MAYO CLINIC

Torino, IT
October 2016

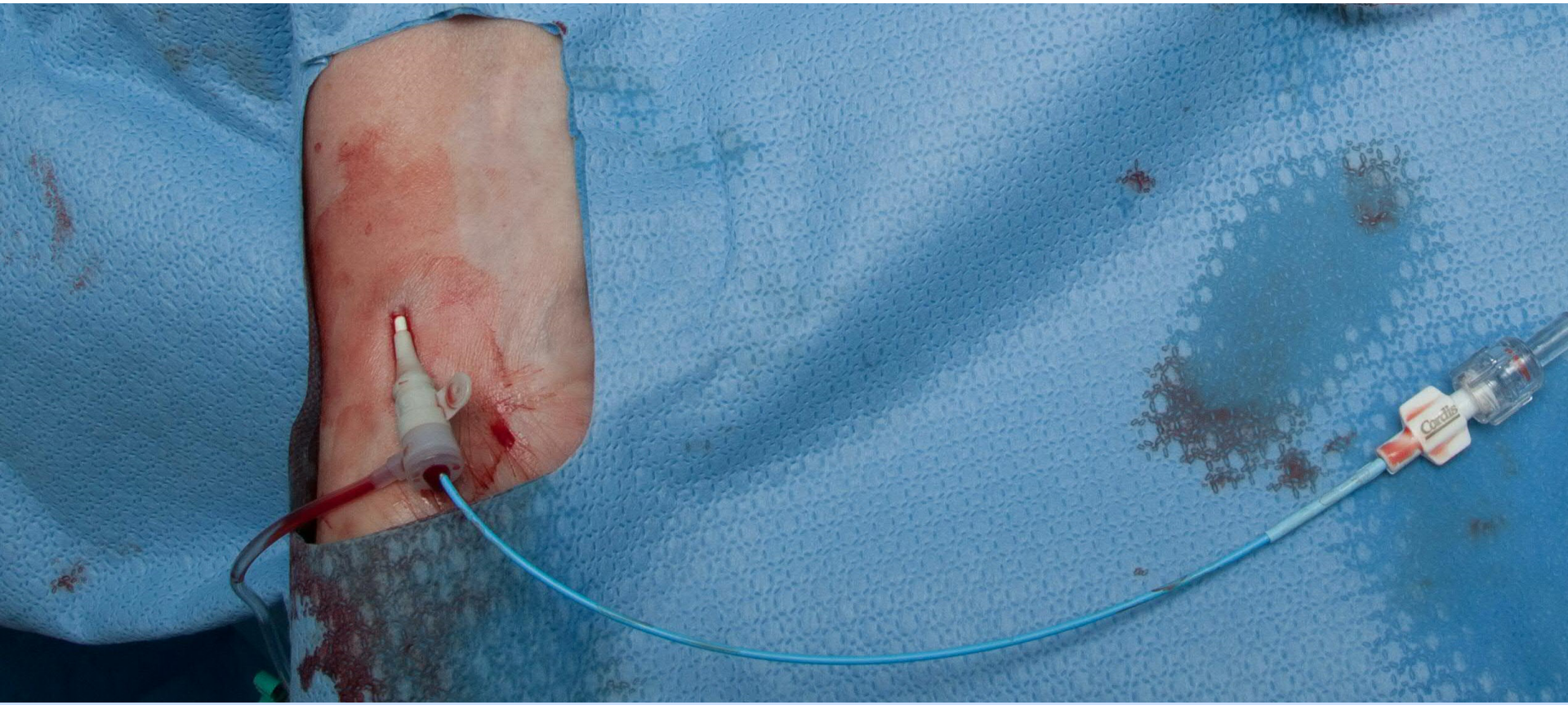
5 Important Trials in Ischemic Heart Disease in the Last Year

Malcolm R. Bell, MBBS, FRACP
Director Ischemic Heart Disease Program
Mayo Clinic, MN, USA

Conflicts and disclosures – none

MAYO CLINIC

MAYO CLINIC



MAYO CLINIC

Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial

*Marco Valgimigli, Andrea Gagnor, Paolo Calabró, Enrico Frigoli, Sergio Leonardi, Tiziana Zaro, Paolo Rubartelli, Carlo Briguori, Giuseppe Andò, Alessandra Repetto, Ugo Limbruno, Bernardo Cortese, Paolo Sganzerla, Alessandro Lupi, Mario Galli, Salvatore Colangelo, Salvatore Ierna, Arturo Ausiello, Patrizia Presbitero, Gennaro Sardella, Ferdinando Varbella, Giovanni Esposito, Andrea Santarelli, Simone Tresoldi, Marco Nazzaro, Antonio Zingarelli, Nicoletta de Cesare, Stefano Rigattieri, Paolo Tosi, Cataldo Palmieri, Salvatore Brugaletta, Sunil V Rao, Dik Heg, Martina Rothenbühler, Pascal Vranckx, Peter Jüni, for the MATRIX Investigators**

Lancet 2015; 385: 2465–76
Published Online
March 16, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60292-6

Summary

Background It is unclear whether radial compared with femoral access improves outcomes in unselected patients with acute coronary syndromes undergoing invasive management.

Methods We did a randomised, multicentre, superiority trial comparing transradial against transfemoral access in patients with acute coronary syndrome with or without ST-segment elevation myocardial infarction who were

