Stroke Prevention Medications:

Latest Research

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Disclosures

Relationships with commercial interests: None

Potential for conflict(s) of interest: None

Presentation Objectives:

By the end of this presentation you will be able to:

- Apply updated knowledge of stroke prevention medications to your clinical practice
- Use best practice information to inform clinical decisions around management of stroke risk factors

Vascular risk factors [% incidence]

Hypertension	50-60%
Diabetes mellitus	20-25%
Dyslipidemia	20-25%
Atrial fibrillation	10-40%

Others: CAD,Smoking, COPD, Lack of Exercise, PVD, VHD, CHF, Obesity, OAC, Alcohol excess, ICH, Previous CAD/TIA/CVA

Primary Stroke Prevention

Lifestyle, lifestyle, lifestyle

Healthy Diet, Healthy exercise, Healthy Sleep, Avoid dumb things

Hypertension

Hypertension

1. Dec’ing BP more important than specific drug, though ACE inhibitor or a diuretic preferred.

2. Target: 140/90;130/90 if DM, VD, or CV risk >10%|20%/ Consider ”Risk Enhancers”

3. If recurrent neurologic symptoms from a stenotic artery at a lowered BP, maintain BP > that threshold

Risk Enhancers

Family hx of early CVD (men <55, women <65)
Metabolic syndrome
Chronic kidney disease
Chronic inflammation (e.g., RA, psoriasis, HIV)
Pre-eclampsia or early menopause
Ethnicity (e.g. South Asian)
hs-CRP ≥2.0mg/dL
Lipoprotein (a) ≥ 125 nmol/L
Apolipoprotein B ≥2.5 mmol/dL

Diabetes Mellitus

Diabetes Mellitus

No ASA*

* Unless High Risk from other causes

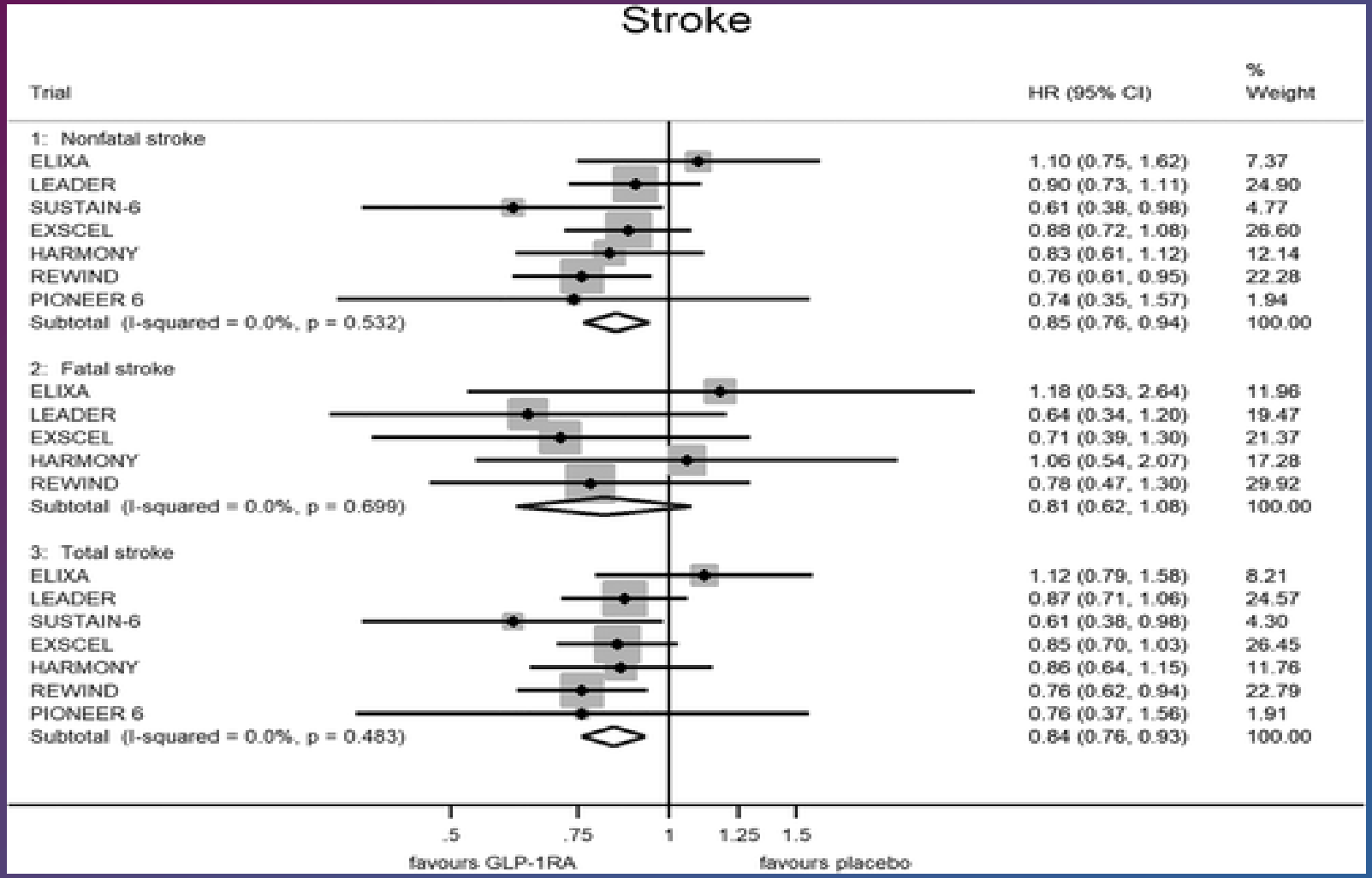
Diabetes Mellitus

SGLT-2 Inhibitors [CREDENCE] 30% dec in CV death, MI, CVA

GLP- agonists- REWIND. 9901Pts, CVD or CVF 5.4 yrs 25% dec. [3.2 vs 4.1 ie 1% absolute]. [Gluc- dec ut 54% & BP ut 14%]

[NB- 1- Dec sulfonylurea 50%, basal insulin 20%; stop DPP4 if GLP-a
2- DAPA-HF]

