L ESSENTIEL du congrès ESC 2019

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Remerciements:

A Baumbach,D Capodanno, C Lam,E Prescott, S Silber

- **Heart failure:**

-DAPA HF,EVALUATE HF, PARAGON, GALACTIC.

- **Secondary Prevention:**

-THEMIS

- **Coronary artery disease/Interventional cardiology:**

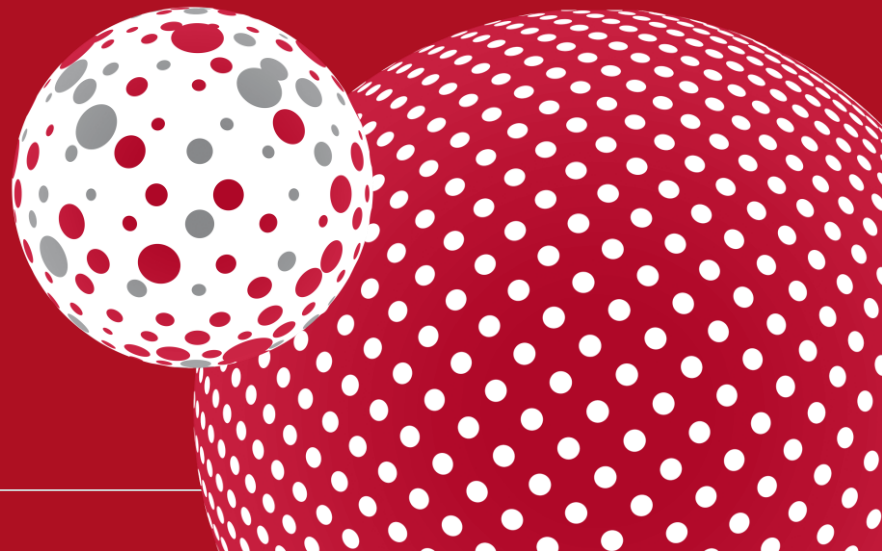
-SYNTAX 10 years, DANAMI 16 years,COMPLETE,ISAR REACT 5,

CLARIFY

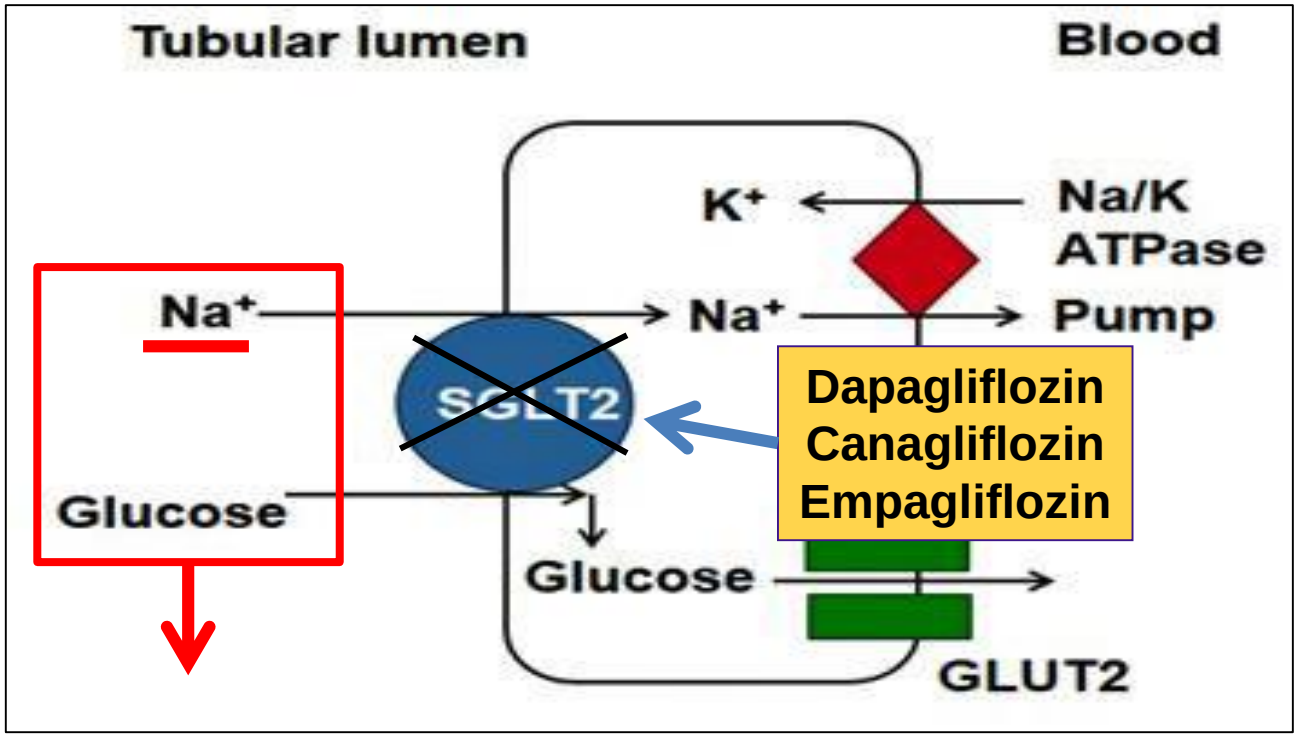
HFrEF

DAPA-HF

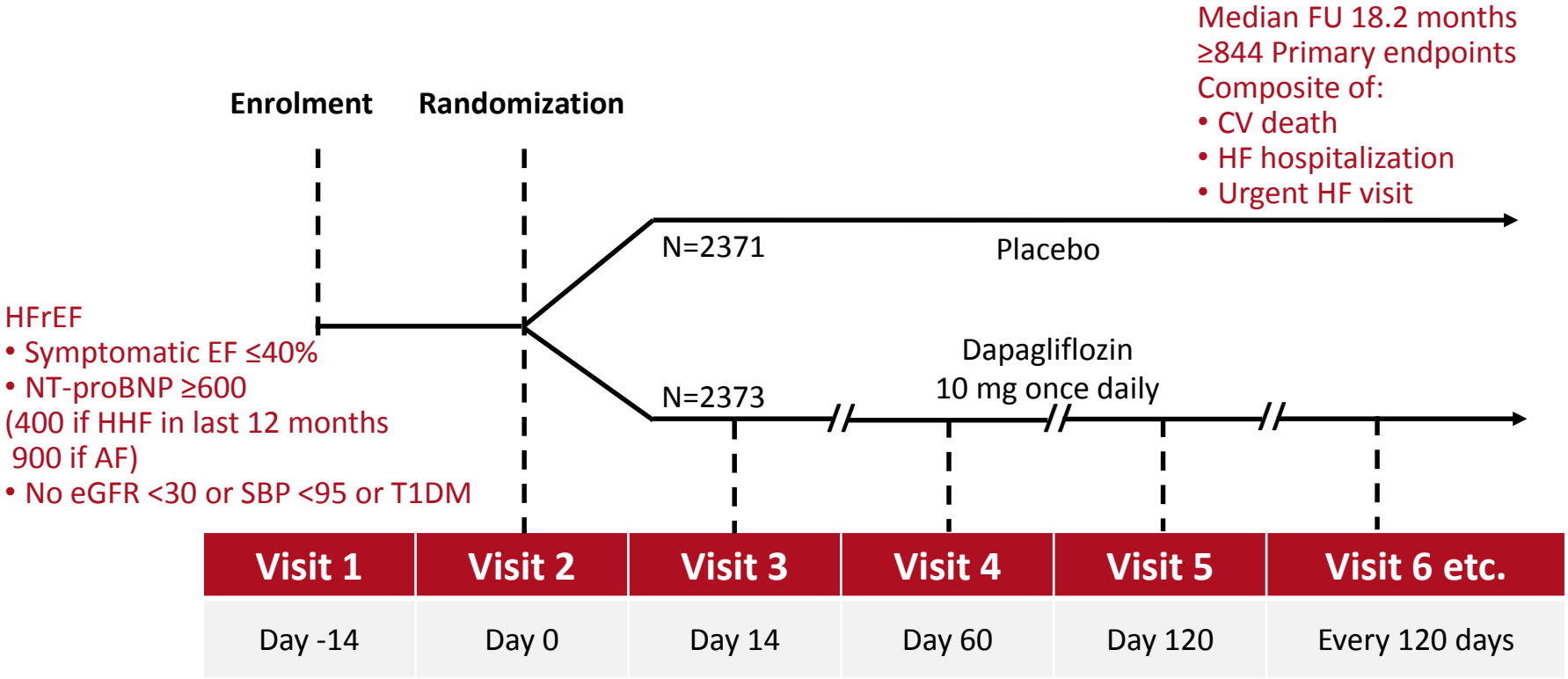
EVALUATE-HF



Sodium Glucose co-transporter inhibitors



Dapagliflozin in patients with HFrEF (DAPA-HF)



Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (yr)	66	67
Male (%)	76	77
NYHA class II/III/IV (%)	68/31/1	67/32/1
Mean LVEF (%)	31	31
Median NT pro BNP (pg/ml)	1428	1446
Mean systolic BP (mmHg)	122	122
Ischaemic aetiology (%)	55	57
Mean eGFR (ml/min/1.73m^2)	66	66
Prior diagnosis T2D (%)	42	42
Any baseline T2D (%)*	45	45

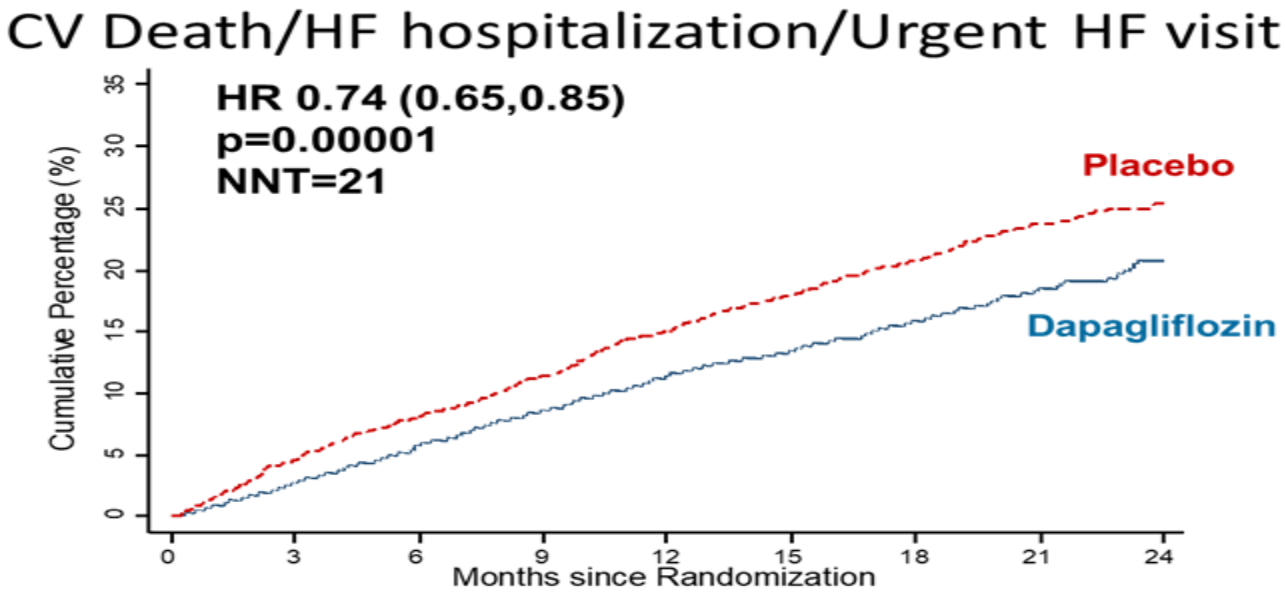
*includes 82 dapagliflozin and 74 placebo patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol)

Treatment (%)	Dapagliflozin (n=2373)	Placebo (n=2371)
Diuretic	93	94
ACE-inhibitor/ARB/ARNI+	94	93
ACE inhibitor	56	56
ARB	28	27
Sacubitril/valsartan	11	11
Beta-blocker	96	96
MRA	71	71
ICD*	26	26
CRT**	8	7

+ARNI = angiotensin receptor neprilysin inhibitor
*ICD or CRT-D **CRT-P or CRT-D

For full details see McMurray JJV et al Eur J Heart Fail.2019 Jul 15. doi: 10.1002/ejhf.1548

