Comparative safety and effectiveness of apixaban versus VKAs and other DOACs in patients with nonvalvular atrial fibrillation: the NAXOS study

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Declaration of interest

- Research contracts (Amarin, Bayer, Sanofi, and Servier)
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Amarin, Amgen, AstraZeneca, Bayer/Janssen, Boehringer-Ingelheim, Bristol-Myers-Squib, Idorsia, Novartis, Novo-Nordisk, Pfizer, Regeneron, Sanofi, Servier)

Disclosures

- **PG.Steg**
  - Research grants (Unité INSERM U-1148): Amarin, Bayer, Sanofi, Servier
  - Consultant or speaker: Amarin, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Idorsia, Novartis, Pfizer, Sanofi, Servier

- **NAXOS** was supported by Bristol-Myers Squibb/Pfizer

- **The NAXOS database was housed at and all analyses were performed by the academic group at PharmacoEpidemiology Lyon**, EA 7425 HESPER health services and performance research, Université Claude-Bernard; Hôpital de la Croix-Rousse , Lyon, France.

Background

- Oral anticoagulants Vitamin K antagonists [VKAs] and three direct oral anticoagulants (DOACs) (dabigatran, rivaroxaban, and apixaban) are used for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) in France.

- While results from pivotal randomized trials comparing VKA and DOACs are available (RELY, ROCKET AF, ARISTOTLE, ENGAGE-AF), there is little data pertaining to the characteristics and outcomes of patients treated with these anticoagulants in routine clinical practice in France.

- In addition, there is no randomized trial comparing DOACs in terms of clinical outcomes

- French regulators have requested "real-life data" to document the therapeutic benefit of apixaban under actual conditions of use, compared with the other standard oral anticoagulant treatments recommended in France in patients with non-valvular AF

Objectives

1. Describe the use of OACs available in France for treating NVAF

2. Evaluate, in OAC-naïve patients with NVAF, the **safety** (risk of major bleeding), **effectiveness** (risk of stroke and systemic thromboembolism) as well as **all-cause mortality** of OACs
   - comparing apixaban with vitamin K antagonists
   - comparing apixaban with rivaroxaban, or dabigatran

The French National Health System claims data

- France (population 66 million) has nearly universal health coverage

- The National Health System* claims data covers > 90% of the population

- The NHS claims data collects information about demographics, medical history, hospital admissions, procedures and diagnoses, treatments, outpatient reimbursements and mortality

* Système National des Données de Santé: SNDS

Study design

- NAXOS is a historical cohort study generated from the French National Health System (NHS) claims data.

- All patients aged ≥18 years with NVAF and newly initiating an OAC* between January 2014 and December 2016 were identified in the NHS and allocated to four different treatment cohorts, according to the OAC started (VKA, Apixaban, Dabigatran or Rivaroxaban).

- The study was approved by the French Institute for Health Data (INDS) on Sept 8, 2015), conducted using anonymised data, approved by the National Informatics and Liberty Committee (CNIL) on 17 March 2016.

- NAXOS is registered at ClinicalTrials.gov (NCT02640222).

* OAC naïve patients could be "OAC experienced" (i.e. have received OAC more than 24 months before enrolment)

Study population

Inclusion criteria :
- Patients aged 18 years or more
- Covered by the French national health insurance general scheme
- With at least one reimbursement of OAC treatment
- Patients having initiated an index OAC treatment, either OAC-naive or not
- Patients diagnosed with AF in the 24 months prior to OAC initiation, identified using a validated algorithm*

Exclusion criteria :
- Multiple OAC treatments, doses or prescribers at index date
- Valvular conditions (detected using a specific validated algorithm)
- OAC for indications other than stroke prevention in AF

*Bouillon K et al. Lancet Haematol 2015;2:e150-9

Outcomes definitions

Effectiveness: risk of stroke and systemic thromboembolic events

Identification of stroke and systemic thromboembolic events was based on <u>main diagnoses of hospital stays</u>, through ICD-10 codes, for:
- Ischemic stroke or not specified
- Hemorrhagic stroke
- Systemic thromboembolism

**Safety: risk of major bleeding by AC treatment**

Identification of major bleeding was based on <u>main diagnoses of hospital stays</u>, through ICD-10 codes, for:
- Intracranial bleeding
- Gastric duodenal and rectum bleeding
- Acute post hemorrhagic anemia
- Intraocular bleeding
- Otorrhagia
- Pericardic
- Respiratory bleeding
- Haemoperitoneum
- Intra articular bleeding
- Uterine and vaginal bleeding
- Other bleeding

Statistical analysis

- Risks were compared using **propensity scores (PS)-adjusted models** –either Cox or Fine and Gray- based on known confounding factors (sociodemographics, specialty of the prescriber who initiated OAC treatment, comorbidities, drugs dispensed within 3 months of index date).

