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## Background

- > Dabigatran and rivaroxaban showed a better benefit-risk than vitamin-K antagonists (VKA) for stroke prevention in non-valvular atrial fibrillation (NVAF), but no randomized trial has compared dabigatran to rivaroxaban.
- > However, our previous results and other studies conducted in real-life settings found similar or better results with dabigatran at either dose than rivaroxaban after 1 or 2 years of follow-up.
- > Dabigatran 150mg and rivaroxaban 20mg are the standard doses. Dabigatran 110mg is a reduced dose indicated in patients with moderate renal impairment, a higher risk of bleeding or in older patients, whereas rivaroxaban 15mg is just recommended for patients with moderate renal impairment.

## **Objectives**

To estimate the comparative effectiveness and safety of standard and reduced doses of dabigatran versus rivaroxaban over a 3-year follow-up in real-life setting.

## Methods

### Study design

Cohorts study in the SNDS (Système National des Données de Santé) nationwide French claims database including all new users of dabigatran (150mg or 110mg), or rivaroxaban (20mg or 15mg) for NVAF in 2013, with three-year history and three-year follow-up in the database (except for patients who did not survive).

### Data source

- SNDS database contains individual pseudonymised information from 66 million persons on:
- Gender, date of birth, area of residence, date of death;
- Long-term disease registration with associated ICD-10 codes for full insurance coverage (with start and end dates);
- Outpatient reimbursed healthcare expenditures: visits, medical procedures, lab tests, drugs ...;
- Hospital discharge summaries with ICD-10 codes for diagnosis (primary, linked and associated diagnoses) for all private and public medical, obstetric and surgery hospitalisations, with the date and duration of hospitalisation, medical procedures.

### > NVAF population

Patients with long-term disease registration, hospitalisation or procedure for atrial fibrillation without valvular disease history, and nor other probable indication using three-year database history.

> Outcomes: during anticoagulant exposure period (on treatment)

- Clinical events: hospital admission with main diagnosis of clinically relevant bleeding (CRB), major bleeding, stroke and systemic embolism (SSE), and acute coronary syndrome (ACS);
- Death (all-cause);
- Composite criterion: first event among CRB, SSE, ACS, or death.

### Data analysis

- 1:1 matched analysis on gender, age  $(\pm 1 \text{ year})$ , date of the first drug dispensing
- $(\pm 14 \text{ days})$ , and high-dimensional propensity score (hdPS)\*  $(\pm 0.01)$ .
- Cumulative incidence of outcomes using Kaplan-Meier estimate (death, composite) or cumulative incidence function (other outcomes).
- Hazard ratios (HR) [95% confidence interval (CI)] of outcomes during first prescribed anticoagulant exposure, using Cox proportional hazard risk (death, composite) or Fine and Gray models (other outcomes) for crude, adjusted and matched patient analyses.

\*Probability to be treated by dabigatran 150mg versus rivaroxaban 20mg or dabigatran 110mg versus rivaroxaban 15mg using a logistic regression model with 500 variables including gender, age, stroke risk factors, bleeding risk factors

## **Declaration of Interest Statement**

This study was funded by an unrestricted grant from Boehringer Ingelheim France. It was designed, conducted, and analysed independently by the Bordeaux PharmacoEpi of the Bordeaux University. It was overseen by independent experts.





# Face-to-face 3-year comparative effectiveness and safety of dabigatran and rivaroxaban, standard and reduced doses, for nonvalvular atrial fibrillation: a cohort study in the French nationwide claims database

