

Clinical trials in 2018

João Morais



8th

CHALLENGES in

CARDIOLOGY



Topics

- Patent foramen ovale closure
- Omega 3 fatty acids and cardiovascular risk
- Coronary artery bypass grafting versus PCI
- TAVI in patients with severe aortic stenosis
- Beta-blockade in patients undergoing noncardiac surgery
- Prevention of early sudden death after AMI



ESC

European Society
of Cardiology

European Heart Journal (2018) **0**, 1–12

doi:10.1093/eurheartj/ehy121



CLINICAL RESEARCH

Interventional cardiology

Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a meta-analysis of randomized controlled trials

Yousif Ahmad, James P. Howard, Ahran Arnold, Matthew Shun Shin, Christopher Cook, Ricardo Petraco, Ozan Demir, Luke Williams, Juan F. Iglesias, Nilesh Sutaria, Iqbal Malik, Justin Davies, Jamil Mayet, Darrel Francis*, and Sayan Sen



Efficacy of closure vs. medical therapy

Closure of PFO resulted in a significant reduction in recurrent stroke (Figure 2; HR 0.32 95% CI 0.13–0.82; $P = 0.018$), though with significant heterogeneity ($I^2 = 73.4\%$). Across all trials, 37 of 1829 patients had a recurrence of stroke in the active arms, compared with 72 of 1611 in the control arms. Overall, the annual weighted risk of recurrent stroke was low in both in the closure (0.61%) and the medical therapy (1.17%) group.

Safety of closure vs. medical therapy

Device closure significantly increased the risk of AF (Figure 3; risk ratio (RR) 4.68, 95% CI 2.19–10.00, $P < 0.001$, heterogeneity $I^2 = 27.5\%$). Across all trials, 76 of 1784 patients had a recurrence of stroke in the active arms, compared with 12 in the control arms. Overall, the annual weighted risk of AF was low (1.38% per year in the device arm and 0.21% per year in the control arm).

Across the four studies which reported major bleeding in both the device and control arms, there was no significant difference between

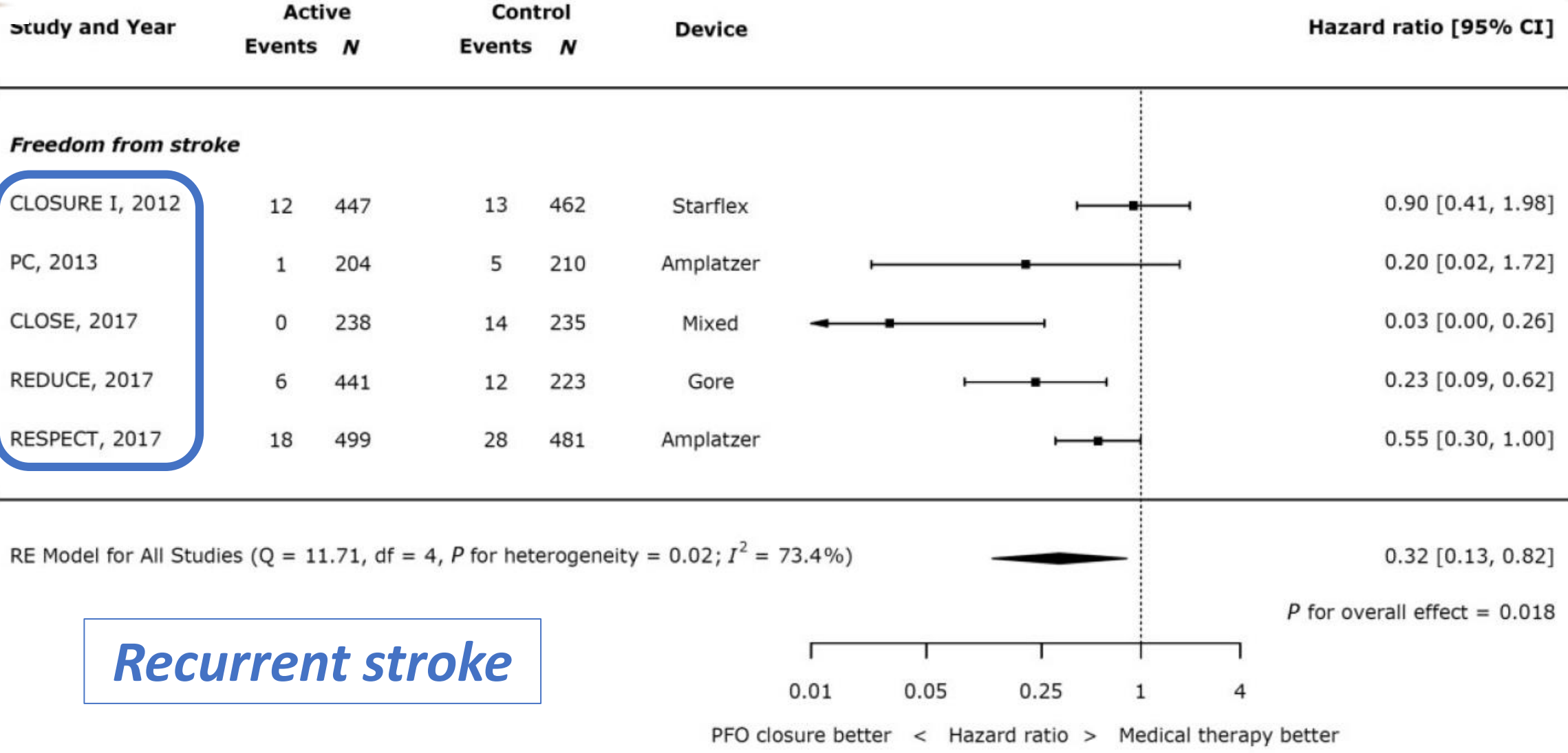
the groups (Figure 4, RR 0.83, 95% CI 0.33–2.09; $P = 0.691$, heterogeneity $I^2 = 41.8\%$).

Procedural-related events were low across the five trials, occurring in 3.2% of patients in CLOSURE-1, 5.9% in CLOSE, 2.5% in REDUCE, 1.5% in PC, and 2.4% of RESPECT.

Impact of shunt size and atrial septal aneurysm

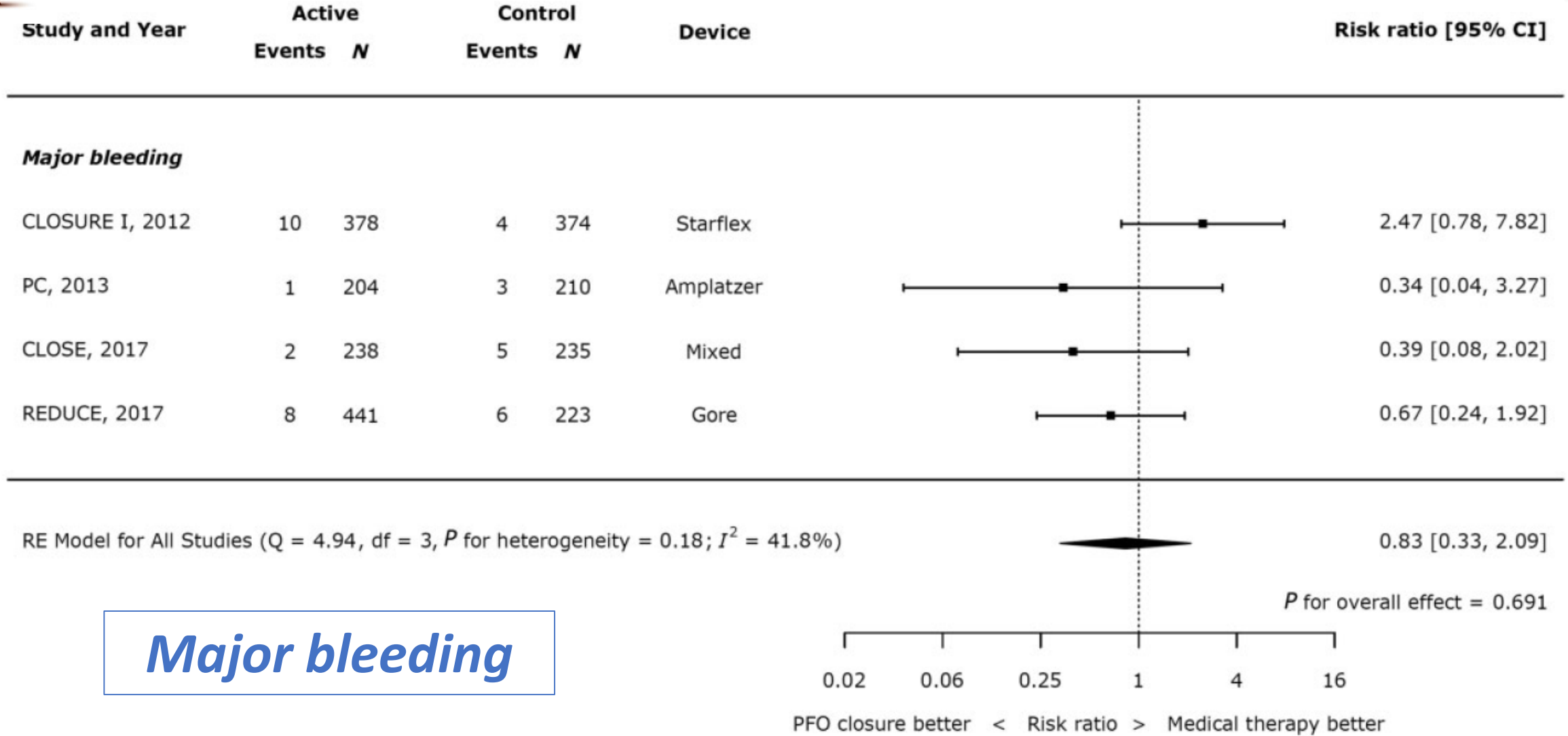
Three trials reported outcomes stratified by shunt size and presence of an atrial septal aneurysm (CLOSURE I, PC, and RESPECT). The CLOSE trial only enrolled patients with either a large shunt or an atrial septal defect (ASD) and therefore there was no appropriate comparator group for either variable.

