Nuovi e vecchi anticoagulanti orali

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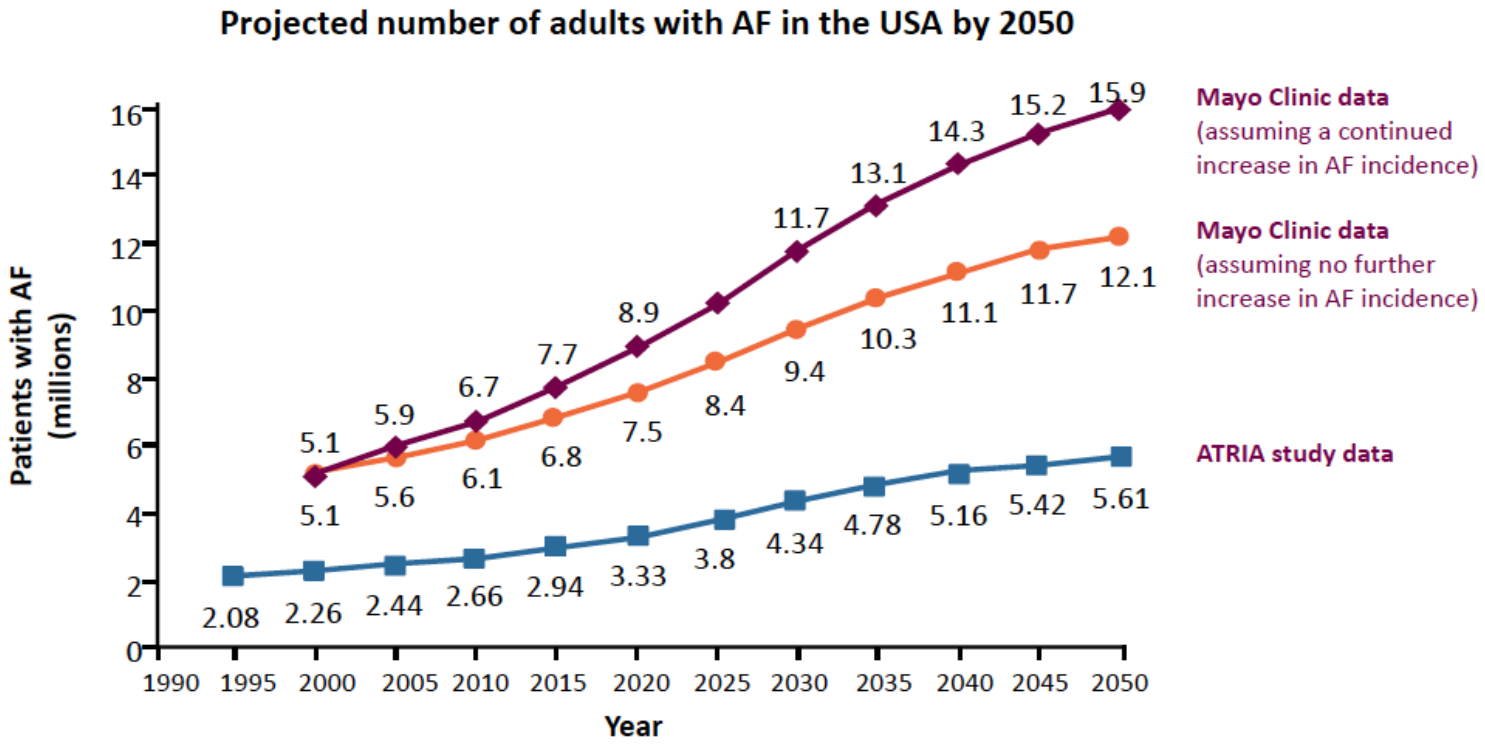
ASL CITTÀ DI TORINO

Fibrillazione atriale

- FA è il più comune disturbo del ritmo cardiaco
- Si stima che 1 individuo su 4 di età ≥ 40 anni svilupperà FA
- A causa dell'invecchiamento della popolazione, si prevede che questo numero raddoppierà entro i prossimi 30 anni [2]

1. Camm et al. Eur Heart J 2010;31:2369–2429.
2. Go et al. JAMA 2001;285:2370–2375.

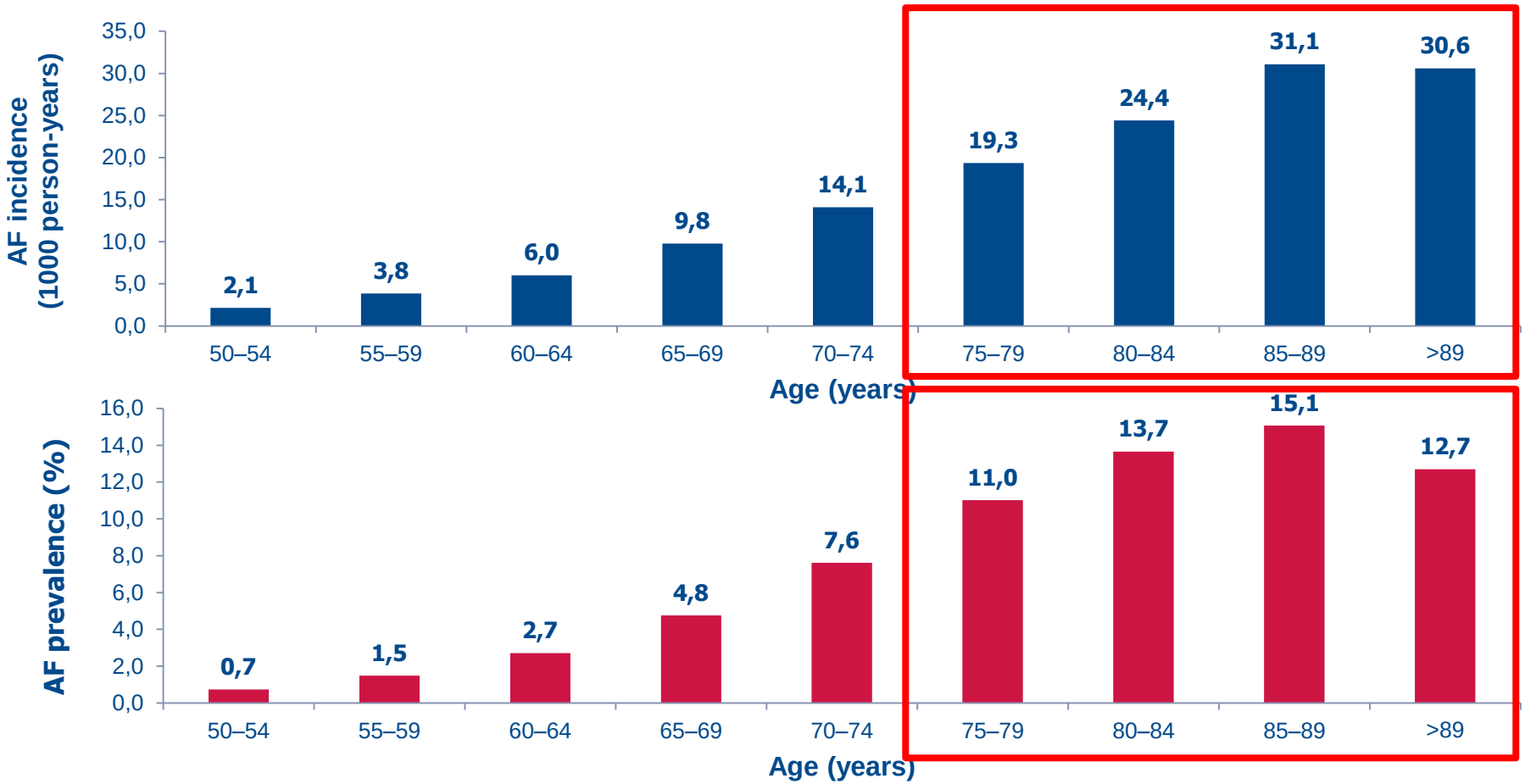
La prevalenza di FA è in continua crescita



- Projected data from population studies suggest that the prevalence of AF will double by 2025

1. Savelieva et al. *Clin Cardiol* 2008;31:55–62.

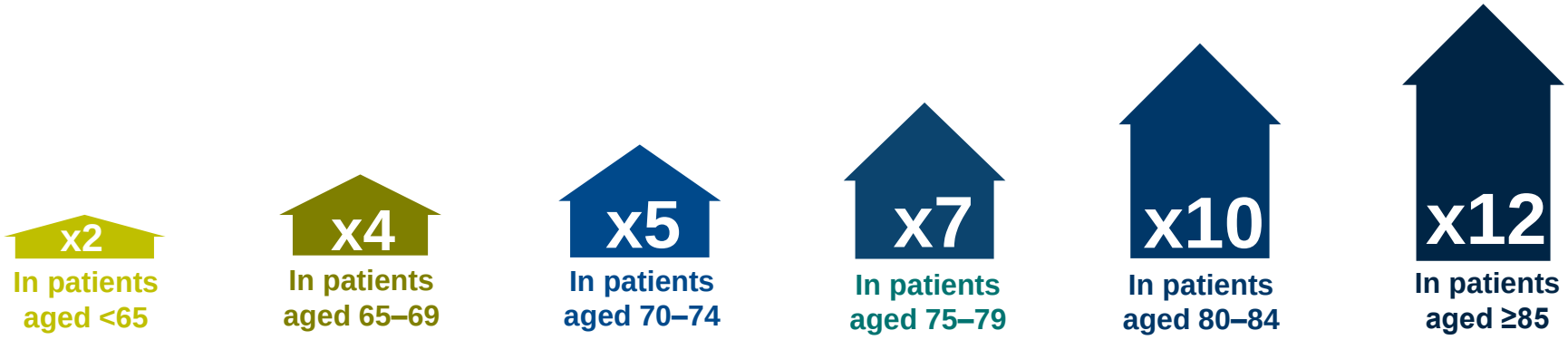
L'incidenza e la prevalenza di FA aumenta con incremento dell'età



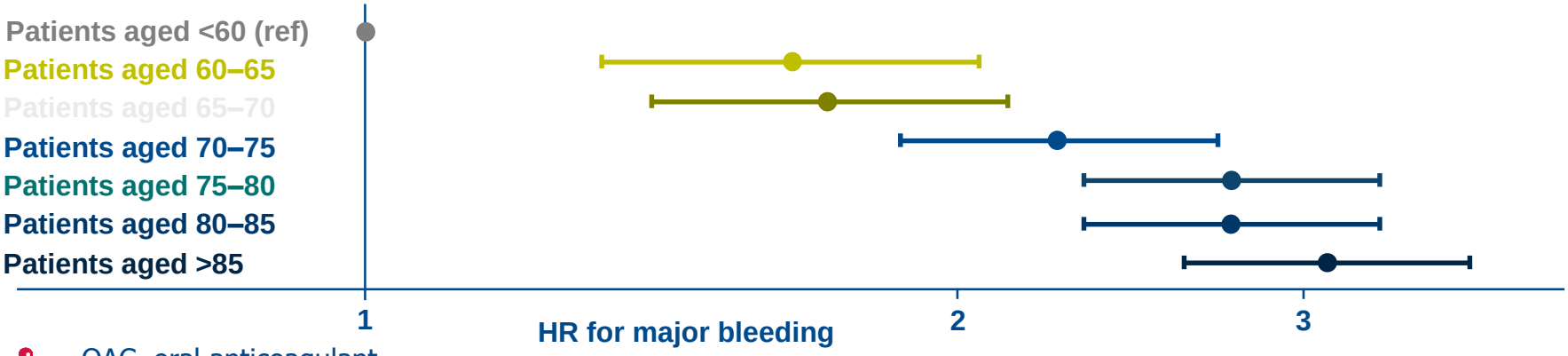
In an analysis of claims data from 8.3 million participants in Germany, of which 176 891 had AF, the incidence and prevalence of AF increased with age[1]

