SOCIETÀ MEDICA DI SANTA MARIA NUOVA

Giornate Mediche di
Santa Maria Nuova 2015

VII EDIZIONE

L'ECCELLENZA DELLE CURE
IN OSPEDALE:
Santa Maria Nuova
si confronta con la sua storia
e con l'innovazione

2 - 3 Ottobre 2015

TAVOLA ROTONDA

La terapia con i Nuovi Anticoagulanti Orali: La gestione «sul campo» di una classe di farmaci innovativi

I Prescrittori: Il Cardiologo

Massimo Milli
Cardiologia SMN
Azienda Sanitaria di Firenze

FIBRILLAZIONE ATRIALE: Epidemiologia

33,5 milioni di persone affette da FA nel 2010

Incidenza nei paesi industrializzati: ***213 nuovi casi/anno/100.000 persone***

Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study

Eur Heart J. 2006 Apr;27(8):949-53.

FIBRILLAZIONE ATRIALE: Epidemiologia

Rischio di sviluppare FA nel corso della vita per un uomo/donna europeo di 55 anni:	***24,8 % (uomini)*** ***22,9 (donne)***

Eta' media dei pz con FA 77 aa Prevalenza di FA nella popolazione > 85 anni:	***15 %***

Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study.
Chugh SS1 et al. Circulation. 2014 Feb 25;129(8):837-47.

Maggiore motivazione al trattamento

Vantaggi clinici

Semplificazione del trattamento

Necessità di acquisire nozioni di base ed esperienza clinica diretta sulle varie molecole a disposizione

Gestione di alcune complessità organizzativo/gestionali

Persistenza di alcune zone d'ombra

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

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

Maggiore motivazione al trattamento

Possibilità di allargare il trattamento anticoagulante a fasce di pz che precedentemente non erano trattati in modo corretto:

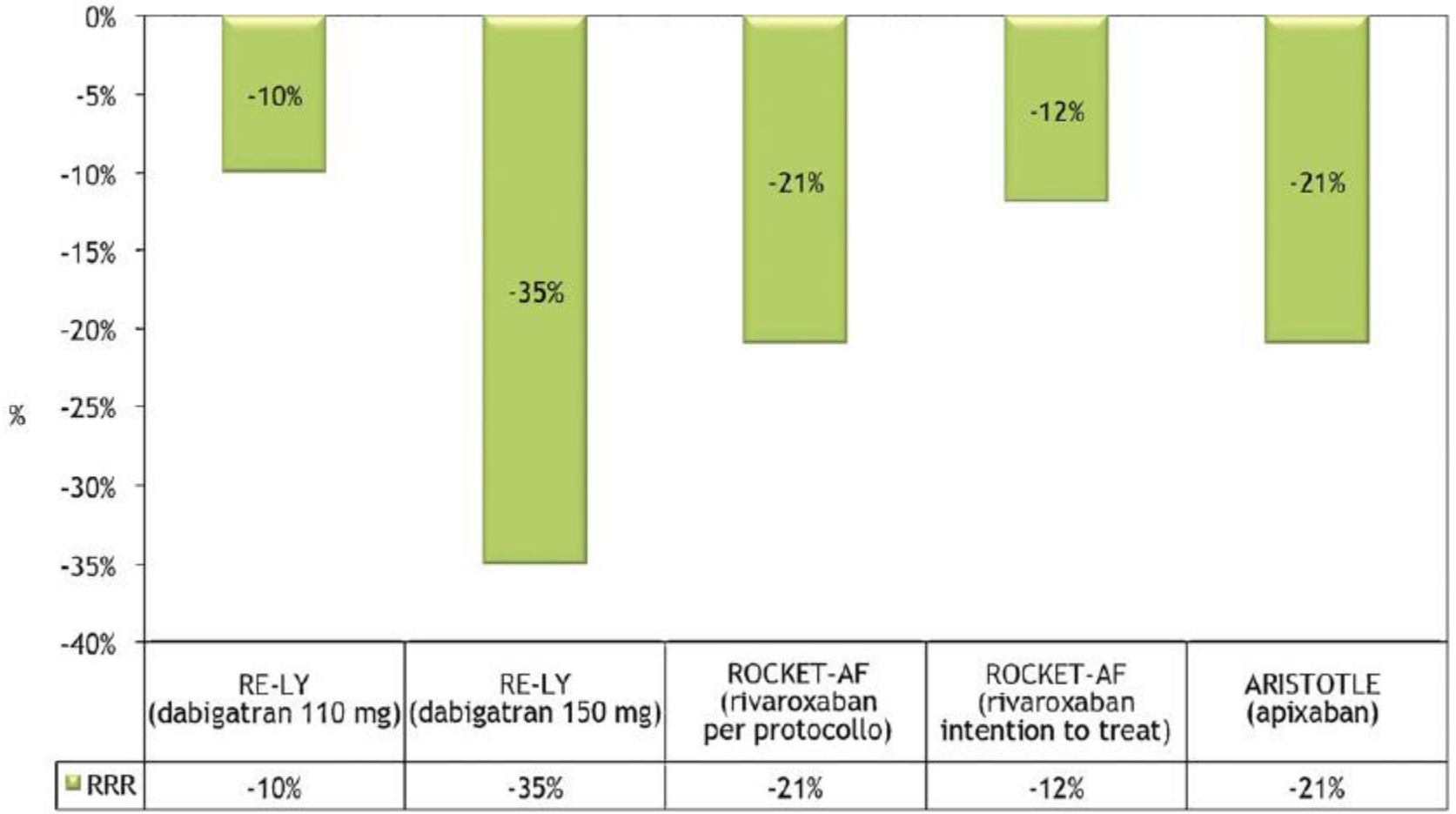
- Pazienti anziani (grande anziano)
- Pazienti con scarsa compliance
- Pazienti con scarso controllo del TTR (TTR medio degli trial con NAO (55-64%)
- Pazienti che rifiutano il trattamento anticoagulante con dicumarolici

Efficacia e sicurezza dei nuovi farmaci anticoagulanti orali rispetto al warfarin nella profilassi cardioembolica del paziente con fibrillazione atriale non valvolare. Più luci che ombre

Efficacy and safety of new oral anticoagulants compared with warfarin in cardioembolic prophylaxis of patients with non valvular atrial fibrillation. More lights than shadows

Luca Masotti [a,*], Mario Di Napoli [b], Walter Ageno [c], Davide Imberti [d], Daniel Godoy [e], Grazia Panigada [f], Niccolò Napoli [f], Giancarlo Landini [g], Roberto Cappelli [h], Ido Iori [i], Domenico Prisco [j], Giancarlo Agnelli [k]

