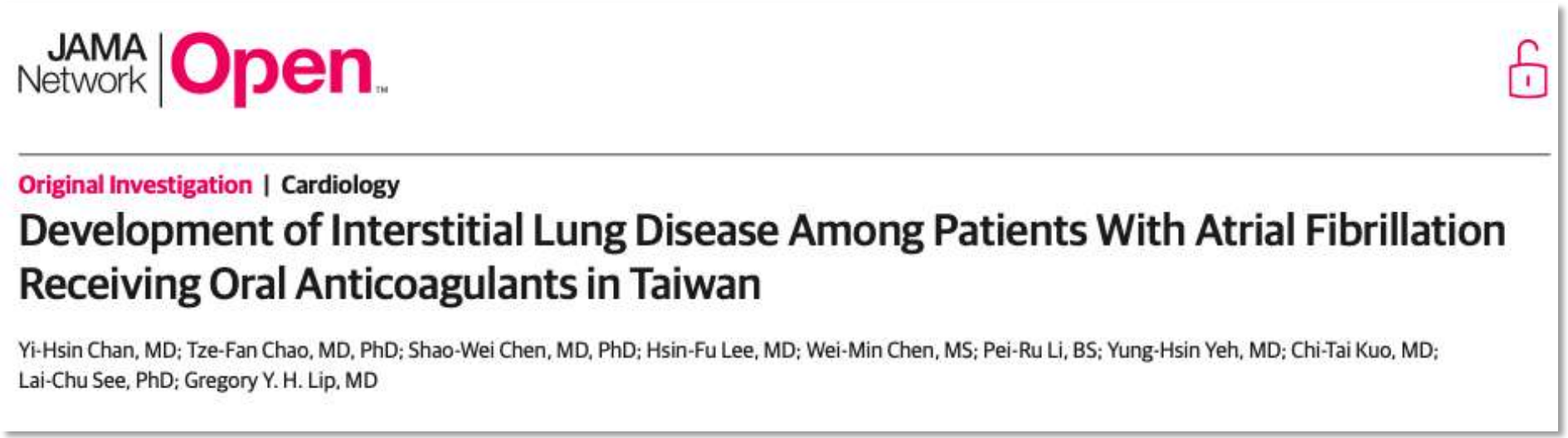
Journal Club



JAMA Netw Open. 2022 Nov 1;5(11):e2243307.

Impact factor: 13.353 (2021)

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Outline

01

Introduction

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Methods

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Discussion

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Conclusion

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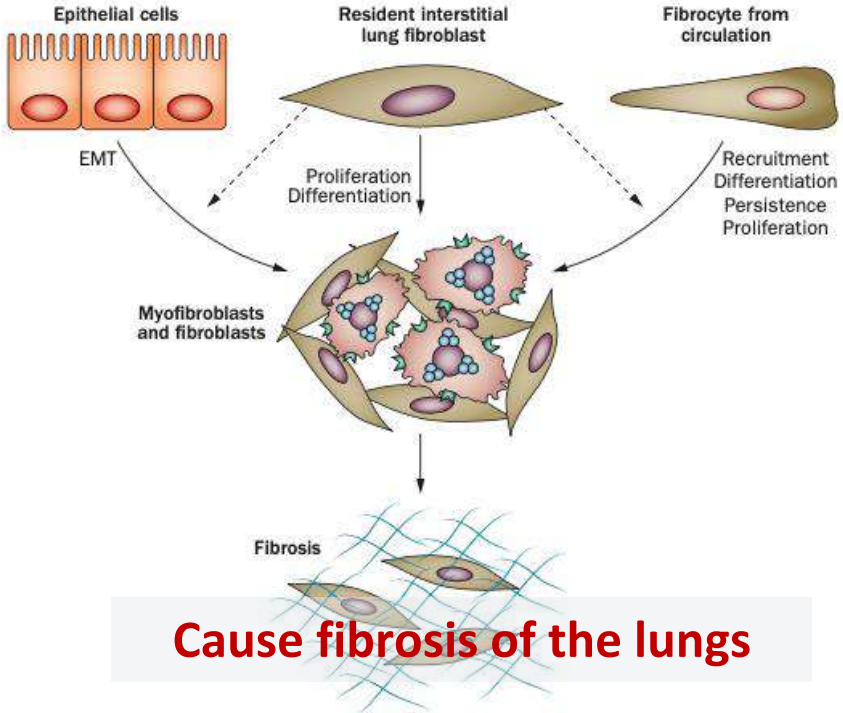
Appraisal

Interstitial Lung Disease

A group of diffuse parenchymal lung disorders

Initiation	Progression	Failed resolution
Epithelial damage	Fibroblast proliferation	Myofibroblast persistence
Endothelial activation	Fibrocyte recruitment	Altered matricellular interaction
Immune-cell infiltration	Epithelial–mesenchymal transition	Perturbed epithelial repair
Inflammation	Ongoing epithelial damage	Ongoing epithelial damage



Cause fibrosis of the lungs

Diagnosis

- ✓ High-resolution computed tomography pattern (HRCT)
- ✓ Histopathologic patterns

Risk factors

Smoking, substances, medications, and specific systemic conditions

Bradley B et al., Thorax. 2008 Wells AU et al., Nat Rev Rheumatol. 2014 Borensztajn K et al., Trends Mol Med. 2008

Drug-induced Interstitial Lung Disease

Immune-mediated

Immune-checkpoint inhibitors
TNF-α inhibitors
Rituximab
Tocilizumab

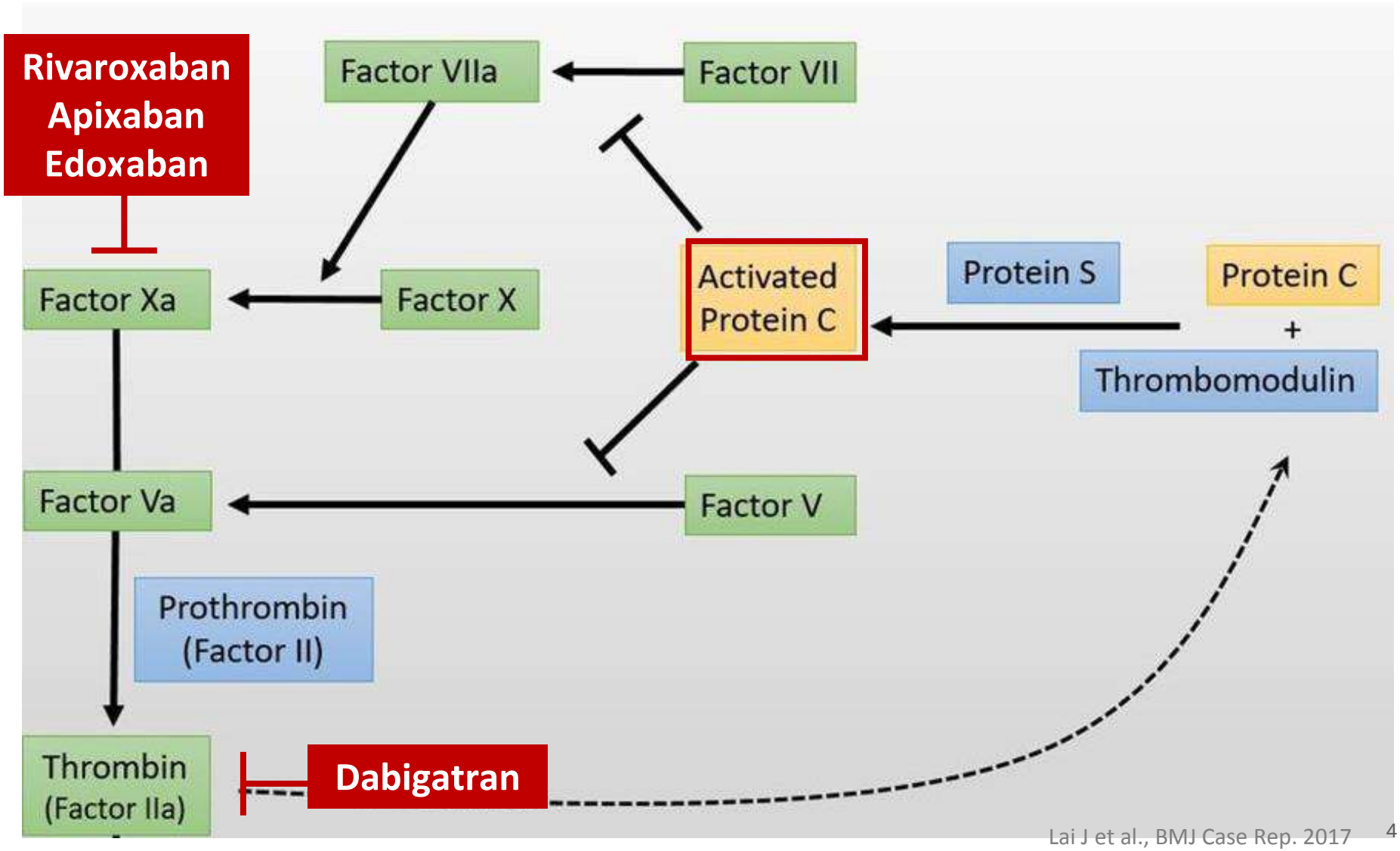
Direct, dose-dependent toxicity

Bleomycin
Methotrexate
Cyclophosphamide
Nitrofurantoin
Sulfasalazine
Amiodarone

Leads to the disruption of the lysosomal membranes of molecules through protein C activation and the subsequent release of toxic oxygen radicals

Matsuno O et al., Respir Res. 2012

Probable Role of Anticoagulant in ILD



Lai J et al., BMJ Case Rep. 2017

Existing Evidence (1)

Development of Interstitial Lung Disease after Initiation of Apixaban Anticoagulation Therapy

- **Case report from Japan**
  - ① Who developed acute respiratory failure while taking **apixaban** and were subsequently diagnosed as having ILD
  - ② Between February 2013 and May 2015

Characteristics	Case 1	Case 2	Case 3	Case 4
Sex	M	M	M	M
Age (years)	91	87	79	81
Ethnicity	Asian	Asian	Asian	Asian
Body weight (kg)	57	45	53	78
Smoker	Yes	Yes	Yes	No
History of lung disease	ILD	None	Emphysema	Tuberculosis
History of ischemic stroke	No	Yes	No	No
Other comorbidities	Pacemaker for sick sinus syndrome	Traumatic ICH	Primary ICH	PCI for silent coronary artery disease
Prior anticoagulant use	No	Warfarin	Warfarin	Rivaroxaban, warfarin
Dosage of apixaban (mg/day)	5	5	5	10

ILD: Interstitial lung disease

Tomari S et al., J Stroke Cerebrovasc Dis. 2016

Existing Evidence (2)

Direct Oral Anticoagulants and Interstitial Lung Disease: Emerging Clues from Pharmacovigilance

Emanuel Raschi[1] · Michele Fusaroli[1] · Igor Diemberger[2] · Elisabetta Poluzzi[1]

Drug	Main analysis ROR (95% CI)	Restricted to suspect reports ROR (95% CI)
DOACs	1.34 (1.25–1.43) [962]	1.32 (1.22–1.42) [716]
Factor-Xa inhibitors	1.60 (1.50–1.72) [821]	1.47 (1.36–1.60) [594]
Apixaban	1.93 (1.73–2.13) [362]	2.04 (1.81–2.3) [279]
Edoxaban	8.04 (6.47–9.79) [94]	5.20 (3.87–6.86) [47]
Rivaroxaban	1.18 (1.06–1.30) [377]	1.04 (0.92–1.17) [272]
Dabigatran	0.98 (0.83–1.14) [151]	0.91 (0.76–1.08) [128]

- ✓ Data source: FAERS, 2004-2019
- ✓ Retrospective pharmacovigilance disproportionality analysis (hypothesis-generating)

- ➢ Investigate the reporting of ILD associated with NOACs
- ➢ A total of 962 cases of ILD receiving NOACs out of 24720 patients

Age ≧ 65	Female	Asia
87%	34%	60%

Consistently emerged with higher-than-expected reporting of ILD

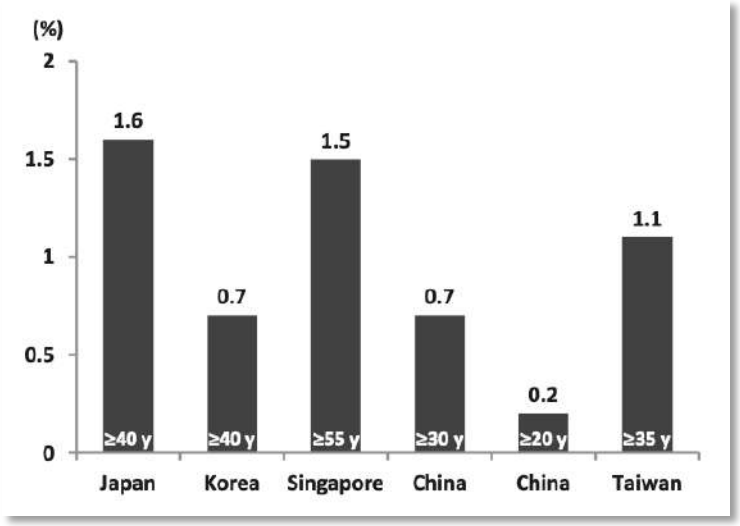
Raschi E et al., Drug Saf. 2020

FAERS: Food and Drug Administration adverse event reporting system, NOAC: Non-Vitamin K antagonist oral anticoagulants, ILD: Interstitial lung disease, ROR: reporting odds ratio

Nonvalvular Atrial Fibrillation in Taiwan

Definition

A supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently **ineffective atrial contraction**



- **Prevalence of AF in Taiwanese is 1.4% in men and 0.7% in women**

2016 Guidelines of the THRS and the TSOC for the management of AF

The First-Ever Stroke Risk

Patients with newly diagnosed AF during 2002-2004 according to inpatient claim **in NHIRD**

Aged 30-55 with none of the CHA_2DS_2-VASc risk factors (excluding sex)

	Number	Case	Follow-up person year	Incidence
AF	790	48	4816	1.00
Non-AF	10173	181	73117	0.25

Sex-adjusted HR (95% CI) 4.09 (2.97-5.62)

AF: Atrial Fibrillation, NHIRD: the National Health Insurance Research Database, CHA2DS2-VASc: Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female)

Chang KC et al., Mayo Clin Proc. 2014

Management of NVAF

Rhythm control

Cardioversion

Antiarrhythmics

Catheter ablation

Rate control

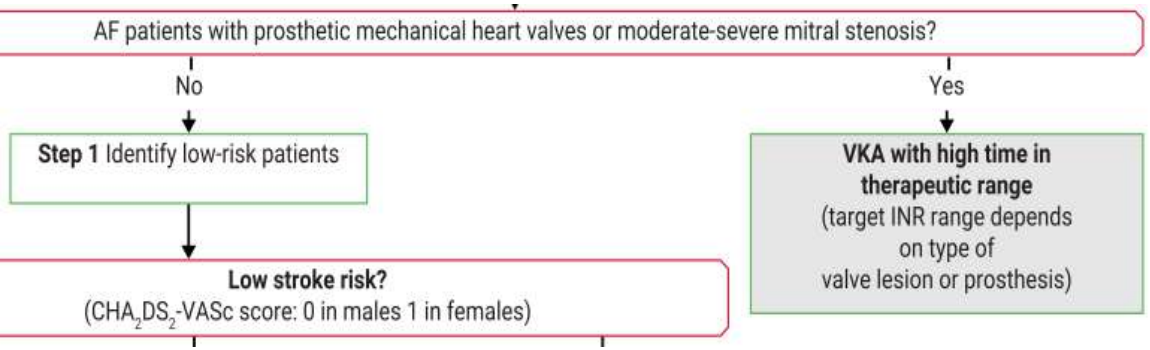
Beta blocker

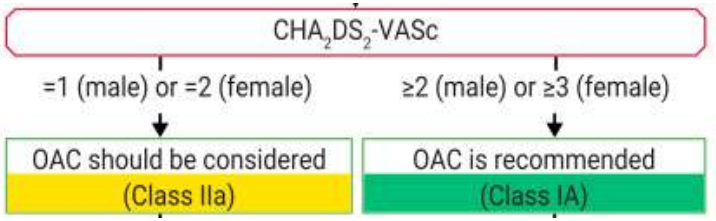
Non-Dihydropyridine CCB

CCB: Calcium channel blockers

Anticoagulant

For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis).[423,424]	I	A
For stroke risk assessment, a risk-factor-based approach is recommended, using the CHA_2DS_2-VASc clinical stroke risk score to initially identify patients at 'low stroke risk' (CHA_2DS_2-VASc score = 0 in men, or 1 in women) who should not be offered antithrombotic therapy.[334,388]	I	A





