



SABATO 2 MARZO

RIVAROXABAN NELLA CARDIOPATIA ISCHEMICA CRONICA E ARTERIOPATIA OBLITERANTE. RAZIONALE E RISULTATI.

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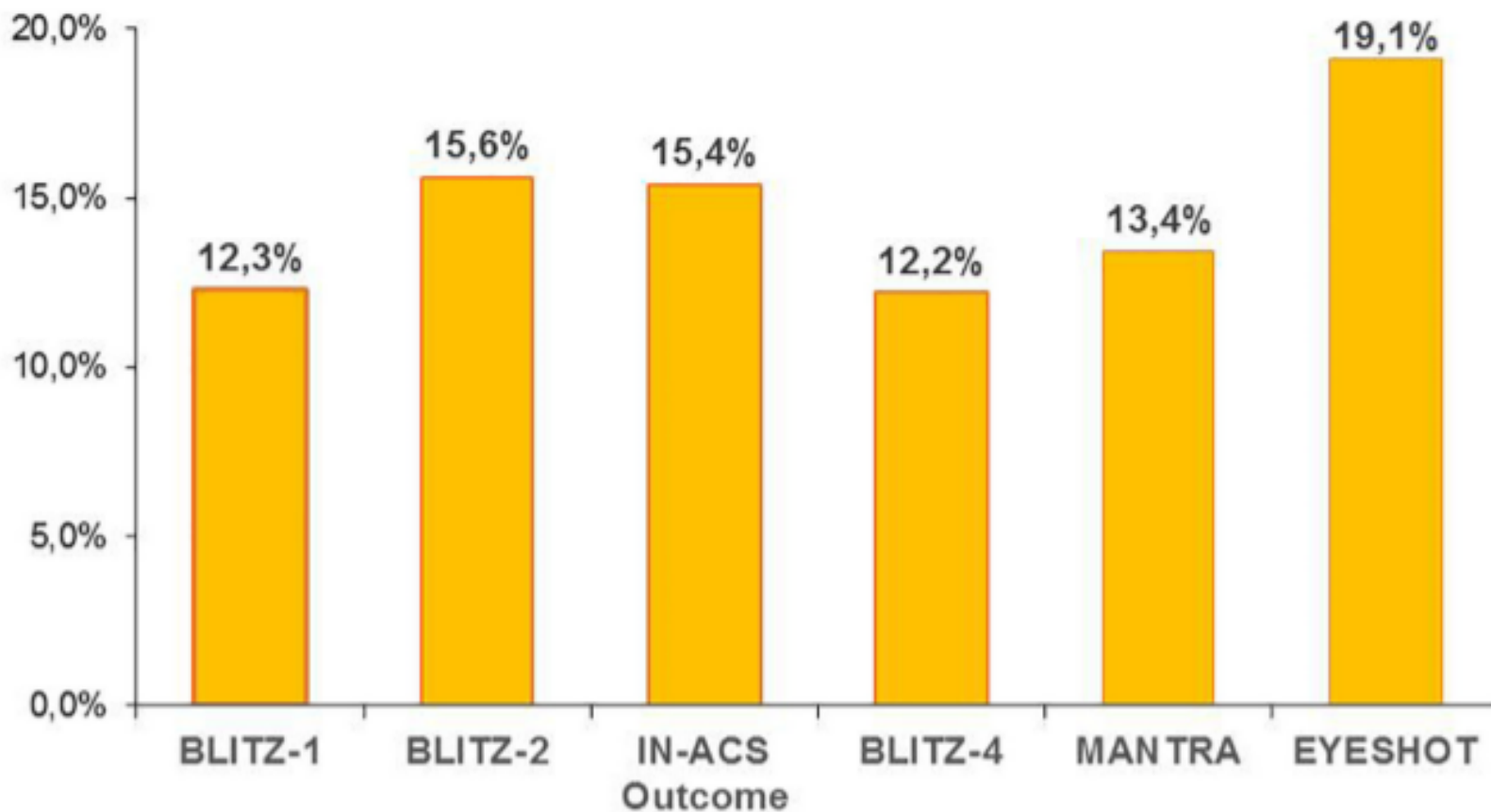
Original Article

Trends in management and outcome of patients with non-ST elevation acute coronary syndromes and peripheral arterial disease



Leonardo De Luca^{a,*}, Giuseppe Di Pasquale^b, Lucio Gonzini^c, Francesco Chiarella^d,
Antonio Di Chiara^e, Alessandro Boccanelli^f, Gianni Casella^b, Zoran Olivari^g, Stefano De Servi^h,
Michele Massimo Guliziaⁱ, Andrea Di Lenarda^j, Stefano Savonitto^k, Leonardo Bolognese^l

Prevalence of PAD among NSTEMACS patients

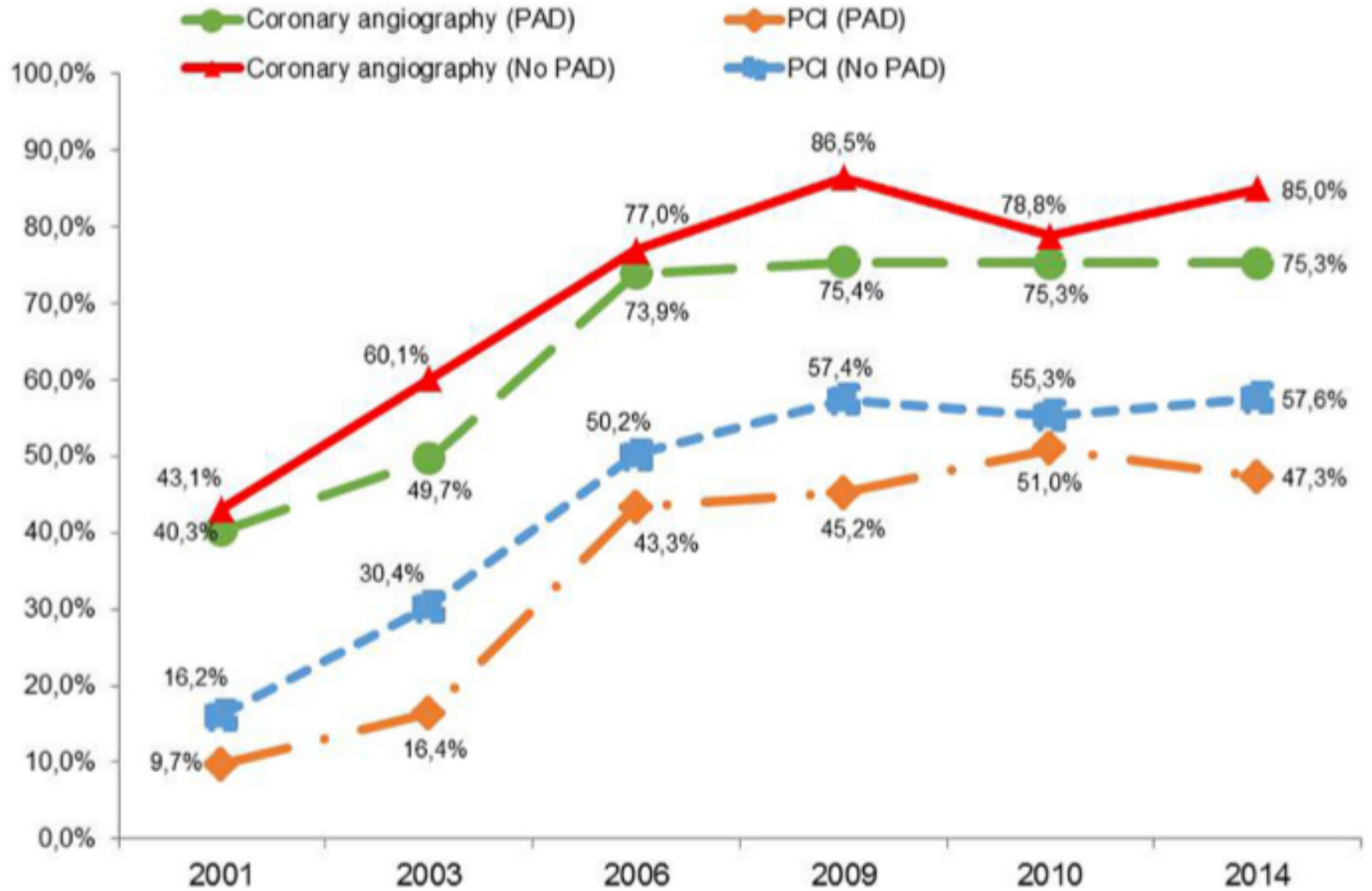


| Year | 2001 | 2003 | 2006-2007 | 2009-2010 | 2009-2010 | 2013-2014 |
|--------------------------|------|------|-----------|-----------|-----------|-----------|
| Centres | 296 | 275 | 38 | 163 | 52 | 203 |
| Total n. of NSTEMACS pts | 585 | 1059 | 3519 | 5786 | 3479 | 1439 |

Clinical characteristics of NSTEMACS patients with PAD

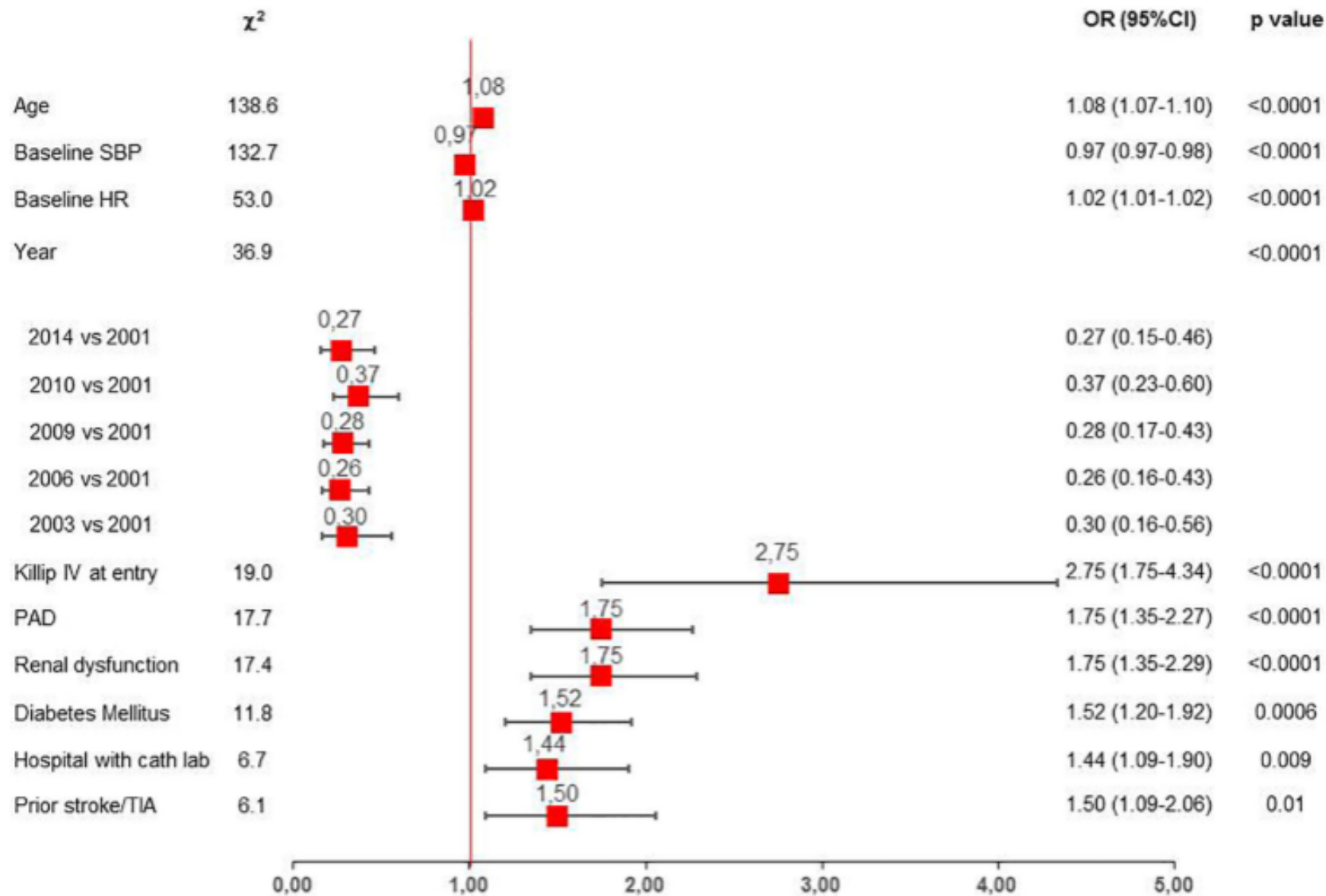
| | No PAD n = 13,641 | PAD n = 2226 | p value |
|-----------------------------------|----------------------|--------------|----------|
| Age, yrs. (mean \pm SD) | 68 \pm 13 | 75 \pm 9 | < 0.0001 |
| Females, n (%) | 4470 (32.8) | 650 (29.2) | 0.0008 |
| Active smokers, n (%) | 3651 (26.8) | 434 (19.5) | < 0.0001 |
| Diabetes mellitus, n (%) | 3698 (27.1) | 1030 (46.3) | < 0.0001 |
| Hypertension, n (%) | 8385 (61.5) | 1748 (78.5) | < 0.0001 |
| Chronic kidney disease, n (%) | 1132 (8.3) | 642 (28.8) | < 0.0001 |
| Previous stroke/TIA, n (%) | 739 (5.4) | 353 (15.9) | < 0.0001 |
| History of HF, n (%) | 537 (3.9) | 251 (11.3) | < 0.0001 |
| History of angina, n (%) | 2533 (18.6) | 735 (33.0) | < 0.0001 |
| Previous MI, n (%) | 2784 (20.4) | 789 (35.4) | < 0.0001 |
| Previous PCI/CABG, n (%) | 2870 (21.0) | 834 (37.5) | < 0.0001 |
| Variables at CCU admission | | | |
| Killip IV, n (%) | 140 (1.0) | 64 (2.9) | < 0.0001 |
| Atrial fibrillation, n (%) | 975 (7.2) | 228 (10.2) | < 0.0001 |
| SBP, mmHg (mean \pm SD) | 141 \pm 25 | 142 \pm 28 | 0.03 |
| HR, bpm (mean \pm SD) | 79 \pm 19 | 82 \pm 21 | < 0.0001 |
| LVEF, % (mean \pm SD) | 51 \pm 10 | 48 \pm 11 | < 0.0001 |