- **Sensitivity analyses** used adjustment for
  - confounding factors,
  - PS matching
  - High-Dimensional Propensity Score (HDPS) matching.

- **Subgroup analyses** performed to compare patients treated with the standard dose of apixaban and of the other OACs using PS-adjusted models.

Patient flow
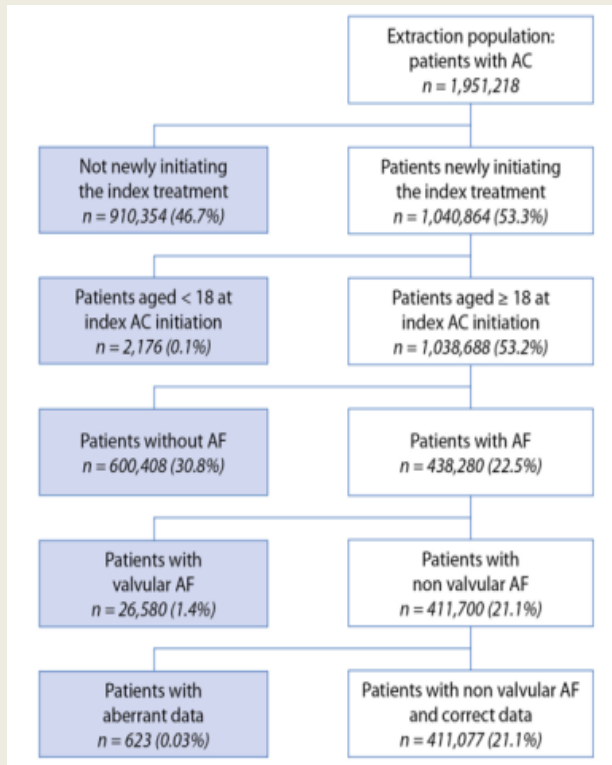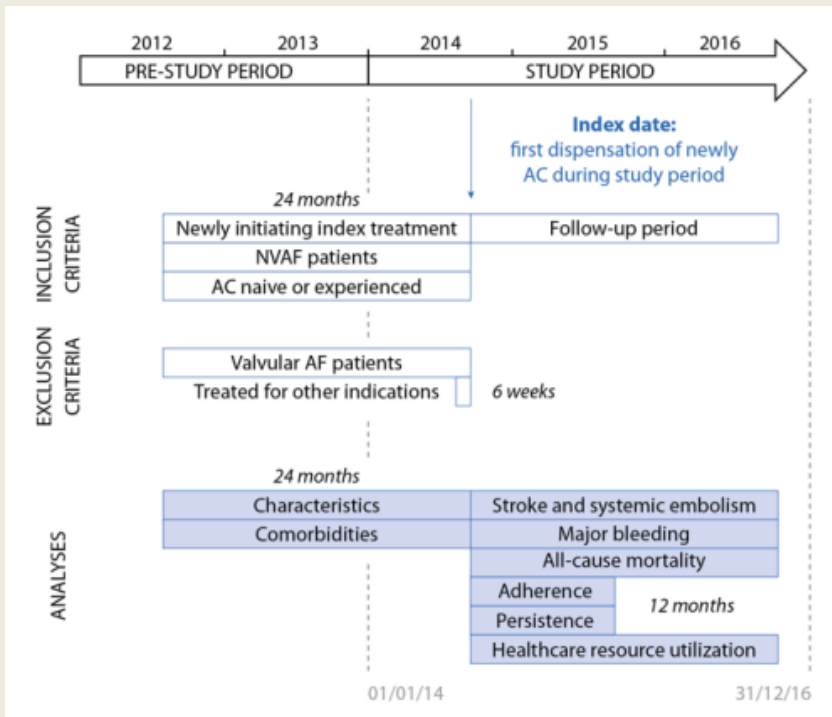
Demographic and clinical characteristics

