Anti-Thrombotic Therapy – Update 2017

Sophia-Antipolis (France), February 23-25 2017

European Heart House

SESSION 6: NOACs BEYOND ATRIAL FIBRILLATION

February 24 2017

16:00-17:00

NOACs in ACS

Raffaele De Caterina

"G. d'Annunzio" University – Chieti and
"G. Monasterio" Foundation – Pisa, Italy

February 24, 2017 – 16:40-16:55 – 15 min. + 5 disc.

Prof. Raffaele De Caterina
Conflicts of Interest

- Co-author ESC Guidelines on Atrial Fibrillation 2010-2012
- Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE-AF, Re-DUAL PCI
- Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck

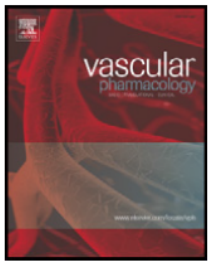
Triple therapy - one common denominator: targeting thrombin receptor or activity

Vascular Pharmacology 81 (2016) 1–14

Contents lists available at ScienceDirect

Vascular Pharmacology

journal homepage: www.elsevier.com/locate/vph



Review

Targeting thrombin long-term after an acute coronary syndrome: Opportunities and challenges

Raffaele De Caterina [a,b,*], Shinya Goto [c]

[a] Institute of Cardiology and Center of Excellence on Aging, G. d'Annunzio University — Chieti-Pescara, Pisa, Italy
[b] G. Monasterio Foundation, Pisa, Italy
[c] Department of Medicine (Cardiology), Tokai University School of Medicine, Isehara, Japan

NOACs in ACS – 2 different scenarios

1. ACS in the setting of AF
2. ACS without AF

EUROPEAN HEART HOUSE

Anti-Thrombotic Therapy – Update 2017

Thursday 23 February – Saturday 25 February, 2017

Thrombosis
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

SESSION 9: COEXSISTING ATRIAL FIBRILLATION AND CAD – Chairs: R. De Caterina and S.D. Kristensen

10:50-11:05 Stable coronary artery disease, elective stenting and atrial fibrillation – K. Huber
11:05-11:10 Discussion
11:10-11:25 After an ACS – R. De Caterina
11:25-11:30 Discussion

NOACs in ACS – 2 different scenarios

1. ACS in the setting of AF
2. ACS without AF

NOACs in ACS – 2 different scenarios

1. ACS in the setting of AF
2. ACS without AF
   a. The Rationale
   b. The Implementation

Easy take-home message:

- Nothing really new in the past two years, but stay tuned, because things may quickly change

NOACs in ACS without AF

- The Rationale
- The Implementation

NOACs in ACS without AF

- The Rationale
- The Implementation

Double Antiplatelet Therapy (ASA + CLOPIDOGREL)

- ✓ CURE
- ✓ PCI-CURE
- ✓ CREDO

- ✓ For all patients, immediate 300 mg loading dose of clopidogrel is recommended, followed by 75 mg clopidogrel daily (I-A). Clopidogrel should be maintained for 12 months unless there is an excessive risk of bleeding (I-A).

New $P2Y_{12}$ ADP receptor antagonists

Drug	Type	Route	Action	Dose	MPI*	Trial
Prasugrel	Hepatic Conv	Oral	Irreversible binding	LD 60 mg - MD 10 mg	70% (<1h)	TRITON
Cangrelor	Direct Inh.	Parenteral	Competitive binding	4 mcg/kg/ min	95% (<5 min)	CHAMPION
AZD-6140 Ticagrelor	Direct Inh.	Oral	Competitive binding	90 mg x 2	95% (2-4h)	PLATO

*MPI = mean platelet inhibition

A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A
• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[e] for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	I	B
• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[e]	I	B
• Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	I	B

European Heart Journal Advance Access published August 29, 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

Thus, there appear to be differences between the 2 new $P2Y_{12}$ oral inhibitors

Prasugrel

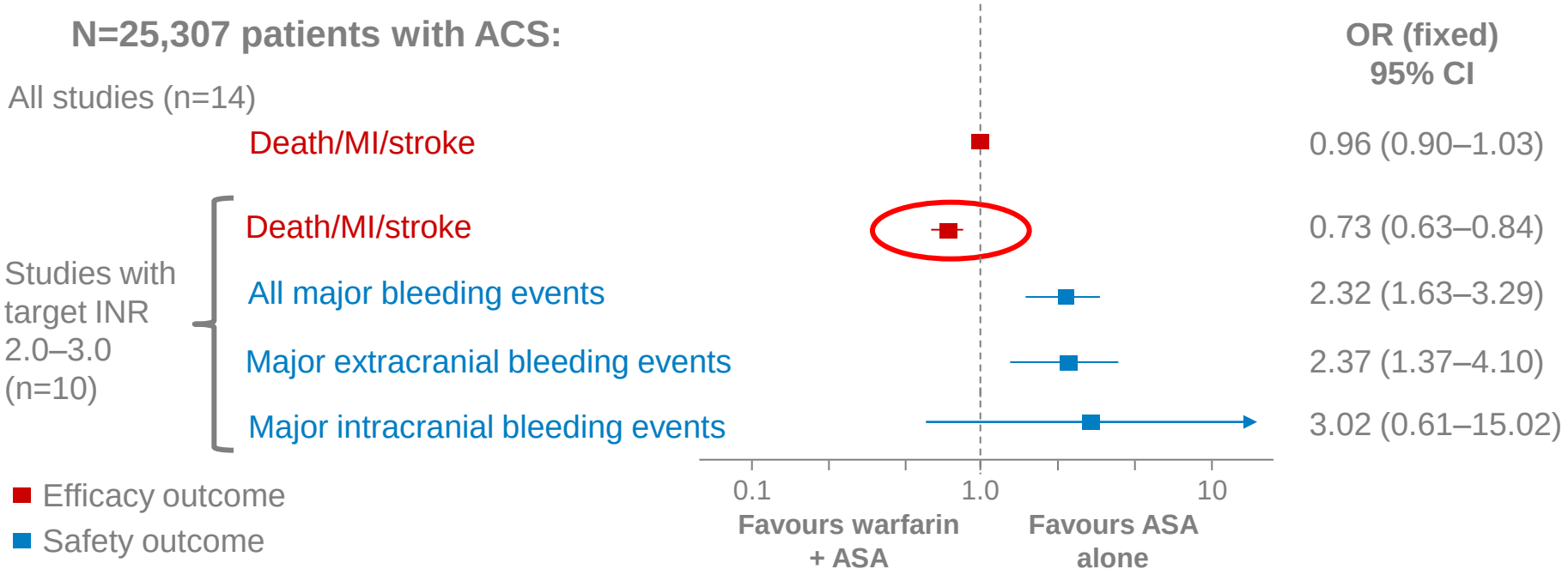
- ✓ Only in patients undergoing PCI
- ✓ Only in clopidogrel-naive patients
- ✓ Not in patients with previous stroke
- ✓ Careful in >75 yo with dose adjustment
- ✓ Not to be given with pretreatment in NSTEMI
- ✓ Irreversible inhibitor

