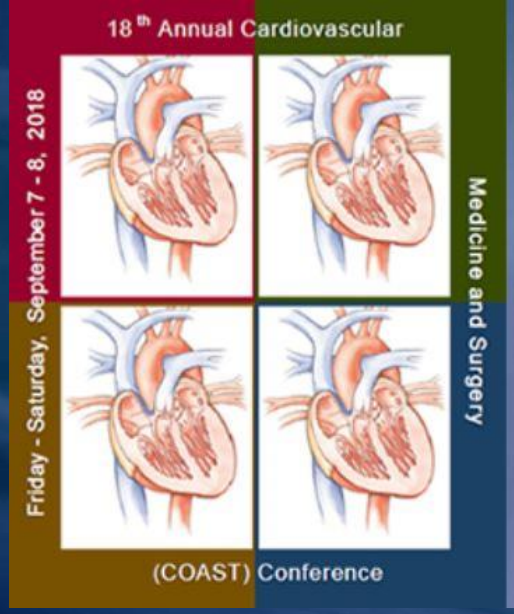

18th Annual Cardiovascular Medicine and Surgery (COAST) Conference

September 7-8, 2018
Mandarin Oriental - Las Vegas, NV

Albert Yuh-Jer Shen, MS, MD
Chief, Dept. of Cardiology
Los Angeles Medical Center

Clinical Professor of Medicine
UCLA School of Medicine

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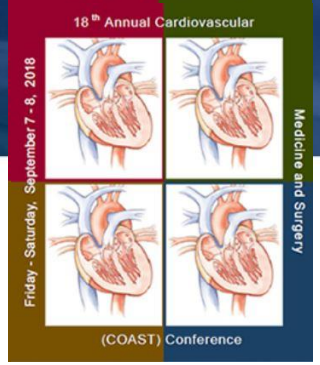

2018 Cardiovascular Medicine Highlights

- *These are <u>some</u> of the clinically relevant studies (IMO) presented and/or published since the last COAST*
- *Most slides were pirated off the original presentation (whenever possible) or from the published manuscript (when I could not find the slides online to pirate from)*
- *If your favorite study is not covered here, take it up with the conference chairman*

Disclosures of Conflict of Interest – None, except for my cynicism and lack of trust of industry and some so-called academic clinicians

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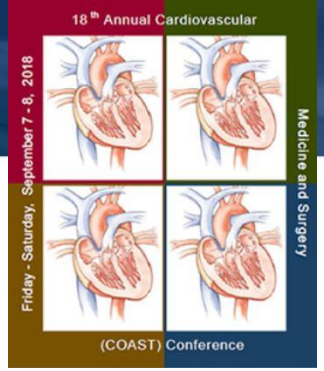
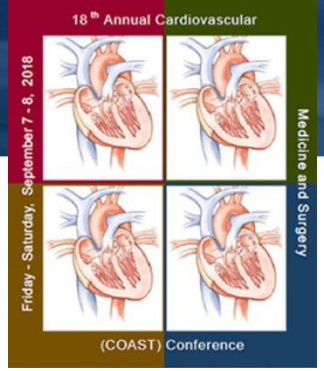


2018 Cardiovascular Medicine Highlights

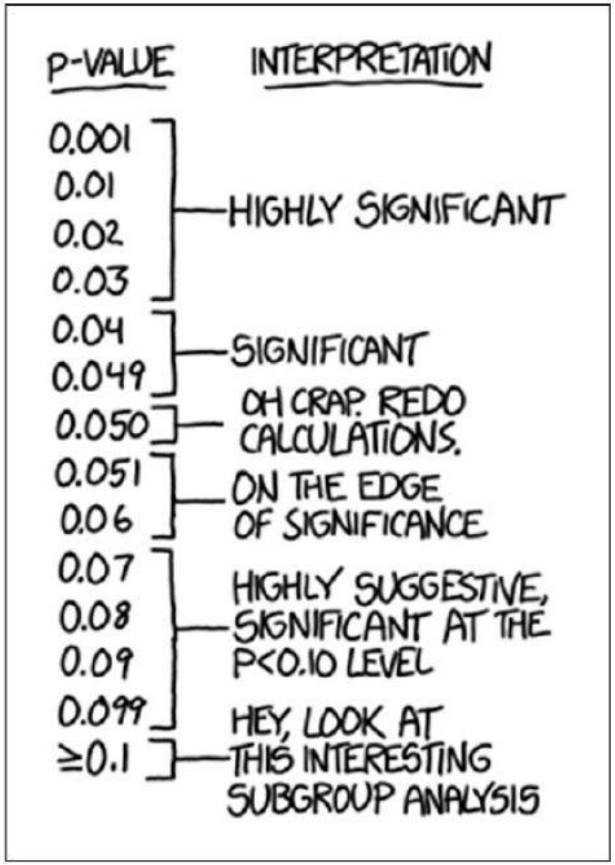
1. ORBITA
2. MITRA-FR
3. POET
4. SMART-DATE
5. CASTLE-AF
6. CABANA
7. POISE 1-Yr Follow-up
8. VEST
9. CECCY
10. Lisinopril or Carvedilol for Prevention of Trastuzumab Induced Cardiotoxicity
11. ODYSSEY Outcomes



How To Interpret The Studies…

Null Hypothesis Significance Testing, aka…

Statistical Hypothesis Inference Testing



Beware of P-hacking

ORBITA
(TCT 2017, Lancet 2018)

- *Over 500 000 PCIs per year worldwide for* stable angina
- *Primarily for angina relief*
- *Size of angina relief beyond placebo unknown*
  - **Unblinded PCI increases exercise time by 96”** (ACME, NEJM 1992)
  - **Single antianginal drug increases exercise time by 48-55”** (MARISA [ranolazine] Circ 2003 and IIG [ivabradine] JACC 2004)

ORBITA
(TCT 2017, Lancet 2018)

Articles

Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial

*Rasha Al-Lamee, David Thompson, Hakim-Moulay Dehbi, Sayan Sen, Kare Tang, John Davies, Thomas Keeble, Michael Mielewczik, Raffi Kaprielian, Iqbal S Malik, Sukhjinder S Nijjer, Ricardo Petraco, Christopher Cook, Yousif Ahmad, James Howard, Christopher Baker, Andrew Sharp, Robert Gerber, Suneel Talwar, Ravi Assomull, Jamil Mayet, Roland Wensel, David Collier, Matthew Shun-Shin, Simon A Thom, Justin E Davies, Darrel P Francis, on behalf of the ORBITA investigators**

Summary

Background Symptomatic relief is the primary goal of percutaneous coronary intervention (PCI) in stable angina and is commonly observed clinically. However, there is no evidence from blinded, placebo-controlled randomised trials to show its efficacy.

Lancet 2018; 391: 31–40
Published Online
November 2, 2017

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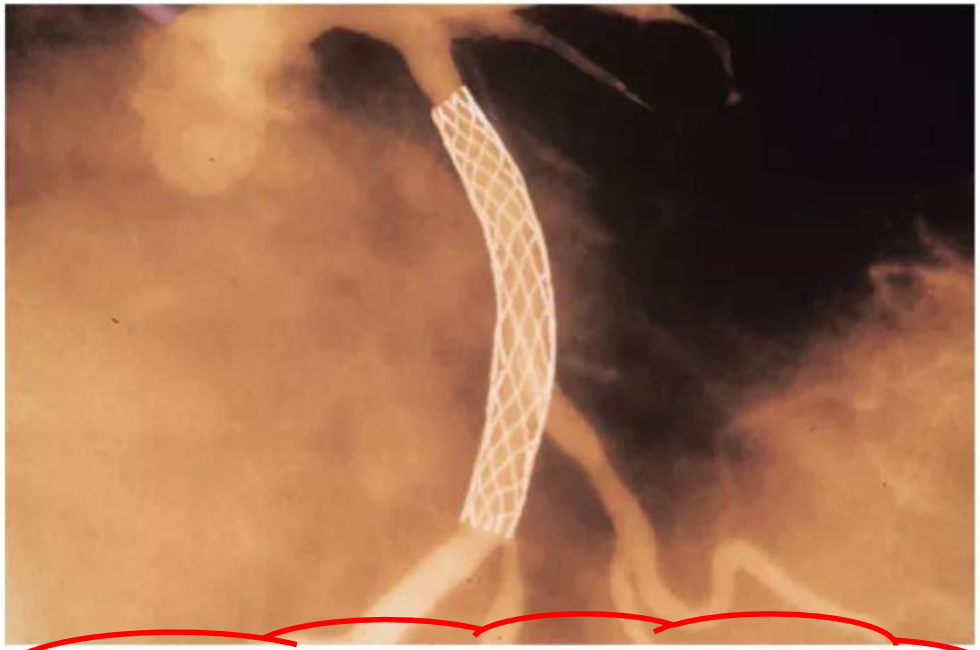
ORBITA
(NYT 2018)

Health

WELL



GJLP, CNRI, VIA SCIENCE SOURCE

‘Unbelievable’: Heart Stents Fail to Ease Chest Pain

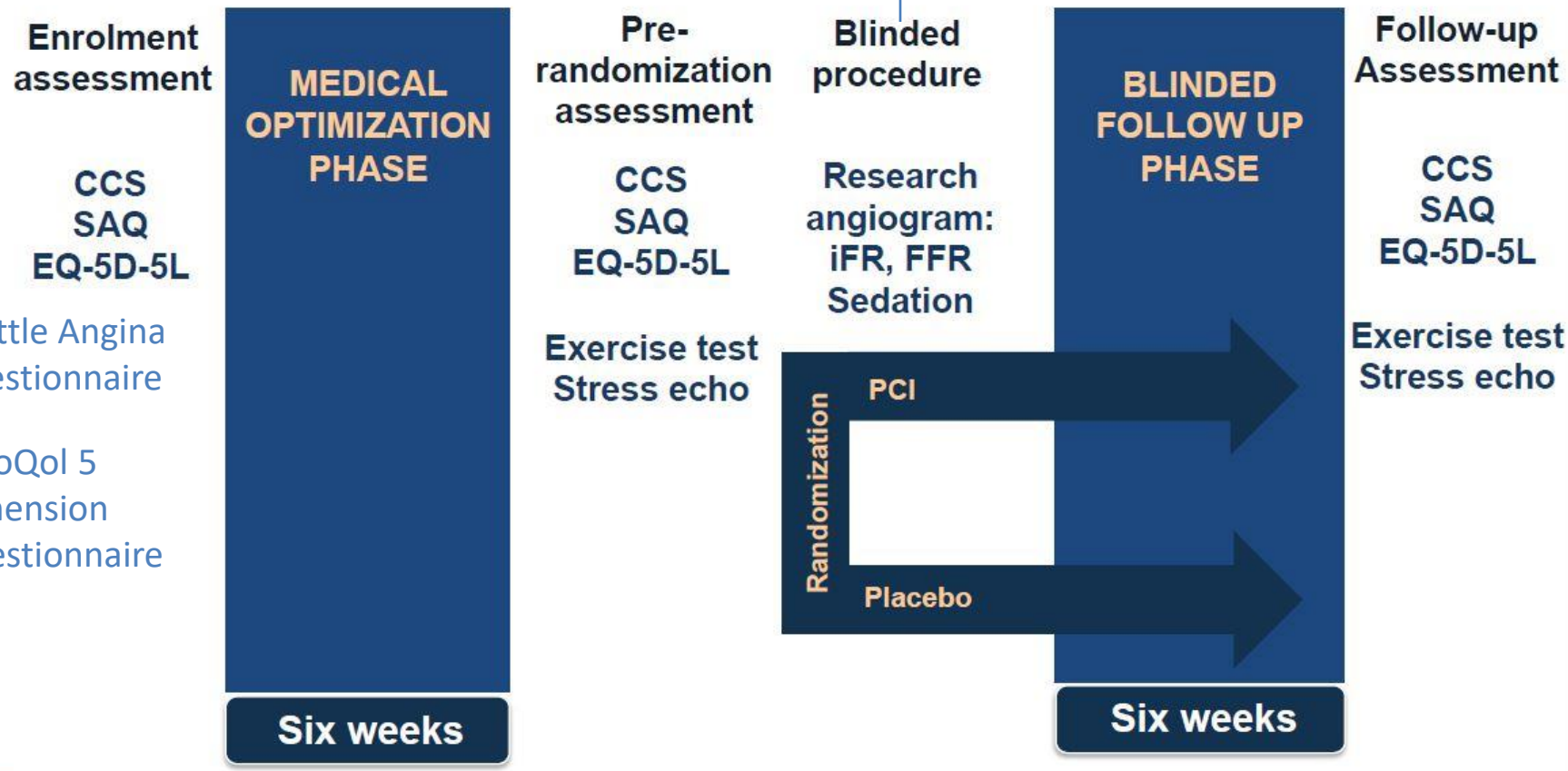
With a sham treatment, British researchers found that a common and often costly cardiac procedure does not relieve discomfort.

1d ago · By GINA KOLATA

ORBITA
Trial design

Cath – SVD

Sham achieved by sedation & auditory isolation



Seattle Angina Questionnaire

EuroQol 5 Dimension Questionnaire

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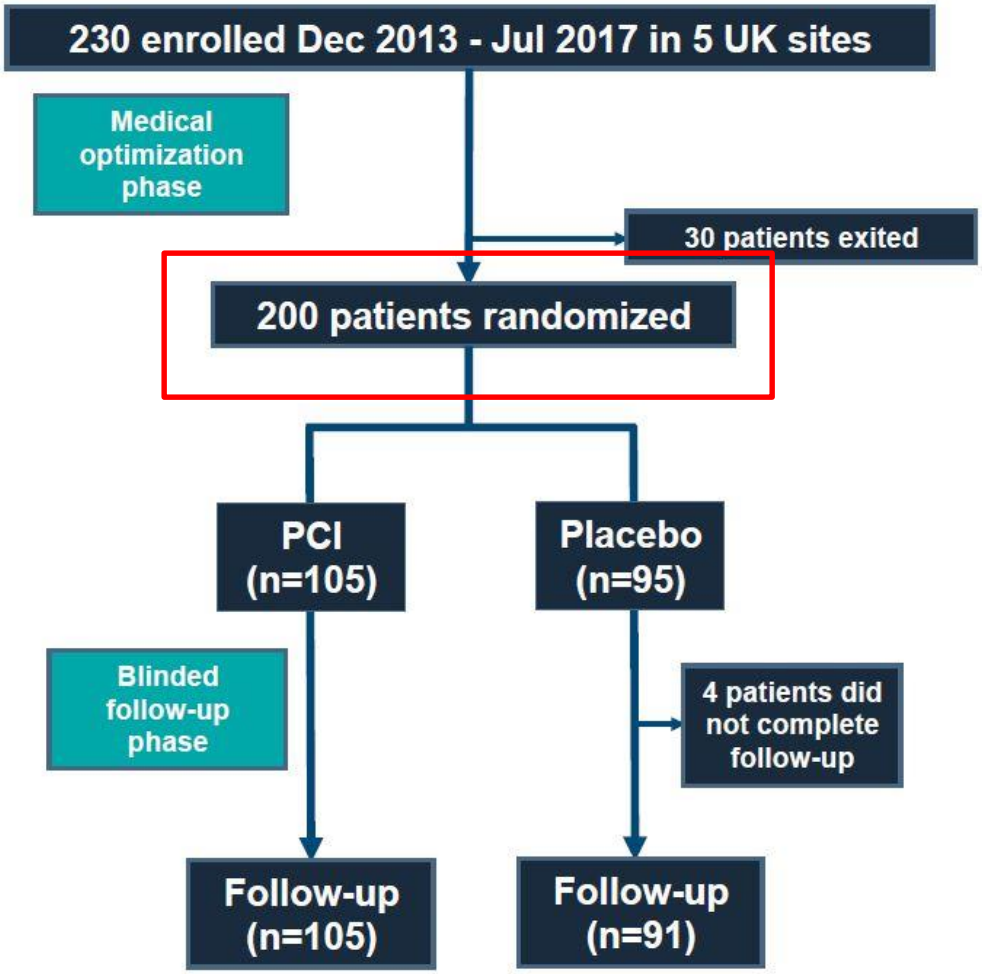
ORBITA



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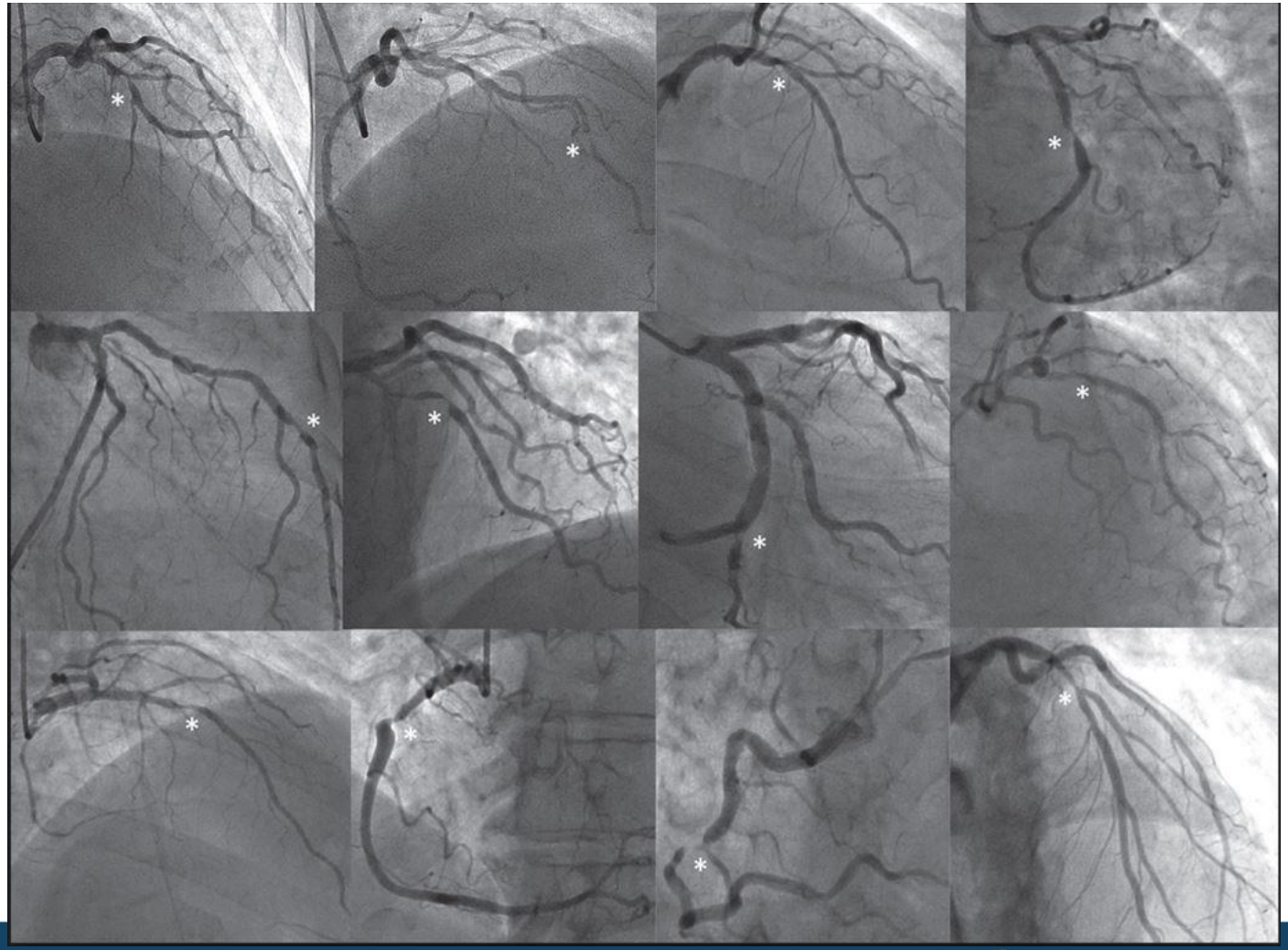
ORBITA



- All single vessel dz
- 70% LAD
- All PCI was w/ DES
- Median stent length 24 mm

ORBITA
Stenosis severity

	PCI n = 105	Placebo n = 95	P
Area stenosis by QCA (%)	84.6 (SD 10.2)	84.2 (SD 10.3)	0.781
FFR	0.69 (SD 0.16)	0.69 (SD 0.16)	0.778
iFR	0.76 (SD 0.22)	0.76 (SD 0.21)	0.751

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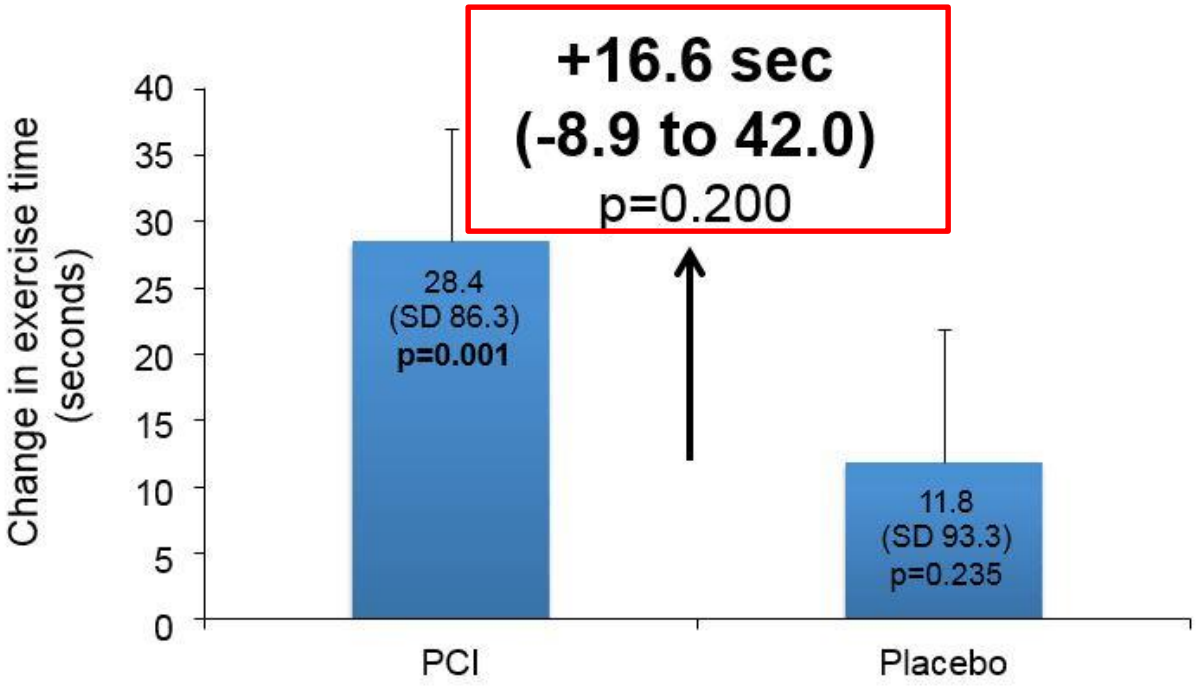
ORBITA

Primary endpoint result

Change in total exercise time



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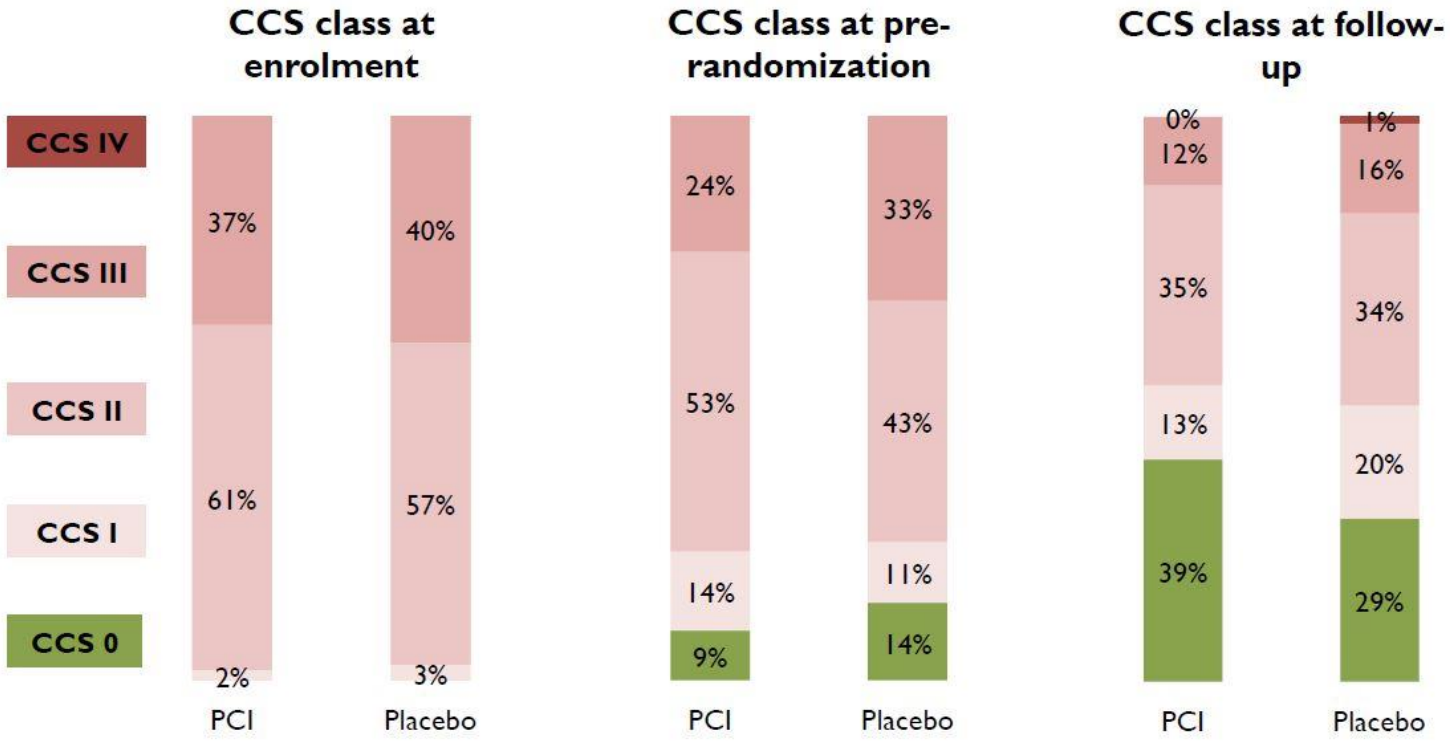
ORBITA

Secondary endpoint results

CCS class improved in both groups



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ORBITA

Secondary endpoint results

Blinded evaluation of ischaemia reduction

Wall motion score:

1. Normal
2. Hypokinetic
3. Akinetic
4. Dyskinetic
5. Aneurysmal

Peak stress wall motion index score	PCI n = 80	Placebo n = 57
Pre-randomization	1.11 (0.18)	1.11 (0.18)
Follow-up	1.03 (0.06)	1.13 (0.19)
Δ (Pre-randomization to follow-up)	-0.08 (0.17)	0.02 (0.16)
	p<0.0001	p=0.433
Difference in Δ between arms	-0.09 (-0.15 to -0.04) **p=0.0011**	

ORBITA

- ORBITA is the first placebo-controlled randomized trial of PCI in stable angina
- Area stenosis QCA 84.4%, FFR 0.69, iFR 0.76
- PCI was safe and physiologically effective
- PCI significantly reduced ischemic burden as assessed by stress echo
- In this single vessel, angiographically guided trial there was no difference in exercise time increment between PCI and placebo

ORBITA

Editorial by David L Brown, Rita F Redberg

Comment

Last nail in the coffin for PCI in stable angina?

Interventional cardiology began in Switzerland in 1977, when Andreas Gruentzig performed the first successful percutaneous transluminal coronary angioplasty (PTCA) on a 38-year-old man with angina and a focal proximal stenosis of the left anterior descending coronary artery. Despite numerous subsequent randomised trials and meta-analyses of these trials, which have shown no reduction in death or myocardial infarction,[1] the use of percutaneous coronary intervention (PCI) has grown exponentially. Some of this growth was driven by data from clinical trials suggesting that PCI was more effective in relieving angina than medical therapy alone. For example, in 1992, the results of the Angioplasty Compared to Medicine (ACME) study,[2] showed that at

NCDR

Cardiovascular Data Registry showed that less than half of patients undergoing PCI were receiving optimal medical therapy, with no increase following the publication of COURAGE.[7] More importantly, despite the known placebo power of invasive procedures, until now, there had not been a blinded clinical trial of PCI in its entire 40 year history.[8]

In a landmark new study in *The Lancet*, the investigators of the Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) group[9] have filled this important gap. We commend them for challenging the existing dogma around a procedure that has become routine, ingrained, and profitable. The results of ORBITA show (once again) why regulatory

BSIP/Getty Images

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November 2, 2017
http://dx.doi.org/10.1016/
S0140-6736(17)32757-5

See Articles page 31

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MITRA-FR
(ESC 2018, NEJM 2018)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation

J.-F. Obadia, D. Messika-Zeitoun, G. Leurent, B. Iung, G. Bonnet, N. Piriou, T. Lefèvre, C. Piot, F. Rouleau, D. Carrié, M. Nejjari, P. Ohlmann, F. Leclercq, C. Saint Etienne, E. Teiger, L. Leroux, N. Karam, N. Michel, M. Gilard, E. Donal, J.-N. Trochu, B. Cormier, X. Armoiry, F. Boutitie, D. Maucort-Boulch, C. Barnel, G. Samson, P. Guerin, A. Vahanian, and N. Mewton, for the MITRA-FR Investigators*

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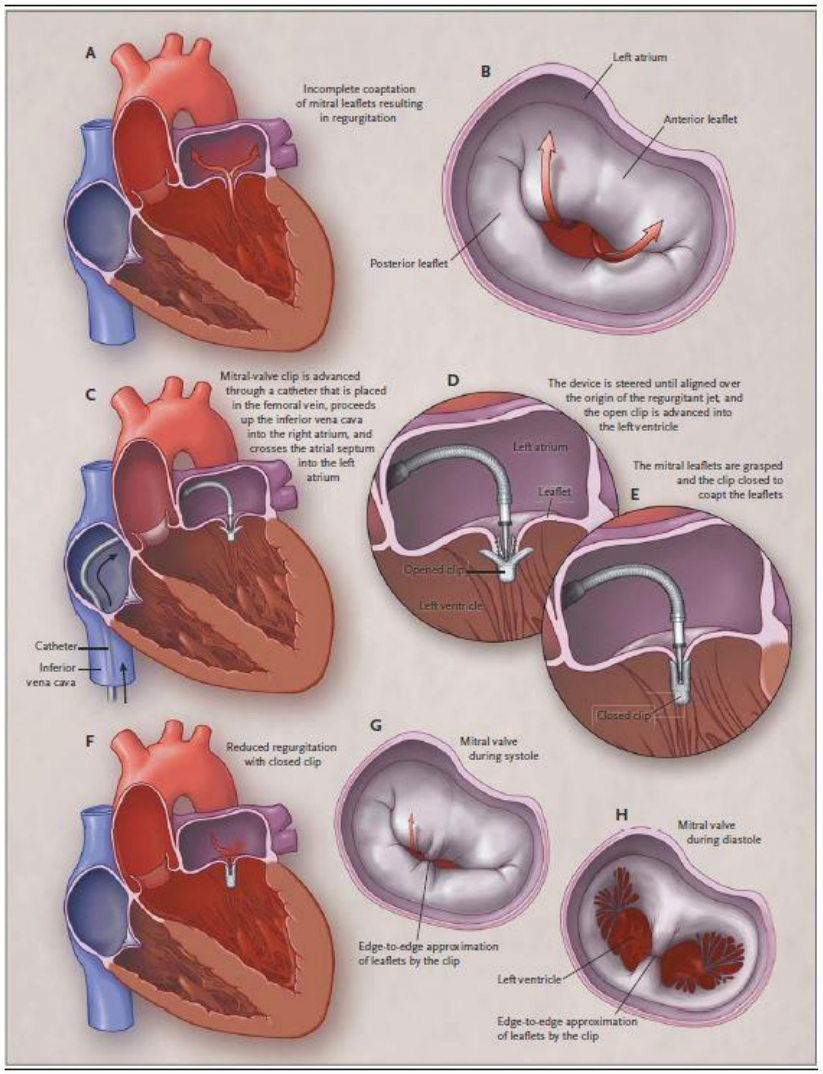
MITRA-FR



- *EVEREST II compared MitraClip v MV surgery in primary (nee structural) MR. This was <u>arguably</u> a "positive" trial for clip (less effective but safer w/ similar clinical outcomes).*
- *MITRA-FR and cousin trials compared clip v GDMT in secondary (nee functional) MR.*
- *Since EVEREST II, the FDA approved MitraClip for Primary MR, whereas the EMA approved it for "general use".*

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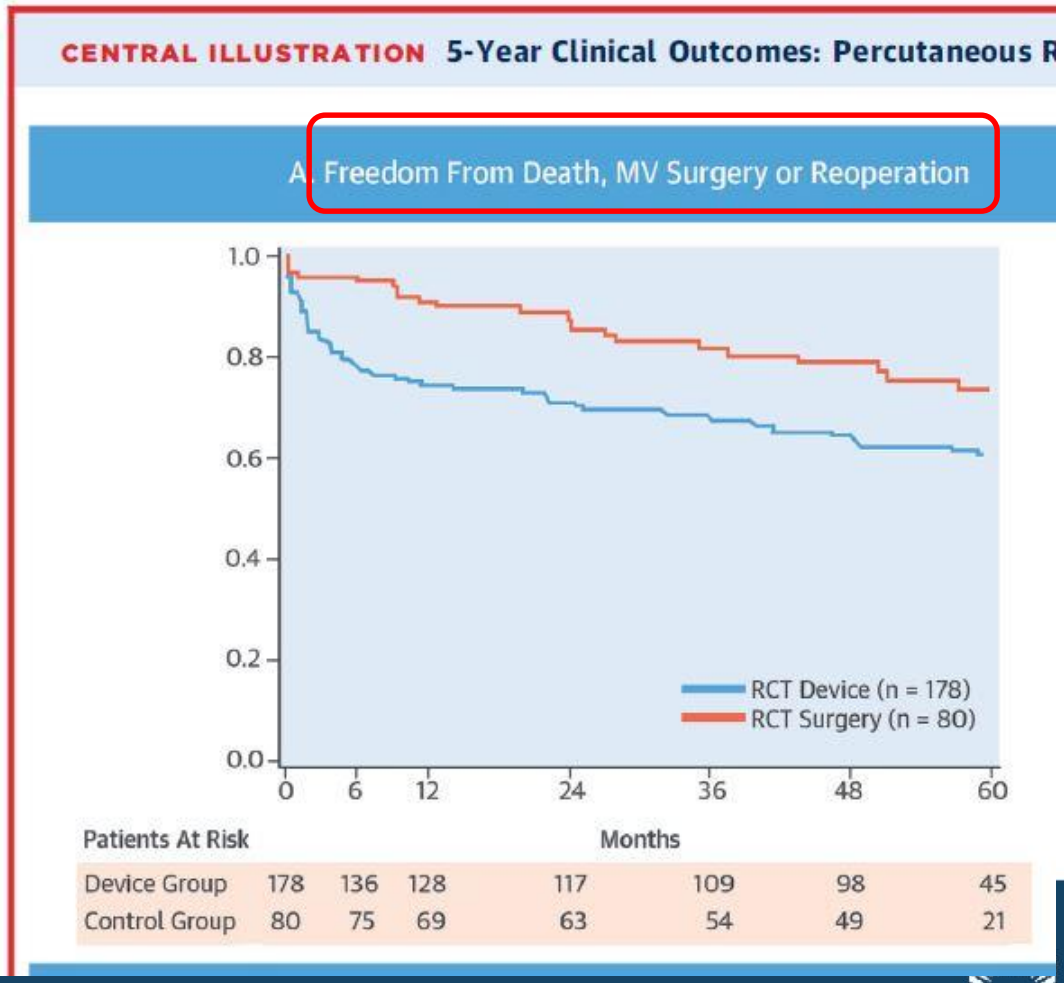
EVEREST II 5-Yr Outcome (JACC 2015)



- *Composite endpoint of freedom from death, surgery, or 3+ or 4+ MR in the as-treated population was 44.2% versus 64.3% in the percutaneous repair and surgical groups, respectively (p = 0.01).*
- *The difference was driven by increased rates of 3+ to 4+ MR (12.3% vs. 1.8%; p = 0.02) and surgery (27.9% vs. 8.9%; p = 0.003) with percutaneous repair.*

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EVEREST II 5 Yr Outcome Editorial

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 66, NO. 25, 2015

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2015.11.007

EDITORIAL COMMENT

Evaluating Catheter-Based Mitral Valve Therapies

Lessons Learned and Future Directions*

Anelechi C. Anyanwu, MD, David H. Adams, MD

JACC 2015

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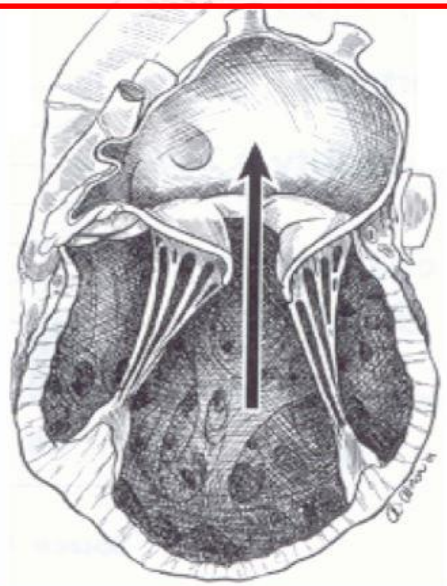
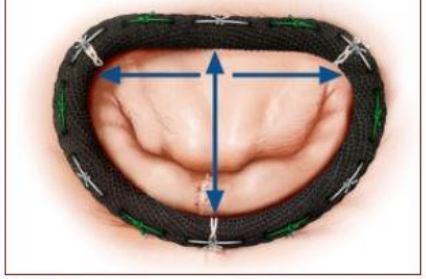
MITRA-FR

Background

Secondary / Functional



Treatment



Recommendations

2017 ESC/EACTS Guidelines

.....a percutaneous edge-to-edge procedure may be considered.....