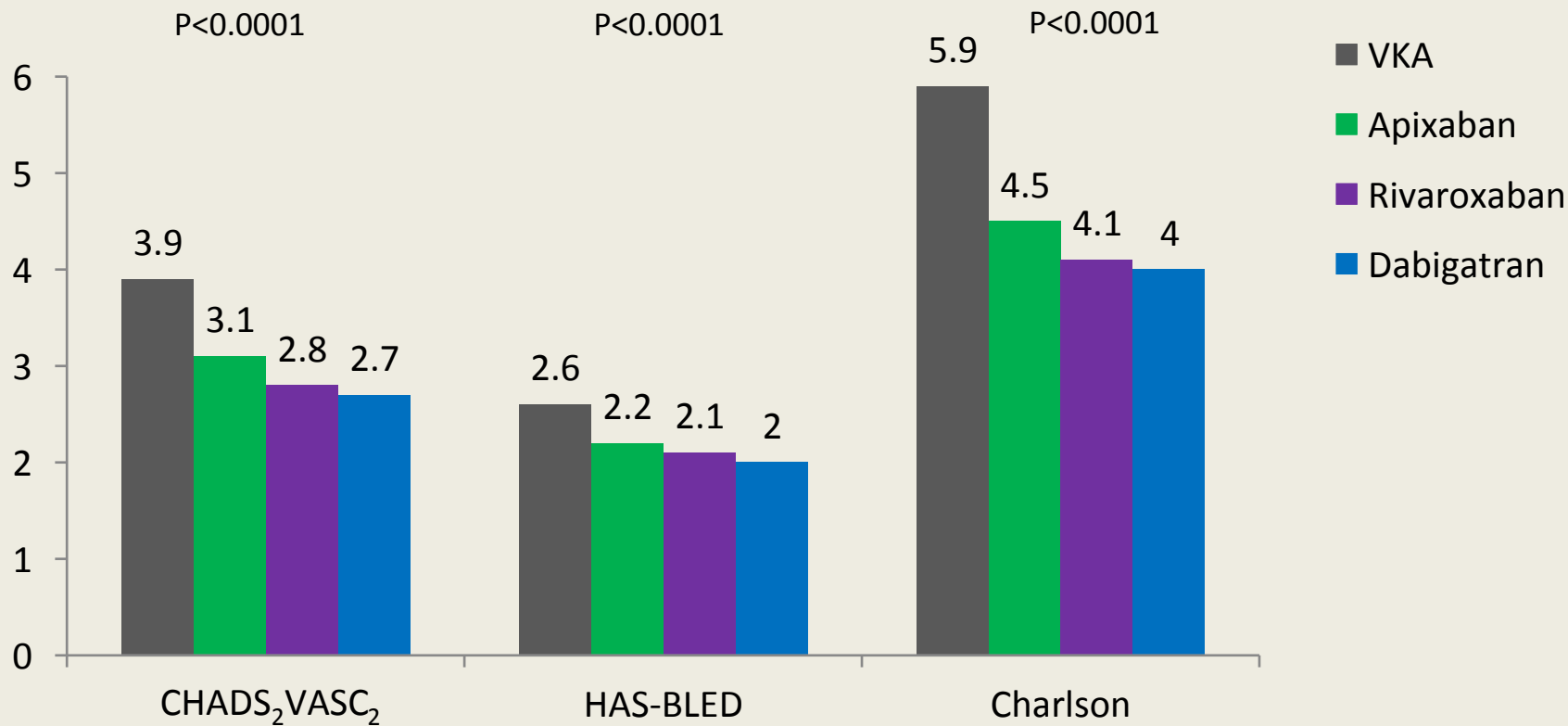|		VKA N=112,628	Apixaban N=87,565	Dabigatran N=21,245	Rivaroxaban N=100,063
Age at index date, years	Mean (SD)	78.5 (11.1)	74.7 (11.5)	72.7 (11.8)	72.0 (12.0)
>80 years	%	54.5	38.5	32.1	29.6
Sex	% Male	48.8	51.2	54.1	55.1
Time between NVAF diagnosis and index date	Months; Mean (SD)	89.4 (189.7)	69.7 (183.5)	73.9 (190.7)	71.7 (187.8)
Past hospital stays*	% of patients	85.4	73.7	69.7	69.0
	Mean number of hospital stays (SD)	2.7 (2.4)	2.1 (1.9)	2.1 (1.6)	2.1 (1.8)
Cumulative duration of past hospital stays	Mean (SD)	22.4 (22.8)	12.5 (14.9)	11.9 (14.9)	11.8 (14.9)

