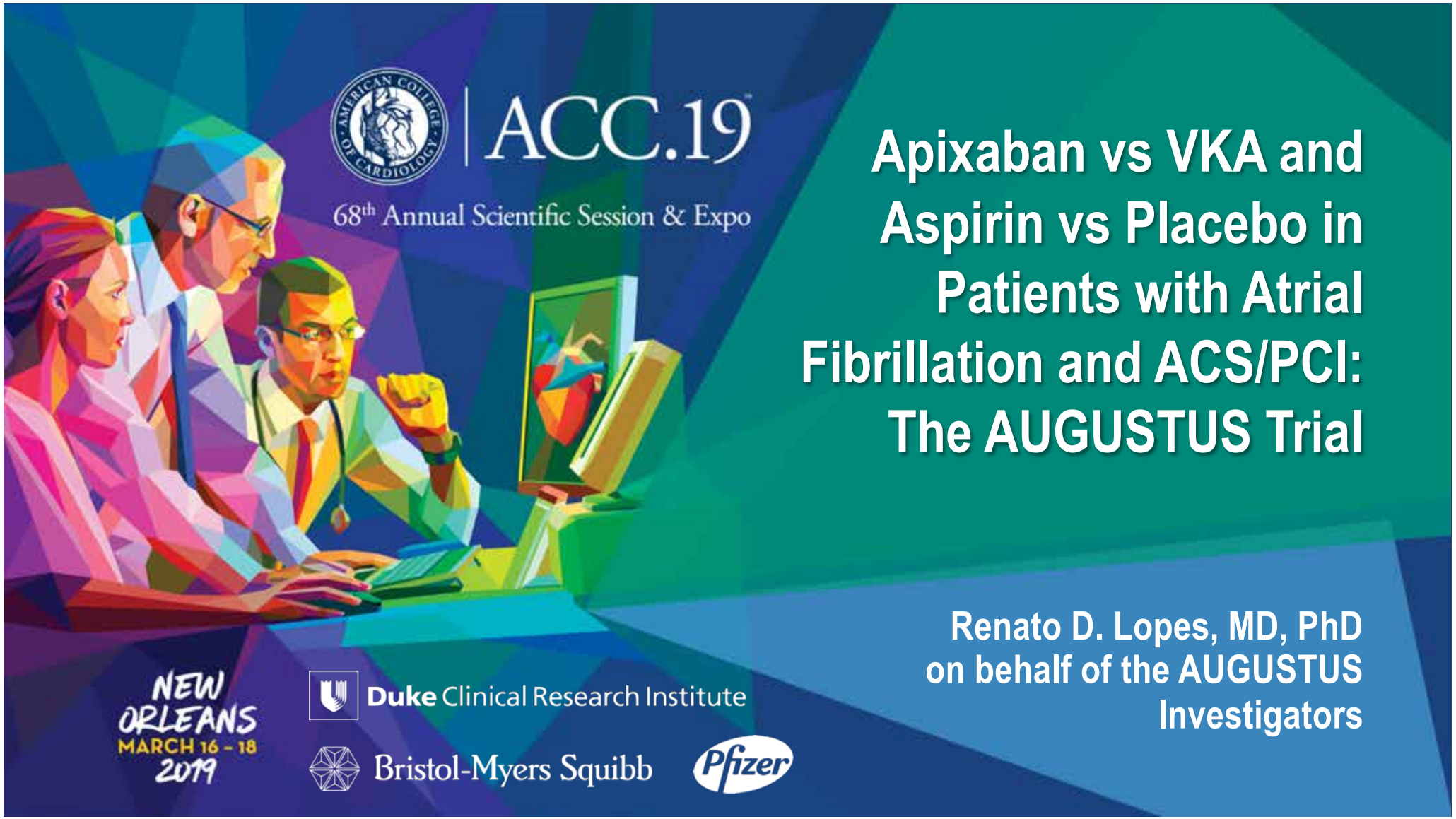


# Apixaban vs VKA and Aspirin vs Placebo in Patients with Atrial Fibrillation and ACS/PCI: The AUGUSTUS Trial

Renato D. Lopes, MD, PhD
on behalf of the AUGUSTUS Investigators

# Background

- The optimal antithrombotic regimen for patients with atrial fibrillation (AF) who have an acute coronary syndrome (ACS) or require percutaneous coronary intervention (PCI) is unclear
- Prior studies were designed to identify strategies to reduce the bleeding associated with triple antithrombotic therapy
  - WOEST (n=573): less bleeding AND fewer ischemic events without aspirin compared with vitamin K antagonist (VKA) + dual antiplatelet therapy (DAPT)
  - PIONEER AF-PCI (n=2124): less bleeding with two reduced-dose rivaroxaban regimens compared with VKA + DAPT
  - RE-DUAL PCI (n=2725): less bleeding with two standard-dose dabigatran regimens, without aspirin, compared with VKA + DAPT
- There are limited data with apixaban in patients with AF requiring DAPT
- Data on the independent effects of aspirin in this population are needed

Dewilde WJ, et al. Lancet 2013;381:1107-15.
Gibson CM, et al. N Engl J Med 2016;375:2423-34.
Cannon CP, et al. N Engl J Med 2017;377:1513-24.

