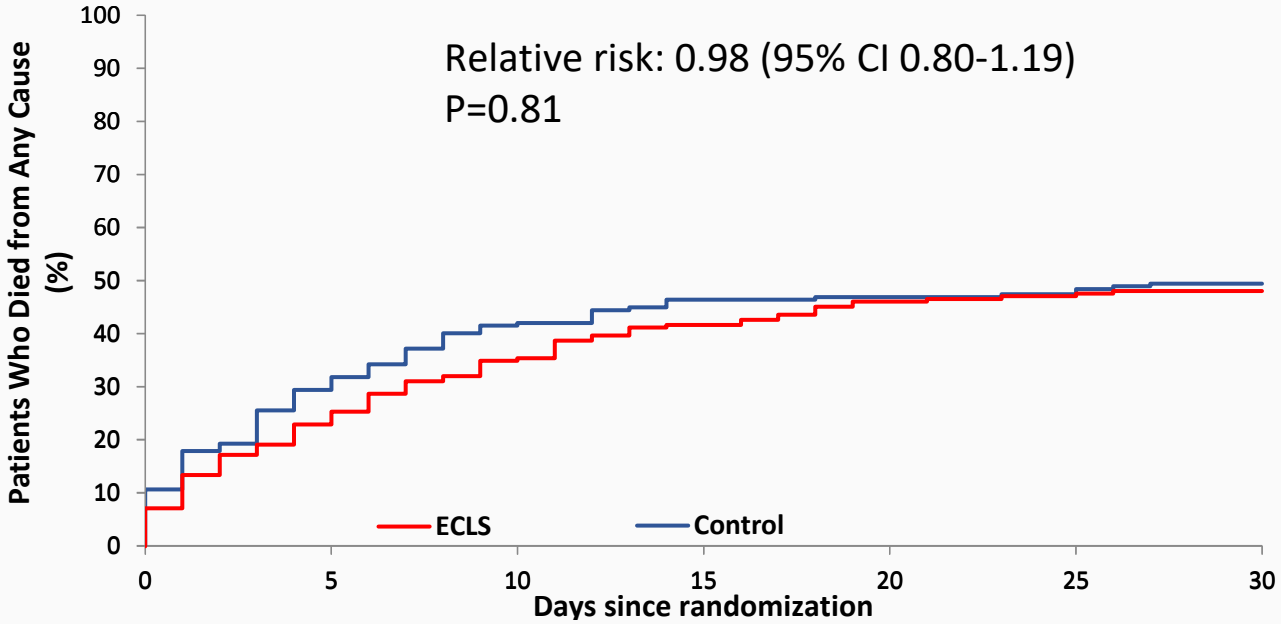
	ECLS (n=209)	Control (n=208)
Age (years); median (IQR)	62 (56 - 69)	63 (57 - 71)
Male sex; n/total (%)	170/209 (81.3)	169/208 (81.3)
Signs of impaired organ perfusion; n/total (%)		
Altered mental status	200/209 (95.7)	198/208 (95.2)
Cold, clammy skin and extremities	202/209 (96.7)	204/208 (98.1)
Oliguria	150/209 (71.8)	150/208 (72.1)
Mean blood pressure (mmHg); median (IQR)	71 (61 - 87)	72 (60 - 88)
STEMI; n/total (%)	135/204 (66.2)	141/207 (68.1)
Resuscitation before randomization; n/total (%)	162/209 (77.5)	162/208 (77.9)
No. of diseased vessels; n/total (%)		
1	71/203 (35.0)	63/200 (31.5)
2	71/203 (35.0)	53/200 (26.5)
3	61/203 (30.0)	84/200 (42.0)
LVEF (%); median (IQR)	30 (20 - 35)	30 (20 - 40)
Laboratory values on admission		
pH; median (IQR)	7.2 (7.1 - 7.3)	7.2 (7.1 - 7.3)
Lactate (mmol/L); median (IQR)	6.8 (4.5 – 9.6)	6.9 (4.6 – 10.0)

Treatment

ECLS-SHOCK

	ECLS (n=209)	Control (n=208)
Type of inital revascularization; n/total (%)		
PCI	199/208 (95.7)	199/204 (97.5)
CABG	1/208 (0.5)	0/204
PCI with emergent transfer to CABG	2/208 (1.0)	0/204
ECLS therapy; n/total (%)	192/209 (91.8)	26/208 (12.5)
Initiation in catheterization laboratory		
Prior revascularization	42/192 (21.9)	4/26 (15.4)
During revascularization	50/192 (26.0)	8/26 (30.8)
After revascularization	100/192 (52.1)	7/26 (26.9)
Initiation after catheterization laboratory		
<24 hours	0/192	3/26 (11.5)
≥24 hours	0/192	4/26 (15.4)
Duration of ECLS therapy (days); median (IQR)	2.7 (1.5 - 4.8)	2.7 (2.2 – 3.8)
Peripheral antegrade perfusion sheath; n/total (%)	183/192 (95.3)	16/19 (84.2)
Active left ventricular unloading in ECLS; n/total (%)	11/191 (5.8)	6/19 (31.6)
Other MCS in patients without ECLS; n/total (%)	0/17	28/182 (15.4)
Invasive mechanical ventilation; n/total (%)	183/203 (90.1)	177/202 (87.6)

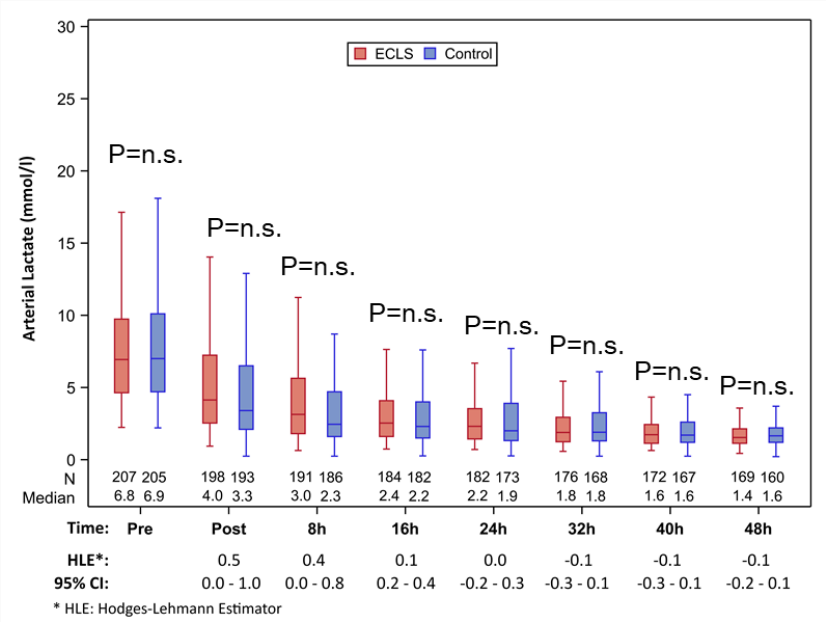
Primary Endpoint – 30-Day All-Cause Mortality



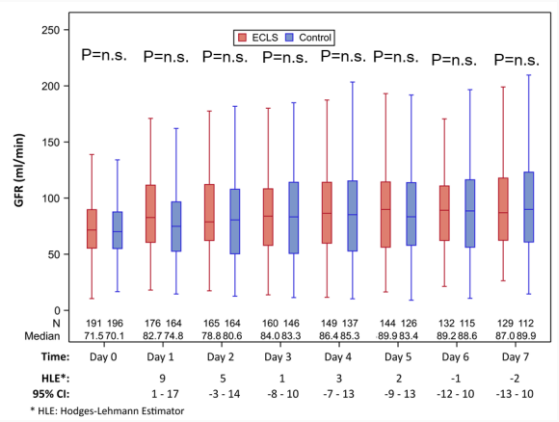
No. at Risk							
Control	208	146	120	109	105	104	100

Key Secondary Endpoints

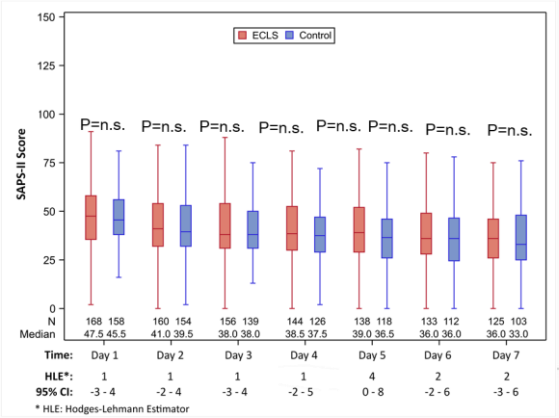
Arterial Lactate



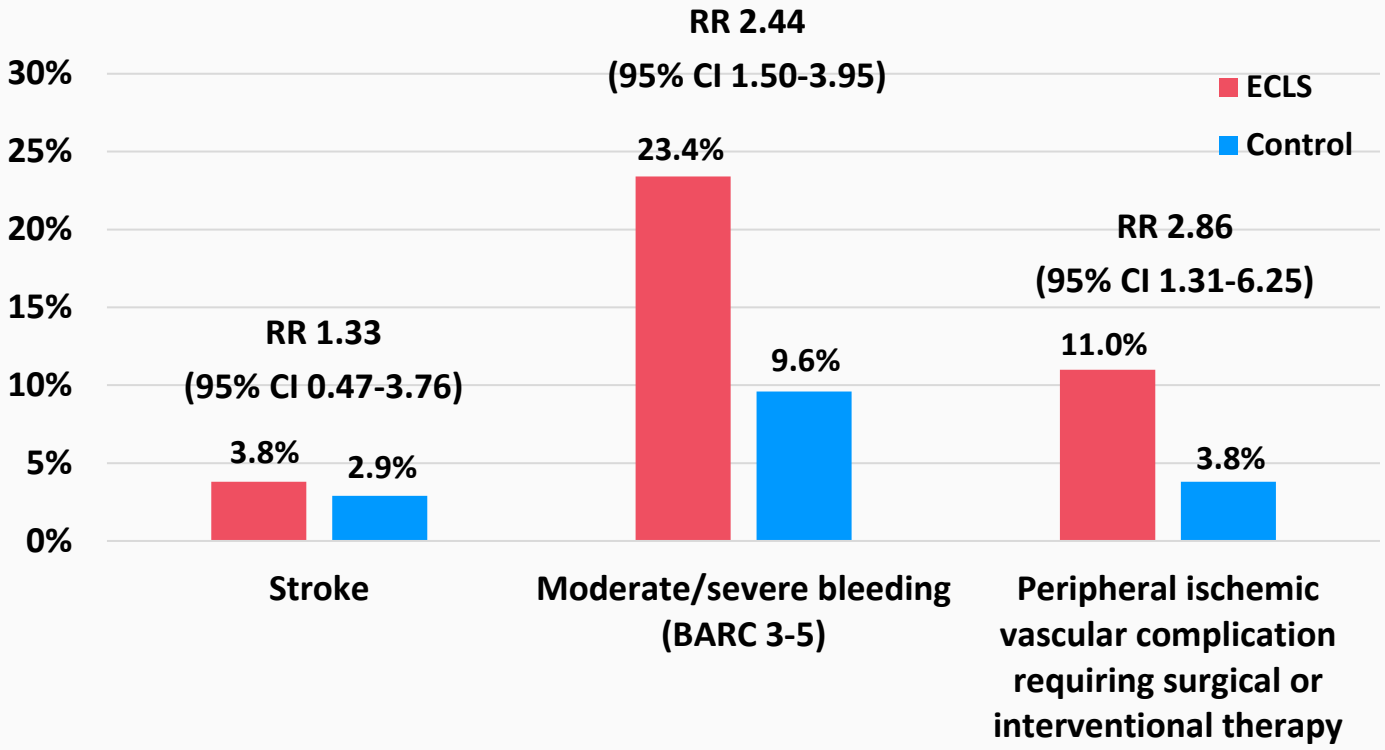
Renal Function - eGFR



SAPS-II



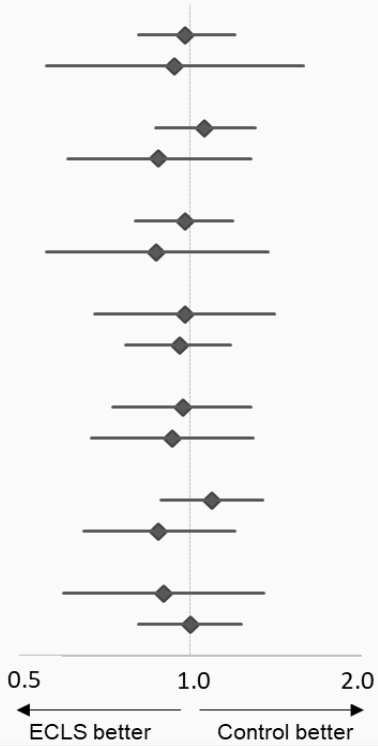
Safety


RR 2.44
(95% CI 1.50-3.95)
30%
25%
20%
15%
10%
5%
0%
ECLS
Control
23.4%
RR 2.86
(95% CI 1.31-6.25)
11.0%
RR 1.33
(95% CI 0.47-3.76)
9.6%
3.8%
2.9%
3.8%
Stroke
Moderate/severe bleeding (BARC 3-5)
Peripheral ischemic vascular complication requiring surgical or interventional therapy

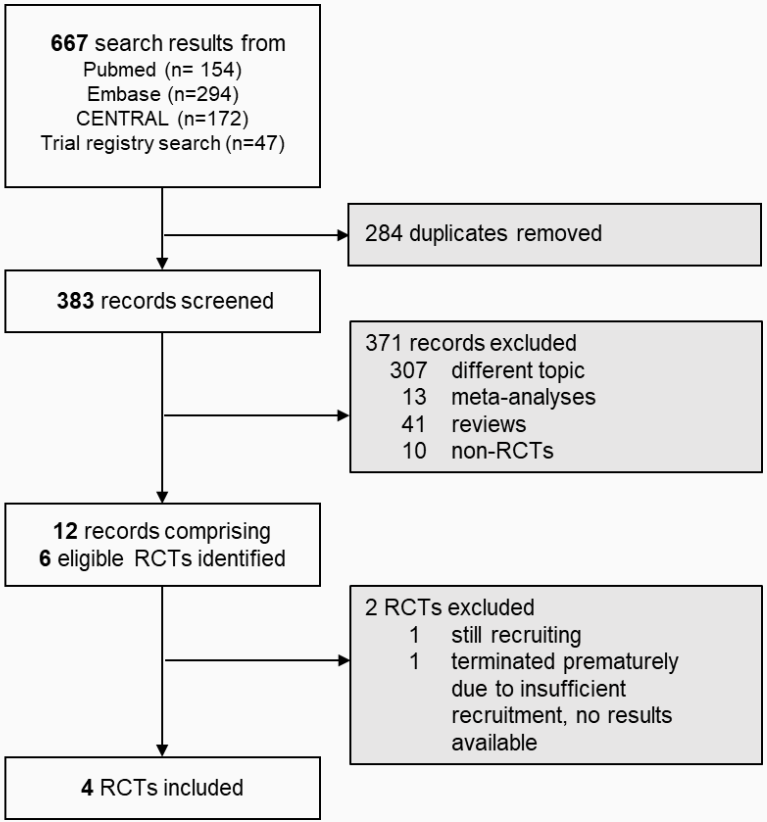
30-Day All-Cause Mortality - Subgroups

ECLS-SHOCK

	30-day all-cause mortality (%) Control No. of patients with event/total no. of patients (%)	ECLS (%)	Relative Risk (95%)
Sex			
Male	79/169 (46.7)	78/170 (45.9)	0.98 (0.81-1.20)
Female	23/39 (59.0)	22/39 (56.4)	0.94 (0.56-1.58)
Age			
<65 years	41/112 (36.6)	50/124 (40.3)	1.06 (0.87-1.30)
>= 65 years	61/96 (63.5)	50/85 (58.8)	0.88 (0.61-1.28)
Diabetes			
No	62/146 (42.5)	57/138 (41.3)	0.98 (0.80-1.19)
Yes	39/60 (65.0)	42/70 (60.0)	0.87 (0.56-1.37)
Type of infarction			
NSTEMI	36/66 (54.5)	37/69 (53.6)	0.98 (0.68-1.41)
STEMI	65/141 (46.1)	59/135 (43.7)	0.96 (0.77-1.18)
STEMI type			
Anterior infarction	39/85 (45.9)	33/75 (44.0)	0.97 (0.73-1.28)
Non-anterior infarction	26/56 (46.4)	25/59 (42.4)	0.93 (0.67-1.29)
Arterial lactate			
<= 6 mmol/l	24/85 (28.2)	30/87 (34.5)	1.09 (0.89-1.34)
> 6 mmol/l	75/120 (62.5)	69/120 (57.5)	0.88 (0.65-1.20)
CPR			
No	24/46 (52.2)	22/47 (46.8)	0.90 (0.60-1.35)
Yes	78/162 (48.2)	78/162 (48.2)	1.00 (0.81-1.23)

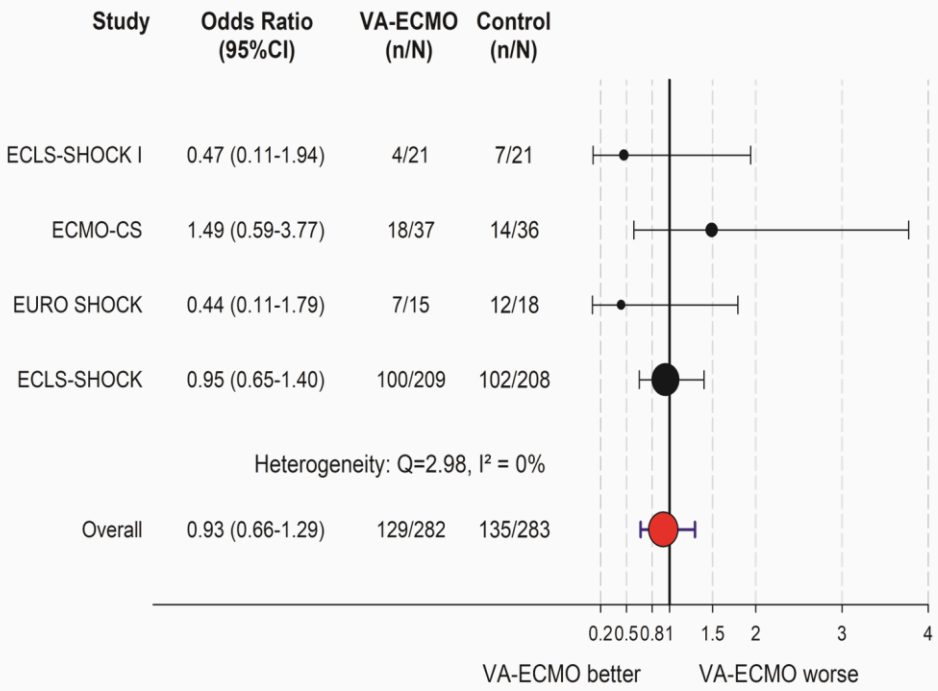


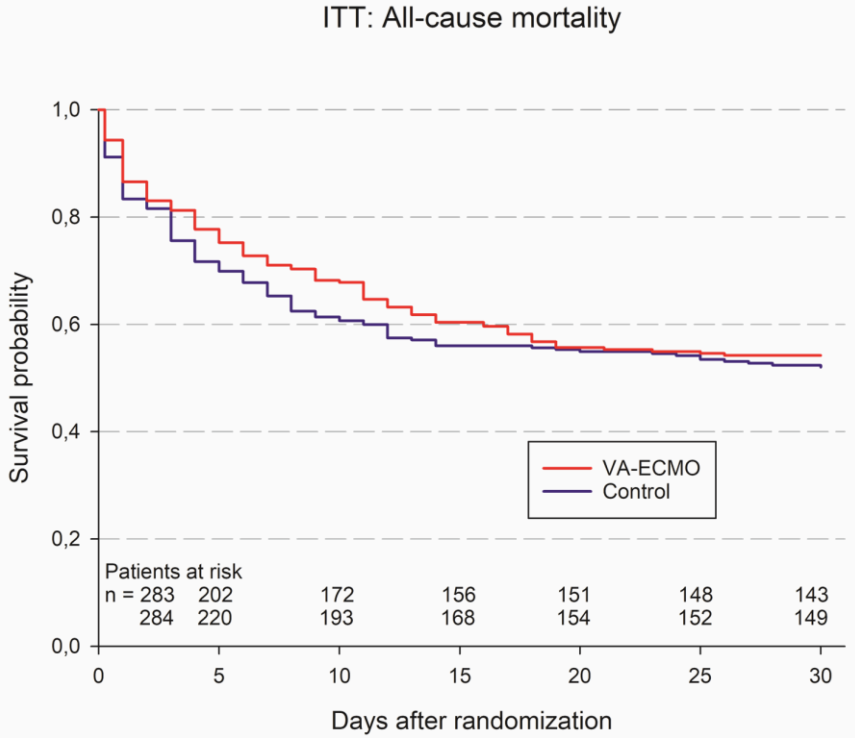
IPD Meta-Analysis VA-ECMO vs No VA-ECMO



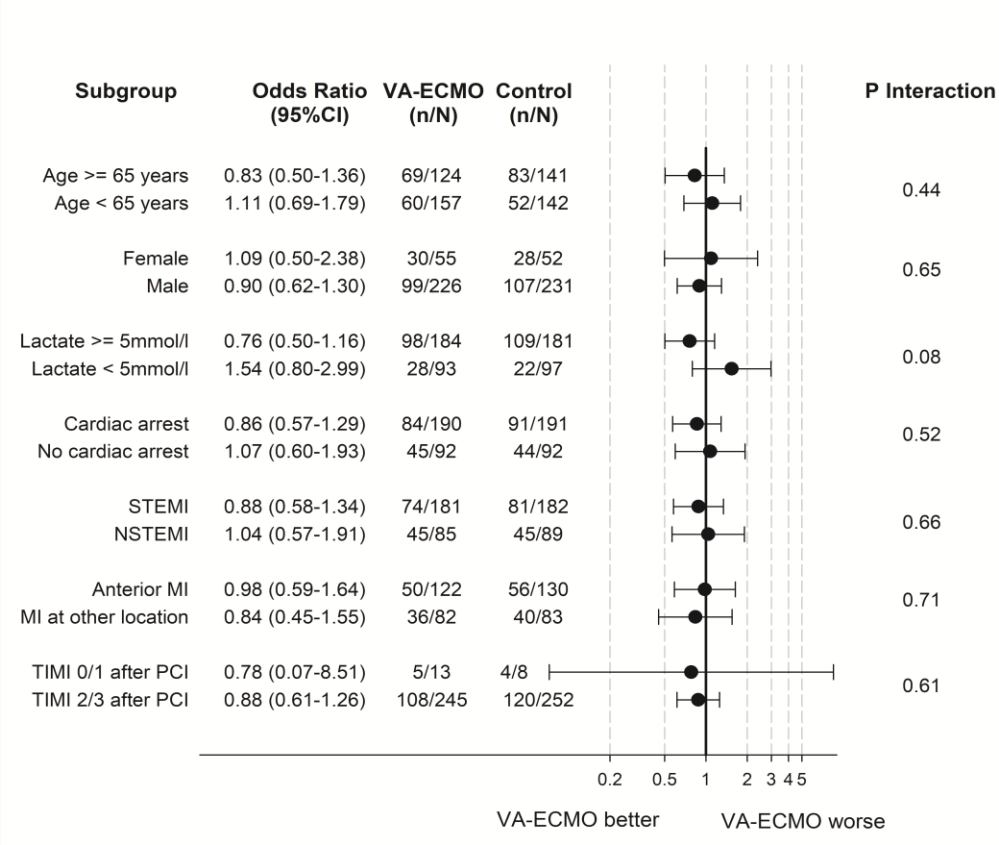
Results

IPD Metaanalysis – 30-Day All-Cause Mortality





IPD Metaanalysis – 30-Day Mortality - Subgroups

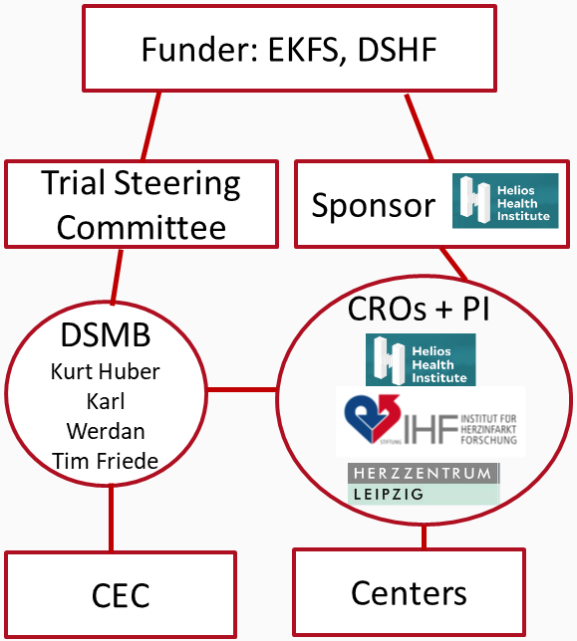


Summary and Conclusions

ECLS-SHOCK

- In patients with acute myocardial infarction and cardiogenic shock with planned revascularization ECLS (VA-ECMO) versus control does not reduce 30-day all-cause mortality.
- This lack of mortality benefit is supported by an IPD metaanalysis of all 4 RCTs comparing ECLS vs control.
- This lack of mortality benefit is further supported by the fact that there were no differences in the secondary endpoints (e.g. lactate, renal function, duration of catecholamines, etc.).
- ECLS is associated with higher rates of moderate or severe BARC bleeding and peripheral ischemic complications requiring intervention.
- The findings challenge current guideline recommendations and clinical practice with increasing rates of mechanical circulatory support in cardiogenic shock.

Acknowledgments and Thank You



Our greatest thanks go to the patients and relatives.

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ECLS-SHOCK

www.nejm.org

www.thelancet.com

ADVENT trial

#ESCCongress

Pulsed field ablation vs. thermal ablation (RF/cryo) for paroxysmal AF

Conclusion

Pulsed field ablation (PFA) is noninferior to thermal ablation in paroxysmal atrial fibrillation (AF).

Impact on clinical practice

PFA is as effective and safe as conventional thermal ablation to treat paroxysmal AF.
Procedure times were faster for PFA than thermal ablation, but there was more X-ray exposure with PFA.

Study objectives

ADVENT was the first randomised controlled trial comparing PFA to conventional ablation (either radiofrequency or cryothermal ablation).

Study population

Patients with drug-resistant, symptomatic paroxysmal AF

Where?

United States — 30 centres

Who and what?

687 patients → 80 roll-in patients to gain experience with the PFA catheter

607 patients

Randomised 1:1

- **PFA**
- **Thermal ablation**: Radiofrequency or Cryothermal

12-month follow-up

Primary efficacy endpoint

Success rate, defined as acute success and chronic success (1-year freedom from recurrent atrial arrhythmias, antiarrhythmic drug use, and cardioversion or repeat ablation)

Rate%

- 73.3%
- 71.3%

Met the prespecified criteria for noninferiority: between-group difference, 2.0%; 95% Bayesian credible interval (BCI), -5.2 to 9.2%; posterior probability of noninferiority >0.999

Secondary efficacy endpoint

Same as the primary efficacy endpoint, but tested for superiority:
did not meet the criteria for superiority
(posterior probability of superiority 0.708)

Primary safety endpoint

Composite of serious adverse events related to use of an ablation catheter or the procedure itself and occurring within 7 days, as well as pulmonary vein stenosis or oesophageal fistula occurring at any time during the 12-month follow up

- 2.1%
- 1.5%

Met the prespecified criteria for noninferiority: between-group difference, 0.6%; 95% BCI, -1.5 to 2.8%; posterior probability of noninferiority >0.999

Secondary safety endpoint

Change in pulmonary vein dimension (i.e., any stenosis or narrowing) from baseline to day 90

Reductions in vein cross-sectional area

- 3.3%
- 19.5%

Met the prespecified criteria for superiority of PFA: posterior probability of superiority >0.999

ESC

OCT vs. IVUS vs. angiography guidance

A real-time updated network meta-analysis

#ESCCongress

Conclusion

Intravascular imaging (IVI)-guided percutaneous coronary intervention (PCI) is associated with a lower rate of target lesion failure compared with angiography-guided PCI.

Impact on clinical practice

These results emphasise the importance of physicians using IVI with either optical coherence tomography (OCT) or intravascular ultrasound (IVUS) to optimise stent outcomes and improve the long-term prognosis of their patients.

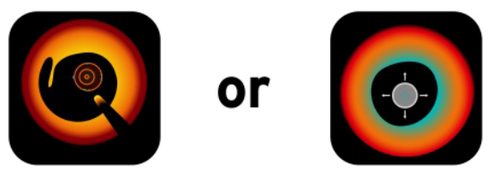
Study objectives

This real-time updated network meta-analysis, integrating data from the ILUMIEN IV and OCTOBER trials with prior studies, examined the effects of IVI-guided PCI versus angiography-guided PCI.

Who and what?

20 trials 12,428 patients randomised

IVI-guided PCI including:
OCT or IVUS



angiography-guided PCI

follow-up

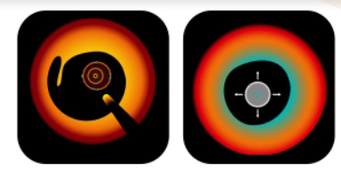
between 6 months and 5 years

Primary endpoint

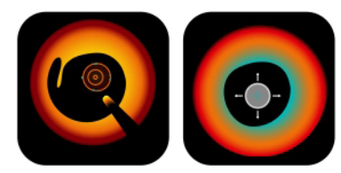
Target lesion failure, defined as a composite of cardiac death, target vessel myocardial infarction, or target lesion revascularisation.

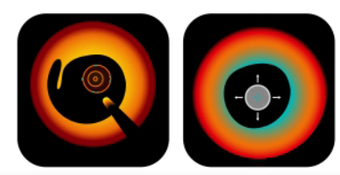
Reduced by 31% with  vs. 

Secondary endpoints

Cardiac death reduced by 46% with  vs. 

Target vessel myocardial infarction reduced by 20% with  vs. 

Target lesion revascularisation reduced by 29% with  vs. 

Stent thrombosis reduced by 52% with  vs. 

ESC

OPT-BIRISK trial

#ESCCongress

Extended clopidogrel monotherapy versus DAPT in high-risk patients

Conclusion

Extended P2Y12 inhibitor monotherapy beyond 12 months after percutaneous coronary intervention (PCI) reduces bleeding and ischaemic events in acute coronary syndrome (ACS) patients at high risk for both types of events.

Impact on clinical practice

Extended P2Y12 inhibitor monotherapy benefits high-risk ACS patients.

Study objectives

The OPT-BIRISK trial examined whether in ACS patients with both high bleeding and ischaemic risk characteristics who remained event-free after a standard course of dual antiplatelet therapy (DAPT) following PCI, an extended course of clopidogrel monotherapy would be superior to ongoing DAPT treatment with aspirin and clopidogrel.