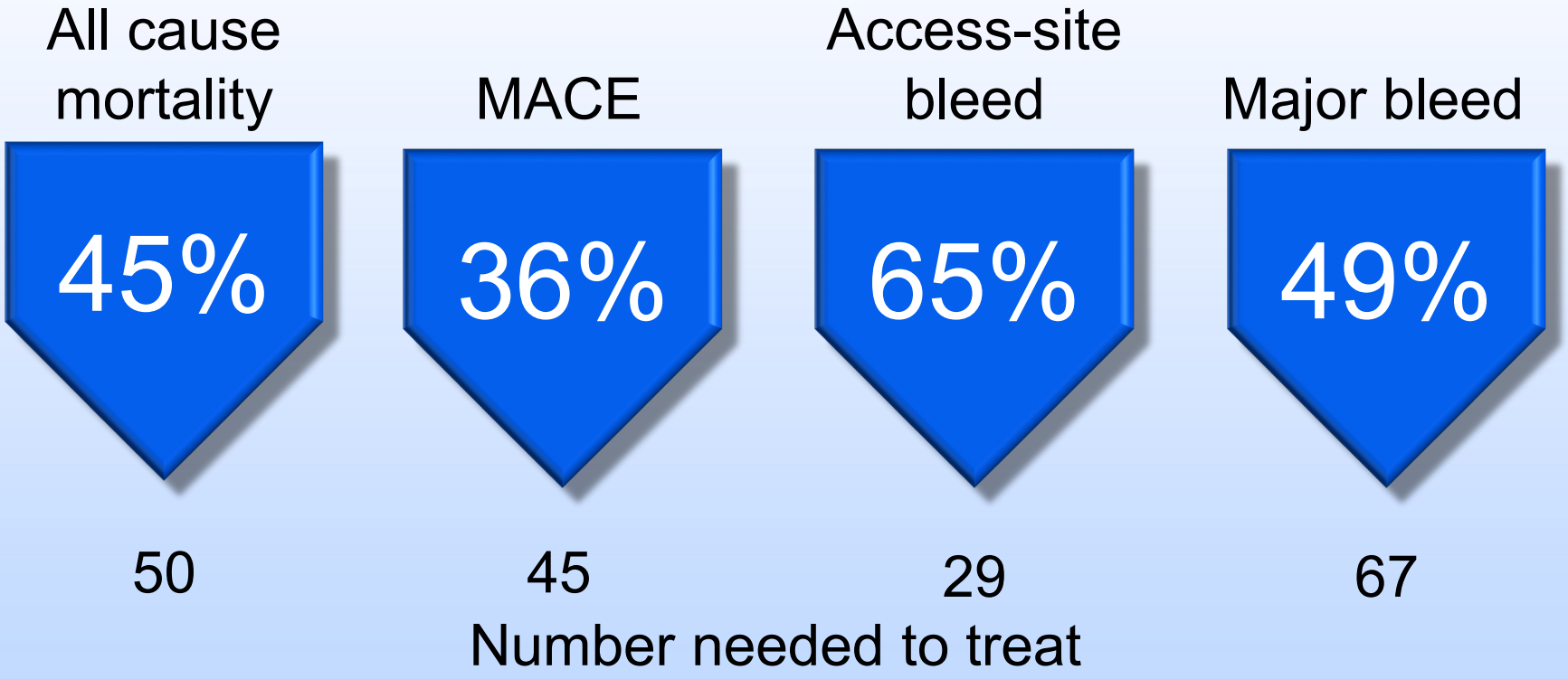
MATRIX

Radial reduced net adverse events compared to femoral access through reduction in major bleeding and all-cause mortality in this 8500-pt ACS population

NNT = 56

Valgimigli M: Lancet 2015

Meta Analysis of Transradial STEMI RCTs
12 Trials and >5000 Patients



Karrowni W: JACC Intv 2013

MAYO CLINIC

2013 STEMI Guidelines
Vascular access choice: Europe *vs* USA

ESC: Class IIa Level B

"If performed by experienced radial operator, radial access should be preferred over femoral access"

ACCF/AHA: No recommendation

"Bleeding rates with radial versus femoral artery access for PCI warrant further prospective study"

Bax JJ: ESC 2013
O'Gara PT: JACC 2013

MAYO CLINIC

European Heart Journal Advance Access published September 11, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv320

ESC GUIDELINES

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Marco Roffi* (Chairperson) (Switzerland), Carlo Patrono* (Co-Chairperson) (Italy), Jean-Philippe Collet† (France), Christian Mueller† (Switzerland), Marco Valgimigli† (The Netherlands), Felicita Andreotti (Italy), Jeroen J. Bax (The Netherlands), Michael A. Borger (Germany), Carlos Brotons (Spain), Derek P. Chew (Australia), Baris Gencer (Switzerland), Gerd Hasenfuss (Germany), Keld Kjeldsen (Denmark), Patrizio Lancellotti (Belgium), Ulf Landmesser (Germany), Julinda Mehilli (Germany), Debabrata Mukherjee (USA), Robert F. Storey (UK), and Stephan Windecker (Switzerland)

	Class	Level
In centres experienced with radial access, a radial approach is recommended for coronary angiography and PCI.	I	A

"*Radial access, performed by experienced operators, is recommended over the transfemoral access in ACS.*

It is recommended that centres treating ACS patients implement a transition from transfemoral to transradial access."

Roffi M: ESC Non-STEMI Guidelines; EHJ 2015

MAYO CLINIC

MAYO CLINIC

Outcomes after thrombus aspiration for ST elevation myocardial infarction: 1-year follow-up of the prospective randomised TOTAL trial

Sanjit S Jolly, John A Cairns, Salim Yusuf, Michael J Rokoss, Peggy Gao, Brandi Meeks, Sasko Kedev, Goran Stankovic, Raul Moreno, Anthony Gershlick, Saqib Chowdhary, Shahar Lavi, Kari Niemela, Ivo Bernat, Warren J Cantor, Asim N Cheema, Philippe Gabriel Steg, Robert C Welsh, Tej Sheth, Olivier F Bertrand, Alvaro Avezum, Ravinay Bhindi, Madhu K Natarajan, David Horak, Raymond C M Leung, Saleem Kassam, Sunil V Rao, Magdi El-Omar, Shamir R Mehta, James L Velianou, Samir Pancholy, Vladimír Džavík, for the TOTAL Investigators

Summary

Background Two large trials have reported contradictory results at 1 year after thrombus aspiration in ST elevation myocardial infarction (STEMI). In a 1-year follow-up of the largest randomised trial of thrombus aspiration, we aimed to clarify the longer-term benefits, to help guide clinical practice.

Methods The trial of routine aspiration ThrOmbecTomy with PCI versus PCI ALone in Patients with STEMI (TOTAL) was a prospective, randomised, investigator-initiated trial of routine manual thrombectomy versus percutaneous coronary intervention (PCI) alone in 10 732 patients with STEMI. Eligible adult patients (aged ≥18 years) from 87 hospitals in 20 countries were enrolled and randomly assigned (1:1) within 12 h of symptom onset to receive routine manual thrombectomy with PCI or PCI alone. Permuted block randomisation (with variable block size) was done by a 24 h computerised central system, and was stratified by centre. Participants and investigators were not masked to treatment assignment. The trial did not show a difference at 180 days in the primary outcome of cardiovascular death, myocardial infarction, cardiogenic shock, or heart failure. However, the results showed improvements in the surrogate outcomes of ST segment resolution and distal embolisation, but whether or not this finding would translate into a longer term benefit remained unclear. In this longer-term follow-up of the TOTAL study, we report the results on the primary outcome (cardiovascular death, myocardial infarction, cardiogenic shock, or heart failure) and secondary outcomes at 1 year. Analyses of the primary outcome were by modified intention to treat and only included patients who underwent index PCI. This trial is registered with ClinicalTrials.gov, number NCT01149044.

Findings Between Aug 5, 2010, and July 25, 2014, 10 732 eligible patients were enrolled and randomly assigned to thrombectomy followed by PCI (n=5372) or to PCI alone (n=5360). After exclusions of patients who did not undergo PCI in each group (337 in the PCI and thrombectomy group and 331 in the PCI alone group), the final study population comprised 10 064 patients (5035 thrombectomy and 5029 PCI alone). The primary outcome at 1 year occurred in 395 (8%) of 5035 patients in the thrombectomy group compared with 394 (8%) of 5029 in the PCI alone group (hazard ratio [HR] 1·00 [95% CI 0·87–1·15], p=0·99). Cardiovascular death within 1 year occurred in 179 (4%) of the thrombectomy group and in 192 (4%) of 5029 in the PCI alone group (HR 0·93 [95% CI 0·76–1·14], p=0·48). The key safety outcome, stroke within 1 year, occurred in 60 patients (1·2%) in the thrombectomy group compared with 36 (0·7%) in the PCI alone group (HR 1·66 [95% CI 1·10–2·51], p=0·015).