OAC: oral anticoagulant

2020 ESC Guidelines for Management of Atrial Fibrillation

Study Aim

- Emerging concern from case reports and pharmacovigilance analyses of a possible risk → **class effect?**
- Major clinical trials have reported adverse events (e.g. cough, dyspnea, and respiratory disorders) associated with common NOACs

O

To evaluate the risk of **incident ILD** associated with the **use of OACs** in **patients with NVAF**

P I C

ILD: Interstitial lung disease, OAC: oral anticoagulant, NVAF: Nonvalvular Atrial Fibrillation

Study Overview and Population

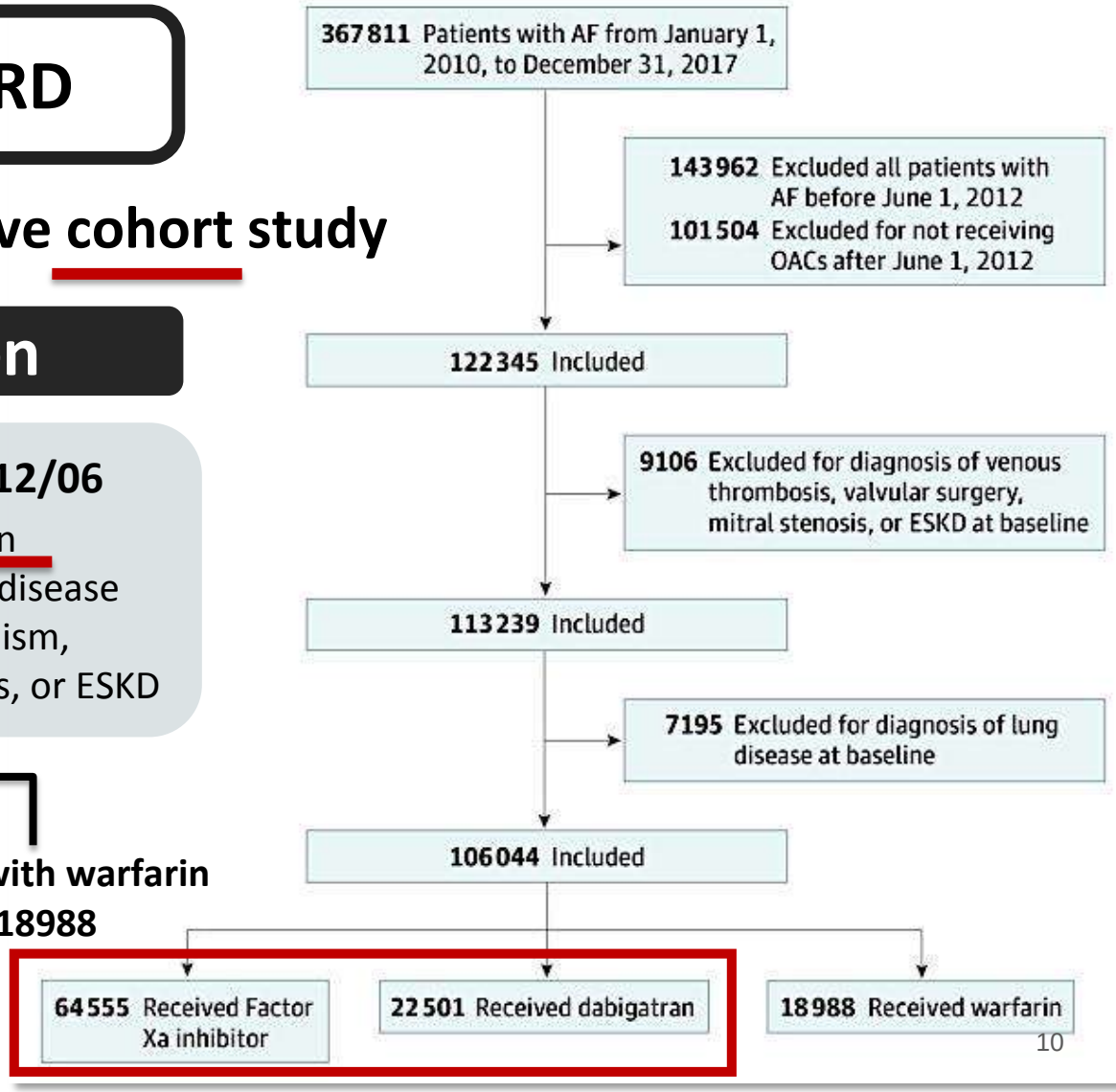
Data source: NHIRD

Study design: retrospective cohort study

Study population

Patients with NVAF after 2012/06

- Treated with NOACs or warfarin
- Without previous chronic lung disease
- Exclude venous thromboembolism, valvular surgery, mitral stenosis, or ESKD



Treated with NOACs n=87056

Treated with warfarin n=18988

NOAC: Non-Vitamin K antagonist oral anticoagulants,
ESKD: End stage kidney disease

Exposure and Outcome of Interest

Study cohort

NOACs n=87056

Warfarin n=18988

Exposure	Number	%
Dabigatran	22501	-
Apixaban	15386	23.83
Rivaroxaban	36756	56.94
Edoxaban	12413	19.23
Warfarin (ref)	18988	-

Primary outcome

New onset idiopathic ILD

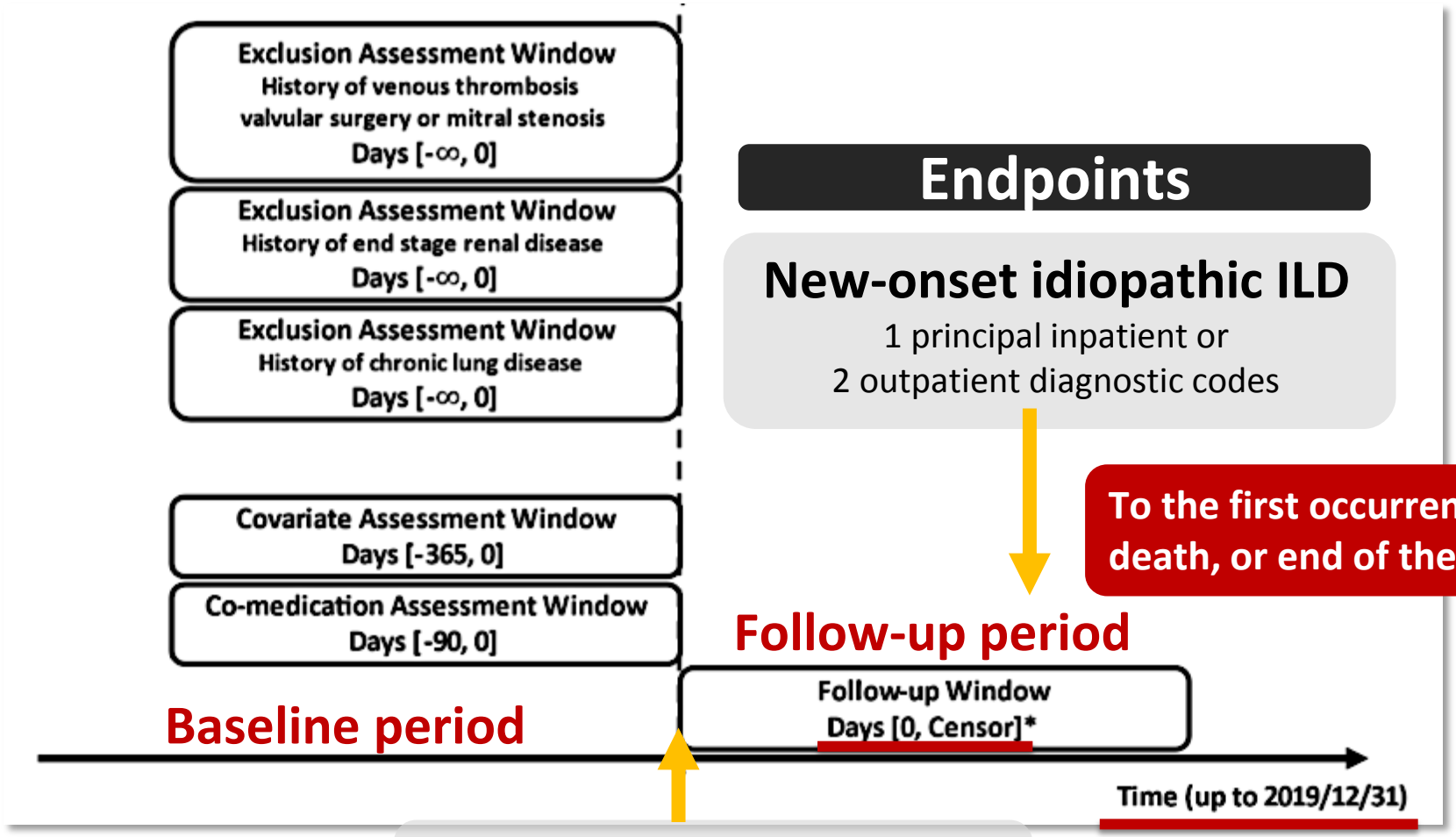
Falsification outcome

Lung cancer
Influenza
Asthma

NOAC: Non-Vitamin K antagonist oral anticoagulants, ILD: Interstitial lung disease

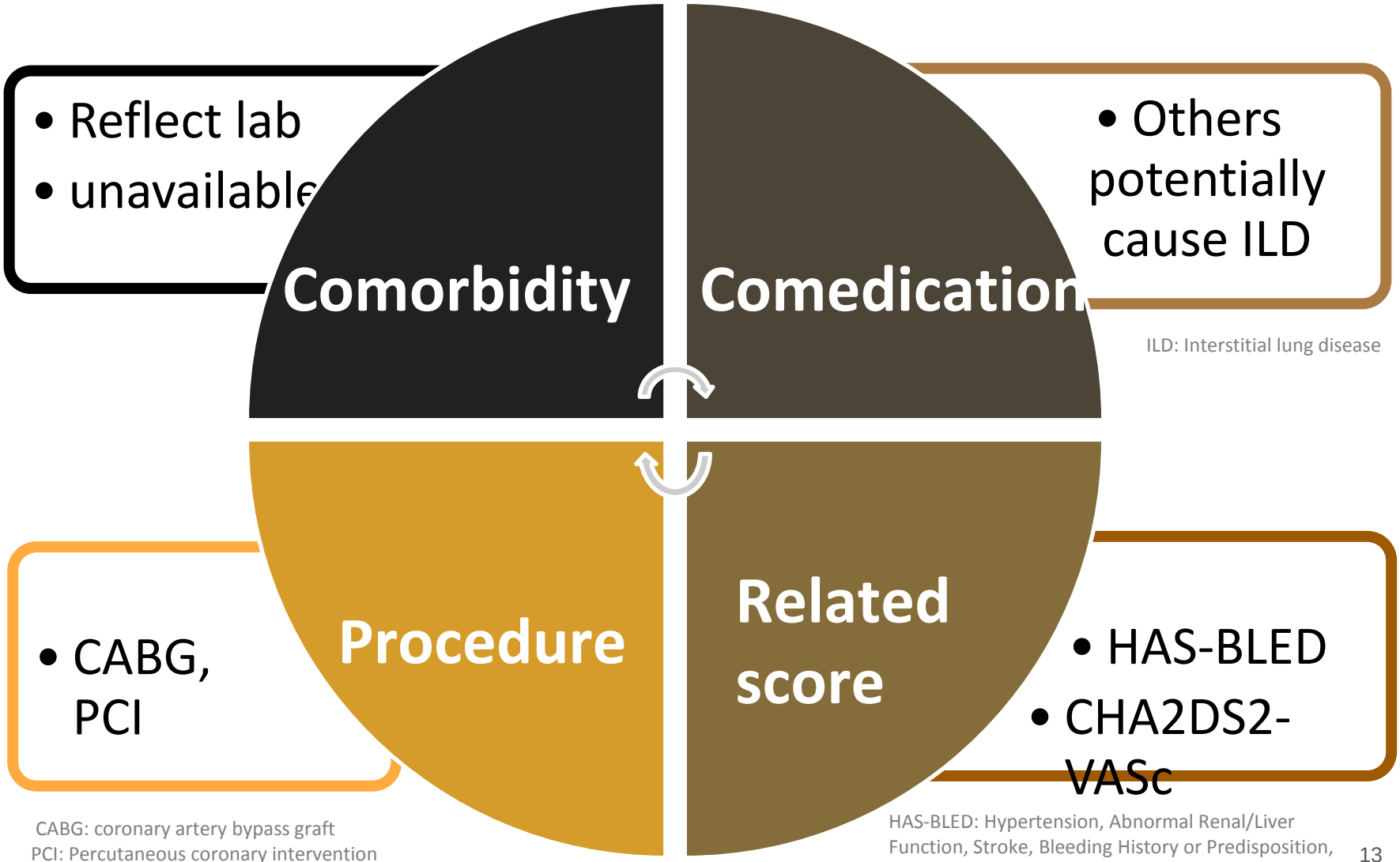
Groenwold RH et al., JAMA. 2013

Follow-up Scheme



NOAC: Non-Vitamin K antagonist oral anticoagulants, ILD: Interstitial lung disease

Baseline Covariates



Statistical Analysis

IPTW + stabilized weight (PSSW)

- |SMD| of 0.1 or less→balanced

Generalized/gradient boosted models

Survival analysis

- Kaplan-Meier curve and cox proportional hazards model

Sensitivity analysis

Subgroup analysis

- Amiodarone

IPTW: inverse probability treatment weighting, PSSW: propensity score stabilized weighting, ASMD: absolute standardized mean difference

Baseline Characteristic (1)

n=106044

Age mean [SD]	73.4 [11.9]
Female n (%)	46049 (43.4%)

Characteristic	Patients, No. (%)			ASMD	
	FXa inhibitor (n = 64 555)	Dabigatran (n = 22 501)	Warfarin (n = 18 988)	FXa inhibitor vs warfarin	Dabigatran vs warfarin
Age					
Mean (SD), y	74.7 (11.2)	73.3 (10.9)	69.4 (14.1)	0.4135	0.3105
<65	11 598 (18.0)	4550 (20.2)	7536 (39.7)	0.5009	0.4693
65-74	19 072 (29.5)	7322 (32.5)	3906 (20.6)	NA	NA
75-84	21 679 (33.6)	7441 (33.1)	4715 (24.8)	NA	NA
≥85	12 206 (18.9)	3188 (14.2)	2831 (14.9)	NA	NA
Sex					
Male	35 646 (55.2)	13 589 (60.4)	10 760 (56.7)	0.0292	0.0757
Female	28 909 (44.8)	8912 (39.6)	8228 (43.3)	NA	NA
CHA_2DS_2-VASc score, mean (SD)	3.3 (1.7)	3.2 (1.6)	2.6 (1.9)	0.3748	0.3140
HAS-BLED score, mean (SD)	2.6 (1.2)	2.5 (1.1)	2.1 (1.3)	0.3975	0.3437

Baseline Characteristic (2)

CHA2DS2-VASc	CHF, HTN, age≧75, diabetes, previous stroke or TIA, vascular disease, age 65-74, female
HAS-BLED	HTN, abnormal kidney or liver function, stroke, bleeding history, labile INR, age≧65 years, antiplatelet drug or alcohol use

Characteristic	Patients, No. (%)			ASMD	
	FXa inhibitor (n = 64 555)	Dabigatran (n = 22 501)	Warfarin (n = 18 988)	FXa inhibitor vs warfarin	Dabigatran vs warfarin
Hypertension	34 387 (53.3)	10 931 (48.6)	7904 (41.6)	0.2347	0.1401
Diabetes	23 317 (36.1)	7786 (34.6)	5702 (30.0)	0.1297	0.0979
Dyslipidemia	29 329 (45.4)	9225 (41.0)	6411 (33.8)	0.2403	0.1500
Chronic liver disease	5569 (8.6)	1767 (7.9)	1485 (7.8)	0.0293	0.0012
CKD	11 238 (17.4)	2647 (11.8)	2600 (13.7)	0.1027	0.0579
Gout	10 235 (15.9)	3110 (13.8)	2590 (13.6)	0.0625	0.0053
CHF	5749 (8.9)	1644 (7.31)	1769 (9.3)	0.0143	0.0729
Chronic IHD	7289 (11.3)	1993 (8.9)	1650 (8.7)	0.0868	0.0059
Stroke	11 900 (18.4)	5382 (23.9)	2459 (13.0)	0.1512	0.2857
Cancer	6822 (10.6)	1920 (8.5)	1665 (8.8)	0.0609	0.0084
RA	223 (0.4)	74 (0.3)	49 (0.3)	0.0159	0.0131
PCI	4694 (7.3)	1161 (5.2)	955 (5.0)	0.0934	0.0059
CABG	354 (0.6)	59 (0.3)	210 (1.1)	0.0616	0.1025
History of bleeding	1029 (1.6)	305 (1.4)	305 (1.6)	0.0010	0.0208

