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Content

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REVIEW

Advances in Clinical Cardiology 2021: A Summary of Key Clinical Trials

Patrick Savage · Brian Cox · Katie Linden · Jaimie Coburn · Michael Shahmohammadi · Ian Menown

MORE NEJM

Advances in Clinical Cardiology 2021:

Key Summary Points

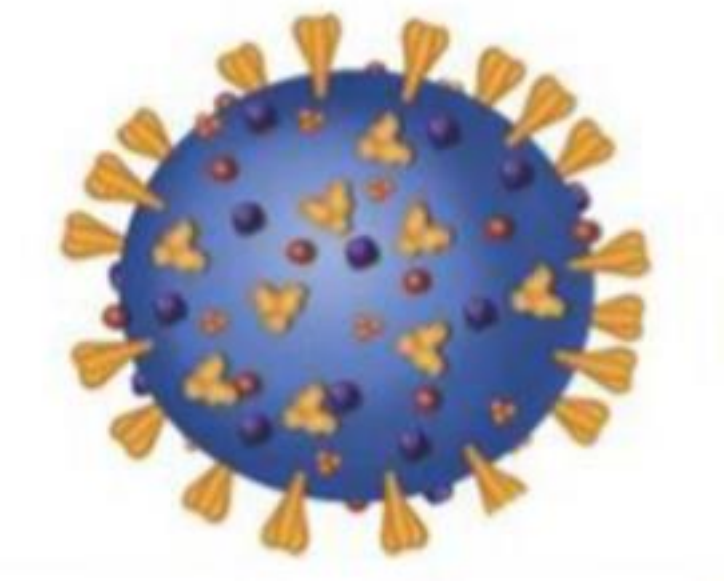
A concise summary of 150 key cardiology trial presented at major international conferences during 2021.

Updates across the spectrum of cardiology including interventional and structural, acute coronary syndromes, antiplatelet therapies, electrophysiology, atrial fibrillation, preventative therapies, and heart failure.

- American College of Cardiology (ACC)
- European Society of Cardiology (ESC)
- American Heart Association (AHA)
- European Heart Rhythm Association (EHRA)
- European Association for Percutaneous Cardiovascular Interventions (EuroPCR)
- Transcatheter Cardiovascular Therapeutics (TCT)
- Society for Cardiovascular Angiography and Interventions (SCAI)
- TVT-The Heart Summit (TVT)
- Cardiovascular Research Technologies (CRT).

Clinically relevant trials with potential to impact and change current practice.

Impacto COVID19:



COVID-19 STEMI

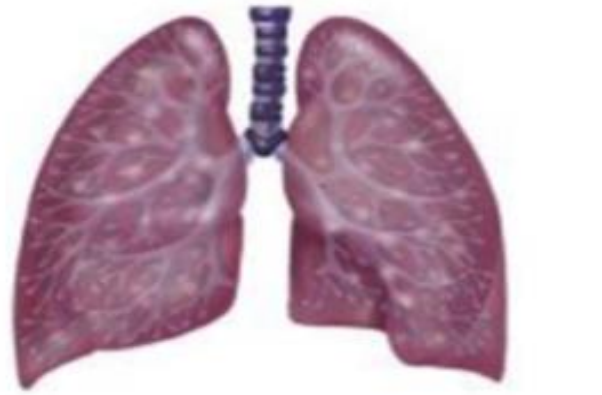
(Initial findings on North American COVID-19 myocardial infarction registry)

COVID Positive Patients (n = 230)

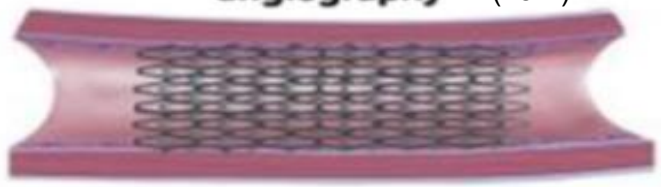
PUI (n = 495)
* suspected positive but subsequently tested negative for COVID-19

Age- and Sex-Matched Control (n = 460)

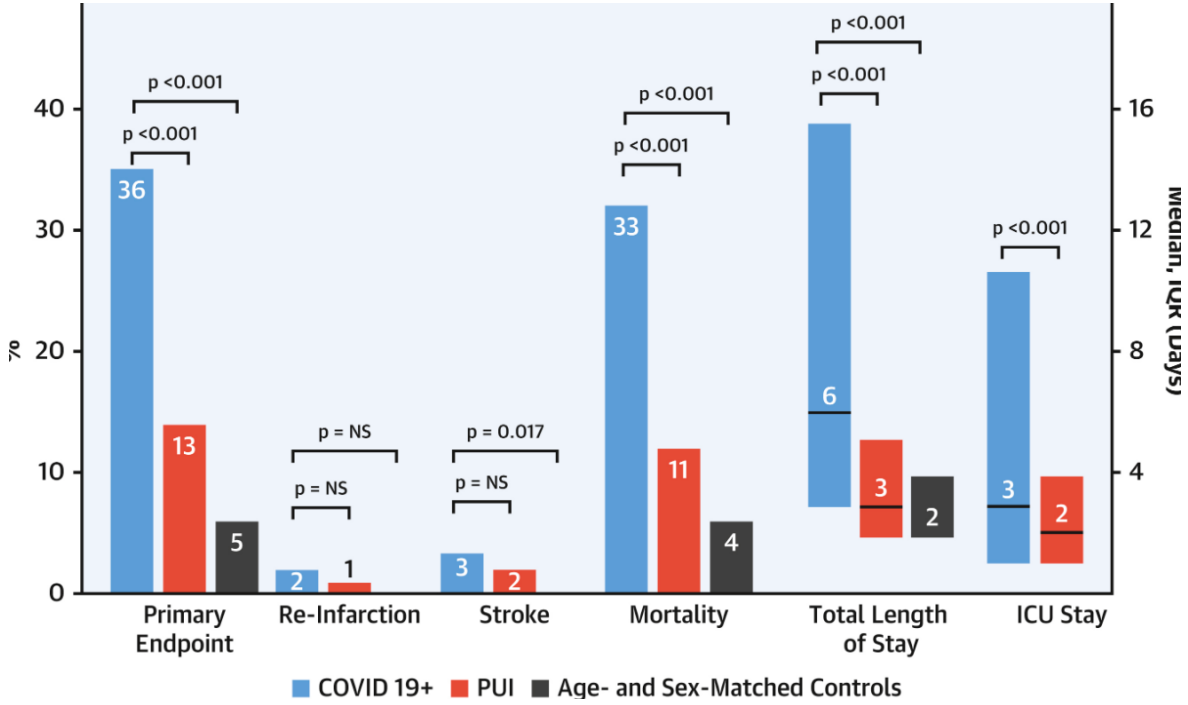
Presentation
Cardiogenic Shock (18%)
Pulmonary Infiltrates (46%)
Dyspnea (54%)



Less likely to receive invasive angiography (78%)



Primary endpoint: composite of in-hospital death, stroke, recurrent myocardial infarction (MI), or unplanned revascularization.



2. Garcia S, Dehghani P, Grines C, et al. Initial findings from the North American COVID-19 myocardial infarction registry. J Am Coll Cardiol. 2021;77(16): 1994–2003. https://doi.org/10.1016/j.jacc.2021.02.055.

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COVID Y SCA:

Question:

The association of COVID with myocardial injury and troponin release is well documented; however, its relative impact on survival is not well understood.

Methods: Retrospective analysis of troponin levels of 4695 patients, 72 h before and 48 h after testing positive for COVID-19.

Results: RISK OF DEATH:

- acutely elevated troponin (47.3% HR 4.72, 95% CI 4.15–5.36)
- chronic myocardial injury (43.0%; HR 4.17, 95% CI 3.44–5.06)
- worse prognostic:
  - if patients < 65 years (p = 0.043)
  - or did not have CAD (p = 0.041)

this data suggests a role for troponin analysis in COVID-19 with regards to risk stratification and prognostication.

71. Kini A, Cao D, Nardin M, et al. Types of myocardial injury and mid-term outcomes in patients with COVID-19. Eur Heart J Qual Care Clin Outcomes. 2021;7(5):438–46. https://doi.org/10.1093/ehjqcco/qcab053.

Miocarditis tras vacunacion COVID19

Initial reports suggested an association between messenger RNA (mRNA) COVID-19 vaccines and the development of myocarditis.

- A recent review of a large Israeli healthcare database of 2.5 million patients: BNT162b2 vaccine (Pfizer)
  - estimated incidence of post-vaccine myocarditis of 2.13 cases per 100,000.
- The highest incidence was reported in male patients between the ages of 16 and 29 years (10.69 cases per 100,000 persons)
- Most cases were classified as mild (76%) and only one case was associated with cardiogenic shock.

These data are reassuring that myocarditis remains rare and mild for the majority of patients affected

70. Witberg G, Barda N, Hoss S, et al. Myocarditis after Covid-19 vaccination in a large health care organization. N Engl J Med. 2021;385(23):2132–9.

Myocarditis after BNT162b2 Vaccination in Israeli Adolescents

A total of 9 cases were adjudicated as probable or definite myocarditis
incidence of 4.8 cases per 100,000 persons
8 cases occurred after the second vaccine dose
All cases of myocarditis were classified as mild,

4 Abnormal electrocardiographic (ECG) results
cardiac and inflammatory markers were elevated in all
median duration of admission was 3 days
Eight patients had a normal ejection fraction
four had a pericardial effusion.

Echocardiographic after hospital discharge (median interval, 10 days).

All echocardiograms showed a normal ejection fraction and resolution of pericardial effusion

Five patients underwent cardiac magnetic resonance imaging with minimal evidence of myocardial scarring or fibrosis,

At a median follow-up of 206 days none had been readmitted to the hospital.

Conclusions: rare adverse event that occurs predominantly in males after the second vaccine dose. The clinical course appears to be mild and benign

Guy Witberg, M.D., M.P.H.
Rabin Medical Center, Petah Tikva, Israel
October 19, 2022
DOI: 10.1056/NEJMc2207270

INFUENZA VACCINATION IN MI

The IAMI (Influenza Vaccination After Myocardial Infarction

Methods:

- double-blind placebo-controlled trial randomising post-MI patients to receive:
  influenza vaccine on discharge (n = 1272)
  or placebo (n = 1260).
- Primary endpoint at 12 months: all-cause death, MI or stent thrombosis

Results:

occurred in 67 (5.3%) with vaccine
vs. 91 (7.2%) with placebo (HR 0.72 [95% CI 0.52–0.99]; p = 0.040).

(the trial was stopped early because of the COVID pandemic and thus may be underpowered)
it still supports a benefit of adding influenza vaccination to standard care in this patient group.

72. Fröbert O, Götberg M, Erlinge D, et al. Influenza vaccination after myocardial infarction: a randomised, double-blind, placebo-controlled, multicenter trial. Circulation. 2021.

Interventional cardiology

Debate about Stable CAD: PCI strategy + medical therapy vs. medical therapy alone

- Extensive meta-analysis of 25 trials involving 19,806 patients PCI+Medical Therapy:

- lower risk of spontaneous MI (RR 0.74; p <0.01)
- lower risk of cardiac death (relative risk (RR) 0.79; p <0.01)
- No significant difference in

all-cause mortality (RR 0.94; p = 0.11)

19. Naverese EP, Lansky AJ, Kereiakes DJ, et al. Cardiac mortality in patients randomised to elective coronary revascularisation plus medical therapy or medical therapy alone: a systematic review and meta-analysis. Eur Heart J. 2021;42(45):4638–51. https://doi.org/10.1093/eurheartj/ehab246.

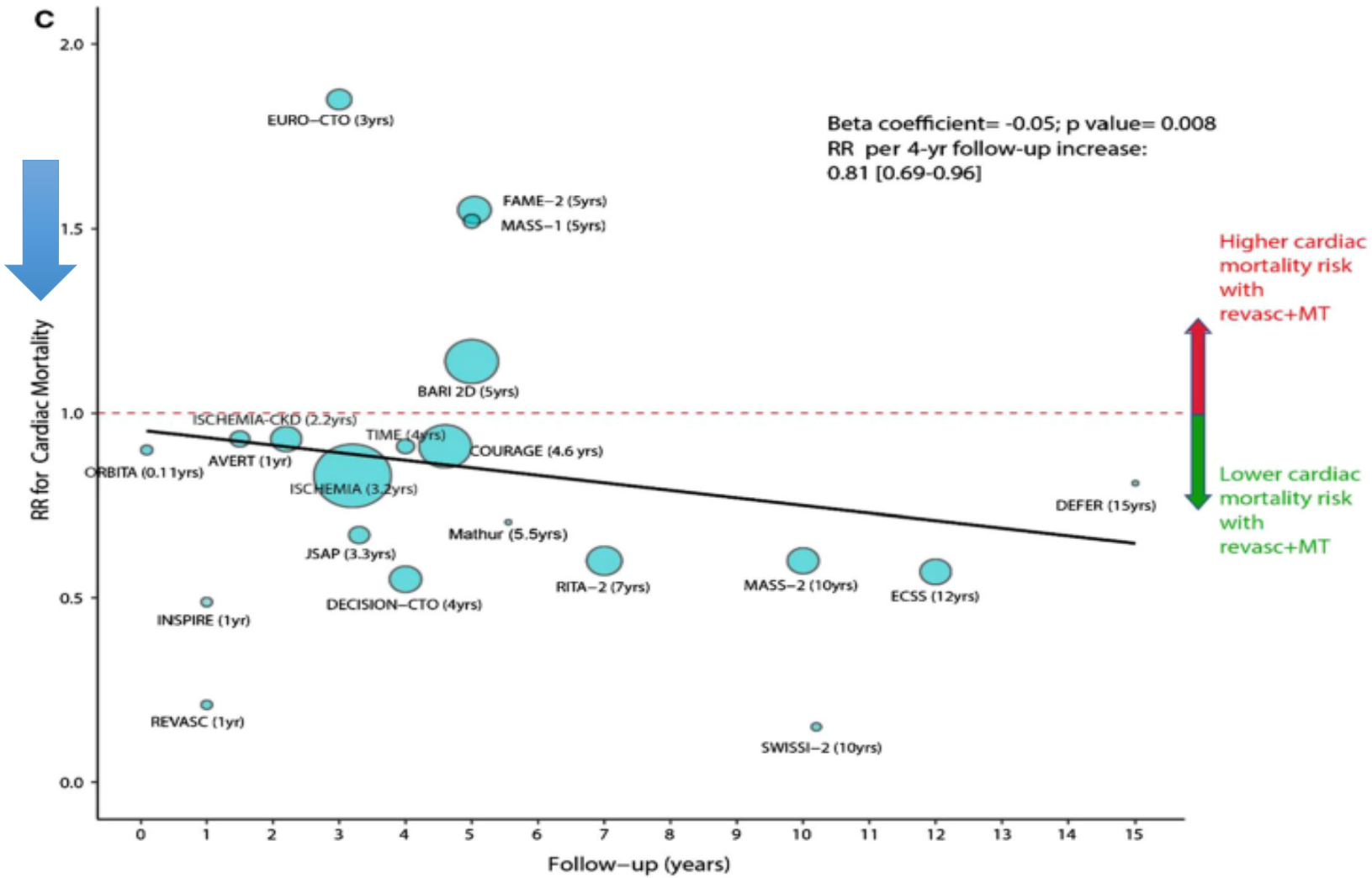

Fig. 2 Figure demonstrating meta-regression of rate ratios for cardiac mortality with revascularisation plus medical therapy vs. medical therapy alone in relation to follow-up duration. The size of the data markers is proportional to the size of trial. Rate ratios lower than 1 indicate cardiac death reduction with revascularisation. The solid line represents the meta-regression slope of the change in cardiac death rate ratio for revascularisation plus medical therapy vs. medical therapy alone with increasing length of follow-up. Reproduced with permission from the *European Heart Journal* (Naverese et al. [19])

While the findings were encouraging, conclusions remain guarded since the meta-analysis included studies dating back to 1979 (when medical therapy was less than optimal).