Interpretation Routine thrombus aspiration during PCI for STEMI did not reduce longer-term clinical outcomes and might be associated with an increase in stroke. As a result, thrombus aspiration can no longer be recommended as a routine strategy in STEMI.

Funding Canadian Institutes of Health Research, Canadian Network and Centre for Trials Internationally, and Medtronic Inc.

Lancet 2016; 387: 127–35

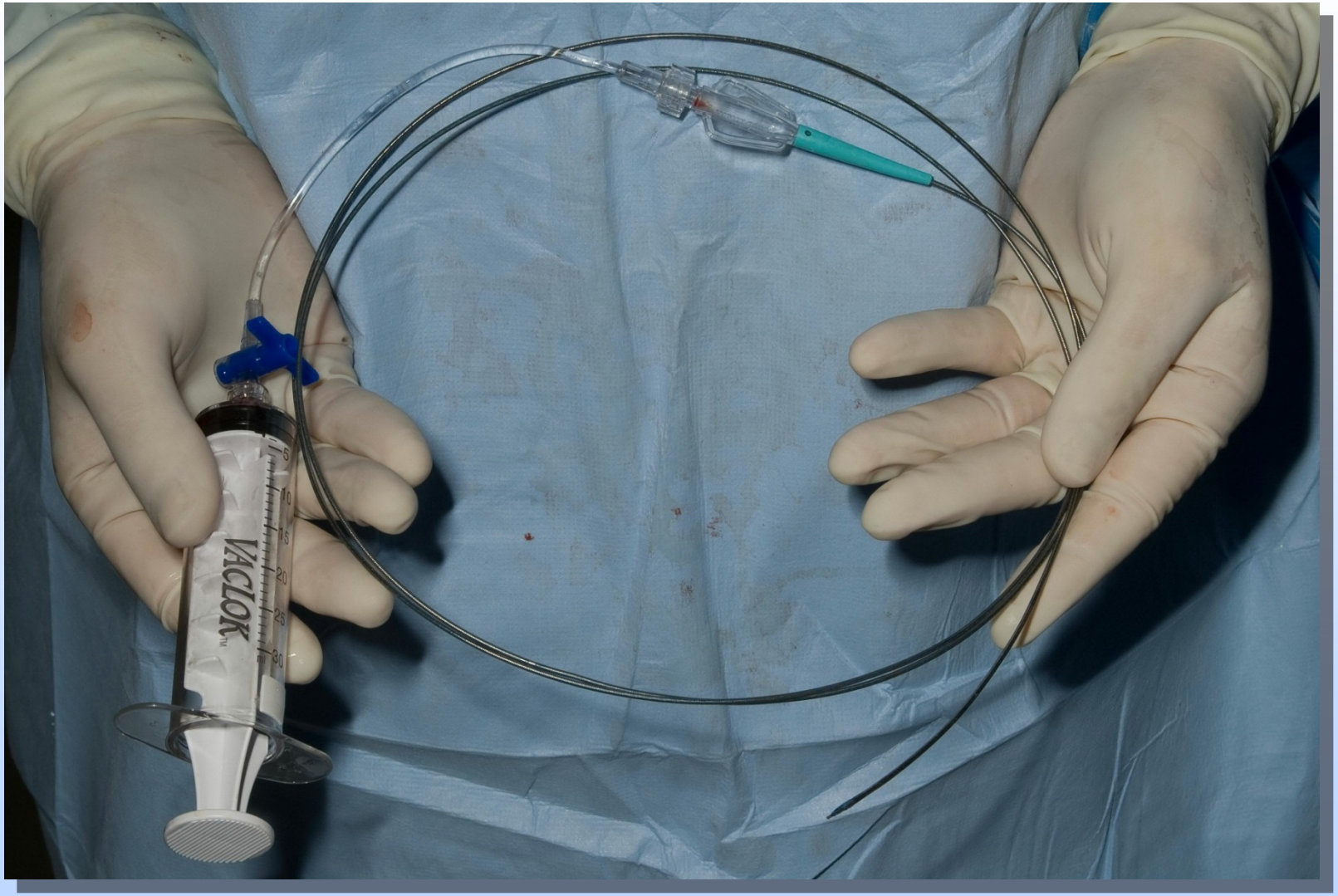
Published Online
October 13, 2015
http://dx.doi.org/10.1016/S0140-6736(15)00448-1

See Comment page 97

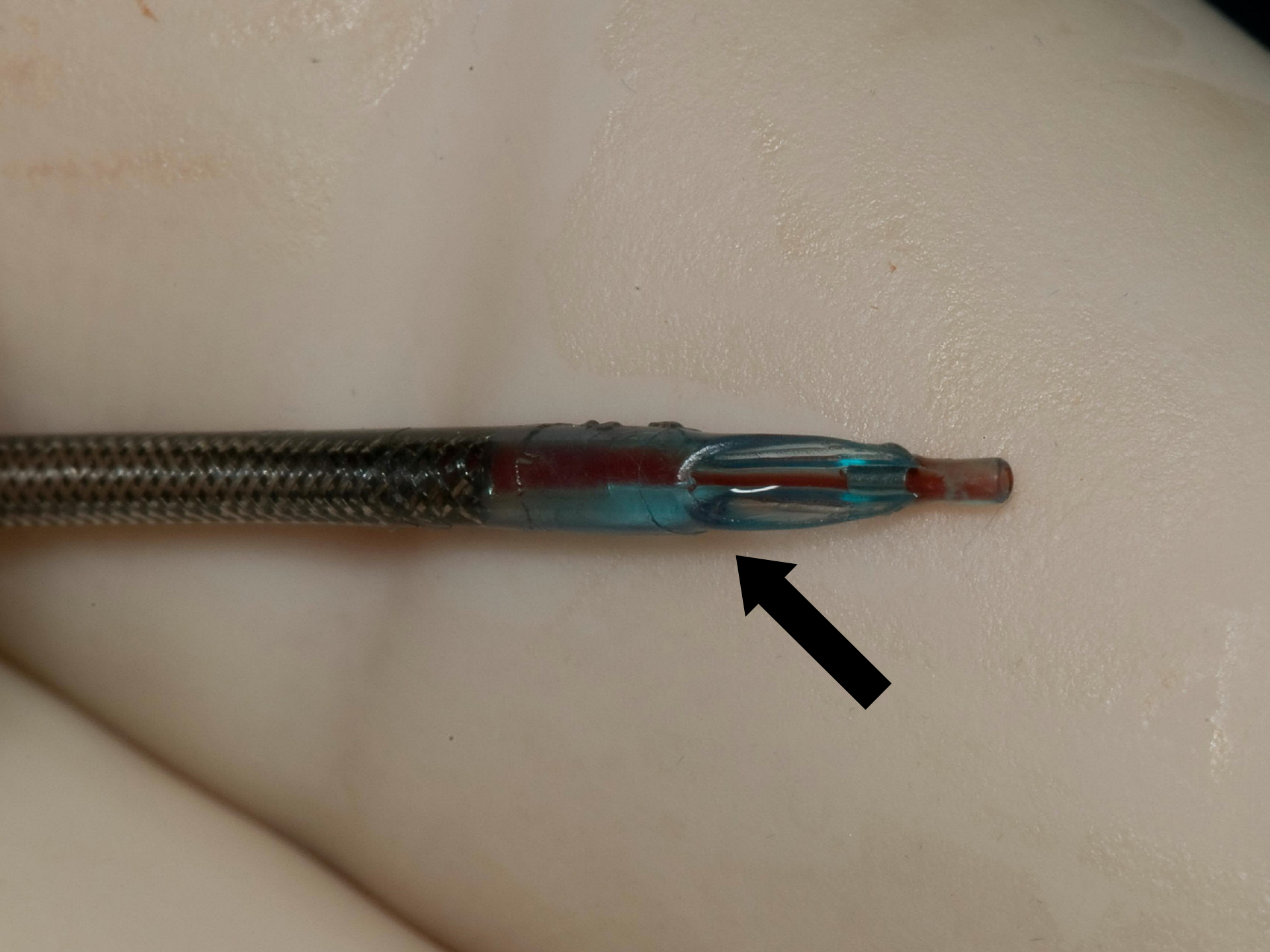
McMaster University and the Population Health Research Institute, Hamilton Health Sciences, Hamilton, ON, Canada (S S Jolly MD, Prof S Yusuf MBBS, M J Rokoss MD, P Gao MSc, B Meeks MEng, T Sheth MD, Prof M K Natarajan MD, Prof S R Mehta MD, J L Velianou MD); University of British Columbia, Vancouver, BC, Canada (Prof J A Cairns MD); London Health Sciences Centre, Department of Medicine, London, ON, Canada (S Lavi MD); Southlake Regional Health Centre, Newmarket, ON, Canada (W J Cantor MD); St Michael's Hospital, Toronto, ON, Canada (A N Cheema MD); Mazankowski Alberta Heart Institute, Department of Medicine, Edmonton, AB, Canada (Prof R C Welsh MD); Quebec Heart-Lung Institute, Laval University, Quebec, QC, Canada (O F Bertrand MD); CK Hui Heart Centre, Edmonton, AB, Canada (R C M Leung MD); Rouge Valley Health System, Toronto, ON, Canada (S Kassam MD); Peter Munk Cardiac Centre, University Health Network, Toronto, ON, Canada (Prof V Džavík MD); University