ASMD: absolute standardized mean difference

Baseline Characteristic (3)

Characteristic	Patients, No. (%)			ASMD	
	FXa inhibitor (n = 64 555)	Dabigatran (n = 22 501)	Warfarin (n = 18 988)	FXa inhibitor vs warfarin	Dabigatran vs warfarin
Use of NSAIDs	15 955 (24.7)	5332 (23.7)	4866 (25.6)	0.0210	0.0448
Use of PPI	7987 (12.4)	2069 (9.2)	2551 (13.4)	0.0317	0.1341
Use of H_2RB	20 309 (31.5)	7140 (31.7)	6132 (32.3)	0.0179	0.0120
Use of ACEI, ARB subtype II	38 543 (59.7)	13 320 (59.2)	10 539 (55.5)	0.0851	0.0747
Use of β-blocker	39 399 (61.0)	13 000 (57.8)	11 739 (61.8)	0.0163	0.0826
Use of verapamil or diltiazem	14 730 (22.8)	4744 (21.1)	4685 (24.7)	0.0436	0.0855
Use of statin	23 061 (35.7)	7751 (34.5)	4835 (25.5)	0.2240	0.1971
Use of APT	34 563 (53.5)	12 156 (54.0)	10 455 (55.1)	0.0305	0.0208
Use of amiodarone	19 787 (30.7)	5567 (24.7)	8065 (42.5)	0.2474	0.3822
Use of dronedarone	2659 (4.1)	353 (1.6)	322 (1.7)	0.1446	0.0100
Use of chemotherapy	988 (1.5)	256 (1.1)	263 (1.4)	0.0121	0.0222
Use of target therapy	999 (1.6)	215 (1.0)	141 (0.7)	0.0757	0.0232
Use of methotrexate	183 (0.3)	56 (0.3)	51 (0.3)	0.0028	0.0039
Use of anti-TNF agent	38 (0.1)	15 (0.1)	11 (0.1)	0.0004	0.0035
Use of corticosteroid	1713 (2.7)	464 (2.1)	583 (3.1)	0.0250	0.0638
Use of quinidine	70 (0.1)	23 (0.1)	49 (0.3)	0.0350	0.0368
Use of rifampicin	194 (0.3)	56 (0.3)	74 (0.4)	0.0152	0.0250
Use of macrolides	1452 (2.3)	387 (1.7)	504 (2.7)	0.0262	0.0639
Use of antifungal agent	571 (0.9)	113 (0.5)	261 (1.4)	0.0464	0.0906

Frequently coprescribed with NOACs in patients with AF

After PSSW, all medication groups were well balanced in all characteristics

AF: Atrial Fibrillation
NOAC: Non-Vitamin K antagonist oral anticoagulants

Main Analysis (1)

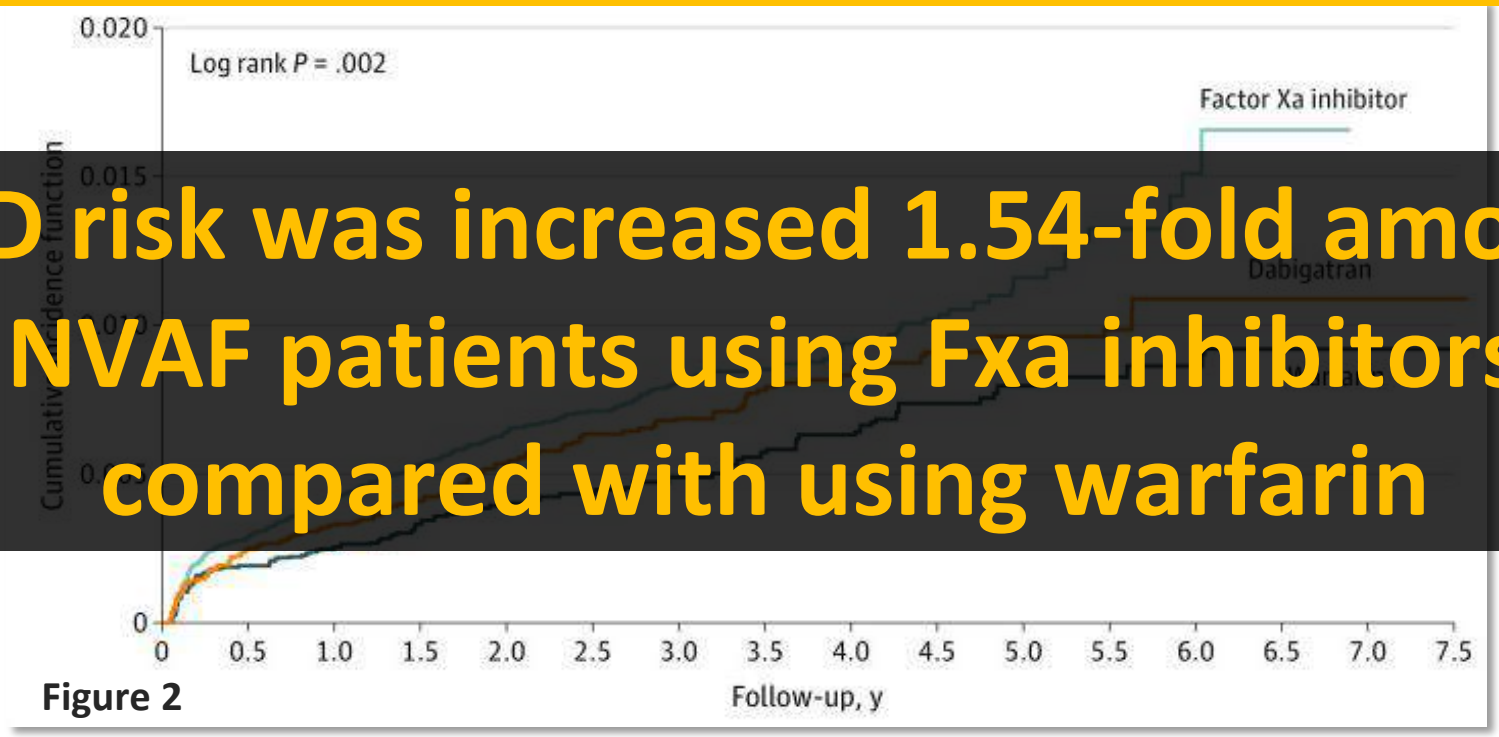


Figure 2

ILD risk was increased 1.54-fold among NVAF patients using Fxa inhibitors compared with using warfarin

	Risk of incident ILD		Absolute risk of incident ILD	
FXa inhibitor	HR=1.54 (1.22-1.94)	P <0.001 Significant	+0.12 (0.29 vs 0.17)	(0.08-0.17)
Dabigatran	HR=1.26 (0.96-1.65)	P =0.09 Non-significant	+0.05 (0.22 vs 0.17)	(−0.001-0.10)

FXa: activated coagulation factor X

Main Analysis (2)

Primary outcome	NOAC, rate per 100 patient-years	Warfarin, rate per 100 patient-years	HR (95% CI)
Interstitial lung disease			
Factor Xa inhibitor	0.29	0.17	1.54 (1.22-1.94)
Dabigatran	0.22	0.17	1.26 (0.96-1.65)

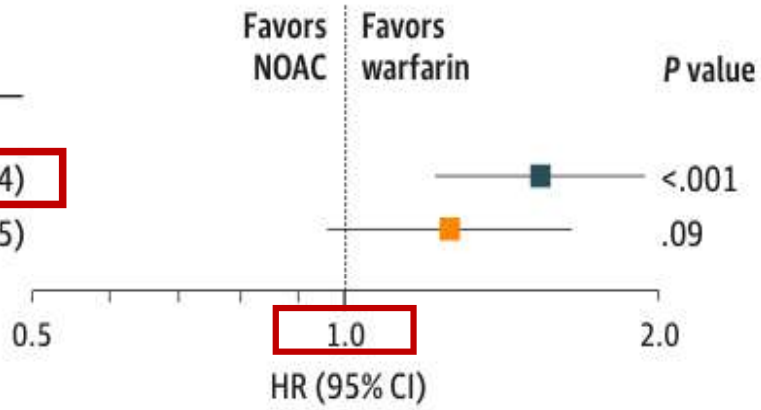
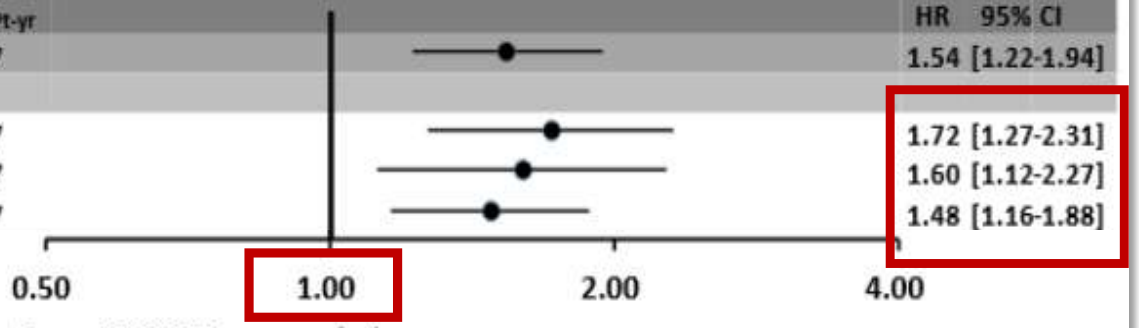


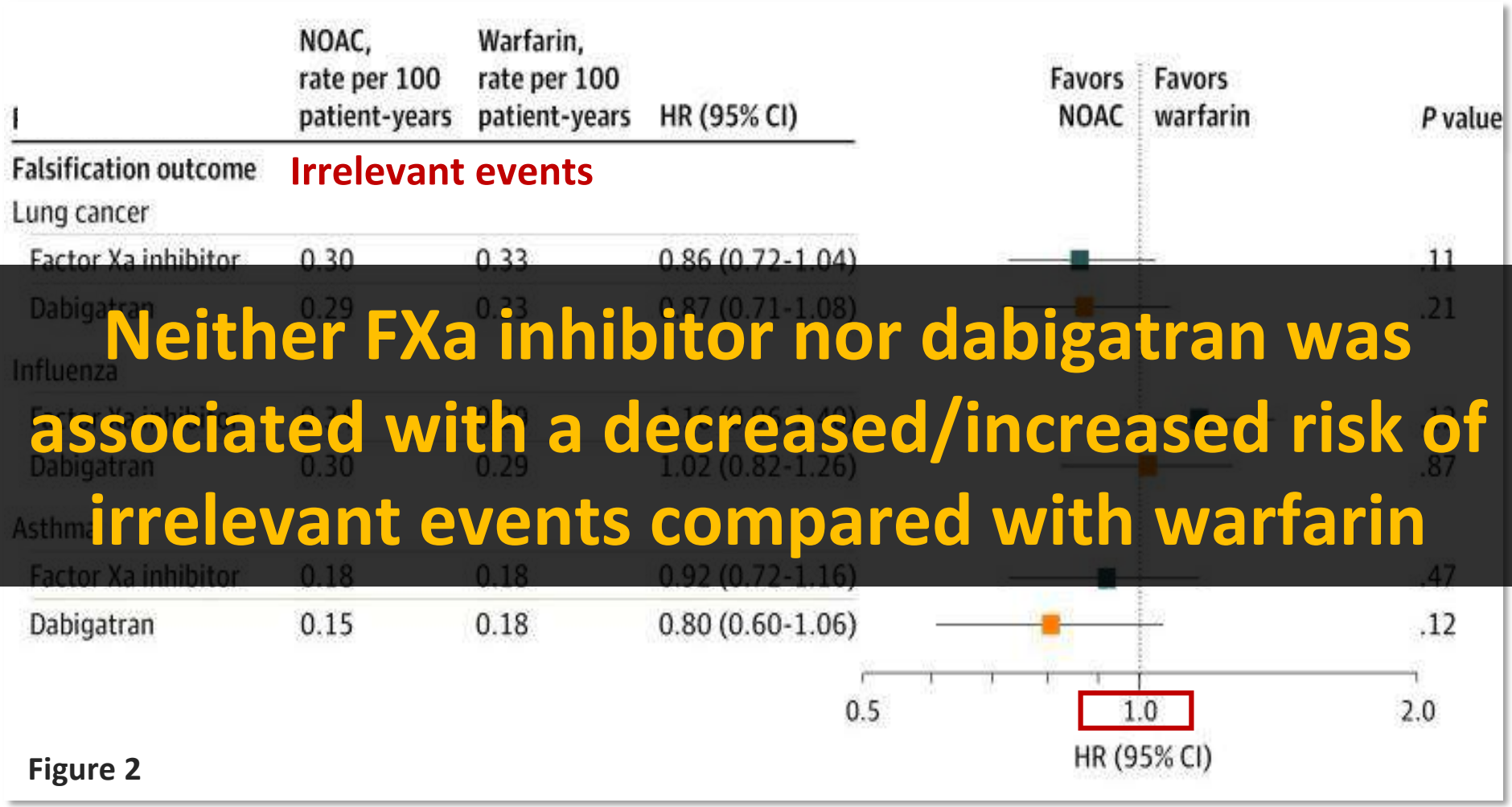
Figure 2

	Xa inhibitor Rate Per 100-Pt-yr	Warfarin Rate Per 100-Pt-yr	HR 95% CI
All	0.29	0.17	1.54 [1.22-1.94]
Xa inhibitor			
Apixaban	0.35	0.17	1.72 [1.27-2.31]
Edoxaban	0.37	0.17	1.60 [1.12-2.27]
Rivaroxaban	0.27	0.17	1.48 [1.16-1.88]



eFigure 2

Falsification Outcomes



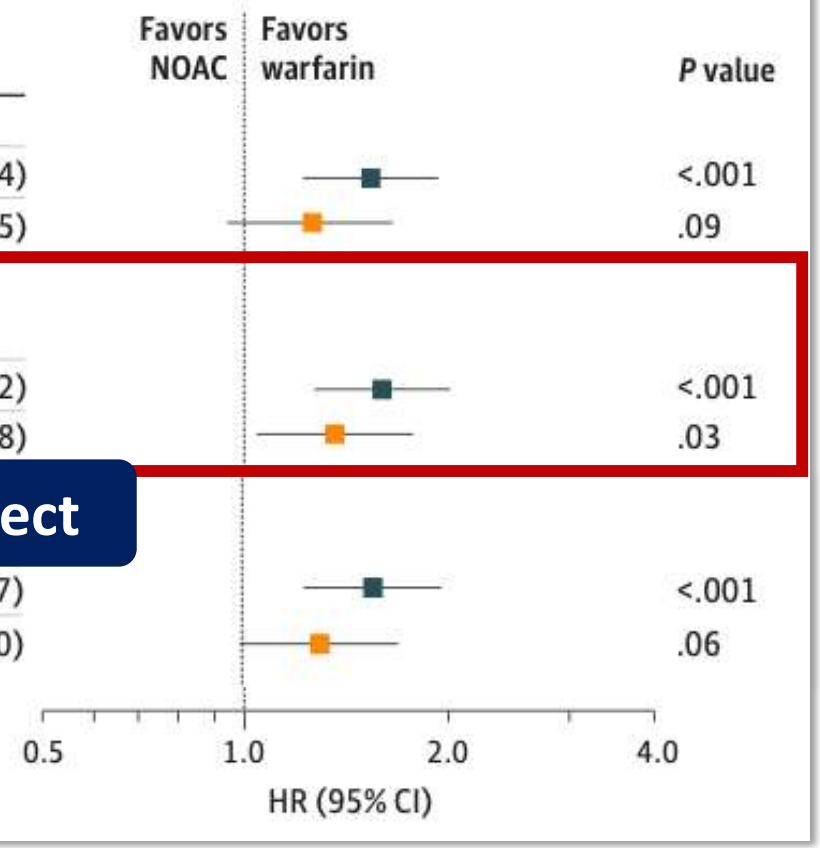
Neither FXa inhibitor nor dabigatran was associated with a decreased/increased risk of irrelevant events compared with warfarin