PCI for Ischemic Left Ventricular Dysfunction

KEY POINTS FROM

Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction

by D. Perera et al.

OCTOBER 13, 2022

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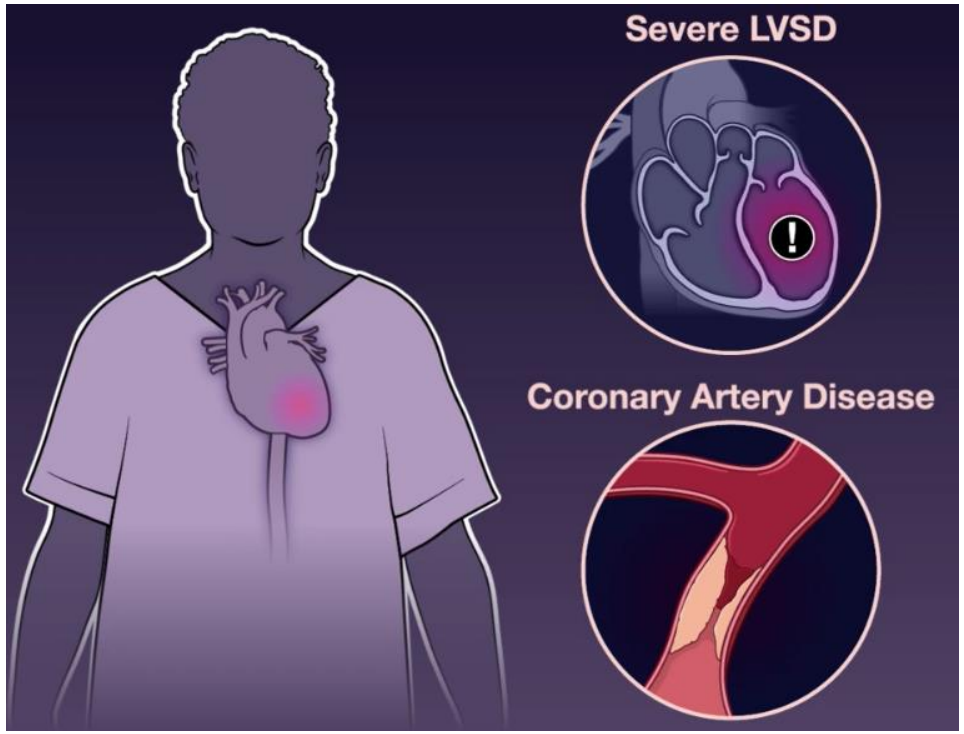
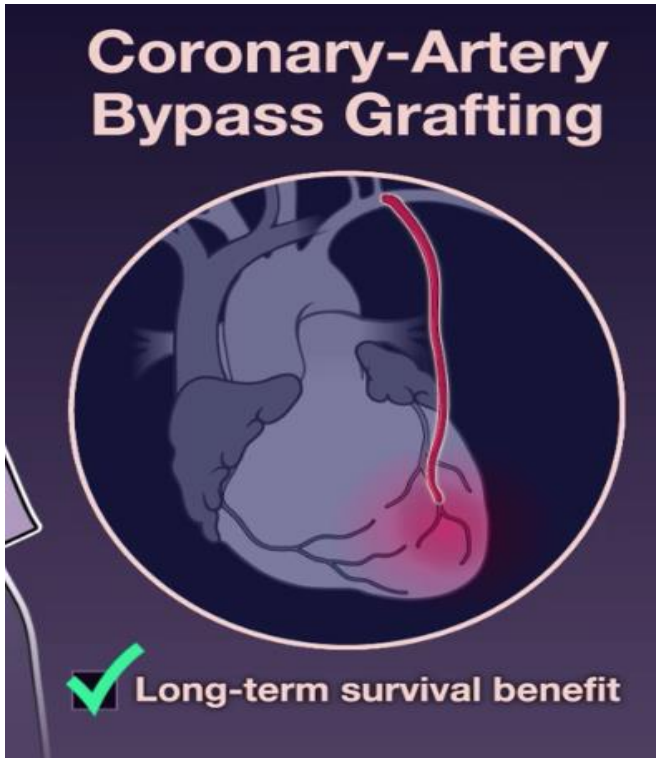

Severe LVSD
Coronary Artery Disease

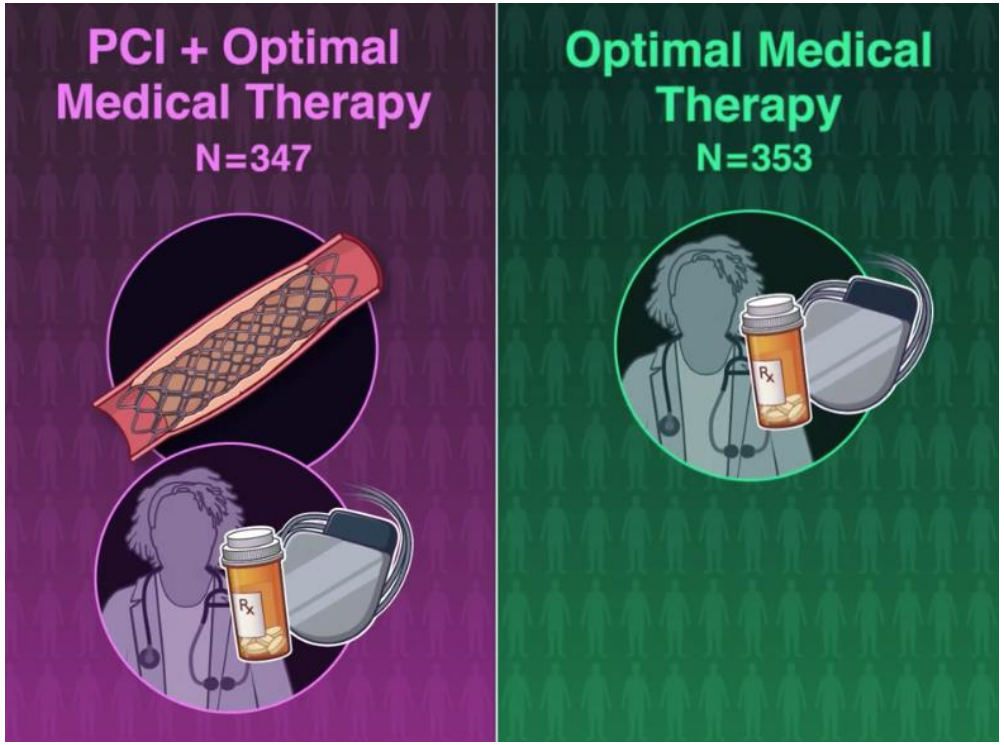

Coronary-Artery Bypass Grafting
Long-term survival benefit

REVIVED Trial

- Prospective
- Multicenter
- Randomized
- Open-label

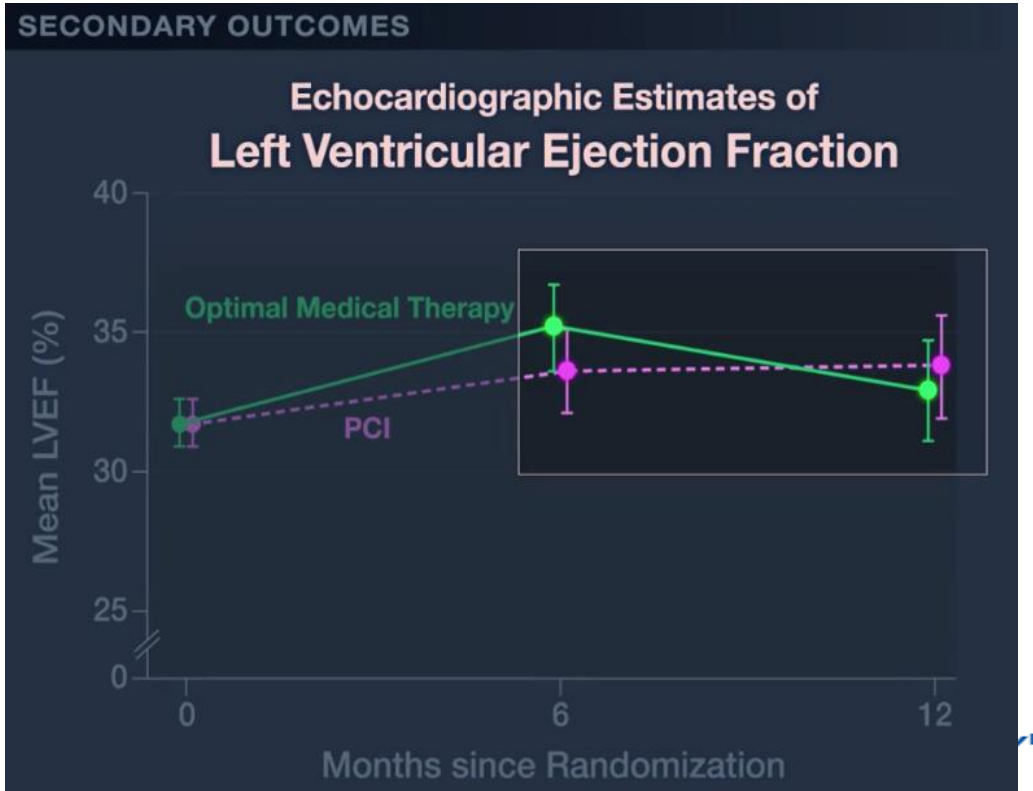
700 Patients

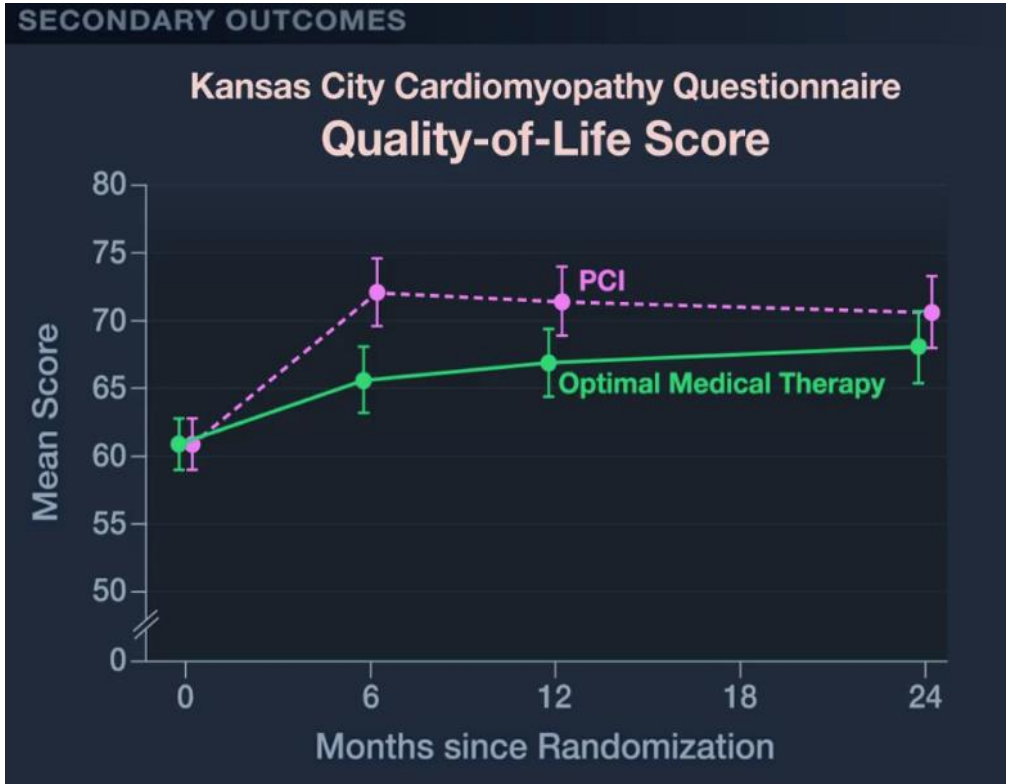
- Left ventricular ejection fraction of ≤35%
- Extensive coronary artery disease
- Viability in ≥4 dysfunctional myocardial segments