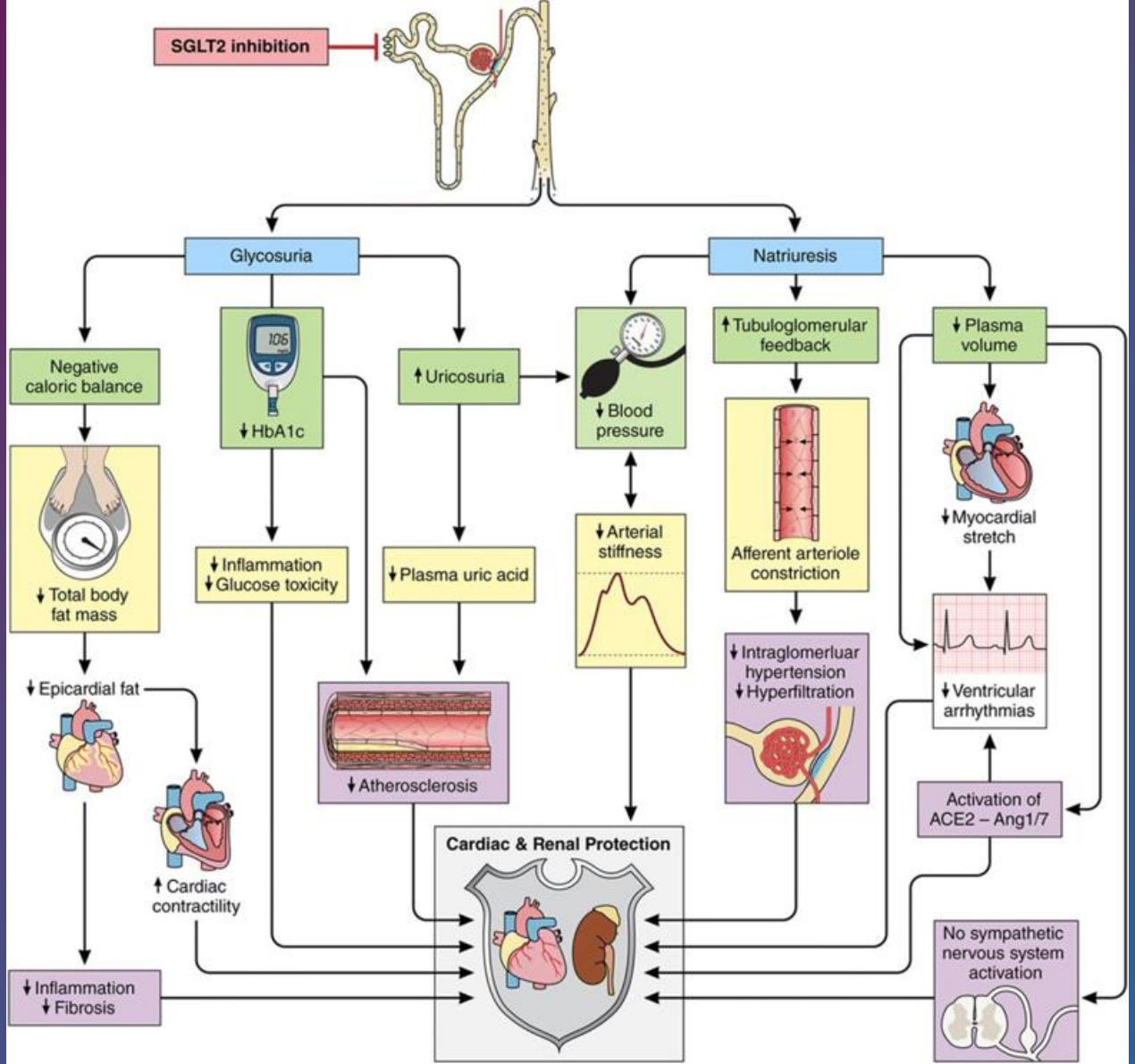
Glucagon-Like Peptide-1 Receptor Agonists



Glucagon-Like Peptide-1 Receptor Agonists and Prevention of Stroke Systematic Review of Cardiovascular Outcome Trials With Meta-Analysis, Giuseppe Bellastella. Stroke.Volume: 51, Issue: 2, Pages: 666-669

Diabetes Mellitus:
SGLT-2 Inhibitors

Diabetes Mellitus: SGLT-2 Inhibitors



Diabetes Mellitus: SGLT-2 Inhibitors

Beneficial effects of SGLT2 inhibitors on stroke risk factors

- Hyperglycemia
- Hypertension
- Obesity
- Decreased HDL-C
- Increased triglycerides

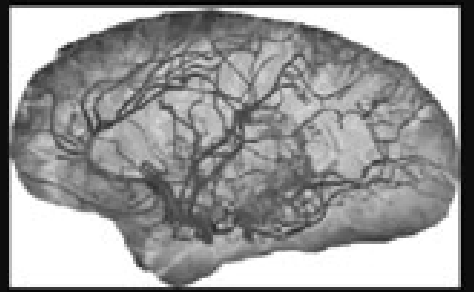
Beneficial effects of SGLT2 inhibitors on structural and functional vascular markers

- Oxidative stress
- Albuminuria
- Arterial stiffness

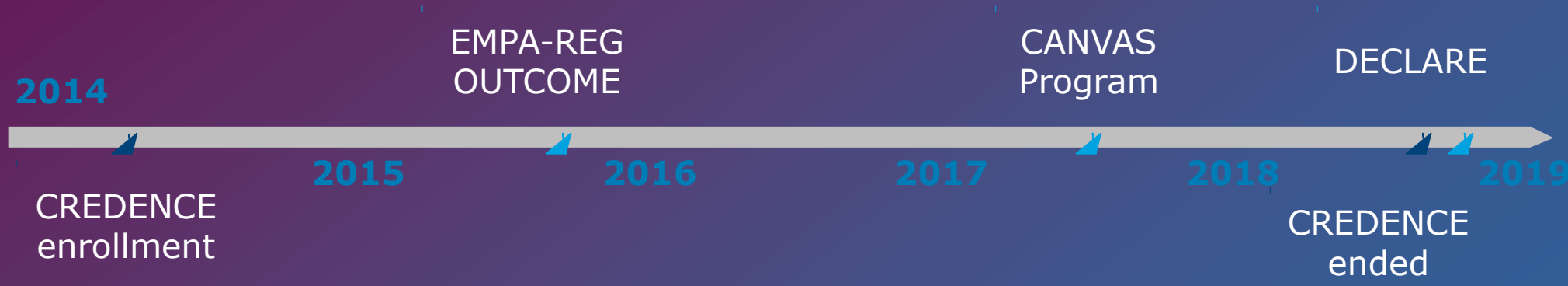
VS

No stroke risk benefits in EMPA-REG

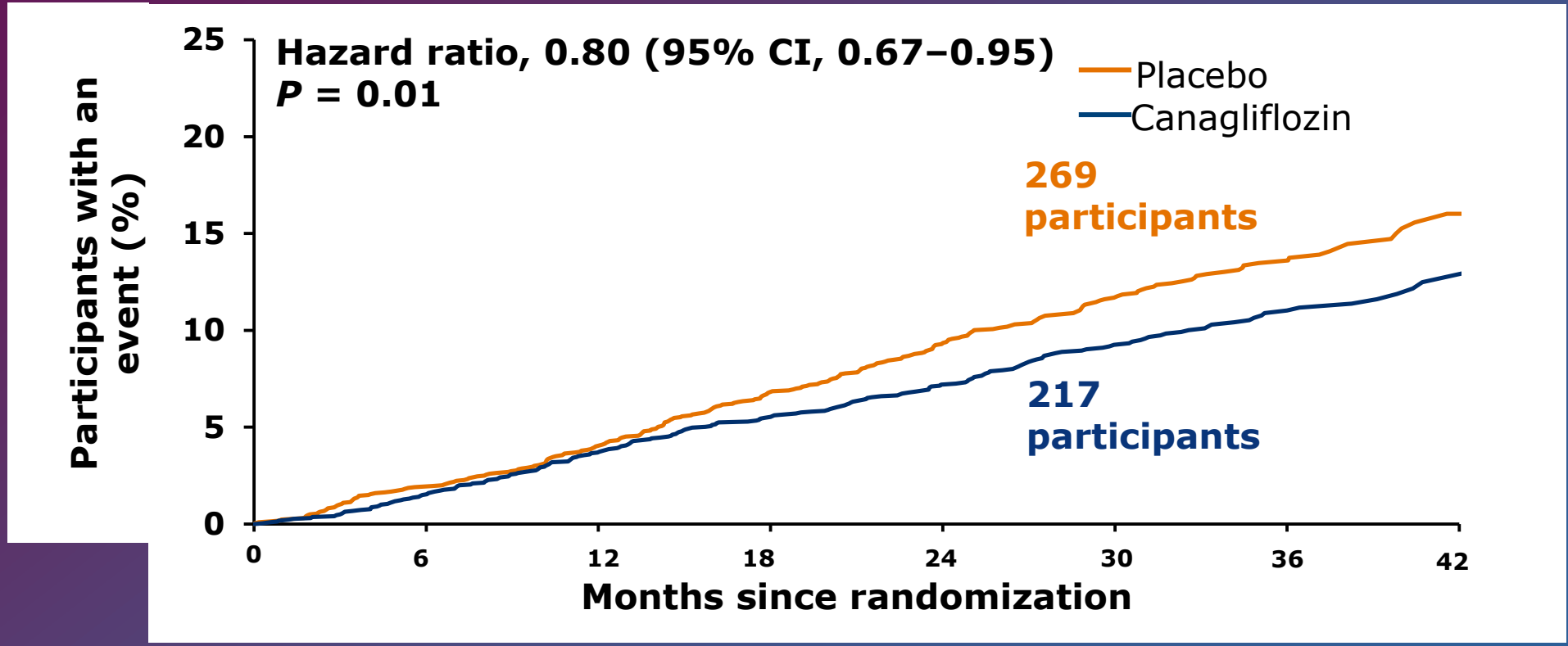
<u>Other factors in play?</u>



SGLT-2i


2014
2015
2016
2017
2018
2019
CREDENCE enrollment
EMPA-REG OUTCOME
CANVAS Program
DECLARE
CREDENCE ended

