# Rivaroxaban e le più recenti evidenze: da XANTUS a COMPASS

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# Relazioni con soggetti portatori di interessi commerciali in campo sanitario

- Ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18, 19 dell'Accordo Stato-Regione del 19 aprile 2012, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:
  - *Bayer*
  - *Sanofi*
  - *BMS/Pfizer*
  - *Boehringer*
  - *Daiichi*
  - *Alfa Wassermann*
  - *IL*

# Established Evidence and New Data

- DOAC (Rivaroxaban) are at least as effective and safe as AVK in primary and secondary prevention in AF patients (Net Clinical Benefit)
- DOAC (Rivaroxaban) are at least as effective and safe as AVK in therapy and secondary prevention of VTE (Net Clinical Benefit)
- DOAC (Dabigatran and Rivaroxaban) may be used in AF patients undergoing PCI (on antiplatelet therapy) for ACS
- New Data on “Real Word” use of these compounds for AF and VTE (quality of these evidences?)
- Concomitant use of DOAC and Antiplatet Therapy in patients with CAD and PAD (Rivaroxaban only).

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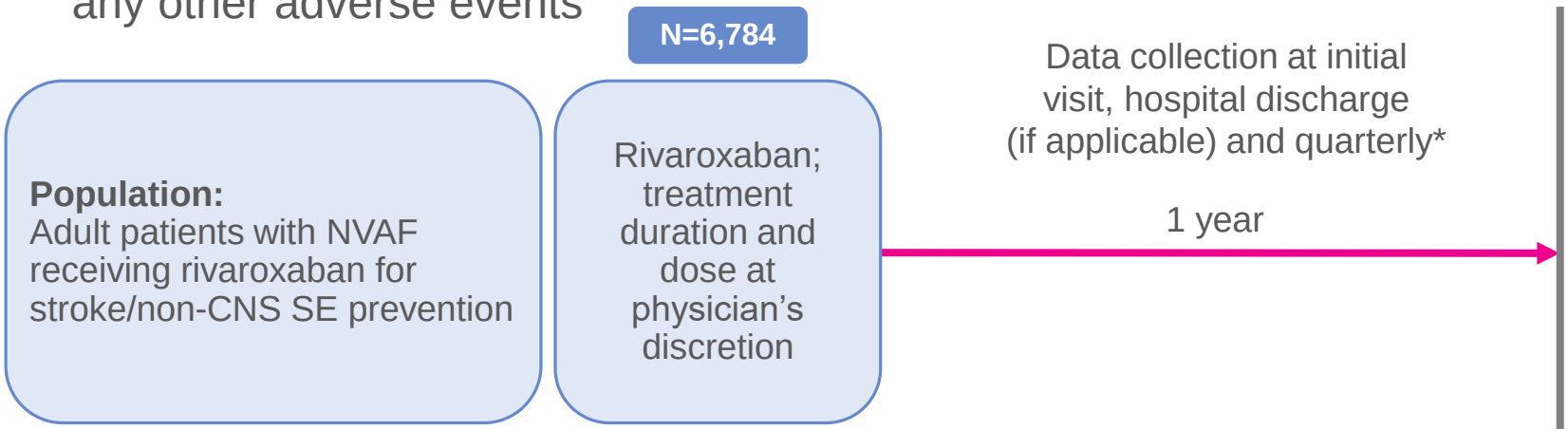
# XANTUS: Study Objective and Design

- To collect real world data on adverse events in patients with NVAF treated with rivaroxaban to determine the safety profile of rivaroxaban across the broad range of patient risk profiles encountered in routine clinical practice
  - Primary outcomes: major bleeding (ISTH definition), all-cause mortality, any other adverse events




Prospective, single-arm, observational, non-interventional phase IV study
Statistical analyses were descriptive and exploratory in nature

*Exact referral dates for follow-up visits not defined (every 3 months recommended); #for rivaroxaban discontinuation ≤1 year, observation period ends 30 days after last dose. Observational design means no interference with clinical practice was allowed

1. Camm AJ *et al*, *Vasc Health Risk Manag* 2014;10:425–434; 2. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

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# XANTUS: Primary and Secondary Outcomes

- Primary outcomes
  - Major bleeding (ISTH definition)
  - All-cause mortality
  - Any other AEs
  - Any other serious AEs
- Secondary outcomes
  - Symptomatic thromboembolic events
  - Non-major bleeding events
    - Any bleeding event that does not meet the criteria for a major haemorrhage
  - AEs and serious AEs across risk scores
  - AEs and serious AEs in important subgroups
  - Other outcomes collected included:
    - Patient treatment satisfaction using standardized questionnaires
    - Persistence with therapy
    - Healthcare resource use
    - Details of interventions and how they were managed
    - Concomitant medication use
    - Reasons for switching/interrupting rivaroxaban therapy

1. Camm AJ *et al*, *Vasc Health Risk Manag* 2014;10:425–434

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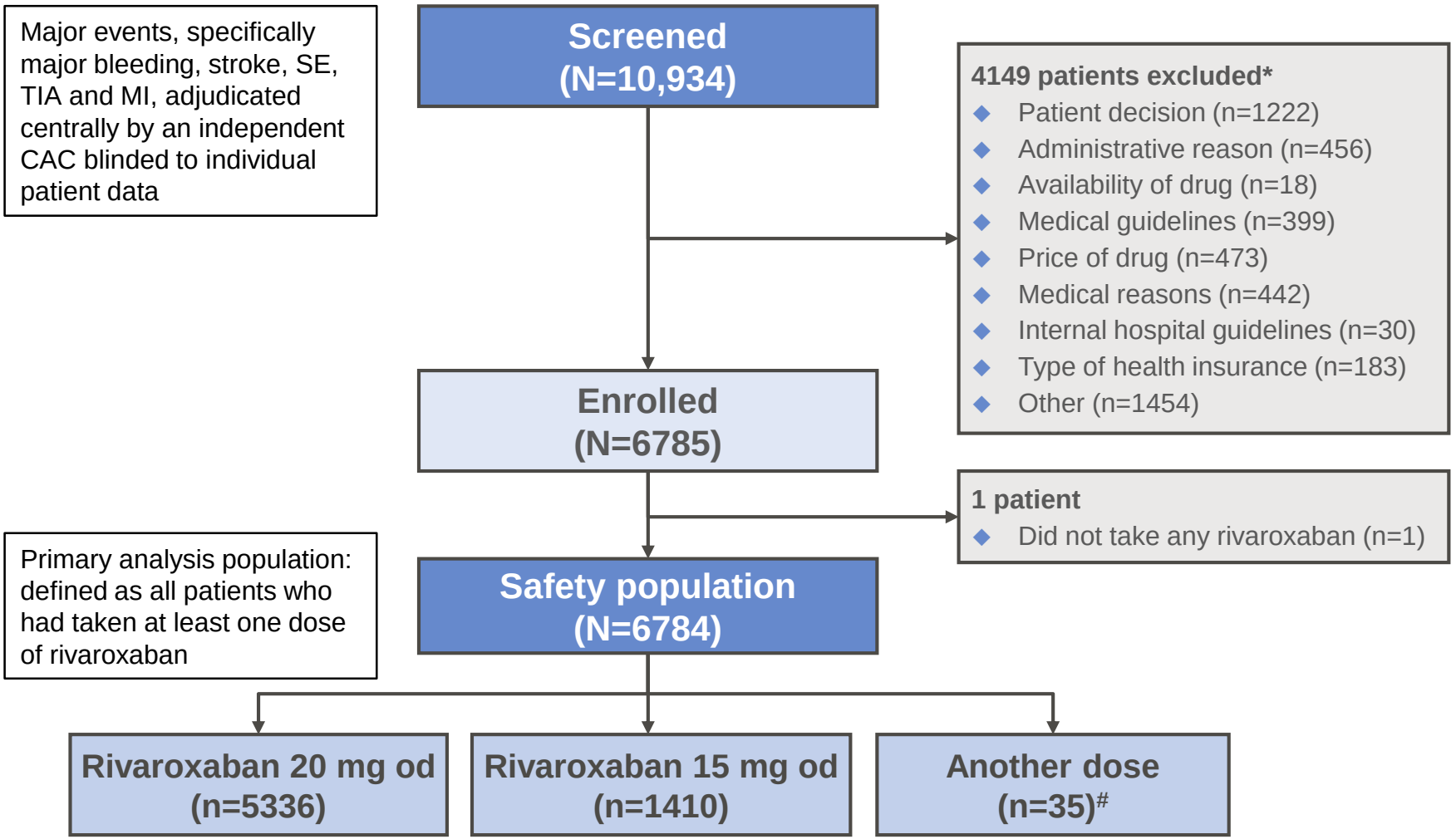
# XANTUS: Patient Flow