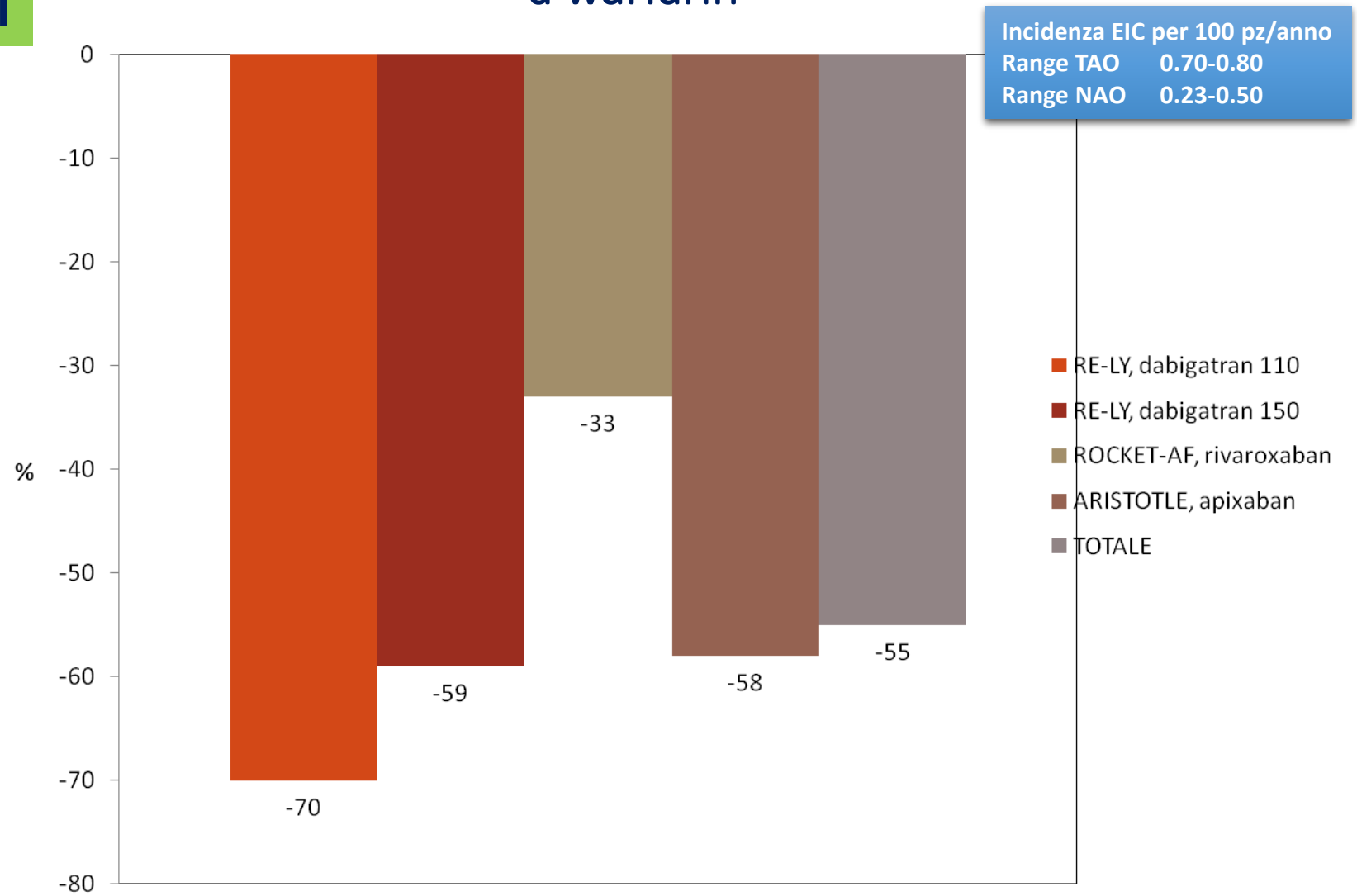
Vantaggi clinici



Riduzione del rischio relativo (RRR) di ictus ischemico ed emorragico e tromboembolismo sistemico dei nuovi anticoagulanti orali rispetto al warfarin.

Vantaggi clinici

RRR delle emorragie intracraniche dei nuovi anticoagulanti rispetto a warfarin



Modificata da Masotti et al. Ital J Med 2012

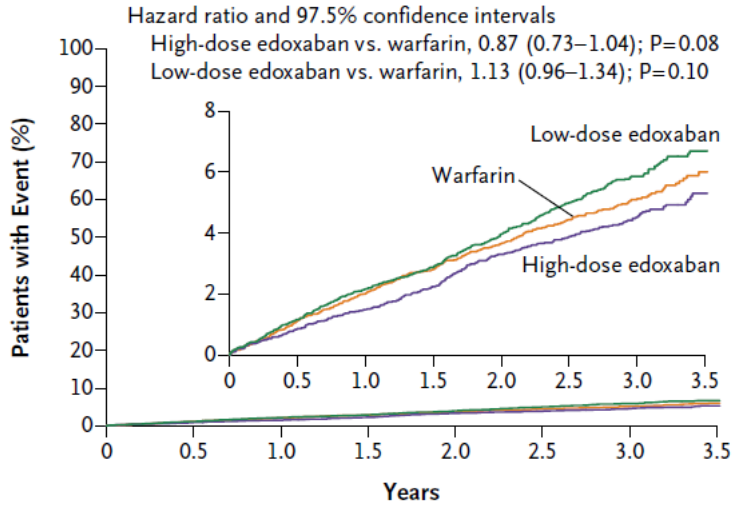
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

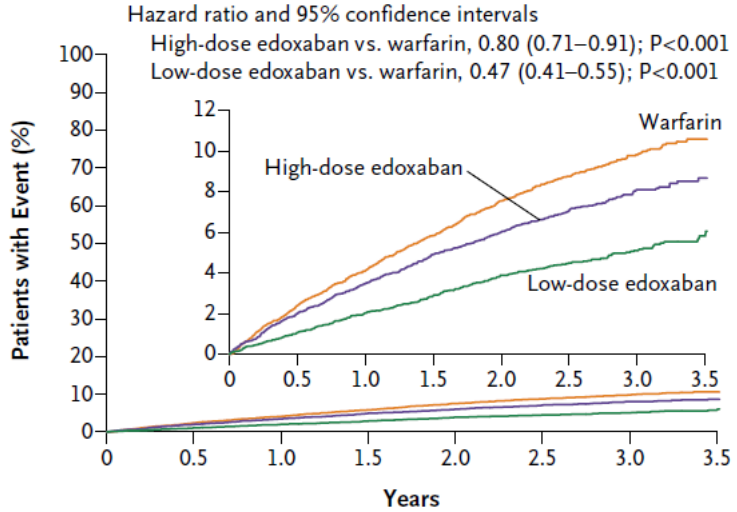
Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*

A Stroke or Systemic Embolic Event



No. at Risk								
Warfarin	7036	6798	6615	6406	6225	4593	2333	536
High-dose edoxaban	7035	6816	6650	6480	6283	4659	2401	551
Low-dose edoxaban	7034	6815	6631	6461	6277	4608	2358	534

B Major Bleeding



Semplificazione del trattamento

- Dosaggio fisso del farmaco
- Non necessario monitoraggio continuo dei parametri della coagulazione
- Assenza di interazione con il cibo e minori interazioni farmacologiche
- Facile switch con eparine BPM
- Possibilità di inizio precoce di terapia anche durante ricovero al DEA
- Semplificazione della procedura di cardioversione elettrica

REVIEW

CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will manage bleeding complications in patients on the new oral anticoagulants

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Practical management of bleeding due to the anticoagulants dabigatran, rivaroxaban, and apixaban

Necessità di acquisire nozioni di base ed esperienza clinica diretta sulle varie molecole a disposizione

TABLE 1

Pharmacokinetic profiles and metabolism of the new oral anticoagulants

Feature	Dabigatran	Rivaroxaban	Apixaban
Prodrug	Yes	No	No
Mode of action	Thrombin inhibition	Factor Xa inhibition	Factor Xa inhibition
Bioavailability	6%–8%	80%	50%
Time to peak	1.5–2 hours	2–3 hours	3 hours
Half-life	14–17 hours	7–11 hours	8–14 hours
Excretion	Renal (unchanged) > 80% Bile 5%–10%	Renal (half inactive) 66% Feces 33%	Renal 25%–30% Feces 56%
Plasma protein binding	35%	95%	87%

DATA FROM REFERENCES 13, 16, AND 18.

Gestione di alcune complessità organizzativo/gestionali : Esperienza Cardiologia SMN

FASE 1

Chi compila il piano ?
Dove ?
Quando ?
Chi lo rinnova ?

FASE 2

Apertura di una Agenda CUP per Ambulatorio NAO gestita dal personale della Reception di Linea Medica (Al momento della prenotazione richiesta di pervenire alla visita con esami ematici non anteriori al mese

Cardiologia SMN

↓

Specialisti non abilitati all'esecuzione del piano (Cardiologi Territoriali Medici di laboratorio) → **AMBULATORIO NAO:**

- **Valutazione del pz**
- **Esecuzione piano terapeutico o rinnovo**
- **invio alla farmacia interna per ritiro del farmaco**
- **Apertura follow-up**

← MMG

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

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

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

Definition of 'non-valvular atrial fibrillation' and eligibility for non-vitamin K antagonist oral anticoagulants

Table I Valvular indications and contraindications for NOAC therapy in AF patients

	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.[8]