Figure 2

FXa: activated coagulation factor X

Sensitivity Analysis (1)

	NOAC, rate per 100 patient-years	Warfarin, rate per 100 patient-years	HR (95% CI)	P value
ILD, main analysis				
Factor Xa inhibitor	0.29	0.17	1.54 (1.22-1.94)	<.001
Dabigatran	0.22	0.17	1.26 (0.96-1.65)	.09
ILD, with death as competing risk				
Factor Xa inhibitor	0.29	0.17	1.60 (1.27-2.02)	<.001
Dabigatran	0.22	0.17	1.36 (1.04-1.78)	.03
ILD, NOAC user without previous warfarin exposure				
Factor Xa inhibitor	0.30	0.17	1.56 (1.23-1.97)	<.001
Dabigatran	0.23	0.17	1.30 (0.99-1.70)	.06



→ Avoid carryover effect

Fxa inhibitor	61713, 95.6%
Dabigatran	21035, 93.5%

Figure 3

NOAC: Non-Vitamin K antagonist oral anticoagulants, ILD: Interstitial lung disease, FXa: activated coagulation factor X

Sensitivity Analysis (2)

	NOAC, rate per 100 patient-years	Warfarin, rate per 100 patient-years	HR (95% CI)	P value
ILD, main analysis				
Factor Xa inhibitor	0.29	0.17	1.54 (1.22-1.94)	<.001
Dabigatran	0.22	0.17	1.26 (0.96-1.65)	.09
ILD, >1 claim within 30-365 d of diagnosis				
Factor Xa inhibitor	0.17	0.10	1.57 (1.16-2.12)	.003
Dabigatran	0.12	0.10	1.20 (0.85-1.71)	.30
IPF				
Factor Xa inhibitor	0.25	0.15	1.47 (1.15-1.88)	.002
Dabigatran	0.19	0.15	1.23 (0.93-1.64)	.15
Rigid IPF				
Factor Xa inhibitor	0.06	0.03	1.96 (1.11-3.47)	.02
Dabigatran	0.03	0.03	1.22 (0.62-2.41)	.56

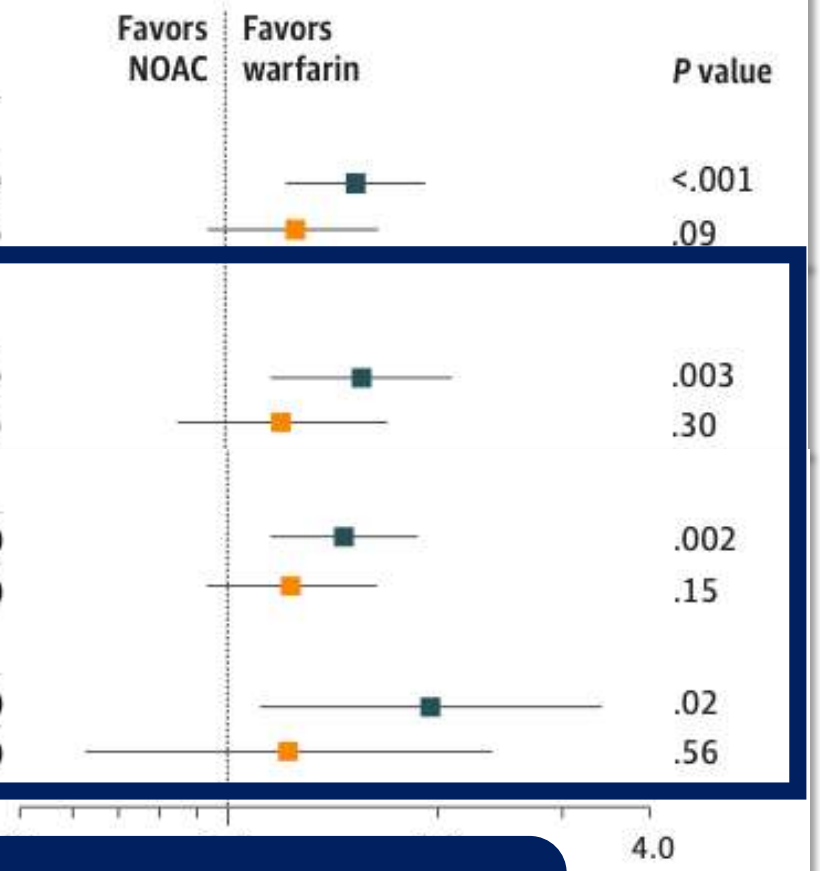
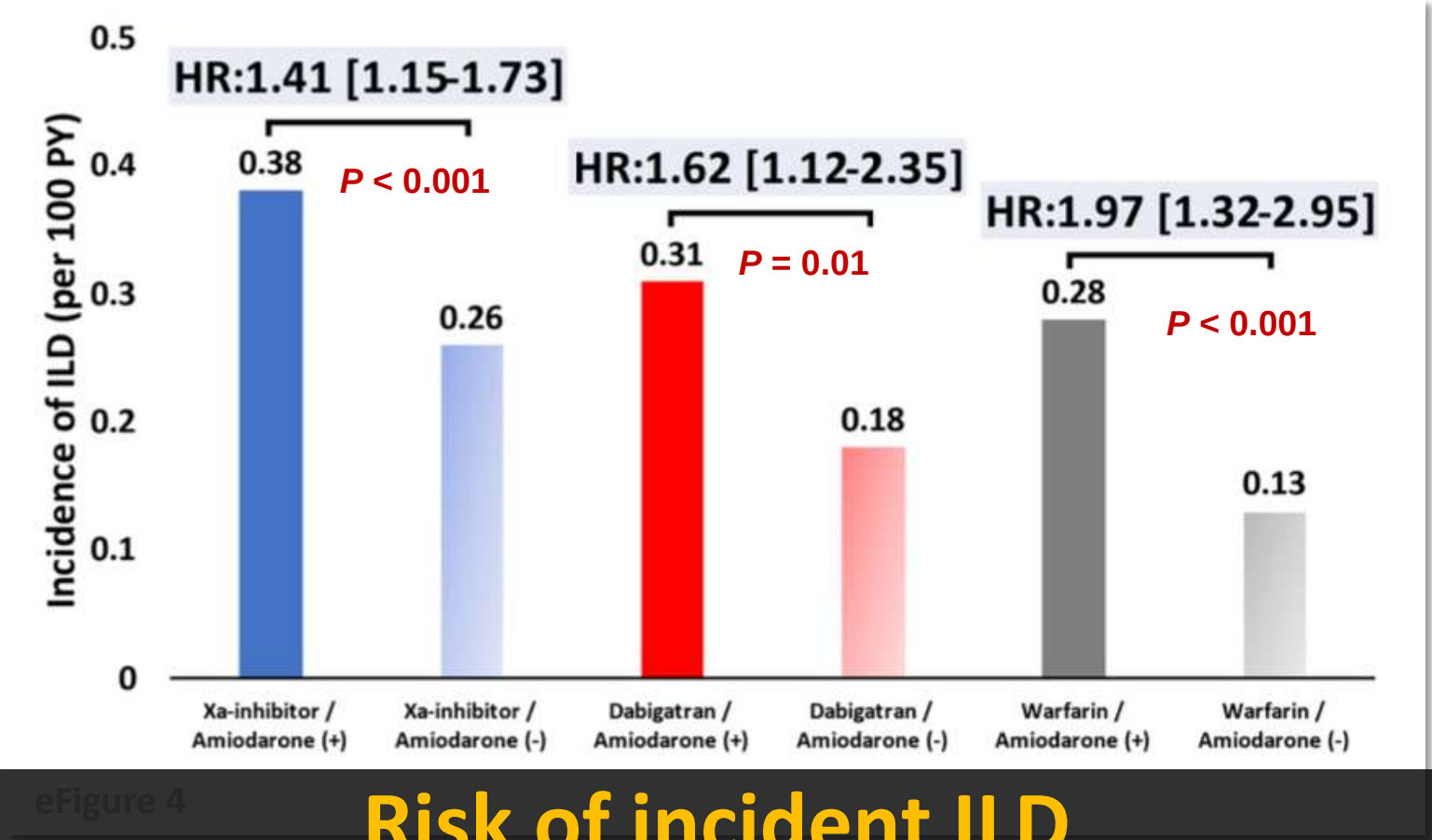


Figure 3

Further restrict the diagnosis of ILD to make sure the certainty of outcome measurement

NOAC: Non-Vitamin K antagonist oral anticoagulants, ILD: Interstitial lung disease, FXa: activated coagulation factor X

Subgroup Analysis



eFigure 4

Risk of incident ILD

The highest: FXa inhibitors w/ amiodarone

The lowest: warfarin w/o amiodarone

Main Finding

Associated with higher risk of incident ILD compared with warfarin

Group \ Analysis	Main	Sensitivity	Subgroup
FXa inhibitor	Significantly	Consistent with main analysis	Amiodarone was a effect modifier
Dabigatran	Non-significantly	Consider death as competing risk	

ILD: Interstitial lung disease, FXa: activated coagulation factor X

Compare with Previous Studies (1)

	Present study	Raschi E et al., Drug Saf. 2020
Population	NVAF	FAERS (non-defined)
Amiodarone	Effect modifier (stratify)	Excluded
Anticancer & anti-rheumatics	Baseline covariates	Excluded

Primary outcome	NOAC, rate per 100 patient-years	Warfarin, rate per 100 patient-years	HR (95% CI)
Interstitial lung disease			
Factor Xa inhibitor	0.29	0.17	1.54 (1.22-1.94)
Dabigatran	0.22	0.17	1.26 (0.96-1.65)

	Xa inhibitor Rate Per 100-Pt-yr	Warfarin Rate Per 100-Pt-yr	HR 95% CI
All	0.29	0.17	1.54 [1.22-1.94]
Xa inhibitor			
Apixaban	0.35	0.17	1.72 [1.27-2.31]
Edoxaban	0.37	0.17	1.60 [1.12-2.27]
Rivaroxaban	0.27	0.17	1.48 [1.16-1.88]

Drug	Main analysis ROR (95% CI)	Restricted to suspect reports ROR (95% CI)
DOACs	1.34 (1.25–1.43) [962]	1.32 (1.22–1.42) [716]
Factor-Xa inhibitors	1.60 (1.50–1.72) [821]	1.47 (1.36–1.60) [594]
Apixaban	1.93 (1.73–2.13) [362]	2.04 (1.81–2.3) [279]
Edoxaban	8.04 (6.47–9.79) [94]	5.20 (3.87–6.86) [47]
Rivaroxaban	1.18 (1.06–1.30) [377]	1.04 (0.92–1.17) [272]
Dabigatran	0.98 (0.83–1.14) [151]	0.91 (0.76–1.08) [128]

Compare with Previous Studies (2)

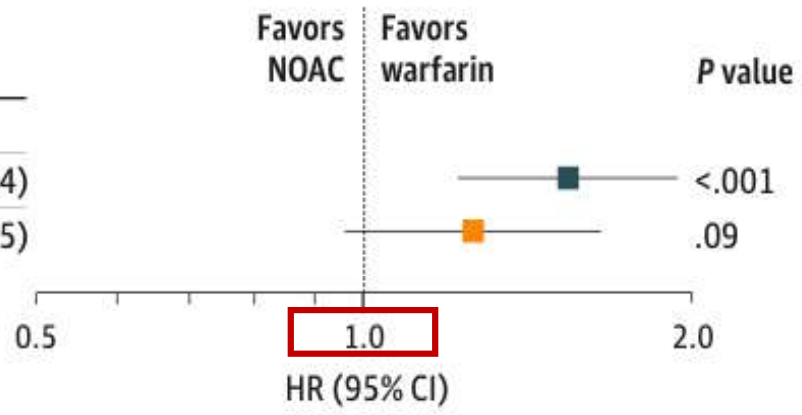
	Raschi E et al., Drug Saf. 2020		Tomari S et al., J Stroke Cerebrovasc Dis. 2016	
Population	FAERS (non-defined)		Taking apixaban for stroke prevention among NVAF (Case report from Japan)	
Previously exposed	unknown		naïve	warfarin→apixaban
			warfarin→apixaban	rivaroxaban→ warfarin→apixaban
Onset (median)	**Fxa inhibitor**	**Dabigatran**	4 days	3 days (misclassification?)
	49 days (15-176.5)	60 days (40-182.5)	3 days (misclassification?)	90 days

Pulse therapy	MP 1 g × 3 days	MP 1 g × 3 days	MP 0.5 g × 3 days	MP 1 g × 3 days
Mechanical ventilation	Yes	No	Yes	Yes
Outcome	Fatal	Recovered	Recovered	Fatal

Subsequent Treatment for ILD

	Antifibrotic agents (per 100 patients) (pirfenidone or nintedanib)	Immunosuppressants (per 100 patients)
FXa inhibitor	**9.18**	68.73
Dabigatran	**5.56**	68.25
Warfarin	**3.03**	74.75

Primary outcome	NOAC, rate per 100 patient-years	Warfarin, rate per 100 patient-years	HR (95% CI)
Interstitial lung disease			
Factor Xa inhibitor	0.29	0.17	1.54 (1.22-1.94)
Dabigatran	0.22	0.17	1.26 (0.96-1.65)



ILD: Interstitial lung disease

Benefit Package of NHI

6.2.7.Nintedanib (Ofev)、pirfenidone (Pirespa)：(106/3/1、106/7/1、108/12/1、109/9/1)

1. 需檢附肺部 HRCT (High resolution computed tomography)影像檢查。
2. 經專科醫師確診為特發性肺纖維化(Idiopathic pulmonary fibrosis, IPF)後，病人的用力肺活量(forced vital capacity, FVC) 在50~80%之間。
3. 用於經專科醫師確診為特發性肺纖維化，且 FVC>80%之病患，需具明顯症狀(病歷須清楚記載如呼吸困難、喘或咳嗽等臨床症狀)。(108/12/1、109/9/1)
4. 停止治療條件:肺功能出現惡化（經確認病人的用力肺活量預測值降低10%或以上情況發生時），得以續用或得申請使用不同機轉藥物治療並觀察12週，如再測之 FVC 未改善應停止使用。(106/7/1、108/12/1、109/9/1)
5. 需經事前審查核准後使用，每24週需檢送評估資料再次申請。
6. Nintedanib 與 pirfenidone 不得同時併用。(106/7/1)

NHI: the National Health Insurance

Limitations (1)

Due to data source (NHIRD)

- Smoking?
- Adherence?
- Renal function?
- Treatment dose?
- INR? TTR? (warfarin group)
- ~~Asian only~~

The use of specific NOACs or warfarin may be guided accordingly

9106 Excluded for diagnosis of venous thrombosis, valvular surgery, mitral stenosis, or ESKD at baseline

NHIRD: the National Health Insurance Research Database, INR: international normalized ratio, TTR: Time in Therapeutic Range

Limitations (2)

Due to unmeasured confounder

- Confounding by indication may still exist
- ILD attributed to unmeasured drugs

Due to operational definition

- Underestimate of outcome?
- ~~Misclassification? COVID-19?~~

Conclusion

- **FXa inhibitors appeared to be associated with higher ILD risk among NVAF patients who were treated with OACs**
  - ① HR=1.54 (1.22-1.94)
  - ② With relative small absolute risk (+0.12)

- **Whereas dabigatran did not**
  - ① HR=1.26 (0.96-1.65)

ILD: Interstitial lung disease, OAC: oral anticoagulant, NVAF: Nonvalvular Atrial Fibrillation, FXa: activated coagulation factor X

Clinical Impact (1)

Risk-benefit assessment

	Incidence (100pt per yr) (95%CI)			Rate difference (100pt per yr) (95%CI)	
	Factor Xa inhibitor (n = 64,393.72)	Dabigatran (n = 22,178.67)	Warfarin (n = 18,469.65)	Factor Xa inhibitor vs. Warfarin	Dabigatran vs. Warfarin
Outcomes					
IS/SE	1.76 (1.69-1.84)	1.91 (1.79-2.02)	2.55 (2.41-2.69)	-0.78 (-0.94, -0.63)	-0.64 (-0.82, -0.46)
Major GI bleeding	1.04 (0.99-1.09)	0.94 (0.86-1.02)	1.32 (1.22-1.42)	-0.28 (-0.40, -0.17)	-0.38 (-0.51, -0.26)
All major bleeding	1.61 (1.54-1.68)	1.38 (1.28-1.47)	2.39 (2.25-2.52)	-0.78 (-0.93, -0.63)	-1.01 (-1.17, -0.84)