P values <0.0001 for all 2 x 2 comparisons

Note that VKA used are 70% fluindione, 3% acenocoumarol, 27% warfarin

Sociodemographic and clinical characteristics of OAC-naive patients

	VKAs N=112,628	Apixaban N=87,565	Dabigatran N=21,245	Rivaroxaban N=100,063	P value Apixaban vs VKA	P value Apix. vs Riva.	P value Apix. vs Dabi.
More frequent LTD status (%)							
Severe heart failure, arrhythmias, valvular cardiomyopathy, congenital heart disease	28.6	24.7	24.5	23.1	<0.0001	<0.0001	0.6305
Diabetes (type 1 or 2)	19.9	15.6	14.4	14.2	<0.0001	<0.0001	<0.0001
Cancer	15.7	13.4	12.5	12.7	<0.0001	<0.0001	0.0002
Coronary heart disease	16.3	11.9	9.2	10.1	<0.0001	<0.0001	<0.0001

Distribution of doses for the DOACs studied
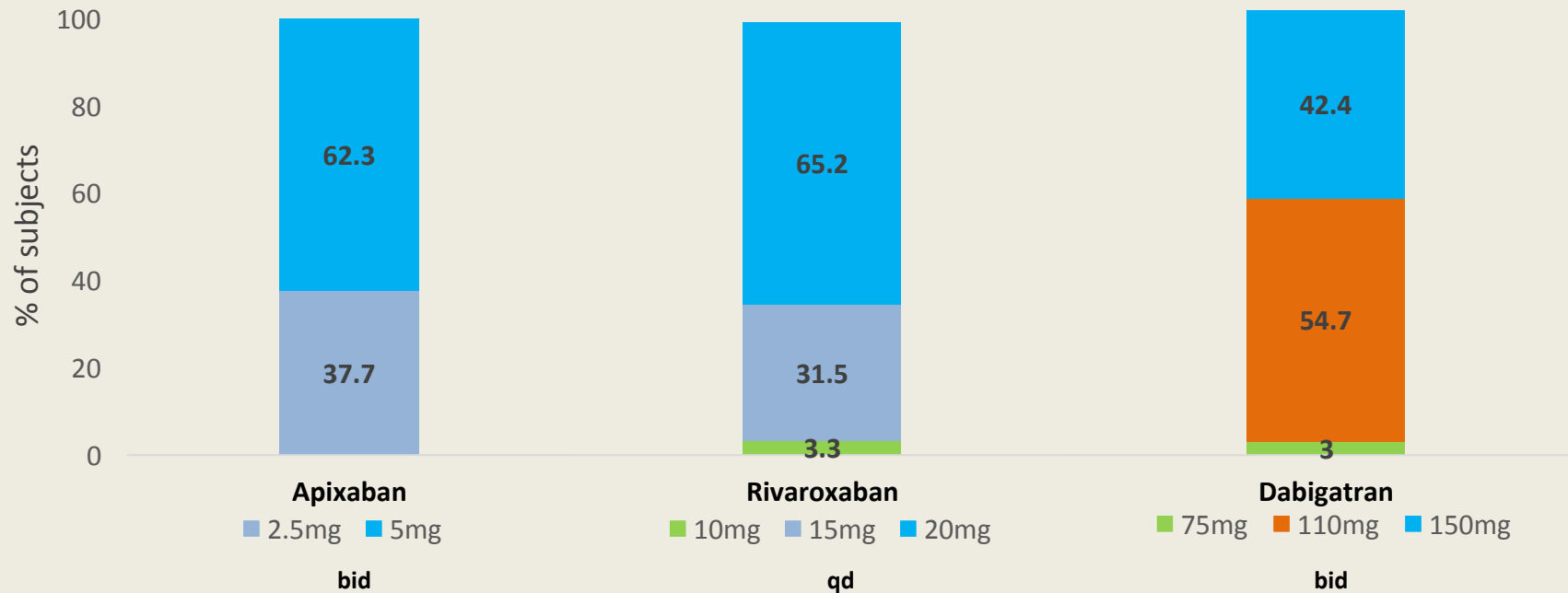
Given the information collected in the NHS database, it is not possible to know which patients fulfilled the criteria for dose reduction.