H. Heidbuchel et al Europace 2015

Patient with atrial fibrillation and coronary artery disease

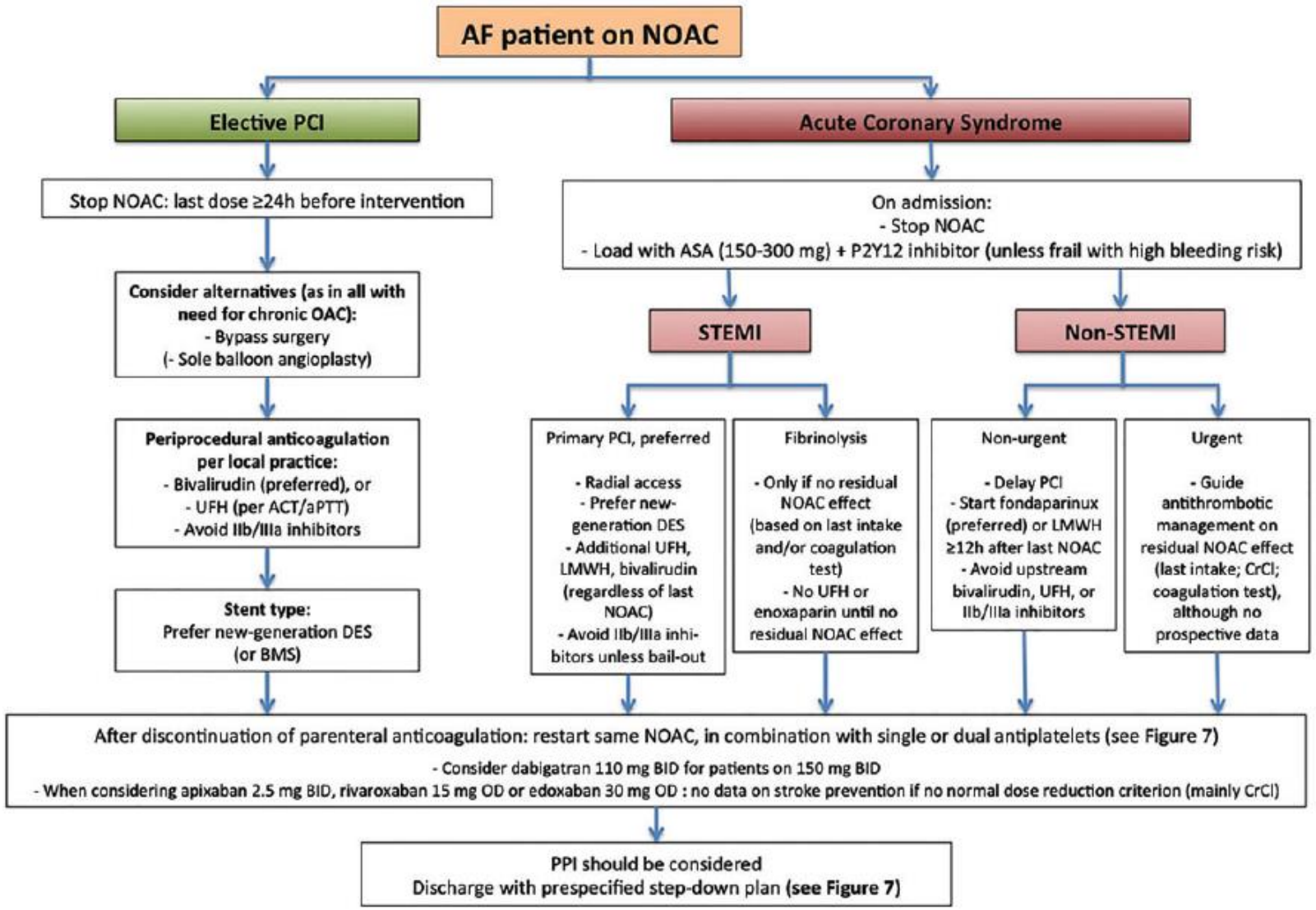


Figure 6 Acute management of revascularization or ACS in AF patients treated with NOAC. See text for further discussion.

H. Heidbuchel et al Europace 2015

Default scenarios and criteria for adaptation for long-term treatment of patients on NOAC therapy after revascularization or ACS

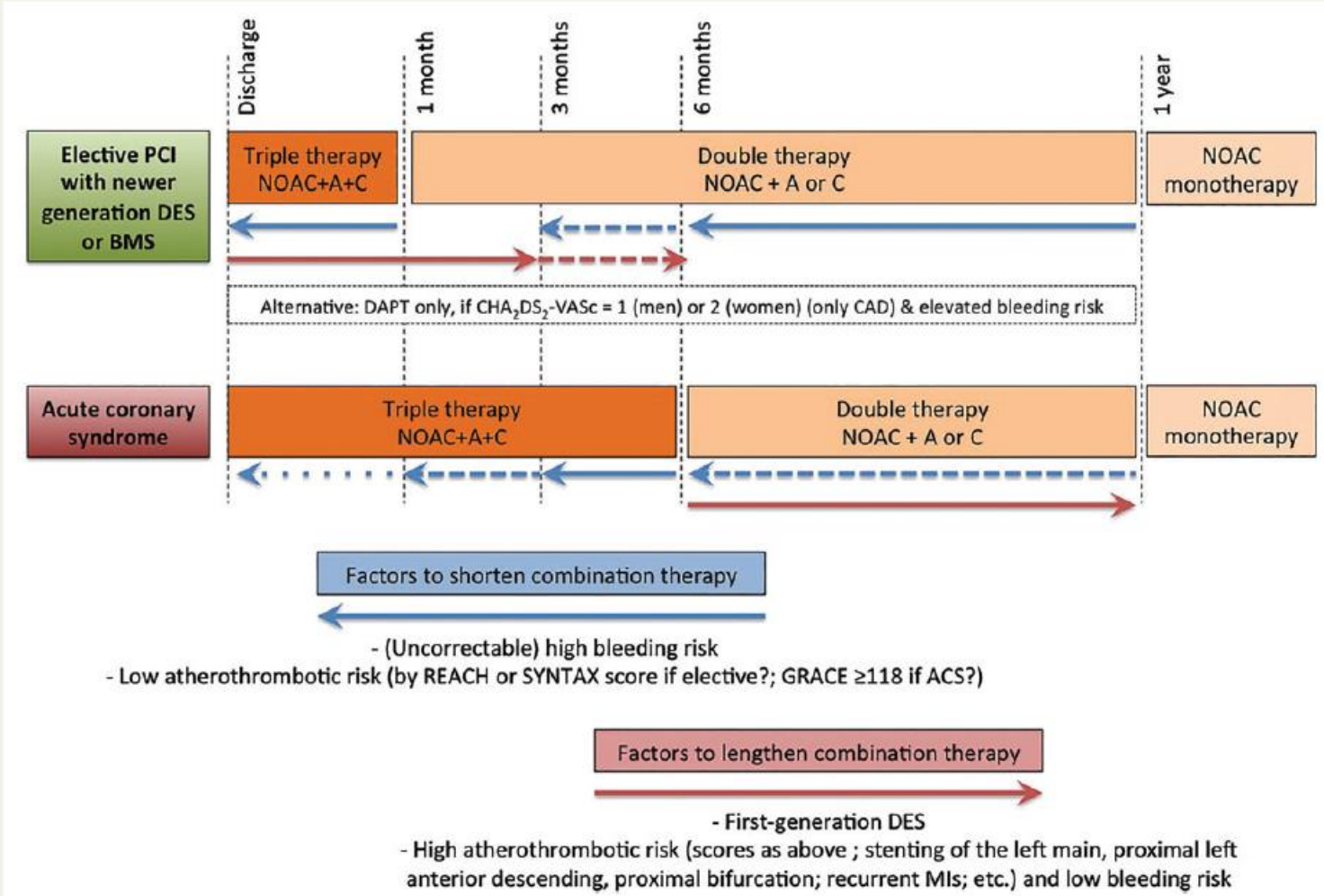


Figure 7 Default scenarios and criteria for adaptation for long-term treatment of patients on NOAC therapy after revascularization or ACS. There are innumerable possible variations on this global theme, as discussed in the text. Patient characteristics and institutional practices should be taken into account to individualize the approach. This figure wants to create a 'backbone' as guidance for such tailored approaches. A: aspirin 75–100 mg OD; C: clopidogrel 75 mg OD.