Ticagrelor

- ✓ Both in patients treated invasively and non-invasively
- ✓ Also in clopidogrel pretreated patients
- ✓ Not in patients with prior ICH
- ✓ No dose adjustment in the elderly >75
- ✓ Pretreatment in STEMI not greatly effective, but not harmful
- ✓ Reversible inhibitor, with faster offset of effect

Why adding an anticoagulant long-term?

Meta-analysis: ASA + warfarin reduced CV outcomes vs ASA alone

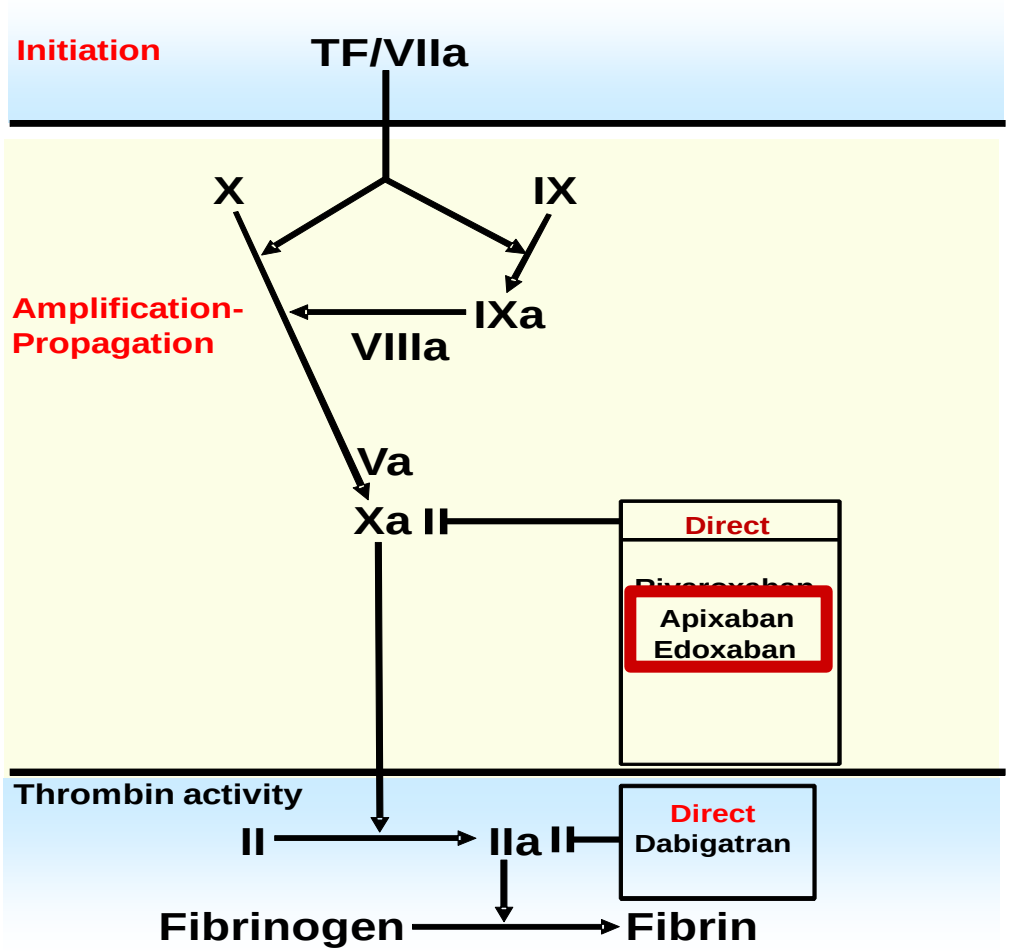


- Warfarin + ASA versus ASA alone:
  - Reduces death/MI/stroke only when the correct therapeutic dose is applied (INR 2.0–3.0)
  - Increases the risk of major bleeding events

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; CI, confidence interval; CV, cardiovascular; INR, international normalized ratio; MI, myocardial infarction; OR, odds ratio.

Andreotti *et al. Eur Heart J* 2006;27:519–26.

