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Torino, IT
October 2017

5 Important Trials in Ischemic Heart Disease in the Last Year

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Conflicts and disclosures – none

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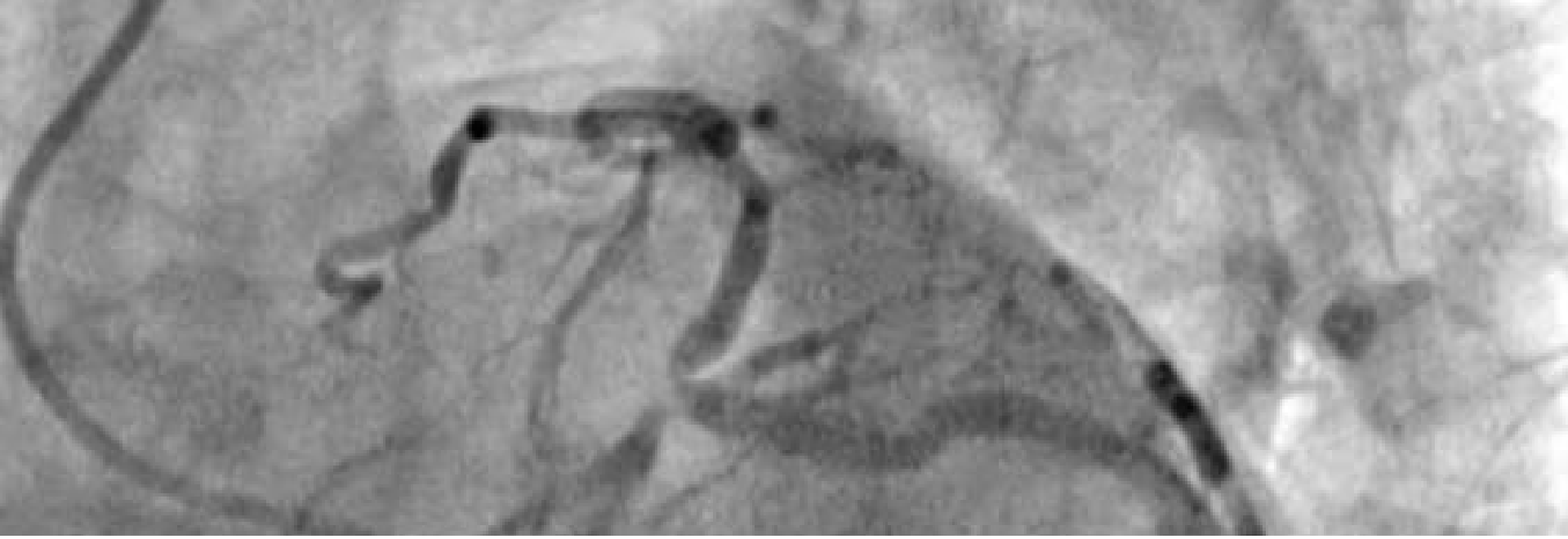

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2016 VOL. 375 NO. 23

Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease

G.W. Stone, J.F. Sabik, P.W. Serruys, C.A. Simonton, P. Généreux, J. Puskas, D.E. Kandzari, M.-C. Morice, N. Lembo, W.M. Brown III, D.P. Taggart, A. Banning, B. Merkely, F. Horkay, P.W. Boonstra, A.J. van Boven, I. Ungi, G. Bogáts, S. Mansour, N. Noiseux, M. Sabaté, J. Pomar, M. Hickey, A. Gershlick, P. Buszman, A. Bochenek, E. Schampaert, P. Pagé, O. Dressler, I. Kosmidou, R. Mehran, S.J. Pocock, and A.P. Kappetein, for the EXCEL Trial Investigators*

EXCEL results

Endpoint	PCI	CABG	Non Inferior	Superior
Primary: Death, CVA or MI - 3 years	15.4%	14.7%	Yes	No
Secondary: Death, CVA or MI - 30 days	4.9%	7.9%	Yes	Yes
Death, CVA, MI or revascularization - 3 years	23.1%	19.1%	Yes	No

Stone GW: NEJM 2016

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EXCEL – noteworthy observations