In patients with a large shunt, PFO closure was associated with a significant reduction in stroke (Figure 5; HR 0.33, 95% CI 0.16–0.72; $P = 0.005$), whilst there was no significant reduction in stroke in patients with a small shunt (HR 0.90, 95% CI 0.50–1.60; $P = 0.712$). Across all trials, 7 of 478 patients with a large shunt had a recurrent



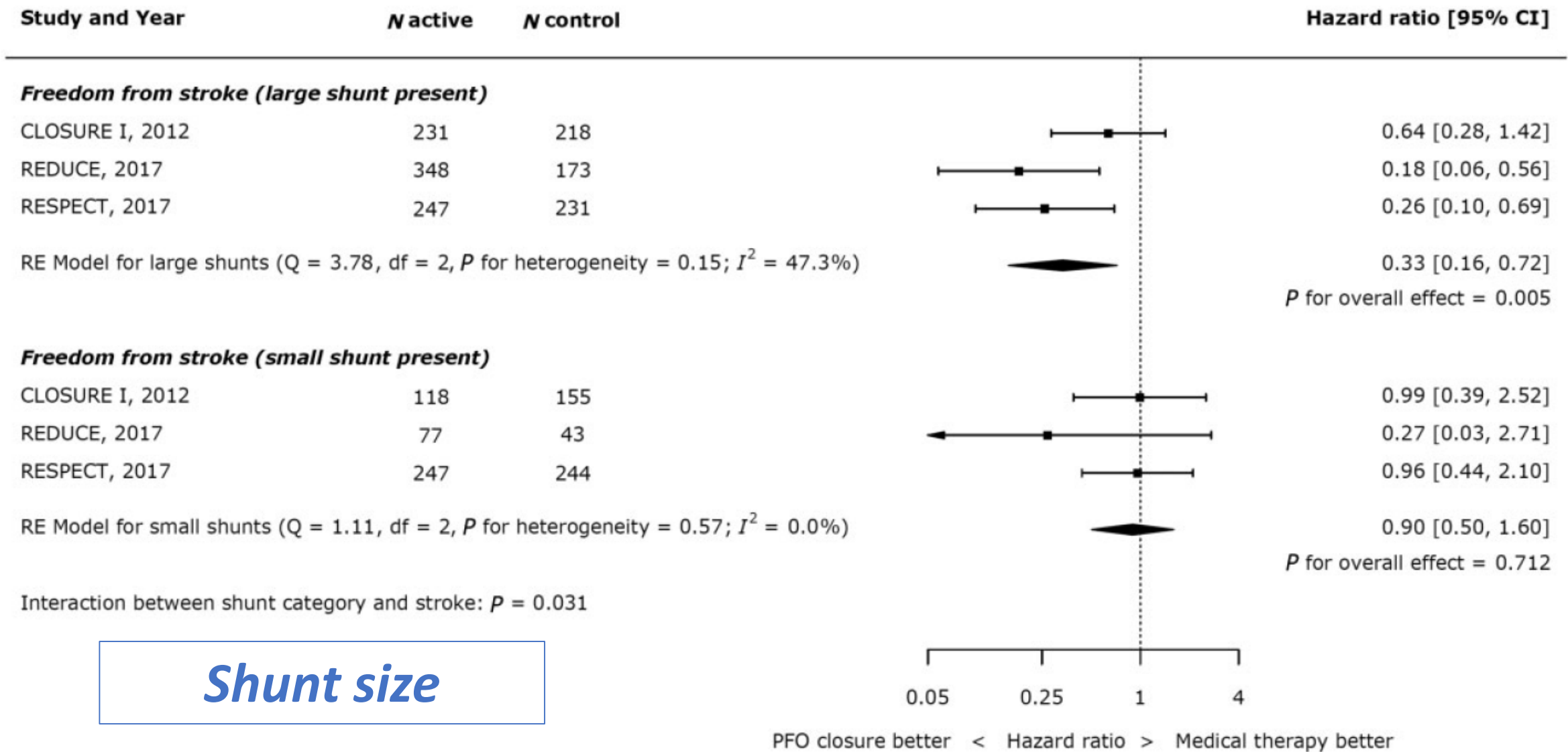
Recurrent stroke

Figure 2 Effect of device closure on recurrent stroke.



Major bleeding

Figure 4 Effect of device closure on major bleeding.



Shunt size

Figure 5 Impact of shunt size on effect of device closure on recurrent stroke.



Conclusions

In selected patients with cryptogenic stroke, PFO closure is superior to medical therapy for the prevention of further stroke: this is particularly true for patients with moderate-to-large shunts. Guidelines should be updated to reflect this.



JAMA Cardiology | **Original Investigation**

Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks

Meta-analysis of 10 Trials Involving 77 917 Individuals

Theingi Aung, MBBS, FRCP; Jim Halsey, BSc; Daan Kromhout, PhD; Hertzell C. Gerstein, MD; Roberto Marchioli, MD; Luigi Tavazzi, MD; Johanna M Geleijnse, PhD; Bernhard Rauch, MD; Andrew Ness, PhD, FFPH; Pilar Galan, MD, PhD; Emily Y. Chew, MD; Jackie Bosch, PhD; Rory Collins, FMedSci, FRCP; Sarah Lewington, DPhil; Jane Armitage, FRCP, FFPH; Robert Clarke, MD, FRCP, FFPH;
for the Omega-3 Treatment Trialists' Collaboration

JAMA Cardiol. doi:[10.1001/jamacardio.2017.5205](https://doi.org/10.1001/jamacardio.2017.5205)

OBJECTIVE To conduct a meta-analysis of all large trials assessing the associations of omega-3 fatty acid supplements with the risk of fatal and nonfatal coronary heart disease and major vascular events in the full study population and prespecified subgroups.

MAIN OUTCOMES AND MEASURES The main outcomes included fatal coronary heart disease, nonfatal myocardial infarction, stroke, major vascular events, and all-cause mortality, as well as major vascular events in study population subgroups.



Table. Characteristics of Included Trials

Study (Year)	Patients, No.	Dose of EPA/ DHA (mg/d)	Male, No (%)	Mean Trial Duration, y	Mean (SD) Age, y	No (%)			
						Prior CHD	Prior Stroke	Prior Diabetes	Statin Use
DOIT (2010)	563	1150/800	563 (100)	3	70 (3)	133 (23.6)	37 (6.6)	46 (8.2)	NA
AREDS-2 (2014)	4203	650/350	1816 (43.2)	4.5	74 (NA)	405 (9.7)	211 (5.0)	546 (13.0)	1866 (44.4)
SU.FOL.OM3 (2010)	2501	400/200	1987 (79.4)	4.7	61 (NA)	1863 (74.5)	638 (25.5)	440 (17.9)	2079 (83.1)
JELIS (2007) ^{a,b}	18 645	1800/NA	5859 (31.4)	4.6	61 (8)	NA	NA	3040 (16.3)	18 645 (100.0)
Alpha Omega (2010)	4837	226/150	3783 (78.2)	3.3	69 (6)	4837 (100.0)	345 (7.2)	1014 (21.0)	4122 (85.2)
OMEGA (2010)	3818	460/380	2841 (74.4)	1	64 (NA)	796 (22.5)	192 (5.5)	948 (27.0)	3566 (94.2)
R&P (2013)	12 505	500/500	7687 (61.5)	5	64 (NA)	Not stated (30)	594 (4.8)	7494 (59.9)	12 505 (100.0)
GISSI-HF (2008)	6975	850/950	5459 (78.3)	3.9	67 (11)	3614 (51.8)	346 (5.0)	1974 (28.3)	NA
ORIGIN (2012)	12 536	465/375	8150 (65.0)	6.2	64 (8)	8094 (64.6)	10 877 (86.8)	11 081 (88.4)	6739 (53.8)
GISSI-P ^b (1999)	11 334	850/1700	9658 (85.2)	3.5	59 (11)	11 334 (100.0)	NA	2139 (18.9)	NA
Total	77 917	NA	47 803 (61.4)	4.4	64	31 076/46 767 (66.4)	13 240/47 938 (27.6)	28 722 (36.9)	49 522 (83.4)



Figure 1. Associations of Omega-3 Fatty Acids With Major Vascular Events

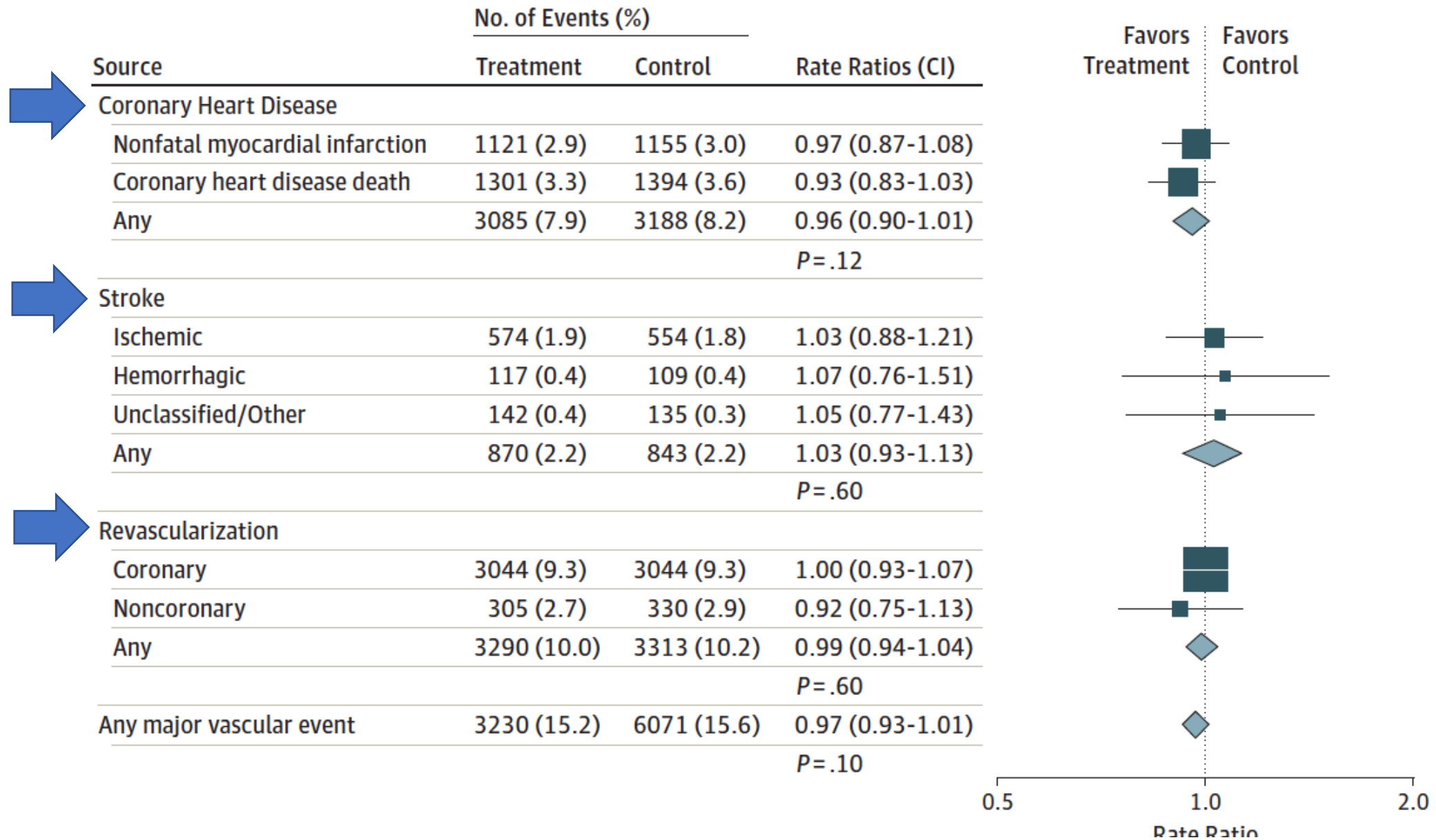
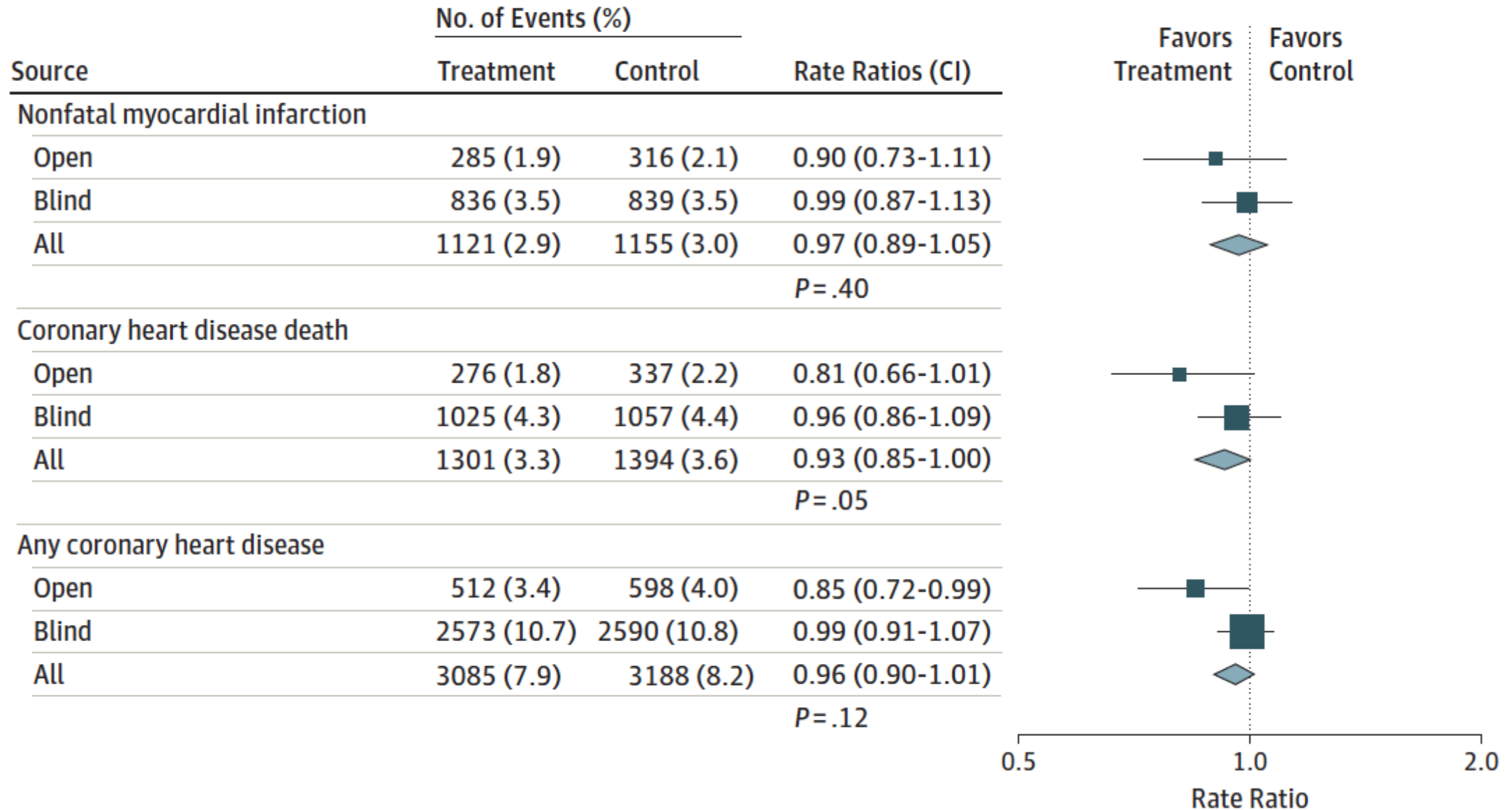