Study population

Patients who

- completed 9 to 12 months of DAPT (aspirin plus either clopidogrel or ticagrelor) after drug-eluting stent implantation for the treatment of ACS
- were free from major adverse clinical events during the prior 6 months
- were at both high bleeding and ischaemic risk

Where?

101 Chinese centres

Who and what?

7,758 patients

randomised 1:1

clopidogrel (75 mg/day) + placebo

clopidogrel (75 mg/day) + aspirin (100 mg/day)

for 9 months

open-label aspirin monotherapy (100 mg/day) for an additional 3 months to exclude rebound events

Primary endpoint

Rate of clinically-relevant bleeding 9 months after randomisation, defined as Bleeding Academic Research Consortium (BARC) types 2, 3, or 5 bleeding.

Rate%

+ placebo — 2.5%

+ aspirin — 3.3%

Hazard ratio 0.75, 95% CI 0.57–0.97
difference -0.8%, 95% CI -1.6% to -0.1%
p=0.03

Key secondary endpoint

Rate of major adverse cardiac and cerebral events (MACCE) 9 months after randomisation, defined as a composite of all-cause death, myocardial infarction, stroke or clinically-driven revascularisation

Rate%

+ placebo — 2.6%

+ aspirin — 3.5%

Hazard ratio 0.74, 95% CI 0.57–0.96
difference -0.9%, 95% CI -1.7% to -0.1%
p<0.001 for non-inferiority, p=0.02 for superiority

ESC

ARREST trial

#ESCCongress

Expedited transfer to a cardiac arrest centre for OHCA

Conclusion

There was no difference in survival at 30 days in patients with resuscitated cardiac arrest in the community who were taken by ambulance to a cardiac arrest centre compared with those delivered to the geographically closest emergency department.

Impact on clinical practice

Ambulances should take cardiac arrest victims to the closest emergency department.

Study objectives

The ARREST trial investigated whether expedited transfer of out-of-hospital cardiac arrest (OHCA) patients to a cardiac arrest centre reduces mortality compared with delivery to the closest emergency department.

Study population

Patients

- successfully resuscitated after an OHCA
- without ST-elevation on their post-resuscitation electrocardiogram (ECG)

Where?

London, UK

7 cardiac arrest centres

32 emergency departments

Who and what?

862 patients

randomised 1:1

expedited delivery to a cardiac arrest centre

delivery to the nearest emergency department

both by the London Ambulance Service

Primary endpoint

All-cause mortality at 30 days in the intention-to-treat population

Rate%

63%

63%

unadjusted risk ratio for survival 1.00
95% CI 0.90 to 1.11, p=0.96
risk difference 0.2%, 95% CI -6.5 to 6.8

Secondary endpoints

3-month all-cause mortality

=

risk ratio 1.02; 95% CI 0.92 to 1.12
risk difference 1.0%, 95% CI -5.6 to 7.5

neurological outcomes at hospital discharge and 3 months

=

modified Rankin scale:
odds ratio 1.00, 95% CI 0.76 to 1.32
cerebral performance category (CPC) score:
0.98, 95% CI 0.74 to 1.30

ESC

ATTRibute-CM trial

#ESCCongress

Acoramidis (AG10) in patients with transthyretin amyloid cardiomyopathy

Conclusion

Acoramidis improves outcomes in patients with transthyretin amyloid cardiomyopathy (ATTR-CM) compared with placebo.

Impact on clinical practice

Acoramidis has the potential to be an effective and safe alternative to tafamidis for the treatment of ATTR-CM.

Study objectives

The ATTRibute-CM trial evaluated the efficacy and safety of acoramidis in patients with ATTR-CM.

Study population

Eligible patients with wild-type or variant symptomatic ATTR-CM.

Who and what?

632 patients

randomised 2:1 *for 30 months*

oral acoramidis 800 mg twice daily

placebo

Patients in both arms had the option of initiating open-label, commercially available tafamidis after 12 months in the study.

Primary endpoint

Analysed at 30 months: a hierarchical analysis by the Finklestein-Schoenfeld method of all-cause mortality, CV-related hospitalisation, NT-proBNP, and 6 minute walk distance (6MWD).

vs.

overall win ratio 1.8
95% CI 1.4 to 2.2
p<0.0001

Secondary endpoints

all-cause mortality:

vs.

absolute risk reduction 6.4%; relative risk reduction 25%
hazard ratio 0.772; 95% CI 0.542 to 1.102; p=0.15

cumulative frequency of CV-related hospitalisation reduced with

vs.

absolute risk reduction: 0.226 CV-related hospitalisations per year
relative risk reduction: 50.4%; 95% CI 30.5% to 64.5%; p<0.0001

change from baseline in NT-proBNP lower with

vs.

ratio of adjusted geometric mean fold-change 0.529; 95% CI 0.463 to 0.604; p<0.0001

decline in change from baseline in 6MWD reduced with

vs.

least squares mean difference 39.64 m;
95% CI 21.07 to 58.22; p<0.0001

ESC

COP-AF trial

#ESCCongress

Colchicine for the prevention of perioperative atrial fibrillation after major thoracic surgery

Conclusion

Colchicine does not significantly reduce perioperative atrial fibrillation (AF) or myocardial injury after non-cardiac surgery (MINS) in patients undergoing major non-cardiac thoracic surgery.

Impact on clinical practice

Despite no significant reduction in the co-primary outcomes with colchicine and an increased risk of non-infectious diarrhoea, several results provided an encouraging signal of benefit for colchicine to reduce the incidence of adverse CV outcomes in these patients.

Study objectives

The COP-AF trial tested the hypothesis that colchicine reduces the incidence of clinically important perioperative AF and MINS in patients undergoing major non-cardiac thoracic surgery.

Study population

Patients

- aged ≥55 years
- were undergoing major non-cardiac thoracic surgery.

Where?

11 countries

45 sites

Who and what?

3,209 patients randomised 1:1

- **Oral colchicine 0.5 mg twice daily**
- **Placebo**

First dose within 4 hours before surgery for a total of 10 days

Follow-up ▶ 14 days

Co-primary outcomes

Clinically important perioperative AF

	Rate%
	6.4%
	7.5%

Hazard ratio 0.85; 95% CI 0.65 to 1.10
absolute risk reduction (ARR) 1.1%;
95% CI -0.7 to 2.8, p=0.22

MINS

	Rate%
	18.3%
	20.3%

Hazard ratio 0.89; 95% CI 0.76 to 1.05
ARR 2.0%; 95% CI -0.8 to 4.7, p=0.16

Post-hoc analyses

Composite outcome of clinically important perioperative AF or MINS

	Rate%
	22.4%
	25.9%

Hazard ratio 0.84; 95% CI 0.73 to 0.97

Composite outcome of vascular mortality, nonfatal MINS, nonfatal stroke or clinically important perioperative AF

	Rate%
	22.6%
	26.4%

Hazard ratio 0.83; 95% CI, 0.72 to 0.96

ESC

Effects of FCM on recurrent HF hospitalisations

An individual participant data meta-analysis

#ESCCongress

Conclusion

In iron-deficient patients with heart failure (HF) and reduced or mildly reduced left ventricular ejection fraction (LVEF), intravenous ferric carboxymaltose (FCM) is associated with a reduced risk of the composite outcome of total CV hospitalisation and CV death through 52 weeks compared with placebo.

Impact on clinical practice

Intravenous FCM should be considered in iron-deficient patients with HF and reduced or mildly reduced LVEF to reduce the risk of hospitalisation due to HF and CV causes.

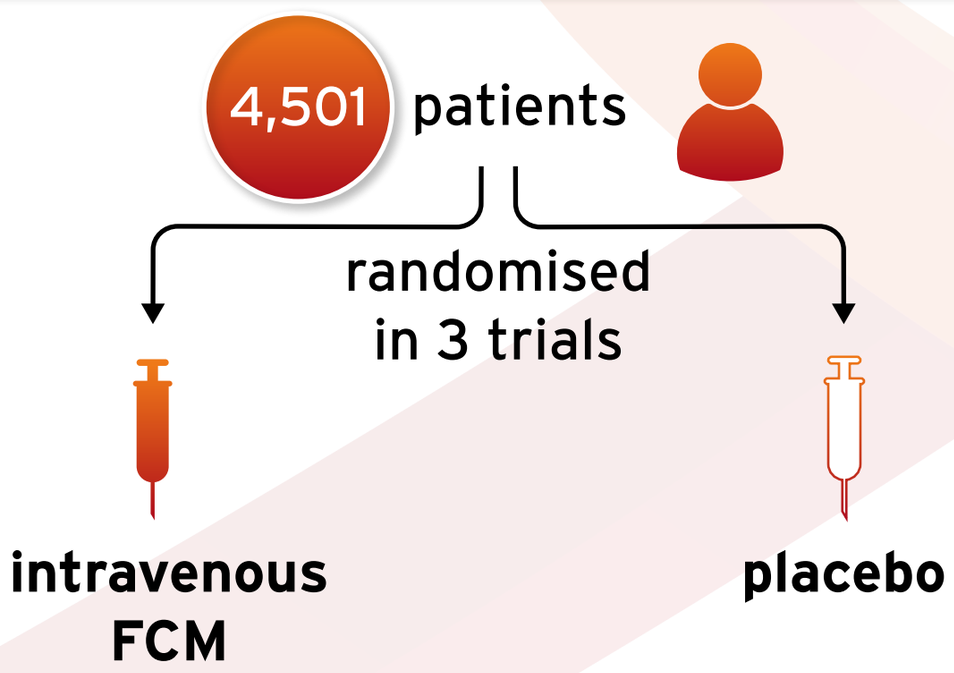
Study objectives

The meta-analysis evaluated the effects of FCM therapy on hospitalisations and mortality in iron-deficient patients with HF and reduced or mildly reduced LVEF.

Study population

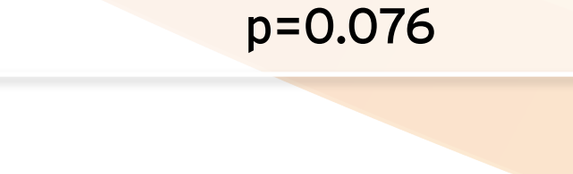
Individual participant data were pooled from 3 randomised, placebo-controlled trials of FCM in adult patients with HF and iron deficiency with ≥52 weeks of follow up: CONFIRM-HF, AFFIRM-AHF and HEART-FID.

Who and what?



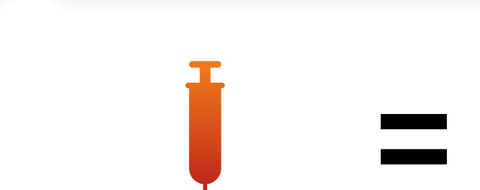
Primary endpoints

composite of total CV hospitalisations and CV death through 52 weeks of follow up reduced with



rate ratio 0.86
95% CI 0.75 to 0.98
p=0.029

composite of total HF hospitalisations and CV death through 52 weeks of follow up no significant difference:



rate ratio 0.87
95% CI 0.75 to 1.01
p=0.076

Secondary endpoints

total CV hospitalisations reduced with	total HF hospitalisations reduced with	CV death: no effect with
vs.	vs.	=
rate ratio 0.83 95% CI 0.73 to 0.96 p=0.009	rate ratio 0.84 95% CI 0.71 to 0.98 p=0.025	

ESC

QUEST trial

#ESCCongress

Qiliqiangxin in patients with heart failure and reduced ejection fraction

Conclusion

The traditional Chinese medicine qiliqiangxin reduces hospitalisation for HF and CV death in patients with heart failure (HF) and a reduced ejection fraction (HFrEF).

Impact on clinical practice

The findings demonstrate meaningful clinical benefit with qiliqiangxin in patients with HFrEF and support its use as an adjunct therapy.

Study objectives

The QUEST trial evaluated the clinical efficacy and safety of qiliqiangxin on major HF outcomes in HFrEF patients.

Study population

Adult HFrEF patients

- with a left ventricular ejection fraction ≤40%
- with NT-proBNP ≥450 pg/ml
- had been on a stable standardised baseline treatment regimen for ≥2 weeks prior to enrolment

Where?

China and Hong Kong SAR of China

133 hospitals

Who and what?

3,110 patients

randomised 1:1

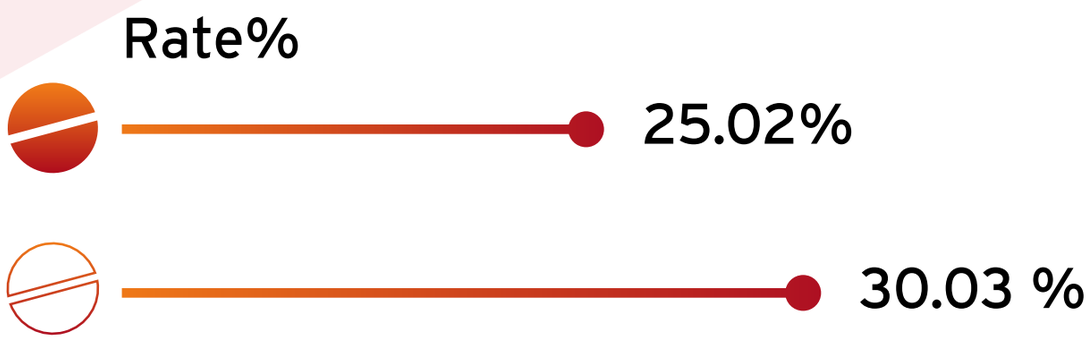
Qiliqiangxin | **Placebo**

4 capsules, 3X daily on top of standard medications for chronic HF

Median follow-up ▶ 18.3 months

Primary endpoint

Composite of rehospitalisation for worsening HF or CV death



Hazard ratio 0.78
95% CI 0.68–0.90; p<0.001

Effect related to

Rehospitalisation for worsening HF reduced with

versus

Hazard ratio 0.76
95% CI 0.64–0.90; p=0.002

CV death reduced with

versus

Hazard ratio 0.83
95% CI 0.68–0.996; p=0.045

ESC

Heliyon

Case report: Woven coronary arteries in a patient with polycythemia vera

--Manuscript Draft--

Manuscript Number:	HELIYON-D-23-31942
Article Type:	Case Report / Case Series
Section/Category:	Medical Sciences
Keywords:	Woven coronary artery; thrombotic recanalization; polycythemia vera; Optical coherence tomography
Abstract:	A 58-year-old female patient was admitted to the Cardiology Department of our hospital for intermittent chest pain for 5 years and aggravation for a week. She had been diagnosed with polycythemia vera 8 years ago.Coronary angiography showed haze lesions in mid right coronary artery, mid left circumflex, and proximal left anterior descending artery. Optical coherence tomography in LAD showed diffused multiple channels within the lumen which are consistent with woven coronary artery. Thromboembolism is the most common complication of polycythemia vera. Therefore, we speculate that the woven coronary artery is caused by thrombotic recanalization.

Case report: Woven coronary arteries in a patient with polycythemia vera

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ABSTRACT

A 58-year-old female patient was admitted to the Cardiology Department of our hospital for intermittent chest pain for 5 years and aggravation for a week. She had been diagnosed with polycythemia vera 8 years ago.Coronary angiography showed haze lesions in mid right coronary artery, mid left circumflex, and proximal left anterior descending artery. Optical coherence tomography in LAD showed diffused multiple channels within the lumen which are consistent with woven coronary artery. Thromboembolism is the most common complication of polycythemia vera. Therefore, we speculate that the woven coronary artery is caused by thrombotic recanalization.

Keywords

Woven coronary artery; thrombotic recanalization; polycythemia vera; Optical coherence tomography

1.Introduction

Woven coronary artery is a rare anomaly characterized by multiple interlacing micro channel bifurcations and woven found incidentally in coronary angiography. Some scholars think that this is a congenital coronary anomaly and benign condition[1].However,others think it might be mimicked by thrombotic recanalization[2]. Thromboembolism is the most common complication of polycythemia vera. Here, we reported a case of woven coronary arteries in a patient with polycythemia vera.

2. Case introduction

A 58-year-old female patient was admitted to the Cardiology Department of our hospital due to intermittent chest pain for 5 years and aggravation for a week. The patient had a history of hypertension for 10 years, with a highest blood pressure of 150/100 mmHg, which was controlled by oral amlodipine 1 tablet once daily and history of cerebral infarction for 23 years. She has been diagnosed with polycythemia vera for 8 years and took hydroxyurea 0.5g once daily. Physical examination: the body temperature was 36.5℃, pulse 76 beats/min, blood pressure 138/70mmHg(1 mmHg=0.133 kPa), and she was not in acute distress. Routine blood test revealed white blood cell count $3.65*10^9$/L (reference interval 3.50-9.50*10^9/L), red blood cell count $8.15*10^{12}$/L (reference interval 3.80-5.10*10^9/L), and hemoglobin count 237g/L (reference interval 115-150g/L). Platelet count $265*10^9$/L (reference interval 125-350*10^9/L); Routine coagulation, liver function, renal function, biochemical, and myocardial injury markers were normal. Bone marrow cytology showed proliferation of granulocyte, red and megakaryocyte lineages, and JAK2-V617 mutation was detected by gene screening. Electrocardiogram showed

sinus rhythm and poor R-wave progression in leads V1-V3 (Figure 1). Echocardiography showed left ventricular ejection fraction 46%, left atrial diameter 44mm, left ventricular end-diastolic diameter 62mm, interventricular septal thickness 12mm, and left ventricular wall segmental motion abnormality. Coronary angiography showed haze lesion in the middle to proximal segment of the left anterior descending artery (LAD) with forward flow TIMI grade 3(Figure 2A). Suspected thrombus in the left circumflex artery (LCX) was observed in the middle to proximal segment and the forward flow of TIMI was grade 3(Figure 2B). The right coronary artery (RCA) showed aneurysmal dilatation in the proximal segment and suspected thrombus in the middle segment with forward flow TIMI grade 3 (Figure 2C). Optical coherence tomography(OCT) performed in LAD showed organized thrombi separate the lumen into multiple micro channels. Clinical diagnosis: Coronary artery heart disease, stable angina, polycythemia vera, Hypertension. Considering the high risk of thrombosis with the condition of the polycythemia vera, and the high possibility of the side branch loss with stenting, the patient was discharged home without coronary intervention. The discharge medicine includingaspirin 100mg once daily, atorvastatin 20mg once daily, metoprolol 47.5mg once daily, amlodipine 1 tablet once daily, hydroxyurea 0.5g once daily. The patient was in stable condition in 3 months follow-up.

3.Discussion

Here we are reporting 1st case of woven coronary arteries in a patient with polythythemia vera. Woven coronary artery is a rare anomaly characterized by multiple interlacing micro channel bifurcations and woven found incidentally in coronary angiography. Some scholars think that this is a congenital anomaly [1], while others believe that it is caused by recanalization of coronary thrombosis [2].At first, it was considered to be a benign condition [3], but later studies found that this variant could cause thrombosis and sudden cardiac death [4, 5].The complex intra-coronary channels affect the flow and causing pressure drop in the distal blood perfusion, particulary for those with more complex micro channel and extended lesion length [5].Although the woven coronary artery showed normal TIMI flow or visual stenosis < 70% on angiography, their sensitivity and specificity in the assessment of ischemia is limited. Intravascular imaging such as OCT can be very helpful in clarifying the intracoronary artery structions and detection of intracoronary thrombus [1].Fractional flow reserve may be the most appropriate method to assess the severity of ischemia [5].Polycythemia vera is the most common disease in myeloproliferative neoplasms and thromboembolism is the most common complication and cause of death[6]. The incidence of thromboembolism is 46%, and the incidence of arterial thrombosis is 2 to 3 times that of venous thrombosis[7]. This patient was hospitalized for cerebral infarction more than 20 years ago, and blood routine examination showed that the red blood cell count was increased abnormally. Polycythemia vera diagnosis was established with bone marrow biopsy 8 years ago. It was speculated and the blood viscosity caused by polycythemia led to cerebral infarction. The coronary artery change confirmed by the OCT are consistent with the organized thrombus based on the angiographic manifestation. We assume the lesion in the LCX and RCA are likely another organized thrombus, which are all complications of polycythemia vera.

Currently, there are no guidelines for the treatment of woven coronary artery. Surgical bypass surgery [1], and coronary artery intervention with stenting has been proposed as treatment options[8]. However, due to the distortion of the channel, the woven coronary artery may lead to the difficulty of wiring and device delivery. Endothelialization of the tissue separating the

multiple channel may cause the occlusion of the side branch. Therefore the treatment strategy should be prudent and individualized for patient with extremely high risk of thromobosis, conservative therapy without stenting probably is safier as with this patient. 3 month follow-up showed that the patient's chest pain was relieved, without any cardiac event.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Baoguo Wang drafted the manuscript as first author. Mingyou Zhang and Jian Zhang provided clinical specimens and information. Weihua Zhang revised the manuscript. All authors read and approved the final manuscript.

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Additional information

Supplementary content related to this article has been published online at [URL].

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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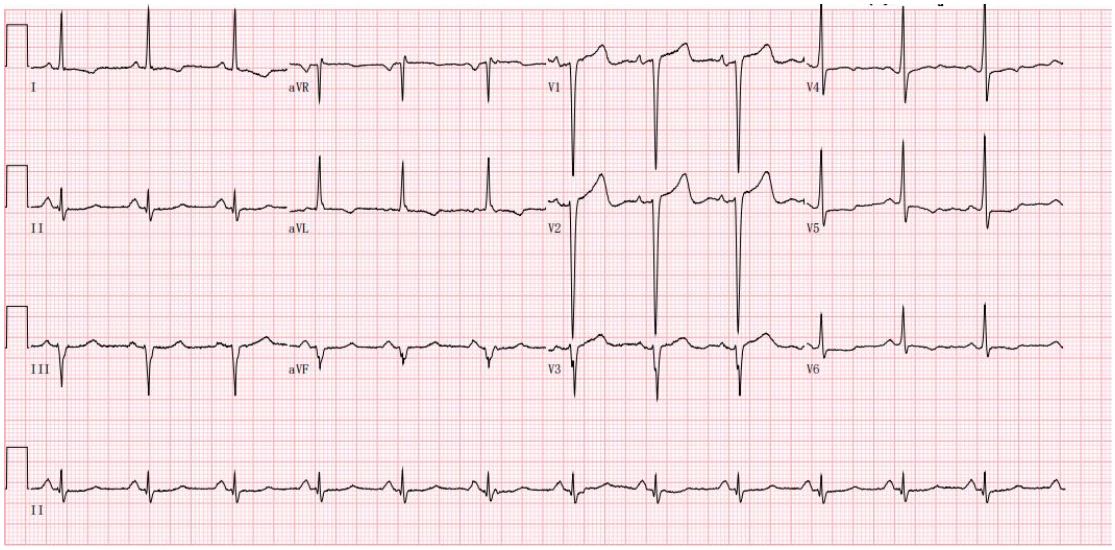
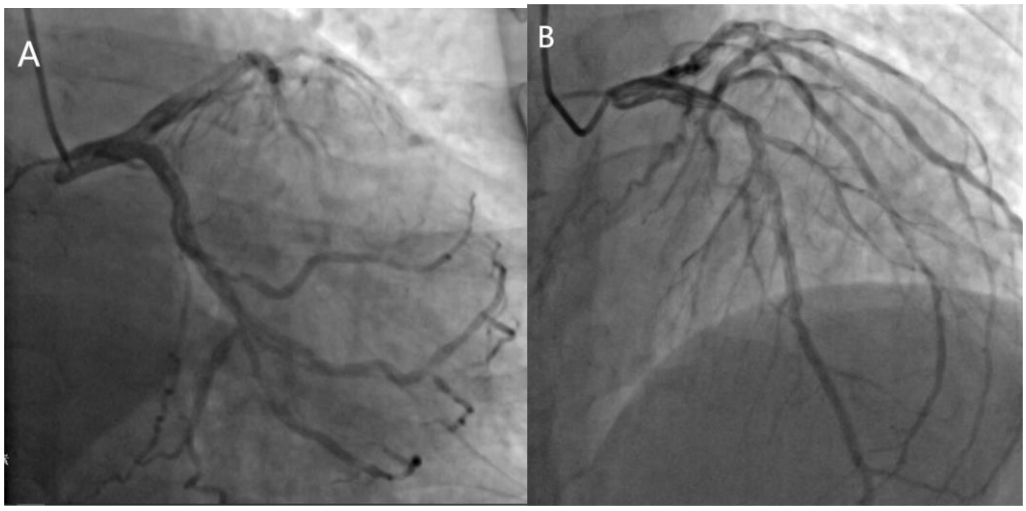


Fig.1. ECG showed sinus rhythm and poor R-wave progression in leads V1-V3.



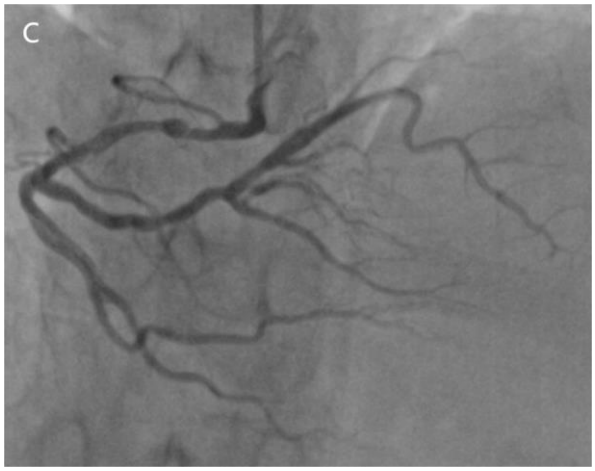


Fig.2. A. The coronary angiography at foot position showed suspected thrombus in the middle to proximal segment of LCX, and the forward flow TIMI grade 3. B. The coronary angiography at head position showed suspected thrombus in the middle to proximal segment of LAD, and the forward flow TIMI grade 3. C. The coronary angiography at head position showed aneurysmal dilatation in the proximal segment and suspected thrombus in the middle segment of RCA with forward flow TIMI grade 3.

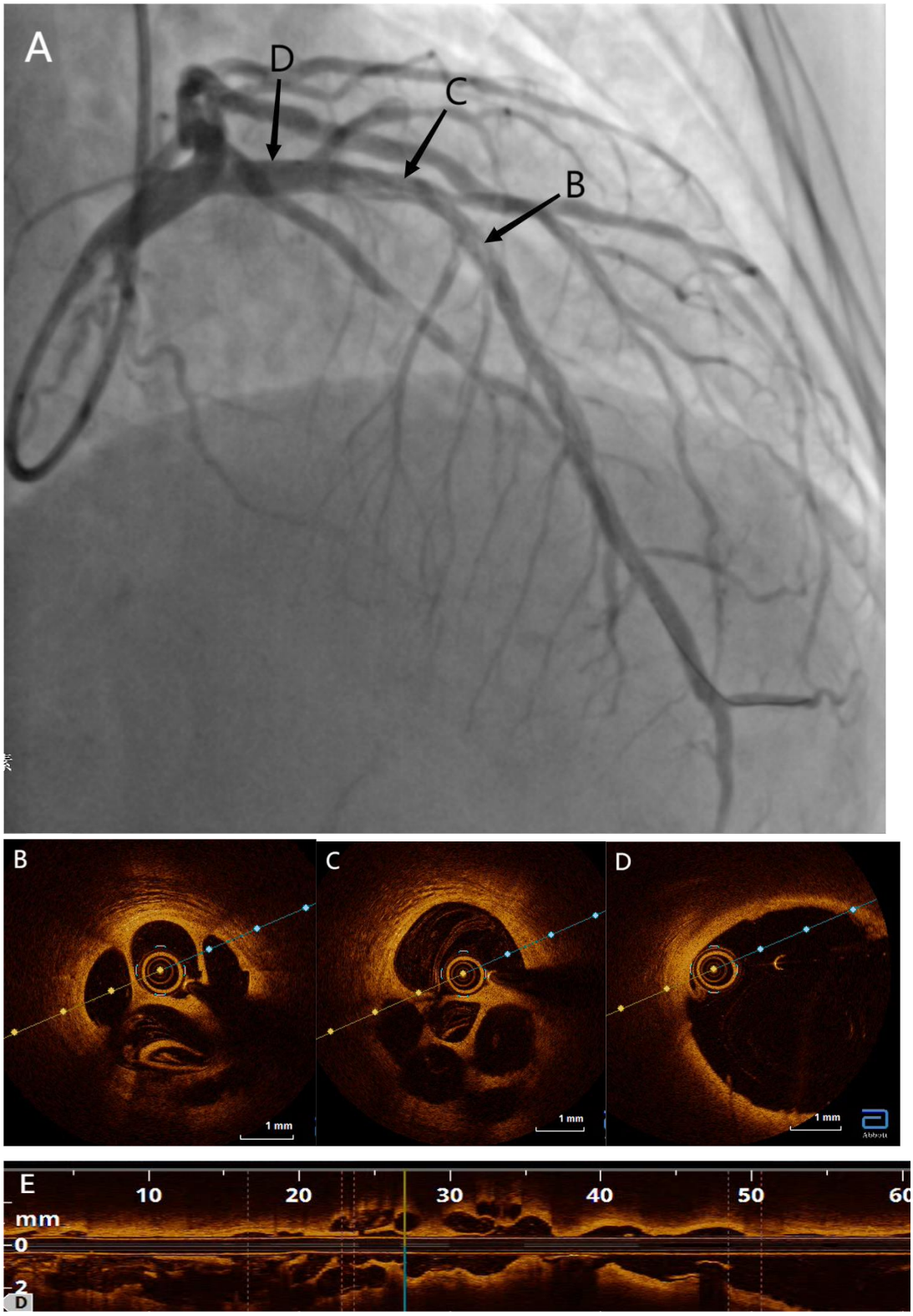


Fig.3. A,B and C. OCT performed in LAD showed organized thrombus separated the lumen into multiple micro channels.D and E. OCT performed in LAD showed multiple micro channels converged into a single lumen at the proximal segment.