A new era in anticoagulation

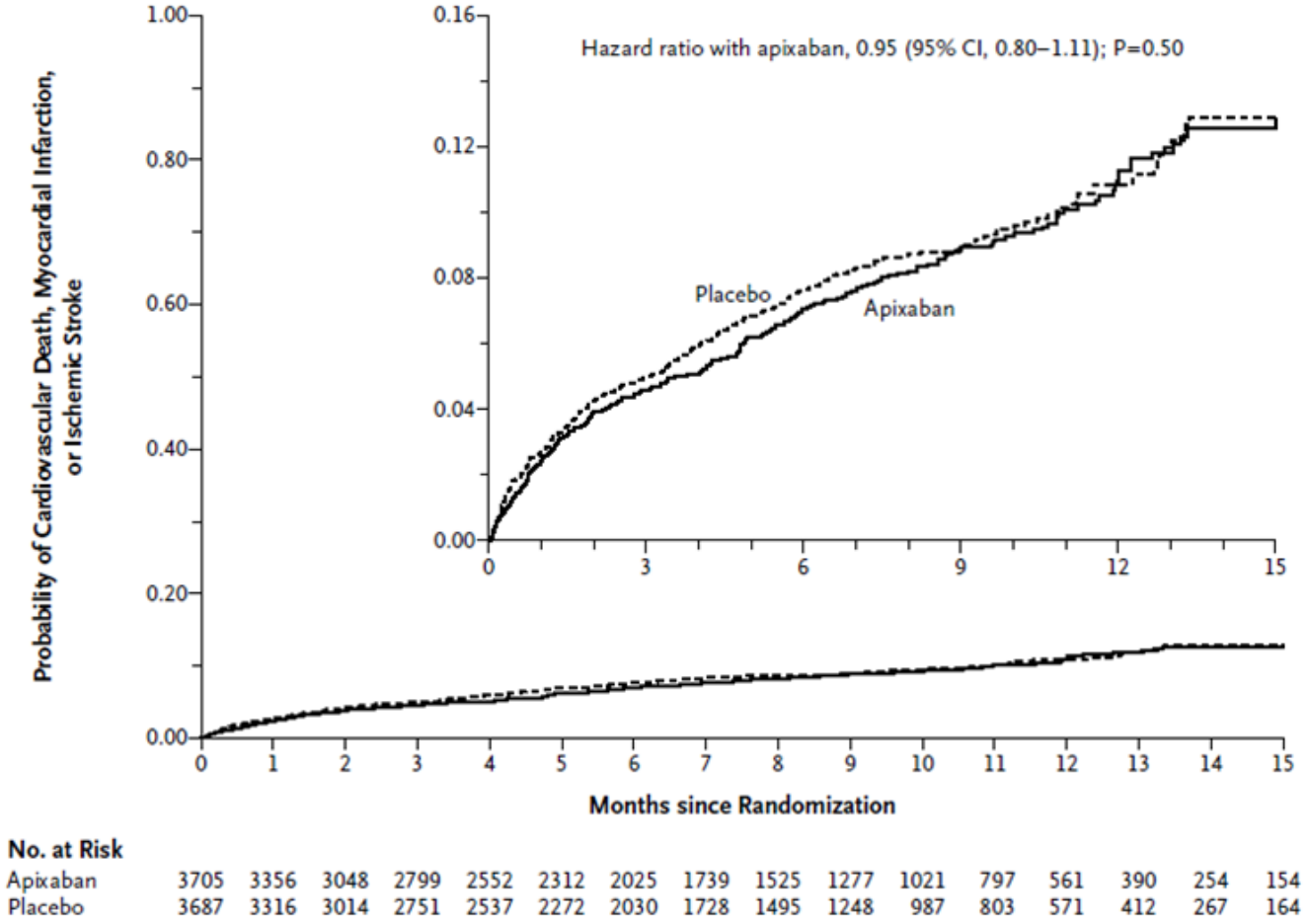


De Caterina *et al. Thromb Haemost* 2013;109:569–79.

NOACs in ACS without AF

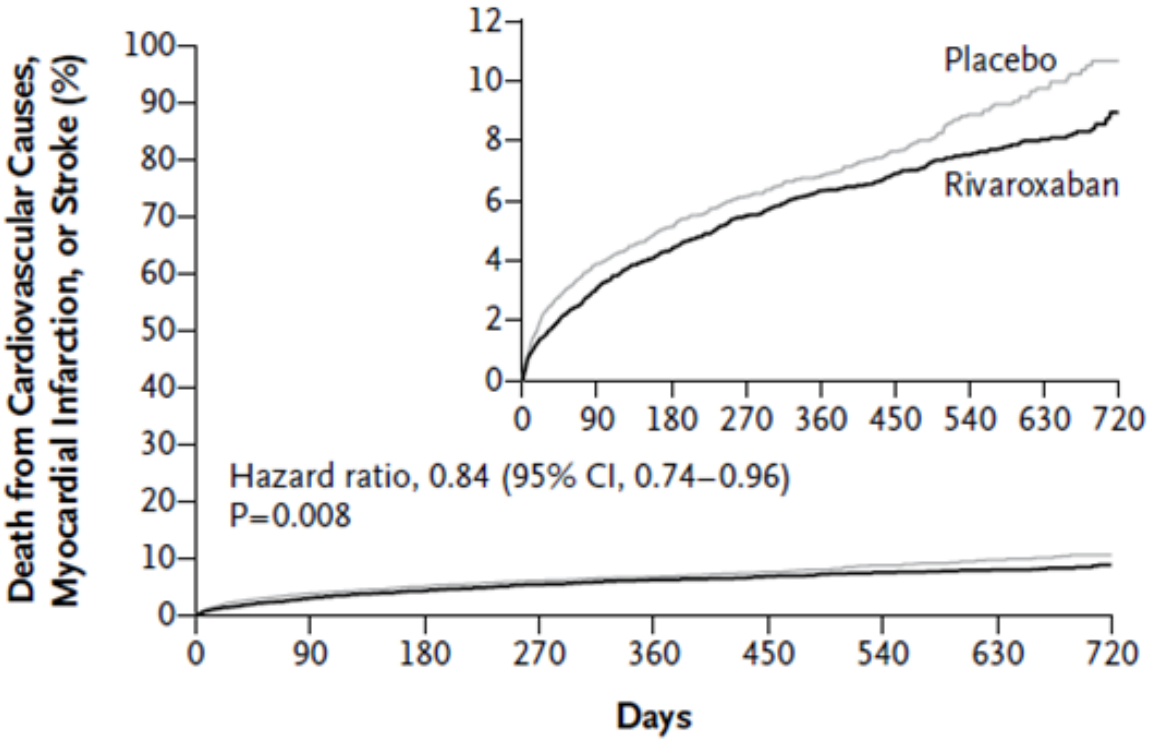
- The Rationale
- The Implementation

APPRAISE-2: Primary efficacy outcome (CV death, MI, stroke)



Alexander *et al. N Engl J Med* 2011;365:699–708.

