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CLINIC



Torino, IT
October 2015



Ischemic Heart Disease: The 5 Most Important Trials in the Last Year

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Mayo Clinic, MN, USA

Conflicts and disclosures – none

Selection of Trials

- Newsworthy and from major journals
- General importance and relevance to your practice
- Might change your practice
- Might impact professional guidelines and appropriate use criteria





Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial

Adeel Shahzad, Ian Kemp, Christine Mars, Keith Wilson, Claire Roome, Rob Cooper, Mohammed Andron, Clare Appleby, Mike Fisher, Aleem Khand, Babu Kunadian, Joseph D Mills, John L Morris, William L Morrison, Shahzad Munir, Nick D Palmer, Raphael A Perry, David R Ramsdale, Periaswamy Velavan, Rod H Stables, for the HEAT-PPCI trial investigators

Summary

Background Bivalirudin, with selective use of glycoprotein (GP) IIb/IIIa inhibitor agents, is an accepted standard of care in primary percutaneous coronary intervention (PPCI). We aimed to compare antithrombotic therapy with bivalirudin or unfractionated heparin during this procedure.



Background to HEAT-PPCI

- Bivalirudin established AC option for PPCI
- Supported by result of HORIZONS-AMI trial
- Consistent reduction in bleeding

But not everyone convinced.....

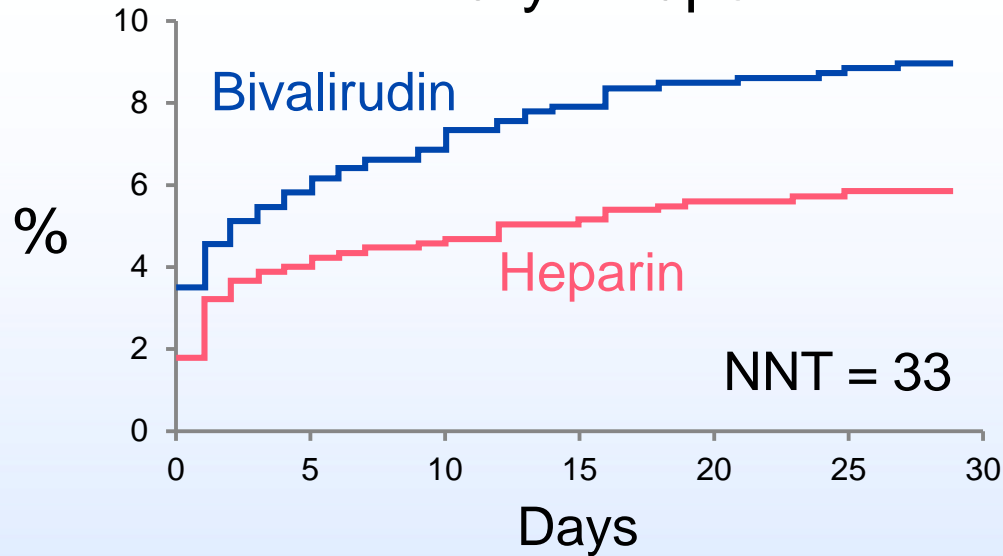
- Prior trial designs
- Acute stent thrombosis more frequent
- 400 fold more expensive



MAIN
ENTRANCE

Reception

Primary Endpoint

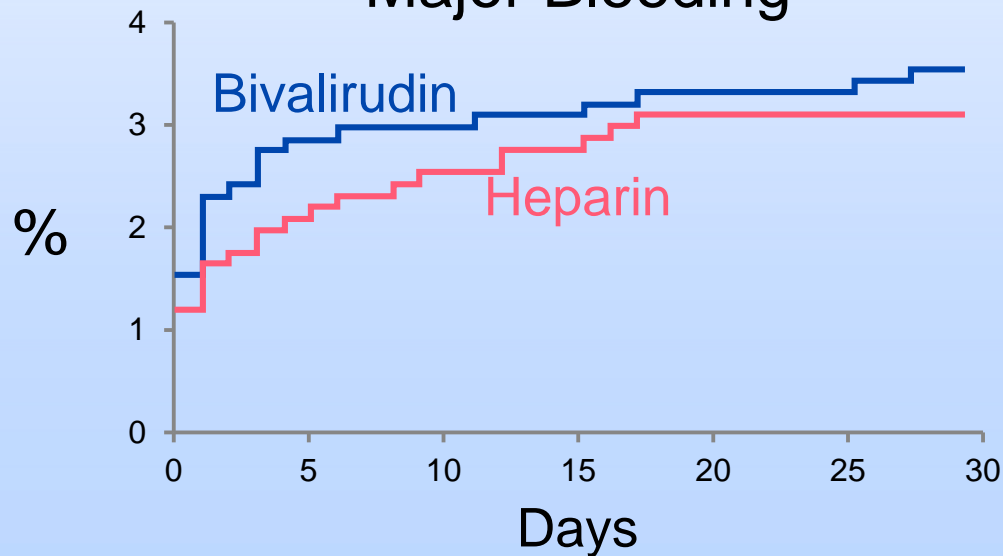


Stent thrombosis



Bivalirudin

Major Bleeding



Shazad A: Lancet, 2014

Implications

- Rethink use of routine Bivalirudin
- Early use of P2Y₁₂ inhibitors
- Minimize use of GP IIb/IIIa inhibitor
- Radial access to reduce risk of bleeding
- Guidelines to change?
- Another trial?