H. Heidbuchel et al Europace 2015

CARDIOVERSIONE ELETTRICA DI FA ED UTILIZZO DEI NAO

- Possibilità di una pianificazione precisa del giorno di effettuazione della procedura al momento dell'inizio della terapia anticoagulante con NAO

- Tempi precisi e brevi di attesa per la cardioversione

- Potenziale percentuale di successo maggiore della procedura (minore è il tempo che intercorre tra l'esordio dell'FA e la cardioversione e maggiore è la possibilità di ripristino di ritmo sinusale)

- Costi gestionali minori

- Sicurezza della procedura sotto trattamento con NAO

- Impossibilità di verificare in modo diretto lo stato di scoagulazione del paziente

↓

necessità di una attestazione firmata dal paziente
dell'avvenuto trattamento e/o di una verifica dei blister utilizzati

Cardioversion in a non-vitamin K antagonist anticoagulant-treated patient

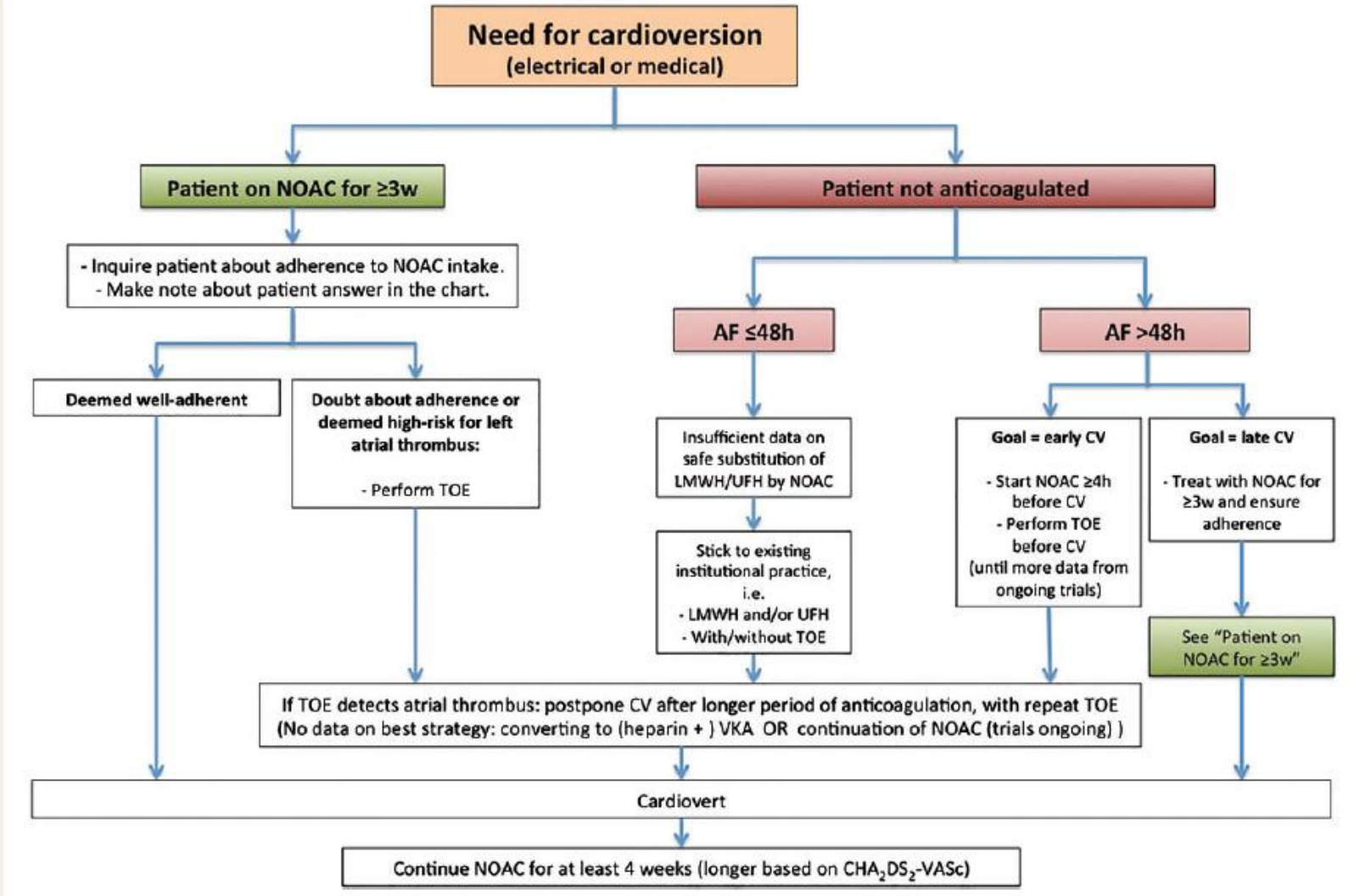


Figure 8 Cardioversion work-flow in AF patients treated with NOAC, depending on the duration of the arrhythmia and prior anticoagulation.

H. Heidbuchel et al Europace 2015

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

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

Special considerations concerning atrial fibrillation ablation and device implantation procedures

Tamponade or haemothorax was reported to be around 1.3% in the worldwide AF ablation survey, although their incidence is decreasing in recent trials.

Recent international consensus statements recommend performing PVI in VKA-treated patients without VKA interruption, since such strategy is associated not only with less thrombo-embolic events but also with less bleeding (uninterrupted VKA therapy with target INR of 2.0–2.5).

NOAC: A number of factors should be considered for the timing of last intake, such as renal function, CHA_2DS_2-VASc risk of the patient, experience of the operator, type and extent of additional ablation beyond PVI, and the presence of periprocedural imaging to guide transseptal puncture.

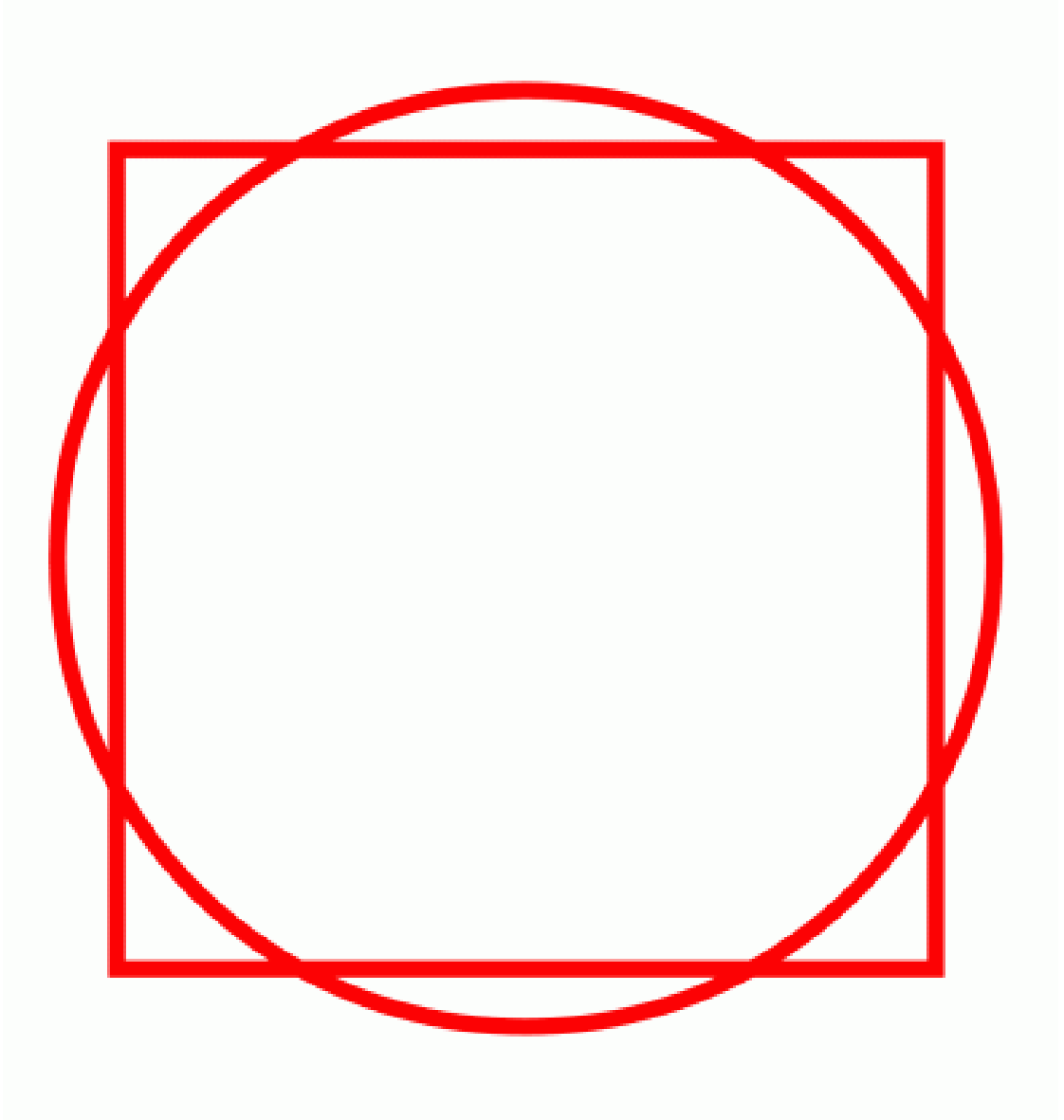
Meta-analysis data indicate that a last intake of NOAC 24 h before the procedure is a viable strategy. Continued intake until the evening before the procedure or even the morning of the procedure seems to be equally safe, especially in experienced centres but more data are needed to make firm statements on the best strategy.