Patient disposition

	VKAs N=112,628	Apixaban N=87,565	Dabigatran N=21,245	Rivaroxaban N=100,063
End of follow-up, n (%)				
Death	13,232 (11.7%)	3,314 (3.8%)	796 (3.7%)	3,776 (3.8%)
Switch to another OAC	9,415 (8.4%)	5,589 (6.4%)	3,626 (17.1%)	10,538 (10.5%)
OAC Discontinuation	47,490 (42.2%)	19,872 (22.7%)	7,131 (33.6%)	32,152 (32.1%)
Follow-up duration (in days)				
Mean (Std)	316.1 (284.8)	285.7 (251.1)	329.1 (332.3)	317.6 (303.9)
Total person-years	97,528.3	68,540.1	19,153.5	87,078.9

Clinical Outcomes

NAXOS
Apixaban in patients with atrial fibrillation in Real Life French Study

| Cumulative incidence of event (t = 3 years) [95% CI]**	VKA	Apixaban	Rivaroxaban	Dabigatran
Major bleeding	**9.7%** [9.2% - 10.1%]	**4.1%** [3.7% - 4.6%]	**6.1%** [5.5% - 6.7%]	**4.1%** [3.6% - 4.7%]
Stroke and systemic embolism	**6.2%** [5.9% - 6.6%]	**2.9%** [2.6% - 3.2%]	**3.1%** [2.8% - 3.3%]	**3.1%** [2.6% - 3.7%]
All cause mortality	**27.7%** [26.8%- 28.6%]	**9.8%** [8.9% - 10.8%]	**9.7%** [9.1% - 10.2%]	**10.1%** [9.1% - 11.0%]

**Taking into account competing risks

Comparative safety and effectiveness
(propensity score adjusted comparison)
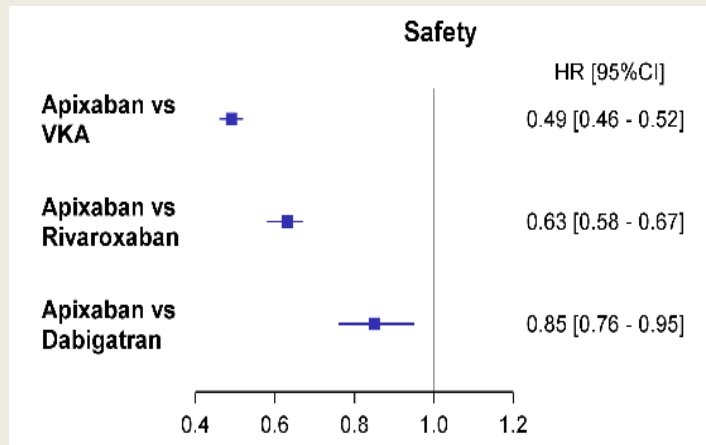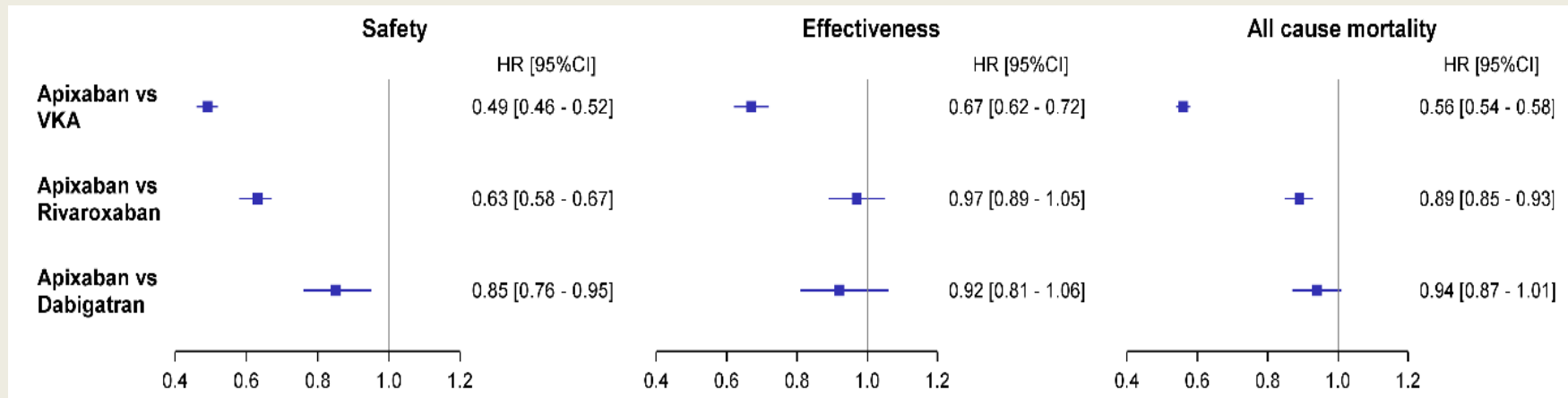