CREDENCE: Major Cardiovascular Events: CV Death, MI, or Stroke

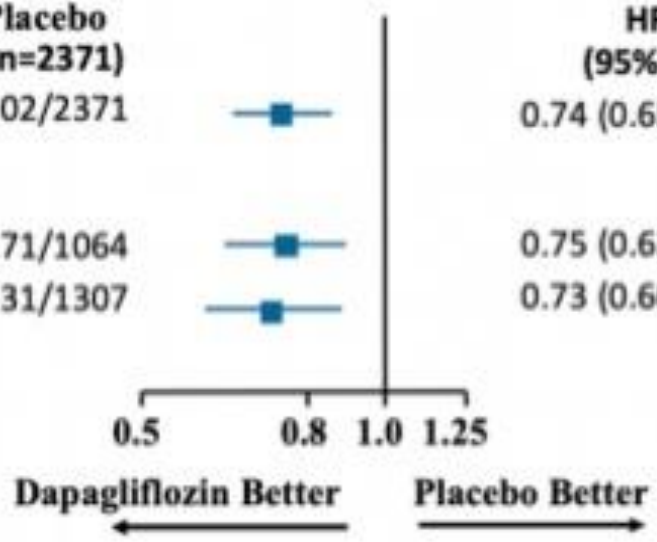


Canagliflozin & Renal Outcomes in Type 2 Diabetes & Nephropathy. N Engl J Med

What about non-Diabetics?

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)

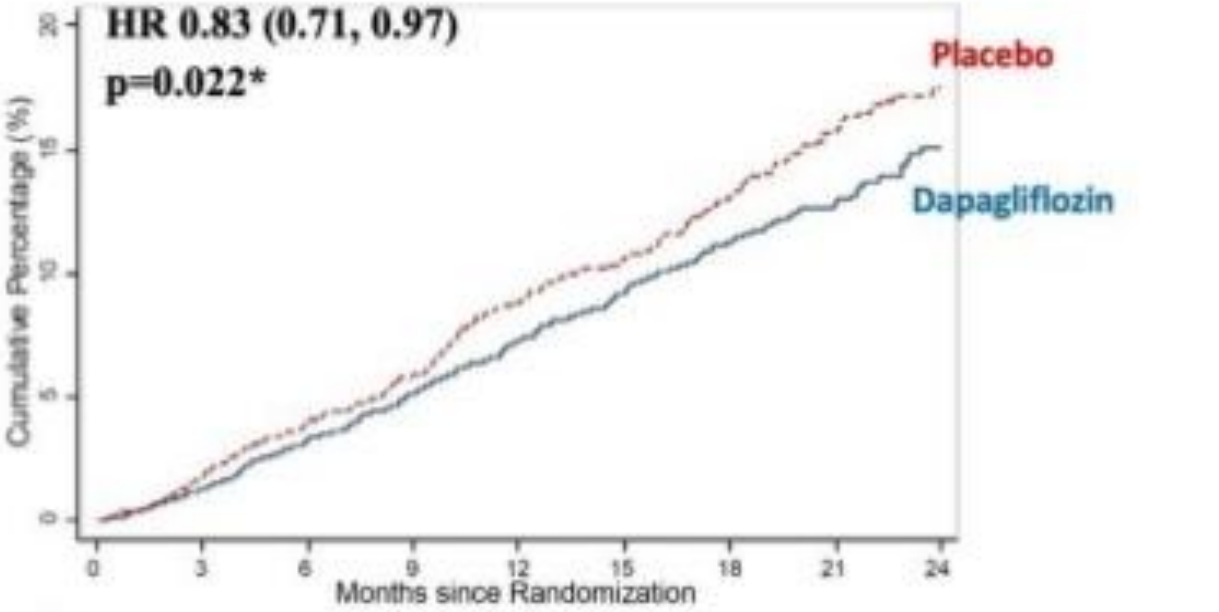


*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

McMurray presentation ESC 2019

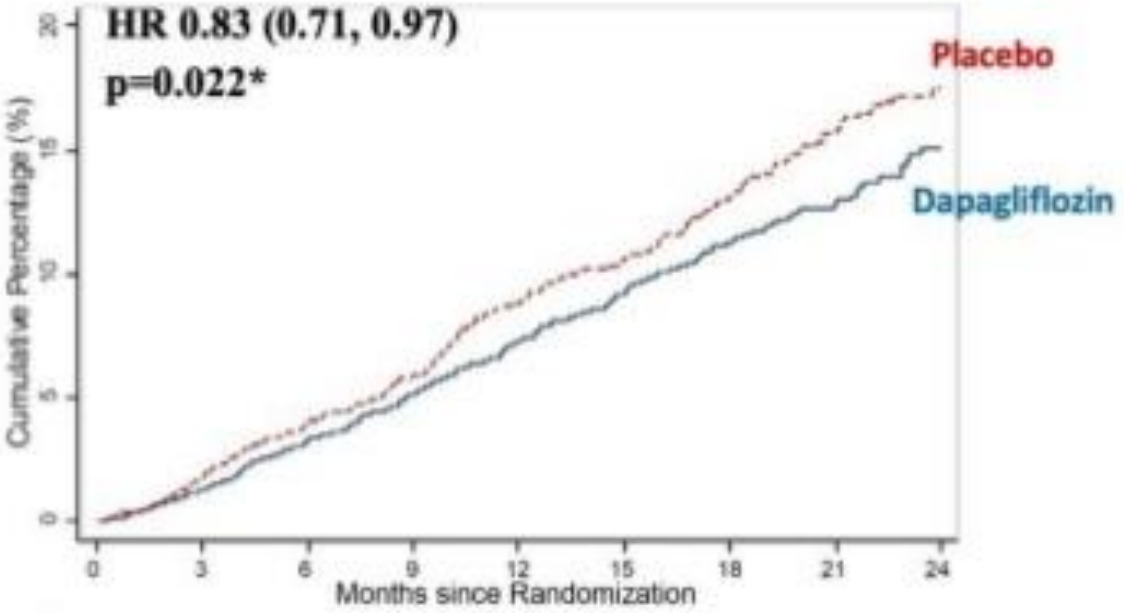
Dapagliflozin in Patients with Heart Failure and Reduced EF. Nov 19. N Engl J Med

All-cause death



McMurray presentation ESC 2019

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

McMurray presentation ESC 2019

ASA [1 Prevention]

ASPREE, ASCEND (2018), & ARRIVE (2018)

In healthy, older pts, low-dose aspirin did not reduce death, dementia, nor physical disability. Aspirin was associated with