*Reasons for not continuing in the study included, but were not limited to, patient decision, administrative or medical reasons. Some patients could have more than one reason for exclusion; #other dose includes any initial daily rivaroxaban dose besides 15/20 mg od (excluding missing information, n=3)

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

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# XANTUS: Baseline Demographics – Clinical Characteristics

| | Rivaroxaban (N=6784) |
|---|---|
| Age (years) | |
| **Mean ± SD** | **71.5±10.0** |
| Age <65, n (%) | 1478 (21.8) |
| Age ≥65–≤75, n (%) | 2782 (41.0) |
| Age >75, n (%) | 2524 (37.2) |
| Gender (male): n (%) | 4016 (59.2) |
| Weight (kg): mean ± SD | 83.0±17.3 |
| BMI (kg/m$^2$): mean ± SD | 28.3±5.0 |
| BMI >30 kg/m$^2$, n (%) | 1701 (25.1) |
| AF, n (%) | |
| First diagnosed | 1253 (18.5) |
| **Paroxysmal** | **2757 (40.6)** |
| Persistent | 923 (13.6) |
| Permanent | 1835 (27.0) |
| Missing | 16 (0.2) |

| | Rivaroxaban (N=6784) |
|---|---|
| Creatinine clearance, n (%) | |
| <15 ml/min | 20 (0.3) |
| ≥15–<30 ml/min | 75 (1.1) |
| ≥30–<50 ml/min | 545 (8.0) |
| ≥50–≤80 ml/min | 2354 (34.7) |
| >80 ml/min | 1458 (21.5) |
| Missing | 2332 (34.4) |
| Existing co-morbidities, n (%) | |
| Hypertension | 5065 (74.7) |
| Diabetes mellitus | 1333 (19.6) |
| Prior stroke/non-CNS SE/TIA | 1291 (19.0) |
| Congestive HF | 1265 (18.6) |
| Prior MI | 688 (10.1) |
| **VKA experienced, n (%)** | **3089 (45.5)** |

. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

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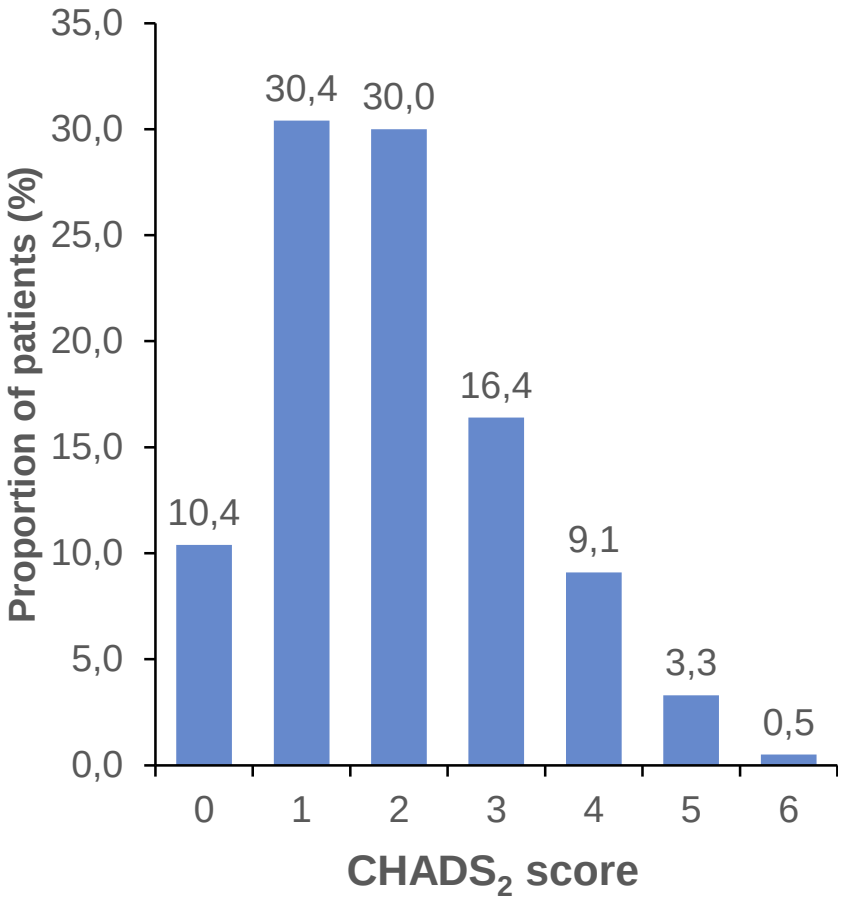
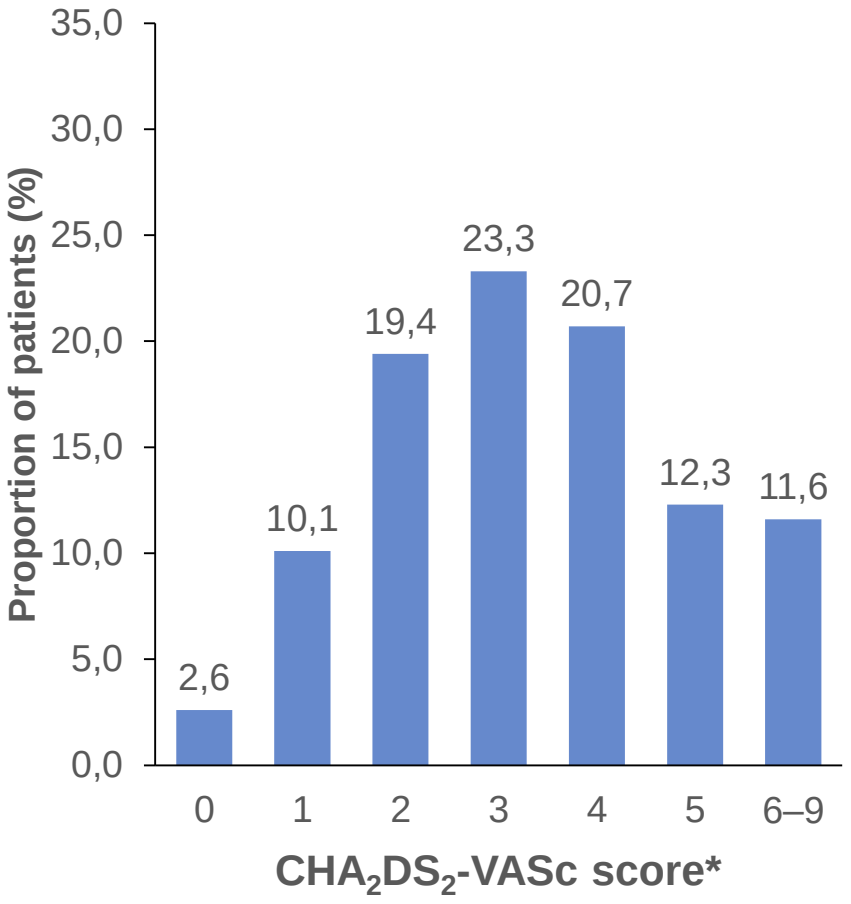
# XANTUS: Baseline Demographics – Distribution of Stroke Risk Factors