Figure 4. Associations of Omega-3 Fatty Acids With Fatal and Nonfatal Vascular Events, by Trial Design





the results of the present meta-analysis provide no support for the recommendations to use approximately 1 g/d of omega-3 FAs in individuals with a history of CHD for the prevention of fatal CHD, nonfatal MI, or any other vascular events. The results of the ongoing trials are needed to assess if higher doses of omega-3 FAs (3-4 g/d) may have significant effects on risk of major vascular events.



Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data

Stuart J Head, Milan Milojevic, Joost Daemen, Jung-Min Ahn, Eric Boersma, Evald H Christiansen, Michael J Domanski, Michael E Farkouh, Marcus Flather, Valentin Fuster, Mark A Hlatky, Niels R Holm, Whady A Hueb, Masoor Kamalesh, Young-Hak Kim, Timo Mäkikallio, Friedrich W Mohr, Grigorios Papageorgiou, Seung-Jung Park, Alfredo E Rodriguez, Joseph F Sabik 3rd, Rodney H Stables, Gregg W Stone, Patrick W Serruys, Arie Pieter Kappetein

We included 11 randomised trials involving 11 518 patients selected by heart teams who were assigned to PCI (n=5753) or to CABG (n=5765).

Lancet 2018; 391: 939–48

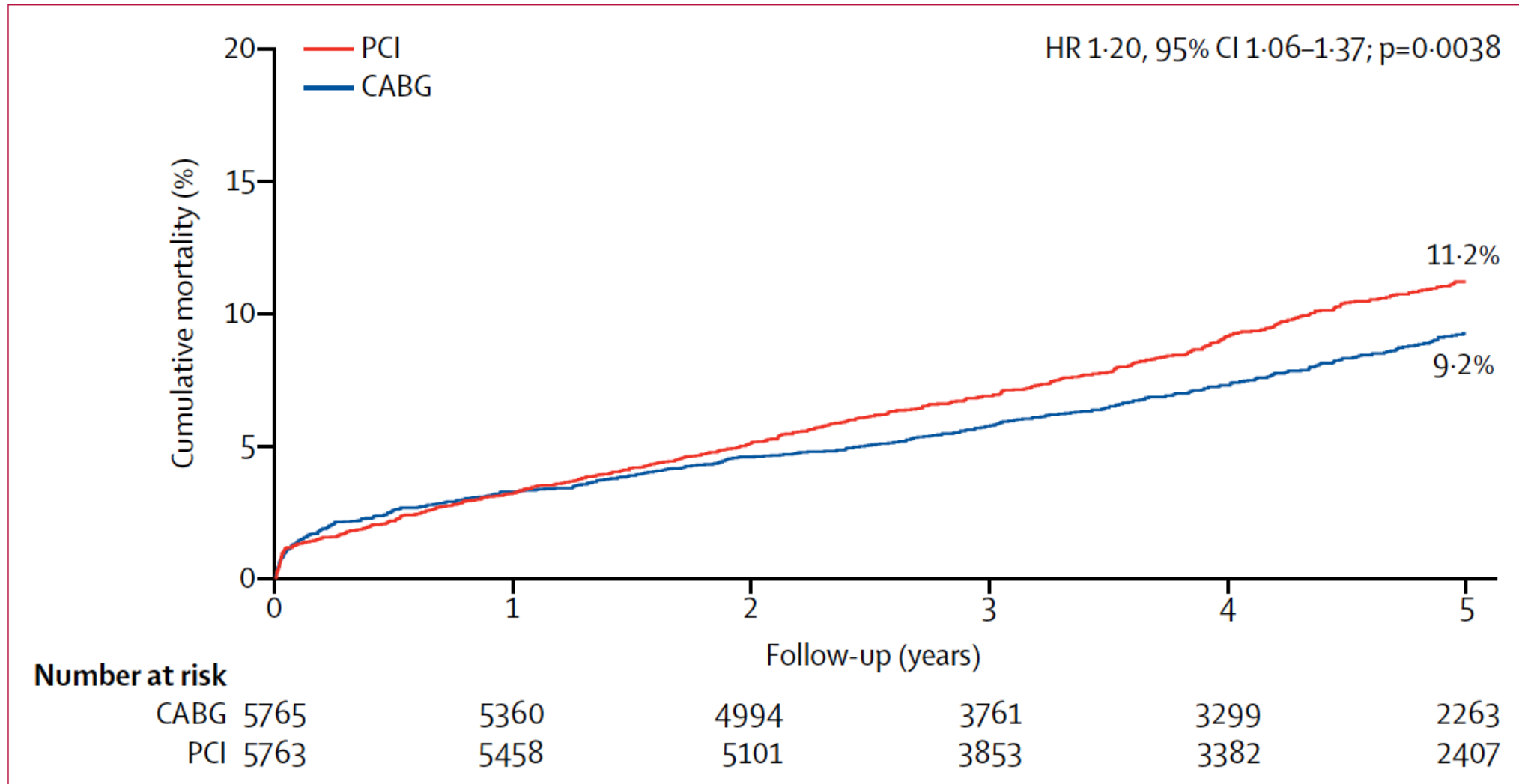


Figure 1: Mortality after CABG versus after PCI during 5 years' follow-up

Kaplan-Meier estimates are from the overall pooled patient population. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. HR=hazard ratio.

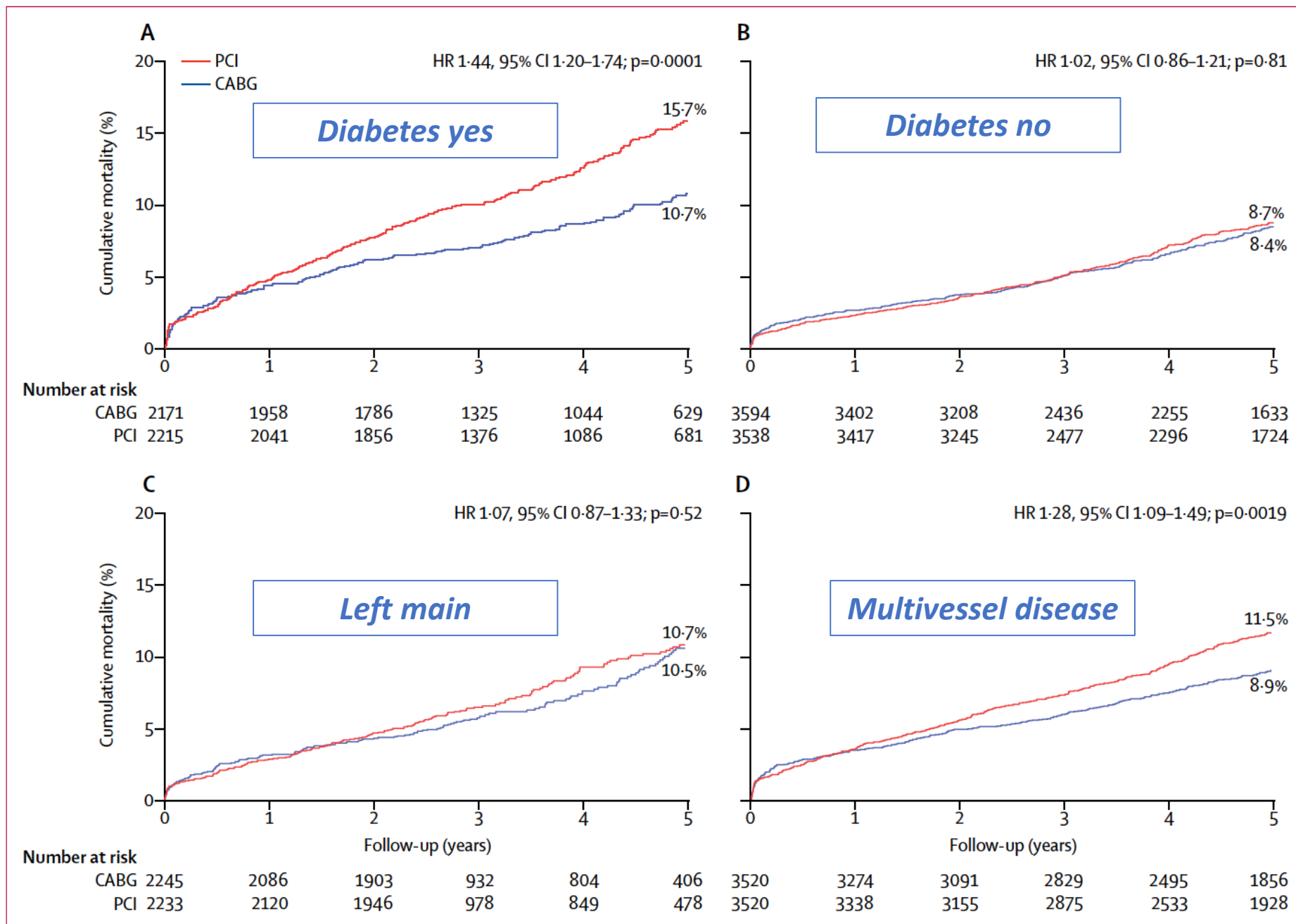


Figure 3: Mortality after CABG versus after PCI during 5 years' follow-up of patients with (A) or without (B) diabetes and with left main disease (C) or multivessel disease (D)



Interpretation CABG had a mortality benefit over PCI in patients with multivessel disease, particularly those with diabetes and higher coronary complexity. No benefit for CABG over PCI was seen in patients with left main disease.