Largest ULMCA trial

Best 2G DES – ST in 0.7%

Optimal surgical procedures

- Arterial conduits, off pump etc

30% had diabetes mellitus

Large periprocedural MI counted for PCI and CABG

SYNTAX Score not discriminatory

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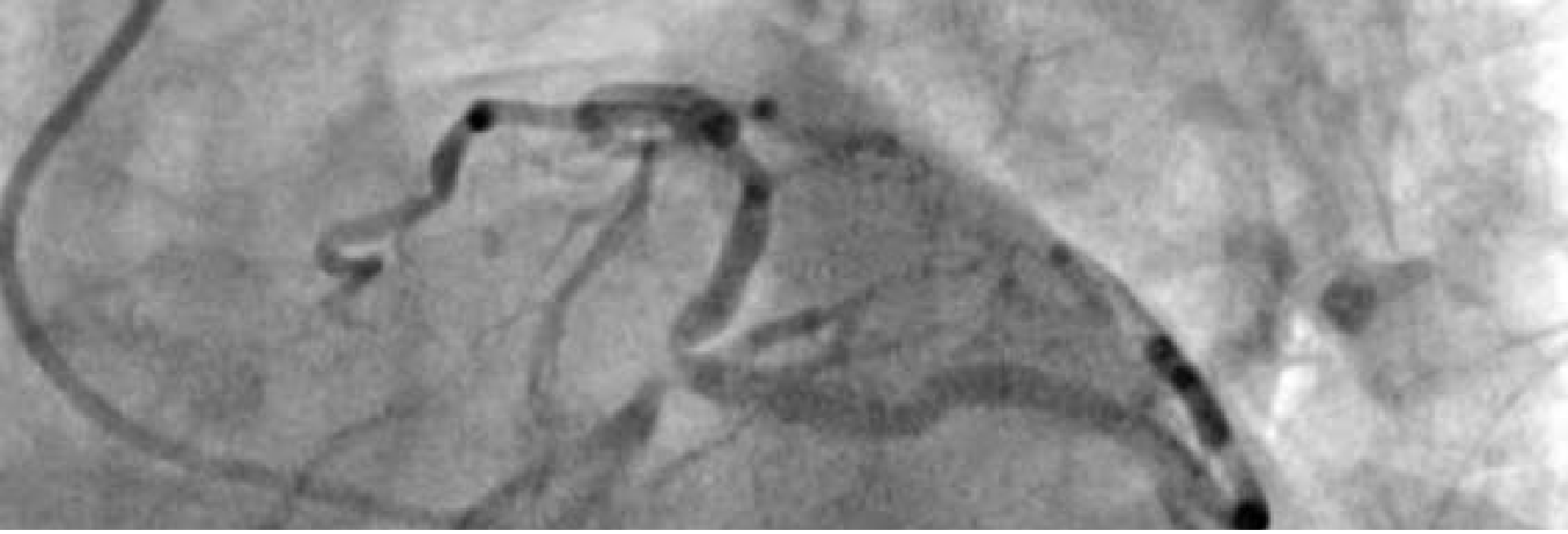

THE LANCET

Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial

*Timo Mäkikallio, Niels R Holm, Mitchell Lindsay, Mark S Spence, Andrejs Erglis, Ian B A Menown, Thor Trovik, Markku Eskola, Hannu Romppanen, Thomas Kellerth, Jan Ravkilde, Lisette O Jensen, Gintaras Kalinauskas, Rikard B A Linder, Markku Pentikainen, Anders Hervold, Adrian Banning, Azfar Zaman, Jamen Cotton, Erlend Eriksen, Sulev Margus, Henrik T Sørensen, Per H Nielsen, Matti Niemelä, Kari Kervinen, Jens F Lassen, Michael Maeng, Keith Oldroyd, Geoff Berg, Simon J Walsh, Colm G Hanratty, Indulis Kumsars, Peteris Stradins, Terje K Steigen, Ole Fröbert, Alastair N J Graham, Petter C Endresen, Matthias Corbascio, Olli Kajander, Uday Trivedi, Juha Hartikainen, Vesa Anttila, David Hildick-Smith, Leif Thuesen, Evald H Christiansen, for the NOBLE study investigators**