Invasive management of NSTEMI/ACS in PAD patients

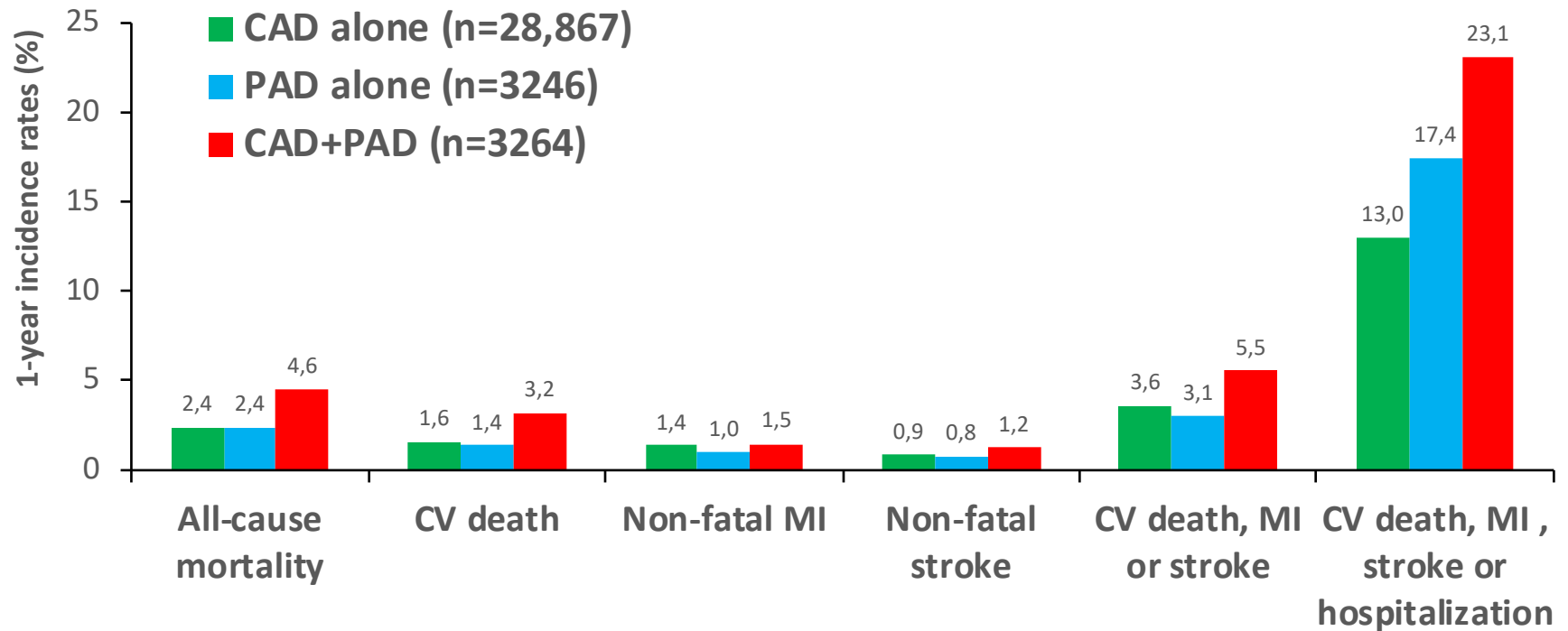


Predictors of in-H mortality among NSTEMI/ACS patients

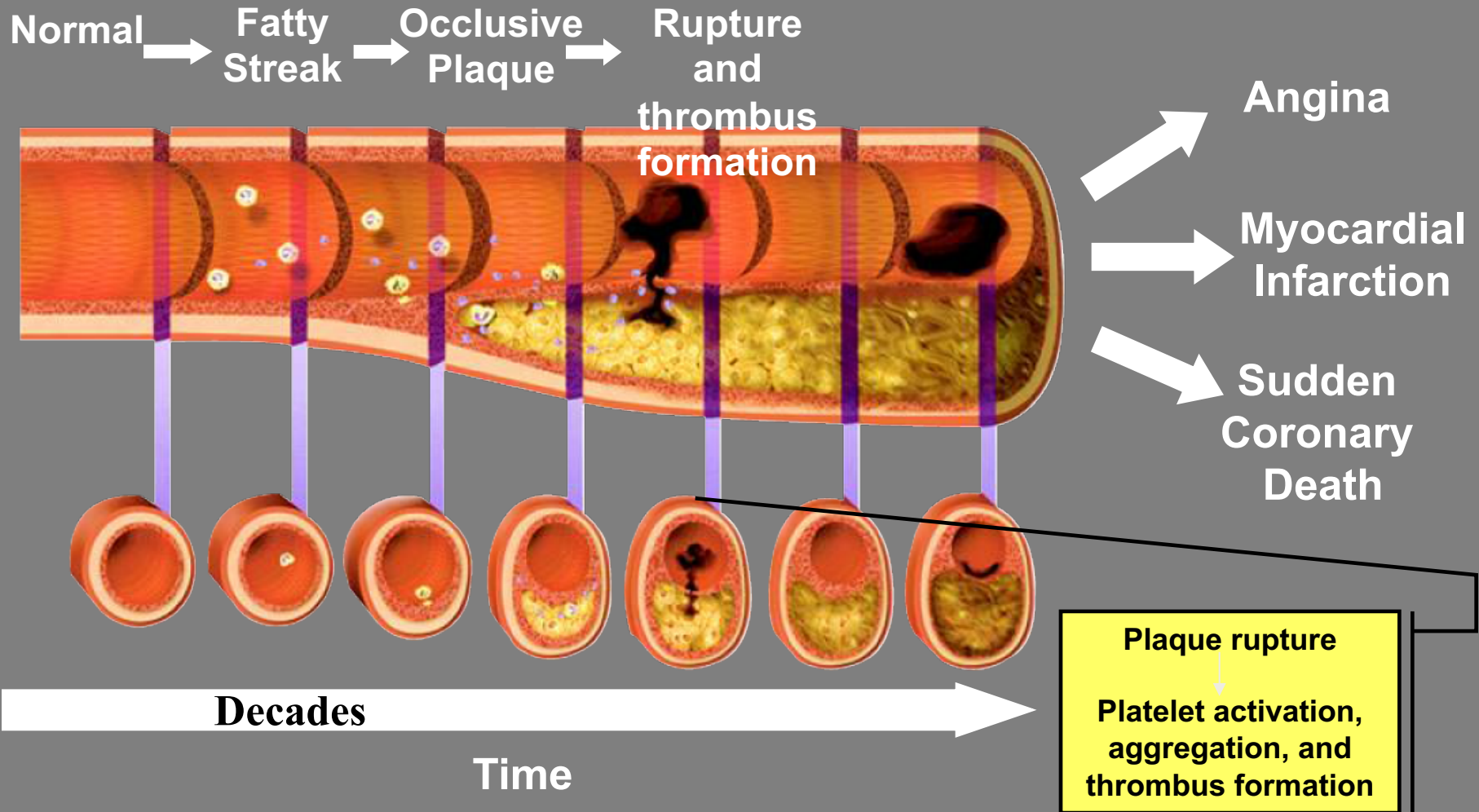
multivariable logistic regression analysis



1-year outcomes in patients with CAD alone, PAD alone or CAD+PAD (REACH registry)

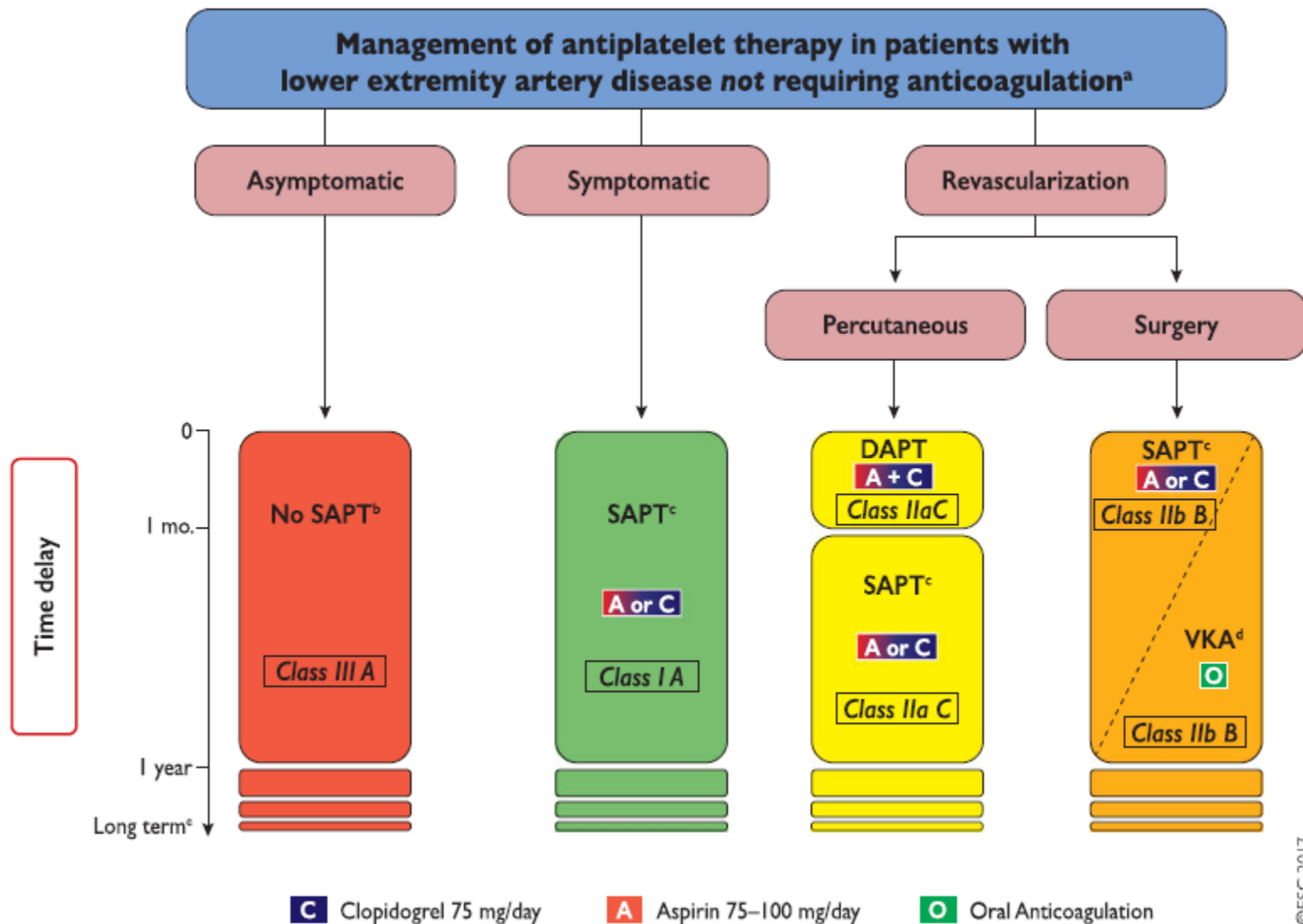


Progression of Atherosclerosis Atherothrombosis

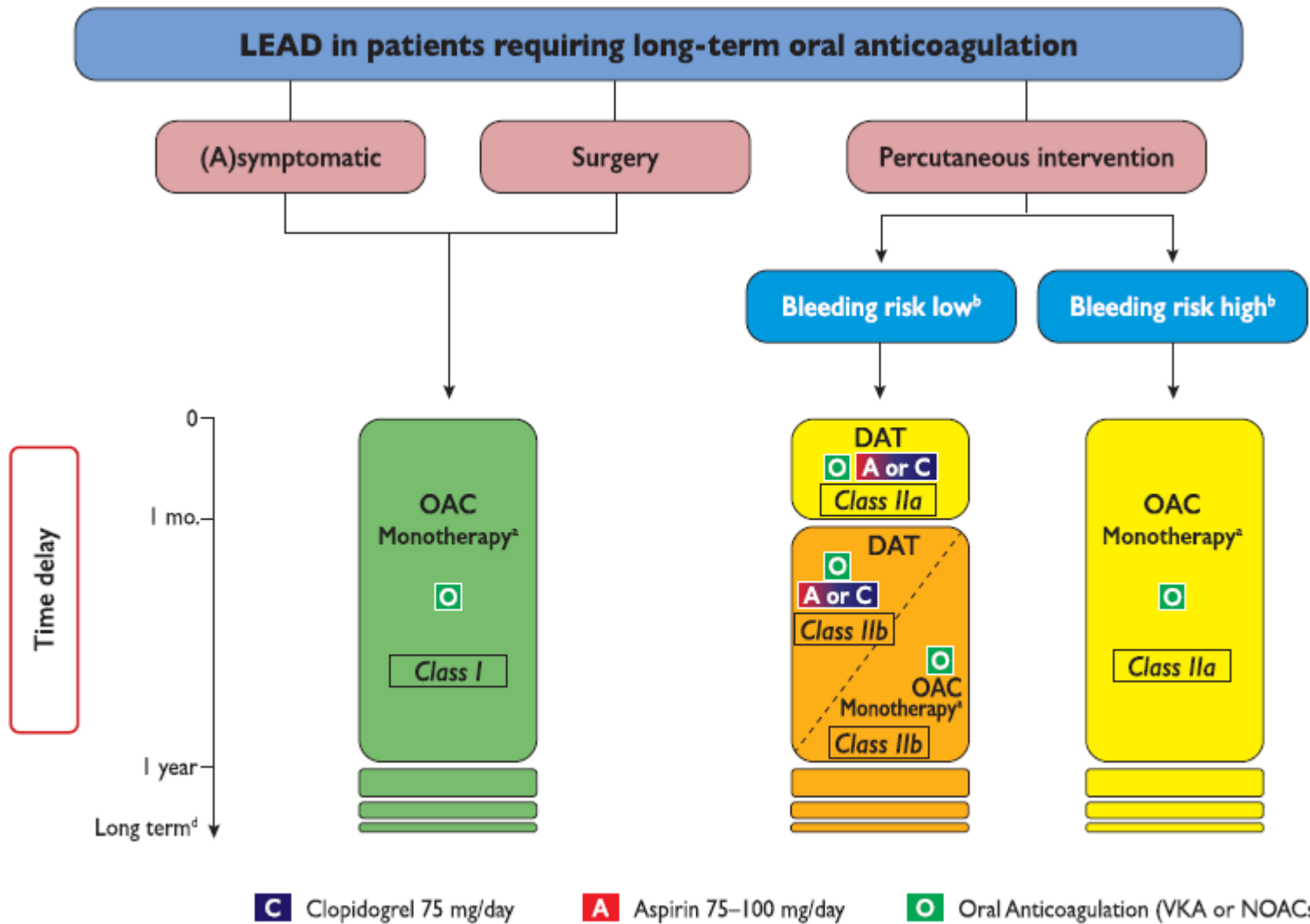


2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases

| Recommendations | Class ^a | Level ^b |
|---|--------------------|--------------------|
| Smoking cessation is recommended in all patients with PADs. ^{27,28} | I | B |
| Healthy diet and physical activity are recommended for all patients with PADs. | I | C |
| Statins are recommended in all patients with PADs. ^{31,32} | I | A |
| In patients with PADs, it is recommended to reduce LDL-C to < 1.8 mmol/L (70 mg/dL) or decrease it by ≥ 50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL). ²⁵ | I | C |
| In diabetic patients with PADs, strict glycaemic control is recommended. | I | C |
| Antiplatelet therapy is recommended in patients with symptomatic PADs. ⁵¹ | I | C ^d |
| In patients with PADs and hypertension, it is recommended to control blood pressure at < 140/90 mmHg. ^{41,42,52} | I | A |



©ESC 2017



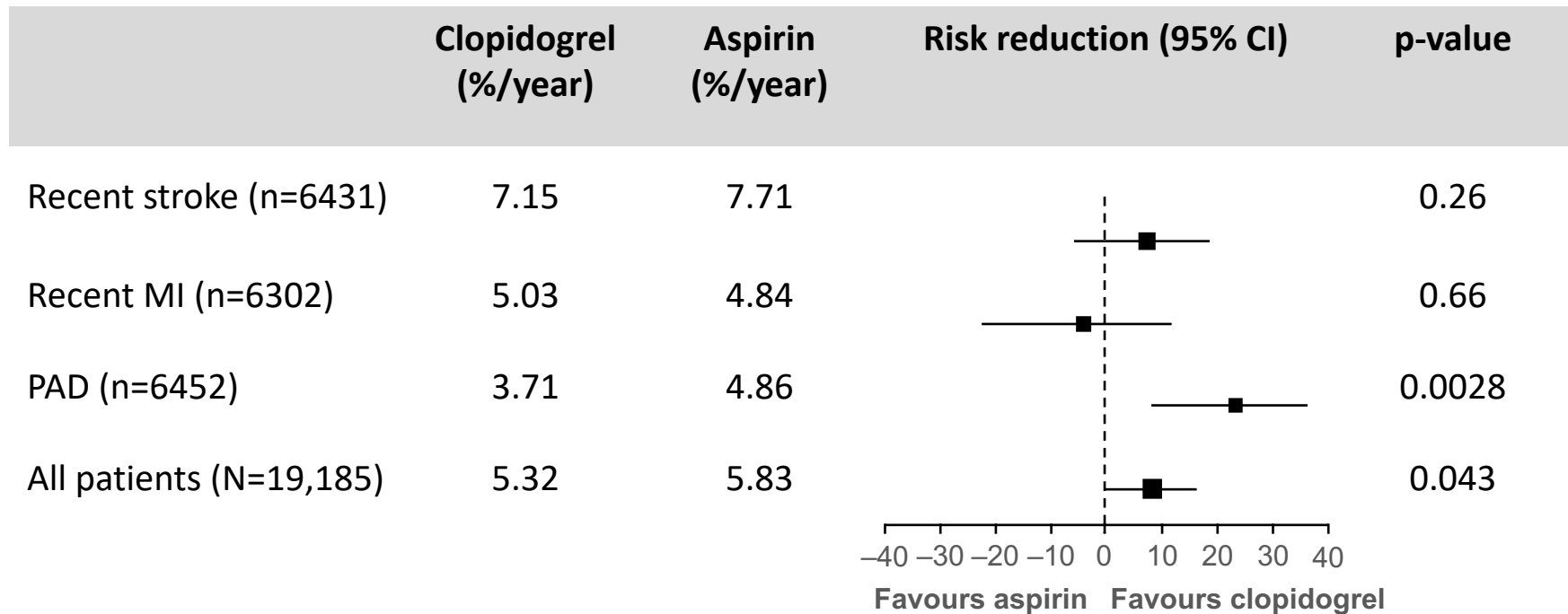
Antithrombotic options are limited in patients with PAD