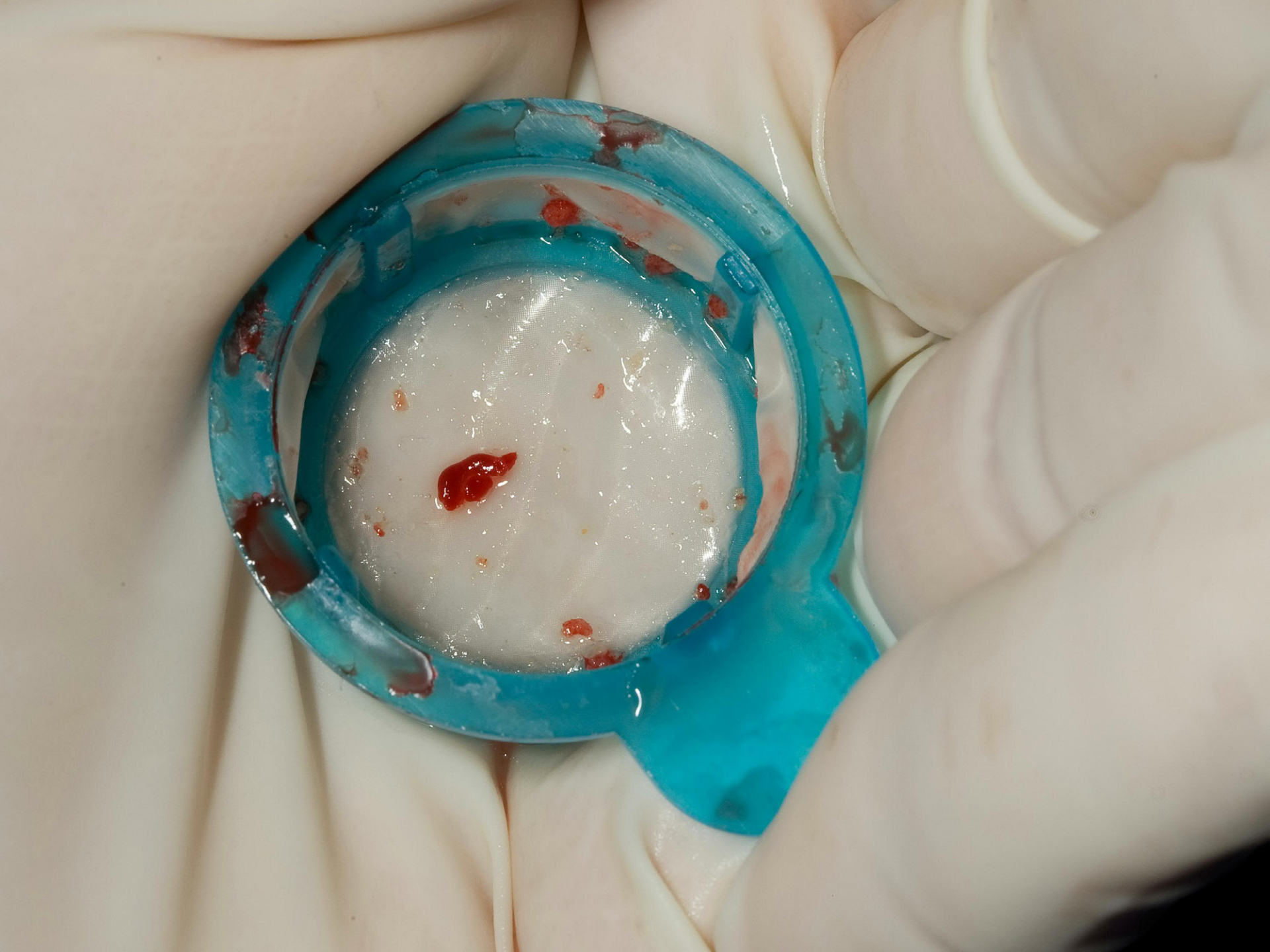
MAYO CLINIC

Intuitive, simple……but crude



MAYO CLINIC





Aspiration Thrombectomy
Evidence leading to Guidelines

TAPAS trial (manual aspiration):

Better myocardial perfusion and 1-year survival

Svilaas T: NEJM 2008 and Vlaar PJ: Lancet 2008

Meta analyses:

Survival benefit but only if *manual aspiration*

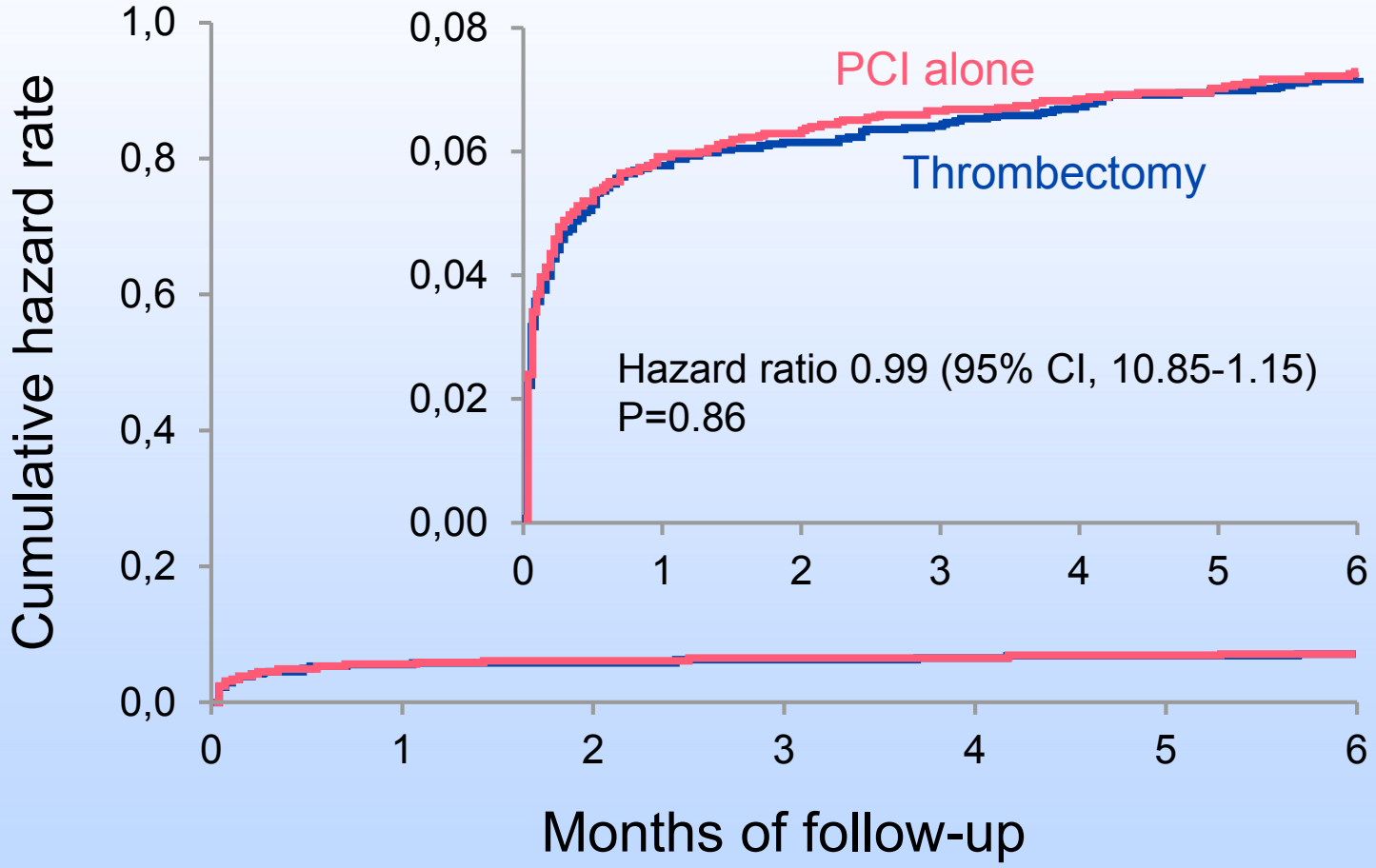
Bavry AA: EHJ 2008 and Burzotta F: EHJ 2009

ACC/AHA 2009 and ESC/EACTS 2010

Class IIa recommendation

MAYO CLINIC

TOTAL Trial – 10,732 randomized patients
Primary Endpoint*

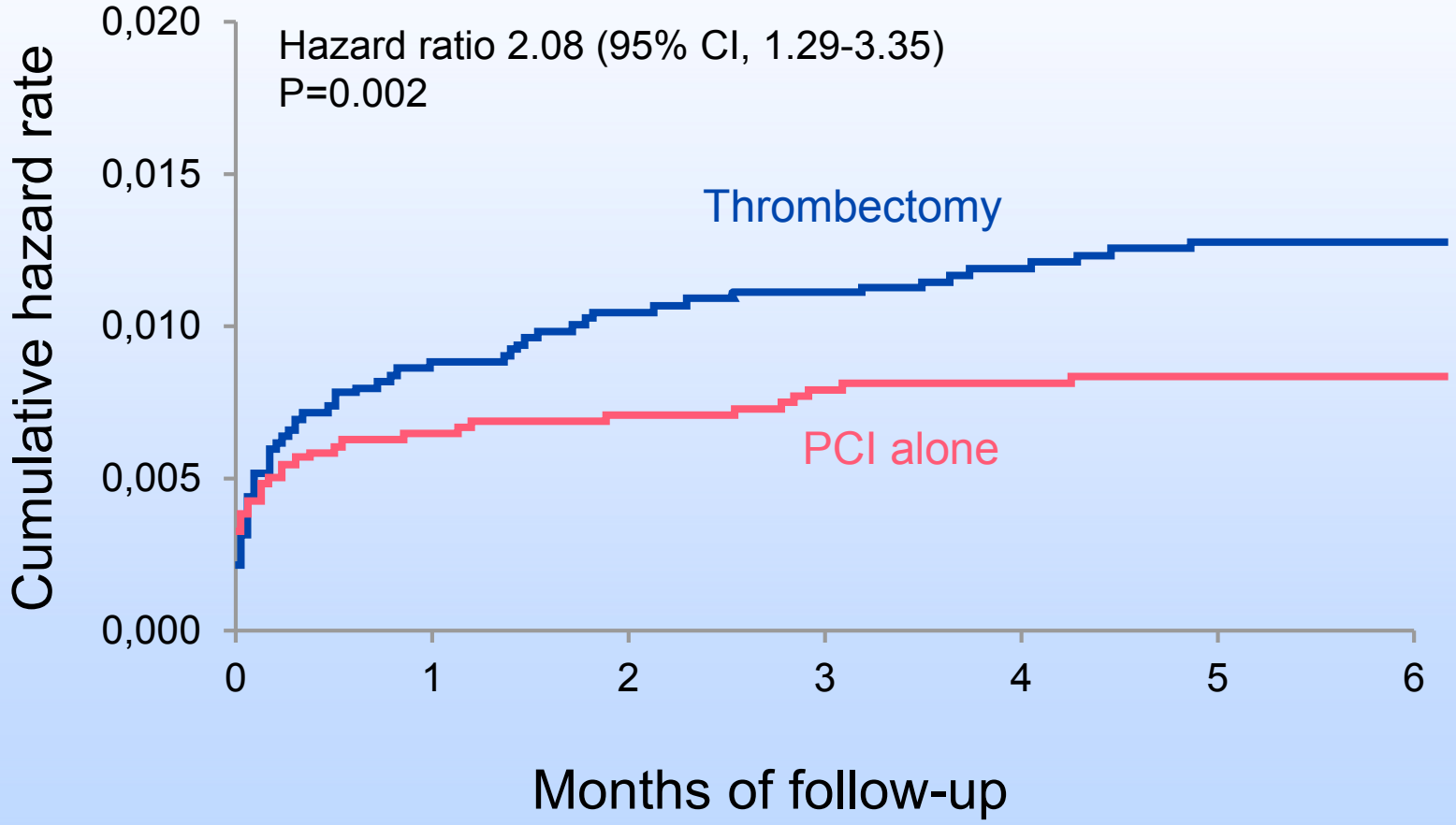


*CV death, MI, shock, NYHA class IV at 180 days

Jolly SS: NEJM 2015

MAYO CLINIC

TOTAL Trial – 10,732 randomized patients
Stroke – key safety endpoint



Jolly SS: NEJM 2015

MAYO CLINIC

Outcomes after thrombus aspiration for ST elevation myocardial infarction: 1-year follow-up of the prospective randomised TOTAL trial