*CARE checklist

CARE Checklist of information to include when writing a case report

Topic	Item	Checklist item description	Reported on Line
Title	**1**	Case report: Woven coronary arteries in a patient with polycythemia vera	
Key Words	**2**	Woven coronary artery; thrombotic recanalization; polycythemia vera; optical coherence tomography;case report	
Abstract (no references)	**3a**	Woven coronary artery is a rare anomaly characterized by multiple interlacing micro channel bifurcations and woven found incidentally in coronary angiographyHere we are reporting 1st case of woven coronary arteries in a patient with polythythemia vera.	
	3b	A 58-year-old female patient was admitted to the Cardiology Department of our hospital due to intermittent chest pain for 5 years and aggravation for a week	
	3c	Clinical diagnosis: Coronary artery heart disease, stable angina, polycythemia vera, Hypertension. Therapeutic interventions: Conservative therapy without stenting. Outcomes: 3 month follow-up showed that the patient's chest pain was relieved, without any cardiac event.	
	3d	Endothelialization of the tissue separating the multiple channel may cause the occlusion of the side branch. Therefore the treatment strategy should be prudent and individualized for this patient with extremely high risk of thromobosis, conservative therapy without stenting probably is safier as with this patient.	
Introduction	**4**	This is the first report of woven coronary arteries in a patient with polythythemia vera,and optical coherence tomography(OCT) performed in LAD showed organized thrombi separate the lumen into multiple micro channels.The treatment strategy should be prudent and individualized for this patient with extremely high risk of thromobosis, conservative therapy without stenting probably is safier as with this patient.	
Patient Information	**5a**	A 58-year-old female patient	
	5b	The patient has been intermittent chest pain for 5 years and aggravation for a week.Optical coherence tomography(OCT) performed in LAD showed organized thrombi separate the lumen into multiple micro channels. She has been diagnosed with polycythemia vera for 8 years and took hydroxyurea 0.5g once daily.	
	5c	The patient had a history of hypertension for 10 years, with a highest blood pressure of 150/100 mmHg, which was controlled by oral amlodipine 1 tablet once daily and history of cerebral infarction for 23 years. She has been diagnosed with polycythemia vera for 8 years and took hydroxyurea 0.5g once daily. Bone marrow cytology showed proliferation of granulocyte, red and megakaryocyte lineages, and JAK2-V617 mutation was detected by gene screening.	
	5d	The hypertension was controlled by oral amlodipine 1 tablet once daily and hydroxyurea 0.5g once daily because of the polycythemia vera.	
Clinical Findings	**6**	She has been diagnosed with polycythemia vera for 8 years and took hydroxyurea 0.5g once daily.Routine blood test revealed red blood cell count 8.15*1012/L (reference interval 3.80-5.10*109/L), and hemoglobin count 237g/L (reference interval 115-150g/L). Bone marrow cytology showed proliferation of granulocyte, red and megakaryocyte lineages, and JAK2-V617 mutation was detected by gene screening.	
Timeline	**7**	The history of cerebral infarction for 23 years,diagnosed with polycythemia vera for 8 years, intermittent chest pain for 5 years and aggravation for a week.	
Diagnostic Assessment	8a	Routine blood test revealed white blood cell count 3.65*109/L (reference interval 3.50-9.50*109/L), red blood cell count 8.15*1012/L (reference interval 3.80-5.10*109/L), and hemoglobin count 237g/L (reference interval 115-150g/L). Platelet count 265*109/L (reference interval 125-350*109/L).Bone marrow cytology showed proliferation of granulocyte, red and megakaryocyte lineages, and JAK2-V617 mutation was detected by gene screening.Electrocardiogram showed sinus rhythm and poor R-wave progression in leads V1-V3 (Figure 1).	

Echocardiography showed left ventricular ejection fraction 46%, left atrial diameter 44mm, left ventricular end-diastolic diameter 62mm, interventricular septal thickness 12mm, and left ventricular wall segmental motion abnormality. Coronary angiography showed haze lesion in the middle to proximal segment of the left anterior descending artery (LAD) with forward flow TIMI grade 3(Figure 2A). Suspected thrombus in the left circumflex artery (LCX) was observed in the middle to proximal segment and the forward flow of TIMI was grade 3(Figure 2B). The right coronary artery (RCA) showed aneurysmal dilatation in the proximal segment and suspected thrombus in the middle segment with forward flow TIMI grade 3 (Figure 2C). Optical coherence tomography(OCT) performed in LAD showed organized thrombi separate the lumen into multiple micro channels.

8b No diagnostic challenges.

8c Clinical diagnosis: Coronary artery heart disease, stable angina, polycythemia vera, Hypertension.

8d No Prognosis

Therapeutic Intervention

9a Type of therapeutic intervention: pharmacologic

9b Aspirin 100mg once daily, atorvastatin 20mg once daily, metoprolol 47.5mg once daily, amlodipine 1 tablet once daily, hydroxyurea 0.5g once daily.

9c No changes in therapeutic intervention

Follow-up and Outcomes

10a The patient was in stable condition in 3 months follow-up.

10b No important follow-up diagnostic and other test results.

10c The patient followed the doctor's advice and adhered to the medication in 3 months follow-up.

10d No adverse and unanticipated events.

Discussion

11a This is the first report of woven coronary arteries in a patient with polythythemia vera.This patient was hospitalized for cerebral infarction more than 20 years ago, and blood routine examination showed that the red blood cell count was increased abnormally.Polycythemia vera diagnosis was established with bone marrow biopsy 8 years ago. It was speculated and the blood viscosity caused by polycythemia led to cerebral infarction. The coronary artery change confirmed by the OCT are consistent with the organized thrombus based on the angiographic manifestation. We assume the lesion in the LCX and RCA are likely another organized thrombus, which are all complications of polycythemia vera.

11b Some scholars think that this is a congenital anomaly [1], while others believe that it is caused by recanalization of coronary thrombosis [2].At first, it was considered to be a benign condition [3], but later studies found that this variant could cause thrombosis and sudden cardiac death [4, 5].The complex intra-coronary channels affect the flow and causing pressure drop in the distal blood perfusion, particulary for those with more complex micro channel and extended lesion length [5].Although the woven coronary artery showed normal TIMI flow or visual stenosis < 70% on angiography, their sensitivity and specificity in the assessment of ischemia is limited. Intravascular imaging such as OCT can be very helpful in clarifying the intracoronary artery structions and detection of intracoronary thrombus [1].Fractional flow reserve may be the most appropriate method to assess the severity of ischemia [5].Polycythemia vera is the most common disease in myeloproliferative neoplasms and thromboembolism is the most common complication and cause of death.Currently, there are no guidelines for the treatment of woven coronary artery. Surgical bypass surgery [1], and coronary artery intervention with stenting has been proposed as treatment options[8].

11c The treatment strategy should be prudent and individualized for patient with extremely high risk of thromobosis, conservative therapy without stenting probably is safier as with this patient.

11d Due to the distortion of the channel, the woven coronary artery may lead to the difficulty of wiring and device delivery. Endothelialization of the tissue separating the multiple channel may cause the occlusion of the side branch. The treatment strategy should be prudent and individualized for patient with extremely high risk of thromobosis, conservative therapy without stenting probably is safier as with this patient.

Patient Perspective

12a The patient's chest tightness was relieved, and the condition was in a stable stage. She took drugs on time and came to the hospital for regular follow-up.

Informed Consent

12b Did the patient give informed consent? Please provide if requested. Yes ☑ No ☐

Intravascular Imaging Guidance for PCI:

A "Real-Time" Updated Network Meta-analysis

Gregg W. Stone MD

on behalf of

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Akiko Maehara, Yousif Ahmad, Ulf Landmesser, Niels R. Holm

Background

- Prior meta-analyses of intravascular imaging (IVI) guidance vs. angiography guidance of PCI procedures have generally shown reductions in MACE with IVI guidance, although none have shown a reduction in all-cause death or all MI, and few prior studies included OCT guidance

- At the 2023 ESC annual scientific sessions, two new major RCTs of OCT-guided vs. angiography-guided PCI have been presented, the international ILUMIEN IV trial in high-risk pts and complex lesions (n=2487) and the EU-based OCTOBER trial in bifurcation lesions (n=1201)

- The ILUMIEN IV and OCTOBER investigators have collaborated to prepare an updated “real-time” network meta-analysis to examine the effects of IVI guidance vs. angiography guidance and OCT vs. IVUS vs. angiography guidance in patients undergoing PCI

Methods 1

- **PRISMA guidance** was followed for systematic reviews and network meta-analyses and this study has been registered with **PROSPERO**
- **A systematic search** was performed for all RCTs of OCT-guided and IVUS-guided PCI
- **The longest available follow-up duration** was used for each trial; outcomes are expressed as relative risks (RR) with 95% confidence intervals (CI)
- **Direct evidence** was generated from 2-stage meta-analysis (prioritizing random effects > fixed effects)
- **Network meta-analysis** was performed to generate **indirect data** and **overall treatment effects** - specified as the **primary analysis** for this study

Methods 2

- **Pre-specified primary analysis:** IVI-guided PCI (OCT-guided or IVUS-guided or both) vs. angiography-guided PCI
- **Pre-specified secondary analyses:** IVUS-guided vs. angiography-guided PCI, OCT-guided vs. angiography-guided PCI, and OCT-guided vs. IVUS-guided PCI
- **Primary outcome measure was TLF** (cardiac death, TV-MI or ID/CD TLR)
- **Secondary outcomes:** TLF components, all-cause death, all MI, ID/CD TVR, definite or probable stent thrombosis
- **Rules for component outcomes:**
  - If cardiac (or CV) death unavailable, use all-cause death
  - If TV-MI unavailable, use all MI
  - If TLR unavailable, use TVR
  - If definite or probable ST unavailable, use definite ST

Summary of Included Studies

20 randomized trials

(publication years 2010 – 2023)

12,428 randomized patients

(range 85 – 2487 pts per trial)

IVUS: 13 randomized arms, 3120 pts

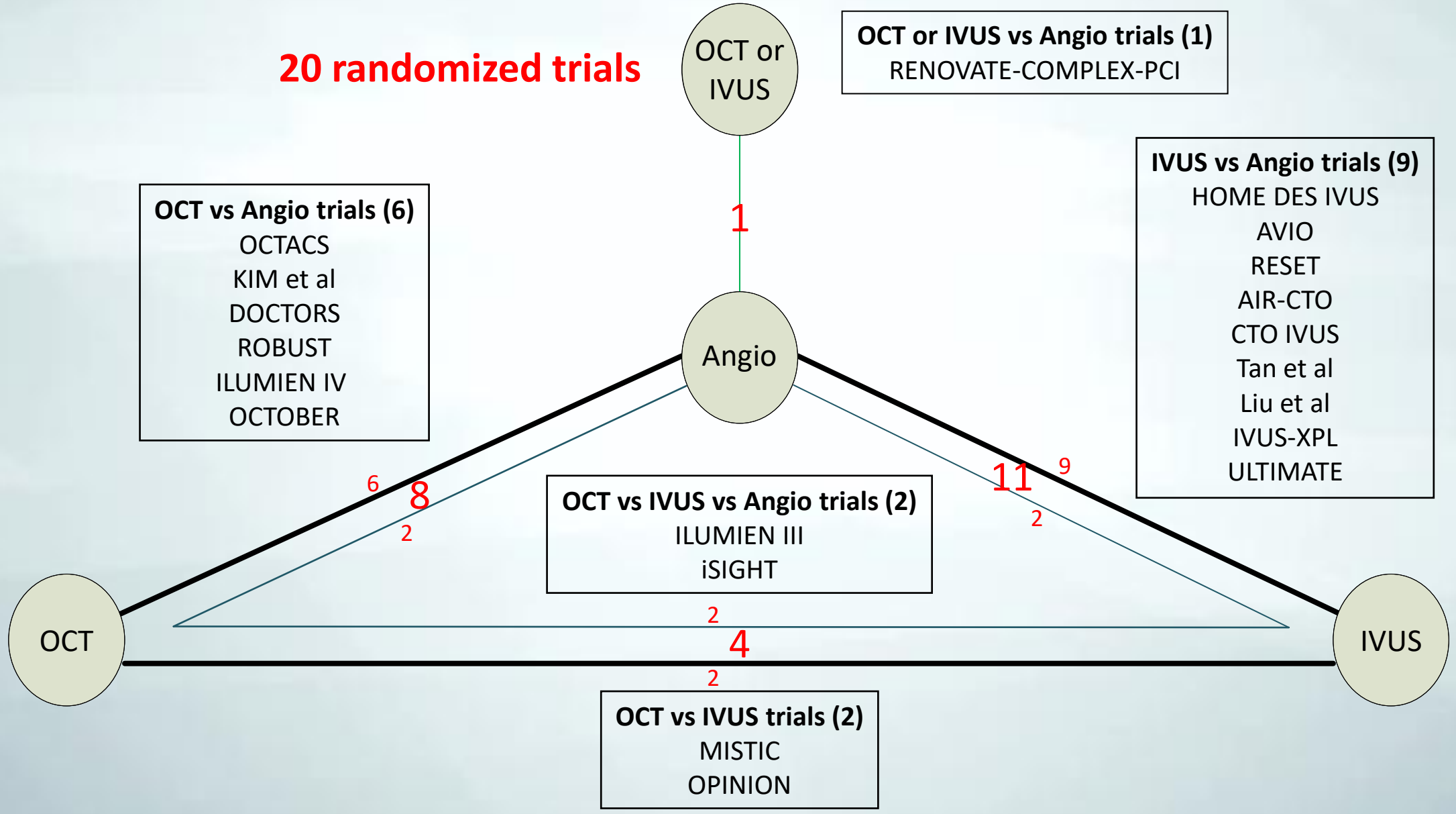
OCT: 10 randomized arms, 2826 pts

OCT or IVUS: 1 randomized arm, 1092 pts

Angiography: 18 randomized arms, 5390 pts

Longest FU: Range 6 – 60 months (weighted mean 26.4 mo)

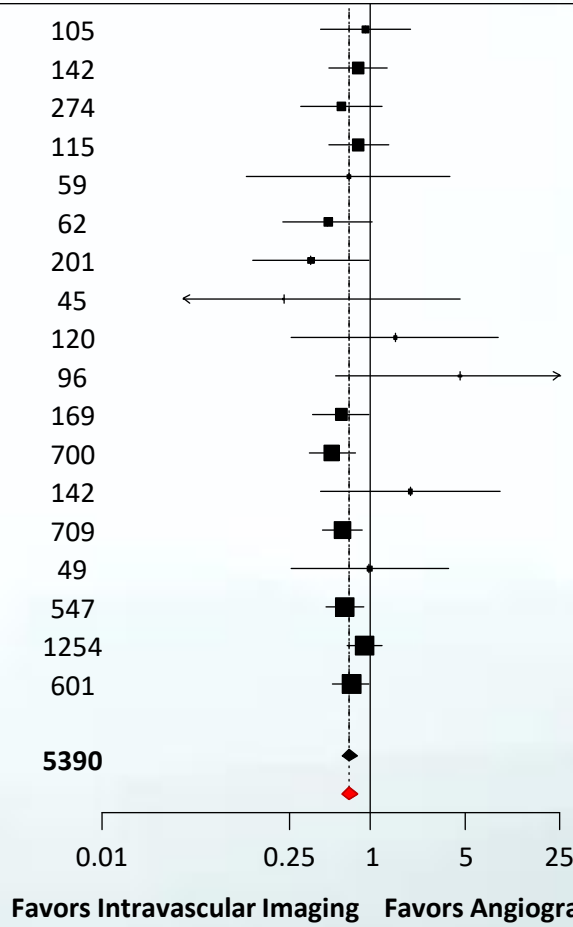
Nodal Map of Direct Relationships



TLF (Direct Evidence): IV Imaging (OCT or IVUS) vs. Angio

18 trials, 11,502 patients, 963 events

Trial and Year	Intravascular Imaging Events	Intravascular Imaging N	Angiography Events	Angiography N	Relative Risk (RR)	RR [95% CI]	Weight (Random)	Weight (Fixed)
HOME DES IVUS, 2010	11	105	12	105		0.92 [0.42, 1.98]	2.5%	2.1%
AVIO, 2013	23	142	29	142		0.79 [0.48, 1.30]	6.1%	5.1%
RESET, 2013	12	269	20	274		0.61 [0.30, 1.23]	3.1%	3.5%
AIR-CTO, 2015	21	115	26	115		0.81 [0.48, 1.35]	5.7%	4.6%
Kim et al, 2015	2	58	3	59		0.68 [0.12, 3.91]	0.5%	0.5%
Tan et al, 2015	8	61	17	62		0.48 [0.22, 1.03]	2.6%	3.0%
CTO-IVUS, 2015	5	201	14	201		0.36 [0.13, 0.97]	1.5%	2.5%
OCTACS, 2015	0	40	2	45		0.22 [0.01, 4.54]	0.2%	0.3%
DOCTORS, 2016	3	120	2	120		1.50 [0.26, 8.82]	0.5%	0.4%
ROBUST, 2018	5	105	1	96		4.57 [0.54, 38.43]	0.3%	0.2%
Liu et al, 2019	22	167	37	169		0.60 [0.37, 0.97]	6.5%	6.5%
IVUS-XPL, 2020	36	700	70	700		0.51 [0.35, 0.76]	10.0%	12.4%
ILUMIEN III, 2021	8	289	2	142		1.97 [0.42, 9.13]	0.6%	0.5%
ULTIMATE, 2021	47	714	76	709		0.61 [0.43, 0.87]	12.4%	13.5%
iSIGHT, 2021	6	101	3	49		0.97 [0.25, 3.72]	0.8%	0.7%
RENOVATE-COMPLEX-PCI, 2023	76	1092	60	547		0.63 [0.46, 0.88]	14.5%	14.2%
ILUMIEN IV, 2023	76	1233	86	1254		0.90 [0.67, 1.21]	16.9%	15.1%
OCTOBER, 2023	59	600	83	601		0.71 [0.52, 0.97]	15.3%	14.7%
Fixed-Effect Model	**420**	**6112**	**543**	**5390**		**0.69 [0.61, 0.78]**	--	**100.0%**
Random-Effect Model (primary analysis)						**0.69 [0.61, 0.78]**	**100.0%**	--



Test for heterogeneity: $I^2 = 0\%$, $\chi^2 = 16.43$ (P=0.49)

Test for overall effect (Fixed): $z = -5.89$ (P<0.0001)

Test for overall effect (Random): $z = -5.87$ (P<0.0001)

RR 0.69, 95% CI 0.61-0.78

OPINION and MISTIC (OCT vs IVUS without an Angio arm) are not included

Cardiac Death (Direct Evidence): IV Imaging vs. Angio

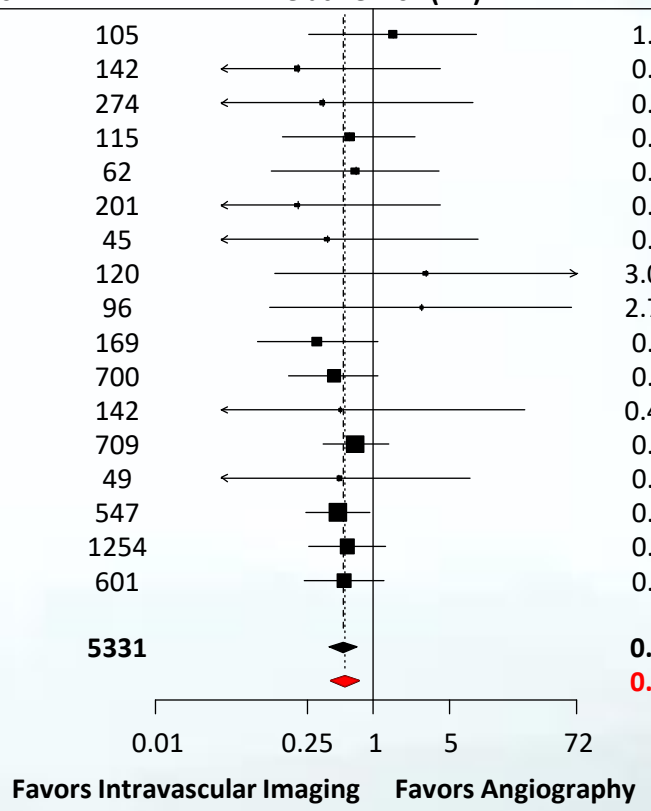
17 trials, 11,385 patients, 174 events

Trial and Year	Intravascular Imaging Events	Intravascular Imaging N	Angiography Events	Angiography N	RR [95% CI]	Weight (Random)	Weight (Fixed)
HOME DES IVUS, 2010	3	105	2	105	1.50 [0.26, 8.79]	3.0%	1.8%
AVIO, 2013	0	142	2	142	0.20 [0.01, 4.13]	1.0%	1.8%
RESET, 2013	0	269	1	274	0.34 [0.01, 8.30]	0.9%	0.9%
AIR-CTO, 2015	3	115	5	115	0.60 [0.15, 2.45]	4.7%	4.4%
Tan et al, 2015	2	61	3	62	0.68 [0.12, 3.91]	3.0%	2.6%
CTO-IVUS, 2015	0	201	2	201	0.20 [0.01, 4.14]	1.0%	1.8%
OCTACS, 2015	0	40	1	45	0.37 [0.02, 8.94]	0.9%	0.8%
DOCTORS, 2016	1	120	0	120	3.00 [0.12, 72.91]	0.9%	0.0%
ROBUST, 2018	1	105	0	96	2.74 [0.11, 66.56]	0.9%	0.0%
Liu et al, 2019	3	167	10	169	0.30 [0.09, 1.08]	5.7%	8.7%
IVUS-XPL, 2020	6	700	14	700	0.43 [0.17, 1.11]	10.2%	12.3%
ILUMIEN III, 2021	0	289	0	142	0.49 [0.01, 24.68]	0.6%	0.0%
ULTIMATE, 2021	13	714	19	709	0.68 [0.34, 1.37]	19.0%	16.8%
iSIGHT, 2021	1	101	1	49	0.49 [0.03, 7.59]	1.2%	1.2%
RENOVATE-COMPLEX-PCI, 2023	16	1092	17	547	0.47 [0.24, 0.93]	20.3%	19.9%
ILUMIEN IV, 2023	9	1233	16	1254	0.57 [0.25, 1.29]	14.0%	13.9%
OCTOBER, 2023	8	600	15	601	0.53 [0.23, 1.25]	12.8%	13.2%
Fixed-Effect Model	**66**	**6054**	**108**	**5331**	**0.53 [0.39, 0.72]**	--	**100.0%**
Random-Effect Model (primary analysis)					**0.54 [0.40, 0.74]**	**100.0%**	--

Test for heterogeneity: $I^2 = 0\%$, $\chi^2 = 6.07$ (P=0.99)

Test for overall effect (Fixed): $z = -4.07$ (P<0.0001)

Test for overall effect (Random): $z = -3.92$ (P<0.0001)

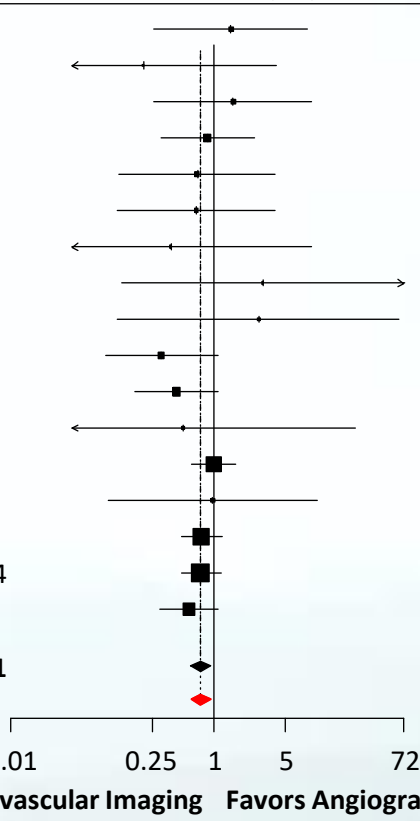


RR 0.54, 95% CI 0.40-0.74

All-cause Death (Direct Evidence): IV Imaging vs. Angio

17 trials, 11,385 patients, 318 events

Study and Year	Intravascular Imaging Events	Intravascular Imaging N	Angiography Events	Angiography N	RR [95% CI]	Weight (Random)	Weight (Fixed)
HOME DES IVUS, 2010	3	105	2	105	1.50 [0.26, 8.79]	1.6%	1.1%
AVIO, 2013	0	142	2	142	0.20 [0.01, 4.13]	0.5%	1.1%
RESET, 2013	3	269	2	274	1.53 [0.26, 9.07]	1.5%	1.1%
AIR-CTO, 2015	6	115	7	115	0.86 [0.30, 2.47]	4.3%	3.9%
Tan et al, 2015	2	61	3	62	0.68 [0.12, 3.91]	1.6%	1.7%
CTO-IVUS, 2015	2	201	3	201	0.67 [0.11, 3.95]	1.5%	1.7%
OCTACS, 2015	0	40	1	45	0.37 [0.02, 8.94]	0.5%	0.5%
DOCTORS, 2016	1	120	0	120	3.00 [0.12,72.91]	0.5%	0.0%
ROBUST, 2018	1	105	0	96	2.74 [0.11, 66.56]	0.5%	0.0%
Liu et al, 2019	3	167	10	169	0.30 [0.09, 1.08]	3.0%	5.5%
IVUS-XPL, 2020	6	700	14	700	0.43 [0.17, 1.11]	5.4%	7.8%
ILUMIEN III, 2021	0	289	0	142	0.49 [0.01, 24.68]	0.3%	0.0%
ULTIMATE, 2021	31	714	31	709	0.99 [0.61, 1.62]	20.5%	17.3%
iSIGHT, 2021	2	101	1	49	0.97 [0.09, 10.44]	0.9%	0.7%
RENOVATE-COMPLEX-PCI, 2023	42	1092	28	547	0.75 [0.47, 1.20]	22.3%	20.7%
ILUMIEN IV, 2023	32	1233	44	1254	0.74 [0.47, 1.16]	24.2%	24.2%
OCTOBER, 2023	13	600	23	601	0.57 [0.29, 1.11]	10.8%	12.8%
Fixed-Effect Model	**147**	**6054**	**171**	**5331**	**0.74 [0.59, 0.92]**	--	**100.0%**
Random-Effect Model (Primary Analysis)					**0.75 [0.60, 0.93]**	**100.0%**	--



Test for heterogeneity: $I^2 = 0\%$, $\chi^2 = 8.90$ (P=0.92)

Test for overall effect (Fixed): $z = -2.75$ (P=0.006)

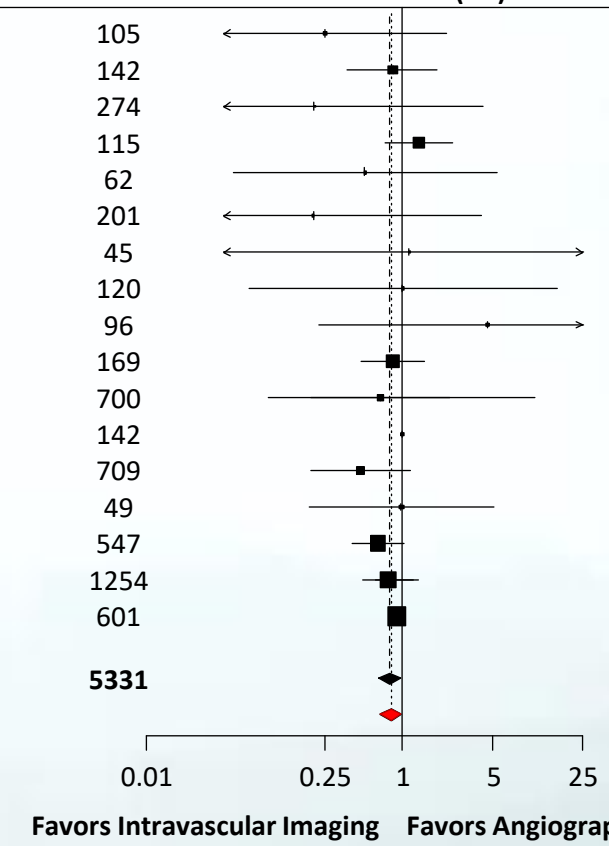
Test for overall effect (Random): $z = -2.61$ (P=0.009)

RR 0.75, 95% CI 0.60-0.93

TV-MI (Direct Evidence): IV Imaging vs. Angio

17 trials, 11,385 patients, 393 events

Trial and Year	Intravascular Imaging Events	Intravascular Imaging N	Angiography Events	Angiography N	RR [95% CI]	Weight (Random)	Weight (Fixed)
HOME DES IVUS, 2010	1	105	4	105	0.25 [0.03, 2.20]	0.8%	1.8%
AVIO, 2013	10	142	12	142	0.83 [0.37, 1.87]	5.8%	5.5%
RESET, 2013	0	269	2	274	0.20 [0.01, 4.22]	0.4%	0.9%
AIR-CTO, 2015	20	115	15	115	1.33 [0.72, 2.47]	9.8%	6.9%
Tan et al, 2015	1	61	2	62	0.51 [0.05, 5.46]	0.7%	0.9%
CTO-IVUS, 2015	0	201	2	201	0.20 [0.01, 4.14]	0.4%	0.9%
OCTACS, 2015	0	40	0	45	1.12 [0.02, 55.33]	0.2%	0.0%
DOCTORS, 2016	1	120	1	120	1.00 [0.06, 15.80]	0.5%	0.5%
ROBUST, 2018	2	105	0	96	4.57 [0.22, 94.07]	0.4%	0.0%
Liu et al, 2019	19	167	23	169	0.84 [0.47, 1.48]	11.6%	10.5%
IVUS-XPL, 2020	4	700	6	700	0.67 [0.19, 2.35]	2.4%	2.8%
ILUMIEN III, 2021	2	289	1	142	0.98 [0.09, 10.75]	0.7%	0.6%
ULTIMATE, 2021	7	714	15	709	0.46 [0.19, 1.13]	4.7%	6.9%
iSIGHT, 2021	4	101	2	49	0.97 [0.18, 5.12]	1.4%	1.2%
RENOVATE-COMPLEX-PCI, 2023	38	1092	30	547	0.63 [0.40, 1.01]	17.1%	18.4%
ILUMIEN IV, 2023	31	1233	41	1254	0.77 [0.49, 1.22]	17.7%	18.7%
OCTOBER, 2023	46	600	51	601	0.90 [0.62, 1.32]	25.6%	23.4%
Fixed-Effect Model	**186**	**6054**	**207**	**5331**	**0.79 [0.65, 0.96]**	--	**100.0%**
Random-Effect Model (primary analysis)					**0.80 [0.66, 0.97]**	**100.0%**	--



Test for heterogeneity: $I^2 = 0\%$, $\chi^2 = 9.81$ (P=0.88)

Test for overall effect (Fixed): $z = -2.42$ (P=0.02)

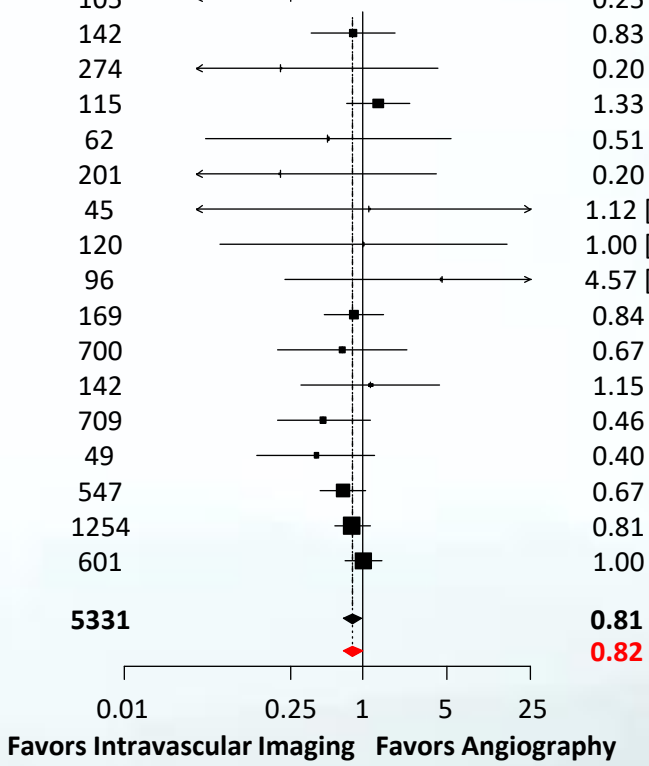
Test for overall effect (Random): $z = -2.25$ (P=0.02)