NOBLE results

Endpoint	PCI	CABG	Non Inferior	Inferior
Primary: Death, CVA, MI, revascularization - 3 years	29%	19%	No	Yes
Death*	12%	9%	* P = NS	
MI	7%	2%		
Revascularization	16%	10%		
CVA*	5%	2%		
ST or symptomatic graft occlusion*	3%	4%		

Makikallio T: Lancet 2016

NOBLE results

Endpoint	PCI	CABG	Non Inferior	Inferior
Primary: Death, CVA, MI, revascularization - 3 years	29%	19%	No	Yes
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ST or symptomatic graft occlusion*	3%	4%		

Makikallio T: Lancet 2016

NOBLE – noteworthy observations

Composite EP included repeat revascularization

Primary endpoint timing changed (event rate low)

1G DES in 11%; BES 89% with ST in 3%

Optimal CABG techniques – not quite?

No routine check for periprocedural MI

Perplexing stroke rate in PCI – play of chance?

SYNTAX Score not discriminatory

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2 Good Options for uLMCA Revascularization

Improved immediate and long term PCI results

Longer follow-up required …
trade-off of fewer early for more later events with PCI?

Challenges CABG as default revascularization option

*"…majority of patients with unprotected left main coronary artery disease….can now be managed **equally well** by means of two strategies of revascularization if carried out by expert, experienced teams…" (Braunwald E)**

*Editorial by Braunwald E: NEJM 2016

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Current practice and guidelines

CABG preferred over PCI

PCI class IB in Europe

PCI class IIA in USA

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ORIGINAL ARTICLE

Bioresorbable Scaffolds versus Metallic Stents in Routine PCI

Joanna J. Wykrzykowska, M.D., Ph.D., Robin P. Kraak, M.D.,
Sjoerd H. Hofma, M.D., Ph.D., Rene J. van der Schaaf, M.D., Ph.D.,
E. Karin Arkenbout, M.D., Ph.D., Alexander J. IJsselmuiden, M.D., Ph.D.,
Joëlle Elias, M.D., Ivo M. van Dongen, M.D., Ruben Y.G. Tijssen, M.D.

Stent thrombosis almost 4x higher with Bioresorbable Scaffold versus Metallic EES

Wykrzkowska JJ: NEJM 2017

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Primer on Coronary Stent Technology

Stent scaffold

- Co-Chromium (permanent)
- Poly (L-lactide) (bioresorbable)

Polymer which elutes the active drug

- Durable or bioresorbable

Polymer-free - passive

Antiproliferative drug

- e.g. everolimus

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Bioresorbable Vascular Scaffold (BVS)

Stent scaffold	poly (L-lactide) (bioresorbable)
Polymer	bioresorbable
Eluted drug	everolimus

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Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial

Patrick W Serruys, Bernard Chevalier, Yohei Sotomi, Angel Cequier, Didier Carrié, Jan J Piek, Ad J Van Boven, Marcello Dominici, Dariusz Dudek, Dougal McClean, Steffen Helqvist, Michael Haude, Sebastian Reith, Manuel de Sousa Almeida, Gianluca Campo, Andrés Iñiguez, Manel Sabaté, Stephan Windecker, Yoshinobu Onuma

Lancet 2016; 388: 2479–91
Published Online

Summary

Background No medium-term data are available on the random comparison between everolimus-eluting bioresorbable vascular scaffolds and everolimus-eluting metallic stents. The study aims to demonstrate two

Failed to meet co-primary endpoints of superior vasomotor function and non-inferior late lumen loss compared to metallic EES (Xience)

late luminal loss, non-inferiority was tested using a one-sided asymptotic test, against a non-inferiority margin of 0·14 mm. The trial is registered at ClinicalTrials.gov, number NCT01425281.

