INDICAZIONI ALLA TERAPIA ANTICOAGULANTE NELLA FIBRILLAZIONE ATRIALE E PRINCIPALI CARATTERISTICHE DEGLI ANTICOAGULANTI ORALI DIRETTI (NOAC)

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ASL IMOLA

GLOBAL PREVALENCE OF A.F.

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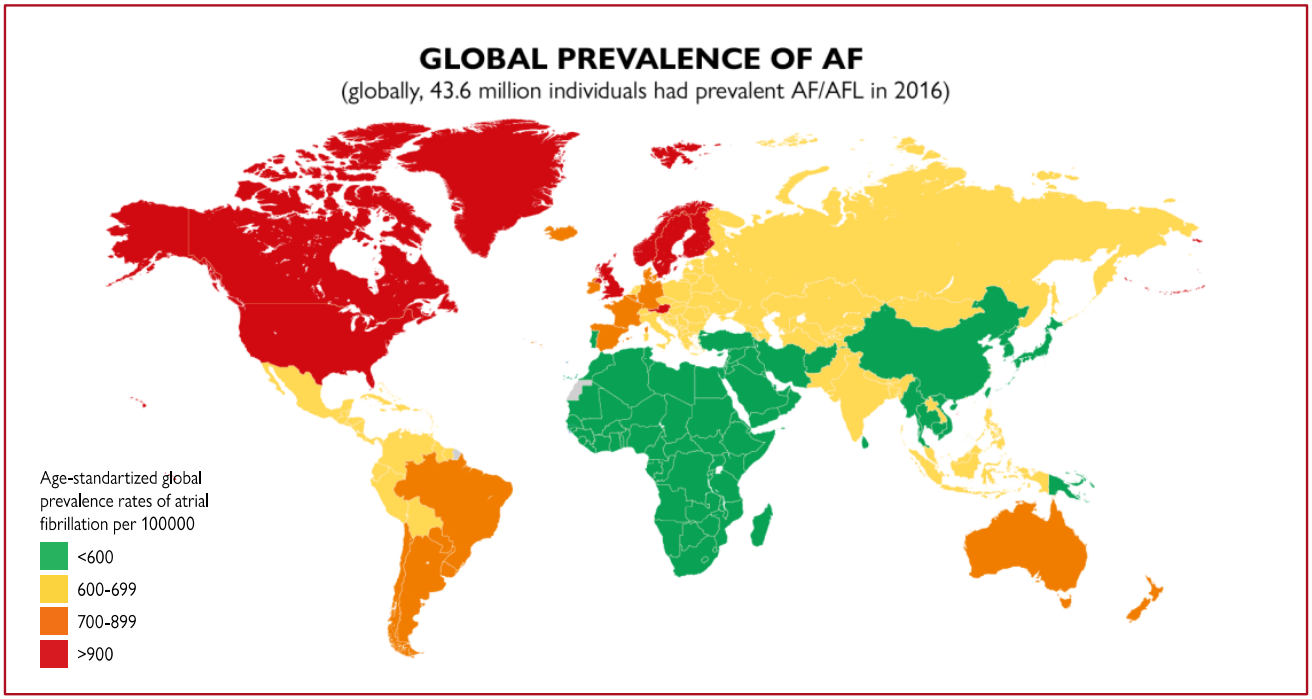
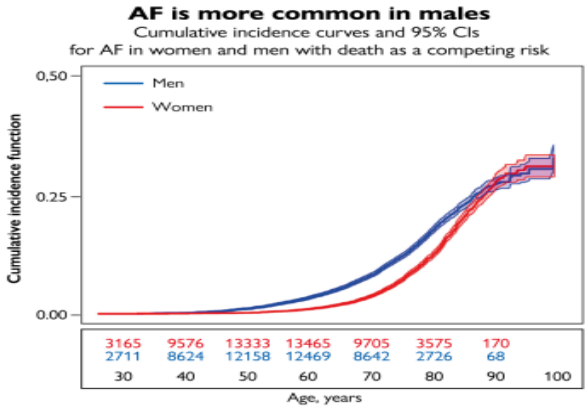


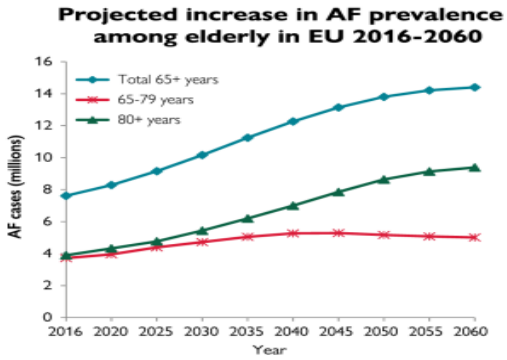
www.escardio.org/guidelines

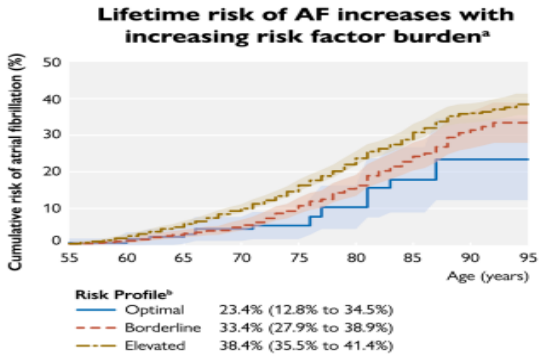
2020 ESC Guidelines for the diagnosis and management of atrial fibrillation
(European Heart Journal 2020-doi/10.1093/eurheartj/ehaa612)

LIFE TIME RISK AND PROJECTED RISE OF A.F.

AF prevalence in adults: 2% – 4% A 2.3 fold rise is expected







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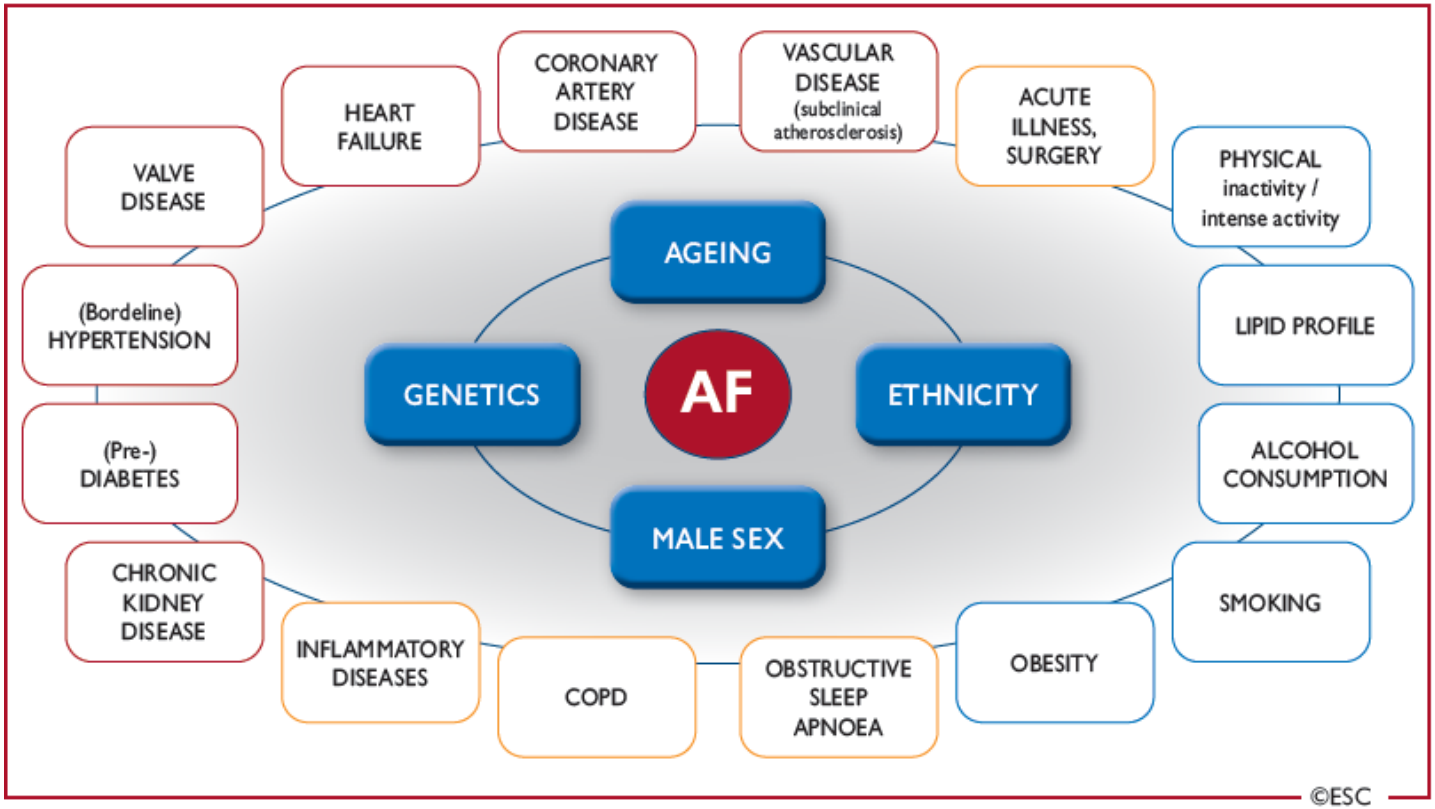
SUMMARY OF RISK FACTORS FOR INCIDENT A.F.



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2020 ESC Guidelines for the diagnosis and management of at
(European Heart Journal 2020-doi/10.1093/eurhe

Fibrillazione Atriale Classificazione

1. ***Di nuova insorgenza***: tutte le F.A. documentate per la prima volta

2. ***Ricorrente***: qualsiasi forma di recidiva di F.A.

3. ***Parossistica***: forme che terminano spontaneamente, generalmente entro 7 giorni (la maggior parte entro le prime 24-48 h)

4. ***Persistente***: forme di durata superiore ai 7 giorni o di durata minore ma che non si interrompono spontaneamente e che necessitano di interventi terapeutici (cardioversione farmacologica o elettrica) per la loro riconversione a ritmo sinusale

5. ***Persistente di lunga durata***: forme che durano più di un anno

6. ***Permanente***: forme nelle quali non sono stati effettuati tentativi di cardioversione o, se effettuati, non hanno avuto successo per mancato ripristino del r.s. o per recidive precoci dell'aritmia che sconsigliano ulteriori tentativi di cardioversione.

Le diverse forme non sono mutuamente esclusive nello stesso pz. e nel tempo ogni forma può virare in un'altra.