ATLAS ACS 2–TIMI 51: Primary efficacy outcome (CV death, MI, stroke)

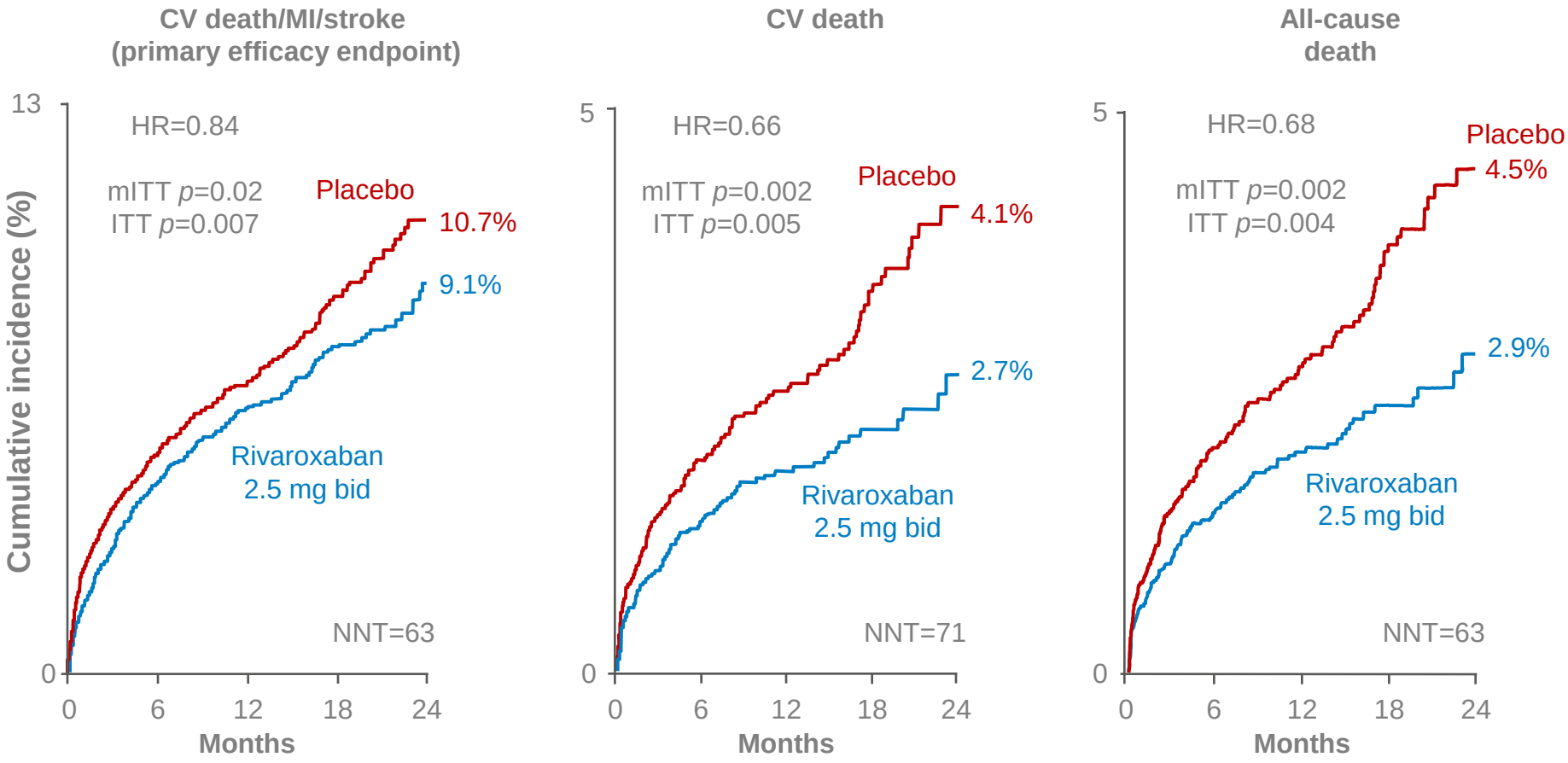


No. at Risk									
Rivaroxaban	10,229	8817	7797	6324	5137	3967	2830	1747	831
Placebo	5,113	4437	3974	3253	2664	2059	1460	878	421

Mega *et al. N Engl J Med* 2012;366:9–19.

