CENTRI EMOSTASI E TROMBOSI, SPECIALISTI OSPEDALIERI E MEDICINA DEL TERRITORIO NELLA GESTIONE DELLE MALATTIE EMORRAGICHE E TROMBOEMBOLICHE

Cremona, 10 marzo 2017

Ospedale di Cremona – Aula Magna

FIBRILLAZIONE ATRIALE

ore 14:00-15:00

Fibrillazione Atriale e prevenzione delle complicanze cardioemboliche – Novità in tema di NOACs

Raffaele De Caterina

Università "G. d'Annunzio" – Chieti e
Fondazione "G. Monasterio" – Pisa, Italia

10 marzo 2017, 14:00-14:20

Prof. Raffaele De Caterina
Conflitti d'interesse

- Co-author ESC Guidelines on Atrial Fibrillation 2010-2012
- Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE-AF, Re-DUAL PCI
- Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck

Selection

1 - NOACs are life-saving drugs

2 - Definition of nonvalvular AF

3 - Risk scores and OAC in low thromboembolic risk

4 - Focus on the elderly

5 - Registries and Subgroups

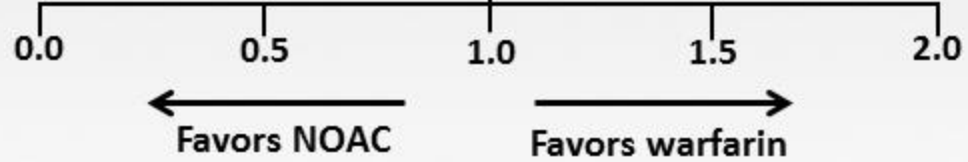
6 - Approved dosing vs trial protocols

7 - Antidotes

Landmark Oral Anticoagulation Trials: Mortality

Head-to-head studies do not exist, so direct comparisons between agents may not be made

	Pts with events (%/yr)			
	NOAC	Warfarin	HR	95% CI
Dabi 110[a]	446 (3.75)	487 (4.13)	0.91	0.80-1.03
Dabi 150[a]	438 (3.64)	487 (4.13)	0.88	0.77-1.00
Riva 20[b]	582 (4.50)	632 (4.90)	0.92	0.82-1.03
Apix 5[c]	603 (3.52)	669 (3.94)	0.89	0.80-0.96
Edox 30[d]	737 (3.80)	839 (4.35)	0.87	0.79-0.96
Edox 60[d]	773 (3.99)	839 (4.35)	0.92	0.83-1.01



Full dose NOAC meta-analysis: **RR (95% CI) = 0.90 (0.85-0.95)** - Ruff et al. Lancet 2014

a. Connolly SJ, et al. *N Engl J Med*. 2009;361(12):1139-1151.
b. Patel MR, et al. *N Engl J Med*. 2011;365(10):883-891.
c. Granger C, et al. *N Eng J Med*. 2011;365(11):981-992.
d. Giugliano RP, et al. *N Engl J Med*. 2013; 369(22):2093-2104.

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European Heart Journal (2014) **35**, 3328–3335
doi:10.1093/eurheartj/ehu352

CURRENT OPINION

What is 'valvular' atrial fibrillation? A reappraisal

Raffaele De Caterina[1] and A. John Camm[2]*

[1]Institute of Cardiology and Center of Excellence on Aging, G. D'Annunzio University – Chieti, and G. Monasterio Foundation, Pisa, Italy; and [2]Division of Clinical Sciences, St George's University of London, London, UK

Received 22 April 2014; revised 18 July 2014; accepted 6 August 2014; online publish-ahead-of-print 29 September 2014

- A truly poorly defined term, often preventing the possible and correct use of NOACs
- We propose the term 'mechanical and rheumatic mitral valvular AF' (acronym: MARM AF) as an accurate description of conditions where NOACs should not be used

De Caterina F & Camm AJ Eur Heart J 2014;35: 3328-35

Valvular Heart Disease Patients on Edoxaban or Warfarin in the ENGAGE AF-TIMI 48 Trial