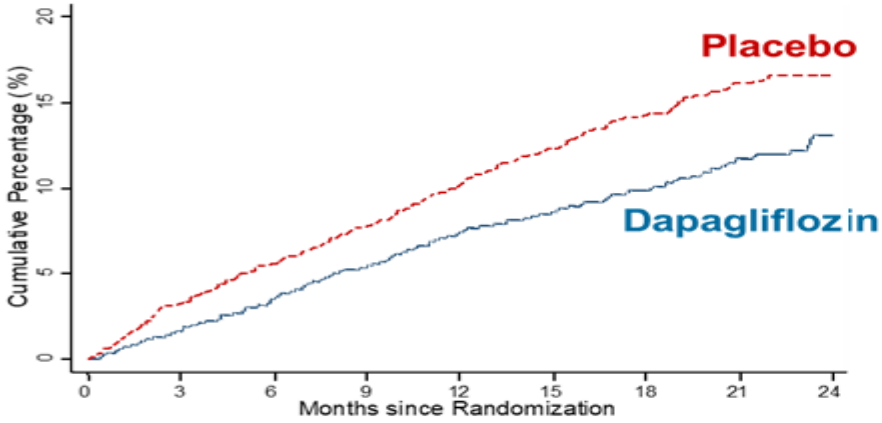
Primary composite outcome



Components of primary outcome

Worsening HF event

HR 0.70 (0.59, 0.83); p=0.00003

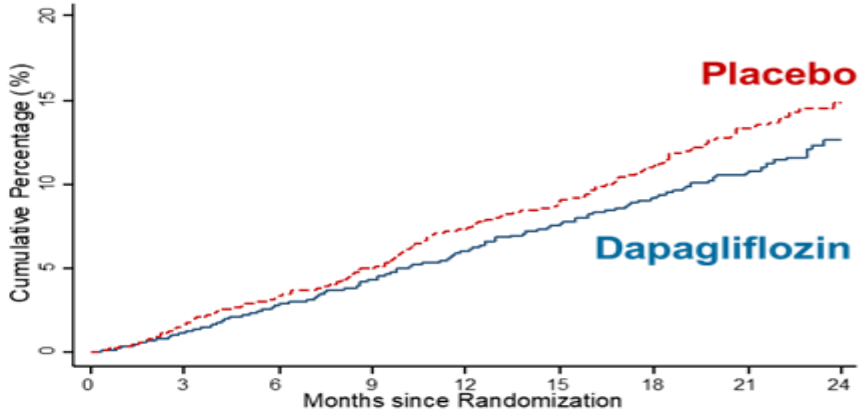


Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

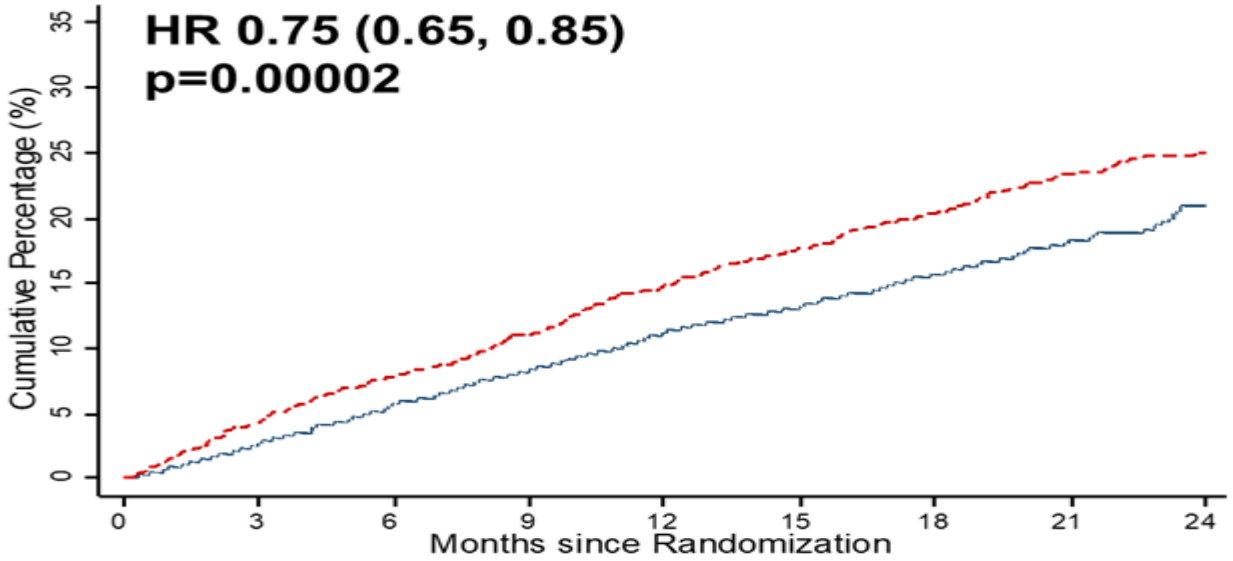
Cardiovascular death

HR 0.82 (0.69, 0.98); p=0.029



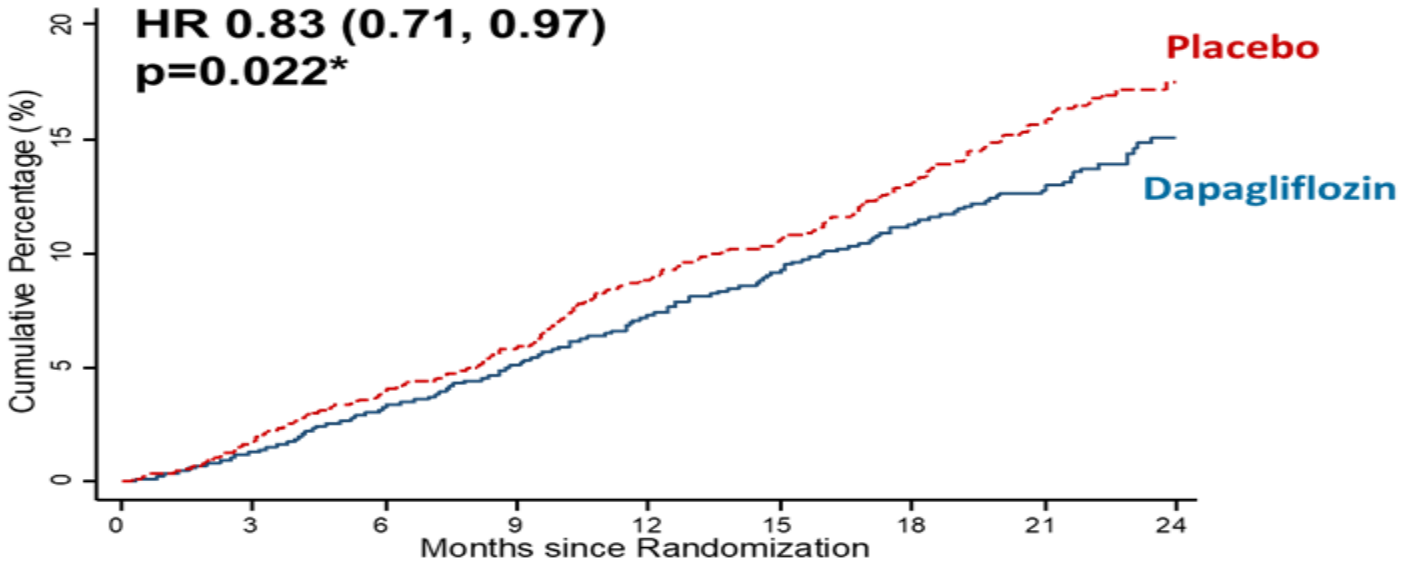
	2373	2339	2293	2248	2127	1664	1242	671	232
	2371	2330	2279	2230	2091	1636	1219	664	234

CV death or HF hospitalization



Number at Risk									
Dapagliflozin	2373	2306	2223	2153	2007	1563	1147	613	210
Placebo	2371	2264	2168	2082	1924	1483	1101	596	212

All cause death

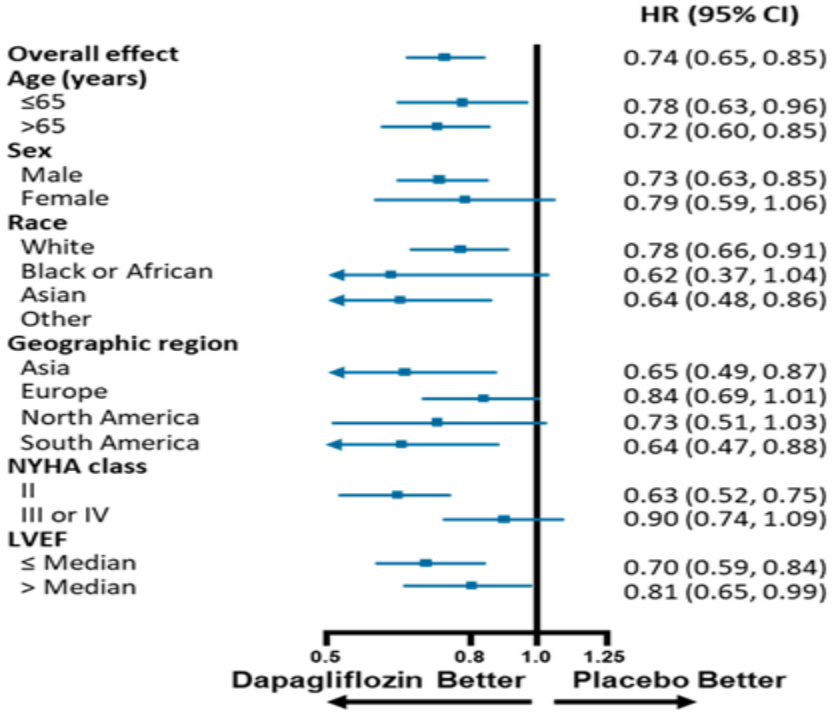


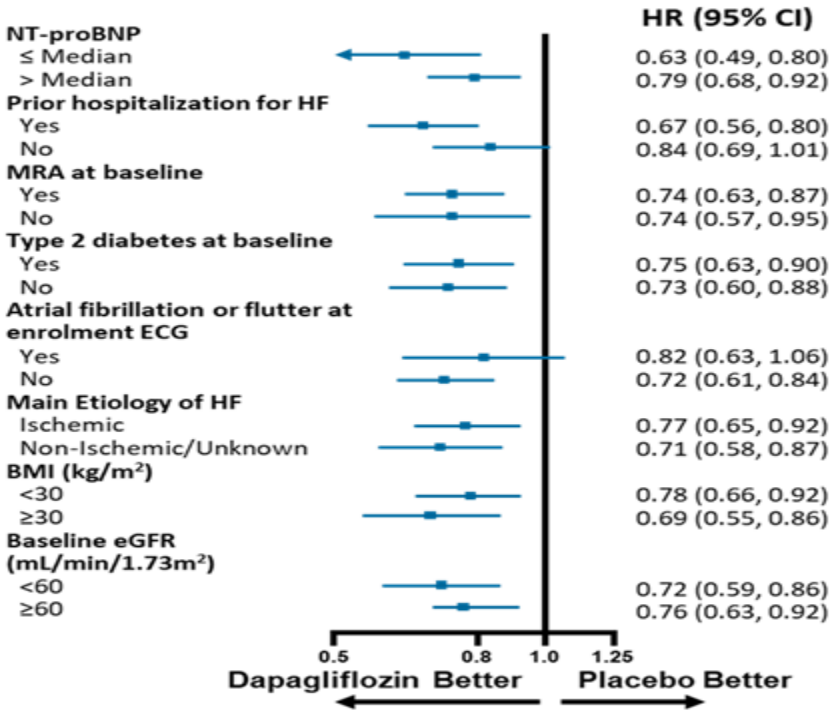
Number at Risk

Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235

*Nominal p value

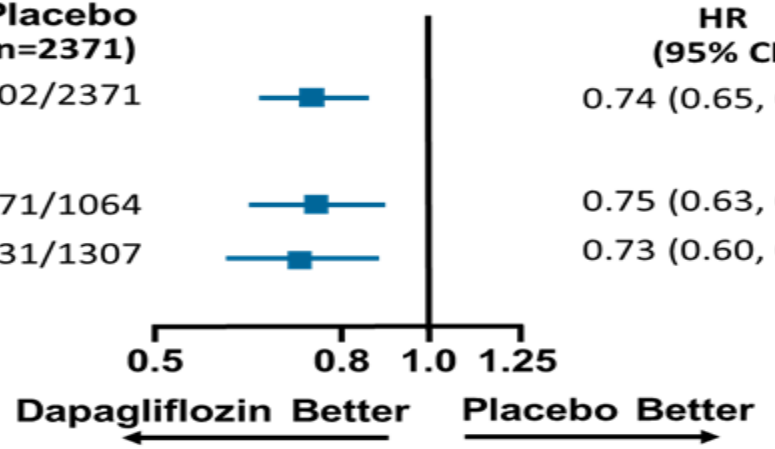
Primary Endpoint: Prespecified Subgroups





No diabetes / Diabetes subgroup
Primary Endpoint

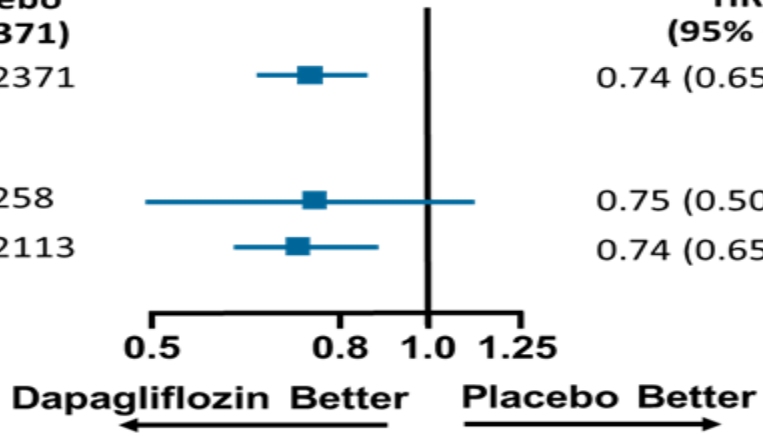
	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)



*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

ARNI/no ARNI *post hoc* subgroup : Primary Endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Angiotensin Receptor Neprilysin Inhibitor (ARNI)			
Yes	41/250	56/258	0.75 (0.50, 1.13)
No	345/2123	446/2113	0.74 (0.65, 0.86)



Kansas City Cardiomyopathy Questionnaire (KCCQ)

Total Symptom Score (TSS): Change from baseline to 8 months

Treatment	Change
Dapagliflozin	**+6.1** ± 18.6
Placebo	**+3.3** ± 19.2

Difference
2.8 points (95% CI 1.6, 4.0)
p<0.001*

Increase in score indicates an improvement

*Calculated from win ratio, incorporating death. Win ratio = 1.18 (CI 1.11, 1.26). Win ratio >1 indicates superiority of dapagliflozin over placebo

Worsening renal function endpoint

Composite of: Sustained* ≥50% reduction in eGFR, end-stage renal disease (ESRD) or death from renal causes

Treatment	No. (%)
Dapagliflozin	28 (1.2)
Placebo	39 (1.6)

Hazard ratio (95% CI)
0.71 (0.44, 1.16)
p=0.17

ESRD consisted of sustained eGFR below 15 ml/min/1.73m^2, sustained dialysis or kidney transplantation

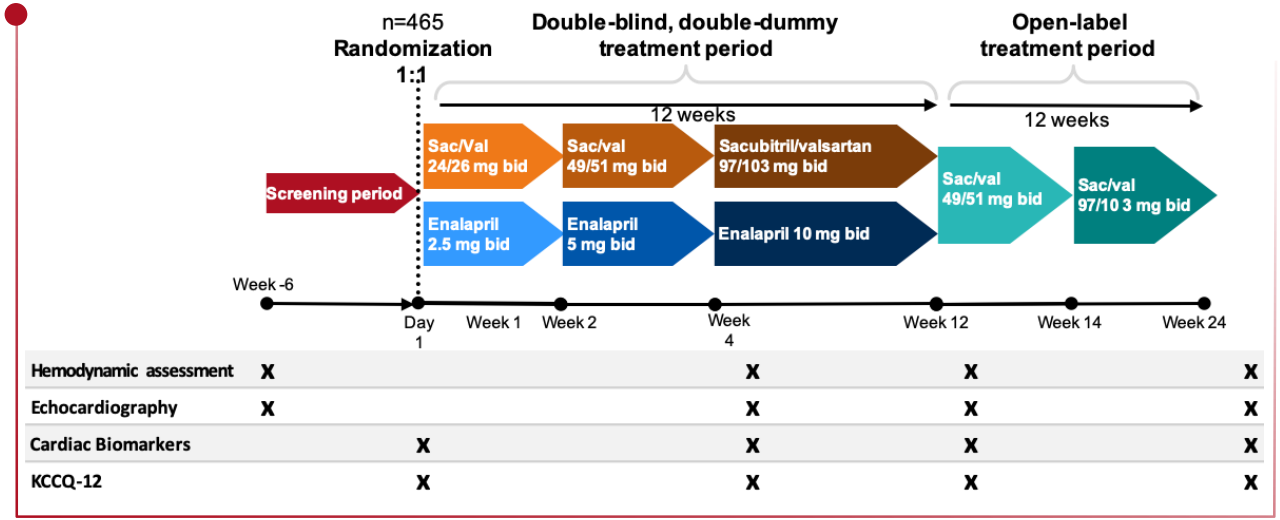
*Sustained = 28 days or more

JAMA | Original Investigation

Effect of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction
A Randomized Clinical Trial

Akshay S. Desai, MD, MPH; Scott D. Solomon, MD; Amil M. Shah, MD; Brian L. Claggett, PhD; James C. Fang, MD; Joseph Izzo, MD; Kevin McCague, MA; Cheryl A. Abbas, PharmD; Ricardo Rocha, MD; Gary F. Mitchell, MD; for the EVALUATE-HF Investigators