Stroke and bleeding risk by age

Compared with patients without AF, the risk of stroke in patients with chronic AF increases by approximately:[1]



Compared with patients without AF, the risk of major bleeding in patients with chronic AF and not receiving OAC increases with age[2]



OAC, oral anticoagulant

1. Rietbrock S et al. Am Heart J 2008; 2. Olesen JB et al. J Thromb Haemost 2011

Clinical course of atrial fibrillation in older adults: the importance of cardiovascular events beyond stroke

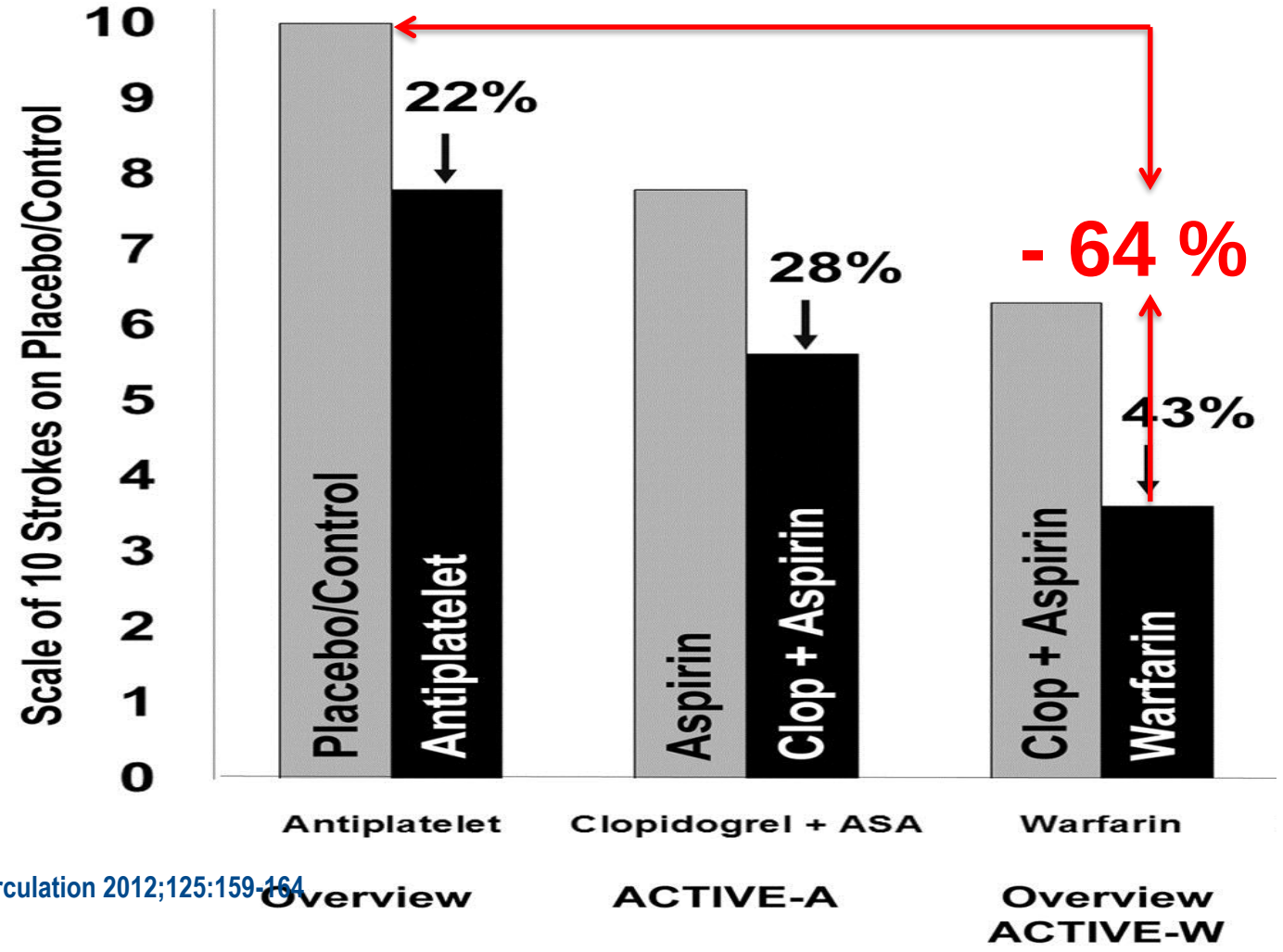
Piccini JP, Eur Heart J 2014

Medicare beneficiaries age >65yrs: n= 186.461

Table 3 Observed cumulative incidence of events over 5 years after the diagnosis of incident atrial fibrillation by the subgroup of the primary study cohort

Subgroup	No. of patients	Cumulative incidence, *n* (%)				
		Mortality	Heart failure	Myocardial infarction	Stroke	Gastrointestinal bleeding
Age group						
67–69 year	16 294	4211 (28.8)	1626 (11.0)	471 (3.3)	728 (5.0)	644 (4.4)
70–74 year	37 153	10 876 (32.3)	4082 (12.1)	1199 (3.6)	1902 (5.7)	1652 (4.9)
75–79 year	44 396	16 155 (40.1)	5401 (13.3)	1538 (3.9)	2749 (6.9)	2375 (5.9)
80–84 year	41 450	19 603 (52.1)	5710 (15.1)	1611 (4.3)	3023 (8.1)	2402 (6.4)
85–89 year	28 657	17 526 (67.0)	4179 (15.8)	1161 (4.4)	2324 (8.9)	1741 (6.6)
≥ 90 year	18 511	14 546 (84.3)	2391 (13.7)	617 (3.6)	1194 (6.9)	934 (5.4)

Stroke prevention: Antithrombotic Therapy in AF



Granger C B Circulation 2012;125:159-164

Stroke prevention

Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial

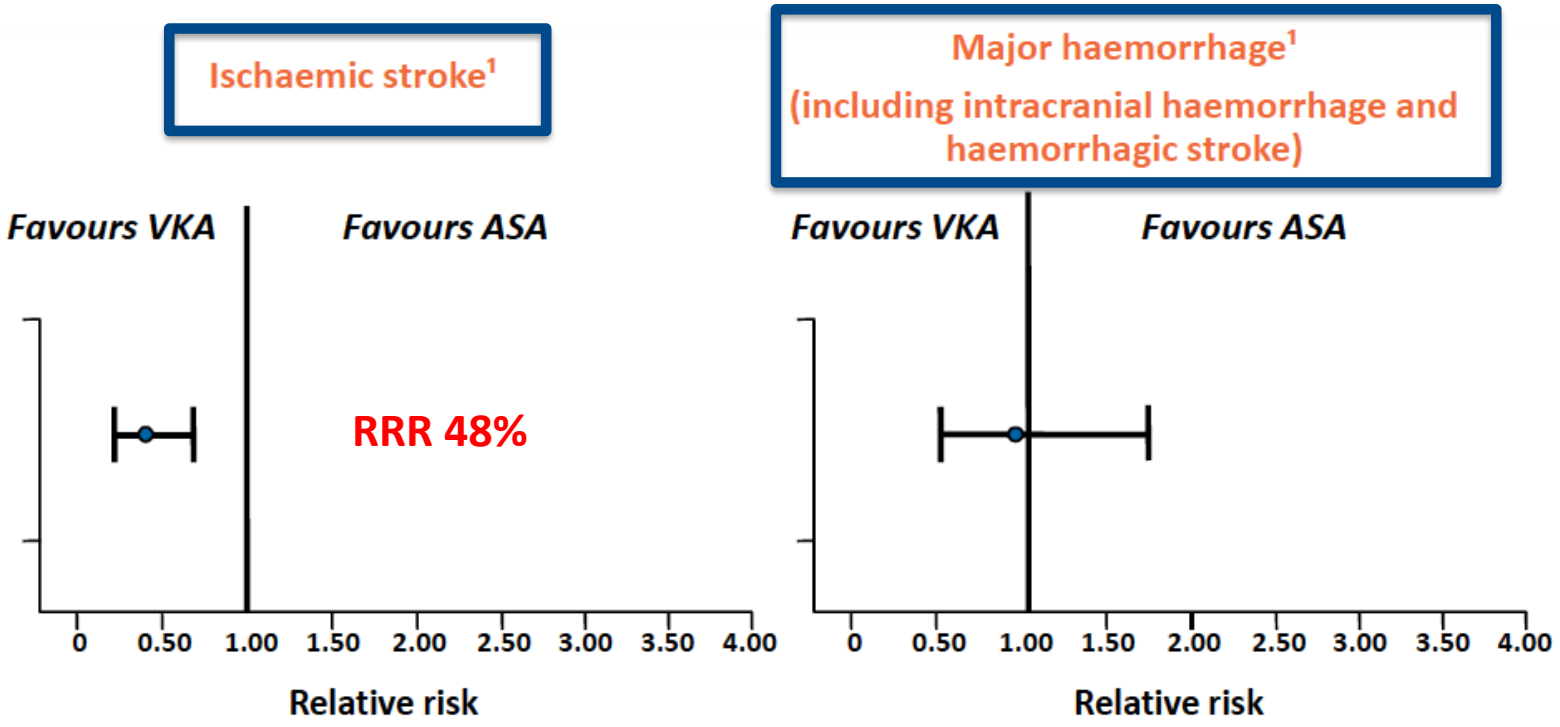
Caratteristiche basali

	Warfarin	Aspirin
Number of patients	488	485
Age (years)	81·5 (4·3)	81·5 (4·2)
Age group		
75–79	197 (40%)	200 (41%)
80–84	196 (40%)	190 (39%)
≥85	95 (19%)	95 (20%)

Mant Lancet 2007; 370 493-503

Warfarin vs Aspirin: BAFTA RCT

996 pz (elderly population with AF)