IIb	C

-Grigioni et al Circulation 2001

-Baumgartner et al. Europ Heart J 2017

MITRA-FR

Study Design*

Objective → to evaluate the clinical efficacy of percutaneous mitral valve repair in addition to medical treatment in patients with heart failure and severe functional/secondary mitral regurgitation versus medical treatment alone.

Primary Endpoint "Composite" → All-Cause Deaths or Unplanned rehospitalization for Heart failure at 12 months

MITRA-FR

Inclusion Criteria

- Symptomatic despite Optimal Treatment (NYHA ≥II).
- At least one hospitalization for HF within 12 months preceding randomization
- Severe Secondary MR ➔ ERO > 20 mm^2 or R.vol>30 mL/beat
- 15% < EF < 40%
- Not eligible for surgery "Heart Team"
- Centralized echocardiographic Corelab

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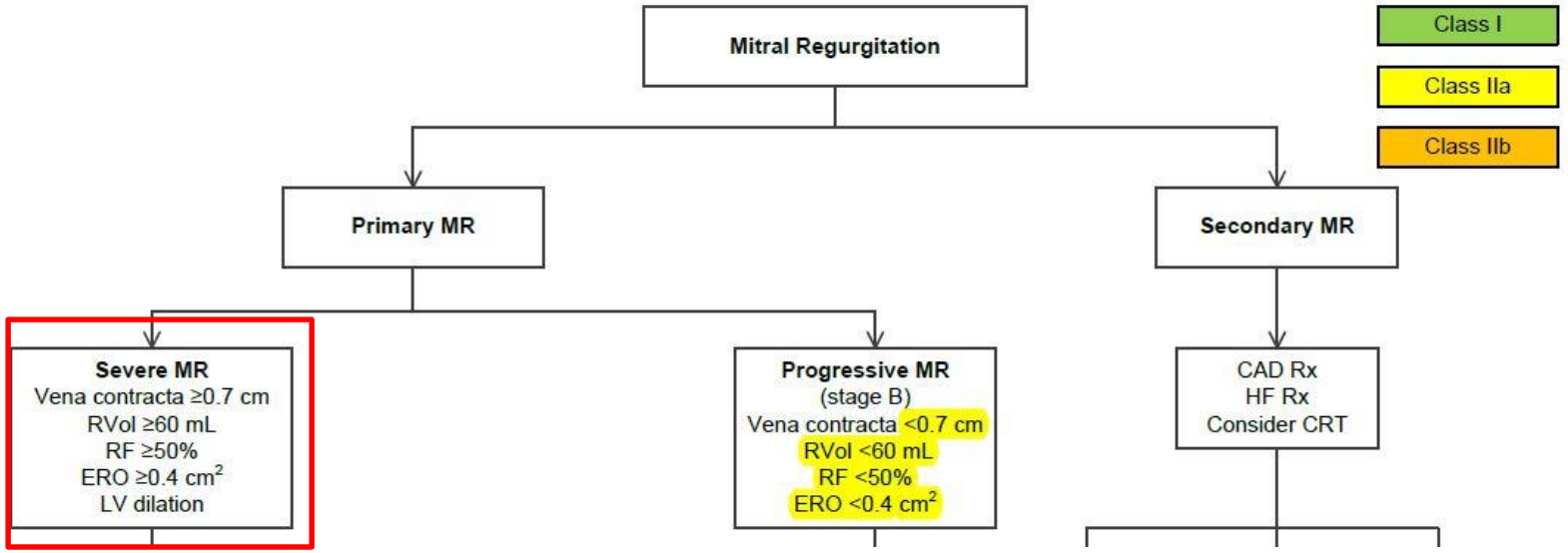
How Much MR Is “Severe”?

Nishimura, et al.
2017 AHA/ACC Focused Update on VHD

Figure 2. Indications for Surgery for MR (Updated Figure 4 From the 2014 VHD guideline)



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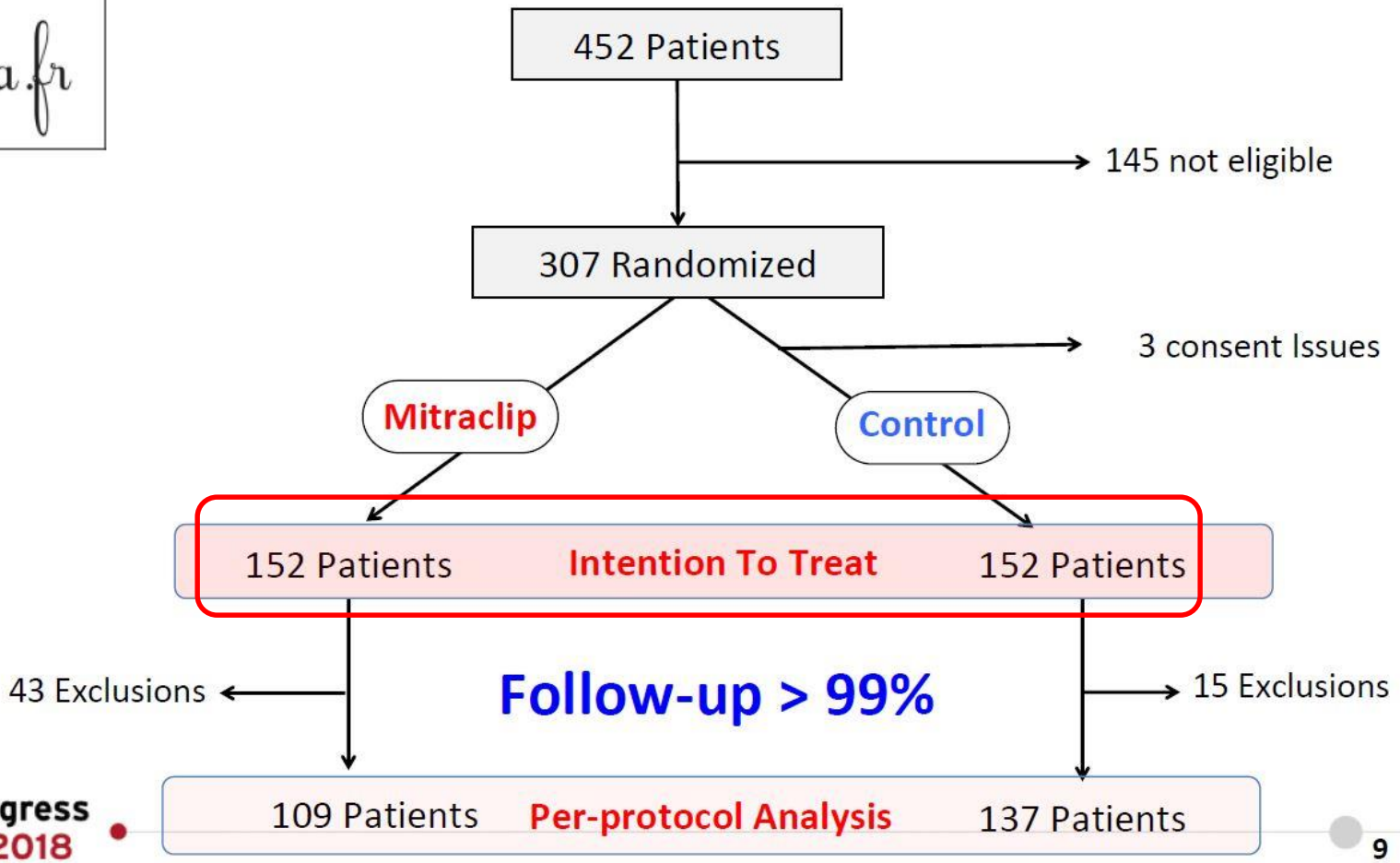

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MITRA-FR

Baseline characteristics

Characteristics	Percutaneous Repair Group (n=152)	Optimal Medical Treatment Group (n=152)	P value
Age year mean (±SD)	70.1 ± 10.1	70.6 ± 9.9	0.69
>75 year n (%)	51 (33.6)	59 (38.8%)	0.40
Males n - (%)	120 (78.9)	107 (70.4%)	0.11
Ischemic Cardiomyopathy n - (%)	95 (62.5)	85 (56.3%)	0.29
NYHA Class II n - (%)	56 (36.8)	44 (28.9%)	
NYHA Class III n - (%)	82 (53.9)	96 (63.2%)	0.27
NYHA Class IV n - (%)	14 (9.2)	12 (7.9%)	
LVEF mean (±SD)	33.3 ± 6.5	32.9 ± 6.7	0.79
Effect regurg. Orif. area - mm^2 mean (±SD)	31 ± 10	31 ± 11	0.42

60%

2/3

EF=33%

S=31mm^2

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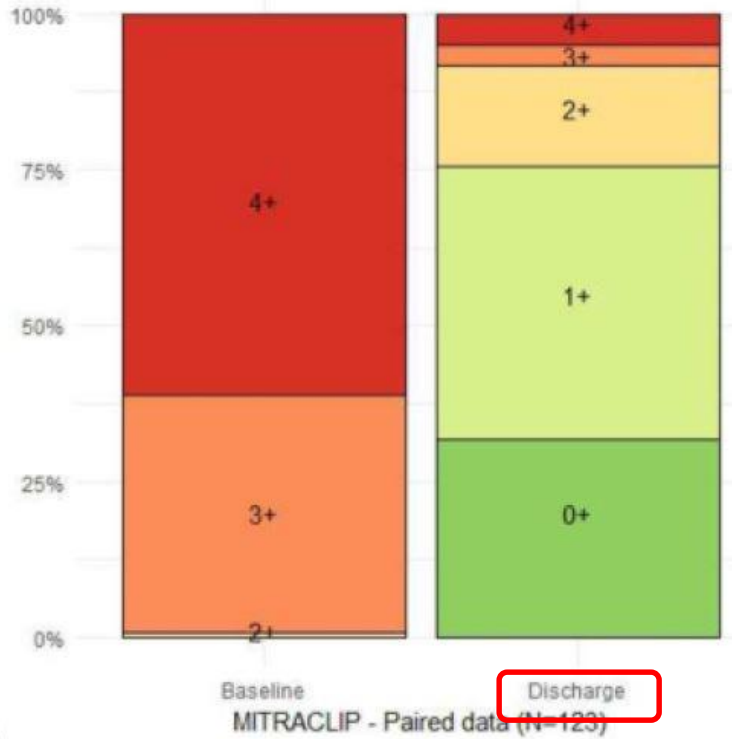
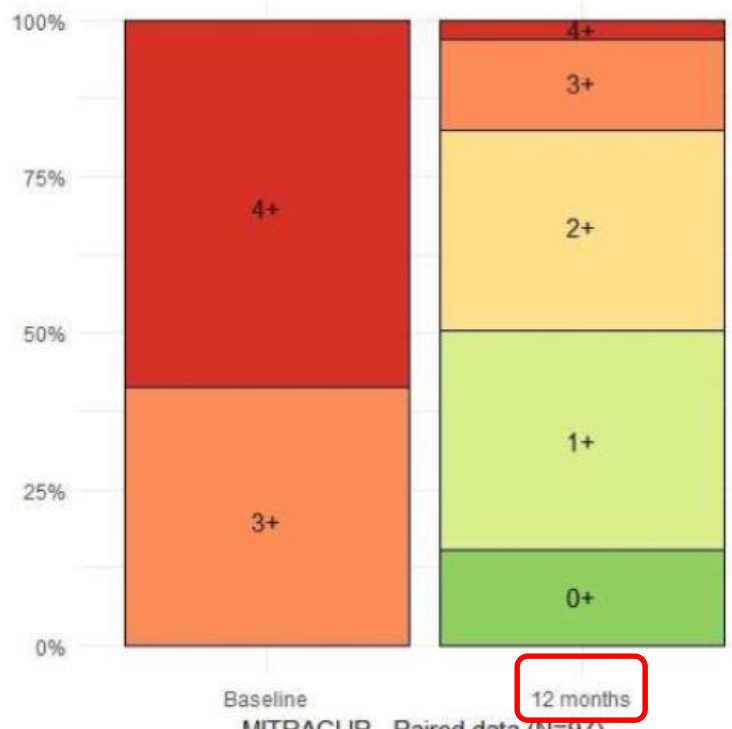
MITRA-FR

Prespecified Secondary Endpoints

MR Grade evolution Corelab

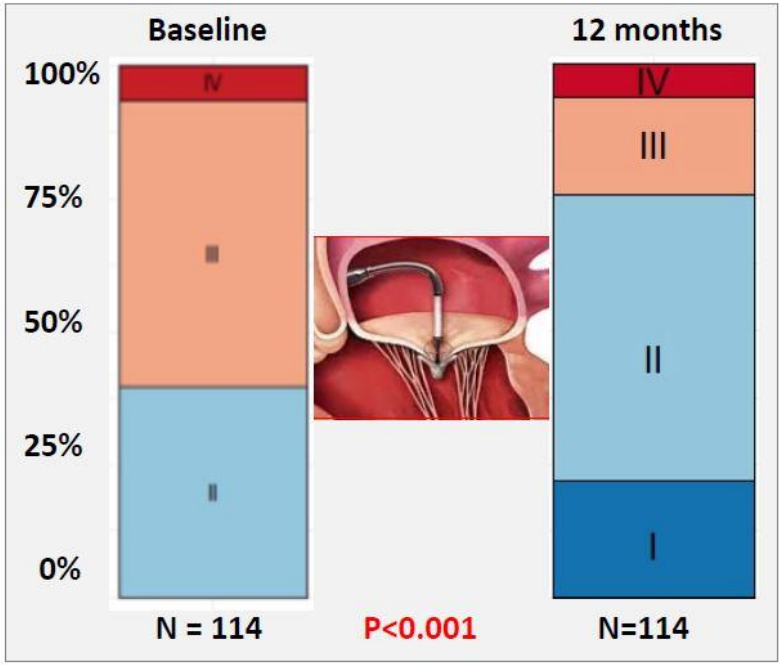




MITRA-FR

Prespecified Secondary Endpoints

NYHA evolution (*123 paired data*)



ESC Congress
Munich 2018

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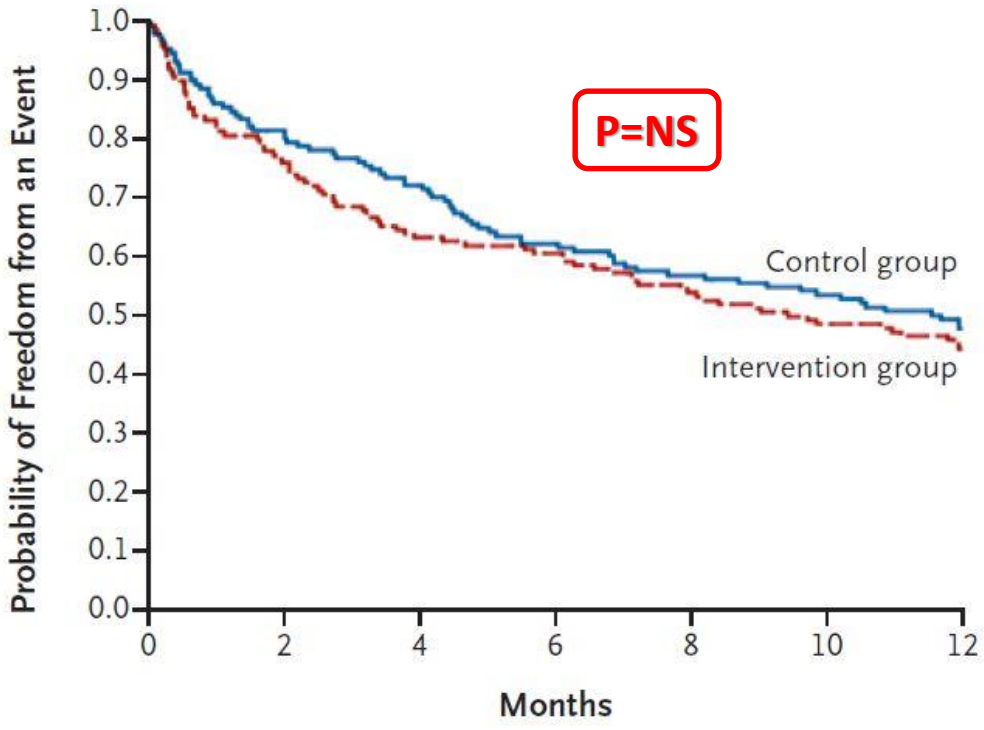
MITRA-FR



No. at Risk							
Control group	152	123	109	94	86	80	73
Intervention group	151	114	95	91	81	73	67

Figure 2. Kaplan–Meier Estimates of Survival without a Primary Outcome Event.

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MITRA-FR

Table 3. Primary Outcome and Secondary Efficacy Outcomes at 12 Months (Intention-to-Treat Population).

Outcome	Intervention Group (N=152)	Control Group (N=152)	Hazard Ratio or Odds Ratio (95% CI)*	P Value†
Composite primary outcome: death from any cause or unplanned hospitalization for heart failure at 12 months — no. (%)	83 (54.6)	78 (51.3)	1.16 (0.73–1.84)	0.53
Secondary outcomes‡				
Death from any cause	37 (24.3)	34 (22.4)	1.11 (0.69–1.77)	
Cardiovascular death	33 (21.7)	31 (20.4)	1.09 (0.67–1.78)	
Unplanned hospitalization for heart failure	74 (48.7)	72 (47.4)	1.13 (0.81–1.56)	
Major adverse cardiovascular events§	86 (56.6)	78 (51.3)	1.22 (0.89–1.66)	

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MITRA-FR

Table 2. Periprocedural Complications and Prespecified Serious Adverse Events (Intention-to-Treat Population).*

Variable	Intervention Group (N=152)	Control Group (N=152)
Periprocedural complications during device implantation — no./total no. (%)†	21/144 (14.6)	NA
Device-implantation failure	6/144 (4.2)‡	NA
Hemorrhage resulting in transfusion or vascular complication resulting in surgical intervention	5/144 (3.5)	NA
Atrial septum lesion or atrial septal defect	4/144 (2.8)	NA
Cardiogenic shock resulting in intravenous inotropic support	4/144 (2.8)	NA
Cardiac embolism, including gas embolism and stroke	2/144 (1.4)	NA
Tamponade	2/144 (1.4)	NA
Urgent conversion to heart surgery	0	NA
Prespecified serious adverse events at 1 year — no. (%)		
All serious adverse events	125 (82.2)	121 (79.6)
Heart transplantation or mechanical cardiac assistance	6 (3.9)	9 (5.9)
Ischemic or hemorrhagic stroke§	7 (4.6)	1 (0.7)
Myocardial infarction	0	2 (1.3)
Need for renal-replacement therapy	5 (3.3)	1 (0.7)
Severe hemorrhage ¶	11 (7.2)	6 (3.9)
Infections	28 (18.4)	27 (17.8)

MITRA-FR

rized in Table 3. The results of the per-protocol analysis were consistent with those of the intention-to-treat analysis (Table S4 in the Supplemen-

Interpretation:

Among patients with severe secondary mitral regurgitation, percutaneous mitral regurgitation repair (MitraClip) was not beneficial. The MitraClip device was not associated with a reduction in the composite (or individual components) of death or hospitalization for heart failure. The MitraClip device was effective since 92% of patients experienced a reduction in mitral regurgitation of at least 2 grades; however, follow-up echocardiographic data was incompletely reported. The lack of benefit was likely due to the poor prognosis of the severe underlying cardiomyopathy.

MitraClip Saga Continues…

TABLE 5 Comparison of Ongoing Randomized Trials of the MitraClip in Patients With Heart Failure and Secondary Mitral Regurgitation

	COAPT	RESHAPE-HF	MITRA-FR
Number of patients and sites	430 patients at 75 U.S. and Canadian sites	800 patients at 50 E.U. sites	288 patients at 18 French sites
Secondary MR grade (core laboratory verified)	≥3+ (EROA ≥30 mm^2 and/or Rvol >45 ml)	≥3+ (EROA ≥30 mm^2 and/or Rvol >45 ml)	Severe (EROA >20 mm^2 + Rvol >30 ml)
NYHA functional class	II, III, or ambulatory IV	III or ambulatory IV	II-IV
LVEF	≥20% to ≤50%	≥15% to ≤40%	≥15% to ≤40%
Surgical criteria	Not appropriate for mitral valve surgery (heart team)	None	None
Left ventricular volume entry criterion	LV end-systolic dimension ≤70 mm	LV end-diastolic dimension ≥55 mm	None
Control arm	Guideline-directed medical therapy (+CRT, if indicated)	Guideline-directed medical therapy (+CRT, if indicated)	Guideline-directed medical therapy (+CRT, if indicated)
Primary efficacy endpoint (superiority)	Heart failure rehospitalizations at 1 yr	Death or heart failure hospitalization at 1 yr	Death or recurrent heart failure hospitalization at 1 yr
Primary safety endpoint (noninferiority)	The composite of: SLDA; device embolization; endocarditis requiring surgery; echocardiography core laboratory-confirmed mitral stenosis requiring surgery; LVAD implant; heart transplant; or any device-related complications requiring nonelective cardiovascular surgery at 12 months	None	None
Health economics	Assessed	Assessed	None
Follow-up, yrs	5	2	2

COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; EROA = effective regurgitant orifice area; LV = left ventricular; LVAD = left ventricular assist device; MITRA-FR = Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation; Rvol = regurgitant volume; RESHAPE-HF = Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation; SLDA = single leaflet device attachment; other abbreviations as in Table 4.

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POET
(ESC 2018, NEJM 2018)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis **POET**

Kasper Iversen, M.D., D.M.Sc., Nikolaj Ihlemann, M.D., Ph.D.,
Sabine U. Gill, M.D., Ph.D., Trine Madsen, M.D., Ph.D., Hanne Elming, M.D., Ph.D.,
Kaare T. Jensen, M.D., Ph.D., Niels E. Bruun, M.D., D.M.Sc.,
Dan E. Høfsten, M.D., Ph.D., Kurt Fursted, M.D., D.M.Sc.,
Jens J. Christensen, M.D., D.M.Sc., Martin Schultz, M.D., Christine F. Klein, M.D.,
Emil L. Fosbøll, M.D., Ph.D., Flemming Rosenvinge, M.D.,
Henrik C. Schønheyder, M.D., D.M.Sc., Lars Køber, M.D., D.M.Sc.,
Christian Torp-Pedersen, M.D., D.M.Sc., Jannik Helweg-Larsen, M.D., D.M.Sc.,
Niels Tønder, M.D., D.M.Sc., Claus Moser, M.D., Ph.D.,
and Henning Bundgaard, M.D., D.M.Sc.

KAISER PERMANENTE®

POET

Background

- Infectious endocarditis is treated with iv antibiotics for up to 6 weeks – in-hospital
- High in-hospital complication- and mortality rates - but mainly in the early phase
- After stabilization the main reason for staying in hospital is to receive iv antibiotics
- Hospital stays *per se* may cause complications

POET

Inclusion criteria:

- Patients ≥18 years of age with infective endocarditis on the left side of the heart
- Stable on intravenous antibiotic therapy for ≥10 days
- Positive blood culture for streptococcus, *Enterococcus faecalis*, *Staphylococcus aureus*, or coagulase negative staphylococci

- Total number of enrollees: 400
- Duration of follow-up: 6 months
- Mean patient age: 67 years
- Percentage female: 25%
- Percentage with diabetes: 18%

Other salient features/characteristics:

- After randomization, continued antibiotic duration was 17 days in the oral group vs. 19 days in the intravenous group (p = 0.48)

POET

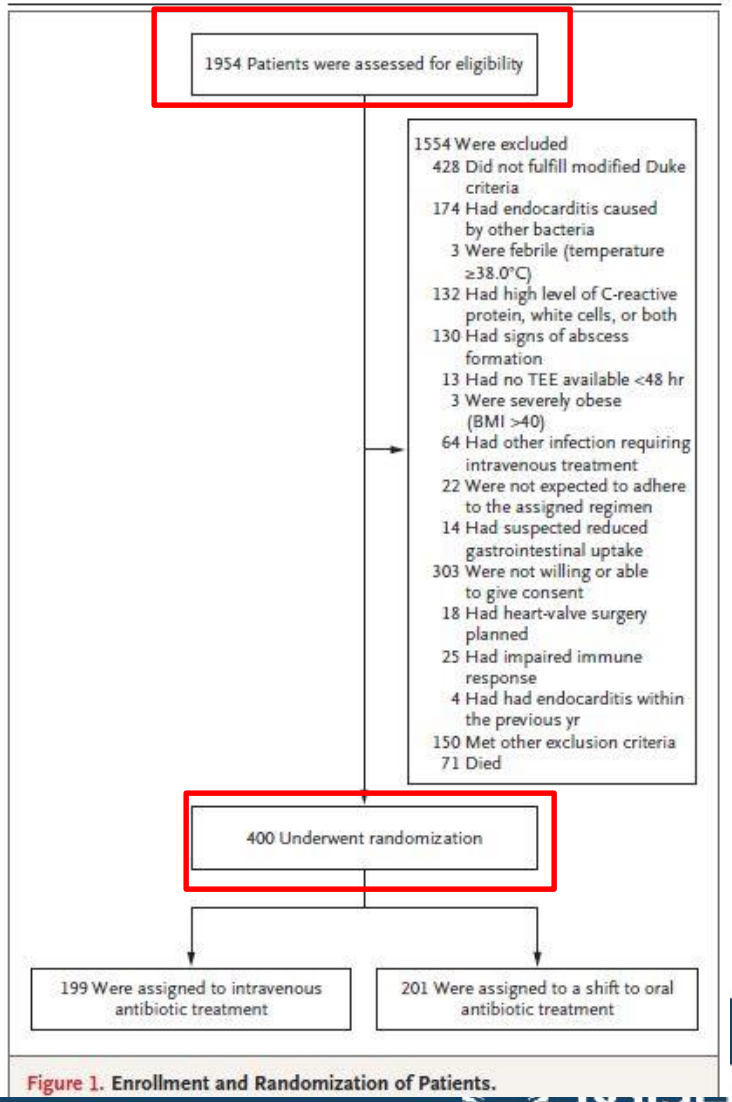


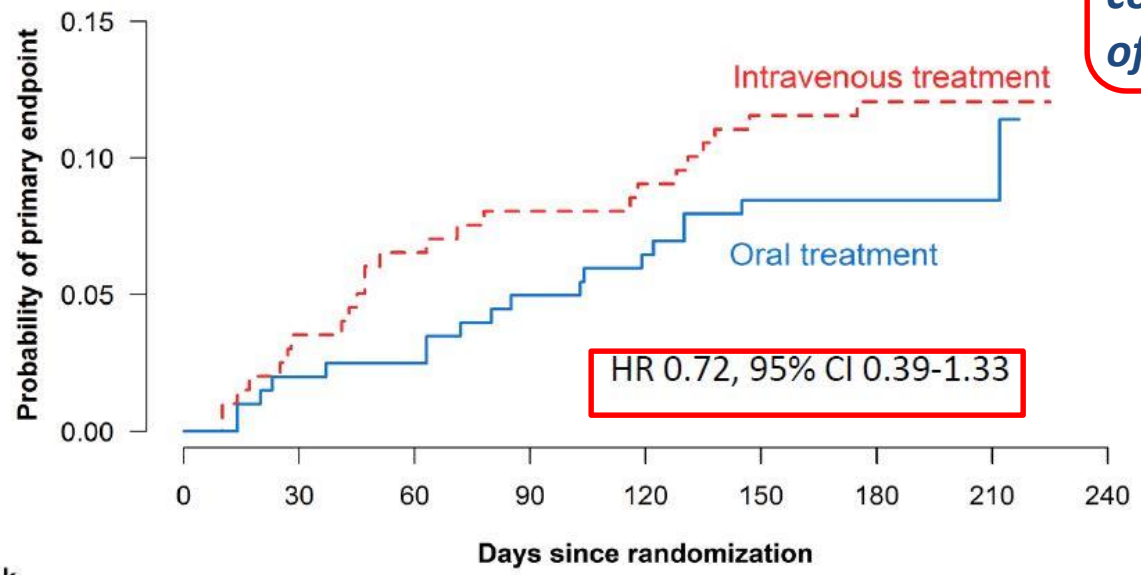
Figure 1. **Enrollment and Randomization of Patients.**

POET
Primary endpoint

(All cause mortality, unplanned cardiac surgery, embolic events or relapse of bacteremia)

Difference 3.1%, 95% CI: -3.4% - 9.6%, Non-inferiority met

At 6 mo after completion of IV Abx



No. at Risk									
Intravenous treatment	199	192	186	183	181	176	174	28	0
Oral treatment	201	197	196	191	188	184	183	36	0

: Congress
nich 2018

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POET

Pathogen — no. (%)†		
Streptococcus	104 (52.3)	92 (45.8)
Enterococcus faecalis	46 (23.1)	51 (25.4)
Staphylococcus aureus‡	40 (20.1)	47 (23.4)
Coagulase-negative staphylococci	10 (5.0)	13 (6.5)
Laboratory results at randomization		
Hemoglobin — mmol/liter	6.3±1.1	6.5±1.0
Leukocytes — $\times 10^{-9}$/liter	7.6±3.6	7.2±2.6
C-reactive protein — mg/liter	24.3±18.4	19.9±16.7
Creatinine — μmol/liter	124±112	141±164

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Preexisting prosthesis, implant, or cardiac disease — no. (%)		
Prosthetic heart valve	53 (26.6)	54 (26.9)
Pacemaker	15 (7.5)	20 (10.0)
Other known valve disease	82 (41.2)	90 (44.8)
Cardiac involvement at randomization — no. (%)§		
Mitral-valve endocarditis	65 (32.7)	72 (35.8)
Aortic-valve endocarditis	109 (54.8)	109 (54.2)
Mitral-valve and aortic-valve endocarditis	23 (11.6)	20 (10.0)
Endocarditis in other locations§	2 (1.0)	0
Pacemaker endocarditis	6 (3.0)	8 (4.0)
Vegetation size >9 mm	7 (3.5)	11 (5.5)
Moderate or severe valve regurgitation	19 (9.5)	23 (11.4)
Valve surgery during current disease course	75 (37.7)	77 (38.3)

POET

Table 2. Distribution of the Four Components of the Primary Composite Outcome.*

Component	Intravenous Treatment (N = 199)	Oral Treatment (N = 201)	Difference	Hazard Ratio (95% CI)
	number (percent)		*percentage points (95% CI)*	
All-cause mortality	13 (6.5)	7 (3.5)	3.0 (–1.4 to 7.7)	0.53 (0.21 to 1.32)
Unplanned cardiac surgery	6 (3.0)	6 (3.0)	0 (–3.3 to 3.4)	0.99 (0.32 to 3.07)
Embolic event	3 (1.5)	3 (1.5)	0 (–2.4 to 2.4)	0.97 (0.20 to 4.82)
Relapse of the positive blood culture†	5 (2.5)	5 (2.5)	0 (–3.1 to 3.1)	0.97 (0.28 to 3.33)

POET

Conclusions

- Efficacy and safety of shifting to oral antibiotic treatment was non-inferior to continued intravenous antibiotic treatment in
  - stabilized patients with left-sided endocarditis caused by
  - streptococcus spp, *Enterococcus faecalis, Staphylococcus aureus*, or coagulase-negative staphylococci
  - across co-morbidities, native vs prosthetic valve and surgically vs conservatively Tx
- Oral antibiotics may safely be administered during approximately
  - half of the recommended antibiotic treatment period
  - potentially as outpatient treatment
- More than 50% of patients with endocarditis may be candidates to partial oral antibiotic treatment

SMART-DATE
(ACC 2018, Lancet 2018)

6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial

Joo-Yong Hahn, Young Bin Song*, Ju-Hyeon Oh, Deok-Kyu Cho, Jin Bae Lee, Joon-Hyung Doh, Sang-Hyun Kim, Jin-Ok Jeong, Jang-Ho Bae, Byung-Ok Kim, Jang Hyun Cho, Il-Woo Suh, Doo-il Kim, Hoon-Ki Park, Jong-Seon Park, Woong Gil Choi, Wang Soo Lee, Jihoon Kim, Ki Hong Choi, Taek Kyu Park, Joo Myung Lee, Jeong Hoon Yang, Jin-Ho Choi, Seung-Hyuk Choi, Hyeon-Cheol Gwon, for the SMART-DATE investigators†*

SMART-DATE

Primary objective of study

To test the efficacy of the reduced 6-month duration of DAPT after second-generation DES implantation in patients with ACS.