Quesiti Aperti

Come conciliare le evidenze della letteratura ed i vantaggi clinico/gestionali con l'attuale piano terapeutico

Come monitorare in termini di politica sanitaria spese e risparmi legati all'utilizzo dei NAO

Quando e come prevedere l'allargamento della prescrivibilità alle altre professionalità (Specialisti ambulatoriali, MMG ecc)



Management of the post-acute phase: ischaemic stroke

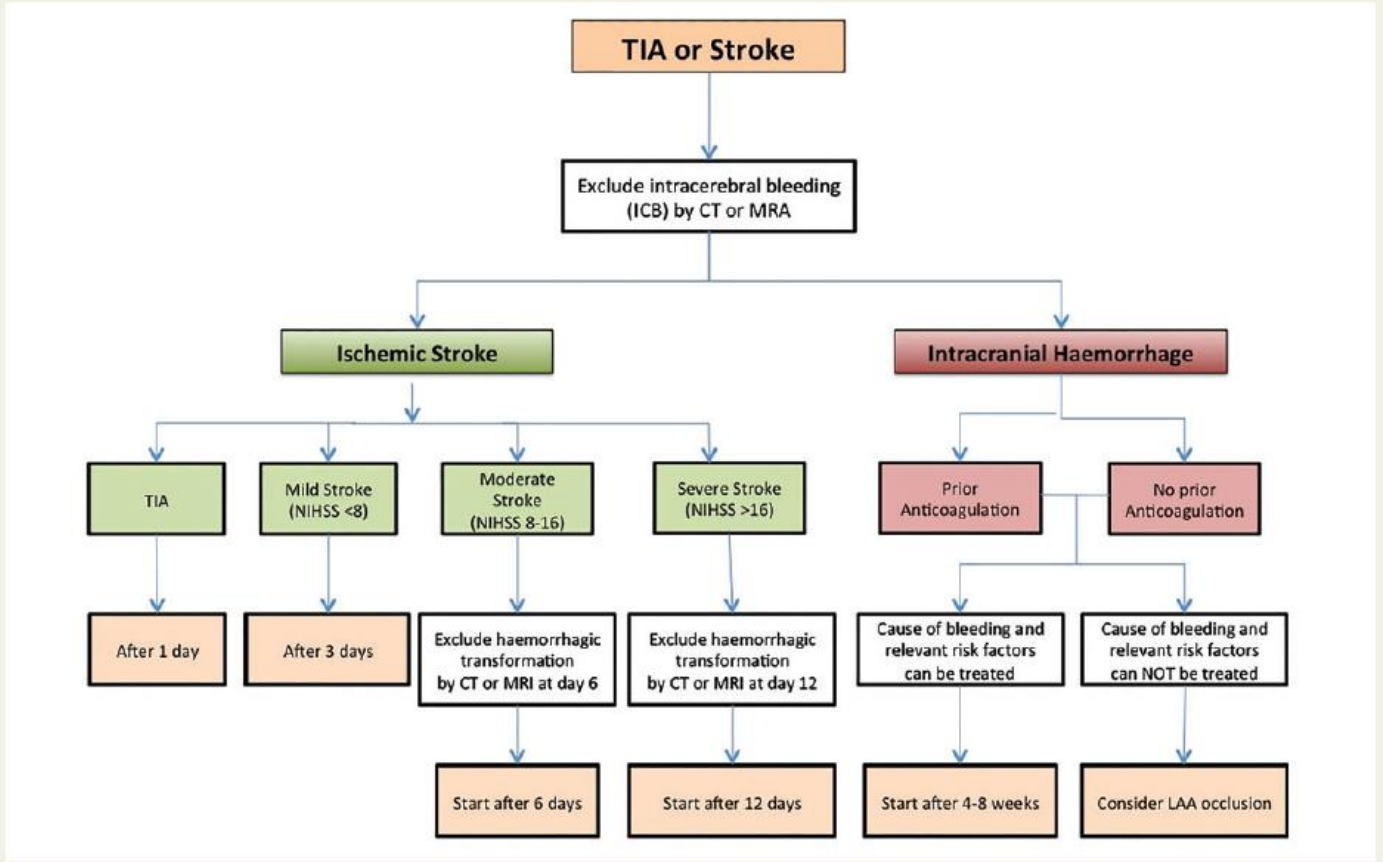
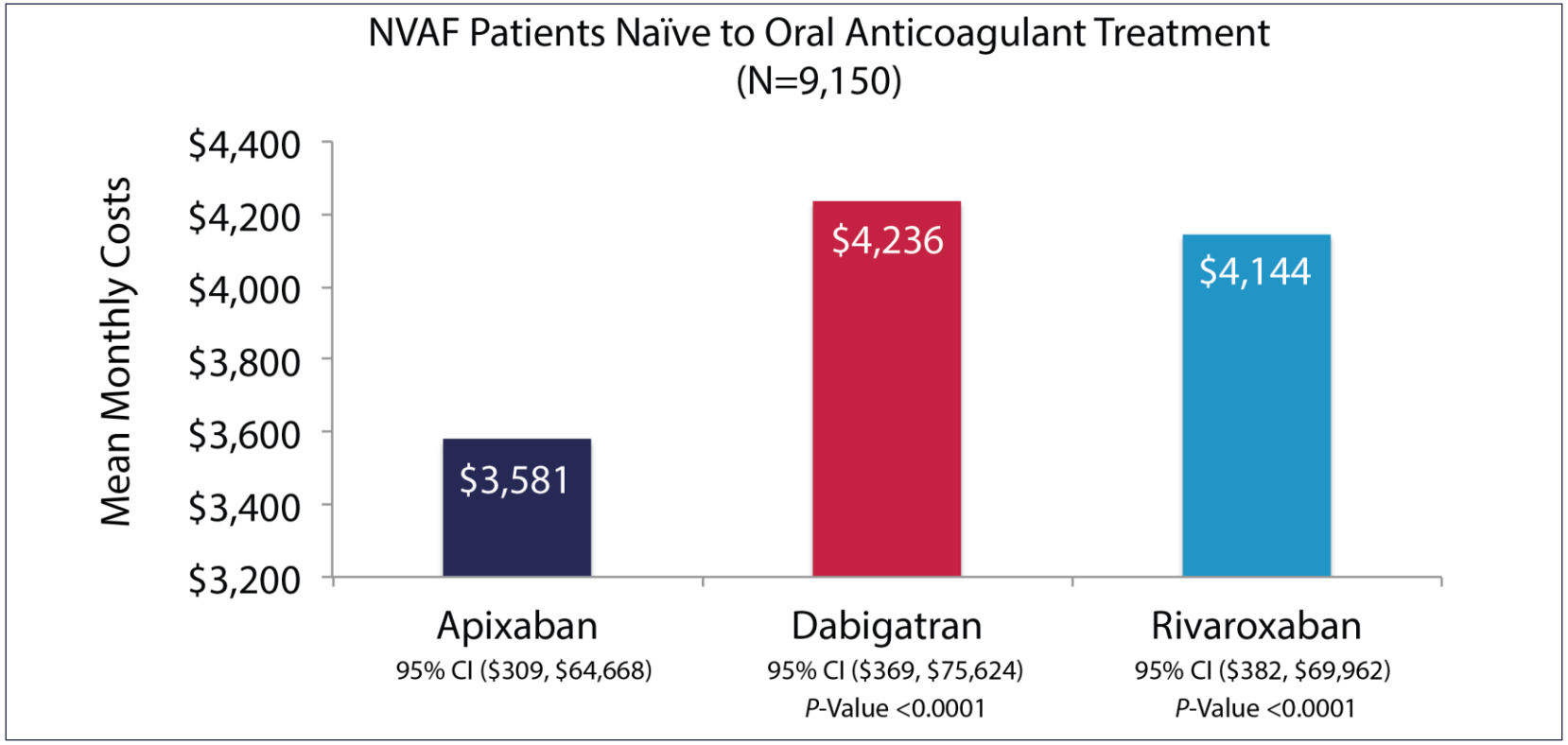


Figure 9 Flowchart for the initiation or re-initiation of anticoagulation after TIA/stroke or intracerebral haemorrhage.