**Mean score±SD = 2.0±1.3**




**Mean score±SD = 3.4±1.7**




*3 patients had missing $CHA_2DS_2$-VASc scores

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

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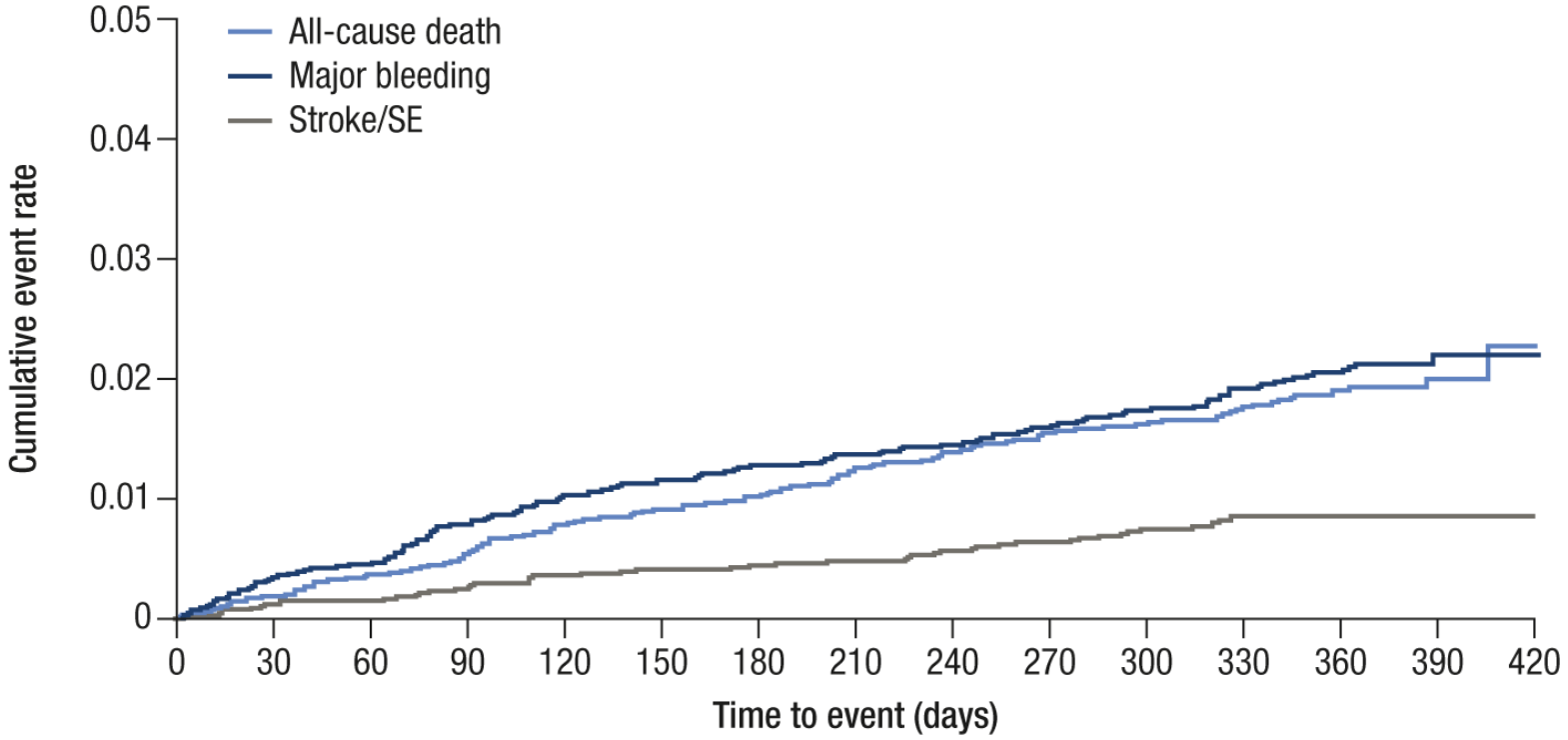
# XANTUS: Cumulative Rates (Kaplan–Meier) for Treatment-Emergent Primary Outcomes



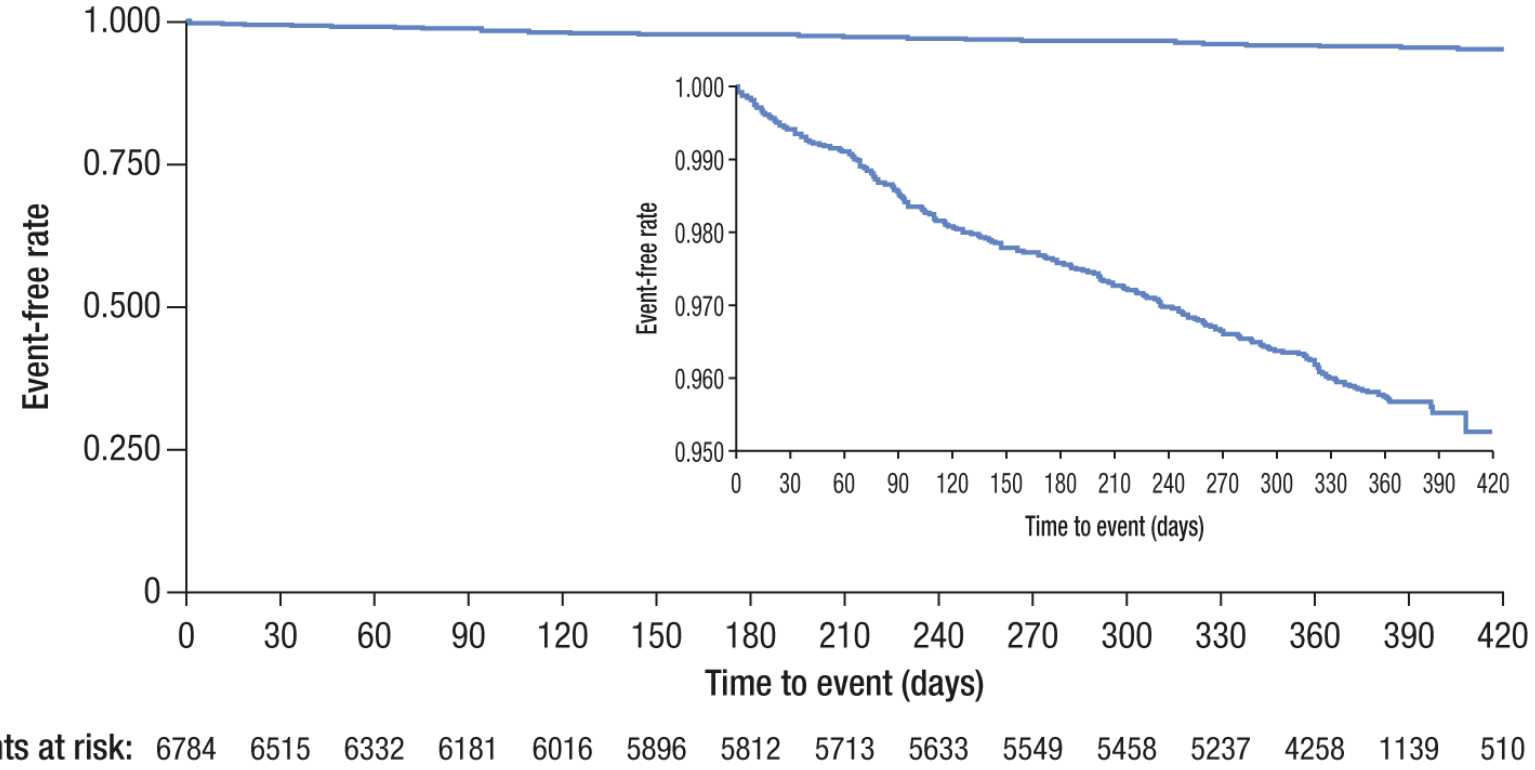

**Patients at risk:**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| All-cause death | 6784 | 6530 | 6349 | 6211 | 6054 | 5938 | 5853 | 5754 | 5679 | 5597 | 5512 | 5295 | 4307 | 1153 | 514 |
| Major bleeding | 6784 | 6522 | 6340 | 6197 | 6033 | 5909 | 5824 | 5726 | 5649 | 5559 | 5471 | 5256 | 4273 | 1144 | 513 |
| Stroke/SE | 6784 | 6532 | 6353 | 6216 | 6053 | 5933 | 5848 | 5752 | 5674 | 5587 | 5499 | 5282 | 4296 | 1149 | 513 |

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

# XANTUS: Event-Free Rate (Kaplan–Meier) for Treatment-Emergent Primary Outcomes

- In total, 6522 (96.1%) patients did not experience any of the outcomes of treatment-emergent all-cause death, major bleeding or stroke/SE




1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

# XANTUS: Major Events

| | Rivaroxaban (N=6784) | |
|---|---|---|
| | Incidence proportion, n (%) | Incidence rate, %/year (95% CI)* |
| Major bleeding | 128 (1.9) | 2.1 (1.8–2.5) |
| Fatal | 12 (0.2) | 0.2 (0.1–0.3) |
| Critical organ bleeding | 43 (0.6) | 0.7 (0.5–0.9) |
| Intracranial haemorrhage | 26 (0.4) | 0.4 (0.3–0.6) |
| Gastrointestinal | 52 (0.8) | 0.9 (0.6–1.1) |
| Non-major bleeding events | 878 (12.9) | 15.4 (14.4–16.5) |
| All-cause death | 118 (1.7) | 1.9 (1.6–2.3) |
| Thromboembolic events (stroke, SE, TIA, and MI) | 108 (1.6) | 1.8 (1.5–2.1) |
| Stroke/SE | 51 (0.8) | 0.8 (0.6–1.1) |