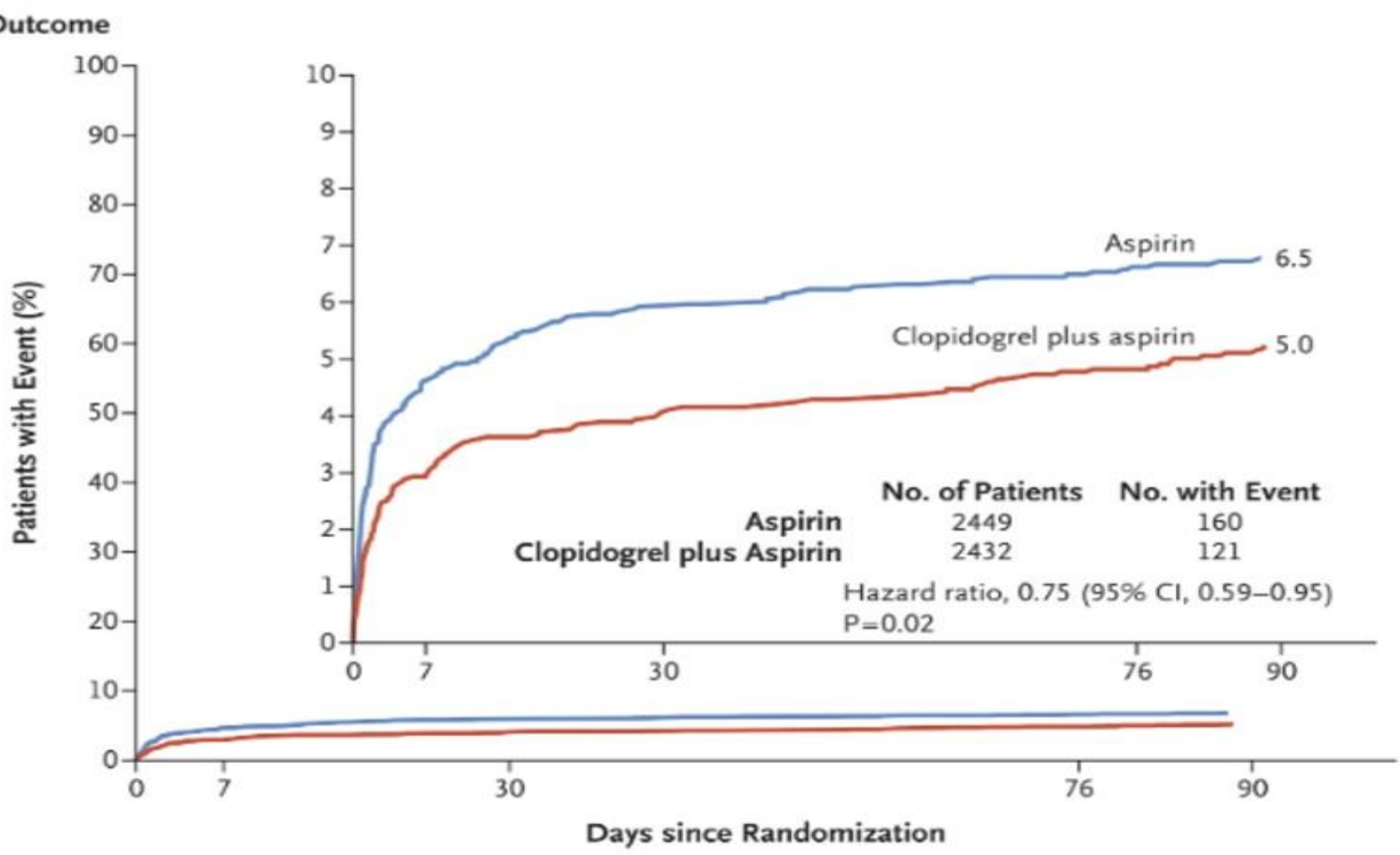
inc’d risk of major hemorrhage.

ASA [2 Prevention]

POINT
THALES/THEMIS

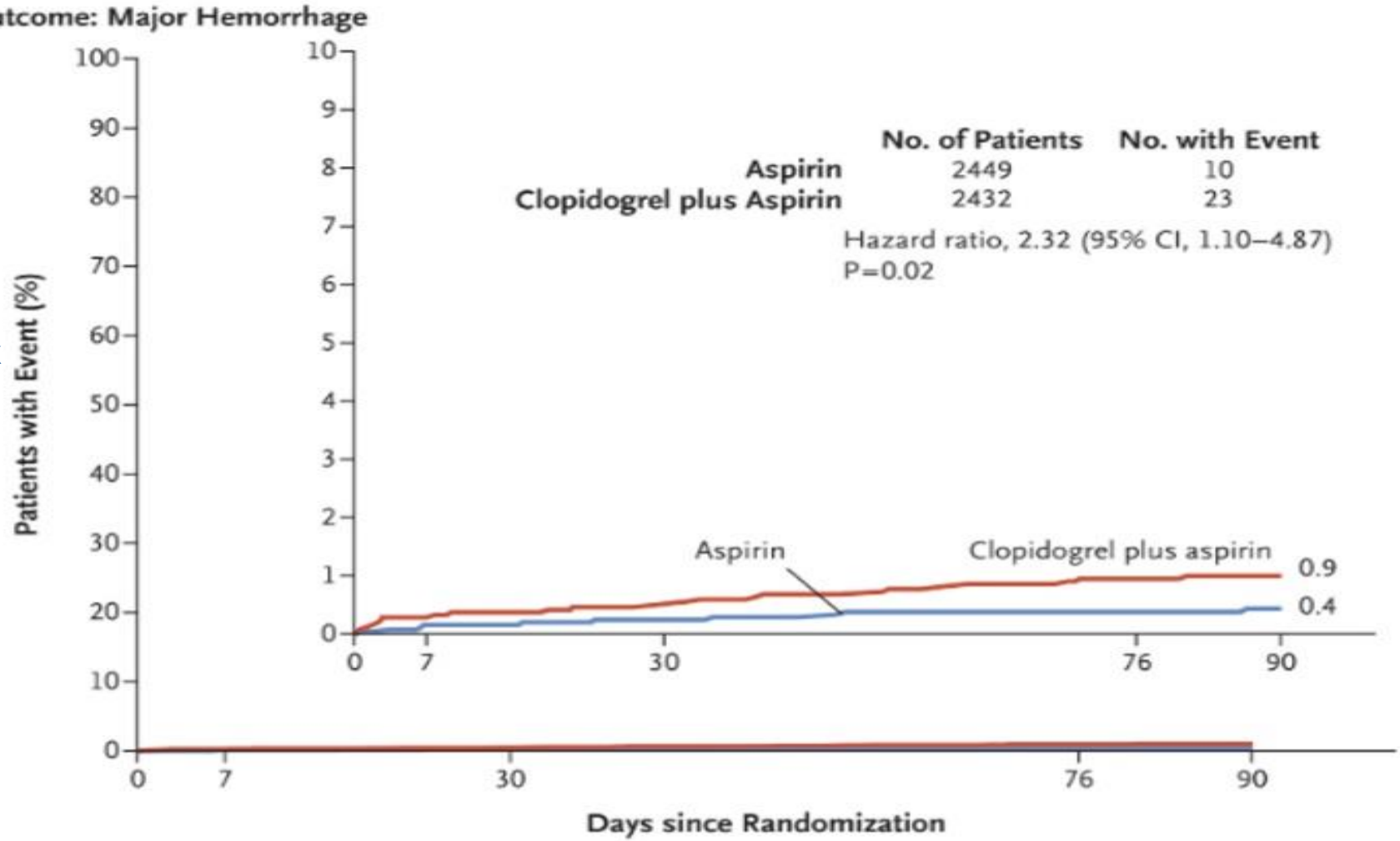
POINT

Clopidogrel & ASA in Acute Ischemic Stroke & High-Risk TIA,NEJM 2018



POINT

Clopidogrel & ASA in Acute Ischemic Stroke & High-Risk TIA,NEJM 2018



The NEW ENGLAND JOURNAL of MEDICINE

THALES

Ticagrelor in Stable Coronary Disease and Diabetes

MULTICENTER, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

19,220
Patients with type 2 diabetes and stable coronary artery disease

	Ticagrelor 60 mg twice daily + low-dose aspirin 75–150 mg once daily (N=9619)		Placebo + low-dose aspirin 75–150 mg once daily (N=9601)
Cardiovascular death, MI, or stroke (median follow-up, 39.9 mo)	7.7% (N=736)	P=0.04	8.5% (N=818)
TIMI major bleeding	2.2% (N=206)	P<0.001	1.0% (N=100)

Ticagrelor + aspirin decreased ischemic cardiovascular events but increased major bleeding

P.G. Steg et al. 10.1056/NEJMoa1908077

Interruption of the blood supply

1-Tissue plasminogen activator (tPA)

2-Endovascular mechanical embolectomy

Neurorestoration re ischemic cascade->cell death /inflammation

1-SCIL-STROKE (S/C IL-1 Receptor Antagonist in Ischemic Stroke)

Acute Post CVA Treatment

Lowering BP to <140/90 within 24 hrs of CVA did not dec death nor disability

Induced Hypertension in noncardioembolic stroke with Phenylephrine to maintain SBP of 200 improved NHISS score by 2

Cholesterol:

How Low Can you Go?