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				Res	sults					
<ul> <li>Populations</li> <li>Of 371,539 new users of dabigatran, rivaroxaban or VKA in 2013 in France, 10,847, 15,532, 18,829 and 11,195 were treated for NVAF with dabigatran 150mg, dabigatran 110mg, rivaroxaban 20mg or rivaroxaban 15mg, respectively.</li> <li>For standard doses comparison, 8,195 patients were matched per arm (76% of dabigatran</li> </ul>					<ul> <li>Benefit-risk of dabigatran 150mg versus rivaroxaban 20mg and dabigatran 110mg versus rivaroxaban 15mg</li> <li>The risk of CRB, major bleeding and the composite criterion was significantly lower with dabigatran 150mg, and with no difference for SSE, ACS, and death.</li> <li>Similar results were found for reduced doses comparison (Figure 2).</li> </ul>					
150mg group and 44% of rivaroxaban 20mg group).						Dabigatran 150mg versus rivaroxa	ban 20mg			
• For reduced doses comparison, <b>7,651 patients were matched per arm</b> (49% of dabigatran							Dabi.150 mg R	iva.20 mg (n)	Events (n)	HR [95% CI]
<ul> <li>Patient characteristics and hdPS distribution showed differences between groups dramatically reduced after matching (Table 1, Figure 1). For both comparisons, after matching, standardized differences were &lt; 5% for all variables, even &lt; 2% for most variables (Figure 1).</li> </ul>					Bleeding Clinically relevant bleeding Crude analysis Adjusted analysis Analysis in matched patients		10847 10847 8195	18829 18829 8195	749 749 348	0.48 [0.40 - 0.57] 0.56 [0.47 - 0.68] 0.53 [0.42 - 0.66]
Table 1. Main patient characteristics in matc	. Main patient characteristics in matched NVAF populations Standard dose Re		Reduce	d dose	Major bleeding Crude analysis Adjusted analysis		10847 10847	18829 18829	280 280	0.45 [0.33 - 0.61] 0.58 [0.42 - 0.79]
	Dabigatran	Rivaroxaban	Dabigatran	Rivaroxaban	Analysis in matched patients		8195	8195	127	0.51 [0.35 - 0.74]
Male, %	n = 8,195 69.6	n = 8,195 69.6	n = 7,651 46.6	n = 7,651 46.6	Stroke and systemic embolism Crude analysis		10847	18829	366	0.73 [0.58 - 0.92]
Age, mean (± SD) Risk factors, %	66.9 (8.7)	66.9 (8.7)	80.5 (7.5)	80.5 (7.5)	Analysis in matched patients Acute coronary syndrome		8195	8195	300 179	0.86 [0.88 - 1.09] 0.78 [0.58 - 1.05]
Hypertension	29.4 19.6	29.3 20.1	43.7	43.9 10.8	Crude analysis Adjusted analysis		10847 10847	18829 18829	284 284	0.89 [0.70 - 1.15] 0.97 [0.75 - 1.27]
Vascular disease history	9.2	9.2	14.4	14.9	Analysis in matched patients		8195	8195	161	1.00 [0.73 - 1.36]
Congestive heart failure Stroke or transient ischemic attack history	9.8 8 3	9.7 7 3	18.7 11 4	20.0 11.6	Crude analysis Adjusted analysis		10847 10847	18829 18829	689 689	0.55 [0.46 - 0.65] 0.82 [0.68 - 0.99]
Abnormal renal function	1.2	1.1	4.8	4.8	Analysis in matched patients		8195	8195	263	0.83 [0.65 - 1.07]
Abnormal liver function $CUA DS = VASe sector > 2$	1.0	0.9	1.3	1.4	Composite criterion Crude analysis	⊢	10847	18829	1941	0.60 [0.54 - 0.66]
HAS-BLED score $\geq 3$	15.9	59.3 15.1	94.1 33.7	94.1 34.6	Adjusted analysis Analysis in matched patients		10847 8195	18829 8195	1941 888	0.75 [0.67 - 0.84] 0.73 [0.64 - 0.84]
Debigetrep 150mg versus riverevek	Dob	igotrop 110mg	vorouo rivorovok	on 15mg		0.30 0.50 1 2				
Dabigatran 150mg versus rivaroxaban 20mg       Dabigatran 110mg versus rivaroxaban 15mg						Dabigatran 110mg versus rivaroxa	ban 15mg			
	10 -						Dabi.110 mg R	iva.15 mg (n)	Events (n)	HR [95% CI]