2017 ESC/ESVS guidelines for the use of antithrombotics in patients with PAD

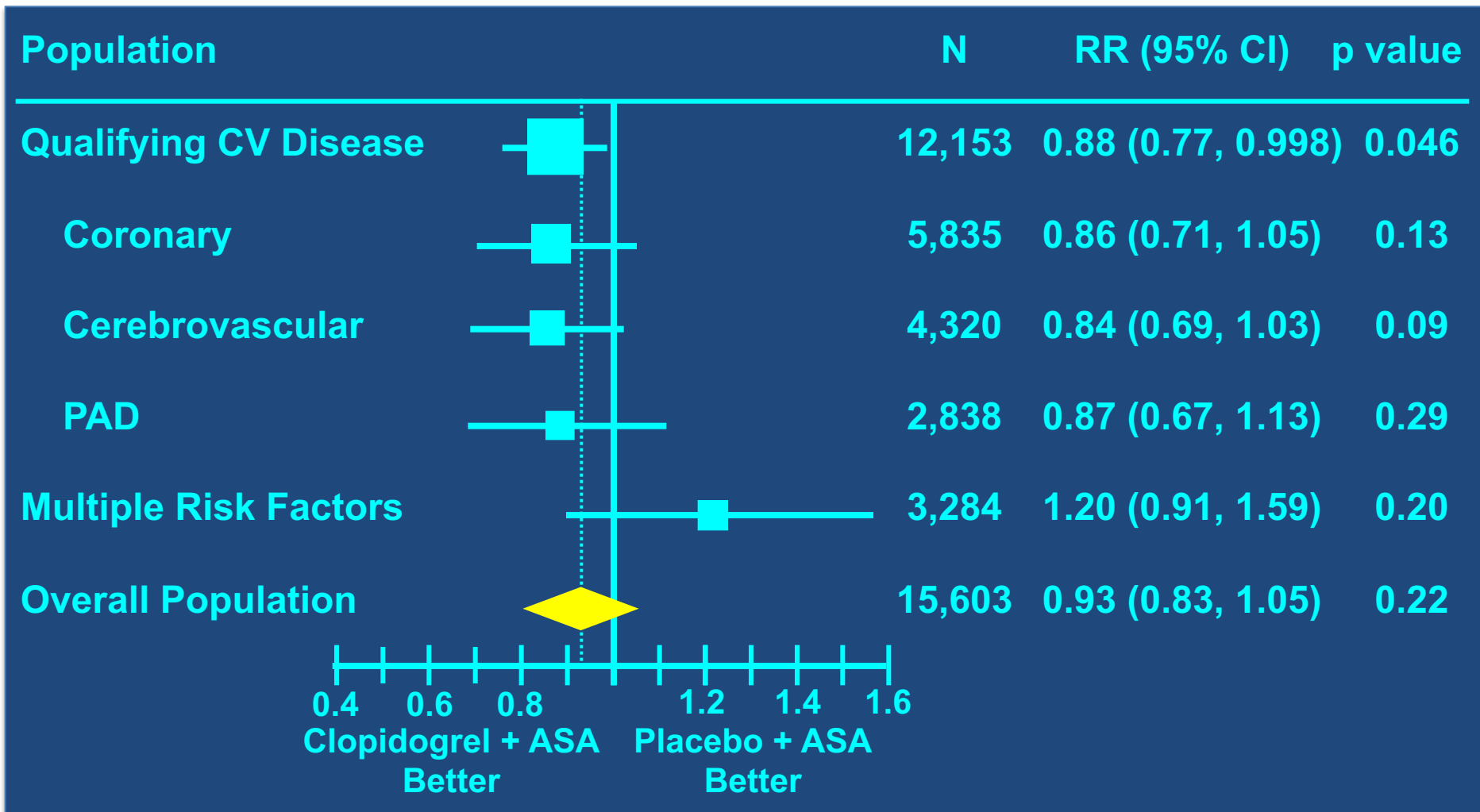
| Recommendation | Class | Level |
|---|-------|-------|
| Long-term single antiplatelet therapy is recommended in symptomatic patients | I | A |
| In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin | IIb | B |

Recommendation for clopidogrel in PAD based on 20-year-old subanalysis data

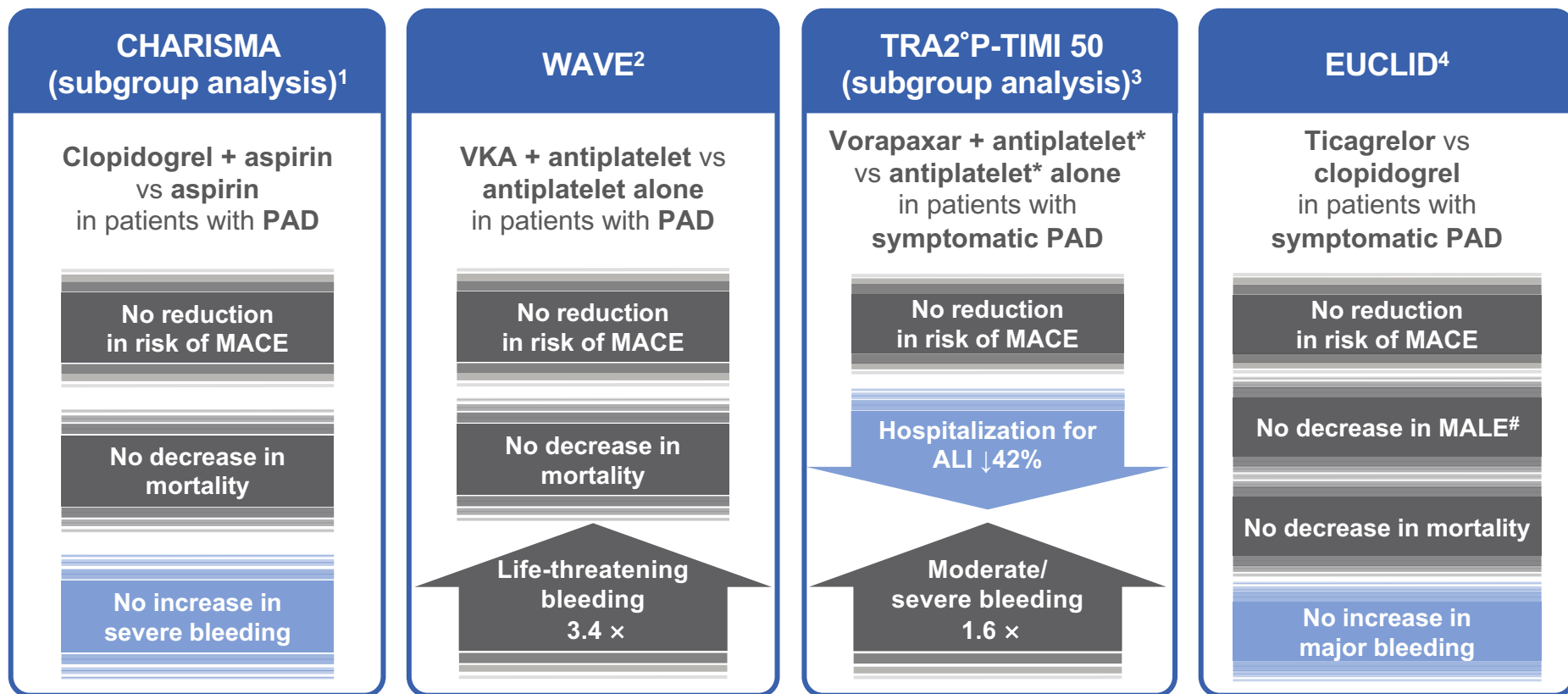
CAPRIE subanalysis: lower risk of CV events with clopidogrel versus aspirin in patients with symptomatic PAD



MI/Stroke/CV Death at 30 months by Category of Inclusion Criteria



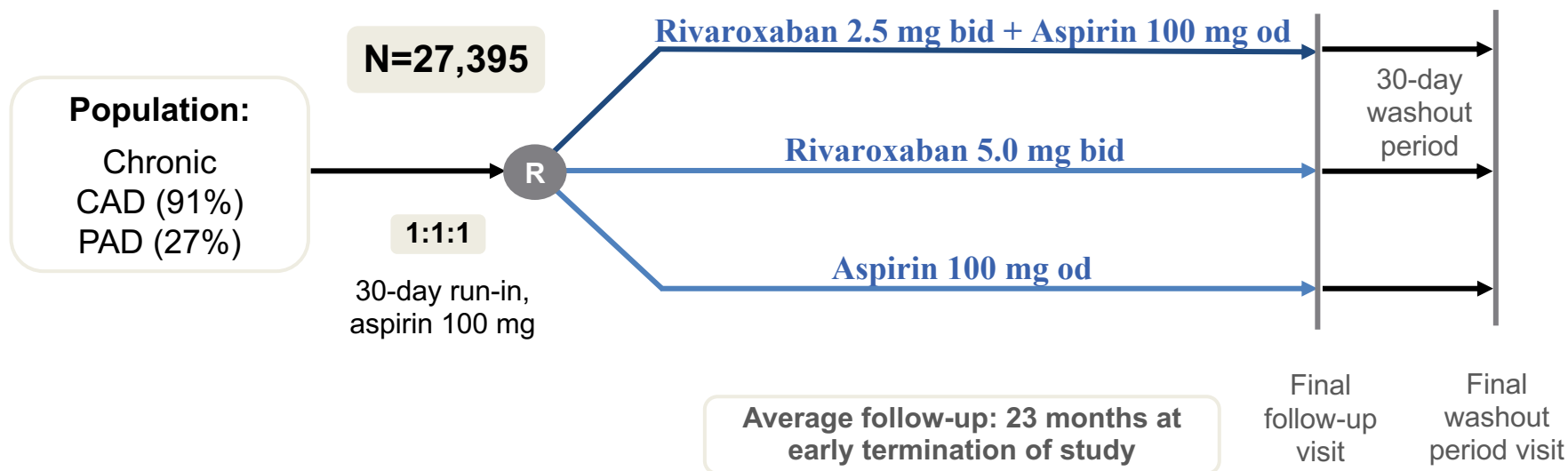
Subsequent trials for antithrombotic therapy in PAD have had limited clinical success



1. Cacoub PP. *Eur Heart J* 2009;30:192–201; 2. Anand S. *N Engl J Med* 2007;357:217–227;
 3. Bonaca MP. *Circulation* 2013;127:1522–1529; 4. Hiatt WR. *N Engl J Med* 2017;376:32–40

COMPASS study design

Primary endpoint: MI, stroke and cardiovascular death in CAD or PAD



Antithrombotic investigations* were stopped 1 year ahead of expectations in Feb 2017 due to overwhelming efficacy in the rivaroxaban 2.5 mg bid + aspirin arm

Inclusion and Exclusion Criteria

Key inclusion criteria

- ◆ Previous peripheral artery revascularization
- ◆ Previous limb or foot amputation for arterial vascular disease
- ◆ Intermittent claudication plus:
 - Low ABI (<0.90), or
 - Significant peripheral artery stenosis (≥50%)
- ◆ Previous carotid revascularization, or asymptomatic carotid artery stenosis ≥50%
- ◆ CAD + low ABI (<0.90)

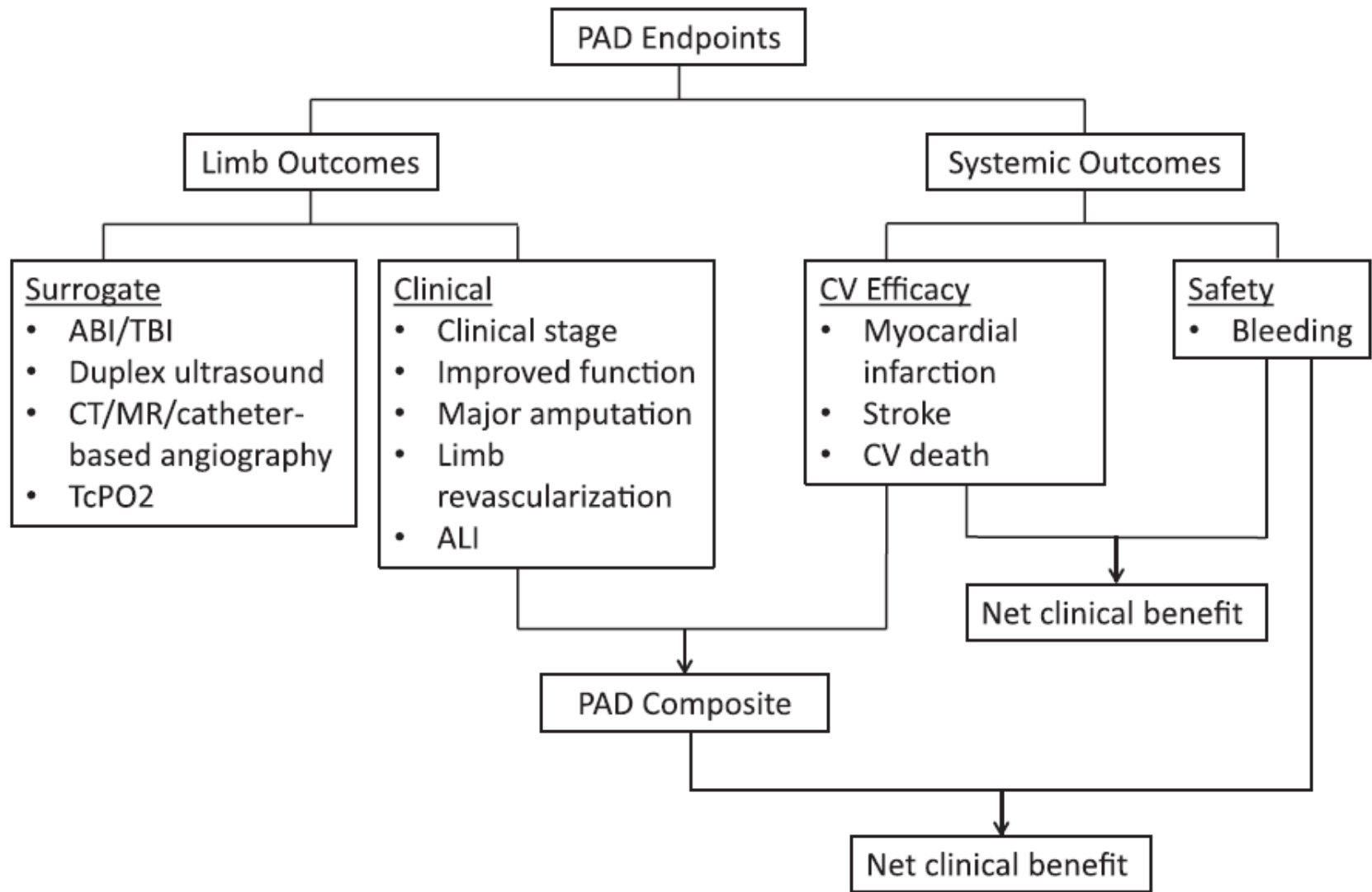
Key exclusion criteria

- ◆ High risk of bleeding
- ◆ Stroke within 1 month
- ◆ History of haemorrhagic/lacunar stroke
- ◆ Severe heart failure (ejection fraction <30%)
- ◆ eGFR <15 ml/min
- ◆ A need for dual antiplatelet therapy
- ◆ A need for non-aspirin antiplatelet therapy
- ◆ An indication for anticoagulation therapy

PAD-Specific Limb Outcomes in COMPASS

- **Primary cardiovascular outcome was MACE, defined as:**
 - **Composite of cardiovascular death, stroke or MI**
- **Key composite outcomes for PAD:**
 - **Primary limb outcome was major adverse limb events (MALE), defined as development of ALI or CLI and major amputations not included in ALI or CLI**
 - **The composite of MACE and MALE**
 - **The composite of MACE, MALE and major amputations not included in ALI or CLI**