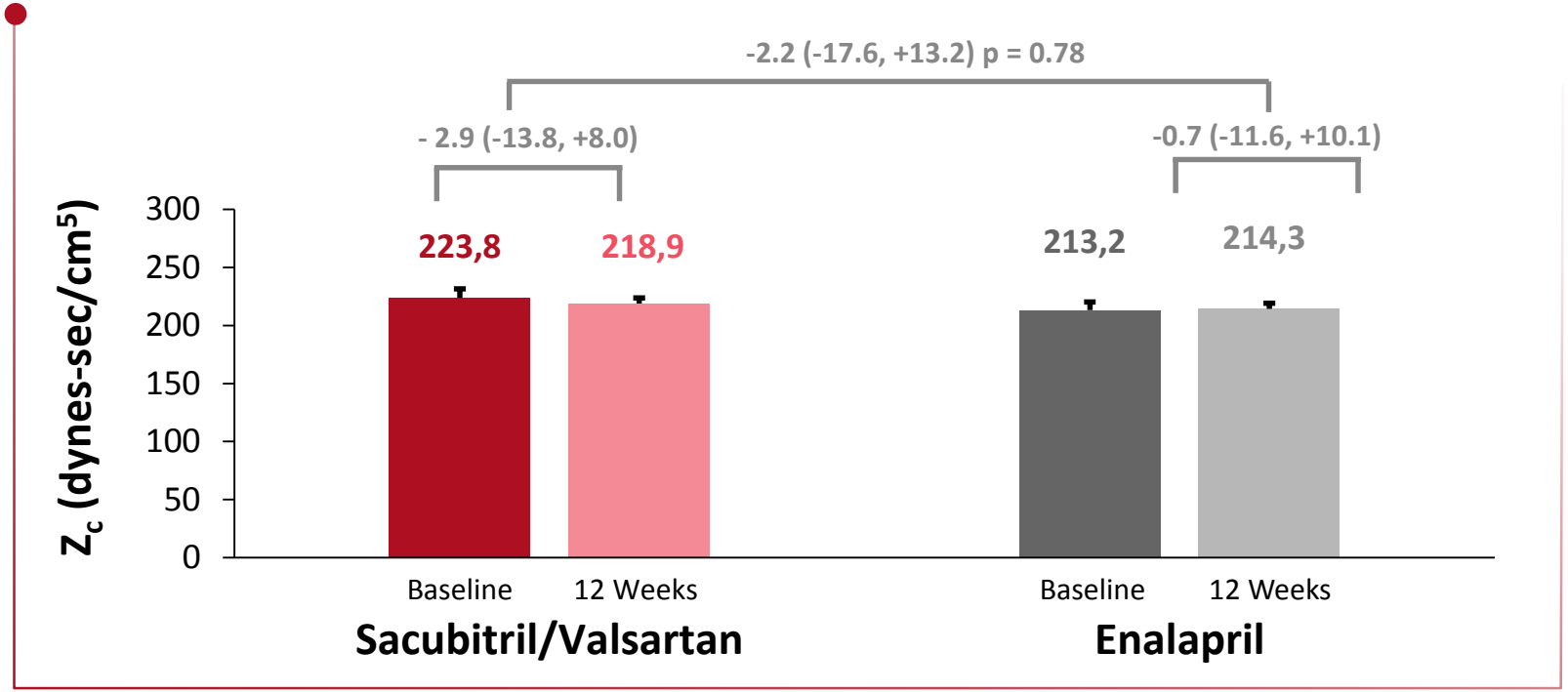
EVALUATE-HF



To determine whether treatment of HFrEF with sacubitril/valsartan improves central aortic stiffness and cardiac remodeling compared with enalapril

A.Desai, JAMA 2019

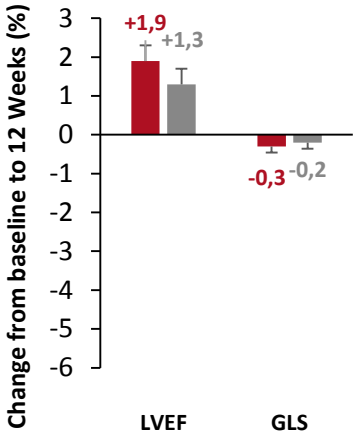
Primary Endpoint: Change in aortic characteristic impedance Z_c



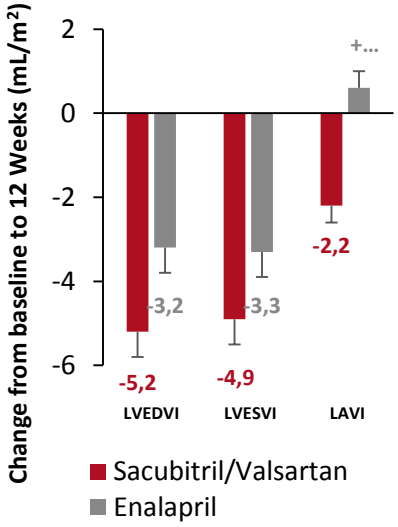
A.Desai, JAMA 2019

Secondary Endpoints: Change in Cardiac Structure and Function from Baseline to 12 weeks, by Treatment

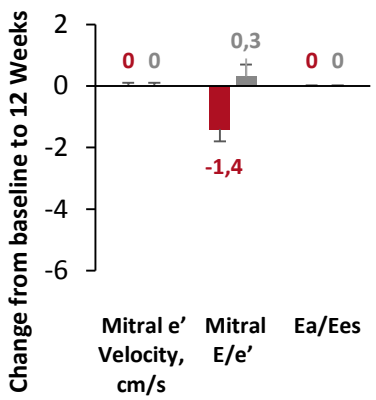
Systolic Function



Cardiac Structure



Diastolic Function and Ventricular-Vascular Coupling



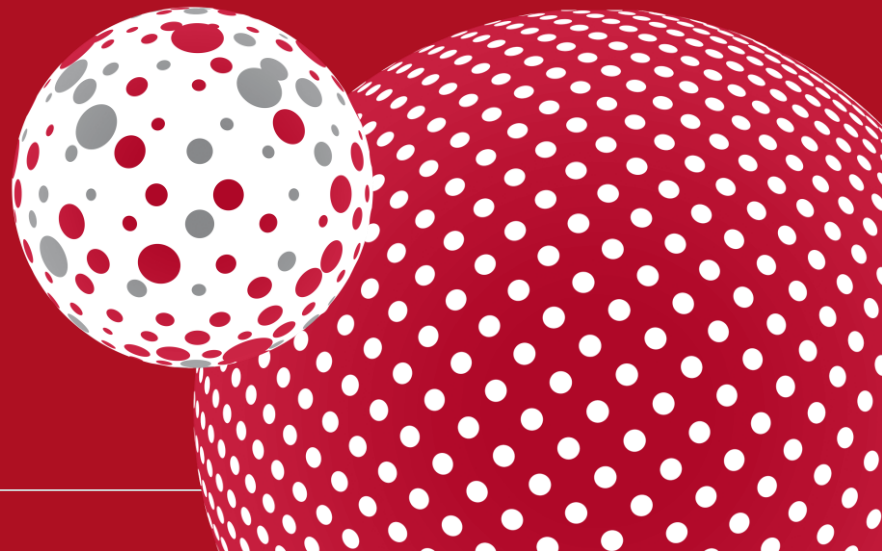
Implications

Clinical benefits of sacubitril/valsartan in HFrEF are likely unrelated to changes in central aortic stiffness or pulsatile load, but might be related to effects on myocardial remodeling and wall stress

A.Desai, JAMA 2019

HFpEF

PARAGON-HF



Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction

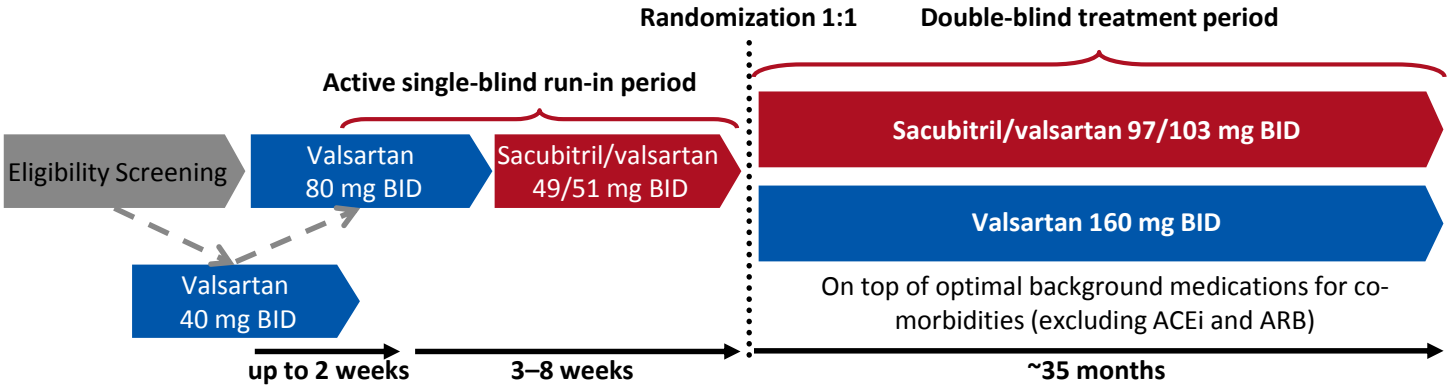
Primary results of the PARAGON-HF trial

Scott D. Solomon, MD, and John J.V. McMurray, MD

for the PARAGON-HF Committees, National Leaders and Investigators

PARAGON-HF study design

Randomized, double-blind, active comparator trial testing the hypothesis that sacubitril/valsartan, compared with valsartan, would reduce the composite outcome of total HF hospitalisations and CV death



Primary Endpoint
Composite of total (first and recurrent) HF hospitalisations and CV death

Secondary Endpoints:
- Improvement in NYHA functional classification at 8 months
- Changes in KCCQ clinical summary score at 8 months
- Time to first occurrence of worsening renal function
- Time to all-cause mortality

Solomon SD, et al. JACC-Heart Fail 2017; 5(7):471-482.

Key Inclusion & Exclusion criteria

KEY INCLUSION CRITERIA

- ≥ 50 years of age and LVEF ≥ 45%
- Heart failure signs/symptoms (NYHA Class II–IV) requiring treatment with diuretic(s) for at least 30 days prior to enrollment
- Structural heart disease (LAE or LVH by echocardiography)
- Elevation in natriuretic peptides
  - NT-proBNP 200 pg/ml if hospitalized for HF within 9 months, and 300 pg/ml if not hospitalized; 3-fold increase for patients in AF at enrollment

KEY EXCLUSION CRITERIA

- Any prior measurement of LVEF < 40%
- Current acute decompensated heart failure
- Alternative reason for signs and symptoms
- SBP < 110 or > 180mm Hg (or > 150mm Hg if patient not taking 3 or more antihypertensive medications)

Baseline Demographics

		Sacubitril/valsartan N = 2,407	Valsartan N = 2,389
Age (years) – mean (SD)		72.7 (8.3)	72.8 (8.5)
Sex – n (%)	Male	1166 (48.4)	1151 (48.2)
	Female	1241 (51.6)	1238 (51.8)
Race – n (%)	Caucasian	82%	81%
	Black	2.2%	2.1%
	Asian	12%	13%
Region – n (%)	North America*	12%	11%
	Latin America	7.9%	7.5%
	Western Europe	29%	29%
	Central Europe	36%	36%
	Asia/Pacific/other**	16%	16%
Baseline LVEF – median [IQR]		57 [51,62]	57 [50,63]
Baseline NT-proBNP (pg/mL) – median (IQR) – Sinus rhythm		583 [370, 1046]	611 [389, 1072]
Baseline NT-proBNP (pg/mL) – median (IQR) – Atrial fibrillation		1633 [1191, 2368]	1536 [1153, 2212]

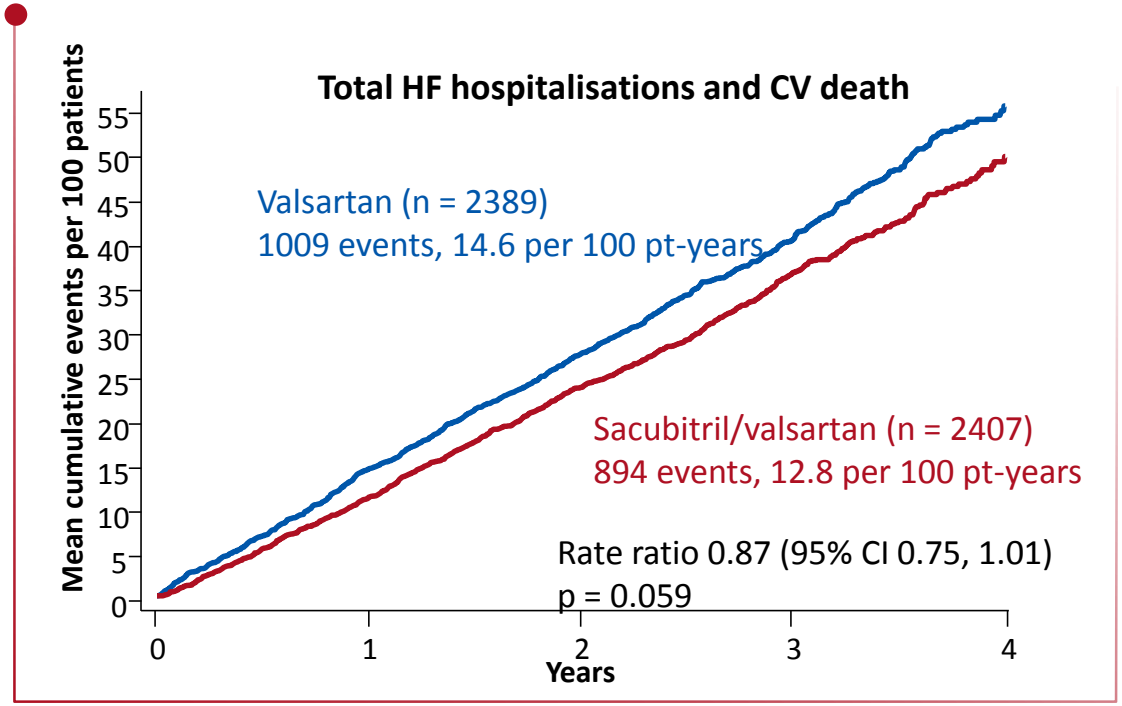
*North America = US and Canada. **Asia/Pacific/Other includes Israel, South Africa, Australia, China, India, Japan, Rep of Korea, Philippines, Singapore, Taiwan.

Baseline Demographics

			Sacubitril/valsartan N=2,407	Valsartan N=2,389
NYHA class at randomization – n (%)		Class I	3.0%	2.7%
		Class II	78%	77%
		Class III	19%	20%
		Class IV	0.3%	0.5%
BMI – mean (SD)			30.2 (4.9)	30.3 (5.1)
Baseline systolic/diastolic blood pressure at randomization – mean (SD)/mean(SD)			130.5 (15.6)/74.3 (10.6)	130.6 (15.3)/74.3 (10.4)
Medical history – n (%)		Hypertension, n (%)	96%	95%
		Diabetes mellitus, n (%)	44%	43%
		Atrial fibrillation at screening ECG, n (%)	32%	33%
		Hospitalization for HF within 9 months	38%	39%
Medications	*Prior to randomization*	ACEi or ARBs	87%	87%
	At randomization	Diuretics	94%	95%
		MRA	24%	27%*
		Beta blockers	79%	79%
		Calcium channel blockers	34%	34%

PARAGONHF

PARAGON-HF primary results
Recurrent event analysis of total HF hospitalisations and CV death*

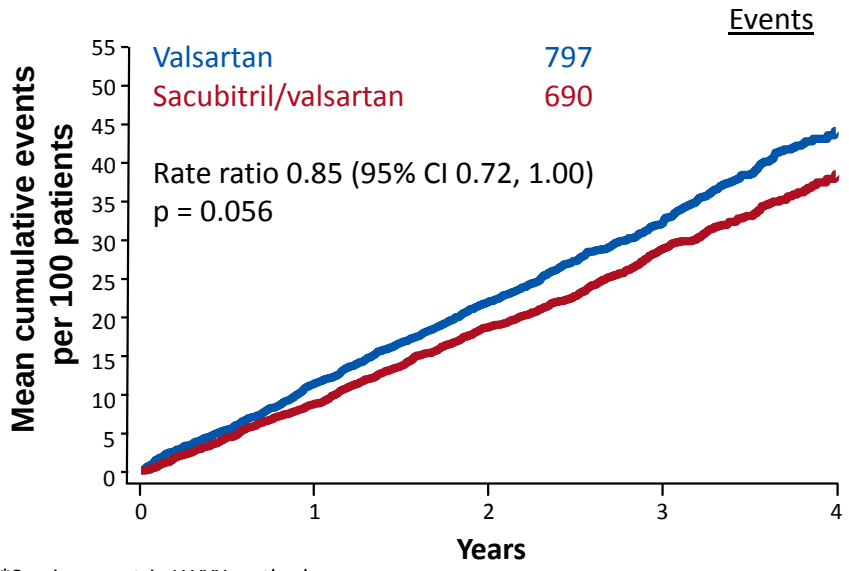


*Semiparametric LWYY method.

