标准剂量或低剂量的达比加群与利伐沙班治疗非瓣膜性心房颤动患者的有效性和安全性比较

Comparative Effectiveness and Safety of Standard or Reduced Dose Dabigatran vs. Rivaroxaban in Nonvalvular Atrial Fibrillation

青岛大学附属医院 李静 孙加琳

2020年03月31日

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01

第一部分

研究背景

Comparative Effectiveness and Safety of Standard or Reduced Dose Dabigatran vs. Rivaroxaban in Nonvalvular Atrial Fibrillation

标准剂量或低剂量的达比加群与利伐沙班治疗非瓣膜性心房颤动患者的有效性和安全性比较

Patrick Blin [1], Caroline Dureau-Pournin [1], Yves Cottin [2], Jacques Bénichou [3,4], Patrick Mismetti [5], Abdelilah Abouelfath [1], Regis Lassalle [1], Cécile Droz [1] and Nicholas Moore [1,3]

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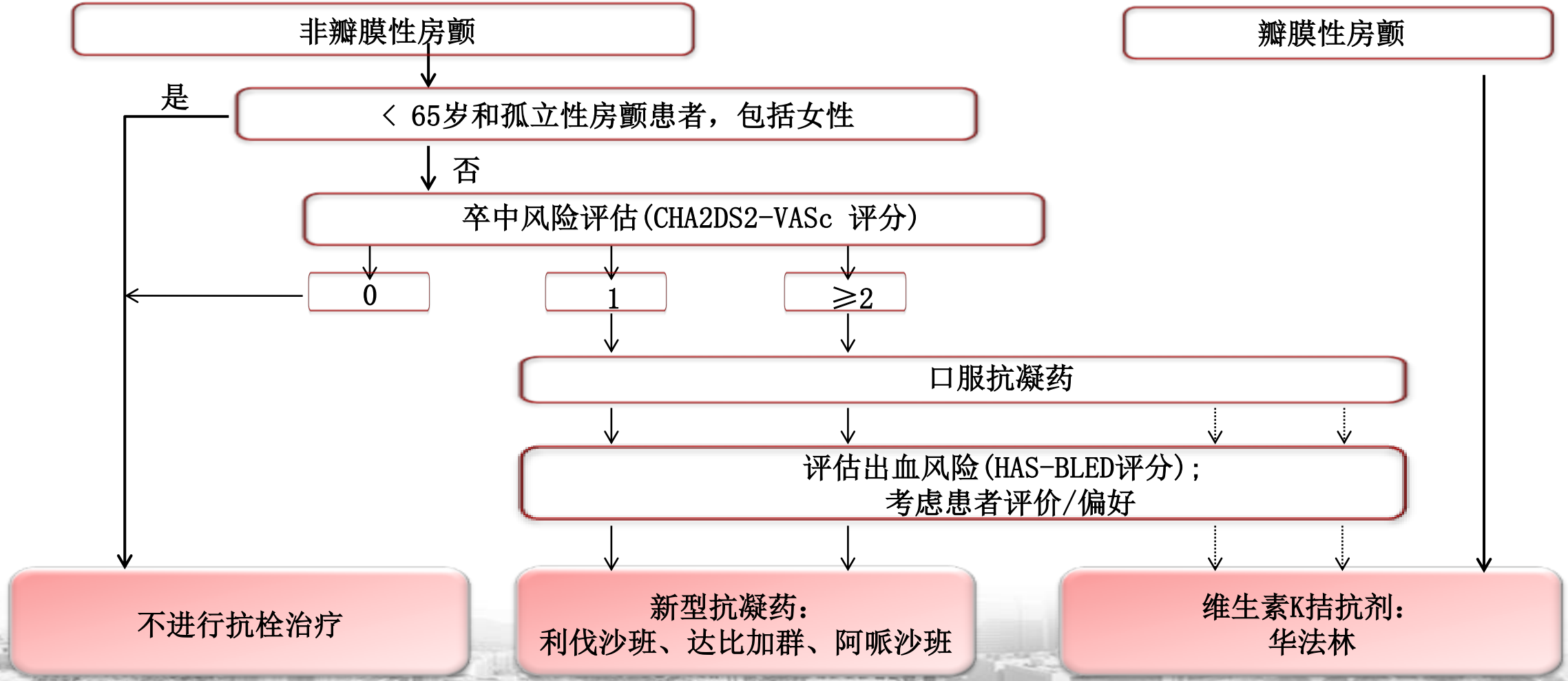
Pharmacology & Pharmacy

抗凝药物的选择策略



2019ESC房颤指南

NOAC的推荐优先于华法林

抗凝	VKA	• 华法林
	DOAC	• 达比加群 • 利伐沙班

- 临床经典用药
- 出血风险大
- 相似或更优的抗凝效果；
- 较低的出血风险

推荐意见	推荐类别	证据级别
在华法林剂量调整用药INR不稳定或相关不良反应，或不能接受INR监测时推荐应用NOACs	I	B
根据净临床获益，大多数的非瓣膜性房颤患者优先选择NOAC而非华法林	IIa	A

试验	RELY[1、2] 达比加群		ROCKET AF[3] 利伐沙班
剂量	150mg bid	110mg bid	20mg od
平均CHADS2评分	2.1		3.5
低（0-1）	3,916(32%)		0
中（2）	4,225(35%)		925(13%)
高（3~6）	3,949(33%)		6,205(87%)
平均 TTR	**64%**		55%
主要终点（ITT） 卒中或全身性栓塞	优效 ↓35%(P<0.001)	非劣效 ↓10%(P=0.29)	非劣效 ↓12%(P=0.12)
缺血性卒中	显著降低 ↓24%(P=0.03)	无显著性 ↑11%(P=0.35)	无显著性 ↓6%(P=0.58)
出血性卒中	显著降低 ↓74%(P<0.001)	显著降低 ↓69%(P<0.001)	显著降低 ↓41%(P=0.024)
出血			
大出血	↓7%(P=0.31)	↓20%(P=0.003)	↑4%(P=0.58)
颅内出血	↓59%(P<0.001)	↓70%(P<0.001)	↓33%(P=0.02)

1. **RELY研究：**
- D110和D150剂量随机分配，D110仅适用于肾功能不全，出血风险较高或老年患者
2. **ROCKET AF研究：**
- 标准剂量为20 mg，对老年患者或肾功能不全患者给予15 mg，但公开数据未对不同剂量进行结果公示
3. **未知**

达比加群 VS 利伐沙班

- 风险？？ 收益？？
- 标准剂量？？
- 降低剂量？？

1. Connolly SJ, et al. N Engl J Med. 2009;361:1139-51.
2. Connolly SJ, et al. N Engl J Med. 2010;363:1875-6.
3. Patel M, et al. N Engl J Med. 2011;365(10):883-91.