Risk of all major bleeding was significantly decreased among NVAF patients using NOACs compared with using warfarin

eTable 4

OAC: oral anticoagulant, NVAF: Nonvalvular Atrial Fibrillation, FXa: activated coagulation factor X

Clinical Impact (2)

For physicians and pharmacists

- Monitoring potential development of ILD in NVAF patients receiving FXa inhibitors
- Especially those co-prescribed with amiodarone

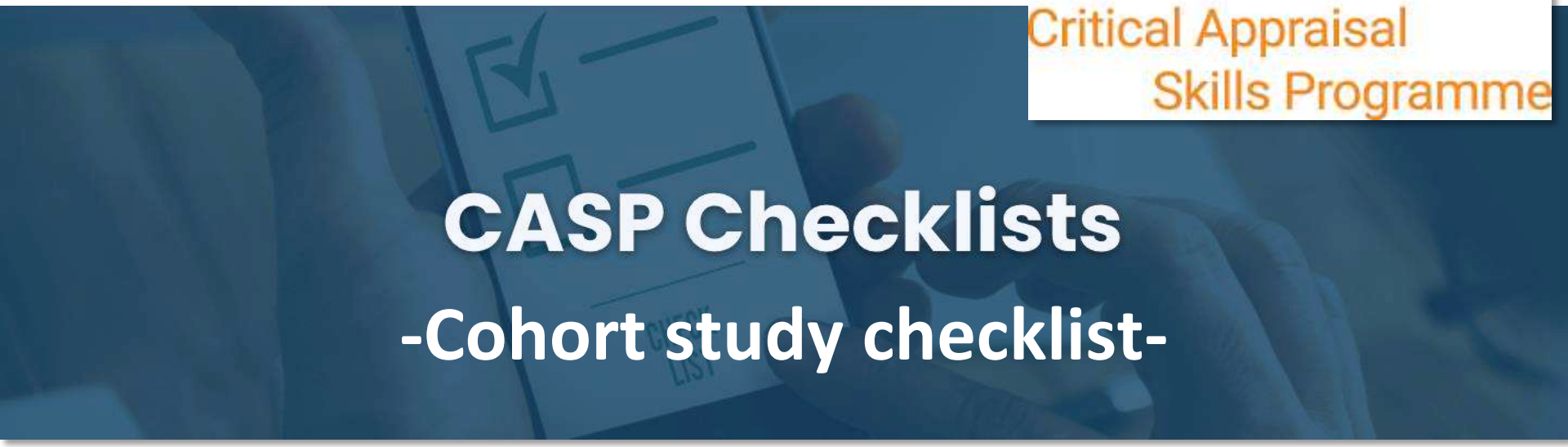
ILD: Interstitial lung disease, NVAF: Nonvalvular Atrial Fibrillation, FXa: activated coagulation factor X

Patients education

- Importance of taking NOACs
- Early respiratory signs identification
- Remain vigilant for adverse lung effects

NOAC: Non-Vitamin K antagonist oral anticoagulants

Appraisal



Section A: Are the results of the study valid?

Section B: What are the results?

Section C: Will the results help locally?

Appraisal (1)

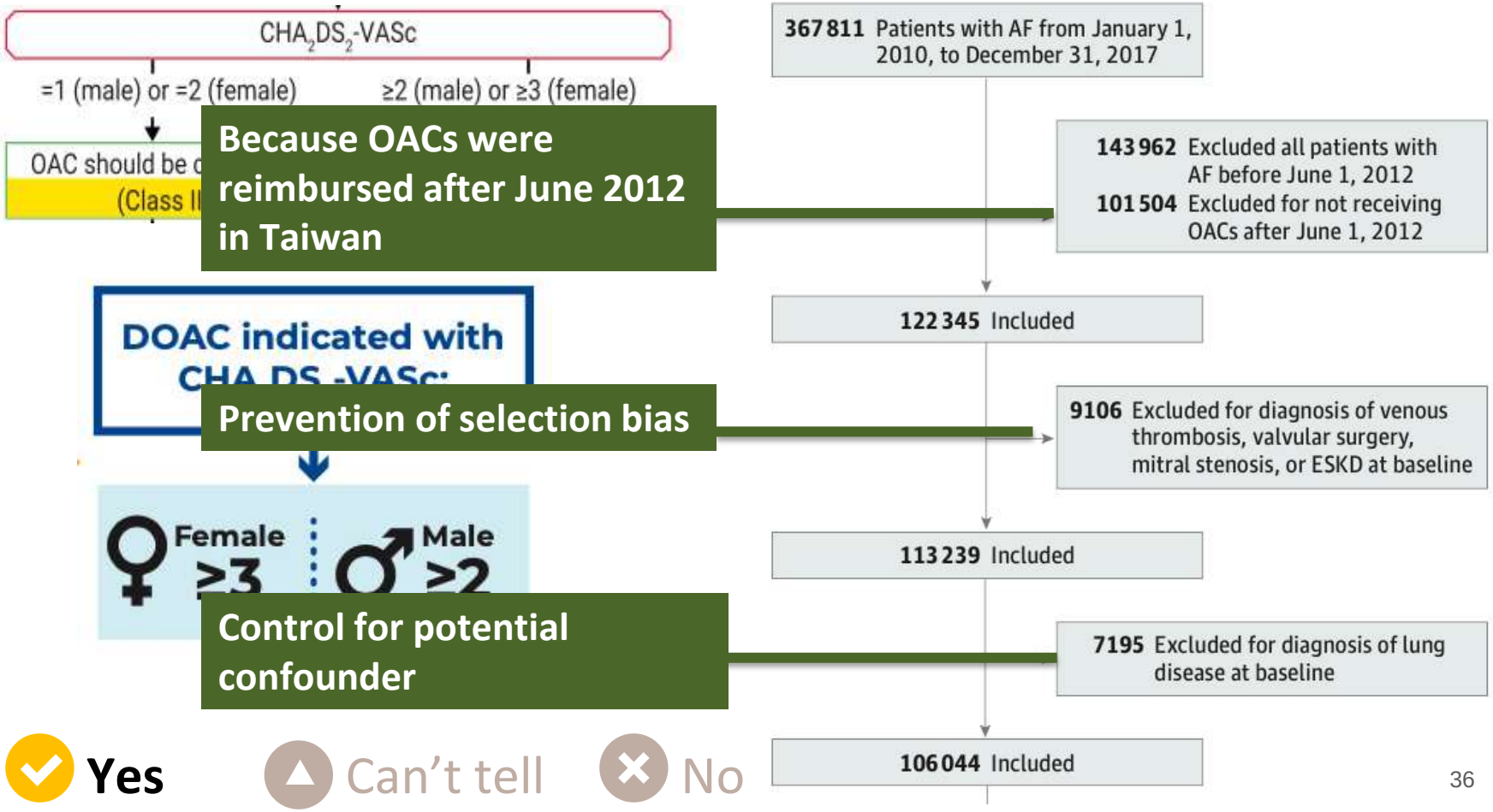
1. Did the study address a clearly focused issue?

OBJECTIVE To evaluate the risk of incident ILD associated with the use of oral anticoagulants (OACs) in patients with nonvalvular atrial fibrillation (NVAF).

DESIGN, SETTING, AND PARTICIPANTS This nationwide retrospective cohort study used data from the Taiwan National Health Insurance Research Database. Patients with NVAF without preexisting lung disease who received OACs from June 1, 2012, to December 31, 2017, were included. Propensity score stabilized weighting (PSSW) was used to balance covariates across the medication groups (FXa inhibitors, dabigatran, and warfarin, with warfarin as the reference). Patients were followed up from the drug index date until the onset of ILD, death, or end of the study (December 31, 2019), whichever occurred first. Data were analyzed from September 11, 2021, to August 3, 2022.

Appraisal (2)

2. Was the cohort recruited in an acceptable way?



Because OACs were reimbursed after June 2012 in Taiwan

Prevention of selection bias

Control for potential confounder

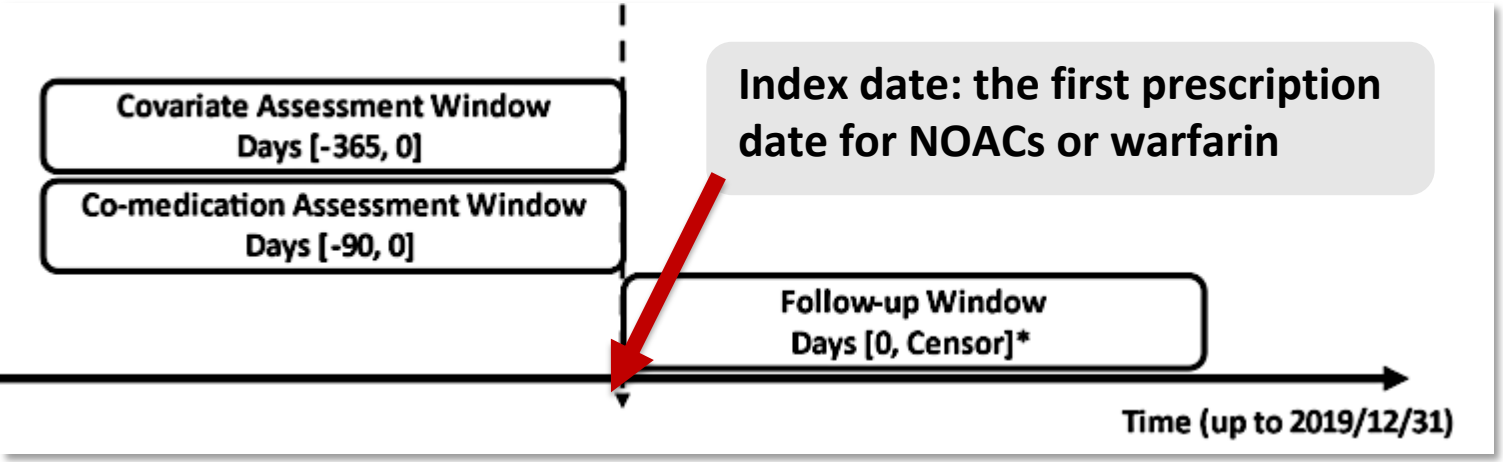
Yes | Can't tell | No

Appraisal (3)

3. Was the exposure accurately measured to minimize bias?

Prevention of immortal time bias (misclassification)

The drug index date was defined as the first prescription date for NOACs or warfarin. The follow-up period was from the drug index date to the first occurrence of study outcome (ILD), death, or end of the study (December 31, 2019), whichever occurred first. This study, similar to most trials,



Adherence?

Yes | Can't tell | No

Appraisal (4)

4. Was the outcome accurately measured to minimize bias?

Outcomes

The study outcome was new-onset idiopathic ILD (*ICD 9-CM* codes 515-516.9; *ICD-10-CM* codes J84-J84.9) with at least 1 principal inpatient or 2 outpatient diagnostic codes after the drug index date. The *ICD-9-CM* and *ICD-10-CM* codes indicating the diagnosis of idiopathic ILD were suggested by the American Thoracic Society in 2016 (eTable 1 in the Supplement).[14] To explore potential

American Lung Association.

To diagnose an ILD, your doctor will probably **order a chest X-ray or CT scan** to get a better look at your lungs. A lung function test may be used to measure your total lung capacity, which may have deteriorated due to the ILD.

Yes | Can't tell | No

Detection bias?

Appraisal (5)

5. (a) Have the authors identified all important confounding factors?

Dose, smoking, INR, TTR…etc

estimates. Second, different NOACs or warfarin had varying degrees of liver or kidney elimination; thus, the decision regarding the use of specific NOACs or warfarin may be guided by each patient's liver or kidney function. However, laboratory data were lacking in the NHIRD.

5. (b) Have they taken account of the confounding factors in the design and/or analysis?

Design

- ✓ Specification (criteria)
- ✓ Propensity score

Analysis

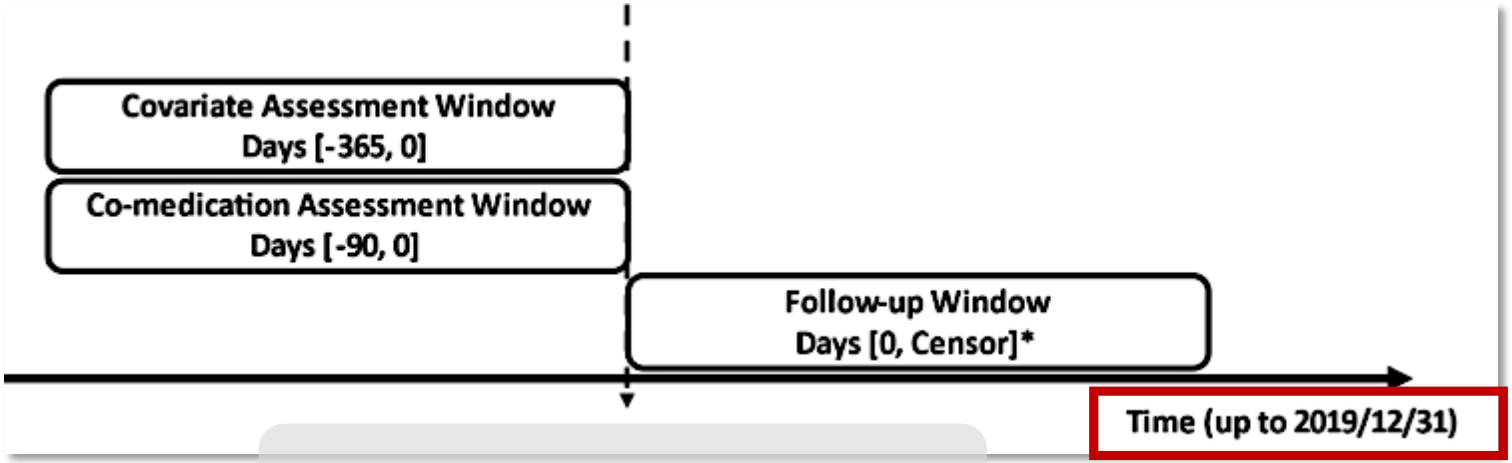
- ✓ Stratification (subgroup)
- ✓ Sensitivity test
- ✓ Adjustment (COX model)

Yes Can't tell No

Appraisal (6)

6. (a) Was the follow up of subjects complete enough?

6. (b) Was the follow up of subjects long enough?