All populatio	8 - 6 - 4 - 2 -		and the second sec		Bleeding Clinically relevant bleeding Crude analysis Adjusted analysis Analysis in matched patients Maior bleeding		15532 15532 7651	11195 11195 7651	827 827 527	0.67 [0.59 - 0.77] 0.71 [0.62 - 0.82] 0.70 [0.58 - 0.83]
♥ 0 0.0 0.2 0.4 0.6 0.8 1.0 <sup>40</sup> Estimated HdPS		0.2 0.4 Estimated	0.6 0.8 1.0 HdPS		Crude analysis Adjusted analysis Analysis in matched patients		15532 15532 7651	11195 11195 7651	410 410 259	0.64 [0.53 - 0.78] 0.69 [0.57 - 0.85] 0.64 [0.50 - 0.82]
—— Dabigatran 150 mg —— Rivaroxaban 20 mg	10 -	– Dabigatran 110 mg –	Rivaroxaban 15 mg		Stroke and systemic embolism Crude analysis Adjusted analysis Analysis in matched patients		15532 15532 7651	11195 11195 7651	446 446 272	0.75 [0.62 - 0.90] 0.79 [0.65 - 0.95] 0.80 [0.63 - 1.02]
<b>i i i i i i i i i i</b>	8 -	,	c-statistic = 0.57		Acute coronary syndrome Crude analysis	<b>⊢</b>	15532	11195	360	0.87 [0.71 - 1.07]
bopu estimat	6 -	/			Adjusted analysis Analysis in matched patients		15532 7651	11195 7651	360 207	0.92 [0.74 - 1.14] 0.85 [0.65 - 1.12]
Matched Kermel densit	4 - 2 - 0 -				All-cause death Crude analysis Adjusted analysis Analysis in matched patients	F- <b>●</b> -1 F- <b>●</b> -1 F- <b>●</b> -1	15532 15532 7651	11195 11195 7651	1723 1723 981	0.85 [0.77 - 0.93] 0.94 [0.86 - 1.04] 0.91 [0.80 - 1.03]
0.0 0.2 0.4 0.6 0.8 1.0	-30 -20 -10 0 10 20 30 Standardized difference (%) •••• Matched patients 0.0	0.2 0.4 Estimated	0.6 0.8 1.0	40 -30 -20 -10 0 10 20 30 Standardized difference (%) •••• Matched patients	Composite criterion Crude analysis	<b>⊢</b> •-	15532	11195	3066	0.79 [0.74 - 0.85]
Estimated HdPS —— Dabigatran 150 mg —— Rivaroxaban 20 mg		– Dabigatran 110 mg –	Rivaroxaban 15 mg		Adjusted analysis Analysis in matched patients		7651	7651	3066 1804	0.86 [0.80 - 0.93] 0.84 [0.77 - 0.92]
Figure 1. hdPS distribution and standardized	differences in all an	d matched po	oulations			0.30 0.50 1 2				
Table 2 3-year cumulative incidence of out	comes for matched N	d patients are	e presented in I	able 2.	Figure 2. Hazard ratios and 95	5% CI of outcomes				
i abre 2. o year oannalarre moraenoe or oatoe	Standard dose		Reduced dose							
Dabigatra	n Rivaroxaban	Dabig	atran R	ivaroxaban		<u> Janones</u>				
n = 8,19 n event % [0	5 n = 8,195 5%Cl1 n event % [95%	n = 7	,651 6 [95%Cl] n event	n = 7,651 % [95%CI]	This real-life nationwid	le study with three-year follo	w-up shov	vs:		
Clinically relevant bleeding (CRB)1133.2 [2Major bleeding401.2 [0Stroke and systemic embolism (SSE)751.8 [1	.6; 3.8]       235       5.5 [4.8; 6         .8; 1.7]       87       2.1 [1.6; 2         .4; 2.3]       104       2.4 [1.9; 2	.6] <b>116 3</b> .208 <b>1</b> .3] <b>208 1</b> .3] <b>208 1</b> .3] <b>208 1</b> .3]	3 [4.5; 6.1]       319         3 [1.8; 2.8]       162         2 [2.6; 3.9]       156	<b>7.8 [6.9; 8.7]</b> 4.0 [3.4; 4.7] <b>3.8 [3.2; 4.5]</b>	<ul> <li>No significant different reduced doses</li> <li>A lower bleeding ris</li> </ul>	rence of effectiveness betwo k of dabigatran at either dos	en the 2	drugs	for s	tandard and
Acute coronary syndrome (ACS)772.1 [1Death (all causes)1133.3 [2Composite criterion (CRB, SSE, ACS, death)3579.6 [8	.6; 2.7] 84 1.9 [1.5; 2 .7; 4.0] 150 3.8 [3.2; 4 .5; 10.7] 531 12.2 [11.2;	.3] 92 2.3 .5] 449 12.3 13.3] 795 21.3	3 [1.8 ; 2.9] 115 9 [11.7; 14.2] 532 1 [19.6; 22.6] 1009	2.6 [2.1; 3.2] 13.9 [12.8; 15.2] 24.1 [22.7; 25.6]	Similar results to t studies with an over	hose after two years of for rall benefit-risk profile in favo	llow-up a our of dab	nd otl igatrar	ner o n for k	bservational both doses