University Hôspital, Barcelona, Spain (A Cequier MD); Hopital de Rangueil, Toulouse, France

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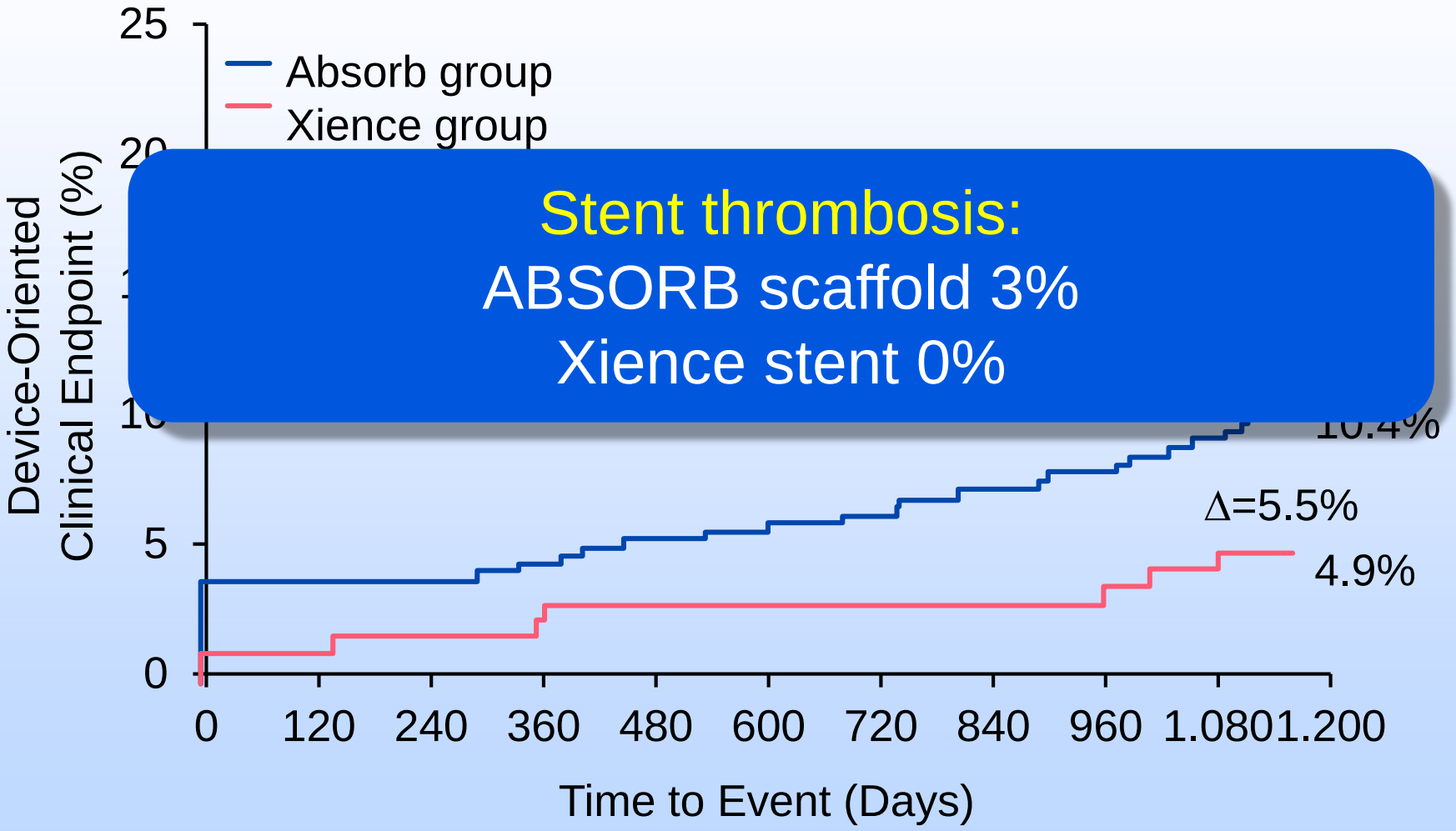
ABSORB II
Device-Oriented Clinical Endpoints



Stent thrombosis:
ABSORB scaffold 3%
Xience stent 0%

Serruys PF et al: Lancet 2016; 388: 2479-91

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2-year results of ABSORB III

Abbott's pivotal trial for US premarket approval

In 2015, 1-year results had shown non inferiority*

Results: Xience DES superior to BVS

- Target vessel failure and MI
- Numerically more cardiac death and TLR
- Numerically more device thrombosis