Working hypothesis

The reduced 6-month duration of DAPT is non-inferior to the conventional 12-month or longer duration of DAPT to prevent major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of all-cause mortality, myocardial infarction (MI), and cerebrovascular event at 18 months after index procedure.

ACC LBCT 2018

SMART-DATE

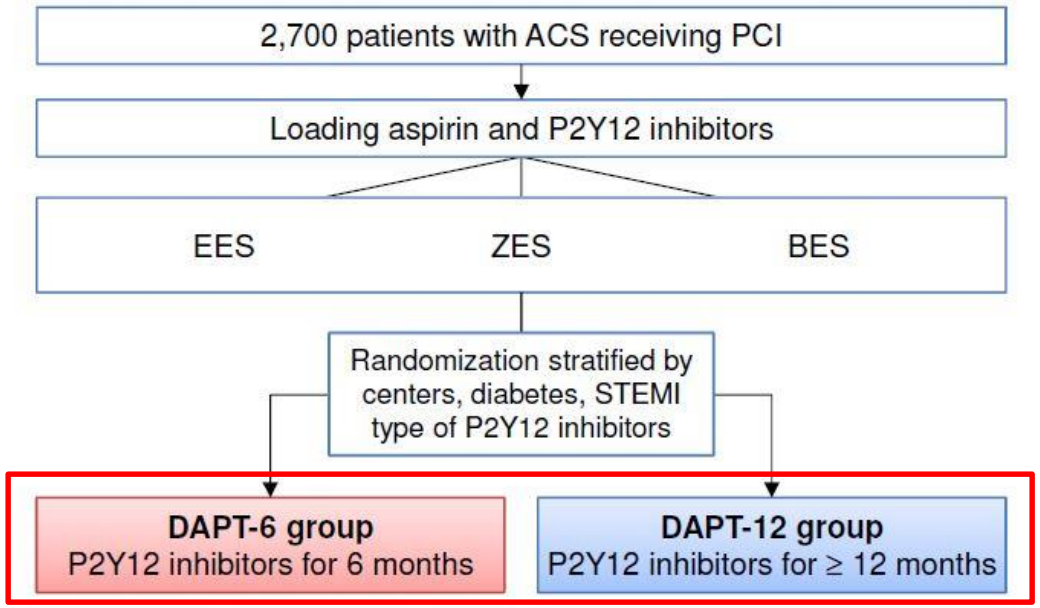
Study endpoints

- **Primary endpoint**
  - Major adverse cardiac and cerebrovascular events (MACCE) at 18 months after the index procedure (A composite of all-cause mortality, myocardial infarction, and cerebrovascular events)
- **Secondary endpoints**
  - The individual components of the primary end point
  - Definite/probable stent thrombosis (ST)
  - Bleeding Academic Research Consortium (BARC) type 2 to 5 bleeding

SMART-DATE

Study design

A prospective, multicenter, randomized, and open-label trial



Primary endpoint: 18-month MACCE
a composite of all-cause mortality, MI, and cerebrovascular events

- PCI=percutaneous coronary intervention
- EES = everolimus eluting stent (Xience Prime)
- ZES = zotarolimus eluting stent (Resolute Integrity)
- BES = biolimus eluting stent (Biomatrix Flex)
- STEMI = ST elevation myocardial infarction
- MI = myocardial infarction

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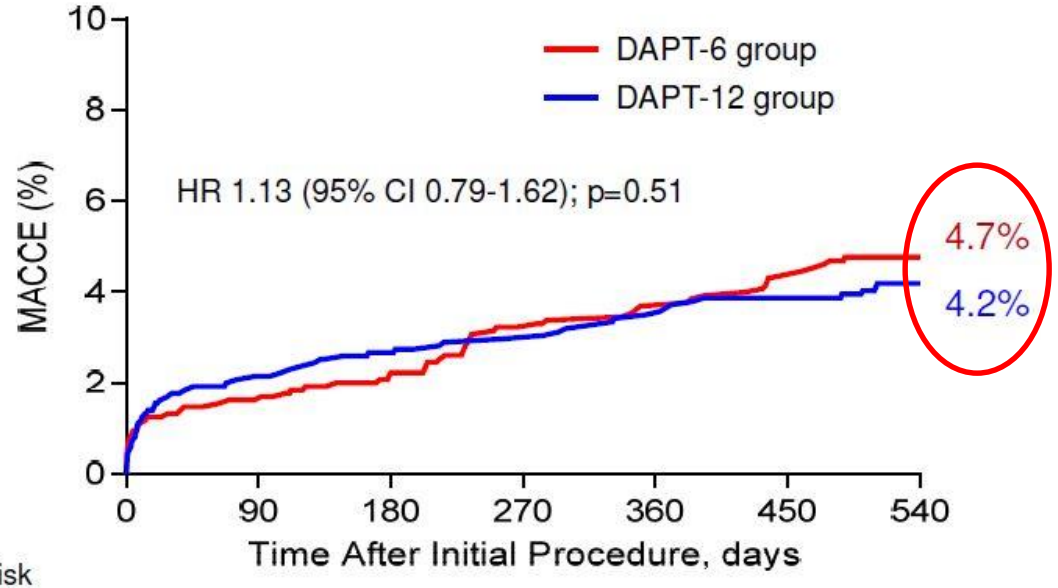
Primary endpoint (MACCE)



No. at risk							
Long-term	1355	1312	1299	1290	1283	1278	1043
Short-term	1357	1318	1296	1271	1264	1255	1032

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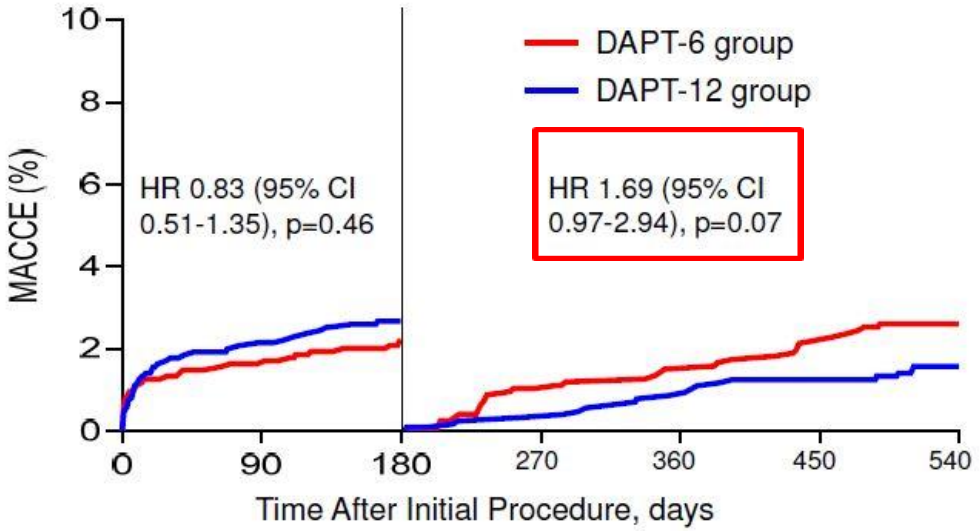
MACCE (Landmark analysis)



No. at risk							
Long-term	1355	1312	1299	1290	1283	1278	1043
Short-term	1357	1318	1296	1271	1264	1255	1032

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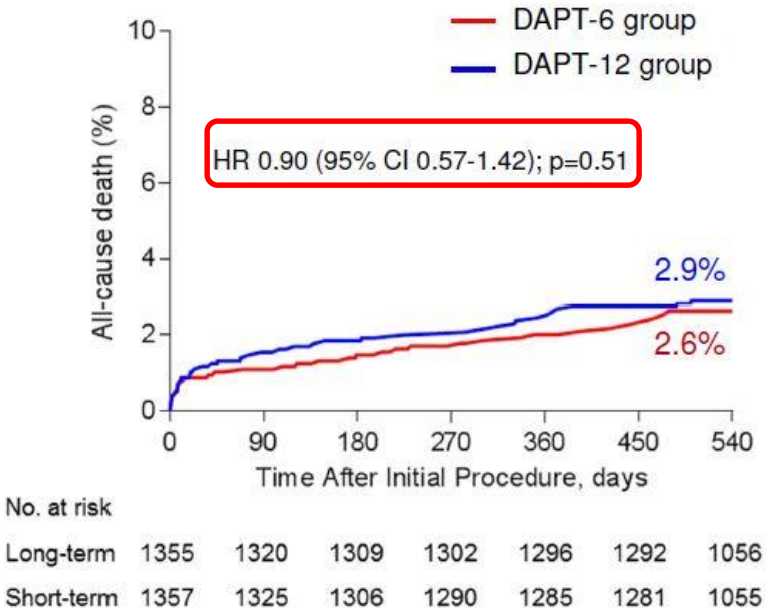
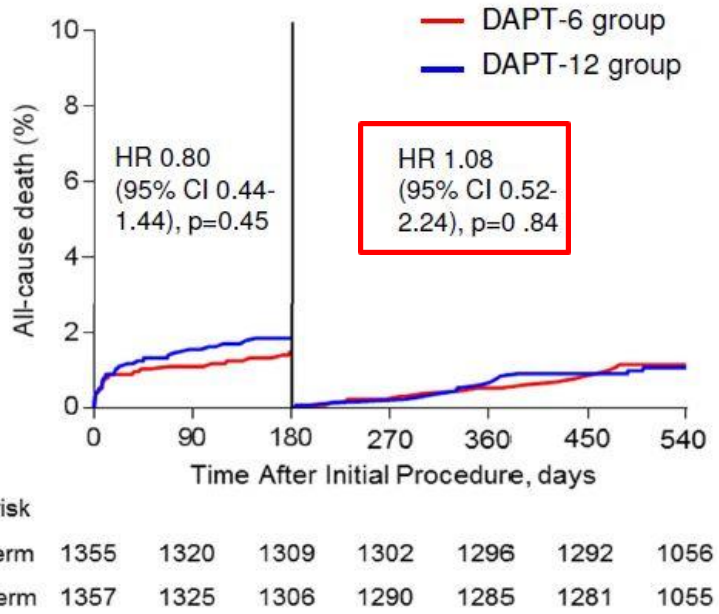
All-cause death (ITT)



No. at risk							
Long-term	1355	1320	1309	1302	1296	1292	1056
Short-term	1357	1325	1306	1290	1285	1281	1055



No. at risk							
Long-term	1355	1320	1309	1302	1296	1292	1056
Short-term	1357	1325	1306	1290	1285	1281	1055

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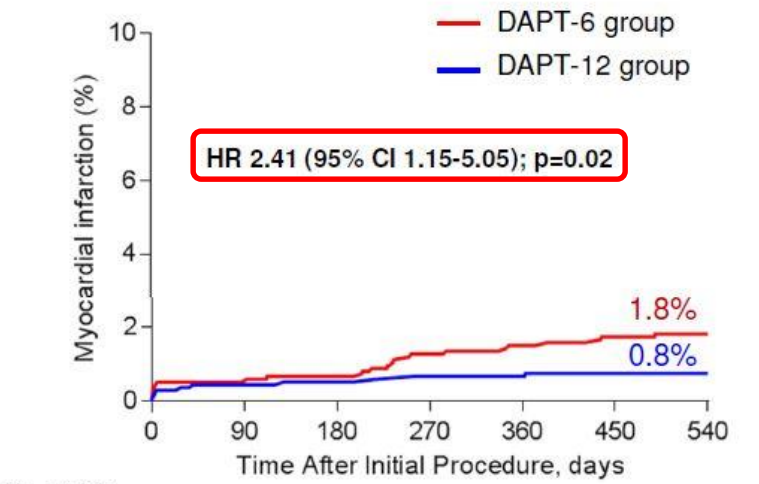
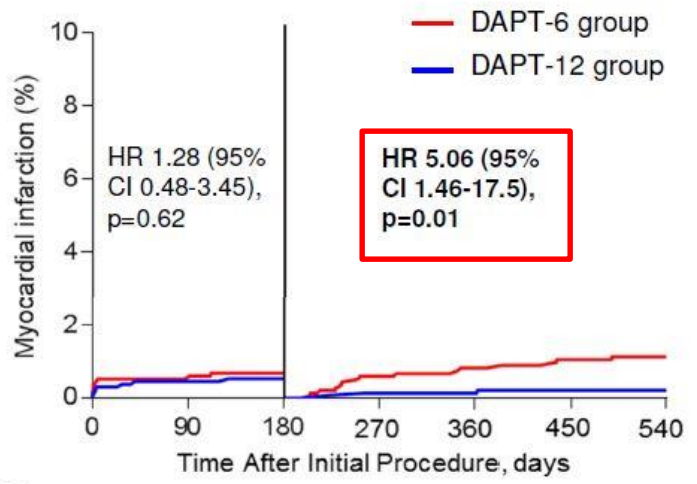
Myocardial infarction (ITT)



No. at risk							
Long-term	1355	1315	1303	1295	1289	1284	1049
Short-term	1357	1321	1300	1277	1270	1263	1039



No. at risk							
Long-term	1355	1315	1303	1295	1289	1284	1049
Short-term	1357	1321	1300	1277	1270	1263	1039

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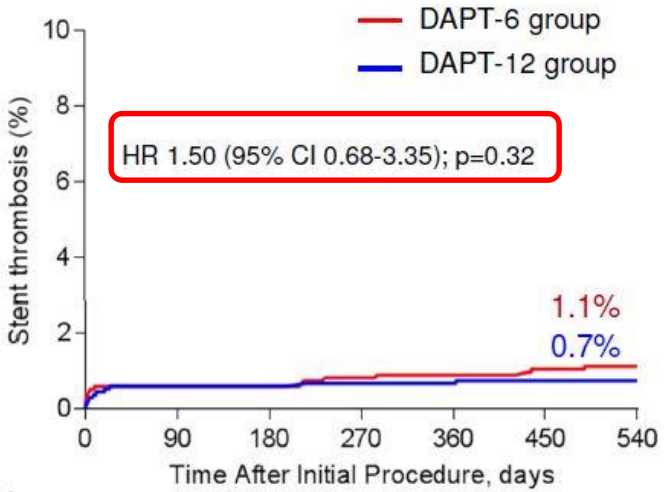
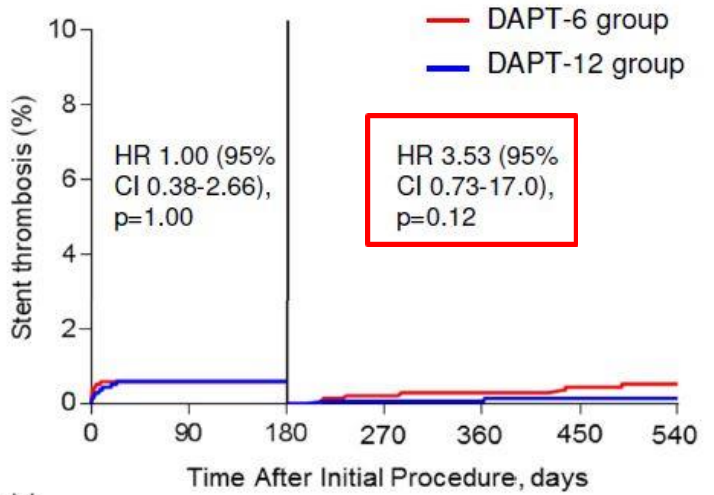
Stent thrombosis (ITT)



No. at risk

Long-term	1355	1316	1305	1298	1292	1287	1051
Short-term	1357	1321	1302	1284	1279	1273	1047



No. at risk

Long-term	1355	1316	1305	1298	1292	1287	1051
Short-term	1357	1321	1302	1284	1279	1273	1047

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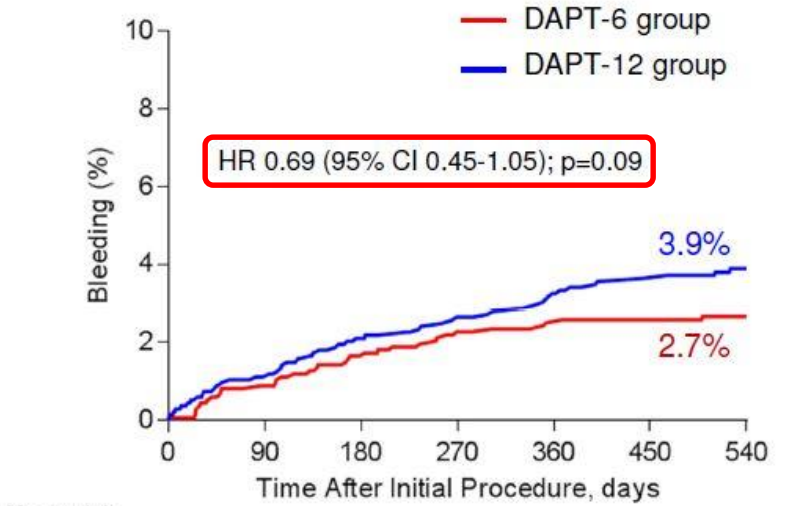
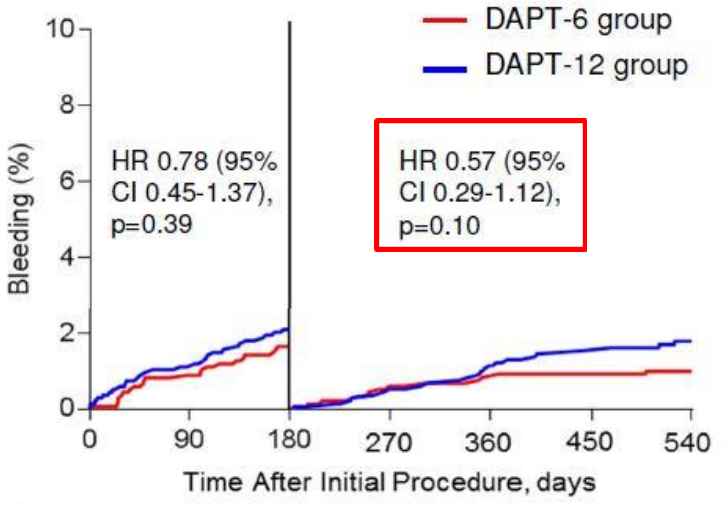
BARC 2-5 Bleeding (ITT)



No. at risk							
Long-term	1355	1307	1285	1271	1260	1251	1023
Short-term	1357	1314	1286	1263	1257	1252	1034



No. at risk							
Long-term	1355	1307	1285	1271	1260	1251	1023
Short-term	1357	1314	1286	1263	1257	1252	1034

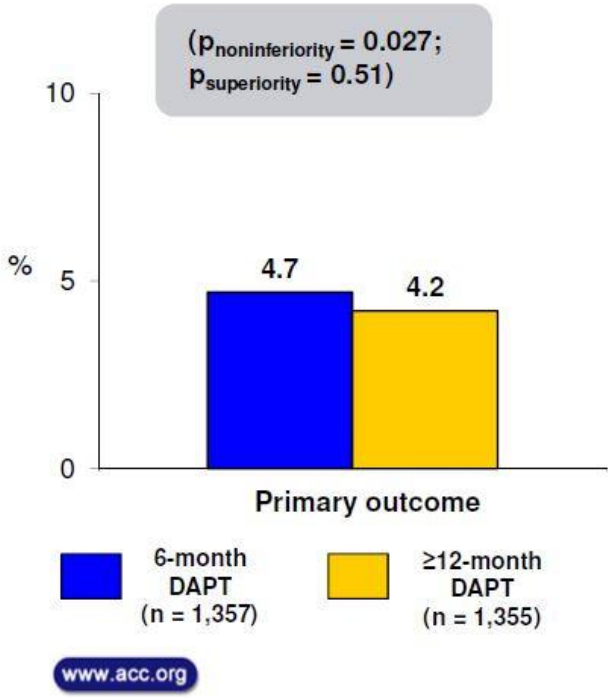
SMART-DATE

Conclusions

- Six-month DAPT was non-inferior to 12-month or longer DAPT for the primary end point of MACCE at 18 months after the index procedure in patients with ACS undergoing PCI with DES.
- However, increased risk of MI with 6-month DAPT prevents us concluding that short-term DAPT is safe in ACS patients undergoing PCI using current DESs.
- Current guidelines that recommend prolonged DAPT in ACS patients without excessive risk of bleeding should be respected.

SMART-DATE

Trial design: Patients with ACS undergoing PCI with a second-generation DES were randomized in a 1:1 fashion to either DAPT for 6 months or ≥12 months. Patients were followed for 18 months.



Results

- Primary outcome, MACCE at 18 months: short-term vs. long-term DAPT: 4.7% vs. 4.2%, p for noninferiority = 0.027; p for superiority = 0.51
- MI: 1.8% vs. 0.8%, p = 0.02; nontarget vessel MI: 0.8% vs. 0.2%, p = 0.07; stent thrombosis: 1.1% vs. 0.7%, p = 0.32
- BARC 2-5 bleeding: 2.7% vs. 3.9%, p = 0.09

Conclusions

- 6-month duration of DAPT is noninferior to ≥12-month duration among patients with ACS undergoing PCI with a second-generation DES; however, there is a higher risk of MI with shorter durations
- Trial validates current guidelines, which recommend at least 12 months of DAPT following DES PCI for ACS

Hahn GY, et al. Lancet 2018;Mar 12:[Epub]

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CASTLE-AF
(ESC 2017, NEJM 2018)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 1, 2018 VOL. 378 NO. 5

Catheter Ablation for Atrial Fibrillation with Heart Failure

Nassir F. Marrouche, M.D., Johannes Brachmann, M.D., Dietrich Andresen, M.D., Jürgen Siebels, M.D., Lucas Boersma, M.D., Luc Jordaens, M.D., Béla Merkely, M.D., Evgeny Pokushalov, M.D., Prashanthan Sanders, M.D., Jochen Proff, B.S., Heribert Schunkert, M.D., Hildegard Christ, M.D., Jürgen Vogt, M.D., and Dietmar Bänsch, M.D., for the CASTLE-AF Investigators*

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CASTLE-AF

Rationale and Objective

- Study the effectiveness of *catheter ablation* of atrial fibrillation in patients with heart failure in *improving hard primary endpoints of mortality and heart failure progression* when compared to conventional standard treatment

CASTLE-AF

Primary Endpoint

- All-cause mortality

1st to study hard endpoints

- Worsening heart failure admissions

CASTLE-AF

- Symptomatic paroxysmal or persistent AF
- Failure or intolerance to ≥ 1 or unwillingness to take AAD
- LVEF ≤ 35%
- NYHA class ≥ II
- ICD/CRT-D with Home Monitoring capabilities already implanted due to primary or secondary prevention

- *PABA-CHF: RFA/PVI > ablate & pace in HF (NEJM 2008)*
- *AATAC: RFA >Amiodarone in HF (Circ 2016)*

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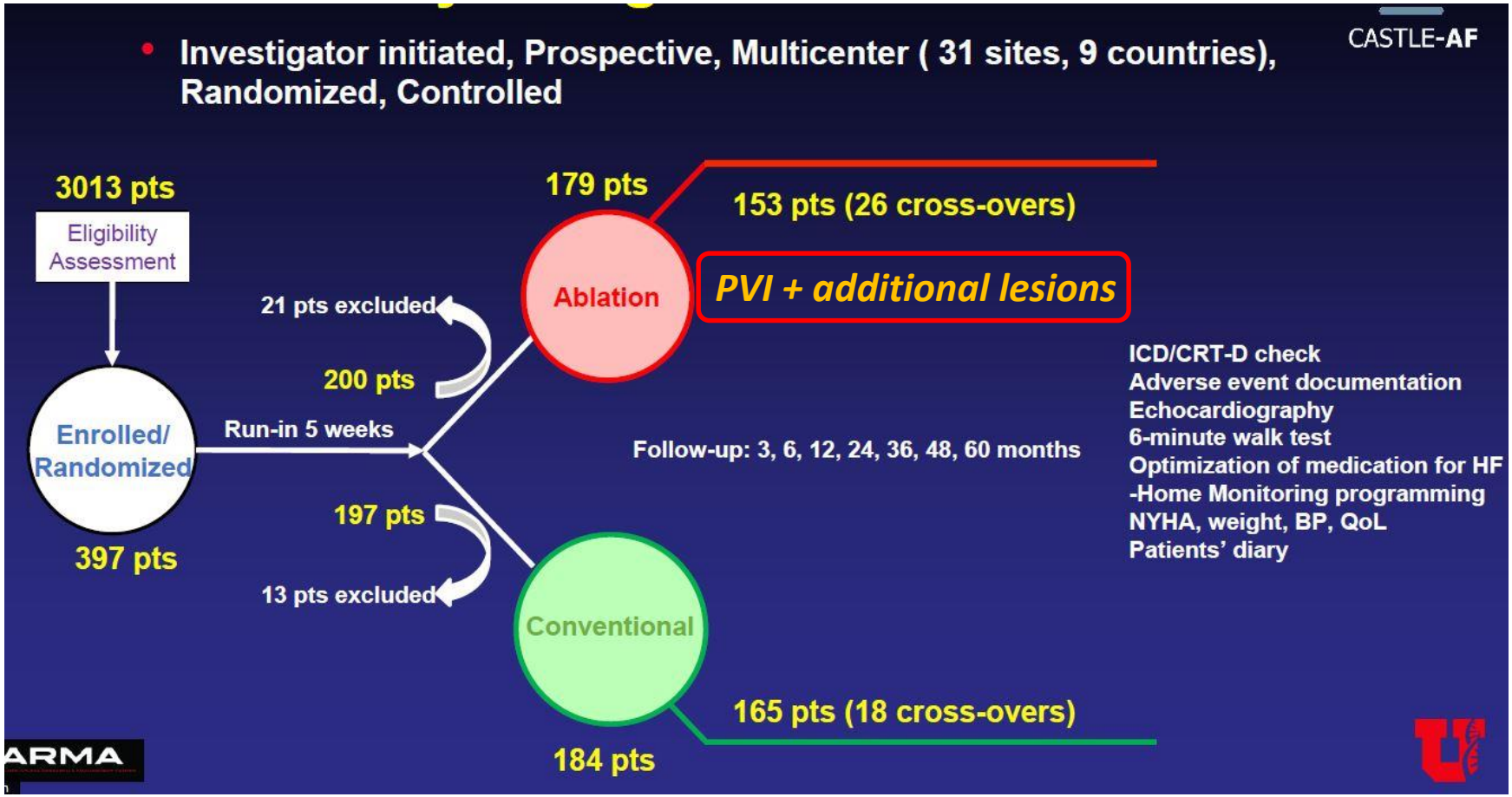

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Treatment Type	
	Ablation (N=179)	Medical Therapy (N=184)
Age — yr		
Median	64	64
Range	56–71	56–73.5
Male sex — no. (%)	156 (87)	155 (84)
Body-mass index†		
Median	29.0	29.1
Range	25.9–32.2	25.9–32.3
New York Heart Association class — no./total no. (%)		
I	20/174 (11)	19/179 (11)
II	101/174 (58)	109/179 (61)
III	50/174 (29)	49/179 (27)
IV	3/174 (2)	2/179 (1)
Cause of heart failure — no. (%)‡		
Ischemic	72 (40)	96 (52)
Nonischemic	107 (60)	88 (48)

A decade younger than your typical AF pt

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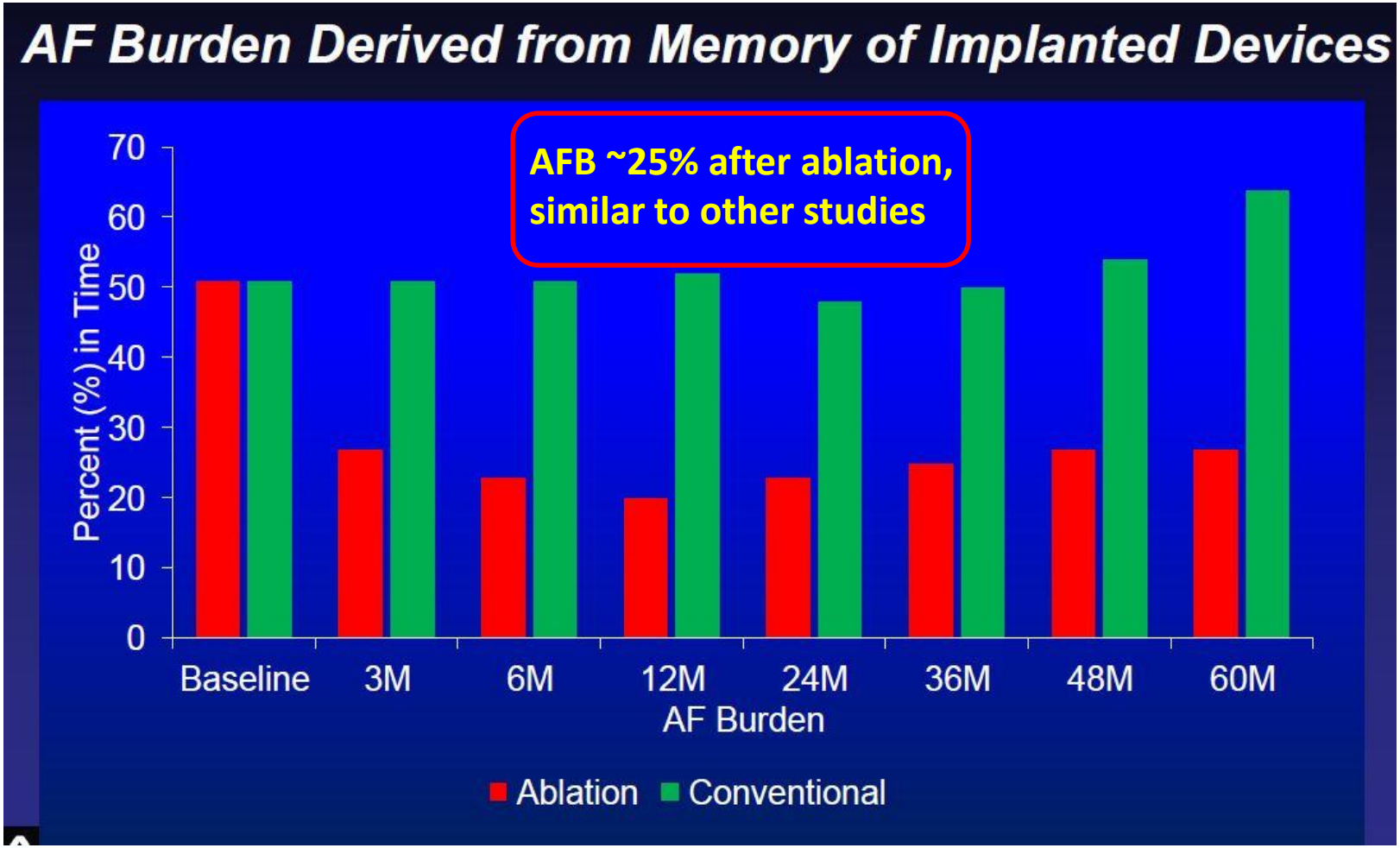

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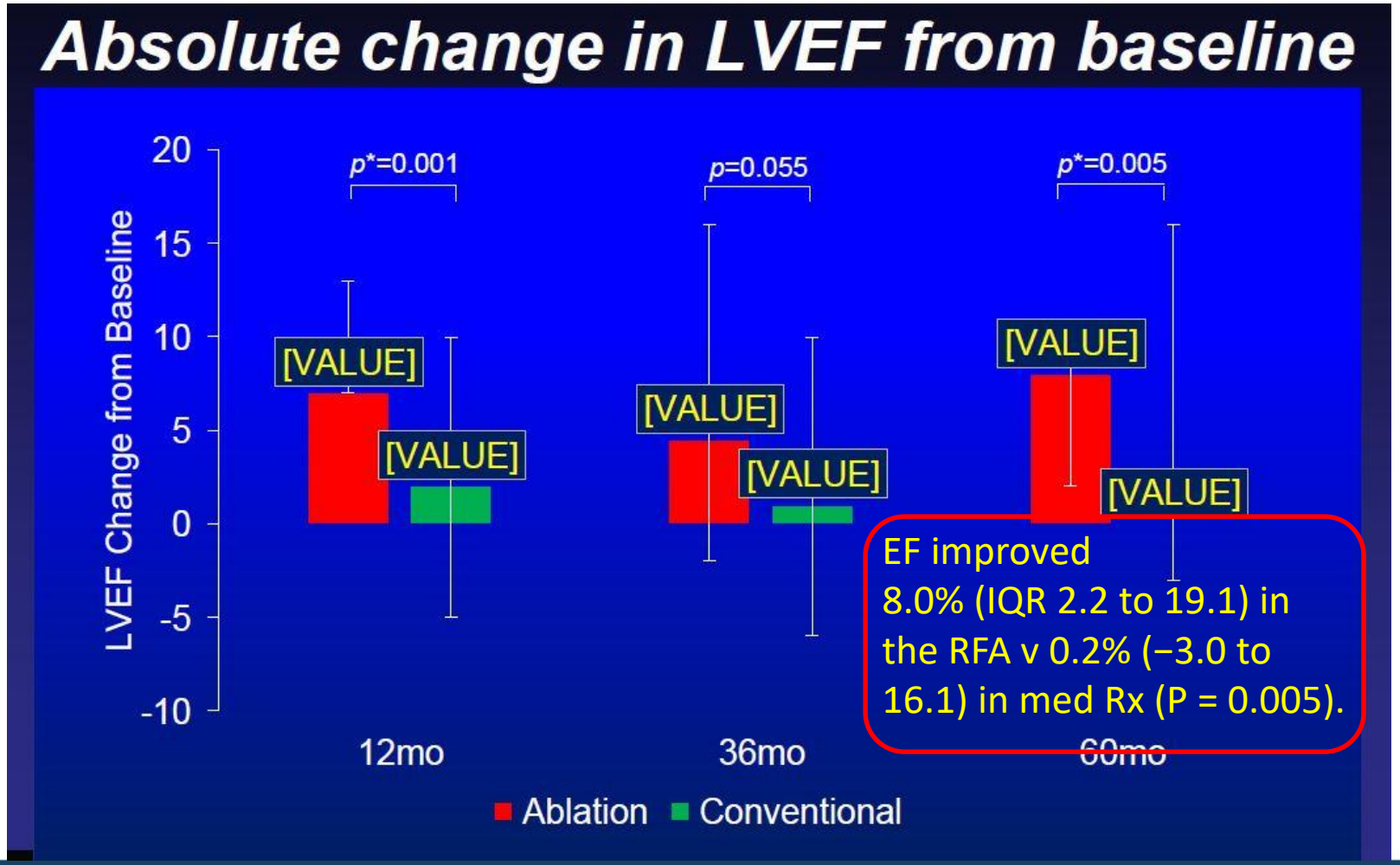