Endpoints for trials in PAD

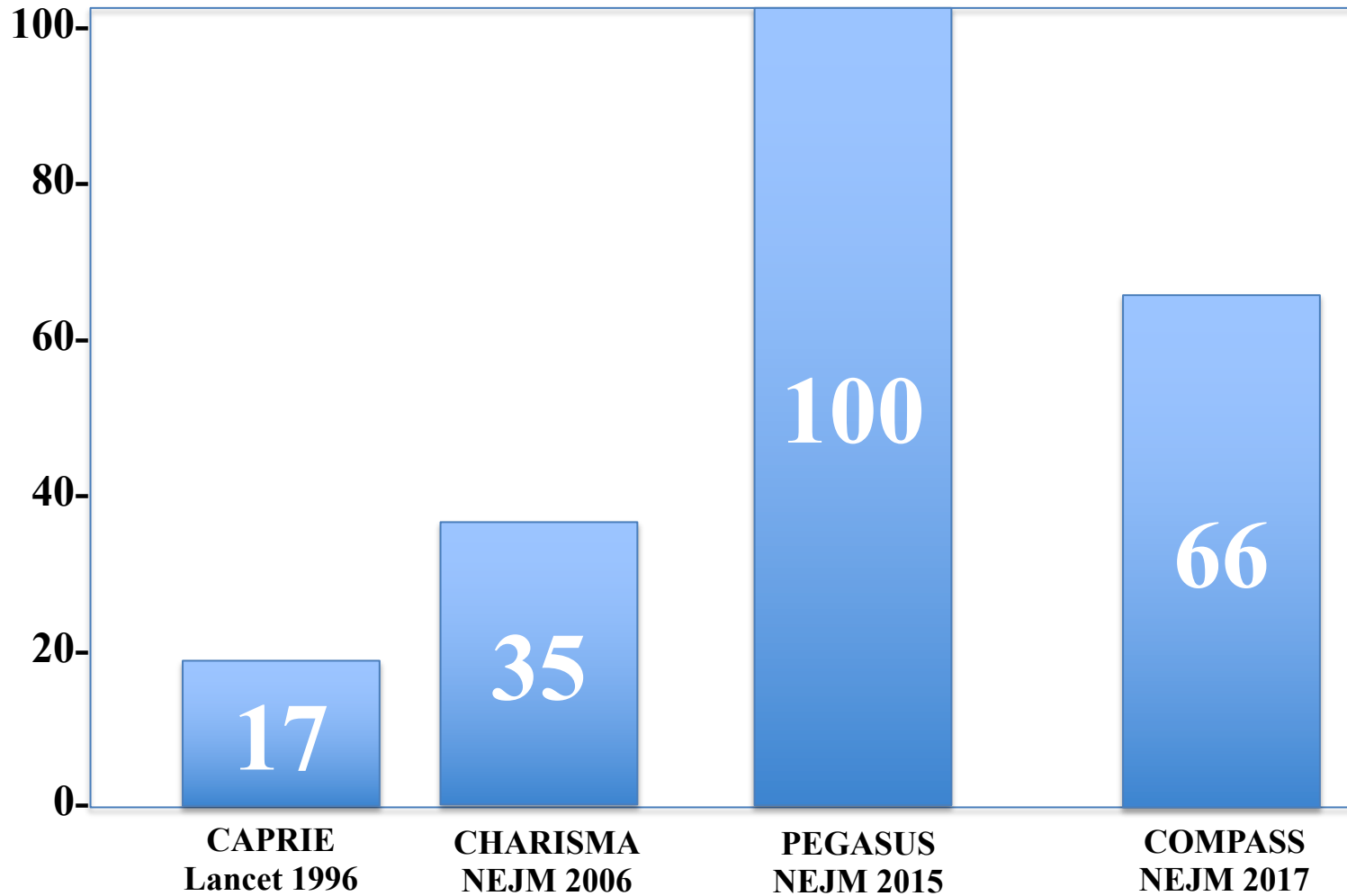


Quality classification of trials in stable PAD

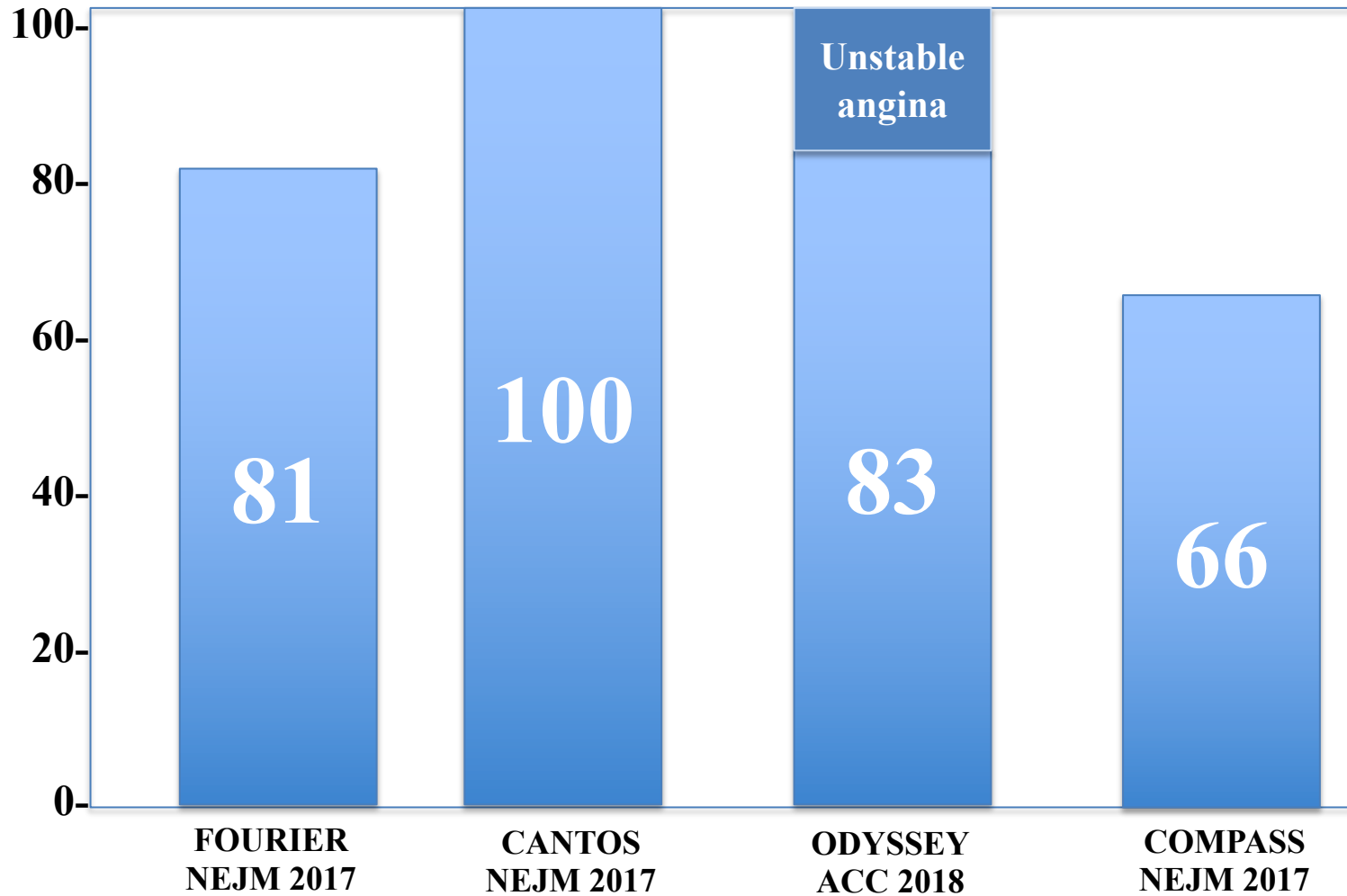
| | Primary PAD population and adjudicated efficacy endpoint | Pre-specified PAD subgroup and adjudicated efficacy endpoint | Post-hoc PAD subgroup or non-adjudicated efficacy endpoint |
|---|--|---|---|
| Adjudicated bleeding using standardized scale | EUCLID ³⁸ WAVE ⁵³ | CHARISMA ³⁹ TRACER ⁵¹ TRA2P ¹¹ COMPASS | PLATO ⁴⁸ PEGASUS ⁴¹ ROCKET-AF ⁵⁵ |
| Adjudicated bleeding using trial-specific scale | AAA ³⁷ | | |
| Non-adjudicated bleeding or bleeding not reported | CLIPS ⁴³ POPADAD ⁴⁴ | CAPRIE ⁴⁰ | Antithrombotic Trialists' Collaboration ^{42,56} |

| Characteristic | Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152 | Rivaroxaban 5 mg bid N=9117 | Aspirin 100 mg N=9126 |
|----------------------------|--|--------------------------------|--------------------------|
| Age, years | 68 | 68 | 68 |
| BP, mmHg | 136/77 | 136/78 | 136/78 |
| Total cholest mg/dL | 162 | 162 | 162 |
| CAD, % | 91 | 90 | 90 |
| PAD, % | 27 | 27 | 27 |
| Previous Stroke, % | 3.8 | 3.8 | 3.7 |
| Previous MI,% | 61.8 | 62 | 62.7 |
| Heart failure,% | 21.4 | 21.5 | 21.7 |
| Diabetes, % | 38 | 38 | 38 |
| Lipid-low drugs, % | 90 | 90 | 89 |
| ACE-i/ARB, % | 71 | 72 | 71 |

