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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ACADEMIC COORDINATING CENTER

Duke Clinical Research Institute

CONTRACT RESEARCH ORGANIZATION

Pharmaceutical Product Development (PPD)

SPONSORS

Bristol-Myers Squibb/
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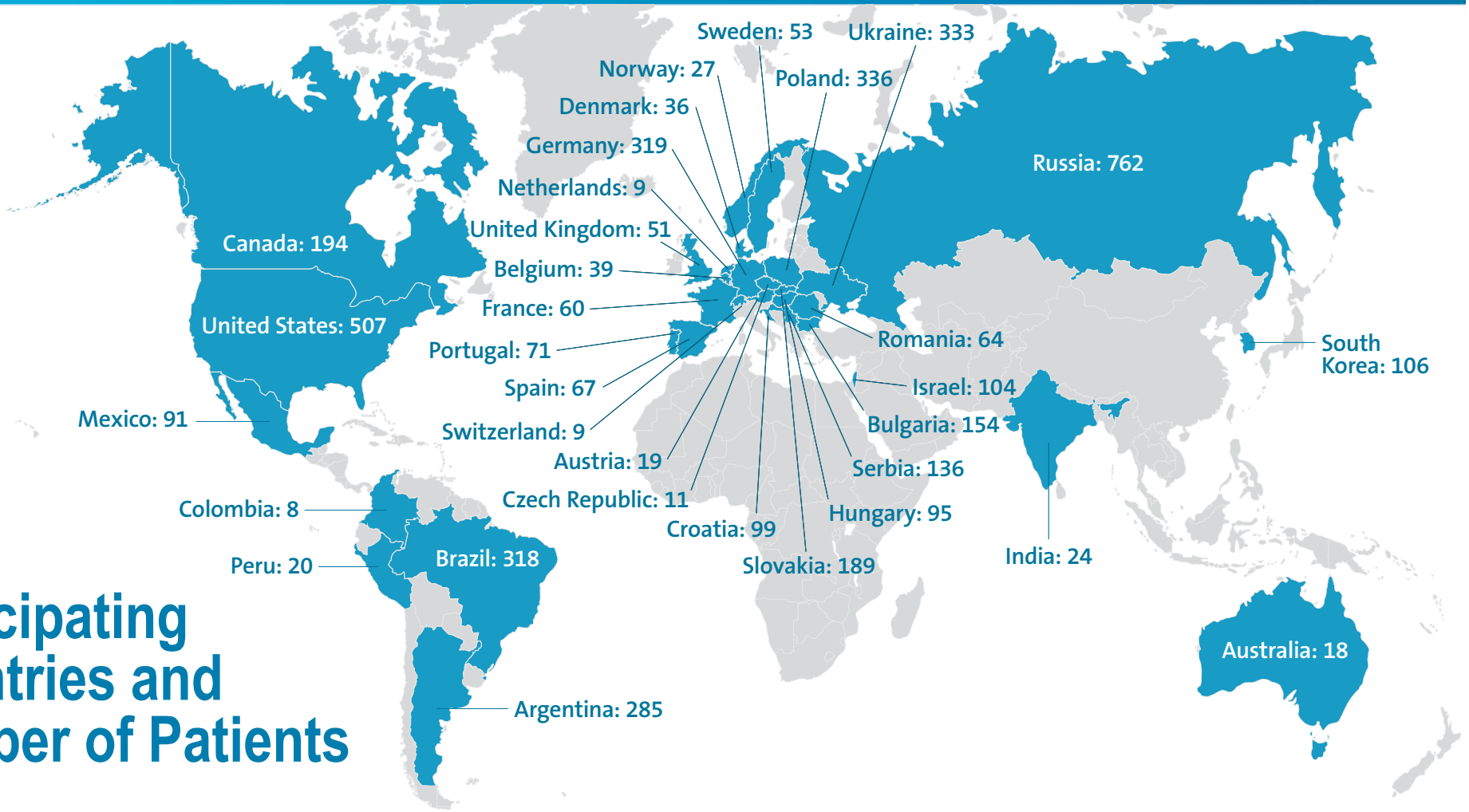
Participating Countries and Number of Patients



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]