TYPES and TRIGGERS of ATRIAL FIBRILLATION

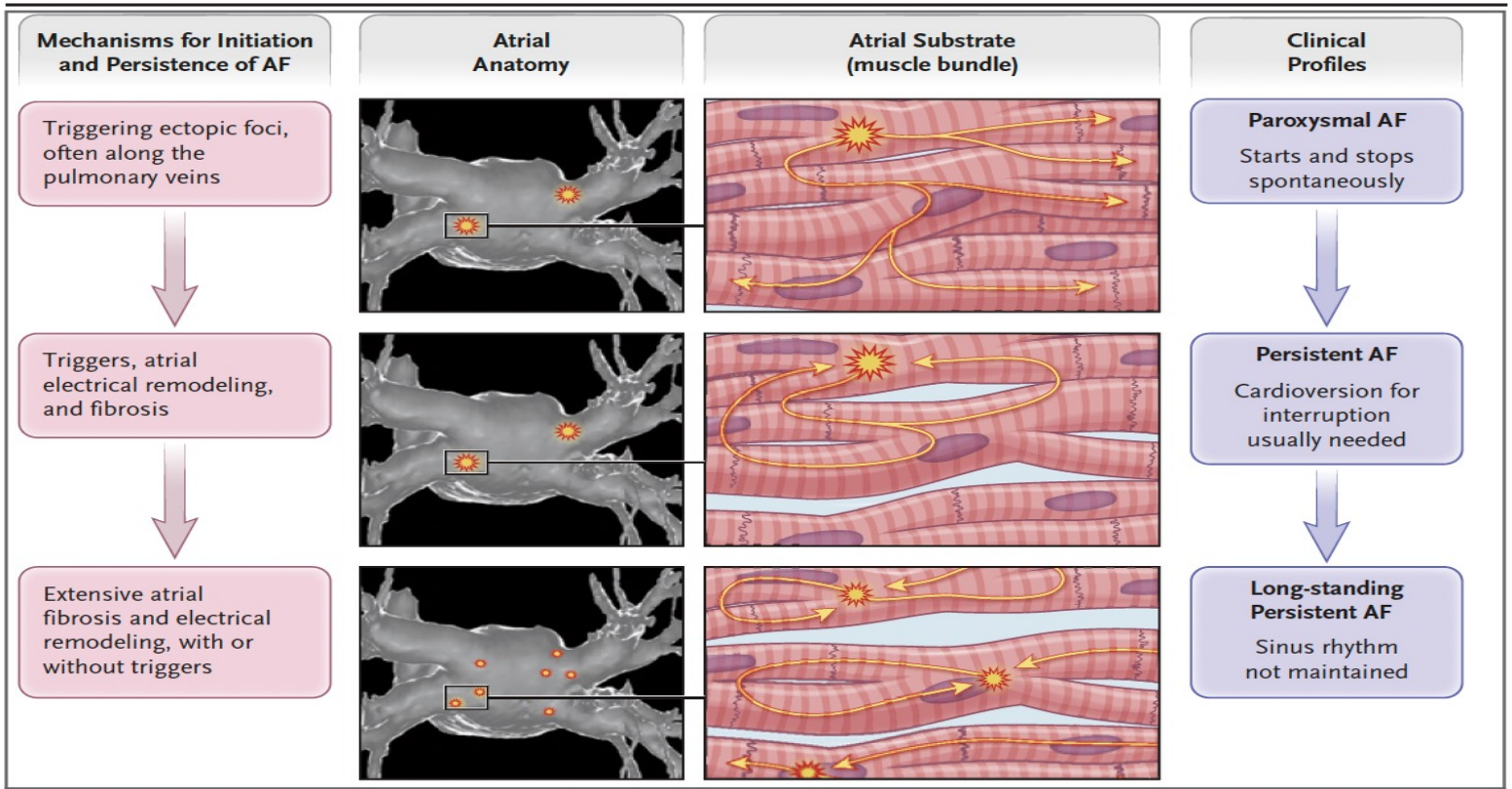

Figure 1. Types and Triggers of Atrial Fibrillation (AF).

Mechanisms for the initiation and persistence of AF and the left atrial anatomy are shown on the left. Clinical profiles of AF related to the underlying atrial substrate at the muscle-bundle level are shown on the right. Paroxysmal AF is associated with triggering foci that are most commonly located in sleeves of muscle along the pulmonary veins. Persistent AF is often characterized by some evidence of atrial remodeling with electrophysiological changes in the atrial myocytes, as well as fibrosis. Triggering foci are also present. In long-standing persistent AF, the atrial remodeling, including fibrosis, is more extensive and severe than in persistent AF.

Gregory F. Michaud, **NEJM 2021 384;4**

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DIAGNOSIS OF CLINICAL A.F.

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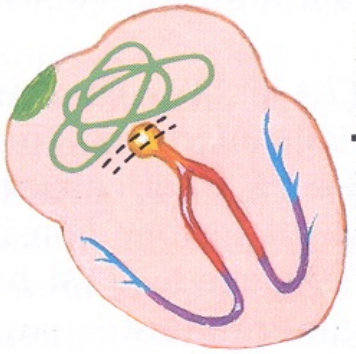
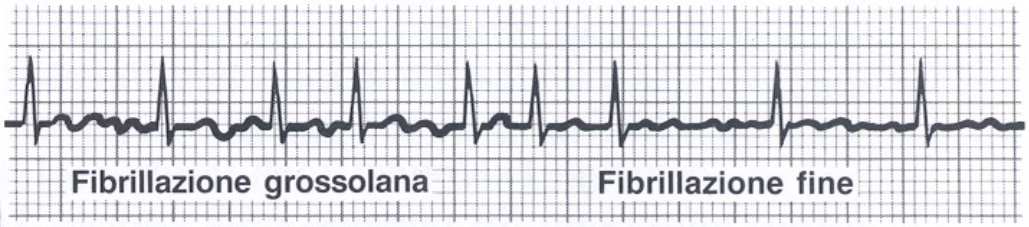
Recommendations	Class[a]	Level[b]
ECG documentation is required to establish the diagnosis of AF. • A standard 12-lead ECG recording or a single-lead ECG tracing of ≥30 s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF.[6]	I	B

J. Fibrillazione atriale

Gli impulsi viaggiano in modo caotico e casuale lungo gli atri





Linea basale finemente o grossolanamente irregolare; assenza di onde P.
Risposta ventricolare (QRS) irregolare, lenta o rapida

DIAGNOSIS OF AHRE/SUBCLINICAL A.F.

Clinical AF

Symptomatic or asymptomatic AF that is documented by surface ECG (ECG single tracing of at least 30 s or entire 12-lead ECG)

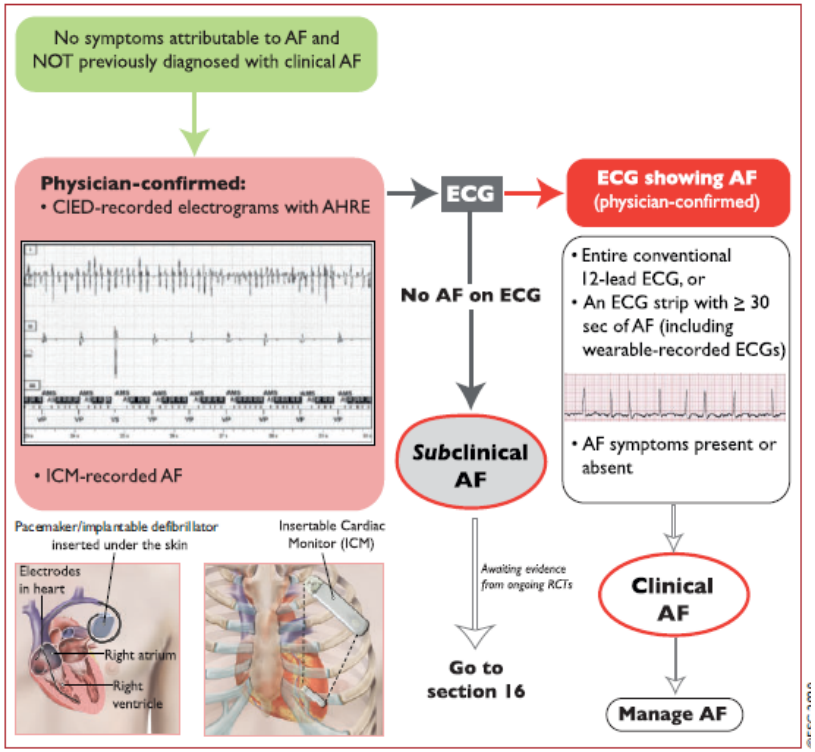
AHRE and subclinical AF

Refers to individuals without symptoms attributable to AF, in whom clinical AF is not previously detectedd (no ECG).

AHRE*: events fulfilling programmed or specified criteria for AHRE that are detected by CIEDs with an atrial lead allowing automated continuous monitoring of atrial rhythm and tracing storage. CIED recorded AHRE need to be visually inspected because some AHRE may be electrical artefacts/false positive.

Subclinical AF includes AHRE confirmed to be AF, AFL or an AT detected by CIED and confirmed by visually reviewed intracardiac electrograms or ECG recorded rhythm.

*Rate criterion for AHRE is ≥ 175 bpm; duration criterion for AHRE is set at ≥ 5 min



Hindricks G et al. Eur Heart J 2020; 42:373-498

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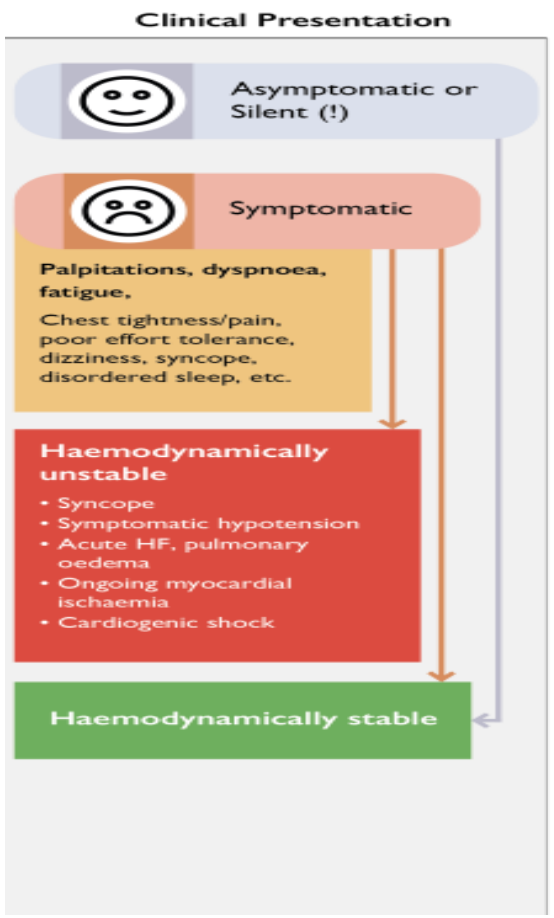
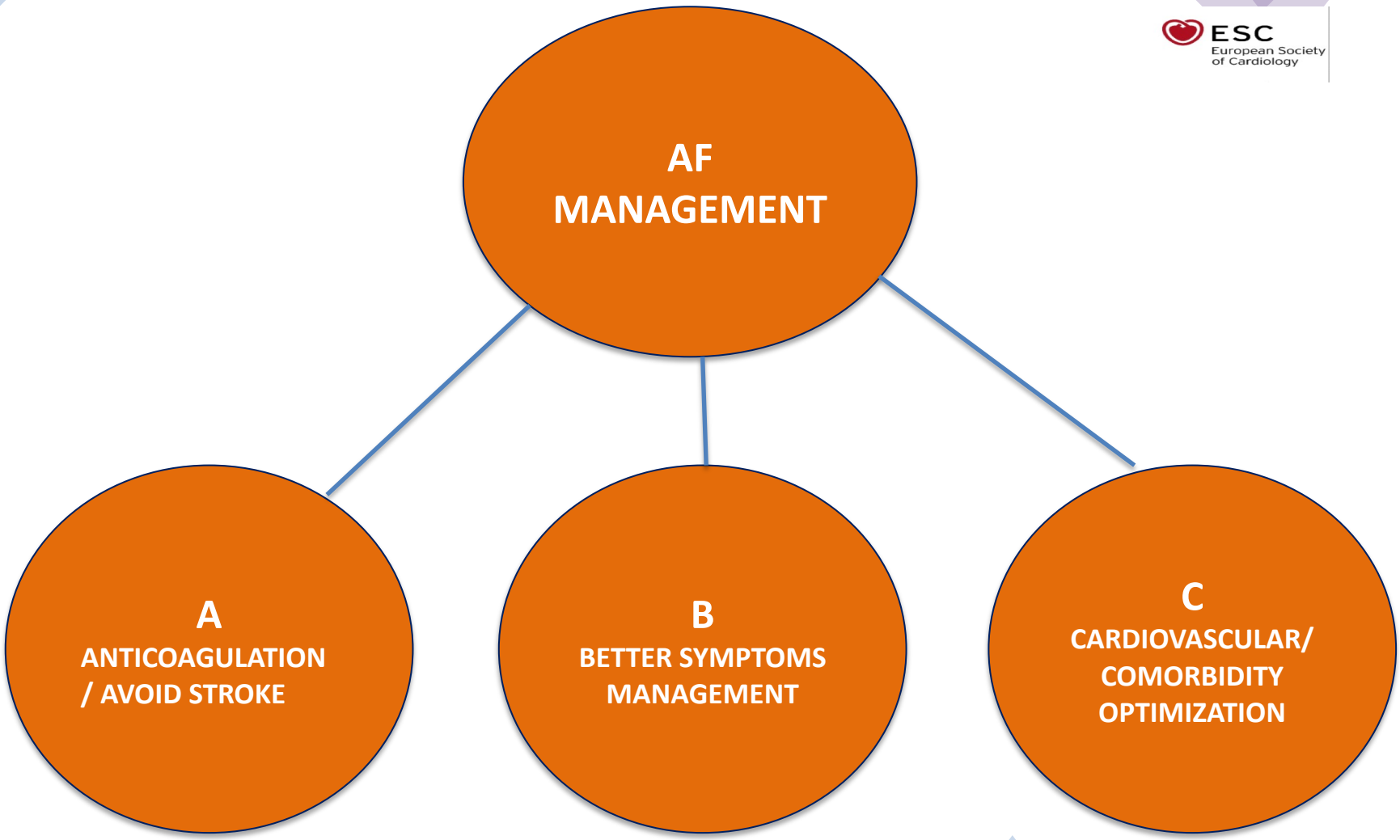
CLINICAL PRESENTATION OF A.F. / OUTCOMES