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SEPTEMBER 10, 2015

VOL. 373 NO. 11

Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes

M. Valgimigli, E. Frigoli, S. Leonardi, M. Rothenbühler, A. Gagnor, P. Calabrò, S. Garducci, P. Rubartelli, C. Briguori, G. Andò, A. Repetto, U. Limbruno, R. Garbo, P. Sganzerla, F. Russo, A. Lupi, B. Cortese, A. Ausiello, S. Ierna, G. Esposito, P. Presbitero, A. Santarelli, G. Sardella, F. Varbella, S. Tresoldi, N. de Cesare, S. Rigattieri, A. Zingarelli, P. Tosi, A. van 't Hof, G. Boccuzzi, E. Omerovic, M. Sabaté, D. Heg, P. Jüni, and P. Vranckx,
for the MATRIX Investigators*



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VOL. 372 NO. 25

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*

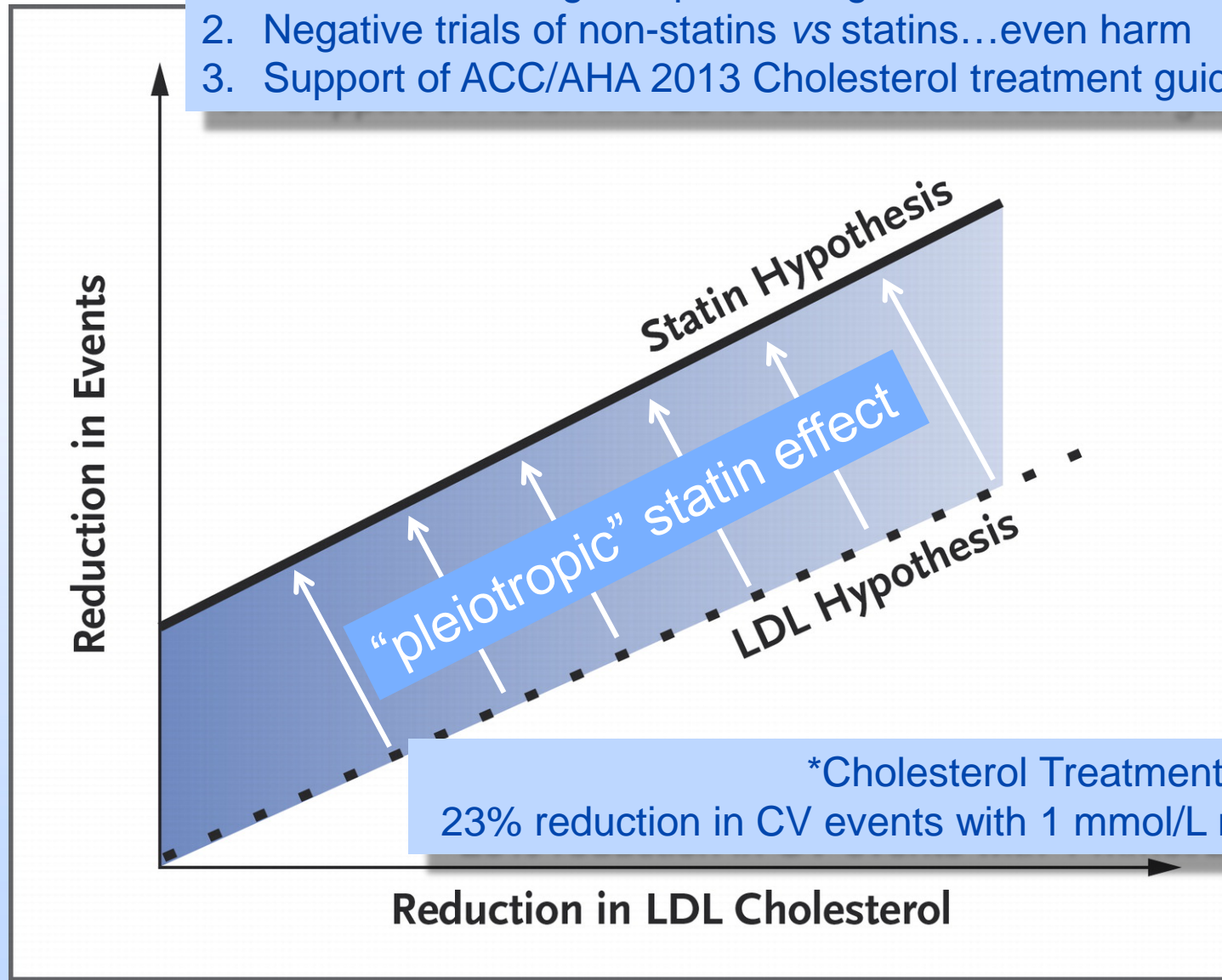
Cannon CP: NEJM 2015

LDL lowering (“lower is better”)

versus

statin effect

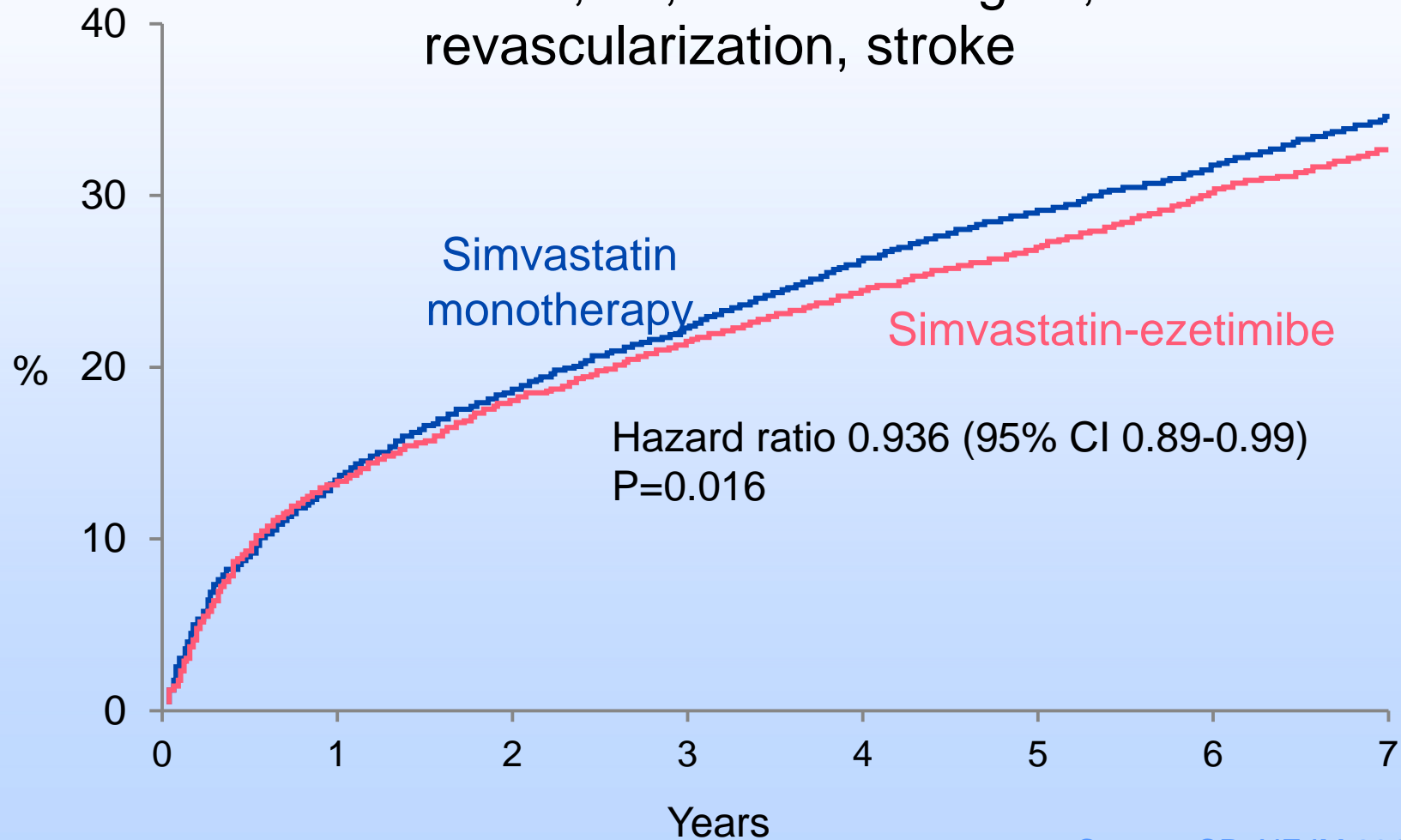
1. Non LDL lowering complex biologic effects of statins
2. Negative trials of non-statins vs statins...even harm
3. Support of ACC/AHA 2013 Cholesterol treatment guidelines