ATLAS ACS 2–TIMI 51: rivaroxaban 2.5 mg bid significantly reduced CV events and death

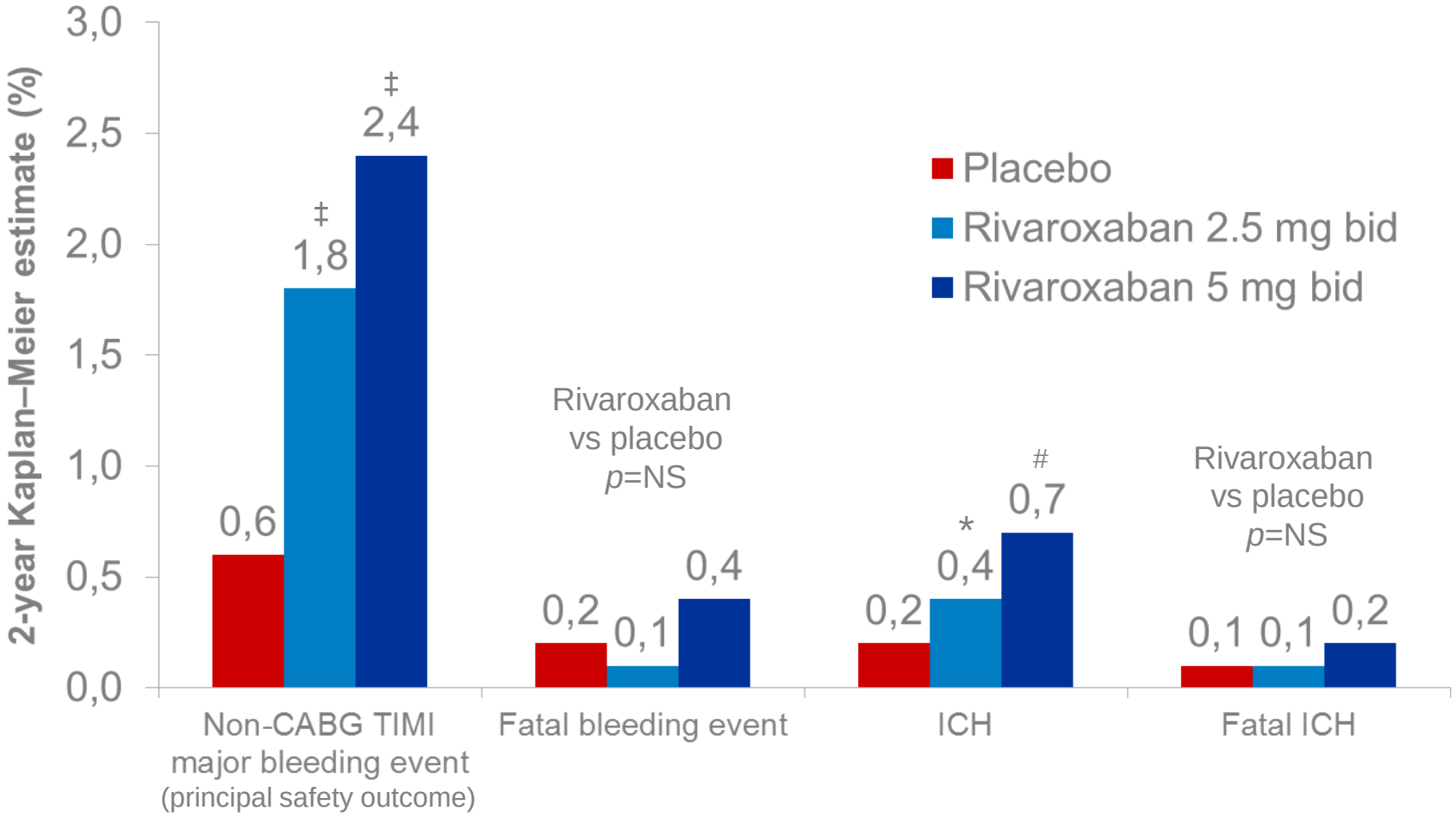
The primary efficacy endpoint reduction was driven by reduced mortality



Both strata. bid, twice daily; CV, cardiovascular; HR, hazard ratio; ITT, intention to treat; MI, myocardial infarction; mITT, modified intention to treat; NNT, number needed to treat.

1. Mega *et al. N Engl J Med* 2012;366:9–19; 2. Gibson *et al. AHA* 2011 (www.clinicaltrialresults.org).

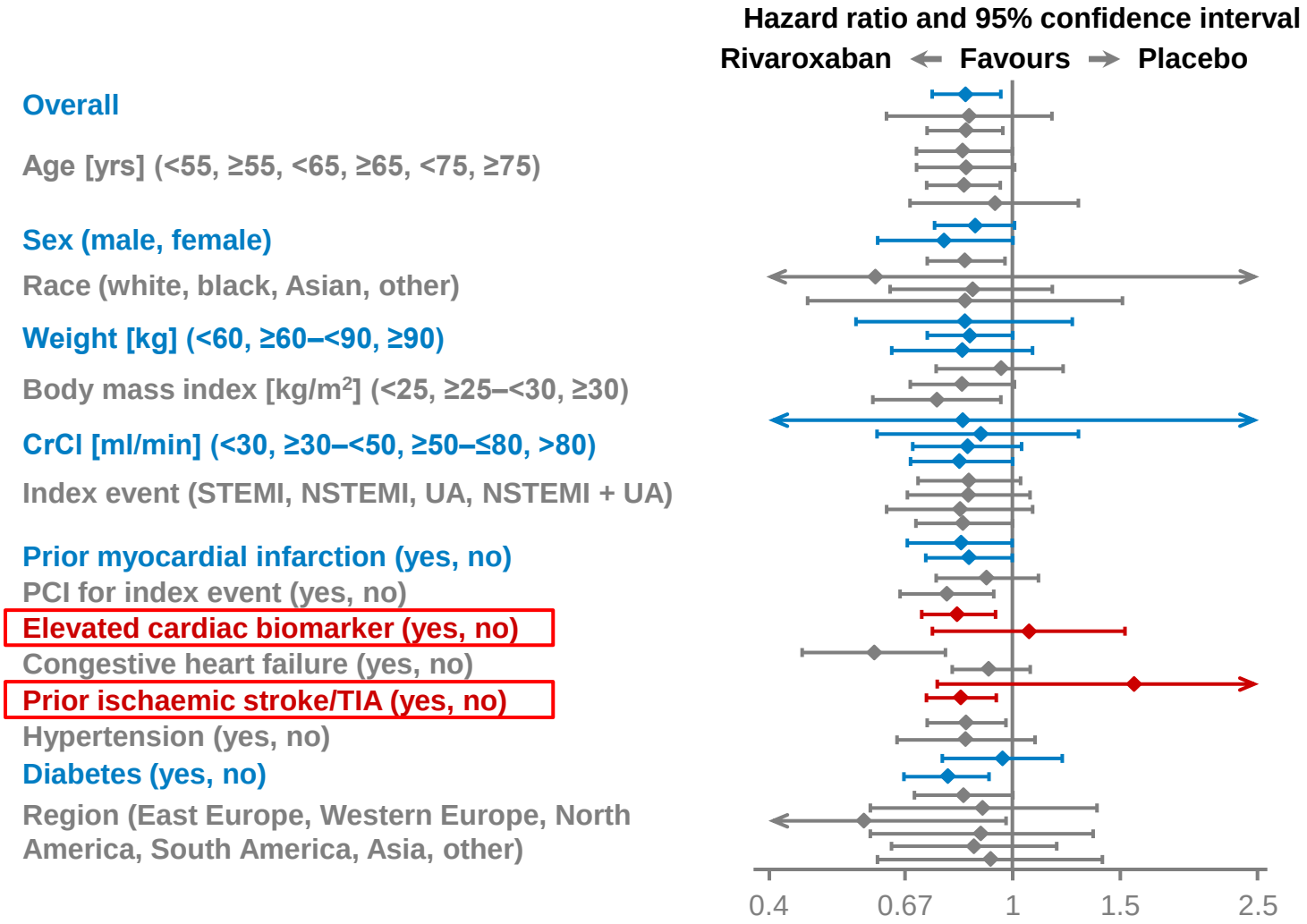
ATLAS ACS 2–TIMI 51: rivaroxaban 2.5 mg bid did not increase fatal bleeding or fatal ICH vs placebo