Longer follow-up is needed to better define mortality differences between the revascularisation strategies.



Five-Year Outcomes From the All-Comers Nordic Aortic Valve Intervention Randomized Clinical Trial in Patients with Severe Aortic Valve Stenosis

H. Gustav Hørsted Thyregod, MD, PhD

Department of Cardiothoracic Surgery
Copenhagen University Hospital, Denmark

On behalf of the NOTION Investigators

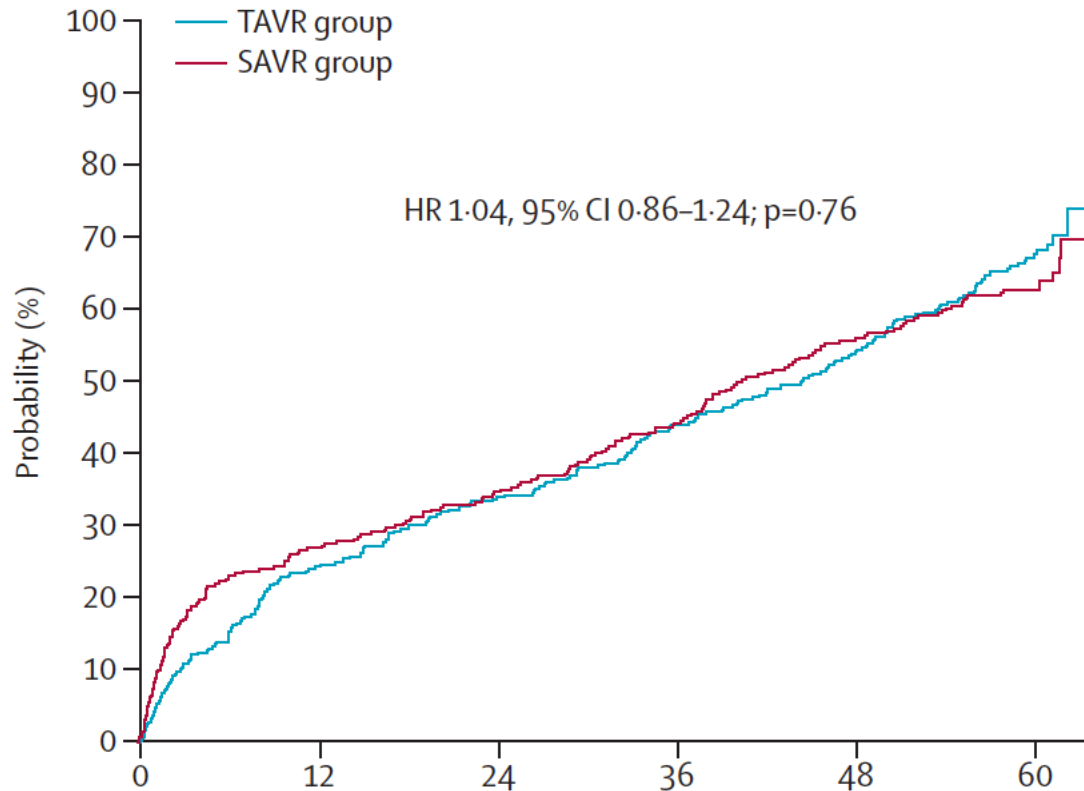


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67th Annual Scientific Session & Expo



TAVR vs. SAVR in High-Risk Patients



All-cause death after 5 years

PARTNER 1

Mack MJ et al, Lancet 2015

Number at risk

TAVR group	348	262	228	191	154	61
SAVR group	351	236	210	174	131	64



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Nordic Aortic Valve Intervention (NOTION) Trial

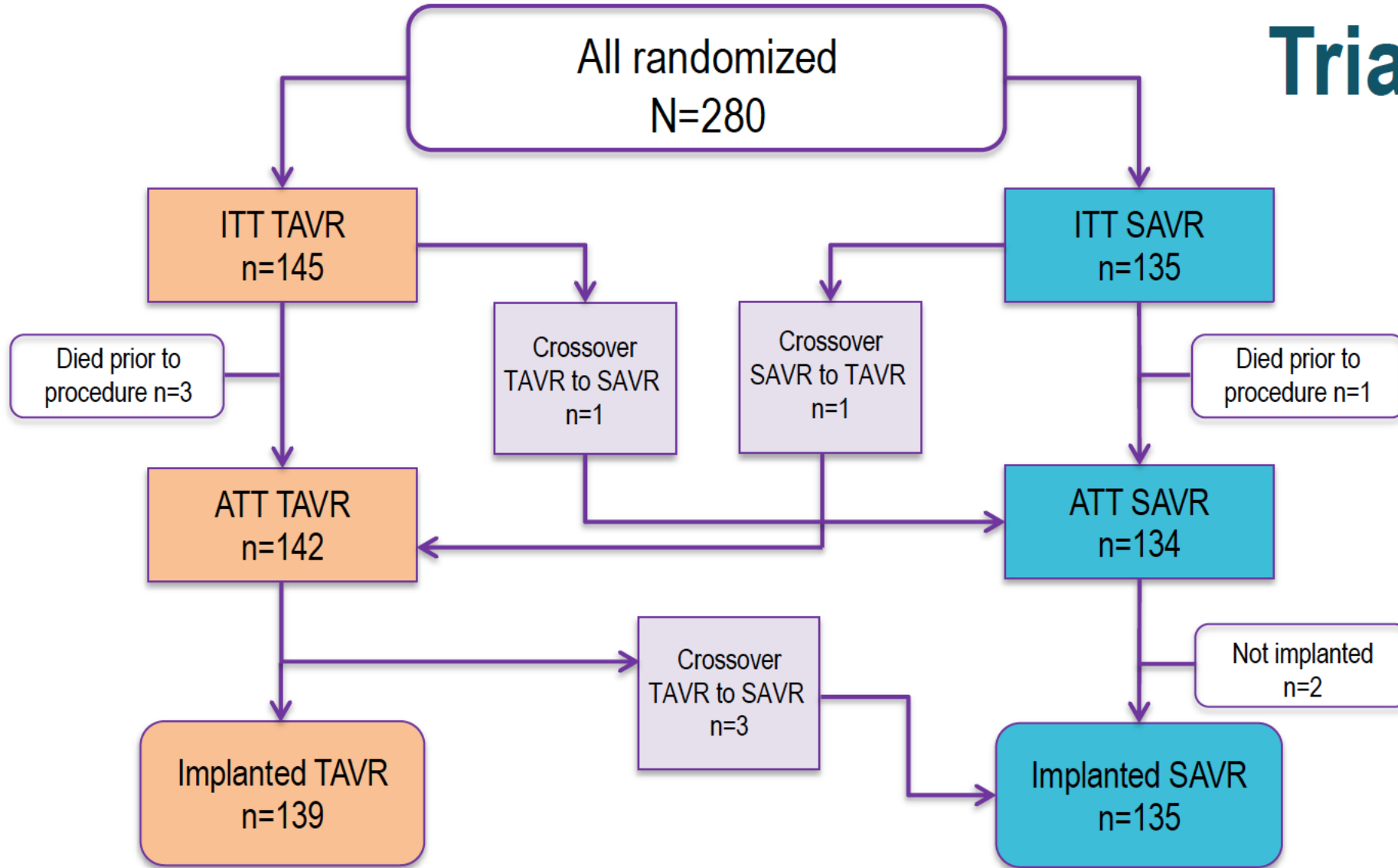


Objective:	To compare TAVR vs. SAVR in patients ≥ 70 years eligible for surgery (all-comers population/consecutive recruitment)
Primary outcome:	Composite rate of all-cause mortality, stroke or myocardial infarction at 1 year (VARC II-defined)
Secondary outcomes:	Safety and efficacy (NYHA), echocardiographic outcomes (VARC II-defined)
Design:	Prospective, multicenter, non-blinded, randomized trial
Enrollment period:	December 2009 - April 2013