Sanjit S Jolly, John A Cairns, Salim Yusuf, Michael J Rokoss, Peggy Gao, Brandi Meeks, Sasko Kedev, Goran Stankovic, Raul Moreno, Anthony Gershlick, Saqib Chowdhary, Shahar Lavi, Kari Niemela, Ivo Bernat, Warren J Cantor, Asim N Cheema, Philippe Gabriel Steg, Robert C Welsh, Tej Sheth, Olivier F Bertrand, Alvaro Avezum, Ravinay Bhindi, Madhu K Natarajan, David Horak, Raymond C M Leung, Saleem Kassam, Sunil V Rao, Magdi El-Omar, Shamir R Mehta, James L Velianou, Samir Pancholy, Vladimír Džavík, for the TOTAL Investigators

Routine thrombus aspiration during PCI for STEMI did not reduce longer-term clinical outcomes and might be associated with an increase in stroke
…. (it) can no longer be recommended as a routine strategy in STEMI

Jolly SS: Lancet 2016

MAYO CLINIC

Lessons learned

Caution with over-interpretation of trials and incorporation into guidelines

- Small trials
- Not powered for major clinical endpoints
- Use of surrogate endpoints

Need large robust and pragmatic trials appropriately powered for important clinical endpoints

MAYO CLINIC

MAYO CLINIC

Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial

Nicolai Tegn, Michael Abdelnoor, Lars Aaberge, Knut Endresen, Pål Smith, Svend Aakhus, Erik Gjertsen, Ola Dahl-Hofseth, Anette Hylen Ranhoff, Lars Gullestad, Bjørn Bendz, for the After Eighty study investigators

Summary

Background Non-ST-elevation myocardial infarction (NSTEMI) and unstable angina pectoris are frequent causes of hospital admission in the elderly. However, clinical trials targeting this population are scarce, and these patients are less likely to receive treatment according to guidelines. We aimed to investigate whether this population would benefit from an early invasive strategy versus a conservative strategy.

Methods In this open-label randomised controlled multicentre trial, patients aged 80 years or older with NSTEMI or unstable angina admitted to 16 hospitals in the South-East Health Region of Norway were randomly assigned to an invasive strategy (including early coronary angiography with immediate assessment for percutaneous coronary intervention, coronary artery bypass graft, and optimum medical treatment) or to a conservative strategy (optimum medical treatment alone). A permuted block randomisation was generated by the Centre for Biostatistics and Epidemiology with stratification on the inclusion hospitals in opaque concealed envelopes, and sealed envelopes with consecutive inclusion numbers were made. The primary outcome was a composite of myocardial infarction, need for urgent revascularisation, stroke, and death and was assessed between Dec 10, 2010, and Nov 18, 2014. An intention-to-treat analysis was used. This study is registered with ClinicalTrials.gov, number NCT01255540.

Findings During a median follow-up of 1·53 years of participants recruited between Dec 10, 2010, and Feb 21, 2014, the primary outcome occurred in 93 (40·6%) of 229 patients assigned to the invasive group and 140 (61·4%) of 228 patients assigned to the conservative group (hazard ratio [HR] 0·53 [95% CI 0·41–0·69], p=0·0001). Five patients dropped out of the invasive group and one from the conservative group. HRs for the four components of the primary composite endpoint were 0·52 (0·35–0·76; p=0·0010) for myocardial infarction, 0·19 (0·07–0·52; p=0·0010) for the need for urgent revascularisation, 0·60 (0·25–1·46; p=0·2650) for stroke, and 0·89 (0·62–1·28; p=0·5340) for death from any cause. The invasive group had four (1·7%) major and 23 (10·0%) minor bleeding complications whereas the conservative group had four (1·8%) major and 16 (7·0%) minor bleeding complications.

Interpretation In patients aged 80 years or more with NSTEMI or unstable angina, an invasive strategy is superior to a conservative strategy in the reduction of composite events. Efficacy of the invasive strategy was diluted with increasing age (after adjustment for creatinine and effect modification). The two strategies did not differ in terms of bleeding complications.

Funding Norwegian Health Association (ExtraStiftelsen) and Inger and John Fredriksen Heart Foundation.

Lancet 2016; 387: 1057–65

Published Online
January 12, 2016
http://dx.doi.org/10.1016/S0140-6736(15)01166-6

See **Comment** page 1029

Department of Cardiology (N Tegn MD, L Aaberge MD, K Endresen MD, Prof S Aakhus MD, Prof L Gullestad MD, B Bendz MD), **Centre for Biostatistics and Epidemiology** (Prof M Abdelnoor PhD), **and Centre for Clinical Heart Research** (Prof M Abdelnoor), **Oslo University Hospital, Oslo, Norway; Faculty of Medicine, University of Oslo, Oslo, Norway** (N Tegn, Prof L Gullestad, Prof P Smith MD, B Bendz); **Department of Cardiology, Akershus University Hospital, Lørenskog, Norway** (Prof P Smith); **Department of Cardiology, Drammen Hospital, Drammen, Norway** (E Gjertsen MD); **Department of Cardiology, Lillehammer Hospital, Lillehammer, Norway** (O Dahl-Hofseth MD); **and Diakonhjemmet Hospital and Department of Clinical Science, University of Bergen, Bergen, Norway** (Prof A H Ranhoff MD)

MAYO CLINIC

Tegn N: Iancet 2016

ACS in Contemporary Practice

Invasive strategy and better medical Rx

- Mortality decreased
- Benefits in younger patients – median age 65
- Guidelines recommend early invasive strategy