# Two Independent Hypotheses

## In patients with AF and ACS or PCI on a $P2Y_{12}$ inhibitor

1. Apixaban is non-inferior to VKA for International Society on Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major (CRNM) bleeding
2. Aspirin is inferior to placebo for ISTH major or CRNM bleeding in patients on oral anticoagulation (OAC)

# Trial Design

Duke Clinical Research Institute

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**INCLUSION**
- Atrial fibrillation (prior, persistent, >6 hr)
  - Physician decision for OAC
- Acute coronary syndrome or PCI
  - Planned $P2Y_{12}$ inhibitor for ≥6 months

**Randomize**
n=4600
patients

**EXCLUSION**
- Contraindication to DAPT
- Other reason for VKA (prosthetic valve, moderate / severe mitral stenosis)

**Apixaban 5 mg BID**
Apixaban 2.5 mg BID in selected patients

Open Label

**VKA**
(INR 2–3)

*Aspirin for all on the day of ACS or PCI*
*Aspirin versus placebo after randomization*

**Aspirin** *Double Blind* **Placebo**

**Aspirin** *Double Blind* **Placebo**

**Primary outcome:** ISTH major / CRNM bleeding
**Secondary outcome(s):** death / hospitalization, death / ischemic events

Lopes RD, et al. Am Heart J. 2018;200:17-23.

# Trial Organization

## EXECUTIVE COMMITTEE

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Roxana Mehran (USA)

Christopher Granger (USA)

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Harald Darius (Germany)

Stephan Windecker (Switzerland)

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## DATA SAFETY MONITORING BOARD

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Robert Harrington

Stuart Pocock

Statistical Support—
Uppsala Clinical Research

## CLINICAL EVENTS CLASSIFICATION (CEC) COMMITTEE

Duke Clinical Research Institute

## ACADEMIC COORDINATING CENTER

Duke Clinical Research Institute

## CONTRACT RESEARCH ORGANIZATION

Pharmaceutical Product Development (PPD)

## SPONSORS

Bristol-Myers Squibb/
Pfizer

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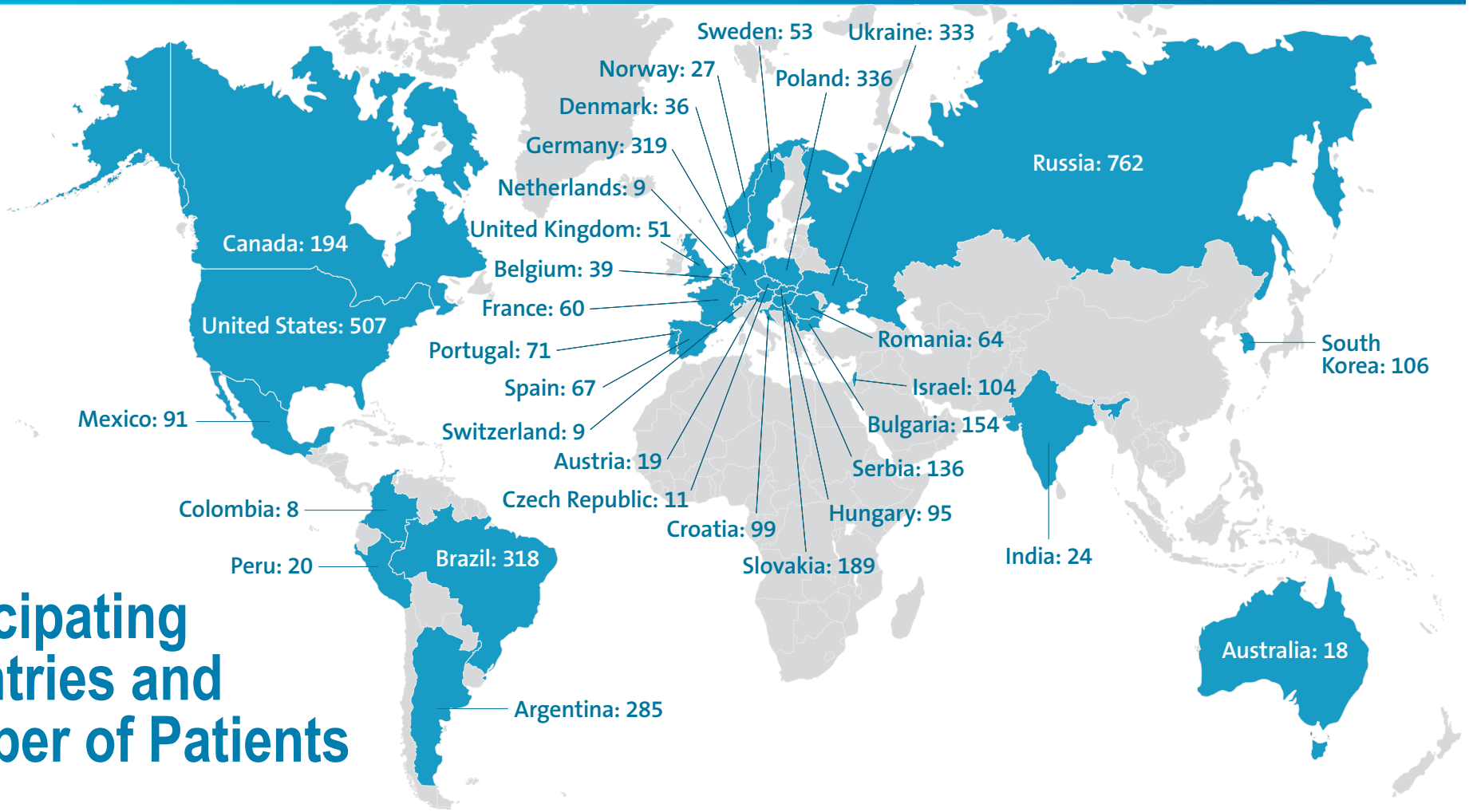
# Participating Countries and Number of Patients