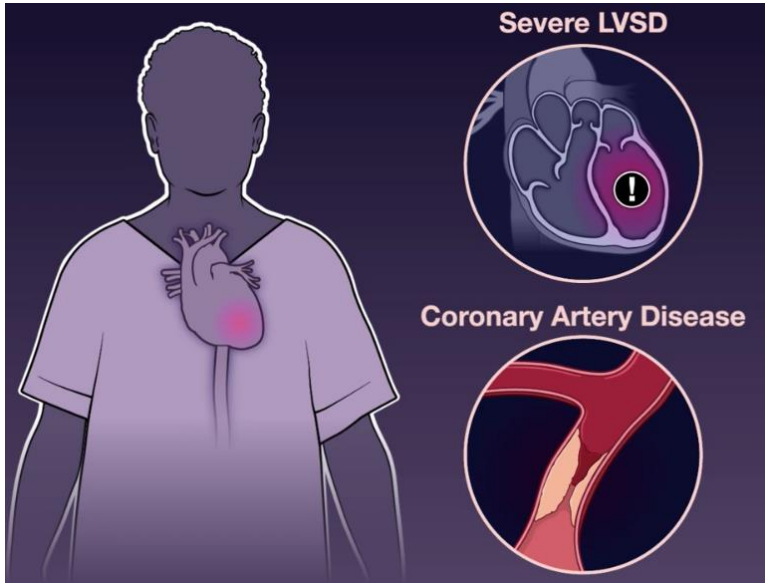

PCI + Optimal Medical Therapy
N=347
Optimal Medical Therapy
N=353
Rx
Rx

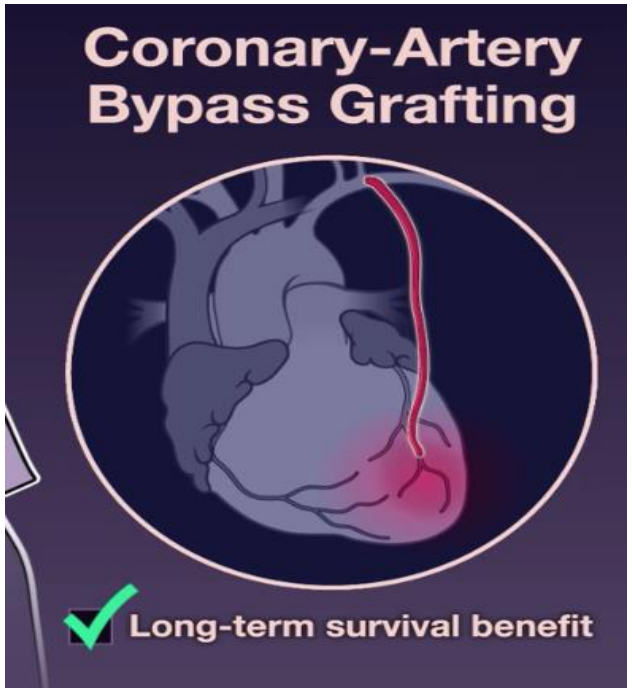

Primary Composite Outcome
RIP
HOSPITAL
YEAR 1
YEAR 2
≥24 Mo of follow-up


PRIMARY COMPOSITE OUTCOME
Death from Any Cause or Hospitalization for Heart Failure
Percentage of Patients
100
80
60
40
20
0
Hazard Ratio, 0.99
95% CI, 0.78 to 1.27
P=0.96
37
38
PCI
N=347
Optimal Medical Therapy
N=353


SECONDARY OUTCOMES
Echocardiographic Estimates of
Left Ventricular Ejection Fraction
Mean LVEF (%)
40
35
30
25
0
Optimal Medical Therapy
PCI
0
6
12
Months since Randomization


SECONDARY OUTCOMES
Kansas City Cardiomyopathy Questionnaire
Quality-of-Life Score
Mean Score
80
75
70
65
60
55
50
0
PCI
Optimal Medical Therapy
0
6
12
18
24
Months since Randomization


Severe LVSD
Coronary Artery Disease


Coronary-Artery Bypass Grafting
Long-term survival benefit

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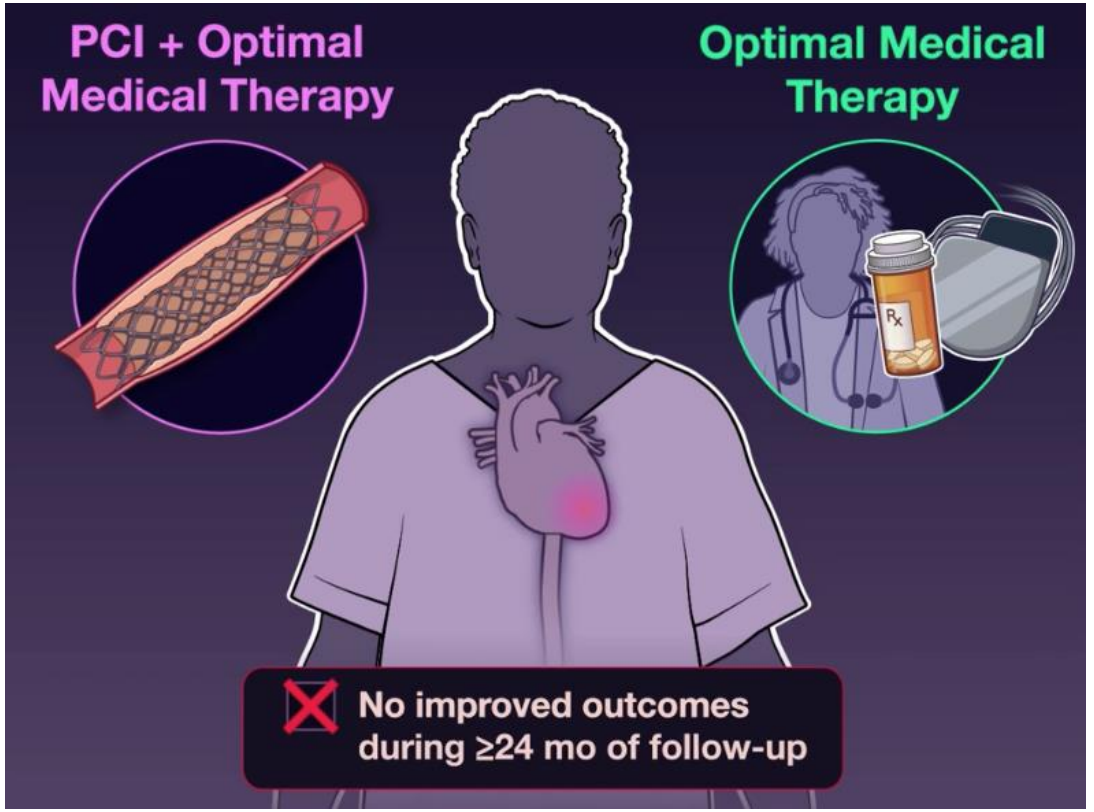
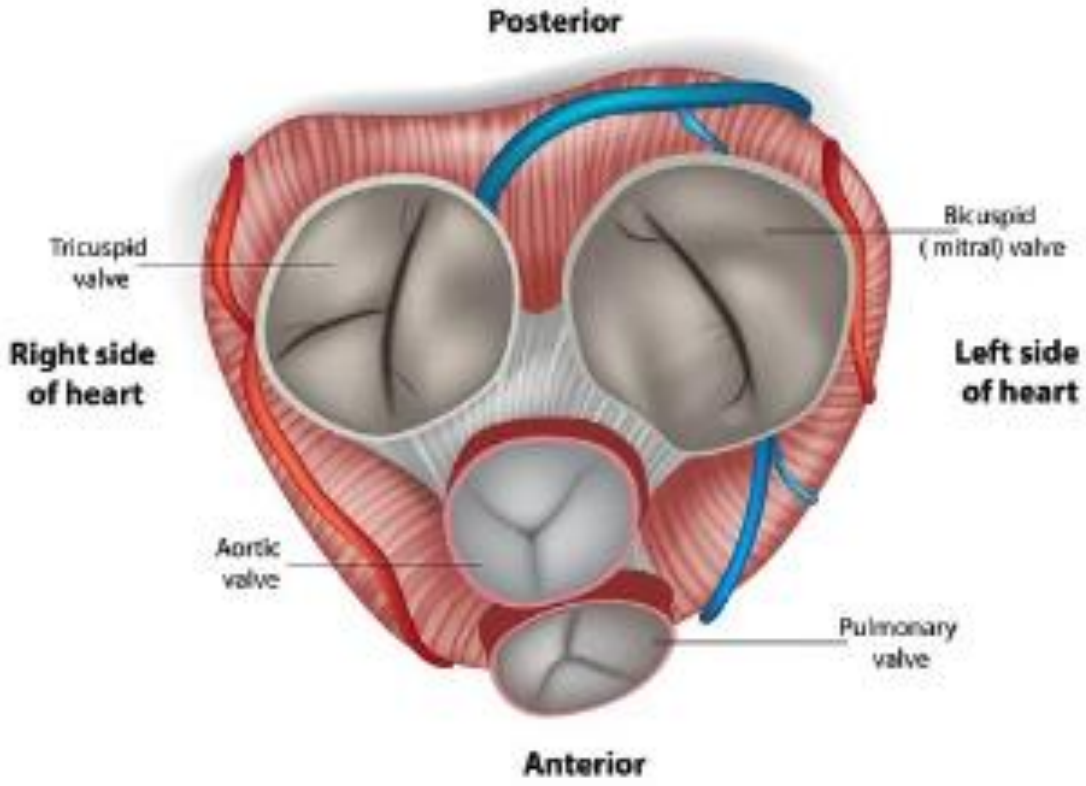

PCI + Optimal Medical Therapy
Optimal Medical Therapy
Rx
No improved outcomes during ≥24 mo of follow-up

Valvulopatias



Aortic Stenosis:

Asymptomatic severe AS with preserved left ventricular (LV) function:

Current guidance:

watchful waiting prior to intervening

1. Kearney A, Linden K, Savage P, Menown IBA. Advances in clinical cardiology 2020: a summary of key clinical trials. Adv Ther. 2021;38(5):2170–200.

Aortic Stenosis:

transcatheter aortic valve replacement (TAVR)

- AVATAR (Aortic Valve ReplAcemenT vs Conservative Treatment in Asymptomatic SeveRe Aortic Stenosis)
  - multicentre randomised trial
  - N=157 patients (mean 67 years, 43% female)
  - early surgery (n = 78) vs. conservative therapy (n = 79).

At 32 months,

- reduction composite primary outcome of all cause death, heart failure, acute MI or stroke:

15.2% vs. 34.7%; p = 0.02)

This signals that early intervention in asymptomatic severe AS may confer a mortality benefit.

39. Banovic M, Putnik S, Penicka M, et al. Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: The avatar trial [published correction appears in Circulation. 2022 Mar;145(9):e761]. Circulation. 2022;145(9):648–658. https://doi.org/10.1161/CIRCULATIONAHA.121.057639.

Aortic Stenosis:

Transcatheter aortic valve replacement (TAVR) self-expanding supraannular bioprosthesis

EVOLUT Low risk trial reported no difference with surgery in the primary outcome of death or disabling stroke at 24 months (1.9% in TAVI vs. 2.1% surgical aortic valve replacement (SAVR); p = 0.742).

(Follow-up to 10 years is planned)

1. Kearney A, Linden K, Savage P, Menown IBA. Advances in clinical cardiology 2020: a summary of key clinical trials. Adv Ther. 2021;38(5):2170–200.

Aortic Stenosis:

https://youtu.be/f20qrZcD1LE

cost analysis versus surgery of 1000 patients undergoing TAVI with the SAPIEN 3 device (PARTNER 3)

- TAVI resulted in shorter:
  - procedure duration (mean 59 vs. 208 min),
  - hospitalisation (mean 1.9 vs. 6.5 days)
  - intensive care unit (ICU) time (mean 0.8 vs. 2.7 days)

Edwards Sapien 3

- hospitalization costs for both TAVI and surgery were comparable ($47,196 vs. $46,606; p = 0.59), largely driven by the TAVR device costs.
- At 2 years there was a notably lower cost in the TAVI group, driven by reduction in follow-up costs vs. SAVR ($19,638 vs. $22,258; p = 0.13).

As more devices enter the market and costs fall as a result of competition, it is possible this cost divergence will grow

40. Cohen DJ. Economic outcomes of TAVR vs. SAVR for low-risk patients: results from the PARTNER 3 trial. Presented at TCT 2021, Orlando, 5 Nov 2021.

Aortic Stenosis,

Current guidance:

Asymptomatic severe AS with preserved left ventricular (LV) function:

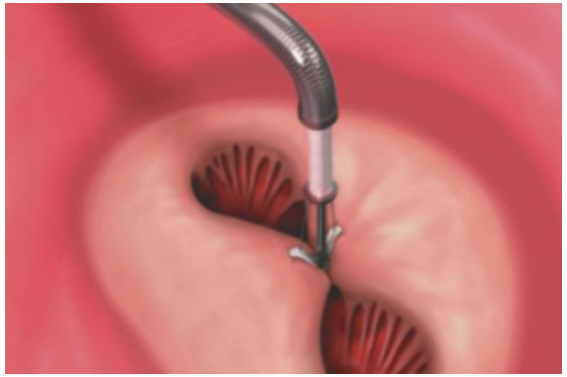
watchful waiting prior to intervening

- the updated 2021 European Society Cardiology (ESC) guidelines released this year have recommended:
  - intervention in patients with asymptomatic severe AS with LV dysfunction (without another cause), IIb recommendation
  - patients over the age of 75 years are offered TAVI in preference to SAVR.

1. Kearney A, Linden K, Savage P, Menown IBA. Advances in clinical cardiology 2020: a summary of key clinical trials. Adv Ther. 2021;38(5):2170–200.