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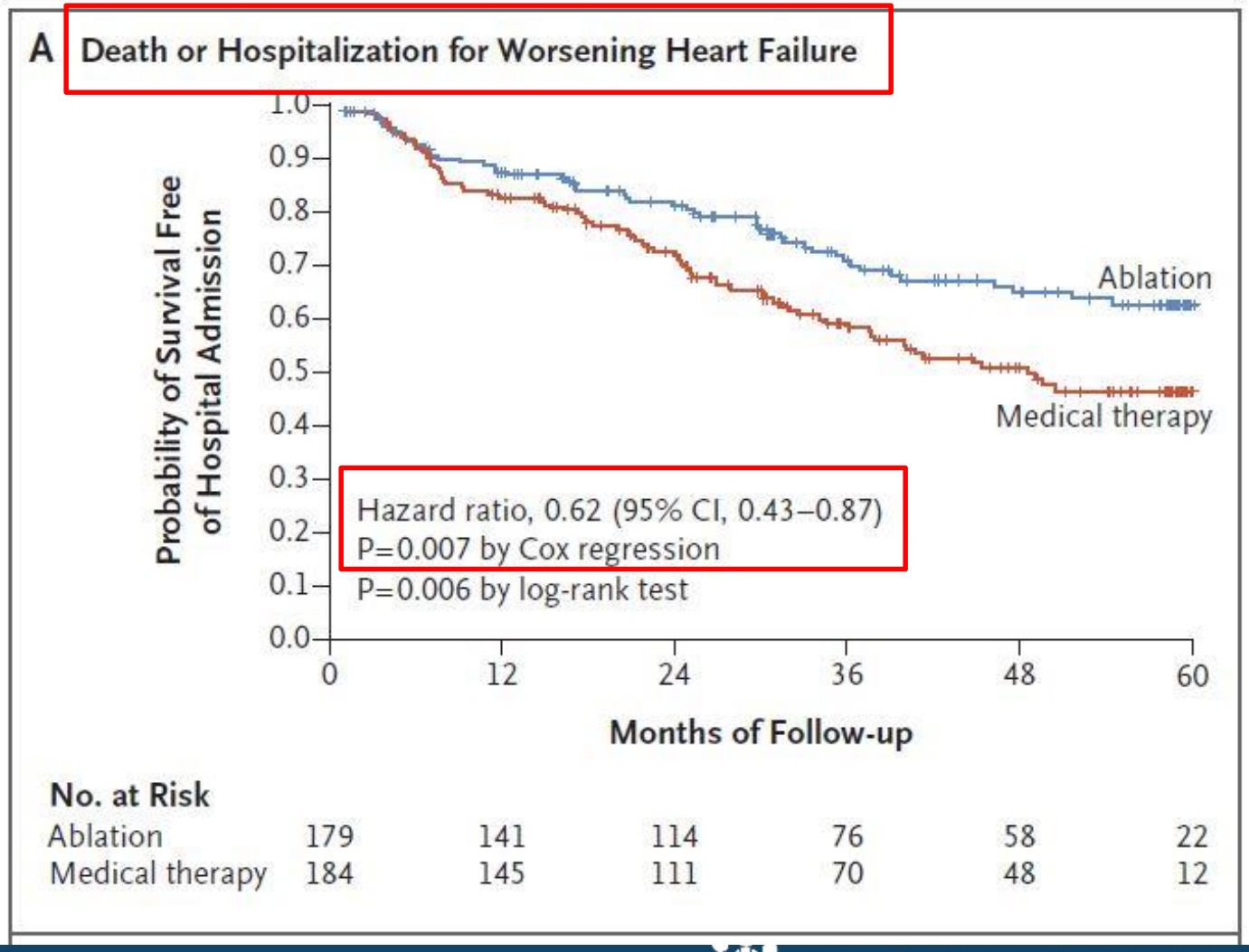

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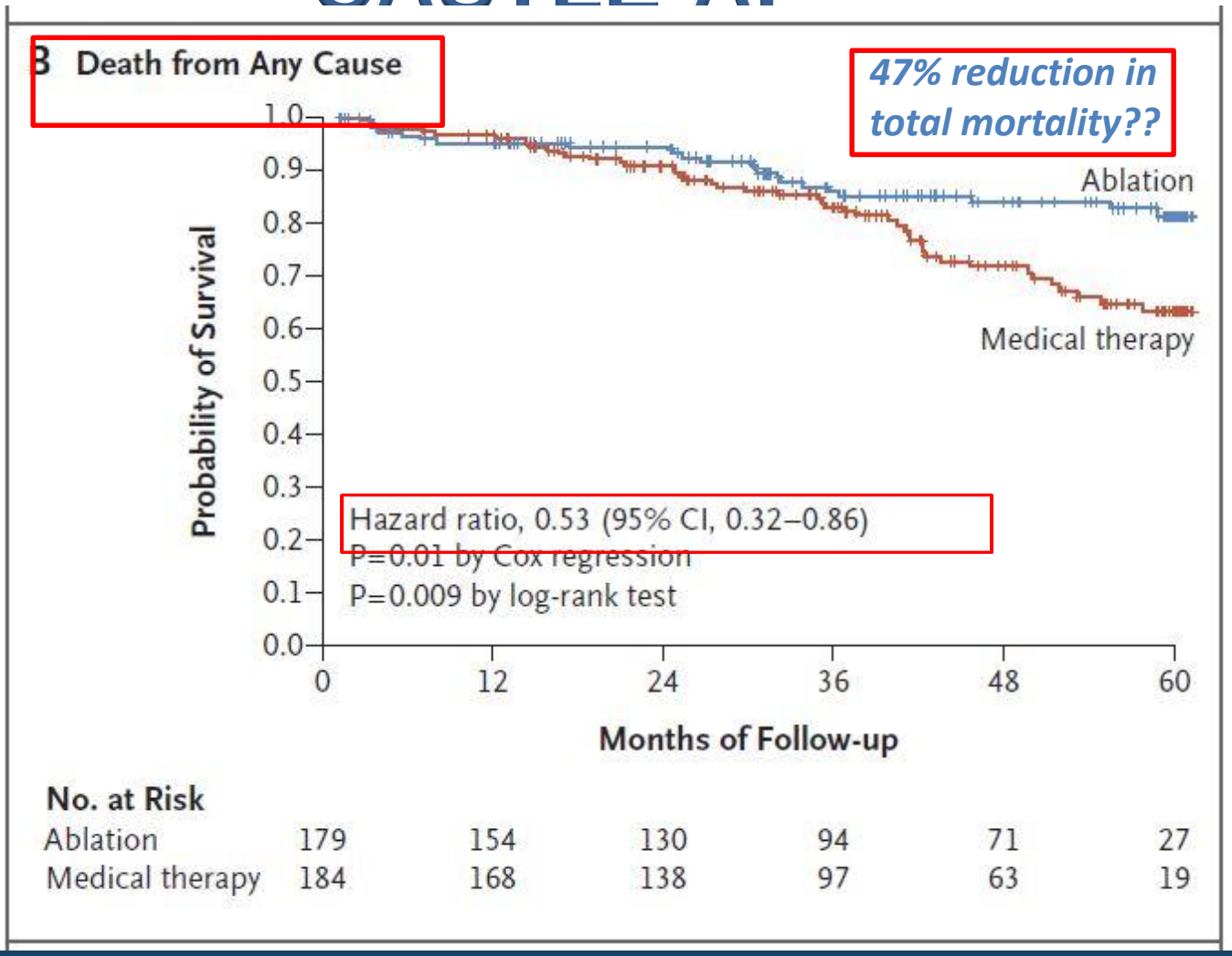

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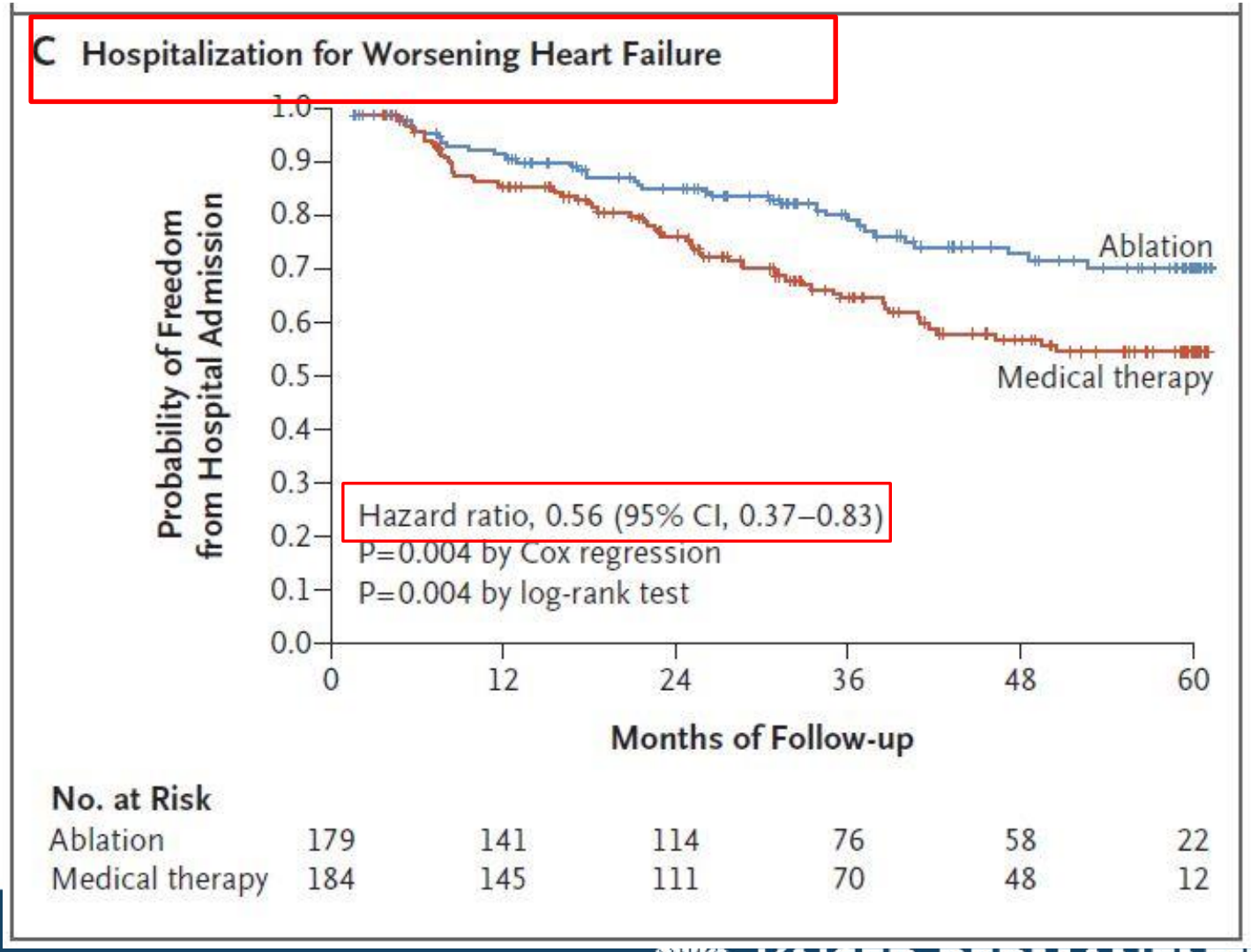

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- ***Catheter ablation*** of atrial fibrillation in patients with heart failure is associated with ***improved all-cause mortality*** and ***fewer admissions for worsening heart failure*** when compared to conventional standard of care treatment
- ***Catheter ablation*** of atrial fibrillation in patients with heart failure is also associated with ***improved cardiovascular mortality*** and ***hospitalization*** when compared to conventional standard of care treatment

CABANA
(HR 2018)

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CABANA

Purpose of CABANA

Compare Ablation to state-of-the-art drug therapy for patients with new onset / undertreated AF

Primary Endpoint

- All-cause mortality, disabling stroke, serious bleeding, or cardiac arrest

Major Secondary Endpoints

- All-cause mortality
- Death (all-cause) or cardiovascular hospitalization

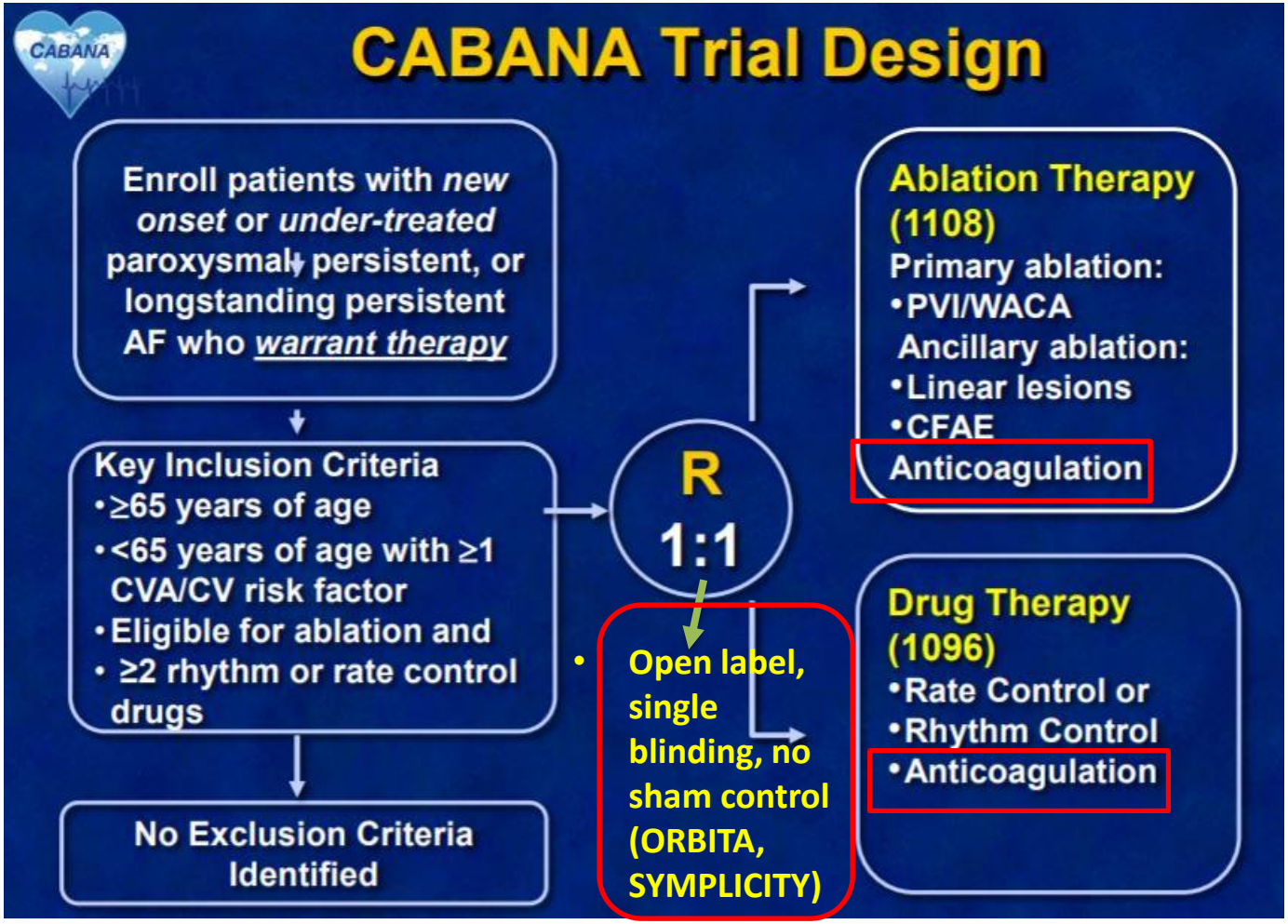
Trial begun in 2009 as mortality trial, changed in 2013 2/2 slow enrollment

CABANA

Arrhythmia History in CABANA

AF Type	Ablation	Drug Therapy
Paroxysmal	42.4%	43.5%
Persistent	47.3%	47.3%
Longstanding Persistent	10.3%	9.2%
Years since onset of AF [Median (Q1,Q3)]	1.1 (0.3, 4.1	1.1 (0.3, 3.9)
CCS Severity of AF		
Class 0-1	34.6%	26.7%
Class 2	31.8%	32.4%
Class 3-4	43.5%	41.0%
Prior hospitalization for AF	40.6%	38.8%

CABANA



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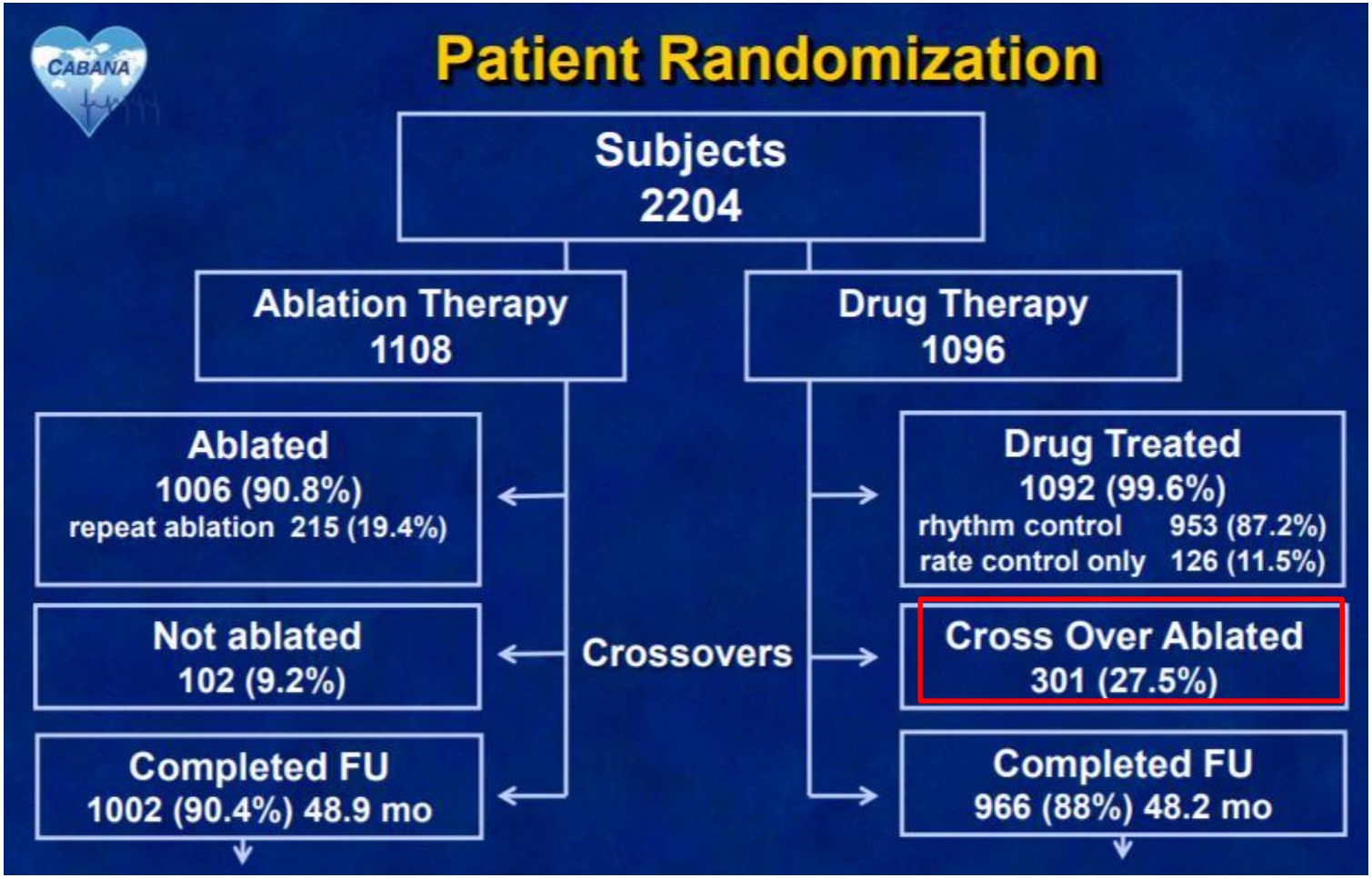

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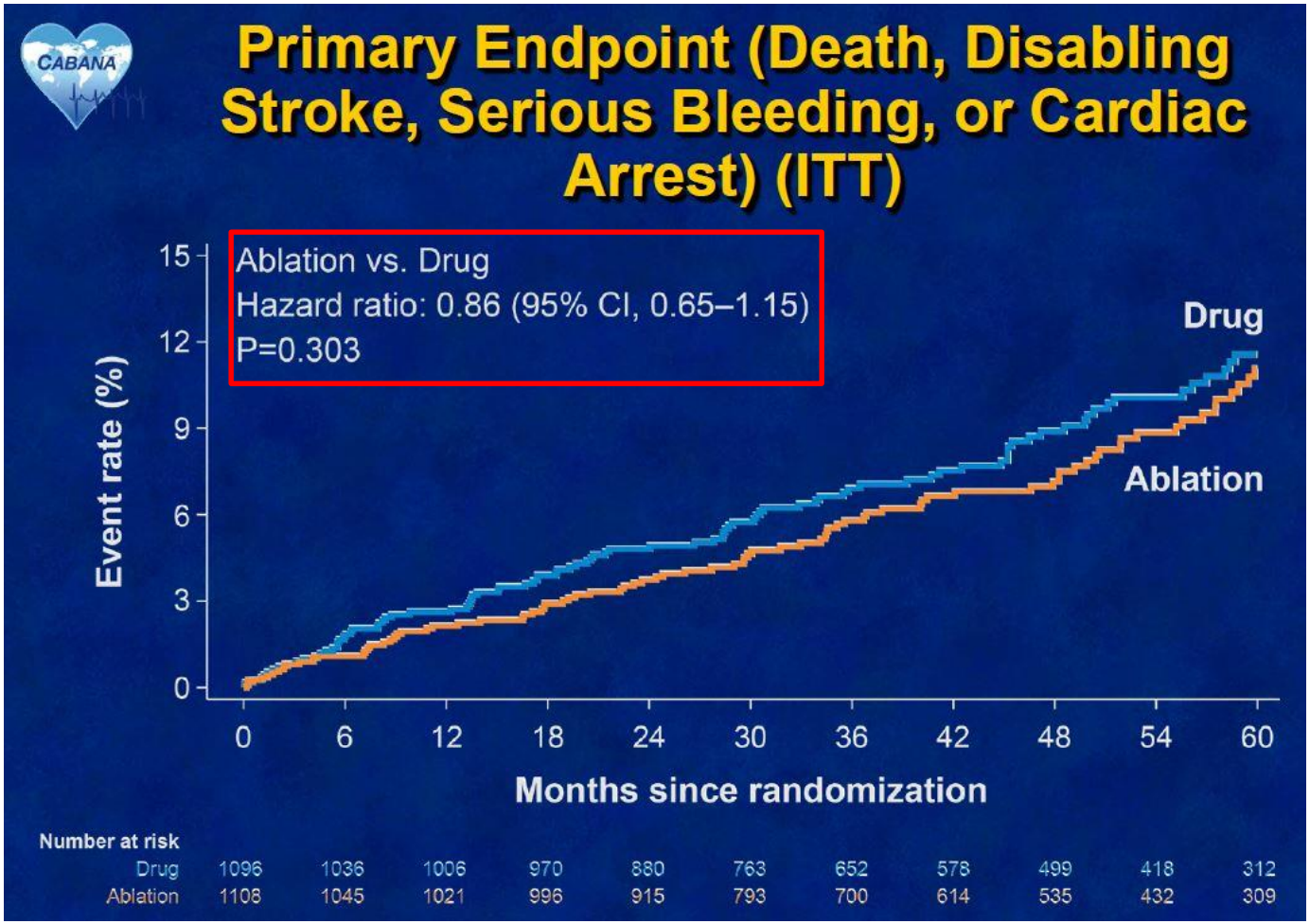

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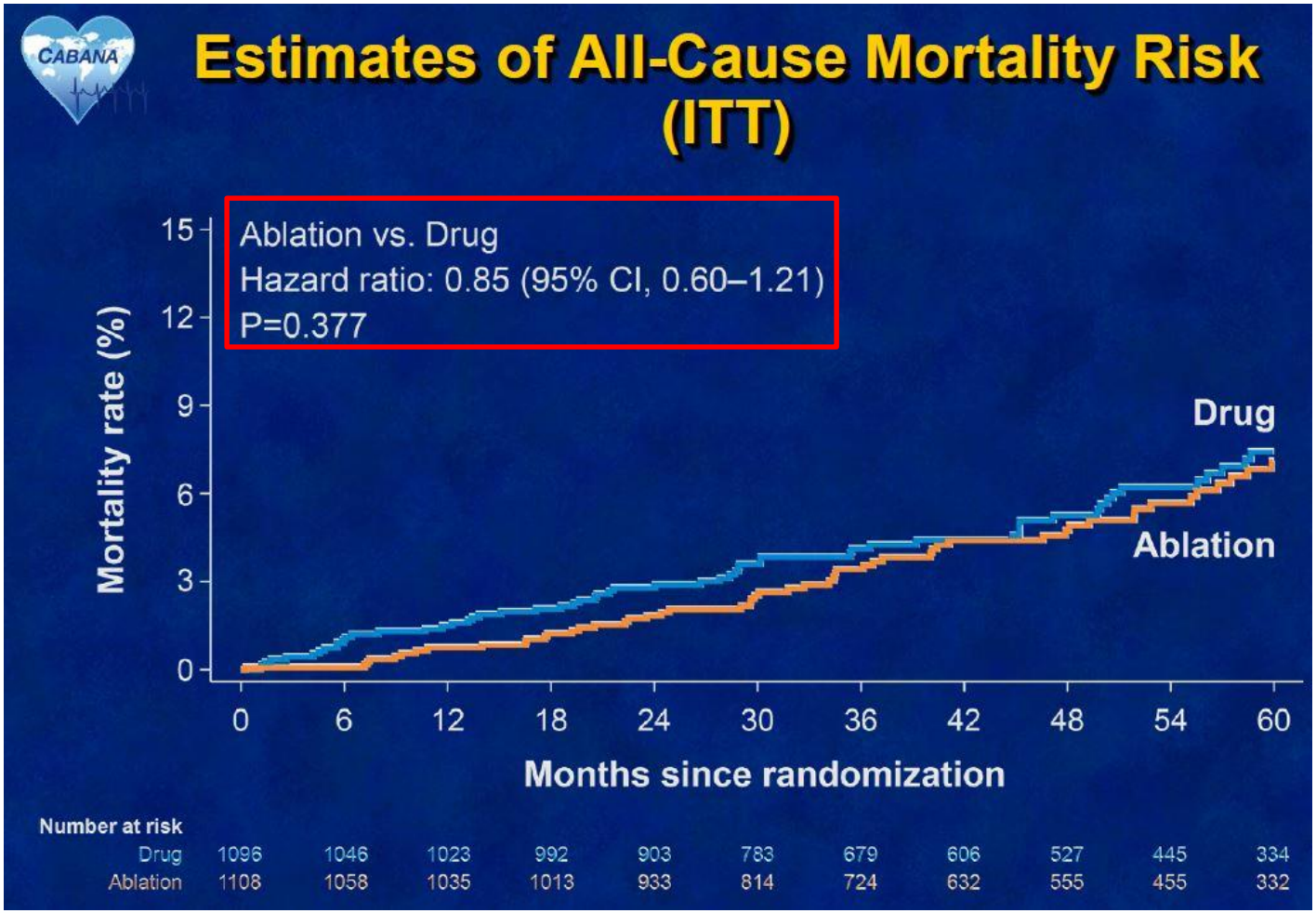

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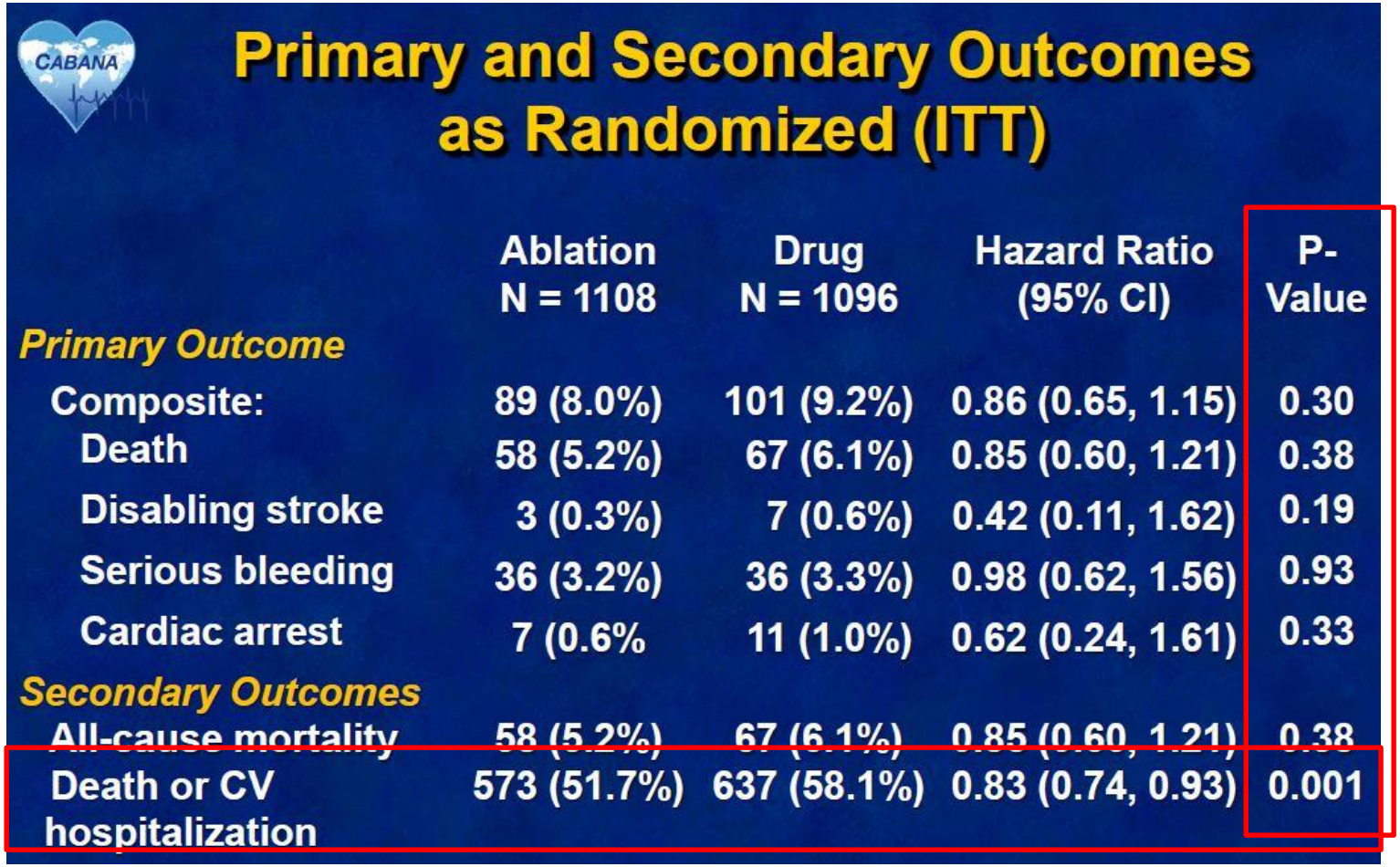

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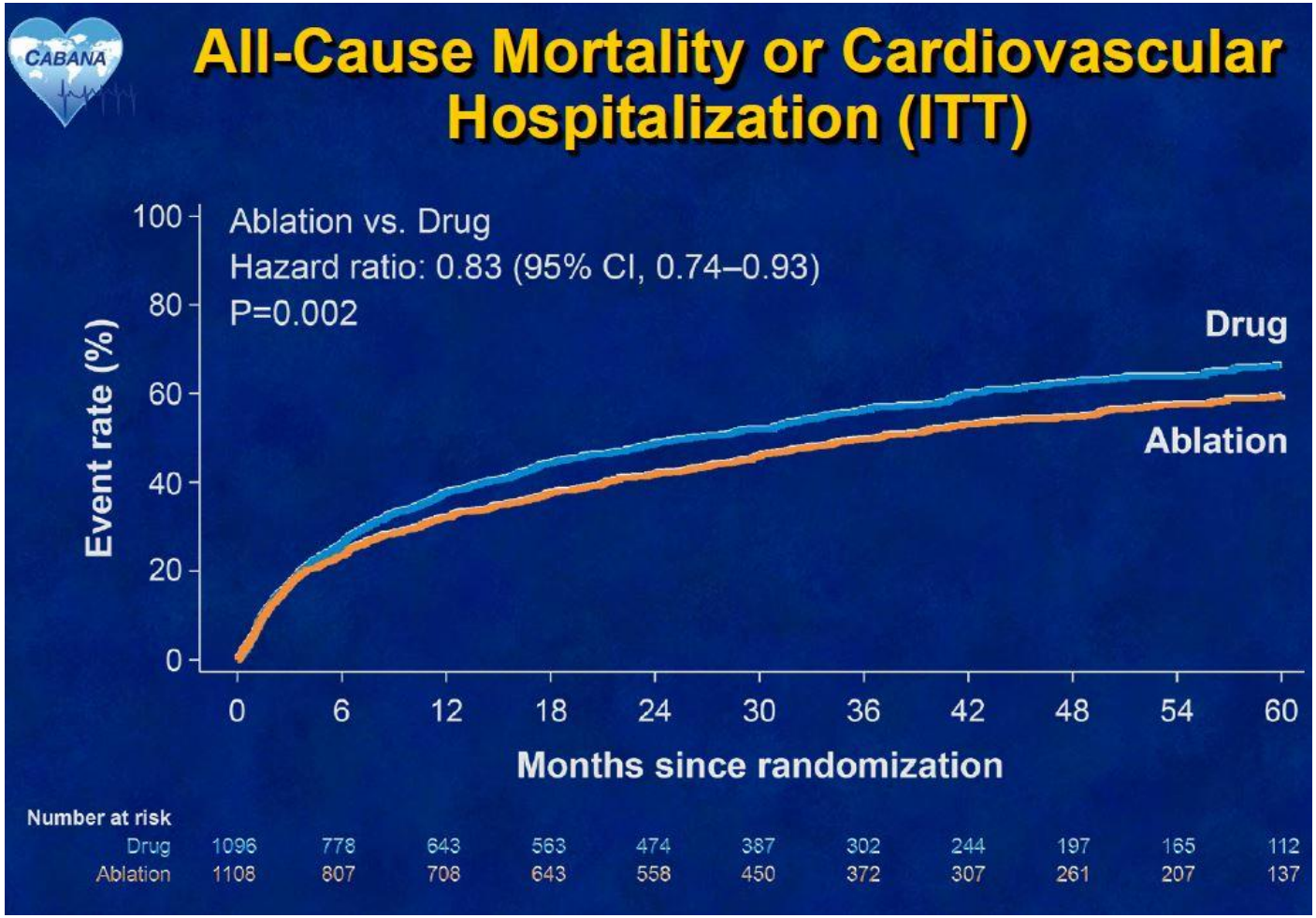