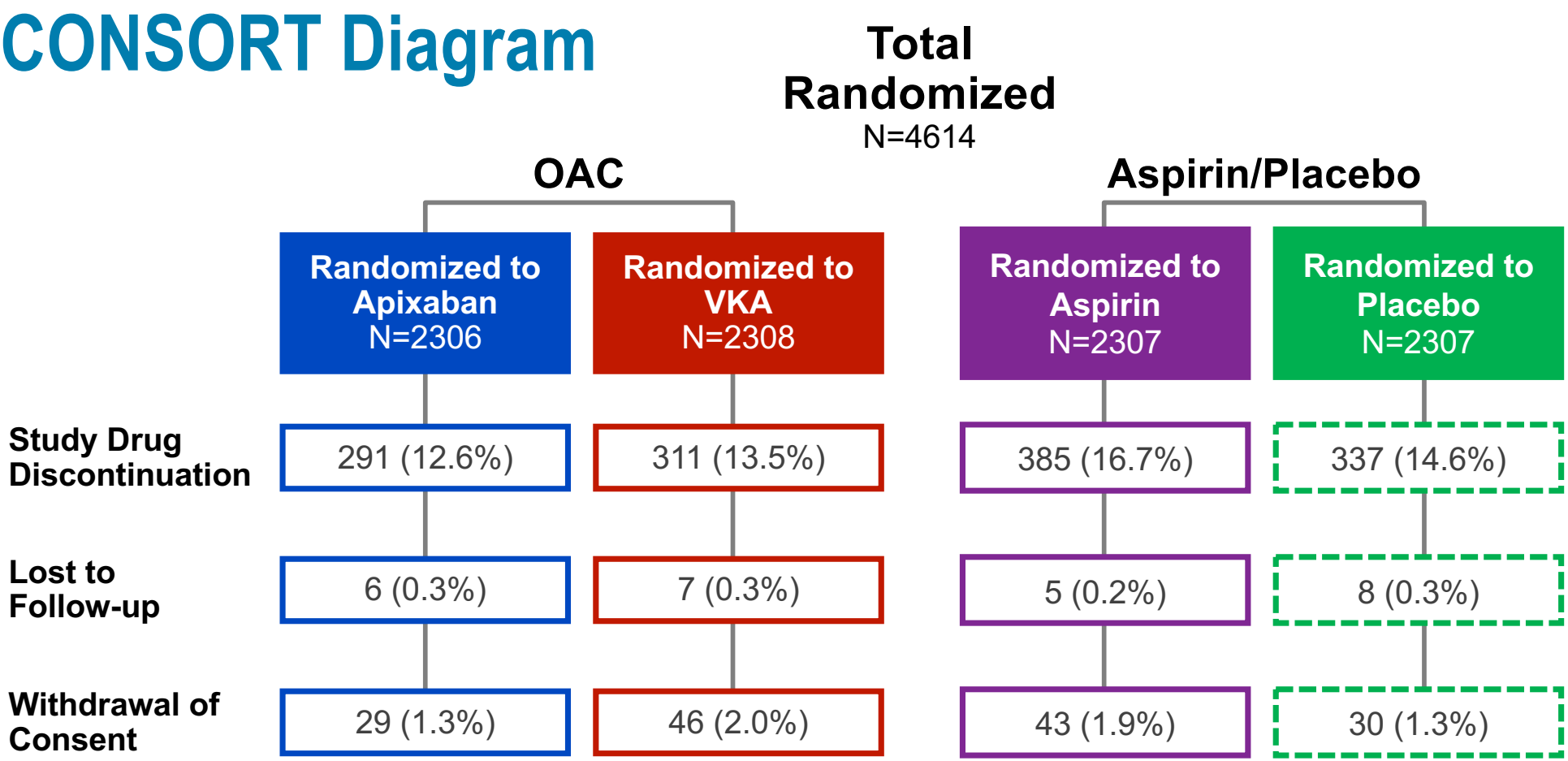
Placebo vs. Aspirin:

- 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

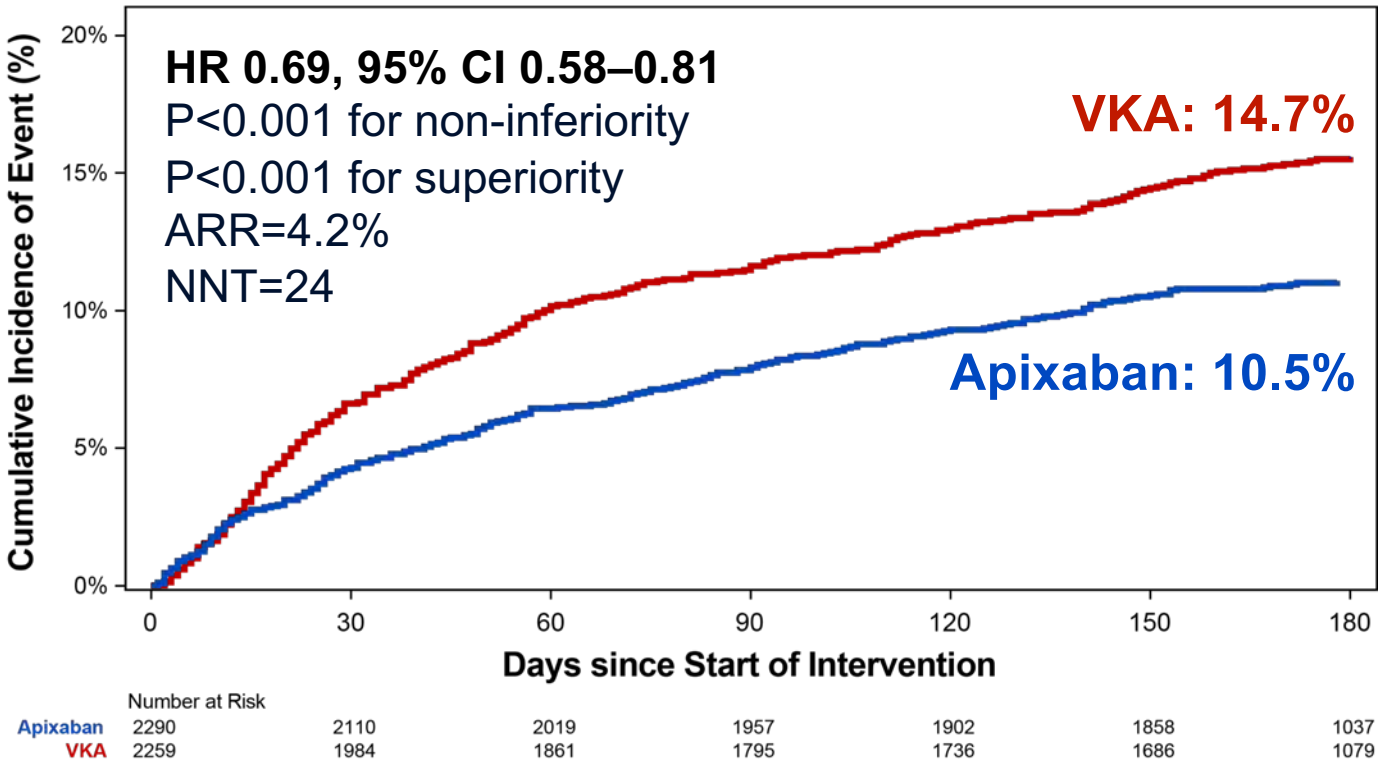
	Total (N=4614)
Age, median (25th, 75th), years	70.7 (64.2, 77.2)
Female, %	29.0
CHA_2DS_2-VASc score, mean (SD)	3.9 (1.6)
HAS-BLED score, mean (SD)	2.9 (0.9)
Prior OAC, %	49.0
$P2Y_{12}$ inhibitor, %	
Clopidogrel	92.6
Qualifying index event, %	
ACS and PCI	37.3
ACS and no PCI	23.9
Elective PCI	38.8