*p=0.04 vs placebo; #p=0.005 vs placebo; ‡p<0.001 vs placebo. bid, twice daily; CABG, coronary artery bypass graft; ICH, intracranial haemorrhage; NS, not significant; TIMI, Thrombolysis in Myocardial Infarction.

1. Mega *et al. N Engl J Med* 2012;366:9–19; 2. Gibson *et al. AHA* 2011 (www.clinicaltrialresults.org).

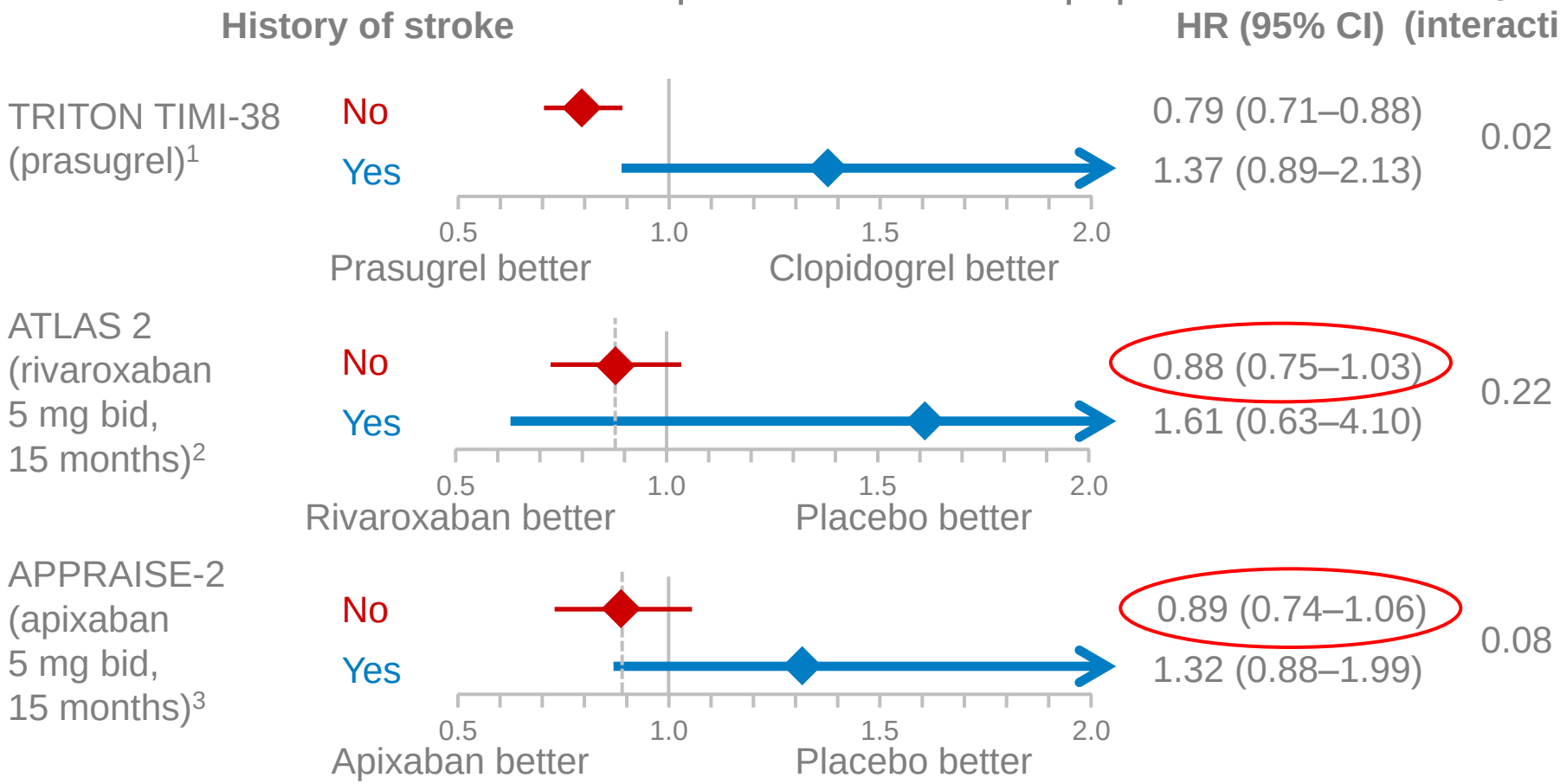
Subgroup analyses for primary efficacy endpoint (mITT/all strata/combined doses)



CrCl, creatinine clearance; mITT, modified intention to treat; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIA, transient ischaemic attack; UA, unstable angina.
FDA briefing information, 23 May 2012.