# Primary Outcome

- **ISTH major bleeding**
  - Results in death
  - Occurs in critical area or organ
  - Results in hemoglobin drop ≥2 g/dL
  - Requires transfusion of ≥2 units of whole blood or packed red blood cells
- **Clinically relevant non-major bleeding**
  - Results in hospitalization
  - Requires medical / surgical evaluation or intervention
  - Requires physician-directed change in antithrombotic regimen

Lopes RD, et al. Am Heart J. 2018;200:17-23.

# Secondary Outcomes

- **Death or Hospitalization**
- **Death or Ischemic Events**
  - Stroke, myocardial infarction, stent thrombosis (definite or probable), urgent revascularization

Lopes RD, et al. Am Heart J. 2018;200:17-23.

# Statistical Analysis—Hierarchical Testing

## Apixaban vs. VKA:

- Major / CRNM Bleeding[NI then Sup]
- Death / Hospitalization[Sup]
- Death / Ischemic Events[Sup]

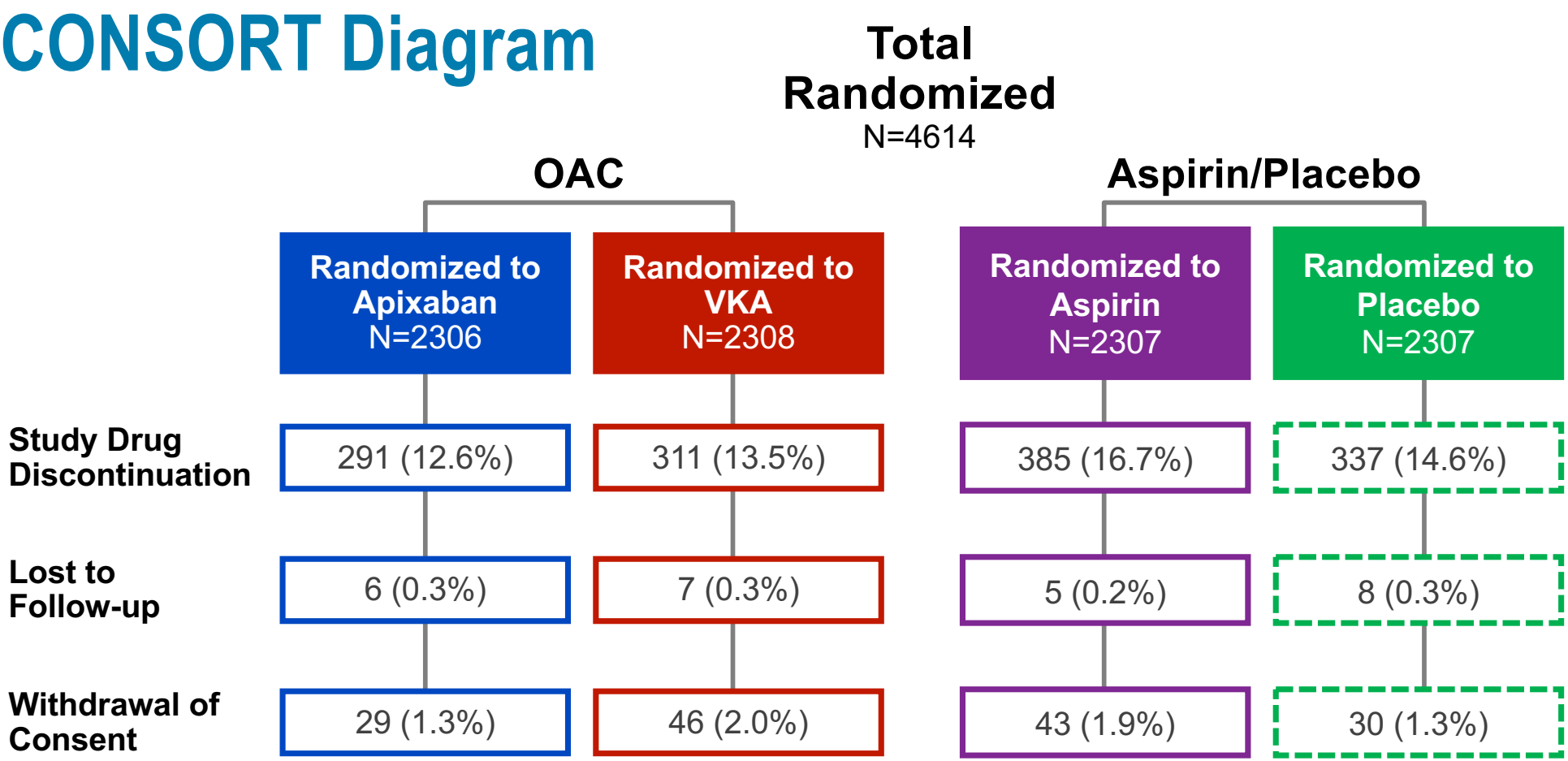
## Placebo vs. Aspirin:

- Major / CRNM Bleeding[Sup]
- Death / Hospitalization[Sup]
- Death / Ischemic Events[Sup]

Lopes RD, et al. Am Heart J. 2018;200:17-23.