H. Heidbuchel et al Europace 2015

Results: Adjusted All-cause Healthcare Costs

Patients treated with apixaban incurred significantly lower average monthly healthcare costs compared to patients treated with dabigatran and rivaroxaban



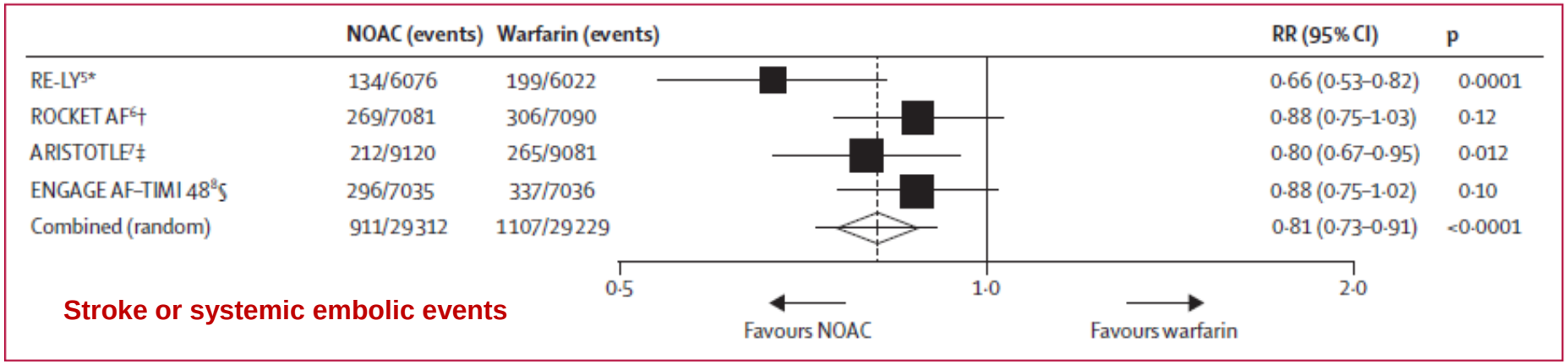
Deitelzweig et al. Poster presentation at ESC Aug/Sept 2015; London, UK Poster/oral poster no.1971 (Rapid Fire Presentation)

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

LANCET DECEMBER 2013

Vantaggi clinici della terapia con NAO

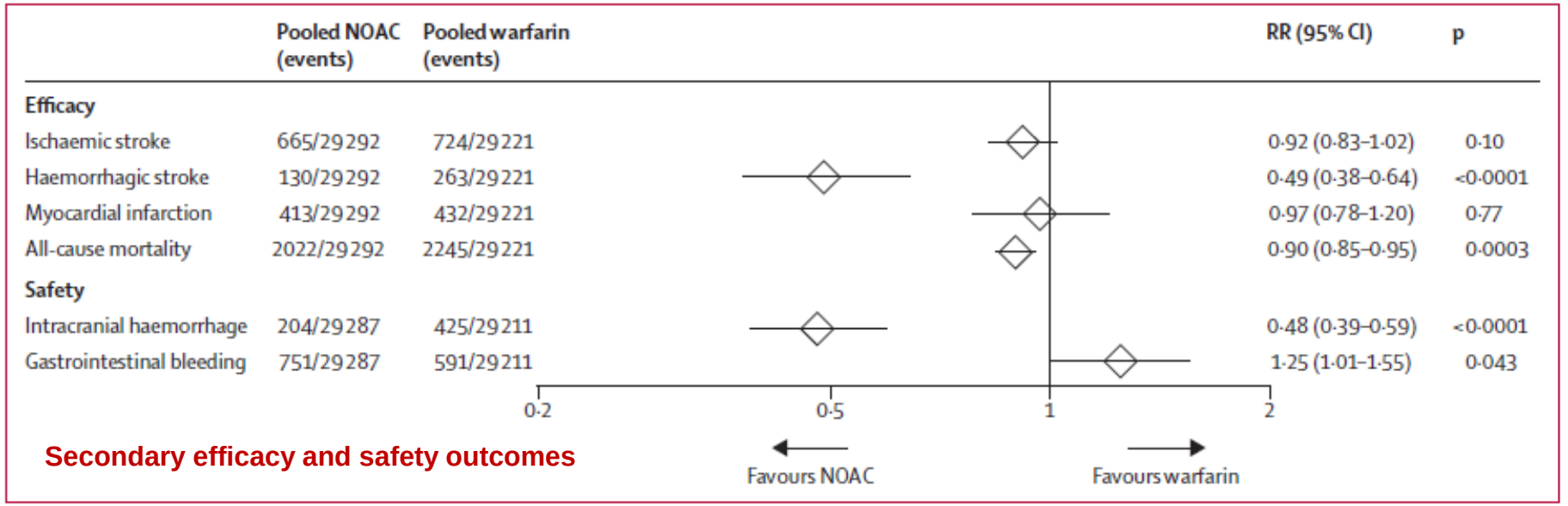


Stroke or systemic embolic events

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

Vantaggi clinici della terapia con NAO



Secondary efficacy and safety outcomes

FIBRILLAZIONE ATRIALE: il fenomeno del reingresso

Studio retrospettivo su 12700 pz dimessi da dipartimento di emergenza dopo accesso per FA

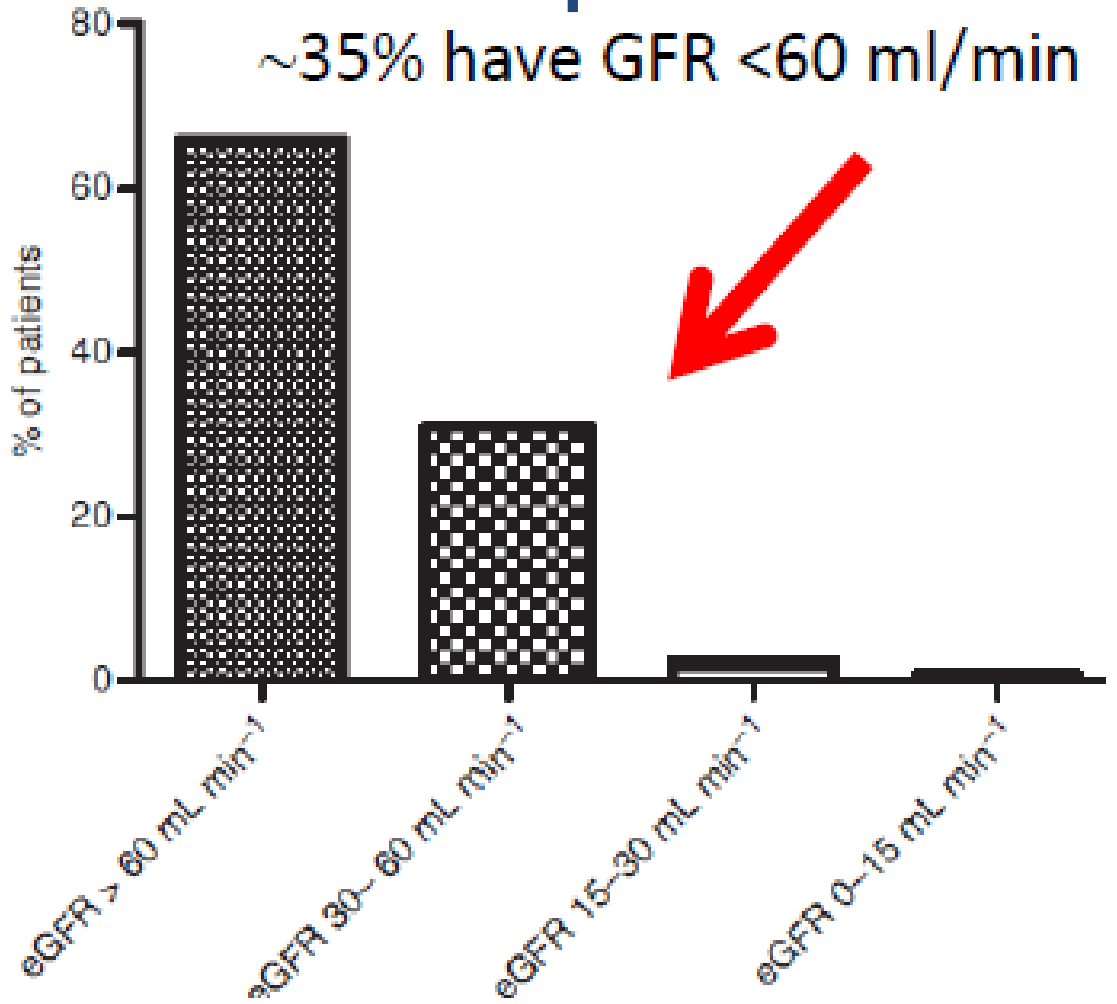
Età media: 77 anni
Mortalità a 14 giorni: 0,7%
Reingresso in DEA: 9% pz entro 14 giorni