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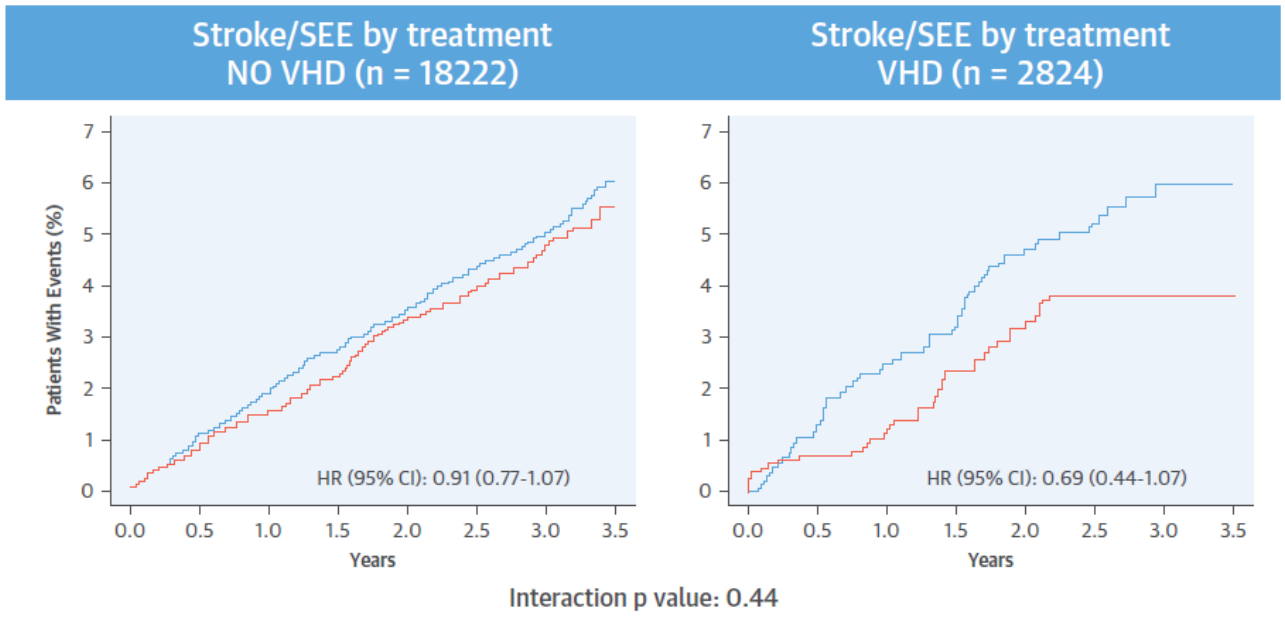
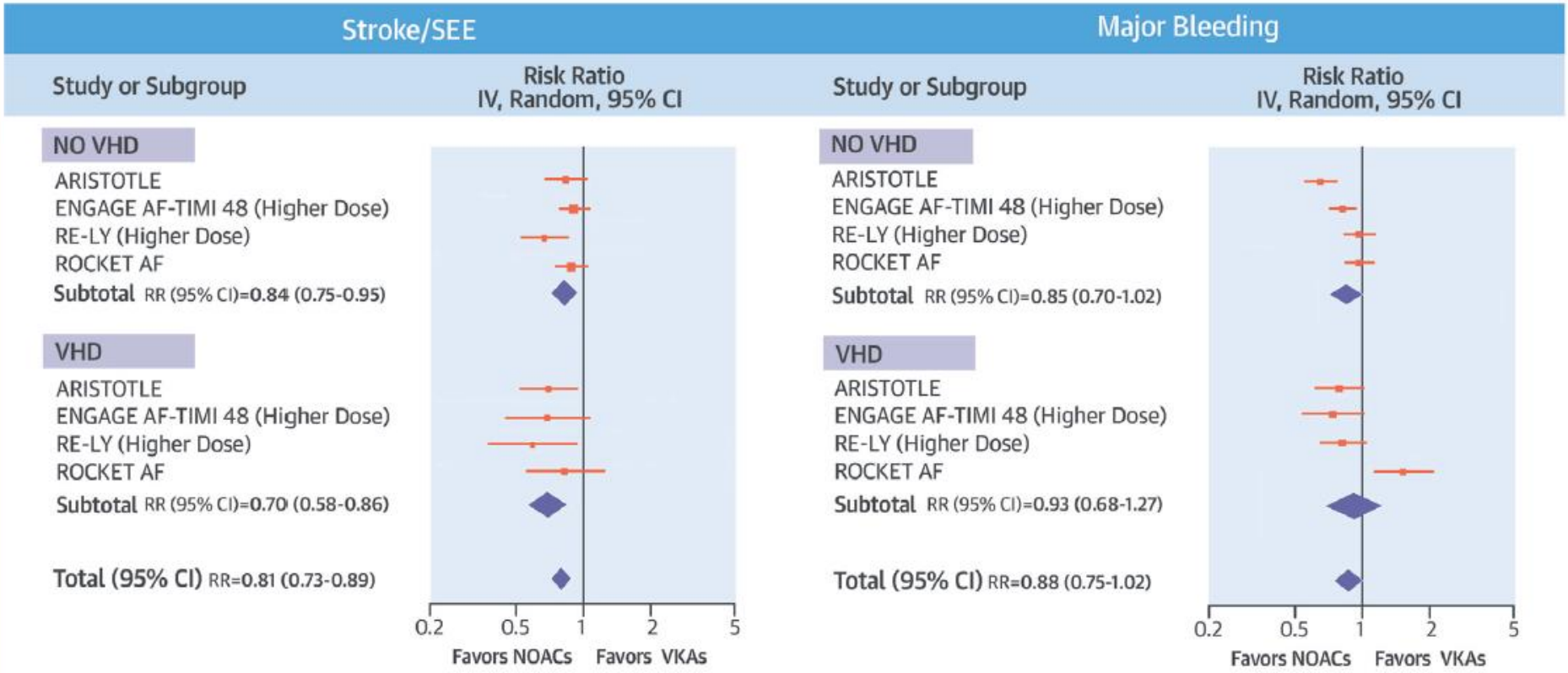
Valvular Heart Disease Patients on Edoxaban or Warfarin in the ENGAGE AF-TIMI 48 Trial

Raffaele De Caterina, MD, PhD,[a] Giulia Renda, MD, PhD,[a] Anthony P. Carnicelli, MD,[b] Francesco Nordio, PhD,[b] Marco Trevisan, MSc,[b] Michele F. Mercuri, MD,[c] Christian T. Ruff, MD, MPH,[b] Elliott M. Antman, MD,[b] Eugene Braunwald, MD,[b] Robert P. Giugliano, MD, SM[b]



De Caterina, R. et al. J Am Coll Cardiol. 2017;69(11): 1372–82.

CENTRAL ILLUSTRATION **SSEE and Major Bleeding in Patients Without and With VHD, Treated With Higher-Dose NOACs or Warfarin**