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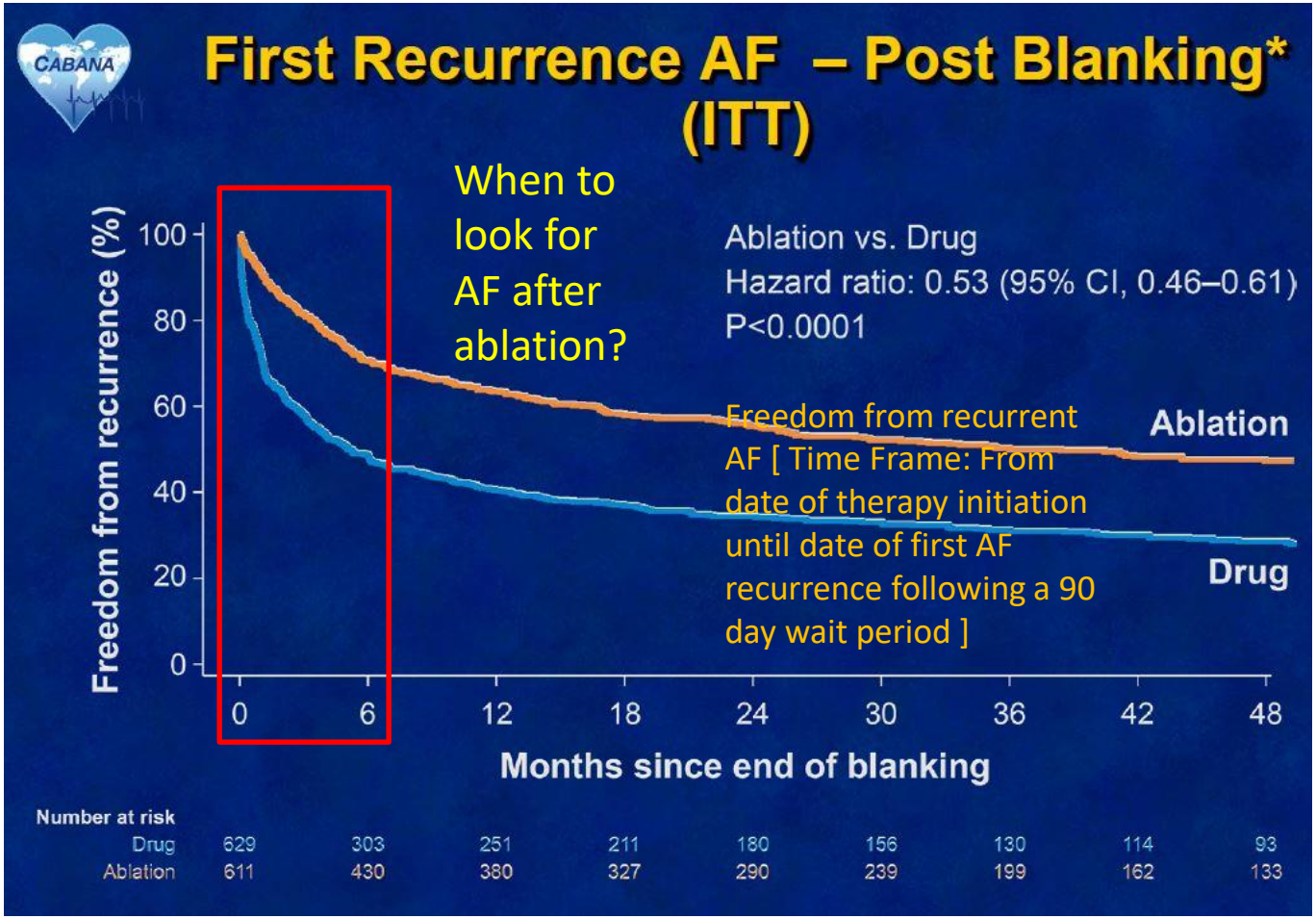

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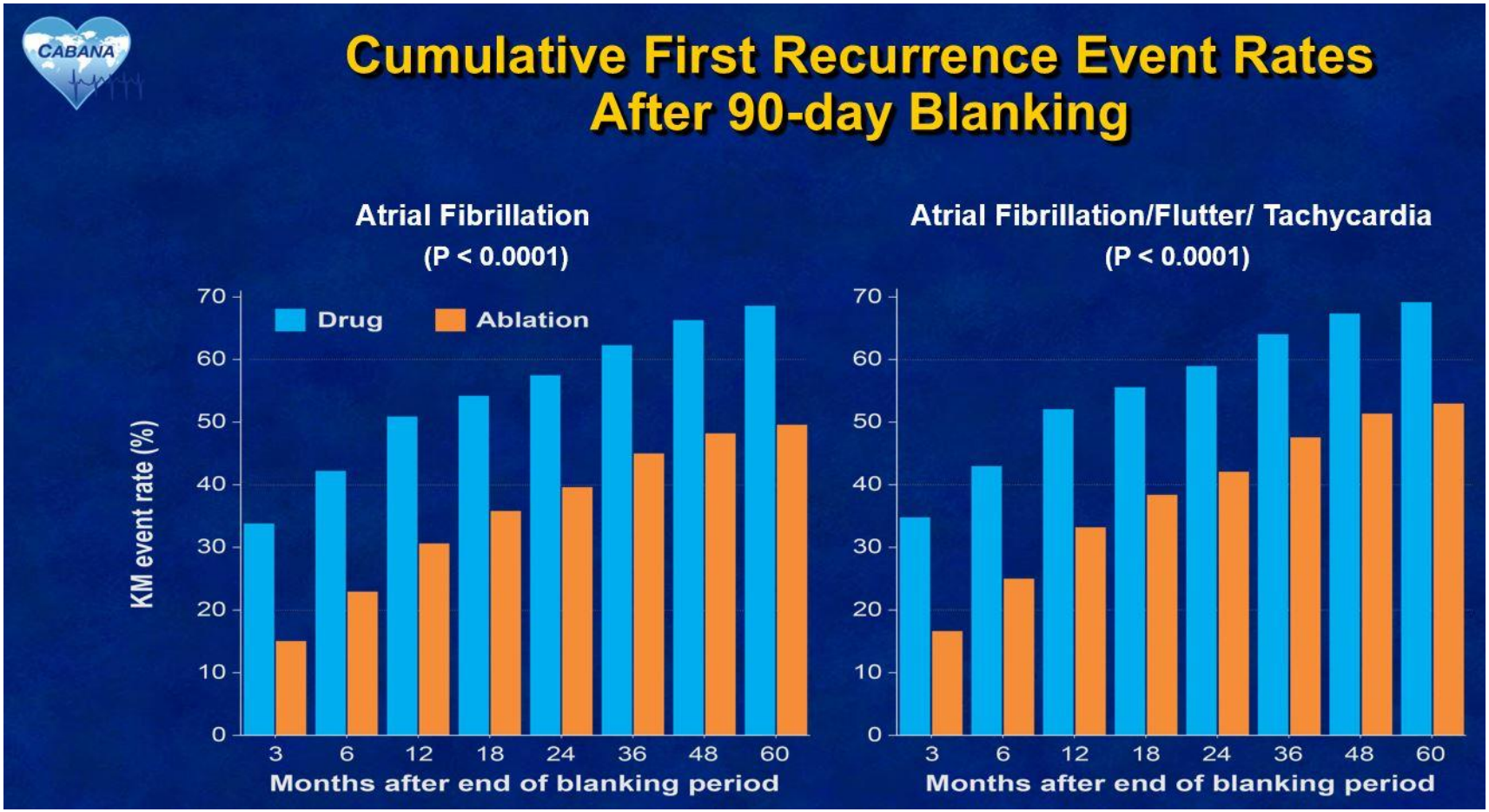

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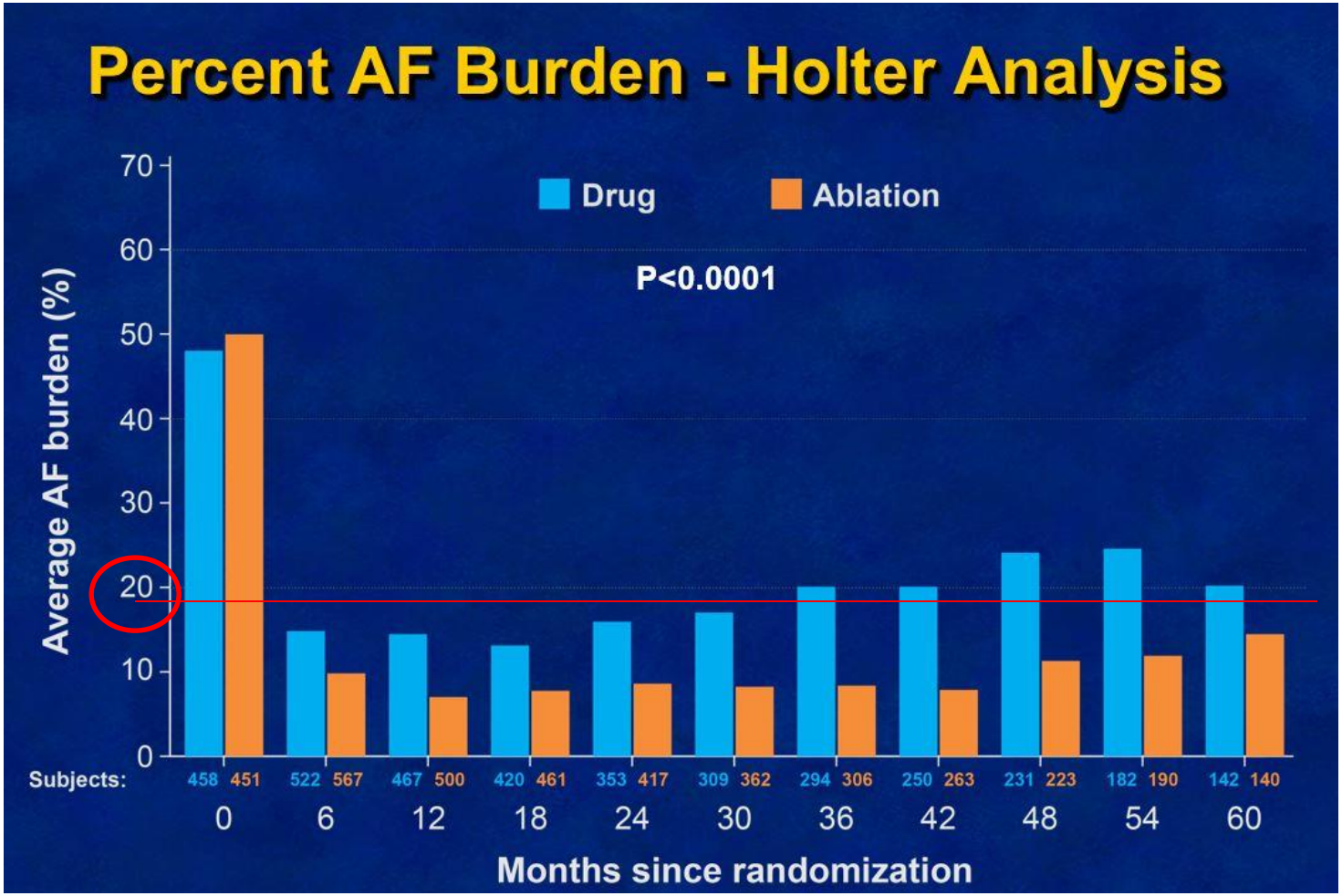

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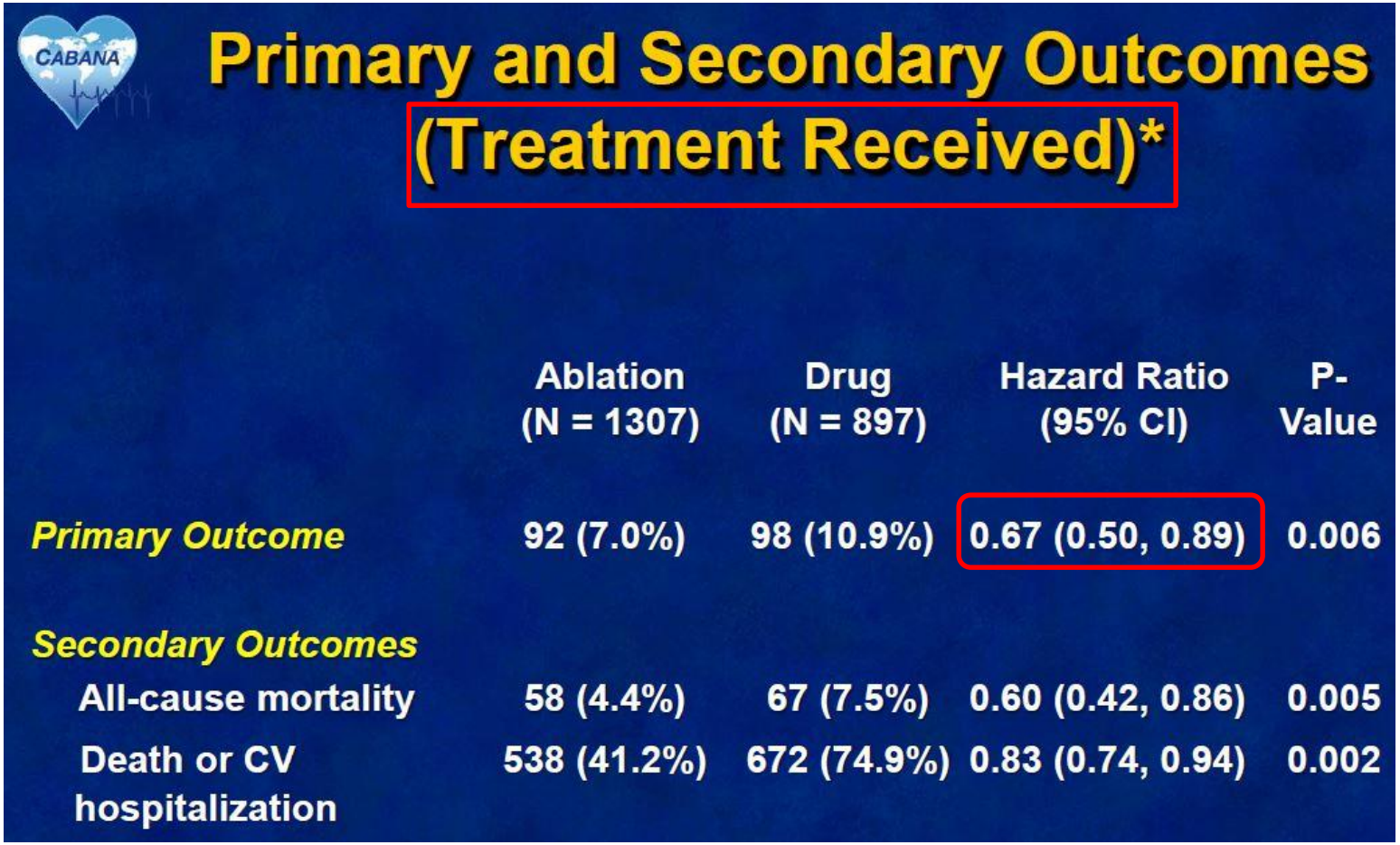
CABANA



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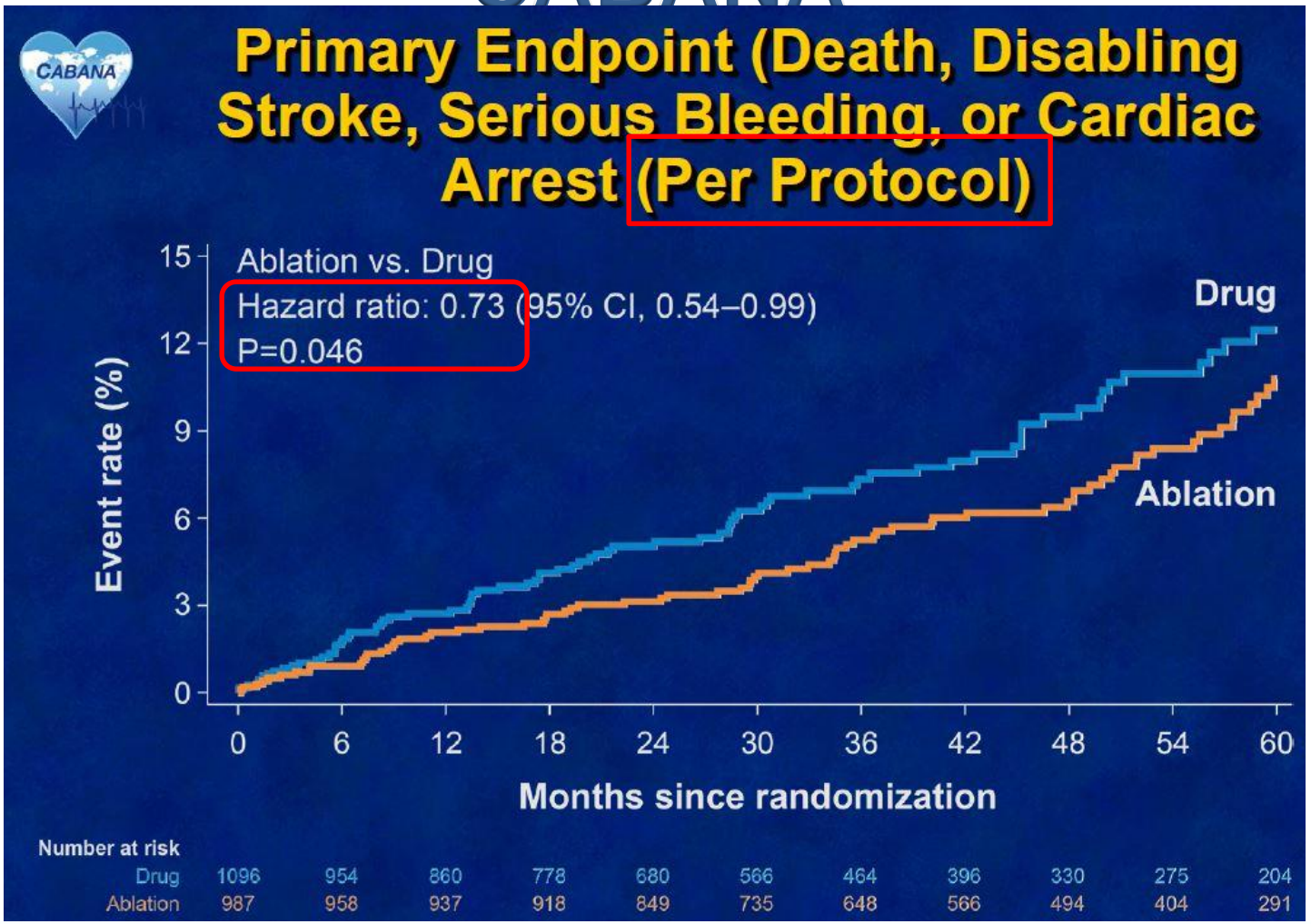
CABANA



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CABANA

Conclusion of the CABANA Trial

- Ablation did not produce a significant reduction in the primary endpoint and all-cause mortality.
- The results were affected by cross-overs in both directions and lower than expected event rates.
- Ablation significantly reduced mortality or CV hospitalization by 17% compared to drug therapy.
- There also was a significant 47% reduction in recurrent AF with ablation compared to drug therapy.
- A 33% reduction in the primary endpoint and 40% mortality risk reduction was present when patients actually *underwent* ablation *(treatment received)*.
- Ablation is an acceptable treatment strategy for treating AF with low adverse event rates even in higher risk patients.

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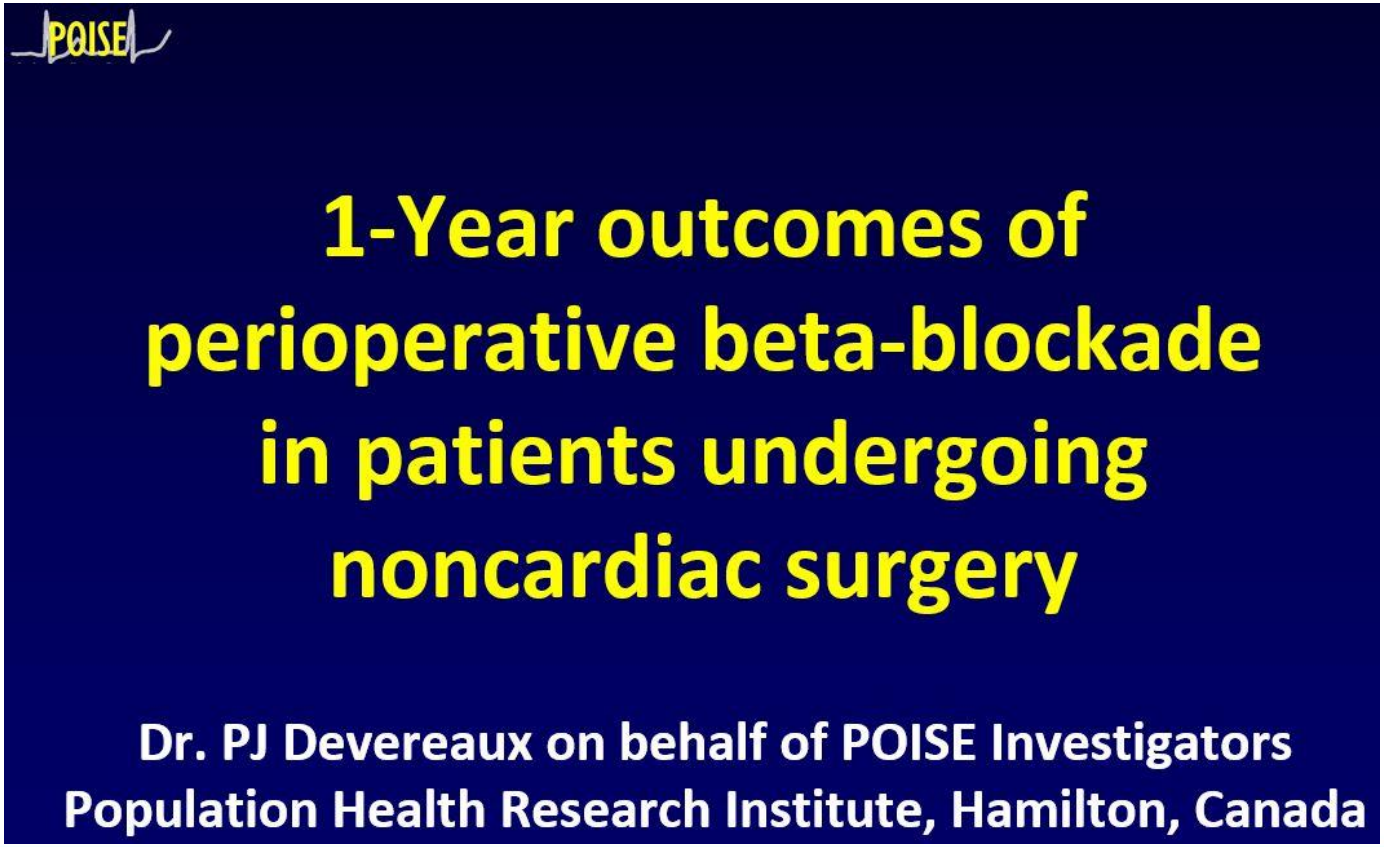
POISE One Yr Follow-up
(ACC 2018)



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POISE - 1

30-d outcome, published in 2008 *Lancet*

Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial

*POISE Study Group**

POISE One Yr Follow-up

- 200 million adults globally undergo noncardiac surgery annually
  - >3 million will suffer MI
- We undertook PeriOperative ISchemic Evaluation (POISE) Trial, because beta-blockers attenuate effects of increased perioperative catecholamine levels
  - we hypothesized that perioperative beta-blockade would decrease risk of perioperative MI and its sequela

POISE One Yr Follow-up

- 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 One Yr Follow-up

- 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

POISE One Yr Follow-up

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%

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POISE One Yr Follow-up

Type of surgery

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

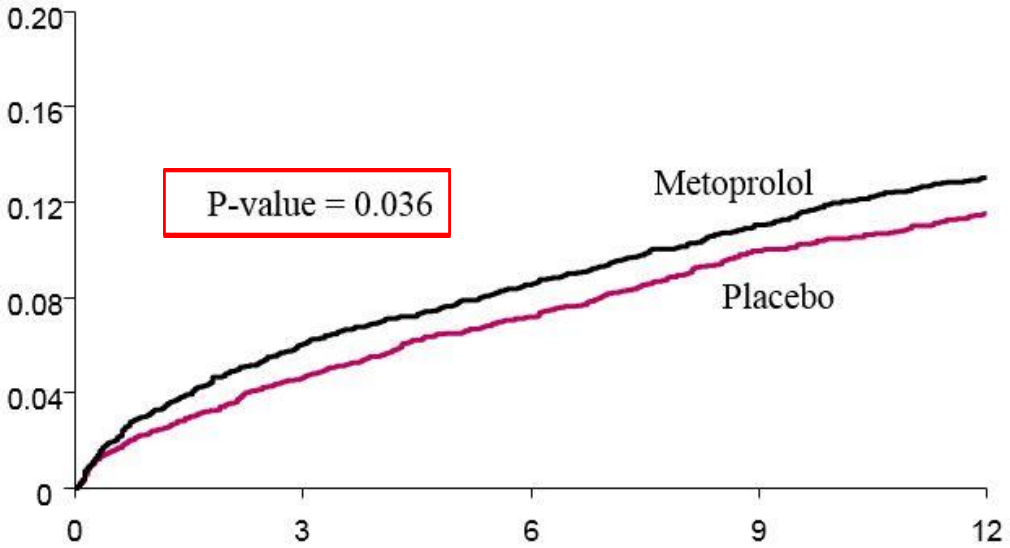
POISE One Yr Follow-up

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

POISE One Yr Follow-up

1-year all-cause mortality



10% v 9%

No. at Risk					
Placebo	4177	2668	2559	2473	2408
Metoprolol	4174	2626	2522	2439	2347

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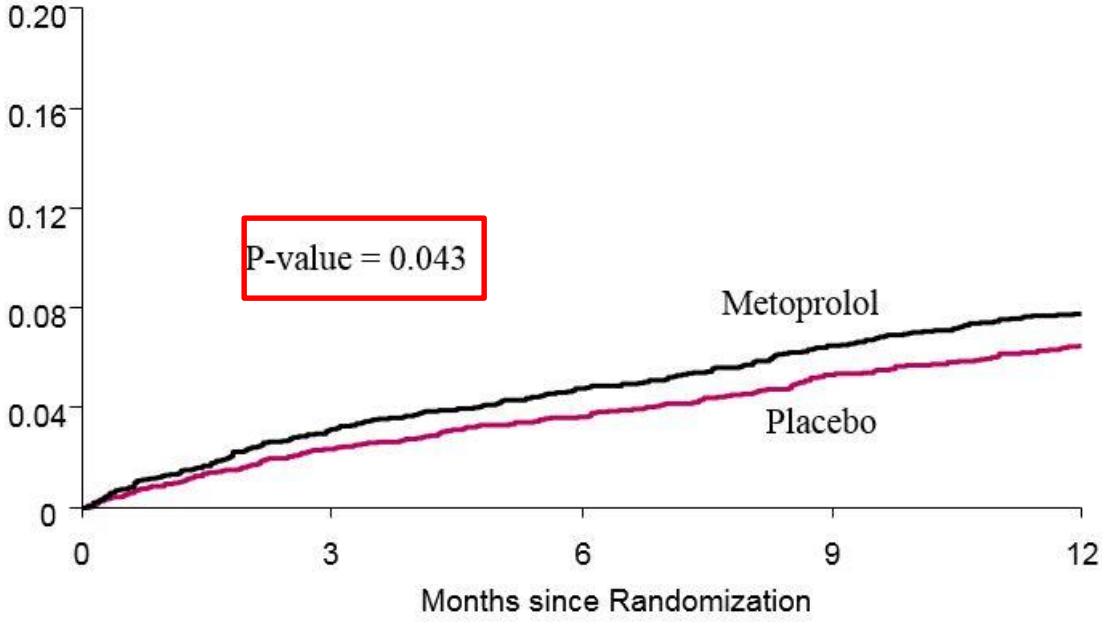
POISE One Yr Follow-up

1-year non-CV mortality



6% v 5%

No. at Risk					
Placebo	4177	2668	2559	2473	2408
Metoprolol	4174	2626	2522	2439	2347

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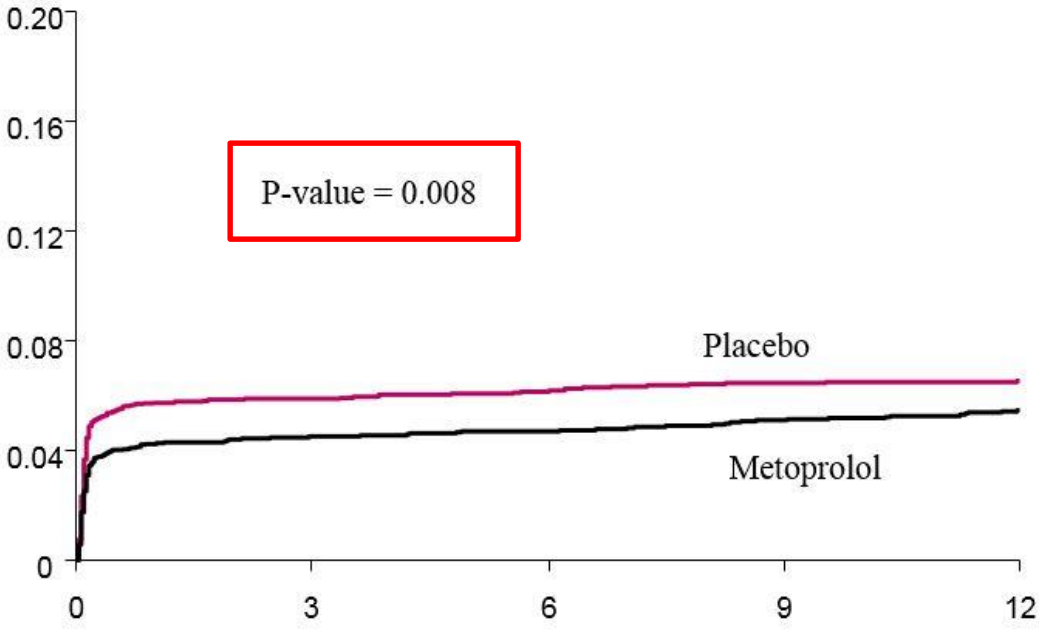
POISE One Yr Follow-up

1-year MI and revasc outcomes

Outcome	metoprolol n=4174 no. (%)	Placebo n=4177 no. (%)	HR (95% CI)	P value
Myocardial infarction	208 (5)	260 (6)	0.78 (0.65-0.94)	0.008
Cardiac revascularization	21 (1)	45 (1)	0.47 (0.28-0.78)	0.004

POISE One Yr Follow-up

1-year myocardial infarction



No. at Risk					
Placebo	4177	2548	2450	2370	2308
Metoprolol	4174	2542	2445	2357	2264

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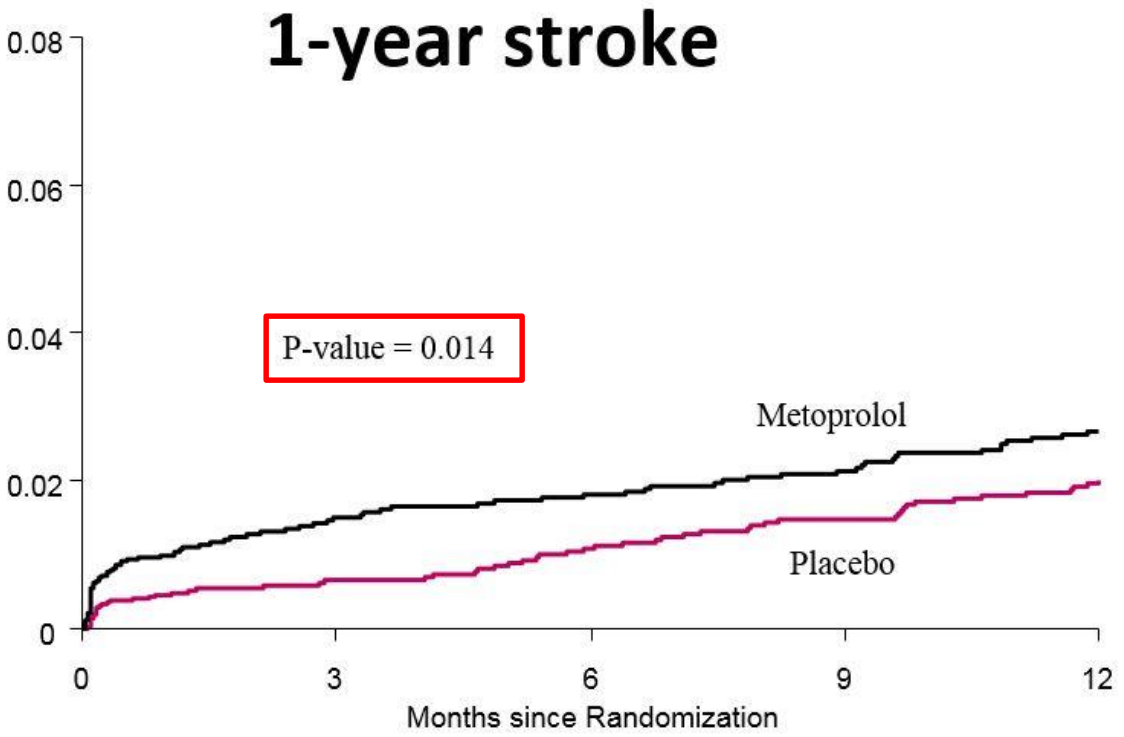
POISE One Yr Follow-up



No. at Risk					
Placebo	4177	2654	2539	2449	2379
Metoprolol	4174	2596	2492	2407	2315

5% v 6%

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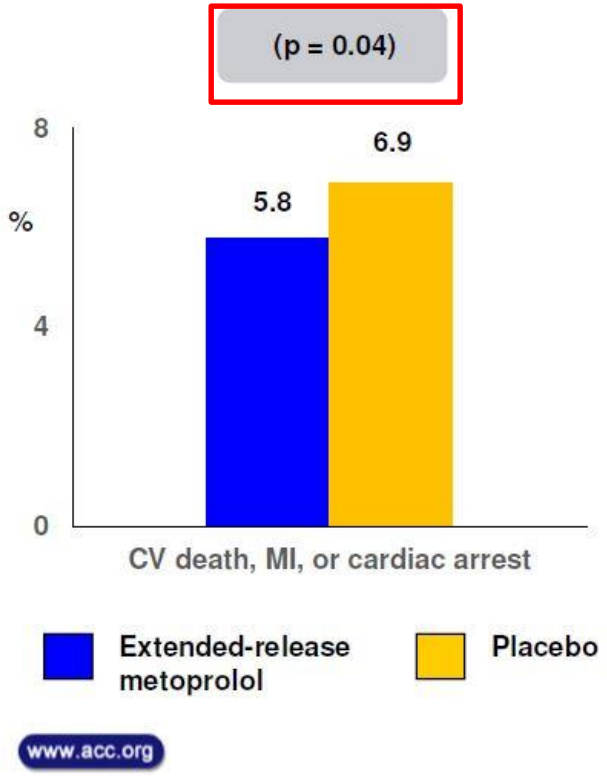
POISE One Yr Follow-up

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

POISE One Yr Follow-up

Trial design: Patients undergoing surgery were randomized in a double-blind manner to treatment with extended-release metoprolol (n = 4,174) vs. placebo (n = 4,177).