GESTIONE POST-DIMISSIONE DEA:
67,8: Assenza di follow-up ambulatoriale
19,4%: Follow-up presso medico di famiglia
12,8%: Follow-up specialistico (cardiologo/internista) → Minor rischio di reingresso
H.R: 0,61, p= 0,003

Evaluating early repeat emergency department use in patients with atrial fibrillation: a population-based analysis.
Am Heart J. 2013, *Atzema CL et al.*

Chronic Kidney Disease is common among AF patients

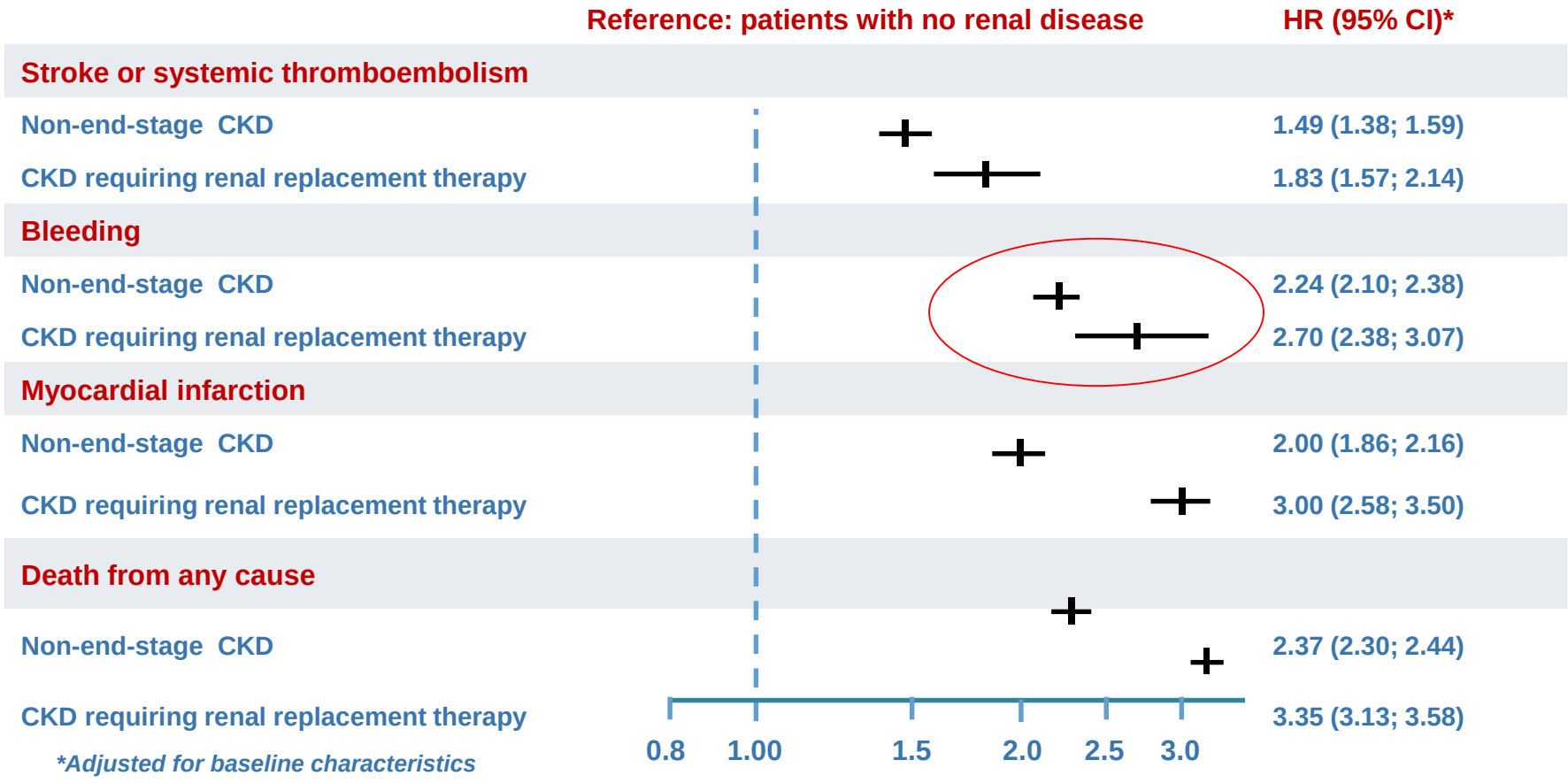
5039 AF patients



Kooiman et al. J Thromb Haemost 2011; 9: 1652-3

Chronic Kidney Disease increases the risk of stroke, bleeding and all-cause death in AF patients

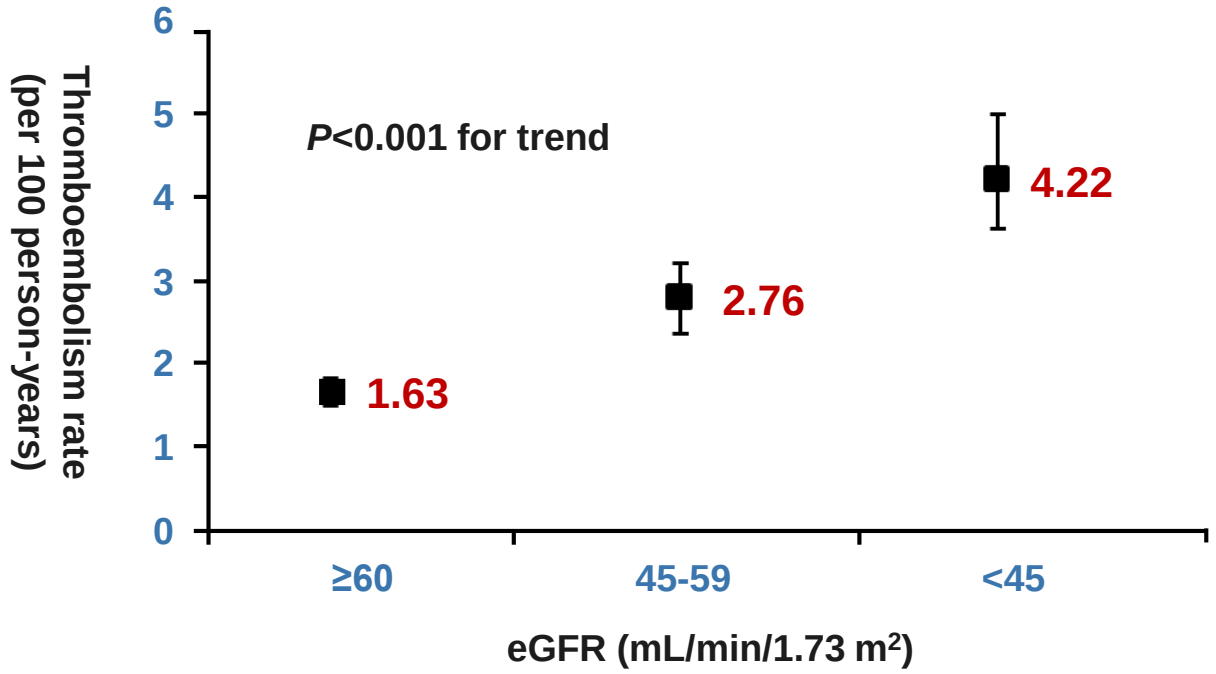
Risk of events in NVAF patients with non-end-stage CKD (n=3587) or with CKD requiring renal replacement therapy (n=901) compared with NVAF patients with no renal disease (n=127,884) - Danish registry (1997-2008)



Adapted from Olesen et al. N Engl J Med 2012;367:625-35.