Incidenza eventi/anno 1.8% gruppo Warfarin vs 3.8% gruppo ASA

Mant J, Lancet 2007

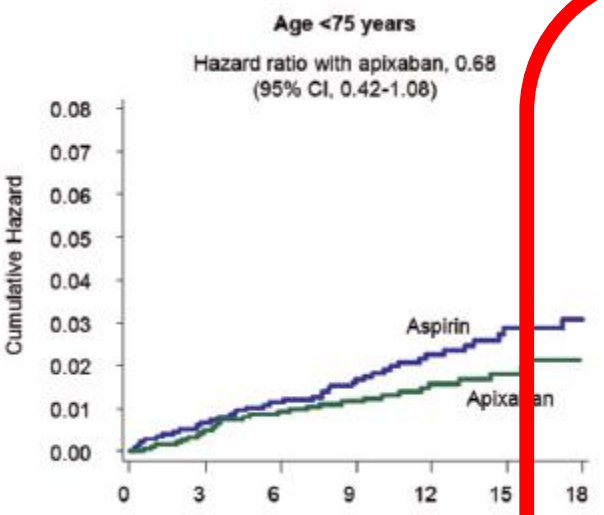
Efficacy and safety of apixaban compared with aspirin in the elderly: a subgroup analysis from the AVERROES trial

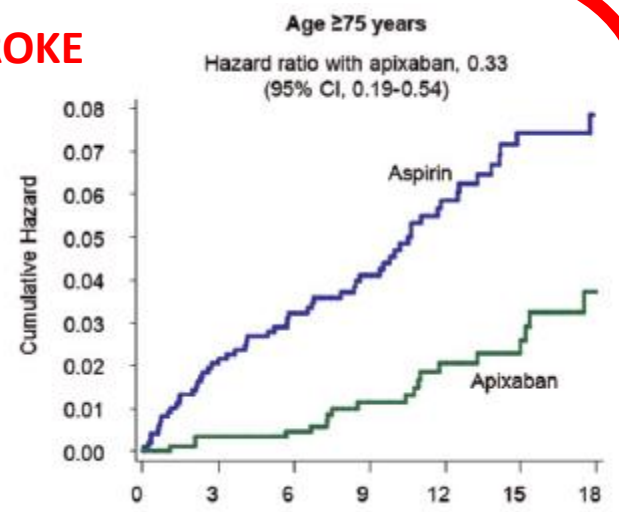
Age and Ageing 2016; **45:** 77–83

KUAN H. NG[1], OLGA SHESTAKOVSKA[1], STUART J. CONNOLLY[1], JOHN W. EIKELBOOM[1], ALVARO AVEZUM[2], RAFAEL DIAZ[3], FERNANDO LANAS[4], SALIM YUSUF[1], ROBERT G. HART[1]

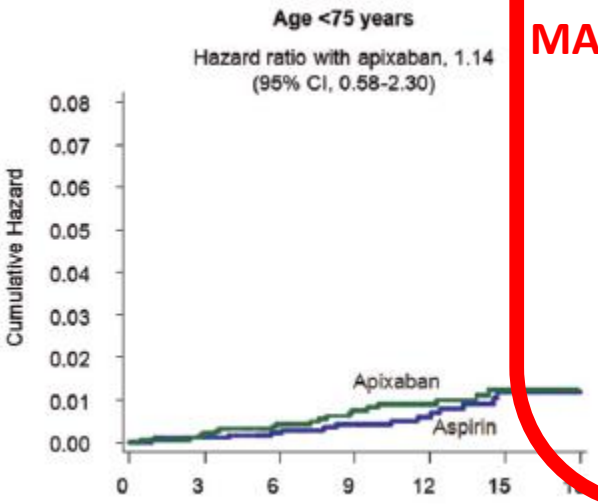
1898 pazienti >=75 anni e 366 pazienti >= 85 anni

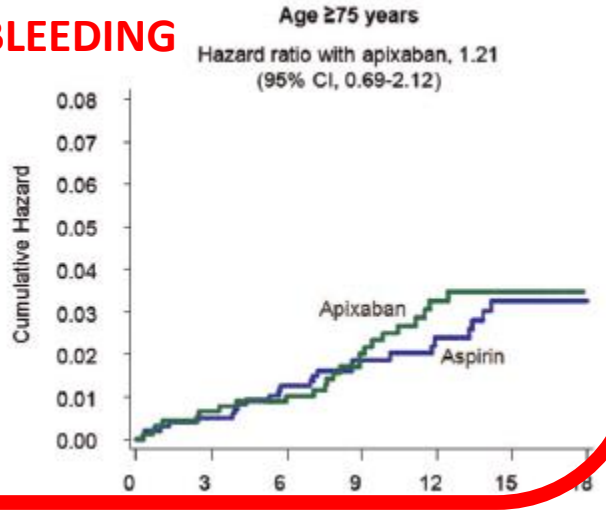
STROKE





MAJOR BLEEDING

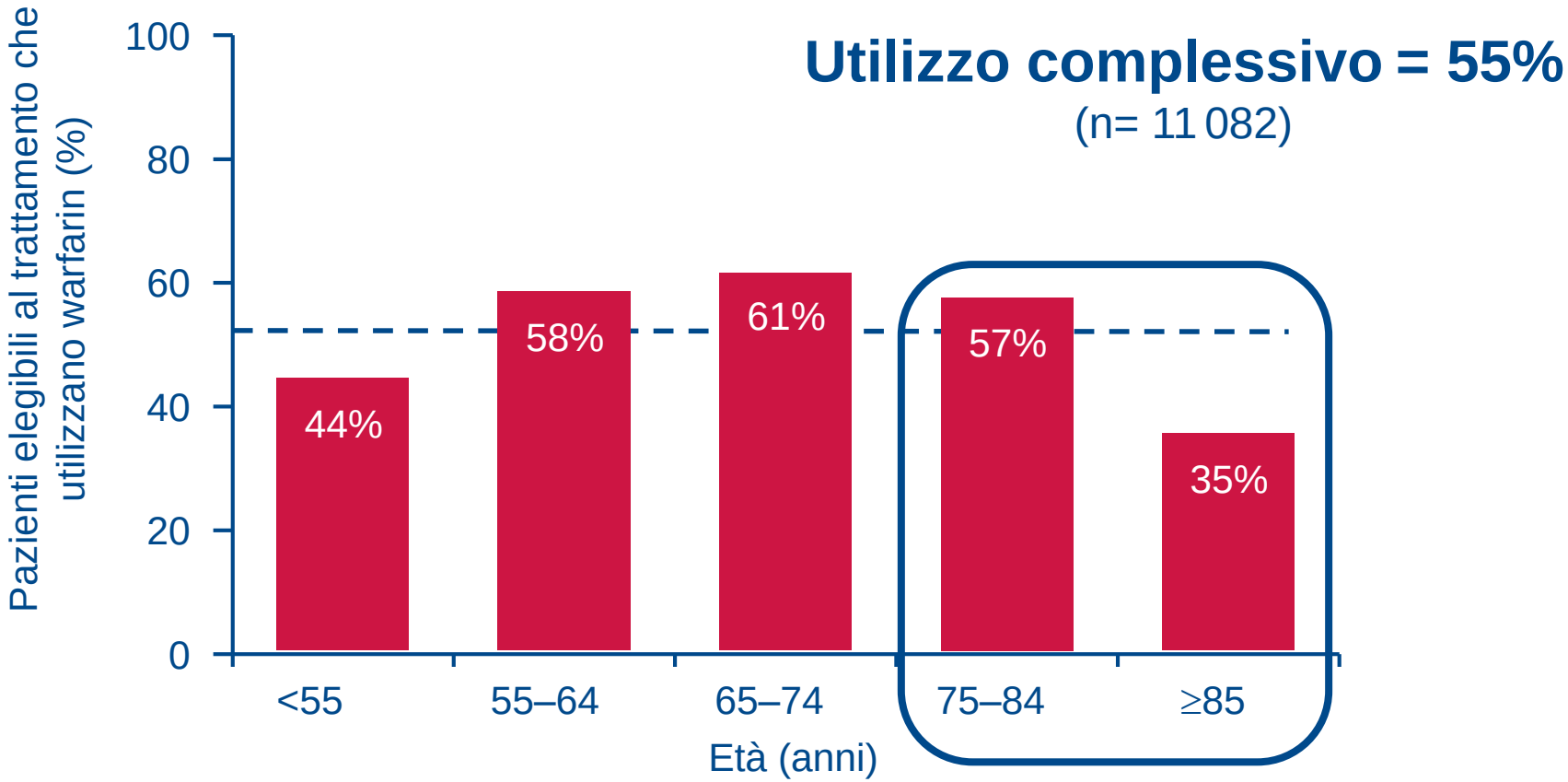




Antithrombotic Therapy in AF in elderly?

Warfarin è utilizzato solo dalla metà dei pazienti con fibrillazione atriale elegibili al trattamento

Sottoutilizzo più marcato in pazienti anziani (i quali hanno un rischio di ictus più elevato)



Go A et al. Ann Intern Med 1999;131:927–34

Current presentation and management of 7148 patients with atrial fibrillation in cardiology and internal medicine hospital centers: The ATA AF study☆

Di Pasquale G, Int J Cardiol 2013

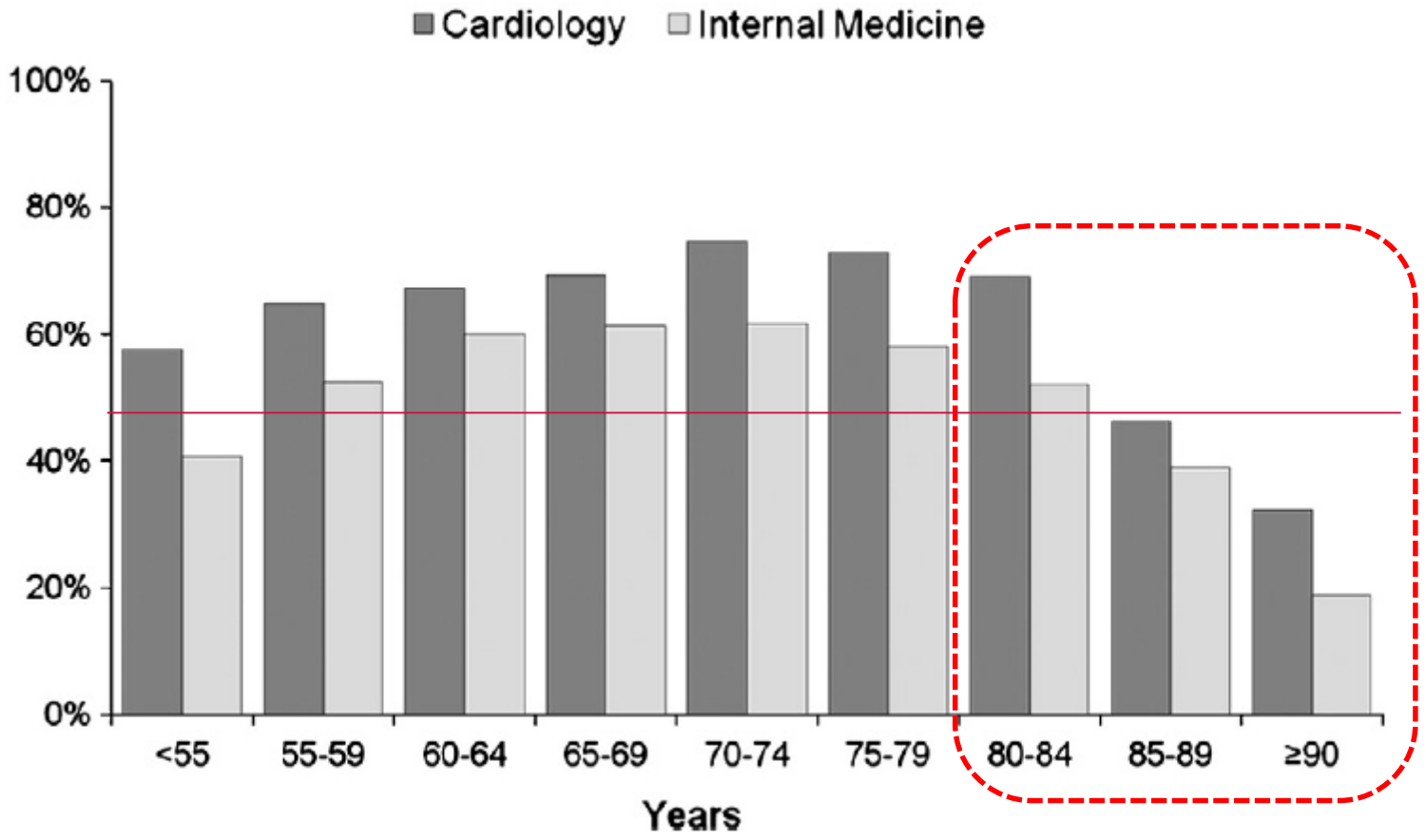


Fig. 5. OAC prescription at discharge from cardiology and internal medicine patients according to the age.