达比加群

V

S

利伐沙班

Standard：
150mg， Bid

Reduced：
110mg， Bid

Standard：
20mg， Qd

Reduced：
15mg， Qd

真实世界研究：队列研究

02

第二部分

PICOST分析

P

SUBJECTS

All adults with a first dispensing of any oral anticoagulant in 2013 (index date), with a diagnosis of definite NVAF based on outpatient chronic disease registration or inpatient diagnosis of AF, as previously described, were identified.[4] Patients had to have a 3-year database history without any dispensing of an anticoagulant before index date. Patients with valvular heart disease, valve replacement or repair, or another indication for anticoagulation, such as deep vein thrombosis, pulmonary embolism, or orthopedic surgery, as well as patients with erroneous or incomplete data were excluded (**Figure 1**). New D110 or D150 NVAF users were 1:1 matched with new R15 or R20 patients users on gender, age at index date (± 1 year), date of the first anticoagulant dispensing (± 2 weeks), and a 500 variable hdPS, using the Greedy method with a caliper of 0.05 (see Statistical Methods section).

入选标准：

成年人；

首次配发口服抗凝剂日期：2013年；

诊断确切：NVAF；

3年内未使用抗凝剂；

排除标准：

患有瓣膜性心脏病，瓣膜置换或修复或其他抗凝适应症（如深静脉血栓形成，肺栓塞或骨科手术）的患者；

数据错误或不完整的患者；

hdPS：

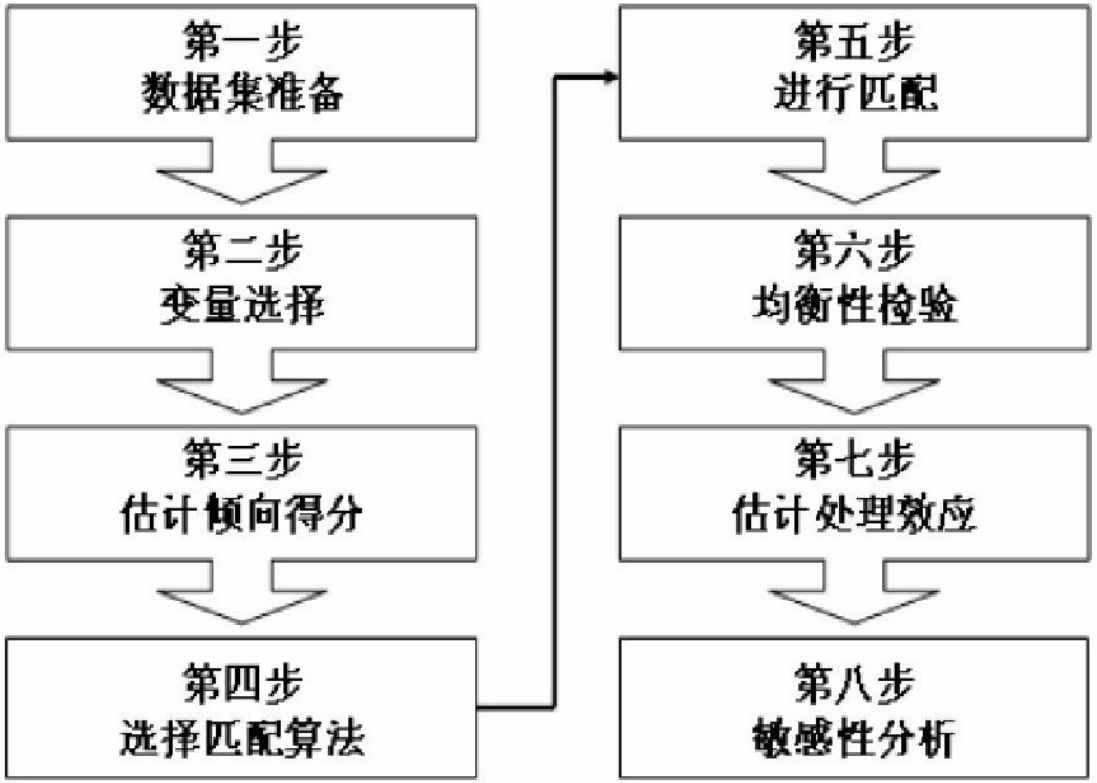
high dimensional propensity score，高维度倾向性评分匹配

倾向性评分法：

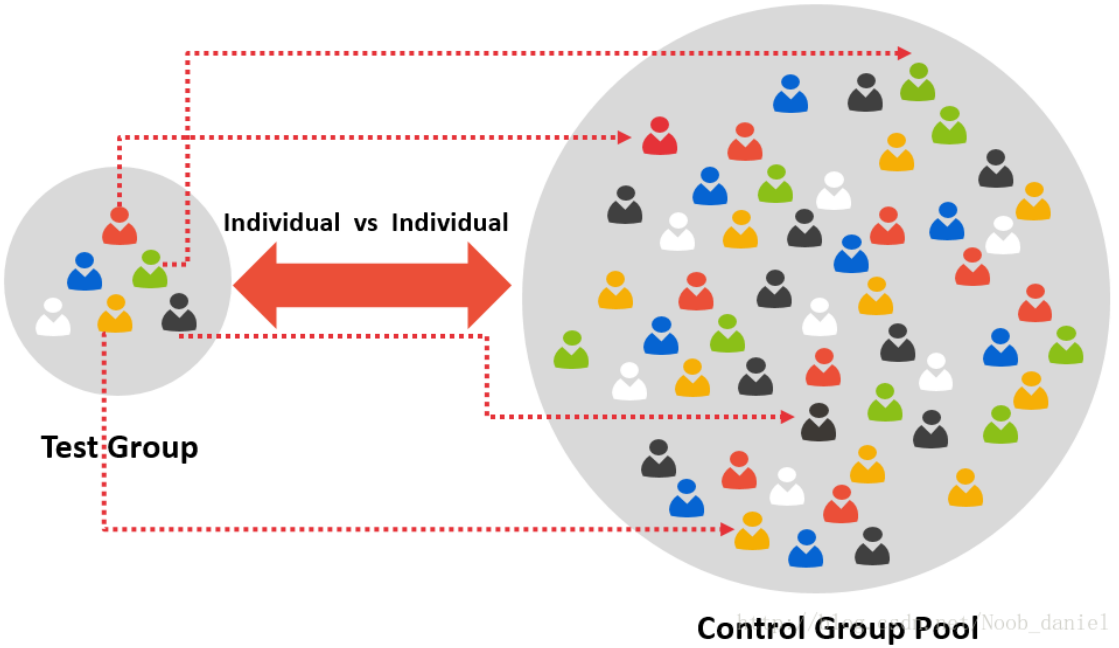
Propensity Score Method（PSM），是指在一定协变量条件下，一个观察对象接受某种暴露/处理因素的可能性，它是一个从0到1的范围内连续分布的概率值。