Solomon S et.al, NEJM 2019

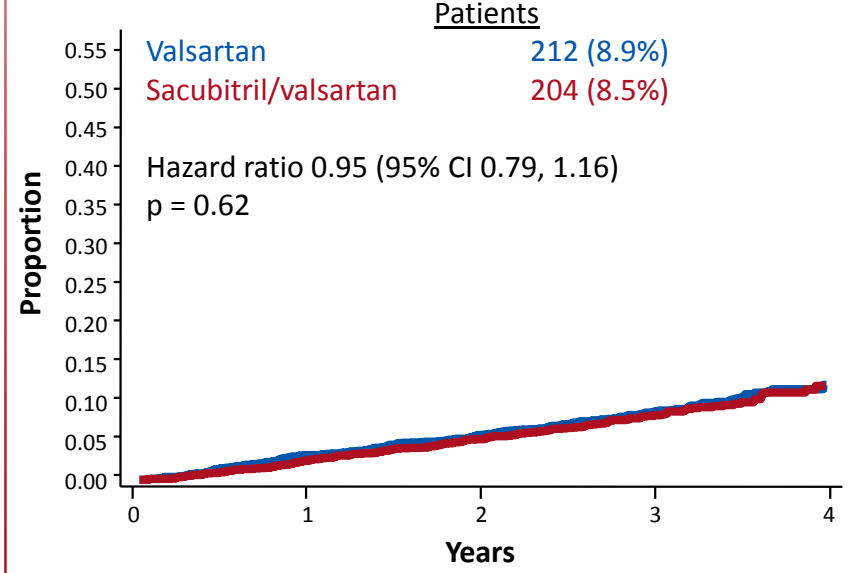
HF hospitalisations and CV death

HF hospitalisations*



*Semiparametric LWYY method

CV death*



Solomon S et.al, NEJM 2019

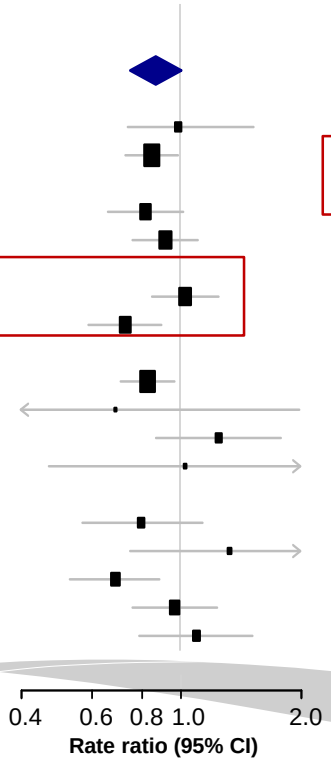
Secondary endpoints

	Sacubitril/valsartan N = 2316	Valsartan N = 2302	Effect size (95% CI)	Nominal P-value
NYHA functional classification at 8 months – Change from baseline (%) **Improved** **Unchanged** **Worsened**	 15.0% 76.3% 8.7%	 12.6% 77.9% 9.6%	OR for improvement 1.45 (1.13, 1.86)	0.004
KCCQ clinical summary score at 8 months – Change from baseline (SE)	-1.6 (0.4)	-2.6 (0.4)	LSM of difference = 1.03 (0.00, 2.1)	0.051
KCCQ responder (> than 5-point improvement)	33.0%	29.6%	OR = 1.30 (1.04, 1.61)	0.019
Worsening Renal Function **Composite of renal death, reaching ESRD, or ≥50% decline in eGFR relative to baseline**	1.4%	2.7%	HR = 0.50 (0.33, 0.77)	0.002
All-cause mortality (%)	14.2%	14.6%	HR = 0.97 (0.84, 1.13)	0.68

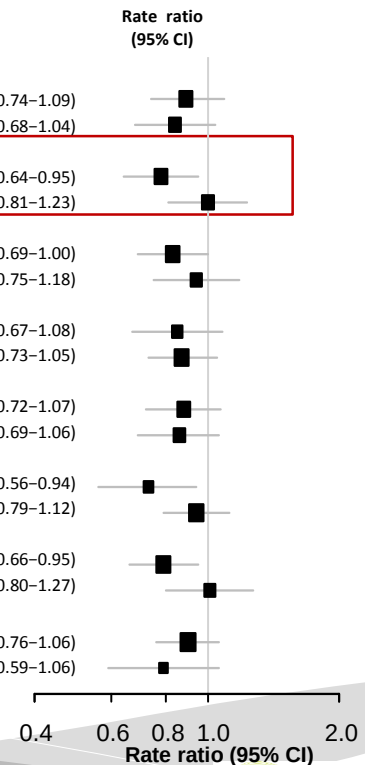
Solomon S et.al, NEJM 2019

Pre-specified subgroups for primary endpoint
Evidence for overall heterogeneity

Subgroup	No. of events /patients	Rate ratio (95% CI)
Overall	**1903/4796**	**0.87 (0.75–1.01)**
Age (years)		
Less than 65 years	276/825	0.99 (0.64–1.53)
65 years or older	1627/3971	0.85 (0.73–0.99)
Age (years)		
Less than 75 years	938/2597	0.82 (0.66–1.02)
75 years or older	965/2199	0.92 (0.76–1.11)
Sex*		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)
Race		
Caucasian	1542/3907	0.83 (0.71–0.97)
Black	89/102	0.69 (0.24–1.99)
Asian	237/607	1.25 (0.87–1.79)
Other	35/180	1.03 (0.47–2.28)
Region		
North America	478/559	0.80 (0.57–1.14)
Latin America	83/370	1.33 (0.75–2.36)
Western Europe	544/1390	0.69 (0.53–0.89)
Central Europe	466/1715	0.97 (0.76–1.24)
Asia/Pacific	332/762	1.10 (0.79–1.52)



Subgroup	No. of events /patients	Rate ratio (95% CI)
Diabetic		
Yes	1041/2069	0.89 (0.74–1.09)
No	862/2727	0.84 (0.68–1.04)
LVEF*		
at or below median (57%)	1048/2495	0.78 (0.64–0.95)
above median (57%)	855/2301	1.00 (0.81–1.23)
History of AF		
Yes	1140/2521	0.83 (0.69–1.00)
No	763/2275	0.94 (0.75–1.18)
Screening NT−proBNP		
at or below median (911 pg/mL)	708/2379	0.85 (0.67–1.08)
above median (911 pg/mL)	1183/2378	0.87 (0.73–1.05)
Screening SBP		
at or below median (137 mmHg)	984/2450	0.88 (0.72–1.07)
above median (137 mmHg)	919/2344	0.86 (0.69–1.06)
MRA use		
Yes	543/1238	0.73 (0.56–0.94)
No	1360/3558	0.94 (0.79–1.12)
Baseline eGFR		
<60 mL/min/1.73m²	1115/2341	0.79 (0.66–0.95)
>=60 mL/min/1.73m²	787/2454	1.01 (0.80–1.27)
NYHA class		
I/II	1402/3843	0.90 (0.76–1.06)
III/IV	499/951	0.79 (0.59–1.06)



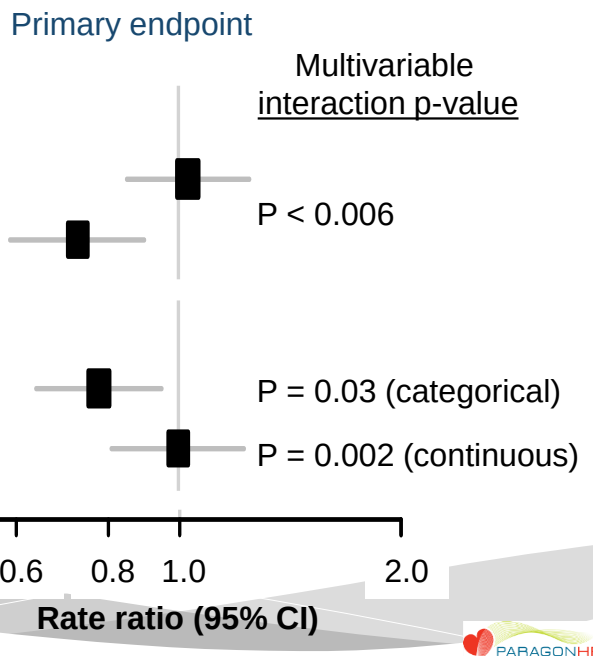
Multivariate interaction p < 0.05.

PARAGONHF

Significant Heterogeneity in Multivariate Analysis by Ejection Fraction and Sex

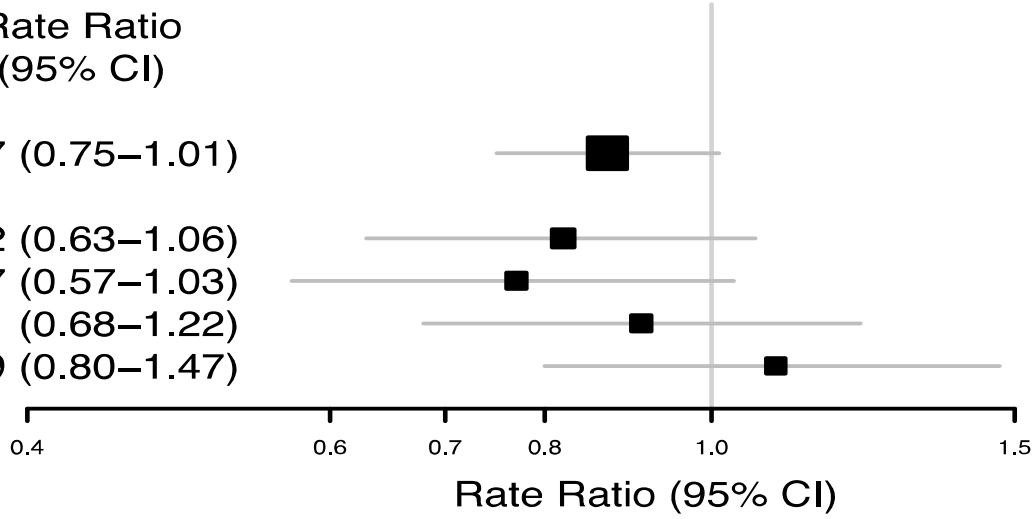
Only interactions for sex and ejection fraction remained nominally significant

Subgroup	No. of events/ patients	Rate ratio (95% CI)
Sex		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)
LVEF		
at or below median (57%)	1048/2495	0.78 (0.64–0.95)
above median (57%)	855/2301	1.00 (0.81–1.23)



Treatment effect by ejection fraction quartiles

Subgroup	No. of Events/Patients	Rate Ratio (95% CI)
Overall	1903/4796	0.87 (0.75–1.01)
EF		
<=50	512/1208	0.82 (0.63–1.06)
>50–57	536/1287	0.77 (0.57–1.03)
>57–63	467/1202	0.91 (0.68–1.22)
>63	388/1099	1.09 (0.80–1.47)



Safety endpoints

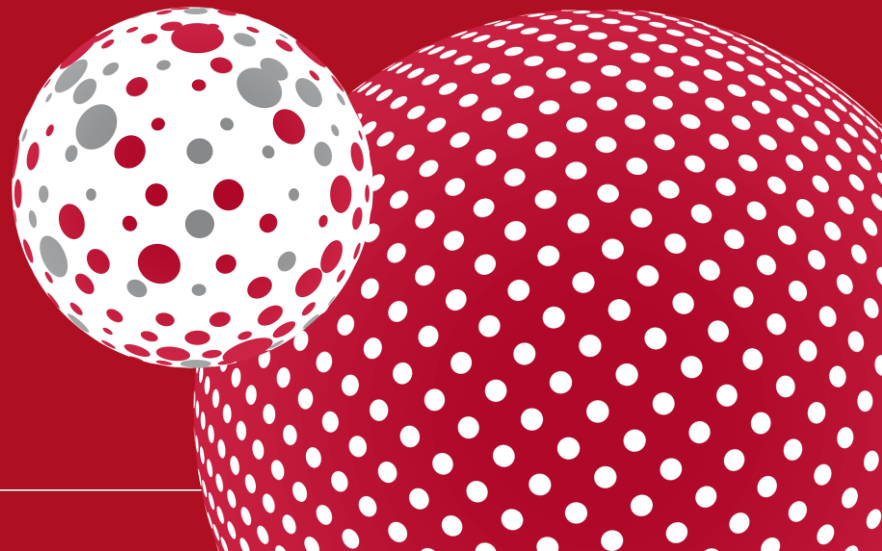
Adverse event		Sacubitril/Valsartan (N = 2407)	Valsartan (N = 2389)	P-value
Hypotension with SBP < 100 mm Hg		15.8%	10.8%	<0.0001
Elevated serum creatinine	≥ 2.0 mg/dl	10.8%	13.7%	0.002
	≥ 2.5 mg/dl	4%	4.6%	0.36
	≥ 3.0 mg/dl	1.6%	1.7%	0.79
Elevated serum potassium	> 5.5 mmol/liter	13.2%	15.3%	0.05
	> 6.0 mmol/liter	3.1%	4.3%	0.04
Angioedema*		0.6%	0.2%	0.02

**Adjudicated*

PARAGONHF

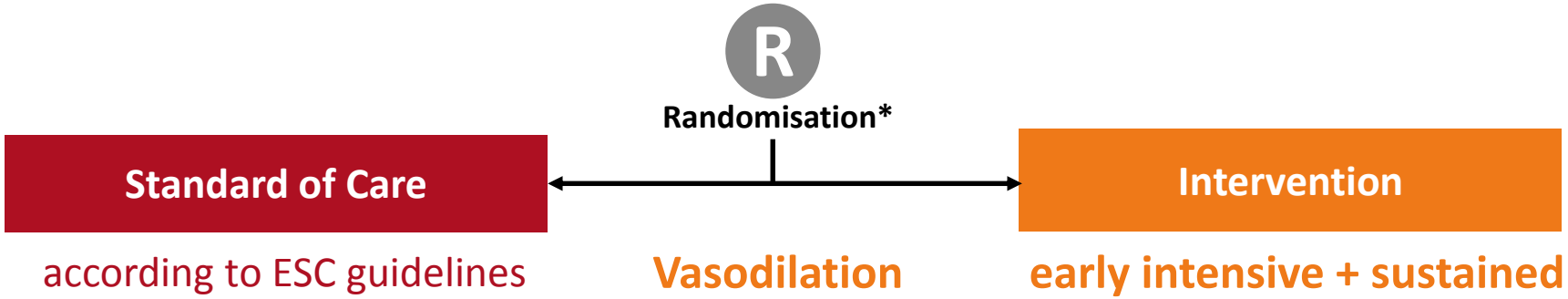
ACUTE HEART FAILURE

GALACTIC



Methods: Design

GALACTIC
novel therapy concept in acute heart failure

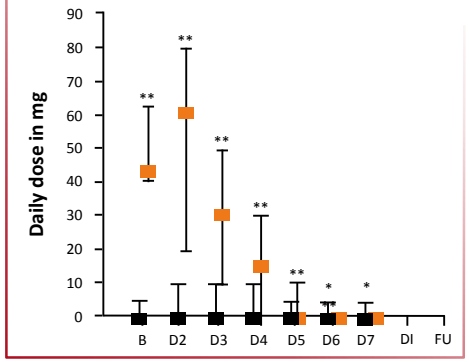


- All other therapies including loop diuretic dose and duration, beta-blockers, aldosterone antagonists, cardiac devices, and follow-up care were according to ESC Guidelines + at the discretion of the treating physician in both groups