Ellis SG: ACC Scientific Sessions March 2017
*Ellis SG: NEJM 2015

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AIDA – Main results at 2 years

Endpoint	Scaffold	Metallic EES	Non Inferior
Primary: Target vessel failure*	11.7%	10.7%	Yes
Safety: Definite device thrombosis	3.5%	0.9%	HR 3.87 (p<0.001)

*Cardiac death, target vessel MI, target vessel revascularization

Wykrzkowska JJ: NEJM 2017

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ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais,

…….canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering

Ridker PM: NEJM 2017

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Inflammation and atherothrombosis

Role for inflammation well documented

Lack evidence demonstrating lower CV events by decreasing vascular inflammation, independent of lipid-lowering (statins)

Canakinumab:

- Human monoclonal Ab inhibits interleukin-1β
- Lowers interleukin-6 and CRP
- Does not lower LDL-C

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CANTOS results

10,061 pts with prior MI and elevated hsCRP

Endpoint (48 months)	Placebo	All doses	P value
Primary: MI, CV death or CVA	4.50%	3.95%	0.02
Secondary: Primary + unstable angina leading to revascularization	5.13%	4.36%	0.003

Ridker PM: NEJM 2017

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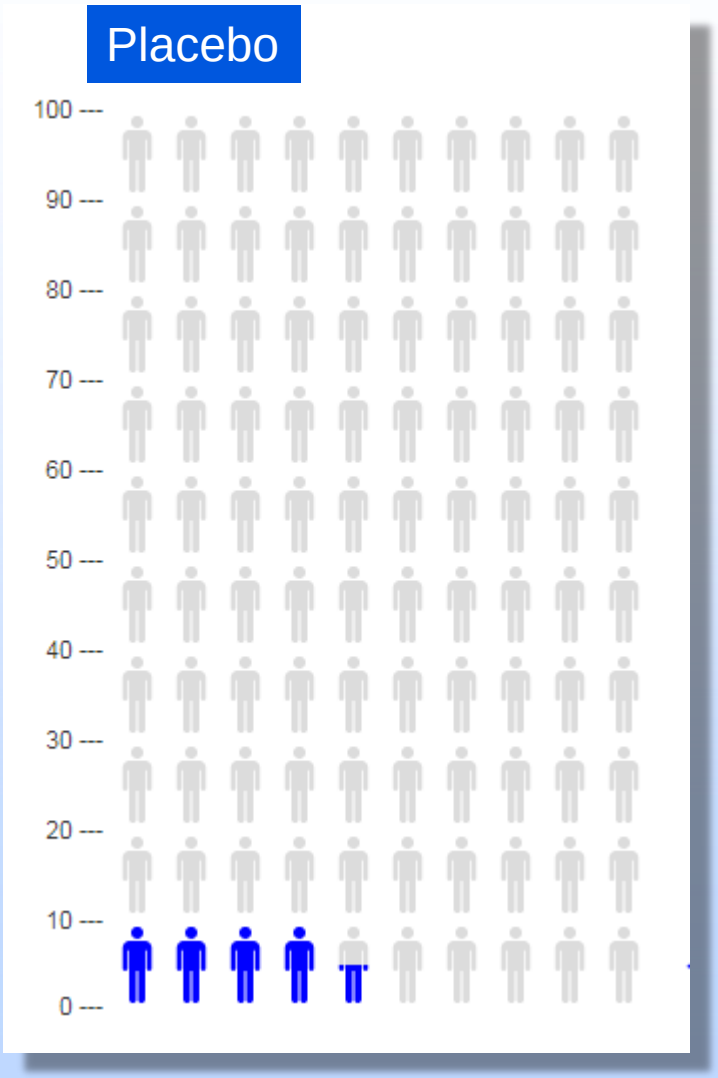
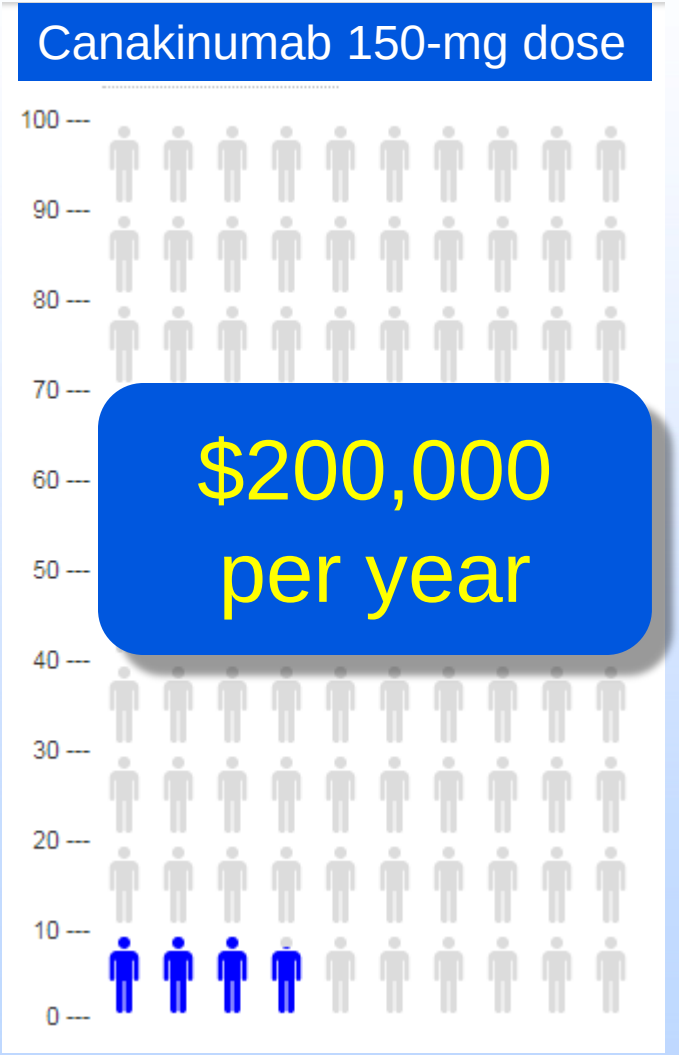
Shared decision making
Magnitude of treatment effect