Adapted from Jarcho JA and Keaney JF: NEJM 2015; *Baigent C: Lancet 2005

IMPROVE-IT results

CV death, MI, unstable angina,
revascularization, stroke



IMPROVE-IT

The key findings

For every 1000 patients treated with Simvastatin and Ezetimibe:

- 17 fewer MIs
- 6 fewer strokes
- 16 fewer urgent revascularizations
- No difference in non CV death
- No difference in cancers

Comments

- Strongest clinical trial support for the LDL-lowering hypothesis
- Applicable to an ACS population and perhaps also those with established CHD
 - Reassurance for use of ezetimibe
- What if higher intensity statins were used?
- Compliance – 7% per year discontinuation
- Is LDL lowering a reliable surrogate for other non statins, e.g. PCSK9 inhibitors?



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Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Laura Mauri, M.D., Dean J. Kereiakes, M.D., Robert W. Yeh, M.D., Priscilla Driscoll-Shempp, M.B.A., Donald E. Cutlip, M.D., P. Gabriel Steg, M.D., Sharon-Lise T. Normand, Ph.D., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., David J. Cohen, M.D., David R. Holmes, Jr., M.D., Mitchell W. Krucoff, M.D., James Hermiller, M.D., Harold L. Dauerman, M.D., Daniel I. Simon, M.D., David E. Kandzari, M.D., Kirk N. Garratt, M.D., David P. Lee, M.D., Thomas K. Pow, M.D., Peter Ver Lee, M.D., Michael J. Rinaldi, M.D., and Joseph M. Massaro, Ph.D., for the DAPT Study Investigators*

DAPT study – DES only

	30 months DAPT	12 months DAPT	P value
Stent thrombosis	0.4%	1.4%	<0.001
MACCE	4.3%	5.9%	<0.001
Myocardial infarction	2.1%	4.1%	<0.001
Death	2.0%	1.5%	0.05
Moderate or severe bleeding	2.5%	1.6%	0.001