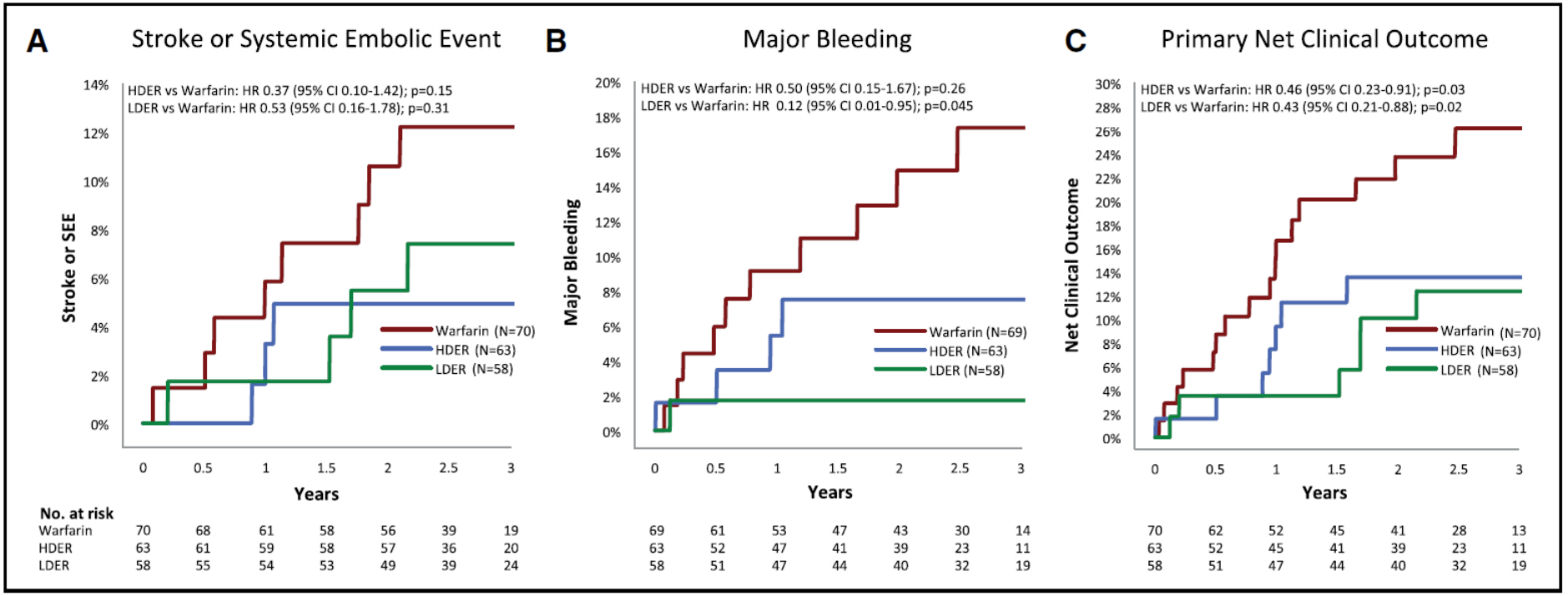


Renda, G. et al. J Am Coll Cardiol. 2017;69(11):1363-71.

Forest plot with individual and summary estimates of the relative risk (RR) and 95% confidence interval (CI) of stroke/SEE and major bleeding for higher-dose NOACs versus warfarin among patients without and with VHD, separately and overall. A random-effect model was applied to estimate RR and 95% CI. Squares and diamond sizes are proportional to study weight. Inter-study heterogeneity, separately reported for no-VHD and VHD groups, and for the overall population, was tested using Cochran's Q test (see text for details). The figure shows that the relative efficacy and safety of NOACs versus warfarin as to the main efficacy (stroke/SEE) and safety (major bleeding) endpoints are similar in no-VHD and VHD patients. CI = confidence interval; IV = inverse variance; NOAC = non-vitamin K antagonist oral anticoagulant; RR =relative risk; SEE = systemic embolic events; VHD = valvular heart disease.

Edoxaban for the Prevention of Thromboembolism in Patients with Atrial Fibrillation and Bioprosthetic Valves

Carnicelli AP, De Caterina R, …Giugliano RP



Circulation 2017; 135:XXX, in press

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4 - Focus on the elderly

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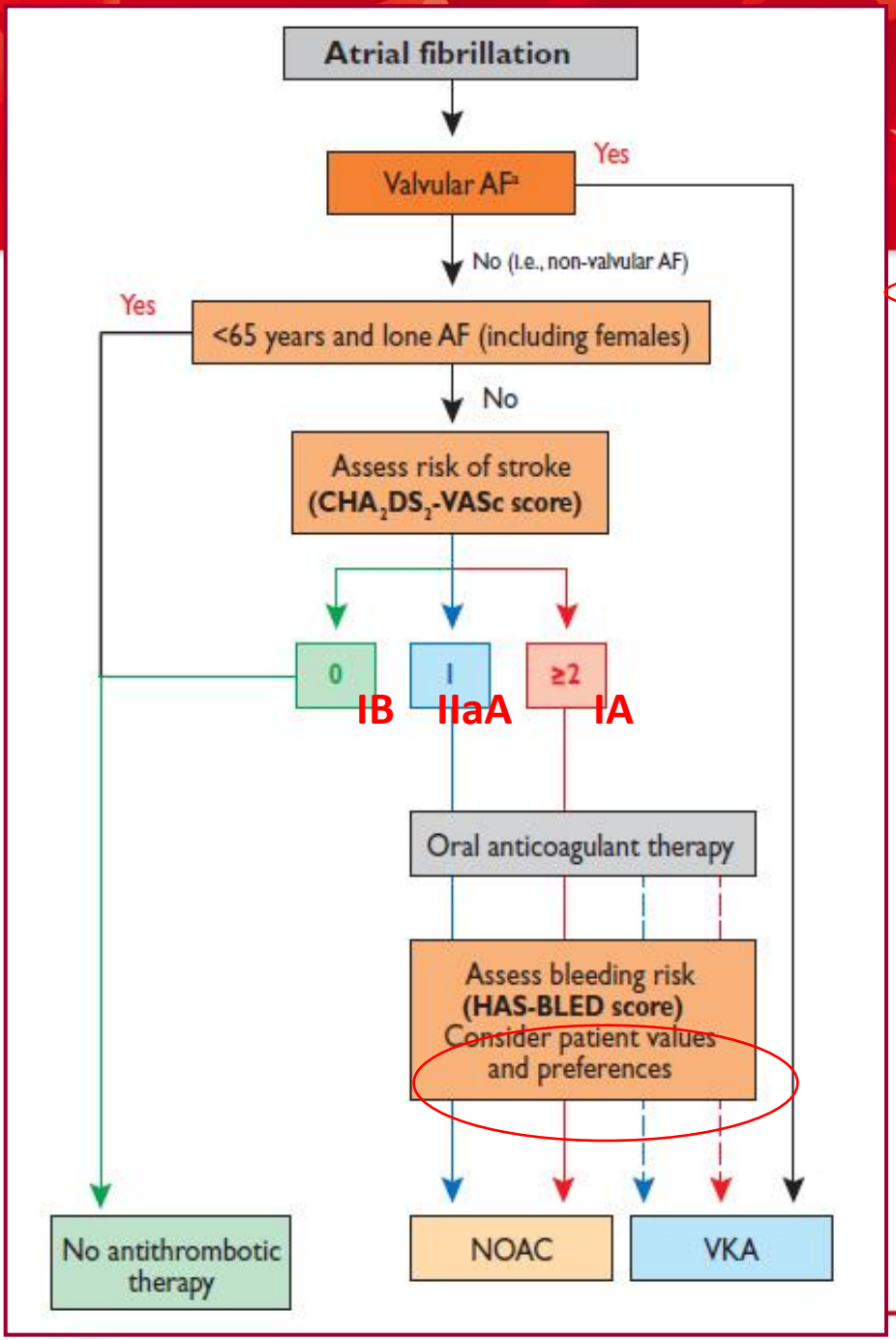