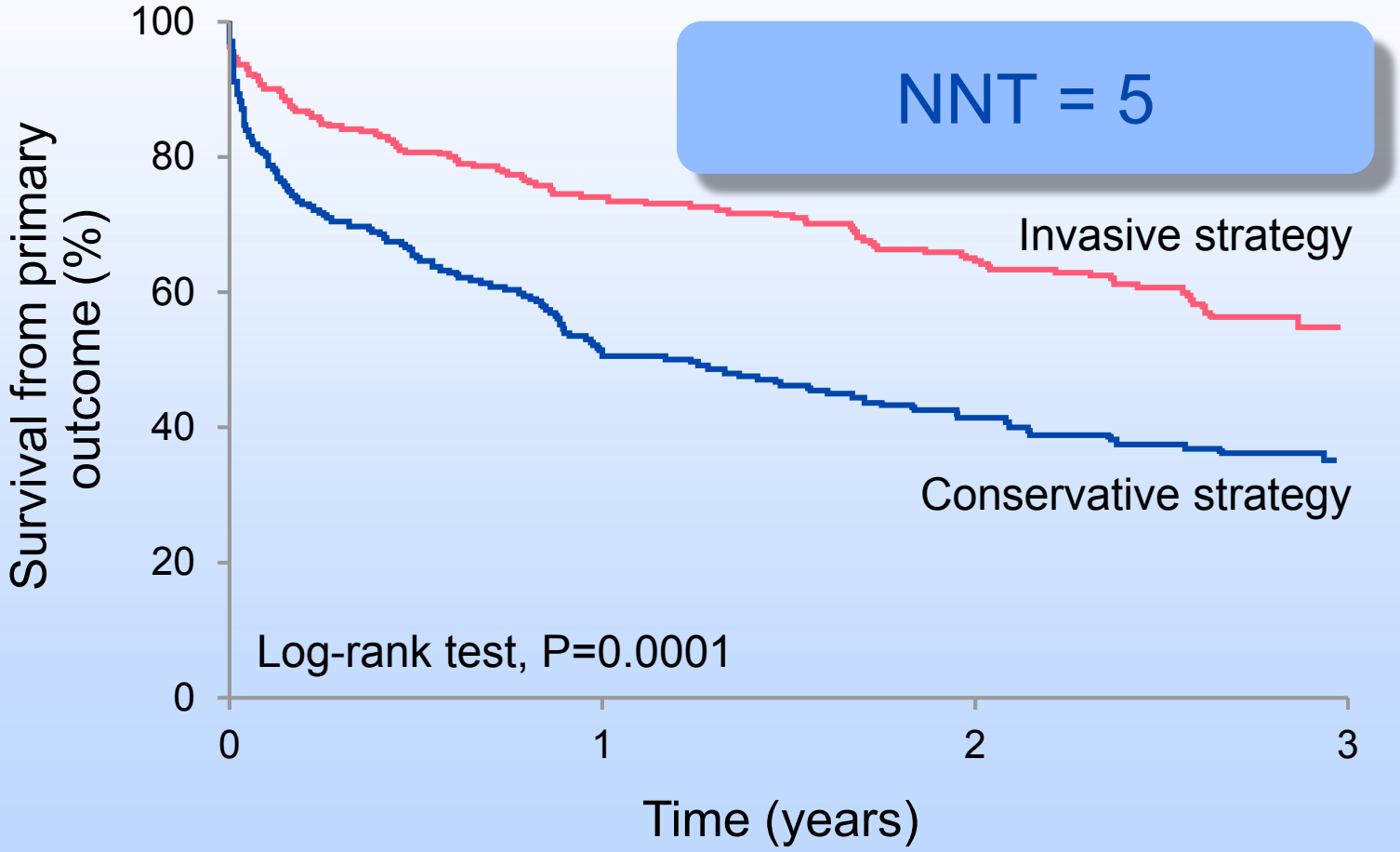
Patients >80 yrs

- Under represented in trials
- Medical and invasive strategy used less
- Risk of adverse outcome higher
- Frequent admissions with ACS

MAYO CLINIC

ACS: Randomized “After 80 Trial”

MI, Death, Urgent Revascularization and CVA

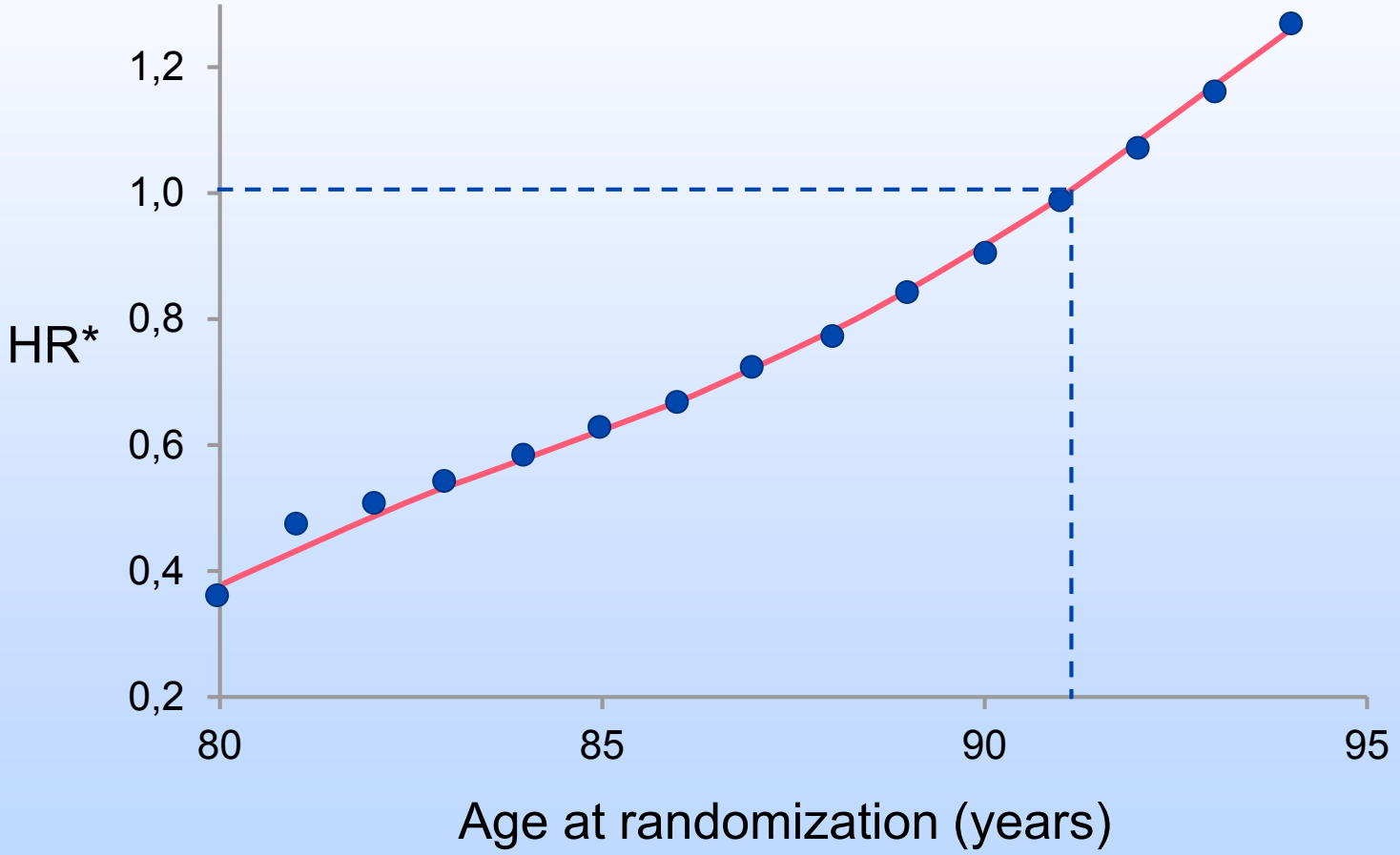


Tegn N: Lancet 2016

MAYO CLINIC

ACS: Randomized “After 80 Trial”

Efficacy of invasive strategy *vs.* age



*Controlling for creatinine

Tegn N: Lancet 2016

MAYO CLINIC

Implications

Support invasive strategy in this older population

- Decrease MI and revascularization
- Bleeding and AKI infrequent

Unclear if benefit extends to nonagenarians

- Individualize and share decision-making

Age not to be used as single criterion in selecting invasive strategy in management of ACS

MAYO CLINIC

MAYO CLINIC

MAYO CLINIC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk

Philip Urban, M.D., Ian T. Meredith, M.B., B.S., Ph.D.,
Alexandre Abizaid, M.D., Ph.D., Stuart J. Pocock, Ph.D.,

LEADERS FREE (BioFreedom Biolimus A9 stent)
Polymer-free, umirolimus coated stent superior to BMS in terms of safety and efficacy

for the LEADERS FREE Investigators*

Urban P: NEJM 2015

MAYO CLINIC

BMS safer than DES: Myth or Reality?