Patients could experience multiple bleeding events in different categories. *Events per 100 patient-years; #numbers are for major mucosal and gastrointestinal bleeding events; ‡representing major bleeding

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

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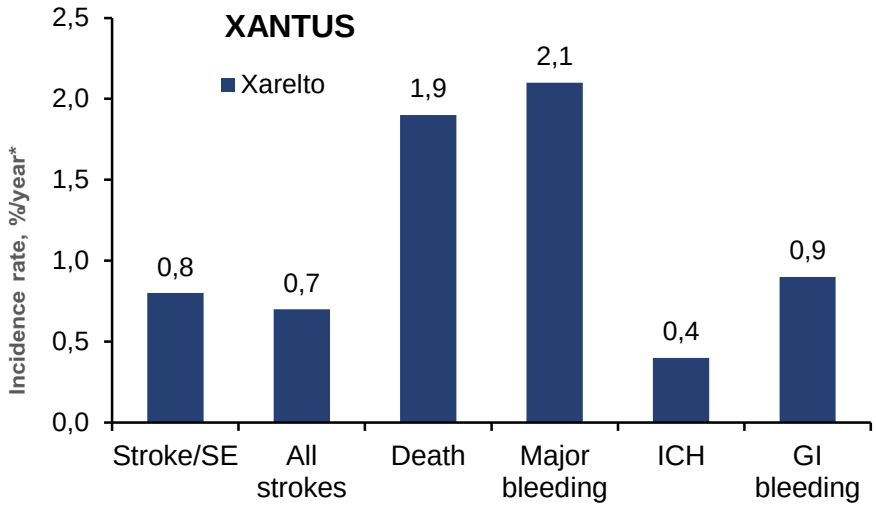
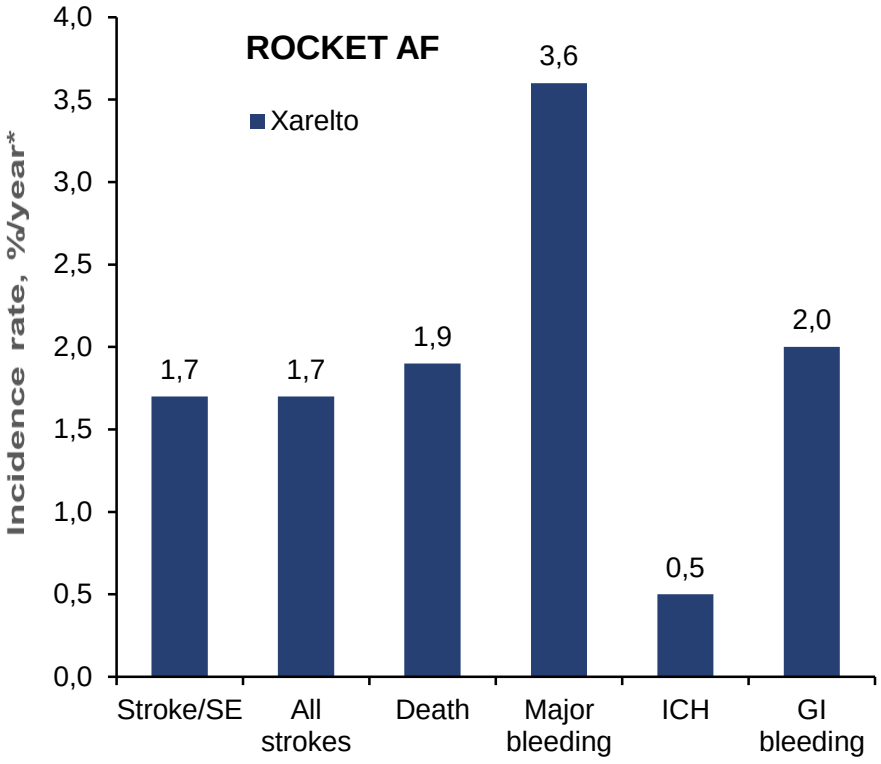
# Comparison of Main Outcomes: XANTUS versus ROCKET AF

| | $CHADS_2$ | Prior stroke[#] |
|---|---|---|
| ROCKET AF[1] | 3.5 | 55% |
| XANTUS[2] | 2.0 | 19% |



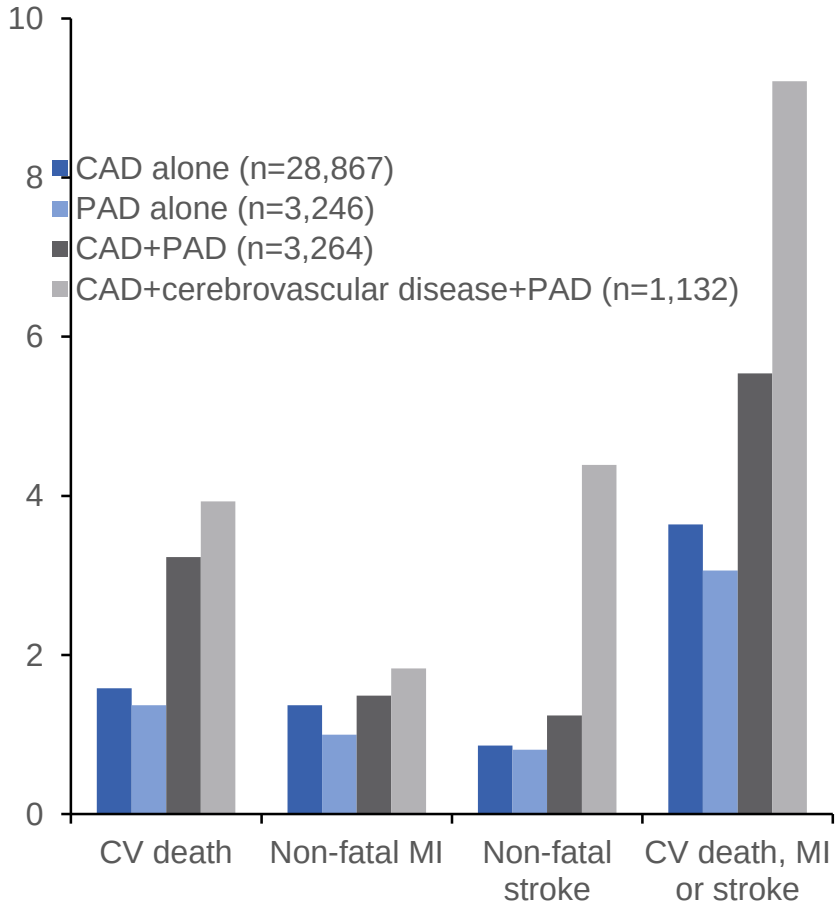

[#]Includes prior stroke, SE or TIA; *Events per 100 patient-years

1. Patel MR *et al, N Engl J Med* 2011;365:883–891; 2. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

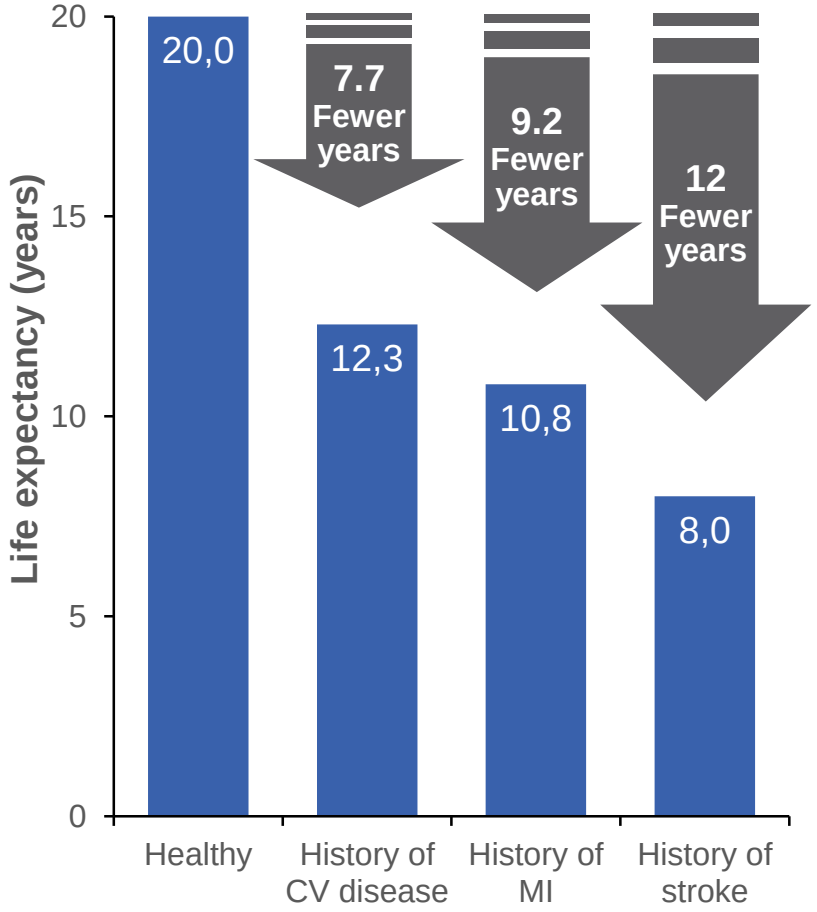
XANTUS

# >17.7 million people worldwide are estimated to have died from CV disease in 2015 (23.6 million/year by 2030)

- 1-year outcomes in patients with atherosclerotic disease[1]