Antiplatelet therapy with aspirin plus clopidogrel, or—less effectively—aspirin only, should be considered in patients who refuse any OAC, or cannot tolerate anticoagulants for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage occlusion, closure or excision may be considered.

Colour: CHA_2DS_2-VASc; green = 0, blue = 1, red ≥2.
Line: solid = best option; dashed = alternative option.
AF = atrial fibrillation; CHA_2DS_2-VASc = see text; HAS-BLED = see text;
NOAC = novel oral anticoagulant; OAC = oral anticoagulant;
VKA = vitamin K antagonist.
[a]Includes rheumatic valvular disease and prosthetic valves.

CHADS-VASc	ESC 2012	AHA 2014
0	none	none IIaB
1	anticoagulation	anticoagulation or aspirin or none IIbC
≥2	anticoagulation	Anticoagulation

Camm AJ et al. Eur Heart J 2012;33:2719-47
January et al. Circulation 2014;130:e199-e267

CHA_2DS_2-VASc score	Patients (n = 73538)	Stroke and thromboembolism event rate at 1 year follow-up (%)
0	6369	0.78
1	8203	2.01
2	12771	3.71
3	17371	5.92
4	13887	9.27
5	8942	15.26
6	4244	19.74
7	1420	21.50
8	285	22.38
9	46	23.64

Adapted from Olesen JB, et al., *Br Med J* 2011;**342**:doi: 10.1136/bmj.d124

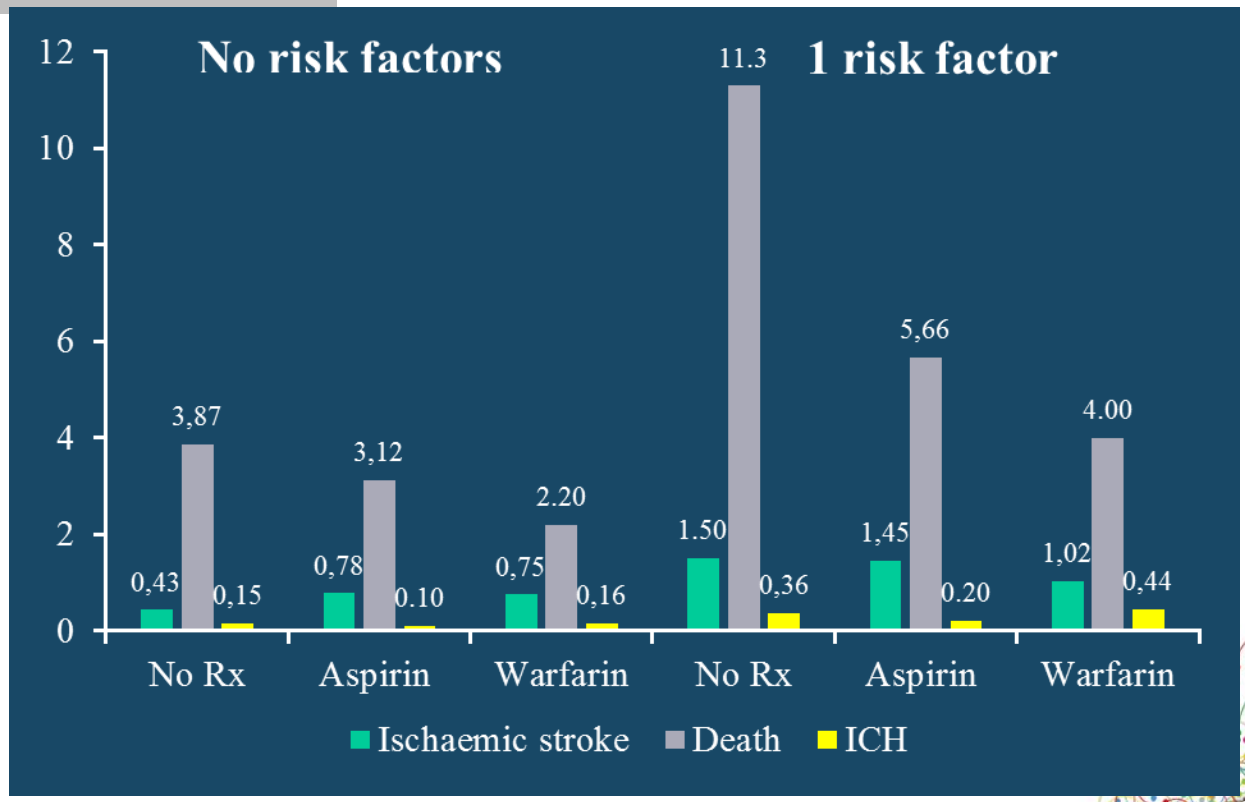
OAC, Aspirin, or No Therapy in Patients With Nonvalvular AF With 0 or 1 Stroke Risk Factor Based on CHA_2DS_2-VASc score