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Proof of concept achieved but what are the clinical implications of CANTOS?

Modest effect but only by decreasing non fatal MI

Excess fatal infections and sepsis

Lower mortality from cancer

Cost in this population is prohibitive

"…cannot justify its routine use in patients with prior MI…"

Harrington RA: NEJM 2017

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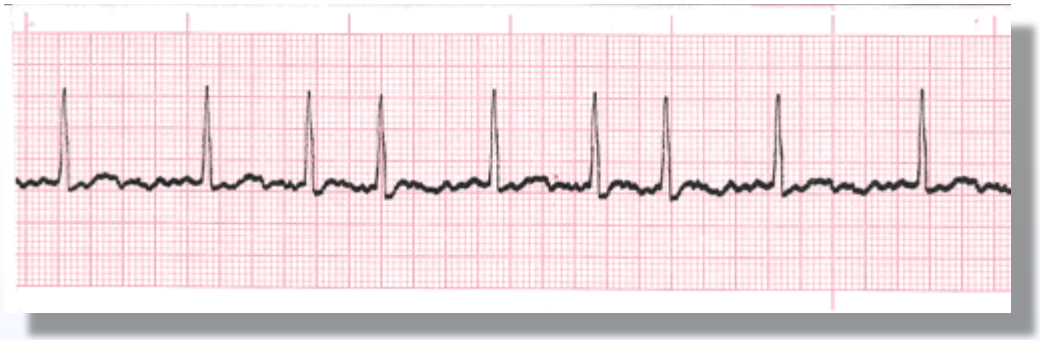