AF-related OUTCOMES

AF-Related Outcome	Frequency in AF	Mechanism(s)
Death	1.5-3.5 fold increase	Excess mortality related to: • HF, comorbidities • Stroke
Stroke	20-30% of all ischaemic strokes, 10% of cryptogenic strokes 3–5 fold increased risk of stroke	• Cardioembolic, or • Related to comorbid vascular atheroma
LV dysfunction / Heart failure	In 20-30% of AF patients	• Excessive ventricular rate • Irregular ventricular contractions • A primary underlying cause of AF
Cognitive decline / Vascular dementia	HR 1.4 / 1.6 (irrespective of stroke history)	• Brain white matter lesions, inflammation, • Hypoperfusion, • Micro-embolism
Depression	Depression in 16-20% (even suicidal ideation)	• Severe symptoms and decreased QoL • Drug side effects
Impaired quality of life	>60% of patients	• Related to AF burden, comorbidities, psychological functioning and medication • Distressed personality type
Hospitalizations	10-40% annual hospitalization rate	• AF management, related to HF, MI or AF related symptoms • Treatment-associated complications

GOALS OF A.F. MANAGEMENT
ABC HOLISTIC PATHWAY



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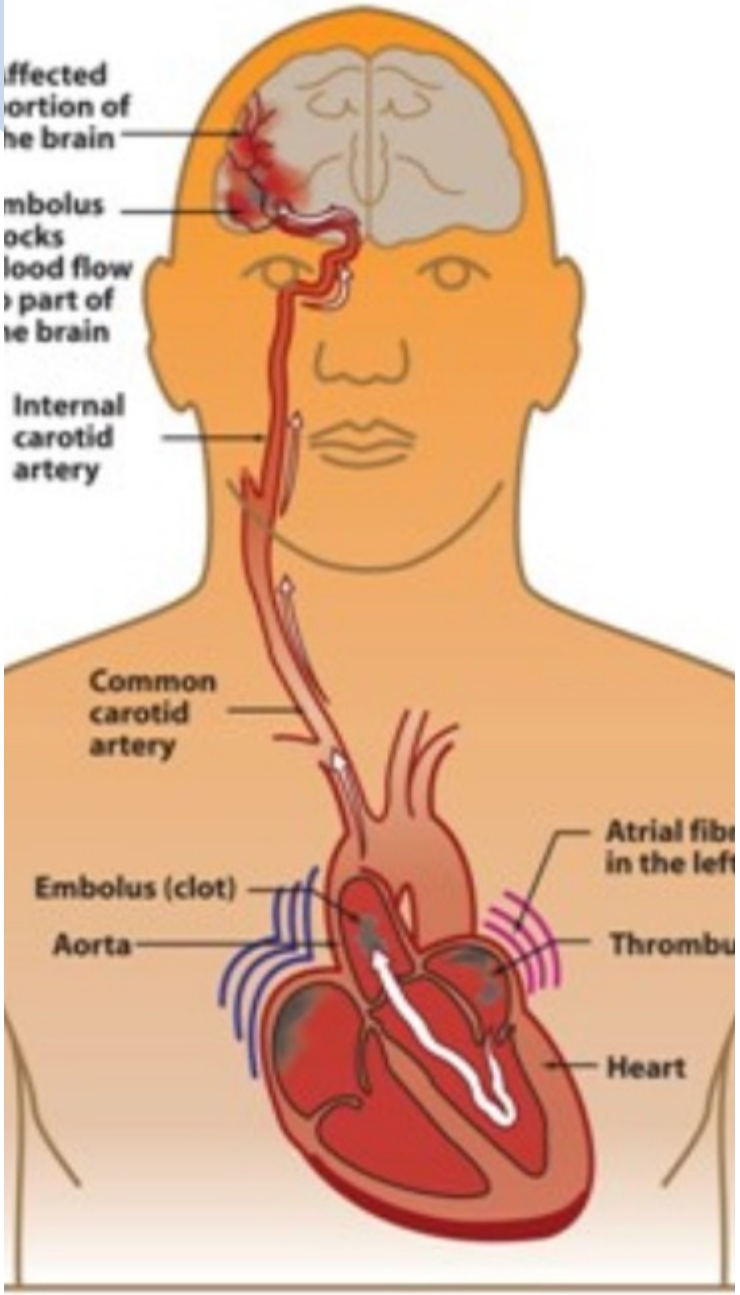


ATRIAL FIBRILLATION AND STROKE

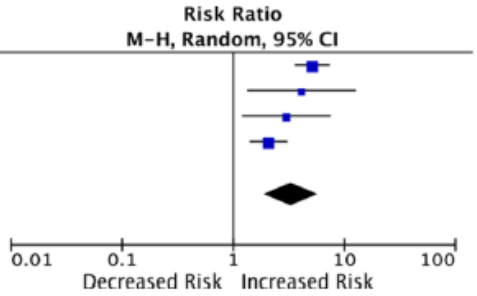
- Stroke is the most common and devasting complication of AF
- AF is associated with a 3–5 fold increased risk of stroke
- AF is an indipendent risk factor for stroke
- Approximately 20% - 30% of all strokes are caused by AF
- Risk of stroke increases with age
- Ischemic stroke associated with AF is often more severe than stroke from other etiology
- Stroke risk persists even in asymptomatic AF

Device-detected atrial high rate episodes and the risk of stroke/ thrombo-embolism and atrial fibrillation incidence: a systematic review and meta-analysis

AHRE: risk of Clinical AF (3.34X)

Study or Subgroup	AHRE Events	AHRE Total	No AHRE Events	No AHRE Total	Weight	Risk Ratio M-H, Random, 95% CI
Healey 2012	41	261	71	2319	33.1%	5.13 [3.57, 7.37]
Nishinarita 2019	8	34	4	70	15.3%	4.12 [1.33, 12.72]
Park 2021	34	344	5	152	19.2%	3.00 [1.20, 7.53]
Witt 2015	27	79	52	315	32.3%	2.07 [1.40, 3.07]
Total (95% CI)		**718**		**2856**	**100.0%**	**3.34 [1.89, 5.90]**
Total events	110		132			

Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 11.24$, df = 3 (P = 0.01); $I^2 = 73\%$
Test for overall effect: Z = 4.14 (P < 0.0001)

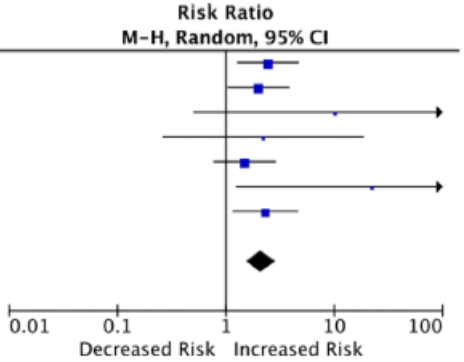


AHRE: risk of Stroke (2,13X)

Lower than the 5x reported with Clinical AF

Study or Subgroup	AHRE Events	AHRE Total	No AHRE Events	No AHRE Total	Weight	Risk Ratio M-H, Random, 95% CI
Healey 2012	11	261	40	2319	24.9%	2.44 [1.27, 4.70]
Li 2019	15	175	18	419	24.4%	2.00 [1.03, 3.87]
Nishinarita 2019	2	34	0	70	1.2%	10.14 [0.50, 205.62]
Park 2021	5	344	1	152	2.3%	2.21 [0.26, 18.75]
Sandgren 2018	13	125	20	286	24.1%	1.49 [0.76, 2.89]
Shanmugam 2012	5	126	0	256	1.3%	22.26 [1.24, 399.43]
Witt 2015	11	79	19	315	21.8%	2.31 [1.15, 4.65]
Total (95% CI)		**1144**		**3817**	**100.0%**	**2.13 [1.53, 2.95]**
Total events	62		98			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.03$, df = 6 (P = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 4.52 (P < 0.00001)



Vitolo M et al. Eur J Intern Med 2021; 92: 100 –106

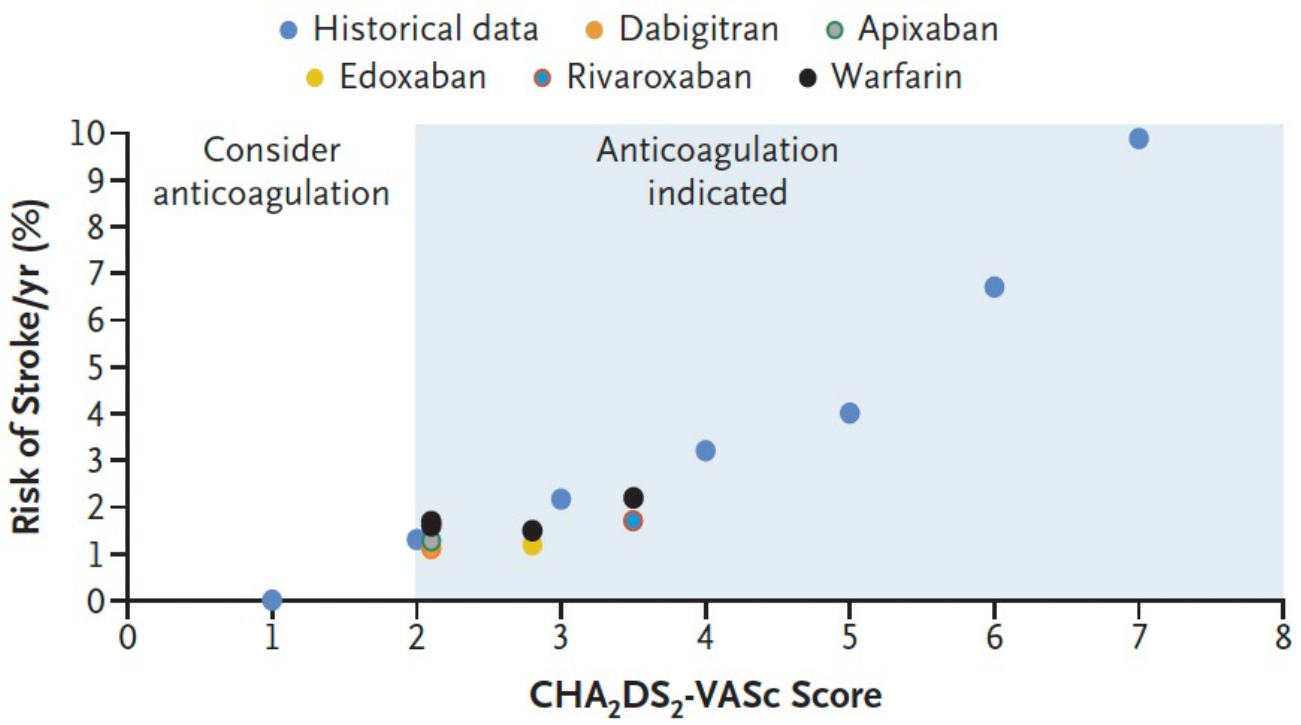
RISCHIO TROMBOEMBOLICO

CHA_2DS_2-VASc punteggio attribuito a ciascun fattore di rischio	
Pregresso ictus/TIA	2
Età ≥75 anni	2
Età 65-74 anni	1
Sesso femminile	1
Scompenso cardiaco recente	1
Ipertensione arteriosa	1
Diabete	1
Vasculopatia	1
Nessuno dei precedenti	0

Punteggio CHA_2DS_2-VASc totale	Rischio di eventi cardioembolici per i diversi punteggi % paz. per anno (IC)
0	0.78 (0.58 - 1.04)
1	2.01 (1.70 - 2.36)
2	3.71 (3.36 - 4.09)
3	5.92 (5.53 - 6.34)
4	9.27 (8.71 - 9.86)
5	15.26 (14.35 - 16.24)
6	19.74 (18.21 - 21.41)
7	21.50 (18.75 - 24.64)
8	22.38 (16.29 - 30.76)
9	23.64 (10.62 - 52.61)