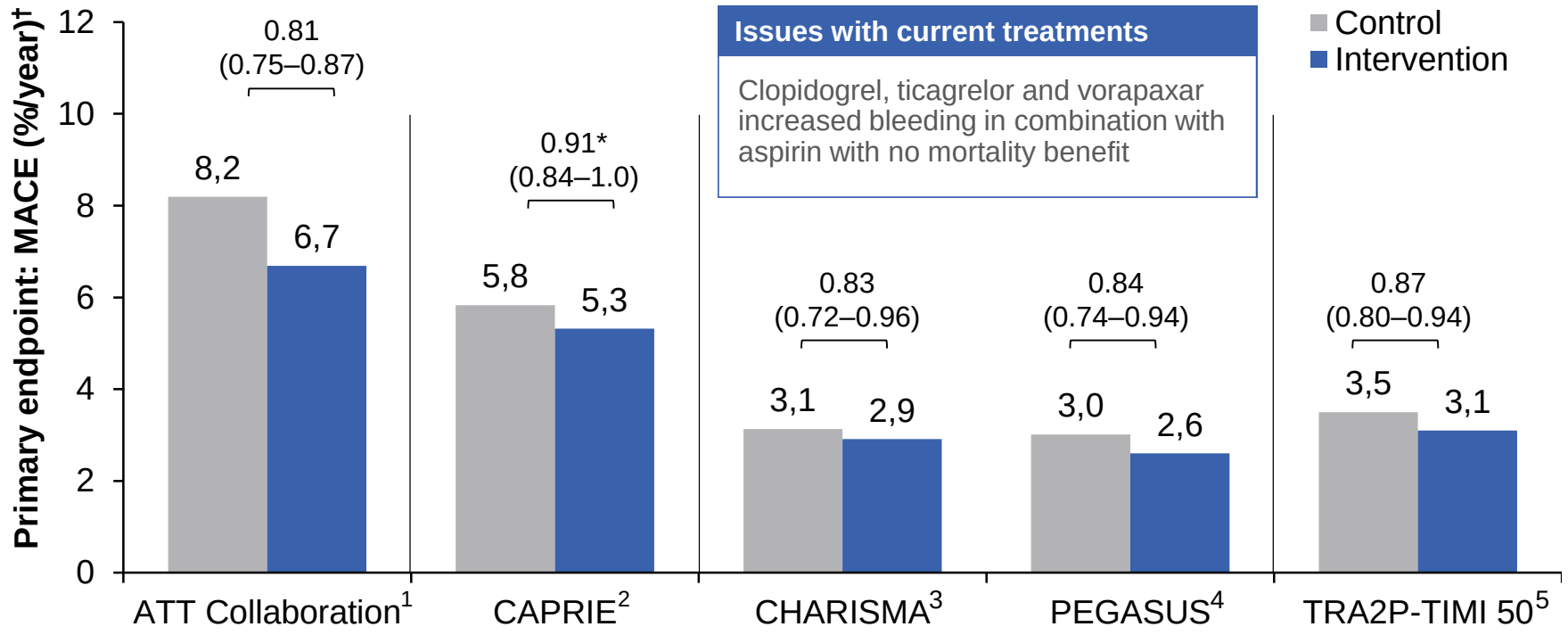



- Life expectancy in patients aged 60 years ± atherosclerosis[2]




1. Steg P *et al*. *JAMA* 2007;297:1197–1206; 2. Peeters A *et al. Eur Heart J* 2002;23:458–466

# Patients with Chronic CAD or PAD Remain At Risk of Vascular Events Despite Current Optimal Medical Therapy




| | | | | | |
|---|---|---|---|---|---|
| *% Use of key therapies in intervention arm* | Control ‖ Aspirin | Aspirin ‖ Clopidogrel | Placebo + Aspirin ‖ Clopidogrel + Aspirin | Placebo + Aspirin ‖ Ticagrelor + Aspirin | Vorapaxar ‖ Placebo + Aspirin ± Thienopyridine |
| *ACEI/ARB* | *Meta-analysis of 16 trials* | *NR* | *up to 85.3* | *80.4* | *73.5* |
| *Statin/ lipid-lowering* | | *NR* | *77.1–89.3* | *92.4* | *91.0* |

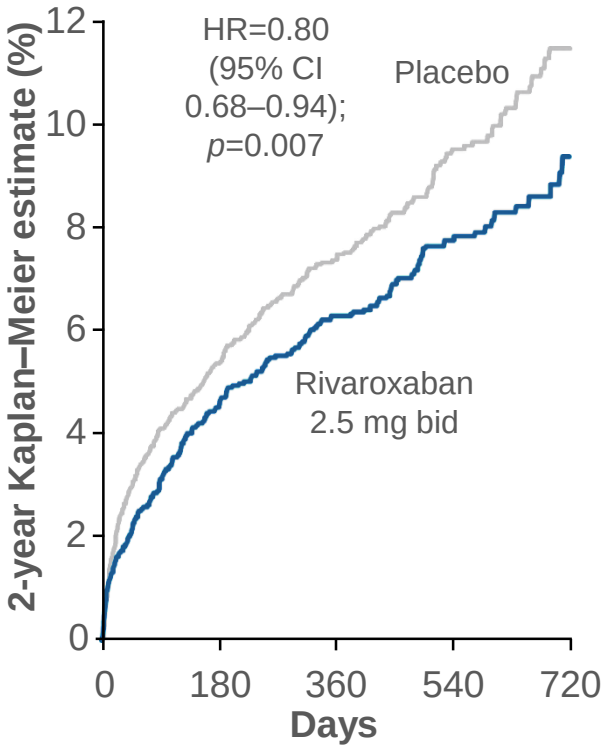
*Estimate calculated from reported relative risk reductions; †Estimate calculated from reported overall % across 28 months of median follow up for CHARISMA; and from reported 3-year Kaplan-Meier event rates for PEGASUS & TRA2P-TIMI50

1. ATT Collaboration. *Lancet* 2009;373:1849–1860; 2. CAPRIE Steering Committee. *Lancet* 1996;348:1329–1339; 3. Bhatt DL *et al*. *J Am Coll Cardiol* 2007;49:1982–1988; 4. Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800; 5. Morrow DA *et al. N Engl J Med* 2012;366:1404–1413