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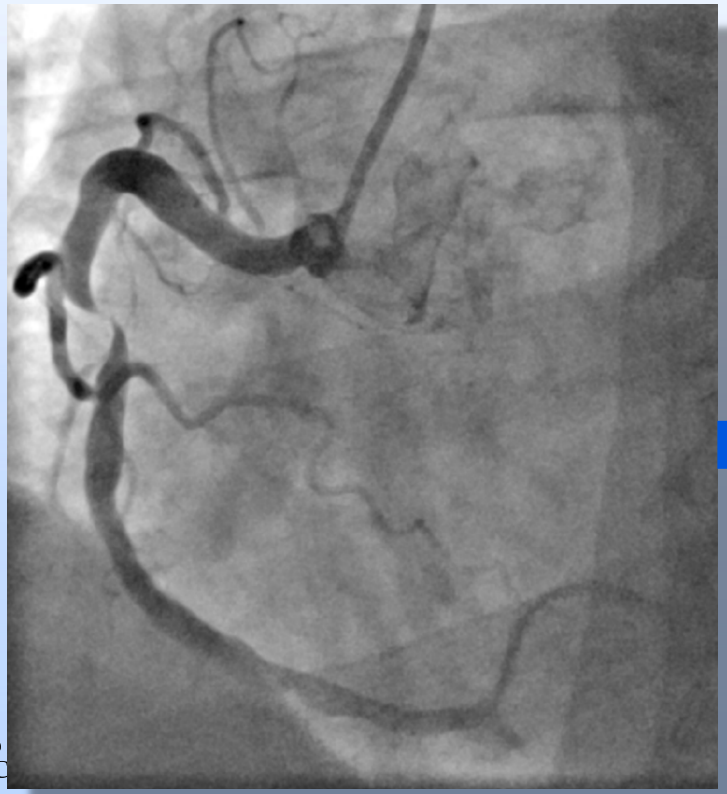

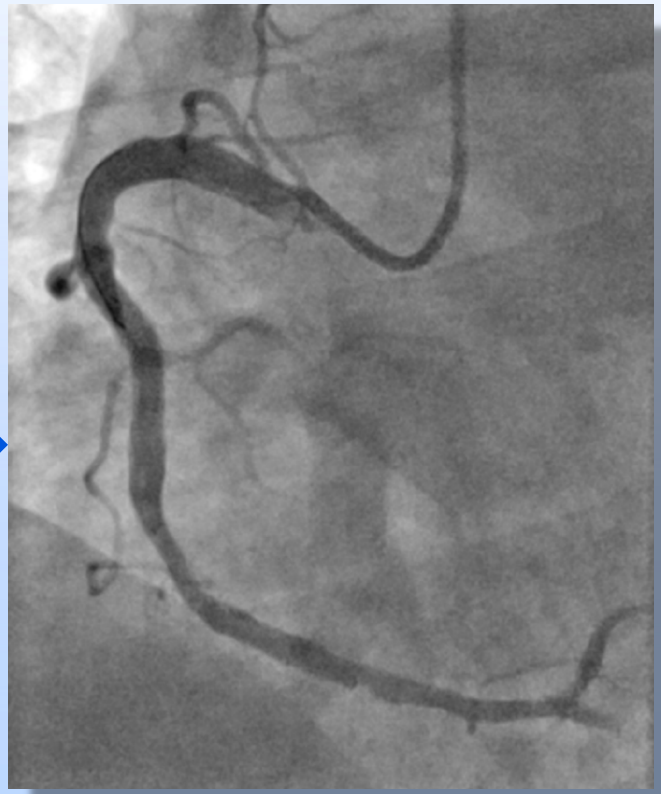

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 19, 2017 VOL. 377 NO. 16

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

Christopher P. Cannon, M.D., Deepak L. Bhatt, M.D., M.P.H., Jonas Oldgren, M.D., Ph.D., Gregory Y.H. Lip, M.D.,

Patients with AF who had PCI, risk of major bleeding was significantly lower with dual therapy (dabigatran and a P_2Y_{12} inhibitor) compared to triple therapy. Adverse ischemic events were similar.