Mitral insufiency:

transcatheter mitral valve (TCMV) repair with the Abbot MitraClip



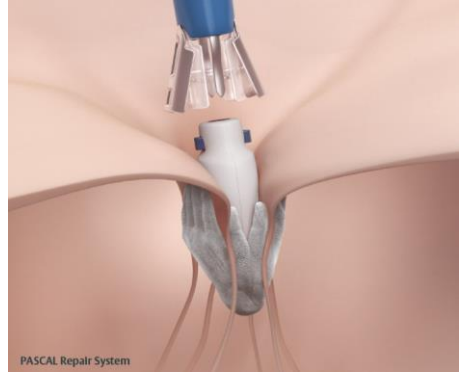
- COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation)

- previously demonstrated that in moderate-to-severe or severe secondary mitral regurgitation (MR) refractory to medical therapy was superior to medical therapy alone

1. Kearney A, Linden K, Savage P, Menown IBA. Advances in clinical cardiology 2020: a summary of key clinical trials. Adv Ther. 2021;38(5):2170–200.

Mitral insufiency:

Edwards PASCALTM transcatheter valve repair system in severe symptomatic MR



The single-arm CLASP (Edwards PASCAL TrAnScatheter Mitral Valve RePair System Study) feasibility study sought to assess the safety and efficacy of the (functional and degenerative severe symptomatic MR).

1-year data: 92% survival and 88% free from heart failure hospitalisation

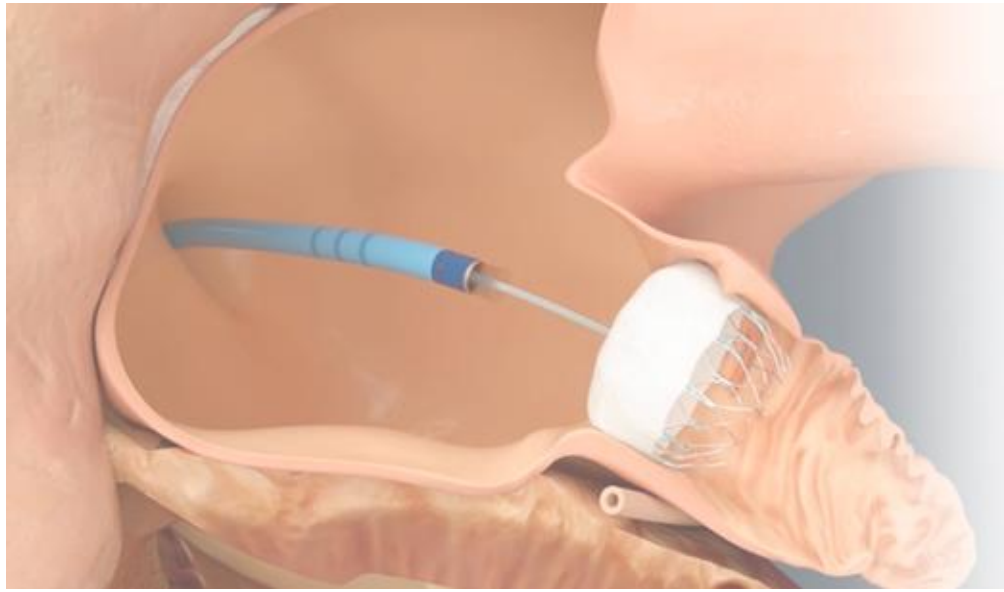
CLASP2: 2-year outcomes from reported an 80% survival rate with 84% free from heart failure hospitalisations.

Optimal device strategy remains unclear and the results of the head-to-head trial between the Abbot and Edwards devices are awaited in the CLASP IID/ IIF trial.

51. Szerlip M, Spargias KS, Makkar R, et al. 2-year outcomes for transcatheter repair in patients with mitral regurgitation from the CLASP study. JACC Cardiovasc Interv. 2021;14(14):1538–48. https://doi.org/10.1016/j.jcin.2021.04.001.

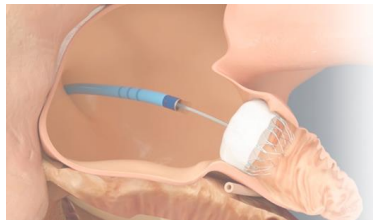
Atrial Fibrilation: Watchman procedure

- left atrial appendage closure (LAA) device (Watchman procedure), Boston Scientific) was approved by the US Food and Drug Administration (FDA), 2015, PROTECT AF and PREVAIL study



62. Price MJ. 1-year clinical outcomes following Watchman transcatheter LAAO for stroke prevention in patients with atrial fibrillation: a report from the NCDR LAAO Registry. Presented at: ACC Virtual 2021. May 15, 2021.

Watchman



National Cardiovascular Data Registry (NCDR) LAA, data first 3-year (2016–18), presented at ACC21 last year:

- 36,681 patients (mean age 76 years; 59% men).
- Mean CHA2DS2-VASc score was 4.8 (SD 1.5)
- mean HAS-BLED score was 3.0 (SD 1.1)
- 69.5% having experienced prior clinically relevant bleeding.

- Stroke rate at 1 year was low at 1.53%, demonstrating a much lower rate (77% less) than would be expected in this high-risk population
- Bleeding rates 6.2%
- All-cause mortality of 8.52%,

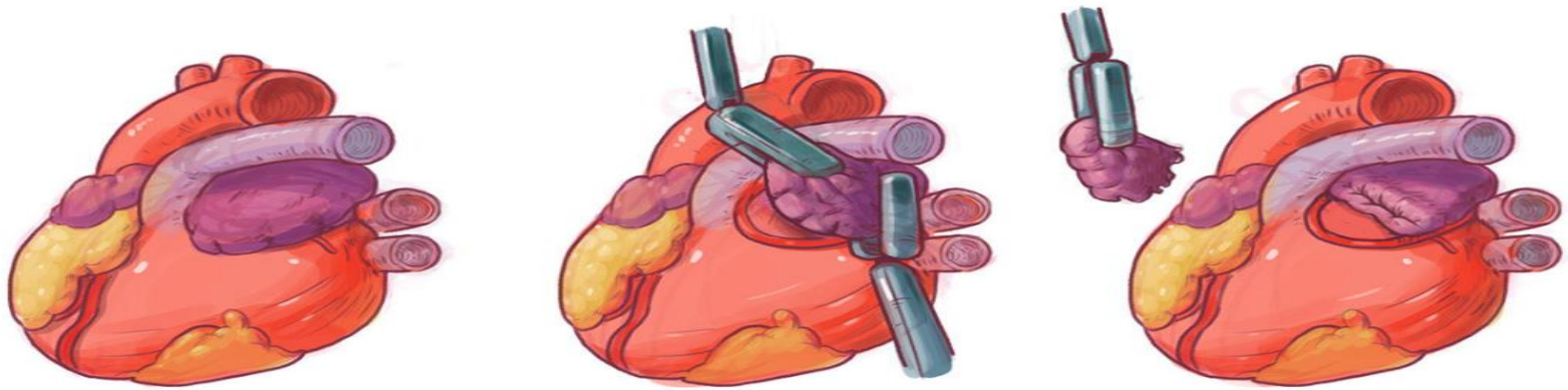
demonstrated favourable procedural success and complication rates:

62. Price MJ. 1-year clinical outcomes following Watchman transcatheter LAAO for stroke prevention in patients with atrial fibrillation: a report from the NCDR LAAO Registry. Presented at: ACC Virtual 2021. May 15, 2021.

Catheter-Based Left Atrial Appendage Closure: LAAOS III (Left Atrial Appendage Occlusion Study III)

- 4811 patients
- 105 centres
- 27 countries

- Mean age 67
- AF and elevated risk of stroke (CHADsVasc 4,2)
- undergoing open-heart surgery for another indication to surgical LAAC vs. no LAAC.



68. Whitlock RP, Belley-Cote EP, Paparella D, et al. Left atrial appendage occlusion during cardiac surgery to prevent stroke. N Engl J Med. 2021;384(22): 2081-91. https://doi.org/10.1056/NEJMoa2101897.

Catheter-Based Left Atrial Appendage Closure: LAAOS III (Left Atrial Appendage Occlusion Study III)

Primary Outcome at 3.8 Years

	LAAO (%)	No LAAO (%)	HR (95% CI)	p-value
Ischemic stroke or systemic embolism	4.8	7.0	0.67 (0.53-0.85)	0.001

OAC usage rates at 3 years were similar between groups (75% vs. 78%) with no significant difference in bleeding between groups noted.

Although not suggestive that LAAO is a replacement to OAC, it does highlight a segmented benefit in stroke risk reduction when added to OAC.

68. Whitlock RP, Belley-Cote EP, Paparella D, et al. Left atrial appendage occlusion during cardiac surgery to prevent stroke. N Engl J Med. 2021;384(22): 2081–91. https://doi.org/10.1056/NEJMoa2101897.

Heart Failure
with Reduced Ejection Fraction (HFrEF)

- The DAPA-HF trial previously reported that the SGLT2 inhibitor dapagliflozin reduced the incidence of CV death and worsening HF in patients with HFrEF. (natriuresis)

127. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008.

- a new analysis reported a significant reduction in the composite of serious ventricular arrhythmia, resuscitated cardiac arrest or sudden death with dapagliflozin vs. Placebo:

(5.9% vs. 7.4%; HR 0.79, 95% CI 0.63–0.99).

128. Curtain JP, Docherty KF, Jhund PS, et al. Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. Eur Heart J. 2021;42(36):3727–38.

Heart Failure
with Reduced Ejection Fraction (HFrEF)

EMPULSE trial (Effect of Empaglifocina on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure With Reduced Ejection Fraction)

530 pt with acute heart failure
Randomised to empagliflozin vs. Placebo

Greater incidence of clinical benefit:

- rates death
- HF events
- time to first HF event
- change in Kansas City Cardiomyopathy Questionnaire-Total Symptom Score (KCCQ-TSS) (53.9% vs. 39.7%; p = 0.0054).

No safety concerns were noted,

126. Voors A. Empagliflozin in patients hospitalised for acute heart failure—EMPULSE. Presented at the American Heart Association Annual Scientific Sessions. Virtual meeting. 14 Nov 2021.

Heart Failure with Reduced Ejection Fraction (HFrEF):

Sacubitril/valsartan in acute miocardial infarct

PARADISE-MI (Prospective ARNI vs. ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction)

BACKGROUND

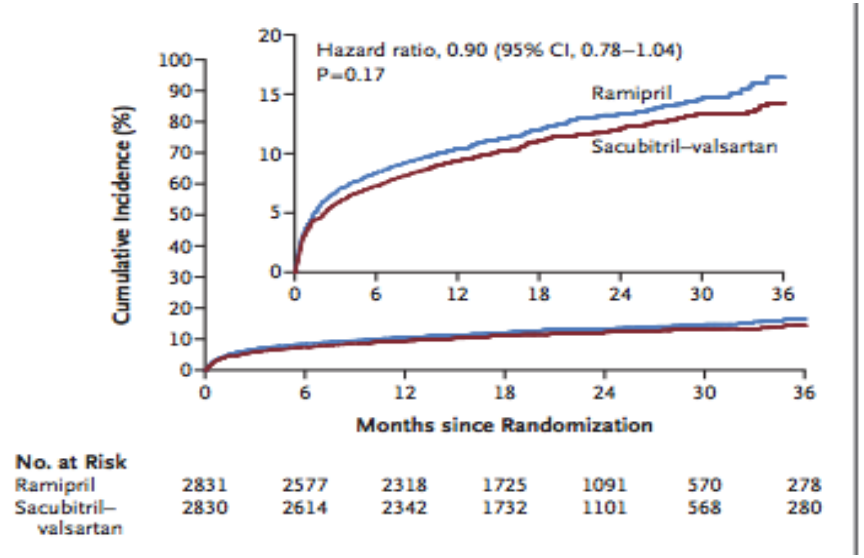
In patients with symptomatic heart failure, sacubitril–valsartan has been found to reduce the risk of hospitalization and death from cardiovascular causes more effectively than an angiotensin-converting–enzyme inhibitor. Trials comparing the effects of these drugs in patients with acute myocardial infarction have been lacking.

Randomisation 5661 patients with acute MI complicated by reduced ejection fraction (< 40%) and/or pulmonary congestion :

2830 patients receive sacubitril/valsartan

- 2831 received ramipril.

The composite endpoint of CV death or HF event occurred in 338 (11.9%) of the sacubitril/valsartan group and 373 (13.2%) of the ramipril group (HR 0.90, 95% CI 0.78–1.04; p = 0.17).



129. Pfeffer MA, Claggett B, Lewis EF, et al. Angiotensin receptor-neprilysin inhibition in acute myocardial infarction. N Engl J Med. 2021;385(20):1845–1855.

Heart Failure with Reduced Ejection Fraction (HFrEF): Sacubitril/valsartan in advanced hearth failure NYHA class IV symptoms

The LIFE study:

N= 335 patients were randomised to receive:
sacubitril/valsartan (n = 167) or valsartan alone (n = 168), followed up for 24 weeks

efficacy was measured by looking at days alive out of hospital and free of HF events

103 days in the sacubitril/valsartan group vs 111 days in the valsartan group (p = 0.45).
No difference in the NT-proBNP in either group vs. baseline.

INTERRETATION: The patients studied in this trial were sicker than previous published work and the results do suggest that the main benefit of this drug may be for patients at an earlier stage in their disease.