Results

- CV death, MI, or cardiac arrest: 5.8% with metoprolol vs. 6.9% with placebo (p = 0.04)
- Total mortality: 3.1% with metoprolol vs. 2.3% with placebo (p = 0.032)
- Stroke: 1.0% with metoprolol vs. 0.5% with placebo (p = 0.0053)

Conclusions

- Among patients undergoing noncardiac surgery, treatment with extended-release metoprolol was associated with a reduction in major adverse cardiac events vs. placebo
- Total mortality and stroke were higher in the metoprolol group

POISE Study Group. Lancet 2008;371:1839-47

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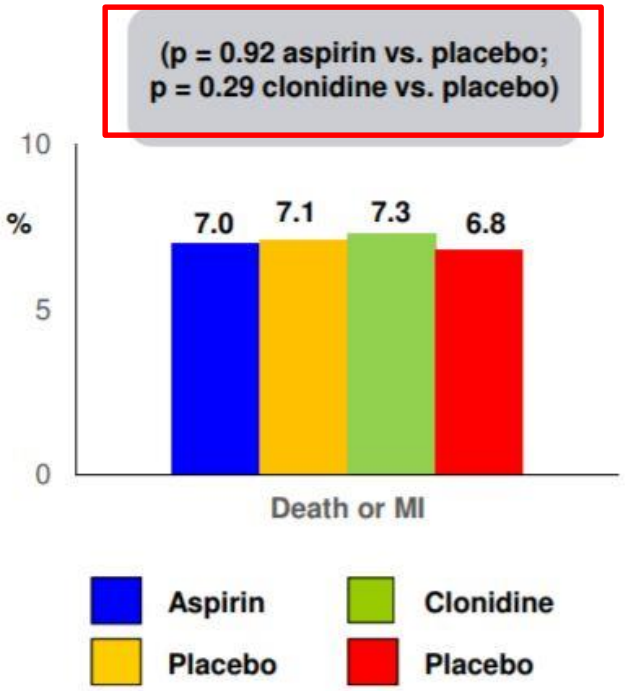
POISE – 2 (ASA & Clonidine, NEJM 2014)

POISE-2

Trial design: Patients undergoing noncardiac surgery were randomized to perioperative aspirin (n = 4,998) vs. placebo (n = 5,012). Patients were also randomized to perioperative clonidine 0.2 mg (n = 5,009) vs. placebo (n = 5,001).



Results

- Death or MI: 7.0% of the aspirin group vs. 7.1% of the placebo group (p = 0.92)
- Major bleeding: 4.6% for aspirin vs. 3.8% for placebo (p = 0.04)
- Death or MI: 7.3% of the clonidine group versus 6.8% of the placebo group (p = 0.29)
- Clinically important hypotension: 47.6% for aspirin vs. 37.1% for placebo (p < 0.001)

Conclusions

- Among patients undergoing noncardiac surgical procedures, neither the perioperative use of aspirin, nor clonidine, was beneficial in reducing death or MI. Aspirin was associated with a significant excess in major bleeding, while clonidine was associated with a significant excess in hypotension.

Devereaux PJ, et al. N Engl J Med 2014;370:1494-1513

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CECCY
(ACC 2018, JACC 2018)

Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity

The CECCY Trial

Mônica Samuel Avila, MD,[a,*] Silvia Moreira Ayub-Ferreira, MD, PhD,[a,*] Mauro Rogerio de Barros Wanderley, Jr, MD,[a] Fatima das Dores Cruz, RN,[a] Sara Michelly Gonçalves Brandão, RN,[a] Vagner Oliveira Carvalho Rigaud, PhD,[a] Marília Harumi Higuchi-dos-Santos, MD, PhD,[c] Ludhmila Abrahão Hajjar, MD, PhD,[b,c] Roberto Kalil Filho, MD, PhD,[b,c] Paulo Marcelo Hoff, MD, PhD,[c] Marina Sahade, MD,[c] Marcela S.M. Ferrari, MD,[c] Romulo Leopoldo de Paula Costa, MD,[c] Max Senna Mano, MD, PhD,[c] Cecilia Beatriz Bittencourt Viana Cruz, MD,[b,c] Maria Cristina Abduch, VMD,[b] Marco Stephan Lofrano Alves, MD, PhD,[b] Guilherme Veiga Guimaraes, PhD,[a] Victor Sarli Issa, MD, PhD,[a] Marcio Sommer Bittencourt, MD, MPH, PhD,[b,c,d] Edimar Alcides Bocchi, MD, PhD[a]

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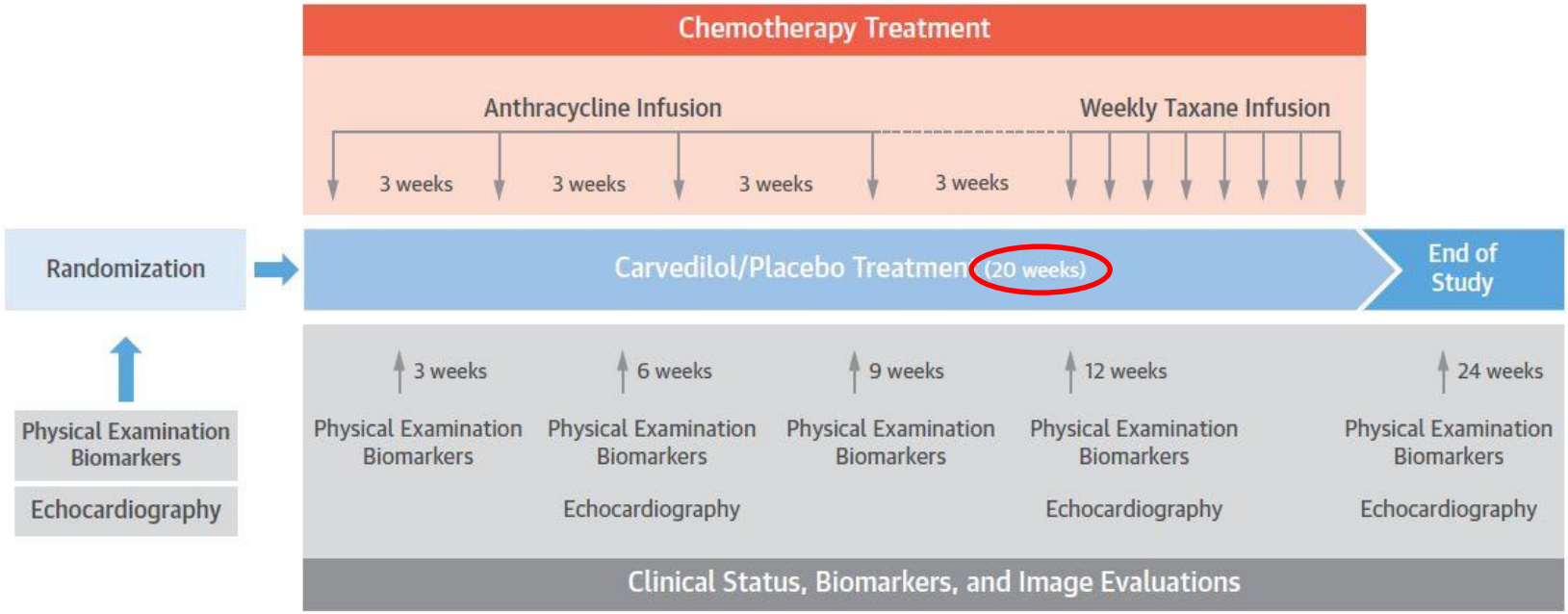
CECCY

The goal of the trial was to evaluate carvedilol compared with placebo among patients with HER2-negative breast cancer undergoing anthracycline (ANT)-based chemotherapy.

- 200 patients with HER2-negative breast cancer tumor status and normal LVEF referred for ANT (240 mg/m^2) randomized to receive carvedilol or placebo until chemotherapy completion.
- Primary endpoint was prevention of a ≥10% reduction in LVEF at 6 months.
- Secondary outcomes were effects of carvedilol on troponin I, B-type natriuretic peptide, and diastolic dysfunction.

CECCY

FIGURE 1 Study Protocol



Biomarkers were collected a mean of 19 days after each anthracycline cycle. The titration of carvedilol/placebo was made every 3 weeks at a maximum dose of 50 mg/day or appearance of symptoms or heart rate ≤60 beats/min or systolic blood pressure <110 mm Hg. Carvedilol was continued until chemotherapy was completed (20 weeks).

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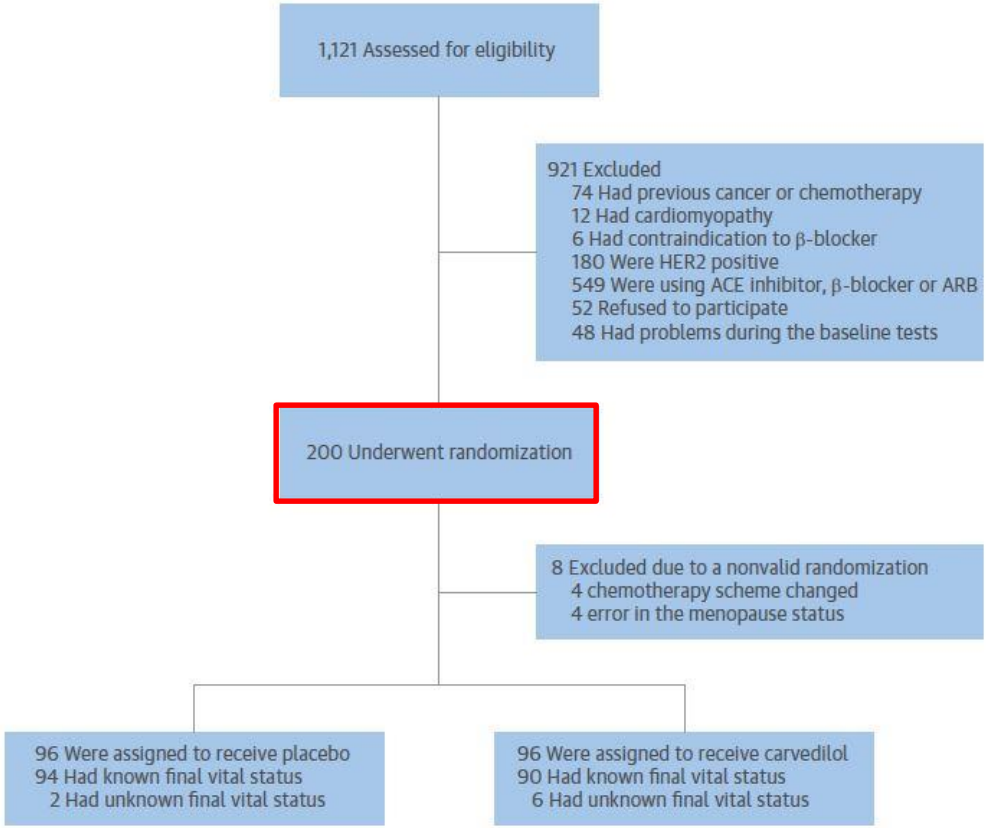
CECCY

FIGURE 2 Screening Criteria and Randomization



The intention-to-treat population included all patients who met the inclusion criteria and had a valid randomization. Problems with baseline tests refer to an impossibility of accomplishing all the baseline examinations before the initiation of chemotherapy. Exclusion due to an invalid randomization refers to patients who after randomization had a change in chemotherapy treatment (n = 4) and an error in the menopausal status (n = 4). ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers.

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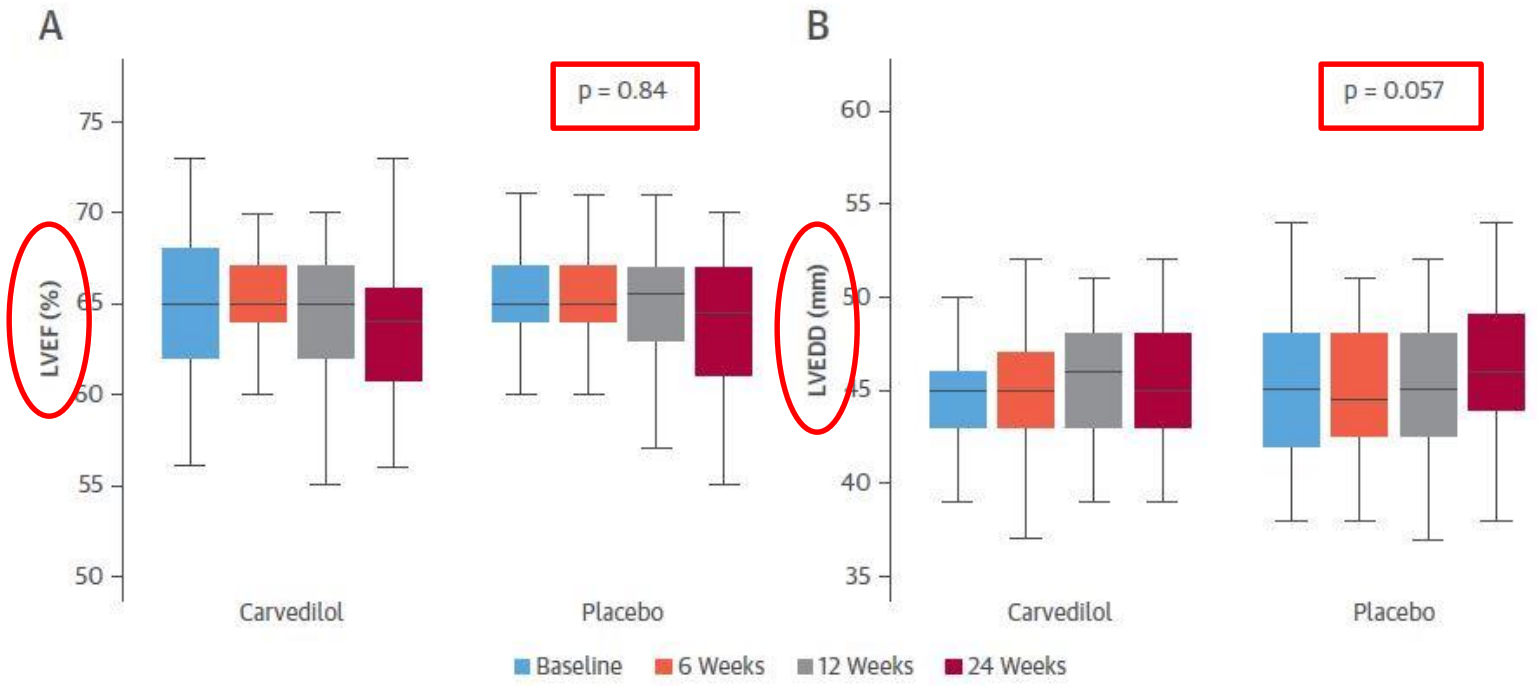
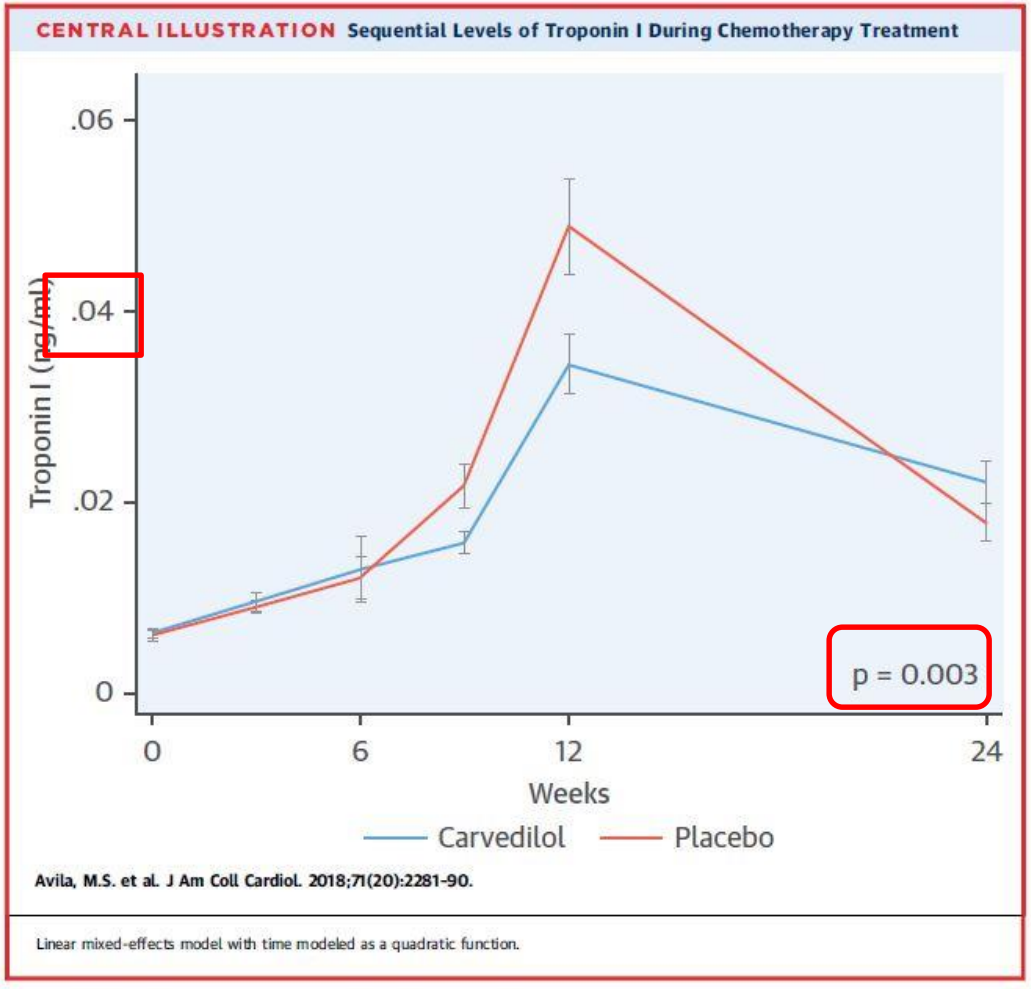
FIGURE 3 Comparison of Placebo and Carvedilol in the Echocardiographic Parameters During Follow-Up



(A) Measurements of left ventricular ejection fraction (LVEF) during the follow-up of chemotherapy treatment and the comparison between carvedilol and placebo group. **(B)** Measurements of left ventricular end-diastolic diameter (LVEDD) during the follow-up of chemotherapy treatment and the comparison between carvedilol and placebo groups.

CECCY



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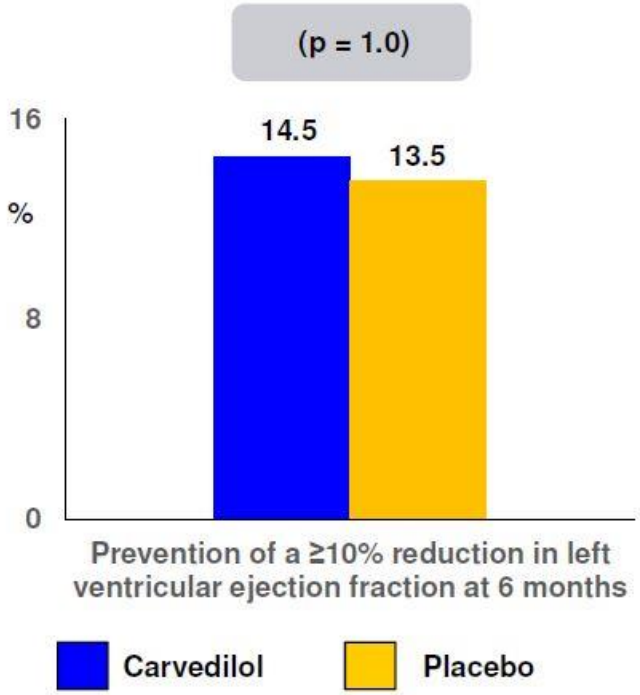
Trial design: Patients with HER2-negative breast cancer undergoing anthracycline-based chemotherapy were randomized to carvedilol (n = 96) vs. placebo (n = 96). Follow-up was 24 weeks.



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Results

- Prevention of a ≥10% reduction in left ventricular ejection fraction (LVEF) at 6 months: 14.5% of the carvedilol group vs. 13.5% of the placebo group (p = 1.0)
- Percentage of patients with troponin I ≥0.04: 26.0% vs. 41.6% (p = 0.003)

Conclusions

- Among patients with invasive breast cancer undergoing anthracycline-based chemotherapy, carvedilol versus placebo was not effective at preventing a reduction in LVEF
- Carvedilol was associated with a lower frequency of detectable troponin I values

Avila MS, et al. J Am Coll Cardiol 2018;Mar 11:[Epub]

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Lisinopril or Carvedilol for Prevention of Trastuzumab Induced Cardiotoxicity (ACC 2018)

- To evaluate lisinopril versus carvedilol versus placebo for prevention of cardiomyopathy among patients undergoing trastuzumab (Herceptin®) chemotherapy for HER2 positive breast cancer.

Lisinopril or Carvedilol for Prevention of Trastuzumab Induced Cardiotoxicity

Introduction: Incidence of Cardiotoxicity

	Overall cardiac dysfunction	NYHA III/IV
Doxorubicin + Cyclophosphamide	8%	4%
Doxorubicin + Cyclophosphamide +Trastuzumab	27%	16%

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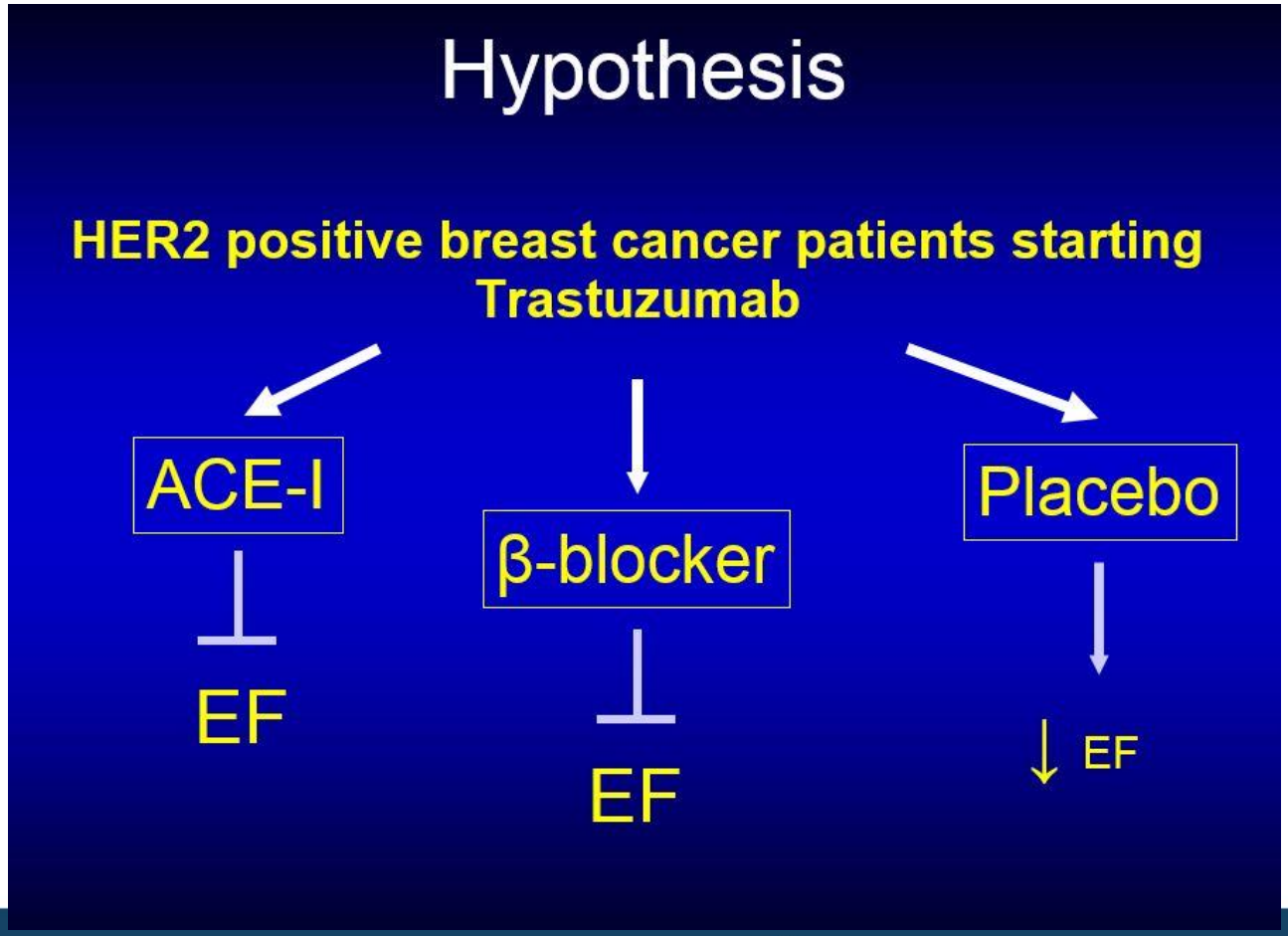
Lisinopril or Carvedilol for Prevention of Trastuzumab Induced Cardiotoxicity

- Patients with breast cancer undergoing trastuzumab chemotherapy were randomized to lisinopril versus carvedilol versus placebo.
- Patients were stratified by treatment with an anthracycline.
- Baseline left ventricular ejection fraction (LVEF) was 63%.
  - N = 468
  - Duration of follow-up: 12 months
  - Mean patient age: 51 years

Lisinopril or Carvedilol for Prevention of Trastuzumab Induced Cardiotoxicity



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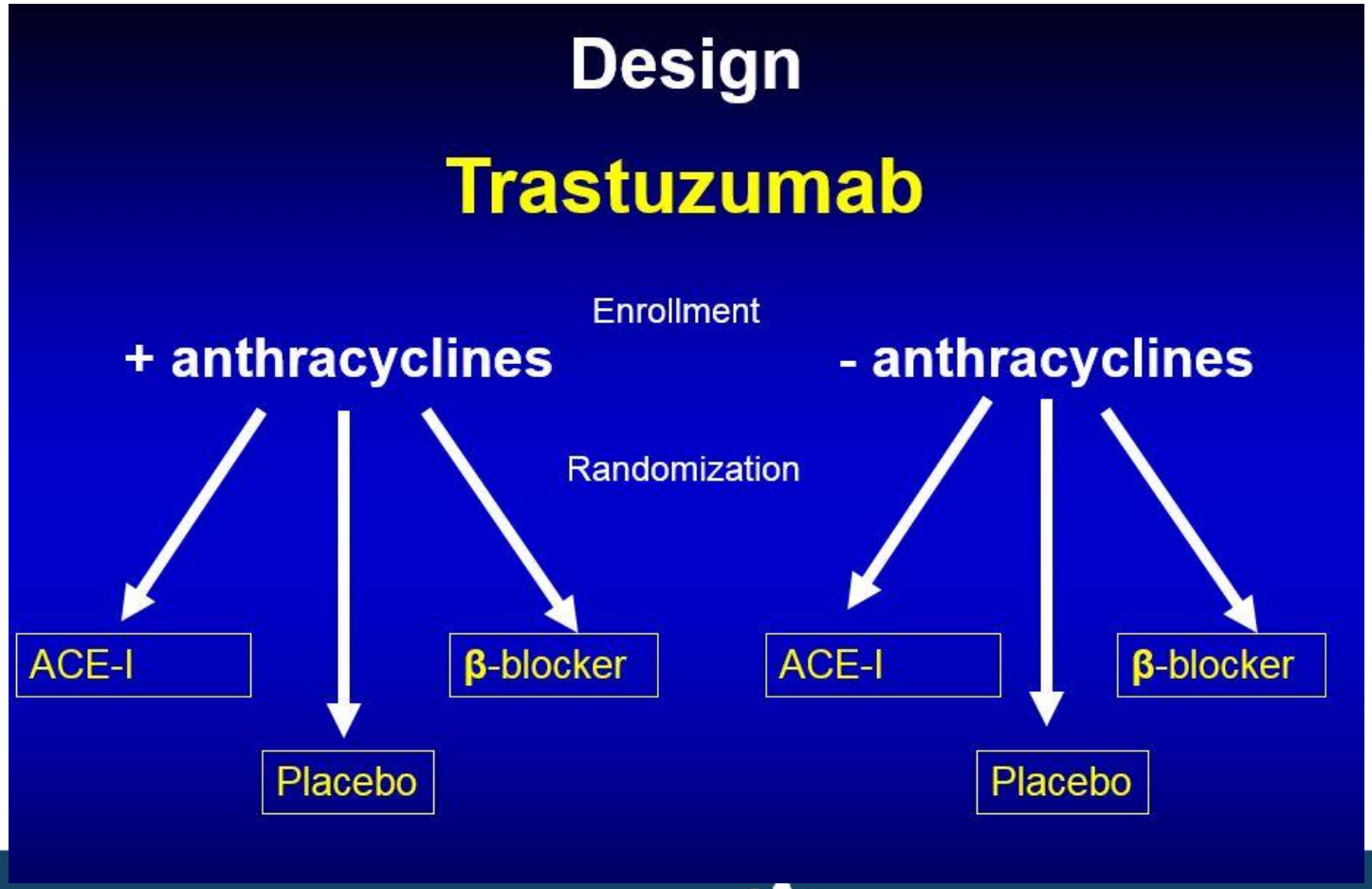
Lisinopril or Carvedilol for Prevention of Trastuzumab Induced Cardiotoxicity



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Lisinopril or Carvedilol for Prevention of Trastuzumab Induced Cardiotoxicity

Definition of Cardiotoxicity

- Decrease from baseline of ≥10% (LVEF) at study follow-up

or

- An absolute decrease ≥ 5% in LVEF if it is < 50% at study follow-up

- The determination of LVEF was made locally at each site. LVEF testing was conducted at baseline, 3, 6, 9, and 12 months.