NI = non-inferiority; Sup = superiority

# CONSORT Diagram



# Baseline Characteristics

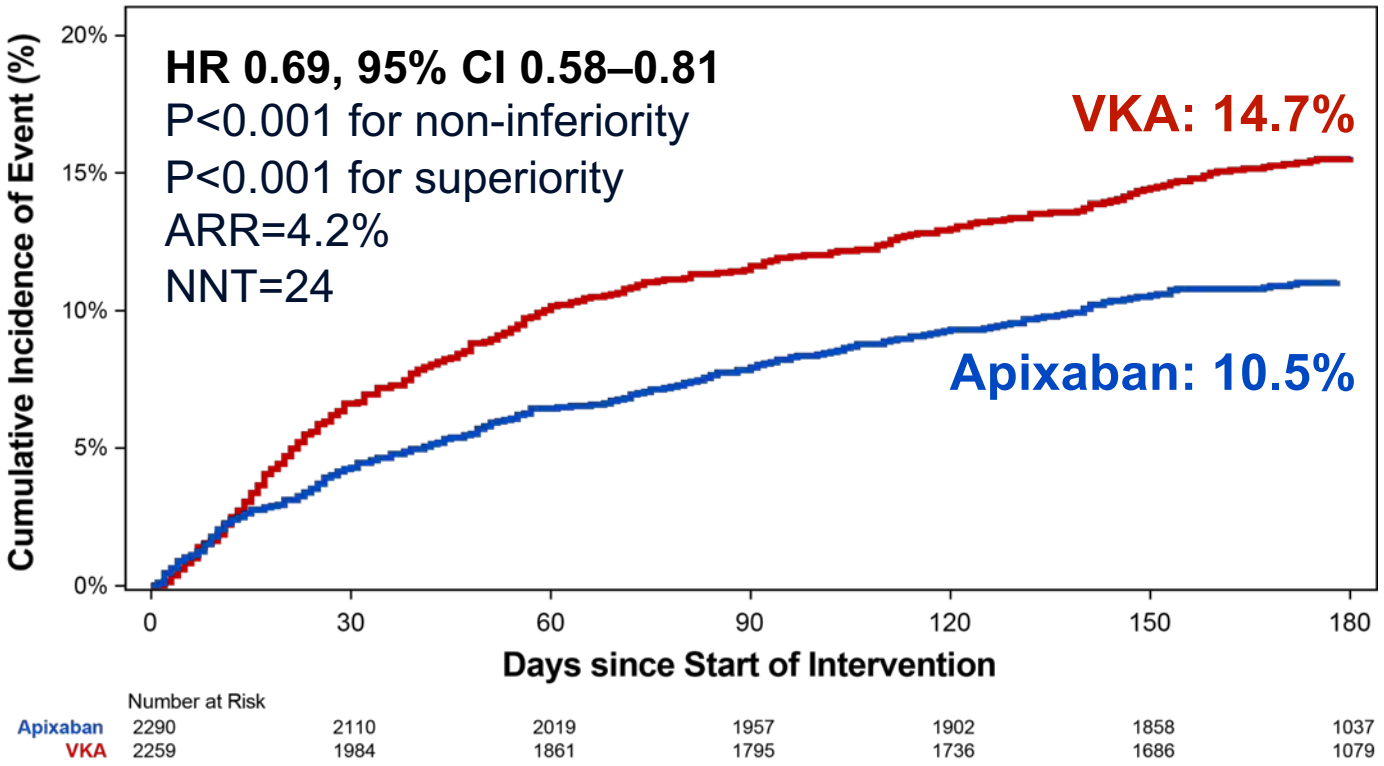
| | **Total** (N=4614) |
|---|---|
| Age, median (25th, 75th), years | 70.7 (64.2, 77.2) |
| Female, % | 29.0 |
| $CHA_2DS_2$-VASc score, mean (SD) | 3.9 (1.6) |
| HAS-BLED score, mean (SD) | 2.9 (0.9) |
| Prior OAC, % | 49.0 |
| $P2Y_{12}$ inhibitor, % | |
| Clopidogrel | 92.6 |
| Qualifying index event, % | |
| ACS and PCI | 37.3 |
| ACS and no PCI | 23.9 |
| Elective PCI | 38.8 |

# No Significant Interactions Between Randomization Factors

## Apixaban / VKA vs. Aspirin / Placebo

- Major / CRNM Bleeding: $P_{interaction} = 0.64$
- Death / Hospitalization: $P_{interaction} = 0.21$
- Death / Ischemic Events: $P_{interaction} = 0.28$