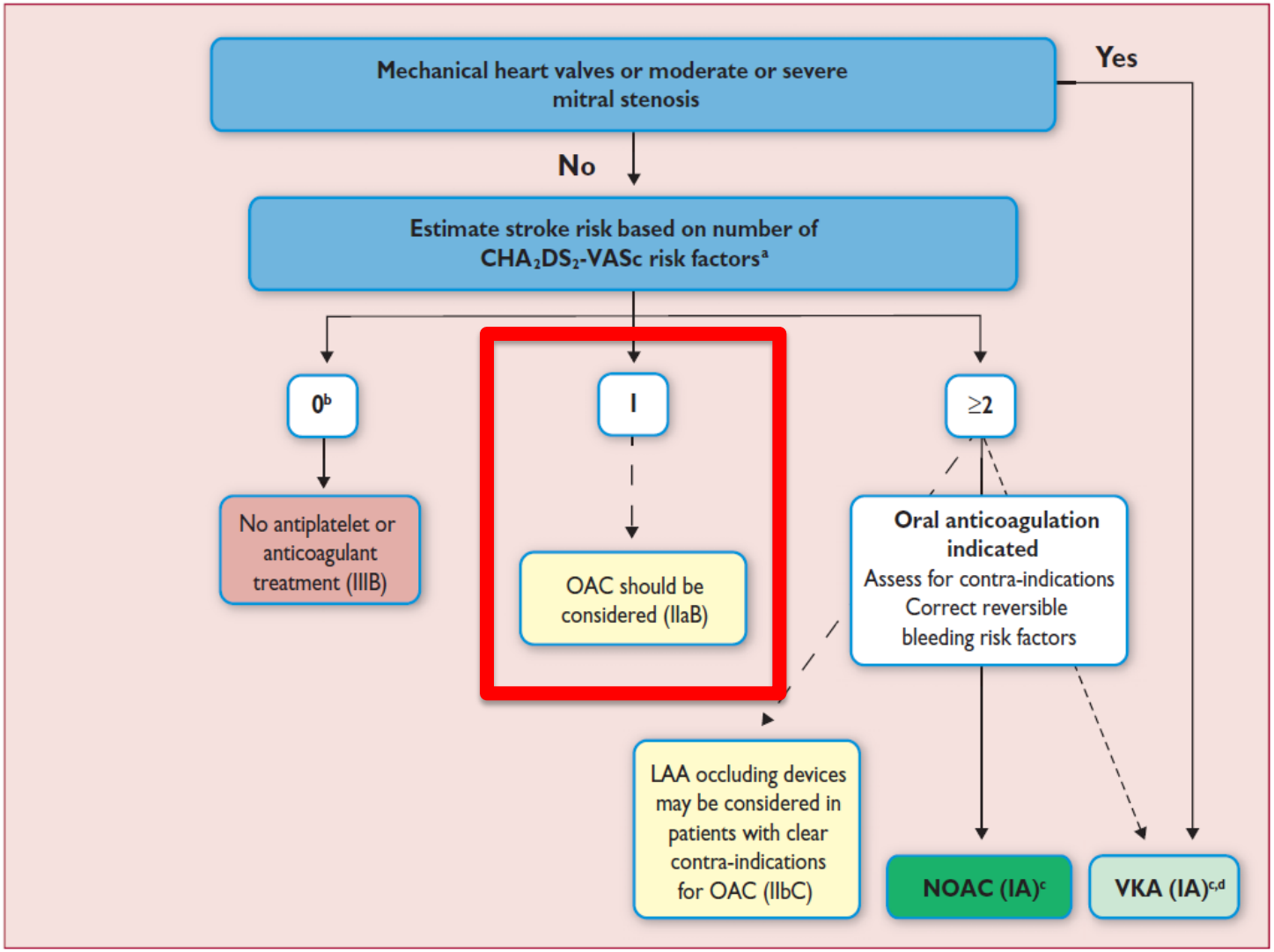
Lip et al J Am Coll Cardiol 2015;65(14):1385-94

Event Rates Per 100 PYs at 1 Year FU According to Treatment Strategy Initiated at Day 14 After Discharge With Incident AF

Low-risk patients have a truly low risk for stroke and bleeding.

With 1 additional stroke risk factor, there was a significant increase in event rates (particularly mortality) if non-anticoagulated.





AF = atrial fibrillation; LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist.
[a]Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, prior Sstroke/TIA/embolus (2 points), Vascular disease, age 65–74 years, female Sex.
[b]Includes women without other stroke risk factors.
[c]IIaB for women with only one additional stroke risk factor.
[d]IB for patients with mechanical heart valves or mitral stenosis.

ESC 2016
Guidelines for AF

- …but I advise for NOACs because of their proven equal safety, but better efficacy, compared with aspirin
- and because of their better safety compared with VKAs