FOURIER

Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

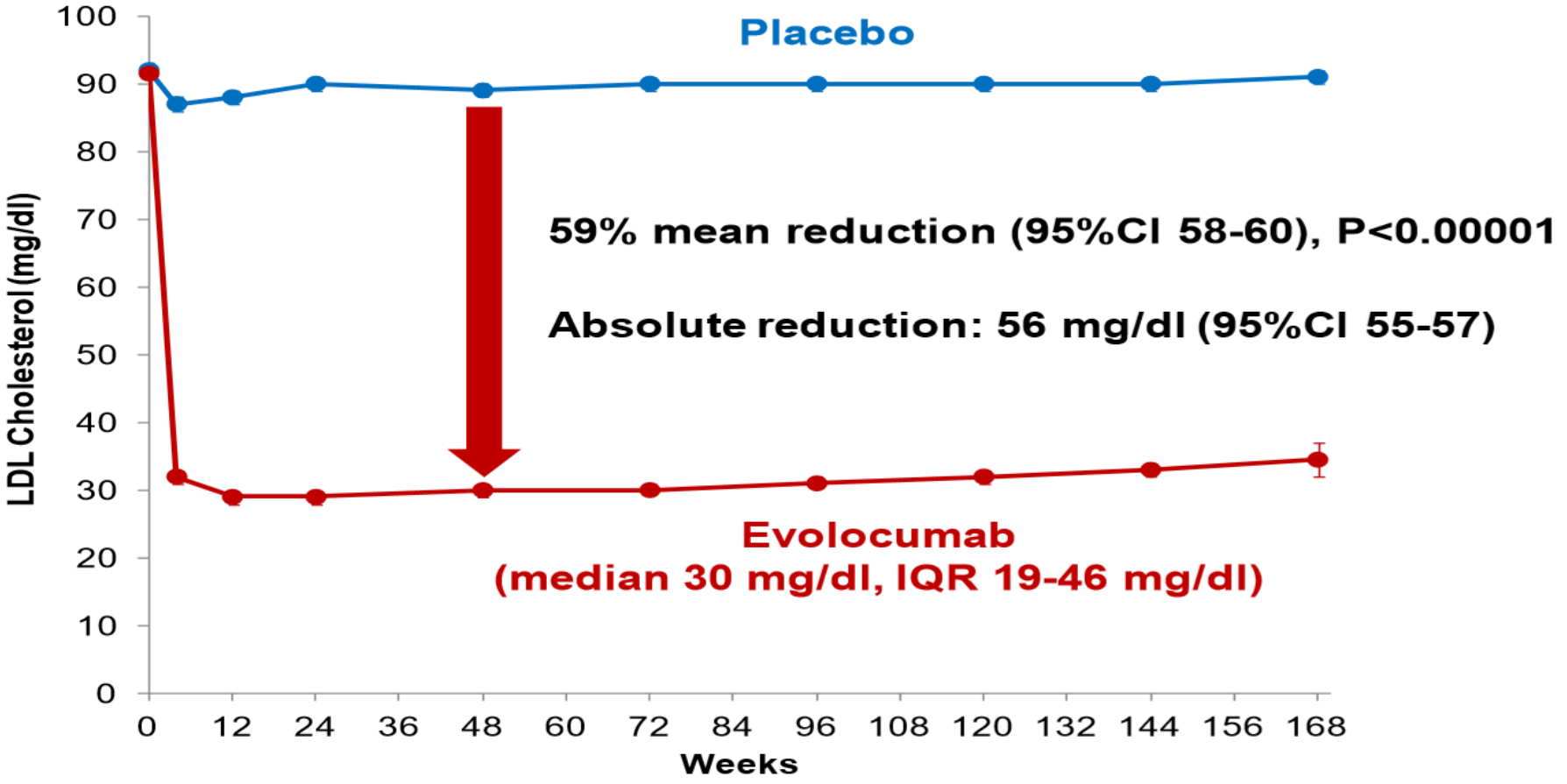
Focus on Cerebrovascular Disease

TR Pedersen*, RP Giugliano, PS Sever, AC Keech, M.S. Murphy, and MS Sabatine,

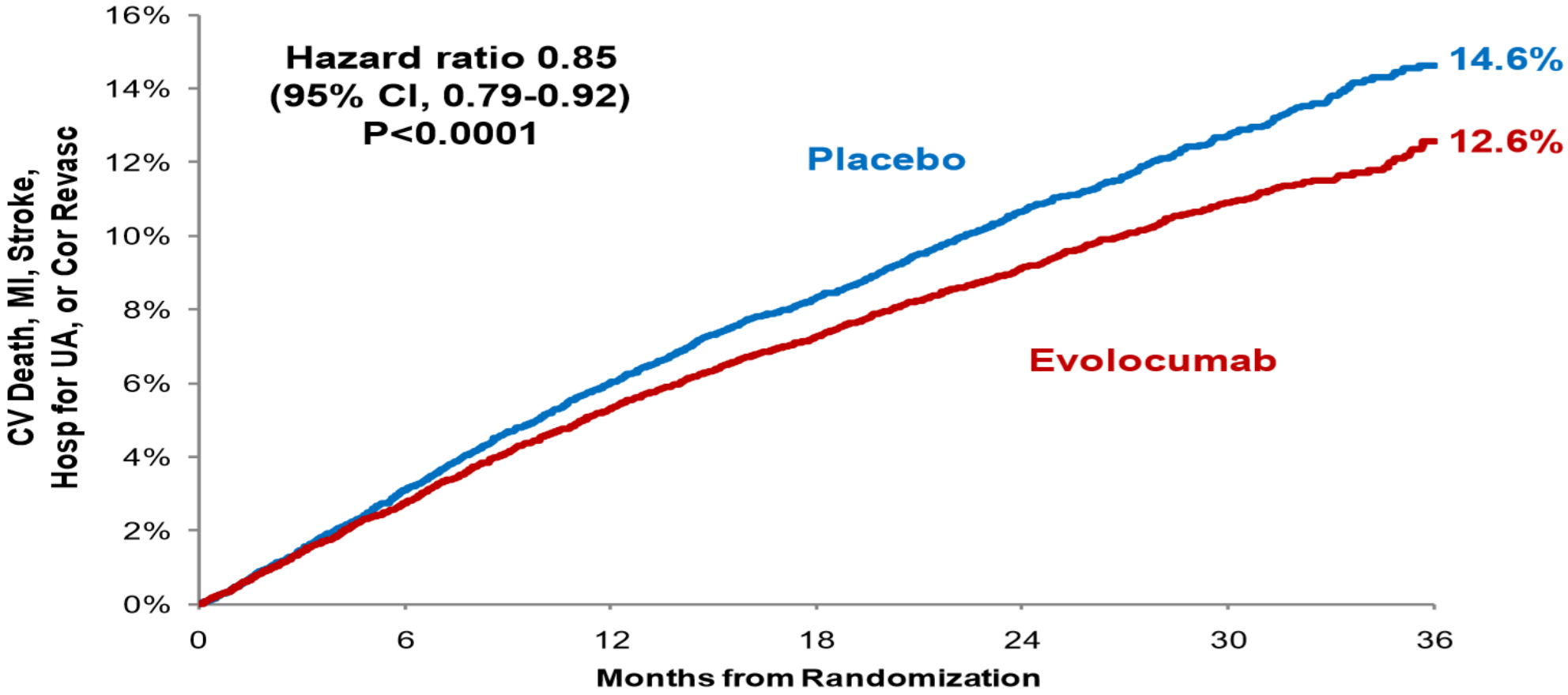
for the FOURIER Steering Committee & Investigators