基本原理：将多个混杂因素的影响**用一个综合的倾向性评分**来表示，从而降低了协变量的维度，减少了自变量的个数，有效的克服了分层分析和多因素调整分析中要求自变量个数不能太多的短板。

倾向性评分匹配 过程：



Greedy method



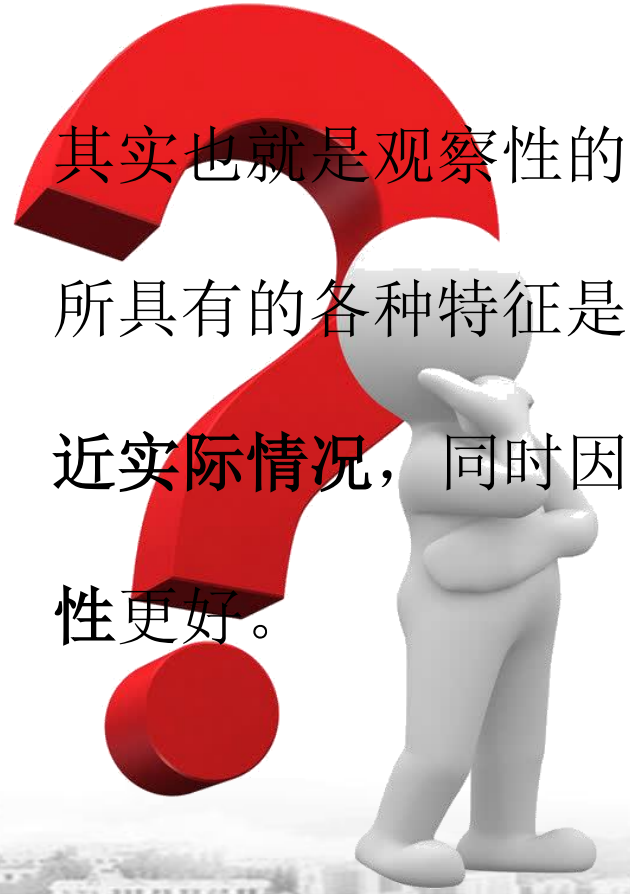
按一定的逻辑从实验组取出一样本，然后在对照池中寻找最佳匹配。

成功后再取另一样本，从**剩余**的对照池中寻找最佳匹配。

若还存在阈值，则每次需检查最佳匹配间的距离是否超过阈值，若超过则需舍弃。

Caliper：0.05

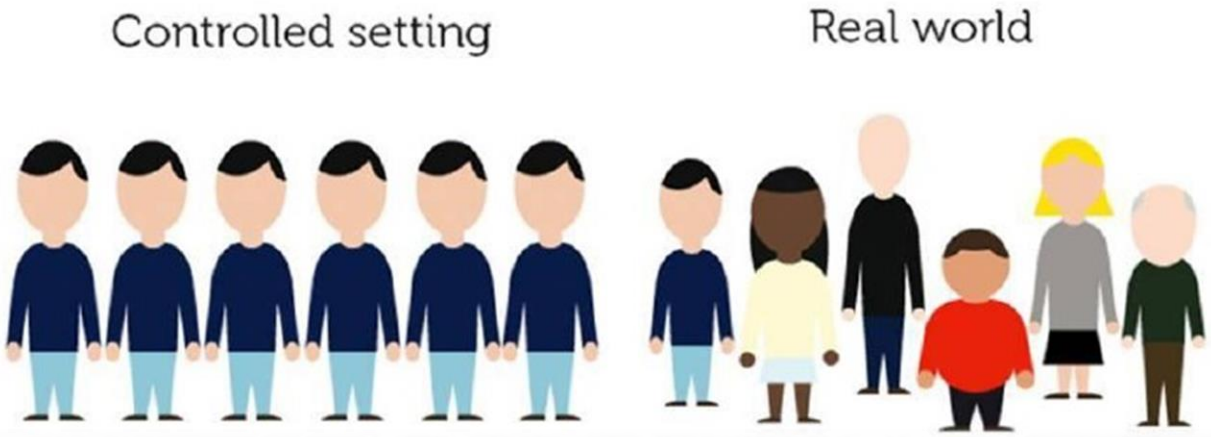
真实世界研究（RWS）



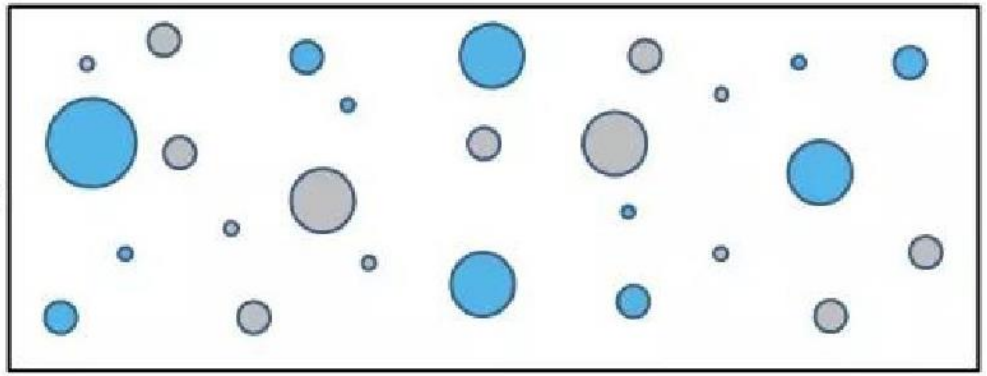
其实也就是观察性的临床研究，相对于RCT研究，观察性临床研究的研究对象所具有的各种特征是**客观存在**的，研究者不能对其进行干预，其研究结果更**接近实际情况**，同时因其较宽的纳入排除标准，使其研究结果更具**外推性**，**实用性**更好。

真实世界研究（RWS）

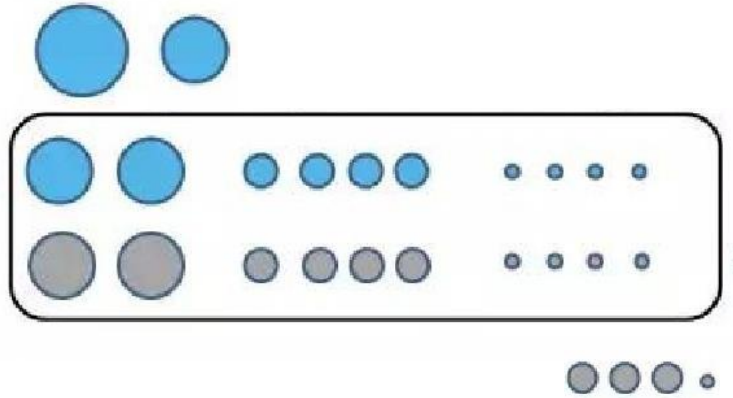
尴尬：相对于RCT研究，观察性的研究因为**没有随机分组**，所以实验组和对照组除了要研究的暴露因素X外，两组基线特征还存在很多差异（也就是**混杂因素**），因此，两组结局事件的发生就**不一定**完全由暴露因素X所引起的。