RR 0.80, 95% CI 0.66-0.97

All MI (Direct Evidence): IV Imaging vs. Angio

17 trials, 11,385 patients, 480 events

Trial and Year	Intravascular Imaging Events	Intravascular Imaging N	Angiography Events	Angiography N	Relative Risk (RR)	RR [95% CI]	Weight (Random)	Weight (Fixed)
HOME DES IVUS, 2010	1	105	4	105		0.25 [0.03, 2.20]	0.6%	1.5%
AVIO, 2013	10	142	12	142		0.83 [0.37, 1.87]	4.7%	4.6%
RESET, 2013	0	269	2	274		0.20 [0.01, 4.22]	0.3%	0.8%
AIR-CTO, 2015	20	115	15	115		1.33 [0.72, 2.47]	8.0%	5.7%
Tan et al, 2015	1	61	2	62		0.51 [0.05, 5.46]	0.5%	0.8%
CTO-IVUS, 2015	0	201	2	201		0.20 [0.01, 4.14]	0.3%	0.8%
OCTACS, 2015	0	40	0	45		1.12 [0.02, 55.33]	0.2%	0.0%
DOCTORS, 2016	1	120	1	120		1.00 [0.06, 15.80]	0.4%	0.4%
ROBUST, 2018	2	105	0	96		4.57 [0.22, 94.07]	0.3%	0.0%
Liu et al, 2019	19	167	23	169		0.84 [0.47, 1.48]	9.4%	8.7%
IVUS-XPL, 2020	4	700	6	700		0.67 [0.19, 2.35]	1.9%	2.3%
ILUMIEN III, 2021	7	289	3	142		1.15 [0.30, 4.37]	1.7%	1.5%
ULTIMATE, 2021	7	714	15	709		0.46 [0.19, 1.13]	3.8%	5.7%
iSIGHT, 2021	5	101	6	49		0.40 [0.13, 1.26]	2.4%	3.1%
RENOVATE-COMPLEX-PCI, 2023	43	1092	32	547		0.67 [0.43, 1.05]	15.3%	16.3%
ILUMIEN IV, 2023	57	1233	72	1254		0.81 [0.57, 1.13]	26.6%	27.3%
OCTOBER, 2023	54	600	54	601		1.00 [0.70, 1.44]	23.5%	20.6%
Fixed-Effect Model	**231**	**6054**	**249**	**5331**		**0.81 [0.68, 0.97]**	--	**100.0%**
Random-Effect Model (primary analysis)						**0.82 [0.69, 0.98]**	**100.0%**	--



Test for heterogeneity: $I^2 = 0\%$, $\chi^2 = 11.99$ (P=0.74)

Test for overall effect (Fixed): $z = -2.34$ (P=0.02)

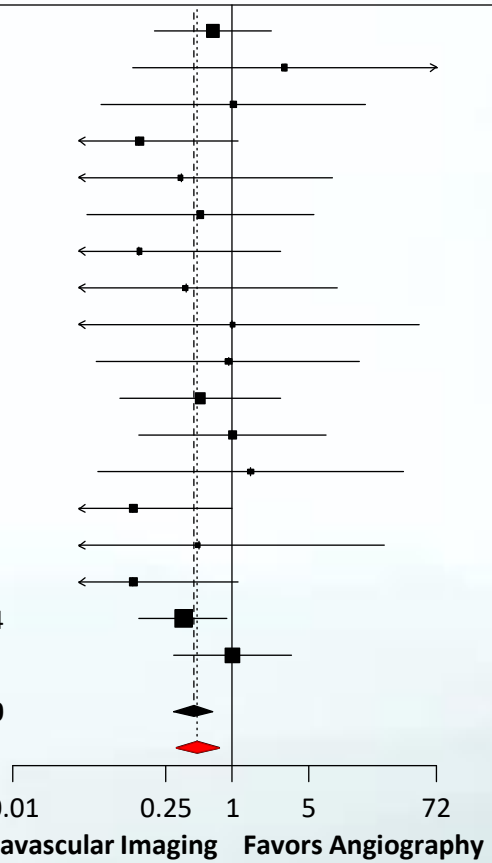
Test for overall effect (Random): $z = -2.18$ (P=0.03)

RR 0.82, 95% CI 0.69-0.98

Stent Thrombosis (Direct Evidence): IV Imaging vs. Angio

18 trials, 11,502 patients, 89 events

	Intravascular Imaging		Angiography					
Trial and Year	**Events**	**N**	**Events**	**N**	**Relative Risk (RR)**	**RR [95% CI]**	**Weight (Random)**	**Weight (Fixed)**
HOME DES IVUS, 2010	4	105	6	105		0.67 [0.19, 2.29]	13.5%	9.0%
AVIO, 2013	1	142	0	142		3.00 [0.12, 73.02]	2.0%	0.7%
RESET, 2013	1	269	1	274		1.02 [0.06, 16.20]	2.7%	1.5%
AIR-CTO, 2015	1	115	7	115		0.14 [0.02, 1.14]	4.8%	10.5%
Kim et al, 2015	0	58	1	59		0.34 [0.01, 8.15]	2.0%	2.2%
Tan et al, 2015	1	61	2	62		0.51 [0.05, 5.46]	3.7%	3.0%
CTO-IVUS, 2015	0	201	3	201		0.14 [0.01, 2.75]	2.4%	5.2%
OCTACS, 2015	0	40	1	45		0.37 [0.02, 8.94]	2.1%	2.1%
DOCTORS, 2016	0	120	0	120		1.00 [0.02, 49.99]	1.4%	0.7%
ROBUST, 2018	1	105	1	96		0.91 [0.06, 14.42]	2.7%	1.6%
Liu et al, 2019	2	167	4	169		0.51 [0.09, 2.73]	7.3%	5.9%
IVUS-XPL, 2020	2	700	2	700		1.00 [0.14, 7.08]	5.4%	3.0%
ILUMIEN III, 2021	1	289	0	142		1.48 [0.06, 36.02]	2.0%	1.0%
ULTIMATE, 2021	1	714	8	709		0.12 [0.02, 0.99]	4.8%	12.0%
iSIGHT, 2021	0	101	0	49		0.49 [0.01, 24.22]	1.4%	1.0%
RENOVATE-COMPLEX-PCI, 2023	1	1092	4	547		0.13 [0.01, 1.12]	4.3%	8.0%
ILUMIEN IV, 2023	6	1233	17	1254		0.36 [0.14, 0.91]	24.0%	25.2%
OCTOBER, 2023	5	600	5	601		1.00 [0.29, 3.44]	13.6%	7.5%
Fixed-Effect Model	**27**	**6112**	**62**	**5390**		**0.44 [0.29, 0.68]**	--	**100.0%**
Random-Effect Model (primary analysis)						**0.48 [0.31, 0.76]**	**100.0%**	--



Test for heterogeneity: $I^2 = 0\%$, $\chi^2 = 10.18$ (P=0.90)

Test for overall effect (Fixed): $z = -3.75$ (P=0.0002)

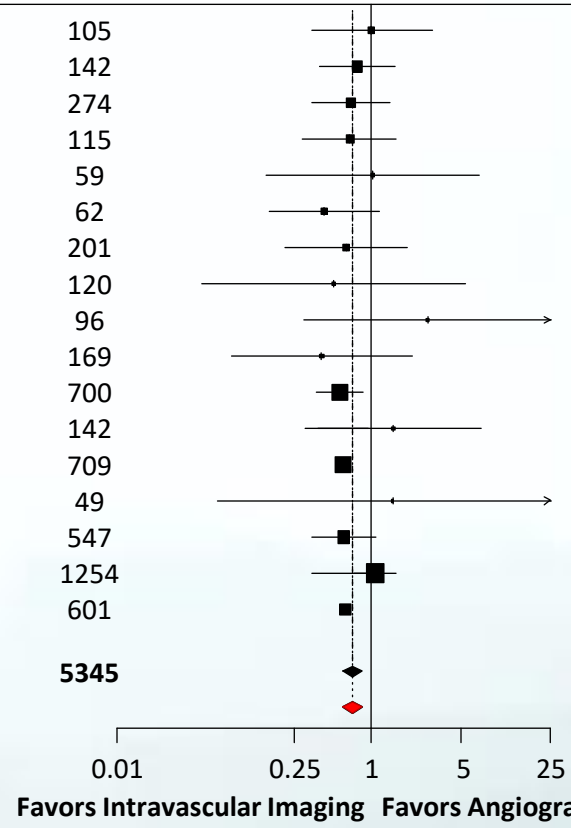
Test for overall effect (Random): $z = -3.14$ (P=0.002)

RR 0.48, 95% CI 0.31-0.76

TLR (Direct Evidence): IV Imaging vs. Angio

17 trials, 11,417 patients, 497 events

	Intravascular Imaging		Angiography					
Trial and Year	**Events**	**N**	**Events**	**N**	**Relative Risk (RR)**	**RR [95% CI]**	**Weight (Random)**	**Weight (Fixed)**
HOME DES IVUS, 2010	6	105	6	105		1.00 [0.33, 3.00]	2.6%	2.1%
AVIO, 2013	13	142	17	142		0.76 [0.39, 1.51]	6.6%	5.9%
RESET, 2013	12	269	18	274		0.68 [0.33, 1.38]	6.1%	6.2%
AIR-CTO, 2015	8	115	12	115		0.67 [0.28, 1.57]	4.2%	4.2%
Kim et al, 2015	2	58	2	59		1.02 [0.15, 6.98]	0.8%	0.7%
Tan et al, 2015	5	61	12	62		0.42 [0.16, 1.13]	3.2%	4.1%
CTO-IVUS, 2015	5	201	8	201		0.62 [0.21, 1.88]	2.5%	2.8%
DOCTORS, 2016	1	120	2	120		0.50 [0.05, 5.44]	0.5%	0.7%
ROBUST, 2018	3	105	1	96		2.74 [0.29, 25.92]	0.6%	0.4%
Liu et al, 2019	2	167	5	169		0.40 [0.08, 2.06]	1.2%	1.7%
IVUS-XPL, 2020	31	700	55	700		0.56 [0.37, 0.86]	16.9%	19.0%
ILUMIEN III, 2021	6	289	2	142		1.47 [0.30, 7.21]	1.2%	0.9%
ULTIMATE, 2021	27	714	45	709		0.60 [0.37, 0.95]	14.2%	15.6%
iSIGHT, 2021	1	101	0	49		1.46 [0.06, 35.27]	0.3%	0.0%
RENOVATE-COMPLEX-PCI, 2023	24	1092	20	547		0.60 [0.34, 1.08]	9.0%	9.2%
ILUMIEN IV, 2023	53	1233	51	1254		1.06 [0.73, 1.54]	21.8%	17.5%
OCTOBER, 2023	16	600	26	601		0.62 [0.33, 1.14]	8.2%	9.0%
Fixed-Effect Model	**215**	**6072**	**282**	**5345**		**0.71 [0.60, 0.84]**	**--**	**100.0%**
Random-Effect Model (primary analysis)						**0.71 [0.59, 0.85]**	**100.0%**	**--**



Test for heterogeneity: $I^2 = 0\%$, $\chi^2 = 11.12$ (P=0.80)

Test for overall effect (Fixed): $z = -3.86$ (P=0.0001)

Test for overall effect (Random): $z = -3.84$ (P=0.0001)

RR 0.71, 95% CI 0.59-0.85

Network Evidence: All Outcomes

IVI-guided (OCT or IVUS) PCI vs Angiography-guided PCI

Outcome	N trials	N pts	N events	Direct estimate	% evidence	Indirect estimate	% evidence	Network estimate
TLF	18	11,502	963	0.69 [0.61, 0.78]	100	-	-	**0.69 [0.61, 0.78]**
- Cardiac death	17	11,385	174	0.54 [0.40, 0.74]	100	-	-	**0.54 [0.40, 0.74]**
- TV-MI	17	11,385	393	0.80 [0.66, 0.97]	100	-	-	**0.80 [0.66, 0.97]**
- ID/CD TLR	17	11,417	497	0.71 [0.59, 0.85]	100	-	-	**0.71 [0.59, 0.85]**
Stent thrombosis	17	11,385	89	0.48 [0.31, 0.76]	100	-	-	**0.48 [0.31, 0.76]**
All-cause death	17	11,385	318	0.75 [0.60, 0.93]	100	-	-	**0.75 [0.60, 0.93]**
All MI	17	11,385	480	0.82 [0.69, 0.98]	100	-	-	**0.82 [0.69, 0.98]**
ID/CD TVR	17	11,417	589	0.71 [0.61, 0.84]	100	-	-	**0.71 [0.61, 0.84]**

Network Evidence: All Outcomes
OCT-guided PCI vs IVUS-guided PCI

Outcome	N trials	N pts	N events	Direct estimate	% evidence	Indirect estimate	% evidence	Network estimate
TLF	4	1316	48	0.89 [0.51, 1.57]	19	1.32 [1.00, 1.73]	81	**1.22 [0.96, 1.56]**
- Cardiac death	4	1316	3	1.32 [0.25, 6.98]	15	1.12 [0.56, 2.27]	85	**1.15 [0.60, 2.20]**
- TV-MI	4	1316	14	0.97 [0.34, 2.79]	14	1.06 [0.69, 1.64]	86	**1.05 [0.70, 1.57]**
- ID/CD TLR	4	1316	34	0.78 [0.39, 1.52]	25	1.51 [1.02, 2.22]	75	**1.28 [0.91, 1.79]**
Stent thrombosis	4	1316	4	0.93 [0.19, 4.51]	26	1.15 [0.45, 2.96]	74	**1.09 [0.48, 2.45]**
All-cause death	4	1316	12	1.26 [0.44, 3.62]	19	0.91 [0.55,1.50]	81	**0.97 [0.61, 1.52]**
All MI	4	1316	21	1.26 [0.52, 3.02]	17	1.12 [0.75, 1.67]	83	**1.14 [0.79, 1.64]**
ID/CD TVR	4	1316	60	1.10 [0.67, 1.80]	34	1.52 [1.07, 2.17]	66	**1.36 [1.02, 1.82]**

TLF (Network Evidence): Bayesian vs. Frequentist Estimates

	Frequentist RR (95% CI)	Bayesian RR (95% CrI)
IVI (OCT or IVUS) vs. Angio		
Direct estimate (18 trials)	0.68 (0.56, 0.84)	0.69 (0.61, 0.79)
Indirect estimate	-	-
Network estimate	0.68 (0.56, 0.84)	0.69 (0.61, 0.79)
IVUS vs. Angio		
Direct estimate (11 trials)	0.63 (0.53, 0.75)	0.62 (0.53, 0.75)
Indirect estimate	0.92 (0.48, 1.76)	1.00 (0.46, 1.95)
Network estimate	0.65 (0.55, 0.77)	0.65 (0.55, 0.77)
OCT vs. Angio		
Direct estimate (8 trials)	0.83 (0.68, 1.02)	0.85 (0.68, 1.06)
Indirect estimate	0.50 (0.27, 0.96)	0.54 (0.27, 1.13)
Network estimate	0.79 (0.65, 0.97)	0.79 (0.65, 0.99)
OCT vs. IVUS		
Direct estimate (4 trials)	0.89 (0.51, 1.57)	0.92 (0.52, 1.69)
Indirect estimate	1.32 (1.00, 1.73)	1.33 (0.98, 1.80)
Network estimate	1.22 (0.96, 1.56)	1.23 (0.93, 1.60)

Limitations

- The limitations of all meta-analyses apply, acknowledging inter-study differences in study design, patient characteristics, geography, operators, technique, collected data, endpoint definitions, and follow-up duration
- The evidence is very robust for all IVI-guided PCI vs angiography-guided PCI, especially for the composite TLF outcome
- Given the fewer numbers of trials and events, the data are less determinative for some of the the pairwise comparisons and non-composite outcomes
  - In particular, prior to this congress, OCT vs. IVUS guidance of PCI had been directly compared in only 4 RCTs (1316 pts)
  - Most of the network evidence for this comparison was therefore “indirect”
  - As the largest completed OCT-guided vs IVUS-guided PCI trial, the just presented OCTIVUS trial will have a major effect on these estimates

Conclusions

The present network meta-analysis from 20 RCTs in 12,428 pts with follow-up ranging from 6-60 months demonstrates that:

- Compared with angiography-guided PCI, IVI-guided PCI with OCT or IVUS reduces **TLF by 31%,** driven by 46%, 20%, and 29% reductions in cardiac death, TV-MI, and ID/CD TLR respectively
- IVI-guided PCI also reduces **stent thrombosis by 52%,** all MI by 18%, and **all-cause death by 25%**
- Outcomes were similar for OCT-guided PCI and IVUS-guided PCI

Implications for Patient Care and Future Research

- **The routine use of OCT or IVUS to guide most PCI procedures will substantially improve patient event-free survival, enhancing both the long-term safety and effectiveness of the procedure**
- Additional investigation is required to determine:
  - Which lesion types most benefit from IVI guidance
  - The optimal technique and procedural objectives for OCT-guided and IVUS-guided stent implantation
  - Whether there are subtle differences in outcomes between OCT and IVUS guidance of PCI procedures

Edoxaban for 3 months versus 12 months in cancer patients with isolated distal deep vein thrombosis: ONCO DVT Study

Yugo Yamashita

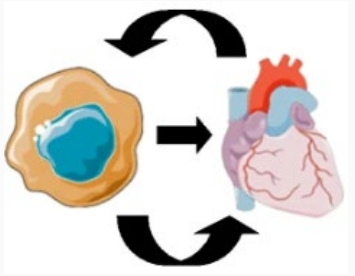
Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University

HOT LINE 9; 28 August 2023; 16:50-

Declaration of interest

- Research contracts : Funding was provided by Daiichi Sankyo Company, Limited, which had no role in the study design, data collection, analysis, interpretation, or writing of the report.
- Others : Dr. Yamashita received lecture fees from Bayer Healthcare, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo, and grant support from Bayer Healthcare and Daiichi Sankyo.

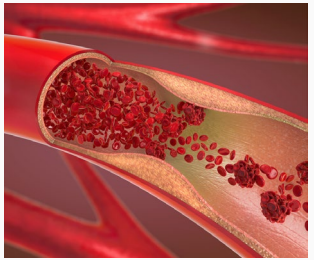
Background



- **Cancer** patients: Surviving longer

---> **Cardiovascular complications ↑↑**: **cardio-oncology**.

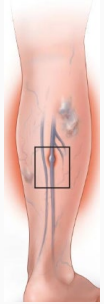
(Eur Heart J. 2022;43:4229-4361.)



- **Venous thromboembolism** (VTE): Risk of **recurrence**.

---> Can be **prevented** by **anticoagulation therapy**.

(Lancet. 2010;376:2032-9.)



- Isolated **distal** deep vein thrombosis (**DVT**): Common

---> More benign or not than a **proximal** DVT?

(Thromb Res. 2014;134:36-40. J Vasc Surg. 2012;55:550-61.)

Background

- **Guidelines recommendations** for isolated distal DVT (ACCP/CHEST)

---> **Anticoagulation of prolonged** duration for **cancer** patients

(**Weak** recommendation, **Low-certainty** evidence)

(Chest. 2021;160:e545-e608.)

- **Previous RCTs** for distal DVT (CACTUS [2016], RIDTS [2022])

---> **Excluded** patients with **active cancer**

(Lancet Haematol. 2016;3:e556-e562. BMJ. 2022;379:e072623.)

- **No RCT** for optimal duration of anticoagulation therapy for **cancer patients**

Purpose of the ONCO DVT study

To compare 12-month edoxaban treatment with 3-month edoxaban treatment in cancer patients with isolated distal DVT in a randomized clinical trial.

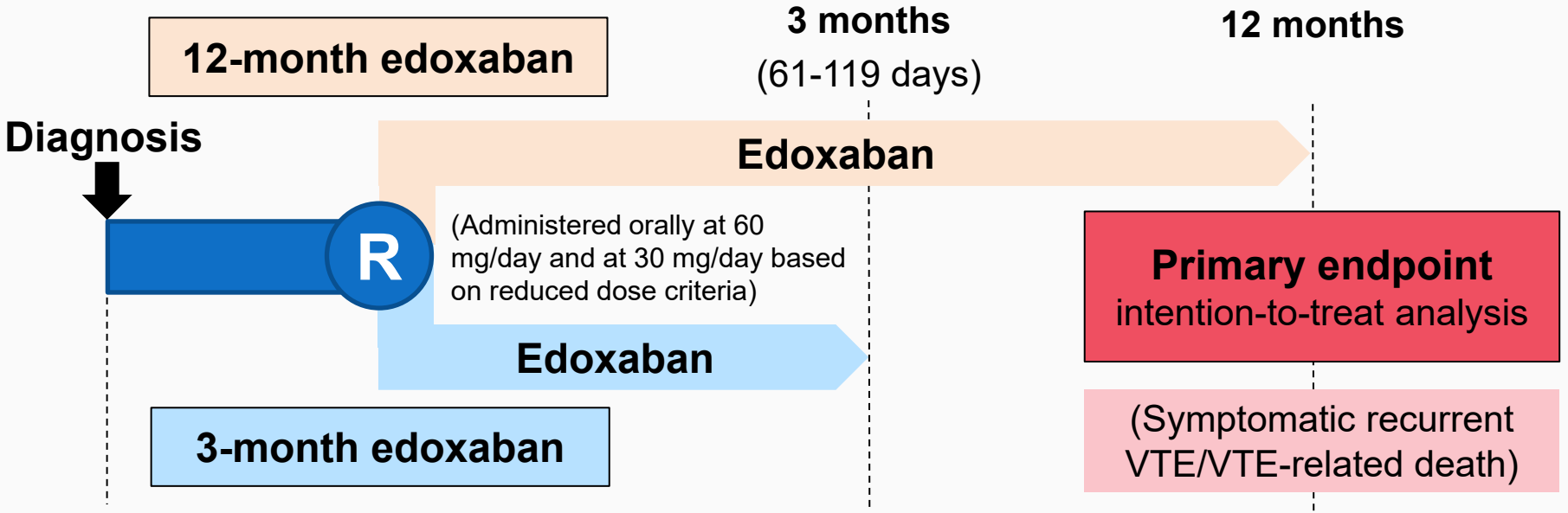
ONCO DVT Study: NCT03895502

(Optimal duration of anticoagulation therapy for isolated distal deep vein thrombosis in patients with cancer study)

Study design: ONCO DVT study

(A multicenter, open-label, adjudicator-blinded, randomized clinical trial)

Patients with active cancer who were newly diagnosed with isolated distal DVT confirmed by ultrasonography were eligible for inclusion.



Inclusion and Exclusion Criteria

Key Inclusion Criteria

- ✓ A new diagnosis of DVT objectively confirmed by ultrasonography
- ✓ With active cancer at randomization
- ✓ Scheduled for DVT treatment with anticoagulation therapy

Key Exclusion Criteria

- ✓ Already on anticoagulation therapy at the time of the diagnosis
- ✓ With pulmonary embolism
- ✓ Expected to have a life prognosis of 3 months or less

Endpoints

- **Primary endpoint (ITT analysis)**
  - ✓ Symptomatic recurrent VTE or VTE-related death at 12 months
- **Major secondary endpoint (ITT analysis)**
  - ✓ A major bleeding event (ISTH criteria definition) at 12 months

Sample Size Calculation

- **Hypothesis: Superiority of 12-month to 3-month edoxaban for the primary endpoint at 12 months**
- Assumption: Event rate at 12-month: 6% (12-month group)
  13% (3-month group)
- Randomization ratio: 1:1
- Power: 80%
- Two-sided alpha: 0.05
- Sample size: 550 patients (275 in each arm)
- Considering the potential dropouts: **600** patients

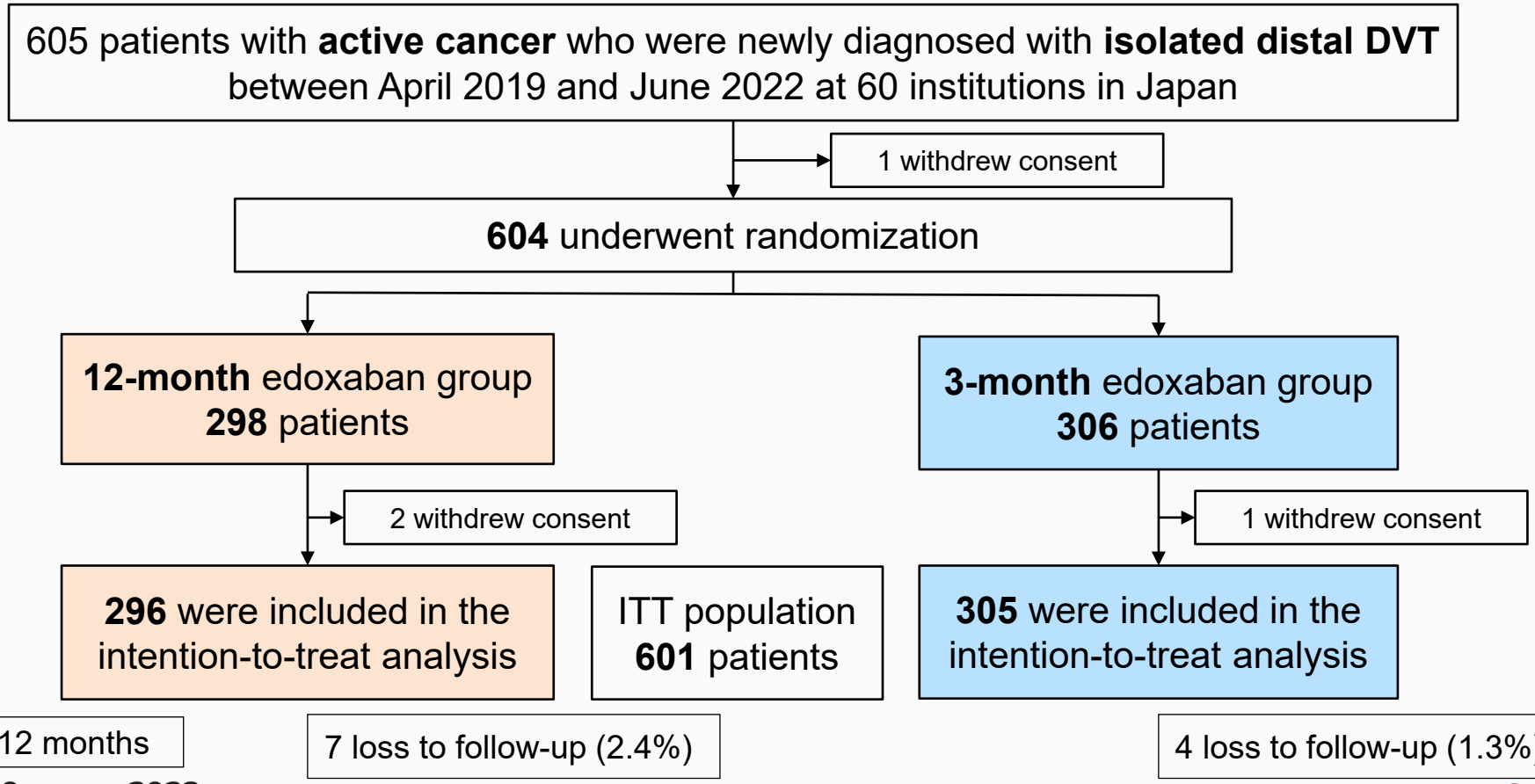
60 participating centers

Kyoto University Hospital
Osaka International Cancer Institute
Saiseikai Noe Hospital
Osaka Red Cross Hospital
Japanese Red Cross Otsu Hospital
Kakogawa Central City Clinics
Cancer Institute Hospital
Kansai Medical University Medical Center
Kyoto Prefectural University of Medicine
Kyorin University Faculty of Medicine
Kindai University Hospital
Kumamoto University Hospital
Kurashiki Central Hospital
Kurume University Hospital
Kuwana City Medical Center
Gunma University
Kobe City Medical Center General Hospital
Kobe University Hospital
Kohka Public Hospital
Fukushima Medical University Hospital
Kokura Memorial Hospital
National Cancer Center Hospital
NHO Okayama Medical Center
NHO Kyoto Medical Center
Saiseikai Yokohamashi Nanbu Hospital
Saiseikai Wakayama Hospital
Saku Central Hospital Advanced Care Center
Shiga General Hospital
Shizuoka Cancer Center
Shizuoka City Shizuoka Hospital
Shimane University Hospital
Shimada General Medical Center
St. Marianna University School of Medicine
Medical Research Institute Kitano Hospital
University of Tsukuba Hospital
Tenri Hospital
Tokyo Women's Medical University Hospital
Tokyo Metropolitan Tama Medical Center
Toho University Ohashi Medical Center
Toho University Omori Medical Center
Tohoku University Hospital
Nagasaki University Hospital
Nara Medical University Hospital
Nippon Medical School Hospital
Japanese Red Cross Wakayama Medical Center
Hyogo Prefectural Amagasaki General Medical Center
Hirakata Kohsai Hospital
Fukui Prefectural Hospital
Saiseikai Yahata General Hospital
Fujisawa City Hospital
Makiminato Central Hospital
Mie University Hospital
Mitsubishi Kyoto Hospital
Japanese Red Cross Musashino Hospital
Yokohama Minami Kyousai Hospital
Yokohama Rosai Hospital
Rakuwakai Otowa Hospital
Niigata University Graduate School of Medicine and Dentistry
Niigata Cancer Center Niigata Hospital
Hyogo College of Medicine

with collaboration of
cardiologists and **oncologists**

ONCO DVT Study

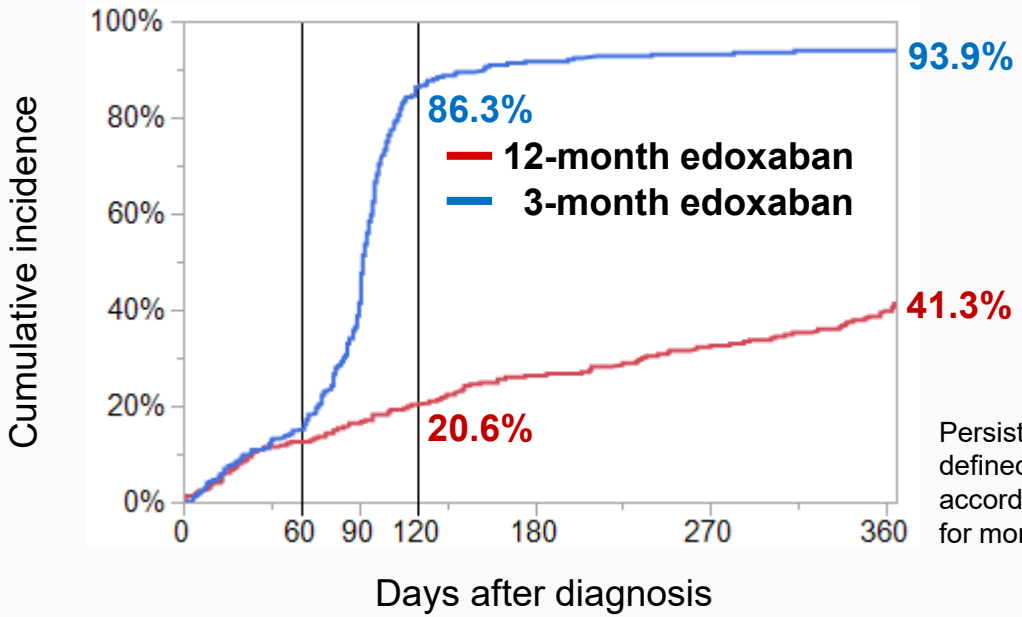
Study Flow


605 patients with **active cancer** who were newly diagnosed with **isolated distal DVT** between April 2019 and June 2022 at 60 institutions in Japan
1 withdrew consent
604 underwent randomization
12-month edoxaban group **298** patients
3-month edoxaban group **306** patients
2 withdrew consent
1 withdrew consent
296 were included in the intention-to-treat analysis
ITT population **601** patients
305 were included in the intention-to-treat analysis
At 12 months
7 loss to follow-up (2.4%)
4 loss to follow-up (1.3%)

Clinical characteristics at baseline

Variables, No. (%)	12-month edoxaban (N=296)	3-month edoxaban (N=305)
Age, years (Mean± SD)	71.6±9.4	70.1±10.3
Male sex	94 (32)	73 (24)
Body weight, kg	56.3±12.1	54.8±11.6
Symptoms at baseline	53 (18)	69 (23)
Lower dose of edoxaban (30 mg/day)	216 (73)	234 (77)
Cancer status		
Metastatic disease	67 (23)	80 (26)
ECOG performance status		
0	161 (54)	150 (49)
1	78 (26)	103 (34)
≥2	57 (19)	52 (17)
History of venous thromboembolism	20 (6.8)	13 (4.3)
Creatinine clearance ≤50 mL/min	69 (23)	62 (20)
Anemia (Hb <13 g/dL for men and <12 g/dL for women)	199 (67)	203 (67)
Platelet count <100,000 per μL	12 (4.1)	19 (6.2)

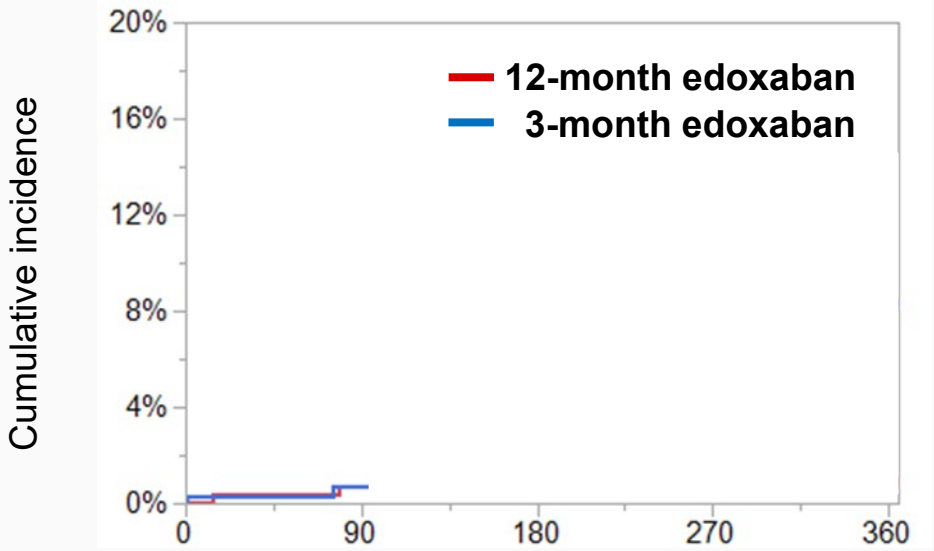
Persistent edoxaban discontinuation



Persistent edoxaban discontinuation was defined as a discontinuation of edoxaban according to the study protocol or lasting for more than 14 days for any reason.