% prior MI in “stable CAD” studies



% prior MI in “stable” CAD studies

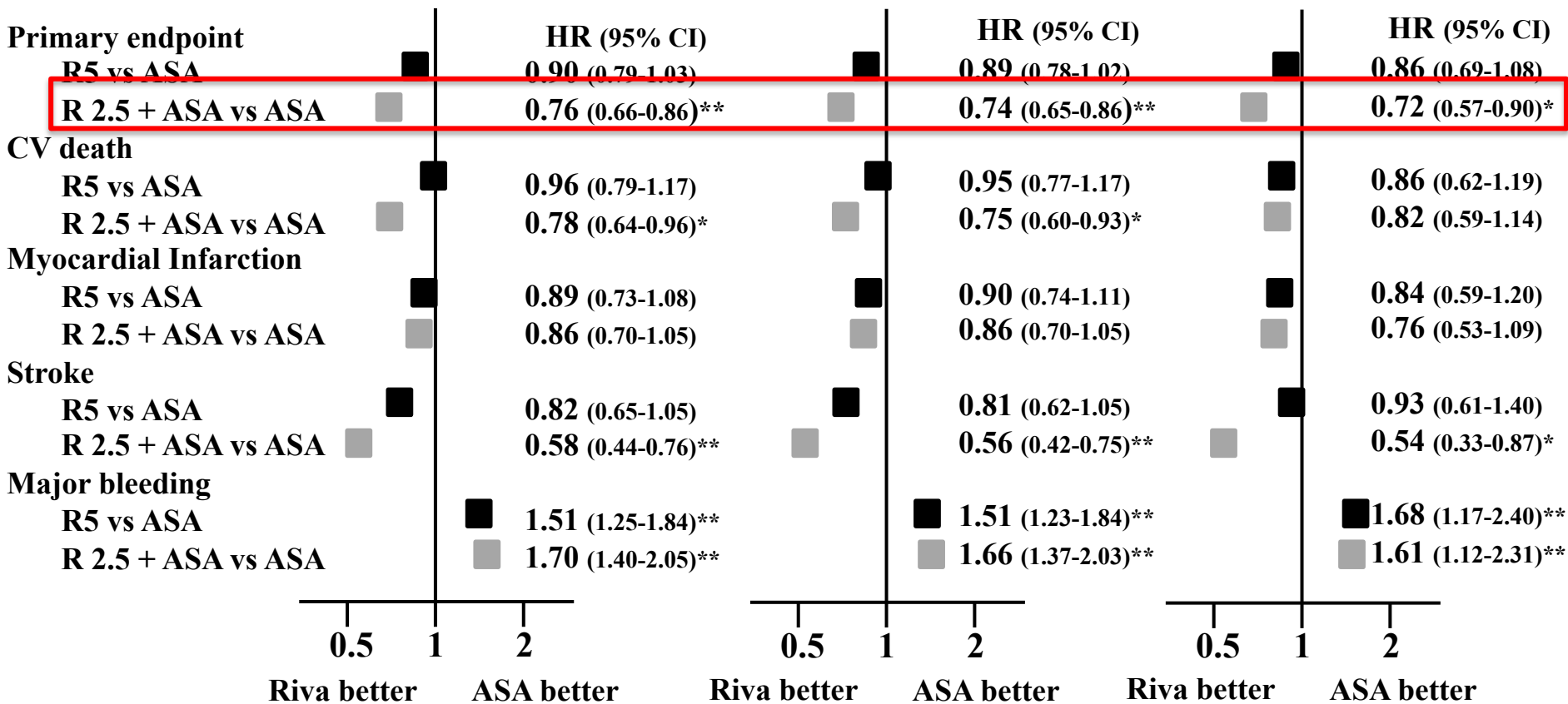


Primary EP: CV death, MI, stroke

**COMPASS
TOTALE**^{ref 17}
N=27.395

**COMPASS
CORONARY**^{ref 18}
N=24.824

**COMPASS
PAD**^{ref 19}
N=7.470



P value: *<0.05; **<0.001

Data: 02 Mar 2019

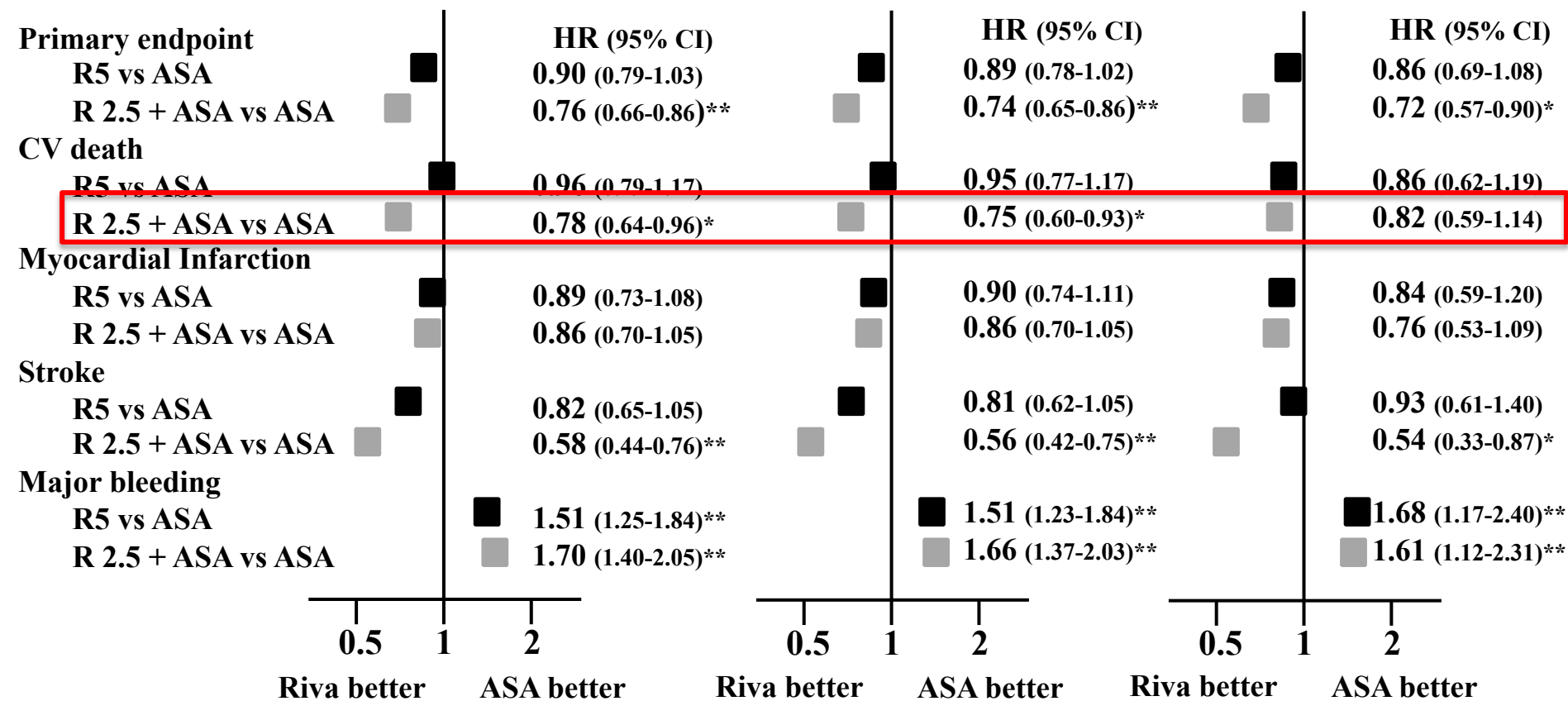
Evento: C&C 2019

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Data: 02 Mar 2019

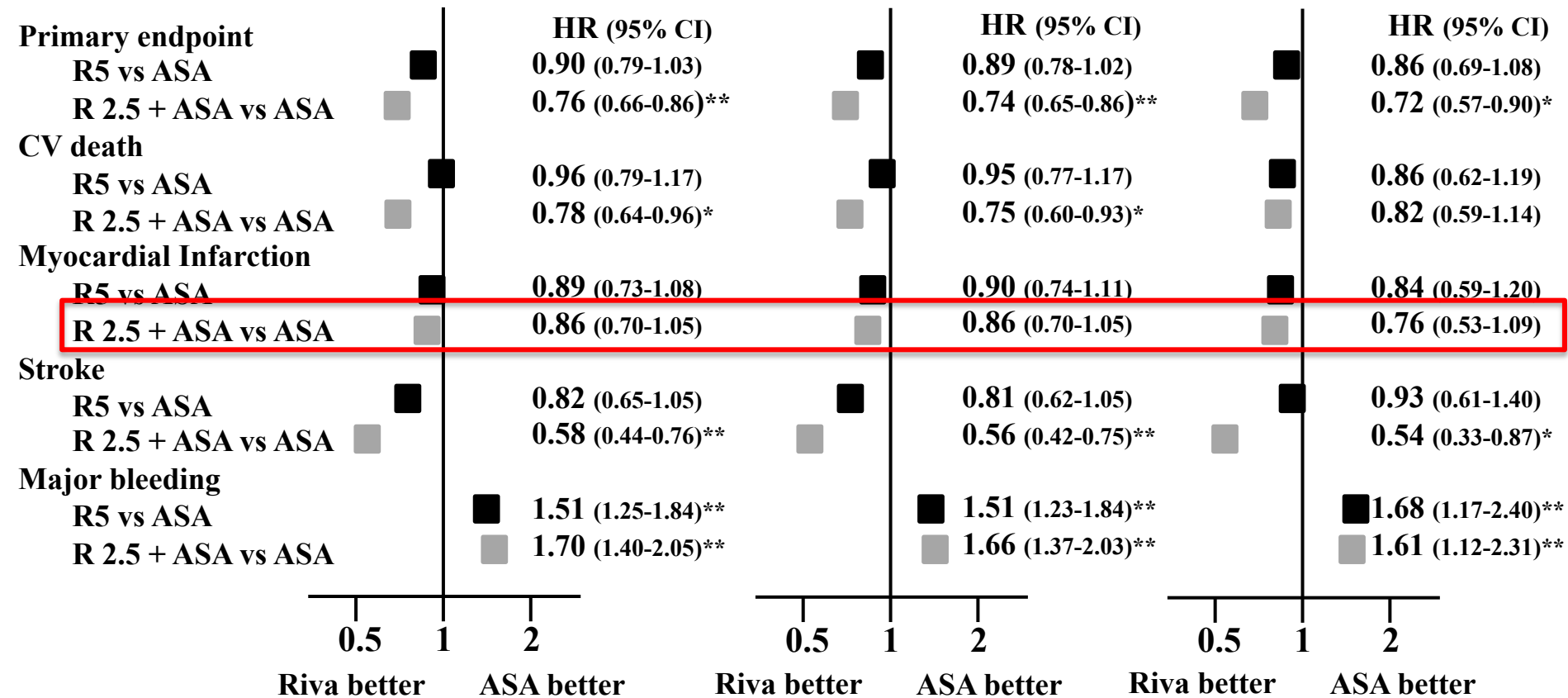
Evento: C&C 2019

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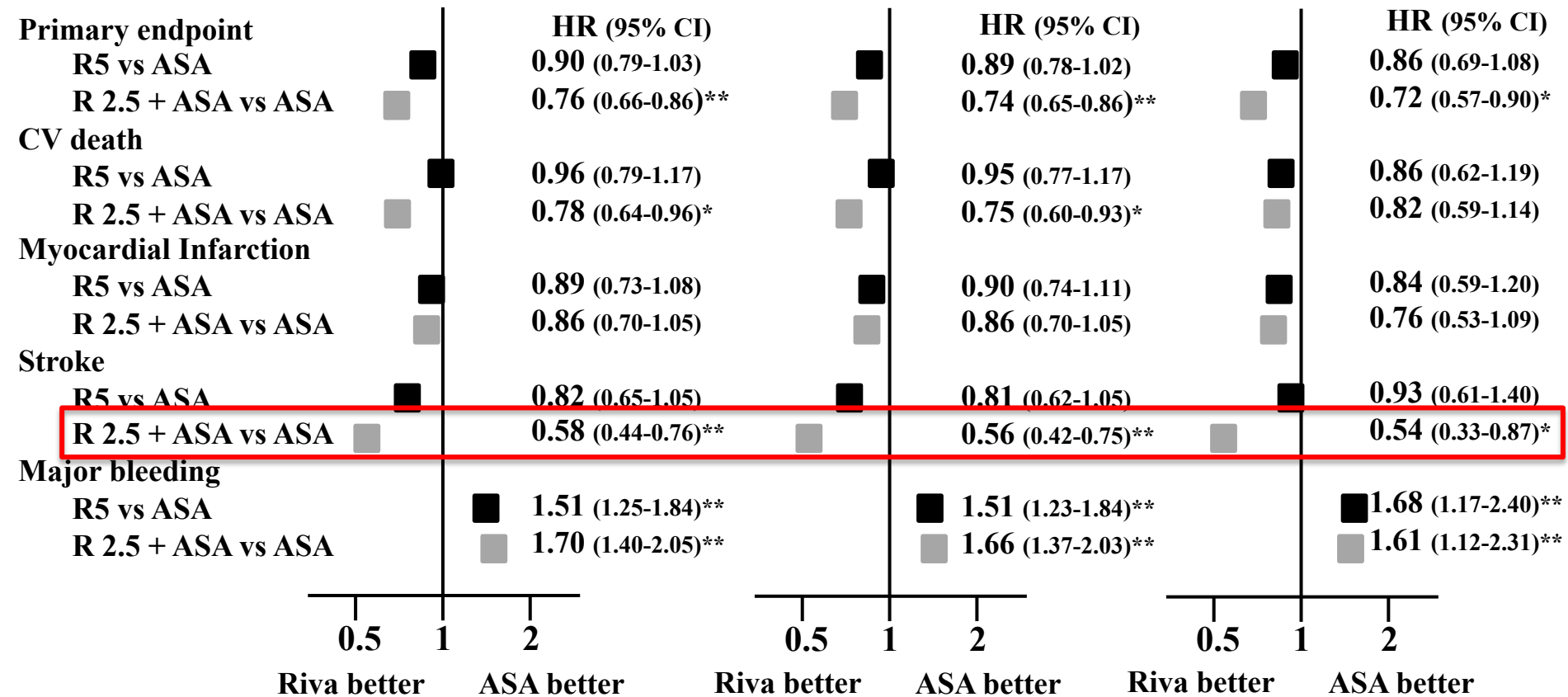
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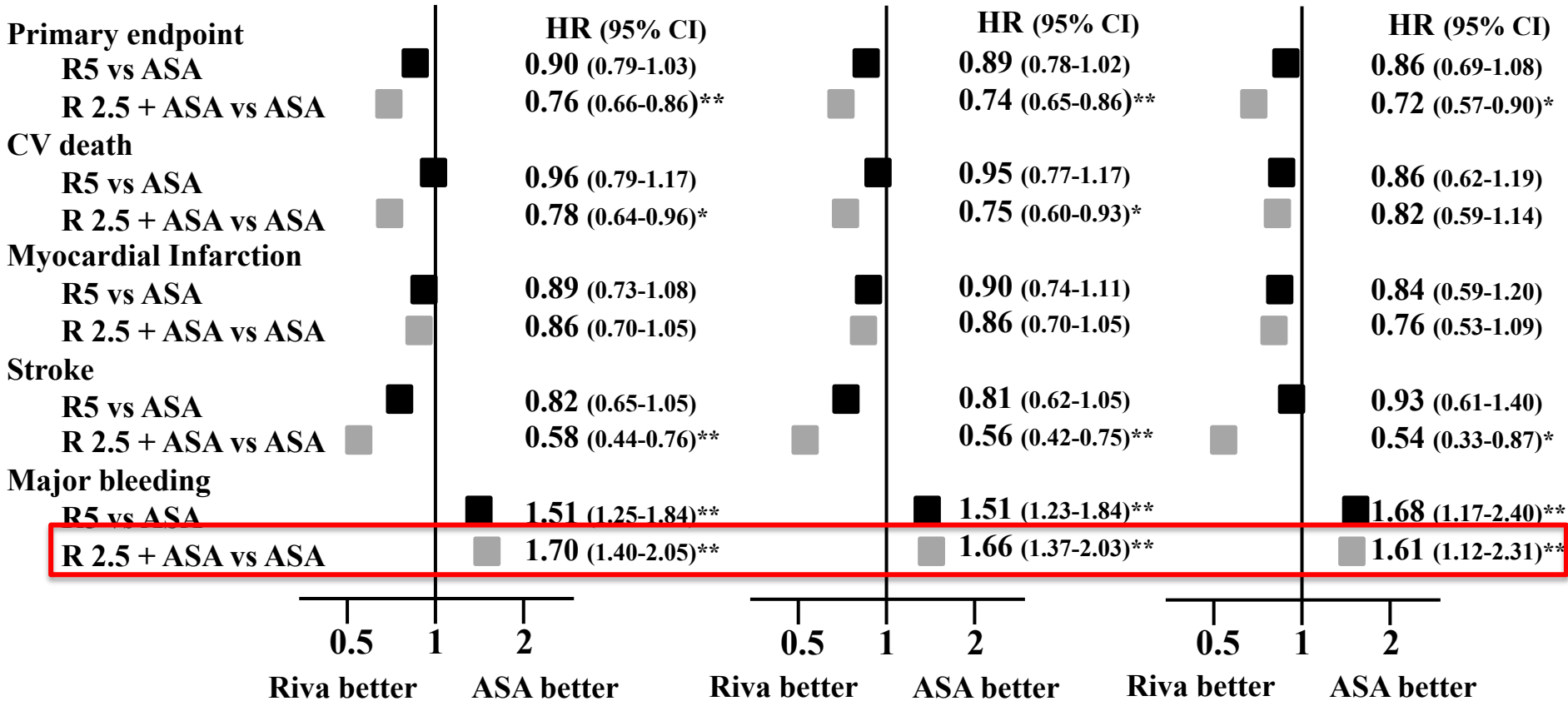
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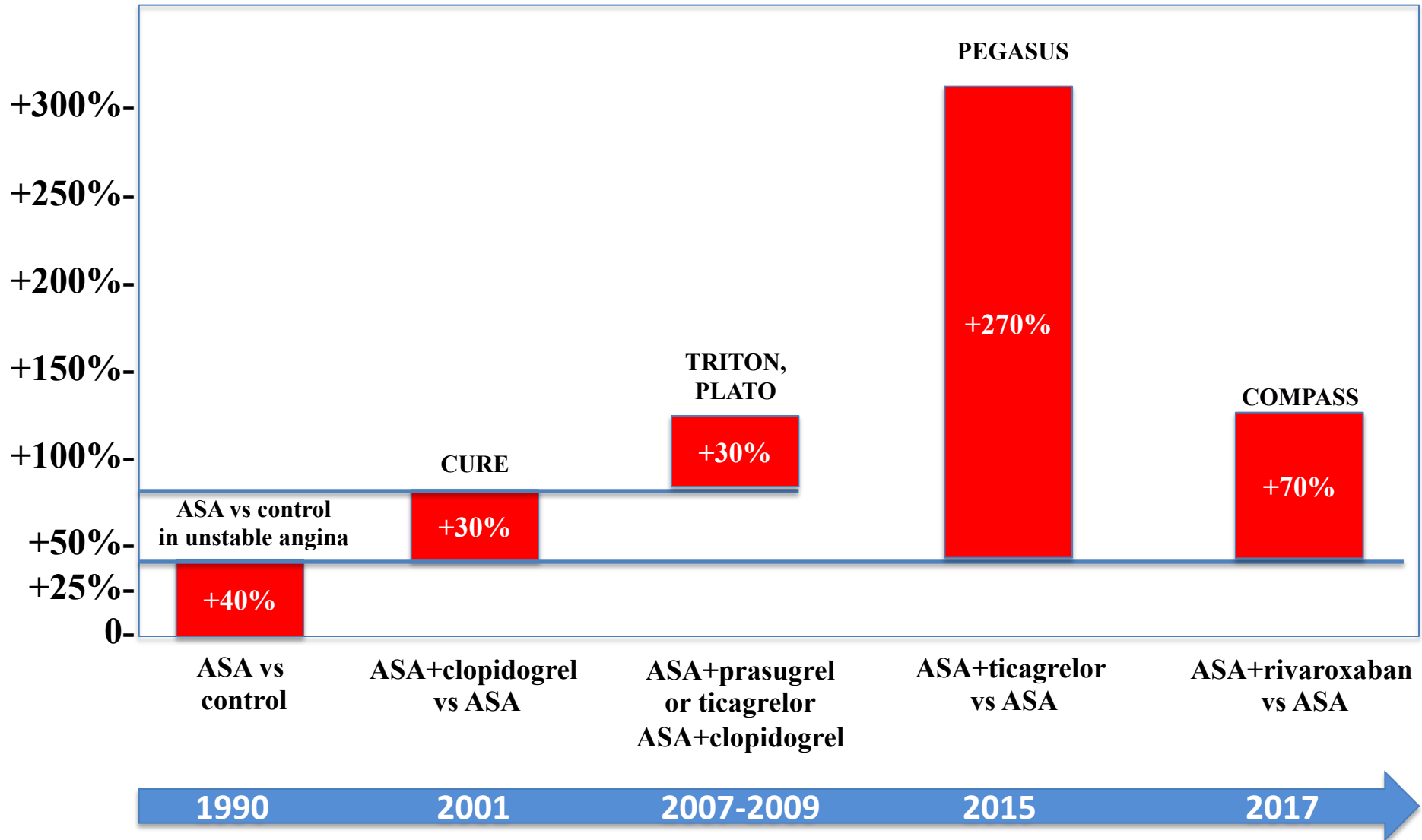