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: $P_{interaction} = 0.28$

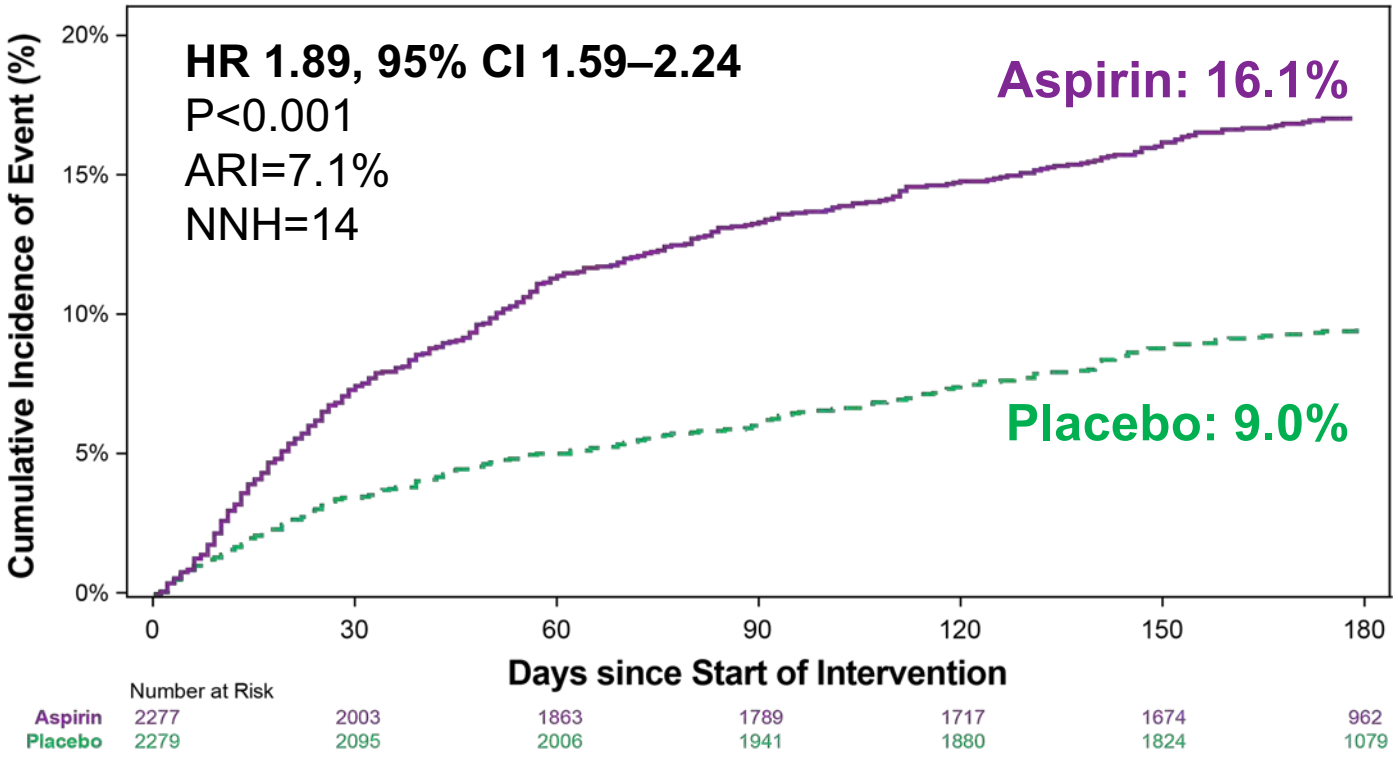
Major / CRNM Bleeding
Apixaban vs. VKA



ARR: absolute risk reduction