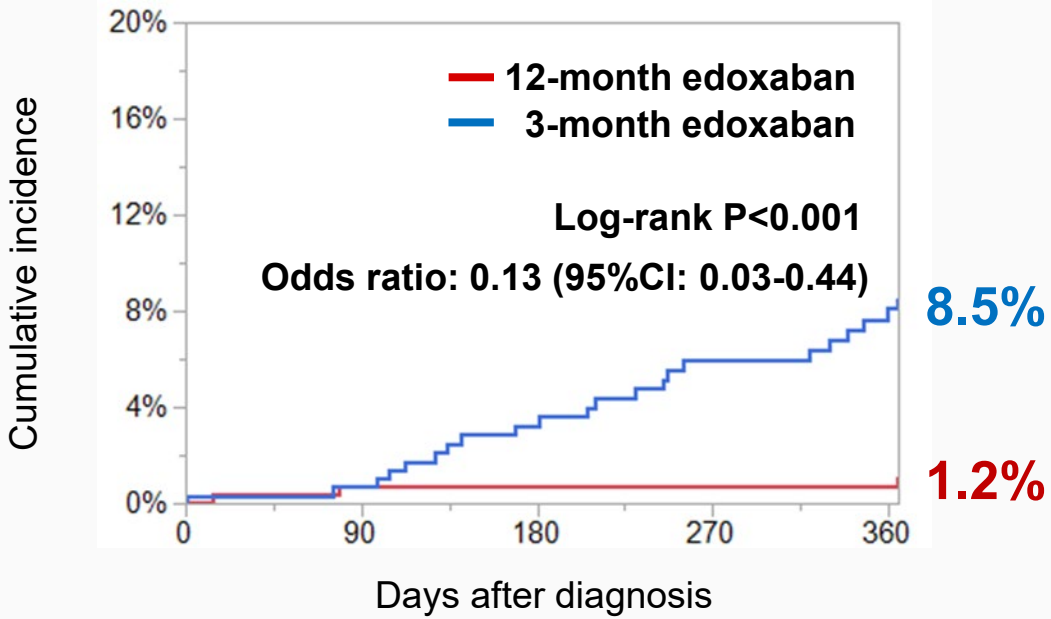
N of patients on edoxaban	0-day	60-day	90-day	120-day	180-day	365-day
12-month edoxaban	296	253	240	224	202	151
3-month edoxaban	305	255	173	40	23	15

Primary endpoint (Symptomatic recurrent VTE or VTE-related death)



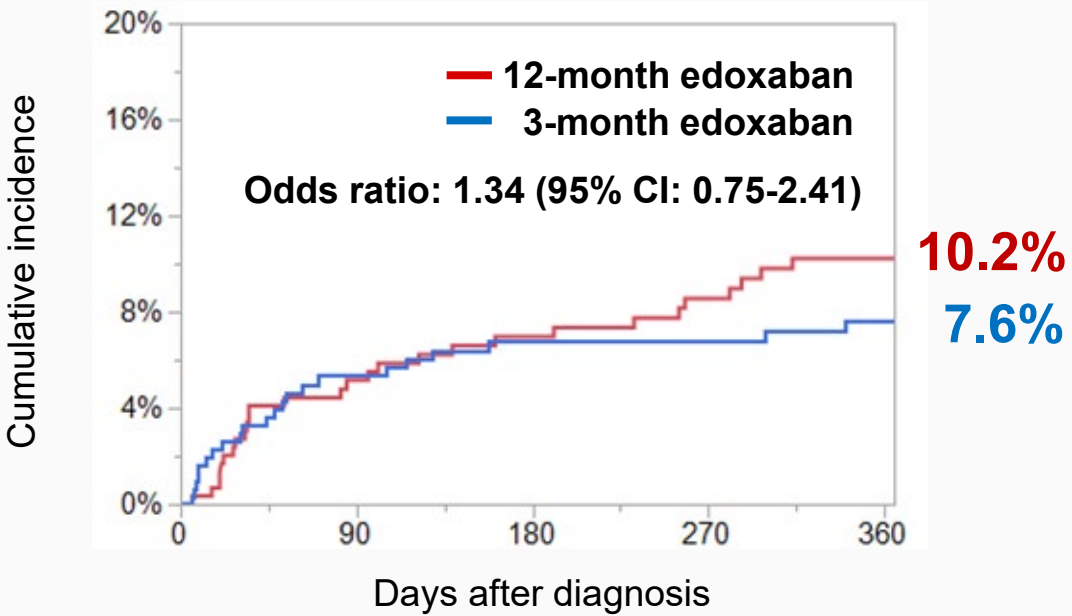
N of patients at risk	0-day	60-day	90-day
12-month edoxaban	296	283	274
3-month edoxaban	305	289	280

Primary endpoint (Symptomatic recurrent VTE or VTE-related death)



N of patients at risk	0-day	60-day	90-day	120-day	180-day	365-day
12-month edoxaban	296	283	274	269	253	222
3-month edoxaban	305	289	280	275	256	210

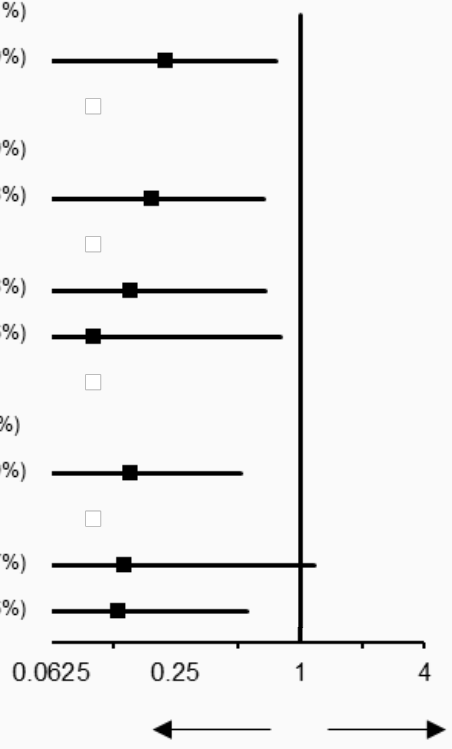
Major secondary endpoint (Major bleeding)

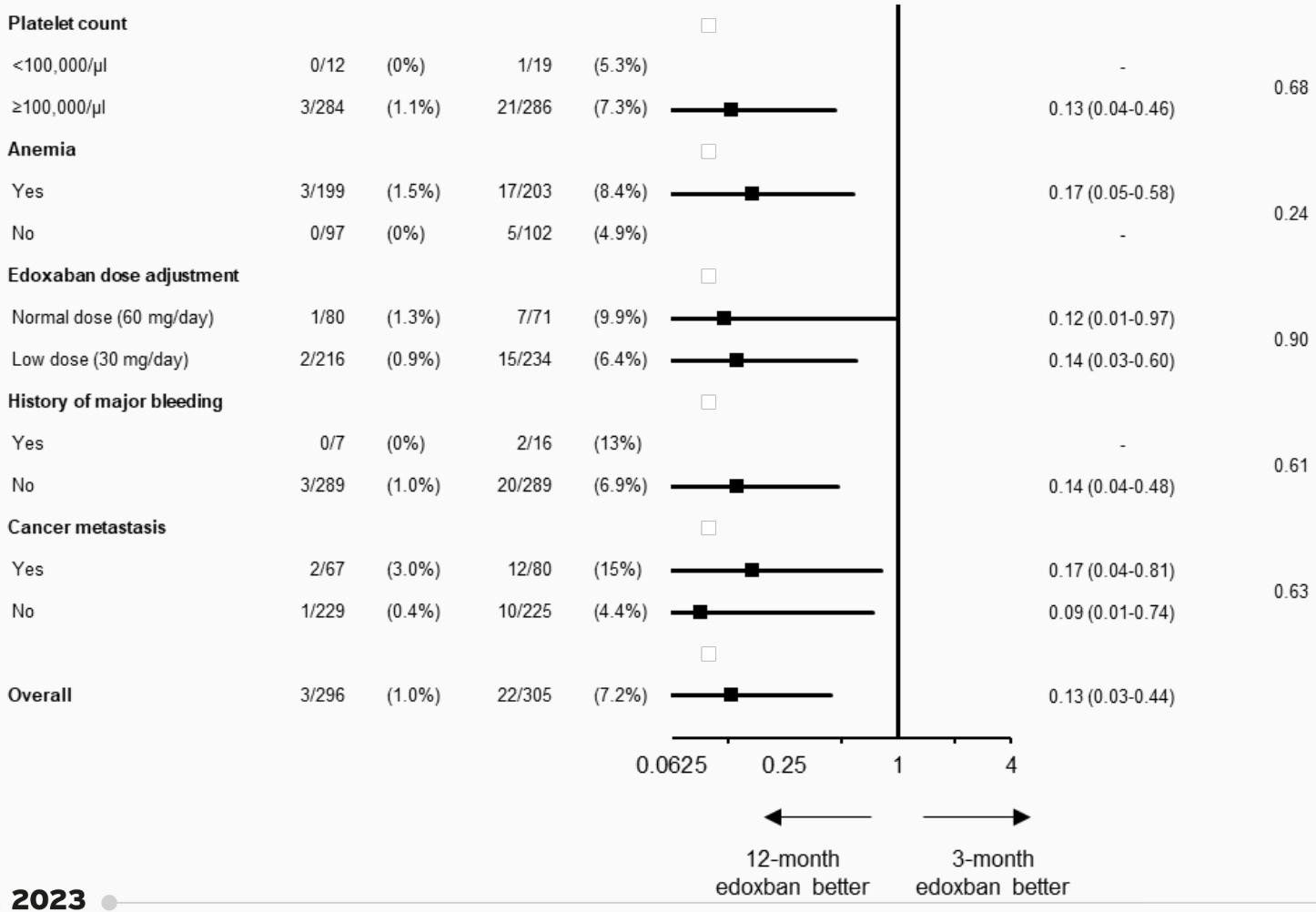


N of patients at risk	0-day	60-day	90-day	120-day	180-day	365-day
12-month edoxaban	296	273	267	261	245	210
3-month edoxaban	305	279	271	264	250	217

Subgroup analyses for the primary endpoint

	12-month edoxaban (N=296)		3-month edoxaban (N=305)		OR (95%CI)	P interaction
Age						
≥75 years	0/131	(0%)	7/114	(6.1%)	-	0.11
<75 years	3/165	(1.8%)	15/191	(7.9%)	0.22 (0.06-0.76)	
Sex						
Male	0/94	(0%)	5/73	(6.9%)	-	0.16
Female	3/202	(1.5%)	17/232	(7.3%)	0.19 (0.06-0.66)	
Weight						
<60 kg	2/199	(1.0%)	14/222	(6.3%)	0.15 (0.03-0.67)	0.74
≥60 kg	1/97	(1.0%)	8/83	(9.6%)	0.10 (0.01-0.80)	
History of VTE						
Yes	0/20	(0%)	2/13	(15%)	-	0.35
No	3/276	(1.1%)	20/292	(6.9%)	0.15 (0.04-0.51)	
Creatinine clearance						
≤50 mL/min	1/69	(1.5%)	6/62	(9.7%)	0.14 (0.02-1.17)	0.95
>50 mL/min	2/227	(0.9%)	16/243	(6.6%)	0.13 (0.03-0.55)	




Platelet count
<100,000/μl 0/12 (0%) 1/19 (5.3%) - 0.68
≥100,000/μl 3/284 (1.1%) 21/286 (7.3%) 0.13 (0.04-0.46)
Anemia
Yes 3/199 (1.5%) 17/203 (8.4%) 0.17 (0.05-0.58) 0.24
No 0/97 (0%) 5/102 (4.9%) -
Edoxaban dose adjustment
Normal dose (60 mg/day) 1/80 (1.3%) 7/71 (9.9%) 0.12 (0.01-0.97) 0.90
Low dose (30 mg/day) 2/216 (0.9%) 15/234 (6.4%) 0.14 (0.03-0.60)
History of major bleeding
Yes 0/7 (0%) 2/16 (13%) - 0.61
No 3/289 (1.0%) 20/289 (6.9%) 0.14 (0.04-0.48)
Cancer metastasis
Yes 2/67 (3.0%) 12/80 (15%) 0.17 (0.04-0.81) 0.63
No 1/229 (0.4%) 10/225 (4.4%) 0.09 (0.01-0.74)
Overall 3/296 (1.0%) 22/305 (7.2%) 0.13 (0.03-0.44)
0.0625
0.25
1
4
12-month edoxban better
3-month edoxban better

Study limitations

- Open-label design (although blinded endpoint adjudication)
- Lower event rates of the primary endpoints than expected
- Not-high adherence to the study protocol as to edoxaban treatment
- Differences of races and a variety of cancer types (generalizability)

Conclusions

In cancer patients with isolated distal DVT, edoxaban treatment for 12 months was superior to 3 months with respect to the composite outcome of a symptomatic recurrent VTE or VTE-related death.

ONCO DVT Study

Circulation

ORIGINAL RESEARCH ARTICLE

Edoxaban for 12 Months versus 3 Months in Cancer Patients with Isolated Distal Deep Vein Thrombosis (ONCO DVT study): An Open-label, Multicenter, Randomized Clinical Trial

Yugo Yamashita, Takeshi Morimoto, Nao Muraoka, Takuya Oyakawa, Michihisa Umetsu, Daijirou Akamatsu, Yuji Nishimoto, Yukihito Sato, Takuma Takada, Kentaro Jujo, Yuichiro Minami, Yoshito Ogihara, Kaoru Dohi, Masashi Fujita, Tatsuya Nishikawa, Nobutaka Ikeda, Go Hashimoto, Kazunori Otsui, Kenta Mori, Daisuke Sueta, Yukari Tsubata, Masaaki Shoji, Ayumi Shikama, Yutaka Hosoi, Yasuhiro Tanabe, Ryuki Chatani, Kengo Tsukahara, Naohiko Nakanishi, Kitae Kim, Satoshi Ikeda, Makoto Mo, Yusuke Yoshikawa, Takeshi Kimura;
On behalf of the ONCO DVT Study Investigators.

Circulation. 2023; DOI: 10.1161/CIRCULATIONAHA.123.066360
https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.123.066360

The QUALIREHAB trial

Early hybrid cardiac rehabilitation in adolescents and young adults with congenital heart disease: a multicentre randomised controlled trial

Pascal AMEDRO

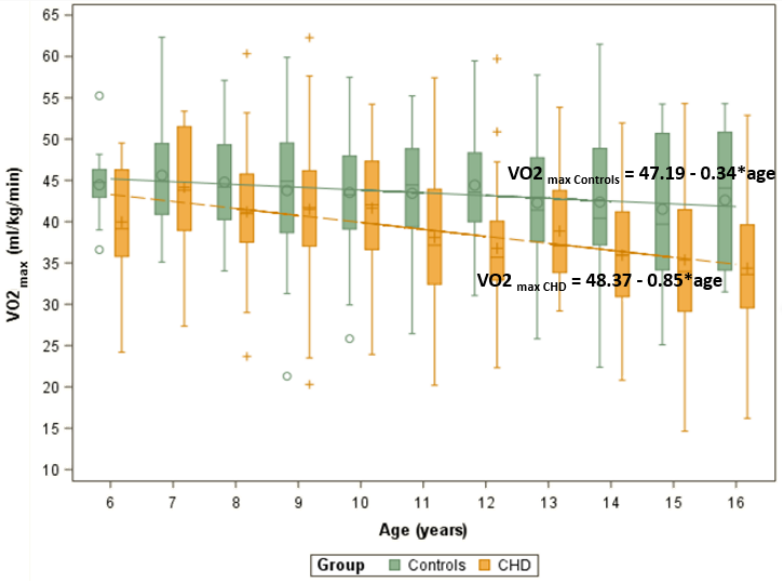
August 25th 2023

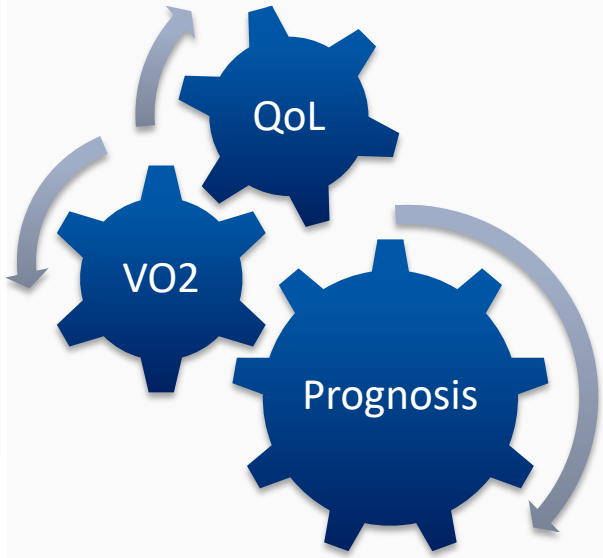
Early onset of physical deconditioning in youth with CHD

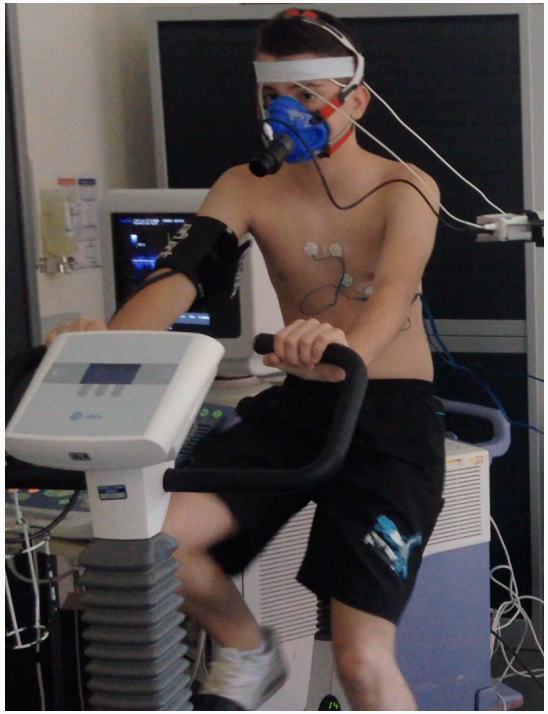
VO_{2max} decrease = -2 % per year vs. -0.4% per year (*P<0.01*)

Low ventilatory anaerobic threshold (VAT): 18% vs 6% (*P<0.01*)

VO_{2max} & VAT correlate with HRQoL in children with CHD

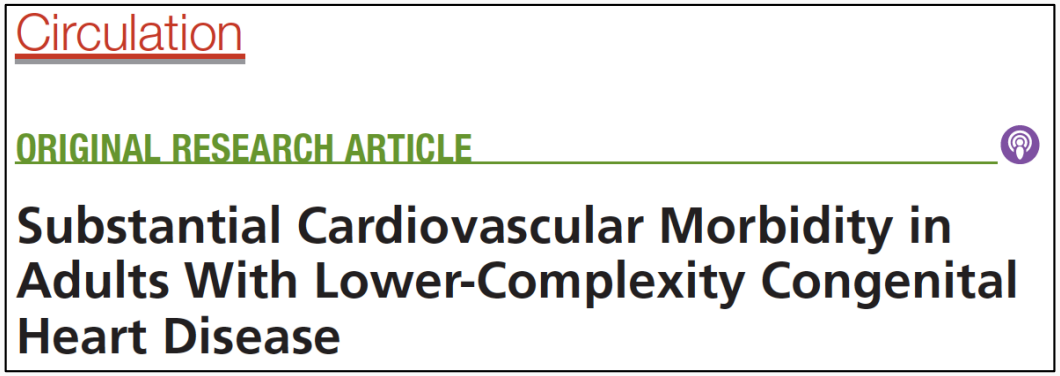






Amedro et al. *Heart* 2018
Amedro et al. *Int J Cardiol* 2019
Gavotto et al. *Int J Cardiol* 2023

Consequences in adult CHD cardiovascular morbidity



Serious alert!

- Adults with CHD: 51% smokers, 30% obese, 69% hypertension, 41% hyperlipidemia, and 7% diabetes mellitus
- High risk for heart failure (HR=13.0)
- High risk for acute coronary syndrome (HR=2.0)

Saha et al. *Circ* 2019

Solution: cardiovascular rehabilitation in youth with CHD as a preventive action

Main goals adapted from adult heart failure cardiovascular rehabilitation:

1. Physical activity training
2. Treatment optimization
3. Patient education

- Class I, level of evidence A in adult heart failure
- ↗ level of evidence in congenital cardiology
- Safe in patients with CHD

Ponikowski et al *EHJ* 2016
Yance et al. *Circ* 2017
Amedro et al. *Press Med* 2017

Early hybrid cardiac rehabilitation : the QUALIREHAB multicentre randomised controlled trial

- PI: Dr. Sophie GUILLAUMONT
- Sponsor: Montpellier University Hospital, France
- Grants: French Ministry of Health, French Society of Cardiology, French Federation of Cardiology
- 12 CHD centres, 9 cardiac rehabilitation centres in France

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Impact of a centre and home-based cardiac rehabilitation program on the quality of life of teenagers and young adults with congenital heart disease: The QUALI-REHAB study rationale, design and methods☆

Pascal Amedro [a,b,*], Arthur Gavotto [a,c], Antoine Legendre [d], Kathleen Lavastre [a], Charlene Bredy [a,s], Gregoire De La Villeon [a,c], Stefan Matecki [a,b], D'Arcy Vandenberghe [a], Manon Ladeveze [a], Fanny Bajolle [d], Gilles Bosser [e], Helene Bouvaist [f], Philippe Brosset [g], Laurence Cohen [h], Sarah Cohen [i], Sonia Corone [j], Claire Dauphin [k], Yves Dulac [l], Sebastien Hascoet [i], Xavier Iriart [m], Magalie Ladouceur [n], Loic Mace [o], Oxana-Anca Neagu [p], Caroline Ovaert [o,u], Marie-Christine Picot [q], Laurent Poirette [r], Frederique Sidney [s], Camille Soullier [t], Jean-Benoit Thambo [m], Nicolas Combes [v], Damien Bonnet [d], Sophie Guillaumont [a,c]

Primary outcome: change from baseline to 12-month follow-up in HRQoL using the PedsQL™ total score in an intention-to-treat analysis.