P value: * <0.05 ; ** <0.001

Data: 02 Mar 2019

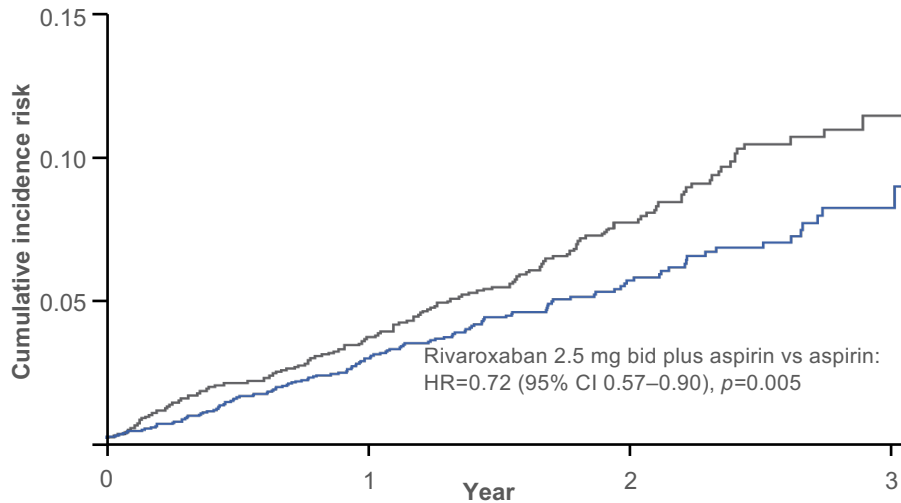
Evento: C&C 2019

L' aumento del rischio emorragico con l' aumento della potenza antitrombotica

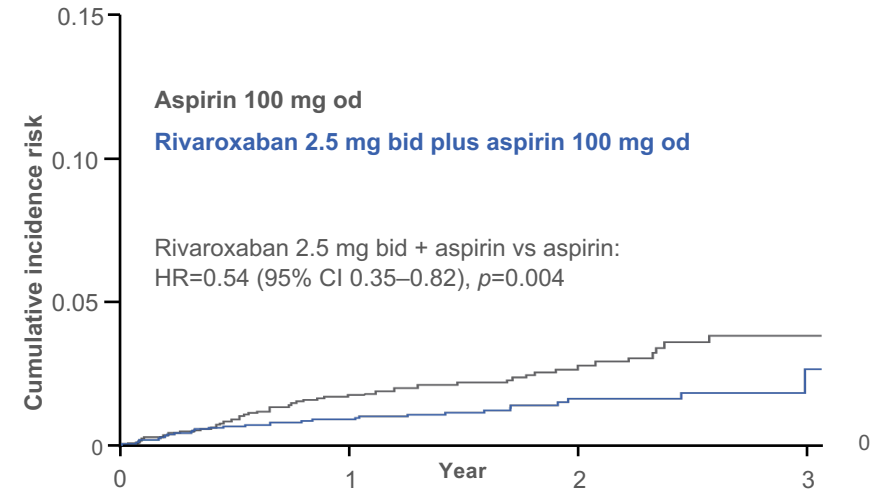


Significantly less MALE with rivaXa 2.5 mg bid plus ASA versus ASA

CV death, MI or stroke

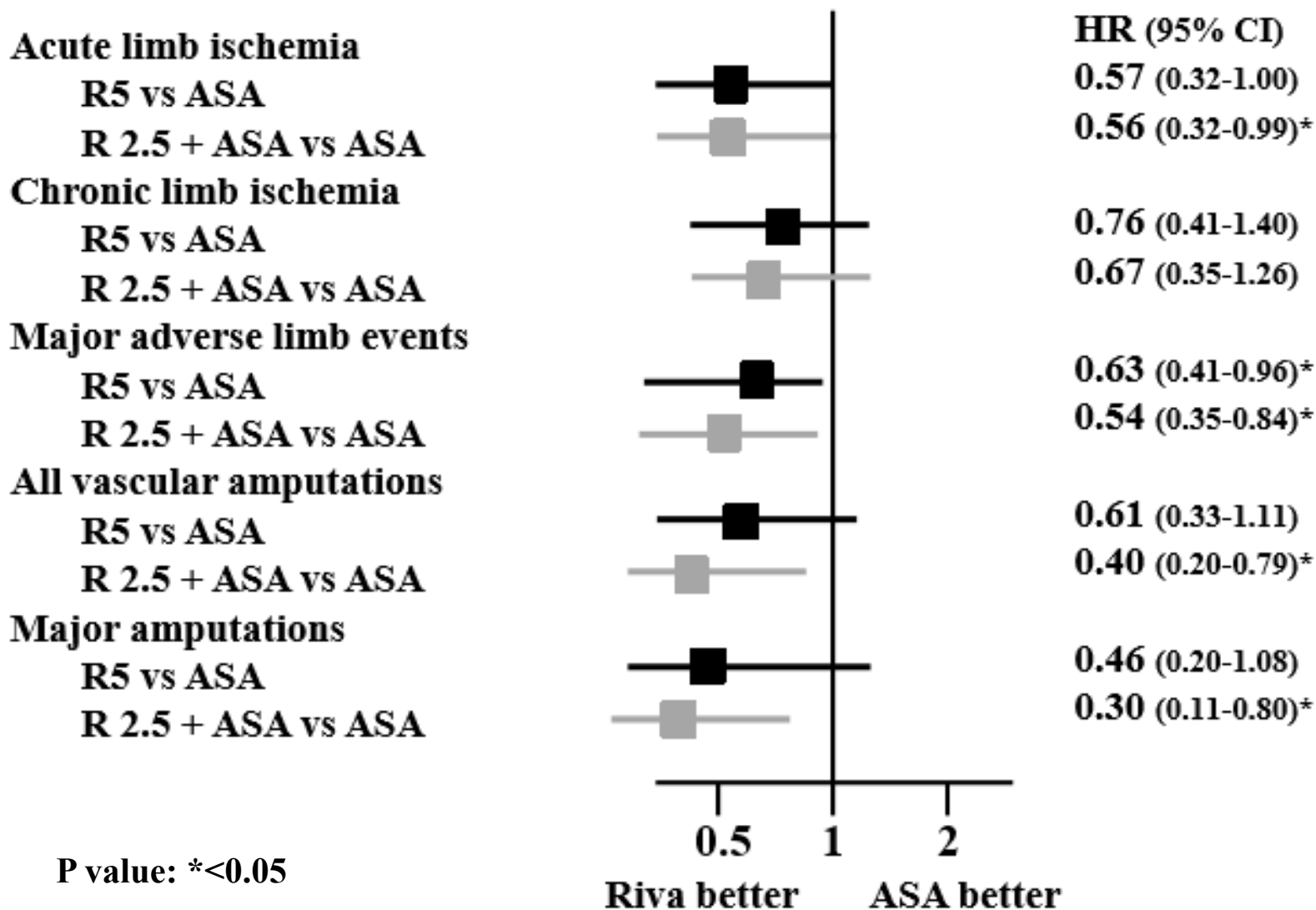


MALE including major amputation



1 in 4 events were limb events

Major Adverse Limb Events



Rivaroxaban 2.5 mg bid + Aspirin Improved Overall Survival in Patients with CAD or PAD

| Study / Treatment arm | Control | Intervention | HR | HR (95% CI) | p-value | NNT |
|----------------------------------|------------------|------------------|------|-------------|---------|------|
| | %/year | %/year | | | | |
| COMPASS¹ | | | | | | |
| Rivaroxaban 2.5 mg bid | 2.1 [†] | 1.8 [†] | 0.82 | | 0.01 | 333 |
| CHARISMA² | | | | | | |
| Clopidogrel 75 mg od | 2.3 [‡] | 2.1 [‡] | 0.91 | | 0.32 | 500 |
| PEGASUS³ | | | | | | |
| Ticagrelor 90 mg bid | 1.7 [¶] | 1.7 [¶] | 1.00 | | 0.99 | n.a. |
| Ticagrelor 60 mg bid | 1.7 [¶] | 1.6 [¶] | 0.89 | | 0.14 | 1000 |
| TRA2P-TIMI 50⁴ | | | | | | |
| Vorapaxar 2.5 mg od | 1.8 [¶] | 1.7 [¶] | 0.95 | | 0.41 | 1000 |

0,5 1 2

Favours intervention Favours control

Rivarovaban 2.5 vs aspirin

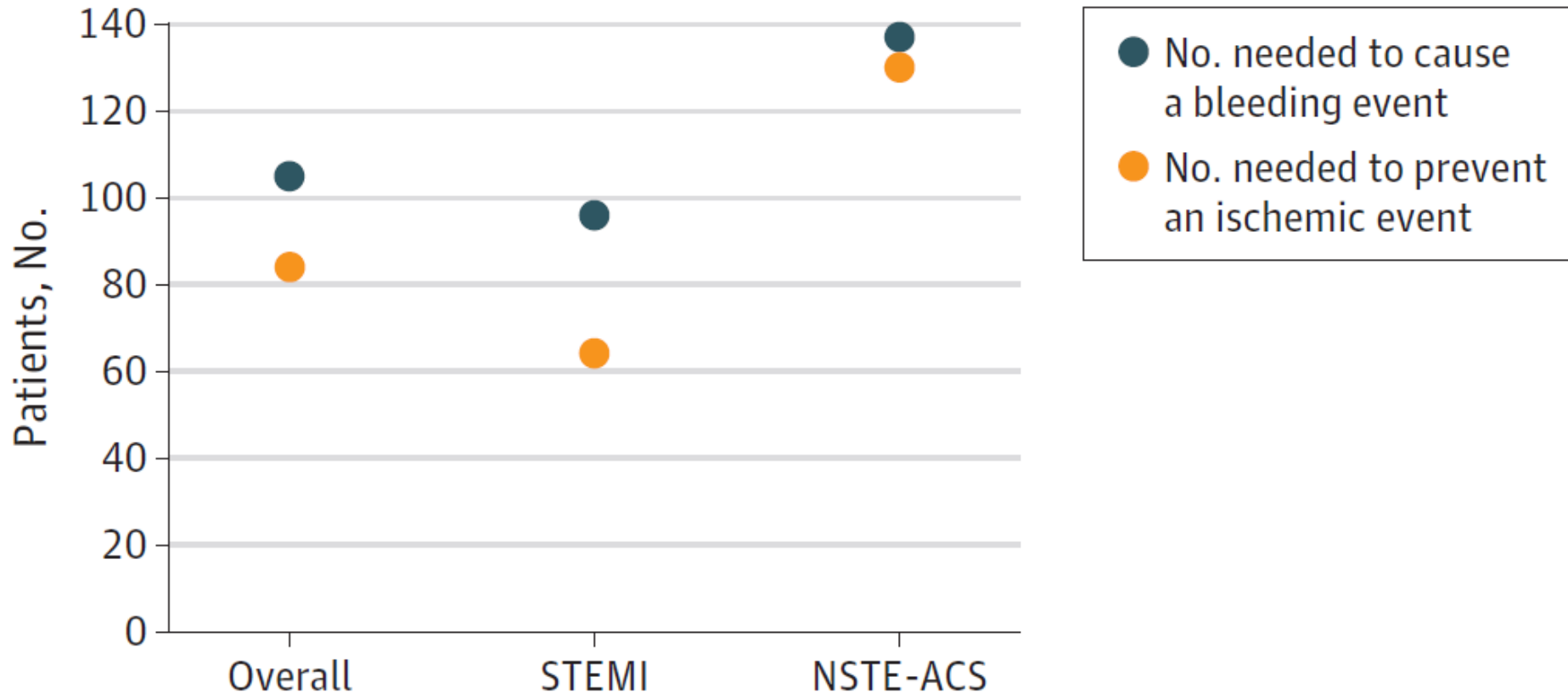
differenze di eventi a 3 anni

(N=18,278)

| | RivaXa 2.5 | Aspirina | NNT/NNH |
|-------------------------|-------------------|-------------------|------------|
| Primary endpoint | 379 (4.1%) | 496 (5.4%) | 77 |
| All-cause death | 313 (3.4%) | 378 (4.1%) | 143 |
| CV death | 160 (1.7%) | 203 (2.2%) | 200 |
| Major bleeding | 288 (3.1) | 170 (1.9) | 83 |

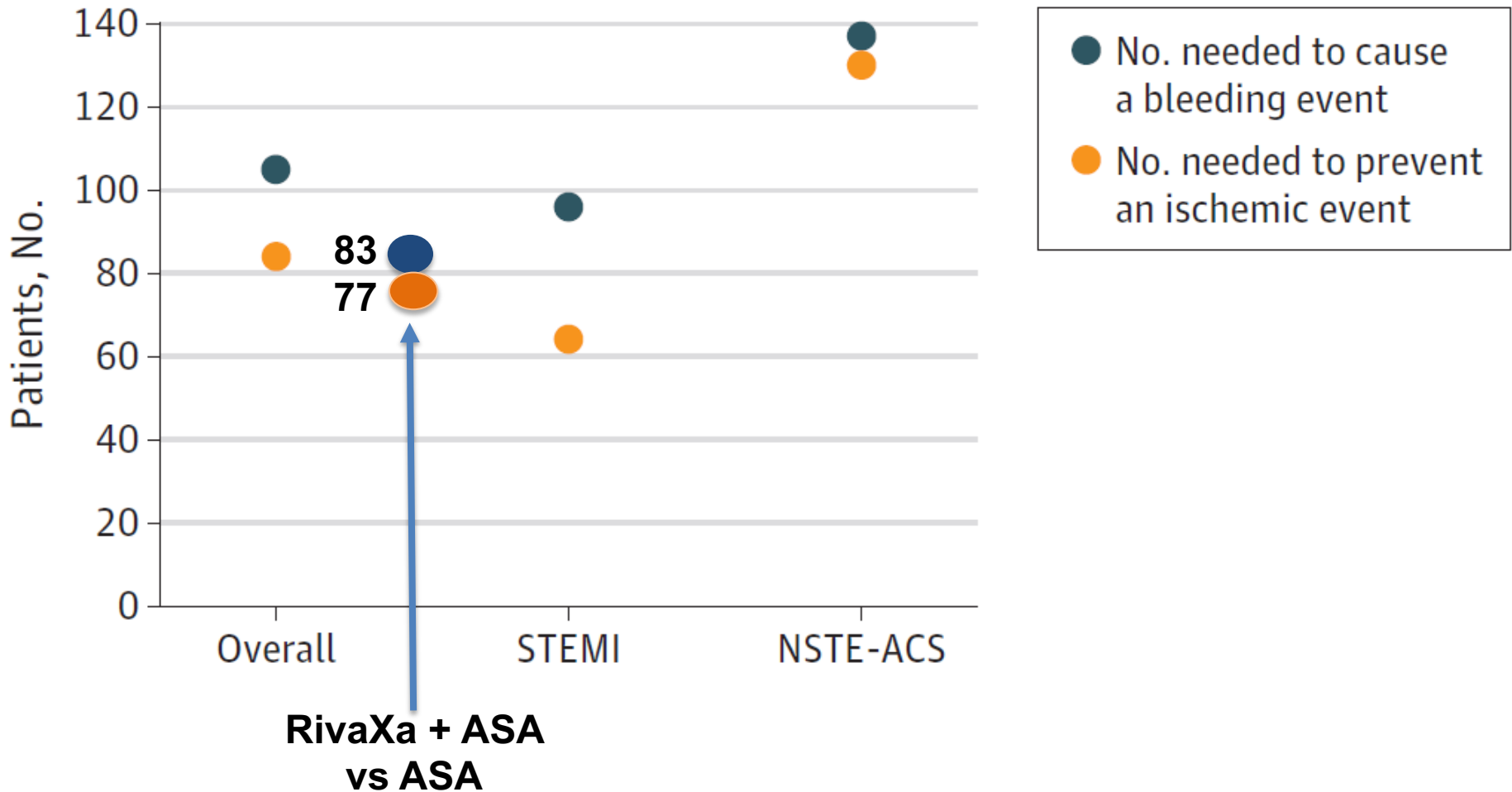
Direct Oral Anticoagulants in Addition to Antiplatelet Therapy for Secondary Prevention After Acute Coronary Syndromes

A Systematic Review and Meta-analysis

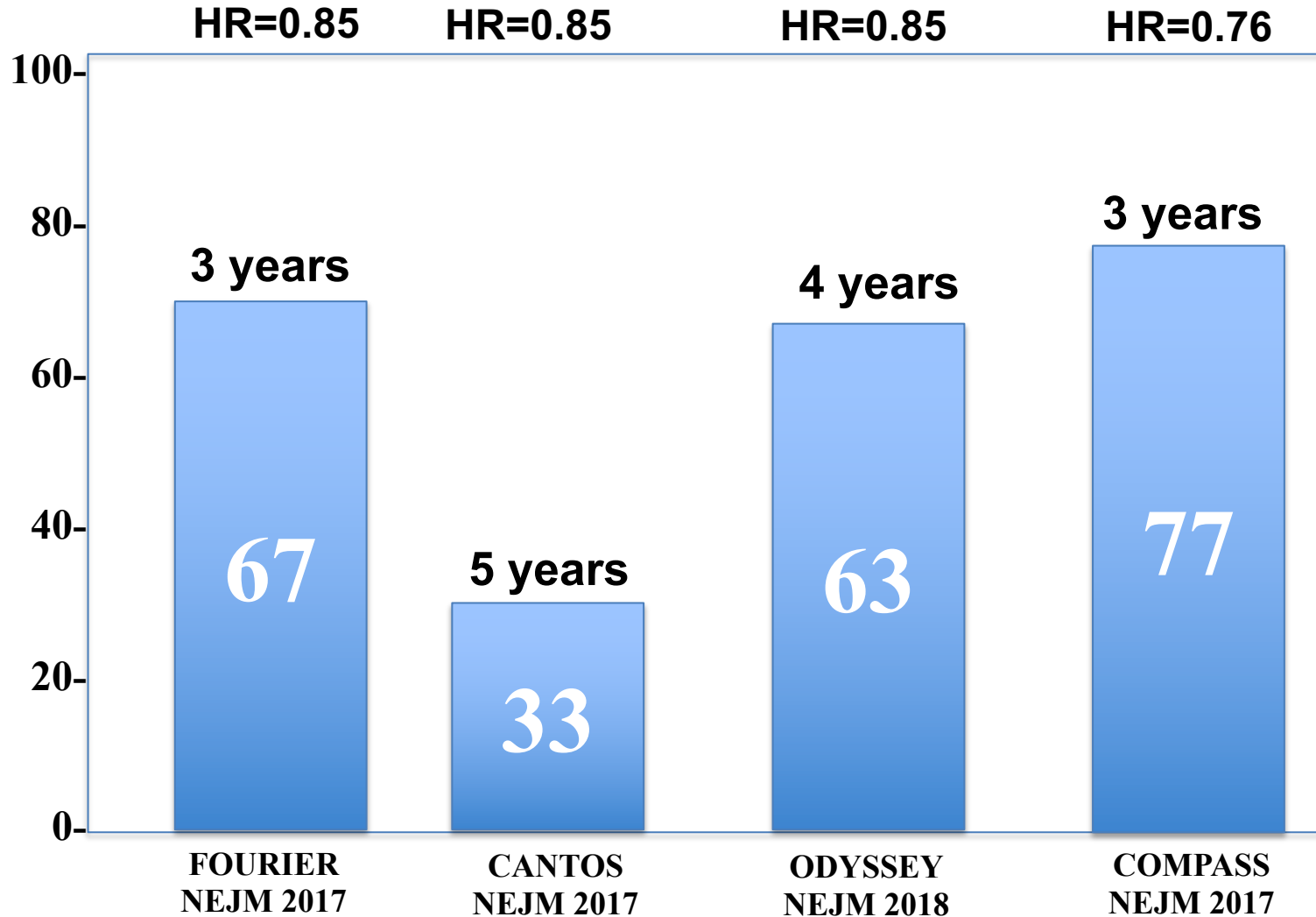


Direct Oral Anticoagulants in Addition to Antiplatelet Therapy for Secondary Prevention After Acute Coronary Syndromes