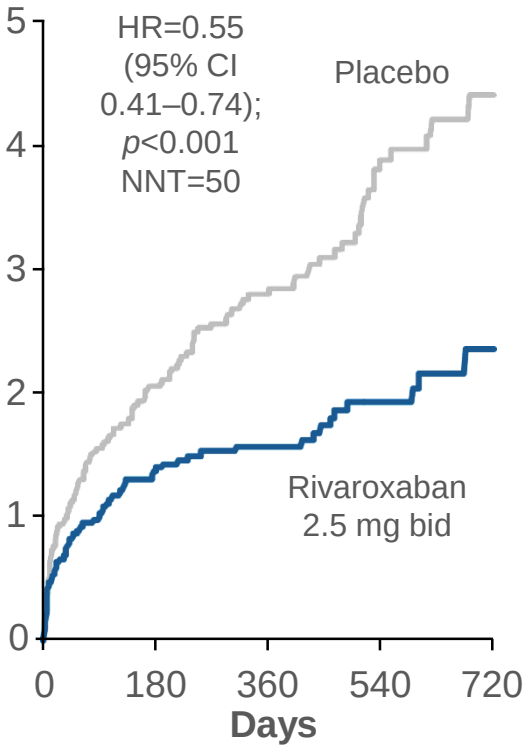
# ATLAS ACS 2 TIMI 51

## Patients with elevated cardiac biomarkers and no prior stroke/transient ischaemic attack

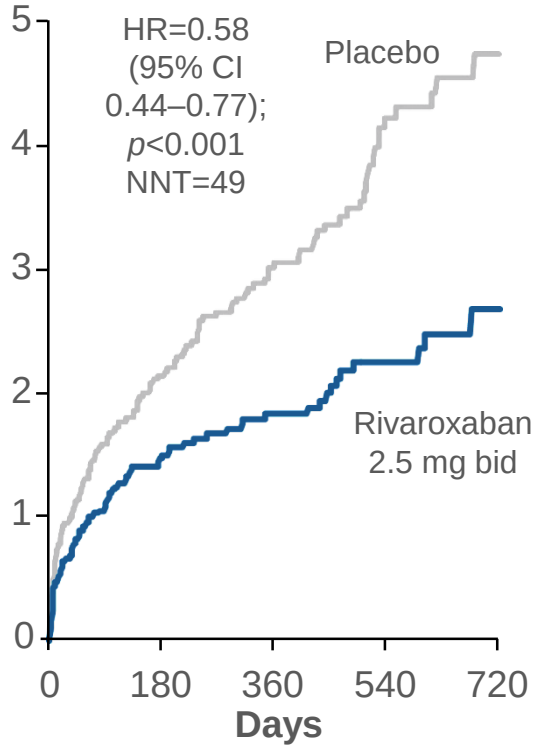
### CV death, MI or stroke




### CV death




### All-cause death



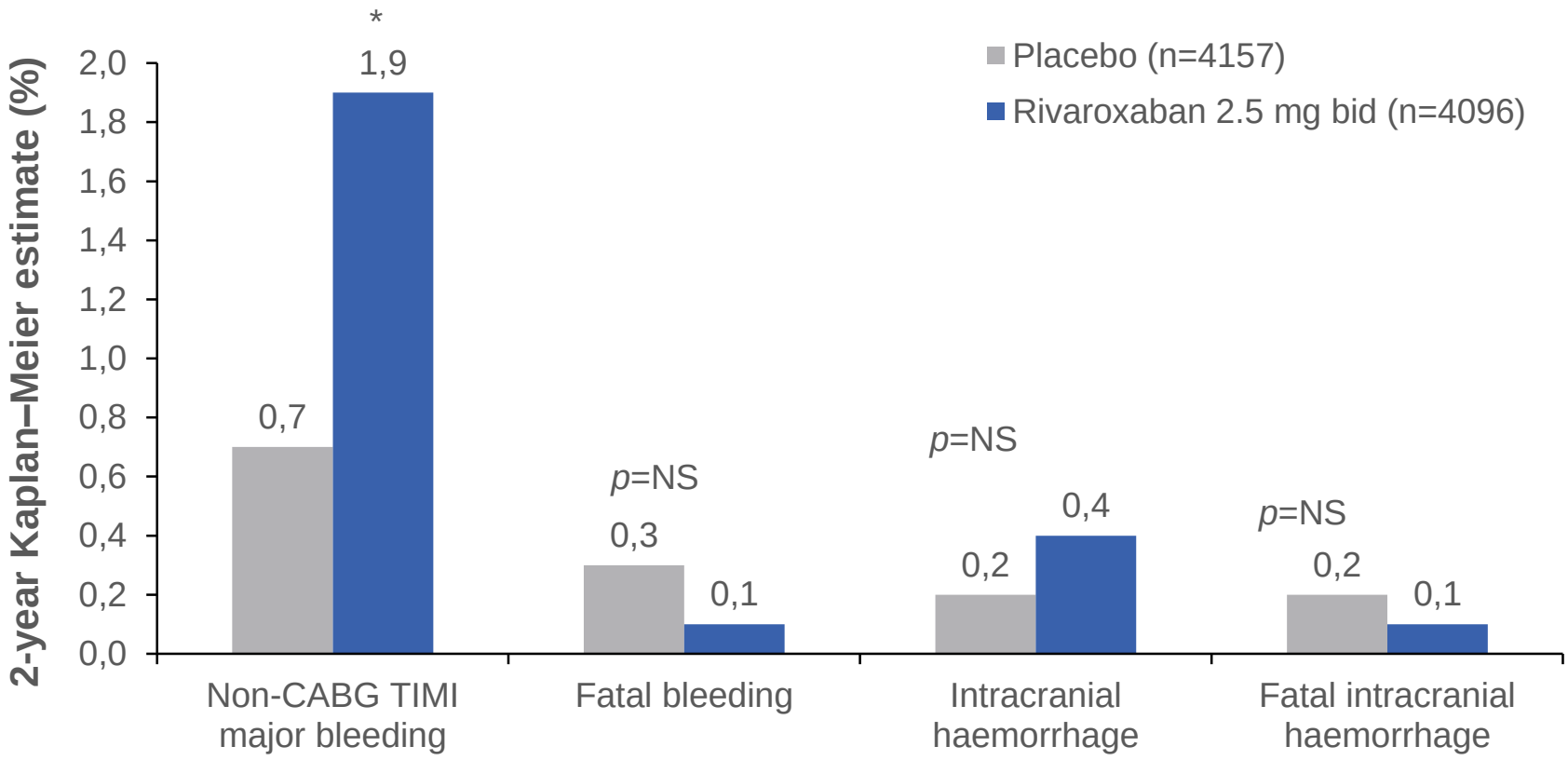

CI, confidence interval; HR, hazard ratio; NNT, number needed to treat
Patients also received antiplatelet standard of care: ASA + thienopyridine (~93%) or ASA alone (~7%)

Mega JL *et al*, *Eur Heart J* 2014;35(Suppl.):992. Abstract P5518 (poster presentation)

ATLAS ACS TIMI 51

# Bleeding Complications

## Patients with elevated cardiac biomarkers and no prior stroke/transient ischaemic attack




CABG, coronary artery bypass grafting; NS, not significant; TIMI, Thrombolysis In Myocardial Infarction
*$p$<0.001 vs placebo

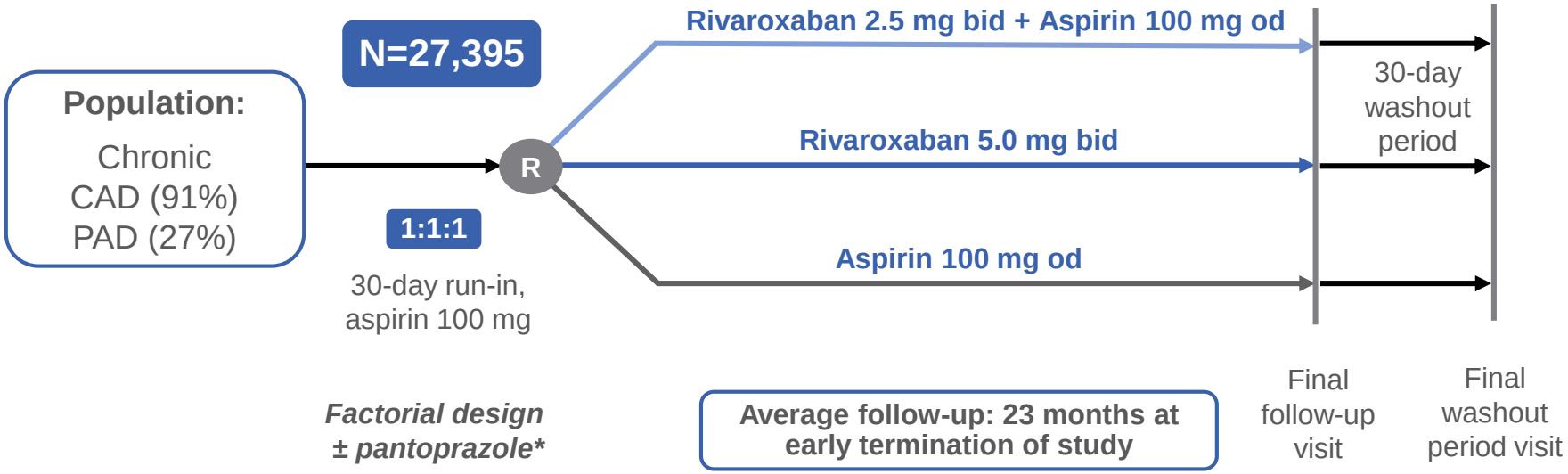
Mega JL *et al*, *Eur Heart J* 2014;35(Suppl.):992. Abstract P5518 (poster presentation)