Limiti della terapia con Warfarin

J Thromb Thrombolysis 2008; 25: 52-60

European Heart Journal (2016) **37**, 2893–2962
doi:10.1093/eurheartj/ehw210

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

- Le più recenti evidenze sottolineano come la prevenzione dell'ictus con i VKA è efficace se il TTR ovvero tempo medio in range terapeutico (INR 2-3) individuale è **almeno >70%**

Tempo trascorso nell'intervallo terapeutico con l'uso di Warfarin nella pratica clinica

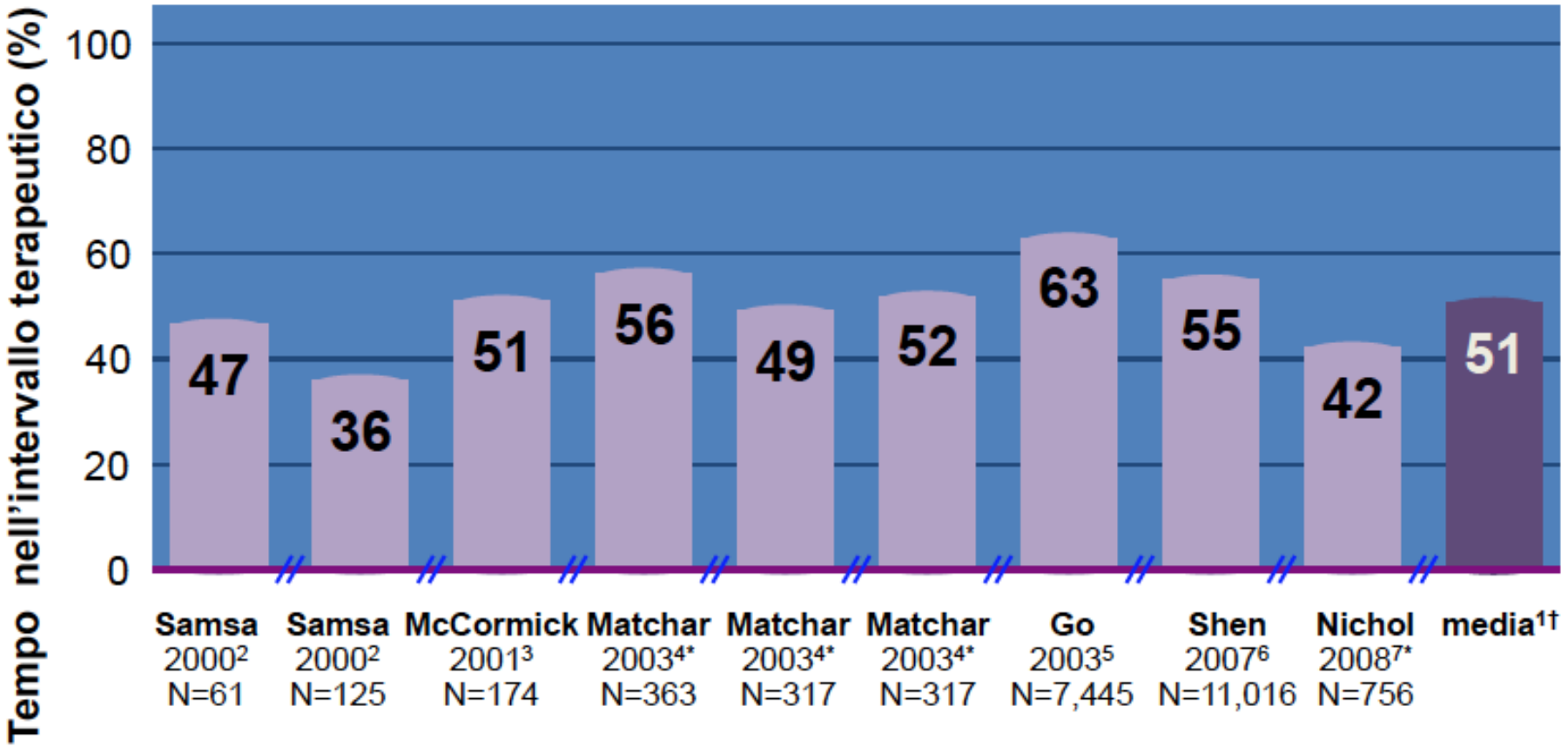


Table 5. Definition of the SAMe-TT_2R_2 Score, Used to Aid Initial Decision Making Between Vitamin K Antagonist (With Good Quality Anticoagulation Control) and a Non–Vitamin K Antagonist Oral Anticoagulant[a]

Definitions	Points
Sex (female)	1
Age (<60 y)	1
Medical history[b]	1
Treatment (interacting drugs, eg, amiodarone for rhythm control)	1
Tobacco use (within 2 y)	
Race (not white)	
Maximum points	

COMORBILITA' influenza la decisione se usare un AVK o un NAO

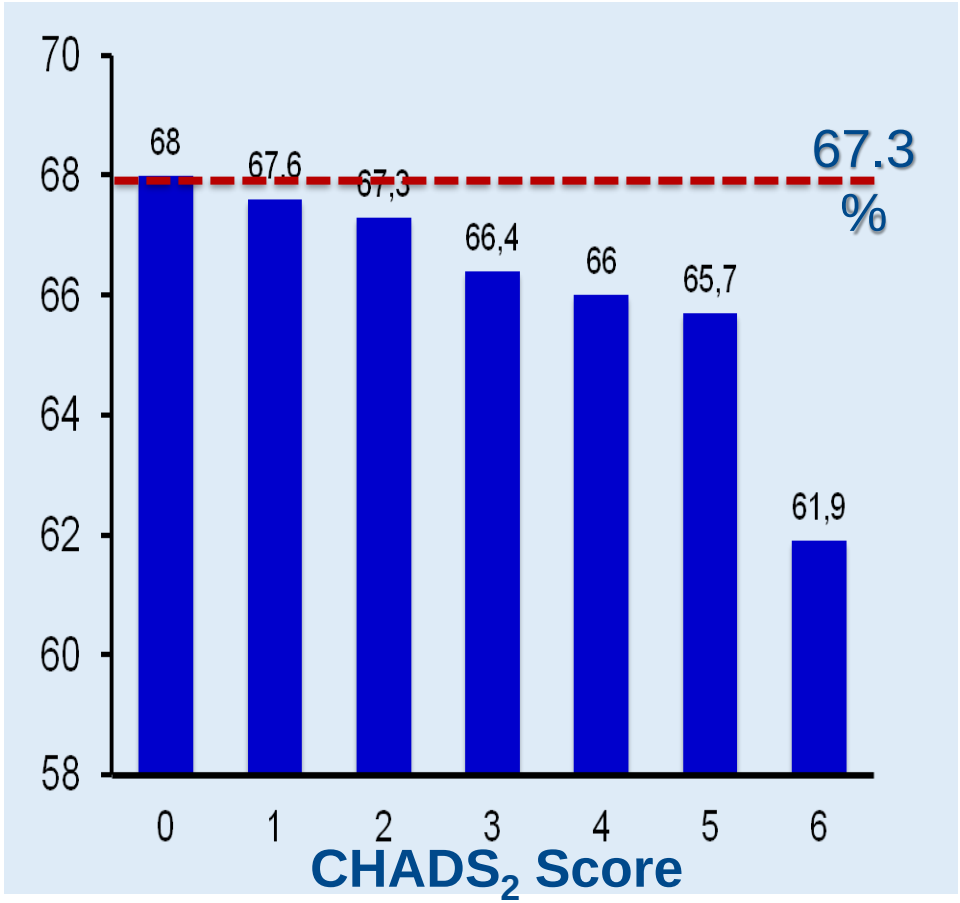
>=2 tra ipertensione, DM, CAD, AOP, CHF, STROKE, BPCO, EPATOPATIA, NEFROPATIA

Score 0-2: probabilità di buona gestione TAO con VKA
Score >2: bassa probabilità di TTR soddisfacente, preferenza per NOACs

Impact of Co-morbidities and Patient Characteristics on International Normalized Ratio Control Over Time in Patients With Nonvalvular Atrial Fibrillation

The relation between TTR and $CHADS_2$ score

(N=23425; Age: 75±10 years, $CHADS_2$ score < 2: 53.9%, 2006-2010)



Longitudinal records collected by the decision support software CoagClinic (Standing Stone, Inc., Westport, Connecticut, USA)

Nelson WW, Am J Cardiol 2013

The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study

Cite this as: *BMJ* 2015;350:h246

Community-based administrative data; 12403 adults aged 66 years or more, with AF, who started warfarin. Kidney function estimated using CKD-EPI equation