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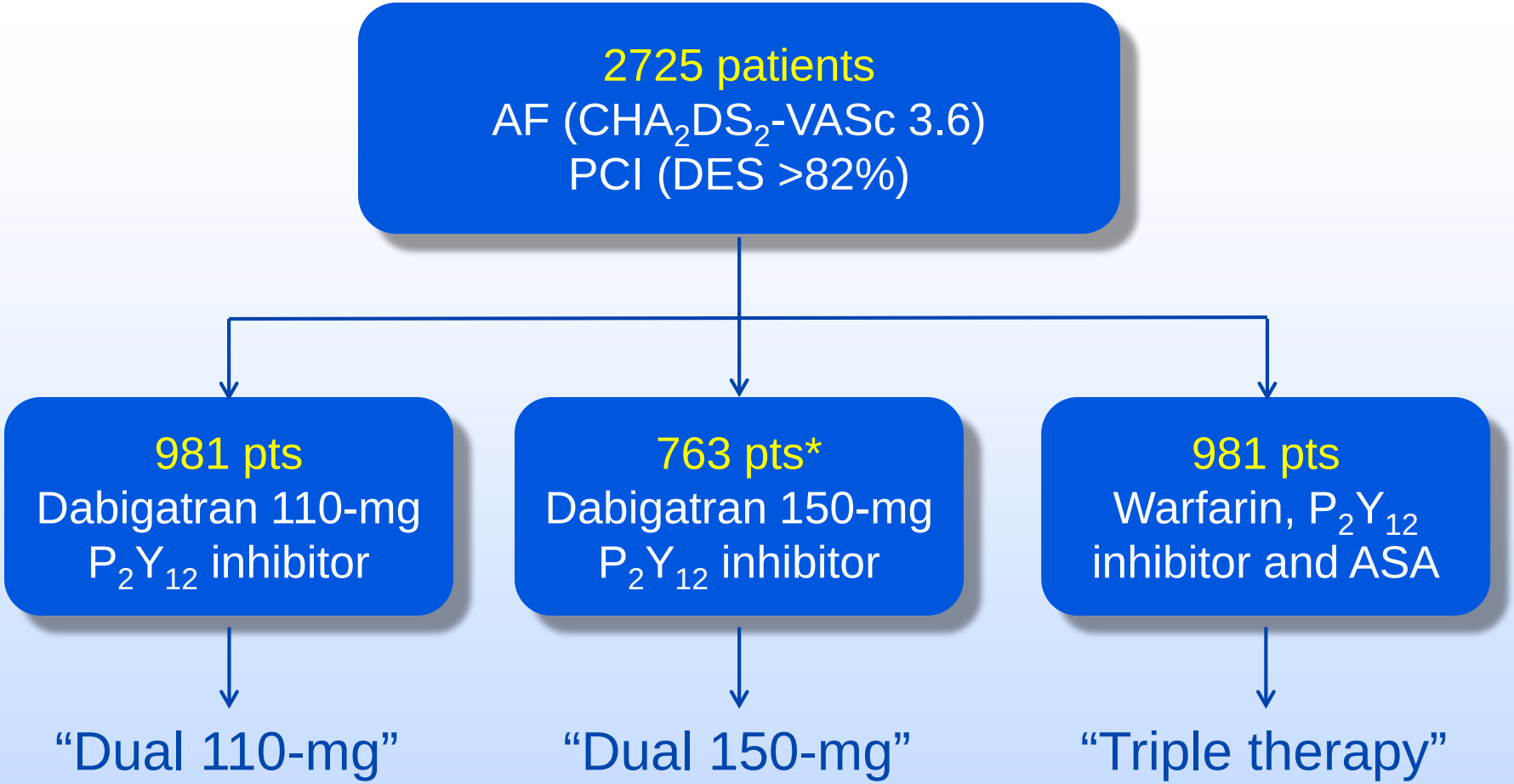

*Excluded elderly pts outside USA

Cannon CP: NEJM 2017

RE-DUAL results at 14 months

Endpoint	Dual 110-mg	Dual 150-mg	Triple therapy	Non inferior
Primary: Major bleeding	15.4%	20.2%	26.9%	Yes
Efficacy: Composite	13.7%		13.4%	Yes
CVA Def stent thrombosis	1.7% 1.5%	1.2% 1.0%	1.2% 0.9%	

Cannon CP: NEJM 2017

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Commentary

Results consistent with 2 prior trials

Dropping ASA results in significant lower risk of major bleeding

No signal of increase in ischemic events

Strongly consider avoiding triple therapy in patients with AF who undergo PCI with DES

Majority were on clopidogrel, not ticagrelor

Ideal combination not known

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