Tabella 2. *Score CHA_2DS_2-VASc per la valutazione del rischio trombo embolico individuale e rispettive percentuali di rischio per ogni punteggio espressi come % paz per anno. (Lip Y et al. Chest 201O; 2010;137;263-272, Olesen JB et al. BMJ 2011;342:d124)*

PREVENZIONE DELLO STROKE NELLA FIBRILLAZIONE ATRIALE



WARFARIN reduced the risk of stroke or systemic embolism by 64% and all- cause mortality by 26%
HART R Ann Intern Med 1999

CHA_2DS_2-VASc	Points
Congestive heart failure	1
Hypertension	1
Age ≥75 yr	2
Diabetes mellitus	1
Stroke, TIA, or thromboembolism	2
Vascular disease	1
Age 65–74 yr	1
Female sex	1

Gregory F. Michaud, **NEJM 2021 384;4**

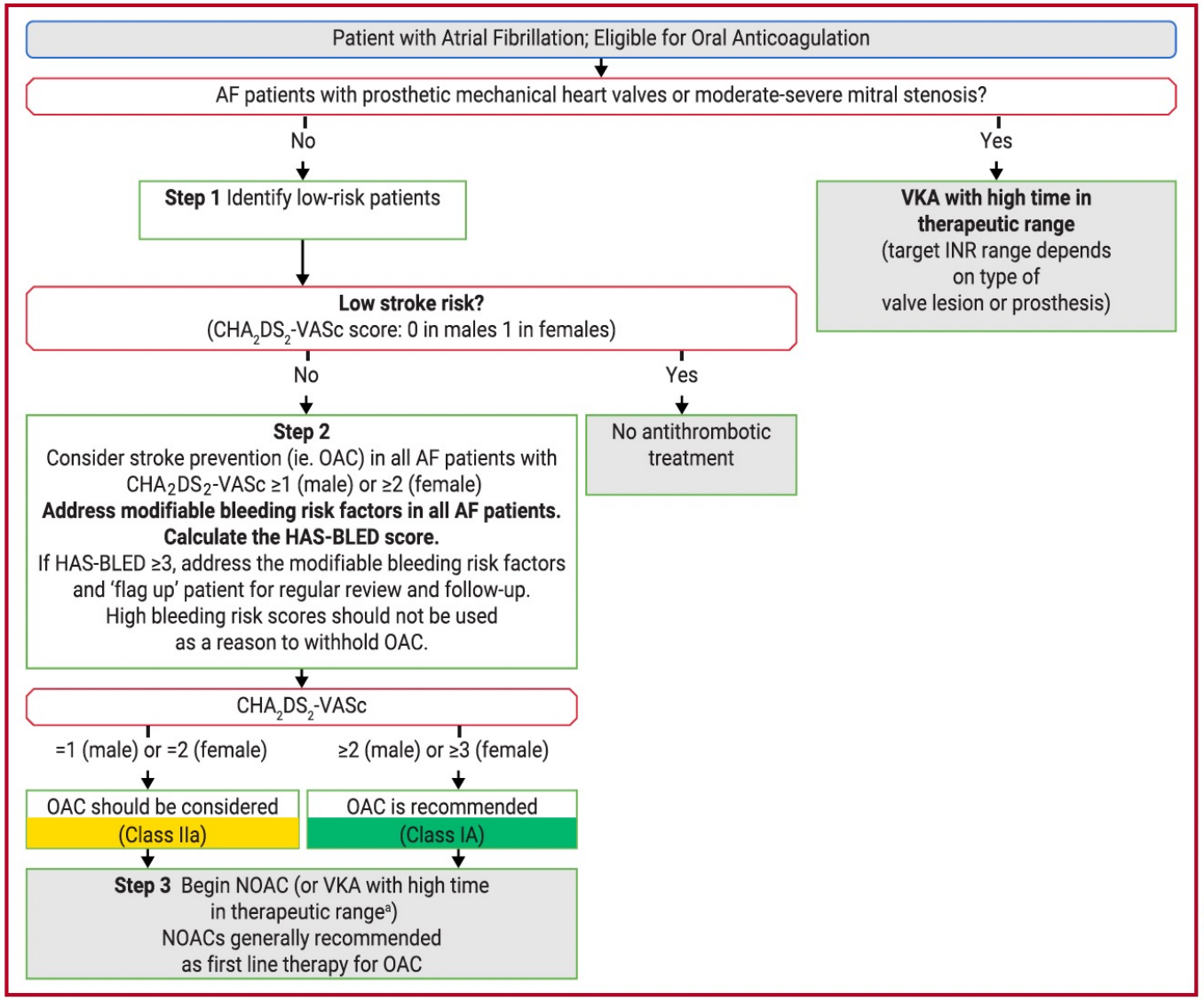
RISCHIO EMORRAGICO

HAS-BLED punteggio attribuito a ciascun fattore di rischio	
Pregresso ictus/TIA	1
Età ≥ 65 anni	1
Storia di emorragia o tendenza emorragica	1
Ipertensione arteriosa	1
Farmaci interferenti con emostasi	1
Alcool	1
INR instabile	1
Ridotta funzionalità epatica o renale (1 punto ciascuna)	1
Nessuno dei precedenti	0

Punteggio HAS-BLED totale	Rischio di emorragie maggiori per i diversi punteggi % paz./anno
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.50
6	...
7	...
8	...
9	...

Tabella 3. *Score HAS-BLED per la valutazione del rischio emorragico individuale e rispettive percentuali di rischio di emorragie maggiori per ogni punteggio espressi come % di paz. per anno. (Pisters R et al. 2010)*

PREVENZIONE DELLO STROKE NELLA FIBRILLAZIONE ATRIALE



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Management of SCAF: ESC Guidelines

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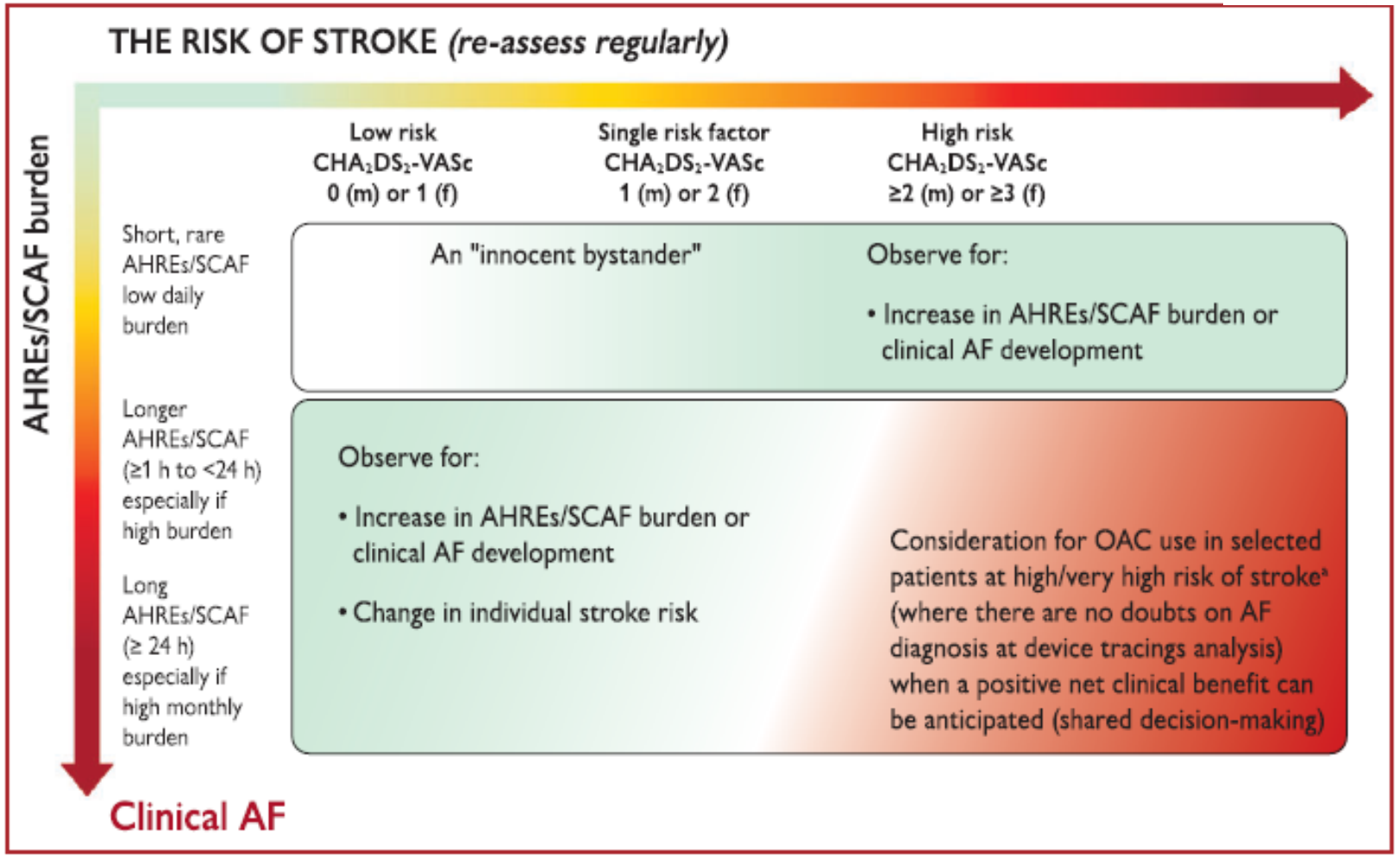


Hindricks G et al. Eur Heart J 2020; 42:373-498

PREVENZIONE DELLO STROKE NELLA FIBRILLAZIONE ATRIALE

Cochrane Library

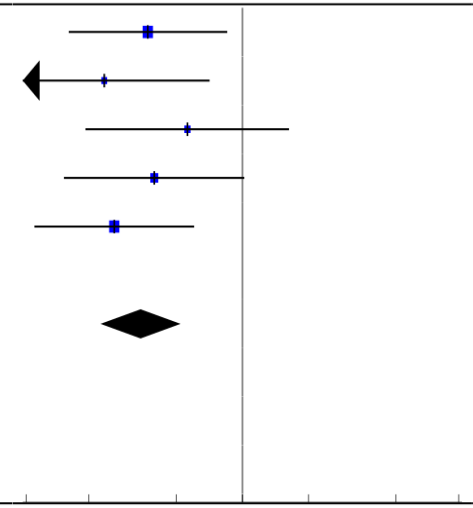
Cochrane Database of Systematic Reviews

Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks (Review)

Aguilar MI, Hart R

Analysis 1.2. Comparison 1 Anticoagulants versus control, Outcome 2 All ischemic stroke (fatal and non-fatal).