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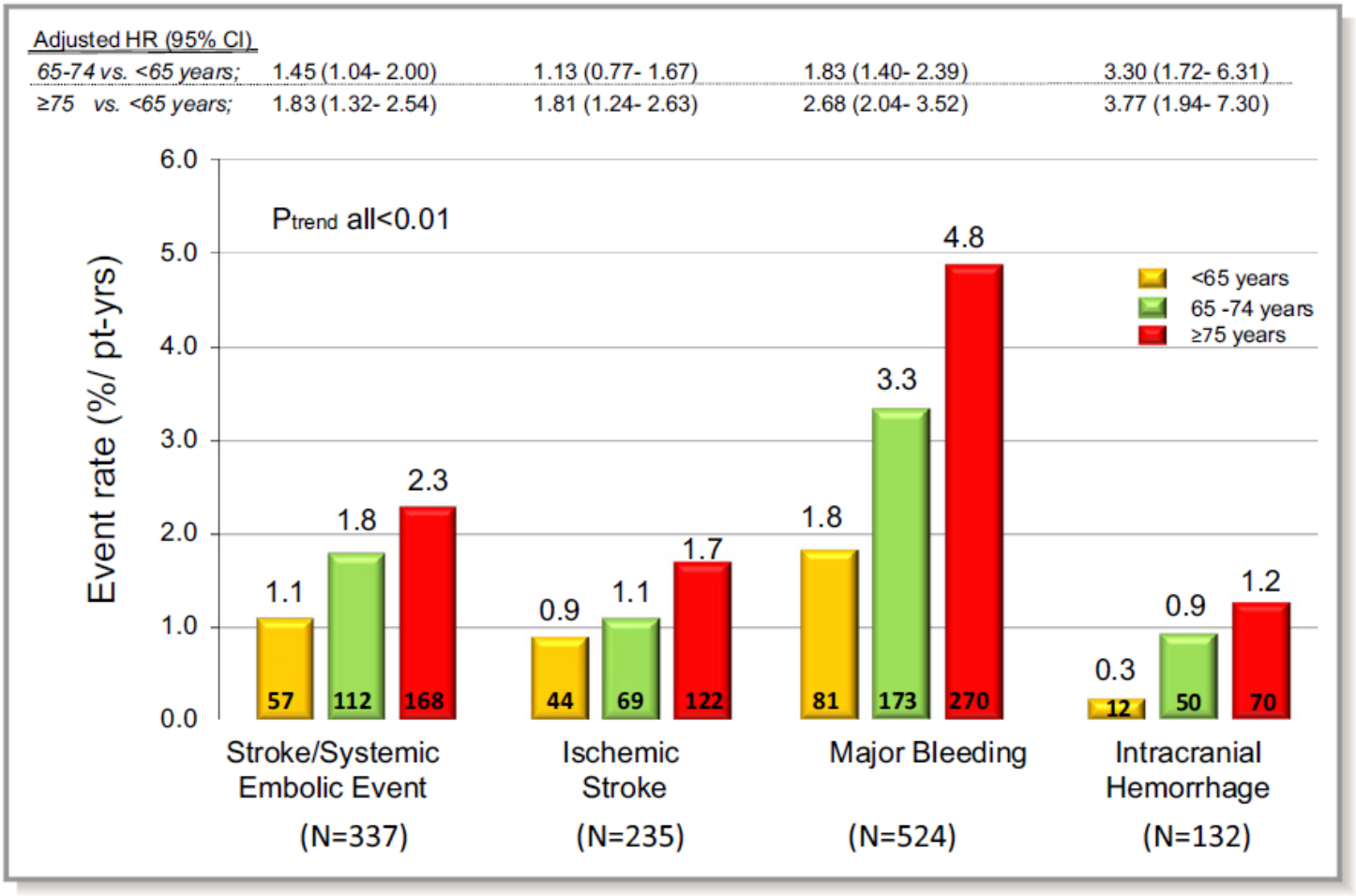
Efficacy and Safety of Edoxaban in Elderly Patients With Atrial Fibrillation in the ENGAGE AF–TIMI 48 Trial

Eri Toda Kato, MD, PhD; Robert P. Giugliano, MD, SM; Christian T. Ruff, MD, MPH; Yukihiro Koretsune, MD, PhD; Takeshi Yamashita, MD, PhD; Robert Gabor Kiss, MD, PhD; Francesco Nordio, PhD; Sabina A. Murphy, MPH; Tetsuya Kimura, MS; James Jin, PhD; Hans Lanz, MD; Michele Mercuri, MD, PhD; Eugene Braunwald, MD; Elliott M. Antman, MD



J Am Heart Assoc. 2016;5: e003432 doi: 10.1161/JAHA.116.003432)

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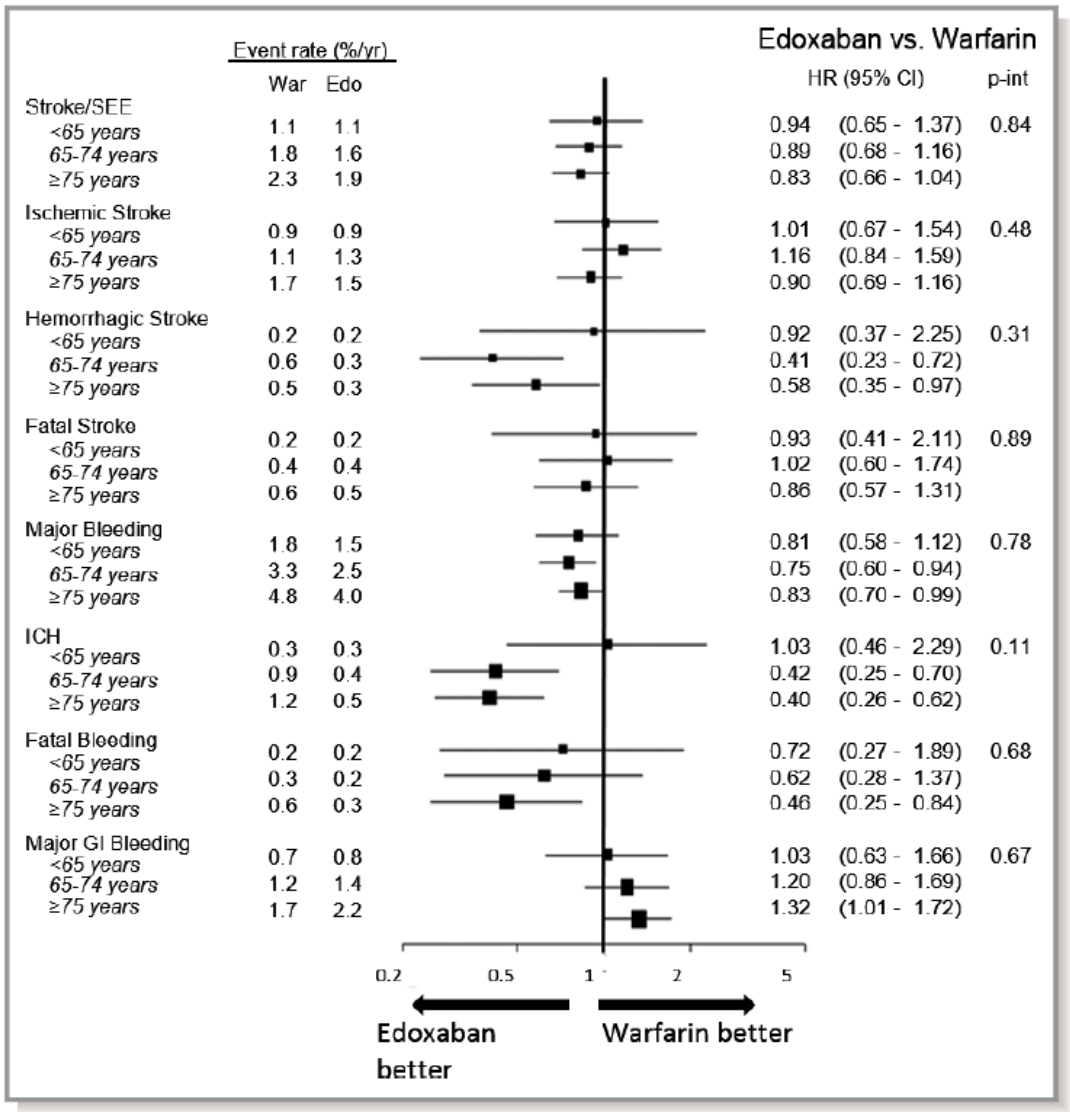