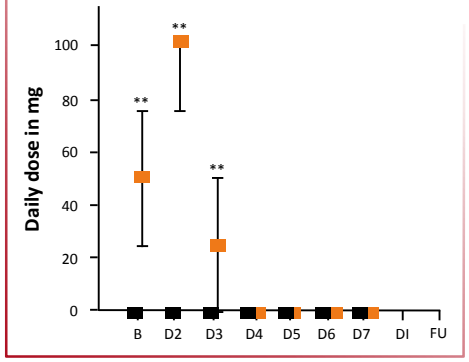
*stratified for site and BNP/NT-proBNP

Results: Intervention

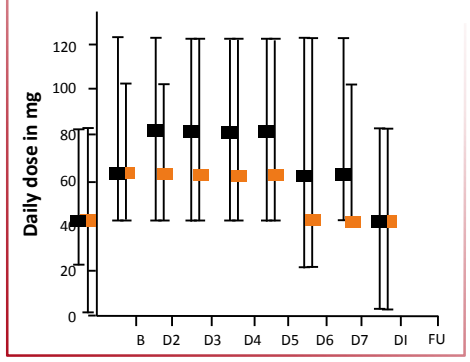
A: Nitroglycerin



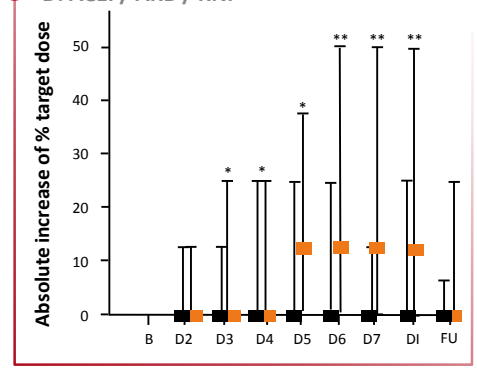
B:Hydralazine



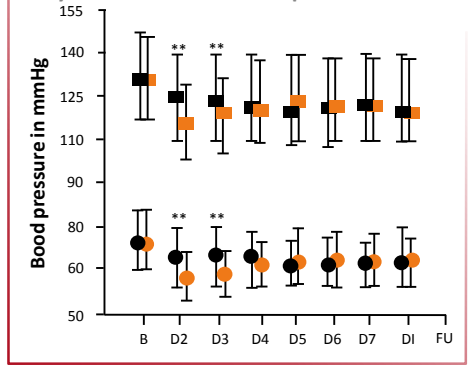
C:Furosemide equivalent dose



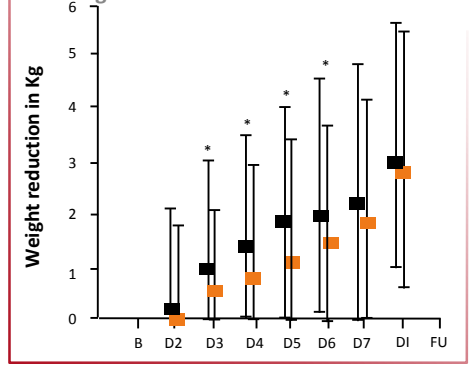
D: ACEI / ARB / RNI



E:Systolic and diastolic blood pressure

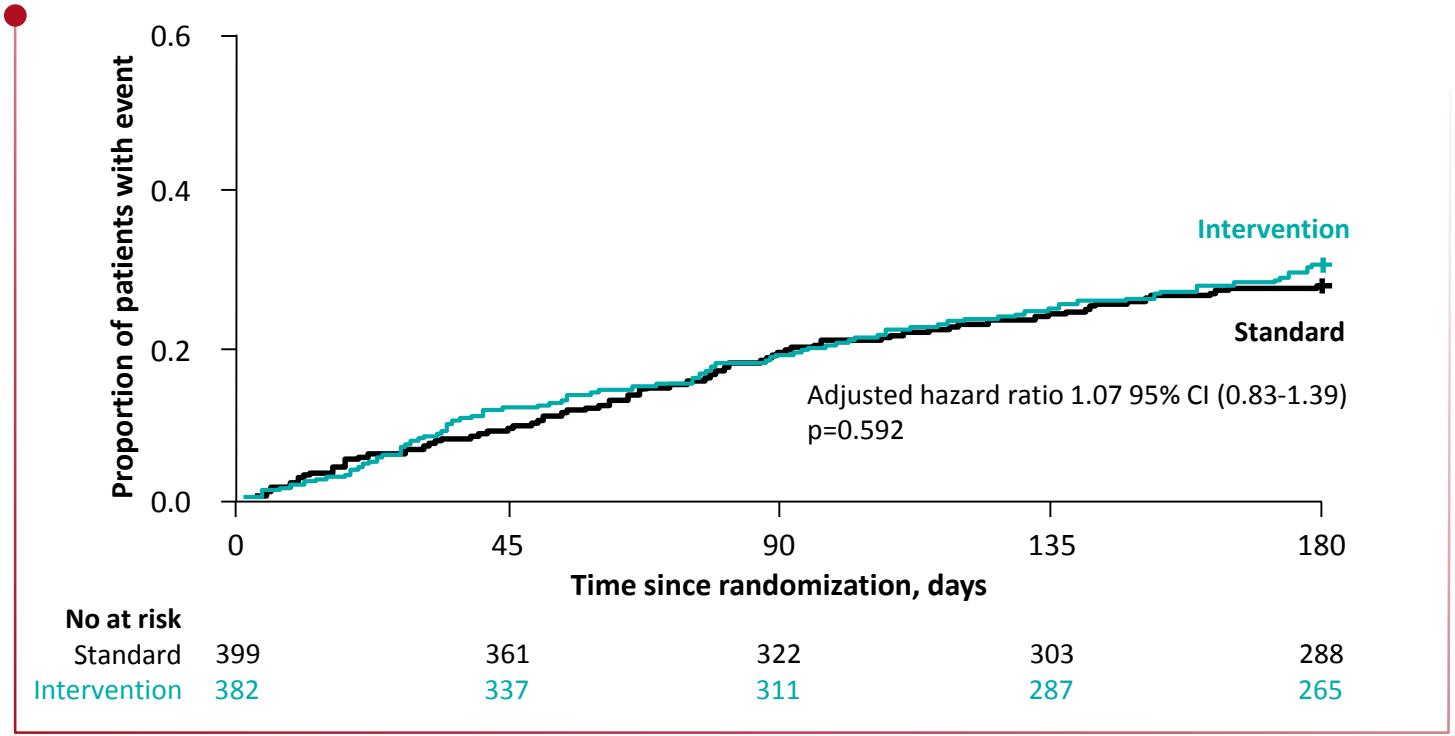


F:Weight reduction



Mueller CE, Hot Line Session 3, FP 3178

Results: Primary Endpoint (Death or AHF)



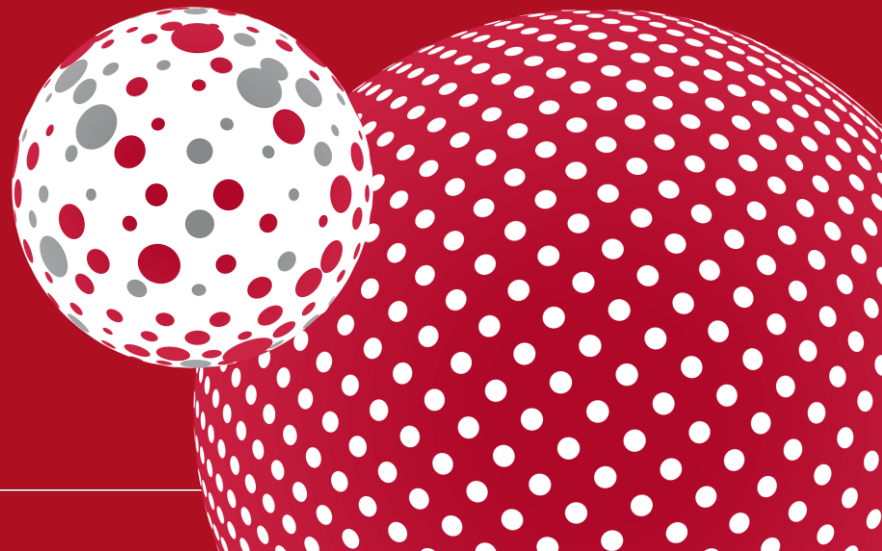
Mueller CE, Hot Line Session 3, FP 3178

PREVENTIVE CARDIOLOGY

BALANCING THROMBOSIS AND BLEEDING IN SECONDARY PREVENTION

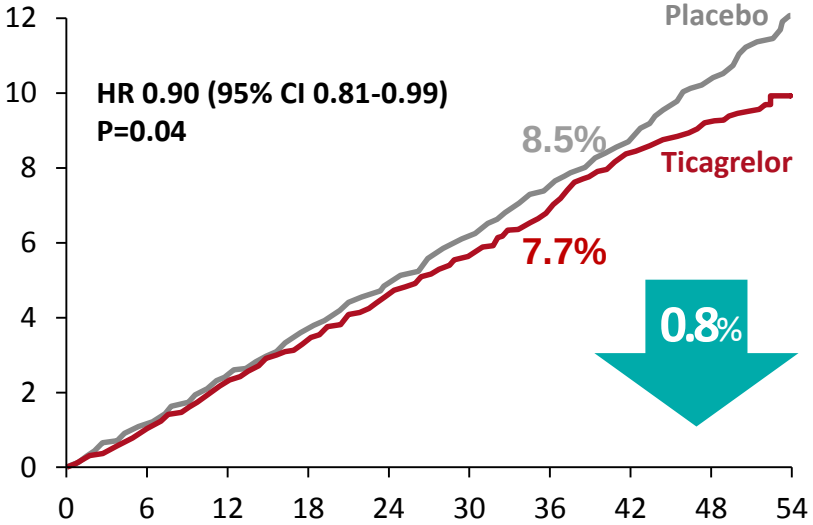
THEMIS and THEMIS-PCI

Tools for the clinician

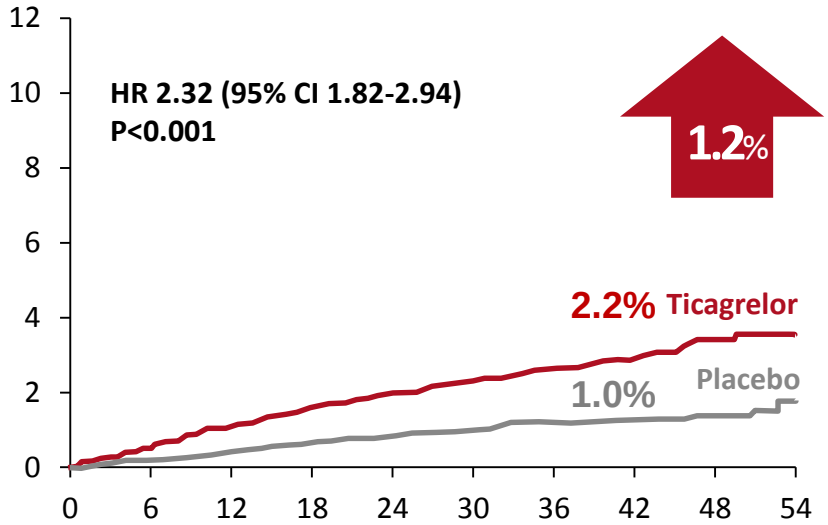


THEMIS

Cardiovascular death/stroke/MI



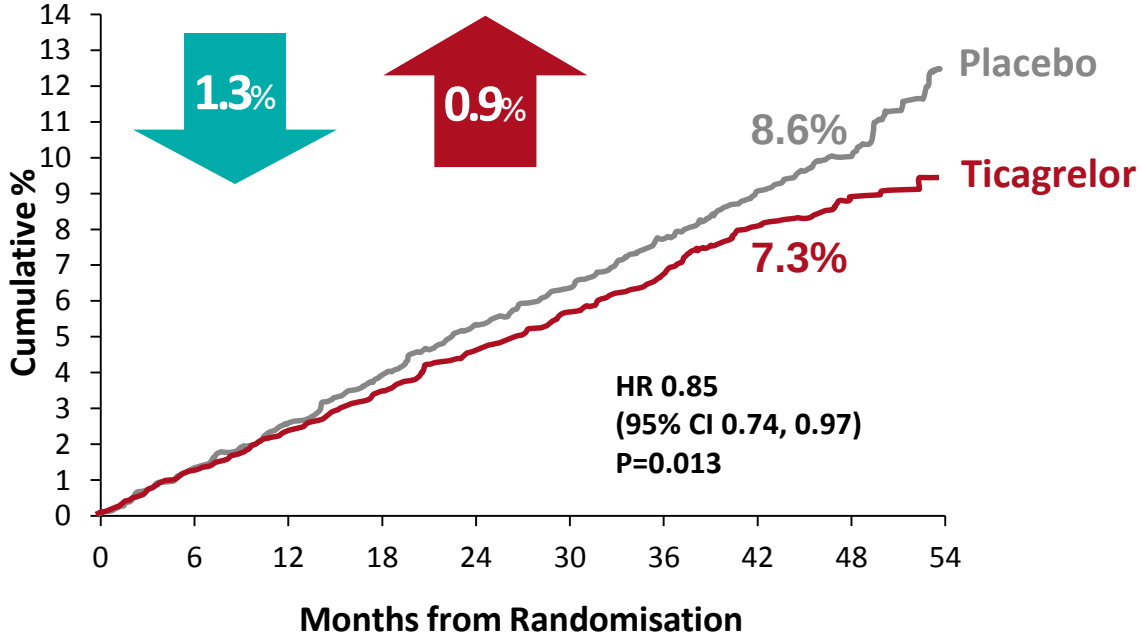
Major bleeding



Steg PG, *et al. NEJM.* 2019

THEMIS-PCI – Prespecified subgroup analysis

- Patients with a history of PCI – N 11,154



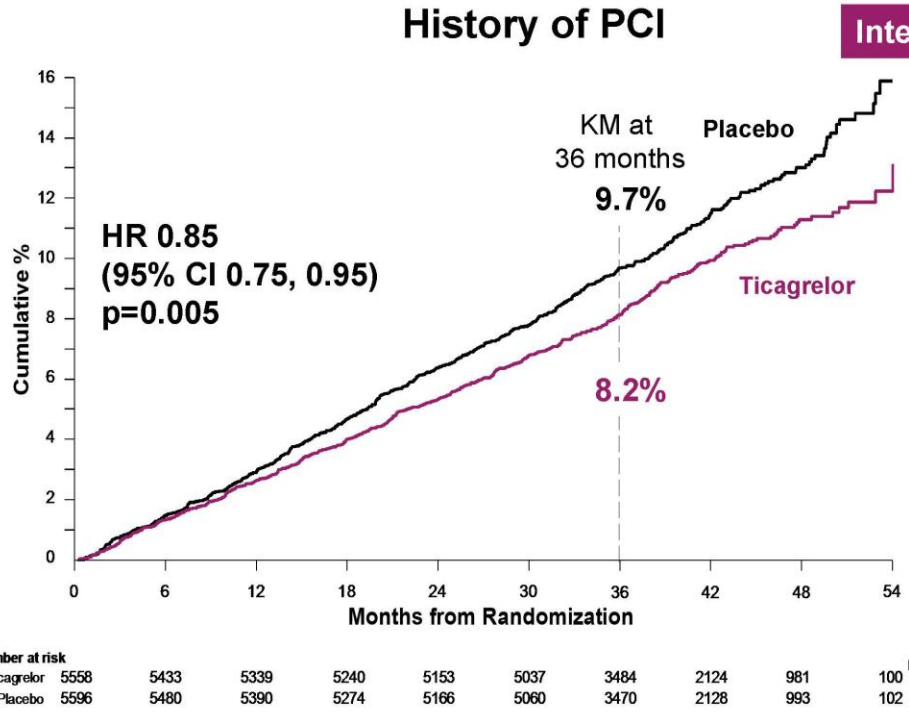
Conclusion

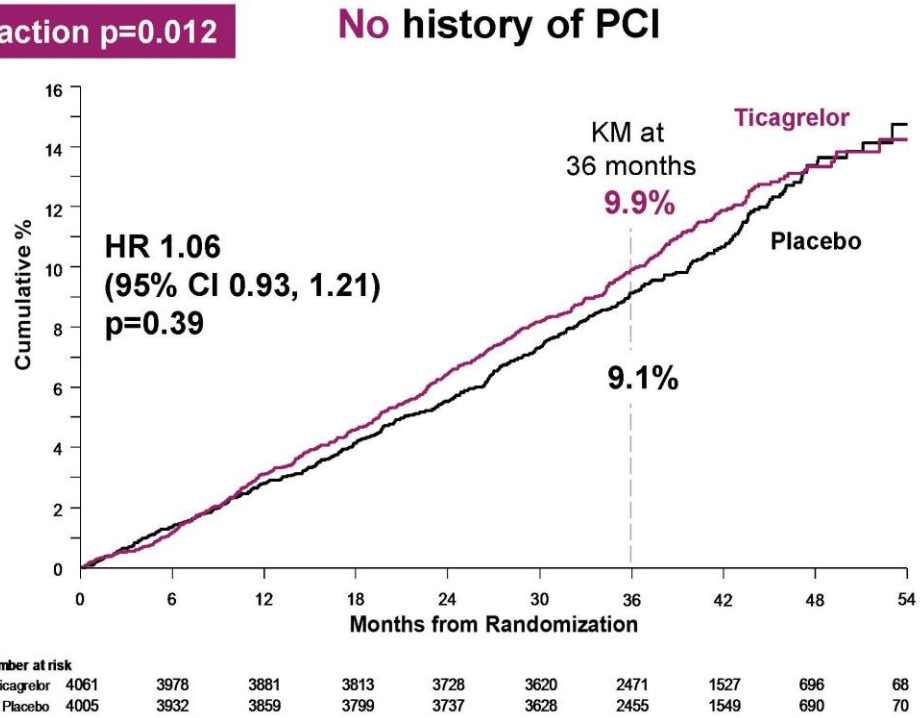
- **In patients with diabetes and CAD the bleeding risk of long-term treatment with ticagrelor and aspirin outweighs the benefit**
- **There may be subgroups where the treatment is beneficial**