NNT: number needed to treat

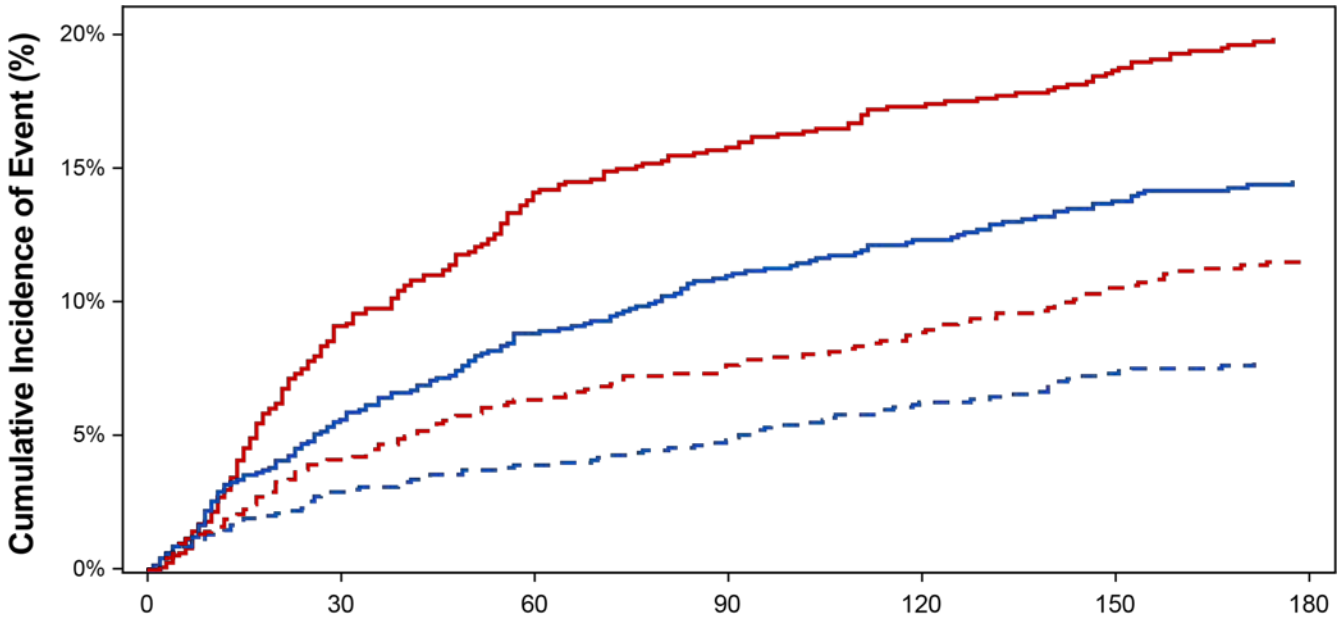
Major / CRNM Bleeding

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%)

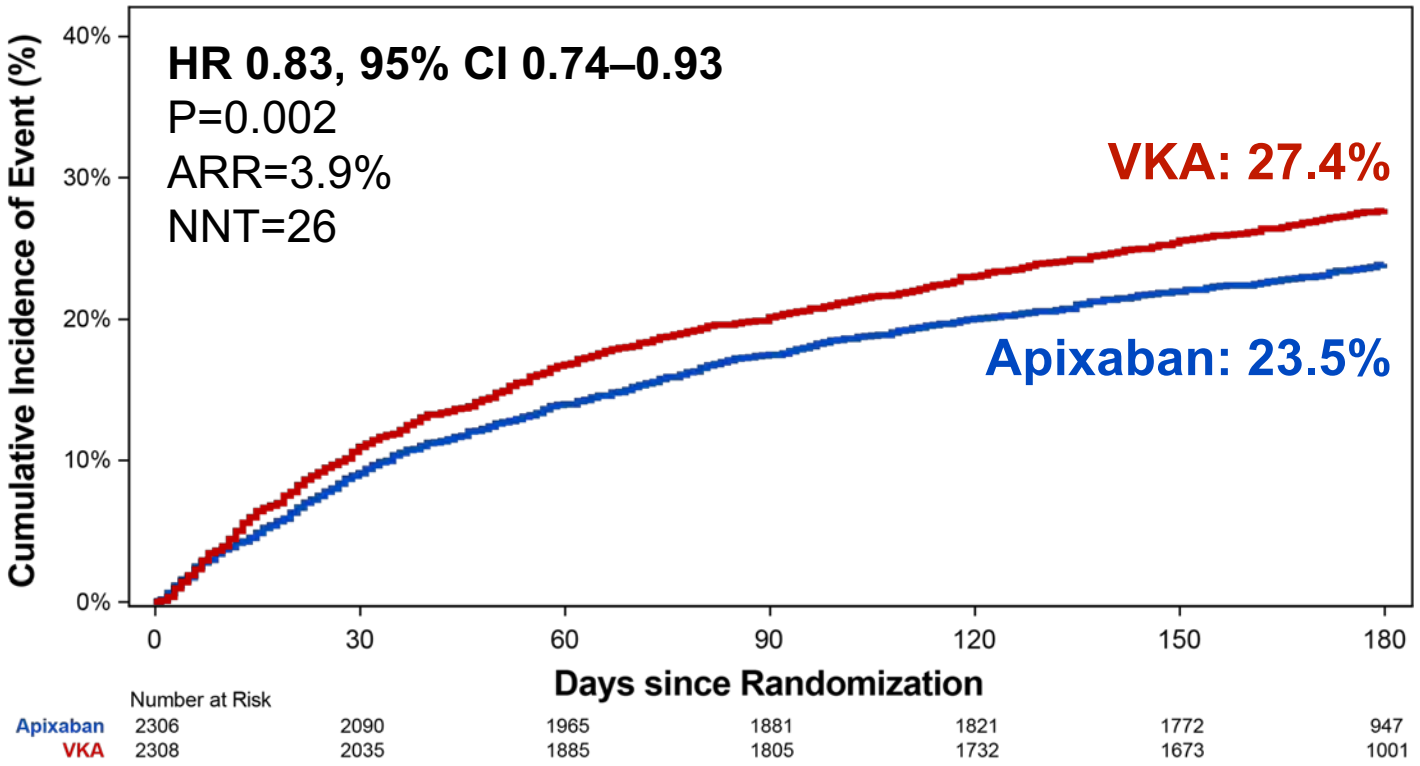
VKA + Placebo (10.9%)