J Am Heart Assoc. 2016;5: e003432 doi: 10.1161/JAHA.116.003432)

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NOAC Prescription Data – The problem of the underdosing

An unexpectedly high proportion of prescriptions for apixaban are for 2.5 mg. Similar patterns are seen with rivaroxaban and dabigatran

	Apixaban		Rivaroxaban			Dabigatran		
	Q4 2014		Q4 2014			Q4 2014		
Country	2.5mg	5mg	10mg	15mg	20mg	75mg	110mg	150mg
UNITED STATES	24%	76%	6%	21%	73%	16%	0%	84%
JAPAN	58%	42%	55%	45%	0%	40%	60%	0%
GERMANY	41%	59%	4%	34%	61%	2%	61%	37%
CANADA	38%	62%	6%	26%	68%	1%	52%	47%
AUSTRALIA	39%	61%	2%	30%	68%	0%	63%	37%
UNITED KINGDOM	42%	58%	6%	22%	71%	3%	51%	46%
SPAIN	37%	63%	5%	33%	63%	3%	60%	38%
FRANCE	46%	54%	0%	0%	0%	0%	0%	0%
BELGIUM	30%	70%	2%	42%	56%	0%	60%	40%
ITALY	35%	65%	2%	37%	61%	0%	63%	36%

Alexander et al. Poster presentation at ESC Aug/Sept 2015; London, UK Poster/oral poster no.2032

- Likely, apixaban 2.5 mg twice daily is being “over-prescribed” in patients with either one or no dose-reduction criteria because of concerns about safety.

Alexander JH, et al. JAMA Cardiol. 2016 Jul 27. doi: 10.1001/jamacardio.2016.1829. [Epub ahead of print]

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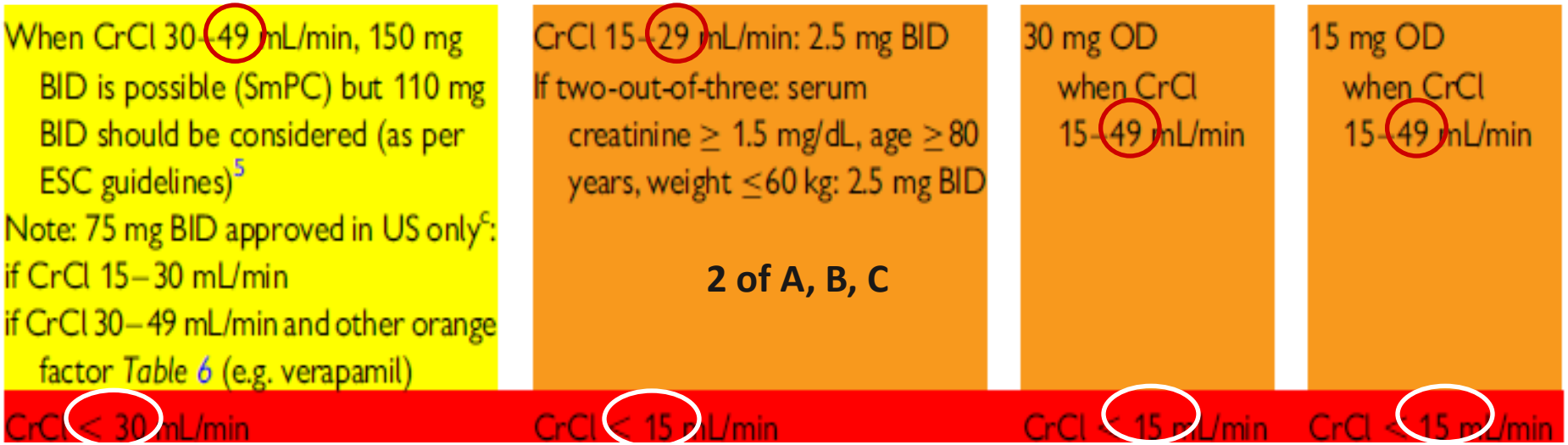
Approved NOAC dose in renal insufficiency