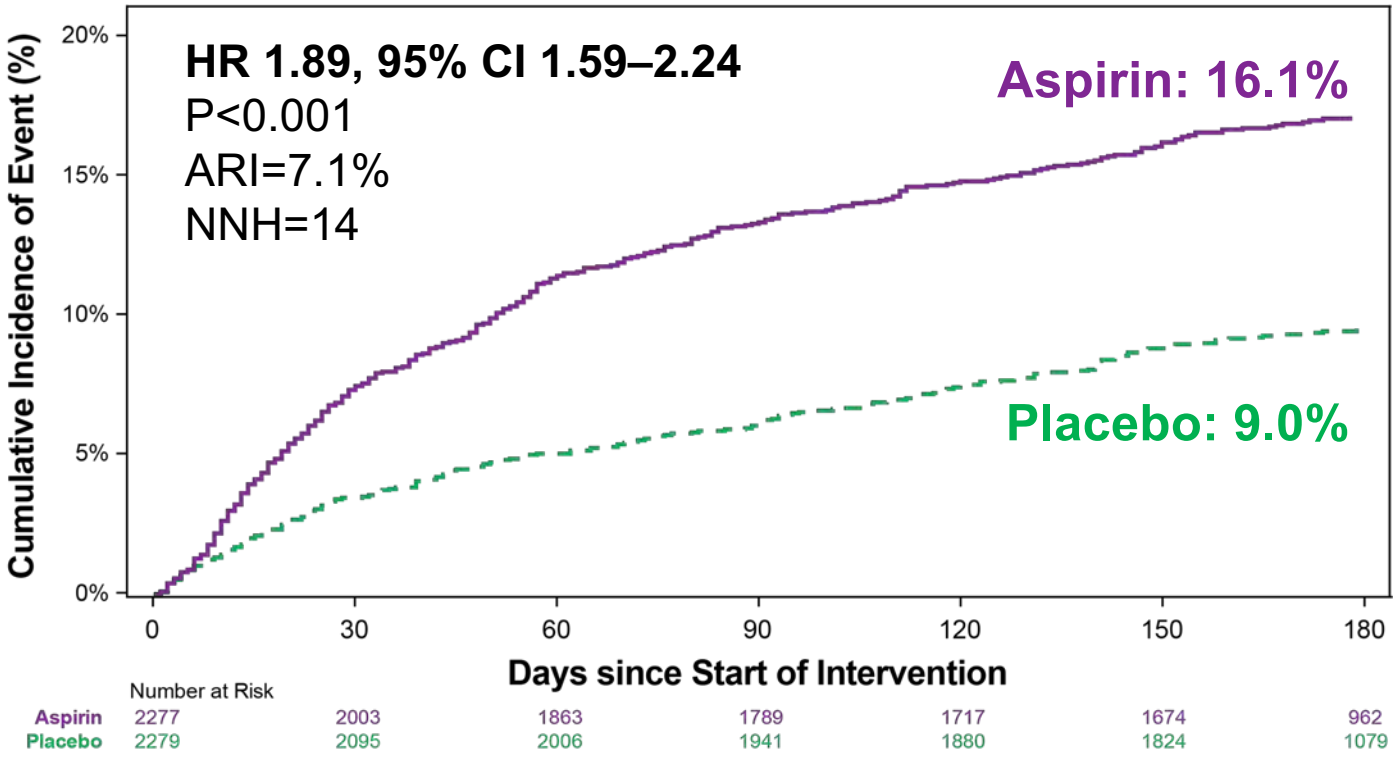
# Major / CRNM Bleeding
## Apixaban vs. VKA