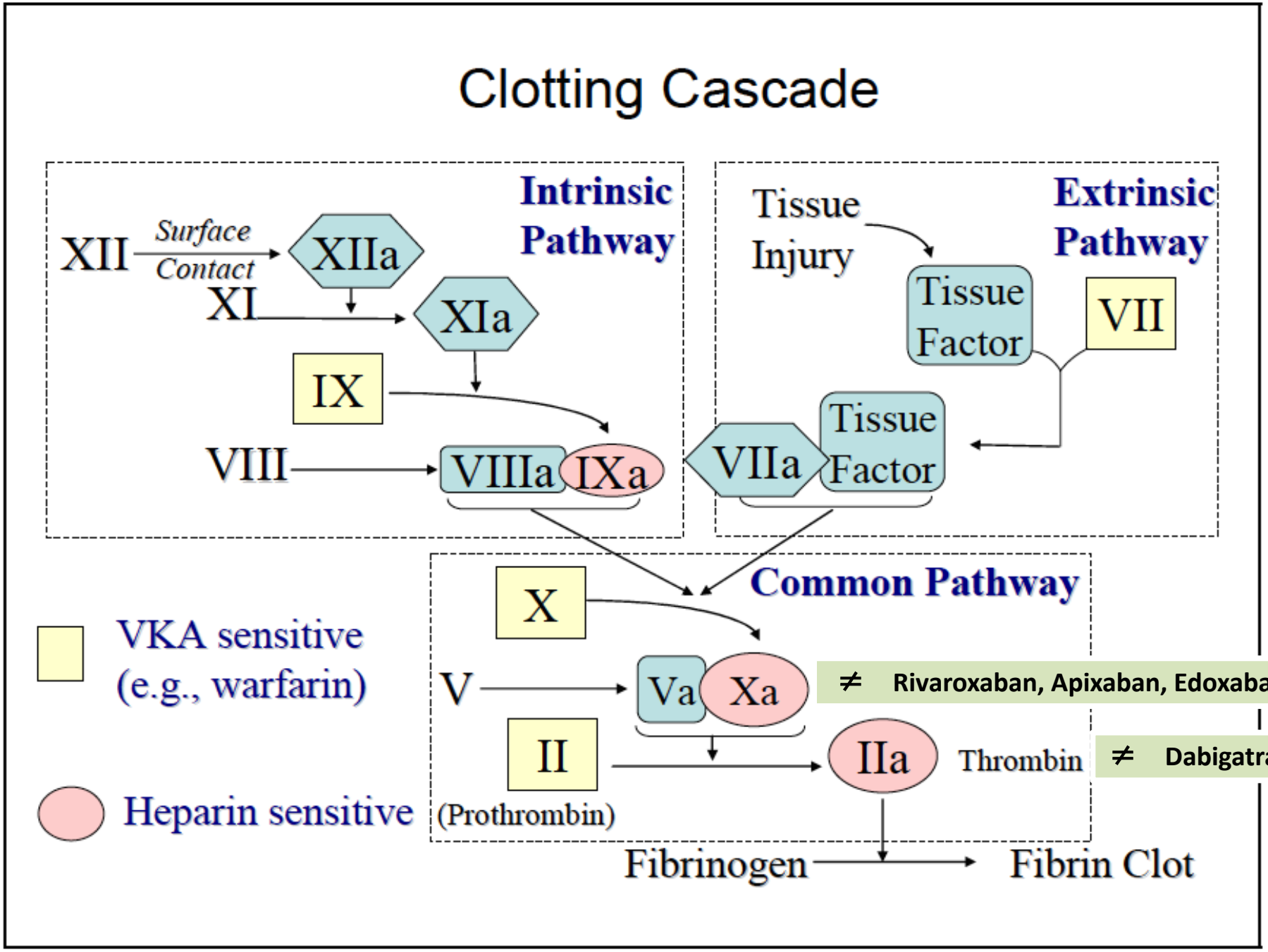
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
AFASAK I	6/315	17/315		25.35%	0.37[0.16,0.85]
BAATAF	2/205	11/201		14.41%	0.24[0.08,0.71]
CAFA	5/181	9/184		15.42%	0.56[0.19,1.63]
SPAF I	5/193	13/194		19.65%	0.4[0.15,1.02]
SPINAF	4/260	19/265		25.17%	0.26[0.11,0.6]
Total (95% CI)	**1154**	**1159**		**100%**	**0.34[0.23,0.52]**
Total events: 22 (Treatment), 69 (Control)					
Heterogeneity: $Tau^2=0$; $Chi^2=1.81$, df=4(P=0.77); $I^2=0\%$					
Test for overall effect: Z=5(P<0.0001)					



The King is Dead (Warfarin): Direct Thrombin and Factor Xa Inhibitors: The Next Diadochian War?

Hans-Christoph Diener

Int. J Stroke 2012



Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011.

FARMACI APPROVATI PER LA PREVENZIONE DEL RISCHIO TROMBOEMBOLICO NELLA FA NON VALVOLARE

	Dabigatran (Pradaxa)	**Apixaban** (Eliquis)	**Edoxaban** (Lixiana)	**Rivaroxaban** (Xarelto)
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Dose	150 mg BID 110 mg BID[a,b] (75 mg BID)[b]	5 mg BID 2.5 mg BID[a]	60 mg OD[c] 30 mg OD[a]	20 mg OD 15 mg OD[a]
Phase III clinical trial	RE-LY[25]	ARISTOTLE[26] AVERROES[27]	ENGAGE-AF[28]	ROCKET-AF[29]

BID, twice a day; OD, once daily.

[a]See further tables and text for discussion on dose reduction considerations.

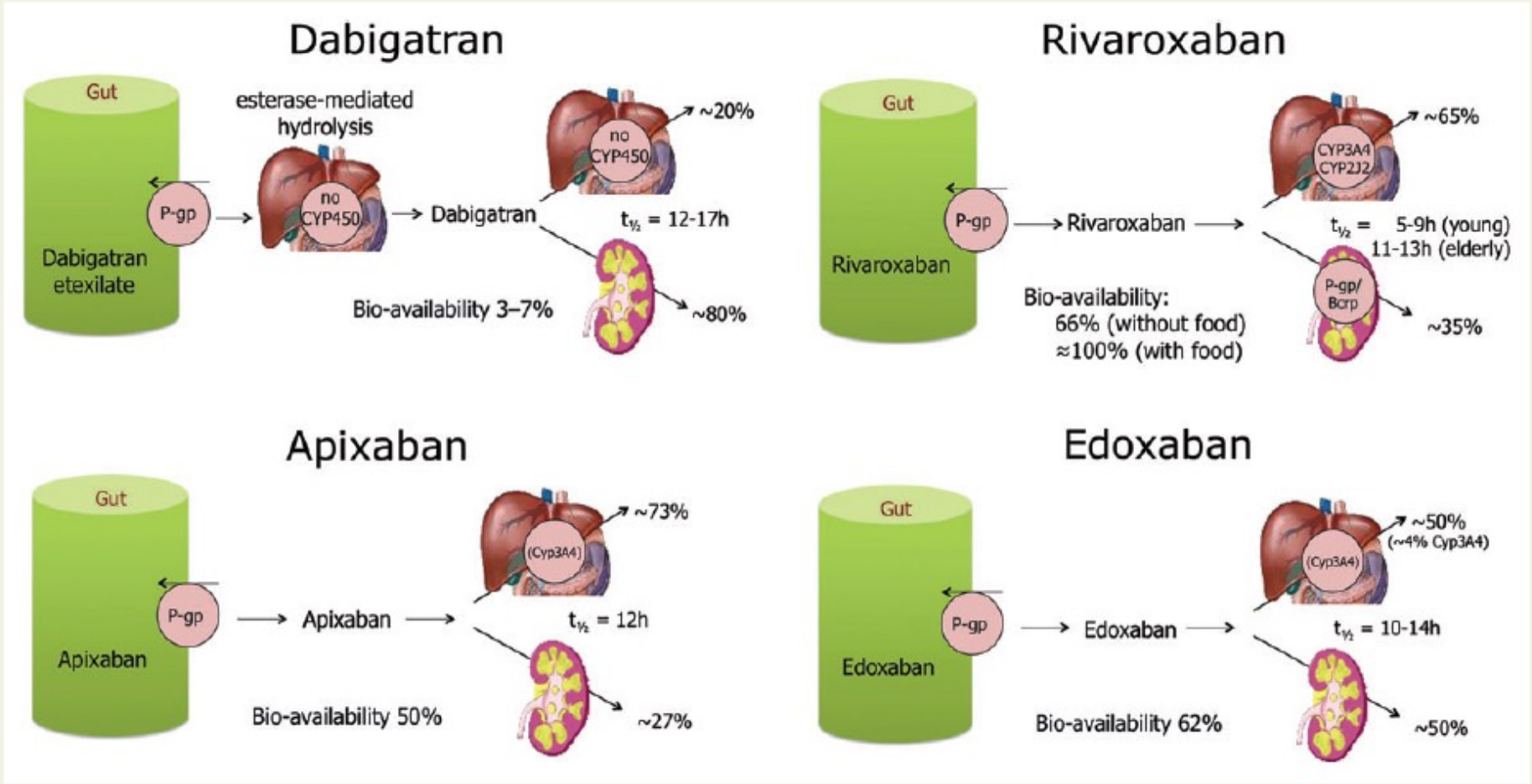
[b]110 mg BID not approved by FDA. 75 mg BID approved in USA only, if CrCl 15–30 mL/min or if CrCl 30–49 mL/min and other 'orange' factor as in *Table 6* (e.g. verapamil).

[c]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients with high creatinine clearance after a careful evaluation of the individual thrombo-embolic and bleeding risk'.

Dose reduction in selected patients	**Dabigatran 110 mg BID if CrCl 30 - 49 mL/min**	Rivaroxaban 15 mg once daily if CrCl 30-49 mL/min	Apixaban 2.5 mg twice daily if at least 2 of age ≥80 years, body weight ≤60 kg or serum creatinine level ≥1.5 mg/dL (133 μmol/L)	Edoxaban 60 mg reduced to 30 mg once daily, and edoxaban 30 mg reduced to 15 mg once daily, if any of the following: creatinine clearance of 30–50 mL/min, body weight ≤60 kg, concomitant use of verapamil or quinidine

Europace 2015

ASSORBIMENTO E METABOLISMO DEI DIFFERENTI NAO



Europace 2015

ASSORBIMENTO E METABOLISMO DEI DIFFERENTI NAO

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	3 to 7%	50%	62%[51]	66% without food. Almost 100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose (if normal renal function; see also 'Patients with chronic kidney disease' section)[a]	20%/80%	73%/27%[52–55]	50%/50%[36,51,56]	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination, moderate contribution)[57]	Minimal (<4% of elimination)	Yes (elimination, moderate contribution)
Absorption with food	No effect	No effect	6–22% more; minimal effect on exposure[58]	+39% more[59]
Intake with food recommended?	No	No	No	Mandatory
Absorption with H2B/PPI	−12 to 30% (not clinically relevant)[60–62]	No effect[63]	No effect	No effect[59,64]
Asian ethnicity	+25%[62]	No effect	No effect[58]	No effect
GI tolerability	Dyspepsia 5 to 10%	No problem	No problem	No problem
Elimination half-life	12 to 17 h[61]	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)

H2B, H2-blocker; PPI, proton pump inhibitor; GI, Gastrointestinal.
[a]For clarity, data are presented as single values, which are the mid-point of ranges as determined in different studies.

Europace 2015

I NUOVI ANTICOAGULANTI ORALI

Overview of design of the pivotal phase III trials of NOAC compared with warfarin in nonvalvular AF

	RELY (NEJM 2009)	ROCKET (NEJM Sep 2011)	ARISTOTLE (NEJM Sep 2011)	ENGAGE AF (NEJM Nov 2013)
Sample size	18,113	14,264	18,201	21,105
New treatment and dose	Dabigatran 110 mg bid Dabigatran 150 mg bid	Rivaroxaban 20 mg qd	Apixaban 5 mg bid	Edoxaban 60 mg qd Edoxaban 30 mg qd
Dose adjustment	No	At randomization	At randomization	At randomization
Design	Noninferiority PROBE	Noninferiority Double blinded	Noninferiority Double blinded	Noninferiority Double blinded
Patients	$CHADS_2$ ≥1 71 years, 64% Men	$CHADS_2$ ≥2 73 years, 60% Men	$CHADS_2$ ≥1 70 years, 65% Men	$CHADS_2$ ≥2 72 years, 62% Men
Primary outcome	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism
Safety outcome	Major bleeding	Major bleeding	Major bleeding	Major bleeding

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NOACs vs. Warfarin

Study Drug vs Warfarin	Dabigatran (RE-LY) 150mg BID 110mg BID*	Rivaroxban (ROCKET-AF) 20mg QD 15mg QD*	Apixaban (ARISTOTLE) 5mg BID 2.5mg BID*	Edoxaban (ENGAGE-TIMI-AF 48) 60mg QD 30mg QD*
Stroke or Systemic Embolism	150mg: ↓ 110mg: Non-inferior	Non-inferior	↓	60mg: ↓ 30mg: Non-inferior
Major Bleeding	150mg: No difference 110mg: ↓	No difference, but demonstrated superiority over warfarin for fatal and critical bleeds	↓	60mg: ↓ 30mg: ↓
GI Bleeding	150mg: ↑	↑	No difference	60mg: ↑ 30mg: ↓
ICH	↓			
Mortality	NS	NS	↓	↓