Bhatt DL, *et al. The Lancet.* 2019

Net Clinical Benefit

All cause death, MI, stroke, fatal bleed or ICH (ITT)*

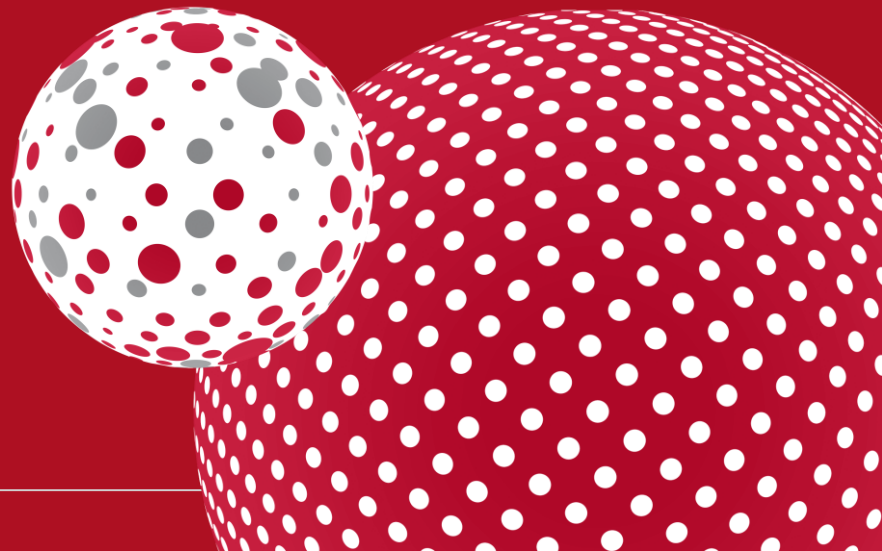




*Prespecified definition of net clinical benefit.

CI=confidence interval; HR=hazard ratio; ICH=intracranial hemorrhage; ITT=intention to treat; MI=myocardial infarction; PCI=percutaneous coronary intervention

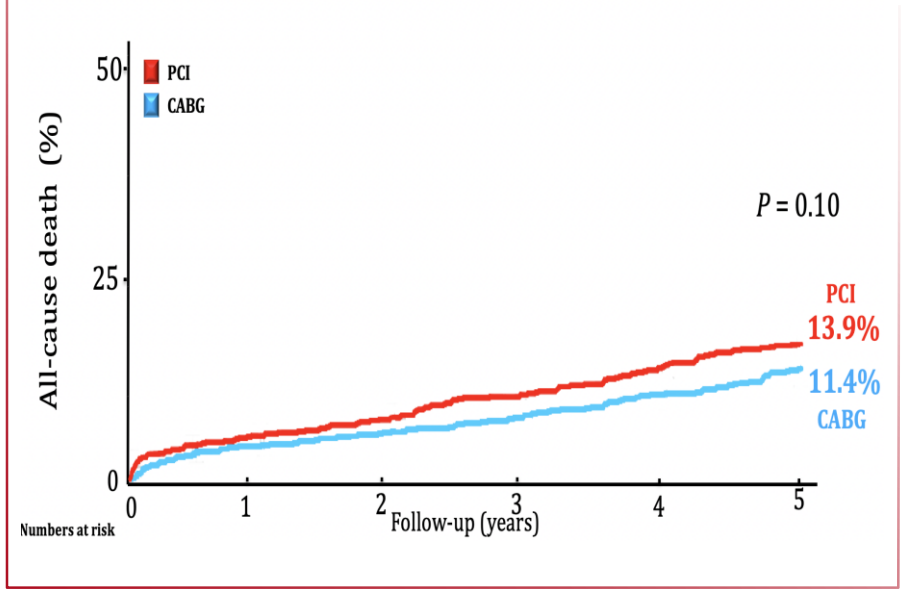
LONG-TERM OUTCOMES



SYNTAXES: background

- **The SYNTAX trial compared stenting with the first generation DES Taxus and CABG in patients with multivessel coronary artery disease and left main stem stenosis**
- **The SYNTAX Score defined three groups of anatomic complexity with different outcomes**
- **The long-term outcome (>5 year) of stent and bypass surgery is of interest**

5 year Mortality



Mohr FW, et al. The Lancet. 2013.

SYNTAXES 10 yr all cause death

62 EU Sites

1 800 patients

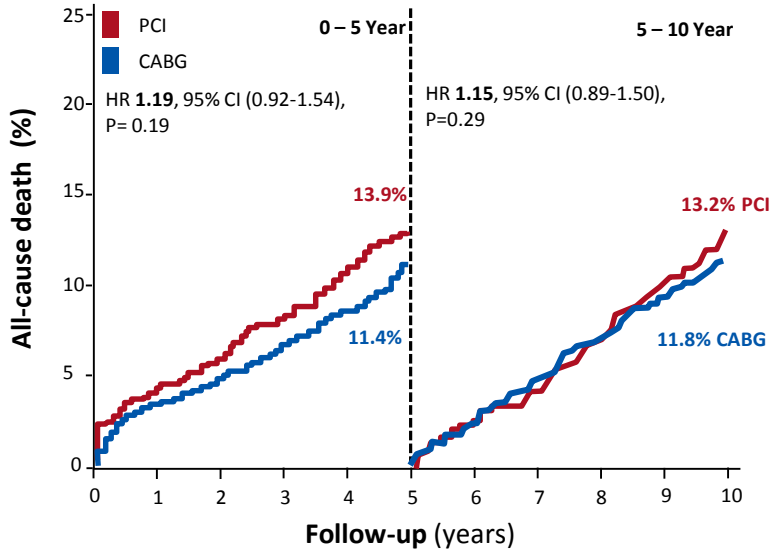
23 US Sites

de novo Three-Vessel and/or Left Main Coronary Artery disease

PCI		CABG
N=903 (100%)	Randomisation	N=897 (100%)
N=871 (96.5%)	5-Year Follow-up	N=805 (89.7%)
N=841 (**93.4%**)	10-Year Follow-up	N=848 (**94.7%**)

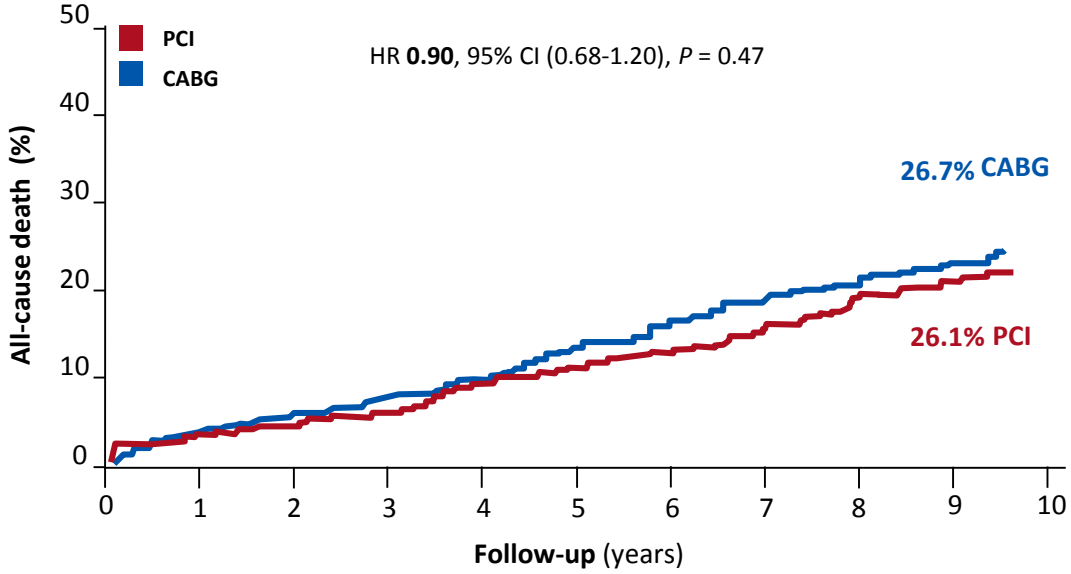
Overall completeness of follow-up: 94%

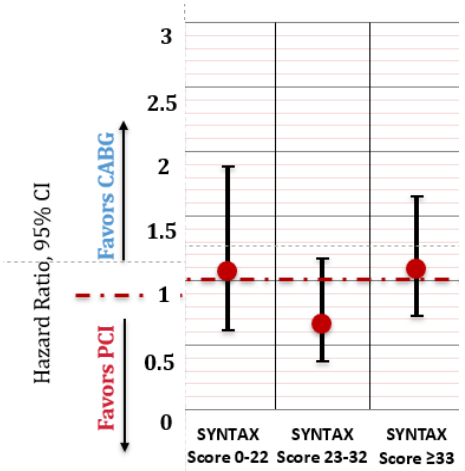
Mortality



Thuijs DJFM, et al. The Lancet. 2019.

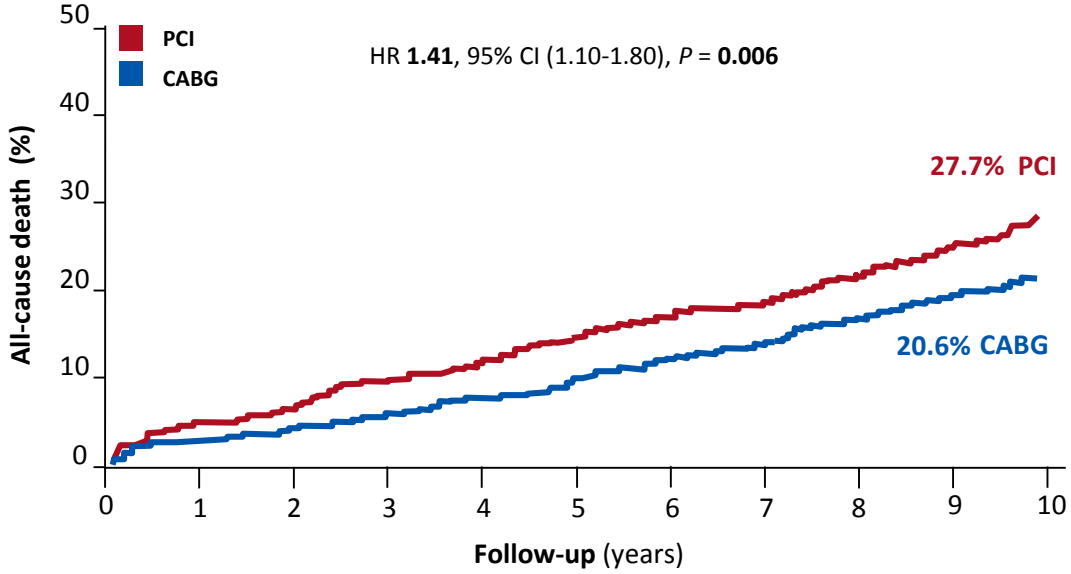
SYNTAX: Left main

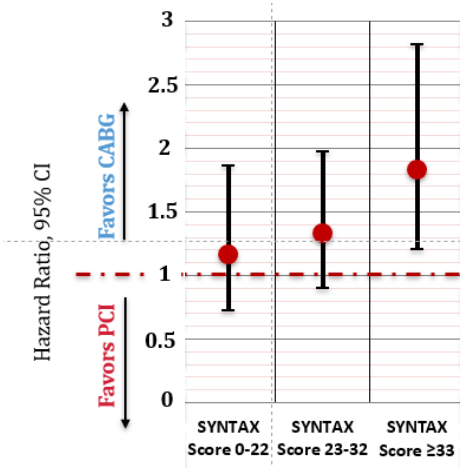




Thuijs DJFM, et al. The Lancet. 2019.

SYNTAXES: Three-vessel disease

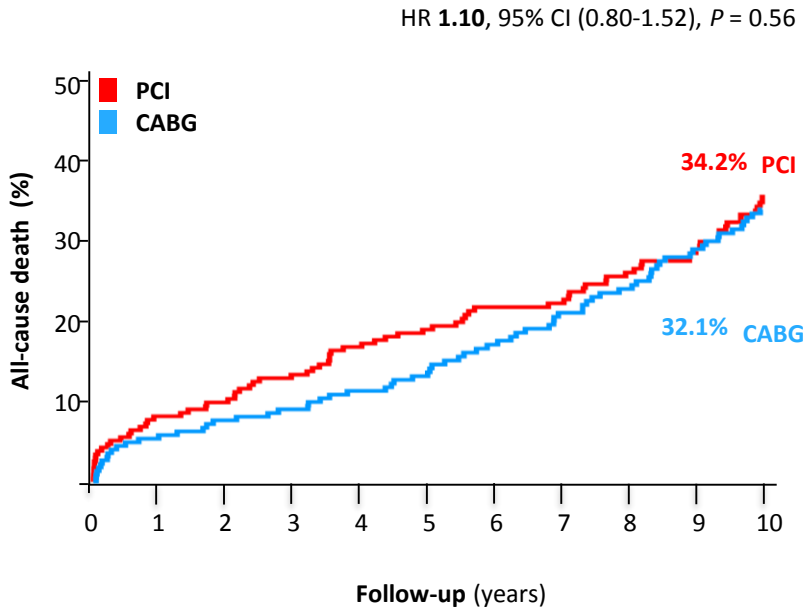




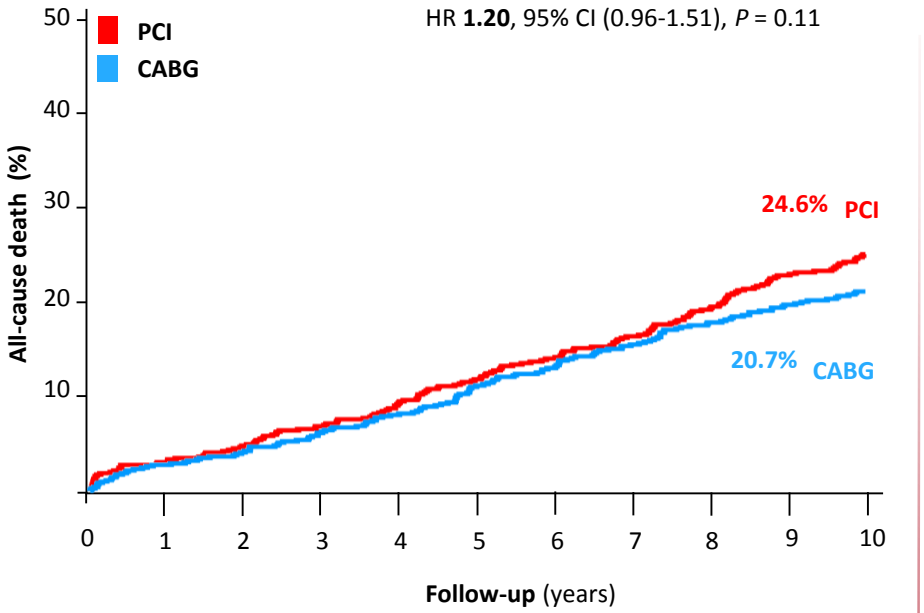
Thuijs DJFM, et al. The Lancet. 2019.