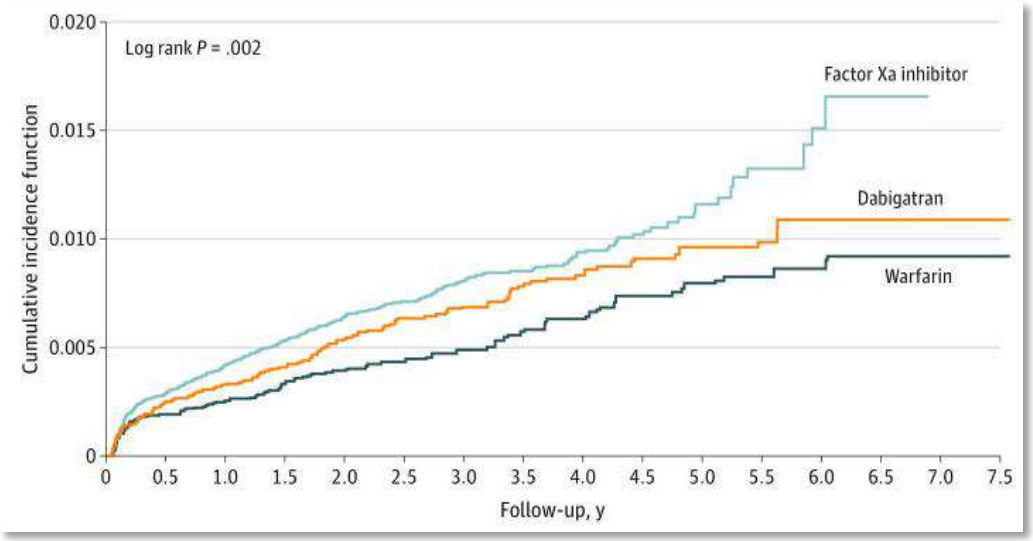
Index date: 2010/1-2017/12

To the first occurrence of ILD, death, or end of the study

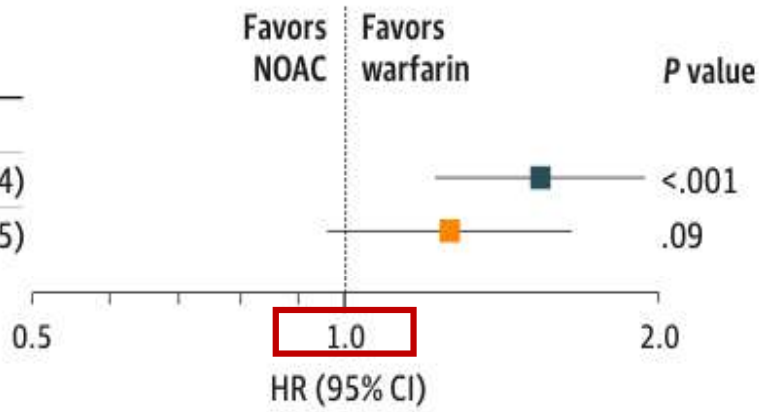
Yes Can't tell No

Appraisal (7)

7. What are the results of this study?

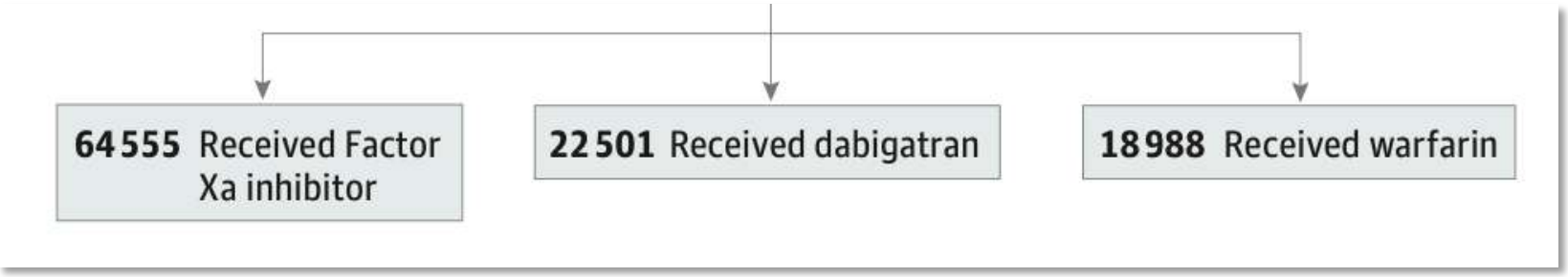


Primary outcome	NOAC, rate per 100 patient-years	Warfarin, rate per 100 patient-years	HR (95% CI)
Interstitial lung disease			
Factor Xa inhibitor	0.29	0.17	1.54 (1.22-1.94)
Dabigatran	0.22	0.17	1.26 (0.96-1.65)



Appraisal (8)

8. How precise are the results?



Sufficient sample size

Primary outcome	NOAC, rate per 100 patient-years	Warfarin, rate per 100 patient-years	HR (95% CI)
Interstitial lung disease			
Factor Xa inhibitor	0.29	0.17	1.54 (1.22-1.94)
Dabigatran	0.22	0.17	1.26 (0.96-1.65)

Acceptable range of confidence interval

Appraisal (9)

9. Do you believe the results?

- Sufficient sample size
- Small range of confidence interval
- Main analysis (overall) was consistent with each of FXa inhibitors in hazard ratio and rage of 95% CI
- Five sensitivity analysis enhanced the robustness of result
- Appropriate methodology in statistical analysis

Yes Can't tell No

Appraisal (10)

10. Can the results be applied to the local population?

Data source: NHIRD

An insured population of more than 22 million people, that is, more than 99% Taiwan population, in the NHI program was established by the

NHI database includes information on birth date, sex, institution codes, type and date of care for inpatient services, diagnoses based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and health care expenditure.

Yes Can't tell No

Appraisal (11)

11. Do the results of this study fit with other available evidence ?

Development of Interstitial Lung Disease after Initiation of Apixaban Anticoagulation Therapy

- **Case report from Japan**

Tomari S et al., J Stroke Cerebrovasc Dis. 2016

Drug Safety (2020) 43:1191–1194
https://doi.org/10.1007/s40264-020-00990-9

RESEARCH LETTER

Direct Oral Anticoagulants and Interstitial Lung Disease: Emerging Clues from Pharmacovigilance

- **Pharmacovigilance disproportionality analysis**

Raschi E et al., Drug Saf. 2020

Yes Can't tell No

Appraisal (12)

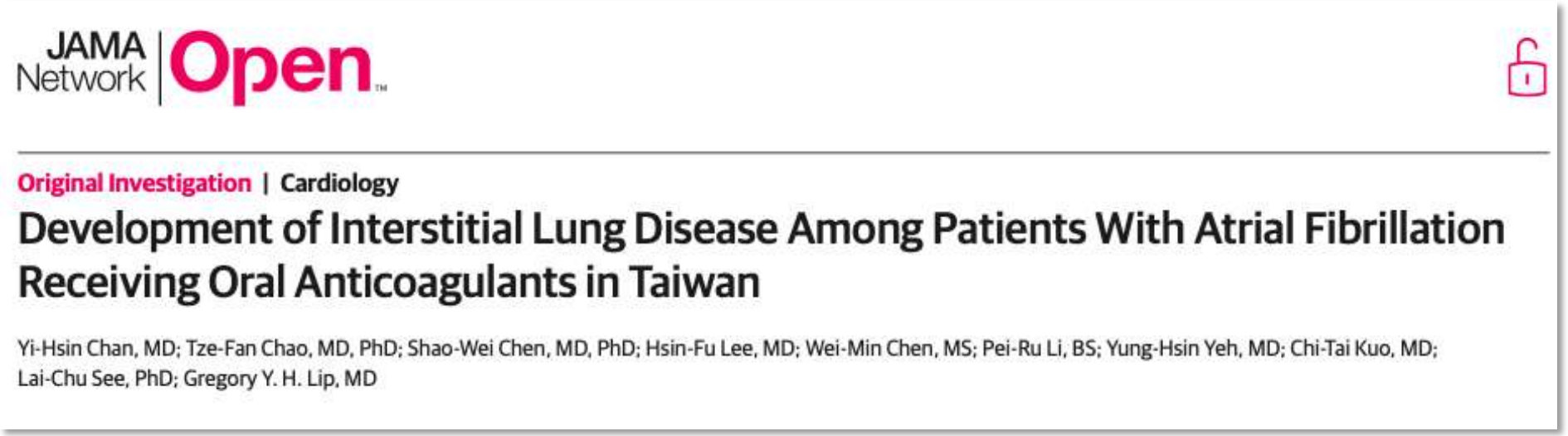
12. What are the implication of this study for practice?

> **Meaning** Findings of the study suggest that physicians should be vigilant in monitoring for any potential adverse lung outcomes of FXa inhibitors.

- Monitoring potential development of ILD in NVAF patients receiving FXa inhibitors
- Especially those co-prescribed with amiodarone

ILD: Interstitial lung disease, FXa: activated coagulation factor X, NVAF: Nonvalvular Atrial Fibrillation

Journal Club


JAMA Network | Open

Original Investigation | Cardiology

Development of Interstitial Lung Disease Among Patients With Atrial Fibrillation Receiving Oral Anticoagulants in Taiwan

Yi-Hsin Chan, MD; Tze-Fan Chao, MD, PhD; Shao-Wei Chen, MD, PhD; Hsin-Fu Lee, MD; Wei-Min Chen, MS; Pei-Ru Li, BS; Yung-Hsin Yeh, MD; Chi-Tai Kuo, MD; Lai-Chu See, PhD; Gregory Y. H. Lip, MD

JAMA Netw Open. 2022 Nov 1;5(11):e2243307.

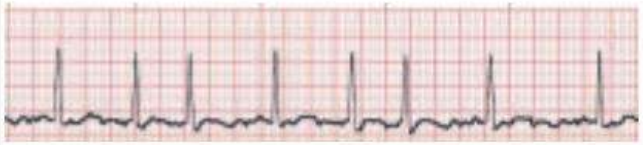
Impact factor: 13.353 (2021)

Thanks For Your Attention

Nonvalvular Atrial Fibrillation

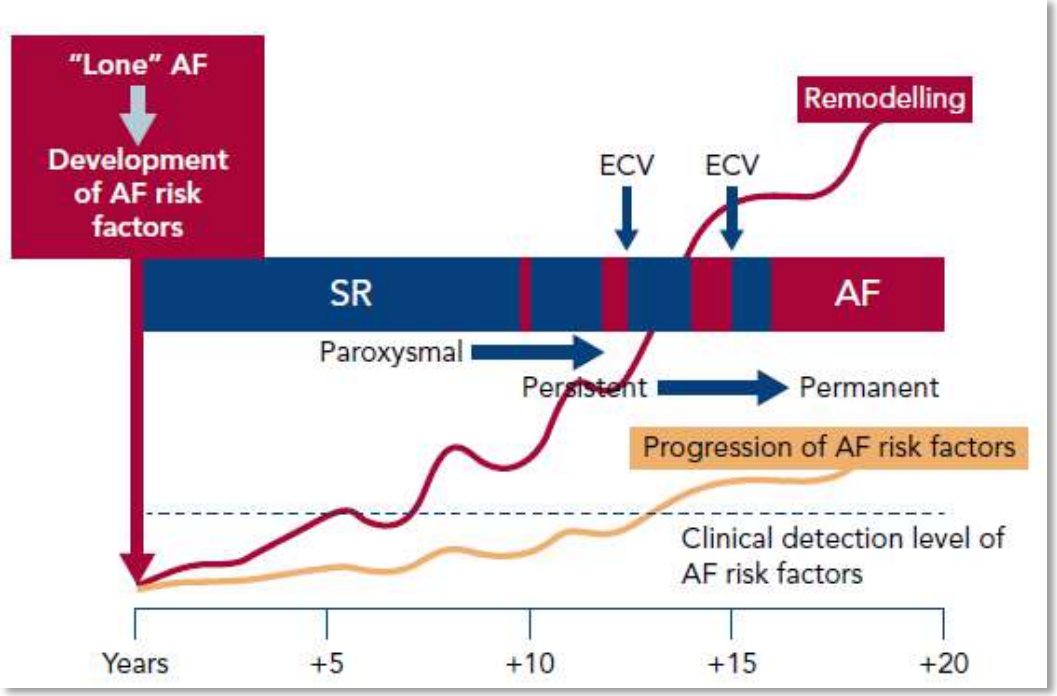
ECG showing AF
(physician-confirmed)

- Entire conventional 12-lead ECG, or
- An ECG strip with ≥ 30 sec of AF (including wearable-recorded ECGs)



- AF symptoms present or absent

Definition
A supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently **ineffective atrial contraction**

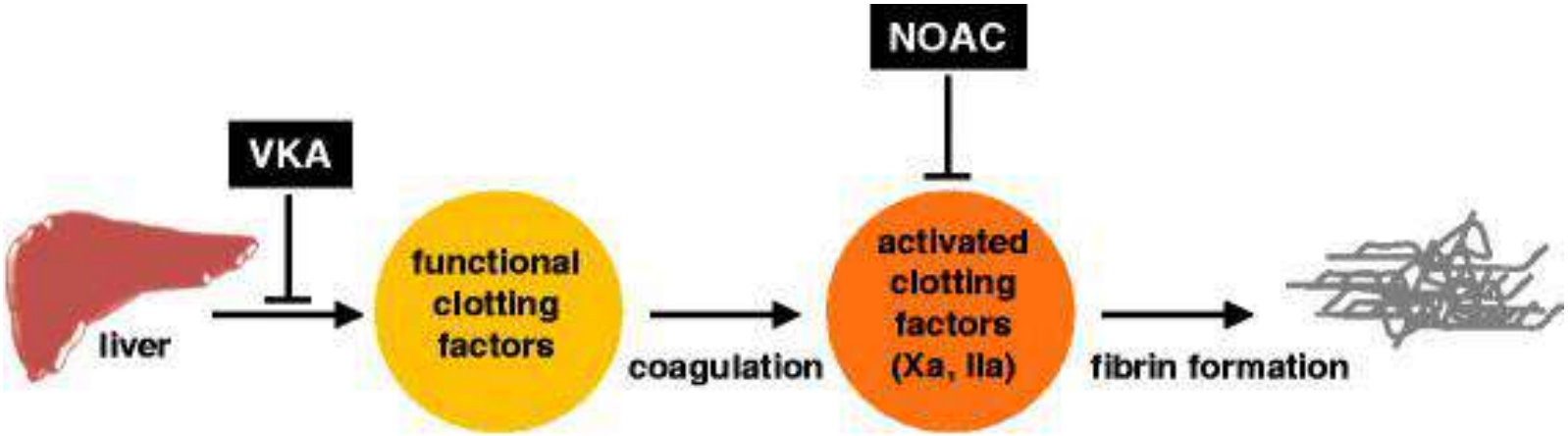


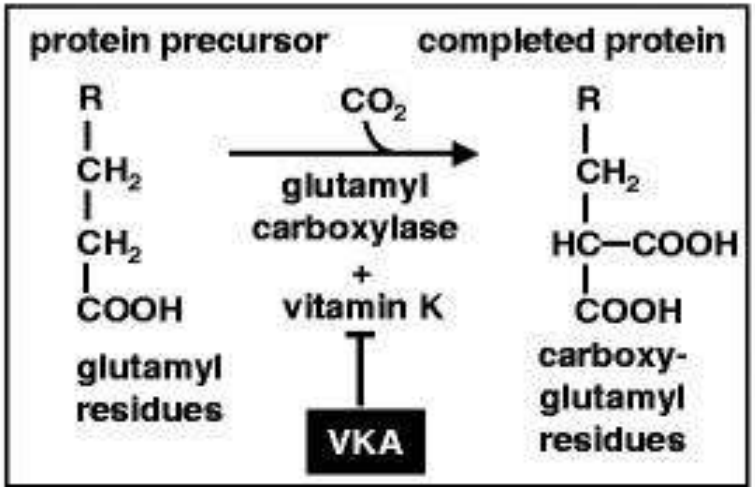
ECG: electrocardiogram, AF: Atrial Fibrillation, SR: sinus rhythm

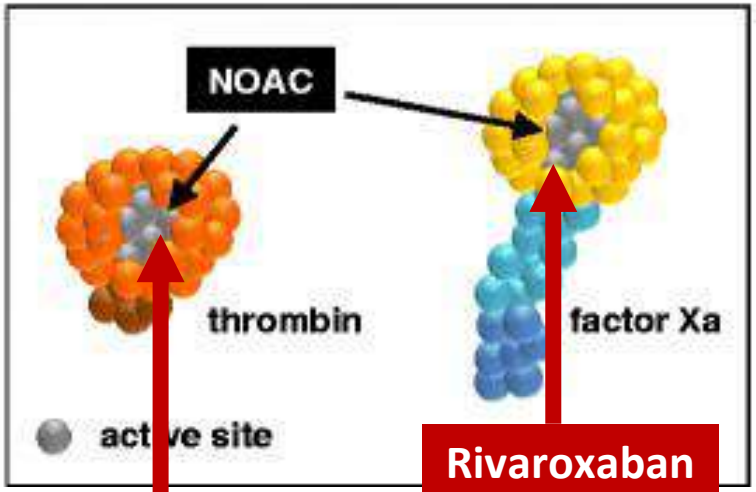
2020 ESC Guidelines for Management of Atrial Fibrillation.