Everolimus DES: MACCE similar while ST reduced 0.7% to 0.3%

30 vs 12 months of DAPT

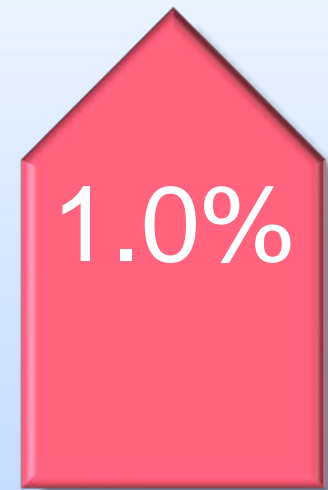
MACCE



Stent
thrombosis



Mod or major
Bleeding



Multiple Meta-analyses

DAPT treatment duration and outcomes

Summary

12 months no better than 3 or 6 months but more major bleeding

Prolonged >12 months

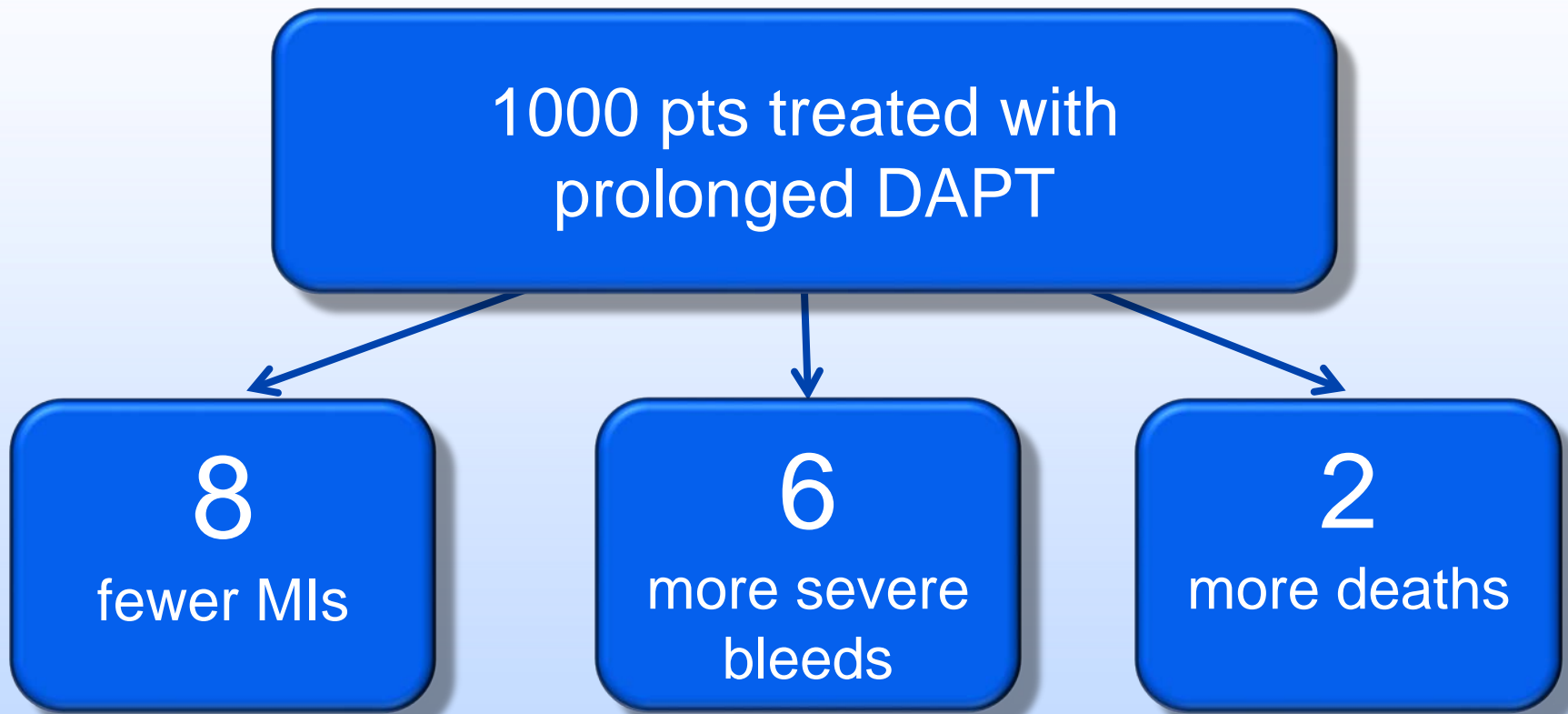
- Less ischemic events
- Less stent thrombosis
- More major bleeding
- More all cause deaths

Palmerini T: JACC 2015;
Navarese EP: BMJ 2015
Palmerini T: Lancet 2015

8 6 2

Choosing short or long duration DAPT

Meta analysis



DAPT duration after PCI

Conclusions

- Optimal DAPT duration remains matter for debate
- Balancing ischemic benefit against bleeding risk
 - 12 months may be a poor compromise
 - Shorter duration for low risk patients?
 - Prolonged duration for high risk patients?
....but who are they?
- Excess mortality with extended DAPT – a concern
- Shared decision making with patient



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color copiers, reduction duplicators and microfilm printers.

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or a General Motors, Xerox can guarantee you a perfect fit.

XEROX

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Original Investigation

Low-Dose Aspirin for Primary Prevention of Cardiovascular Events in Japanese Patients 60 Years or Older With Atherosclerotic Risk Factors

A Randomized Clinical Trial

Yasuo Ikeda, MD; Kazuyuki Shimada, MD; Tamio Teramoto, MD; Shinichiro Uchiyama, MD; Tsutomu Yamazaki, MD; Shinichi Oikawa, MD; Masahiro Sugawara, MD; Katsuyuki Ando, MD; Mitsuru Murata, MD; Kenji Yokoyama, MD; Naoki Ishizuka, PhD

IMPORTANCE Prevention of atherosclerotic cardiovascular diseases is an important public health priority in Japan due to an aging population.

OBJECTIVE To determine whether daily, low-dose aspirin reduces the incidence of cardiovascular events in older Japanese patients with multiple atherosclerotic risk factors.

← Editorial

+ Supplemental content at jama.com

ASA and Primary Prevention of CHD

- Major health goal of many countries
- ASA often recommended in men and women
- Guidelines no higher than IIa
- Evidence is thin
- ASA never shown to save lives
- Cost-effectiveness and risk-benefit questioned

2014 FDA announcement

BREAKING NEWS:

The Surprising **FDA**

REVERSAL

on *Aspirin*



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Japanese Primary Prevention Project

- >14,000 patients aged 60-85 yrs
- HT, diabetes or dyslipidemia
- ASA 100 mg vs none
- CV death, non fatal MI or non fatal CVA

Stopped for futility

Implications

- Low event rates and impact of statin use
- Adds further doubt that any benefit of ASA
- No trial has ever shown that ASA saves lives
- Do not recommend ASA for primary prevention
- Guidelines – will get even weaker

Further reading:

Meta analysis by Seshasai S: Arch Int Med 2012







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JANUARY 1, 2015

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A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