Chronic Kidney Disease increases the risk of thromboembolism in AF patients not receiving warfarin

Crude rate of thromboembolism (% person-year)* - ATRIA cohort (n=10,908 NVAF patients off warfarin – 1995-2003)



ATRIA: Assembly of the Anticoagulation and Risk Factors in Atrial Fibrillation
eGFR: estimated glomerular filtration rate
MDRD: modification of diet in renal disease

***676 validated thromboembolic events (637 ischaemic strokes, 39 other thromboembolism)**

Go AS et al. Circulation. 2009;119:1363-1369

Results (cont.)
US comparative real world research on major bleeding

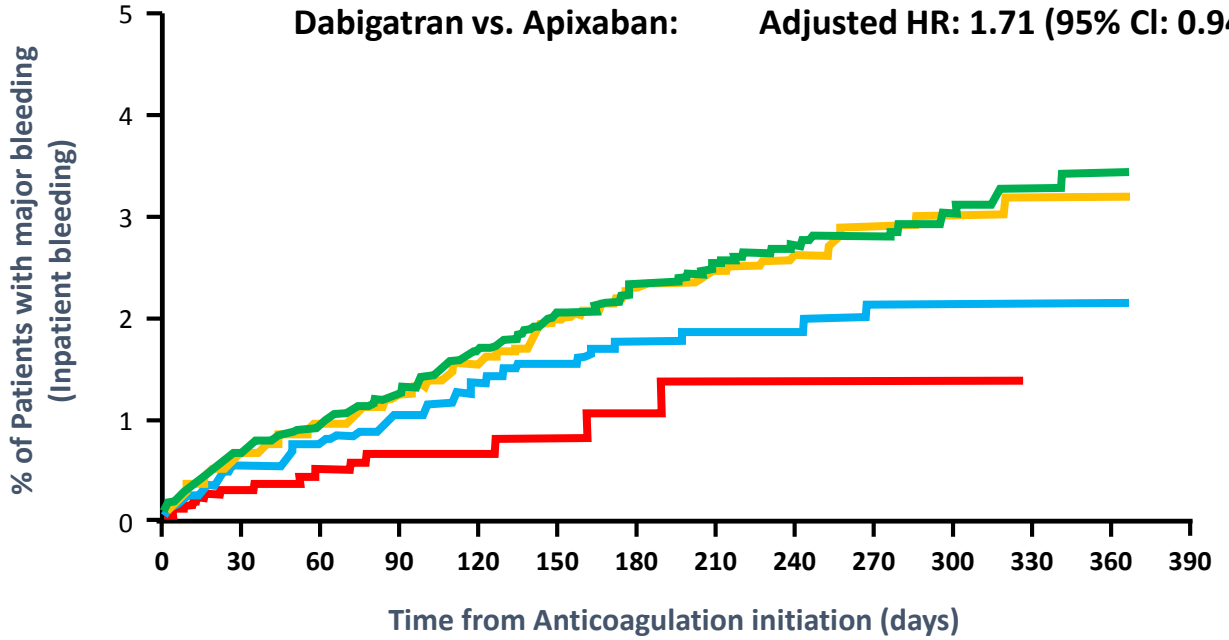
- **The cumulative incidence of major bleeding for new initiation on anticoagulants is represented in the figure below.**

Cumulative incidence of major bleeding

Warfarin vs. Apixaban: **Adjusted HR: 1.93 (95% CI: 1.12–3.33) *P*=0.018**

Rivaroxaban vs. Apixaban: **Adjusted HR: 2.19 (95%CI: 1.26 –3.79) *P*=0.0052**

Dabigatran vs. Apixaban: **Adjusted HR: 1.71 (95% CI: 0.94–3.10) *P*= 0.079**



Apixaban
Warfarin
Dabigatran
Rivaroxaban

Apixaban (N=2,402)	
5 mg	NR
N=2,057	N=345

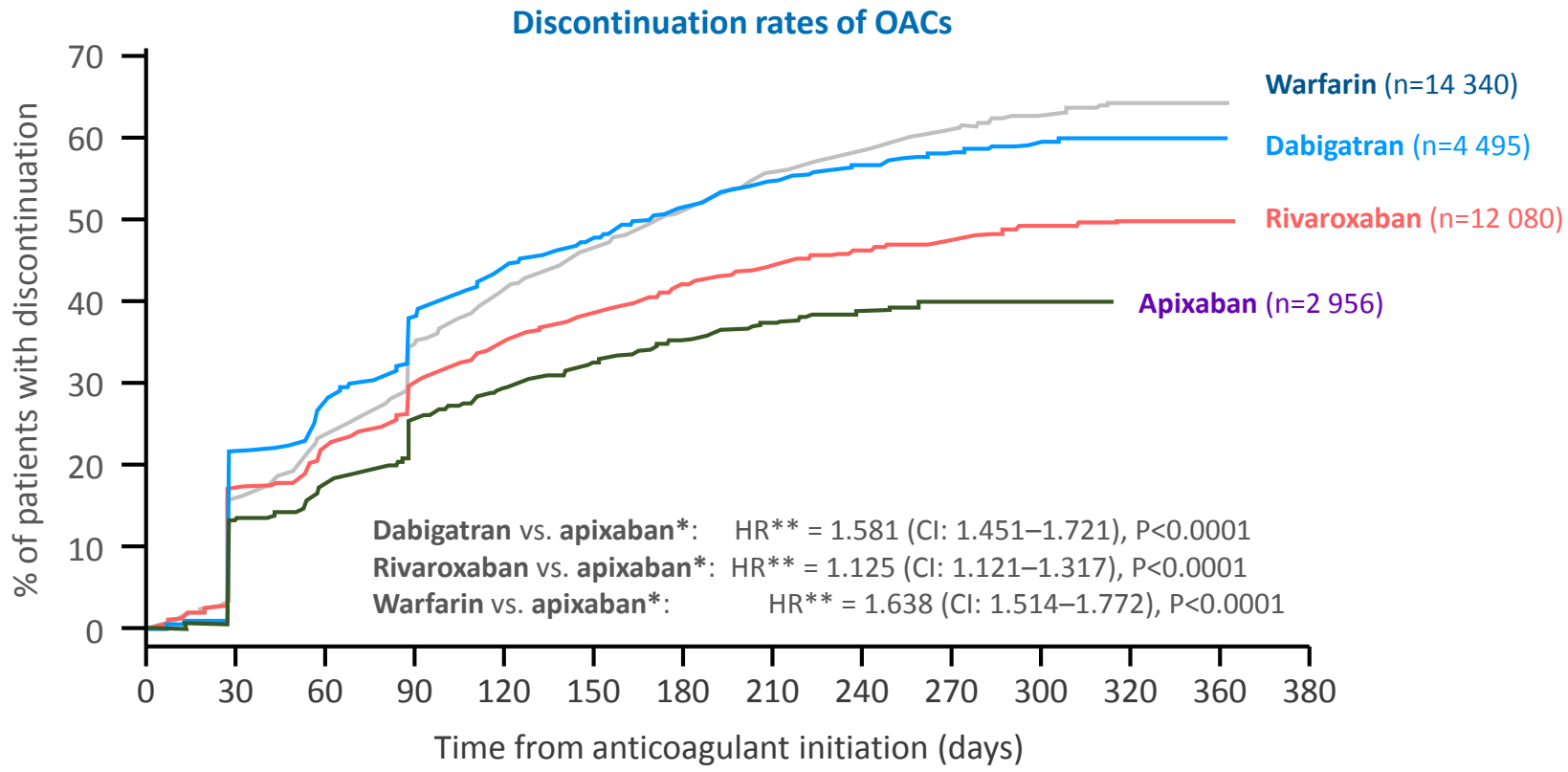
Dabigatran (N=4,173)	
150 mg	NR
N=3,768	N=405

Rivaroxaban (N=10,050)	
20 mg	NR
N=8,066	N=1,984

Warfarin (N=12,713)

Lip et al. Poster presentation at ESC Aug/Sept 2015; London, UK Poster/oral poster no.P6217

Discontinuation rates of NOACs in real world



* Effect size is versus apixaban which acts as a reference category.

** Analysis controlled for other variables including age, gender, onset of embolic or primary ischemic stroke, dyspepsia or stomach discomfort, congestive heart failure, coronary artery disease, diabetes, hypertension, renal disease, myocardial infarction, history of TIA or stroke and history of bleeding.

Retrospective cohort study NVAF patients newly prescribed a NOAC or newly prescribed warfarin without knee/hip replacement surgeries in the time period of Jan 1 – Dec 31, 2013

Pan *et al.* Presented at the ESC Congress 2014. Abstract #5112.