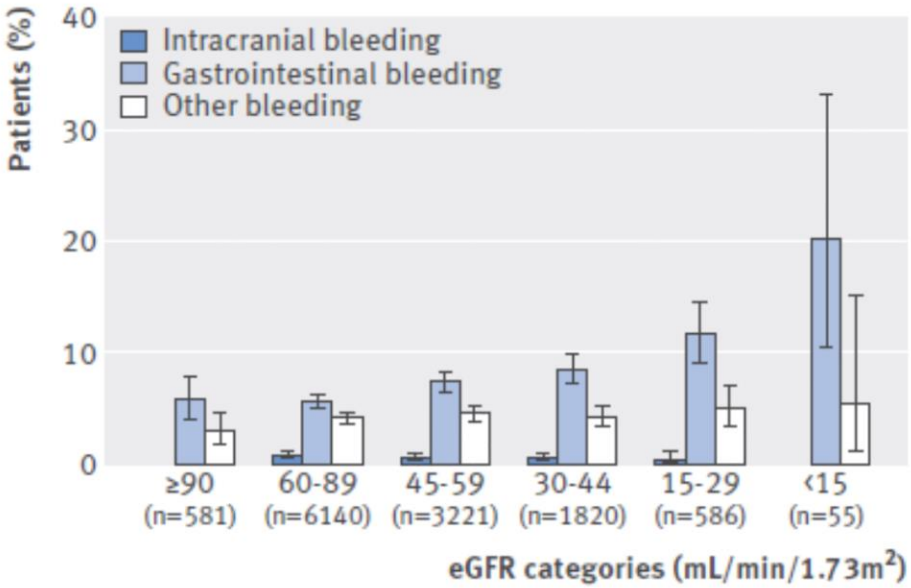


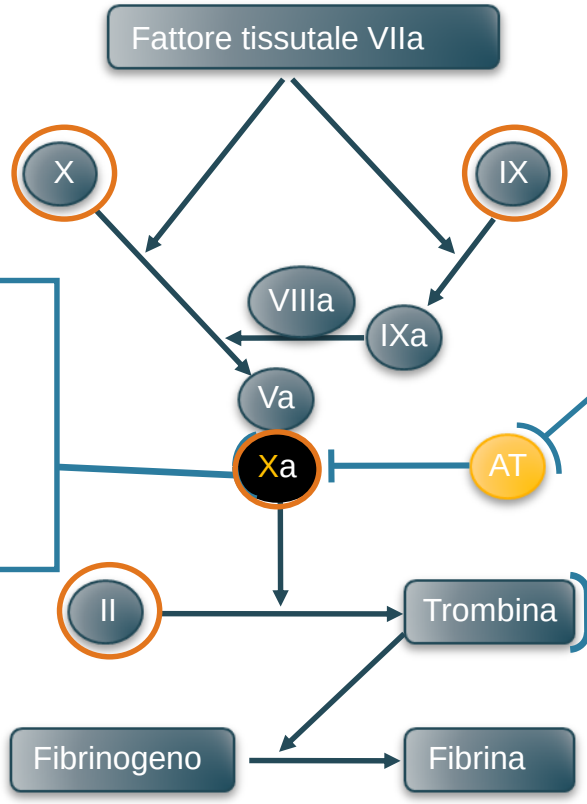
Fig 2 | Percentage of cohort experiencing a major bleeding episode, by type (intracranial bleeding, gastrointestinal bleeding, or other bleeding) and estimated glomerular filtration rate (eGFR). Results represent percentage of cohort experiencing major bleeding over the duration of study follow-up; bars represent 95% confidence intervals

During 2.1 years 1443 (11.6%) experienced a major bleeding episode. Adjusted rates of MBE increased at lower eGFR categories. Across all eGFR categories, rates of MBE were higher during the first 30 days of warfarin treatment

L'anticoagulante "Ideale"

- ***Farmacodinamica semplificata*** (attività diretta sui singoli componenti funzionali del sistema emocoagulativo)
- ***Bassa Variabilità*** farmacocinetica interindividuale (possibilità di dose fissa senza monitoraggio)
- ***Efficace***
- ***Sicuro*** (bassa incidenza di eventi emorragici)
- ***Scarse interazioni farmacologiche e con gli alimenti***
- ***Assunzione orale***
- ***Antidoto***

Non-vitamin K anticoagulant (NOAC)



Antagonisti della vitamina K:

Tecarfarin (Fase II completata)

Inibitori diretti del FATTORE Xa:

Apixaban
Rivaroxaban
Edoxaban

Inibitori indiretti del fattore Xa:

Idraparinux (Fase II completata)
Idrabiotaparinux (sospeso nel 2009)

Inibitori diretti della TROMBINA:

Dabigatran

Non-vitamin K anticoagulant (NOAC)

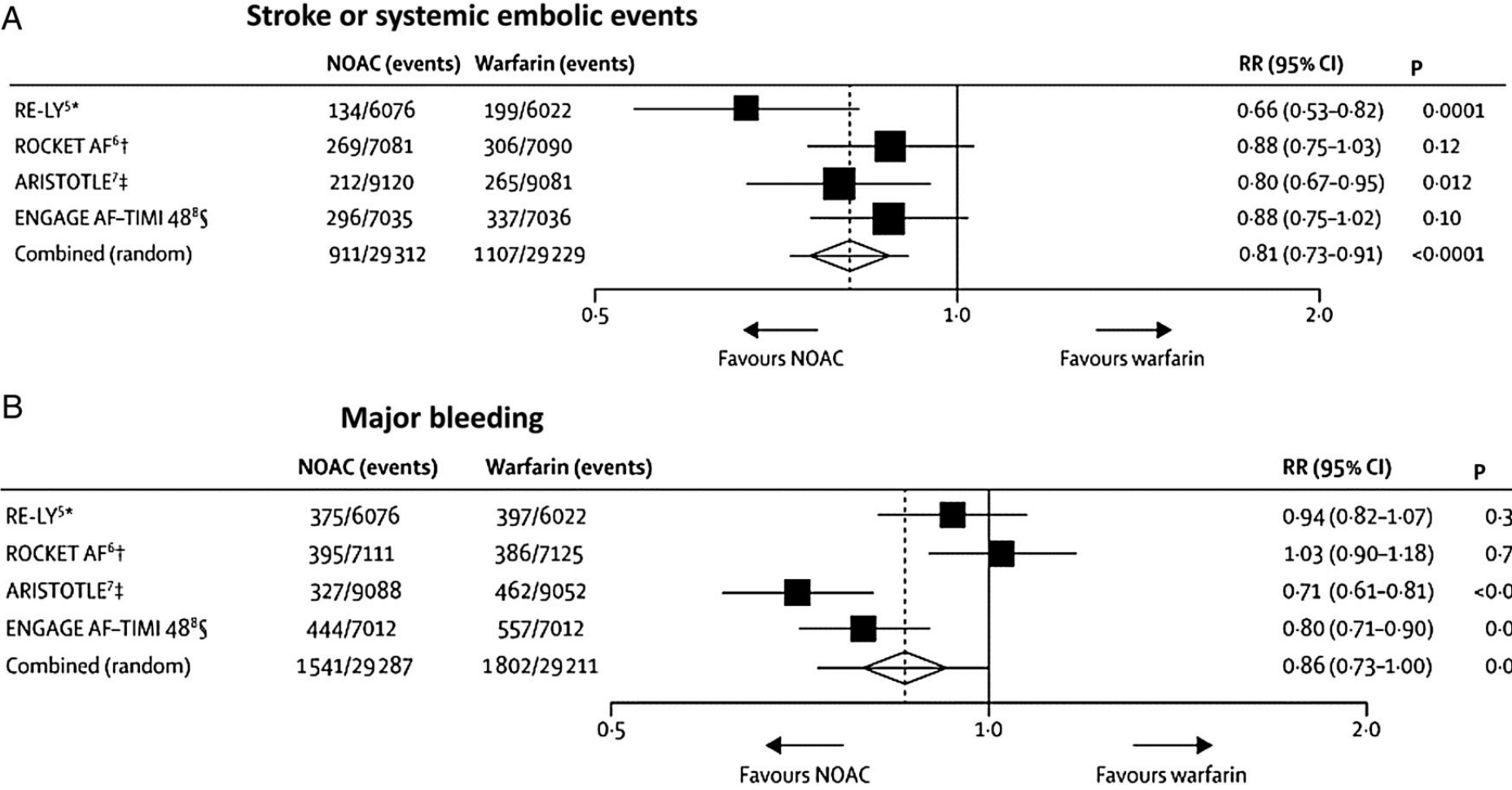
	Dabigatran (RE-LY) [318, 425]	Rivaroxaban (ROCKET-AF) [320, 426]	Apixaban (ARISTOTLE) [319, 427]	Edoxaban (ENGAGE AF-TIMI 48) [321]
Renal clearance	80%	35%	25%	50%
Number of patients	18 113	14 264	18 201	21 105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg (or 30 mg) once daily
Exclusion criteria for CKD	CrCl <30 mL/min	CrCl <30 mL/min	Serum creatinine >2.5 mg/dL or CrCl <25 mL/min	CrCl <30 mL/min
Dose adjustment with CKD	None	15 mg once daily if CrCl 30–49 mL/min	2.5 mg twice daily if serum creatinine ≥1.5 mg/dL (133 µmol/L) plus age ≥80 years or weight ≤60 kg	30 mg (or 15 mg) once daily if CrCl <50 mL/min
Percentage of patients with CKD	20% with CrCl 30–49 mL/min	21% with CrCl 30–49 mL/min	15% with CrCl 30–50 mL/dL	19% with CrCl <50 mL/min
Reduction of stroke and systemic embolism	No interaction with CKD status	No interaction with CKD status	No interaction with CKD status	NA
Reduction in major haemorrhages compared to warfarin	Reduction in major haemorrhage with dabigatran was greater in patients with eGFR >80 mL/min with either dose	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

NOAC: Advantages

• Rapid onset of action	No need for bridging
• Specific coagulation enzyme target	Low risk of off-target adverse effects
• Low potential for food interactions	No dietary precautions
• Low potential for drug interactions	Few drug restrictions
• **Predictable anticoagulant effect**	**NO need for routine coagulation monitoring**