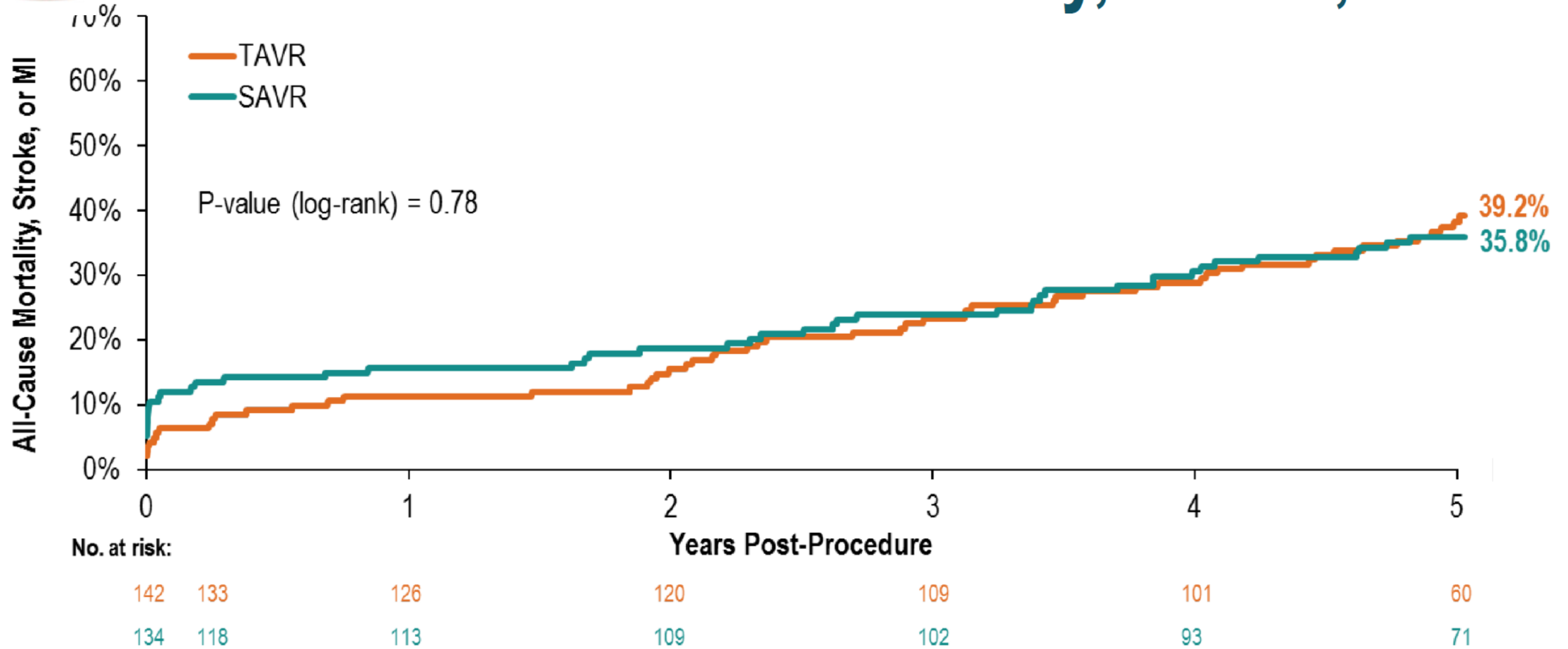


Trial Flowchart

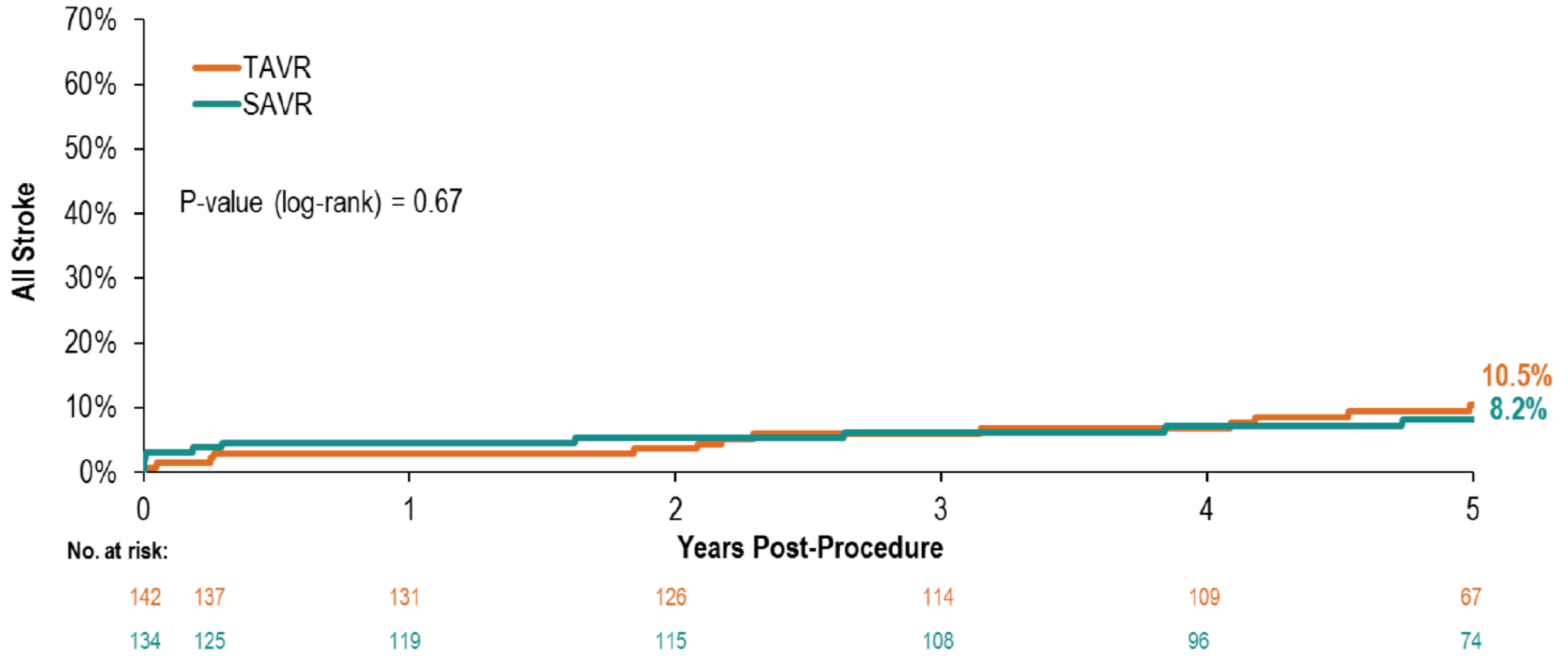




All-Cause Mortality, Stroke, or MI

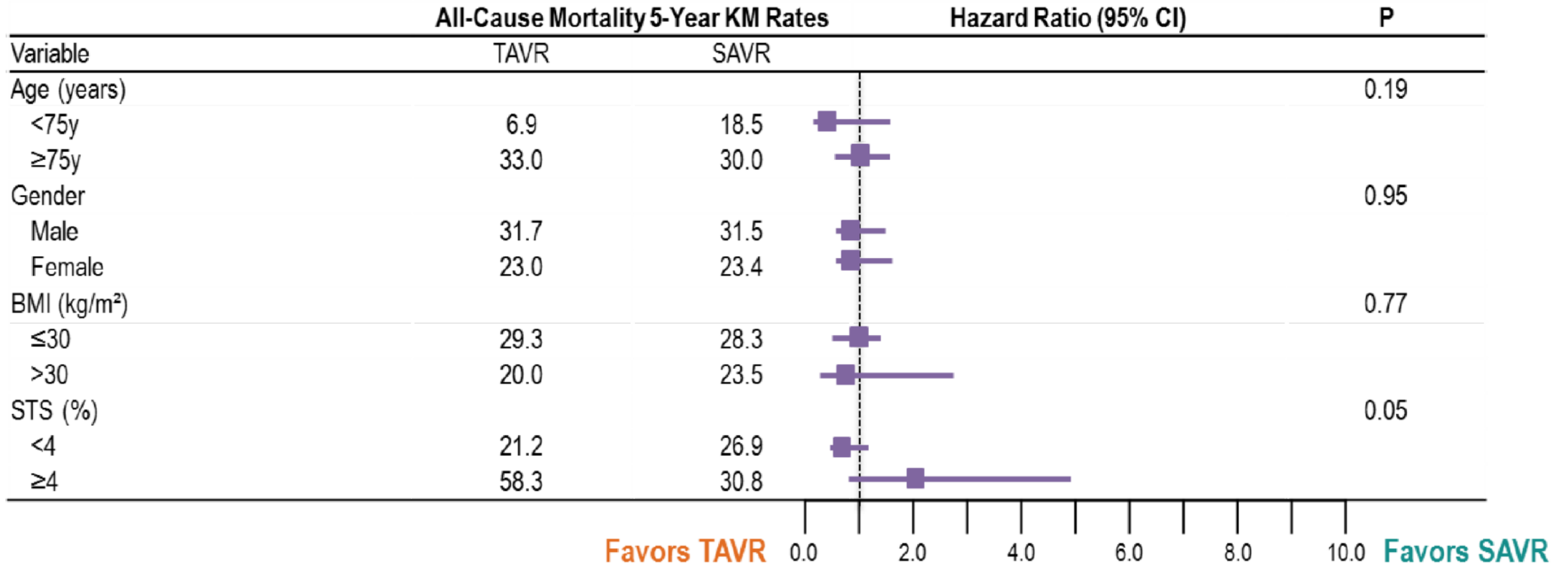


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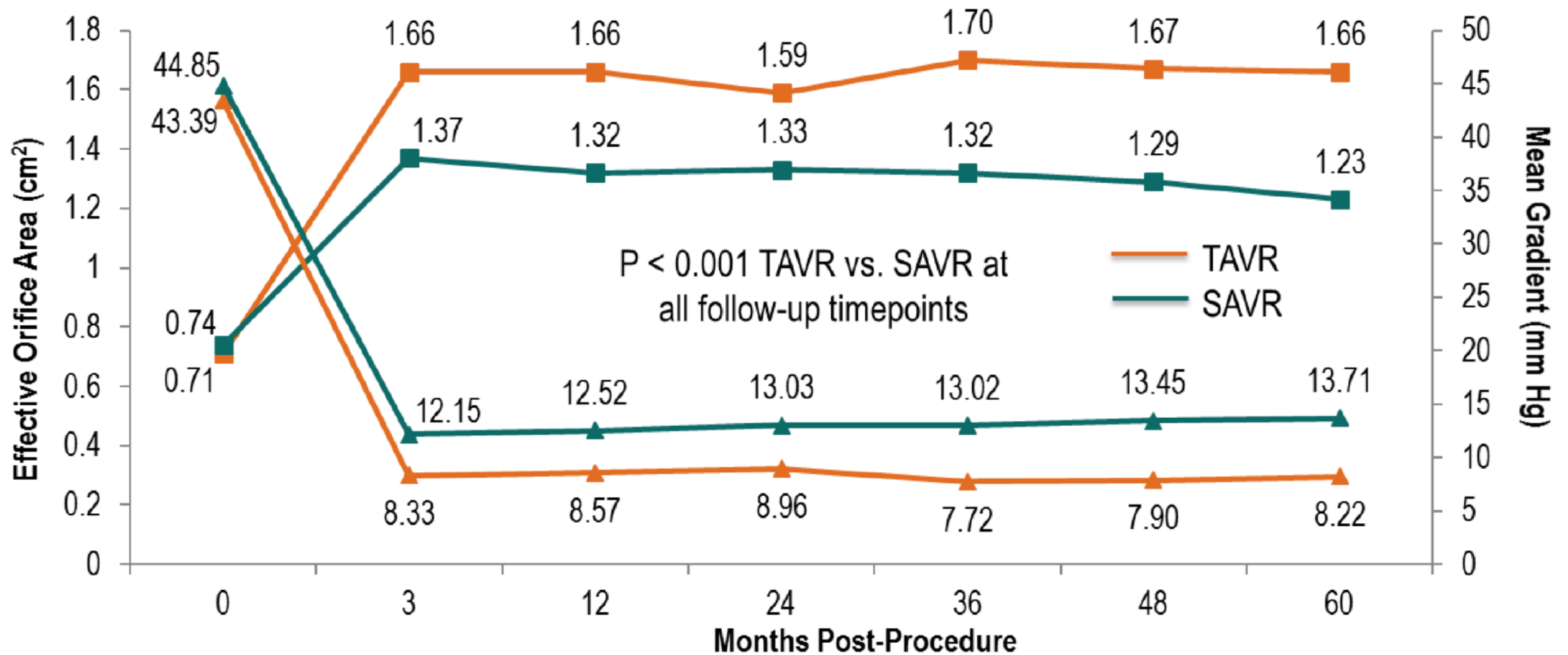
Subgroup Analysis for 5-Year Mortality