				Res	ults				
<ul> <li>Populations</li> <li>Of 371,539 new users of dabigatran, riven 18,829 and 11,195 were treated for rivaroxaban 20mg or rivaroxaban 15mg,</li> <li>For standard doses comparison, 8,195</li> </ul>	<b>7</b> , <b>15,532</b> , n 110mg, abigatran	<ul> <li>Benefit-risk of dabigatran 150mg versus rivaroxaban 20mg and dabigatran 110mg versus rivaroxaban 15mg</li> <li>The risk of CRB, major bleeding and the composite criterion was significantly lower with dabigatran 150mg, and with no difference for SSE, ACS, and death.</li> <li>Similar results were found for reduced doses comparison (Figure 2).</li> </ul>							
150mg group and 44% of rivaroxaban 20mg group).						Dabigatran 150mg versus	s rivaroxaban 20mg		
<ul> <li>For reduced doses comparison, 7,651 patients were matched per arm (49% of dabigatran 110mg group and 68% of rivaroxaban 15mg group).</li> </ul>							Dabi.150 mg  I (n)	Riva.20 mg Eve (n) (n)	<sup>nts</sup> HR [95% CI]
<ul> <li>Patient characteristics and hdPS distribution showed differences between groups dramatically reduced after matching (Table 1, Figure 1). For both comparisons, after matching, standardized differences were &lt; 5% for all variables, even &lt; 2% for most variables (Figure 1).</li> <li>Table 1. Main patient characteristics in matched NVAE populations</li> </ul>					Bleeding Clinically relevant bleeding Crude analysis Adjusted analysis Analysis in matched patients Maior bleeding		10847 10847 8195	18829 749 18829 749 8195 348	0.48 [0.40 - 0.57] 0.56 [0.47 - 0.68] 0.53 [0.42 - 0.66]
	Standard dose		Reduced dose		Crude analysis Adjusted analysis		10847 10847	18829       280         18829       280         18829       280         18829       280	0.45 [0.33 - 0.61] 0.58 [0.42 - 0.79]
	Dabigatran n = 8,195	Rivaroxaban n = 8,195	Dabigatran n = 7,651	Rivaroxaban n = 7,651	Analysis in matched patients Stroke and systemic embolism		8195	8195 127	0.51 [0.35 - 0.74]
Male, % Age, mean (± SD) Risk factors %	69.6 66.9 (8.7)	69.6 66.9 (8.7)	46.6 80.5 (7.5)	46.6 80.5 (7.5)	Crude analysis Adjusted analysis Analysis in matched patients		10847 10847 8195	18829 366 18829 366 8195 179	0.73 [0.58 - 0.92] 0.86 [0.68 - 1.09] 0.78 [0.58 - 1.05]
Hypertension Diabetes mellitus Vascular disease history	29.4 19.6 9.2	29.3 20.1 9.2	43.7 19.8 14 4	43.9 19.8 14 9	Crude analysis Adjusted analysis Analysis in matched patients		10847 10847 10847 8195	18829 284 18829 284 8195 161	0.89 [0.70 - 1.15] 0.97 [0.75 - 1.27] 1.00 [0.73 - 1.36]
Congestive heart failure Stroke or transient ischemic attack history	9.8 8.3 1.2	9.7 7.3 1 1	18.7 11.4 4 8	20.0 11.6 4.8	All-cause death Crude analysis Adjusted analysis Analysis in matched patients		10847 10847 8195	18829 689 18829 689 8195 263	0.55 [0.46 - 0.65] 0.82 [0.68 - 0.99] 0.83 [0.65 - 1.07]
Abnormal liver function $CHA_2DS_2$ -VASc score $\geq 2$ $HAS_{-}BLED$ score $\geq 3$	1.0 58.6 15.9	0.9 59.3 15.1	1.3 94.1 33.7	1.4 94.1 34.6	<b>Composite criterion</b> Crude analysis Adjusted analysis Analysis in matched patients		10847 10847 8195	18829 1941 18829 1941 8195 888	0.60 [0.54 - 0.66] 0.75 [0.67 - 0.84] 0.73 [0.64 - 0.84]
		10.1	00.7			0.30 0.50 1	2		
Dabigatran 150mg versus rivaroxaban 20mg       Dabigatran 110mg versus rivaroxaban 15mg						Dabigatran 110mg versus	s rivaroxaban 15mg		
							Dabi.110 mg I (n)	Riva.15 mg Eve (n) (n)	nts HR [95% CI]
All populatio	6 - 4 - 2 -		and the second sec		Bleeding Clinically relevant bleeding Crude analysis Adjusted analysis Analysis in matched patients Major bleeding		15532 15532 7651	11195 827 11195 827 7651 527	0.67 [0.59 - 0.77] 0.71 [0.62 - 0.82] 0.70 [0.58 - 0.83]