SYNTAXES: Diabetes

DIABETES



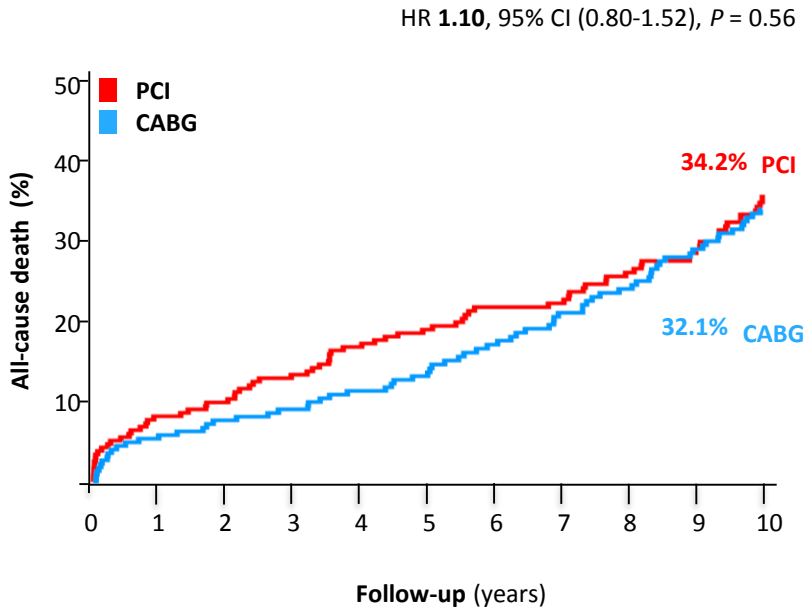
NO DIABETES



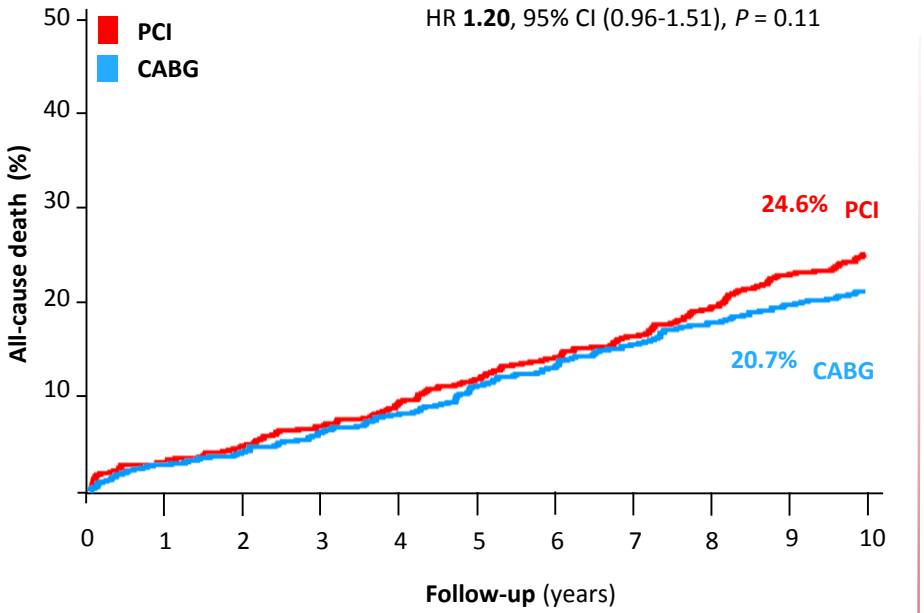
Thuijs DJFM, et al. The Lancet. 2019.

SYNTAXES: Diabetes

DIABETES

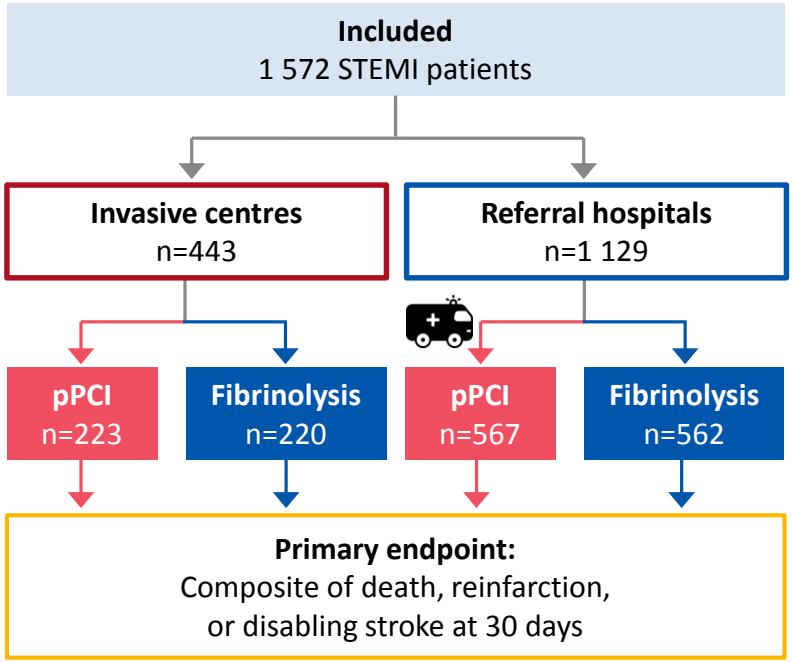


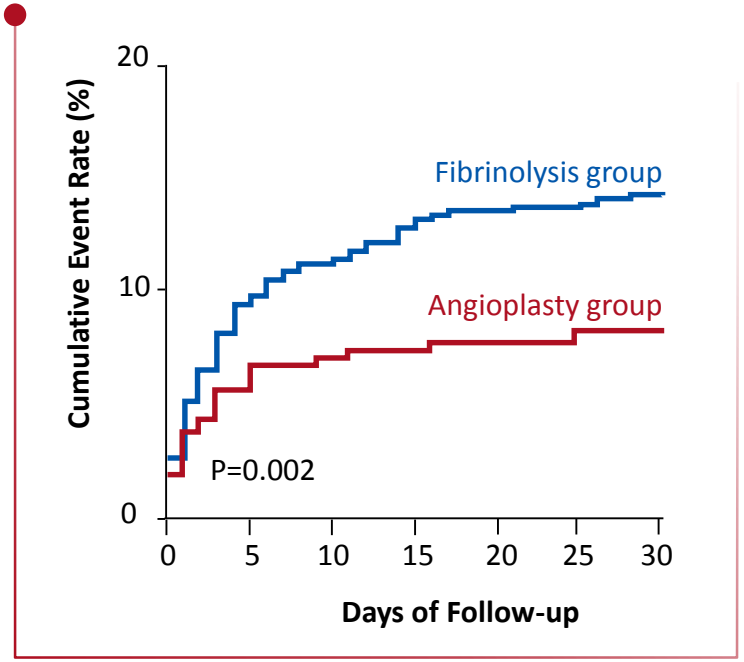
NO DIABETES



Thuijs DJFM, et al. The Lancet. 2019.

DANAMI-2 16 Years: Background

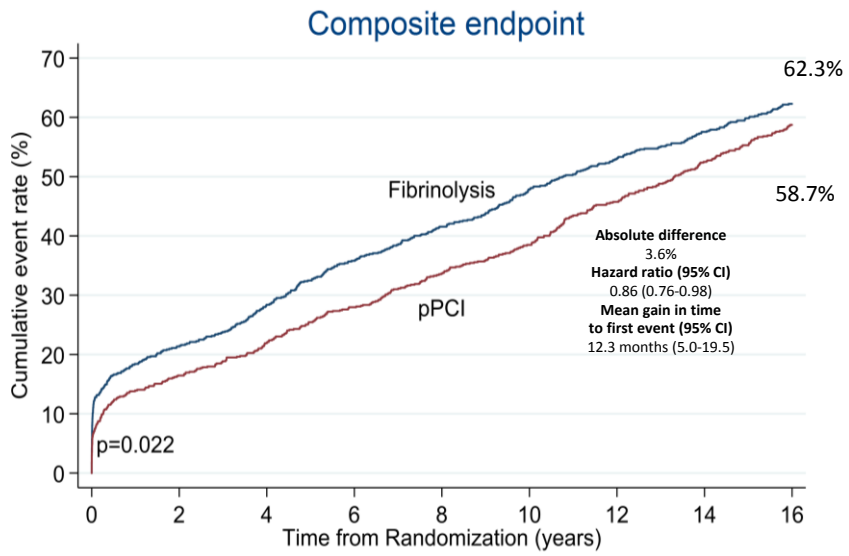




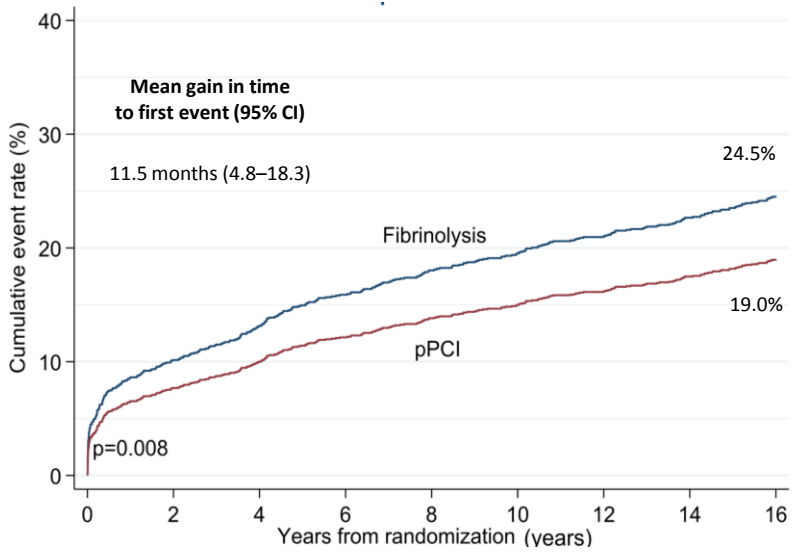
Thrane PG, et al. EHJ. 2019.

DANAMI-2: 16 years later

COMPOSITE ENDPOINT



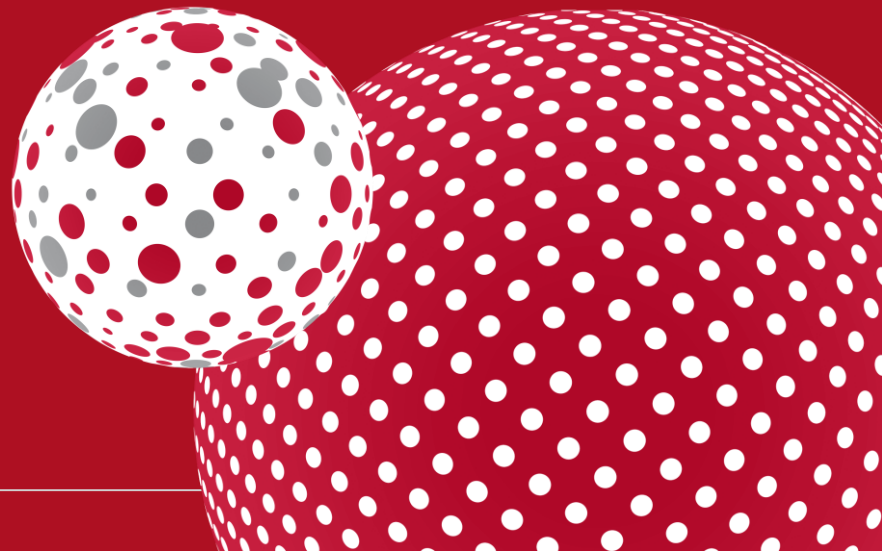
REINFARCTION



Thrane PG, et al. EHJ. 2019

INTERVENTION FOR STEMI

Multivessel strategy



COMPLETE: Background

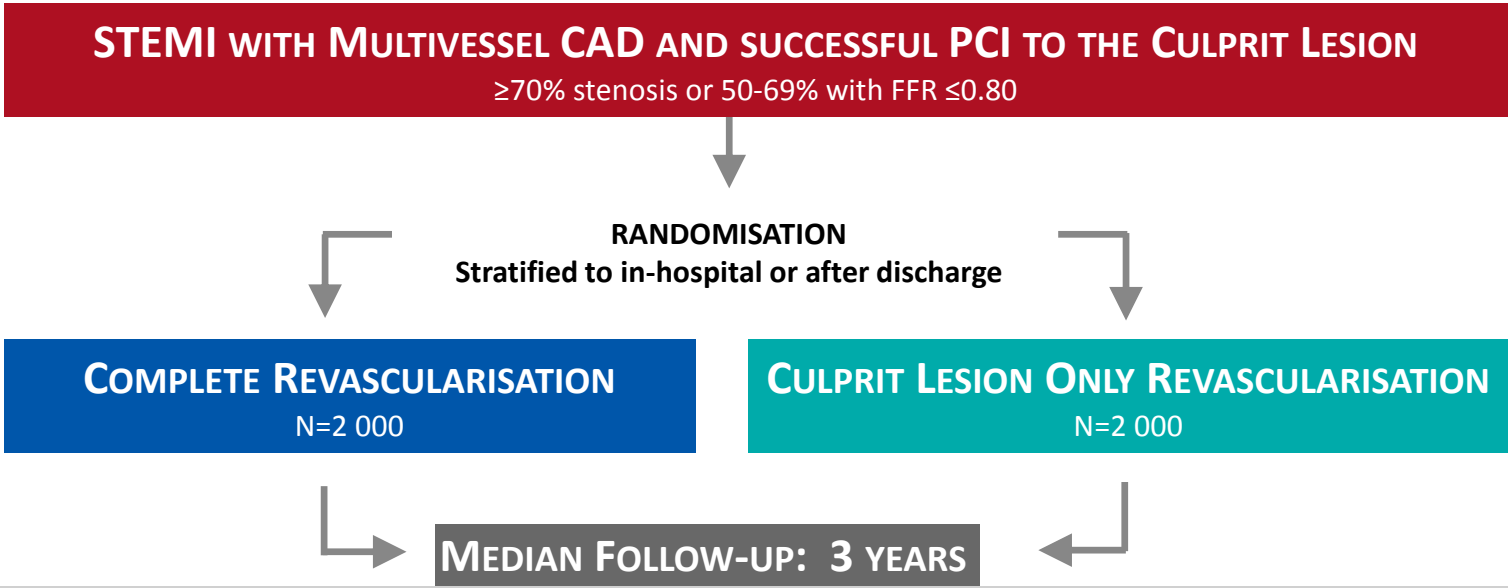
- **Patients undergoing primary PCI of the culprit lesion for STEMI are often found to have multivessel CAD, with 1 or more angiographically significant non-culprit lesions.**

- **There is uncertainty about how best to manage these non-culprit lesions**
  - Routinely revascularise them with PCI?
  - Manage them conservatively with guideline-directed medical therapy alone?

- **While prior RCTs have shown non-culprit lesion PCI reduces revascularisation, none were powered to detect moderate reductions in hard clinical outcomes such as CV death or MI.**

Mehta SR, et al. NEJM. 2019.