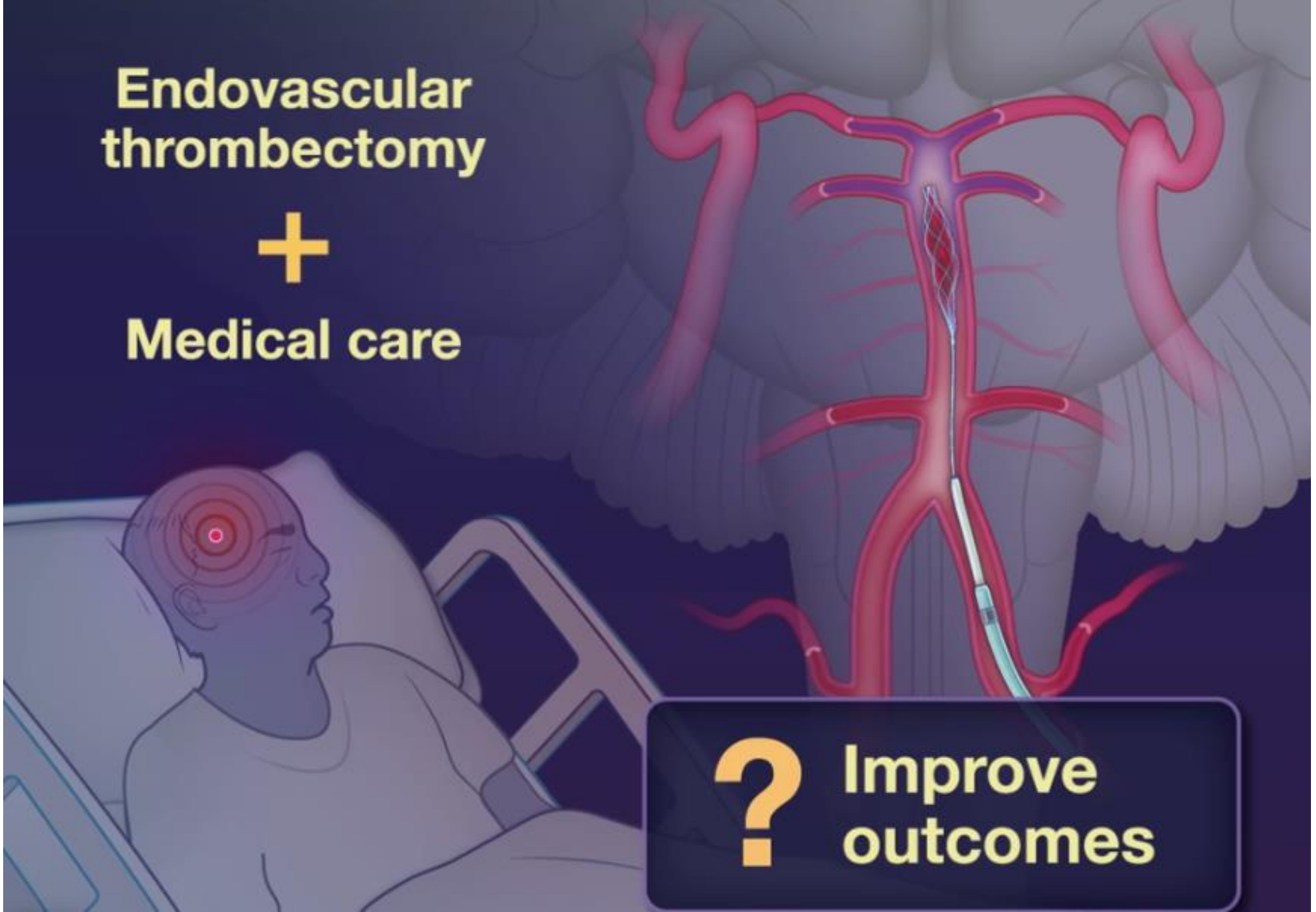
130. Mann DL, Givertz MM, Vader JM, et al. Effect of treatment with Sacubitril/Valsartan in patients with advanced heart failure and reduced ejection fraction: a randomised clinical trial. JAMA Cardiol. 2021;e214567.

- More NEJM…

Trial of Endovascular Treatment of Acute Basilar-Artery Occlusion

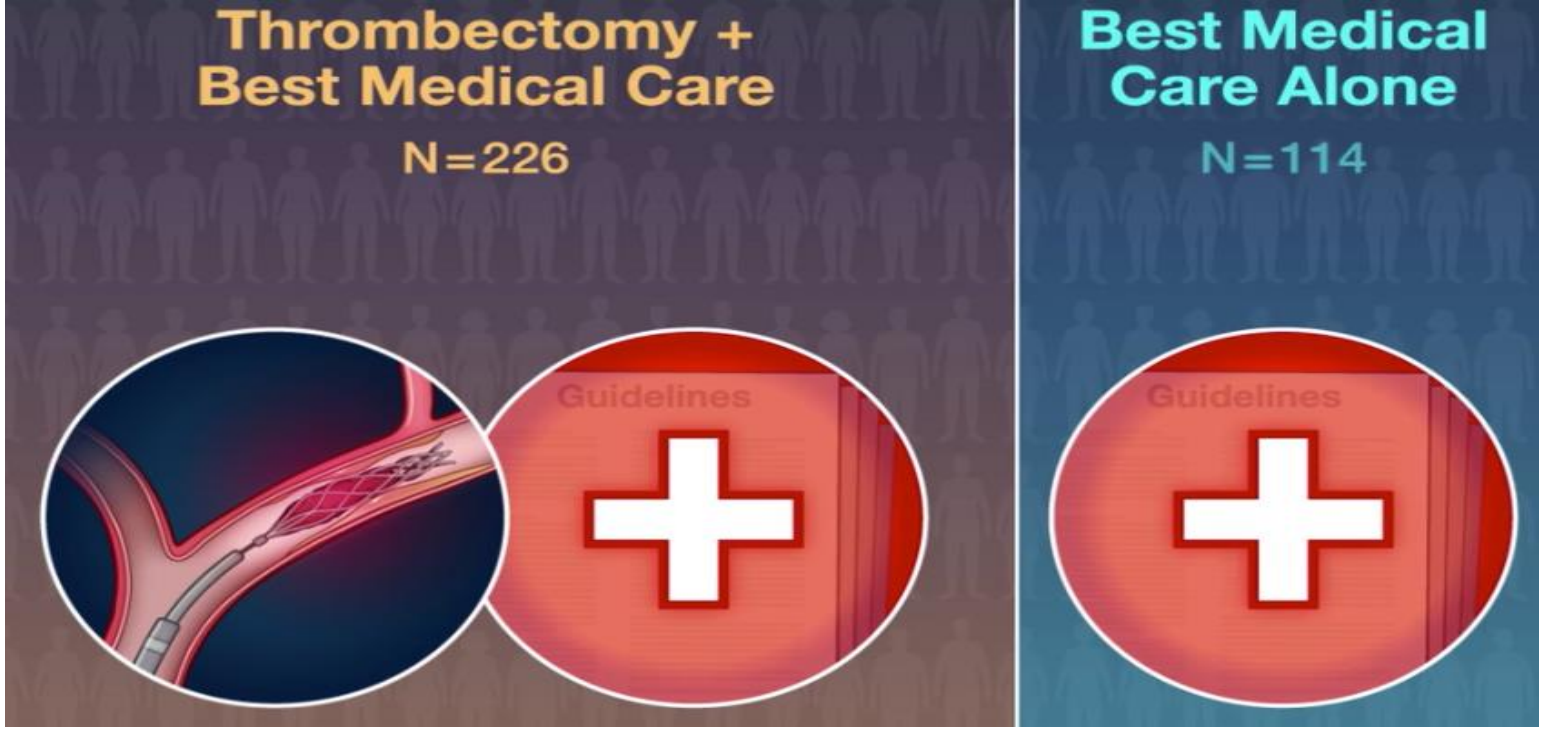
by C. Tao et al.

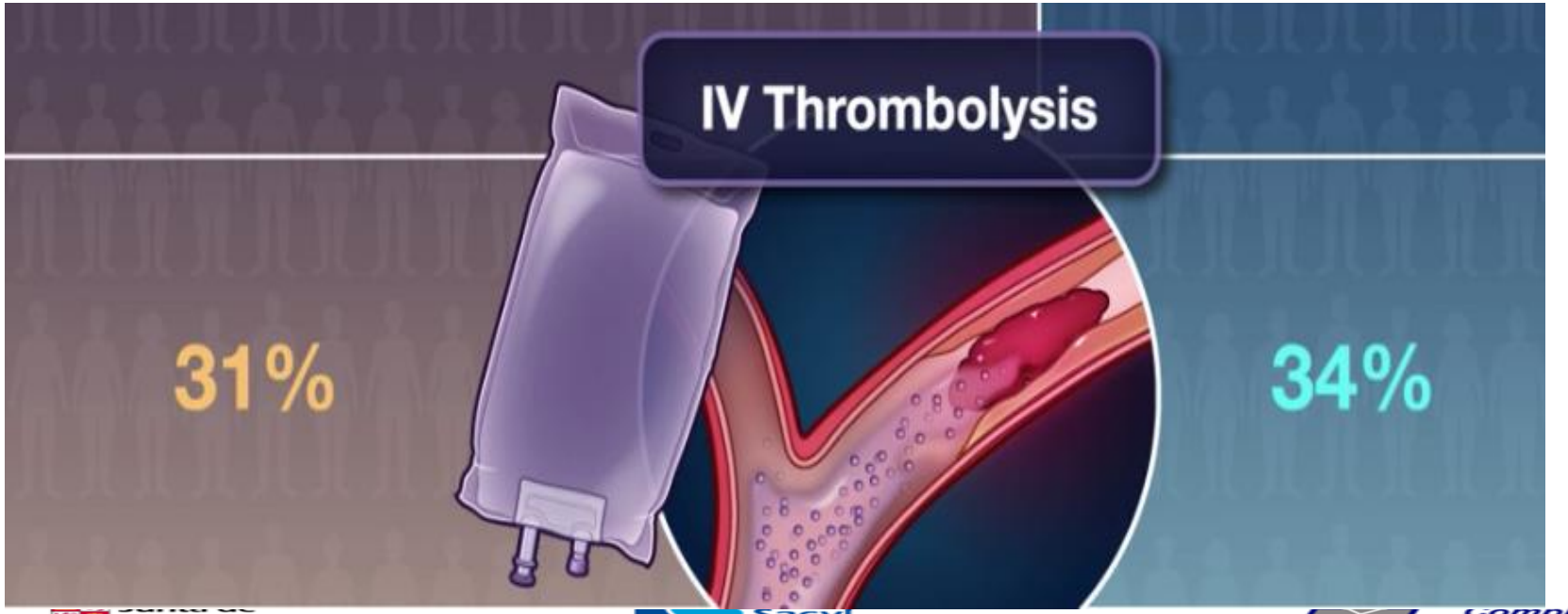
10.1056/NEJMoa2206317


Endovascular thrombectomy
+
Medical care
? Improve outcomes

- Multicenter
- Randomized
- Open-label
- Controlled

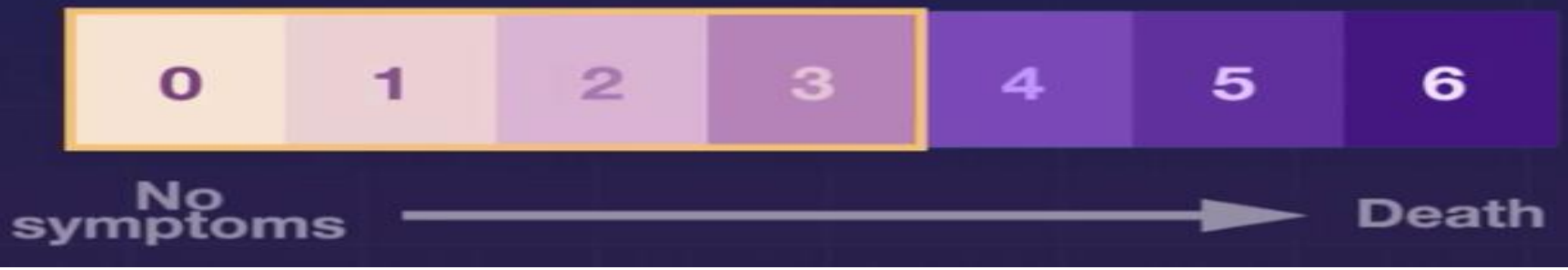
- 340 adults in China
- Moderate or severe ischemic stroke caused by basilar-artery occlusion
- Presented within 12 hours


Thrombectomy +
Best Medical Care
N=226
Guidelines
Best Medical
Care Alone
N=114
Guidelines