* : Oslo University Hospital, Center For Preventive Medicine

LDL-Cholesterol

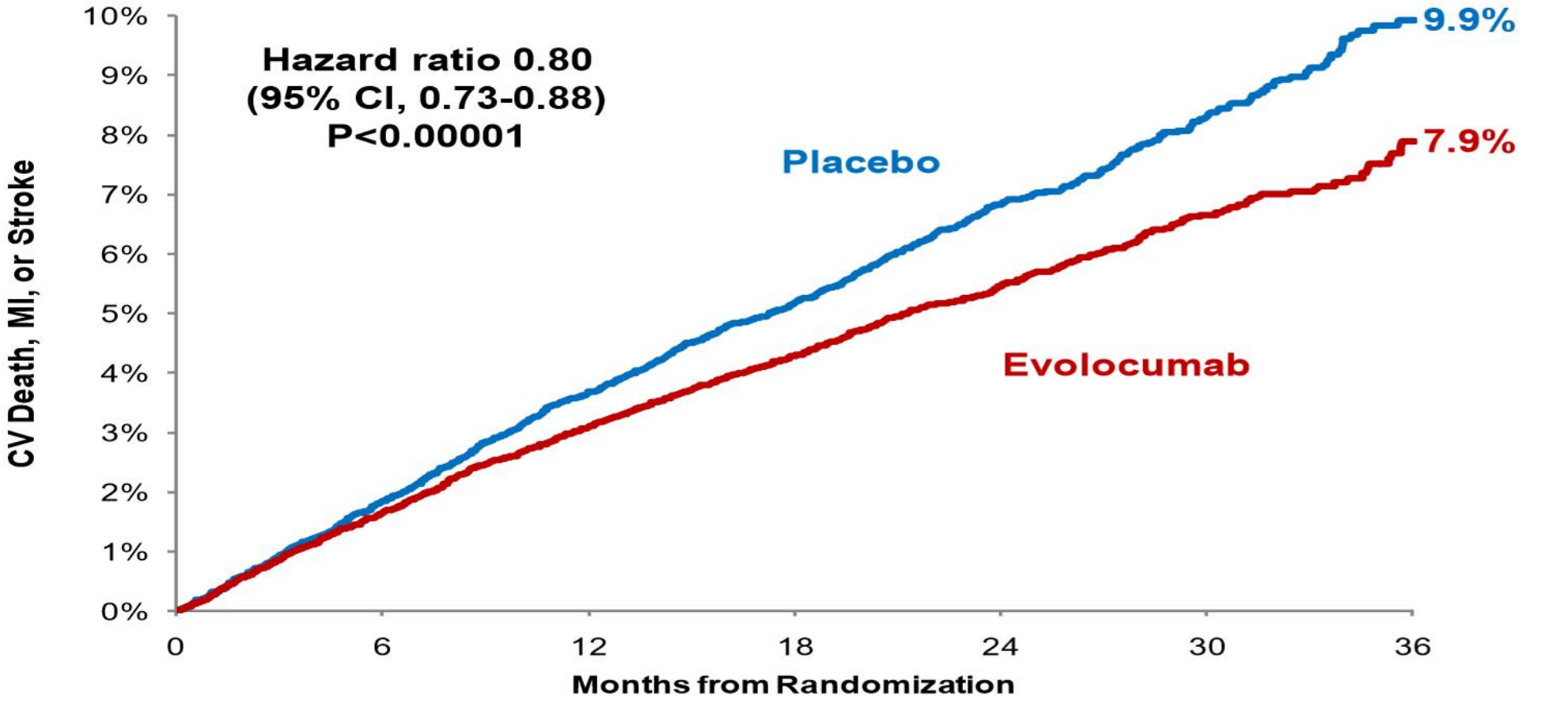


Primary Endpoint
Entire Study Population



Sabatine MS. et al. NEJM 2017;376:1713-22

Key Secondary Endpoint
Entire Study Population



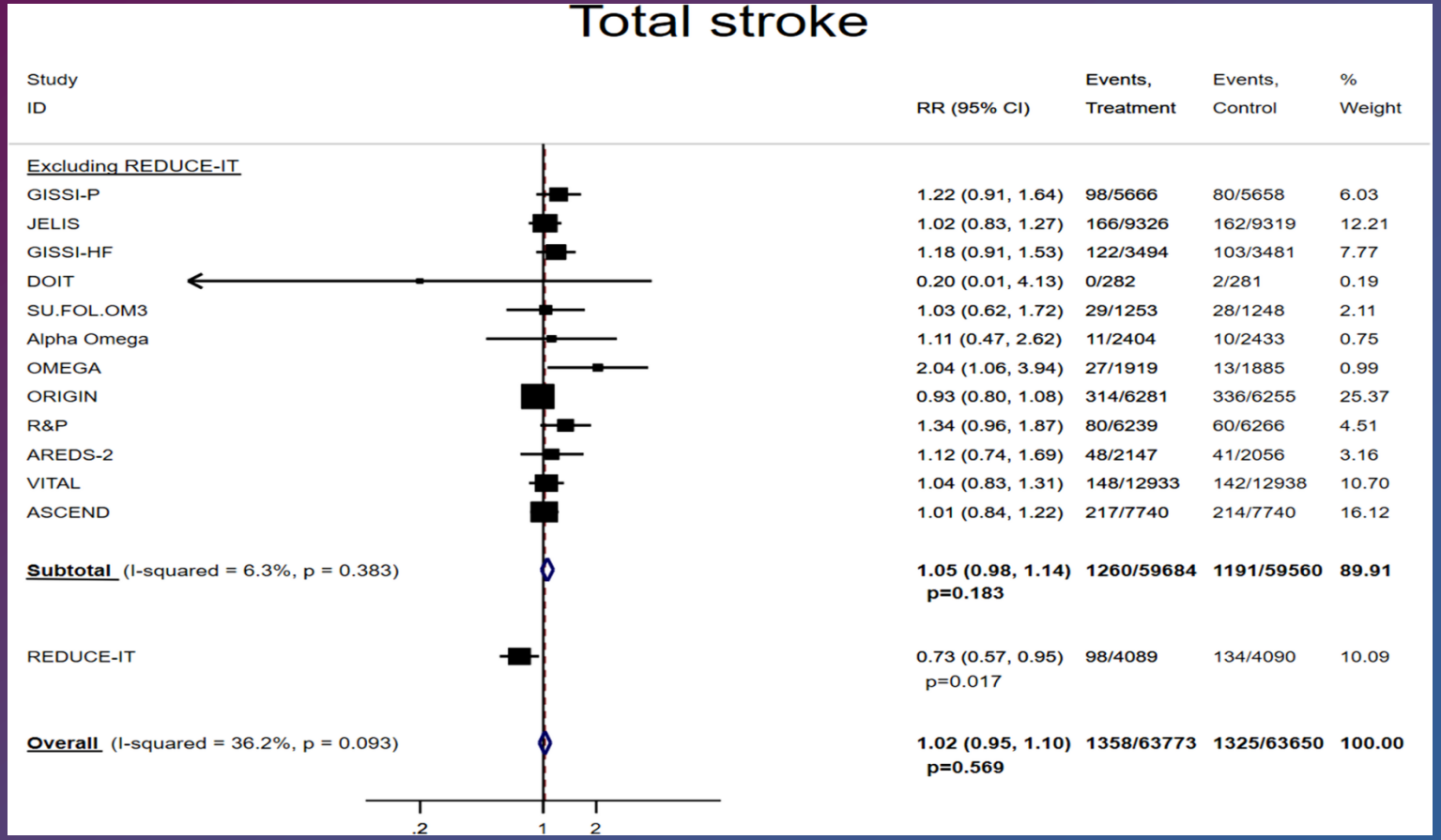
Sabatine MS, et al. NEJM 2017;376:1713-22