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman

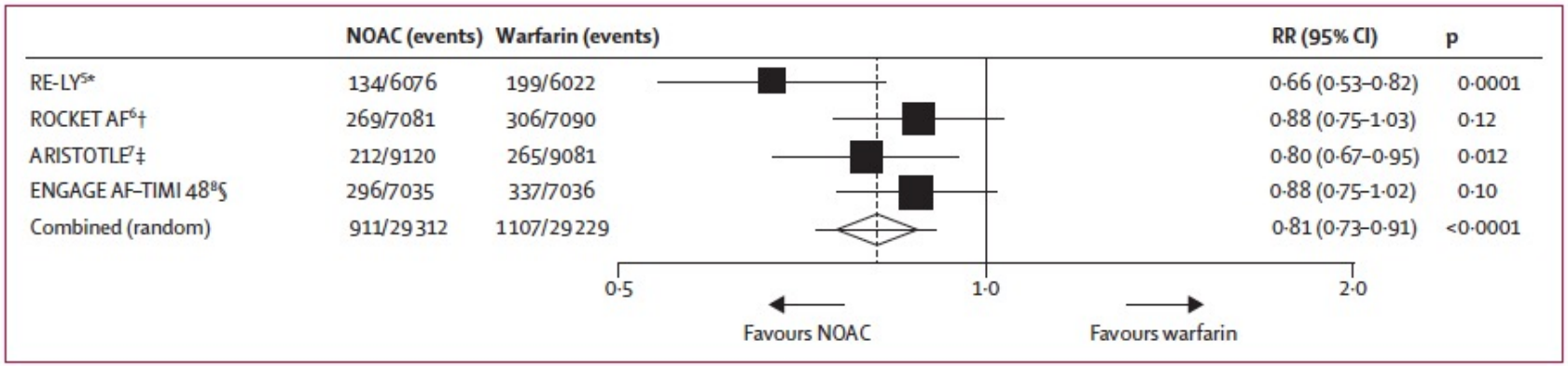

***Figure 1*: Stroke or systemic embolic events**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

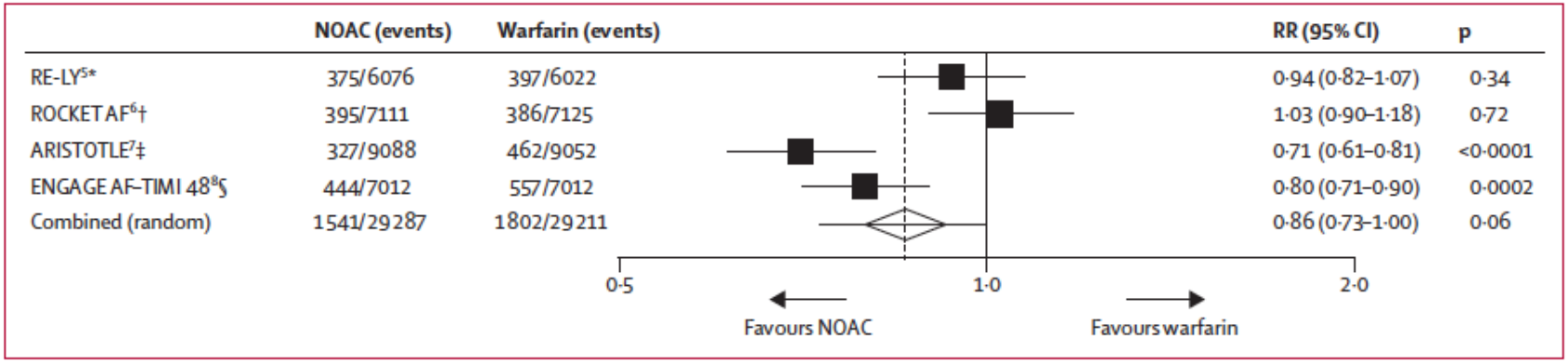

***Figure 3*: Major bleeding**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Lancet 2014

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

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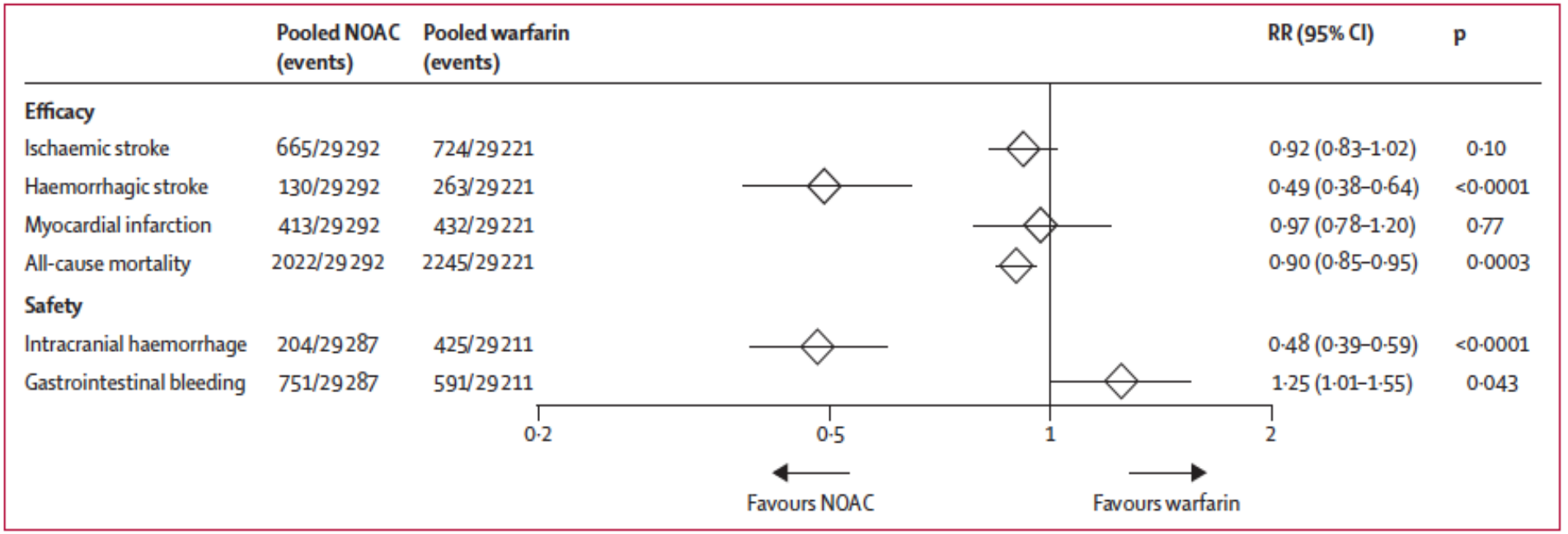


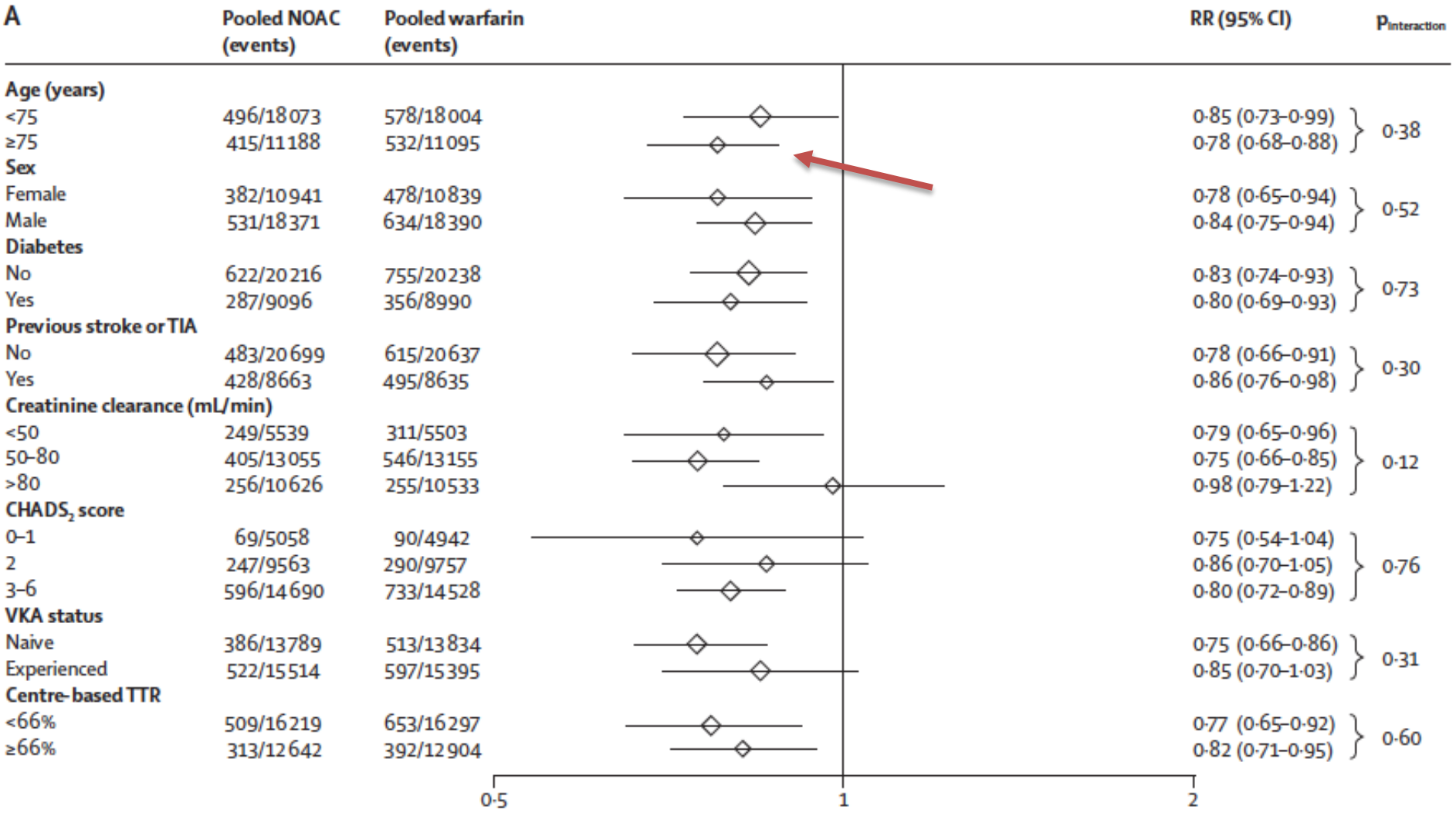
***Figure 2*: Secondary efficacy and safety outcomes**

Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I^2=32%, p=0·22; haemorrhagic stroke I^2=34%, p=0·21; myocardial infarction I^2=48%, p=0·13; all-cause mortality I^2=0%, p=0·81; intracranial haemorrhage I^2=32%, p=0·22; gastrointestinal bleeding I^2=74%, p=0·009. NOAC=new oral anticoagulant. RR=risk ratio.

Lancet 2014

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

STROKE OR SYSTEMIC EMBOLIC EVENTS SUBGROUPS



Lancet 2014

The NEW ENGLAND JOURNAL of MEDICINE

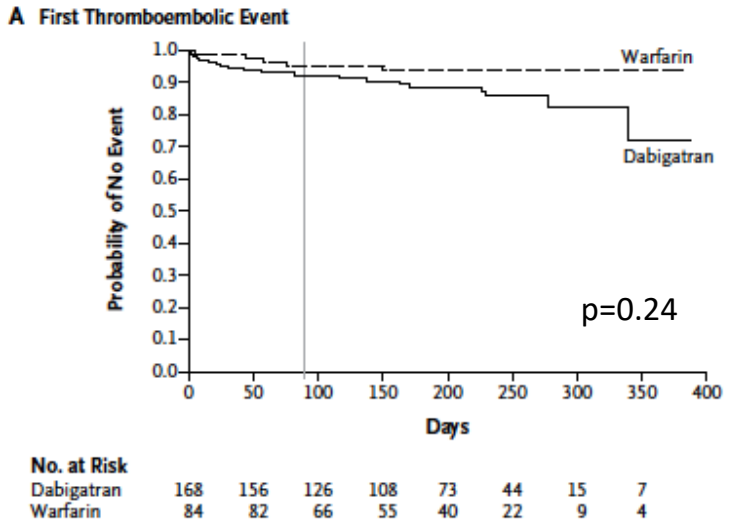
ORIGINAL ARTICLE

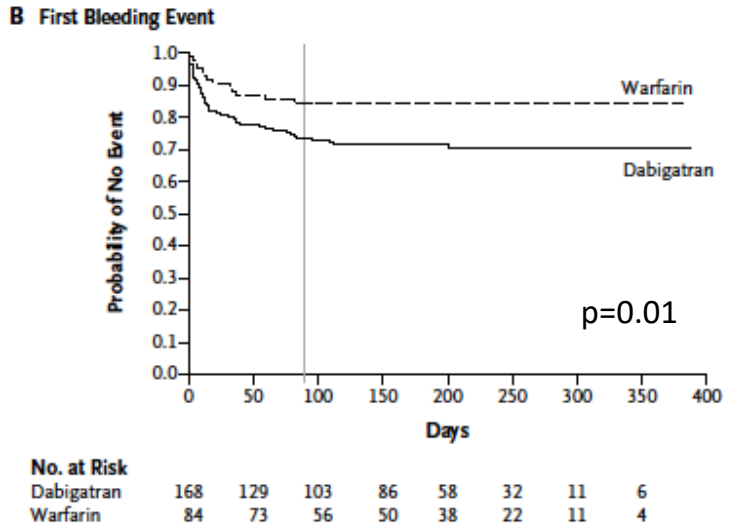
Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

RE-ALIGN TRIAL

- 252 pts with mechanical heart valves who had undergone aortic- or mitral-valve replacement within the past 7 days (199 pts-population A) or at least 3 months earlier (53 pts-population B);
- Randomly assigned in a 2:1 ratio to receive either dabigatran (168 pts) or warfarin (84 pts).
- Initial dabigatran dose (150, 220, or 300 mg twice daily) was based on kidney function and adjusted to obtain a trough plasma level of at least 50 ng/ml. The warfarin dose was adjusted to obtain an international normalized ratio of 2 to 3 or 2.5 to 3.5 on the basis of thromboembolic risk.
- The primary end point was the trough plasma level of dabigatran; Additional outcomes included stroke, systemic embolism, transient ischemic attack, valve thrombosis, bleeding, venous thromboembolism, myocardial infarction, and death.
- Valve location was aortic in 68%, mitral in 28%, and both in 4%; mean duration of treatment with the assigned study drug in population A was 143 days in the dabigatran group and 152 days in the warfarin group, the corresponding mean durations in population B were 136 days and 143 days.