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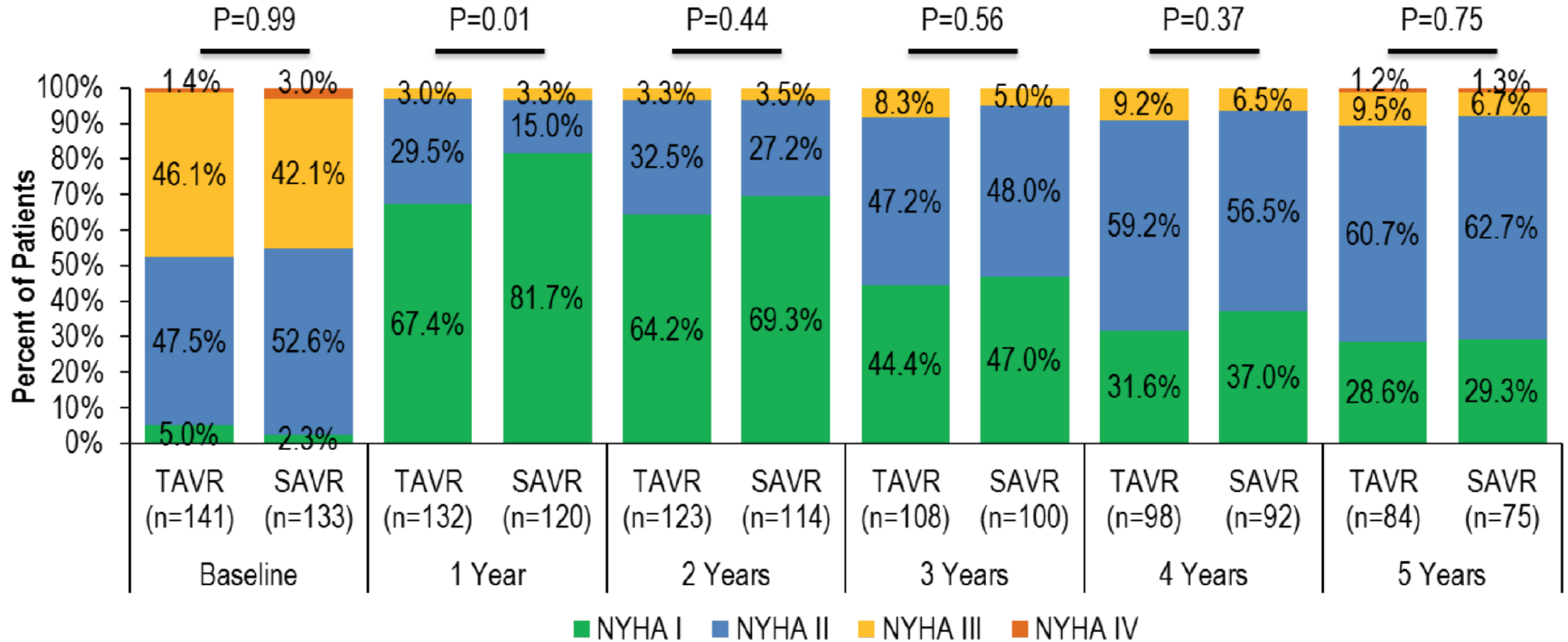


Aortic Valve Performance





NYHA Class



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Conclusion



- NOTION is the first trial to report on 5-year outcomes after TAVR vs. SAVR in lower risk patients (82% with STS < 4%)
- After 5 years, there were no differences in all-cause mortality, stroke, myocardial infarction, or these combined
- There was no difference in prosthetic valve re-intervention
- Prosthetic opening area was larger and mean gradient lower for TAVR and remained unchanged over time
- TAVR continued to have more mild/moderate prosthetic regurgitation
- New pacemaker implantation after TAVR trended to be associated with increased mortality
- Determining the longevity of TAVR prostheses will require longer term follow-up





1-Year outcomes of perioperative beta-blockade in patients undergoing noncardiac surgery

**Dr. PJ Devereaux on behalf of POISE Investigators
Population Health Research Institute, Hamilton, Canada**



Background

- POISE randomized patients undergoing noncardiac surgery to receive beta-blocker or placebo
- **We previously reported 30-day** results demonstrating that extended-release metoprolol
 - **reduced risk of MI** (HR, 0.73; 95% CI, 0.60-0.89) but
 - **increased risk of stroke** (HR, 2.17; 95% CI, 1.26-3.74) and mortality (HR, 1.33; 95% CI, 1.03-1.74)
 - risk of death due to sepsis/infection 36 vs 18 deaths P=0.016
- To facilitate insights into longer-term impact of perioperative beta-blockade, we designed POISE to evaluate secondary outcomes at 1 year after surgery



POISE Trial design

- Design – blinded RCT
- Eligibility – age ≥ 45 yrs, undergoing noncardiac surgery, and have or be risk of atherosclerotic disease
- Intervention – metoprolol CR or placebo
 - **100 mg given 2-4 hrs preop and at 6 hours after surgery**
 - Day after surgery for 30 days patients received 200 mg of study drug
 - dose decreased to 100 mg daily if patient became hypotensive or bradycardic



Baseline characteristics



Characteristics	Metoprolol (N=4174)	Placebo (N=4177)
Age – (mean yrs)	69	69
Male	63%	64%
Preoperative		
heart rate - mean	78	78
blood pressure - mean	139/78	139/79
History of		
coronary artery disease	43%	43%
peripheral arterial disease	42%	40%
stroke	15%	15%



Type of surgery

	Metoprolol (N=4174)	Placebo (N=4177)
Surgery %		
vascular	42	41
intraperitoneal	21	22
orthopedic	21	21
other	16	16

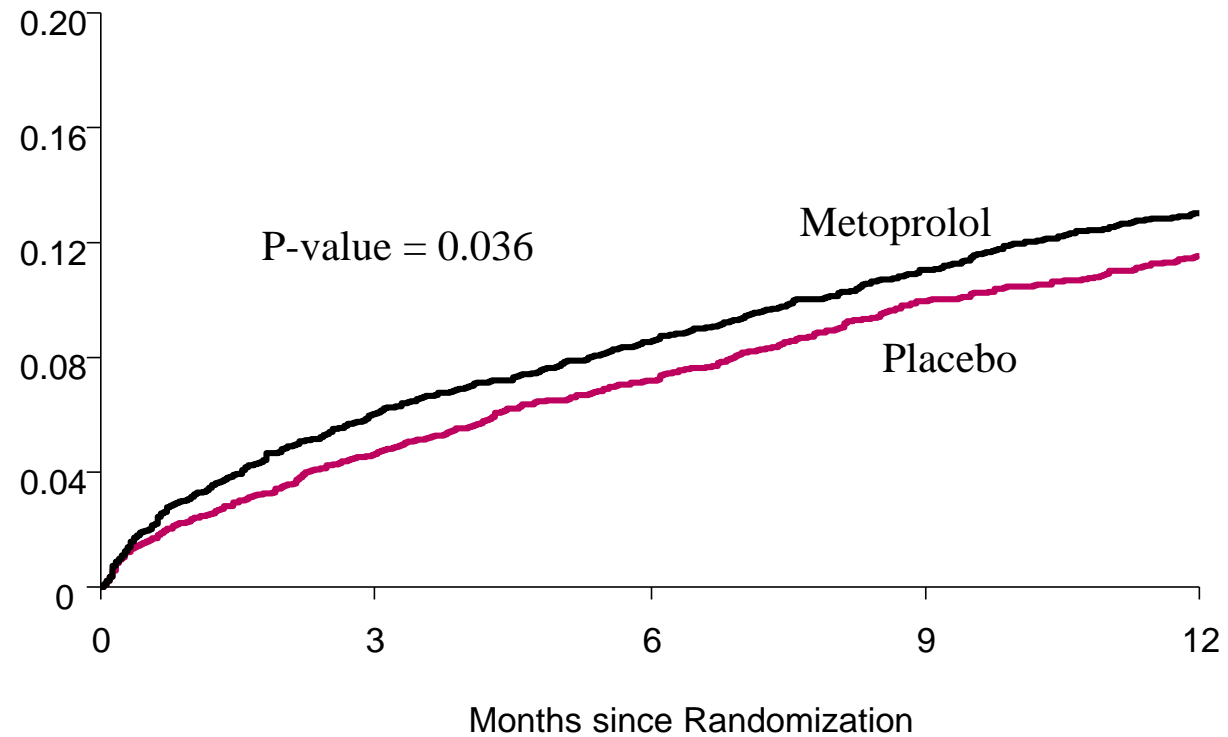


1-year mortality outcomes

Outcome	metoprolol n=4174 no. (%)	Placebo n=4177 no. (%)	HR (95% CI)	P value
All cause mortality	410 (10)	356 (9)	1.16 (1.01-1.34)	0.036
CV mortality	182 (4)	167 (4)	1.10 (0.89-1.36)	0.37
Non-CV mortality	228 (6)	189 (5)	1.22 (1.01-1.48)	0.043