ARR: absolute risk reduction
NNT: number needed to treat

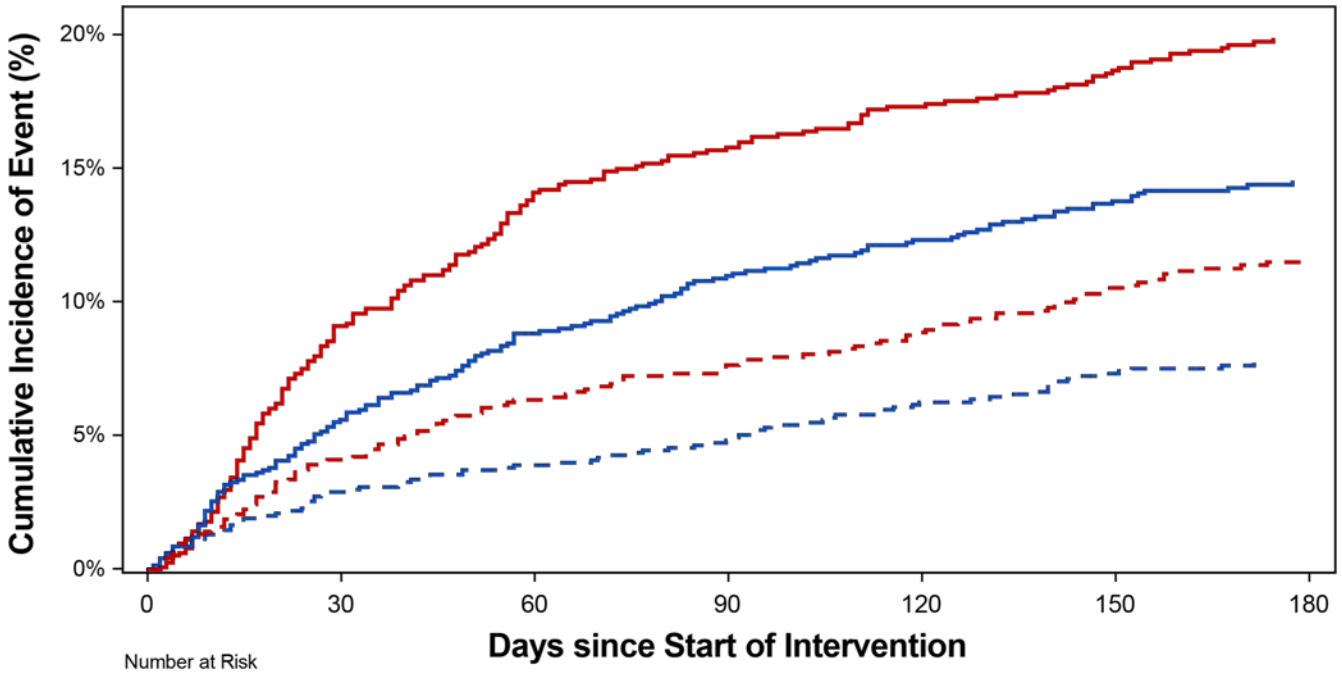
# Major / CRNM Bleeding

## Aspirin vs. Placebo




ARI: absolute risk increase
NNH: number needed to harm

# Major / CRNM Bleeding




| Number at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Apixaban and Aspirin | 1145 | 1036 | 975 | 937 | 903 | 880 | 485 |
| Apixaban and Placebo | 1143 | 1075 | 1044 | 1007 | 975 | 947 | 536 |
| VKA and Aspirin | 1123 | 962 | 881 | 838 | 800 | 776 | 467 |
| VKA and Placebo | 1126 | 1007 | 947 | 917 | 883 | 851 | 528 |