Simpler to be used

NOAC Trials: efficacy and safety outcomes

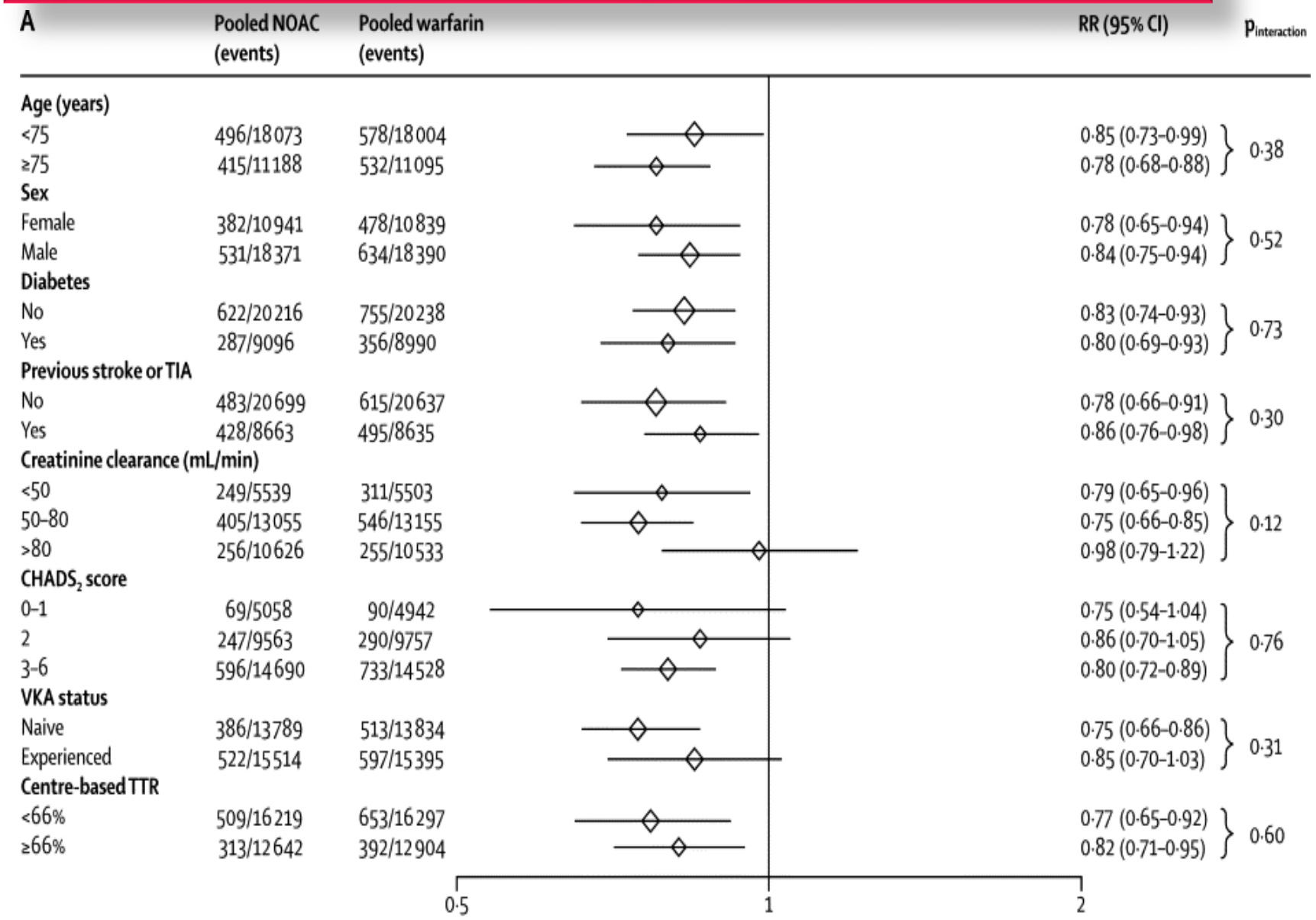


(A)Stroke or systemic embolic events - (B) Major bleeding.

Data are n/N, unless otherwise indicated. Heterogeneity: I2 = 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.

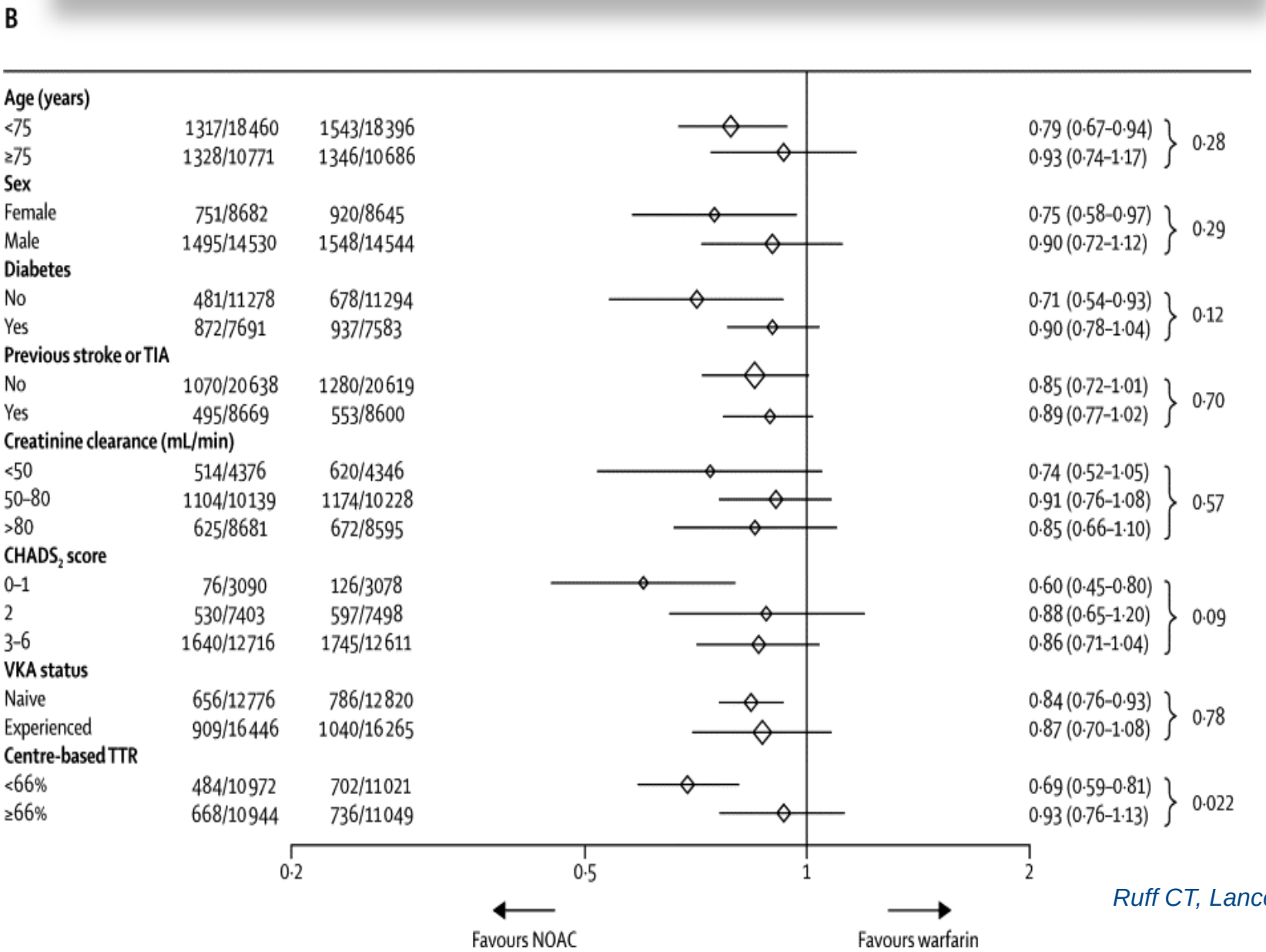
Reproduced from Ruff et al.36 with permission. Ruff et al. Lancet 2014;383:955-62

A. Sottogruppi per stroke e SEE



Ruff CT, Lancet 2014

B. Sottogruppi per sanguinamenti maggiori



Ruff CT, Lancet 2014

ESC European Society of Cardiology
European Heart Journal (2018) 39, 1330–1393
doi:10.1093/eurheartj/ehy136

Non-Eligibility for NOAC

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

	Eligible	Contra-indicated
Mechanical prosthetic valve		✓
Moderate to severe mitral stenosis (usually of rheumatic origin)		✓
Mild to moderate other native valvular disease	✓	
Severe aortic stenosis	✓ Limited data. Most will undergo intervention	
Bioprosthetic valve[a]	✓ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	✓ (except for the first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk)	
Hypertrophic cardiomyopathy	✓ (but no prospective data)	

PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
[a]American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.

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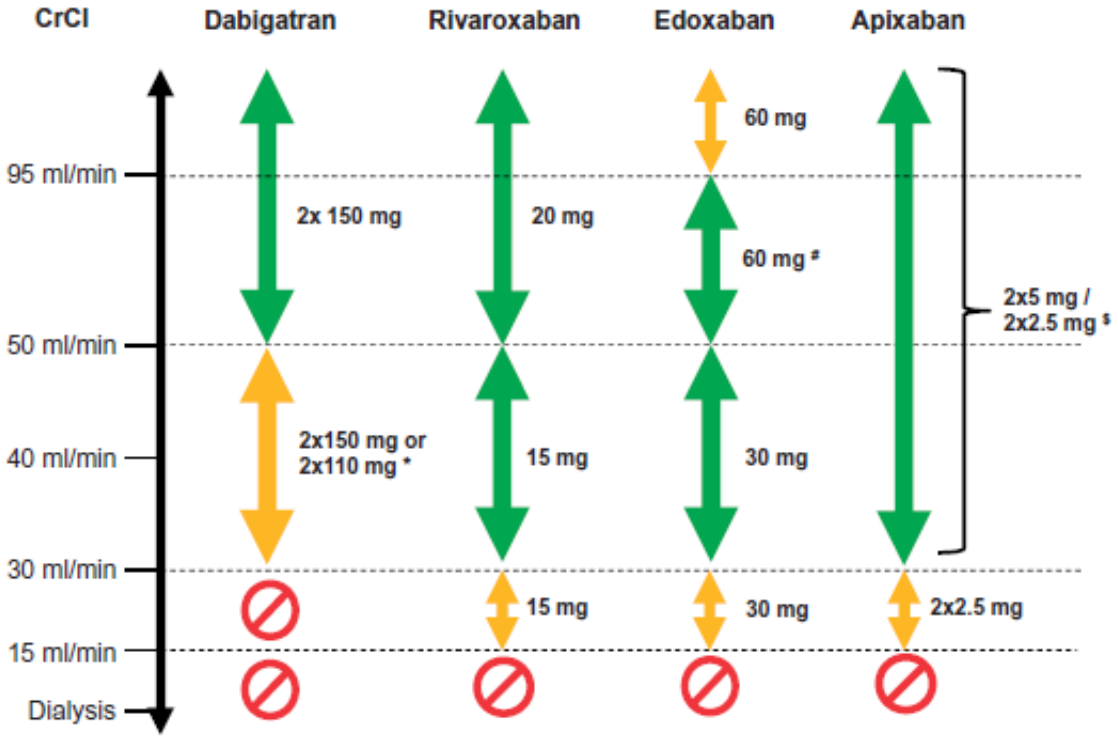
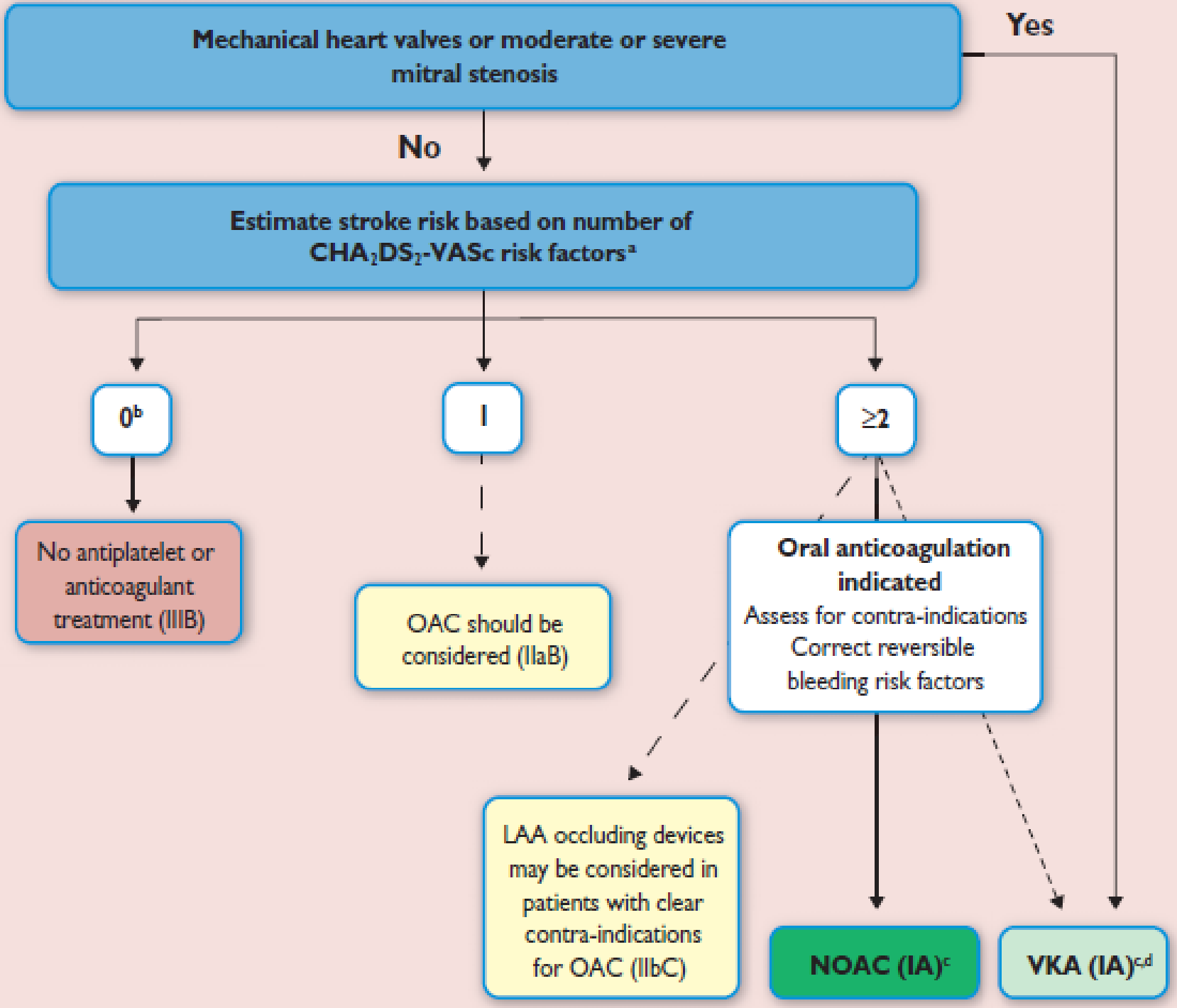