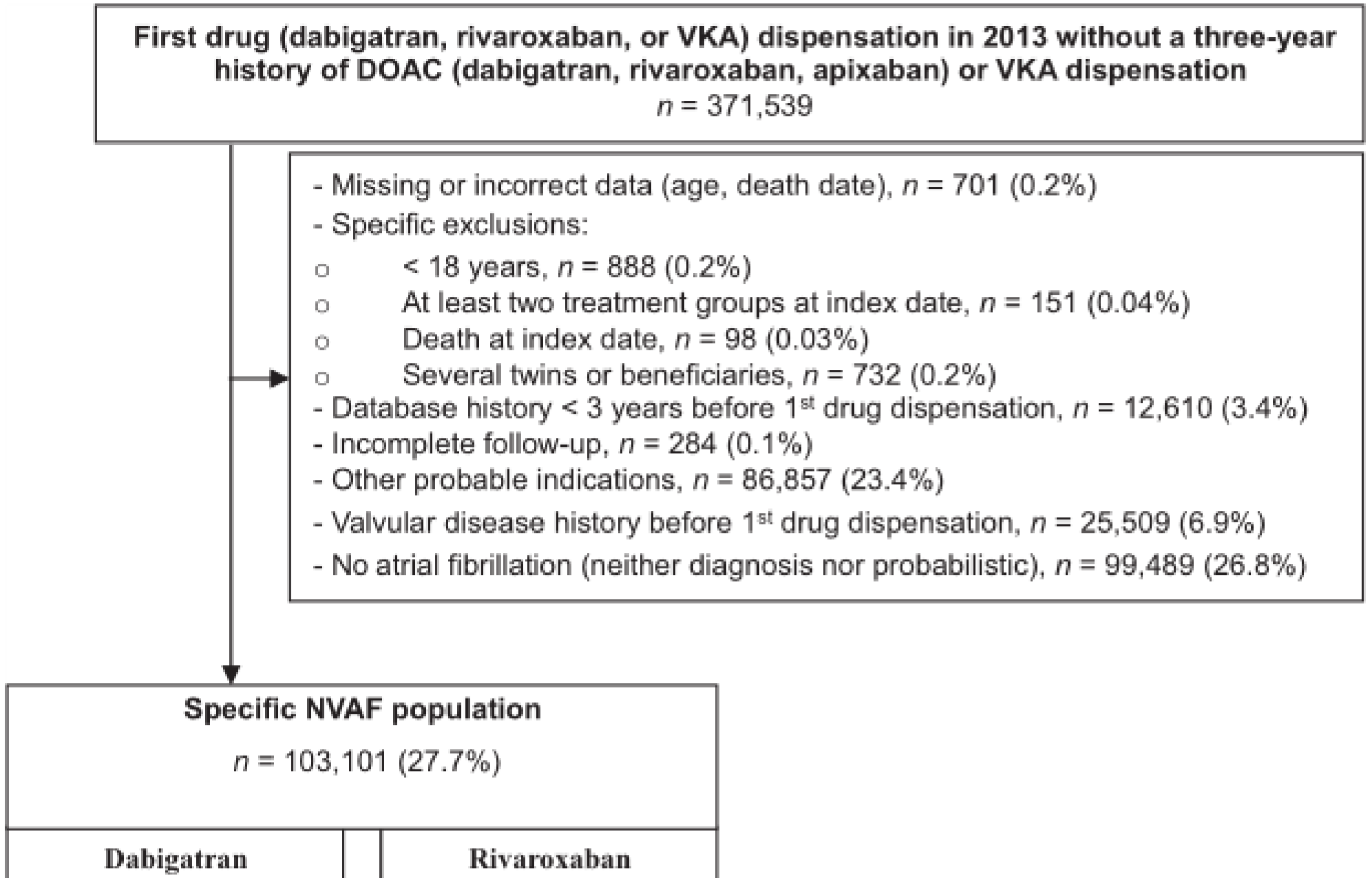
真实世界研究（RWS）



Population with varying characteristics



Study group with maching


First drug (dabigatran, rivaroxaban, or VKA) dispensation in 2013 without a three-year history of DOAC (dabigatran, rivaroxaban, apixaban) or VKA dispensation
n = 371,539
- Missing or incorrect data (age, death date), n = 701 (0.2%)
- Specific exclusions:
o < 18 years, n = 888 (0.2%)
o At least two treatment groups at index date, n = 151 (0.04%)
o Death at index date, n = 98 (0.03%)
o Several twins or beneficiaries, n = 732 (0.2%)
- Database history < 3 years before 1st drug dispensation, n = 12,610 (3.4%)
- Incomplete follow-up, n = 284 (0.1%)
- Other probable indications, n = 86,857 (23.4%)
- Valvular disease history before 1st drug dispensation, n = 25,509 (6.9%)
- No atrial fibrillation (neither diagnosis nor probabilistic), n = 99,489 (26.8%)
Specific NVAF population
n = 103,101 (27.7%)
Dabigatran
Rivaroxaban

I

Exposure

The drug exposures considered were dabigatran 150 mg b.i.d. vs. rivaroxaban 20 mg once a day (standard doses) and dabigatran 110 mg b.i.d. vs. rivaroxaban 15 mg once a day (reduced doses). The drug-exposure period started at the index date and ended 30 days after the last dispensing or at dispensing of a different anticoagulant (switch). Last dispensing was defined as a dispensing that was not followed by another dispensing of the same drug within 60 days.[4] A patient who died within these 60 days would be considered as exposed.

试验组：

标准剂量组：达比加群150 mg，Bid

低剂量组：达比加群110 mg，Bid

药物暴露期：用药日起，至末次用药后30天或换药日。

末次用药：60天内未复用试验药物。60天内发生死亡，仍视为暴露。

C

Exposure

The drug exposures considered were dabigatran 150 mg b.i.d. vs. rivaroxaban 20 mg once a day (standard doses) and dabigatran 110 mg b.i.d. vs. rivaroxaban 15 mg once a day (reduced doses). The drug-exposure period started at the index date and ended 30 days after the last dispensing or at dispensing of a different anticoagulant (switch). Last dispensing was defined as a dispensing that was not followed by another dispensing of the same drug within 60 days.[4] A patient who died within these 60 days would be considered as exposed.