Brandes A et al., Arrhythm Electrophysiol Rev. 2018
2016 Guidelines of the THRS and the TSOC for the management of AF

Anticoagulant Use in NVAF







Brinkman HJ et al., Thromb J. 2015

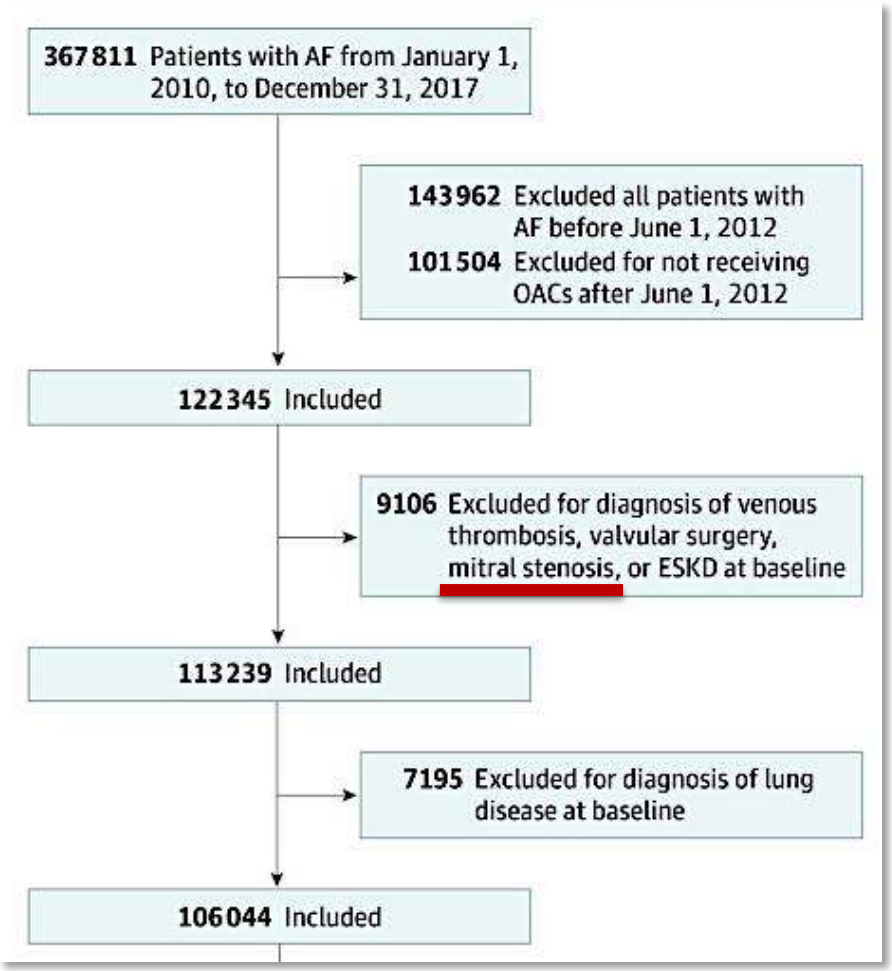
Introduction

Table 13 **Drugs for rate control in AF[a]**

	Intravenous administration	Usual oral maintenance dose	Contraindicated
Beta-blockers[b]			
Metoprolol tartrate	2.5 - 5 mg i.v. bolus; up to 4 doses	25 - 100 mg *b.i.d.*	In case of asthma use beta-1-blockers Contraindicated in acute HF and history of severe bronchospasm
Metoprolol XL (succinate)	N/A	50 - 400 mg *o.d.*	
Bisoprolol	N/A	1.25 - 20 mg *o.d.*	
Atenolol[c]	N/A	25 - 100 mg *o.d.*	
Esmolol	500 µg/kg i.v. bolus over 1 min; followed by 50 - 300 µg/kg/min	N/A	
Landiolol	100 µg/kg i.v. bolus over 1 min, followed by 10 - 40 µg/kg/min; in patients with cardiac dysfunction: 1 - 10 µg/kg/min	N/A	
Nebivolol	N/A	2.5 - 10 mg *o.d.*	
Carvedilol	N/A	3.125 - 50 mg *b.i.d.*	
Non-dihydropyridine calcium channel antagonists			
Verapamil	2.5 - 10 mg i.v. bolus over 5 min	40 mg b.i.d. to 480 mg (extended release) o.d.	Contraindicated in HFrEF Adapt doses in hepatic and renal impairment
Diltiazem	0.25 mg/kg i.v. bolus over 5 min, then 5 - 15 mg/h	60 mg t.i.d. to 360 mg (extended release) o.d.	

Exclusion Criteria

Recommendations	Class[a]	Level[b]
Anticoagulation		
Long-term treatment with an oral anticoagulant is recommended in all patients with AF, HF, and CHA_2DS_2-VASc score ≥2 in men or ≥3 in women.[7]	I	A
DOACs are recommended in preference to VKAs in patients with HF, except in those with moderate or severe mitral stenosis or mechanical prosthetic heart valves.[528,558]	I	A
Long-term treatment with an oral anticoagulant should be considered for stroke prevention in AF patients with a CHA_2DS_2-VASc score of 1 in men or 2 in women.[7,559]	IIa	B



Limitation NHIRD

2021 ESC Guidelines forthe diagnosis and treatment of acute and chronic heart failure (12. cardiovascular comorbidities)

Covariates

Table 10 Clinical risk factors in the HAS-BLED score[395]

Risk factors and definitions		Points awarded
H	**Uncontrolled hypertension** SBP >160 mmHg	1
A	**Abnormal renal and/or hepatic function** Dialysis, transplant, serum creatinine >200 µmol/L, cirrhosis, bilirubin > × 2 upper limit of normal, AST/ALT/ALP >3 × upper limit of normal	1 point for each
S	**Stroke** Previous ischaemic or haemorrhagic[a] stroke	1
B	**Bleeding history or predisposition** Previous major haemorrhage or anaemia or severe thrombocytopenia	1
L	**Labile INR[b]** TTR <60% in patient receiving VKA	1
E	**Elderly** Aged >65 years or extreme frailty	1
D	**Drugs or excessive alcohol drinking** Concomitant use of antiplatelet or NSAID; and/or excessive[c] alcohol per week	1 point for each
Maximum score		**9**

Covariates after PSSW

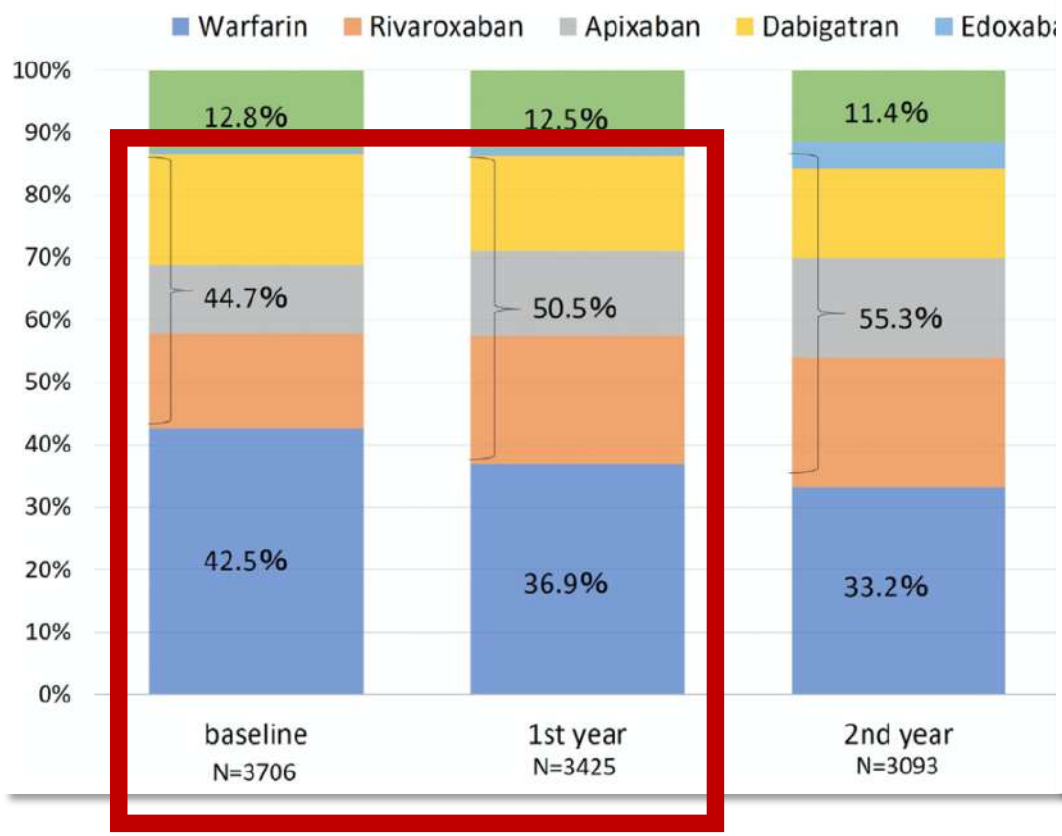
	Factor Xa inhibitor	Dabigatran	Warfarin	ASMD	
				Factor Xa inhibitor vs. Warfarin	Dabigatran vs. Warfarin
	(n = 64,393.72)	(n = 22,178.67)	(n = 18,469.65)		
Age					
(mean ± STD)	73.6±11.6	73.5±11.4	73.3±12.2	0.0265	0.0195
<65	14318.70 (22.24%)	4890.67 (22.05%)	4160.75 (22.53%)	0.0282	0.0282
65-74	18435.32 (28.63%)	6372.68 (28.73%)	5143.34 (27.85%)		
75-84	20559.84 (31.93%)	7103.54 (32.03%)	5905.56 (31.97%)		
>85	11079.86 (17.21%)	3811.78 (17.19%)	3260.00 (17.65%)		
Male	36421.26 (56.56%)	12599.74 (56.81%)	10398.16 (56.30%)	0.0053	0.0104
CHA_2DS_2-VASc (mean ± STD)	3.2±1.7	3.2±1.7	3.2±1.7	0.0038	0.0037
HAS-BLED (mean ± STD)	2.5±1.2	2.5±1.2	2.5±1.2	0.0336	0.0285
Hypertension	32361.67 (50.26%)	11071.96 (49.92%)	9214.61 (49.89%)	0.0074	0.0006
Diabetes mellitus	22339.79 (34.69%)	7703.44 (34.73%)	6430.42 (34.82%)	0.0026	0.0018
Dyslipidemia	27326.59 (42.44%)	9346.67 (42.14%)	7687.20 (41.62%)	0.0167	0.0107
Chronic live disease	5333.76 (8.28%)	1820.47 (8.21%)	1506.09 (8.15%)	0.0047	0.0020
Chronic kidney disease	10034.06 (15.58%)	3407.56 (15.36%)	2936.50 (15.90%)	0.0088	0.0149
Gout	9672.22 (15.02%)	3290.48 (14.84%)	2797.60 (15.15%)	0.0036	0.0088
Congestive heart failure	5566.95 (8.65%)	1873.72 (8.45%)	1676.50 (9.08%)	0.0153	0.0225
Chronic ischemic heart disease	6651.41 (10.33%)	2271.33 (10.24%)	1900.64 (10.29%)	0.0013	0.0016
Stroke	11992.68 (18.62%)	4116.23 (18.56%)	3399.75 (18.41%)	0.0056	0.0040
Cancer	6335.71 (9.84%)	2142.37 (9.66%)	1825.70 (9.88%)	0.0015	0.0077
Rheumatoid arthritis	209.77 (0.33%)	65.86 (0.30%)	47.37 (0.26%)	0.0129	0.0078
PCI	4146.51 (6.44%)	1401.84 (6.32%)	1173.05 (6.35%)	0.0036	0.0013
CABG	365.05 (0.57%)	103.56 (0.47%)	102.00 (0.55%)	0.0020	0.0121
History of bleeding	991.11 (1.54%)	328.14 (1.48%)	300.86 (1.63%)	0.0072	0.0122

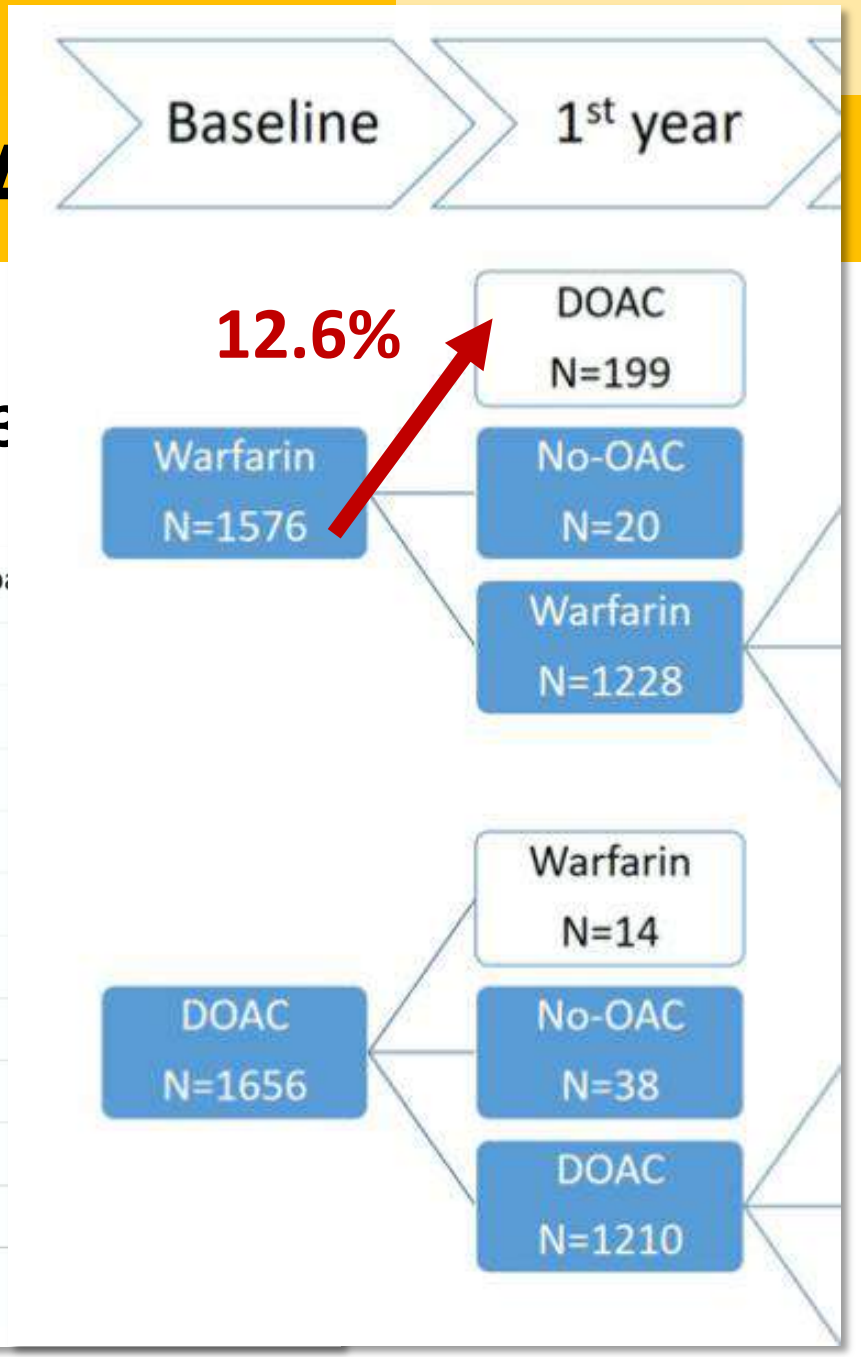
Covariates after PSSW

	Factor Xa inhibitor	Dabigatran	Warfarin	ASMD	
				Factor Xa inhibitor vs. Warfarin	Dabigatran vs. Warfarin
	(n = 64,393.72)	(n = 22,178.67)	(n = 18,469.65)		
Use of NSAIDs	15909.02 (24.71%)	5460.48 (24.62%)	4548.21 (24.63%)	0.0019	0.0001
Use of PPI	7653.56 (11.89%)	2584.31 (11.65%)	2197.10 (11.90%)	0.0003	0.0076
Use of H_2 blocker	20365.21 (31.63%)	7044.47 (31.76%)	5931.67 (32.12%)	0.0106	0.0077
Use of ACEI or ARB	37938.29 (58.92%)	13069.26 (58.93%)	10936.28 (59.21%)	0.0061	0.0059
Use of beta-blocker	38981.94 (60.54%)	13392.62 (60.39%)	11195.55 (60.62%)	0.0016	0.0048
Use of verapamil or diltiazem	14689.91 (22.81%)	5005.83 (22.57%)	4282.69 (23.19%)	0.0090	0.0148
Use of statin	21675.78 (33.66%)	7433.07 (33.51%)	6037.39 (32.69%)	0.0208	0.0177
Use of antiplatelet	34701.04 (53.89%)	12004.07 (54.12%)	10132.04 (54.86%)	0.0196	0.0149
Use of amiodarone	20276.05 (31.49%)	6910.87 (31.16%)	5911.67 (32.01%)	0.0113	0.0184
Use of dronedarone	2032.89 (3.16%)	656.91 (2.96%)	560.31 (3.03%)	0.0072	0.0043
Use of chemotherapy	913.69 (1.42%)	291.56 (1.31%)	257.77 (1.40%)	0.0020	0.0071
Use of target therapy	822.63 (1.28%)	260.13 (1.17%)	219.26 (1.19%)	0.0082	0.0013
Use of methotrexate	174.96 (0.27%)	52.40 (0.24%)	45.92 (0.25%)	0.0046	0.0025
Use of anti-TNF agent	34.71 (0.05%)	12.13 (0.05%)	6.53 (0.04%)	0.0088	0.0092
Use of steroid	1669.95 (2.59%)	542.90 (2.45%)	497.37 (2.69%)	0.0063	0.0156
Use of quinidine	73.58 (0.11%)	22.60 (0.10%)	18.90 (0.10%)	0.0037	0.0001
Use of rifampicin	191.63 (0.30%)	59.22 (0.27%)	54.59 (0.30%)	0.0004	0.0054
Use of macrolides	1428.78 (2.22%)	466.90 (2.11%)	420.71 (2.28%)	0.0040	0.0119
Use of anti-fungal agent	565.49 (0.88%)	184.01 (0.83%)	168.97 (0.91%)	0.0039	0.0093