Types of CV Outcomes

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CV death, MI, or stroke	**7.9**	**9.9**	**0.80 (0.73-0.88)**
Cardiovascular death	**2.5**	**2.4**	**1.05 (0.88-1.25)**
Death due to acute MI	0.26	0.32	0.84 (0.49-1.42)
Death due to stroke	0.29	0.30	0.94 (0.58-1.54)
Other CV death	1.9	1.8	1.10 (0.90-1.35)
MI	**4.4**	**6.3**	**0.73 (0.65-0.82)**
Stroke	**2.2**	**2.6**	**0.79 (0.66-0.95)**

Marine Omega-3 Supplementation and Cardiovascular Disease

Marine Omega-3 Supplementation and Cardiovascular Disease: An Updated Meta-Analysis of 13 Randomized Controlled Trials 30 Sep 2019



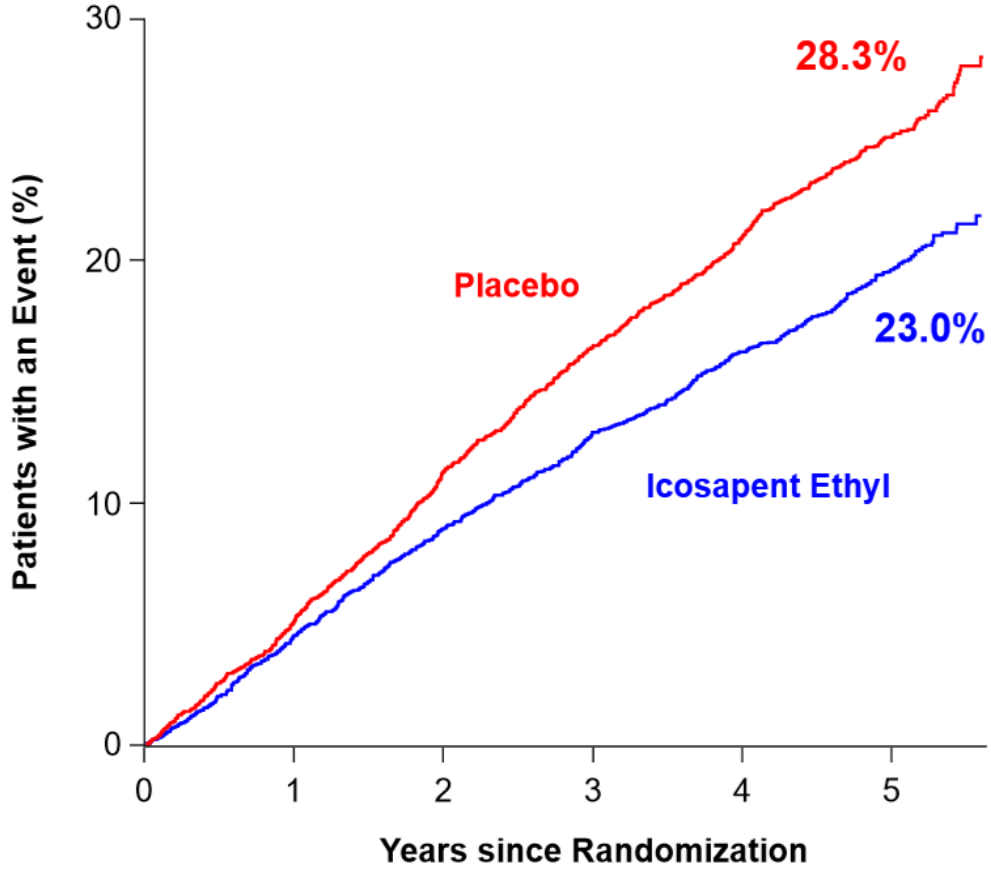
Yang Hu. Journal of the American Heart Association. Marine Omega-3 Supplementation and Cardiovascular Disease: Involving 127,477 Participants, Volume: 8, Issue: 19,

reduce-it

Reduction in Total Ischemic Events in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

Deepak L. Bhatt, MD, MPH, Ph. Gabriel Steg, MD, Michael Miller, MD, Eliot A. Brinton, MD, Terry A. Jacobson, MD, Steven B. Ketchum, PhD, Ralph T. Doyle, Jr., BA, Rebecca A. Juliano, PhD, Lixia Jiao, PhD, Craig Granowitz, MD, PhD, Jean-Claude Tardif, MD, John Gregson, PhD, Stuart J. Pocock, PhD, Christie M. Ballantyne, MD, on Behalf of the **REDUCE-IT** Investigators

Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

RRR = 24.8%

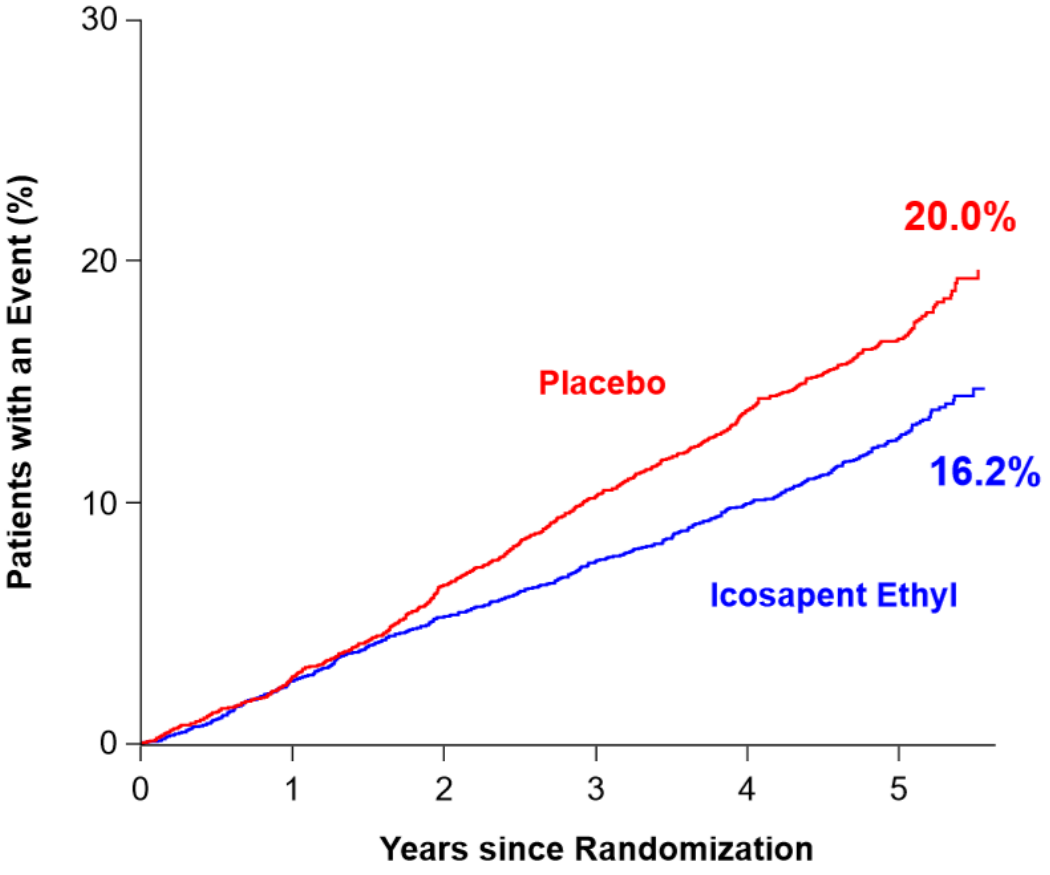
ARR = 4.8%

NNT = 21 (95% CI, 15–33)