1-year all-cause mortality



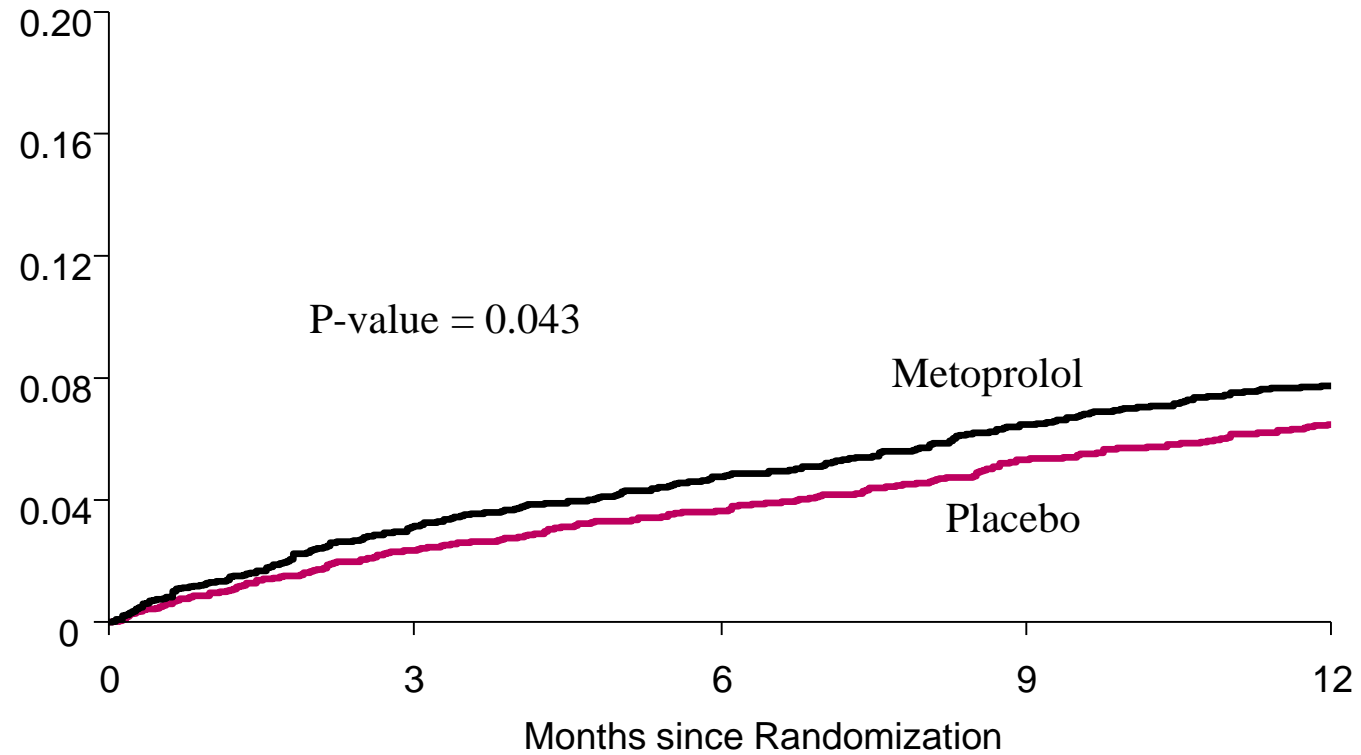
No. at Risk

Placebo 4177 2668 2559 2473 2408

Metoprolol 4174 2626 2522 2439 2347



1-year non-CV mortality

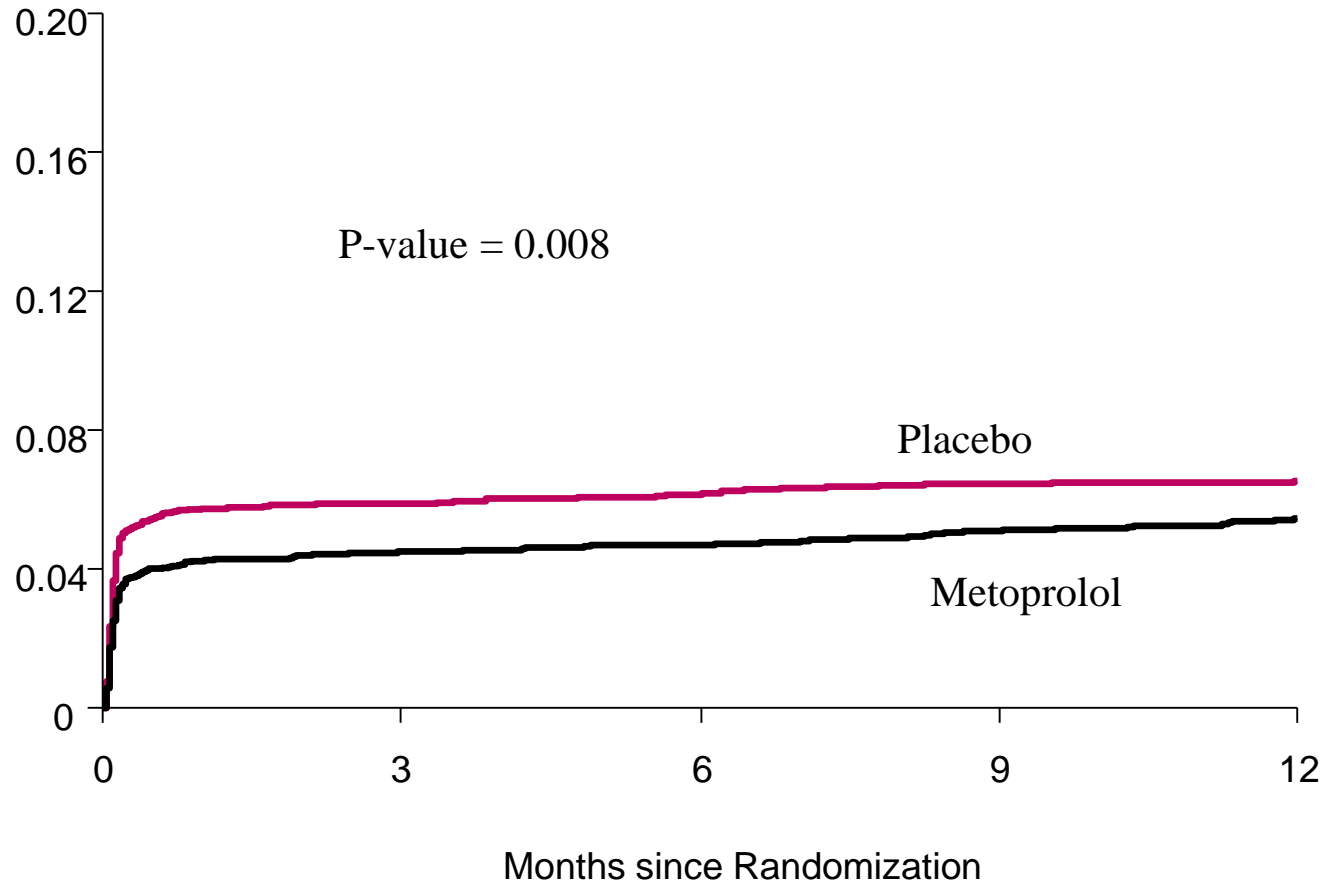


No. at Risk

Placebo	4177	2668	2559	2473	2408
Metoprolol	4174	2626	2522	2439	2347



1-year myocardial infarction



No. at Risk

Placebo	4177	2548	2450	2370	2308
Metoprolol	4174	2542	2445	2357	2264



1-year outcomes

Outcome	metoprolol n=4174 no. (%)	Placebo n=4177 no. (%)	HR (95% CI)	P value
Stroke	85 (2)	59 (1)	1.52 (1.09-2.12)	0.014
Cardiac arrest	24 (1)	26 (1)	0.93 (0.53-1.62)	0.79
Pulmonary embolism	15 (<1)	11 (<1)	1.36 (0.63-2.97)	0.43



Independent predictors of 1-year mortality

	Frequency of complication no. (%)	OR (95% CI)
Myocardial infarction	468 (6)	3.07 (2.39-3.94)
Coronary revascularization	66 (1)	0.31 (0.13-0.76)
Stroke	144 (2)	5.94 (4.16-8.48)
Cardiac arrest	50 (1)	11.80 (6.51-21.3)
Pulmonary embolism	26 (<1)	11.6 (5.32-25.20)



Implications and conclusions

- POISE results suggest at 1 year, for every 1000 patients having noncardiac surgery, metoprolol CR would
 - prevent 12 patients from experiencing an MI and 6 from undergoing cardiac revascularization but
 - result in excess of 13 deaths and 6 strokes
- Research is needed to establish way to derive benefit of perioperative beta-blockade while mitigating risk

ACC Late Breaking Clinical Trials 2018



UCSF

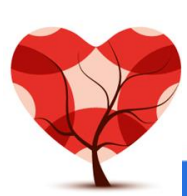
University of California
San Francisco

Vest Prevention of Early Sudden Death Trial (VEST)

Jeffrey Olgin, MD, FACC

Division of Cardiology, UCSF

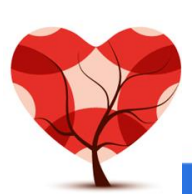
On behalf of the VEST Investigators



Background: VEST rationale

- ICD not indicated in immediate post-MI period
- Some early mortality not due to arrhythmias immediately post-MI, thus not preventable by ICD
- LVEF may recover over 3 months post-MI

Can a wearable cardioverter defibrillator (WCD) reduce SD mortality in the immediate post-MI period (<90 days) in patients with reduced LVEF, as a bridge to evaluation for ICD?



Methods: Intervention-WCD

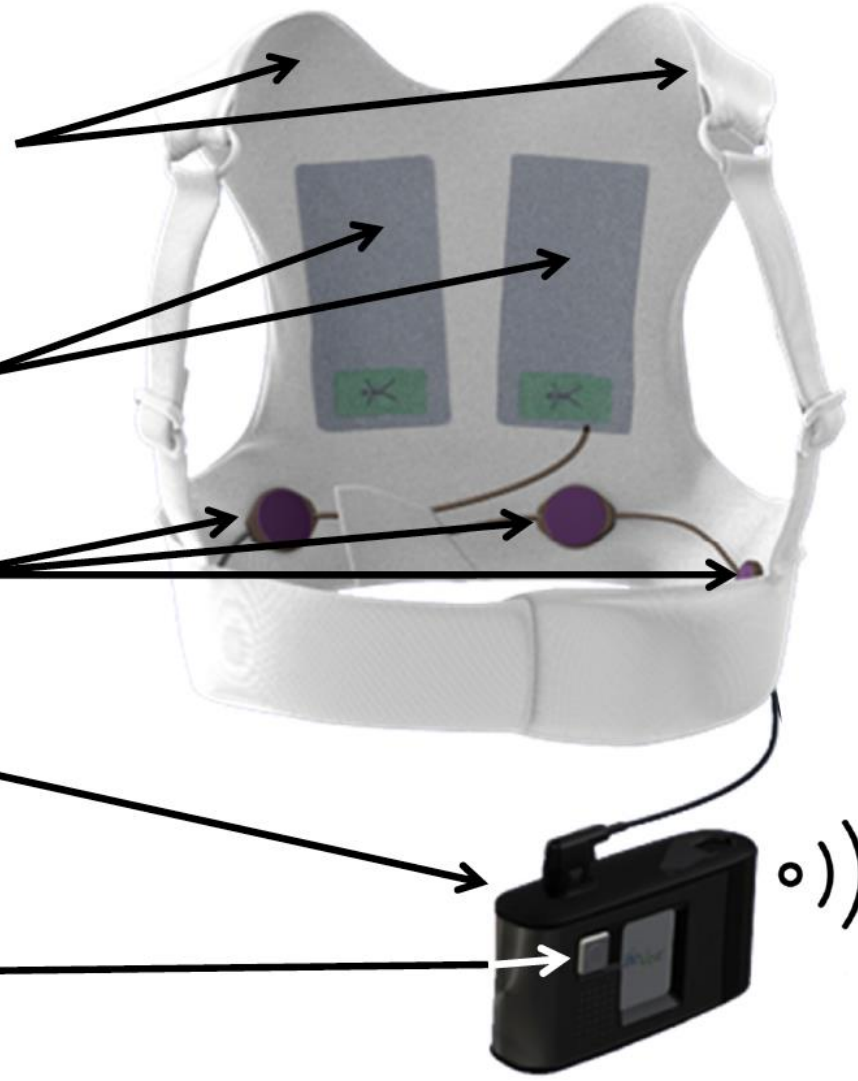
Washable-
Interchangeable
Garment

Self-Gelling
Defibrillation
Electrodes

Dry ECG
Electrodes

Rechargeable
Monitor &
Battery Pack

Response
Buttons



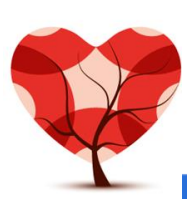
Monitors

- Wear-time
- Noise
- Device warning
- Asystole
- VT/VF

Treatment

- VT/VF





Methods: Inclusion & exclusion

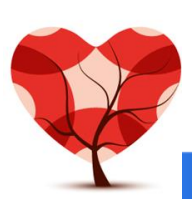
Inclusion Criteria

- ≤ 7 days of hospital discharge for acute MI
- EF $\leq 35\%$ assessed:
 - ≥ 8 hrs after MI
 - ≥ 8 hrs after PCI
 - ≥ 48 hrs after CABG

Exclusion Criteria

- Existing ICD
- Significant valve disease
- Unipolar pacing system
- Chronic hemodialysis
- Chest too small/large for WCD
- Discharge to SNF for >7 days
- Pregnancy

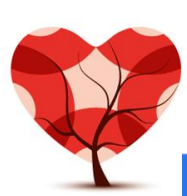




Results: Participant characteristics

Characteristic	WCD Group (N=1524)	Control Group (N=778)
Age, mean \pm SD	60.9 \pm 12.6	61.4 \pm 12.3
Men, n (%)	1107 (72.8%)	577 (74.7%)
Body mass index, Mean \pm SD	28.4 \pm 5.5	28.6 \pm 6.6
Smoker, n(%)	561 (36.9%)	273 (35.5%)
Race n (%)		
White	1278 (84.1%)	636 (82.6%)
Black	143 (9.4%)	75 (9.7%)
Asian	23 (1.5%)	14 (1.8%)
Native American/Alaskan	25 (1.7%)	12 (1.6%)
Pacific Islander/Hawaiian	1 (0.1%)	0 (0%)
Mixed	20 (1.3%)	14 (1.8%)
Hispanic, n (%)	85 (5.6%)	34 (4.4%)