- **The trial was terminated prematurely because the use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin**.





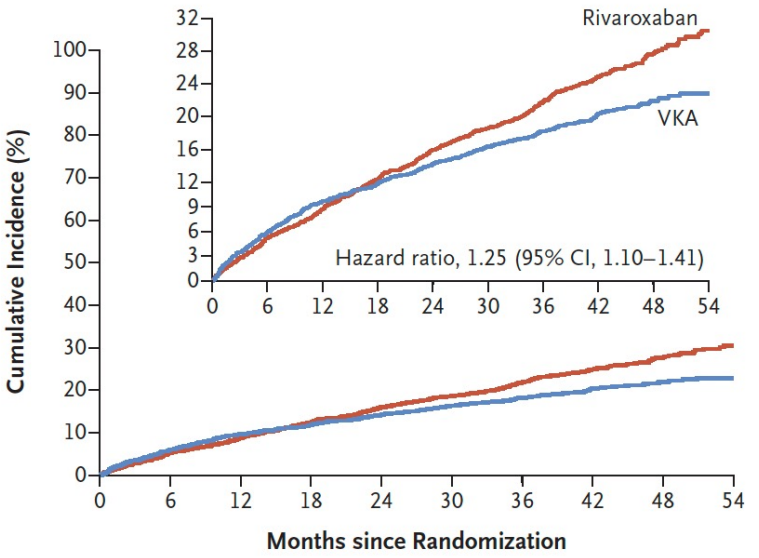
NEJM 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban in Rheumatic Heart Disease–Associated Atrial Fibrillation

INVICTUS TRIAL



No. at Risk										
Rivaroxaban	2275	2124	2023	1931	1838	1750	1356	876	451	144
VKA	2256	2100	2003	1944	1880	1809	1392	881	462	138

Figure 1. Cumulative Incidence of the Composite of Stroke, Systemic Embolism, Myocardial Infarction, or Death from Vascular or Unknown Causes (Primary Outcome).

Vascular causes could be cardiac or noncardiac. The inset shows the same data on an expanded y axis. VKA denotes vitamin K antagonist.

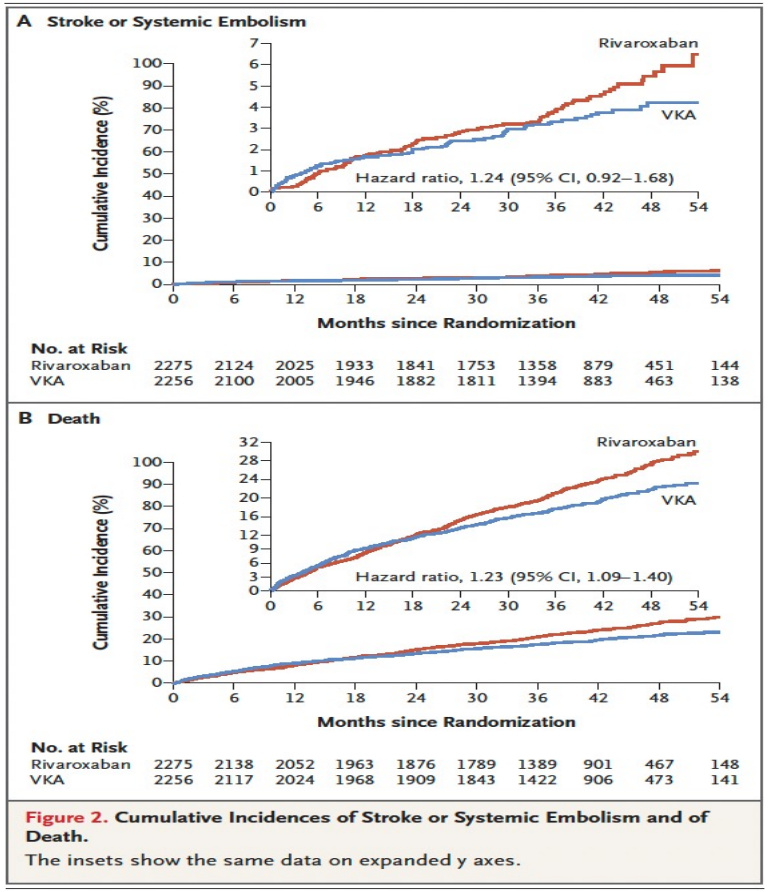


Figure 2. Cumulative Incidences of Stroke or Systemic Embolism and of Death.

The insets show the same data on expanded y axes.

S.J. Connolly, NEJM 2022 DOI: 10.1056/NEJMoa2209051

INDICAZIONI AL TRATTAMENTO ANTICOAGULANTE CON NAO

Table 2. History of VHD in Patients Randomized in ARISTOTLE, ROCKET-AF, and RE-LY

	ARISTOTLE Total (N=18 197)	RE-LY Total (N=18 113)	ROCKET-AF Total (N=14 171)
At least moderate VHD, n (%)	4808 (26.4)	3950 (21.8)	2003 (14.1)
Mitral regurgitation	3526 (19.4)	3101 (17.1)	1756 (89.6)
Mitral stenosis	131 (0.7)	193 (1.1)	. . .
Aortic regurgitation	887 (4.9)	817 (4.5)	486 (24.8)
Aortic stenosis	384 (2.1)	471 (2.6)	215 (11.0)
Tricuspid regurgitation	2124 (11.7)	1179 (6.5)	. . .
Valve surgery	251 (1.4)	. . .	. . .
Prior cardiac valvular procedure	. . .	. . .	106 (5.3)
Other	. . .	. . .	11 (0.6)

VHD indicates valvular heart disease; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RE-LY, Randomized Evaluation of Long Term Anticoagulation Therapy.

Use of Direct Oral Anticoagulants in Patients With Atrial Fibrillation and Valvular Heart Lesions; J Am Heart Assoc *2016*

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

POSITION PAPER

EHRA PRACTICAL GUIDE

Condition	Eligibility for NOAC	Comment
Mechanical prosthetic valve	Contraindicated	Excluded from pivotal RCTs Data indicating worse outcome[15,16]
Moderate to severe mitral stenosis (usually rheumatic)	Contraindicated	Excluded from pivotal RCTs Little rationale for less efficacy and safety vs. VKA
Other mild to moderate valvular disease (e.g. degenerative aortic stenosis, mitral regurgitation etc.) Bioprosthetic valve/valve repair (after >3 months postoperative)	Included in NOAC trials Acceptable	Data regarding efficacy and safety overall consistent with patients without valvular heart disease[12,17–22] Some data from NOAC RCTs Single RCT indicating non-inferiority to VKA[24] Patients without AF usually on ASA after 3–6 months post-surgery, hence NOAC therapy acceptable for stroke prevention if diagnosed with AF
Severe aortic stenosis	Limited data (excluded in RE-LY)	No pathophysiological rationale for less efficacy and safety Most will undergo intervention
Transcatheter aortic valve implantation	Acceptable	Single RCT + observational data May require combination with APT[25,26]
Percutaneous transluminal aortic valvuloplasty	With caution	No prospective data May require combination with APT
Hypertrophic cardiomyopathy	Acceptable	No rational for less efficacy and safety vs. VKA Observational data positive for NOACs[33–36]

Europace (2021) 00, 1–65 doi:10.1093/europace/euab065

RECOMMENDATION FOR THE PREVENTION OF THROMBO-EMBOLIC EVENTS IN A.F.

Hindricks G et al. Eur Heart J 2020; 42:373-498

Recommendations	Class[a]	Level[b]
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 is recommended for stroke prevention in AF patients with CHA_2DS_2-VASc score ≥2 in men or ≥3 in women.[412]	I	A
OAC should be considered for stroke prevention in AF patients with a CHA_2DS_2-VASc score of 1 in men or 2 in women. Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences.[338,378,380]	IIa	B
For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment is recommended to help identify non-modifiable and address modifiable bleeding risk factors in all AF patients, and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up.[388,395,404,406]	I	B
For a formal risk-score-based assessment of bleeding risk, the HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score ≥3) for early and more frequent clinical review and follow-up.[388,395,404,406]	IIa	B
Stroke and bleeding risk reassessment at periodic intervals is recommended to inform treatment decisions (e.g. initiation of OAC in patients no longer at low risk of stroke) and address potentially modifiable bleeding risk factors.[c389,478,479]	I	B
In patients with AF initially at low risk of stroke, first reassessment of stroke risk should be made at 4 - 6 months after the index evaluation.[385–387]	IIa	B
If a VKA is used, a target INR of 2.0 - 3.0 is recommended, with individual TTR≥70%.[414]	I	B
In patients on VKAs with low time in INR therapeutic range (e.g. TTR<70%), recommended options are: • Switching to a NOAC but ensuring good adherence and persistence with therapy[415,416]; or	I	B
• Efforts to improve TTR (e.g. education/counselling and more frequent INR checks).[480]	IIa	B
Antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) is not recommended for stroke prevention in AF.[440,441,480,481]	III	A
Estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention.	III	A
Clinical pattern of AF (i.e. first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication to thromboprophylaxis.[160]	III	B

EFFECT OF DRUG-DRUG INTERACTIONS ON NOAC PLASMA LEVELS AND ANTICOAGULANT EFFECTS

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EHRA PRACTICAL GUIDE 2021

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[519]
Antiarrhythmic drugs					
Amiodarone	Moderate P-gp inhibition	+12% to 60%[SmPC]	No PK data[a]	+40%[521-523]	Minor effect[a]
Digoxin	P-gp competition	No effect[SmPC]	No effect[524]	No effect[523]	No effect[525]
Diltiazem	Weak P-gp and CYP3A4 inhibition	No effect[SmPC]	+40%[526]	No data yet	No effect
Dronedarone	P-gp and CYP3A4 inhibition	+70% to 100%	With caution	+85%[b 523] (dose reduction to 30 mg once daily by label)	Moderate effect; should be avoided
Quinidine	P-gp inhibition	+53%[SmPC]	No data yet	+77%[523] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp inhibition and weak CYP3A4 inhibition	+12% to 180%[SmPC] (if taken simultaneously) (110 mg BID by label)	No PK data	+53% (SR)[523] (no dose reduction required by label)	+40%[527] (probably not relevant)[528]
Other cardiovascular drugs					
Atorvastatin	P-gp inhibition and CYP3A4 competition	No relevant interaction[529]	No data yet	No effect[523]	No effect[530]
Ticagrelor (see also 'Patients with atrial fibrillation and coronary artery disease' section)	P-gp inhibition	+24% to 65%[SmPC] (give loading dose 2h after dabigatran)[d]	No data – carefully monitor	No data – carefully monitor	No data – carefully monitor
Antibiotics					
Clarithromycin; Erythromycin	P-gp inhibition and strong CYP3A4 inhibition	Clarithromycin: +19% AUC; +15% C_{max} (SmPC)	Clarithromycin: +60% AUC; +30% C_{max} (SmPC)	Erythromycin: +85% AUC; +68% C_{max}[531] (dose reduction to 30 mg once daily by label)	Clarithromycin: +50% AUC; +40% C_{max} Erythromycin: +30% AUC; +30% C_{max} (SmPC)
Rifampicin	P-gp/ BCRP and CYP3A4 induction	– 66% AUC; – 67% Cmax (SmPC)	– 54% AUC; – 42% Cmax (SmPC)	– 35% AUC, (but with compensatory increase of active metabolites)[532]	– 50% AUC; – 22% Cmax (SmPC)