Sensitivity A

Changes in the proportions of anticoagulants from baseline to year 3 (Japan data)





Miyazaki S et al., J Cardiol. 2022

Diagnosis of Idiopathic Pulmonary Fibrosis

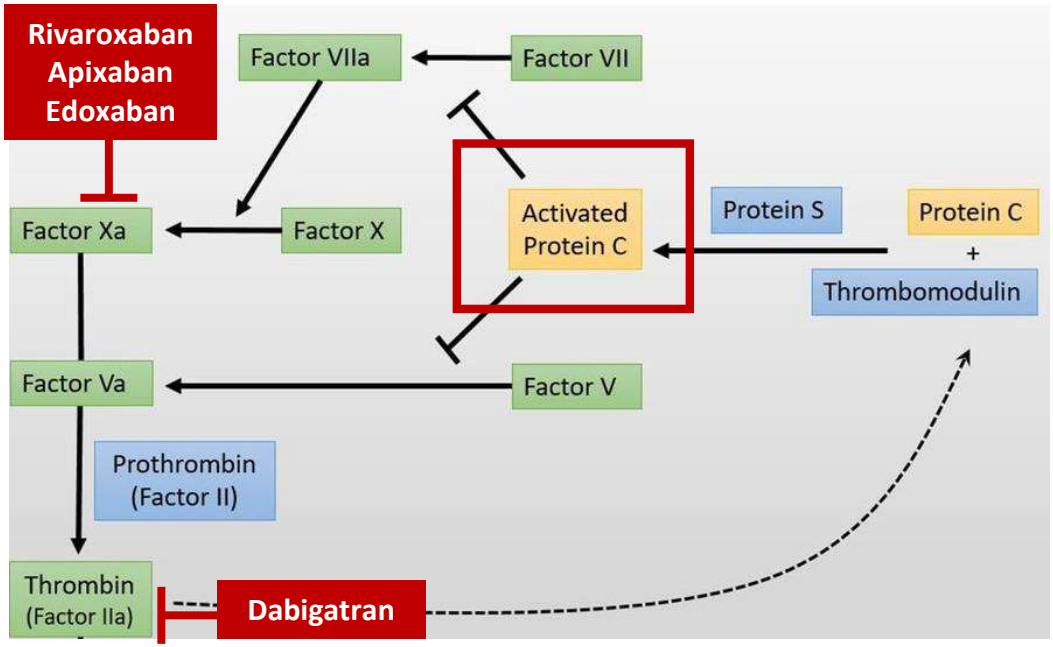
IPF suspected*		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP	Alternative diagnos
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable	IPF	IPF	IPF (Likely)**	Non-IPF dx
	Indeterminate for UIP	IPF	IPF (Likely)**	Indeterminate for IPF ***	Non-IPF dx
	Alternative diagnos	IPF (Likely)** /non-IPF dx	Non-IPF dx	Non-IPF dx	Non-IPF dx

- Moderate to severe traction bronchiectasis/bronchiolectasis in a man over aged 50 or in a woman over aged 60
- Extensive (0.30%) reticulation on HRCT scan and an age >70 years
- Increased neutrophils and/or absence of lymphocytosis in BAL fluid
- MDD reaches a confident diagnosis of IPF

- Without an adequate biopsy, unlikely to be IPF
- With an adequate biopsy, may be reclassified to a more specific diagnosis after MDD and/or additional consultation

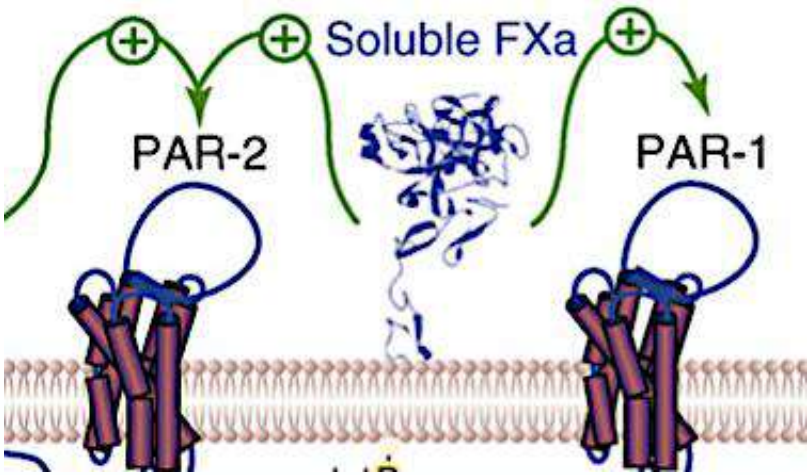
MDD: multi-disciplinary discussion, HRCT: high-resolution computed tomography, IPF: Idiopathic pulmonary fibrosis, UIP: usual interstitial pneumonia

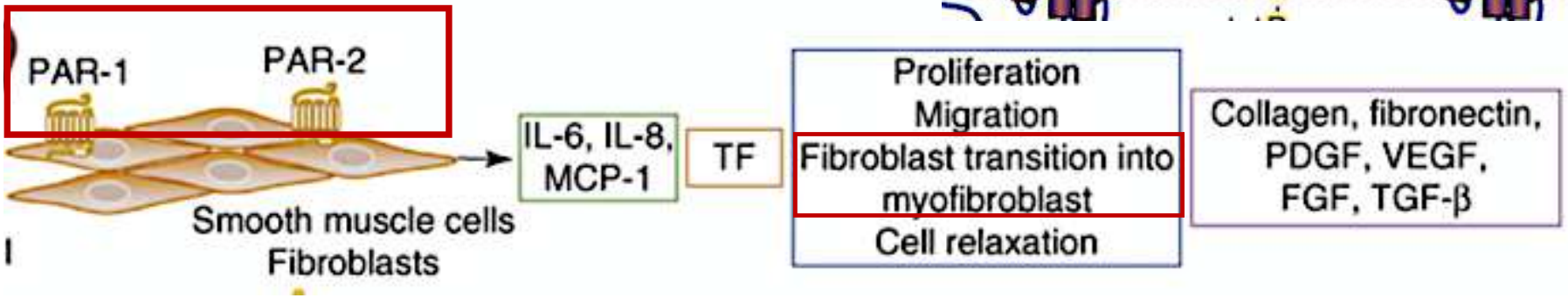
Controversial Mechanism?



Lai J et al., BMJ Case Rep. 2017

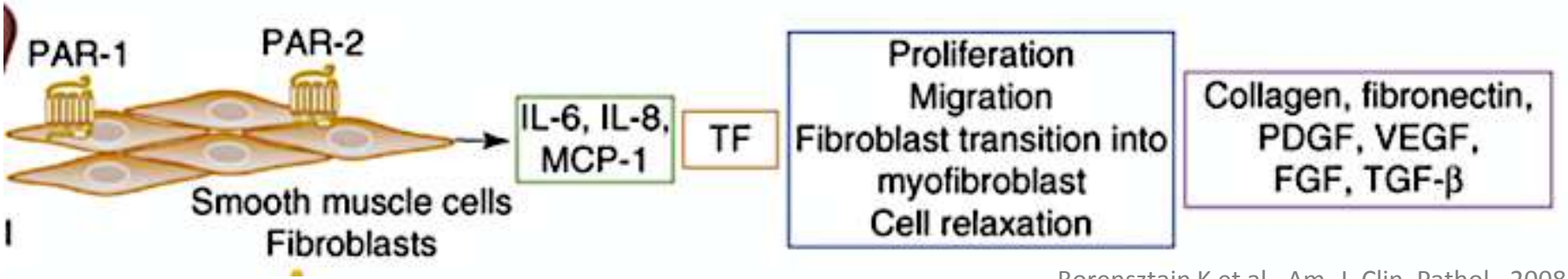
Controversial?





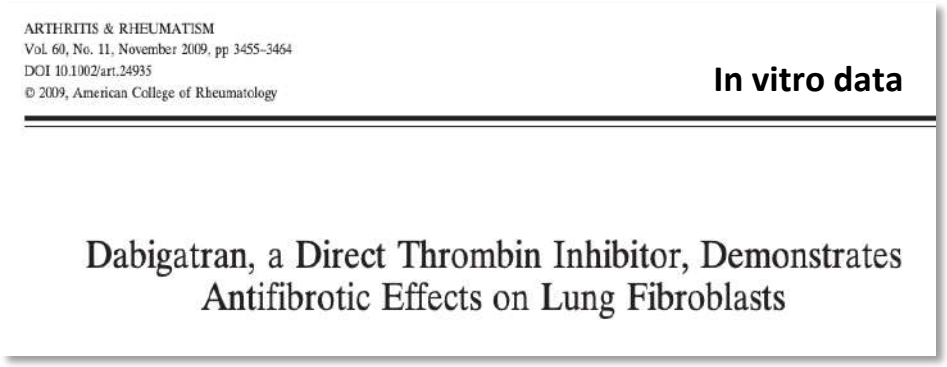
Borensztajn K et al., Am. J. Clin. Pathol., 2008

Controversial Mechanism?



Borensztajn K et al., Am. J. Clin. Pathol., 2008

- PAR-1: The main receptor for thrombin
- PAR-2: As a key player in the progression of a wide pattern of pathologies at the fibro-proliferative interface


ARTHRITIS & RHEUMATISM
Vol. 60, No. 11, November 2009, pp 3455–3464
DOI 10.1002/art.24935
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In vitro data

Dabigatran, a Direct Thrombin Inhibitor, Demonstrates Antifibrotic Effects on Lung Fibroblasts

- When treated with dabigatran scleroderma lung myofibroblasts produce less CTGF, α-SMA, and collagen type I
- **Dabigatran** restrains important profibrotic events in lung fibroblasts and that this oral direct thrombin inhibitor warrants study as a **potential anti-fibrotic drug** for the treatment of fibrosing lung diseases

α-SMA: α-smooth muscle actin, CTGF: connective tissue growth factor

Bogatkevich GS et al., Arthritis Rheum. 2009

Management of Drug Induced ILD

Grade 2

RECOMMENDED

- Immediate **discontinuation of the anticancer drug**[f]
- **Steroid therapy**: 1-2 mg/kg/day prednisone or equivalent
- Consider antibiotic therapy when an overlapping infection cannot be excluded (fever, increased CRP and/or neutrophil counts)
- Consider TMP-SMX prophylaxis for opportunistic infections with high-dose steroids

Grade 3

RECOMMENDED IN REFRACTORY GRADE 2 AND IN GRADE 3 DIILD

- **Consider hospitalisation** and **oxygen therapy** until resolution of respiratory failure
- Timely and definitive **discontinuation of the anticancer drug**
- **Steroid therapy**: 1-2 mg/kg/day methylprednisolone or equivalent
- Consider antibiotic therapy when an overlapping infection cannot be excluded
- Consider TMP-SMX prophylaxis for opportunistic infections with high-dose steroids

Grade 4

RECOMMENDED

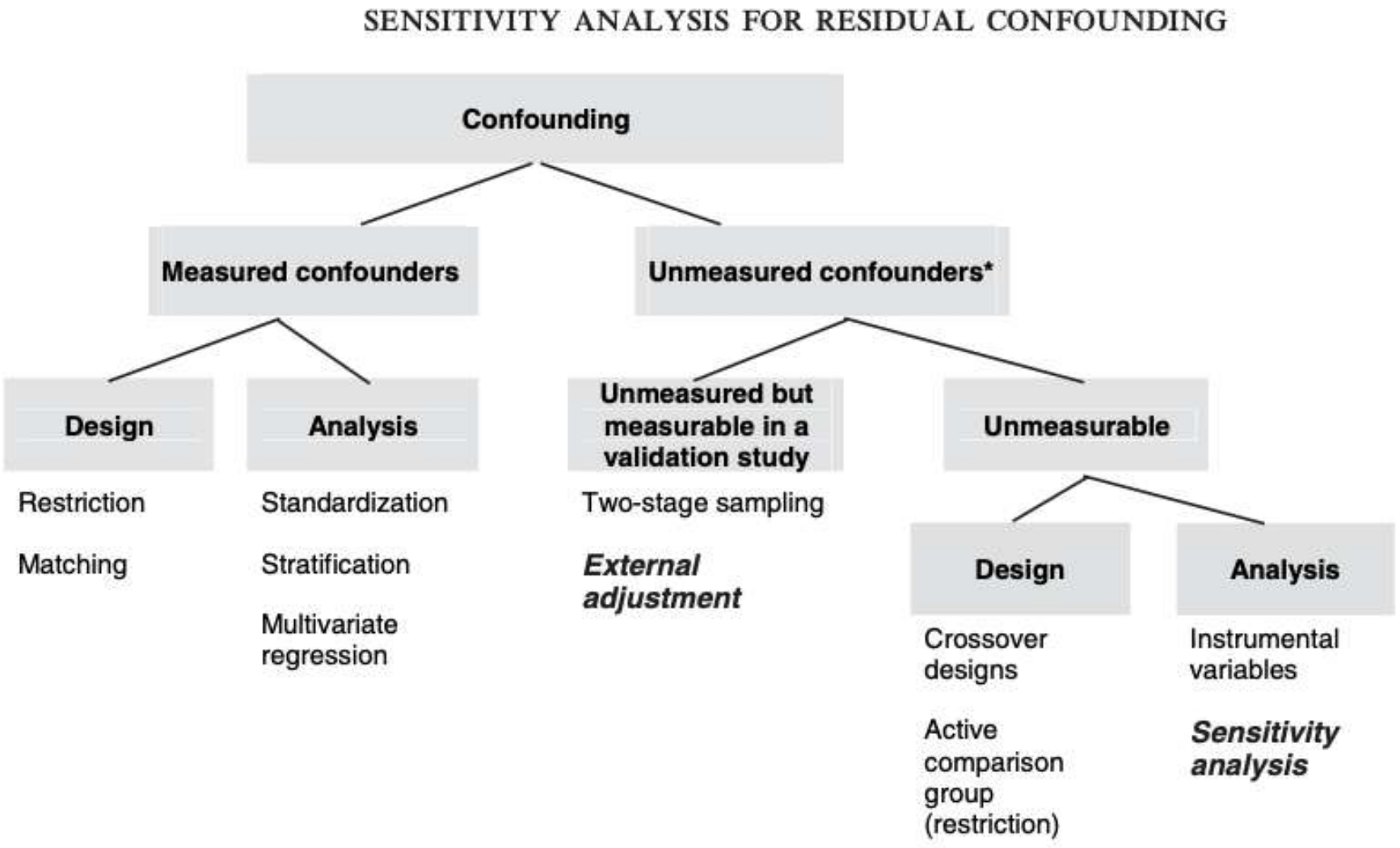
- **Hospitalization, oxygen therapy, supportive therapies**
- **Non-invasive or invasive mechanical ventilation** according to the patient's clinical conditions and the life expectancy associated with the underlying pathology
- Immediate and definitive **discontinuation of anticancer drug**
- **Steroid therapy:** 2 mg/kg/day intravenous (methyl)prednisolone or equivalent[g]
- Consider antibiotic therapy when an overlapping infection cannot be excluded
- TMP-SMX prophylaxis for opportunistic infections with high-dose steroids

[g]Duration of steroid therapy to be determined according to the evolution of the clinical-radiological course, considering a possible therapy extension for up to 6 months, including tapering

PULSE THERAPY TO BE CONSIDERED IN SEVERE CASES

Methylprednisolone 500-1000 mg/day
for 3 consecutive days
↓
Prednisolone 1-2 mg/kg/day
for 2-4 weeks
↓
Tapering

Appraisal (5)



Schneeweiss S et al., Pharmacoepidemiol Drug Saf. 2006