Contraction of the second seco	20 -10 0 10 20 30 tandardized difference (%) **** Crude analysis	0.2 0.4 Estimated	0.6 0.8 1.0 HdPS	0 -30 -20 -10 0 10 20 30 Standardized difference (%) **** Crude analysis	Crude analysis Adjusted analysis Analysis in matched patients Stroke and systemic embolism		15532 15532 7651	11195 410 11195 410 7651 259	0.64 [0.53 - 0.78] 0.69 [0.57 - 0.85] 0.64 [0.50 - 0.82]
Dabigatran 150 mg Rivaroxaban 20 mg	10 -	— Dabigatran 110 mg —	Rivaroxaban 15 mg		Crude analysis Adjusted analysis Analysis in matched patients		15532 15532 7651	11195 446 11195 446 7651 272	0.75 [0.62 - 0.90] 0.79 [0.65 - 0.95] 0.80 [0.63 - 1.02]
c-statistic = 0.56	8 - 6 -		c-statistic = 0.57		Acute coronary syndrome Crude analysis Adjusted analysis Analysis in matched patients		15532 15532 7651	11195 360 11195 360 7651 207	0.87 [0.71 - 1.07] 0.92 [0.74 - 1.14] 0.85 [0.65 - 1.12]
Kernel density A - PERCI - PERCI	4 - 2 - 0 -				<b>All-cause death</b> Crude analysis Adjusted analysis Analysis in matched patients	F- <b>♦</b> -1 F- <b>♦</b> -1 F- <b>♦</b> -1	15532 15532 7651	11195 1723 11195 1723 7651 981	0.85 [0.77 - 0.93] 0.94 [0.86 - 1.04] 0.91 [0.80 - 1.03]
0 0.0 0.2 0.4 0.6 0.8 1.0 Estimated HdPS Dabigatran 150 mg Rivaroxaban 20 mg	-20 -10 0 10 20 30 Standardized difference (%) •••• Matched patients 0.0	0.2 0.4 Estimated Dabigatran 110 mg —	0.6 0.8 1.0 HdPS —— Rivaroxaban 15 mg	-40 -30 -20 -10 0 10 20 30 Standardized difference (%) *** Matched patients	<b>Composite criterion</b> Crude analysis Adjusted analysis Analysis in matched patients	+ <b>◆</b> -    <b>◆</b> -    <b>◆</b> -	15532 15532 7651	11195 3066 11195 3066 7651 1804	0.79 [0.74 - 0.85] 0.86 [0.80 - 0.93] 0.84 [0.77 - 0.92]
Figure 1. hdPS distribution and standardized d	fferences in all an	d matched pop	oulations			0.30 0.50 1	2		
The 3-year cumulative incidence of outcom Table 2. 3-year cumulative incidence of outcom	omes for matche es for matched N	d patients are /AF population	e presented in Teatment	Fable 2.	Figure 2. Hazard ratios and 95	% CI of outcomes			****
S	andard dose		Reduced dose			• • • • • • • • • • • • • • • • • • •			
Dabigatran n = 8 195	Rivaroxaban n = 8.195	Dabig	atran R 1651	livaroxaban n = 7.651					
n event % [95%	Cl] n event % [95%	bCl] n event %	% [95%CI] n event	% [95%CI]	<ul> <li>Ins real-life nationwide</li> <li>No significant different</li> </ul>	e study with three-ye	ear tollow-up shows between the 2	NS: druge for	standard and
Clinically relevant bleeding (CRB) 113 3.2 [2.6; 3.8] 235 5.5 [4.8; 6.3] 208 5.3 [4.5; 6.1] 319 7.8 [6.9; 8.7] Maior bleeding 40 1 2 [0 8: 1 7] 87 2 1 [1 6: 2 6] 97 2 3 [1 8: 2 8] 162 4 0 [3 4: 4 7] reduced doses									
Stroke and systemic embolism (SSE) 75 1.8 [1.4; 2.3] 104 2.4 [1.9; 2.9] 116 3.2 [2.6; 3.9] 156 3.8 [3.2; 4.5]									
Acute coronary syndrome (ACS)       77       2.1 [1.6; 2.7]       84       1.9 [1.5; 2.3]       92       2.3 [1.8; 2.9]       115       2.6 [2.1; 3.2]         Death (all causes)       113       3.3 [2.7; 4.0]       150       3.8 [3.2; 4.5]       449       12.9 [11.7; 14.2]       532       13.9 [12.8; 15.2]         Composite criterion (CRB, SSE, ACS, death)       357       9.6 [8.5; 10.7]       531       12.2 [11.2; 13.3]       795       21.1 [19.6; 22.6]       1009       24.1 [22.7; 25.6]       • Similar results to those after two years of follow-up and other observational studies with an overall benefit-risk profile in favour of dabigatran for both doses									





36<sup>th</sup> ICPE International Society for Pharmacoepidemiology - September 17-18, 2020, Virtual event [Abstract # 4733]