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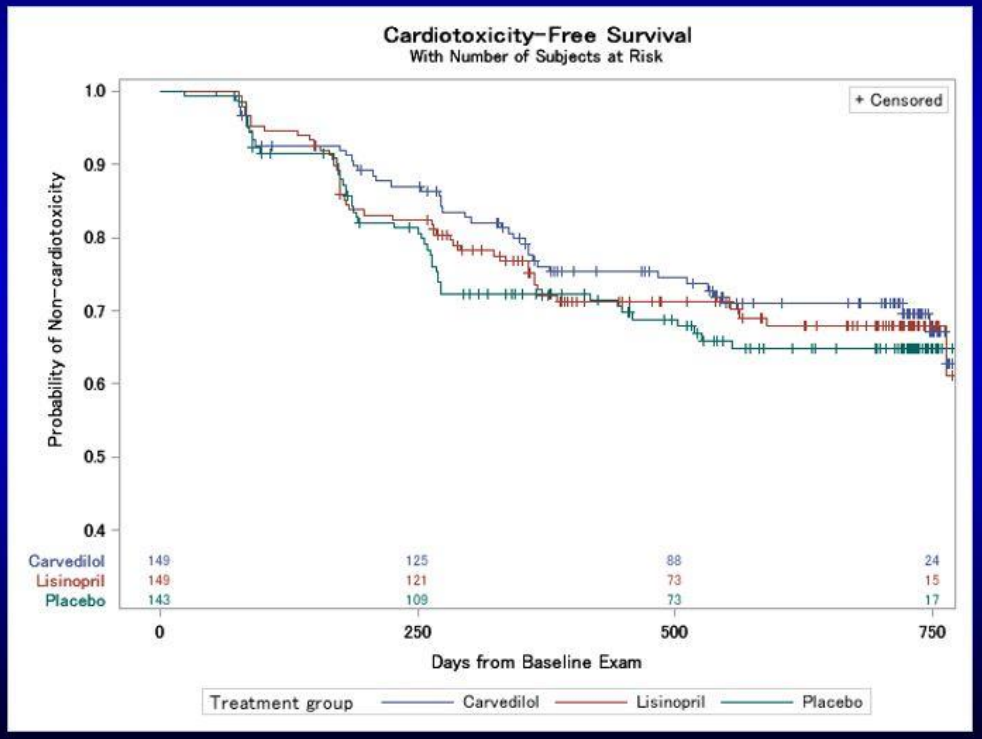
Lisinopril or Carvedilol for Prevention of Trastuzumab Induced Cardiotoxicity

Cardiotoxicity-free survival for the whole study cohort



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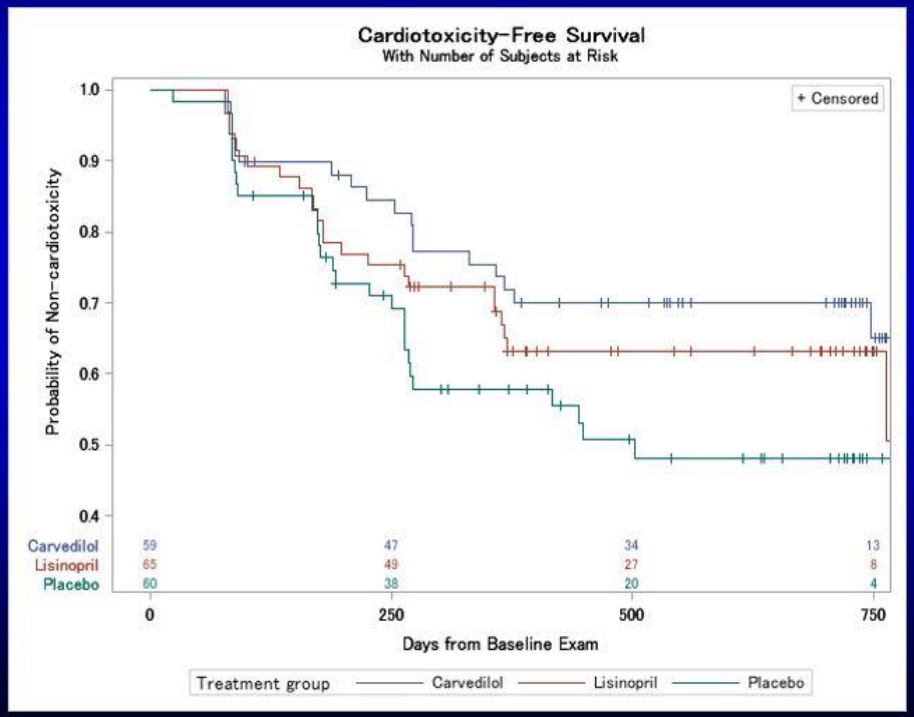
Lisinopril or Carvedilol for Prevention of Trastuzumab Induced Cardiotoxicity

Cardiotoxicity-free survival for the cohort with Trastuzumab and anthracycline exposure



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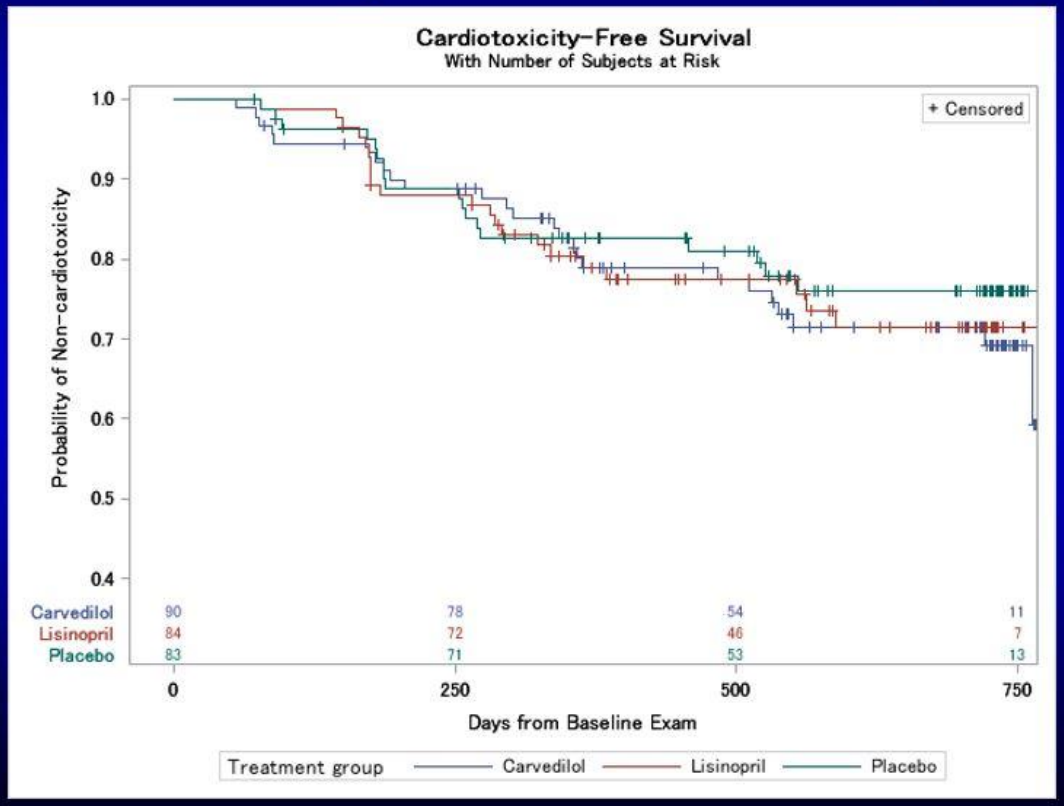
Lisinopril or Carvedilol for Prevention of Trastuzumab Induced Cardiotoxicity

Cardiotoxicity-free survival for the cohort with Trastuzumab exposure without anthracyclines



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Lisinopril or Carvedilol for Prevention of Trastuzumab Induced Cardiotoxicity

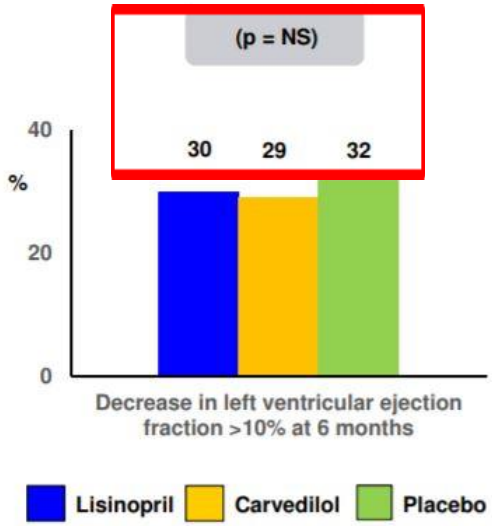
Conclusions

- In patients with HER2 positive breast cancer treated with trastuzumab, the cardiotoxic events were similar on placebo, lisinopril or carvedilol with comparable treatment interruptions.
- Both lisinopril and carvedilol were effective in preventing cardiotoxicity in patients who were treated with both trastuzumab and anthracyclines.
- Cardiotoxicity associated with Trastuzumab superimposed on prior or current exposure to anthracyclines can be prevented with lisinopril or carvedilol.
- In high risk patients who may benefit from an anthracycline-containing regimen, the use of lisinopril or carvedilol is justified and should be considered to off-set cardiotoxic events by the use of anthracyclines in combination with trastuzumab.

Lisinopril or Carvedilol for Prevention of Trastuzumab Induced Cardiotoxicity

Lisinopril or Carvedilol for Cardiotoxicity

Trial design: Patients with breast cancer undergoing trastuzumab chemotherapy were randomized to lisinopril vs. carvedilol vs. placebo. They were followed for 12 months.



Results

- Decrease in left ventricular ejection fraction (LVEF) >10%: 30% of the lisinopril group vs. 29% of the carvedilol group vs. 32% of the placebo group (p = not significant)
- Among those who received an anthracycline, decrease in LVEF >10%: 37% of the lisinopril group vs. 31% of the carvedilol group vs. 47% of the placebo group (p = 0.009)

Conclusions

- Among patients with breast cancer undergoing chemotherapy with trastuzumab, neither lisinopril nor carvedilol was effective at preventing cardiomyopathy compared with placebo

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Presented by Dr. Maya Guglin at ACC 2018

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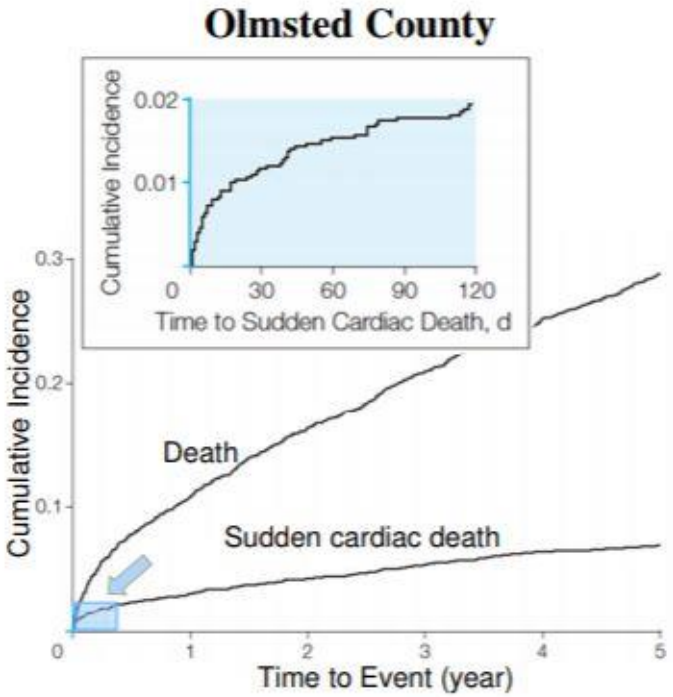
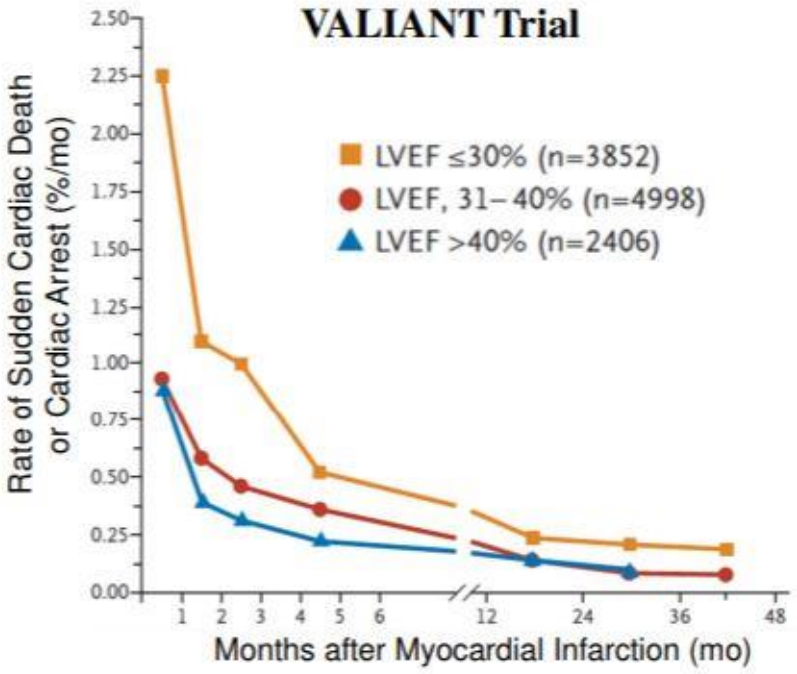
VEST
(ACC 2018)

Background: SCD is high after MI



Adabag, *et al.* JAMA 2008



VALIANT—Solomon, *et al.* NEJM 2005

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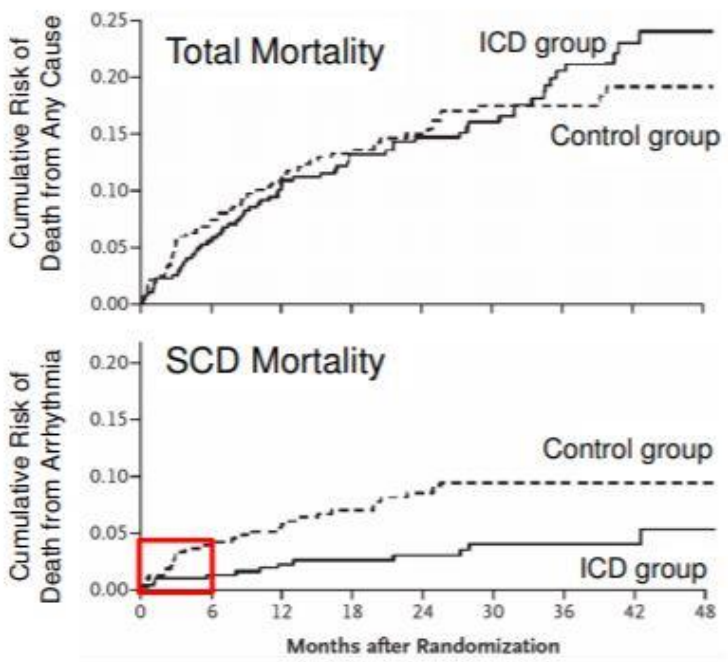
VEST

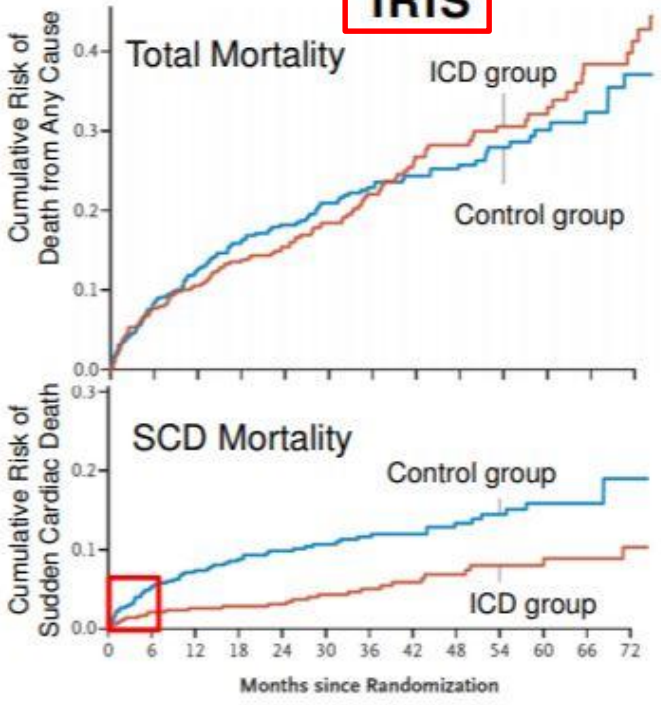
Background: No benefit from early ICD

DINAMIT



DINAMIT: Hohnloser, *et al*. NEJM 2004

IRIS



IRIS: Steinbeck, *et al*. NEJM 2009

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VEST

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?

VEST

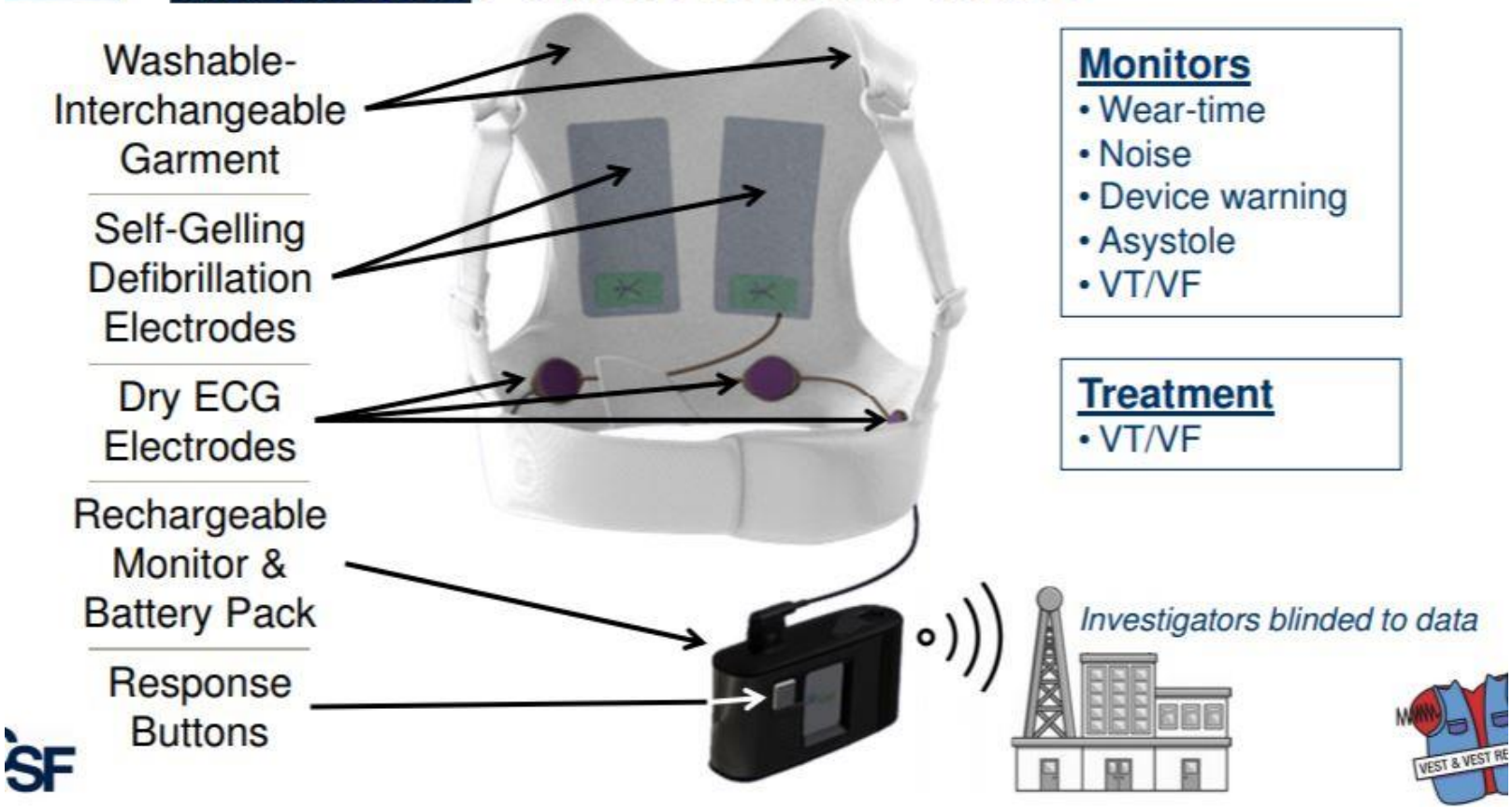
Methods: Study design

- **Multi-center, randomized, open-label trial**
- **Participants enrolled within 7 days of hospital d/c with acute MI and EF≤35%**
- **Randomized 2:1 to receive:**
  - Wearable cardioverter defibrillator (WCD) + guideline-directed therapy **or**
  - Guideline-directed medical therapy alone
- **MD's & sites blinded to detected arrhythmias**
- **Crossovers & ICDs prohibited (except for secondary prevention during follow-up)**

VEST

Basically a shock box – no pacing/ATP

Methods: Intervention-WCD



VEST

Methods: Outcomes

- **Follow-up at 1 month & 3 months**
- **Search NDI at end of study**
- **Primary Outcome: SCD & death due to ventricular arrhythmias**
- **Secondary outcomes**
  - Total mortality & Non-sudden death
  - Cause-specific death
  - Non-fatal outcomes
    - CV Hospitalizations
    - WCD compliance
    - Adverse events

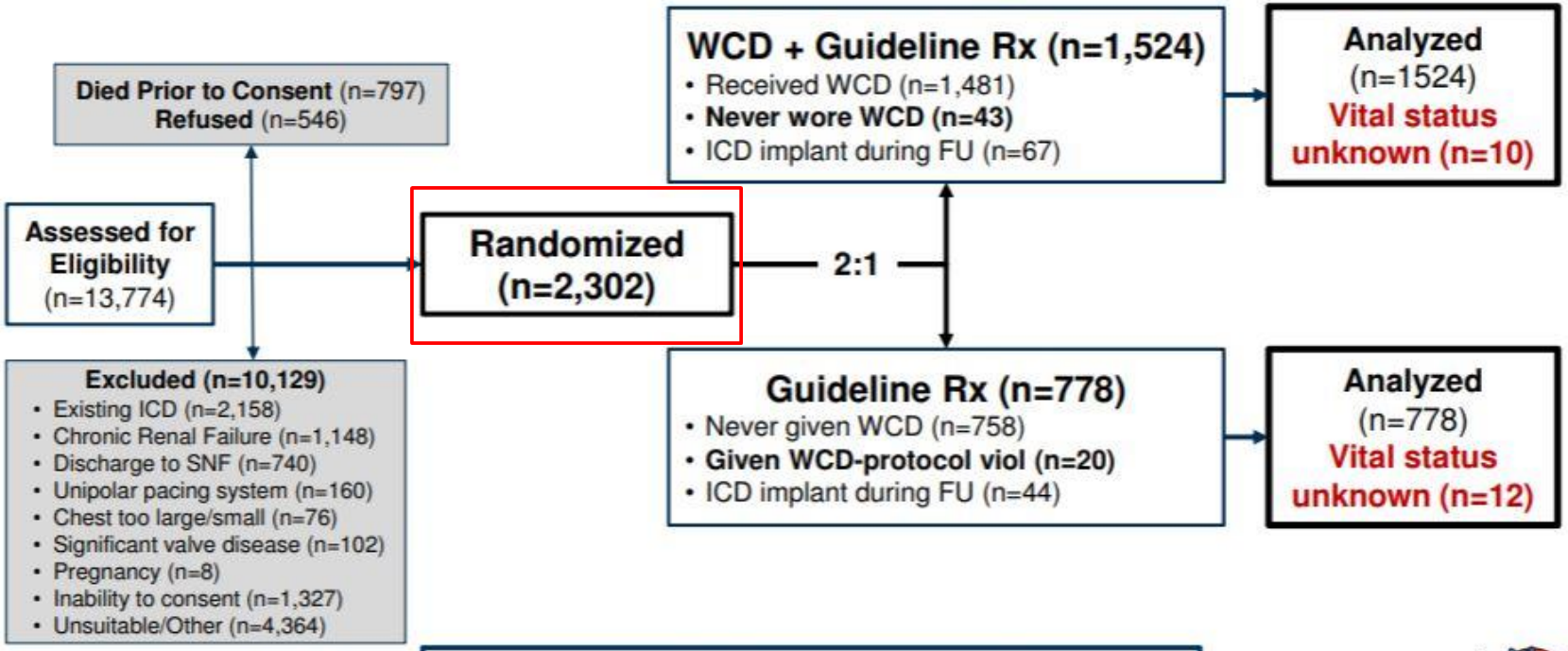
VEST

Methods: Analysis plan

- **Primary Analysis: Intention-to-treat**
  - Participants with indeterminate causes of death or unknown vital status are treated as not having primary outcome
- **Secondary Analyses**
  - Weighted sensitivity analyses excluding unknown vital status and indeterminate causes of death from denominator

VEST

Results: CONSORT diagram



Mean Follow-up = 84.3 ± 15.6 days

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VEST

Zoll LifeVest should be worn except when bathing

Results: Crossover treatment

Characteristic	WCD Group (N=1524)	Control Group (N=778)
WCD received, n (%)	**1455 (95.5%)**	20 (2.6%)*
Average hours/day WCD worn	**14.1 ± 9.3**	0.8 ± 3.9*
ICD during follow up (<90 days), n (%)	67 (4.4%)	44 (5.7%)
ICD Implant timing (days since randomization), median (IQR)	62 (24-81)	58 (25-77)

*P <0.001

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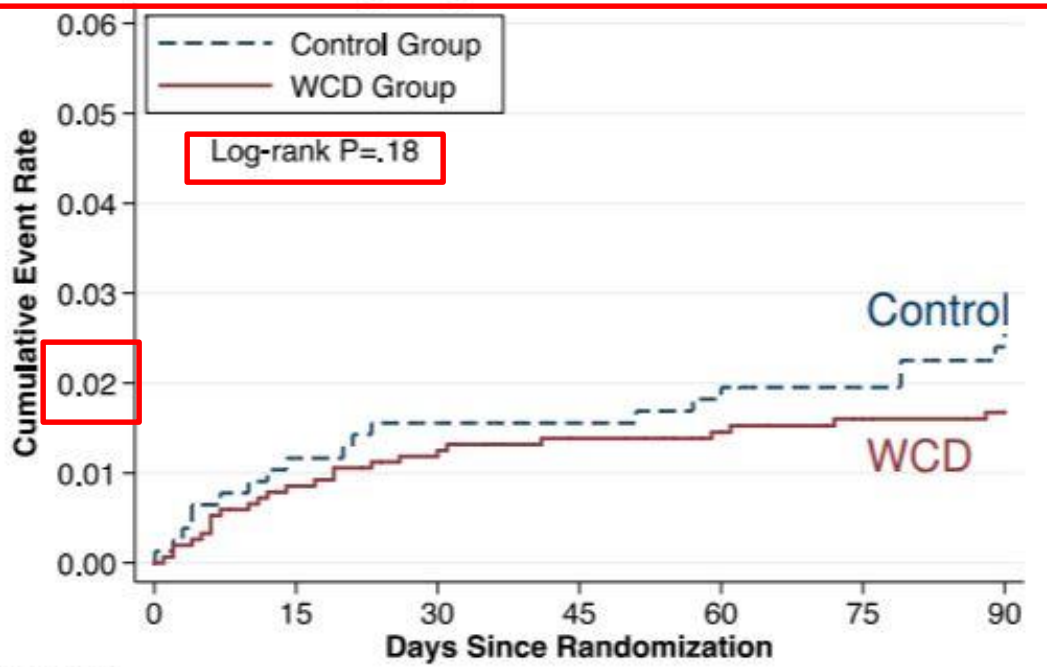
VEST

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

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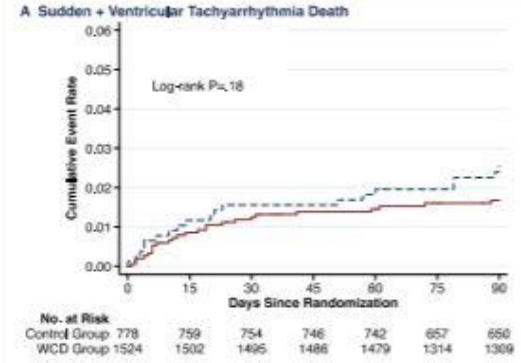
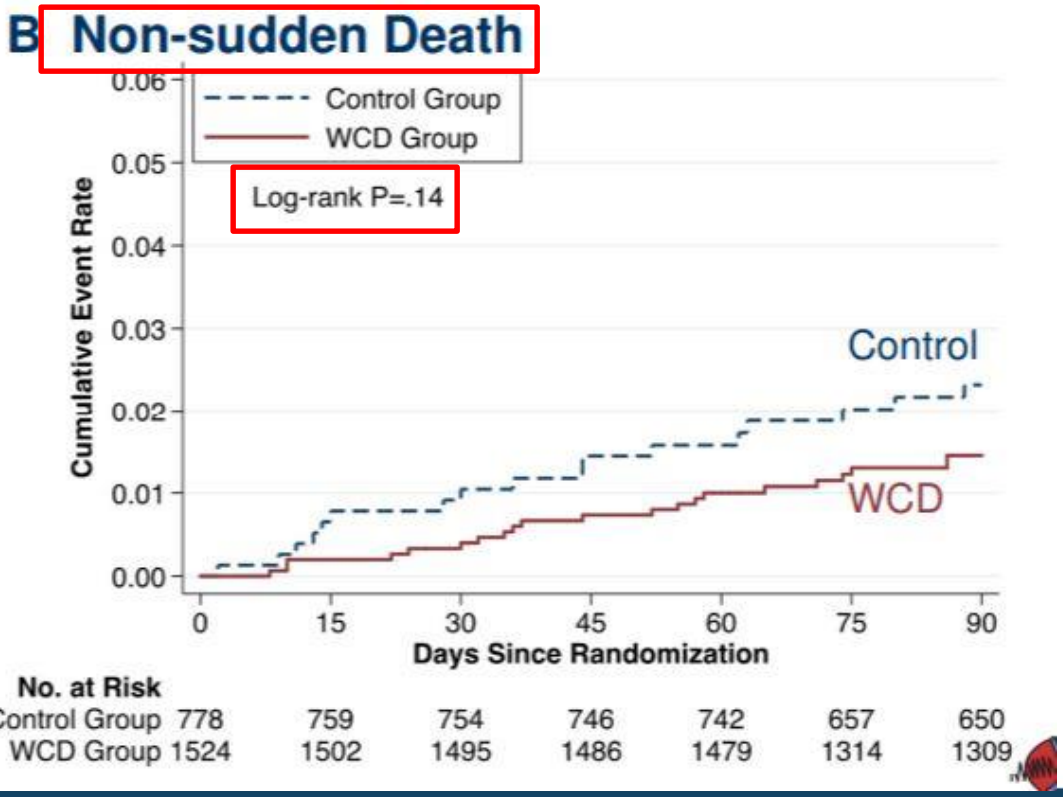
VEST

Results: Outcomes, intention-to-treat

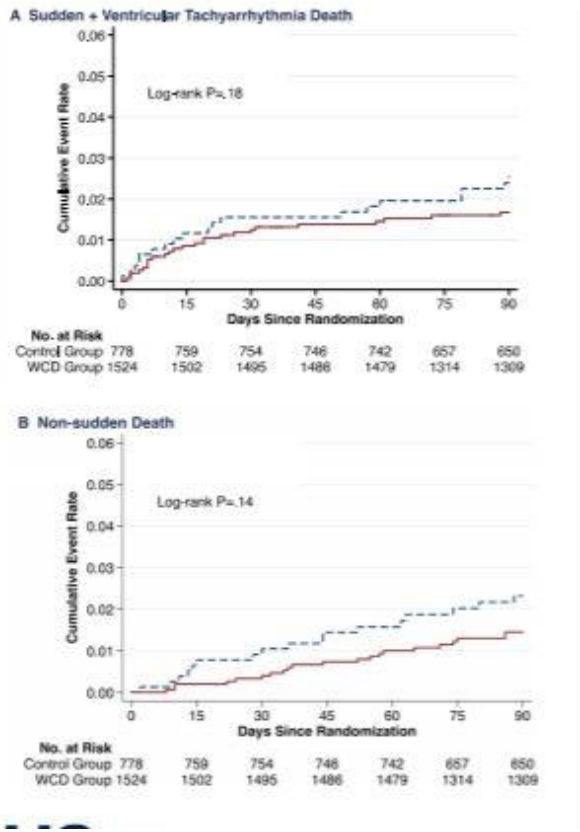


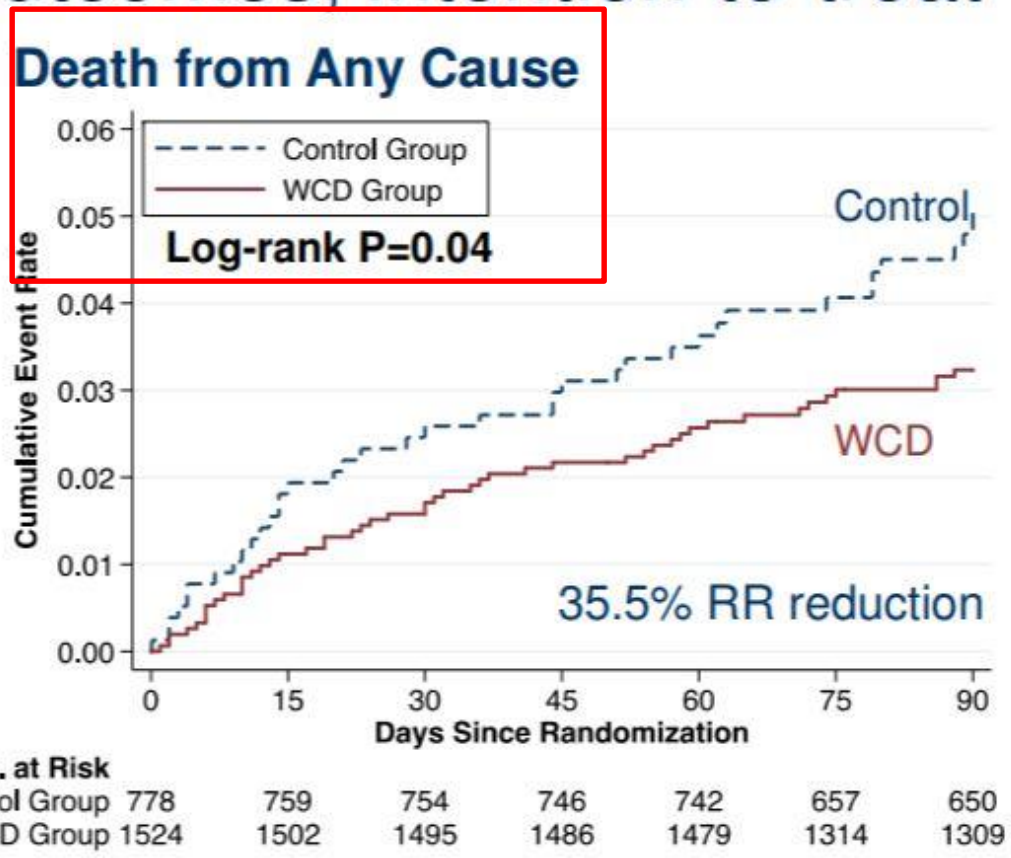


KAISER PERMANENTE®

VEST

Results: Outcomes, intention-to-treat





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VEST

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

VEST

Results: WCD therapies & events

Therapies	WCD Group (N=1524)	Control Group (N=778)
Appropriate shocks (p=0.002)		
1 appropriate shock	13 (0.9%)	0 (0%)
≥2 appropriate shocks	7 (0.5%)	1 (0.1%)
Inappropriate shocks (p=0.05)		
1 inappropriate shock	8 (0.5%)	0 (0%)
≥2 inappropriate shocks	2 (0.1%)	0 (0%)
Aborted shocks (p<0.001)		
1 aborted shock	43 (2.8%)	0 (0%)
≥2 aborted shocks	12 (0.8%)	0 (0%)
>5 aborted shocks	15 (1.0%)	0 (0%)

VEST

- **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

More touches = better care in general, irrespective of WCD.

Seriously?

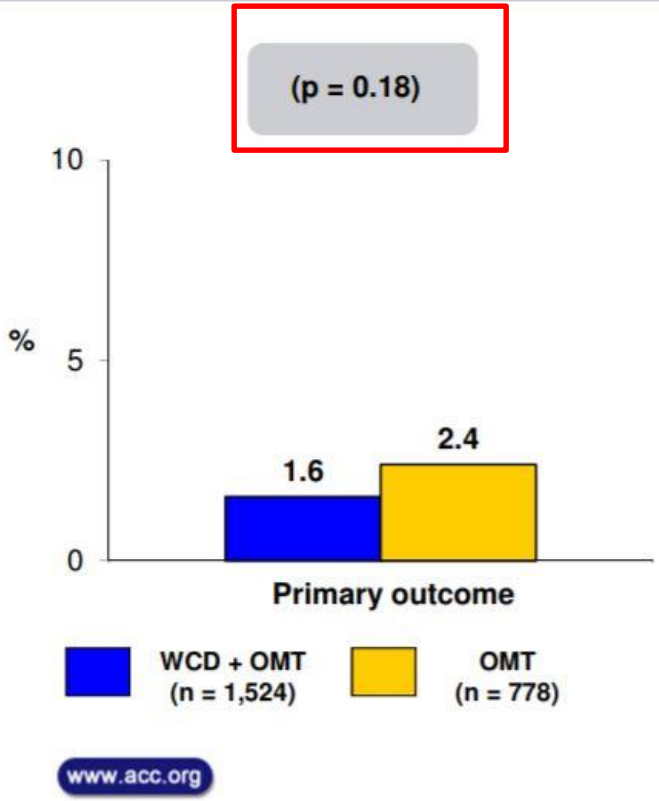
VEST

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 ≤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

VEST

Trial design: Immediate post-MI patients with EF <35% were randomized in a 2:1 fashion to either a wearable cardioverter-defibrillator (WCD) + optimal medical treatment (OMT) vs. OMT alone. Patients were followed for 90 days.