Severe renal impairment and liver disease

Child–Pugh category	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
A (5–6 points)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B (7–9 points)	Use with caution	Use cautiously	Use cautiously	Do not use
C (10–15 points)	Do not use	Do not use	Do not use	Do not use



EUROPEAN SOCIETY OF CARDIOLOGY®

Limiti dei NOACs

1. Aumentato rischio di sanguinamento GEL
2. Aderenza: difficile da controllare.
3. Efficacia e sicurezza non note in categorie di pazienti esclusi dai trials clinici
4. Pazienti con FA e CAD
5. Interazioni con altri farmaci

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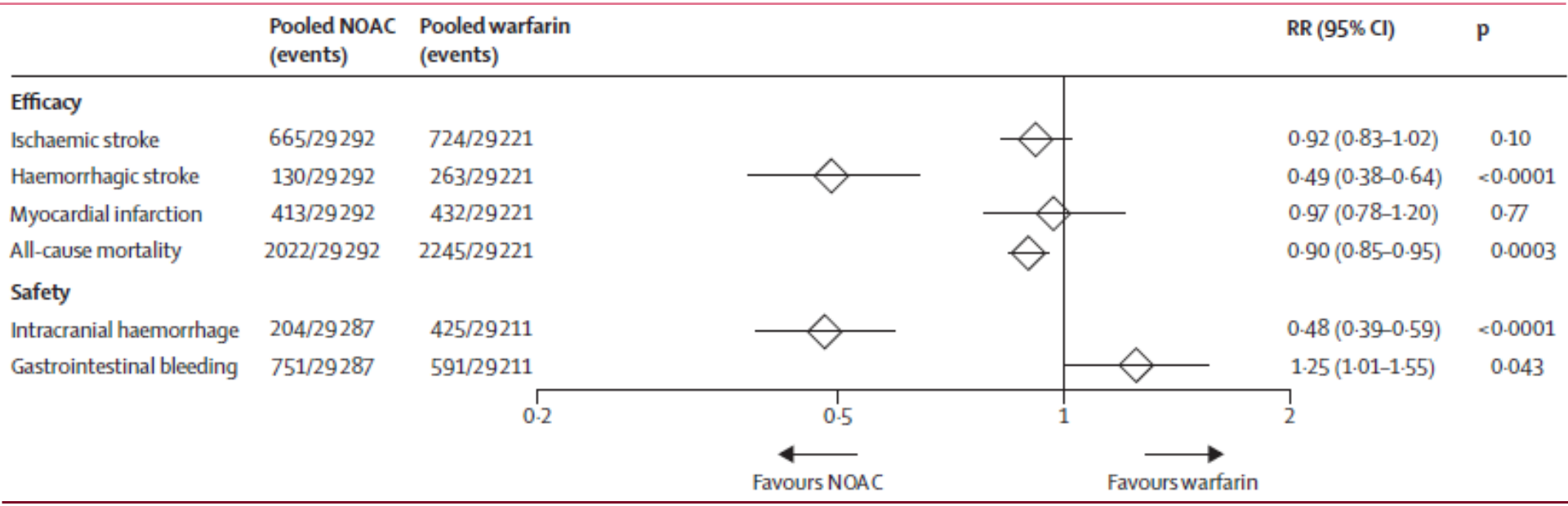

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

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Limiti dei NOACs

1. Aumentato rischio di sanguinamento GEL

2. Aderenza: difficile da controllare
   - Mancanza di test di laboratorio di routine per monitorare livello di scoagulazione

   - Nei trial segnalata alta percentuale di sospensione della terapia

	Discontinuation Rate: Study Drug	Discontinuation Rate: Warfarin
RELY: Dabigatran	21%	18%
ROCKET AF: Rivaroxaban	24%	22%
ARISTOTLE: Apixaban	25%	28%

Limiti dei NOACs

1. Aumentato rischio di sanguinamento GEL
2. Aderenza: difficile da controllare.
3. Efficacia e sicurezza non note in categorie di pazienti esclusi dai trials clinici
4. Pazienti con FA e CAD
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Limiti dei NOACs

Efficacia e sicurezza non note in categorie di pazienti esclusi dai trials clinici ed a rischio emorragico di per se più elevato

- Difetti di coagulazione congeniti e/o acquisiti
- Patologie gastro-intestinali (angiodisplasie; epatopatie; etc)
- Insufficienza renale dialitica
- Insufficienza epatica
- Emorragia cerebrale atipica
- Paziente “fragile” , a rischio di cadute
- Pazienti affetti da demenza
- Cardiomiopatie

CONSIDERA CHIUSURA PERCUTANEA DELL’AURICOLA SINISTRA

Limiti dei NOACs

1. Aumentato rischio di sanguinamento GEL
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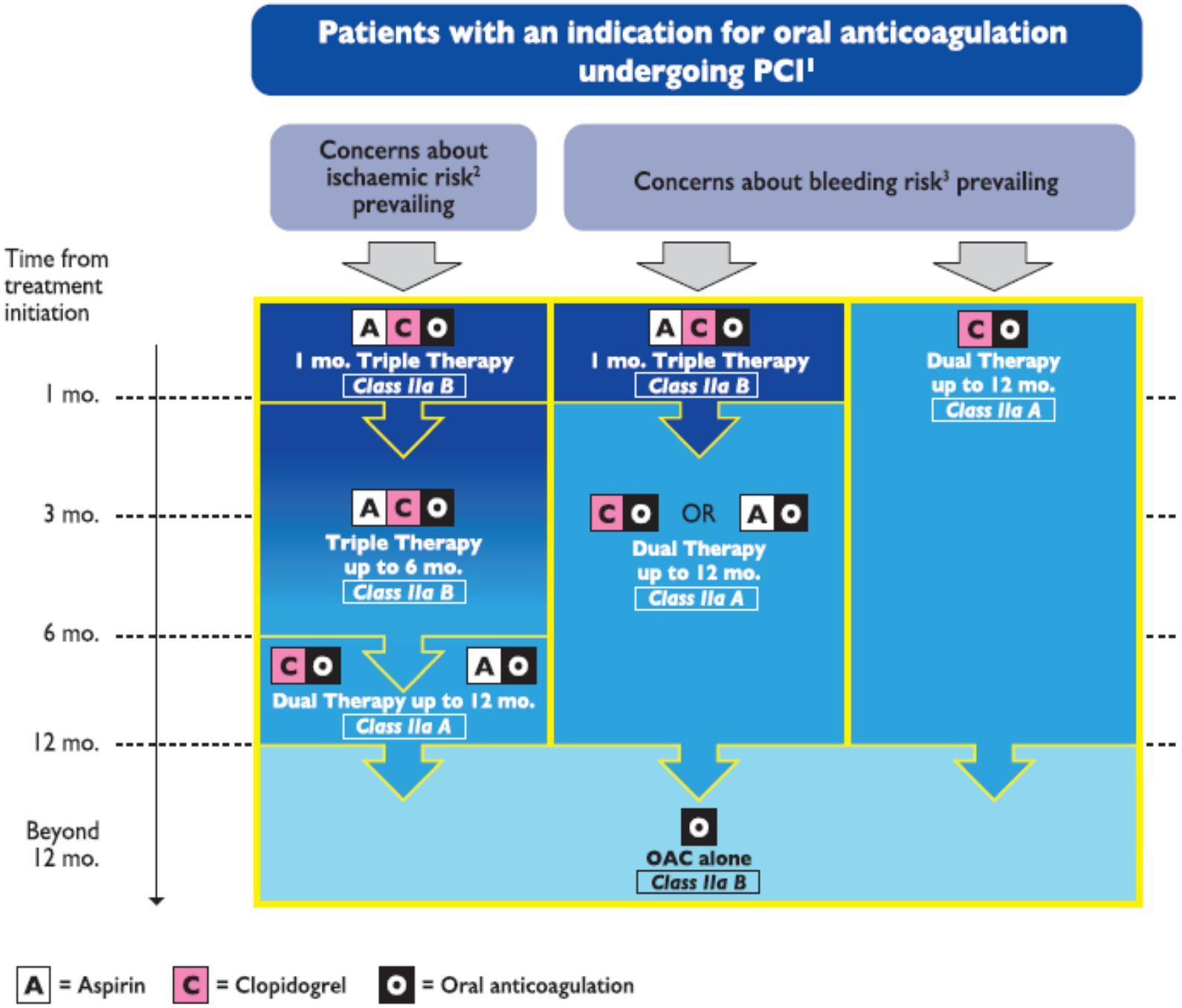
ESC
European Society of Cardiology
European Heart Journal (2018) **39**, 213–254
doi:10.1093/eurheartj/ehx419

ESC GUIDELINES

2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS

The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)