Secondary outcomes: change in cardiovascular parameters, cardiopulmonary fitness, and mental health

Amedro et al. *Int J Cardiol*. 2019

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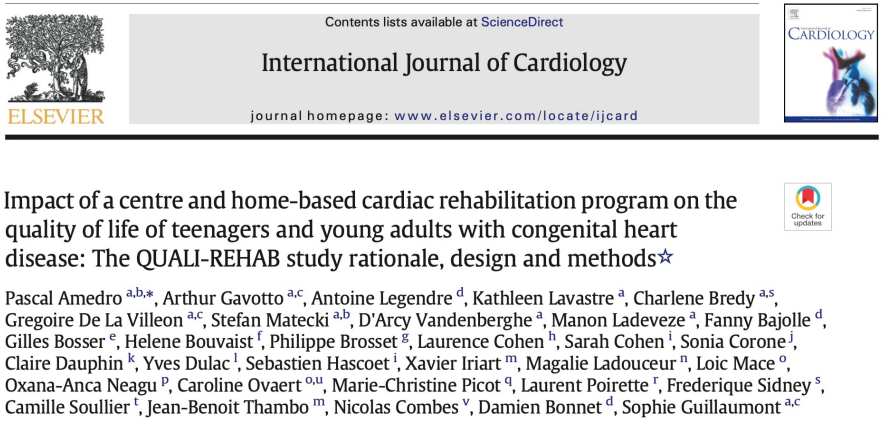
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- Principal Investigator: **Dr. Sophie GUILLAUMONT**
- Sponsor: **Montpellier University Hospital**, France
- Grants: **French Ministry of Health**, French Society of Cardiology, French Federation of Cardiology
- **French national CHD network**: 12 CHD centres, 9 cardiac rehabilitation centres

Amedro et al. *Int J Cardiol*. 2019

The QUALIREHAB trial

Main inclusion criteria

- 13-25 year old CHD patients
- VO_{2max} <80% and/or VAT <55%

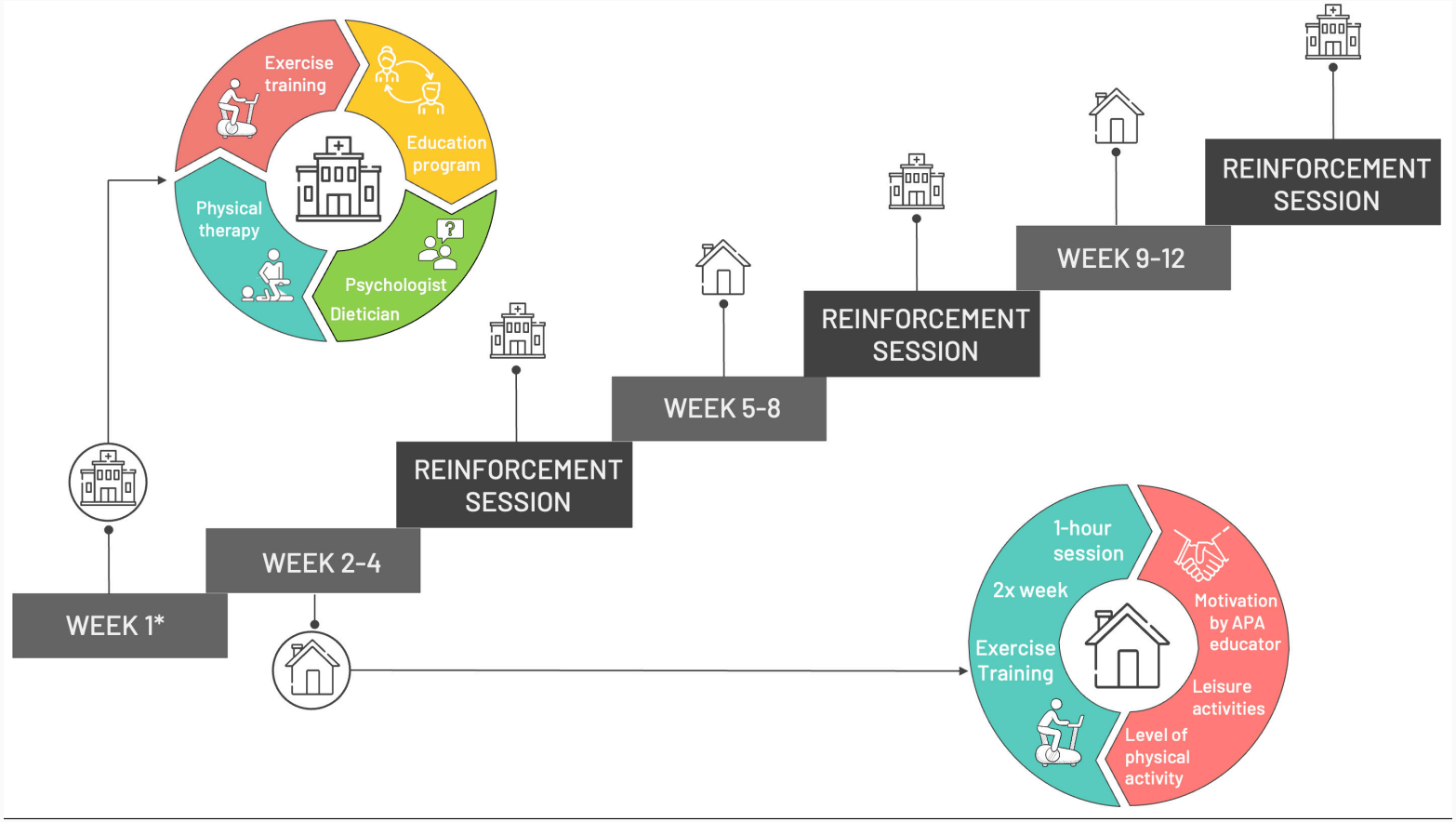
12-month follow-up

Rehabilitation center

12-week rehabilitation program

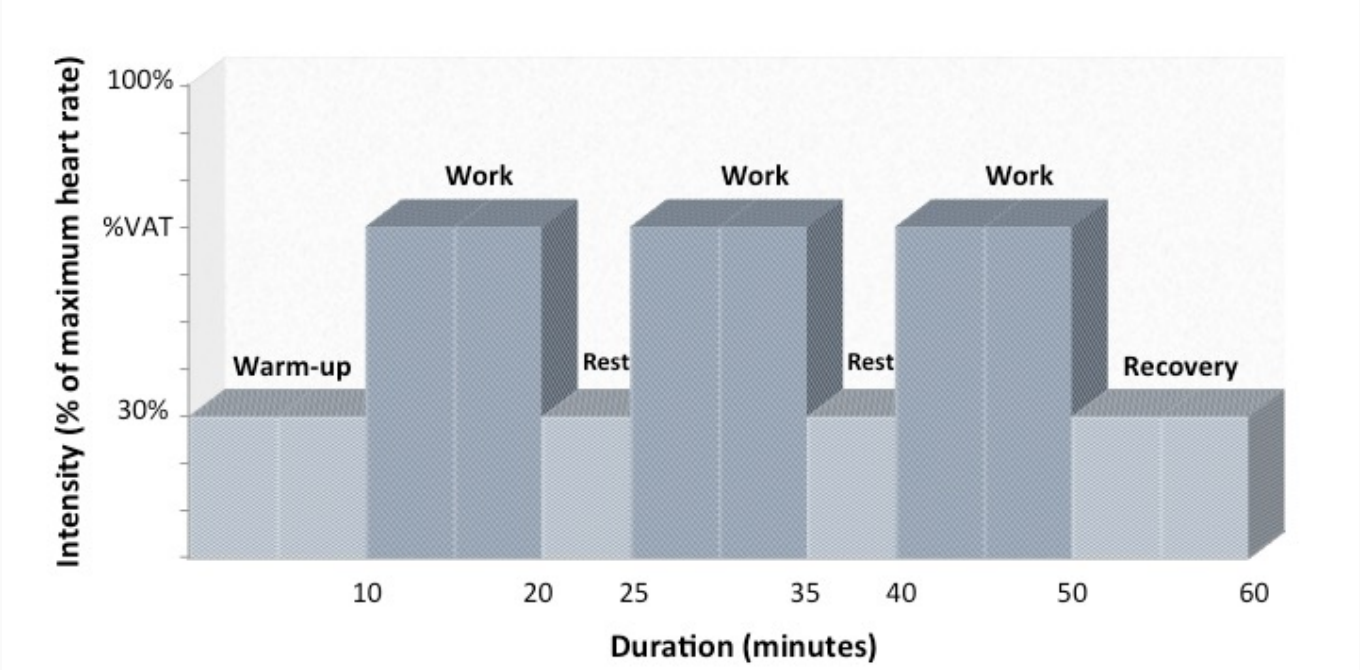
Home

The QUALIREHAB home-based & centre-based program



Interval training exercise at VAT level

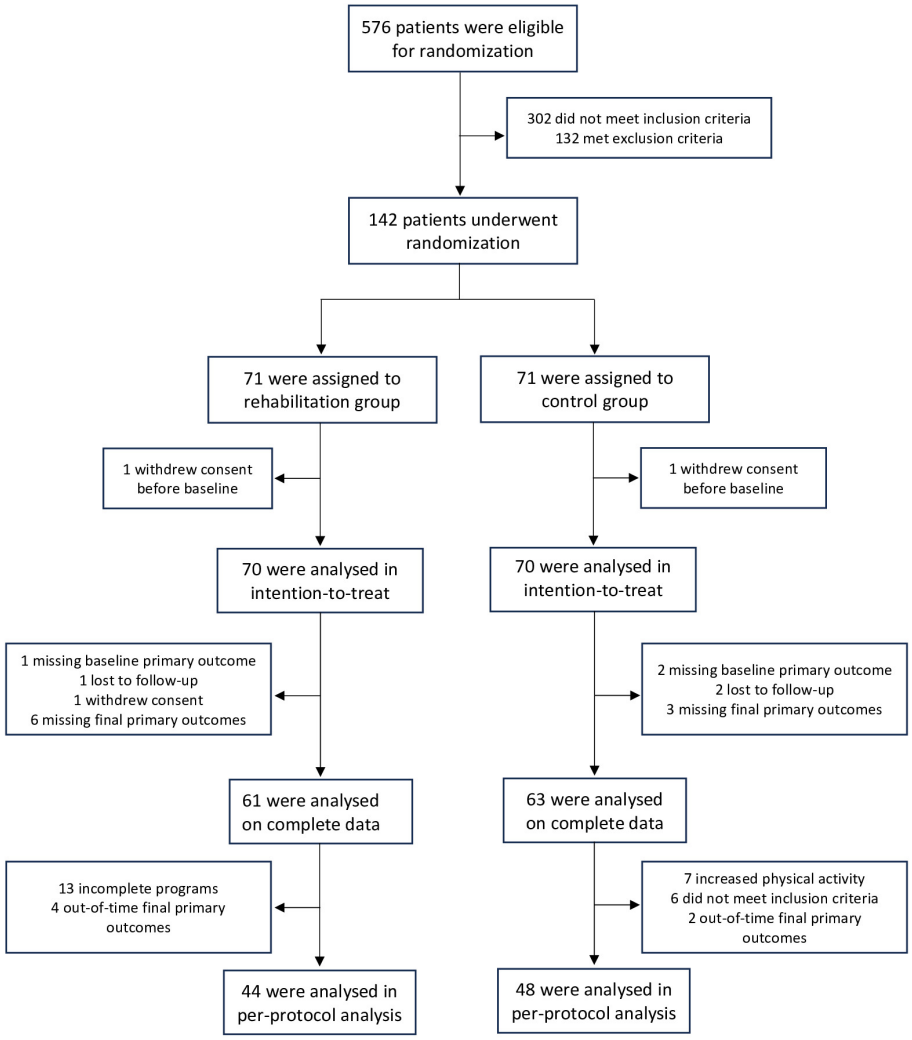
Moderate intensity (60% to 80 % VO_{2max})



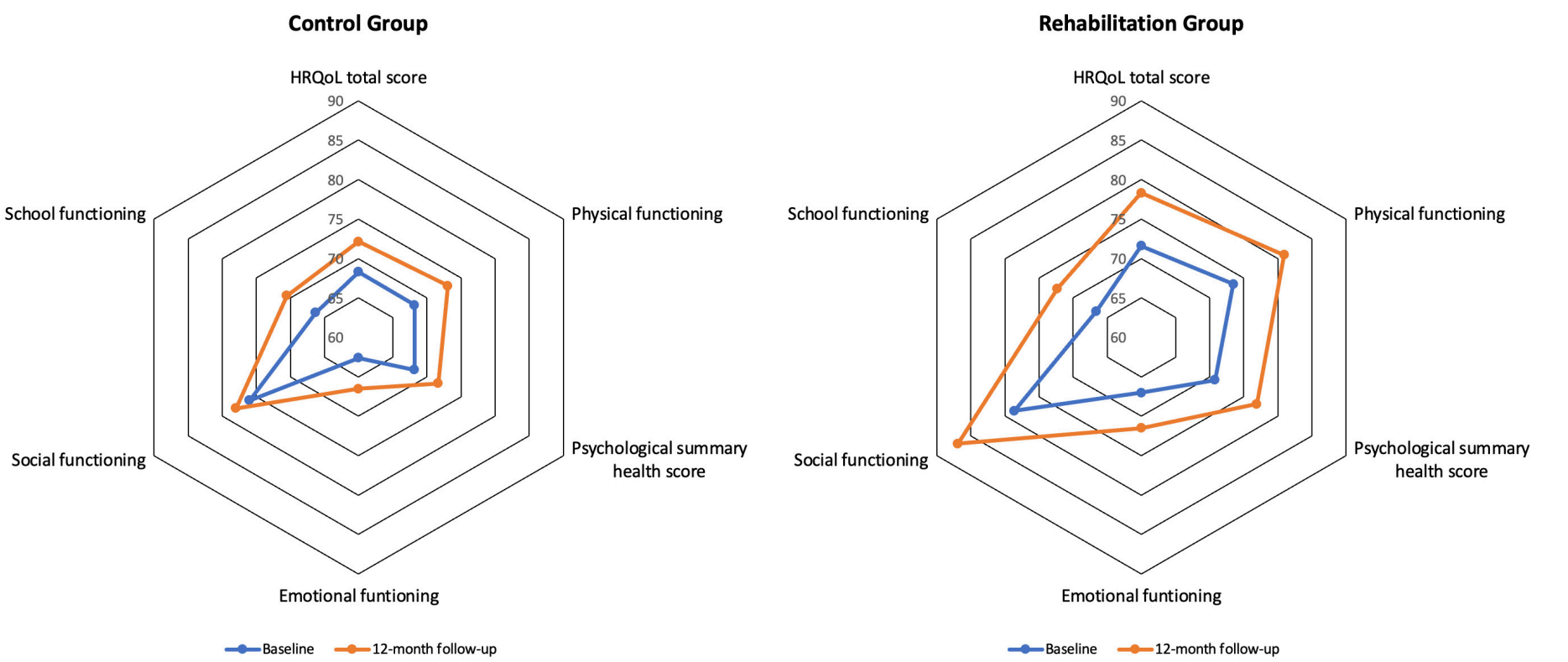
Amedro et al. *Perf Ped* 2021

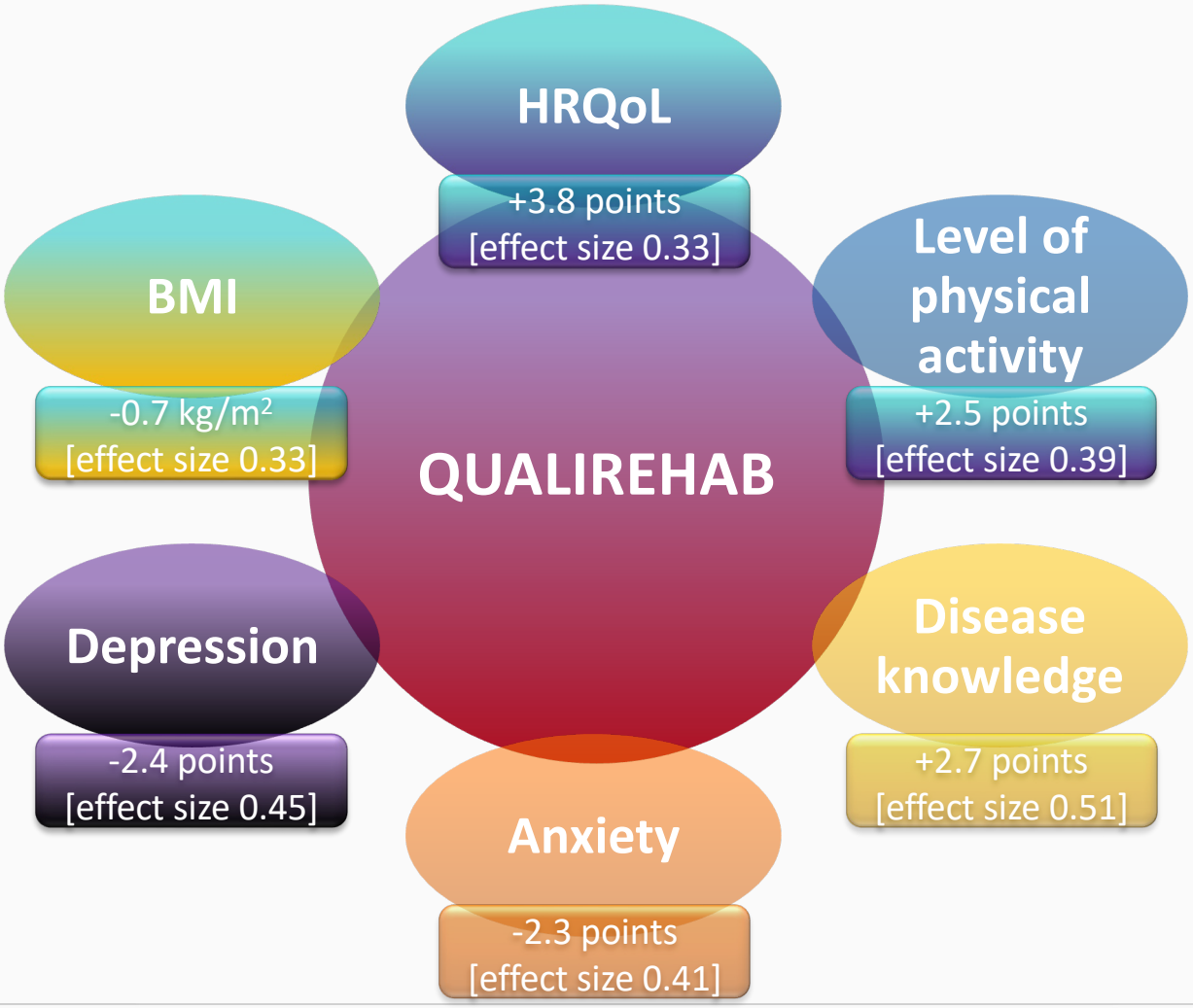
Population characteristics

- N = 142 participants
- Mean age 17.4 ± 3.4 years
- 52% female
- All types of CHD
- ≥ 1 cardiac surgery = 83%
- ≥ 1 intervention catheter = 44%
- Similar baseline group characteristics

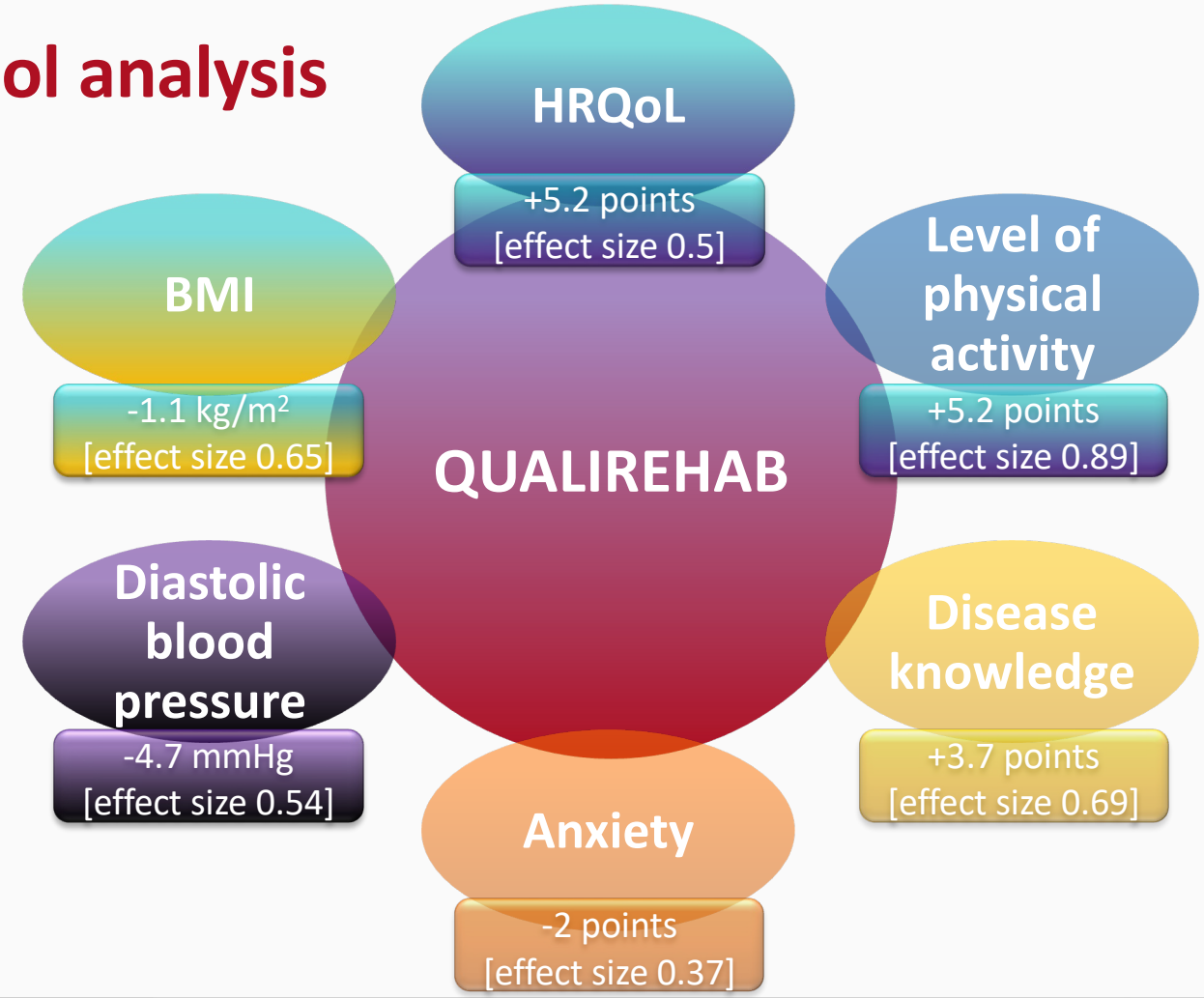


Positive change in the primary outcome: HRQoL total PedsQL™ score at 12 months



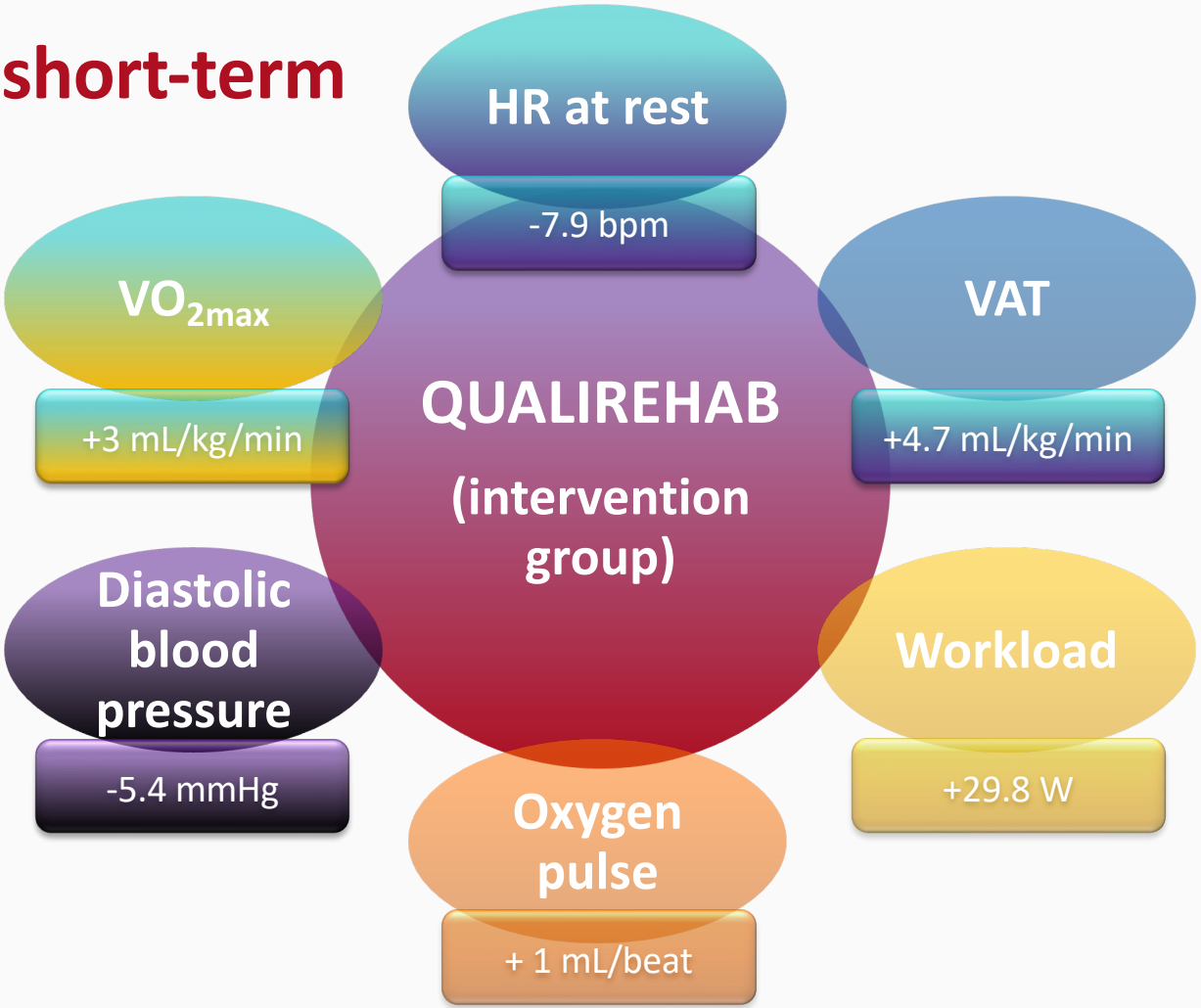

HRQoL
+3.8 points
[effect size 0.33]
BMI
-0.7 kg/m²
[effect size 0.33]
Level of physical activity
+2.5 points
[effect size 0.39]
QUALIREHAB
Depression
-2.4 points
[effect size 0.45]
Disease knowledge
+2.7 points
[effect size 0.51]
Anxiety
-2.3 points
[effect size 0.41]

Per protocol analysis

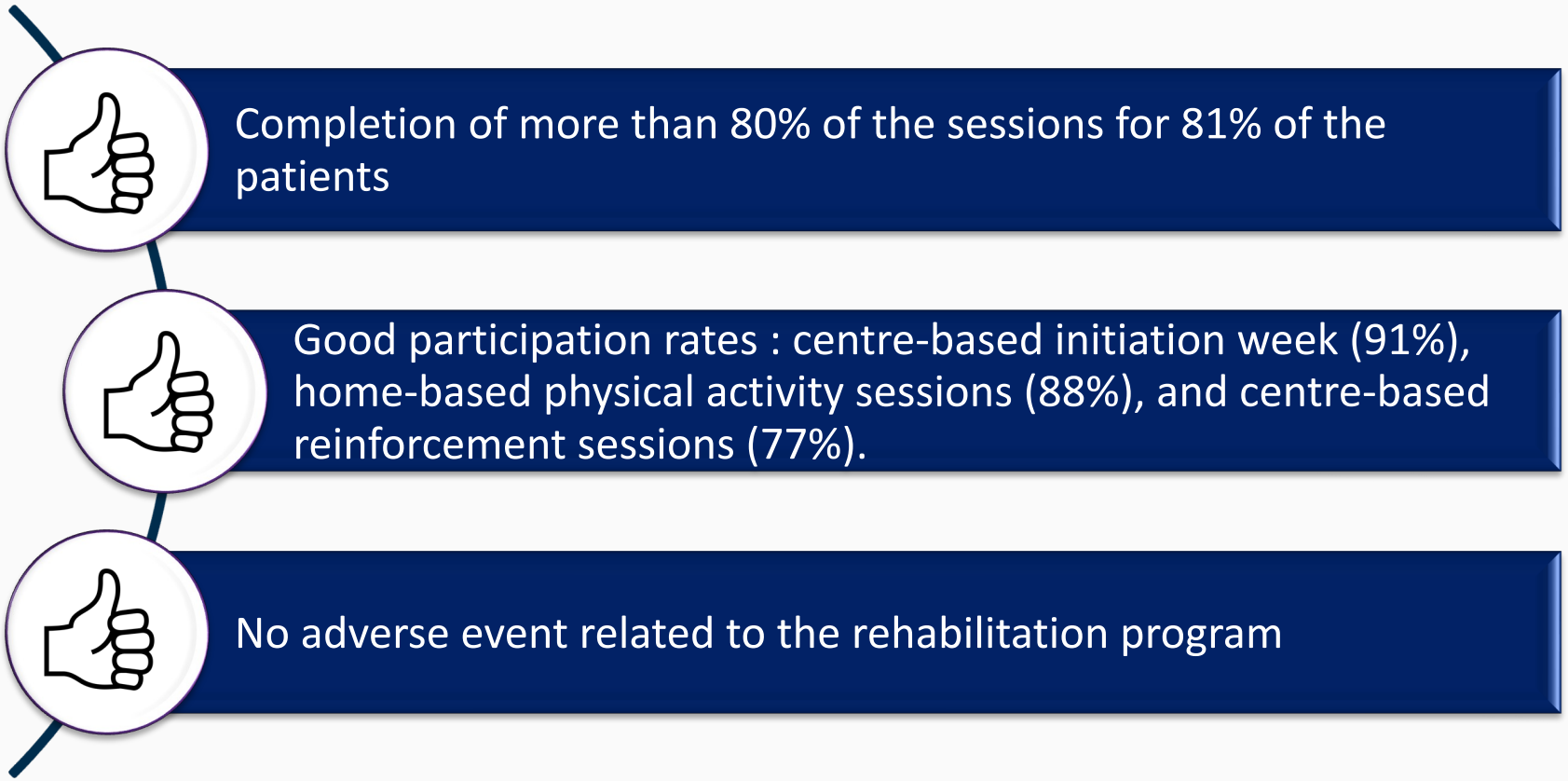


Significant short-term effects

12-week end of program assessment

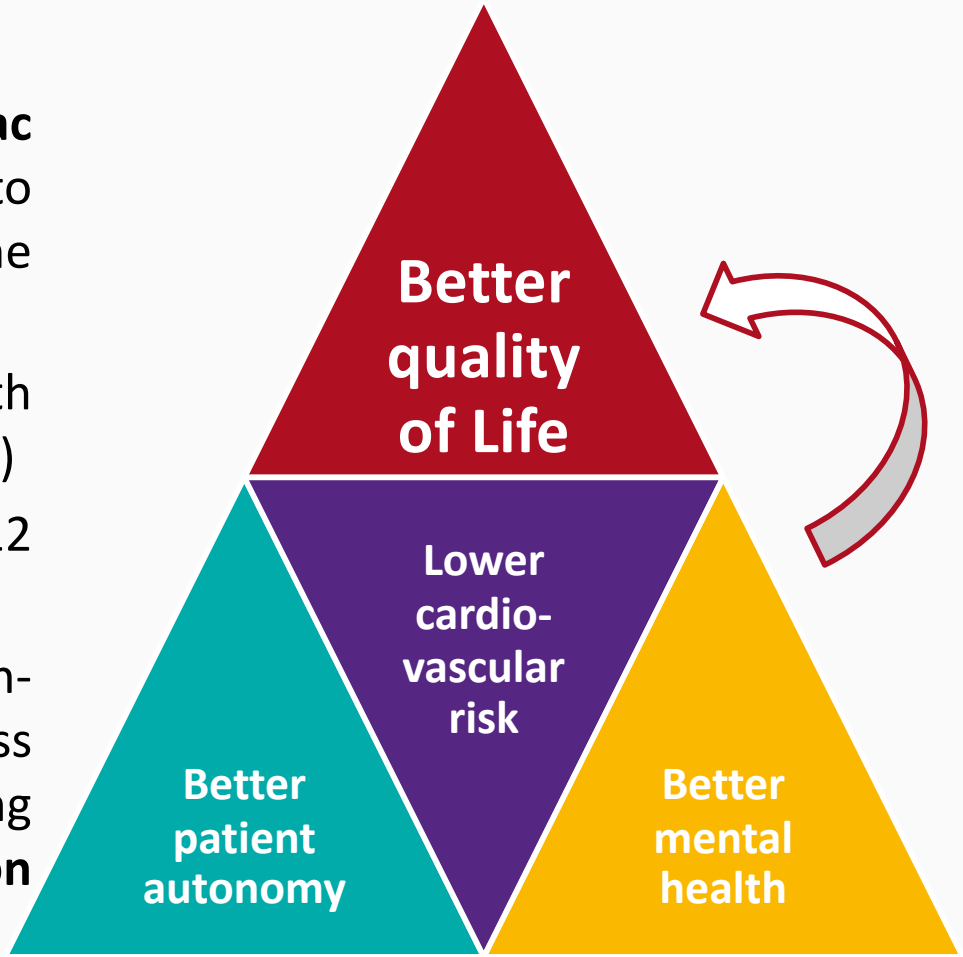


Acceptability and safety of the intervention

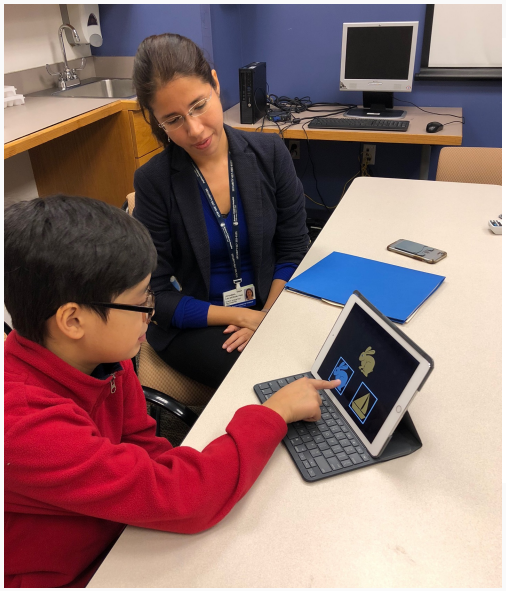


Conclusions

- The QUALIREHAB **early hybrid cardiac rehabilitation program** opens the field to implement **prevention programs** in the usual care of young patients with CHD
- Applicable to other paediatric diseases with adult cardiovascular risk (childhood cancer)
- Main limit: VO_{2max} increased at week 12 but not at 12-month follow-up
- Future programs could combine high-intensity exercise, exercise progress monitoring, various patterns of training (i.e., exergame), and **post-rehabilitation support**.