Less stent thrombosis than DES?

Immune from very late stent thrombosis?

Require shorter duration of DAPT?

Preferred if patient at high risk of bleeding?

MAYO CLINIC

Not your grandfather's DES

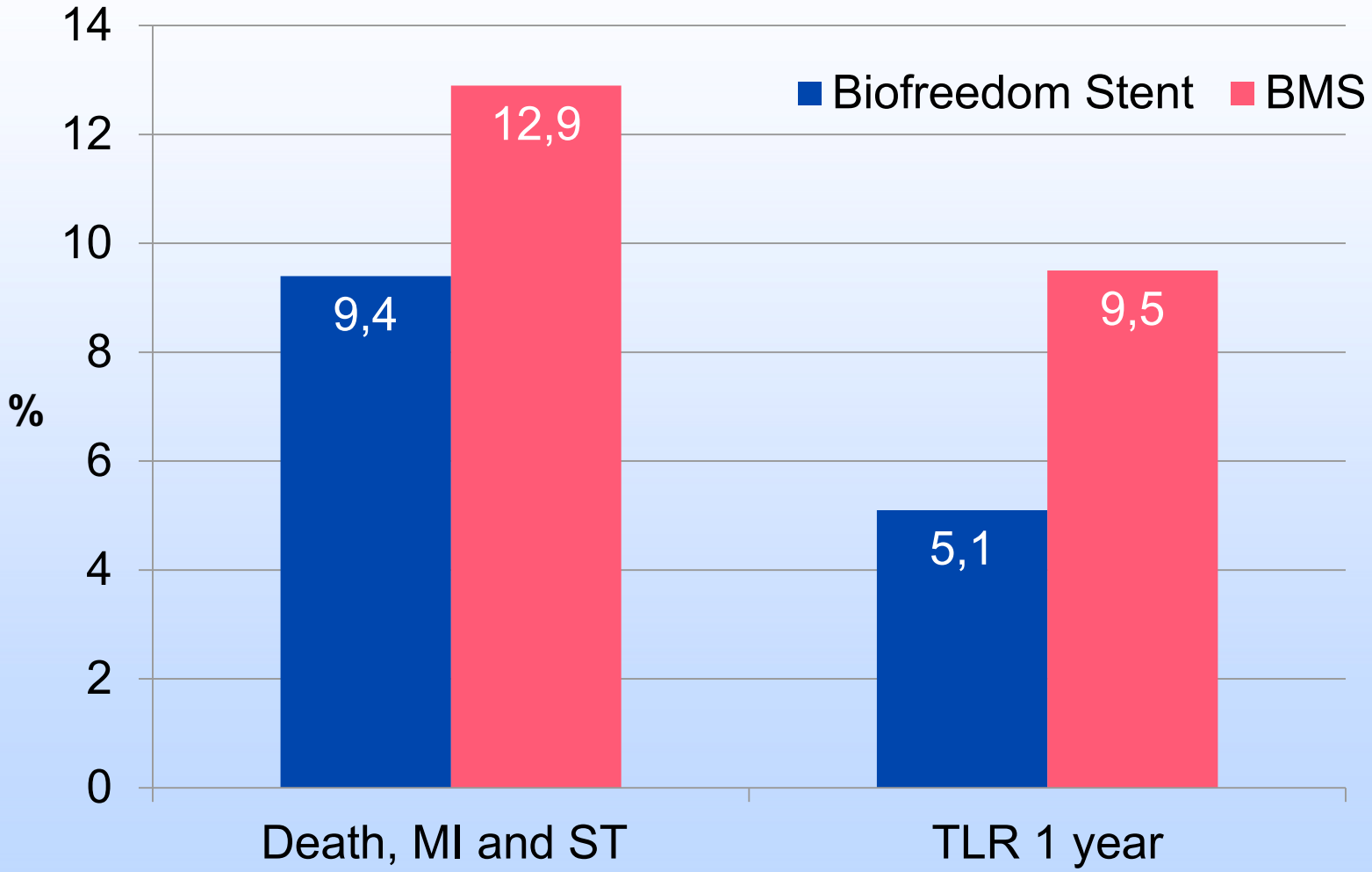
2G DES
better and **safer**
than BMS

Reduction in
restenosis, stent thrombosis, MI and death

Sarno G: EHJ 2012; Palmerini T: Lancet 2012; Bangalore S: BMJ 2013;
Femi R: Circ Cardiovasc Interv 2014

MAYO CLINIC

LEADERS-FREE Trial Results



Urban P: NEJM 2015

MAYO CLINIC

Implications for Clinical Practice

Challenges practice of preferential use of BMS in patients with high bleeding risk or in those with need for short duration of DAPT

Applicable to current 2G DES (everolimus-eluting stents)?

MAYO CLINIC

MAYO CLINIC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease

K.H. Bønaa, J. Mannsverk, R. Wiseth, L. Aaberge, Y. Myreng, O. Nygård, D.W. Nilsen, N.-E. Kløw, M. Uchto, T. Trovik, B. Bendz, S. Stavnes, R. Bjørnerheim, A.-I. Larsen, M. Slette, T. Steigen, O.J. Jakobsen, Ø. Bleie, E. Fossum, T.A. Hanssen, Ø. Dahl-Eriksen, I. Njølstad, K. Rasmussen, T. Wilsgaard, and J.E. Nordrehaug, for the NORSTENT Investigators*

NORSTENT Results at 6 years

Endpoint	DES	BMS	P value
Primary: MI or death	16.8%	17.1%	0.66
Secondary: Repeat revascularization	16.5%	19.8%	<0.001
Definite stent thrombosis	0.8%	1.2%	0.0498

Bonaa KH: NEJM 2016

MAYO CLINIC

NORSTENT Commentary

60% of all PCI procedures 2008-11 and > 72% of eligible patients were randomized

Caveats

- Open label design
- Relatively young patients (median 62.6 yrs.)
- Only 12% had diabetes mellitus
- Clopidogrel for 9 months in both groups

MAYO CLINIC

NORSTENT Conclusions and Implications

Continued advances in PCI in both BMS and DES technology with improved efficacy and safety

Parity in death and MI with DES and BMS

2G DES better than BMS in decreasing target lesion revascularization by decreasing restenosis and stent thrombosis: NNT = 30

BMS reasonable and safe when needed

- caution extrapolating if <9 months clopidogrel (e.g. in patients at high risk of bleeding)

MAYO CLINIC

bell.malcolm@mayo.edu