**VKA + Aspirin (18.7%)**

**Apixaban + Aspirin (13.8%)**

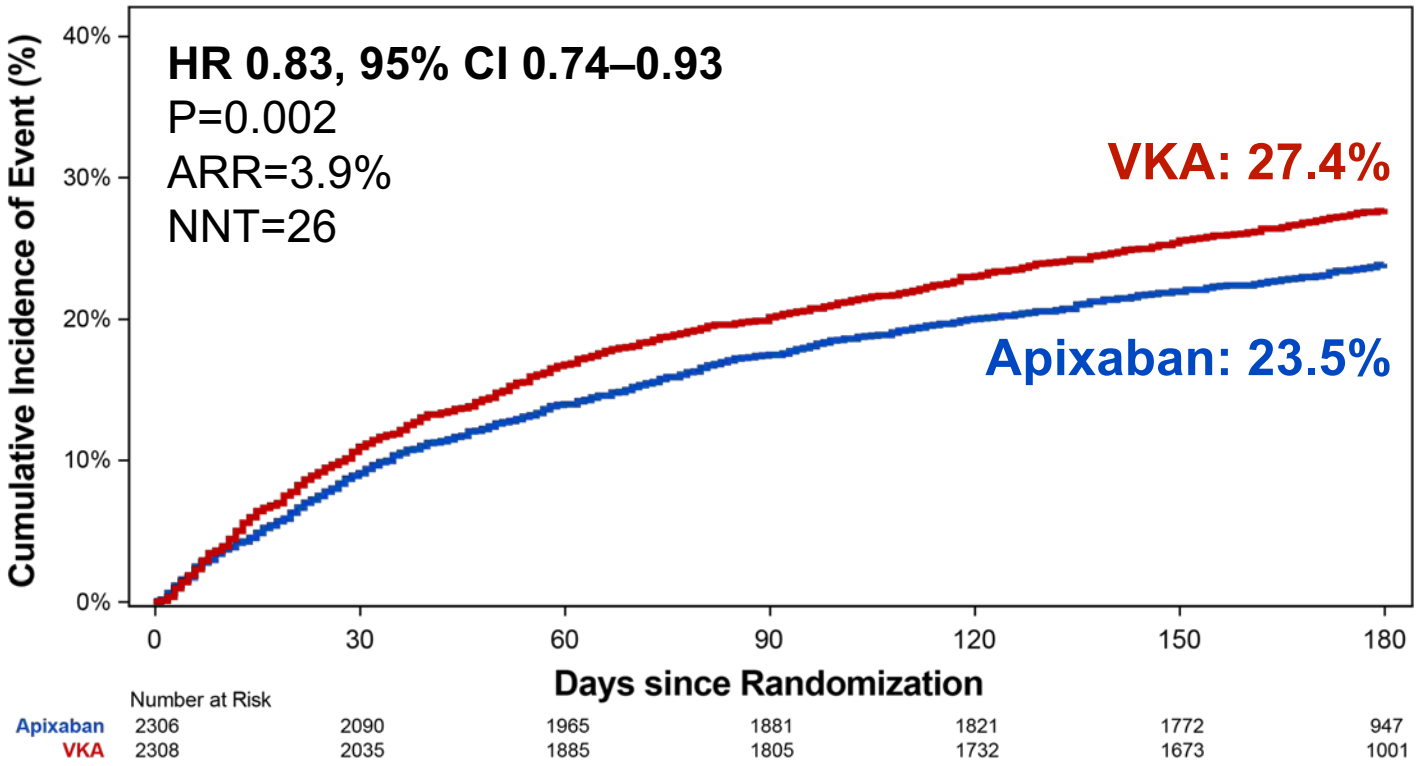
**VKA + Placebo (10.9%)**

**Apixaban + Placebo (7.3%)**

**Apixaban + Placebo vs. VKA + Aspirin:**
11.4% absolute risk reduction (NNT=9)

# Death / Hospitalization

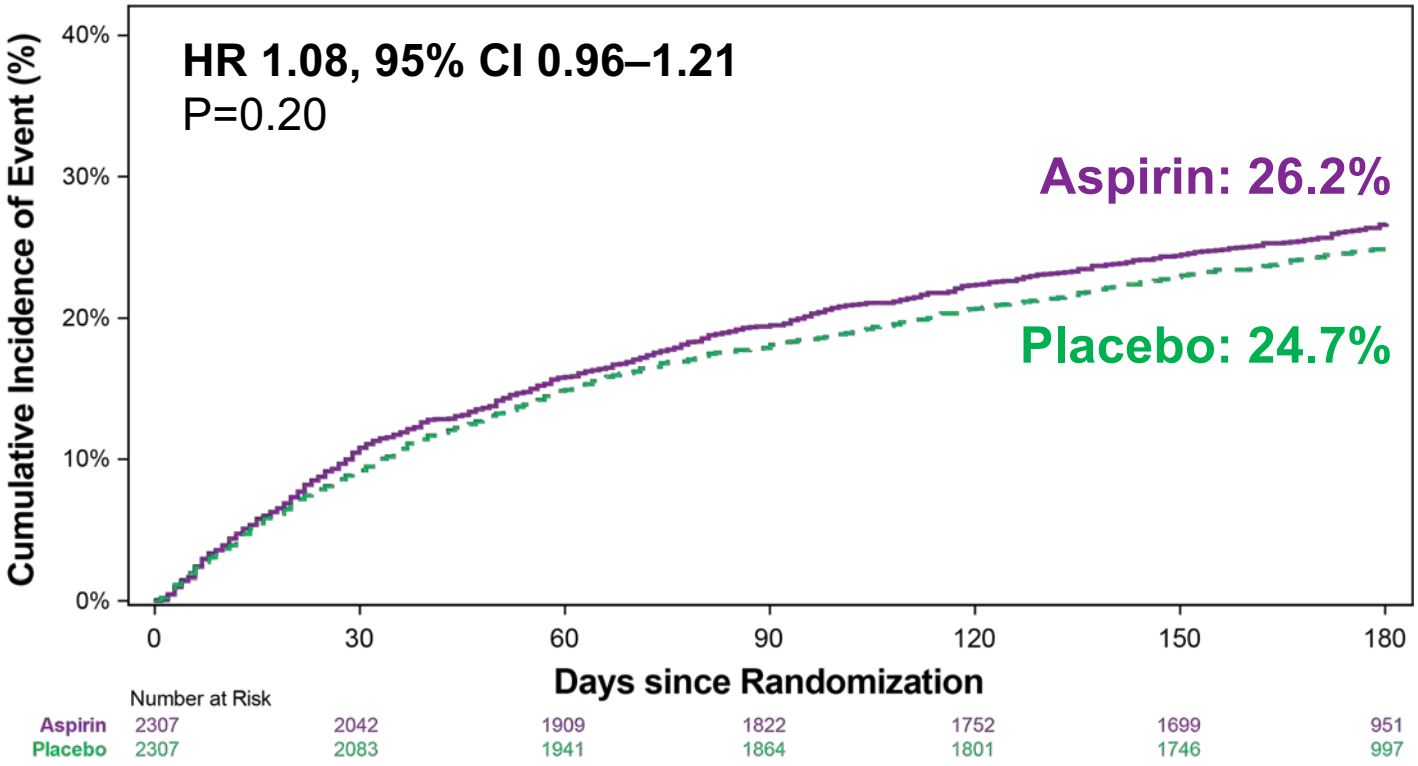
## Apixaban vs. VKA



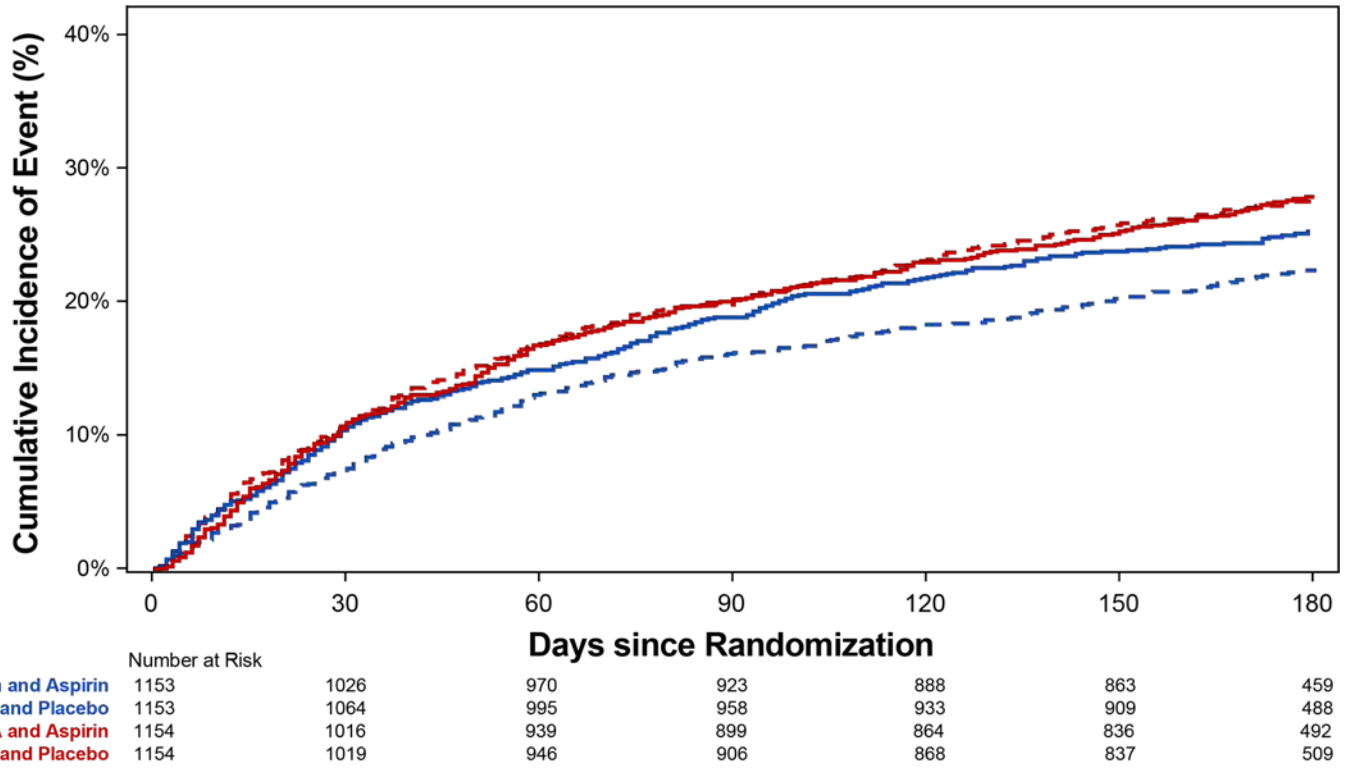

ARR: absolute risk reduction
NNT: number needed to treat

# Death / Hospitalization

## Aspirin vs. Placebo



# Death / Hospitalization




| Number at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Apixaban and Aspirin | 1153 | 1026 | 970 | 923 | 888 | 863 | 459 |
| Apixaban and Placebo | 1153 | 1064 | 995 | 958 | 933 | 909 | 488 |
| VKA and Aspirin | 1154 | 1016 | 939 | 899 | 864 | 836 | 492 |
| VKA and Placebo | 1154 | 1019 | 946 | 906 | 868 | 837 | 509 |

**VKA + Aspirin (27.5%)**
**VKA + Placebo (27.3%)**
**Apixaban + Aspirin (24.9%)**
**Apixaban + Placebo (22.0%)**

**Apixaban + Placebo vs. VKA + Aspirin:**
5.5% absolute risk reduction (NNT=18)

# Ischemic Outcomes
## Apixaban vs. VKA

| Endpoint | Apixaban (N=2306) | VKA (N=2308) | HR (95% CI) |
|---|---|---|---|
| Death / Ischemic Events (%) | 6.7 | 7.1 | 0.93 (0.75–1.16) |
| Death (%) | 3.3 | 3.2 | 1.03 (0.75–1.42) |
| CV Death (%) | 2.5 | 2.3 | 1.05 (0.72–1.52) |