IV Thrombolysis
31%
34%

PRIMARY OUTCOME

Good Functional Status at 90 Days: Modified Rankin Scale Score of 0–3

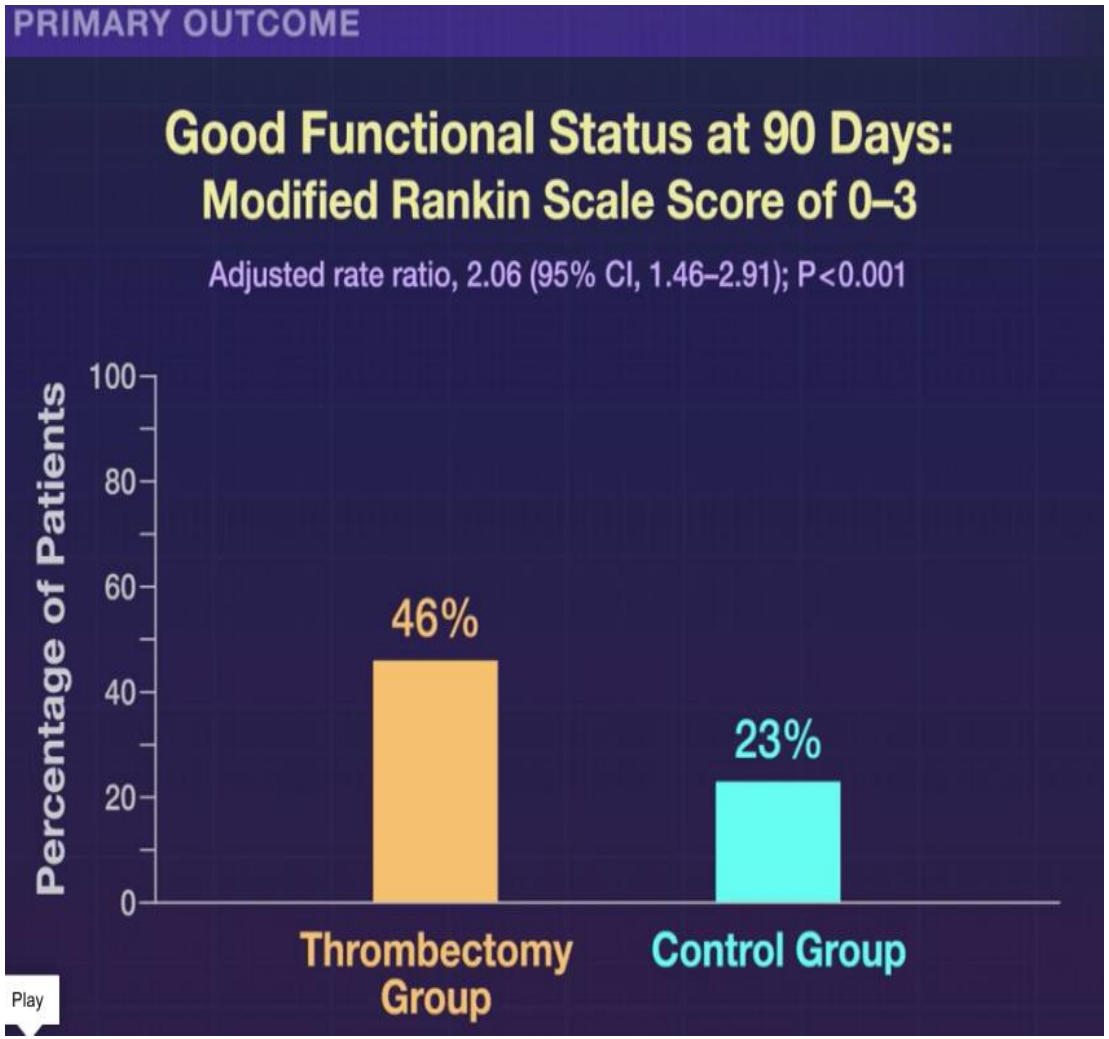


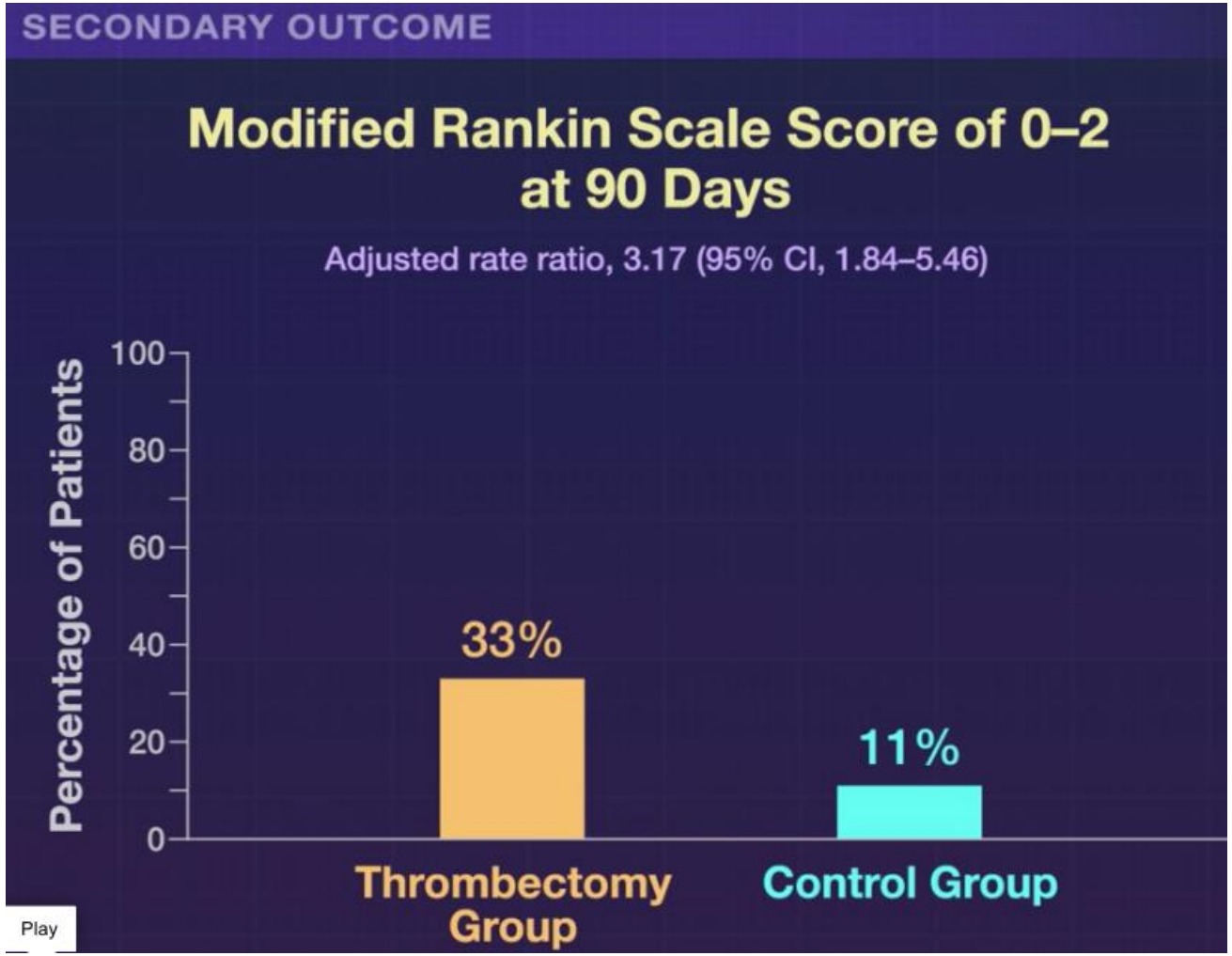
SECONDARY OUTCOME

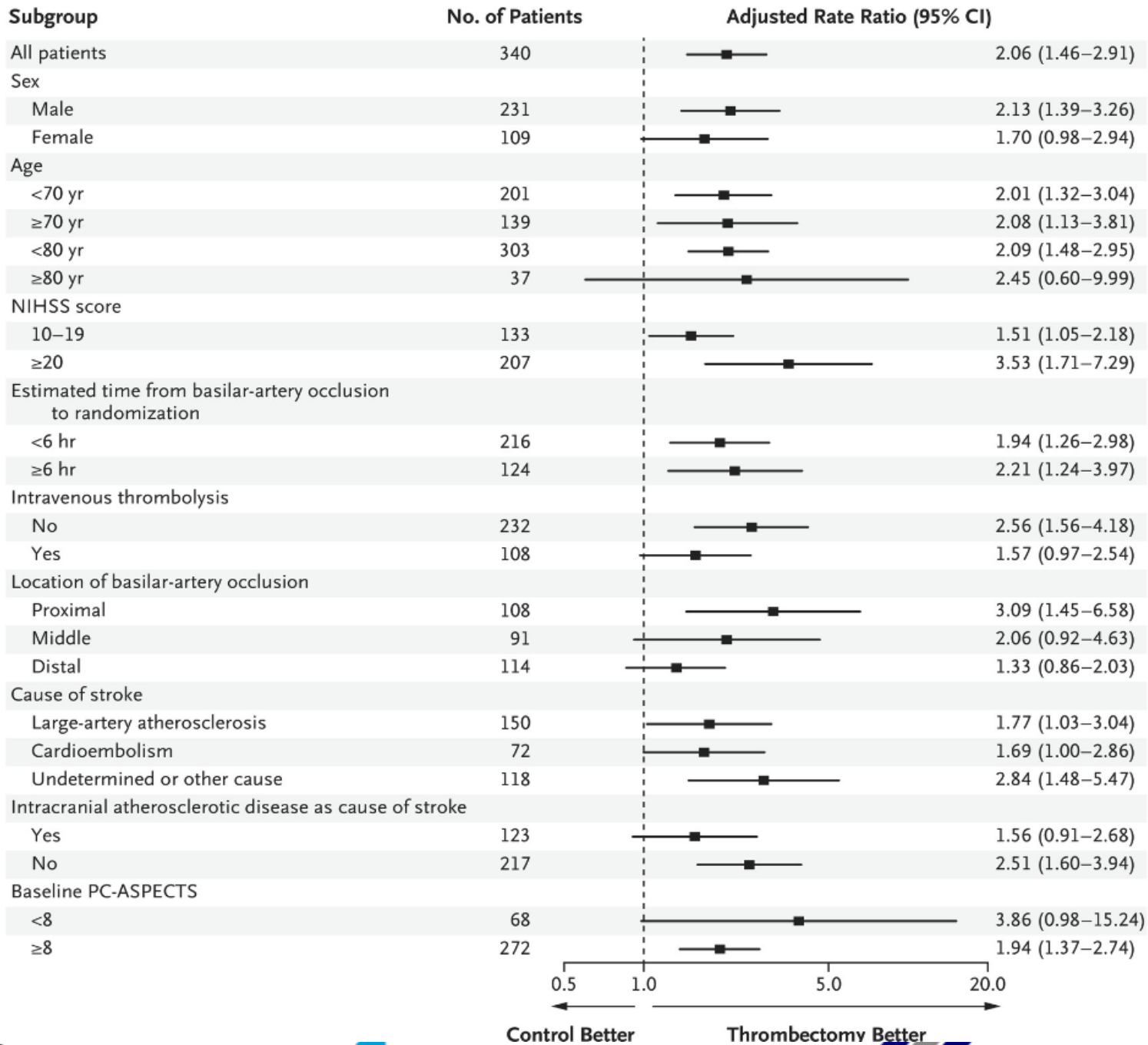
Modified Rankin Scale Score of 0–2 at 90 Days

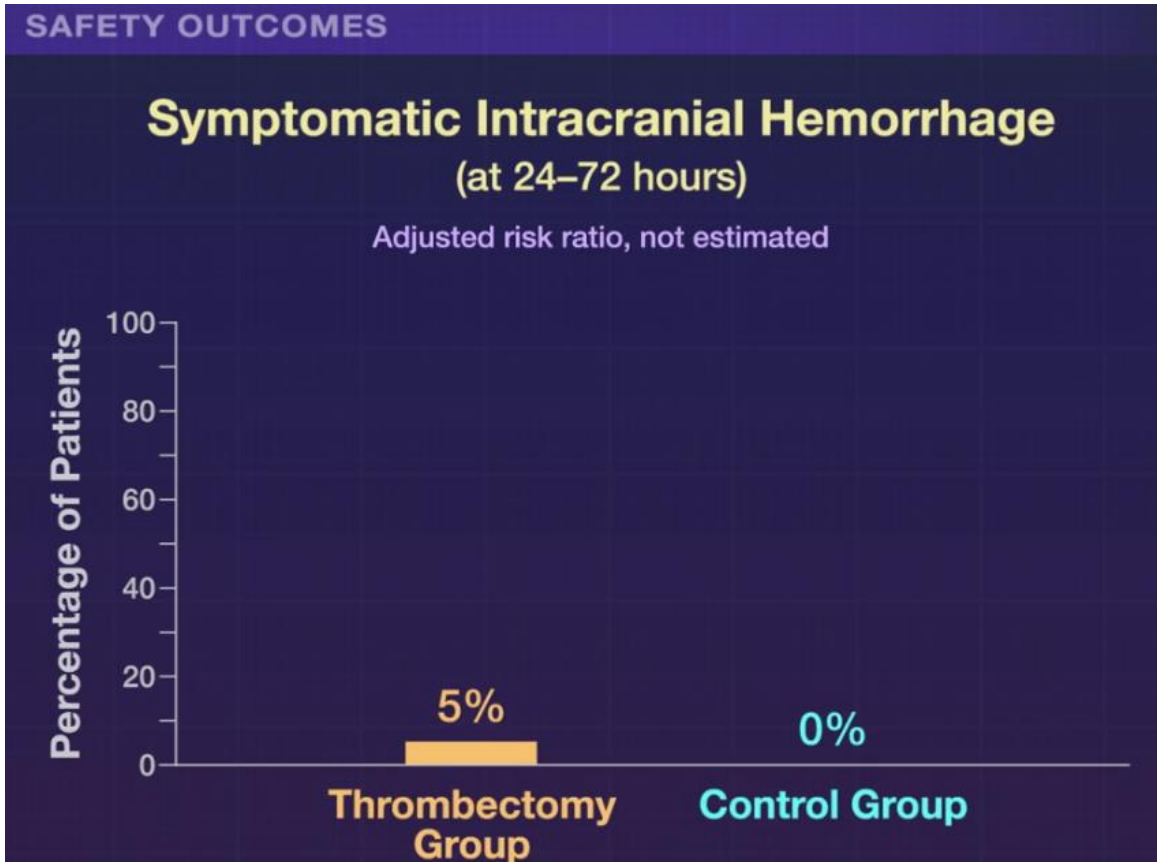
Table 1. Characteristics of the Patients at Baseline.*