O.A. Berkhemer, P.S.S. Fransen, D. Beumer, L.A. van den Berg, H.F. Lingsma, A.J. Yoo, W.J. Schonewille, J.A. Vos, P.J. Nederkoorn, M.J.H. Wermer, M.A.A. van Walderveen, J. Staals, J. Hofmeijer, J.A. van Oostayen, G.J. Lycklama à Nijeholt, J. Boiten, P.A. Brouwer, B.J. Emmer, S.F. de Bruijn, L.C. van Dijk, L.J. Kappelle, R.H. Lo, E.J. van Dijk, J. de Vries, P.L.M. de Kort, W.J.J. van Rooij, J.S.P. van den Berg, B.A.A.M. van Hasselt, L.A.M. Aerden, R.J. Dallinga, M.C. Visser, J.C.J. Bot, P.C. Vroomen, O. Eshghi, T.H.C.M.L. Schreuder, R.J.J. Heijboer, K. Keizer, A.V. Tielbeek, H.M. den Hertog, D.G. Gerrits, R.M. van den Berg-Vos, G.B. Karas, E.W. Steyerberg, H.Z. Flach, H.A. Marquering, M.E.S. Sprengers, S.F.M. Jenniskens, L.F.M. Beenen, R. van den Berg, P.J. Koudstaal, W.H. van Zwam, Y.B.W.E.M. Roos, A. van der Lugt, R.J. van Oostenbrugge, C.B.L.M. Majoie, and D.W.J. Dippel, for the MR CLEAN Investigators*