The QUALINEUROREHAB RCT: a home-based neuro-cardiac rehabilitation program



QUALI
NEURO REHAB

"Mens sana in corpore sano"

EUROPEAN JOINT PROGRAMME
RARE DISEASES

University Hospitals Birmingham NHS
NHS Foundation Trust

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RATE-AF trial wearables study

Dipak Kotecha FESC, Professor of Cardiology

on behalf of Simrat Gill, the BigData@Heart Consortium, the cardAIc group and the RATE-AF trial team

FUNDED BY NIHR | National Institute for Health and Care Research

efpia | imi innovative medicines initiative

Disclosures

Collaborative research: Bayer, AstraZeneca, Merck, Menarini, Daiichi Sankyo, GlaxoSmithKline, Novartis, Servier, Amomed, Protherics Medicines

Research grants and advisory board fees: Bayer, Amomed and Protherics Medicines

Funders:

FUNDED BY NIHR | National Institute for Health and Care Research

Department of Health & Social Care

ESC European Society of Cardiology

EHRA European Heart Rhythm Association

British Heart Foundation FIGHT FOR EVERY HEARTBEAT bhf.org.uk

Funded by the European Union

UKRI

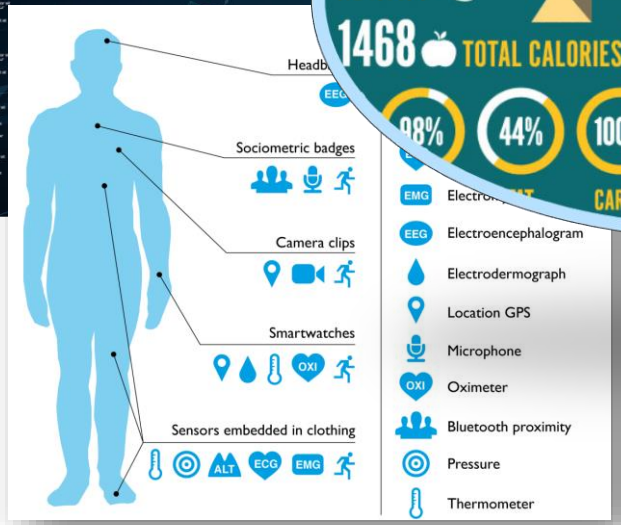
efpia

imi innovative medicines initiative

THE COOK AND WOLSTENHOLME CHARITABLE TRUST

Department for Business, Energy & Industrial Strategy

The potential for wearable devices



Piwek; PLoS Med. 2016;13:e1001953

The RATE-AF trial

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(1) Is digoxin inferior to beta-blockers for AF rate control?
(2) Can wearables account for individual physical activity?
(3) Can wearable data predict clinical progress?

RATE AF

Embedded within a clinical trial

Permanent atrial fibrillation in need of heart rate control with symptoms of heart failure

RANDOMISED

Low-dose digoxin (62.5-250 mcg/daily)

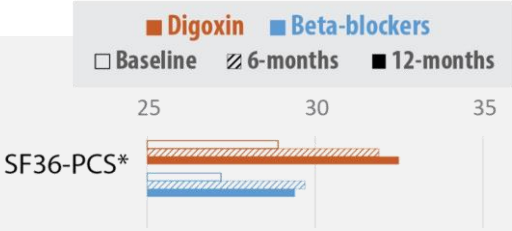
Beta-blockers (Bisoprolol 1.25-10 mg/daily)

160 patients randomised

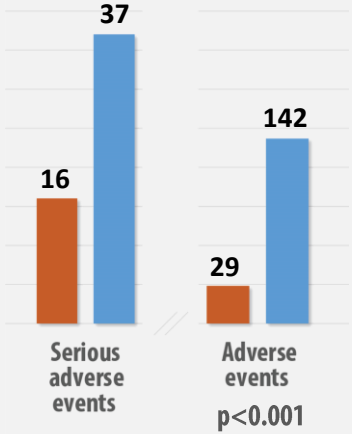
Average age 76

46% women

Symptoms: Moderate Severe



Significantly improved NYHA/mEHRA and NTpro-BNP with digoxin (p<0.01)



BMJ Open 2017;7:e015099

Cardiology 2020;145:666-675

heart 2021;107:902-908

European Heart Journal 2021;42:2411-2414

JAMA 2020;324:2497-2508

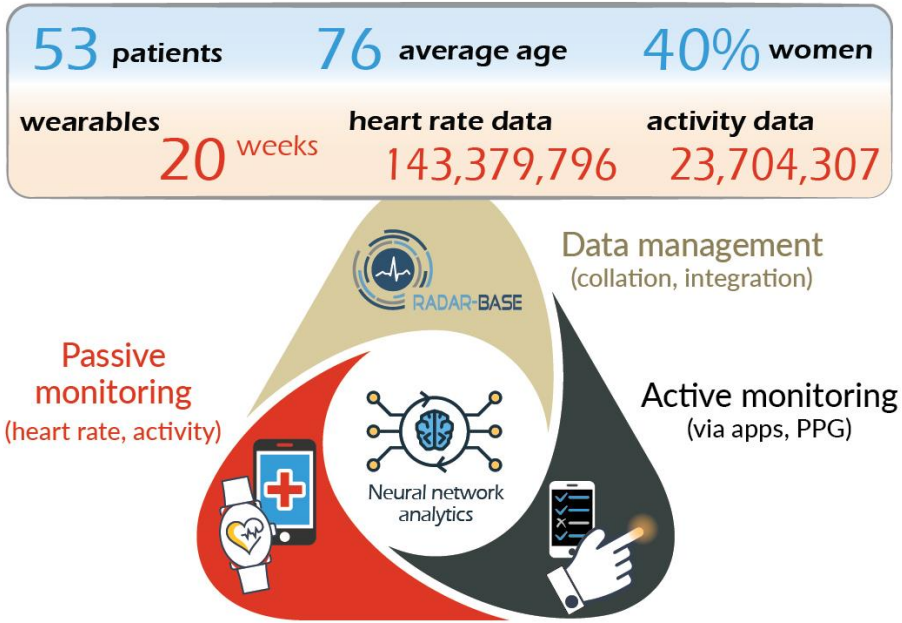
ESC Congress 2023
Amsterdam & Online

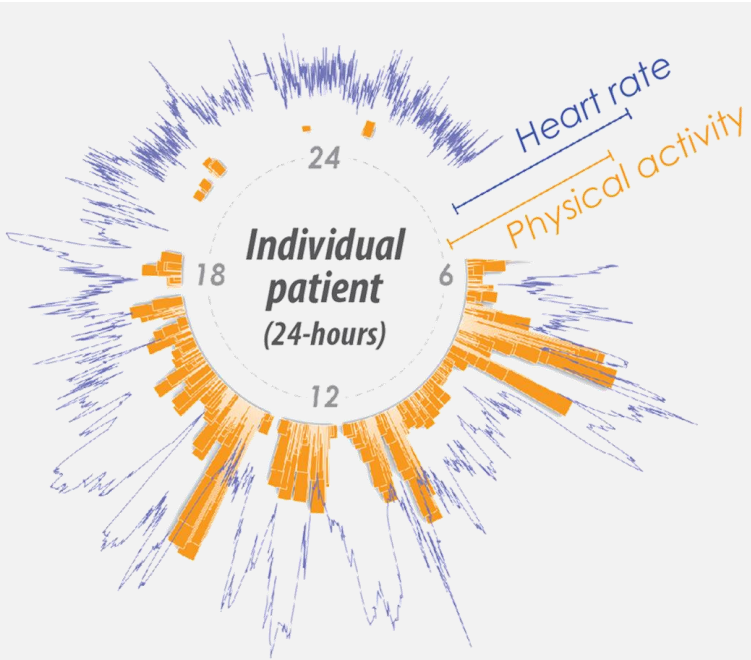
Approach

RATE AF

53 patients | 76 average age | 40% women

wearables: 20 weeks | heart rate data: 143,379,796 | activity data: 23,704,307





Mean number of heart rate data points per patient = **2.7 million** over a 20-week period

(1) Digoxin vs beta-blockers for heart rate control

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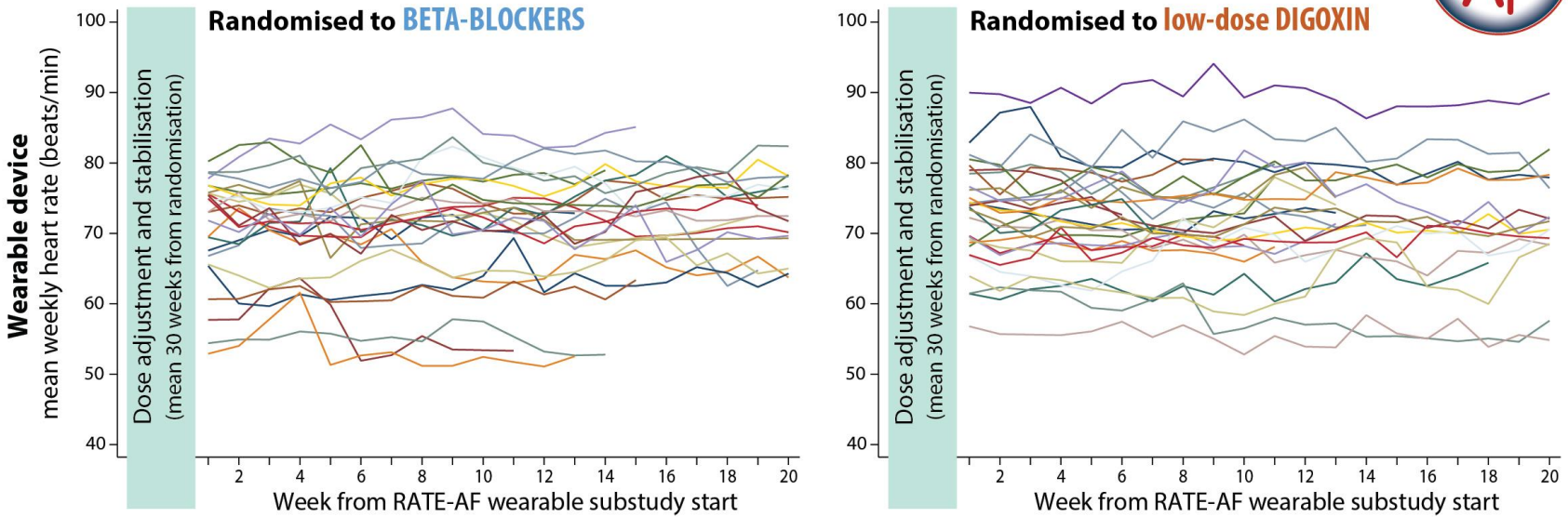
A Trajectory for individual patients



(1) Digoxin vs beta-blockers for heart rate control (cont.)

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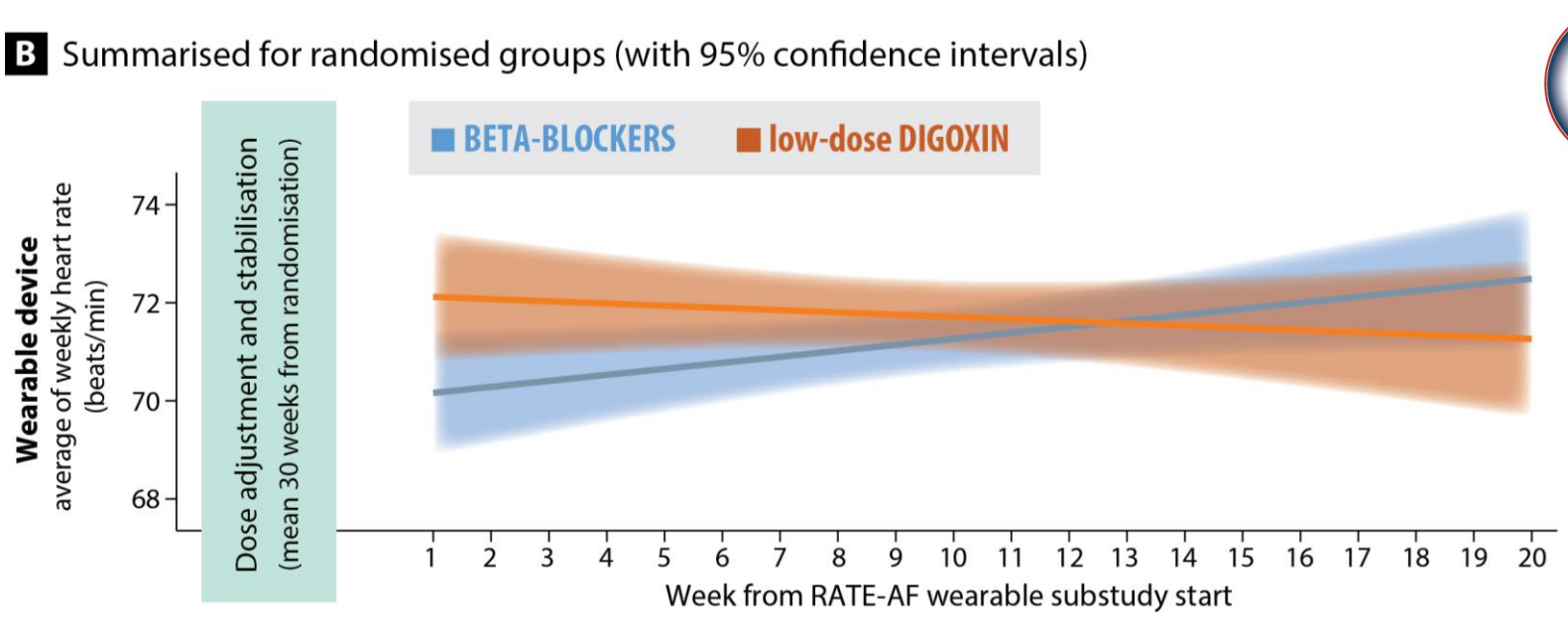


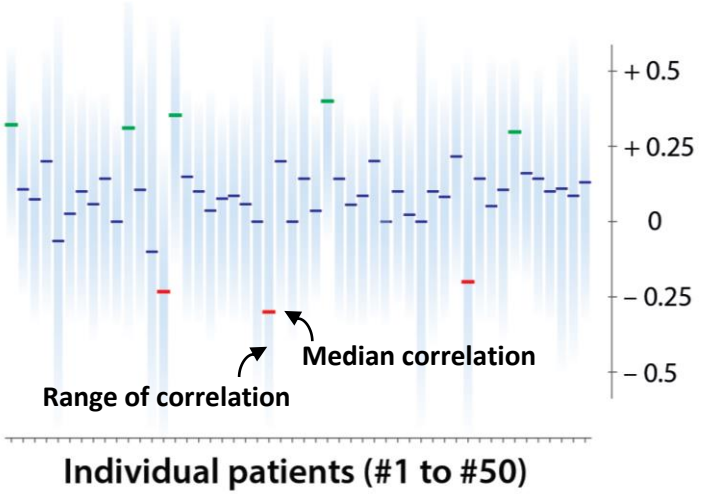
No difference in heart rate comparing digoxin and beta-blocker therapy using the wearable sensors:

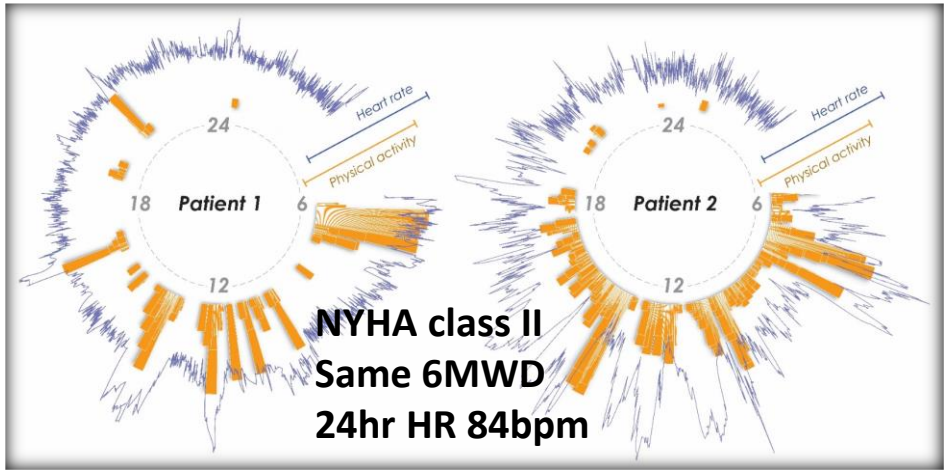
- **Unadjusted regression coefficient: 1.22 (95% CI -2.82 to 5.27; p=0.55)**
- **Adjusted for age, gender, diagnosis of heart failure and NT-proBNP: 0.66 (95% CI -3.45 to 4.77; p=0.75)**

(2) Accounting for physical activity

RATE AF

Correlation between heart rate and physical activity in rate-controlled patients with AF





No difference in heart rate comparing digoxin and beta-blocker therapy using the wearable sensors:

- **No difference after accounting for physical activity (p=0.74)**
- **No difference in any activity ranges:**
  - **<15,000 steps/week; p=0.48**
  - **15-30,000 steps/week; p=0.47**
  - **≥30,000 steps/week; p=0.97**

(3) Prediction of clinical progress

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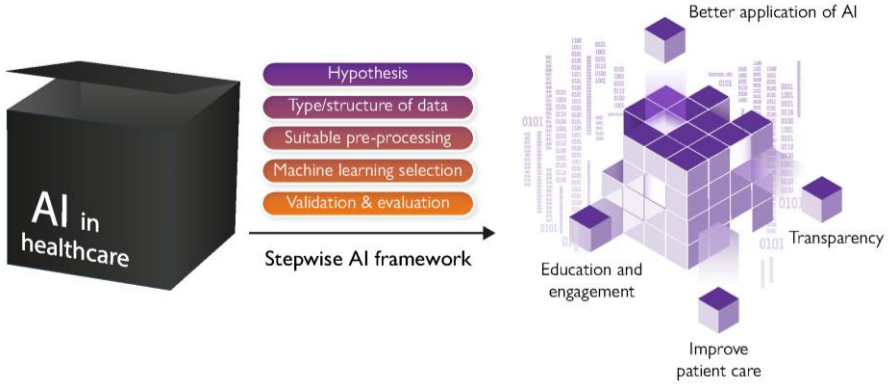
AI FRAMEWORK:

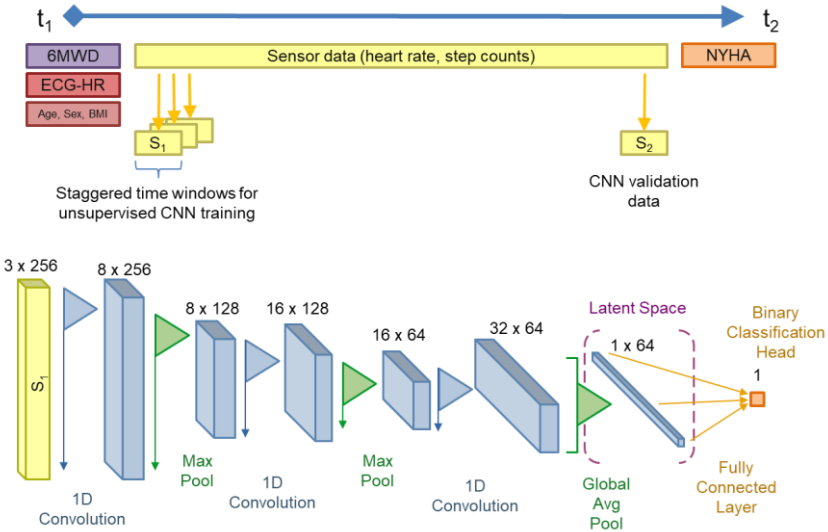


cardAIc

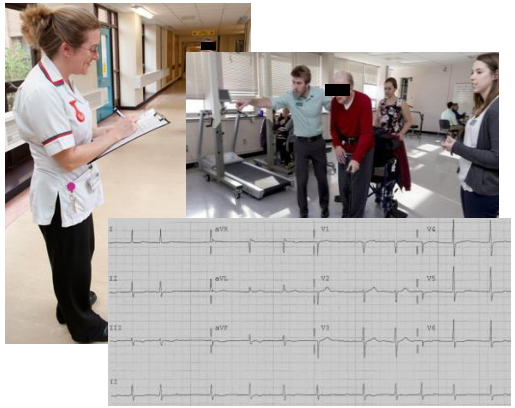
Gill… Kotecha: Eur Heart J 2023;44:713-725
https://doi.org/10.1093/eurheartj/ehac758

BigData@Heart

SELF-SUPERVISING CONVOLUTIONAL NEURAL NETWORK (CNN):

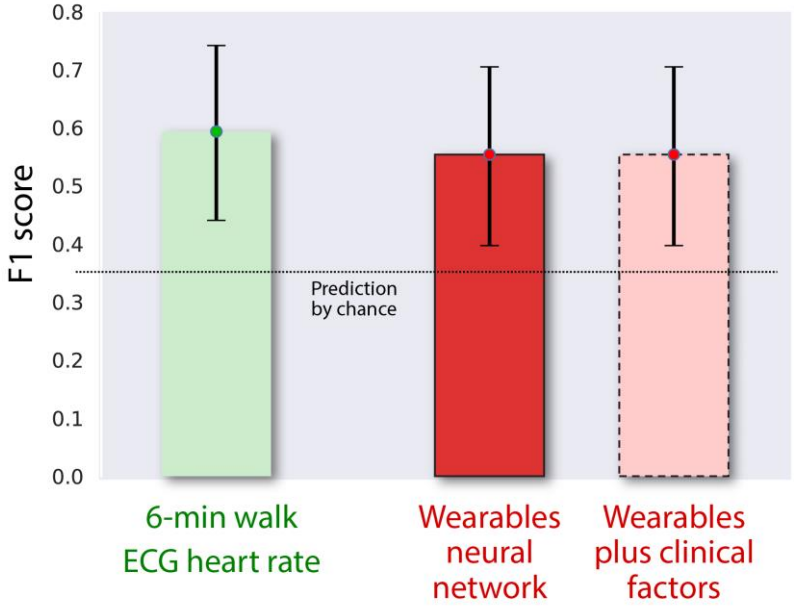


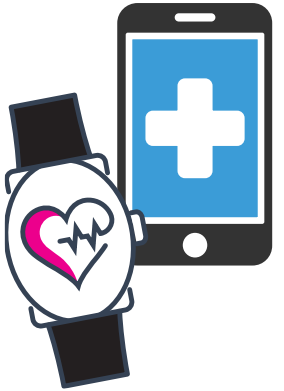
(3) Prediction of clinical progress (cont.)



RATE AF

Prediction of NYHA class
(average of 5 months later)



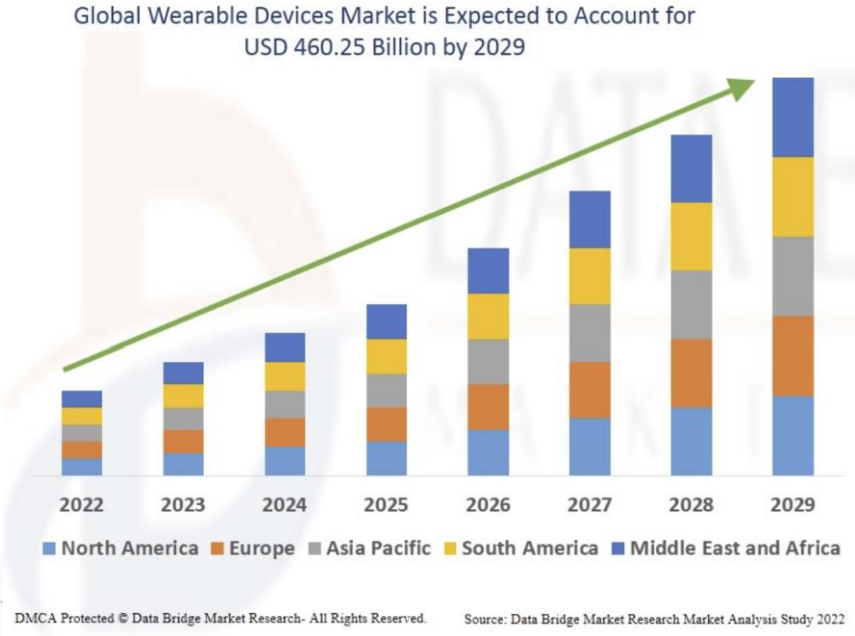


p=0.72

Summary, opportunities & limitations

- Consumer wearable devices are an exciting opportunity to gain information on dynamic physiological parameters
- Noisy and missing data are frequent, and required a novel neural network approach to avoid over-estimating the value of wearable data

- Digoxin and beta-blockers have equivalent effects on non-acute heart rate control in patients with AF, regardless of physical activity
- Dispels the preconception that digoxin is of limited use in highly-active patients



Post-procedural anticoagulation after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a multicentre, randomised, double-blind trial

Shaoping Nie, M.D., Ph.D., FESC, FACC, FSCAI

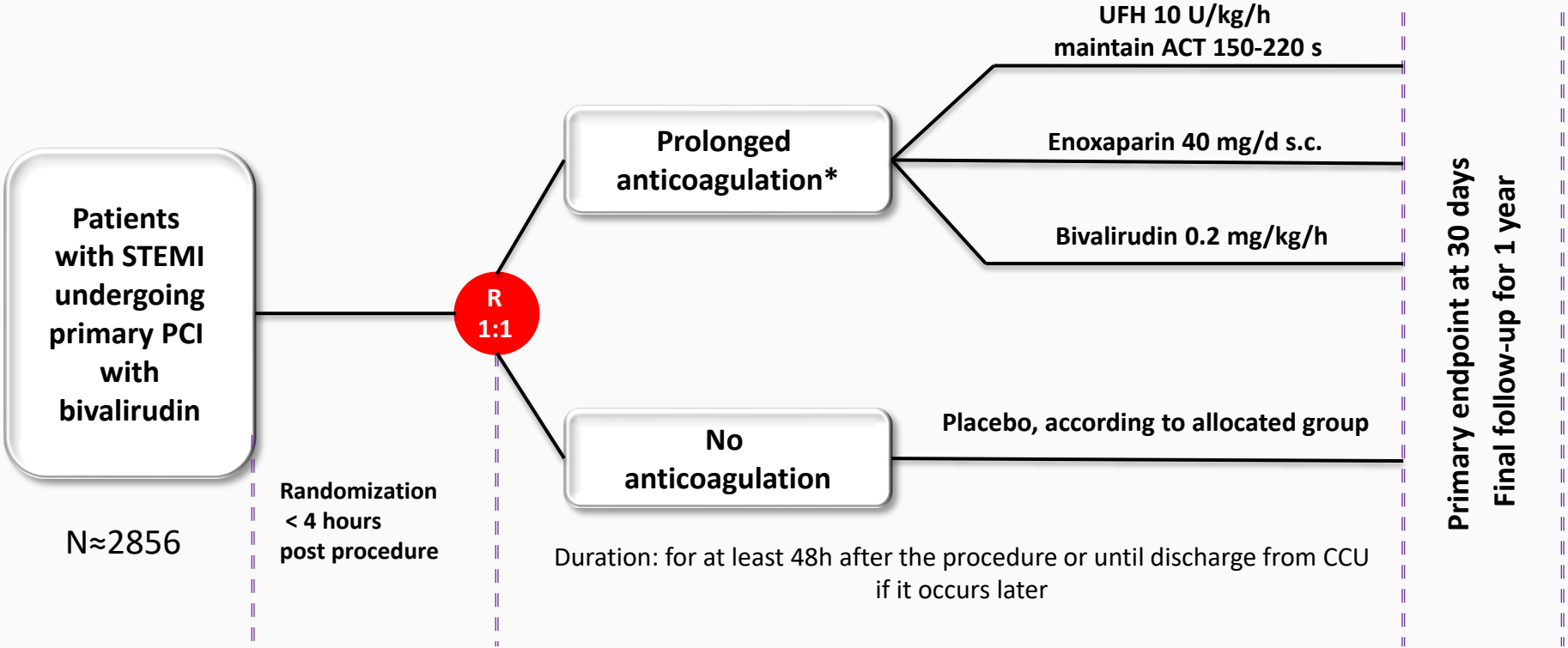
Beijing Anzhen Hospital, Capital Medical University, Beijing, China

National Clinical Research Center of Cardiovascular Diseases, China

On behalf of G Montalescot, Y Li, J Lu, Y Yan and the RIGHT trial investigators

Study Design

RIGHT



* Each center will use only one anticoagulant in all patients randomized at this center

Yan Y. et al. Am Heart J 2020;227:19-30; RIGHT ClinicalTrials.gov number, NCT 03664180

Study Endpoints

RIGHT

- **Primary efficacy endpoint**

  Composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, stent thrombosis (definite) or urgent revascularization (of any vessel) at 30 days

- **Primary safety endpoint**

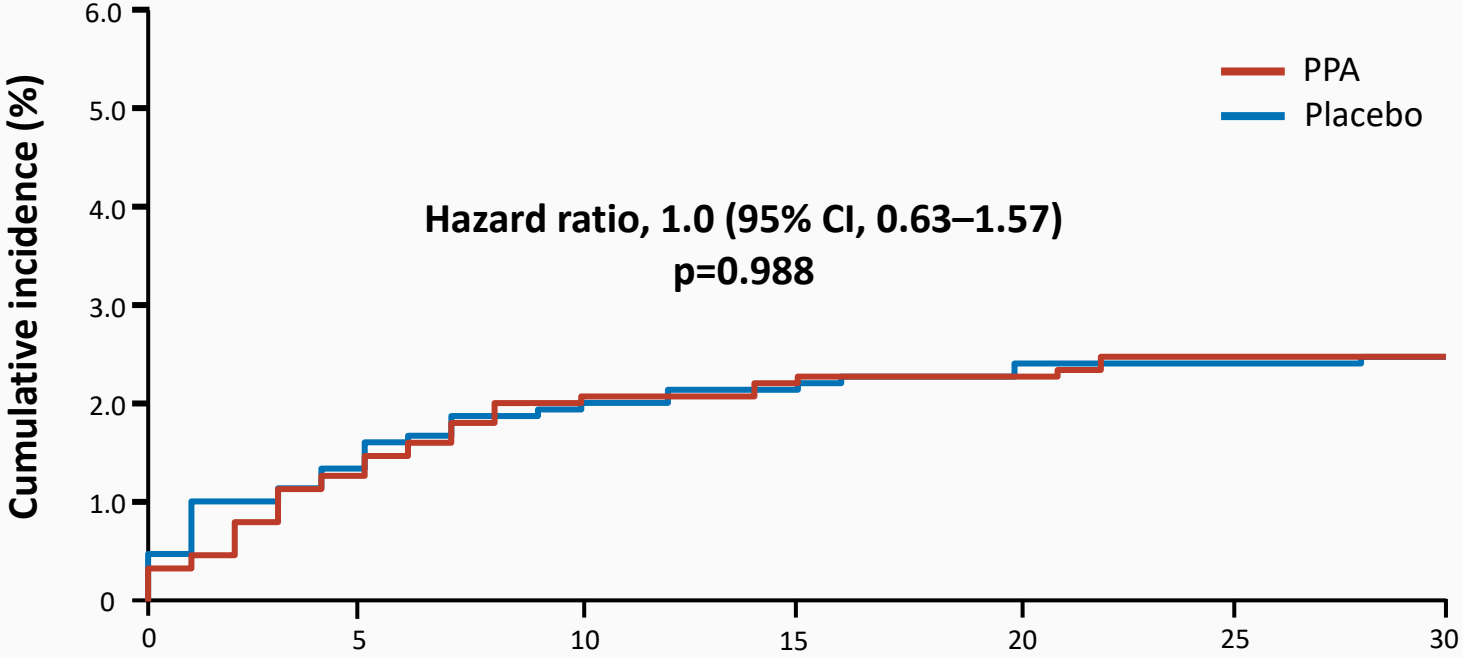
  Major bleeding (BARC definition type 3 to 5) at 30 days