P=0.00000001

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)

RRR = 26.5%

ARR = 3.6%

NNT = 28 (95% CI, 20–47)

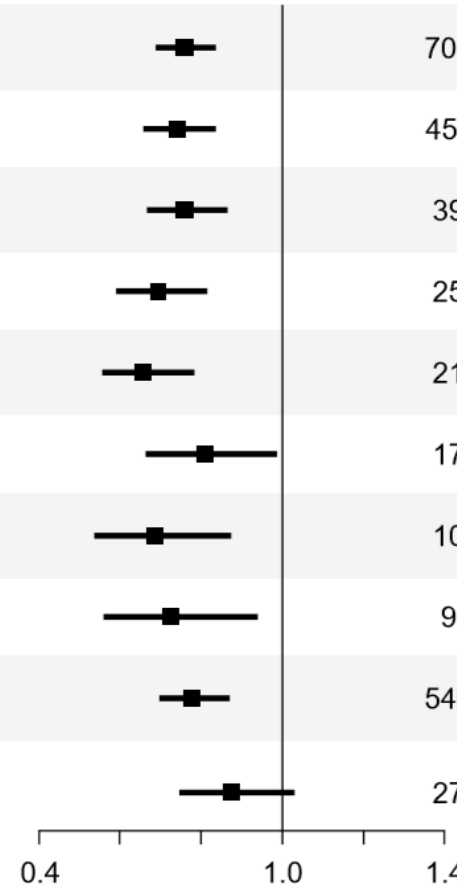
P=0.0000006

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

Prespecified Hierarchical Testing

reduce-it

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09



RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

ANYTHING ELSE?

Efficacy & Safety of Low-Dose Colchicine after MI

MI < 30 dys, any PCI procedures completed, & optimally treated including intensive statins

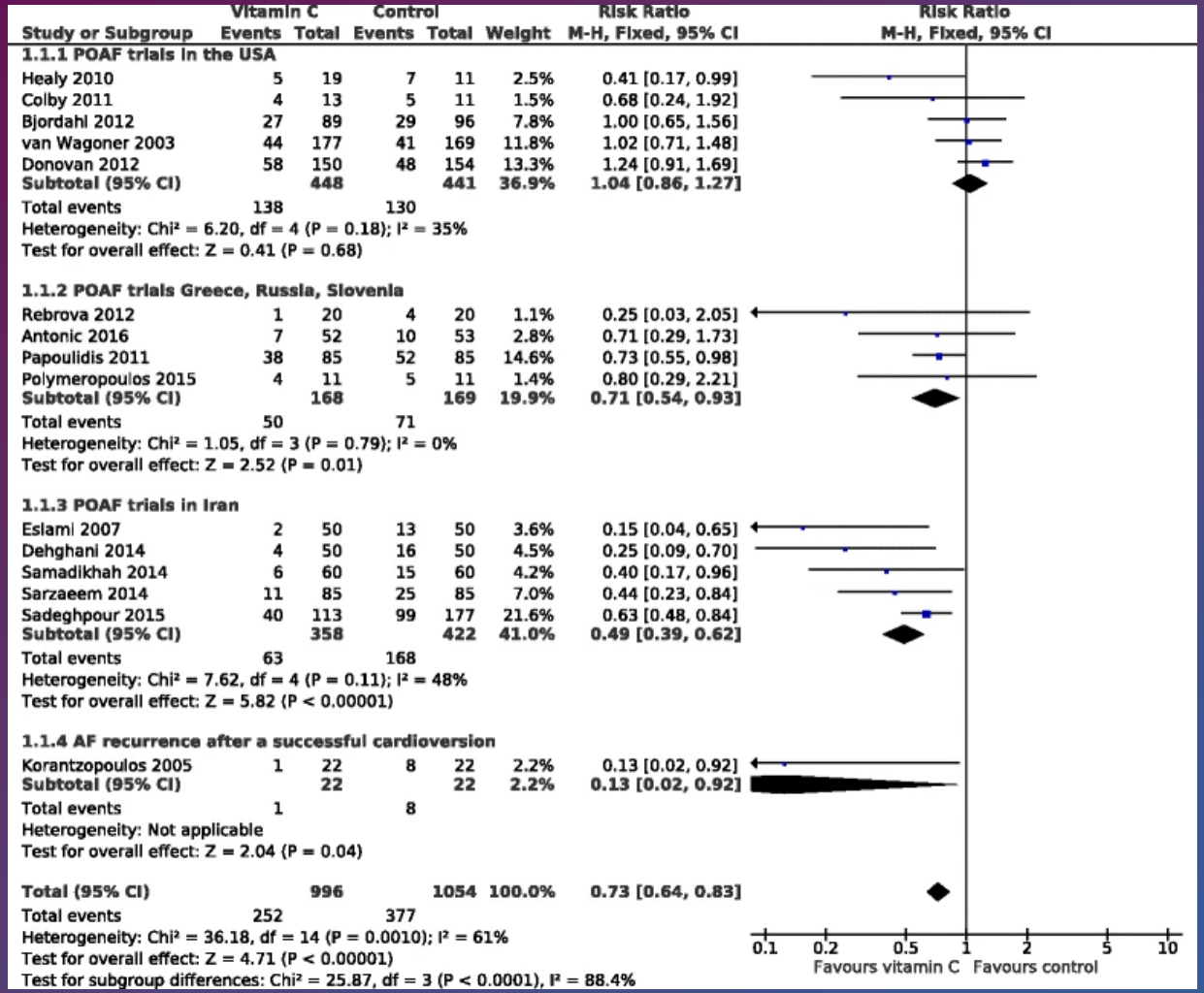
Jean-Claude Tardif et al; N Engl J Med; December 26, 2019 381:2497-2505

Table 2. Major Clinical End Points (Intention-to-Treat Population).*

End Point	Colchicine (N=2366)	Placebo (N=2379)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary composite end point	131 (5.5)	170 (7.1)	0.77 (0.61–0.96)	0.02†
Components of primary end point				
Death from cardiovascular causes	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)	
Resuscitated cardiac arrest	5 (0.2)	6 (0.3)	0.83 (0.25–2.73)	
Myocardial infarction	89 (3.8)	98 (4.1)	0.91 (0.68–1.21)	
Stroke	5 (0.2)	19 (0.8)	0.26 (0.10–0.70)	
Urgent hospitalization for angina leading to revascularization	25 (1.1)	50 (2.1)	0.50 (0.31–0.81)	
Secondary composite end point‡	111 (4.7)	130 (5.5)	0.85 (0.66–1.10)	
Death	43 (1.8)	44 (1.8)	0.98 (0.64–1.49)	
Deep venous thrombosis or pulmonary embolus	10 (0.4)	7 (0.3)	1.43 (0.54–3.75)	
Atrial fibrillation	36 (1.5)	40 (1.7)	0.93 (0.59–1.46)	

* Only the initial event was counted in the analyses of time to first event for the primary composite end point and for the secondary composite end point. In the component analysis, the different types of events were counted separately.
† The log-rank test and the multivariable Cox proportional-hazards model including age, history of diabetes, previous coronary revascularization, and previous heart failure yielded similar P values.
‡ The secondary composite end point included death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, and stroke.

Vitamin C: Prevention atrial fibrillation in high risk patients: systematic review & meta-analysis



Two g vitamin C was given before CV & afterwards 1 g/day of vitamin C for 7 days. After a successful CV, participants were followed for 7 days

?'s

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