Berkhemer OA: NEJM 2015

Ischemic Stroke

IV-tPA is standard of care for ischemic stroke

- Limited application

Catheter-based therapy trials disappointing

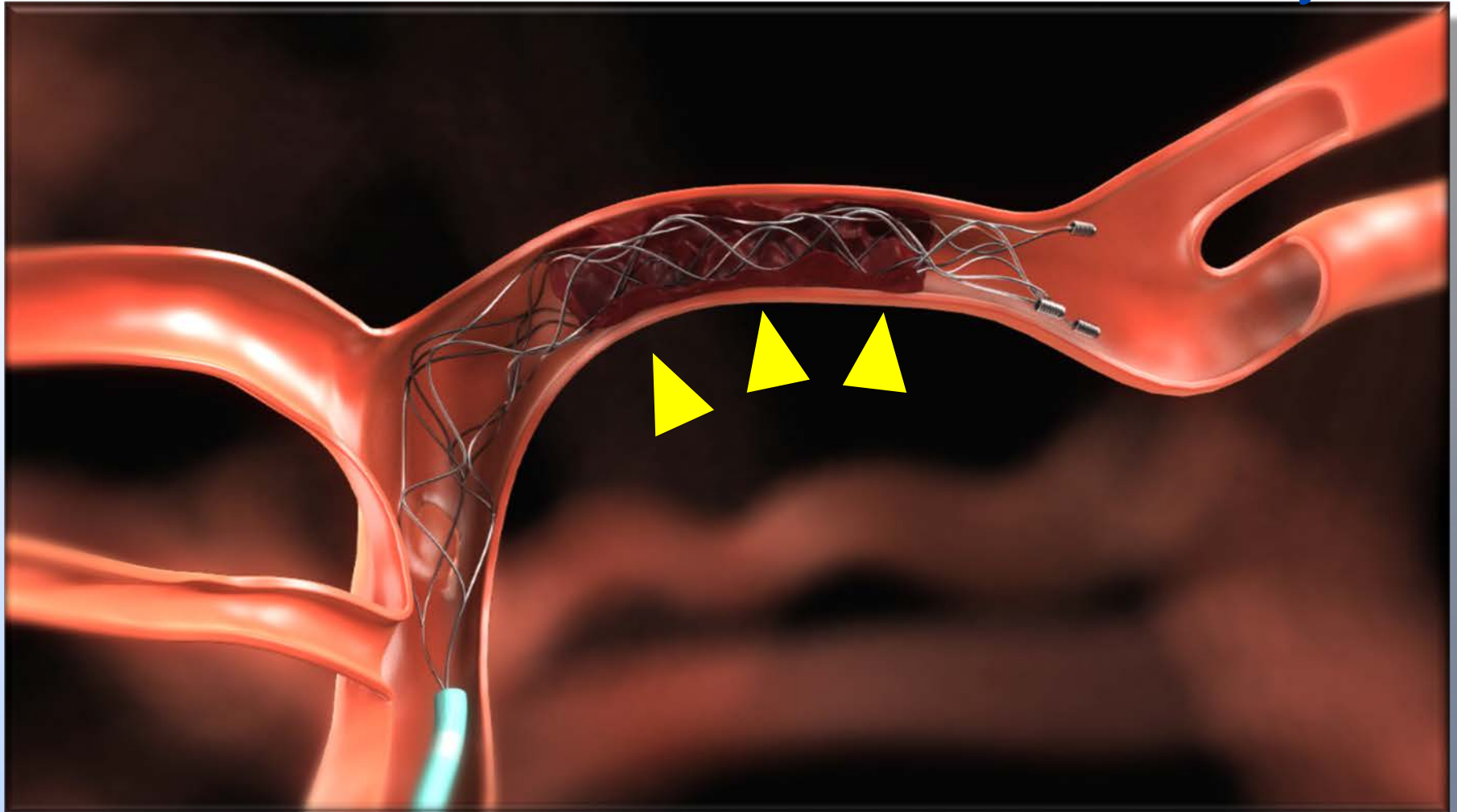
MR CLEAN study design

Open label – 500 patients

90% received IV-tPA

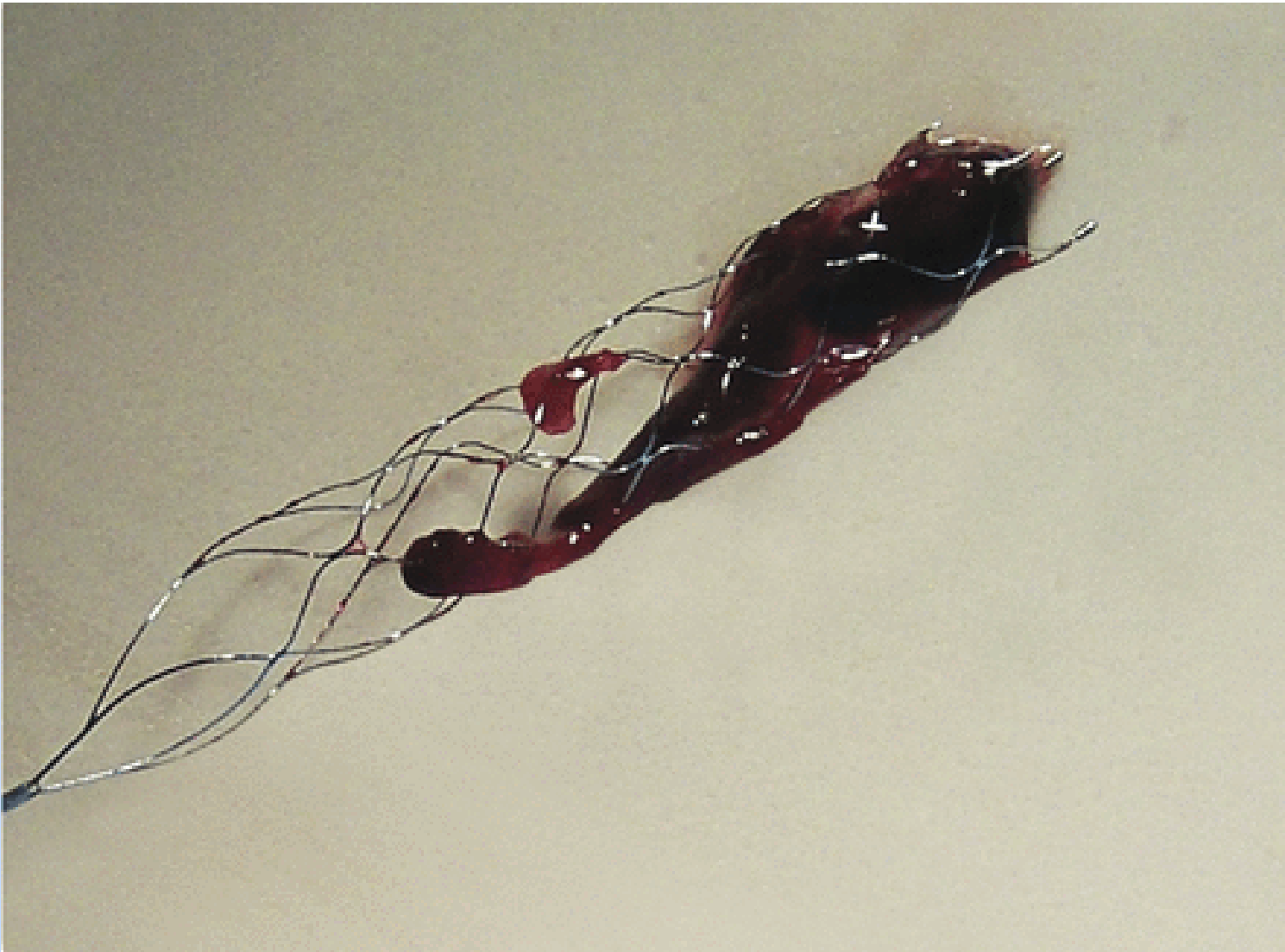
Randomized to thrombectomy or usual care