Patients with an indication for oral anticoagulation undergoing PCI[1]
Concerns about ischaemic risk[2] prevailing
Concerns about bleeding risk[3] prevailing
Time from treatment initiation
1 mo.
3 mo.
6 mo.
12 mo.
Beyond 12 mo.
A C O
1 mo. Triple Therapy
Class IIa B
A C O
1 mo. Triple Therapy
Class IIa B
C O
Dual Therapy up to 12 mo.
Class IIa A
A C O
Triple Therapy up to 6 mo.
Class IIa B
C O OR A O
Dual Therapy up to 12 mo.
Class IIa A
C O
A O
Dual Therapy up to 12 mo.
Class IIa A
O
OAC alone
Class IIa B
A = Aspirin
C = Clopidogrel
O = Oral anticoagulation

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SPECIAL ARTICLE

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

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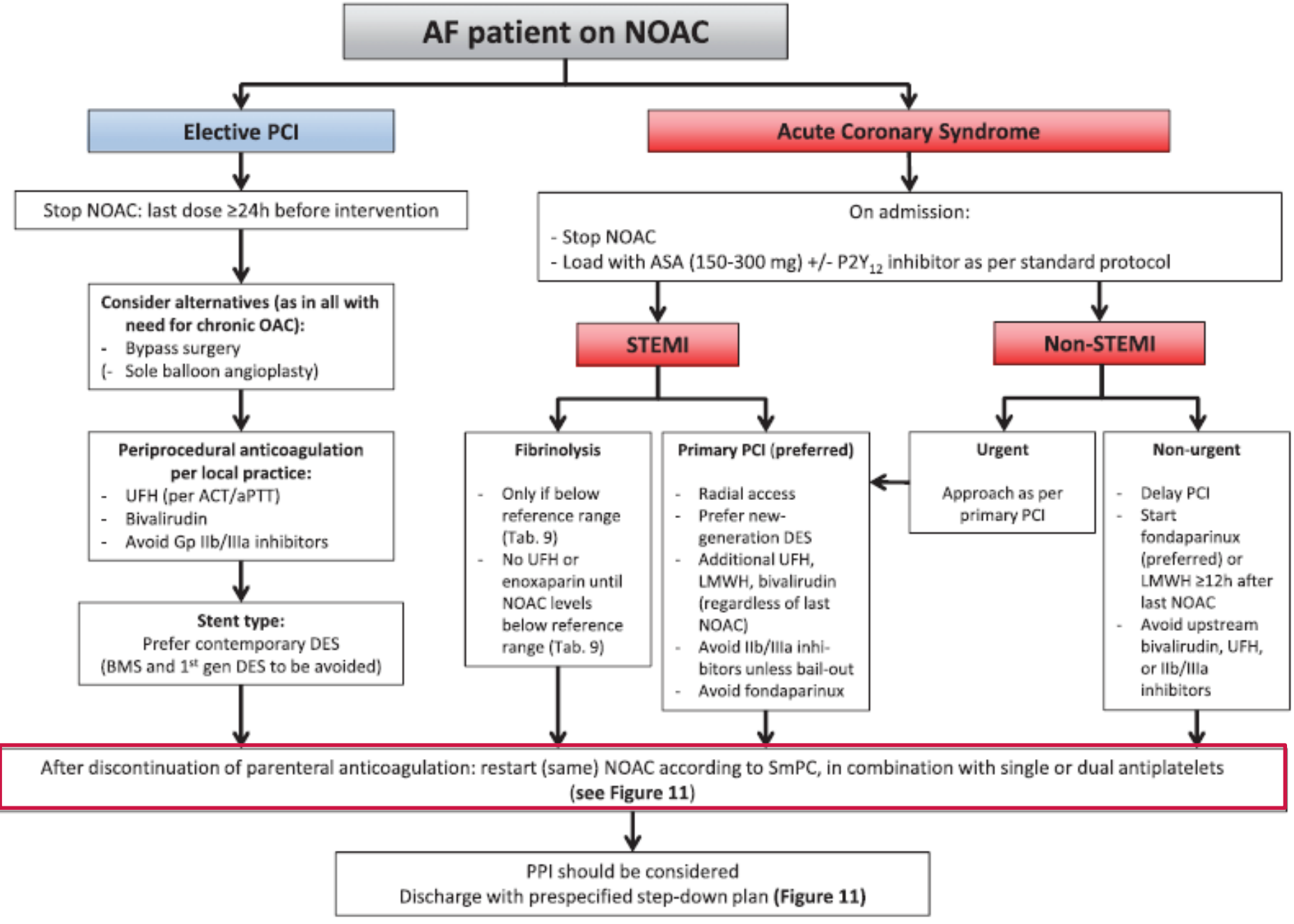
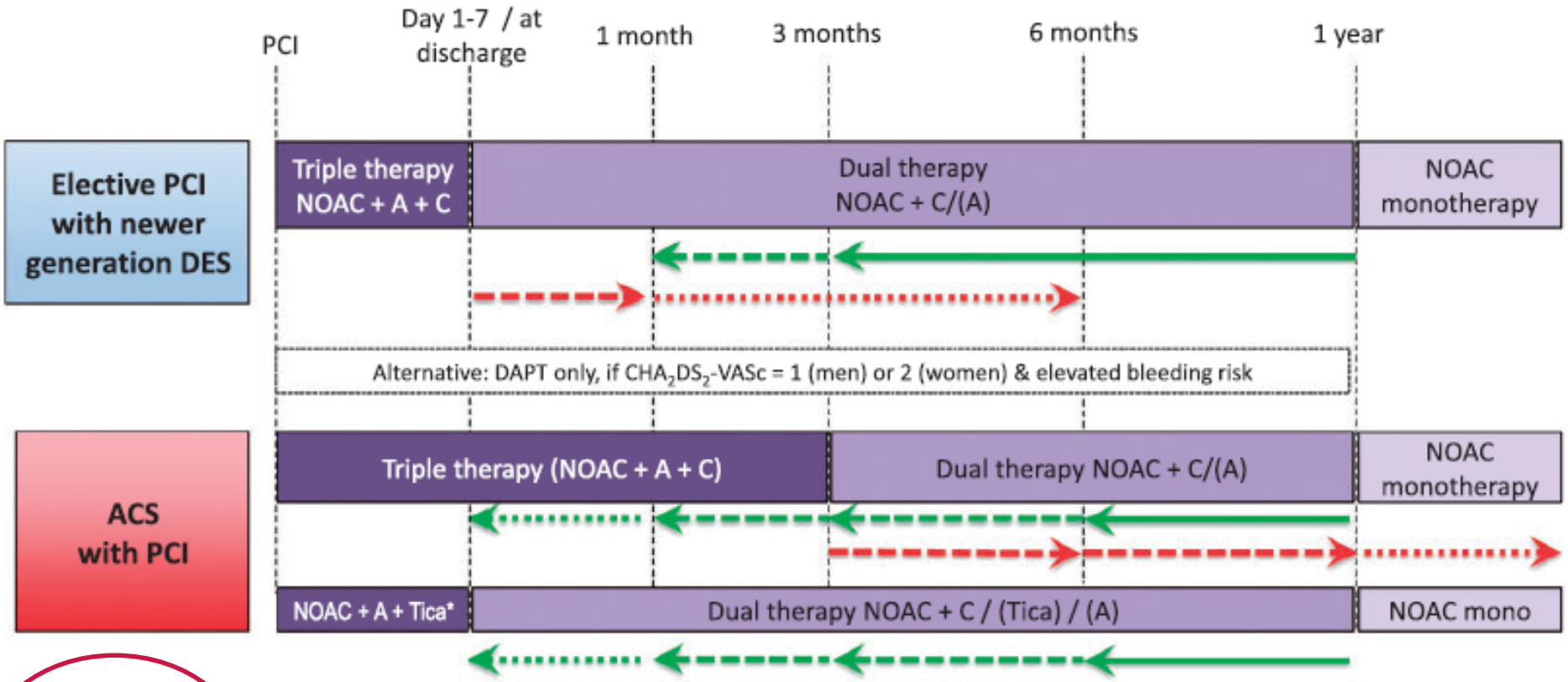

AF patient on NOAC
Elective PCI
Acute Coronary Syndrome
Stop NOAC: last dose ≥24h before intervention
On admission:
- Stop NOAC
- Load with ASA (150-300 mg) +/- P2Y12 inhibitor as per standard protocol
Consider alternatives (as in all with need for chronic OAC):
- Bypass surgery
(- Sole balloon angioplasty)
STEMI
Non-STEMI
Periprocedural anticoagulation per local practice:
- UFH (per ACT/aPTT)
- Bivalirudin
- Avoid Gp IIb/IIIa inhibitors
Fibrinolysis
- Only if below reference range (Tab. 9)
- No UFH or enoxaparin until NOAC levels below reference range (Tab. 9)
Primary PCI (preferred)
- Radial access
- Prefer new-generation DES
- Additional UFH, LMWH, bivalirudin (regardless of last NOAC)
- Avoid IIb/IIIa inhibitors unless bail-out
- Avoid fondaparinux
Urgent
Approach as per primary PCI
Non-urgent
- Delay PCI
- Start fondaparinux (preferred) or LMWH ≥12h after last NOAC
- Avoid upstream bivalirudin, UFH, or IIb/IIIa inhibitors
Stent type:
Prefer contemporary DES
(BMS and 1st gen DES to be avoided)
After discontinuation of parenteral anticoagulation: restart (same) NOAC according to SmPC, in combination with single or dual antiplatelets (see Figure 11)
PPI should be considered
Discharge with prespecified step-down plan (Figure 11)



TAILORED-THERAPY

Factors to shorten combination therapy

- (Uncorrectable) high bleeding risk
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CONSIDERA CHIUSURA PERCUTANEA DELL'AURICOLA SINISTRA

- First-generation DES
- High atherothrombotic risk (scores as above ; stenting of the left main, proximal LAD, proximal bifurcation; recurrent MIs; stent thrombosis etc.) and low bleeding risk

AND HIGH BLEEDING RISK?

Limiti dei NOACs

1. Aumentato rischio di sanguinamento GEL
2. Aderenza: difficile da controllare.
3. Efficacia e sicurezza non note in categorie di pazienti esclusi dai trials clinici
4. Pazienti con FA e CAD
5. Interazioni con altri farmaci

Antiarrhythmic drugs

Antibiotics

Fungostatics

Anthracyclines/Anthracenediones

Hormonal agents

Immune-modulating agents

Cyclosporine	Strong-to-moderate P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC	SmPC	+73%[143]	
Dexamethasone	Strong CYP3A4/P-gp induction; CYP3A4/P-gp competition				
Tacrolimus	Strong-to-moderate P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC			
Prednisone	Moderate CYP3A4 induction; CYP3A4 competition				
Temsirolimus, Sirolimus	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Everolimus	CYP3A4 competition; No relevant interaction anticipated				

Conclusioni

1. I NOAC si sono dimostrati farmaci sicuri ed efficaci rispetto al warfarin

2. L'adesione al trattamento è essenziale per l'efficacia e la sicurezza

3. I NOAC Hanno cambiato la qualità della vita dei pazienti

4. I NOAC rappresentano l'alternativa di scelta nella maggior parte dei pazienti, ma non in tutti

5. Nei pazienti che presentano controindicazioni alla terapia anticoagulante o troppo elevato rischio di sanguinamento, considerare la chiusura percutanea dell'auricola sinistra

ASL CITTÀ DI TORINO