Apixaban + Placebo (7.3%)

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

Death / Hospitalization

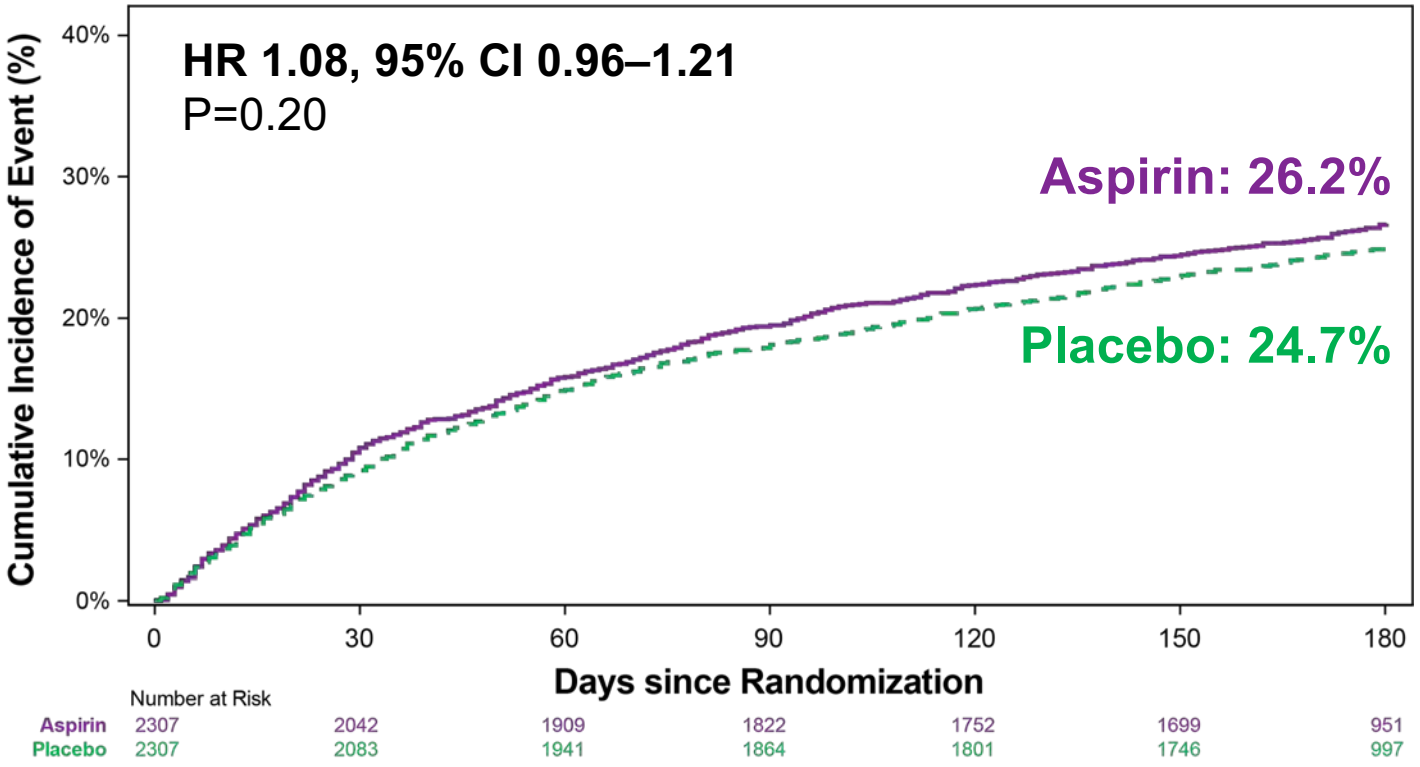
Apixaban vs. VKA