对照组：

标准剂量组：利伐沙班20 mg，Qd

低剂量组：利伐沙班15mg，Qd

药物暴露期：用药日起，至末次用药后30天或换药日。

末次用药：60天内未复用试验药物。60天内发生死亡，仍视为暴露。

O

Study outcomes

The primary outcomes were hospitalization with a main diagnosis of ischemic SSE or MB and all-cause death.

Secondary outcomes included ACS (myocardial infarction or unstable angina), CRB, and specific bleeding sites.

CRBs were all hospitalizations with a main diagnosis of bleeding. Specific bleeding sites were intracerebral hemorrhage, GI bleeding, urogenital bleeding, other critical organ or site bleeding, and other bleeding. MB was intracerebral hemorrhage, critical organ bleeding, any CRB with blood transfusion, acute posthemorrhagic anemia, or death during hospital stay.[32]

结局指标：

主要结局指标：中风或全身性栓塞（SSE）、大出血（MB）、全因死亡

次要结局指标：急性冠状动脉综合征（ACS，包括心肌梗塞或不稳定型心绞痛）、临床相关出血（CRB）、特定的出血部位

Style

To estimate the real-life comparative benefits and risks of standard (D150 vs. R20) or reduced doses (D110 vs. R15) on SSE, MB, or death, as used in clinical practice in the French population, high-dimensional propensity score (hdPS)-matched cohort studies were undertaken, using the French nationwide claims and hospitalization database, Système National des Données de Santé (SNDS).[19]

真实世界队列研究：

基于法国国家医保和住院数据库SNDS

hdPS匹配：

四个维度、数百个变量：

所有可测量的出血和栓塞风险因素、常见的死亡风险因素、过去3年的疾病史、用药史

Time

Study design

This was an hdPS-matched cohort study of all new users of standard or reduced doses of dabigatran or rivaroxaban (D150, D110, R20, or R15) for NVAF in 2013, followed for 2 years in the French national healthcare data system SNDS.[19]

Follow-up

Follow-up began on index date and continued until patient death, treatment discontinuation, occurrence of an outcome of interest (for that outcome only), or the end of the study period (1 year), whichever came first. There was no loss to follow-up.

研究周期：

自2013年入组，为期2年。

随访周期：

自入组开始，直至患者死亡；或者治疗终止，或者感兴趣的结果发生，或者研究结束。结局指标。全部病例纳入分析。

03

第三部分

结果解读

S

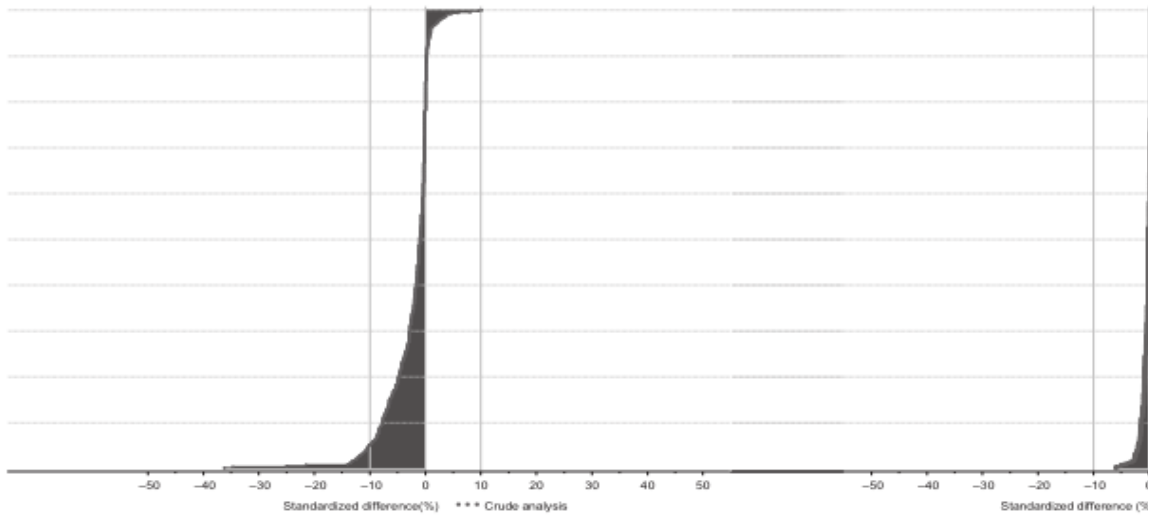
R

Table 2 (Continued)

All patients

Dabigatran 110 mg

Demographics



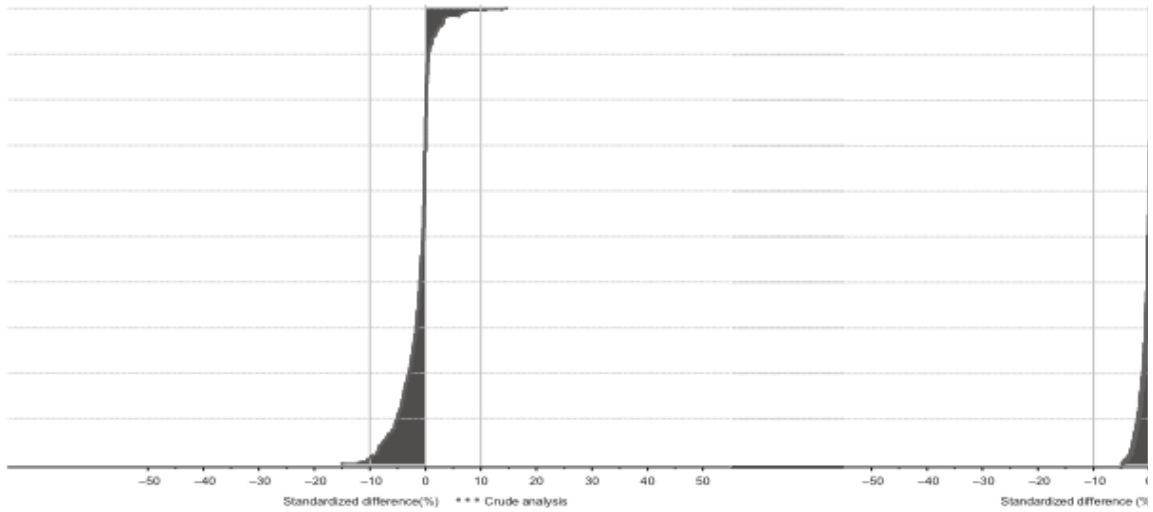


Table 2 (Continued)