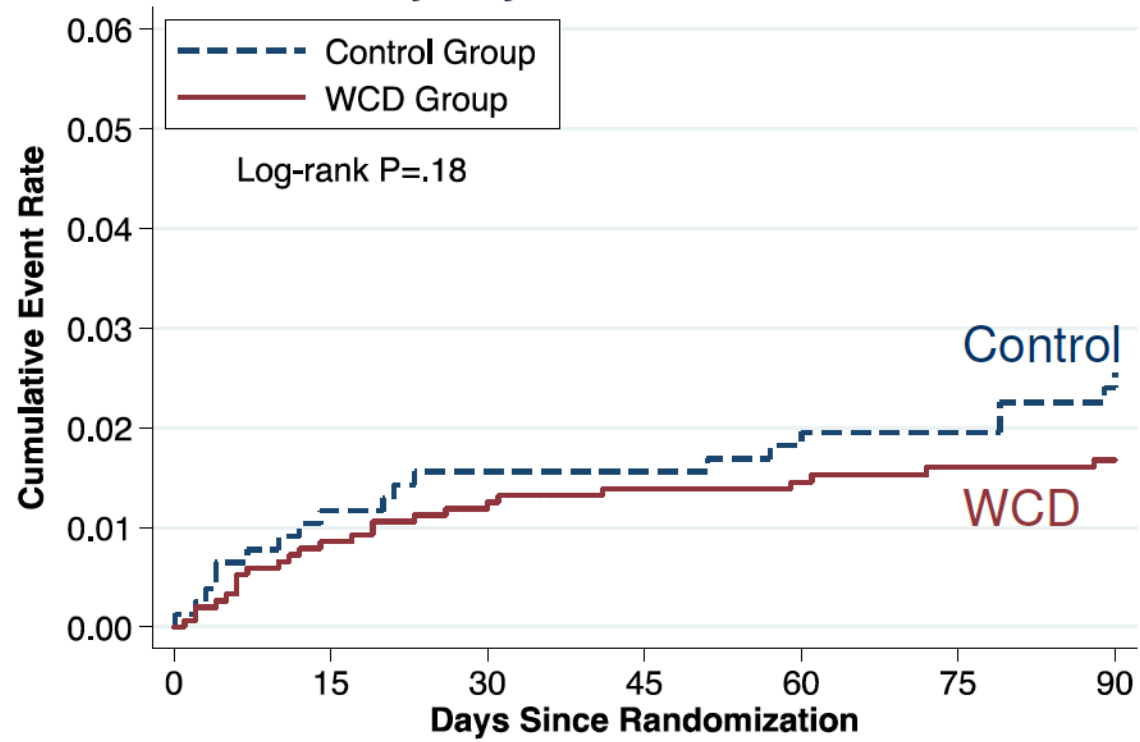
Results: Characteristics of index MI

Characteristic	WCD Group (N=1524)	Control Group (N=778)
LVEF	28.2 ± 6.1%	28.2 ± 5.9%
PCI during MI hospitalization	1272 (84.2%)	650 (84.1%)
Thrombolytics during MI hospitalization	118 (7.8%)	71 (9.2%)
CABG during index hospitalization	14 (0.9%)	12 (1.5%)
Cardiac Arrest/VF	169 (11.2%)	70 (9.1%)
Pulmonary Edema requiring Intubation	162 (10.7%)	88 (11.4%)
Intra-aortic Balloon Pump	173 (11.5%)	93 (12.0%)
Cardiogenic Shock	136 (9.0%)	79 (10.2%)



Results: Outcomes, intention-to-treat

A Sudden + Ventricular Tachyarrhythmia Death



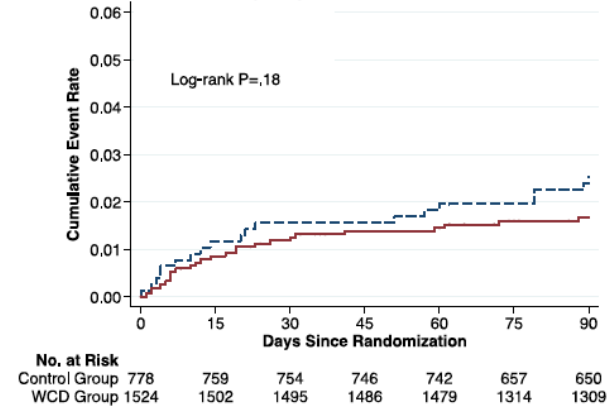
No. at Risk							
Control Group	778	759	754	746	742	657	650
WCD Group	1524	1502	1495	1486	1479	1314	1309



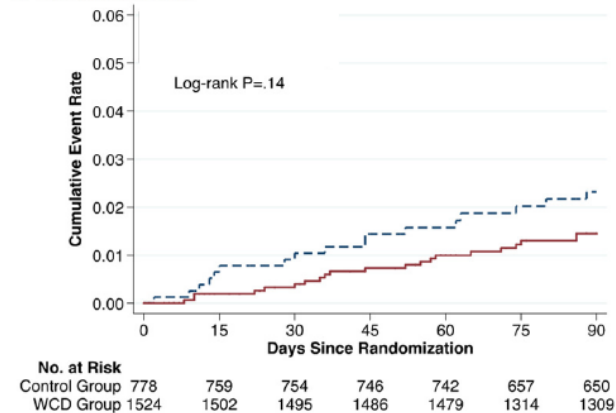


Results: Outcomes, intention-to-treat

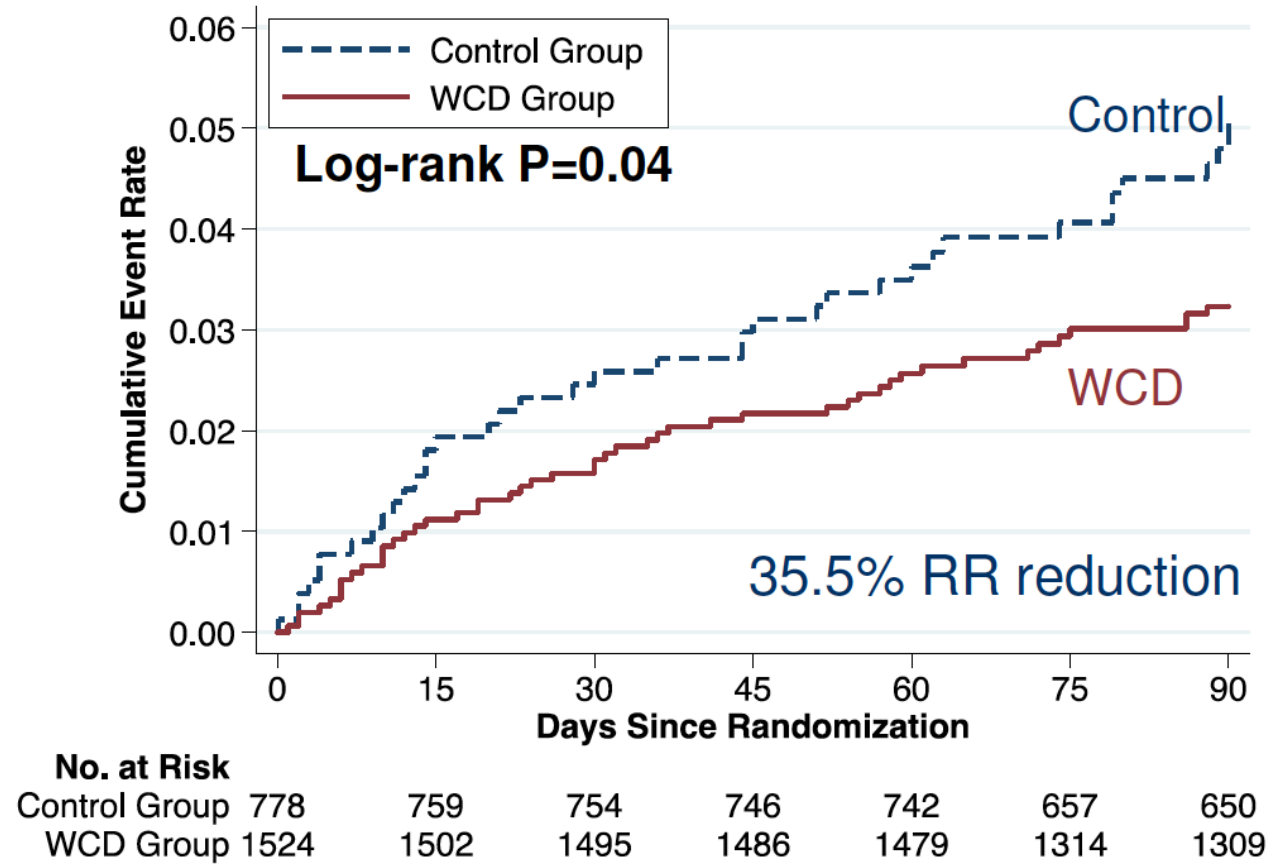
A Sudden + Ventricular Tachyarrhythmia Death



B Non-sudden Death



C Death from Any Cause





Results: Cause-specific death

Clinical event type	WCD (N=1524)	Control (N=778)	P value*
FATAL EVENTS, n (%)			
Sudden Death (1° outcome)	25 (1.6%)	19 (2.4%)	0.18
Non-sudden death	21 (1.4%)	17 (2.2%)	0.15
Congestive heart failure death	10 (0.7%)	5 (0.6%)	1.0
Recurrent MI death	1 (0.1%)	1 (0.1%)	1.0
Stroke death	0 (0.0%)	4 (0.5%)	0.01
Other cardiovascular death	5 (0.3%)	3 (0.4%)	1.0
Other death	5 (0.3%)	4 (0.5%)	0.72
Indeterminate death	2 (0.1%)	2 (0.3%)	0.83
Death, any cause	48 (3.1%)	38 (4.9%)	0.04
NON-FATAL EVENTS, n (%)			
Rehospitalization, cardiovascular	334 (22%)	174 (22%)	0.81
Rehospitalization, any cause	475 (31%)	253 (33%)	0.51



Discussion: Sudden death outcome

- **Possible misclassification of sudden deaths**
 - Reducing power for SD outcome but not total mortality
 - 14 of 20 participants who received an appropriate shock survived to 90 days
- **WCD may confer additional protection beyond SD**
 - Earlier care for bradycardia, NSVT or aborted shocks
 - Lower stroke death in WCD group
- **Reduced anxiety or increased medication compliance**
 - More shortness of breath in controls





Conclusions

- The WCD did not statistically significantly reduce sudden death mortality
- The WCD did reduce total mortality in the first 90 days post-MI in patients with LVEF $\leq 35\%$
 - Relative risk reduction of 35.5%
- VEST represents the first randomized, controlled trial of the WCD
- Prescribing the WCD is reasonable to protect high-risk patients with a low LVEF post-MI until evaluation for an ICD at 40-90 days



Clinical trials in 2018

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