Results

- Primary outcome, sudden cardiac death (SCD) + ventricular tachyarrhythmia death: WCD vs. control: 1.6% vs. 2.4%, p = 0.18
- Nonsudden death: 1.4% vs. 2.2%, p = 0.15, all-cause mortality: 3.1% vs. 4.9%, p = 0.04
- All-cause rehospitalization: 31% vs. 33%, p = 0.51

Conclusions

- WCD does not reduce SCD up to 90 days among patients with low EF immediately post-MI compared with controls on background of OMT
- Mortality reduction is hypothesis generating; no easy explanation
- High rate of cross-over; compliance with WCD use diminished with time

Presented by Dr. Jeffrey E. Olgin at ACC 2018

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ODYSSEY Outcomes
(ACC 2018)
Residual Risk After Acute Coronary Syndrome

- Remains high despite evidence-based preventive therapies
- Is related, in part, to levels of low-density lipoprotein cholesterol (LDL-C)
- Is reduced when LDL-C is lowered by
  - Statin therapy, compared with placebo[1]
  - High-intensity, compared with moderate-intensity statin therapy[2]
  - Ezetimibe, compared with placebo, added to statin[3]

- MIRACL
- PROVE IT (TIMI-22)
- IMPROVE IT (TIMI 40)

ODYSSEY Outcomes

Alirocumab

- PCSK9 is a validated target for risk reduction in stable atherosclerotic cardiovascular disease[1–3]
- A fully human monoclonal antibody against PCSK9
- Produces substantial and sustained reductions in LDL-C and other atherogenic lipoproteins[2]
- Has been safe and well-tolerated in studies to date[4]

ODYSSEY Outcomes

Study Hypothesis

Alirocumab, versus placebo, reduces cardiovascular (CV) morbidity and mortality after recent acute coronary syndrome (ACS) in patients with elevated levels of atherogenic lipoproteins despite intensive or maximum-tolerated statin therapy

ODYSSEY Outcomes

Main Inclusion Criteria

- **Age** ≥40 years
- **ACS**
  - 1 to 12 months prior to randomization
  - Acute myocardial infarction (MI) or unstable angina
- **High-intensity statin therapy***
  - Atorvastatin 40 to 80 mg daily or
  - Rosuvastatin 20 to 40 mg daily or
  - Maximum tolerated dose of one of these agents for ≥2 weeks
- **Inadequate control of lipids**
  - LDL-C ≥70 mg/dL (1.8 mmol/L) or
  - Non-HDL-C ≥100 mg/dL (2.6 mmol/L) or
  - Apolipoprotein B ≥80 mg/dL

ODYSSEY Outcomes

- FOURIER (TIMI 59) - studied the clinical efficacy of fixed dose evolocumab (Repatha®) in pts with stable CAD or PAD
- ODYSSEY – studied the clinical efficacy of flex dose alirocumab (Praluent®) in pts with recent ACS (1 month to 1 year) and up-titrated drug dose to achieve an LDL-C to < 50 mg/dL

ODYSSEY Outcomes

Primary Efficacy Outcome

Time of first occurrence of:

- **Coronary heart disease (CHD) death, or**
- **Non-fatal MI, or**
- **Fatal or non-fatal ischemic stroke, or**
- **Unstable angina requiring hospitalization***

ODYSSEY Outcomes

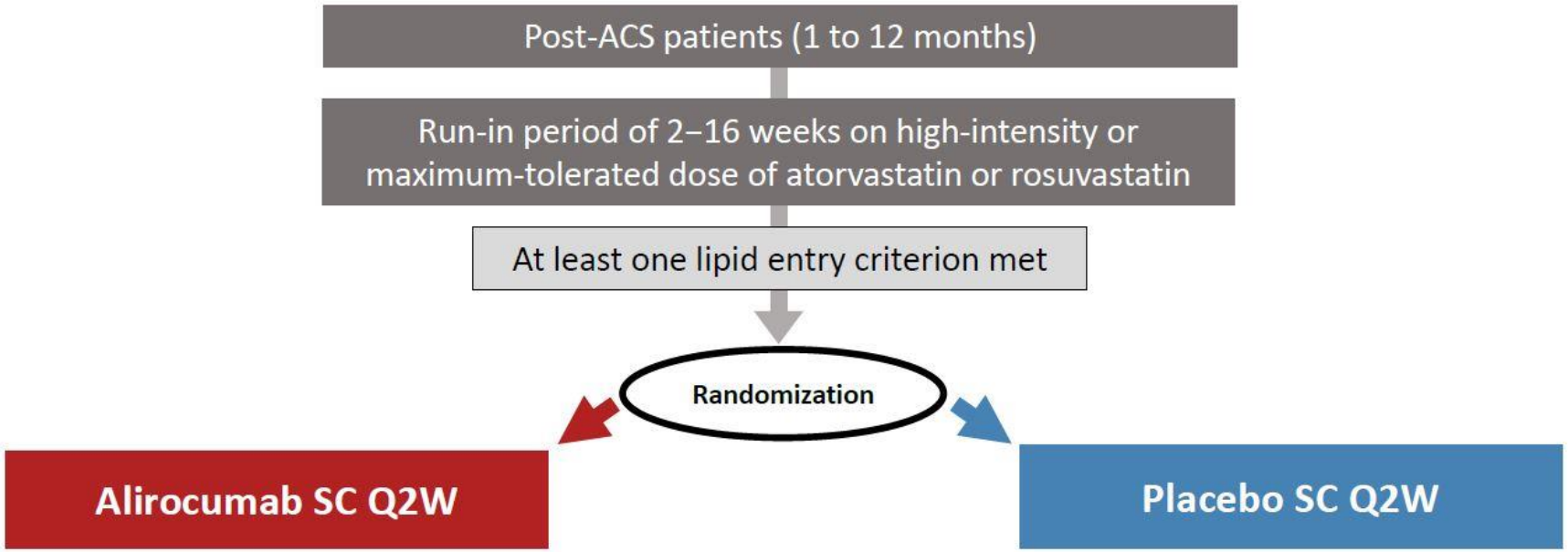
Major Secondary Efficacy Endpoints

Tested in the following hierarchical sequence:

- **CHD event**: CHD death, non-fatal MI, unstable angina requiring hospitalization, or ischemia-driven coronary revascularization*
- **Major CHD event**: CHD death or non-fatal MI
- **CV event:** CV death, non-fatal CHD event, or non-fatal ischemic stroke
- **All-cause death, non-fatal MI, non-fatal ischemic stroke**
- **CHD death**
- **CV death**
- **All-cause death**

ODYSSEY Outcomes

Treatment Assignment

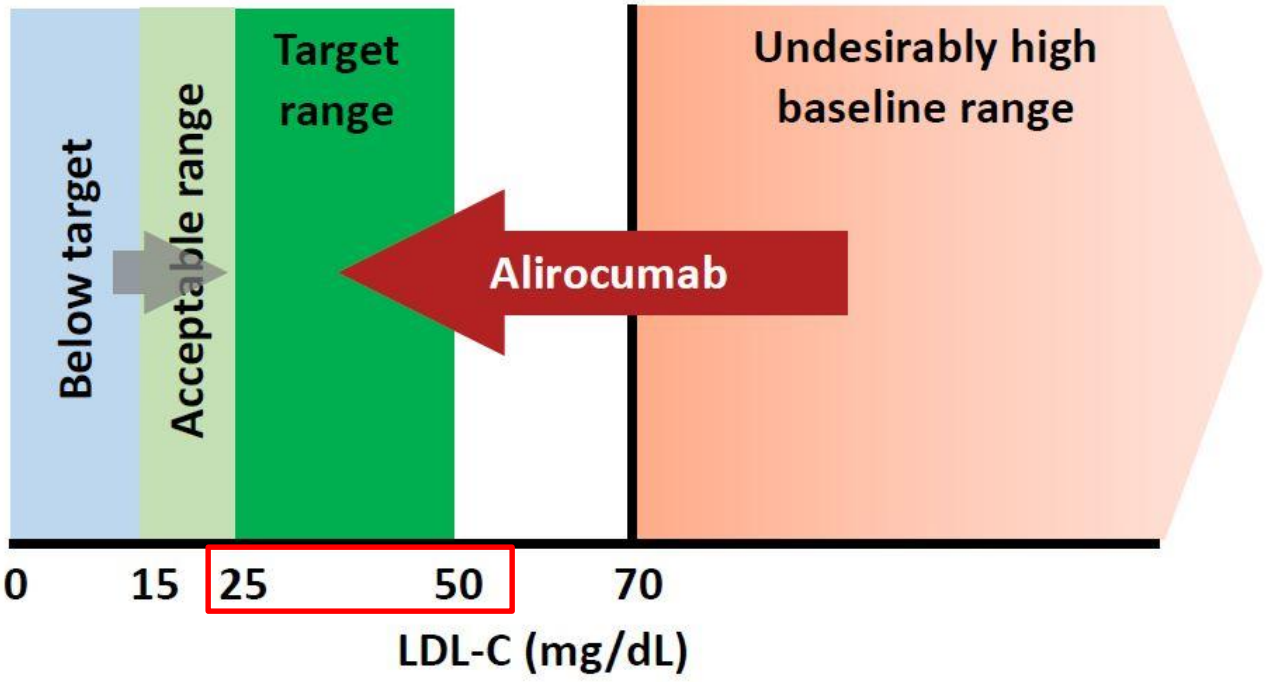


Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

ODYSSEY Outcomes

A Target Range for LDL-C

We attempted to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.



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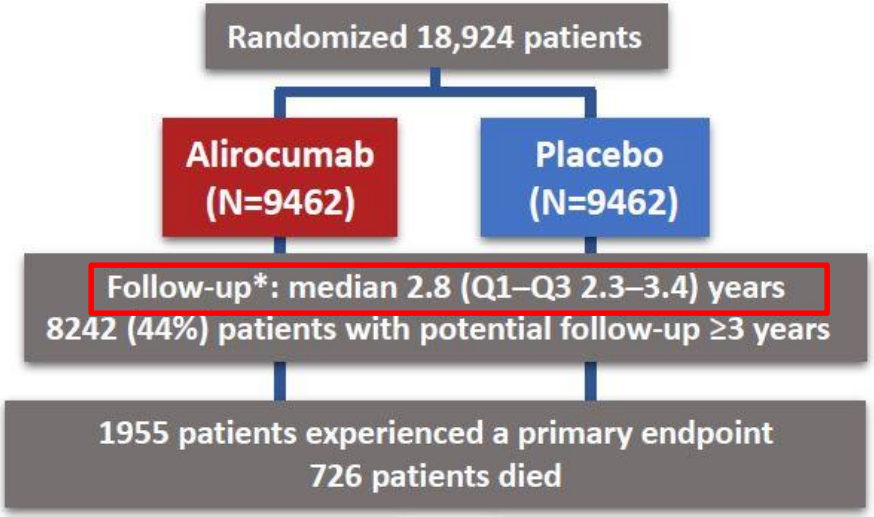
ODYSSEY Outcomes

Statistical Considerations

- All analyses conducted by independent academic statistical team at State University of New York (SUNY) Downstate School of Public Health, in parallel with the sponsor
- Efficacy analysis by intention-to-treat (ITT)
- Assumptions
  - Cumulative incidence of primary endpoint in placebo group 11.4% at 48 months
  - Baseline LDL-C 90 mg/dL; reduction to 45 mg/dL with alirocumab
  - **15% expected hazard reduction for primary endpoint**
  - Loss to follow-up at 24 months: 1%
  - Log-rank test with 1-sided 2.5% significance level
  - Continuation of the trial until **1613** patients with a primary endpoint (for 90% power) **AND** all surviving patients followed for **≥2 years** (for adequate safety assessments), **whichever came later***

ODYSSEY Outcomes

Patient Disposition



• Premature treatment discontinuation	1343 (14.2%)	1496 (15.8%)
• Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)	730 (7.7%)	Not applicable
• Patients lost to follow-up (vital status)	14	9

*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively

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ODYSSEY Outcomes

Baseline Lipid Characteristics

Characteristic, mg/dL, median (Q1–Q3)	Alirocumab (N=9462)	Placebo (N=9462)
LDL-C	87 (73–104)	87 (73–104)
Non-HDL-C	115 (99–136)	115 (99–137)
Apolipoprotein B	79 (69–93)	80 (69–93)
HDL-C	43 (37–50)	42 (36–50)
Triglycerides	129 (94–181)	129 (95–183)
Lipoprotein(a)	21 (7–59)	22 (7–60)

92.5% of patients qualified on the basis of LDL-C ≥70 mg/dL

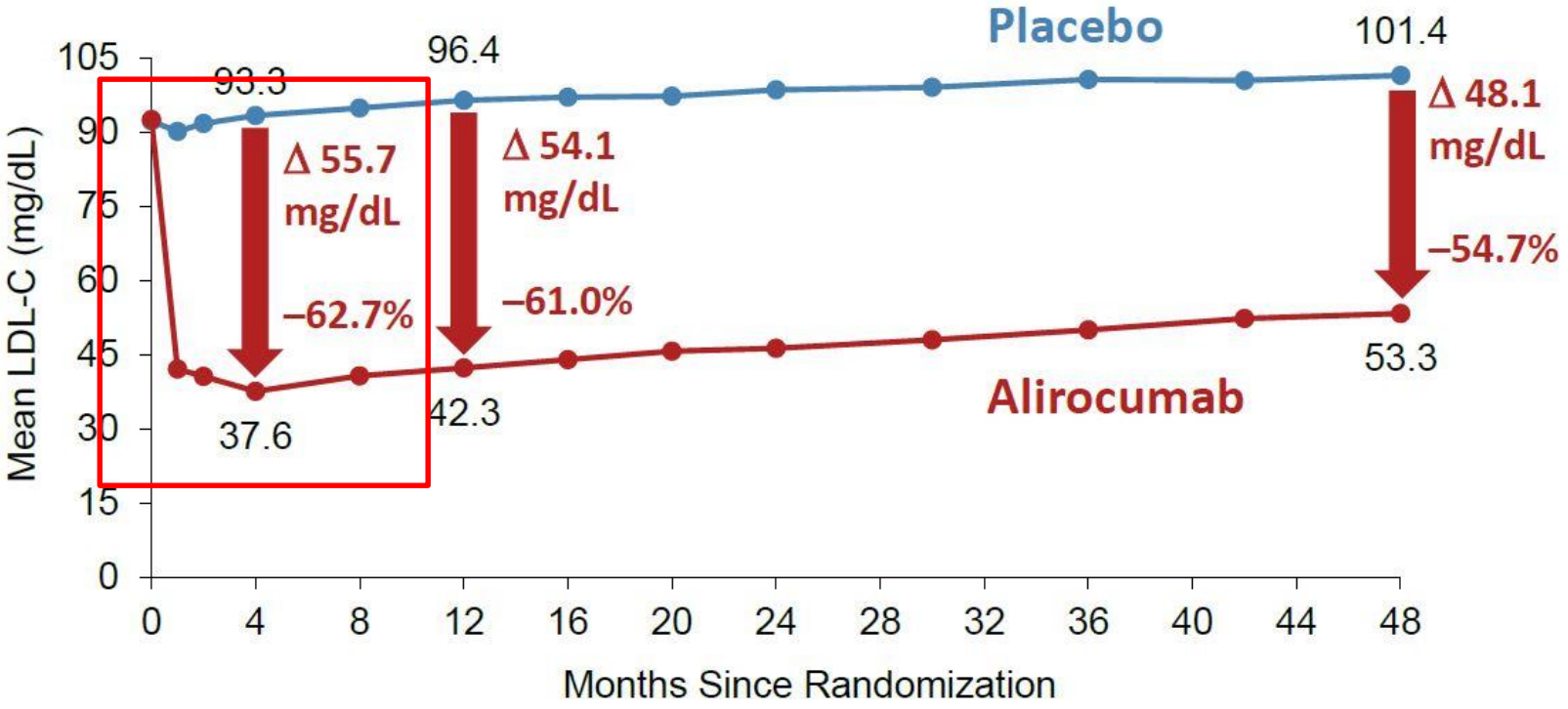
ODYSSEY Outcomes

Baseline Lipid-Lowering Therapy

Therapy, n (%)	Alirocumab (N=9462)	Placebo (N=9462)
High-dose atorvastatin/rosuvastatin	8380 (88.6)	8431 (89.1)
Low-/moderate-dose atorvastatin/rosuvastatin	830 (8.8)	777 (8.2)
Other statin	19 (0.2)	27 (0.3)
Ezetimibe, with or without statin	269 (2.8)	285 (3.0)
No lipid-lowering therapy*	87 (0.9)	91 (1.0)

ODYSSEY Outcomes

LDL-C: On-Treatment Analysis



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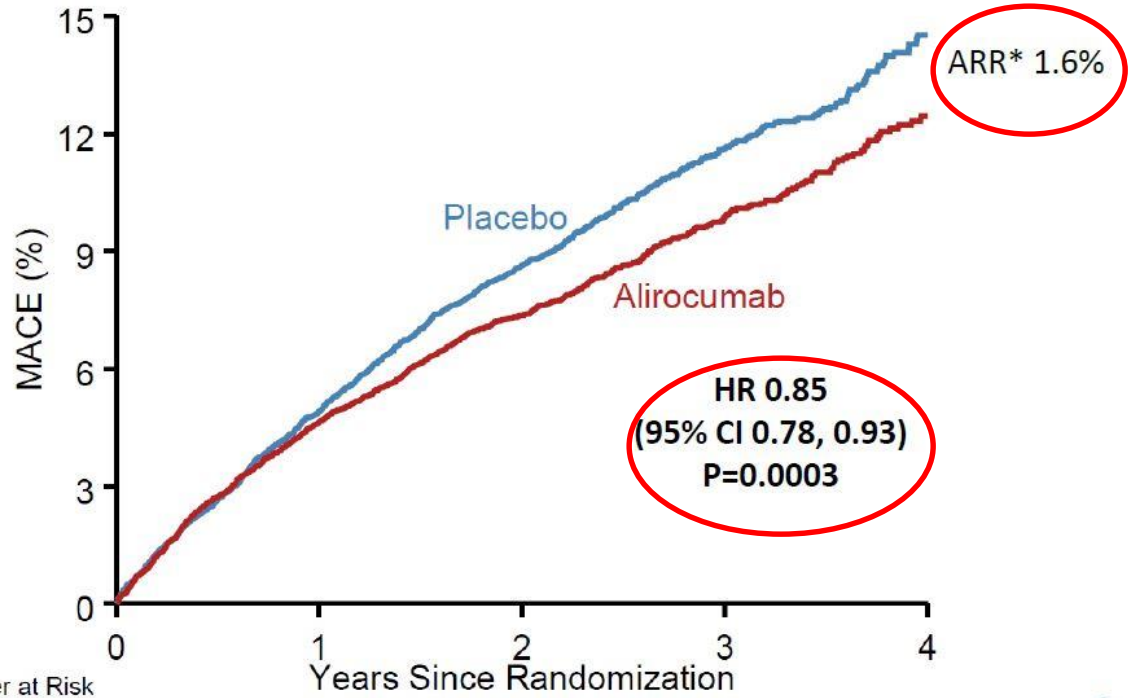
ODYSSEY Outcomes

Primary Efficacy Endpoint: MACE



MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

Number at Risk

Placebo	9462	8805	8201	3471	629
Alirocumab	9462	8846	8345	3574	653

*Based on cumulative incidence

ODYSSEY OUTCOMES

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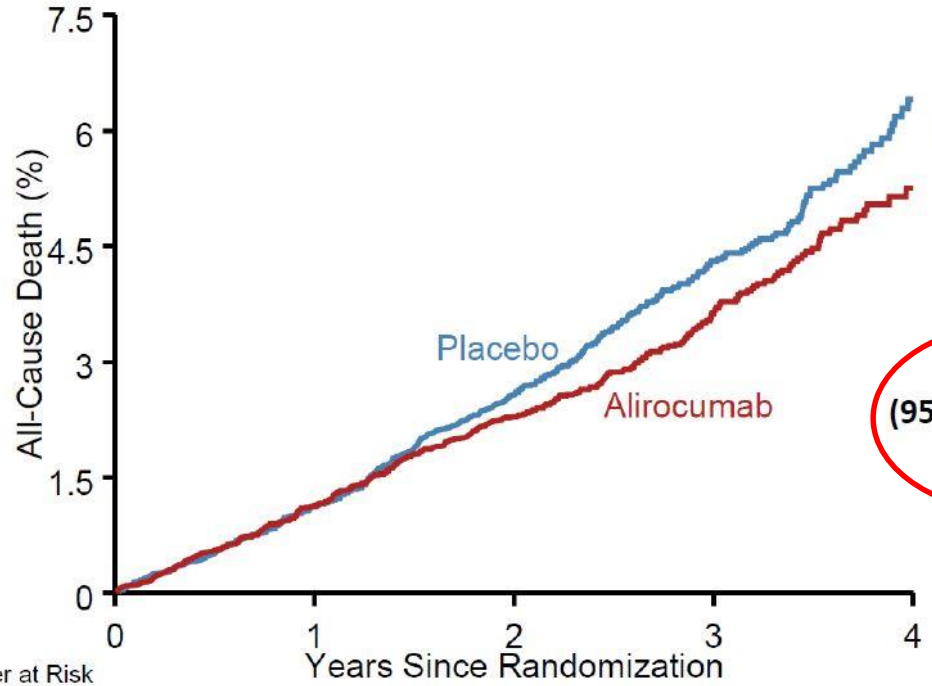
ODYSSEY Outcomes

All-Cause Death



ARR† 0.6%

HR 0.85
(95% CI 0.73, 0.98)
P=0.026*

Number at Risk

Placebo	9462	9219	8888	3898	737
Alirocumab	9462	9217	8919	3946	746

*Nominal P-value
†Based on cumulative incidence

ODYSSEY OUTCOMES

KAISER PERMANENTE®

ODYSSEY Outcomes

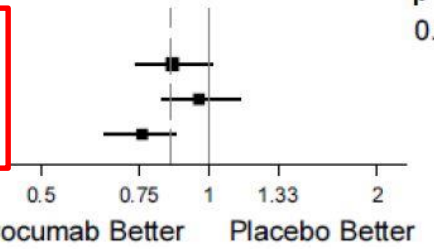
Other Efficacy Endpoints

Endpoint n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
Ischemia-driven coronary revascularization	731 (7.7)	828 (8.8)	0.88 (0.79, 0.97)	0.009
Hospitalization for CHF	176 (1.9)	179 (1.9)	0.98 (0.79, 1.20)	0.84

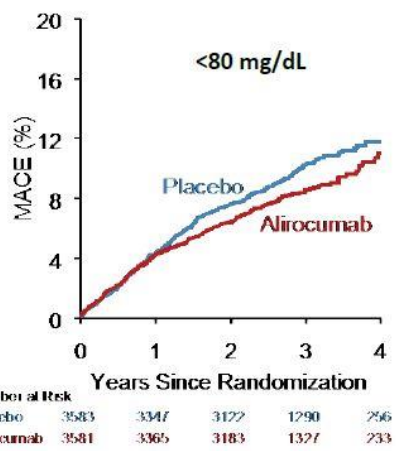
ODYSSEY Outcomes

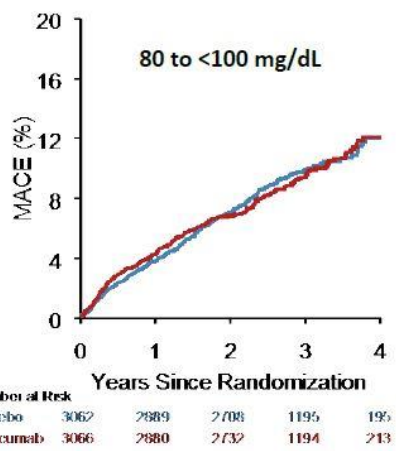
Primary Efficacy in Main Prespecified Subgroups

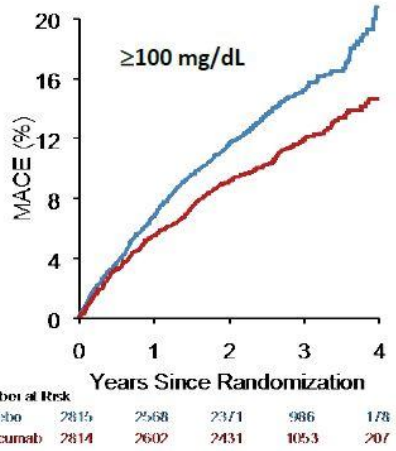
Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	



*P-values for interaction







ODYSSEY OUTCOMES

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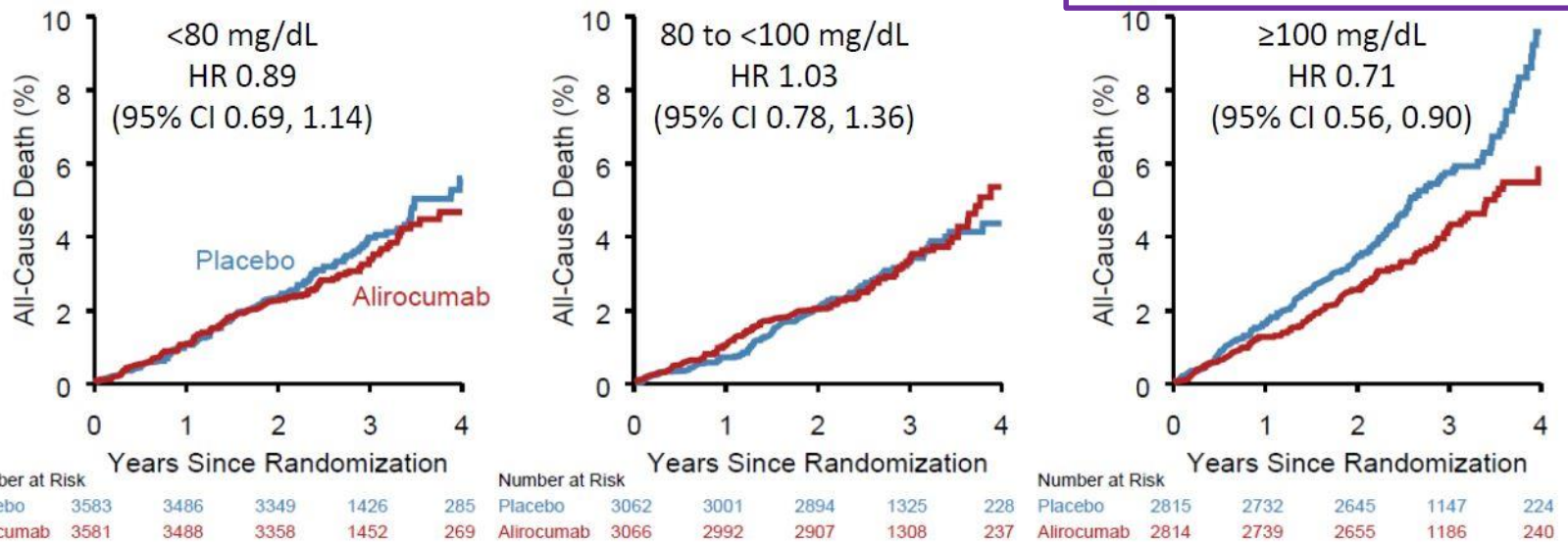
ODYSSEY Outcomes

Post Hoc Analysis: All-Cause Death by Baseline LDL-C Subgroups

ARR* 1.7% $P_{interaction}$=0.12



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ODYSSEY Outcomes

Efficacy: Subgroup with Baseline LDL-C ≥100 mg/dL (Median Baseline LDL-C 118 mg/dL)

Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	Absolute risk reduction (%)	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	3.4	**0.76** (0.65, 0.87)
CHD death	69 (2.5)	96 (3.4)	1.0	**0.72** (0.53, 0.98)
CV death	81 (2.9)	117 (4.2)	1.3	**0.69** (0.52, 0.92)
All-cause death	114 (4.1)	161 (5.7)	1.7	**0.71** (0.56, 0.90)

ODYSSEY Outcomes

Safety (1)

Treatment-emergent adverse events, n (%)	Alirocumab (N=9451)	Placebo (N=9443)
Any	7165 (75.8)	7282 (77.1)
Serious	2202 (23.3)	2350 (24.9)

Laboratory value	Alirocumab	Placebo
ALT >3 × ULN, n/N (%)	212/9369 (2.3)	228/9341 (2.4)
Creatine kinase >10 × ULN, n/N (%)	46/9369 (0.5)	48/9338 (0.5)

ODYSSEY Outcomes

Safety (2)

Event	Alirocumab (N=9451)	Placebo (N=9443)
Diabetes worsening or diabetic complications: *pts w/DM at baseline*, n/N (%)	506/2688 (18.8)	583/2747 (21.2)
New onset diabetes; *pts w/o DM at baseline*, n/N (%)	648/6763 (9.6)	676/6696 (10.1)
General allergic reaction, n (%)	748 (7.9)	736 (7.8)
Hepatic disorder, n (%)	500 (5.3)	534 (5.7)
Local injection site reaction, n (%)*	360 (3.8)	203 (2.1)
Neurocognitive disorder, n (%)	143 (1.5)	167 (1.8)
Cataracts, n (%)	120 (1.3)	134 (1.4)
Hemorrhagic stroke, n (%)	9 (<0.1)	16 (0.2)

ODYSSEY Outcomes

Conclusions

Compared with placebo in patients with recent ACS, alirocumab 75 or 150 mg subcutaneous Q2W targeting LDL-C levels 25–50 mg/dL, and allowing levels as low as 15 mg/dL:

1. Reduced MACE, MI, and ischemic stroke
2. Was associated with a lower rate of all-cause death
3. Was safe and well-tolerated over the duration of the trial

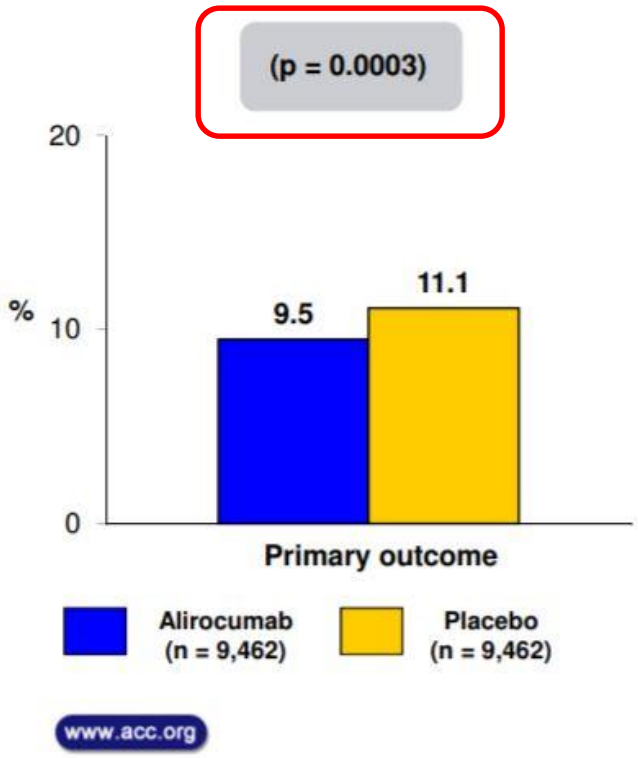
ODYSSEY Outcomes

Clinical Perspective

- In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥3 years, there was no safety signal with alirocumab other than injection site reactions
- Among patients with ACS and baseline LDL-C ≥100 mg/dL, alirocumab reduced MACE by 24% (ARR 3.4%) and all-cause death by 29% (ARR 1.7%) compared with placebo
  - ➢These are the patients who may benefit most from treatment

ODYSSEY Outcomes

Trial design: Patients 1-12 months out from an ACS event were randomized in 1:1 fashion to alirocumab q2 weeks subcutaneously or placebo. Drug was titrated to keep the LDL-C between 25 and 50 mg/dl, but above 15 mg/dl. Patients were followed for 48 months.



Results

- Primary outcome, MACE: alirocumab vs. placebo: 9.5% vs. 11.1%, p = 0.0003; ↑ benefit if LDL ≥100
- CHD death: 2.2% vs. 2.3%, p = 0.38; all-cause mortality: 3.5% vs. 4.1%, p = 0.026
- MI: 6.6% vs. 7.6%, p = 0.006; stroke 1.2% vs. 1.6%, p = 0.01; unstable angina: 0.4% vs. 0.6%, p = 0.02

Conclusions

- Landmark trial; indicates that the use of alirocumab q2 weeks significantly reduces ischemic events, including all-cause mortality and MI, among patients with an ACS event within the preceding 1-12 months; 90% were on high dose of a potent statin
- Cost-effectiveness analyses important for these expensive medications; cost-benefit ratio may be most favorable in patient population with LDL ≥100 mg/dl

Presented by Dr. Philippe Steg at ACC 2018

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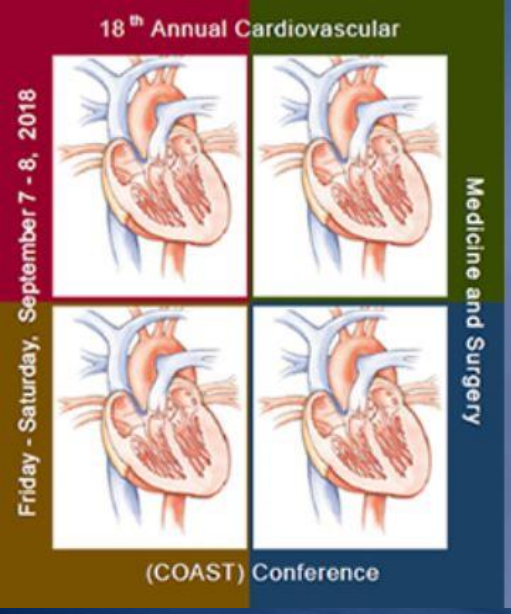

18th Annual Cardiovascular Medicine and Surgery (COAST) Conference

September 7-8, 2018
Mandarin Oriental - Las Vegas, NV

THE END

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