| **Stroke** (%) | **0.6** | **1.1** | **0.50 (0.26–0.97)** |
| Myocardial Infarction (%) | 3.1 | 3.5 | 0.89 (0.65–1.23) |
| Definite or Probable Stent Thrombosis (%) | 0.6 | 0.8 | 0.77 (0.38–1.56) |
| Urgent Revascularization (%) | 1.7 | 1.9 | 0.90 (0.59–1.38) |
| **Hospitalization** (%) | **22.5** | **26.3** | **0.83 (0.74–0.93)** |

# Ischemic Outcomes
## Aspirin vs. Placebo

| Endpoint | Aspirin (N=2307) | Placebo (N=2307) | HR (95% CI) |
|---|---|---|---|
| Death / Ischemic Events (%) | 6.5 | 7.3 | 0.89 (0.71–1.11) |
| Death (%) | 3.1 | 3.4 | 0.91 (0.66–1.26) |
| CV Death (%) | 2.3 | 2.5 | 0.92 (0.63–1.33) |
| Stroke (%) | 0.9 | 0.8 | 1.06 (0.56–1.98) |
| Myocardial Infarction (%) | 2.9 | 3.6 | 0.81 (0.59–1.12) |
| Definite or Probable Stent Thrombosis (%) | 0.5 | 0.9 | 0.52 (0.25–1.08) |
| Urgent Revascularization (%) | 1.6 | 2.0 | 0.79 (0.51–1.21) |
| Hospitalization (%) | 25.4 | 23.4 | 1.10 (0.98–1.24) |

# Conclusion

In patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a $P2Y_{12}$ inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in ischemic events than regimens that included a vitamin K antagonist, aspirin, or both

# Acknowledgement

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ORIGINAL ARTICLE

# Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

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