COMPLETE Trial design



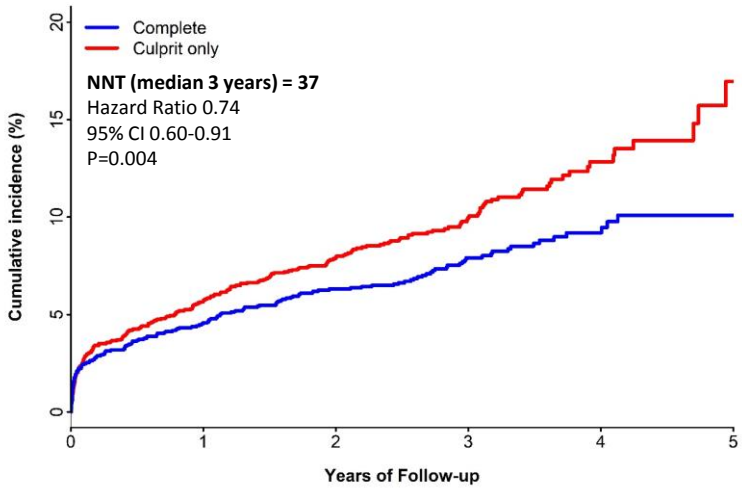
CO-PRIMARY OUTCOMES: 1. Composite of CV death or new MI
2. Composite of CV death, new MI or ischaemia-driven revascularisation

KEY SECONDARY OUTCOME: CV death, new MI, IDR, unstable angina, NYHA class IV heart failure

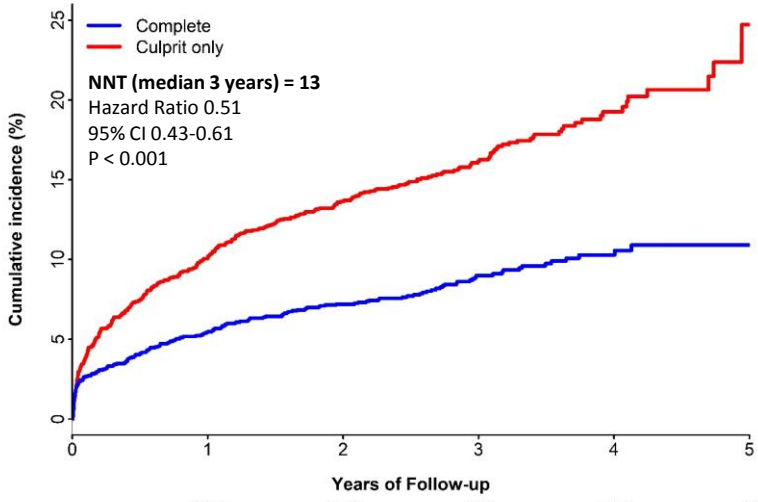
Mehta SR, et al. Am Heart J. 2019.

COMPLETE: Main results

First Co-Primary Outcome: CV Death or New MI



2nd Co-Primary Outcome: CV Death, MI, or IDR

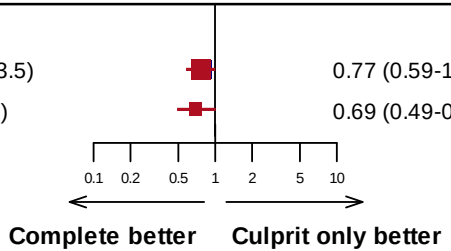


Mehta SR, et al. NEJM. 2019.

COMPLETE: Timing of non-culprit lesion PCI: During or after initial hospitalisation

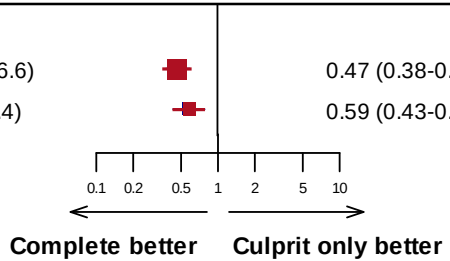
CV death or New MI

	Complete	Culprit Only	HR (95% CI)	Interaction P
	no. of events/total no. (%/yr)			
Intent to perform non-culprit lesion PCI				0.62
During initial hospitalization	101/1353 (2.7)	130/1349 (3.5)	0.77 (0.59-1.00)	
After initial hospitalization	57/663 (2.7)	83/676 (3.9)	0.69 (0.49-0.97)	



CV death, New MI, or IDR

	Complete	Culprit Only	HR (95% CI)	Interaction P
	no. of events/total no. (%/yr)			
Intent to perform non-culprit lesion PCI				0.27
During initial hospitalization	113/1353 (3.0)	227/1349 (6.6)	0.47 (0.38-0.59)	
After initial hospitalization	66/663 (3.1)	112/676 (5.4)	0.59 (0.43-0.79)	



Median Time to study NCL PCI in Complete Group

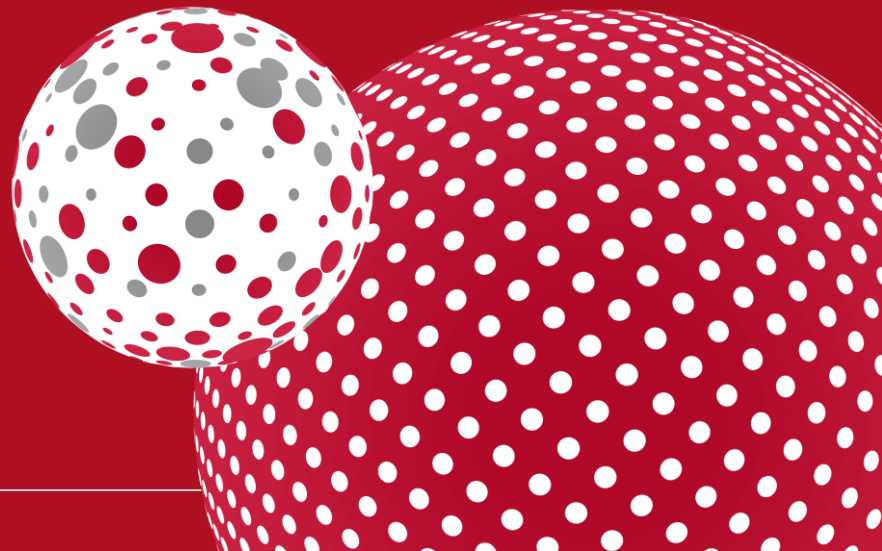
During initial hospitalisation: 1 day (IQR 1-3)

After Hospital discharge: 23 days (IQR 12.5-33.5)

Mehta SR, et al. NEJM. 2019.

ANTIPLATELET THERAPY

ISAR-REACT 5



Antiplatelet therapy for ACS in the ESC Guidelines

Recommendations on $P2Y_{12}$ inhibitor selection	Class	Level
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin[a] is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contraindications	I	B
In patients with ACS undergoing PCI, prasugrel (60 mg loading dose, 10 mg daily dose) on top of aspirin is recommended for $P2Y_{12}$ inhibitor-naive patients with NSTE-ACS or initially conservatively managed STEMI if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization[a] unless there is a high risk of life-threatening bleeding or other contraindications	I	B

[a] Contraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds. Contraindications for prasugrel: previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack or ongoing bleeds. prasugrel is not recommended for patients ≥75 years of age or with a body weight <60 kg.

2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *EHJ.* https://doi.org/10.1093/eurheartj/ehx419.

ISAR-REACT 5

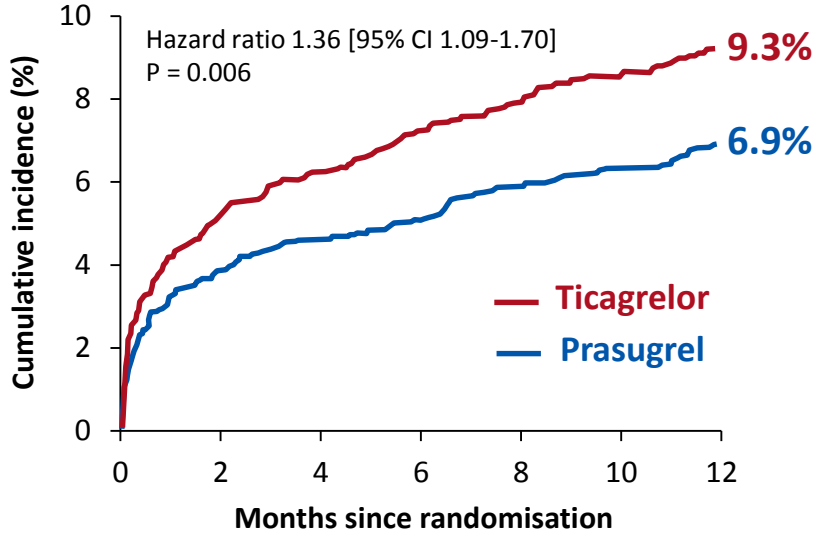
ISAR-REACT 5

4,018 pts with invasively managed ACS
(STEMI 41%, NSTEMI 46%, UA 13%)

Patient-level randomisation
Open label

Prasugrel N=2,006	Ticagrelor N=2,012
Loading dose after coronary angiography in NSTE-ACS and at randomisation in STEMI with dose reduction as per IFU	Loading dose at randomisation irrespective of clinical presentation
CONTROL ARM	INVESTIGATIONAL ARM

DEATH, MI OR STROKE AT 12 MONTHS (PRIMARY ENDPOINT, ITT)



Schüpke S, *et al. NEJM*. 2019

ISAR-REACT 5

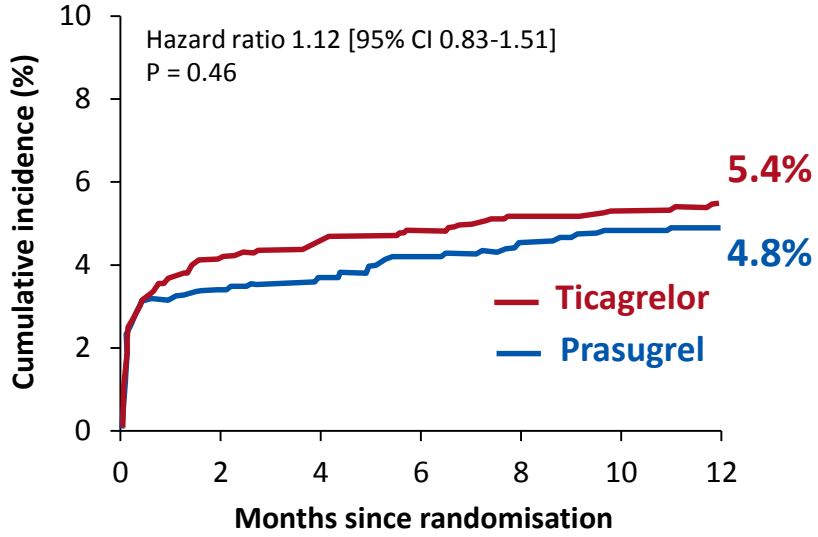
ISAR-REACT 5

4,018 pts with invasively managed ACS
(STEMI 41%, NSTEMI 46%, UA 13%)

Patient-level randomisation
Open label

Prasugrel N=2,006	Ticagrelor N=2,012
Loading dose after coronary angiography in NSTE-ACS and at randomisation in STEMI with dose reduction as per IFU	Loading dose at randomisation irrespective of clinical presentation
CONTROL ARM	INVESTIGATIONAL ARM

BARC TYPE 3, 4, 5 BLEEDING (SAFETY ENDPOINT, mITT)



Schüpke S, *et al. NEJM*. 2019

CLARIFY a prospective observational Longitudinal Registry of patients with stable coronary artery disease

32,703 patients
45 countries

2898 physicians
to consecutively enrol 10-15 patients

Enrolment: 2009 - 2010
Database locked: 2016

Yearly visit
Median follow-up: 5.0 years

Medical care at the discretion of each physician

Inclusion criteria for chronic coronary syndromes, non-mutually exclusive:

- **prior myocardial infarction >3 months**
- **prior revascularisation >3 months**
- **proven symptomatic myocardial ischaemia**
- **angiographic coronary stenosis >50%**

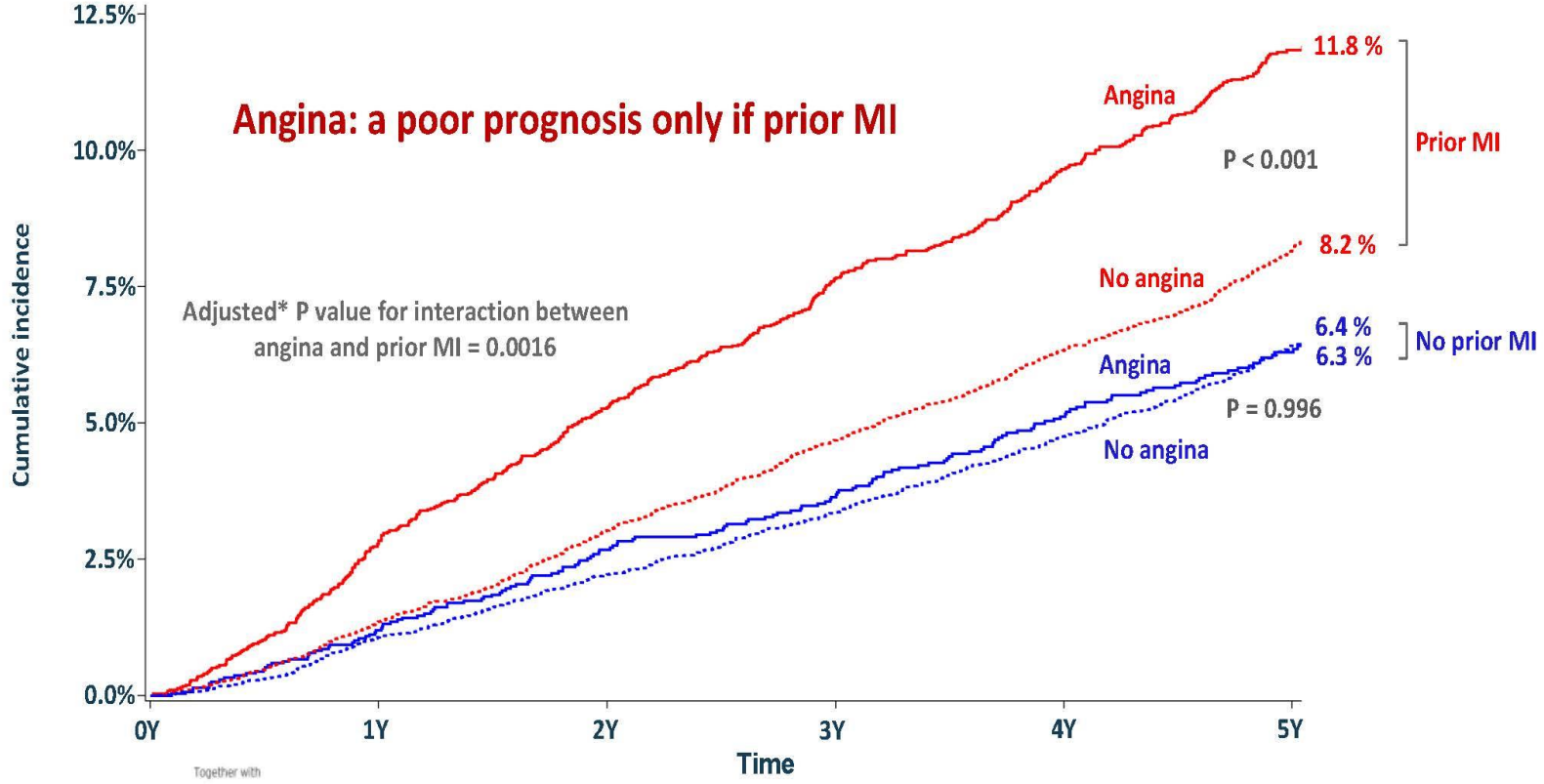
Exclusion criteria:

- conditions interfering with life expectancy
- advanced heart failure

E. Sorbets et al, Clinical Cardiology 2017;40:797

CLARIFY

According to angina and prior MI
5-year incidence of CV death or non-fatal MI



* Multivariable analysis (Cox proportional hazards model) including: age, gender, diabetes, smoking status, history of hypertension, MI, PCI, CABG, hospitalisation for heart failure, asthma/COPD, atrial fibrillation/flutter, prior stroke, cerebrovascular disease, peripheral artery disease, current angina, blood pressure <140/90 mm Hg, geographical zones