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EFFECT OF DRUG-DRUG INTERACTIONS ON NOAC PLASMA LEVELS AND ANTICOAGULANT EFFECTS

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	via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Antiviral Drugs					
HIV protease inhibitors (e.g., ritonavir)	P-gp and BCRP inhibition or induction; CYP3A4 inhibition	Variable increase / decrease [533, 534]	Strong increase	No data yet	+153% AUC +55% C_{max} (Ritonavir 600 BID) [94]
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% AUC; +30% C_{max} (if given systemically) [94]
Itraconazole; Ketoconazole	Potent P-gp and BCRP competition; strong CYP3A4 inhibition	+140 to 150% (ketoconazole) (US: 2 × 75 mg if CrCl 30-50 mL/min)	+100% AUC; +64% C_{max} (ketoconazole) [526]	+87% AUC; +89% C_{max} (dose reduction to 30 mg once daily by label) (ketoconazole) [531]	+160% AUC; +72% C_{max} (ketoconazole, SmPc)
Voriconazole	Strong CYP3A4 inhibition	No data yet	SmPC	No data yet	SmPC
Posaconazole	Mild to moderate P-gp inhibition, strong CYP3A4 inhibition	SmPC	SmPC		SmPC
Other drugs					
Naproxen	P-gp competition; pharmacody-namically (increased bleeding time)	No data yet	+55% AUC; +61% C_{max} [535]	No difference in AUC [536]	No relevant increase of AUC [537]
H_2-blockers; PPI; Al-Mg-hydroxide	GI absorption	Minor effect, not clinically relevant [SmPC]	No effect	Minor effect, not clinically relevant [SmPC]	No effect [105, 538]
SSRIs; SNRIs	Pharmacodynamic effect on platelets	SmPC	SmPC	SmPC	SmPC
St. John's wort	P-gp/ BCRP and CYP3A4 induction				
Other factors					
Age ≥ 80 years	Potential for *increased* plasma levels	110mg BID (SmPC)	b	c	
Age ≥75 years	Potential for *increased* plasma levels			c	
Weight ≤ 60 kg (see 'NOACs in high- and low body weights' section)	Potential for *increased* plasma levels		b	(dose reduction to 30mg according to label) b	
Weight ≥ 120 kg (see 'NOACs in high- and low body weights' section)	Potential for *decreased* plasma levels				
Chronic kidney disease	Potential for *increased* plasma levels				
Other factors with potentially increased bleeding risk		For example : • Concomitant antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants • Severe Frailty / falls risk • History of bleeding or predisposition (anemia, thrombocytopenia)			

EFFECT OF DRUG-DRUG INTERACTIONS ON NOAC PLASMA LEVELS AND ANTICOAGULANT EFFECTS

POSITION PAPER

EHRA PRACTICAL GUIDE 2021

	Via[426, 539-541]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Brivaracetam	–	No relevant interaction known/assumed			
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	-29%[542]	-50% (SmPC)	SmPC	SmPC
Ethosuximide	CYP3A4 competition	No relevant interaction known/assumed			
Gabapentin	–	No relevant interaction known/assumed			
Lacosamide	–	No relevant interaction known/assumed			
Lamotrigine	P-gp competition	No relevant interaction known/assumed			
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/possible P-gp induction		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC[543]	SmPC	SmPC	SmPC
Pregabalin	–	No relevant interaction known/assumed			
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction/inhibition				Ref 544
Zonisamide	CYP3A4 competition; weak P-gp inhibition	No relevant interaction known/assumed (SmPc)			

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EFFECT OF DRUG-DRUG INTERACTIONS ON NOAC PLASMA LEVELS AND ANTICOAGULANT EFFECTS *POSITION PAPER*

EHRA PRACTICAL GUIDE 2021

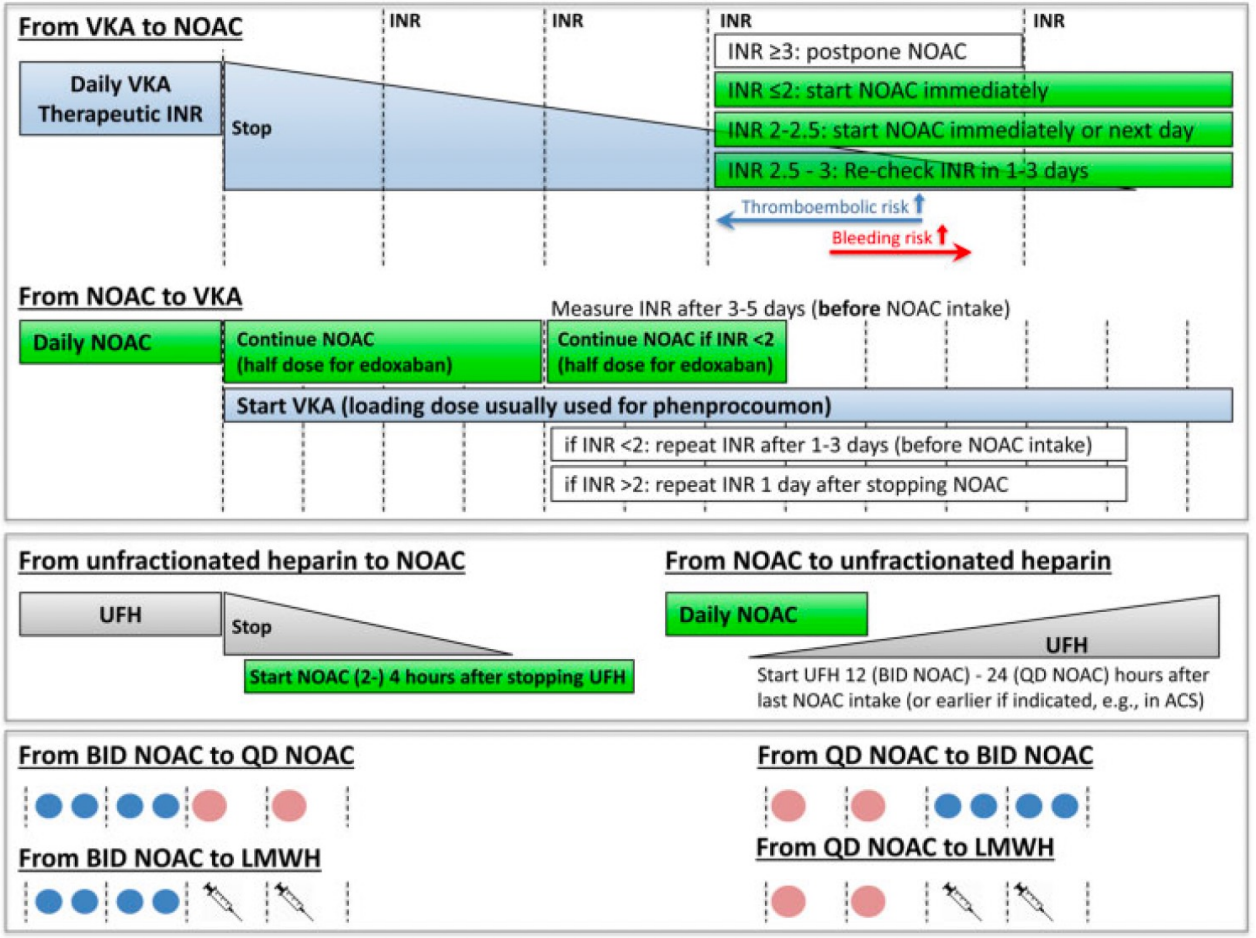
	Via [545, 546; 547]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Curcumin	P-gp inhibition				
Echinacea purpurea	Mild CYP3A4 inhibition				
Garlic	Mild CYP3A4 inhibition; anticoagulation / antiplatelet effect				
Ginger	Anticoagulation / antiplatelet effect				
Ginkgo biloba	P-gp inhibition; anticoagulation / antiplatelet effect				
Ginseng	Anticoagulation / antiplatelet effect				
Green Tea	P-gp inhibition; anticoagulation / antiplatelet effect				
Horse chestnut	Anticoagulation / antiplatelet effect				
St. John's wort iperico	P-gp/ BCRP and CYP3A4 induction	Should be avoided (per SmPc)	"With caution" (per SmPc)	"With caution" (per SmPc)	Should be avoided (per SmPc)
Valerian	Mild CYP3A4 inhibition				

Europace 2021

Grazie di

a tutti!

Switching between NOACs and other Anticoagulants



NAO NELL'INSUFFICIENZA RENALE CRONICA

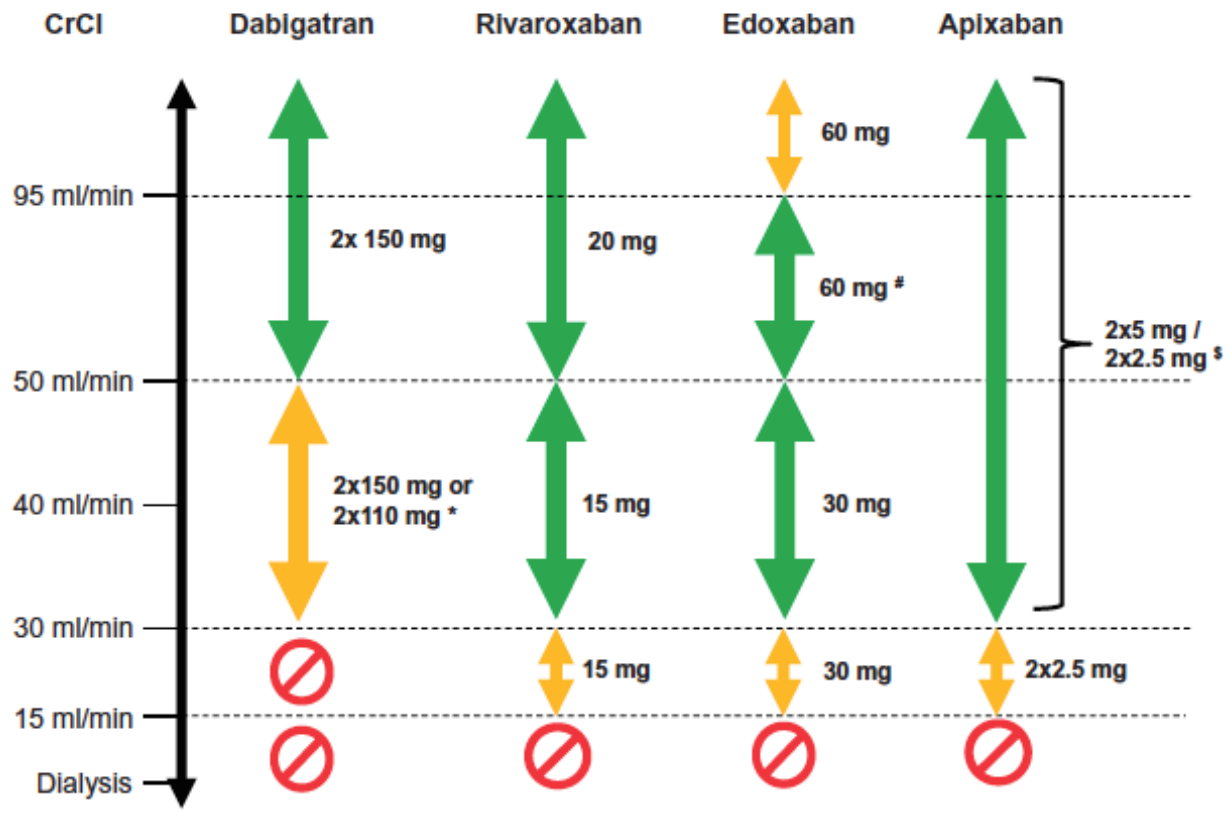


Figure 4 Use of non-vitamin K antagonist oral anticoagulants according to renal function. *2 × 110 mg in patients at high risk of bleeding (per SmPc). #Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). $2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function); see text for details.

Europace 2015