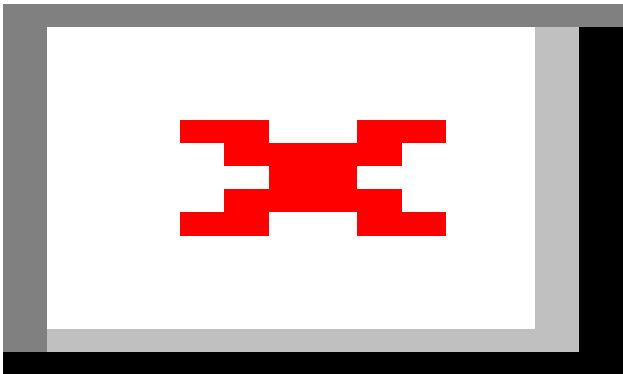major bleeding events leading to hospitalisation

Comparative safety and effectiveness
(propensity score adjusted comparison)
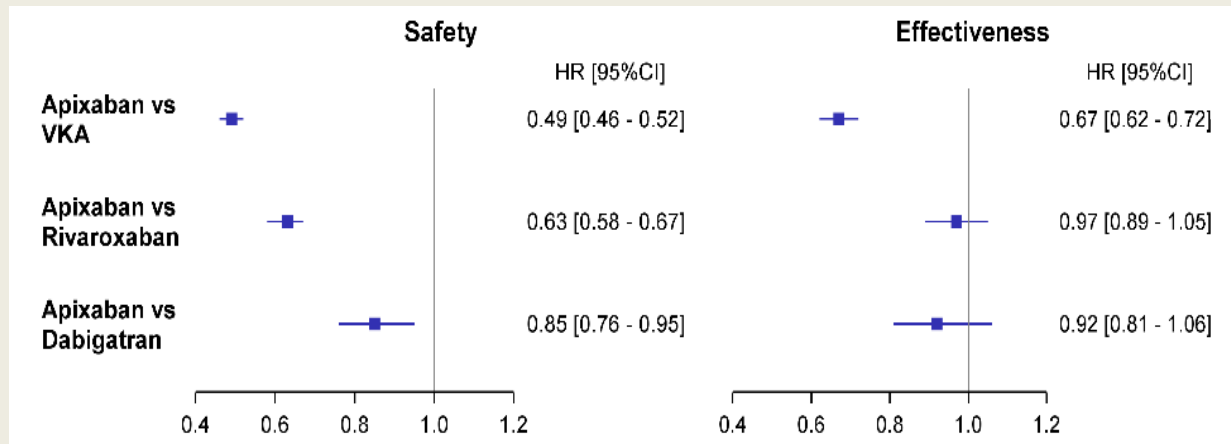
major bleeding events leading to hospitalisation

Stroke and systemic thromboembolism

Comparative safety and effectiveness
(propensity score adjusted comparison)