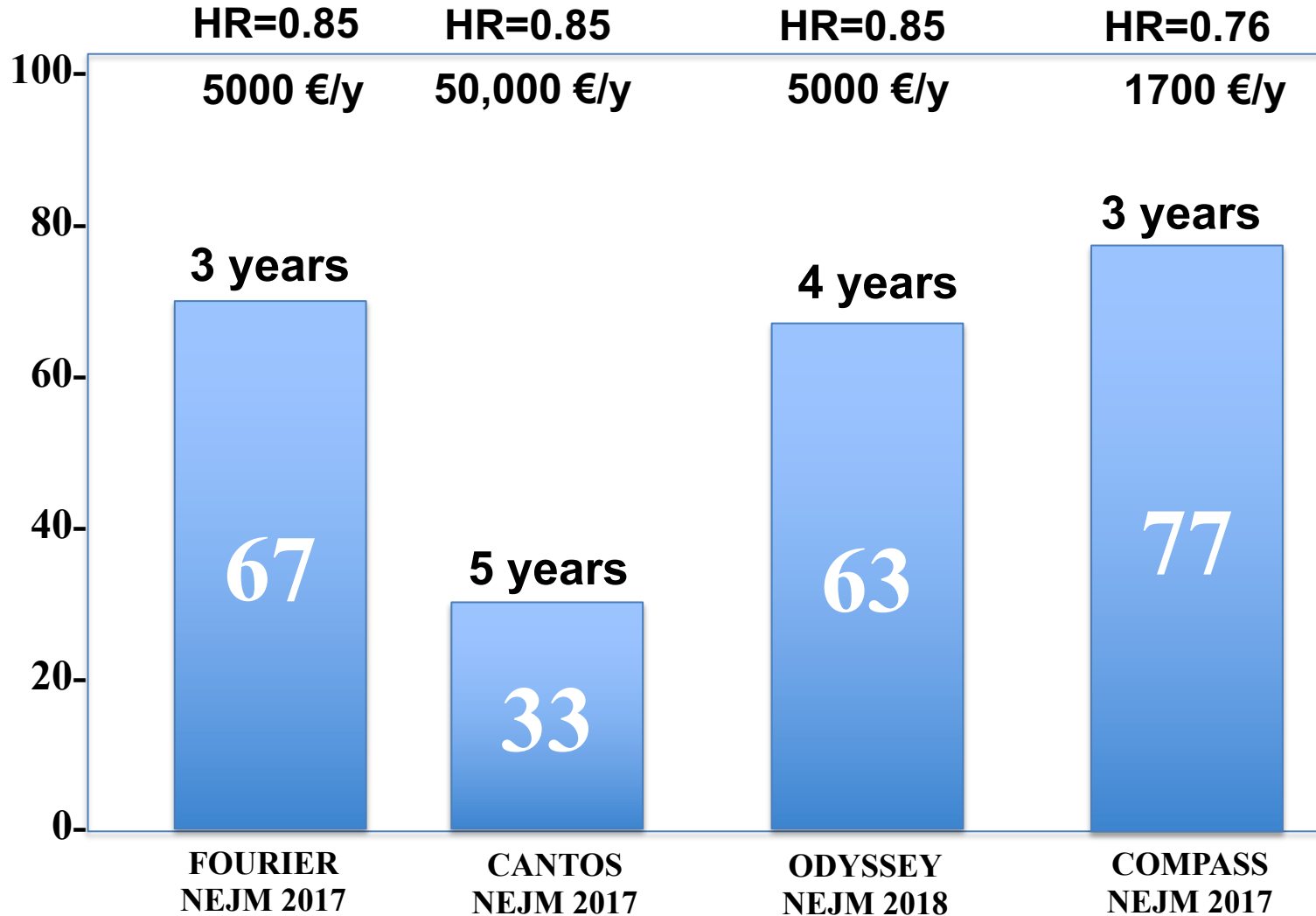
A Systematic Review and Meta-analysis



NNT to prevent 1 major CVE (CV death, MI, stroke)



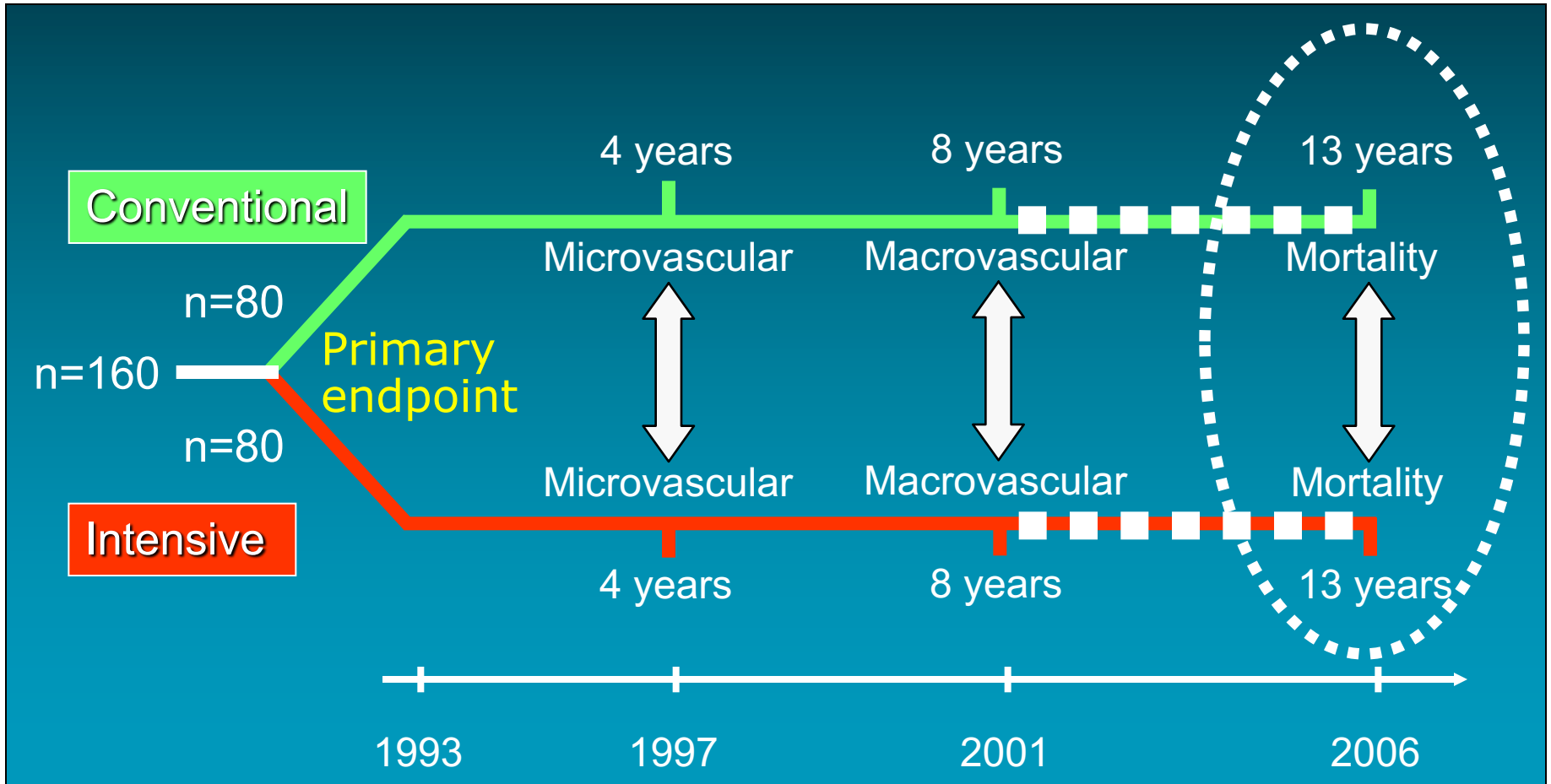
NNT to prevent 1 major CVE (CV death, MI, stroke)



Multifactorial intervention in type 2 diabetes

The Steno 2 study – 13 years follow up

Extendend study protocol



Multifactorial intervention in type 2 diabetes

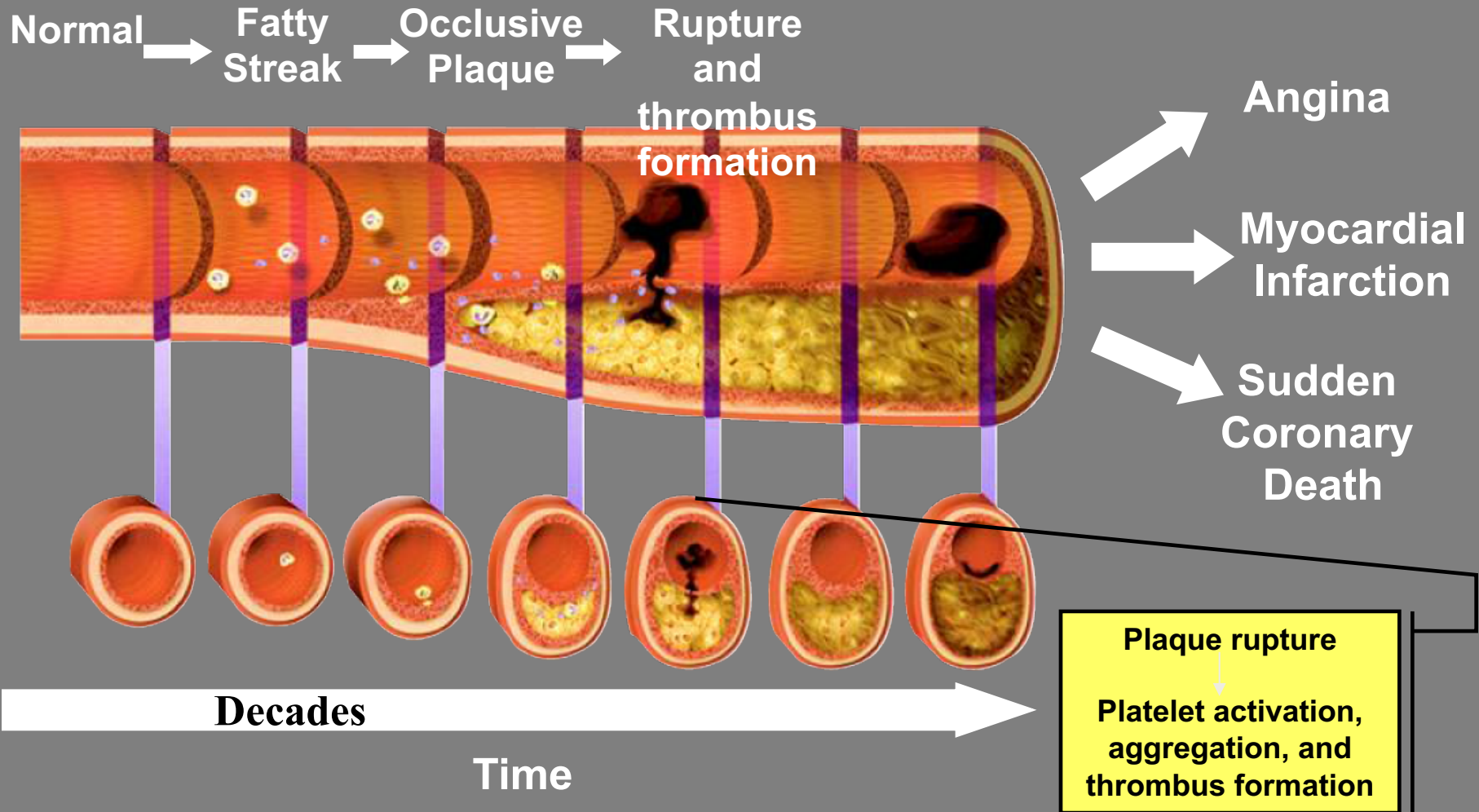
The Steno 2 study - 13 year follow up

| Impact of intensive therapy on | OR | 95% CI | ARR | p-value |
|--------------------------------|------|-----------|-----|---------|
| All-cause mortality | 0.54 | 0.32-0.89 | 20% | 0.015 |
| Cardiovascular mortality | 0.43 | 0.19-0.94 | 13% | 0.036 |
| Major cardiovascular events | 0.41 | 0.25-0.63 | 29% | <0.001 |

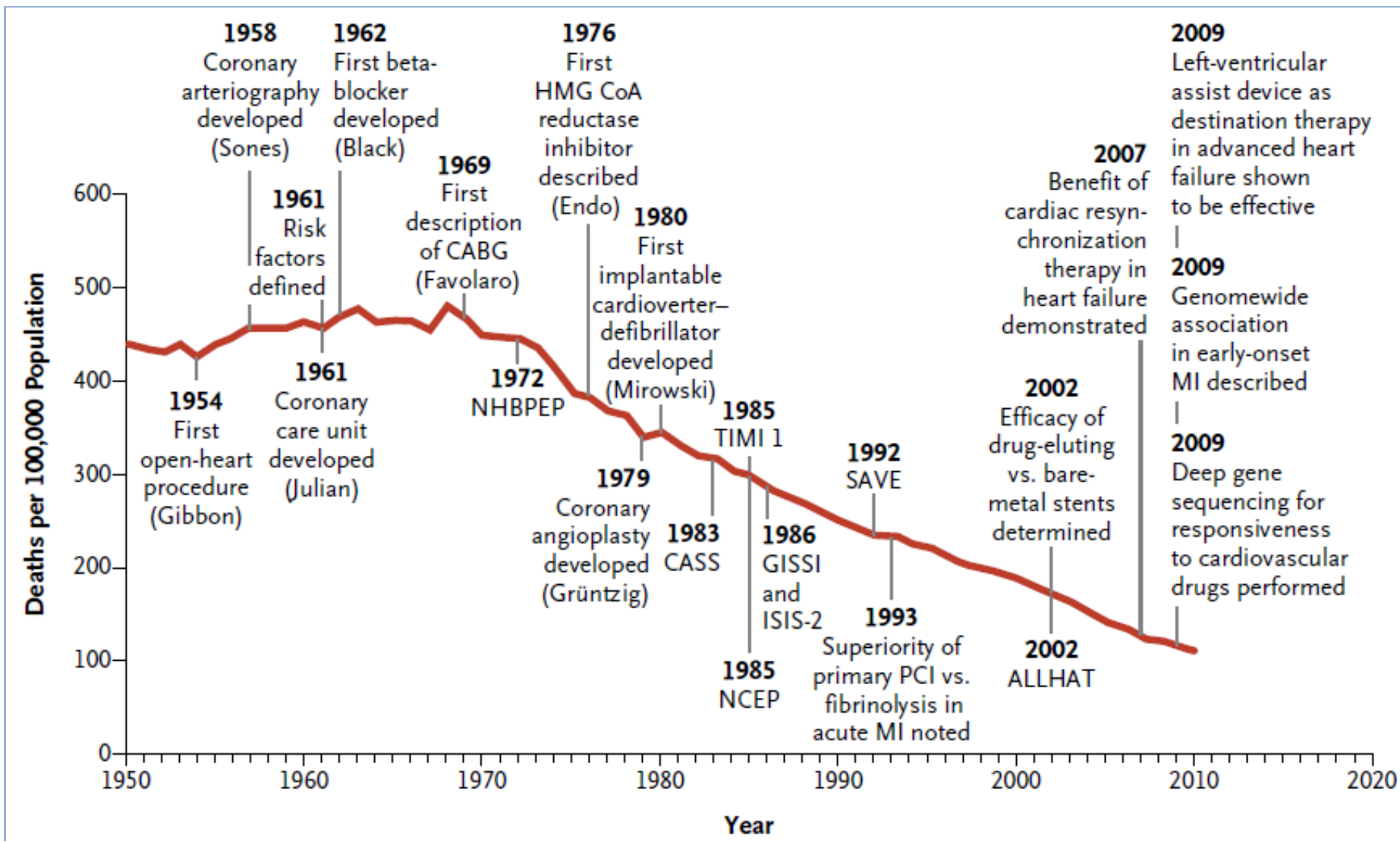
Number of patients needed to treat (NNT)
 to avoid one...