All patients

Dabigatran 110 mg

Table 2 (Continued)

	All patients		Matched patients		Standardized difference (%)	
	Dabigatran 110 mg n = 15,532	Rivaroxaban 15 mg n = 11,195	Dabigatran 110 mg n = 7,639	Rivaroxaban 15 mg n = 7,639	Crude	Matched
B01AB06—Nadroparin	28 (0.2)	17 (0.2)	10 (0.1)	9 (0.1)	—	—
B01AC22—Prasugrel	19 (0.1)	14 (0.1)	6 (0.1)	8 (0.1)	—	—
B01AB04—Dalteparin	8 (0.1)	5 (0.0)	6 (0.1)	2 (0.0)	—	—
B01AC24—Ticagrelor	10 (0.1)	17 (0.2)	3 (0.0)	10 (0.1)	—	—
B01AC05—Ticlopidine	8 (0.1)	5 (0.0)	5 (0.1)	5 (0.1)	—	—
Antiarrhythmics, n (%)						
C01BC04—Flecainide	755 (4.9)	685 (6.1)	412 (5.4)	416 (5.4)	−5.5	−0.2
C01BD01—Amiodarone	797 (5.1)	751 (6.7)	455 (6.0)	432 (5.7)	−6.7	1.3
C01BC03—Propafenone	79 (0.5)	66 (0.6)	39 (0.5)	48 (0.6)	−0.4	−0.5
C01BG07—Cibenzoline	42 (0.3)	24 (0.2)	29 (0.4)	16 (0.2)	—	—
C01BA03—Disopyramide	26 (0.2)	19 (0.2)	9 (0.1)	11 (0.1)	—	—
C01BA—Antiarrhythmics	6 (0.0)	4 (0.0)	4 (0.1)	3 (0.0)	—	—
Medical visits and lab tests in the 3 years before index date						
At least one medical visit, n (%)	15,472 (99.6)	11,166 (99.7)	7,614 (99.7)	7,616 (99.7)	−0.6	−0.1
Mean per patient, mean (± SD)	31.8 (19.8)	33.2 (20.1)	32.0 (19.3)	32.2 (19.1)	—	—
Median per patient	28.0	29.0	28.0	28.0	—	—
[p25–p75%]	[19.0–41.0]	[20.0–43.0]	[19.0–41.0]	[19.0–42.0]	—	—
At least one general practitioner visit, n (%)	15,279 (98.4)	11,018 (98.4)	7,530 (98.6)	7,528 (98.5)	0.4	0.2
Mean per patient, mean (± SD)	23.5 (15.7)	24.5 (16.1)	23.7 (15.7)	23.9 (15.5)	—	—
Median per patient	20.0	21.0	20.0	20.0	—	—
[p25–p75%]	[14.0–30.0]	[14.0–31.0]	[14.0–30.0]	[14.0–30.0]	—	—
At least one cardiologist visit, n (%)	8,673 (55.8)	6,685 (59.7)	4,435 (58.1)	4,485 (58.7)	−7.7	−1.3
Mean per patient, mean (± SD)	3.0 (3.2)	3.3 (3.5)	3.1 (3.3)	3.1 (3.2)	—	—
Median per patient	2.0	2.0	2.0	2.0	—	—
[p25–p75%]	[1.0–4.0]	[1.0–4.0]	[1.0–4.0]	[1.0–4.0]	—	—
At least one other specialist visit, n (%)	13,009 (83.8)	9,486 (84.7)	6,413 (84.0)	6,427 (84.1)	—	—
Mean per patient, mean (± SD)	7.1 (8.1)	7.2 (7.2)	6.9 (7.3)	6.9 (6.7)	—	—
Median per patient	5.0	5.0	5.0	5.0	—	—
[p25–p75%]	[2.0–9.0]	[3.0–9.0]	[2.0–9.0]	[2.0–9.0]	—	—
At least one lab test, n (%)	15,137 (97.5)	10,987 (98.1)	7,487 (98.0)	7,492 (98.1)	−3.1	−0.3

ATC, anatnomic, therapeutic, chemical; hdPS, high-dimensional propensity score; ICD-10, International Classification of Disease 10th edition; LTD, long-term disease.

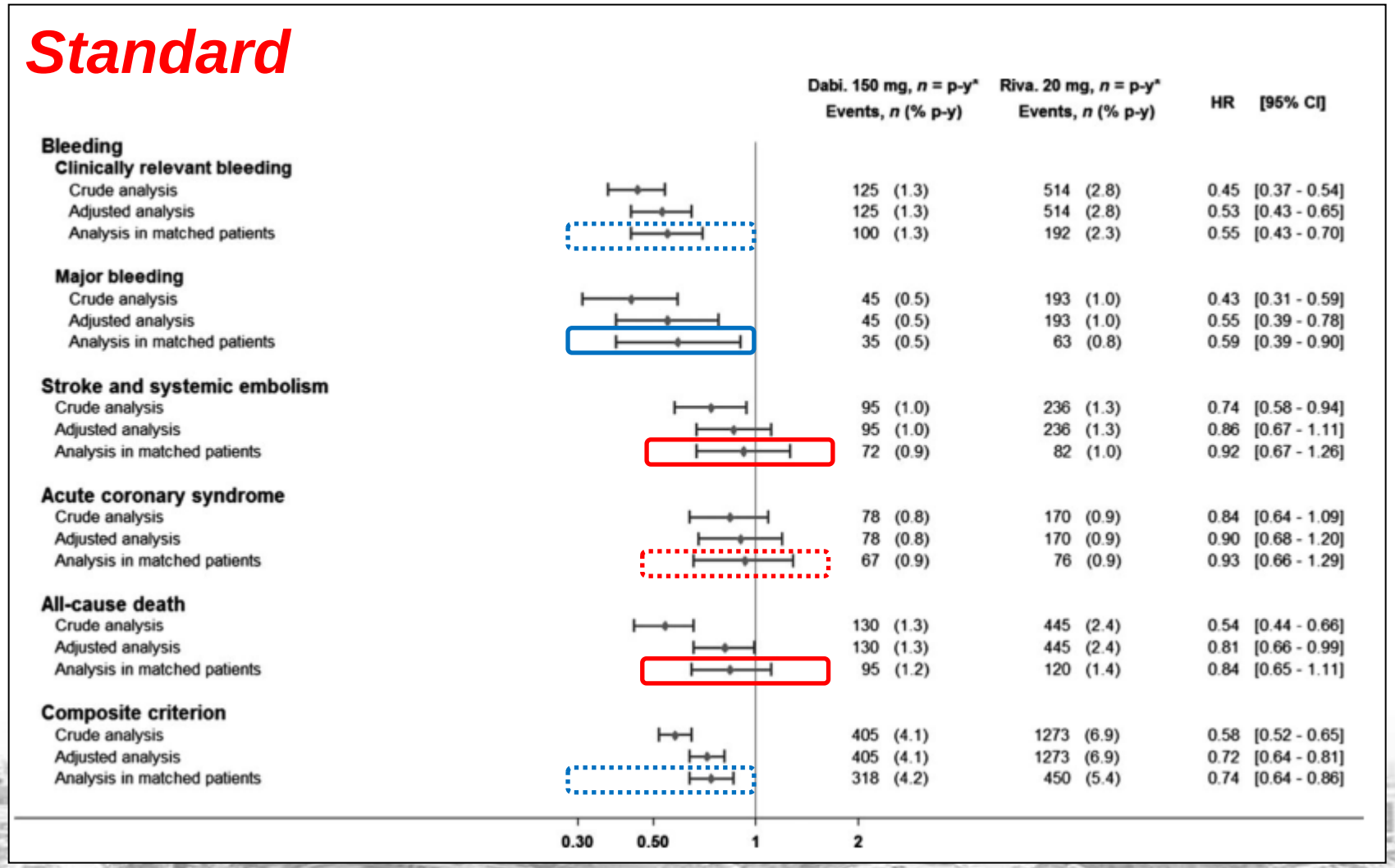
One difference between rivaroxaban and dabigatran is that the reduced dose of dabigatran is indicated in older and higher-risk patients, whereas this is not the case for rivaroxaban, which is only indicated in patients with renal failure. Prescribers might, however, not be aware of these distinctions.