ATLAS ACS TIMI 51

CAD PAD

# A Dual Pathway Approach Targeting Chronic Patients with CAD or PAD was Investigated in COMPASS

**Objective:** To determine the efficacy and safety of rivaroxaban, vascular dose of rivaroxaban plus aspirin or aspirin alone for reducing the risk of 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**

*Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design); the PPI pantoprazole component of the study is continuing; data will be communicated once complete


1. Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118;
2. Bosch J *et al. Can J Cardiol* 2017;33(8):1027–1035


COMPASS

# Inclusion and Exclusion Criteria

## Key inclusion criteria*

- PAD
- CAD with ≥1 of:
  - Age ≥65 years
  - Age <65 years plus atherosclerosis in ≥2 vascular beds or ≥2 additional risk factors
    - Current smoker
    - Diabetes mellitus
    - Renal dysfunction (eGFR<60 ml/min)
    - Heart failure
    - Non-lacunar ischemic stroke ≥1 month ago

## Key exclusion criteria‡

- Stroke ≤1 month or any haemorrhagic or lacunar stroke
- Severe HF with known ejection fraction <30% or NYHA class III or IV symptoms
- **Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy, or oral anticoagulant therapy**
- eGFR <15 ml/min

#Including but not limited to; ‡any other exclusion criteria in conjunction with the local Product Information and any other contraindication listed in the local labelling for rivaroxaban or the comparator have to be considered

www.clinicaltrials.gov/ct2/show/NCT01776424 [accessed 21 Mar 2017];
Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035

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# Main Study Outcomes

## Primary efficacy outcome

- Composite of MI, stroke or CV death

## Secondary efficacy outcomes

- Composite of major thrombotic events
  - Coronary heart disease death, MI, ischaemic stroke, acute limb ischaemia
  - Cardiovascular death, MI, ischaemic stroke, acute limb ischaemia
- Mortality (all cause)

## Primary safety outcome

- Modified ISTH major bleeding
  - Fatal bleeding, *and/or*
  - Symptomatic bleeding in a critical area or organ, such as intracranial, *or*
  - Bleeding into the surgical site requiring re-operation, *and/or*
  - Bleeding leading to hospitalization

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

# Key Baseline Characteristics

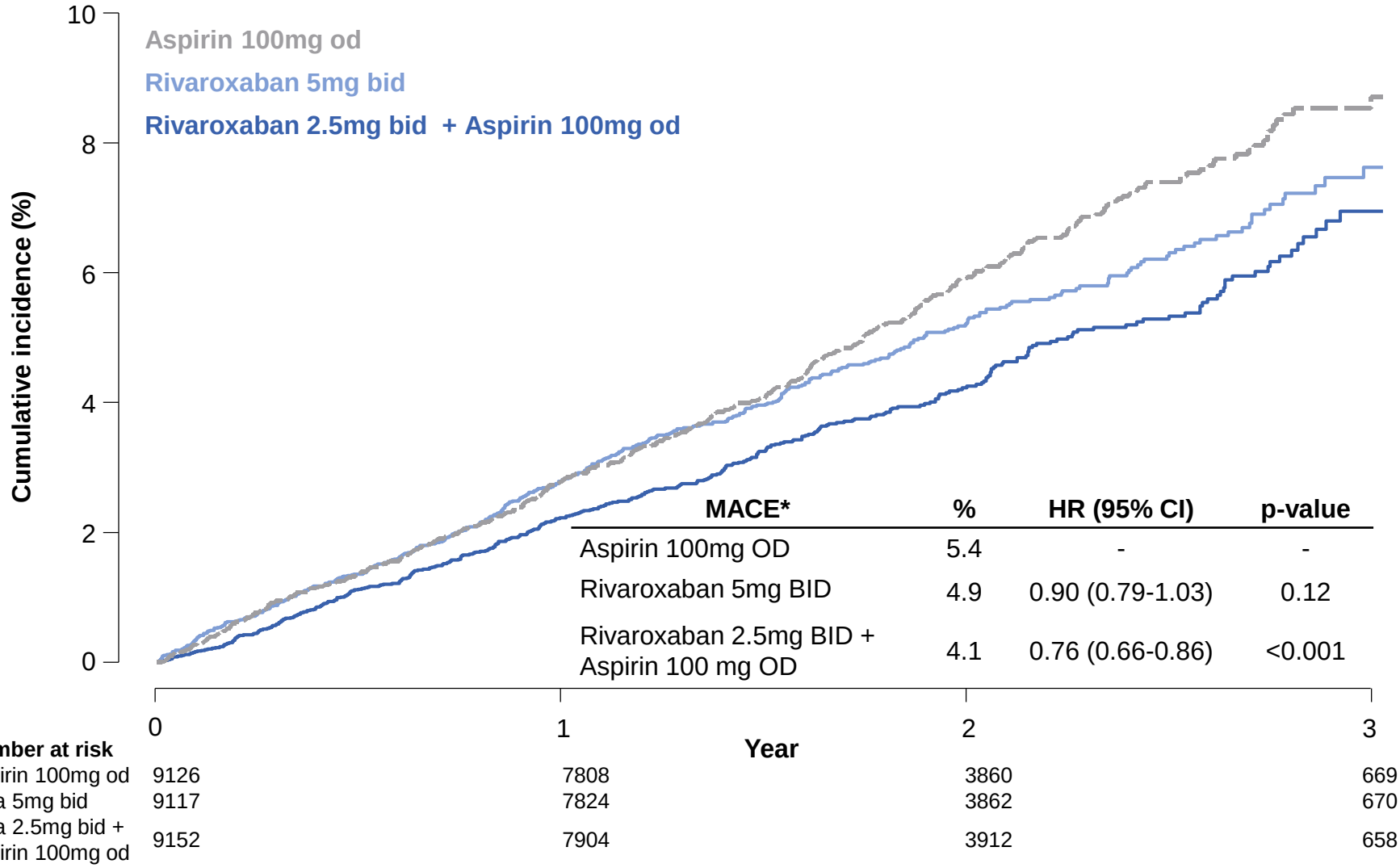
| Characteristic | Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152 | Rivaroxaban 5 mg bid N=9117 | Aspirin 100 mg N=9126 |
|---|---|---|---|
| Age, years | 68 | 68 | 68 |
| Blood pressure, mmHg | 136/77 | 136/78 | 136/78 |
| Total cholesterol, mmol/L | 4.2 | 4.2 | 4.2 |
| CAD, % | 91 | 90 | 90 |
| PAD, % | 27 | 27 | 27 |
| Diabetes, % | 38 | 38 | 38 |
| Lipid-lowering drugs, % | 90 | 90 | 89 |
| ACE inhibitors/ARB, % | 71 | 72 | 71 |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker

*Excluding <7 days before randomization

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

# Efficacy End Point




| MACE* | % | HR (95% CI) | p-value |
|---|---|---|---|
| Aspirin 100mg OD | 5.4 | - | - |
| Rivaroxaban 5mg BID | 4.9 | 0.90 (0.79-1.03) | 0.12 |
| Rivaroxaban 2.5mg BID + Aspirin 100 mg OD | 4.1 | 0.76 (0.66-0.86) | <0.001 |

| Number at risk | | | | |
|---|---|---|---|---|
| Aspirin 100mg od | 9126 | 7808 | 3860 | 669 |
| Riva 5mg bid | 9117 | 7824 | 3862 | 670 |
| Riva 2.5mg bid + Aspirin 100mg od | 9152 | 7904 | 3912 | 658 |

*Rates as at mean follow up of 23 months

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

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# Major Endpoints

| Outcomes, n (%) | Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152 | Aspirin 100 mg N=9126 | Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg | |
|---|---|---|---|---|
| | | | HR (95% CI) | *p*-value |
| CV death, stroke, or MI | 379 (4.1) | 496 (5.4) | 0.76 (0.66–0.86) | <0.001 |
| CV death | 160 (1.7) | 203 (2.2) | 0.78 (0.64–0.96) | 0.02 |
| Stroke | 83 (0.9) | 142 (1.6) | 0.58 (0.44–0.76) | <0.001 |
| MI | 178 (1.9) | 205 (2.2) | 0.86 (0.70–1.05) | 0.14 |

| Rates at mean follow-up of 23 months | Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152 | Aspirin 100 mg N=9126 | Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg | |
|---|---|---|---|---|
| | | | HR (95% CI) | *p*-value |
| **Modified major ISTH bleeding** | 288 (3.1%) | 170 (1.9%) | 1.70 (1.40–2.05) | <0.001 |
| Fatal | 15 (0.2%) | 10 (0.1%) | 1.49 (0.67–3.33) | 0.32 |
| Non-fatal ICH* | 21 (0.2%) | 19 (0.2%) | 1.10 (0.59–2.04) | 0.77 |
| Non-fatal other critical organ* | 42 (0.5%) | 29 (0.3%) | 1.43 (0.89–2.29) | 0.14 |

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

# Net Clinical Benefit: Rivaroxaban 2.5 mg bid + Aspirin Versus Aspirin

- **Definition:** composite of CV death, stroke, MI, fatal bleeding or symptomatic bleeding into a critical organ

| Outcome | Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152 | Aspirin 100 mg N=9126 | Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg | |
|---|---|---|---|---|
| | | | HR (95% CI) | *p*-value |
| Net clinical benefit | 431 (4.7%) | 534 (5.9%) | 0.80 (0.70–0.91) | <0.001 |

NNT 83!!!