| | |
|----------------------------|---|
| Death | 5 |
| Cardiovascular death | 8 |
| Major cardiovascular event | 3 |
| Progression to nephropathy | 5 |

Progression of Atherosclerosis Atherothrombosis

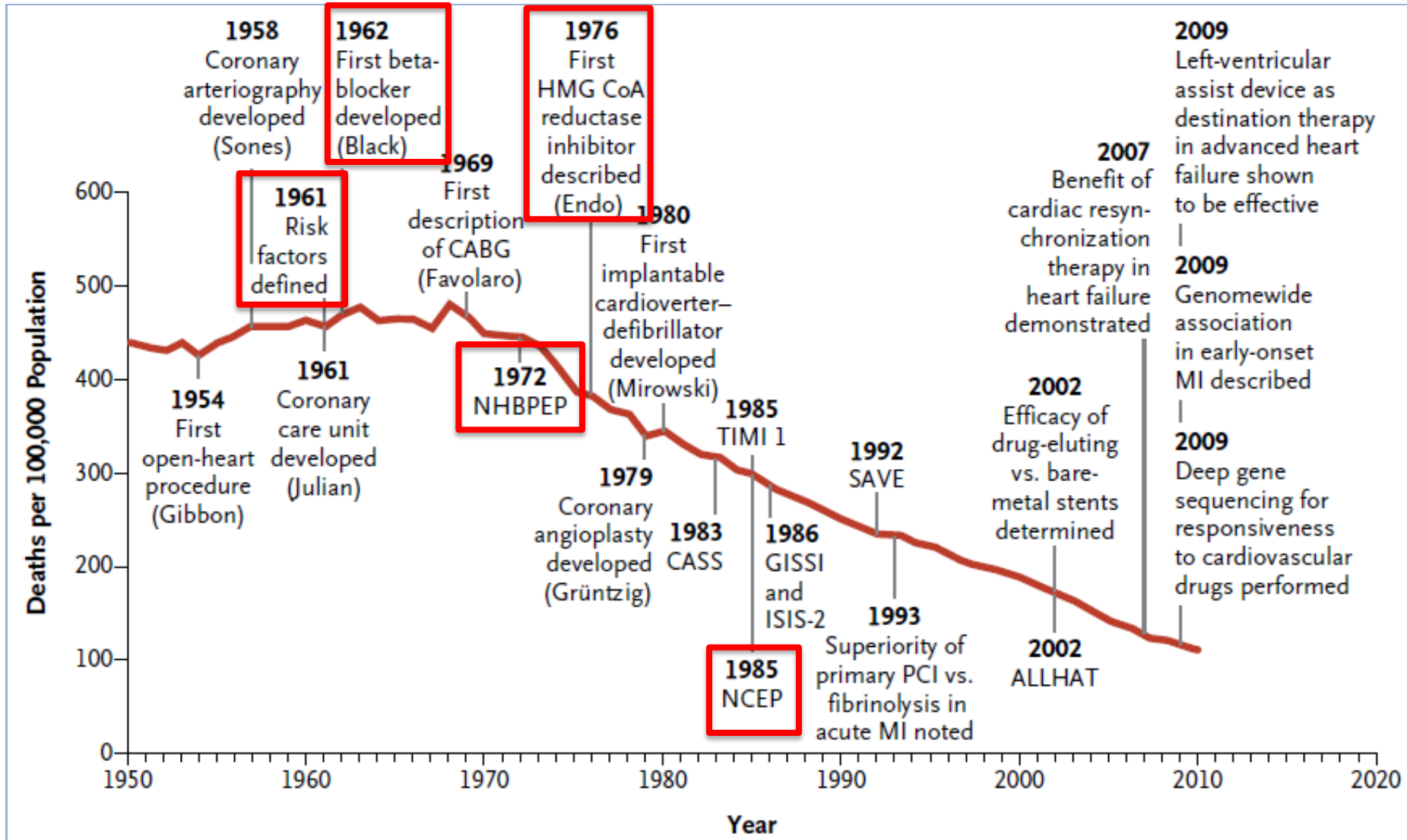


Decline in deaths from CV disease in relation to scientific advances



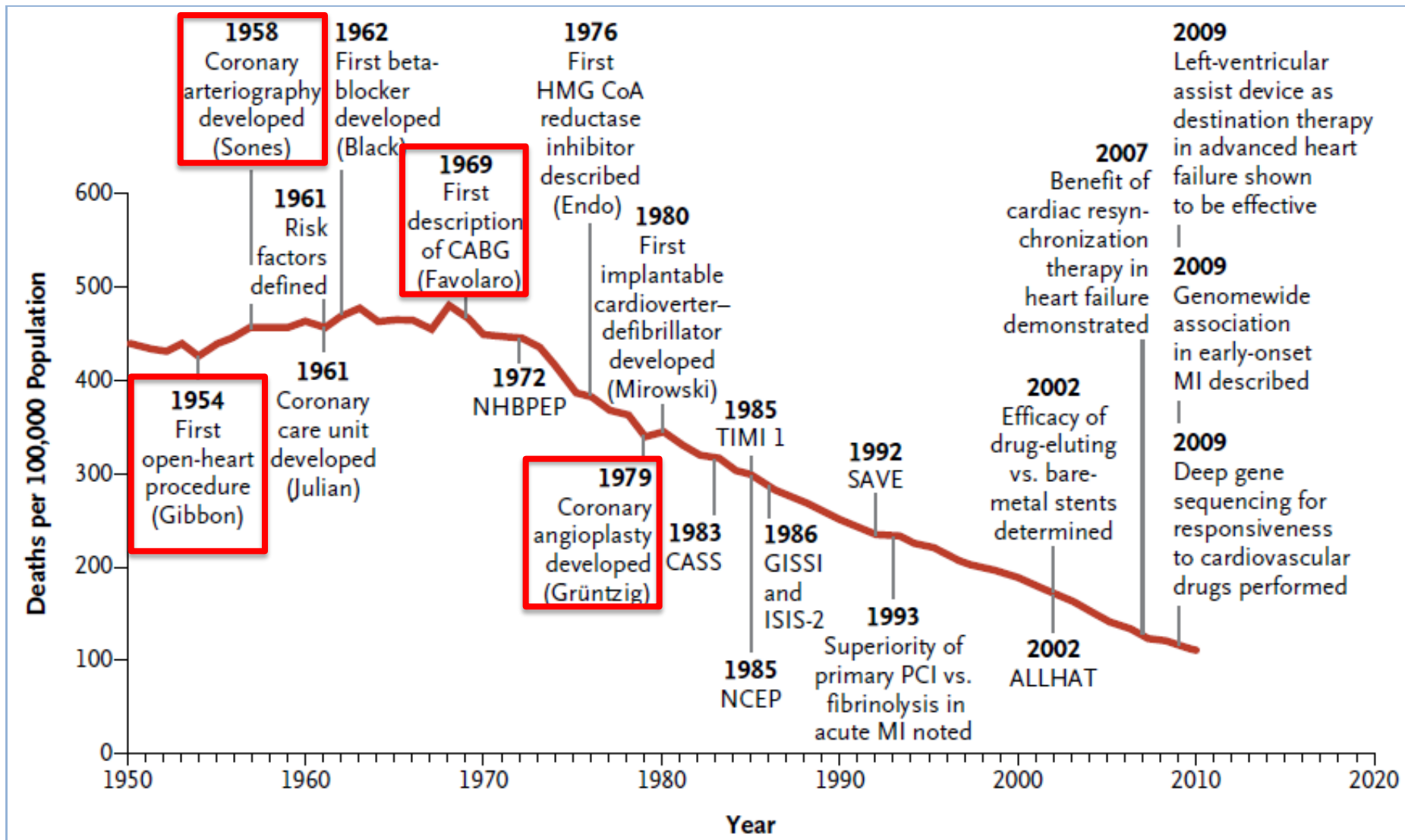
Decline in deaths from CV disease and scientific advances

I. Wide application of effective drug therapies



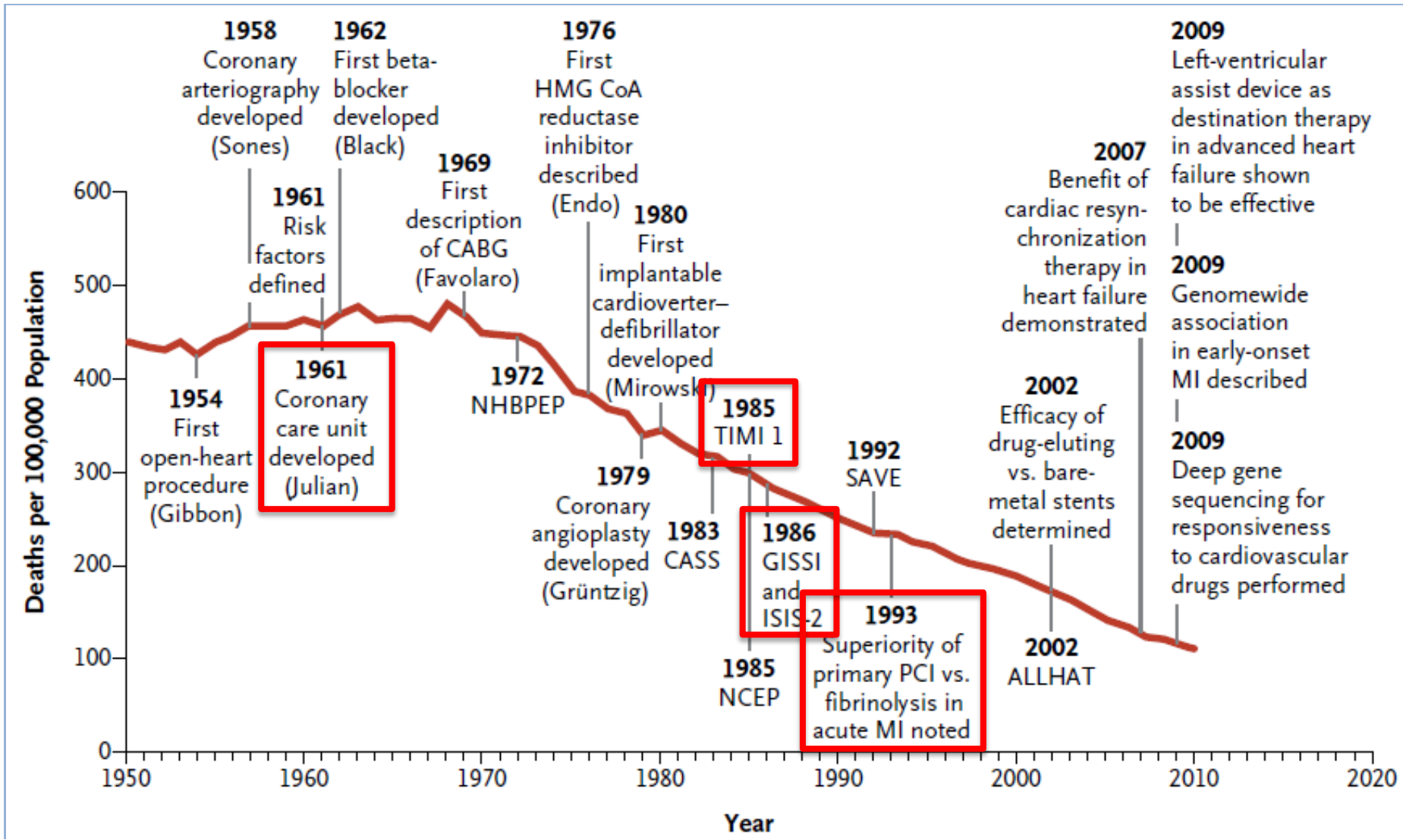
Decline in deaths from CV disease and scientific advances

II. coronary revascularization



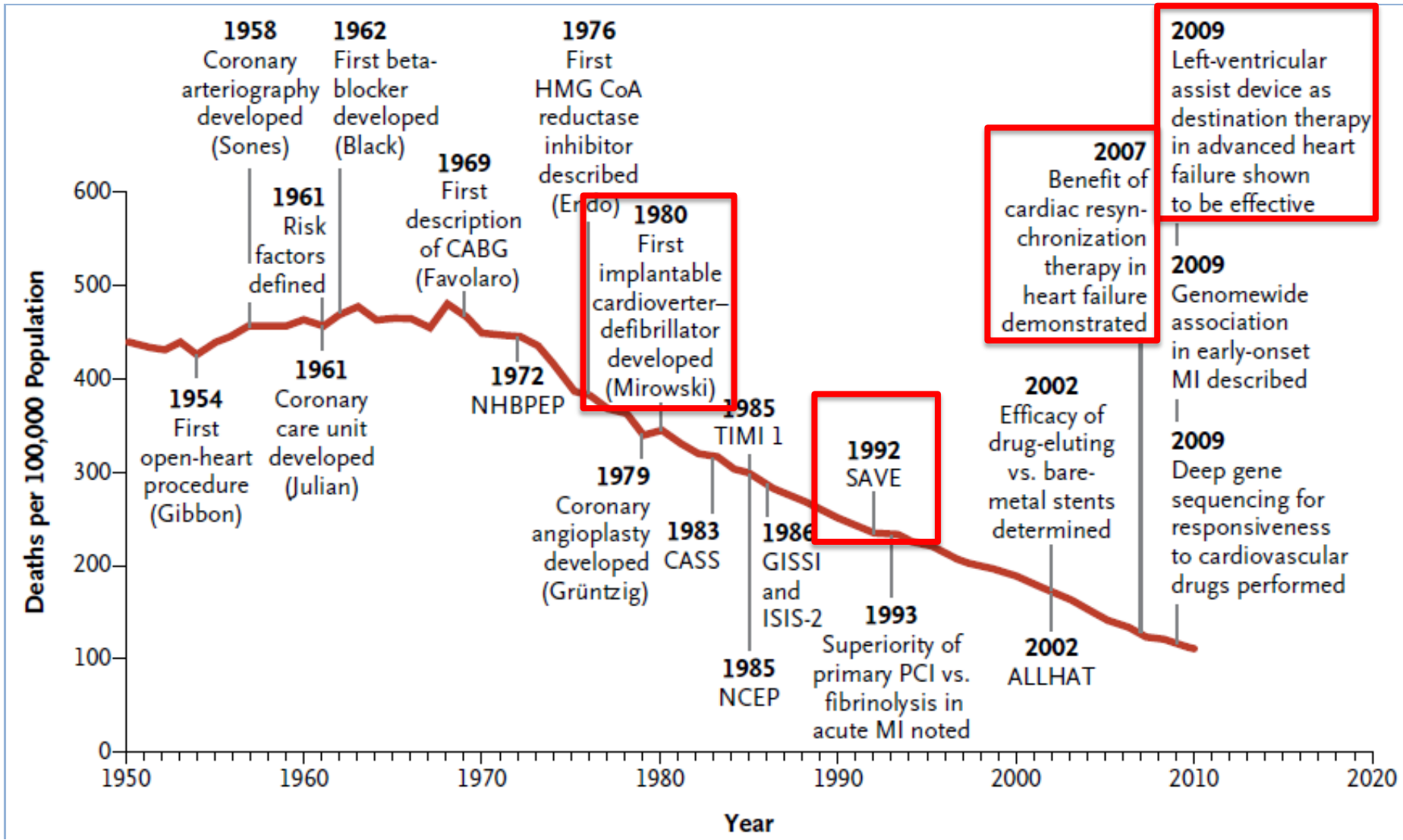
Decline in deaths from CV disease and scientific advances

III. Advances in acute care and reperfusion therapy for AMI



Decline in deaths from CV disease and scientific advances

IV. Advances in care fo heart failure



CONCLUSIONI

- **Le terapie antitrombotiche hanno un ruolo certo nella PREVENZIONE SECONDARIA degli eventi cardiovascolari**
- **Aspirina alla dose di 75-100 mg ha dimostrato un favorevole rapporto rischio-beneficio in questa indicazione**
- **Lo studio COMPASS ha confermato l'ulteriore riduzione di eventi ischemici con rivaroxaban 2.5 mg x 2 associato ad aspirina**
- **Come per l'associazione tra farmaci antiplastrinici, l'eccesso di sanguinamento di rivaroxaban associato ad aspirina richiede una adeguata selezione e informazione del paziente**
- **L'associazione di rivaroxaban e aspirina presenta un favorevole rapporto costo-beneficio tra le recenti terapie di prevenzione secondaria.**
- **Il beneficio maggiore è ottenuto dal CONTROLLO AGGRESSIVO DEI FATTORI DI RISCHIO**