There is good clinical rationale to exclude patients with prior stroke/TIA

- Patients with prior stroke/TIA do not appear to benefit, consistent results seen with other compounds in this sub-population



bid, twice daily; CI, confidence interval; HR, hazard ratio; TIA, transient ischaemic attack.

1. Wiviott *et al. N Engl J Med* 2007;357:2001–15; 2. FDA briefing information, 16 January 2014; 3. Alexander *et al. N Engl J Med* 2011;365:699–708.

Rivaroxaban 2.5 mg bid in ATLAS ACS 2–TIMI 51 vs standard antiplatelet therapy showed…

- Greater efficacy, including fewer deaths and reduction in stent thrombosis (not shown)
- An important increase in bleeding, including intracranial haemorrhage (ICH), but without any increase in fatal bleeding or fatal ICH
- Even greater benefits in patients with elevated cardiac biomarkers and without previous stroke/TIA

De Caterina *et al. J Am Coll Cardiol* 2012;59:1413–25

Overview on rivaroxaban 2.5 mg bid subgroups compared with overall study population

	Subgroup	Primary composite endpoint (CV death/MI/ stroke)	CV death	NCB* Efficacy: non-bleed CV death, MI, ischaemic stroke events prevented Safety: fatal bleeding, symptomatic ICH
1	Overall study population	HR 0.84 CI: 0.72–0.97 (ARR: 1.6%) NNT: 63	HR 0.66 CI: 0.51–0.86 (ARR: 1.4%) NNT: 71	Efficacy: –125 Safety: +10
2	Exclude prior stroke/TIA	HR 0.81, CI: 0.69–0.94 (ARR: 1.8%) NNT: 56	HR 0.63, CI: 0.48–0.82 (ARR: 1.5%) NNT: 67	Efficacy: –143 Safety: +8
3	Restrict to elevated biomarkers Exclude prior stroke/TIA	**HR 0.80** CI: 0.68–0.94 (ARR: 2.1%) NNT: 48	**HR 0.55** CI: 0.41–0.74 (ARR: 2.0 %) NNT: 50	**Efficacy: –159** **Safety: +3**

*Excess number of events in 10,000 patient-years. ARR: absolute risk reduction based on 2-year K–M estimates; bid, twice daily; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ICH, intracranial haemorrhage; MI, myocardial infarction; NCB, net clinical benefit; NNT: number needed to treat; TIA, transient ischaemic attack.

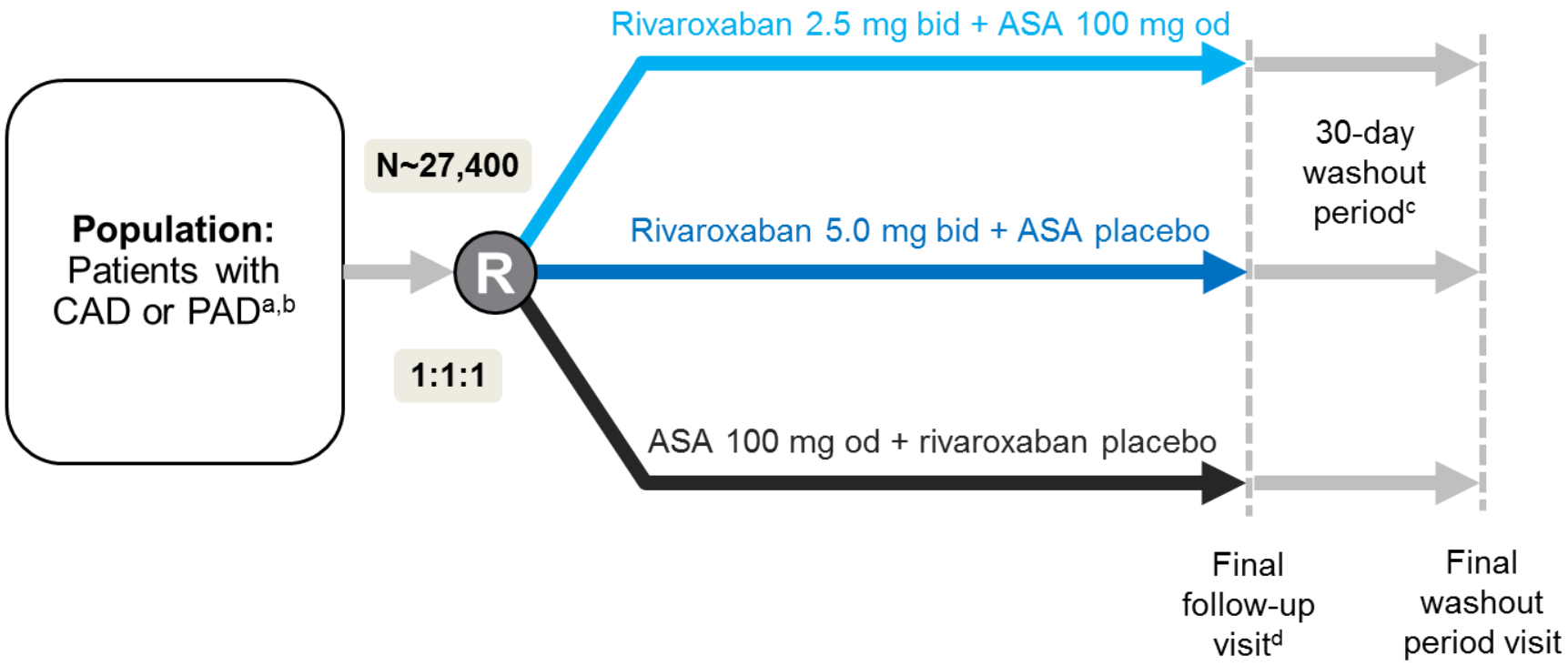
1. EMA Assessment Report, 21 March 2013; 2. FDA briefing information, 16 January 2014.