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

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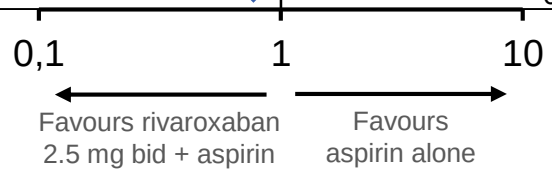
# Efficacy Across All Subgroups

| Subgroup | Rivaroxaban 2.5 mg bid + aspirin n/N (%) | Aspirin alone n/N (%) | HR (95% CI) | *p*-value |
|---|---|---|---|---|
| All participants | 379/9152 (4.1) | 496/9126 (5.4) | 0.76 (0.66–0.86) | |
| Age | | | | 0.20 |
| <65 years | 79/2150 (3.7) | 126/2184 (5.8) | 0.63 (0.48–0.84) | |
| 65–75 years | 179/5078 (3.5) | 238/5045 (4.7) | 0.74 (0.61–0.90) | |
| ≥75 years | 121/1924 (6.3) | 132/1897 (7) | 0.89 (0.69–1.14) | |
| Sex | | | | 0.75 |
| Male | 300/7093 (4.2) | 393/7137 (5.5) | 0.76 (0.66–0.89) | |
| Female | 79/2059 (3.8) | 103/1989 (5.2) | 0.72 (0.54–0.97) | |
| Body weight | | | | 0.64 |
| ≤60 kg | 41/901 (4.6) | 45/836 (5.4) | 0.83 (0.55–1.27) | |
| >60 kg | 335/8241 (4.1) | 448/8285 (5.4) | 0.75 (0.65–0.86) | |
| Estimated GFR | | | | 0.95 |
| <60 mL/min | 132/2054 (6.4) | 177/2114 (8.4) | 0.75 (0.60–0.94) | |
| ≥60 mL/min | 247/7094 (3.5) | 319/7012 (4.5) | 0.76 (0.64–0.90) | |
| CAD | | | | 0.47 |
| Yes | 347/8313 (4.2) | 460/8261 (5.6) | 0.74 (0.65–0.86) | |
| No | 32/839 (3.8) | 36/865 (4.2) | 0.89 (0.55–1.43) | |
| PAD | | | | 0.61 |
| Yes | 126/2492 (5.1) | 174/2504 (6.9) | 0.72 (0.57–0.90) | |
| No | 253/6660 (3.8) | 322/6622 (4.9) | 0.77 (0.66–0.91) | |

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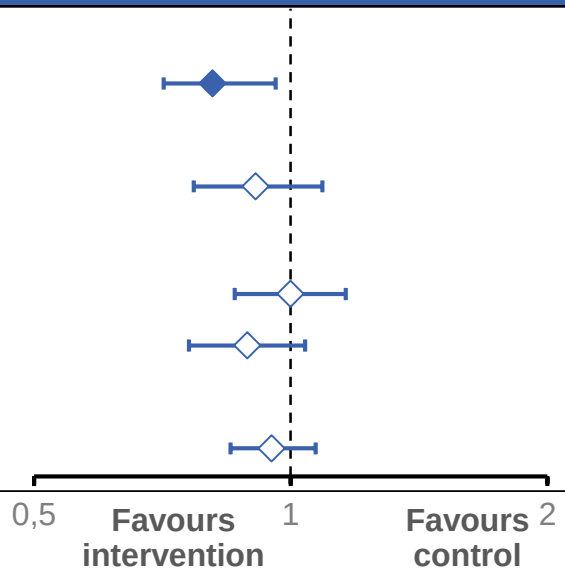
# Overall Survival in Patients with CAD or PAD

| Outcome | Rivaroxaban 2.5 mg bid + aspirin 100 mg | Aspirin 100 mg | Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg | |
|---|---|---|---|---|
| | | | HR (95% CI) | *p*-value* |
| CHD death, ischaemic stroke, MI, ALI | 329 (3.6%) | 450 (4.9%) | 0.72 (0.63–0.83) | <0.001 |
| CV death, ischaemic stroke, MI, ALI | 389 (4.3%) | 516 (5.7%) | 0.74 (0.65–0.85) | <0.001 |
| Mortality (all-cause) | 313 (3.4%) | 378 (4.1%) | 0.82 (0.71–0.96) | 0.01 |

| Study / Treatment arm | Control %/year | Intervention %/year | HR | HR (95% CI) | *p*-value |
|---|---|---|---|---|---|
| **COMPASS[1]** | | | | | |
| Rivaroxaban 2.5 mg bid | 2.1† | 1.8† | 0.82 | | 0.01 |
| **CHARISMA[2]** | | | | | |
| Clopidogrel 75 mg od | 2.3‡ | 2.1‡ | 0.91 | | 0.32 |
| **PEGASUS[3]** | | | | | |
| Ticagrelor 90 mg bid | 1.7¶ | 1.7¶ | 1.00 | | 0.99 |
| Ticagrelor 60 mg bid | 1.7¶ | 1.6¶ | 0.89 | | 0.14 |
| **TRA2P-TIMI 50[4]** | | | | | |
| Vorapaxar 2.5 mg od | 1.8¶ | 1.7¶ | 0.95 | | 0.41 |




1. Eikelboom *et al. N Engl J Med* 2017; 2. Bhatt *et al. J Am Coll Cardiol* 2007; 3. Bonaca *et al. N Engl J Med* 2015; 4. Morrow *et al. N Engl J Med* 2012;

# MALE and Major Amputation

| Outcome | Rivaroxaban 2.5 mg bid + aspirin N=2492 N (%) | Rivaroxaban 5 mg bid N=2474 N (%) | Aspirin N=2504 N (%) | Rivaroxaban 2.5 mg bid + aspirin vs aspirin HR (95% CI) | Rivaroxaban 2.5 mg bid + aspirin vs aspirin *p*-value | Rivaroxaban 5 mg bid vs aspirin HR (95% CI) | Rivaroxaban 5 mg bid vs aspirin *p*-value |
|---|---|---|---|---|---|---|---|
| MALE | 30 (1) | 35 (1) | 56 (2) | 0.54 (0.35–0.84) | 0.0054 | 0.63 (0.41–0.96) | 0.032 |
| Major amputation | 5 (<1) | 8 (<1) | 17 (<1) | 0.30 (0.11–0.80) | 0.011 | 0.46 (0.20–1.08) | 0.068 |
| MALE plus major amputation* | 32 (1) | 40 (2) | 60 (2) | 0.54 (0.35–0.82) | 0.0037 | 0.67 (0.45–1.00) | 0.046 |

*An additional 11 major amputations of a vascular cause were done that were unlinked to acute or chronic limb ischaemia, two in the low-dose rivaroxaban plus aspirin group, five in the rivaroxaban alone group, and four in the aspirin alone group

Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

# Conclusions

- XANTUS is the first, high quality, large, international prospective study to describe rivaroxaban use in a broad patient population with NVAF
- Over 96% patients receiving rivaroxaban did not experience any of the outcomes of stroke/SE, treatment-emergent major bleeding or all-cause death
- Rivaroxaban vascular dose 2.5 mg bid plus aspirin reduced the composite endpoint of stroke, MI or CV death by 28% (MALE by 46% ,Major amputations by 70%) with no significant increase was observed in fatal or critical organ bleeding