Key Baseline Characteristics

Variables	PPA (n=1494)	Placebo (n=1495)
Age, years; mean (SD)	60.7 (12.4)	61.1 (12.3)
Male sex	1195/1494 (80.0)	1175/1495 (78.6)
Current smoking	763/1494 (51.1)	712/1495 (47.6)
Hypertension	830/1494 (55.6)	800/1495 (53.5)
Diabetes	359/1494 (24.0)	372/1495 (24.9)
Dyslipidaemia	637/1494 (42.6)	623/1495 (41.7)
Prior myocardial infarction	107/1494 (7.2)	92/1495 (6.2)
Chronic kidney disease	30/1494 (2.0)	28/1495 (1.9)
Anterior STEMI	640/1494 (42.8)	658/1495 (44.0)
Door-to-balloon time, minutes; median (IQR)	74 (55, 99)	75 (53, 103)
Aspirin before angiography	1467/1494 (98.2)	1458/1495 (97.5)
$P2Y_{12}$ inhibitor loading before angiography	1425/1494 (95.4)	1407/1495 (94.1)

Primary Efficacy Endpoint

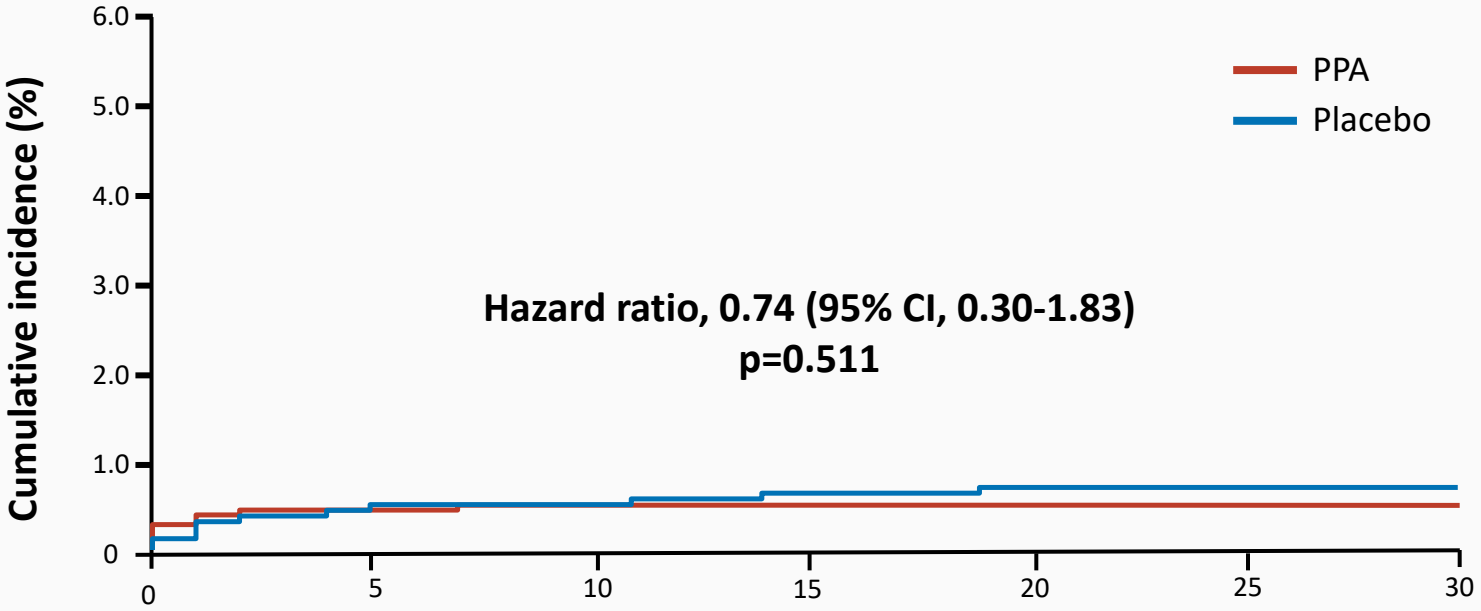
RIGHT



No. at risk							
Placebo	1495	1475	1466	1463	1461	1459	1458
PPA	1494	1475	1464	1461	1460	1457	1457

Primary efficacy endpoint: Death, MI, stroke, stent thrombosis or urgent revascularization at 30 days

Primary Safety Endpoint



No. at risk							
Placebo	1488	1470	1462	1458	1457	1456	1456
PPA	1468	1448	1440	1438	1437	1435	1435

Primary safety endpoint: Major bleeding (BARC 3 to 5) at 30 days

Secondary Exploratory Findings

A **Primary efficacy outcome in three anticoagulation regimen groups**

Subgroup	PPA	Placebo	Hazard ratio (95%CI)	*p for interaction 0·015*
	no./total no. (%)			
Enoxaparin	10/474 (2·1)	21/471 (4.5)		0·46 (0·22-0·98)
UFH	11/510 (2·2)	3/512 (0·6)		3·71 (1·03-13·28)
Bivalirudin	16/510 (3·1)	13/512 (2·5)		1·24 (0·60-2·59)

B **Primary safety outcome in three anticoagulation regimen groups**

Subgroup	PPA	Placebo	Hazard ratio (95%CI)	*p for interaction 0·679*
	no./total no. (%)			
Enoxaparin	3/466 (0·6)	5/470 (1·1)		0·60 (0·14-2·52)
UFH	2/503 (0·4)	4/508 (0·8)		0·50 (0·09-2·75)
Bivalirudin	3/499 (0·6)	2/510 (0·4)		1·54 (0·26-9·24)

Conclusion & Clinical Implications

RIGHT

- Routine PPA using low-dose anticoagulation after primary PCI is safe but does not improve ischaemic outcome at 30 days
- Our data suggest that the three anticoagulants may not be equivalent in the prevention of 30-day ischaemic events but this finding deserves confirmation in future studies

Outcomes of mitral transcatheter edge to edge repair versus isolated mitral surgery for the treatment of severe mitral regurgitation:

data from a nationwide analysis.

Pierre Deharo, MD, PhD, FESC; on behalf of all co authors

CHU la Timone, Marseille, France

25 August 2023

Background

Mitral regurgitation (MR) is the more prevalent valvular disease in western countries

In all registries, MR is undertreated and/or at a late stage

MR treatment is associated with poor prognosis (in older patients)

When considering MR, 1ary and 2ary MR could be differentiated

Background

Treatment of MR is indicated by the severity of MR

Isolated mitral surgery (repair/replace) has been the only curative treatment for severe MR

From 2011, transcatheter edge-to-edge repair (TEER) has offered an alternative to surgery for the treatment of severe MR

Objective

To compare long-term outcomes of TEER vs. isolated mitral valve surgery at a nation wide level in France

To compare long-term outcomes of TEER vs. isolated mitral valve repair at a nation wide level in France

To evaluate long-term outcomes of TEER vs. isolated mitral valve surgery in *1ary and 2ary MR* at a nation wide level in France

Methodology

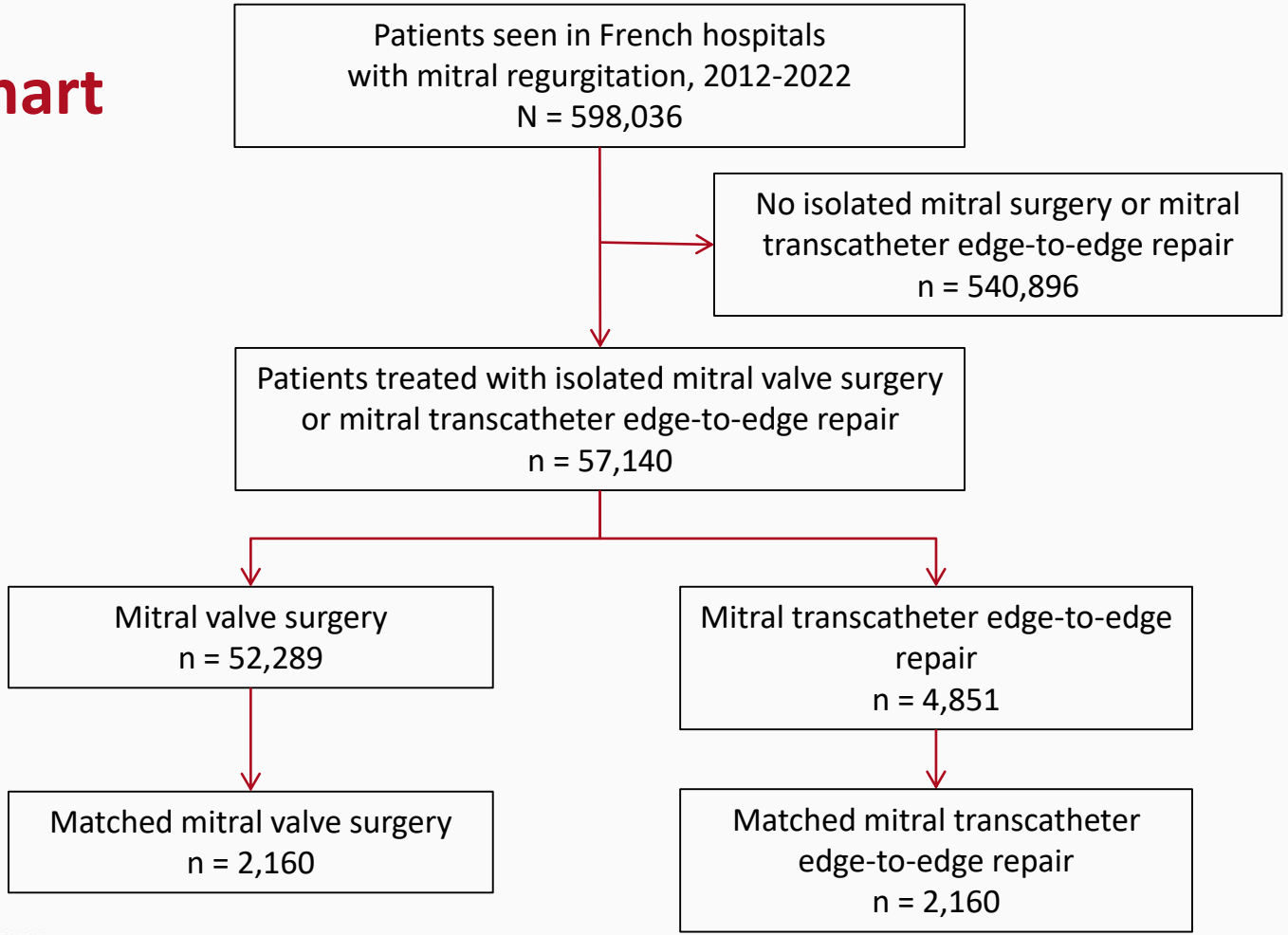
Nationwide analysis

From PMSI database including all patients admitted for severe MR in France from January 2012 to June 2022

Identification and distinction of procedures based on their CCAM codes

Distinction between 1ary and 2ary MR based on codes

Flow chart



FUP 1.0 (± 1.2) year

Baseline characteristics (unmatched)

	Isolated mitral valve surgery (n=52289)	Mitral TEER (n=4741)	p
Age (years), mean±SD	65.9±12.3	79.7±9.2	<0.0001
Coronary artery disease, n (%)	19870 (38.0)	2584 (54.5)	<0.0001
Chronic kidney disease, n (%)	4460 (8.5)	1084 (22.9)	<0.0001
Lung disease, n (%)	8162 (15.6)	1083 (22.8)	<0.0001
Previous cancer, n (%)	4220 (8.1)	857 (18.1)	<0.0001
Poor nutrition, n (%)	6317 (12.1)	1293 (27.3)	<0.0001
Cognitive impairment, n (%)	494 (0.9)	162 (3.4)	<0.0001
Charlson comorbidity index, mean±SD	3.1±2.8	4.2±2.7	<0.0001
Frailty index, mean±SD	7.0±7.6	9.4±8.6	<0.0001
Year of inclusion, mean±SD	2016.7±3.0	2019.8±1.5	<0.0001

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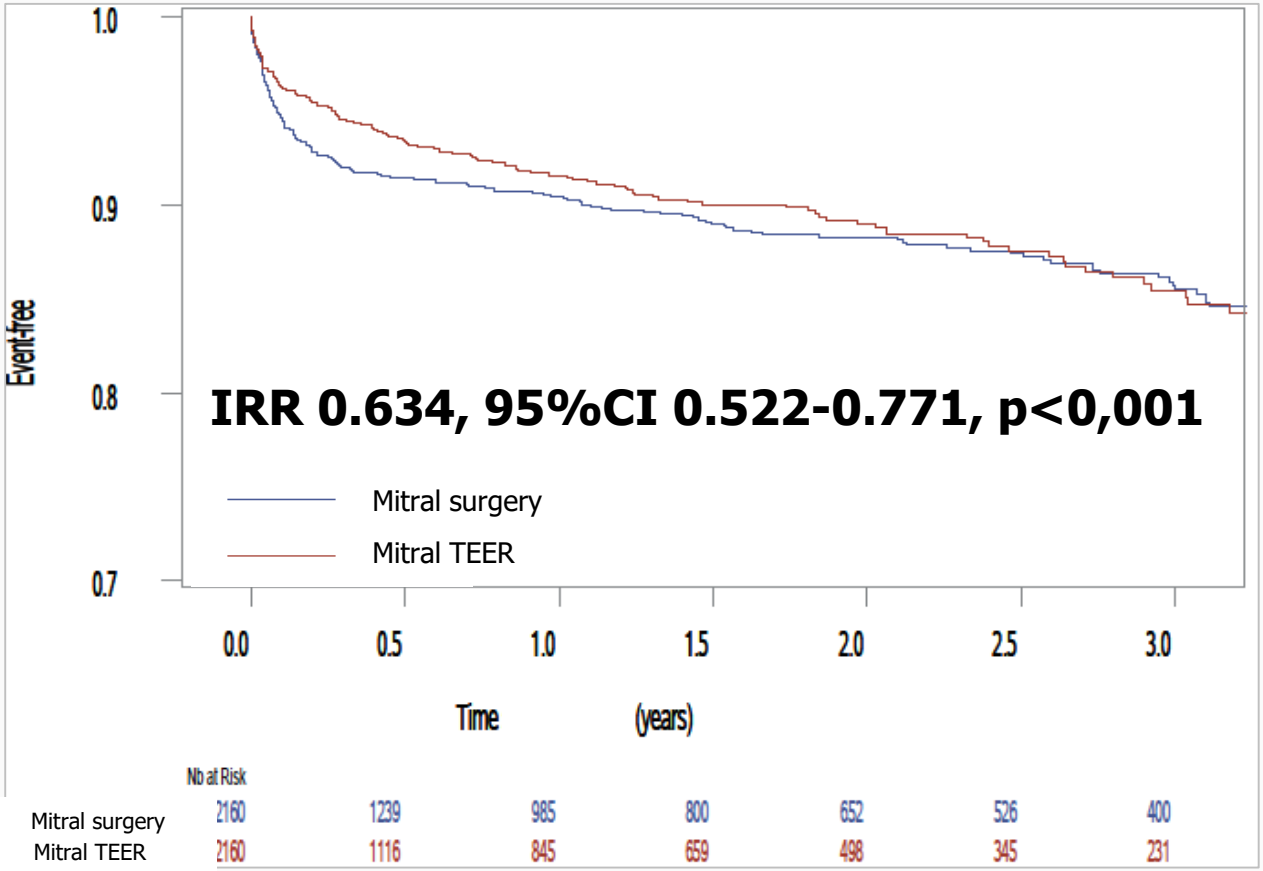
Baseline characteristics (matched)

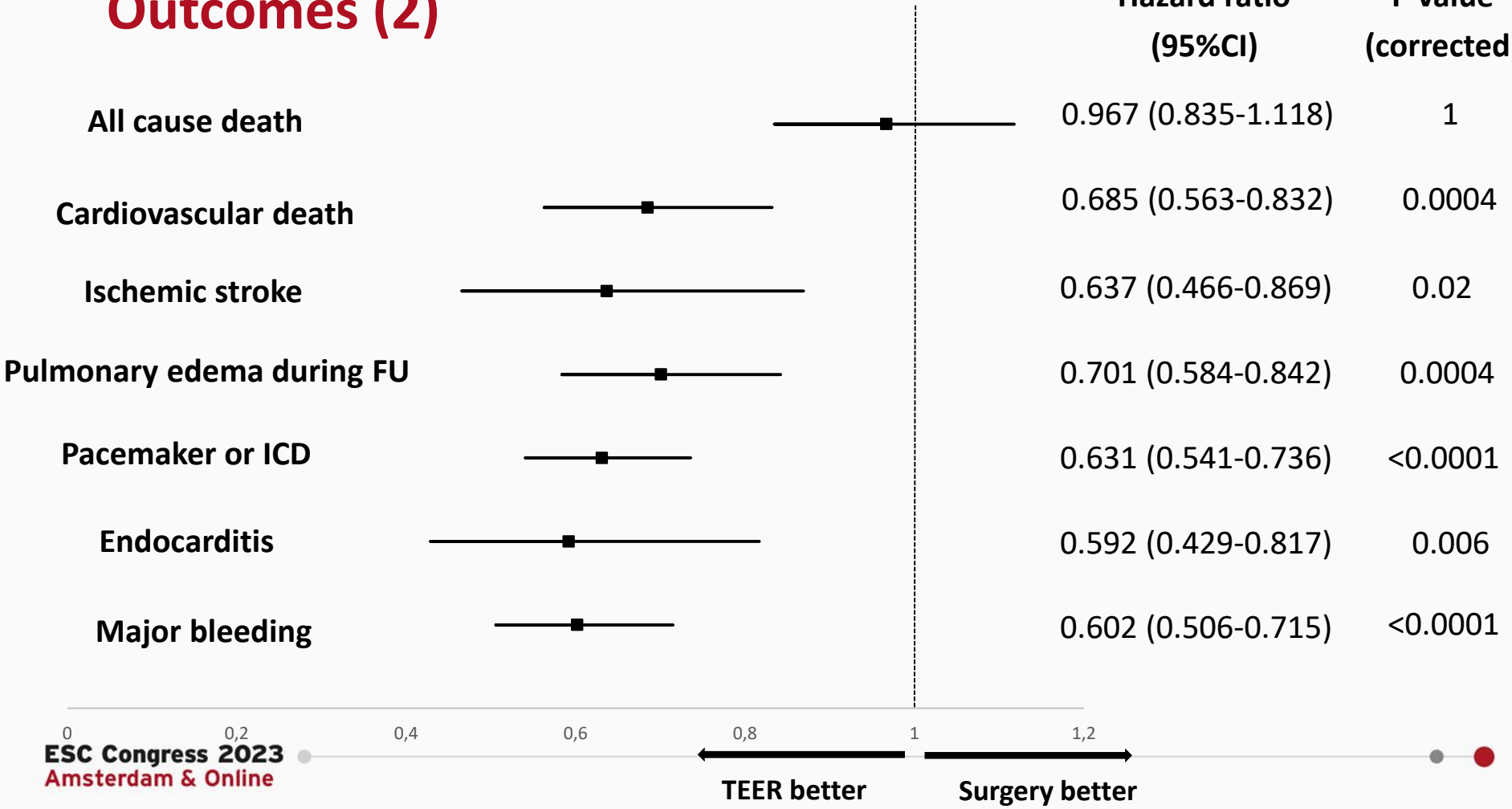
	Isolated mitral valve surgery (n=2160)	Mitral transcatheter edge-to-edge repair (n=2160)	p
Age (years), mean±SD	76.0±8.5	76.0±8.5	1.00
Coronary artery disease, n (%)	1090 (50.5)	1065 (49.3)	0.45
Chronic kidney disease, n (%)	335 (15.5)	380 (17.6)	0.07
Lung disease, n (%)	459 (21.3)	477 (22.1)	0.51
Previous cancer, n (%)	358 (16.6)	353 (16.3)	0.84
Poor nutrition, n (%)	490 (22.7)	522 (24.2)	0.25
Cognitive impairment, n (%)	44 (2.0)	52 (2.4)	0.41
Charlson comorbidity index, mean±SD	3.8±2.8	4.0±2.6	0.19
Frailty index, mean±SD	9.1±8.6	9.0±8.5	0.60
EuroSCORE II, mean±SD	3.9±1.2	3.9±1.2	0.29
Year of inclusion, mean±SD	2019.5±1.5	2019.5±1.5	1.00

Outcomes (1)

Cardiovascular death



Outcomes (2)


Hazard ratio (95%CI)
P value (corrected)
All cause death
0.967 (0.835-1.118)
1
Cardiovascular death
0.685 (0.563-0.832)
0.0004
Ischemic stroke
0.637 (0.466-0.869)
0.02
Pulmonary edema during FU
0.701 (0.584-0.842)
0.0004
Pacemaker or ICD
0.631 (0.541-0.736)
<0.0001
Endocarditis
0.592 (0.429-0.817)
0.006
Major bleeding
0.602 (0.506-0.715)
<0.0001
0
0,2
0,4
0,6
0,8
1
1,2
TEER better
Surgery better

Interaction between subgroups and cardiovascular mortality

Cardiovascular death	Surgery (n=2160)		TEER (n=2160)					
	Number of patients	Number of events	Number of patients	Number of events	Hazard ratio (95% CI)	p value	HR for interaction	p value for interaction
Age <75 yrs	744	51	744	53	0.973 (0.662-1.430)	0.89		
Age ≥75 yrs	1416	119	1416	119	0.608 (0.484-0.764)	<0.0001	**0.611** (0.391-0.955)	**0.03**
EuroSCORE II <4	1274	66	1290	74	1.078 (0.773-1.502)	0.66		
EuroSCORE II ≥4	886	181	870	98	0.539 (0.421-0.689)	<0.0001	**0.487** (0.322-0.736)	**0.0006**

Outcomes (3)

When comparing long-term outcomes of TEER vs. isolated mitral valve repair, cardiovascular death was lower in TEER group versus surgery (IRR 0.698, 0.561-0.869, p 0.001).

When differentiating 1ary versus 2ary MR, cardiovascular death was lower in TEER group versus surgery when treating 2ary MR (IRR 0.664, 0.522-0.846, p 0.001).

In 1ary MR the differences did not reach significance (p 0.08).

Conclusion (1)

Largest propensity matched comparison of mitral TEER versus isolated mitral valve surgery for patients with severe MR

During follow-up we observed that mitral TEER was associated with lower rates of cardiovascular death, pulmonary edema, atrial fibrillation, pacemaker implantation, stroke, major bleeding and endocarditis in matched cohort

Conclusion (2)

We showed a significant interaction between age > 75 years and Euroscore ≥ 4 and reduced cardiovascular and all-cause mortality after TEER versus surgery.

Same differences were reported when including only isolated mitral valve repair (excluding replacement) versus mitral TEER.

In 2ary MR, TEER was associated with lower incidences of cardiovascular death than isolated surgery.

Thank you

Pierre Deharo MD, PhD**, Jean Francois Obadia** MD, PhD**, Thomas Cuisset** MD, PhD**, Patrice Guerin** MD, PhD**, Jean Francois Avierinos** MD, PhD**, Gilbert Habib** MD, PhD**, Olivier Torras** MD**, Arnaud Bisson** MD**, Pascal Vigny** MD**, Christophe Saint Etienne** MD**, Carl Semaan** MD**, Mickael Guglieri** MD, PhD**, Nicolas Dumonteil** MD**, Frederic Collart** MD, PhD**, Martine Gilard** MD, PhD**, Thomas Modine** MD, PhD**, Erwan Donal** MD, PhD**, Bernard Iung** MD, PhD and **Laurent Fauchier** MD, PhD**.**

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COP-AF TRIAL

Colchicine For the Prevention of Peri-Operative Atrial Fibrillation After Major Thoracic Surgery

International, Prospective, Randomized Trial

OBJECTIVE: To evaluate the effect of colchicine on the incidence of perioperative atrial fibrillation (AFib) and myocardial injury after noncardiac thoracic surgery (MINS)

3,209

(1,608 COLCHICINE, 1,601 PLACEBO) PATIENTS

INCLUSION CRITERIA:

- Patients age ≥ 55 undergoing major noncardiac thoracic surgery under general anesthesia without a history of AFib or contraindication to colchicine use

1:1 RANDOMIZATION TO COLCHICINE

VS.

PLACEBO

PRIMARY ENDPOINT

CO-PRIMARY OUTCOMES OF CLINICALLY IMPORTANT PERIOPERATIVE AFIB OR PROGNOSTICALLY IMPORTANT POSTOPERATIVE ISCHEMIC TROPONIN ELEVATION WITHIN 14 DAYS OF SURGERY

SECONDARY ENDPOINTS

COMPOSITE OF ALL-CAUSE MORTALITY, NONFATAL MINS, OR NONFATAL STROKE

COMPOSITE OF ALL-CAUSE MORTALITY, NONFATAL MI, OR NONFATAL STROKE

MINS NOT FULFILLING THE STANDARD MYOCARDIAL INFARCTION DEFINITION

MYOCARDIAL INFARCTION

CONCLUSION

Colchicine did not significantly reduce the incidence of clinically significant perioperative AFib or MINS following major noncardiac thoracic surgery

Conen D, Devereaux PJ, Healey JS, et al. Colchicine for the Prevention of Peri-Operative Atrial Fibrillation After Major Thoracic Surgery. *Lancet* 2023;Aug 25:[Epublished].

Developed and reviewed by Heather Wheat, MD

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DICTATE-AHF

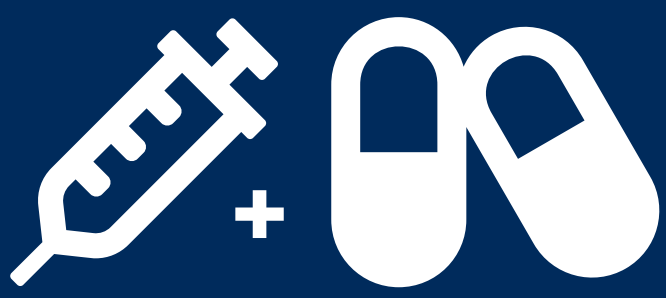
Early Initiation of Dapagliflozin Benefits Patients with Acute Heart Failure

Multicenter, Prospective, Randomized, Open-Labeled Trial Funded By AstraZeneca

OBJECTIVE: To evaluate the efficacy and safety of early inpatient initiation of combination Dapagliflozin and IV loop diuretics in hospitalized patients admitted with acute decompensated heart failure (ADHF).

240
PATIENTS

INCLUSION CRITERIA:
- Recently admitted patients (within 24 hours) with ADHF who are receiving IV loop diuretics
- eGFR>/=25mL/min/1.73m2
- With or without Type 2 diabetes



SYRINGE + PILLS

VS.

SYRINGE

PRIMARY ENDPOINT

THE PRIMARY OUTCOME OF DIURETIC EFFICIENCY (CUMULATIVE WEIGHT CHANGE/CUMULATIVE IV AND ORAL LOOP DIURETIC) FAVORED DAPAGLIFLOZIN (OR 0.65, 95% CI 0.41-1.01, P=0.06).

SECONDARY ENDPOINTS

EARLY DAPAGALIFLOZIN SIGNIFICANTLY IMPROVED NATURIESIS (P=0.025); TIME TO COMPLETING IV DIURETIC THERAPY (P=0.006); AND TIME TO HOSPITAL DISCHARGE (P=0.007). DAPAGLIFLOZIN WAS SAFE ACROSS ALL DIABETIC AND CARDIORENAL IN-HOSPITAL OUTCOMES.

CONCLUSION

Early initiation of dapagliflozin to facilitate decongestion and GDMT optimization is safe and improves diuretic efficiency in patients with ADHF.

Cox Z, et al.; Efficacy and Safety of Dapagliflozin in Acute Heart Failure (DICTATE-AHF; NCTO4298229); Presented at ESC Congress 2023, Amsterdam; Aug. 27, 2023

Developed and reviewed by Katherine Fell, MD

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Sex Differences in FLAVOUR Trial

Sex Differences in Fractional Flow Reserve (FFR)- or Intravascular Ultrasound (IVUS)-Guided Percutaneous Coronary Intervention (PCI)

Multicenter, International, Open-Label, Noninferiority, Investigator-Initiated Randomized Trial

OBJECTIVE: Secondary analysis to identify sex differences in procedural characteristics, treatment and clinical outcomes according to the use of FFR or IVUS for PCI guidance.

1,619
PATIENTS

INCLUSION CRITERIA:
- Ischemic heart disease suspected
- Intermediate stenosis on angiography
- Target vessel 2.5 mm in diameter
- IVUS or FFR performed as assigned in original trial

WOMEN (482)

VS.

MEN (1,137)

PRIMARY ENDPOINT

COMPOSITE OF CARDIAC DEATH, TARGET VESSEL MI AND TARGET VESSEL REVASCULARIZATION AT 24 MONTHS WAS LOWER IN WOMEN THAN IN MEN (2.4% vs. 4.5%).

SECONDARY ENDPOINTS

WOMEN RECEIVED FEWER TOTAL INTERVENTIONS:

TOTAL: 40.8% PCI vs. 47.9% PCI

FFR GROUP: 25.0% vs. 36.8%

IVUS GROUP: 58.4% vs. 59.3%

CONCLUSION

In patients undergoing coronary angiography found to have intermediate stenosis, women had lower rates of target vessel failure than men despite undergoing fewer PCI.

Zhang J, Jiang J, Hu X, et al. Sex Differences in Fractional Flow Reserve- or Intravascular Ultrasound-Guided Percutaneous Coronary Intervention. *JACC: Cardiovasc Interv* 2023;Aug 27:[Epublished]

Developed and reviewed by Kent Brummel, MD

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