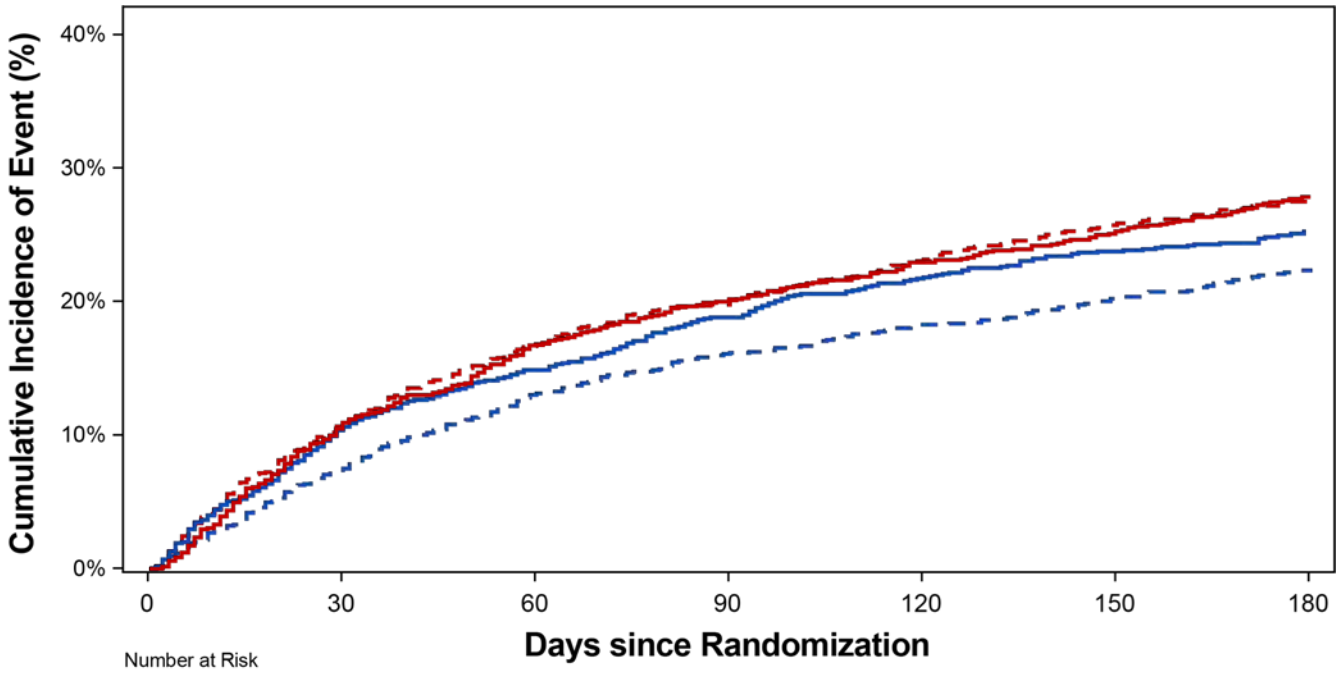
ARR: absolute risk reduction
NNT: number needed to treat

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