	Safety	Effectiveness	All cause mortality
	HR [95%CI]	HR [95%CI]	HR [95%CI]
Apixaban vs VKA	0.49 [0.46 - 0.52]	0.67 [0.62 - 0.72]	0.56 [0.54 - 0.58]
Apixaban vs Rivaroxaban	0.63 [0.58 - 0.67]	0.97 [0.89 - 1.05]	0.89 [0.85 - 0.93]
Apixaban vs Dabigatran	0.85 [0.76 - 0.95]	0.92 [0.81 - 1.06]	0.94 [0.87 - 1.01]

major bleeding events leading to hospitalisation

Stroke and systemic thromboembolism

Sensitivity Analyses - Outcomes comparisons

Adjusted: n=200,193	Adjusted: n=187,628	Adjusted: n=108,810
Matched on PS: n= 175,766	Matched on PS: n= 181,809	Matched on PS: n= 42,490
Adjusted on hdPS:	Adjusted on hdPS:	Adjusted on hdPS:
Safety n=154,890	Safety n=175,242	Safety n=42,149
Effectiveness n=154,124	Effectiveness n=175,352	Effectiveness n=42,125
All-cause death n=157,026	All-cause death n=175,412	All-cause death n=42,152

Strengths and limitations

Strengths

– Population-based nationwide cohort, minimizing the potential for selection bias

– Use of validated algorithms to identify the target population

– Large size, providing power

– Results consistent across a range of sensitivity analyses using various methods to minimize confounding

Limitations

– Patients with mild disease may have been excluded (eg. Paroxysmal uncomplicated AF)

– No collection of primary care diagnoses

– Some CV risk factors were identified from proxies and information missing for some confounders (smoking, weight, diet, physical activity, socioeconomic status)

– **Residual confounding may always be present in observational analyses**

Conclusions

- In this large observational population-based comparison of OACs initiation in patients with NVAF, apixaban use was associated with superior safety, superior effectiveness and lower mortality than VKAs, consistent with the results from ARISTOTLE.

- Apixaban use was associated with lower bleeding and similar effectiveness as rivaroxaban or dabigatran.

- However, given the observational nature of these analyses, they should be viewed as hypothesis-generating.

- Given the lack of randomised comparisons between DOACs, these observations are of interest to patients, clinicians, regulators and payers.

- The magnitude of some differences between DOACs suggest that head-to-head RCTs appear warranted.

Sunday September 1st : 10h05- 10h55
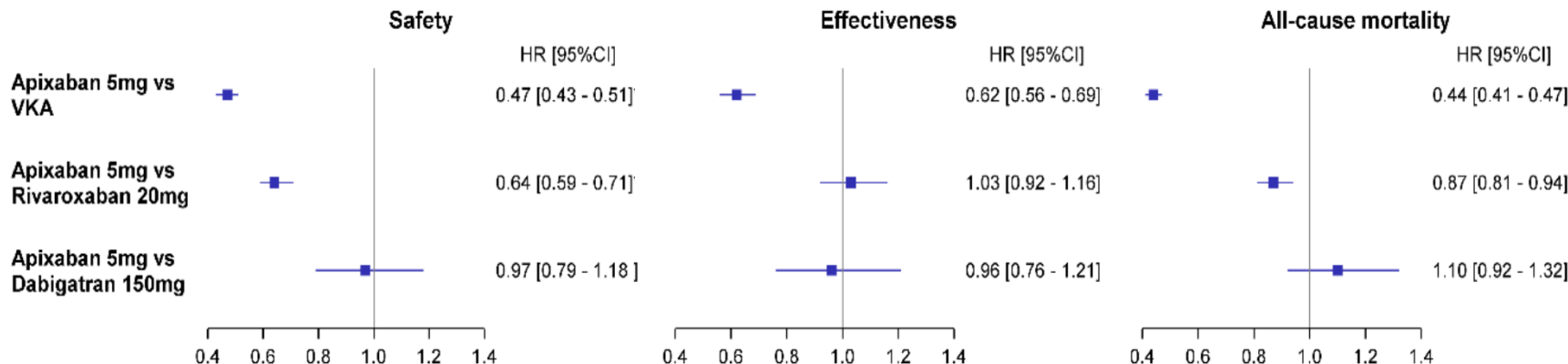
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Comparative safety and effectiveness of standard doses of apixaban versus dabigatran, rivaroxaban, and VKAs in non-valvular atrial fibrillation patients in France: the NAXOS study

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Comparative safety and effectiveness <u>for standard doses</u> (propensity score adjusted comparison)