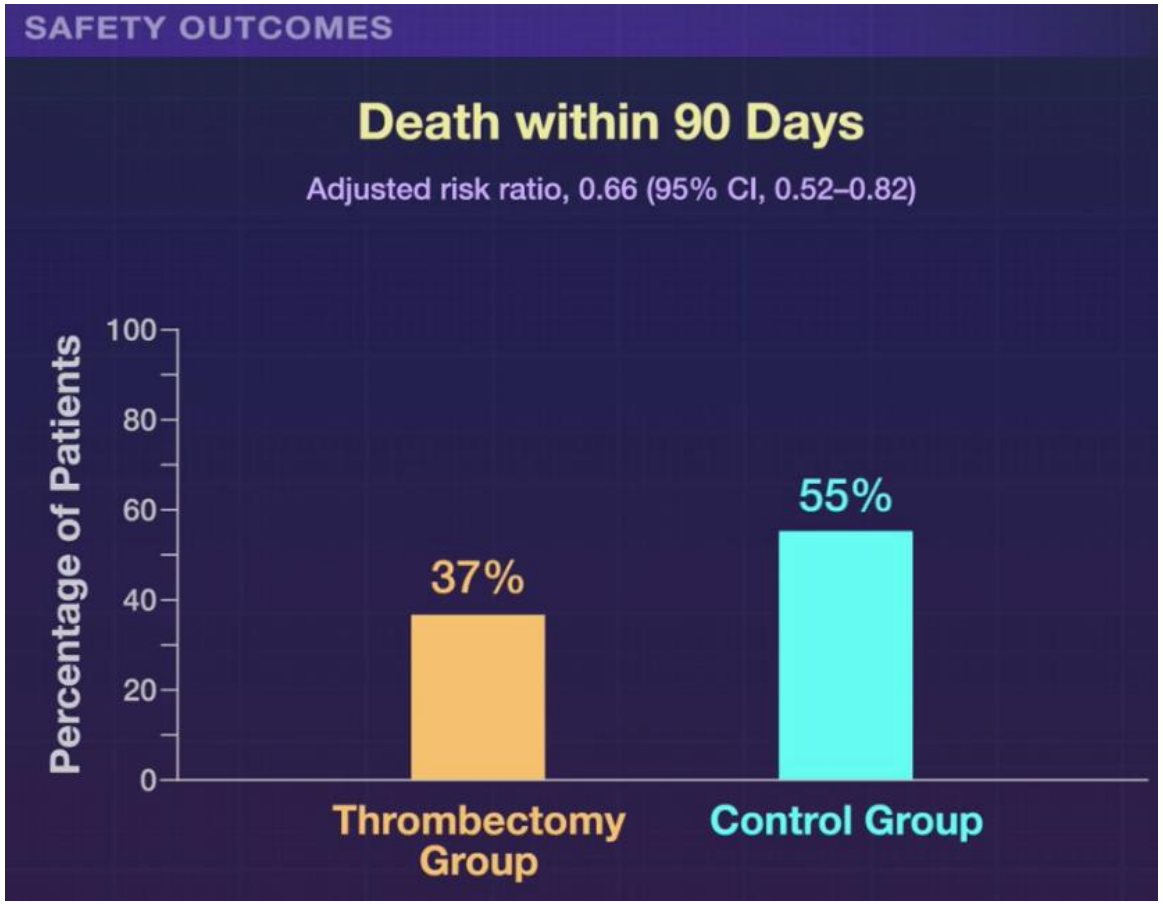
Characteristic	Thrombectomy (N = 226)	Control (N = 114)
Age — yr	66.0±11.1	67.3±10.2
Male sex — no. (%)	149 (66)	82 (72)
Modified Rankin scale score of 1 or 2 before stroke onset — no. (%)†	25 (11)	14 (12)
Median NIHSS score (IQR)‡	24 (15–35)	24 (14–35)
Median PC-ASPECTS (IQR)§	9 (8–10)	10 (8–10)
Cause of stroke — no. (%)¶		
Large-artery atherosclerosis	108 (48)	42 (37)
Intracranial	90 (40)	33 (29)
Extracranial	18 (8)	9 (8)
Cardioembolism	46 (20)	26 (23)
Undetermined cause	69 (31)	46 (40)
Other determined cause	3 (1)	0
Basilar-artery occlusion site — no./total no. (%)‖		
Vertebral artery V4	20/225 (9)	6/114 (5)
Proximal basilar artery	69/225 (31)	39/114 (34)
Middle basilar artery	62/225 (28)	29/114 (25)
Distal basilar artery	74/225 (33)	40/114 (35)
Intravenous thrombolysis — no. (%)**	69 (31)	39 (34)
Alteplase	60 (27)	35 (31)
Urokinase	9 (4)	4 (4)
Median duration (IQR) — hr††		
From stroke onset to randomization	5.1 (3.6–7.2)	4.9 (3.5–7.0)
From stroke onset to groin puncture	5.6 (3.5–7.5)	NA
From stroke onset to revascularization	6.9 (5.0–8.8)	NA
From groin puncture to revascularization	1.2 (0.8–1.8)	NA
Final modified TICI score of 2b or 3 — no./total no. (%)‡‡	208/223 (93)	NA

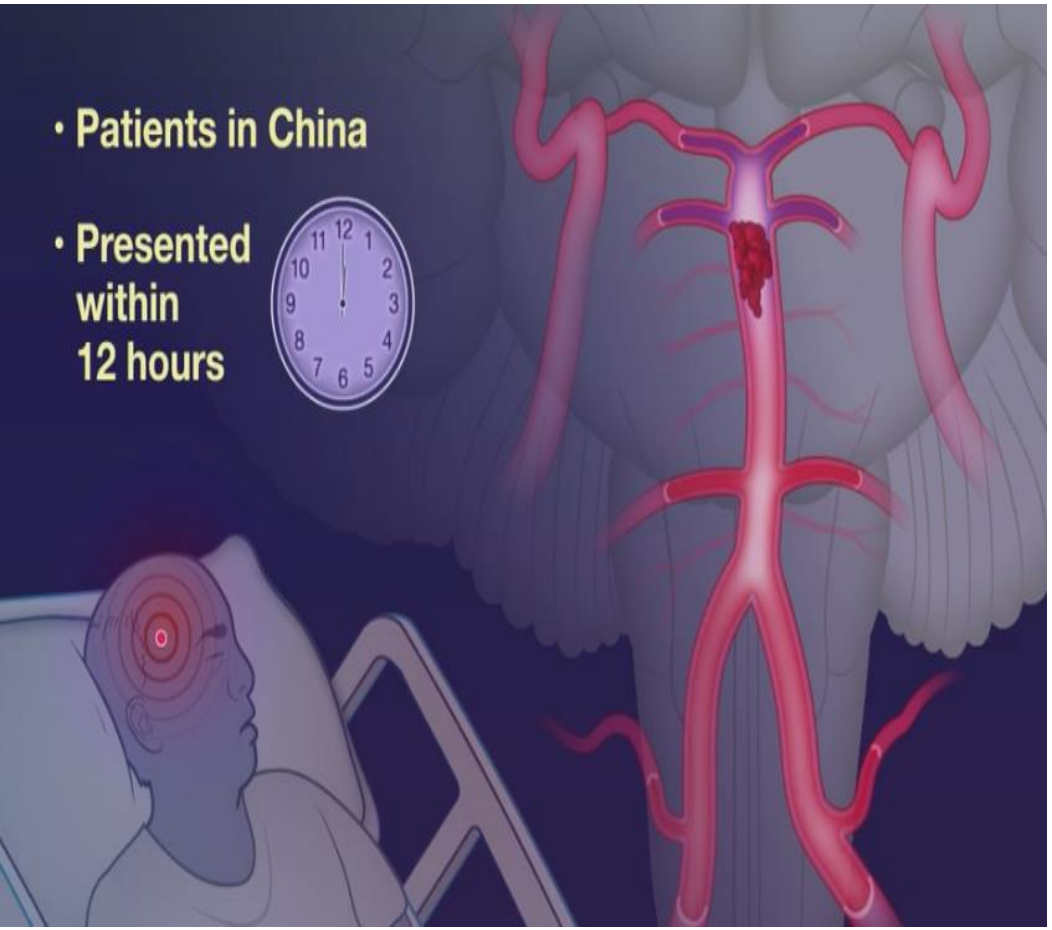

PRIMARY OUTCOME
Good Functional Status at 90 Days:
Modified Rankin Scale Score of 0–3
Adjusted rate ratio, 2.06 (95% CI, 1.46–2.91); P<0.001
Percentage of Patients
100
80
60
40
20
0
46%
23%
Thrombectomy Group
Control Group
Play

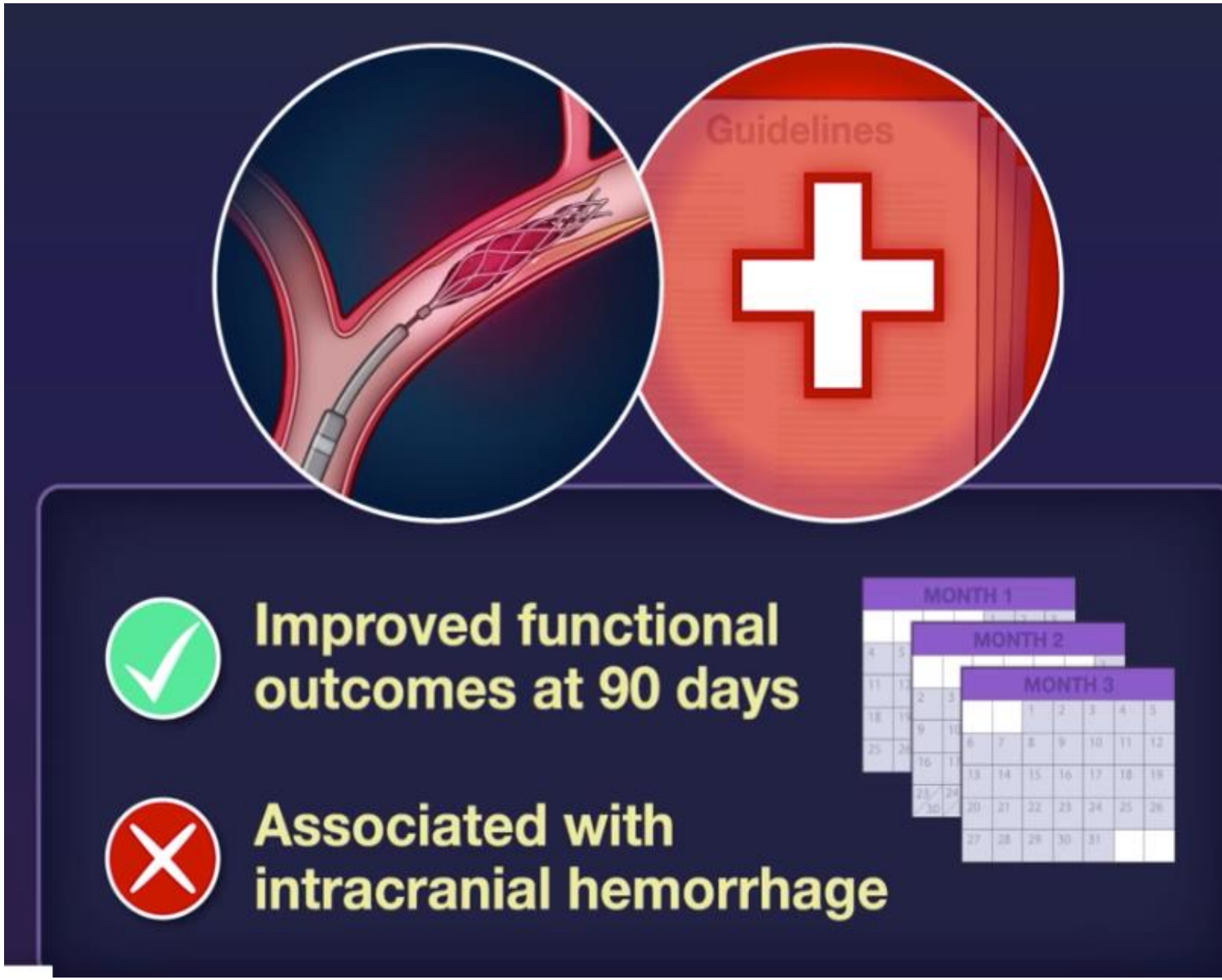

SECONDARY OUTCOME
Modified Rankin Scale Score of 0–2
at 90 Days
Adjusted rate ratio, 3.17 (95% CI, 1.84–5.46)
Percentage of Patients
100
80
60
40
20
0
33%
11%
Thrombectomy Group
Control Group
Play




SAFETY OUTCOMES
Symptomatic Intracranial Hemorrhage
(at 24–72 hours)
Adjusted risk ratio, not estimated
Percentage of Patients
100
80
60
40
20
0
5%
0%
Thrombectomy Group
Control Group


SAFETY OUTCOMES
Death within 90 Days
Adjusted risk ratio, 0.66 (95% CI, 0.52–0.82)
Percentage of Patients
100
80
60
40
20
0
37%
55%
Thrombectomy Group
Control Group


• Patients in China
• Presented within 12 hours


Guidelines
Improved functional outcomes at 90 days
Associated with intracranial hemorrhage
MONTH 1
MONTH 2
MONTH 3

Five-Year Outcomes of the Danish Cardiovascular Screening (DANCAVAS) Trial

Lindholt JS et al. DOI: 10.1056/NEJMoa2208681

CLINICAL PROBLEM

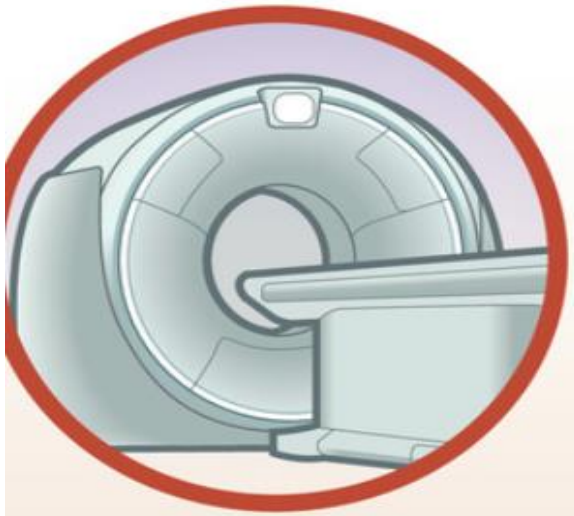
Cardiovascular disease remains a leading cause of death, even though many cardiac events and strokes could be prevented through early detection and treatment of risk factors or subclinical atherosclerosis. Evidence has been lacking to support population-based screening for cardiovascular disease.

CLINICAL TRIAL

Design: A population-based, parallel-group, randomized, controlled trial assessed the effect on mortality of inviting men for comprehensive cardiovascular screening.