RE-LY, which was not the case for rivaroxaban and which had been widely publicized. We attempted to protect against such selection by including in the matching criteria the coronary risk factors.

The unmeasured confounders that could be involved in this case might be smoking and body mass index (BMI). Although we do

结果

Standard



结局指标：

主要结局指标：

中风或全身性栓塞（SSE）、全因死亡：相近

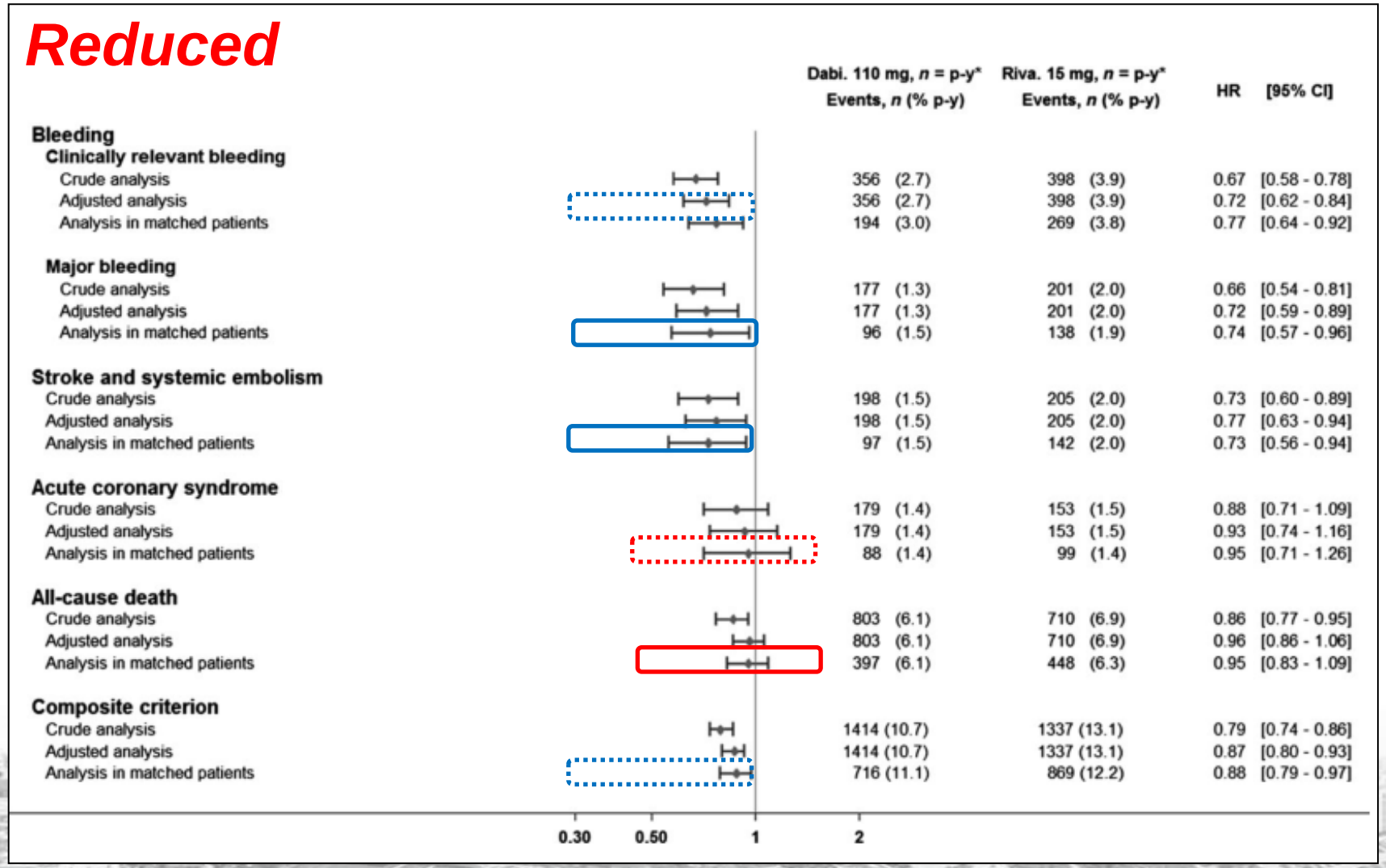
大出血（MB）：达比加群少

次要结局指标：

急性冠状动脉综合征（ACS）：相近

临床相关出血（CRB）、其他复合指标：达比加群少

Reduced



结局指标：

主要结局指标：

全因死亡：相近

中风或全身性栓塞（SSE）、大出血（MB）：达比加群少

次要结局指标：

急性冠状动脉综合征（ACS）：相近

临床相关出血（CRB）、其他复合指标：达比加群少

Table 3 HRs for secondary outcomes, hdPS-matched analyses, standard and reduced doses