Intra arterial mechanical thrombectomy



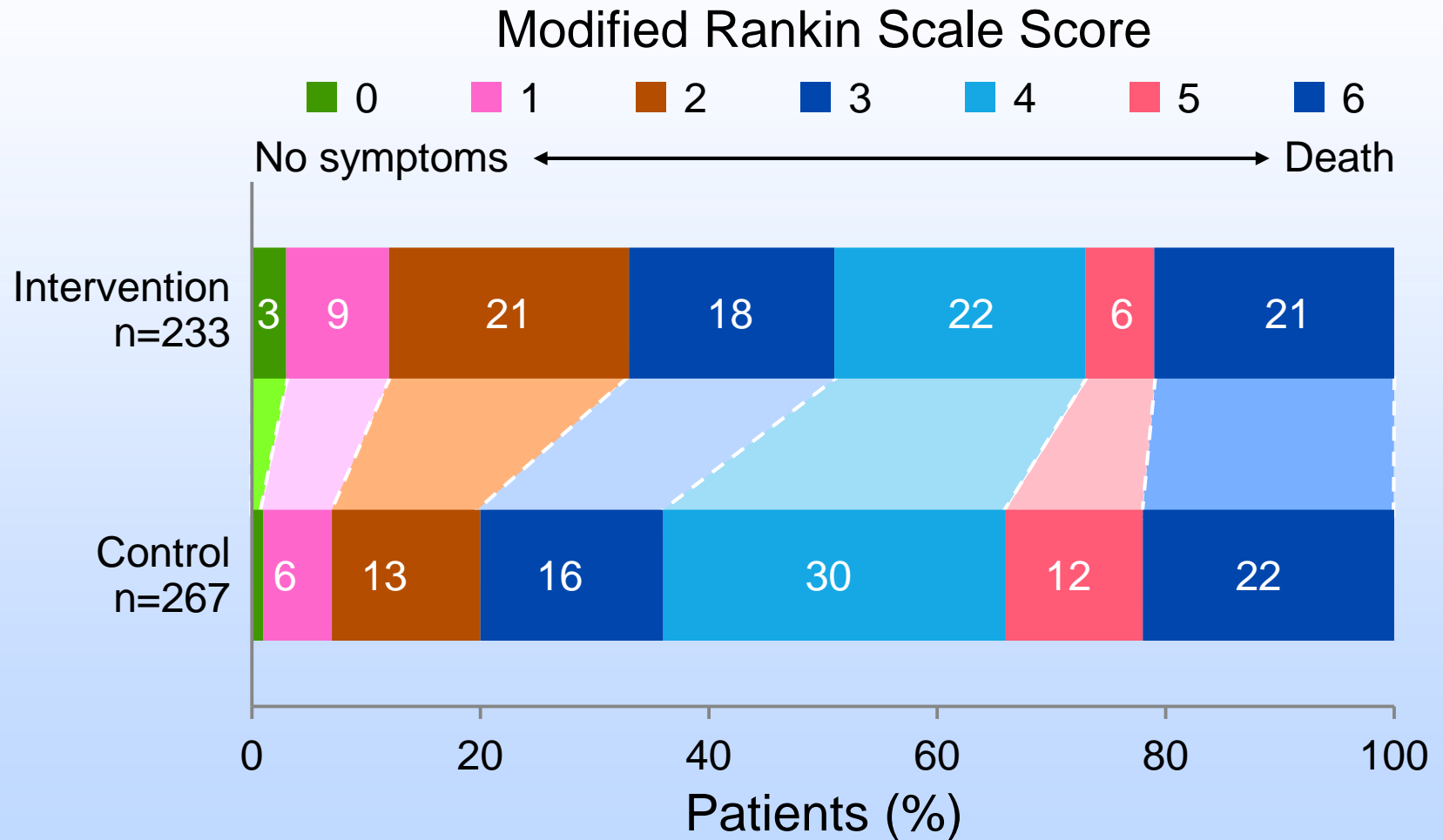
Solitaire™ FR Retriever stent

Covidien: www.ev3.net



Davalos A: Stroke 2012

MR CLEAN Results at 90 Days



Berkhemer OA: NEJM 372:11, 2015

4 more confirmatory trials in 2015

Trial	Result	Terminated early for efficacy	Source
EXTEND IA	++	Yes	Campbell BC: NEJM 2015
ESCAPE	++	Yes	Goyal M: NEJM 2015
SWIFT PRIME	++	Yes	Saver JL: NEJM 2015
REVASCAT	++	No	Jovin TG: NEJM 2015

NNT to achieve functional independence in one person
< 7

Treat stroke now!

“Wake up call” for neuro-radiologists

- 10-20% CVAs eligible?
- 6-hour time window
- Stroke centers
 - Resources and expertise?
 - Logistics?
- Role for interventional cardiologists?

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