Intervention: 46,611 men 65 to 74 years of age

Screening Methods



Noncontrast ECG-Gated CT

- Coronary-artery calcium score
- Aneurysms
- Atrial fibrillation

Ankle–Brachial Blood-Pressure Measurements

- Peripheral artery disease
- Hypertension

Blood Sample

- Diabetes mellitus
- Hypercholesterolemia

Enf. Coronaria

Aneurisma

Arteriopatia periférica

FA

HTA

Diabetes

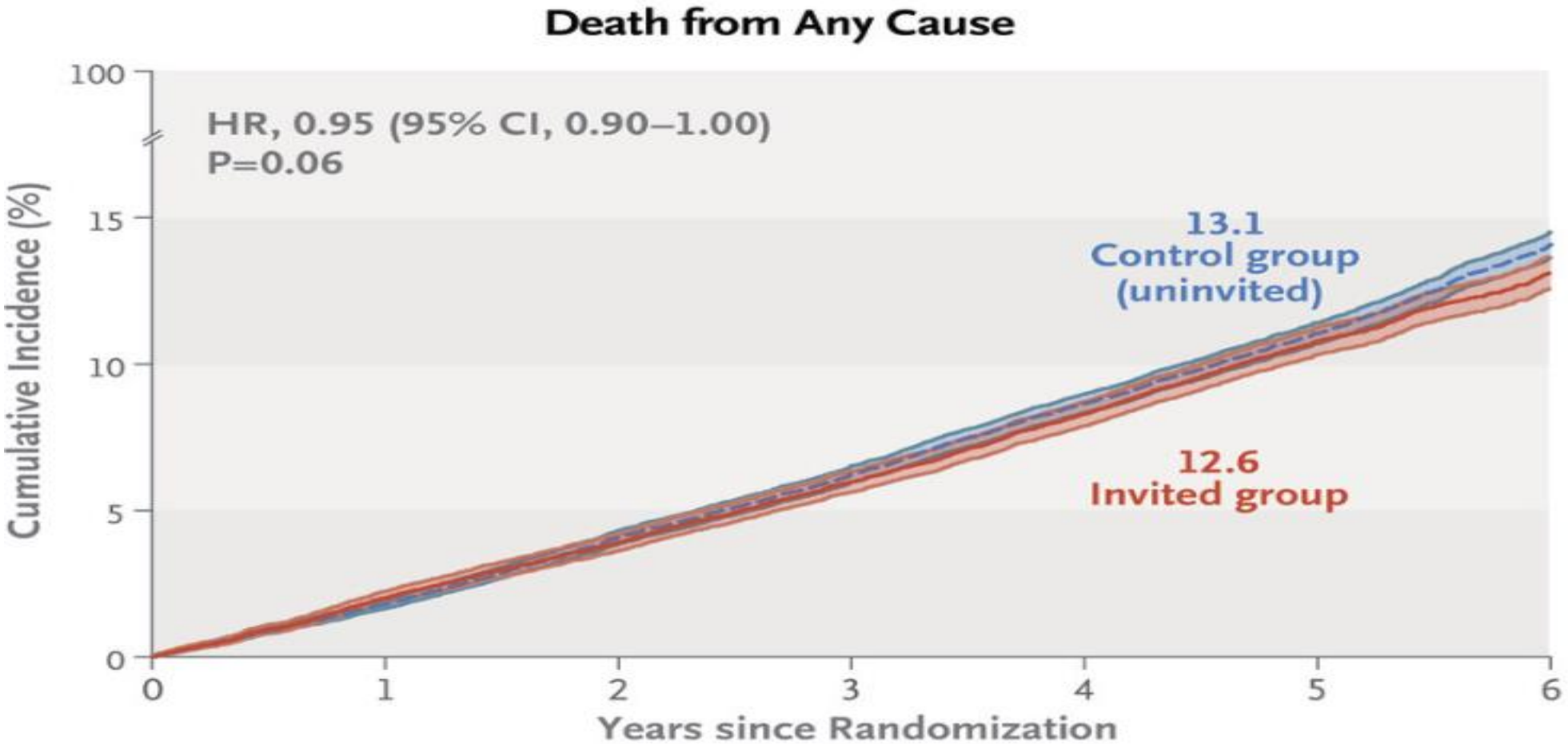
Hiperlipidemia

Table 1. Definitions of Positive Findings and Recommended Preventive Actions.*

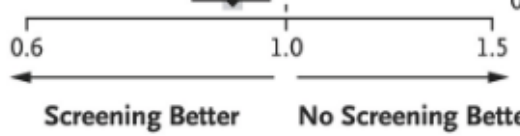
Criteria for Positive Finding	Recommended Action
Increased coronary-artery calcification (coronary-artery calcium score greater than the median sex- and age-specific score)	Provide recommendations regarding general cardiovascular prevention† Provide referral to cardiology department if angina pectoris is suspected
Ascending aortic aneurysm ≥45 mm in maximal diameter at the site where the anterior–posterior and transverse diameters are equivalent on axial CT	Provide recommendations regarding general cardiovascular prevention† If ≥55 mm, provide referral for surgical evaluation If ≥50 mm, perform echocardiography to detect bicuspid aortic valve; if not detected, perform annual control CT, and if detected, provide referral for surgical evaluation If 45–49 mm, assess with CT after 5 yr
Aortic arch aneurysm ≥40 mm on axial CT	Provide recommendations regarding general cardiovascular prevention† If ≥55 mm, provide referral for surgical evaluation If <55 mm, perform annual control CT
Descending aortic aneurysm ≥35 mm on axial CT	Provide recommendations regarding general cardiovascular prevention† If ≥55 mm, provide referral for surgical evaluation If 45–54 mm, perform annual control CT If 35–44 mm, perform control CT every second yr
Abdominal aortic aneurysm ≥30 mm on axial CT	Provide recommendations regarding general cardiovascular prevention† If ≥55 mm, provide referral for surgical evaluation If 50–54 mm, perform control CT twice a year If 45–49 mm, perform annual control CT If 30–44 mm, perform control CT every second yr
Iliac aneurysm ≥20 mm on axial CT	Provide recommendations regarding general cardiovascular prevention† If ≥35 mm, provide referral for surgical evaluation If 30–34 mm, perform annual control CT If 20–29 mm, perform control CT every second yr
Peripheral artery disease (ankle–brachial blood-pressure index value ≤0.90 or >1.40)	Provide recommendations regarding general cardiovascular prevention† Provide instructions regarding walking exercise Provide referral to vascular surgical department if critical limb ischemia suspected because of pain at rest, ulcers, or gangrene
Atrial fibrillation (irregular rhythm on ECG-gated monitor)	Confirm by 12-lead ECG If not confirmed, no action If confirmed, provide referral for cardiac evaluation and initiate anticoagulant medication (unless contraindicated)
Potential hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg)	Provide referral to general practitioner for confirmation and treatment
Suspected diabetes mellitus (glycated hemoglobin level ≥48 mmol/mole)	Provide referral to general practitioner for confirmation and treatment
Hypercholesterolemia (total cholesterol level ≥8.0 mmol/liter)	Provide referral to general practitioner for confirmation and treatment

RESULTS

Efficacy: At a median follow-up of 5.6 years, the incidence of death from any cause did not differ significantly between the groups.



Subgroup	Screened Invited Participants	Unscreened Invited Participants	Hazard Ratio (95% CI)
	no. of events per 1000 person-yr		
Age			
<70 yr	18.73	20.90	0.89 (0.83–0.96)
≥70 yr	30.71	30.33	1.01 (0.94–1.09)
Cardiovascular disease			
No	20.32	21.40	0.95 (0.89–1.01)
Yes	47.50	47.93	0.99 (0.89–1.10)
Stroke			
No	22.64	23.65	0.96 (0.90–1.01)
Yes	42.57	44.19	0.97 (0.80–1.17)
Ischemic heart disease			
No	23.03	24.26	0.95 (0.90–1.00)
Yes	35.10	34.02	1.03 (0.82–1.29)
Heart failure			
No	22.31	23.44	0.95 (0.90–1.00)
Yes	79.61	80.07	0.99 (0.81–1.21)
Peripheral occlusive arterial disease			
No	22.35	23.72	0.94 (0.89–0.99)
Yes	81.96	72.74	1.13 (0.91–1.40)
Aortic aneurysm			
No	23.09	24.25	0.95 (0.90–1.00)
Yes	48.37	53.80	0.90 (0.66–1.21)
Hypertension at baseline			
No	18.95	19.66	0.96 (0.88–1.05)
Yes	27.71	29.20	0.95 (0.89–1.01)
Diabetes mellitus at baseline			
No	21.63	22.54	0.96 (0.90–1.02)
Yes	36.41	39.91	0.91 (0.81–1.03)
Lipid-lowering therapy at baseline			
No	22.21	22.27	1.00 (0.93–1.07)
Yes	25.63	28.54	0.90 (0.83–0.97)

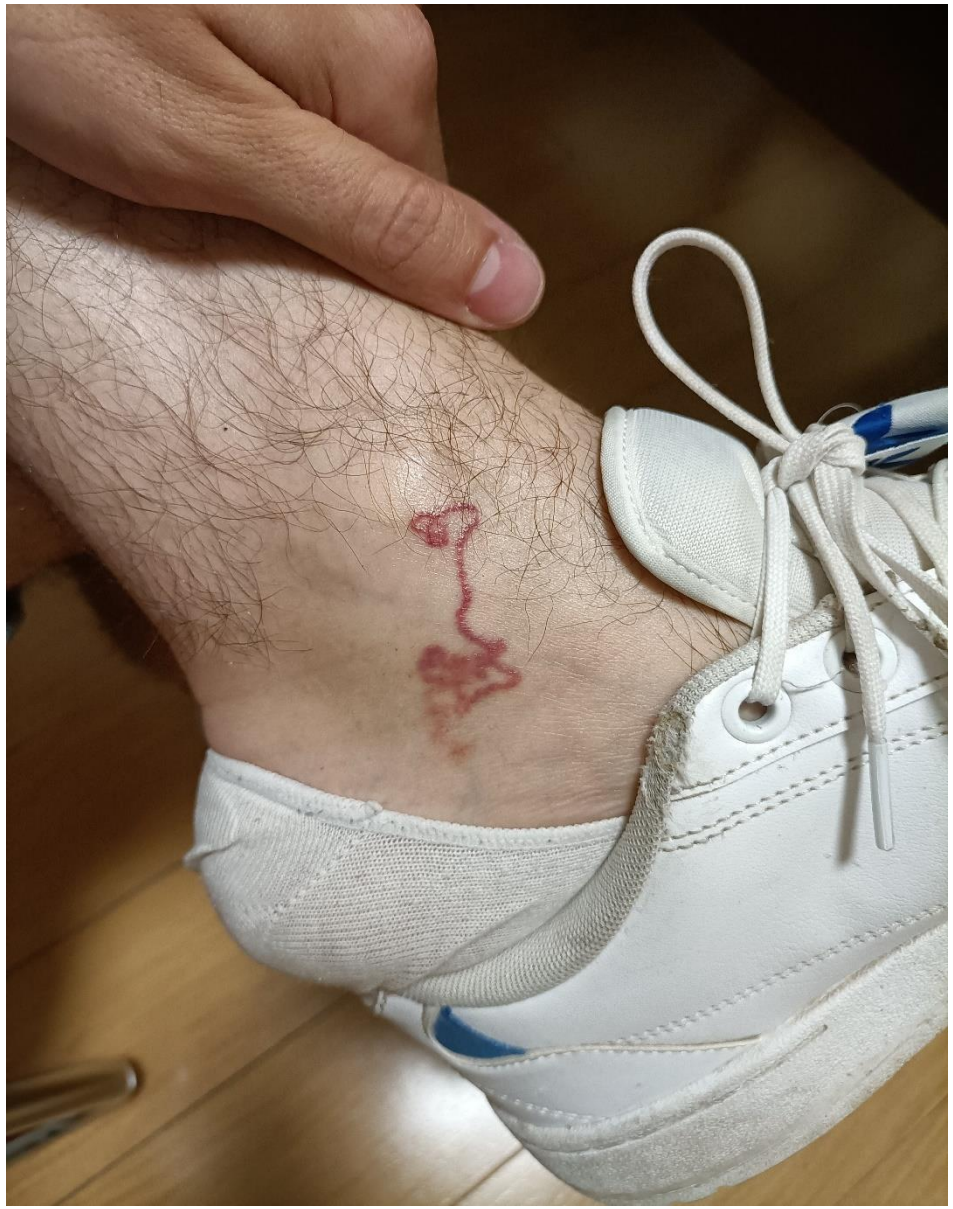


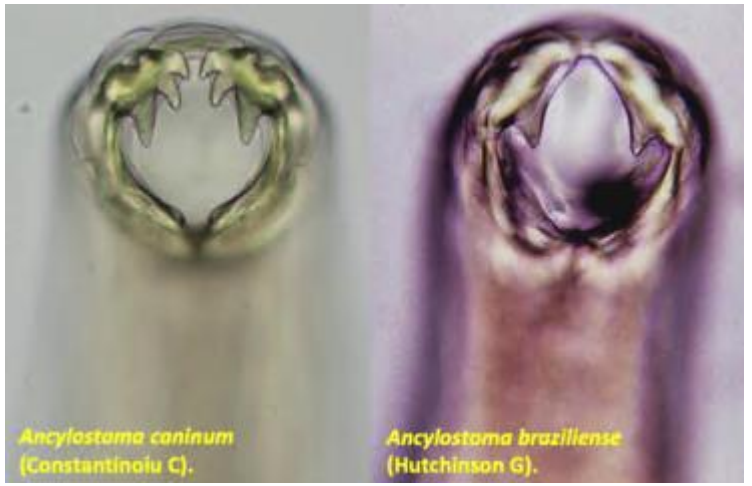
CONCLUSIONS

Among older men, an invitation to undergo comprehensive cardiovascular screening did not significantly reduce the incidence of death at 5.6 years' follow-up.

LIMITATIONS

- The trial included only men 65 to 74 years of age who lived in Denmark.
- Only 63% of men who were invited to be screened actually participated.
- Longer-term follow-up is needed.




Ancylostoma caninum
(Constantinoiu C).
Ancylostoma braziliense
(Hutchinson G).

FIN

18-11-22