	Dabigatran 150 mg *n* = 8,290	Rivaroxaban 20 mg *n* = 8,290	HR [95% CI]	Dabigatran 110 mg *n* = 7,639	Rivaroxaban 15 mg *n* = 7,639	HR [95% CI]
Person-years of drug exposure, *n*	7,639	8,276	—	6,459	7,135	—
Stroke and systemic embolism, *n* (%)	72 (0.9)	82 (1.0)	—	97 (1.3)	142 (1.9)	—
% Person-years [95% CI]	0.9 [0.7–1.2]	1.0 [0.8–1.2]	0.92 [0.67–1.26]	1.5 [1.2–1.8]	2.0 [1.7–2.3]	0.73 [0.56–0.94]
Ischemic or undefined stroke, *n* (%)	47 (0.6)	54 (0.7)	—	70 (0.9)	95 (1.2)	—
% Person-years [95% CI]	0.6 [0.4–0.8]	0.7 [0.5–0.8]	0.90 [0.61–1.33]	1.1 [0.8–1.3]	1.3 [1.1–1.6]	0.79 [0.58–1.07]
Systemic arterial embolism, *n* (%)	25 (0.3)	29 (0.3)	—	28 (0.4)	48 (0.6)	—
% Person-years [95% CI]	0.3 [0.2–0.5]	0.4 [0.2–0.5]	0.92 [0.53–1.57]	0.4 [0.3–0.6]	0.7 [0.5–0.9]	0.63 [0.39–1.00]
Clinically relevant bleeding, *n* (%)	100 (1.2)	192 (2.3)	—	194 (2.5)	269 (3.5)	—
% Person-years [95% CI]	1.3 [1.1–1.6]	2.3 [2.0–2.6]	0.55 [0.43–0.70]	3.0 [2.6–3.4]	3.8 [3.3–4.2]	0.77 [0.64–0.92]
Intracerebral hemorrhage, *n* (%)	5 (0.1)	18 (0.2)	—	15 (0.2)	40 (0.5)	—
% Person-years [95% CI]	0.1 [0.0–0.2]	0.2 [0.1–0.3]	0.29 [0.11–0.76]	0.2 [0.1–0.3]	0.6 [0.4–0.7]	0.41 [0.23–0.74]
Other critical organ or site bleeding, *n* (%)	11 (0.1)	12 (0.1)	—	17 (0.2)	35 (0.5)	—
% Person-years [95% CI]	0.1 [0.1–0.3]	0.1 [0.1–0.3]	0.98 [0.43–2.22]	0.3 [0.1–0.4]	0.5 [0.3–0.7]	0.52 [0.29–0.93]
Other bleeding, *n* (%)	84 (1.0)	163 (2.0)	—	163 (2.1)	197 (2.6)	
% Person-years [95% CI]	1.1 [0.9–1.3]	2.0 [1.7–2.3]	0.55 [0.42–0.71]	2.5 [2.1–2.9]	2.8 [2.4–3.1]	0.88 [0.72–1.08]
Gastrointestinal bleeding, *n* (%)	46 (0.6)	75 (0.9)	—	100 (1.3)	92 (1.2)	—
% Person-years [95% CI]	0.6 [0.4–0.8]	0.9 [0.7–1.1]	0.66 [0.45–0.95]	1.5 [1.2–1.8]	1.3 [1.0–1.6]	1.16 [0.87–1.53]
Urogenital bleeding, *n* (%)	23 (0.3)	41 (0.5)	—	27 (0.4)	40 (0.5)	—
% Person-years [95% CI]	0.3 [0.2–0.4]	0.5 [0.3–0.6]	0.59 [0.35–0.98]	0.4 [0.3–0.6]	0.6 [0.4–0.7]	0.72 [0.44–1.17]
Other bleeding subtype, *n* (%)	17 (0.2)	48 (0.6)	—	39 (0.5)	72 (0.9)	—
% Person-years [95% CI]	0.2 [0.1–0.3]	0.6 [0.4–0.7]	0.38 [0.22–0.66]	0.6 [0.4–0.8]	1.0 [0.8–1.2]	0.58 [0.39–0.85]
Major bleeding, *n* (%)	35 (0.4)	63 (0.8)	—	96 (1.3)	138 (1.8)	—
% Person-years [95% CI]	0.5 [0.3–0.6]	0.8 [0.6–0.9]	0.59 [0.39–0.90]	1.5 [1.2–1.8]	1.9 [1.6–2.3]	0.74 [0.57–0.96]
Acute coronary syndrome, *n* (%)	67 (0.8)	76 (0.9)	—	88 (1.2)	99 (1.3)	—
% Person-years [95% CI]	0.9 [0.7–1.1]	0.9 [0.7–1.1]	0.93 [0.66–1.29]	1.4 [1.1–1.6]	1.4 [1.1–1.7]	0.95 [0.71–1.26]
STEMI, *n* (%)	24 (0.3)	16 (0.2)	—	19 (0.2)	28 (0.4)	—
% Person-years [95% CI]	0.3 [0.2–0.4]	0.2 [0.1–0.3]	1.58 [0.84–2.97]	0.3 [0.2–0.4]	0.4 [0.2–0.5]	0.73 [0.41–1.31]
NSTEMI, *n* (%)	6 (0.1)	18 (0.2)	—	23 (0.3)	12 (0.2)	—
% Person-years [95% CI]	0.1 [0.0–0.2]	0.2 [0.1–0.3]	0.35 [0.14–0.89]	0.4 [0.2–0.5]	0.2 [0.1–0.3]	2.07 [1.03–4.16]
Unstable angina, *n* (%)	45 (0.5)	46 (0.6)	—	53 (0.7)	71 (0.9)	—
% Person-years [95% CI]	0.6 [0.4–0.8]	0.6 [0.4–0.7]	1.03 [0.68–1.56]	0.8 [0.6–1.0]	1.0 [0.8–1.2]	0.79 [0.55–1.13]

CI, confidence interval; hdPS, high-dimensional propensity score; HR, hazard ratio; NSTEMI, non-ST-elevated myocardial infarction; STEMI, ST-elevated myocardial infarction.

CONCLUSION

This countrywide propensity score-matched new user cohort study found in real life that dabigatran as used seems to be, at both standard and reduced doses, at least as effective as and safer than rivaroxaban in the same conditions for the prevention of thromboembolic events in NVAF.

不同剂量组研究显示：

有效性：达比加群酯**等效**甚至**优效**于利伐沙班；

安全性：达比加群酯出血事件更少、**更安全**。

04

第四部分

文章品评

优点

●该研究给出了真实世界研究的一个好的方法（高维度倾向性分析），该方法在存在众多混杂因素的情况下，最大限度地减少混杂因素的干扰；

●病例数据来源广泛可靠，观察指标全面；

●所有病例纳入分析，结果外推性较好。

存在问题

●基于数据库的研究，存在混杂因素多、信息偏倚、数据缺失等问题，如患者的社会地位、工作性质、不

开展严谨的、受试对象明确的RCT研究是有必要的！

●文中几处信息存在疑问。

●卡钳值0.05（0.02，0.03）

谢谢！