Difficulties in buying this concept

- Triple therapy in ACS is more complicated than DAPT using ticagrelor (or prasugrel)
- Identifying candidate patients is somewhat complicated
- Clopidogrel perceived as «an old drug»
- Is the lower mortality with rivaroxaban real? «*One swallow does not make spring*»
- Difficulties in accepting the much higher rates of bleeding

COMPASS Study Design

Objective: Efficacy and safety of rivaroxaban, low-dose rivaroxaban plus ASA or ASA alone for reducing risk of MI, stroke or CV death in patients with CAD or PAD



De Caterina R and Goto S, Vascul Pharmacol 2016; 81:1-14

Bayer AG
Communications and
Public Affairs
51368 Leverkusen
Germany
Tel. +49 214 30-0
www.news.bayer.com

News Release

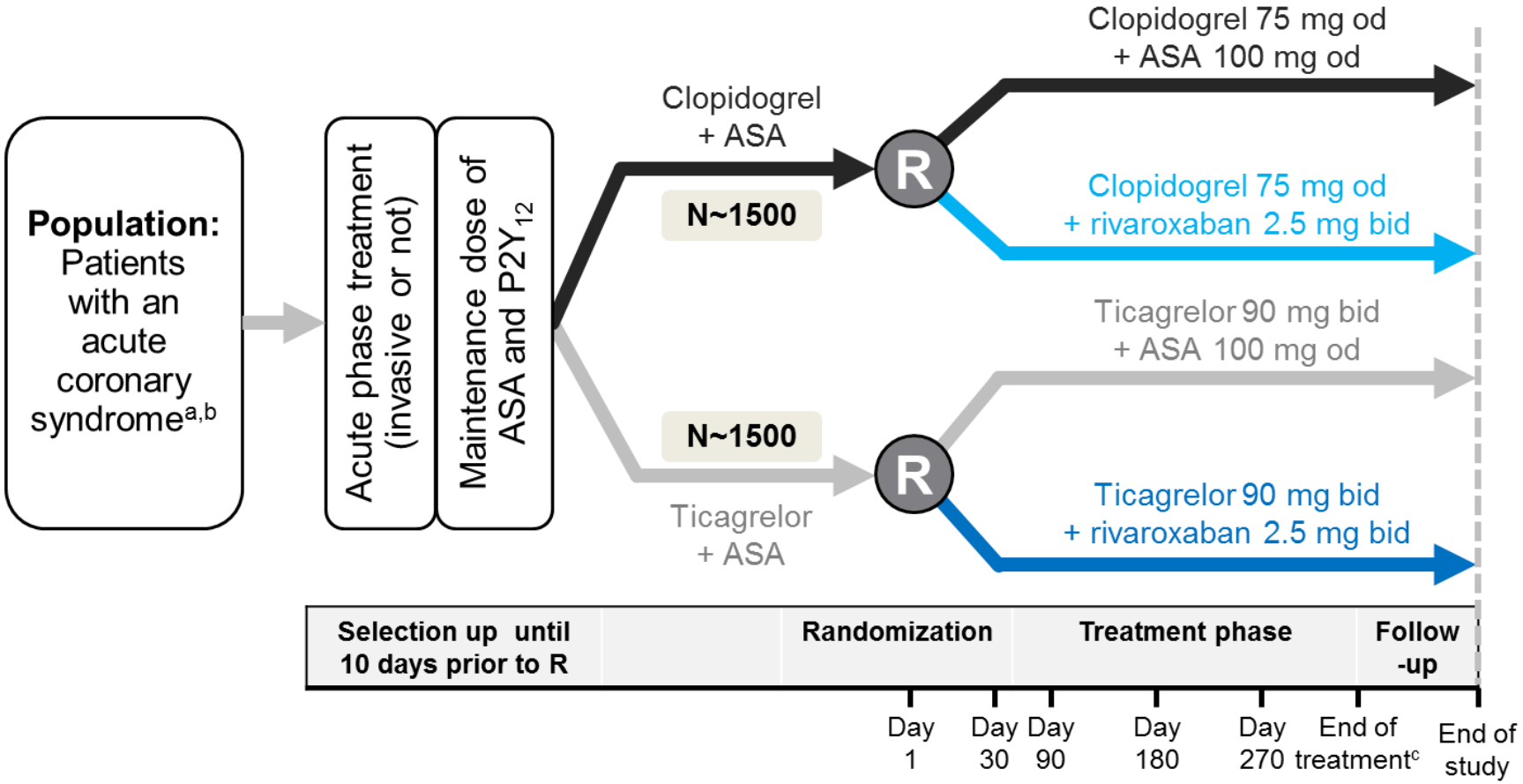
Not intended for U.S. and UK Media

Phase III COMPASS study with Bayer's Rivaroxaban in Patients with Coronary or Peripheral Artery Disease Shows Overwhelming Efficacy and Meets Primary Endpoint Early

08 Feb 2017

GEMINI-ACS-1 Study Design

Objective: Safety of rivaroxaban versus ASA in addition to either clopidogrel or ticagrelor therapy in patients with a recent ACS



De Caterina R and Goto S, Vascul Pharmacol 2016; 81:1-14

Stay tuned!

Thank you!