consider dose reduction

reduce dose

not recommended

Cr Cl / 10 = interval in months to recheck renal function

Heidbuchel H et al. Europace 2015; Aug 31

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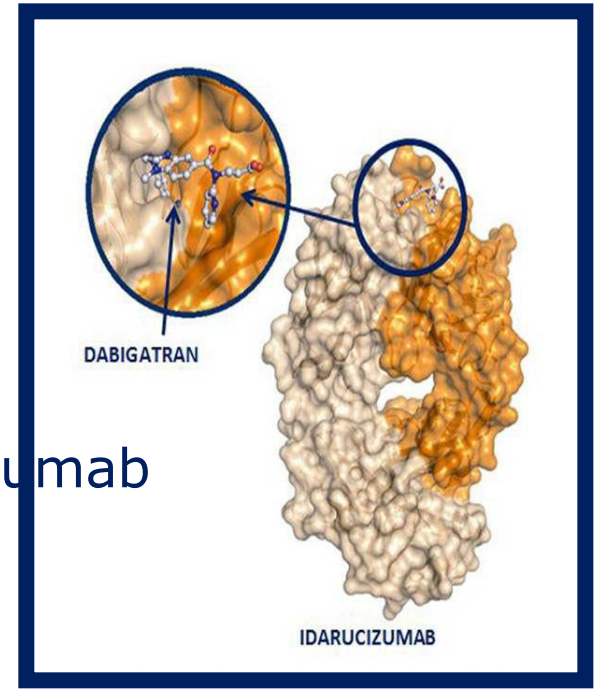
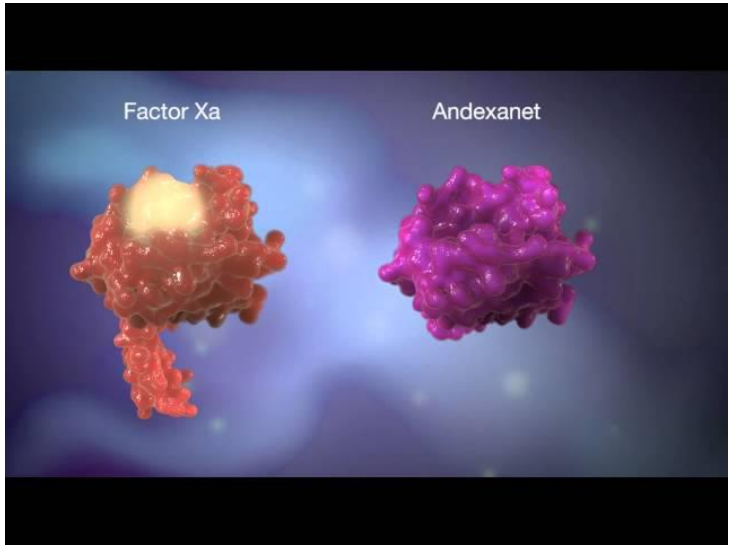
Antidotes

Idarucizumab

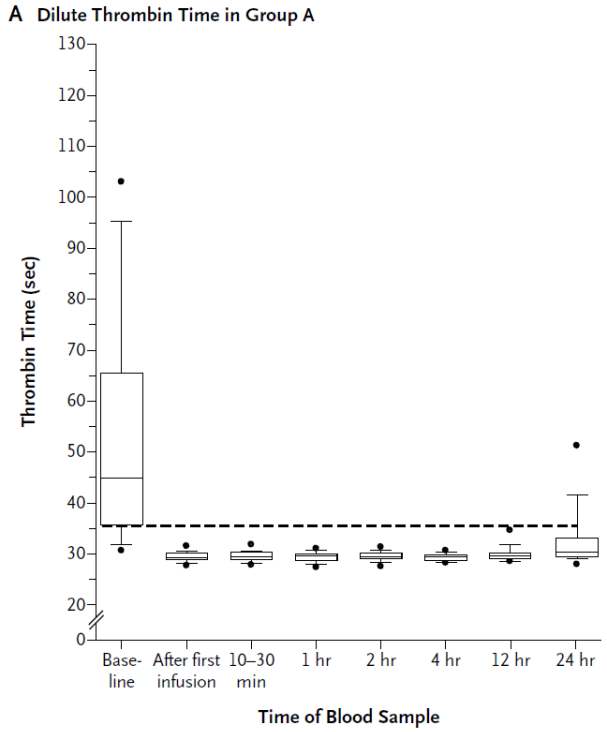


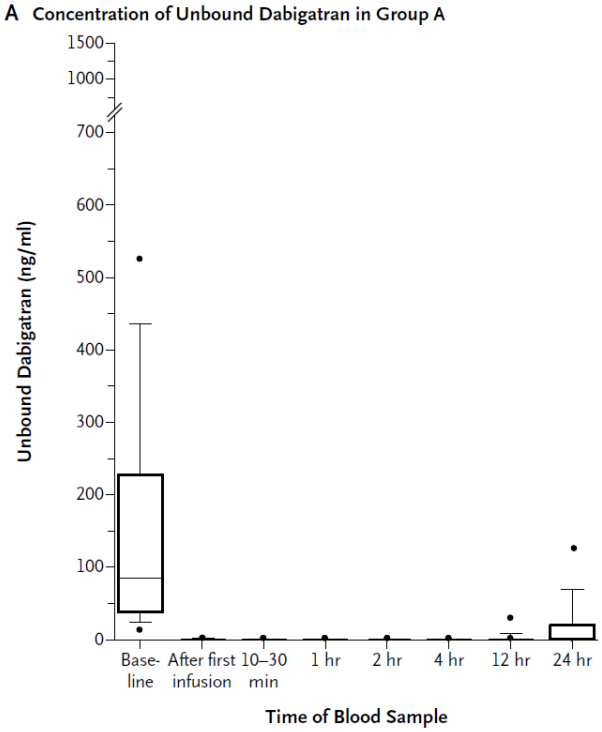


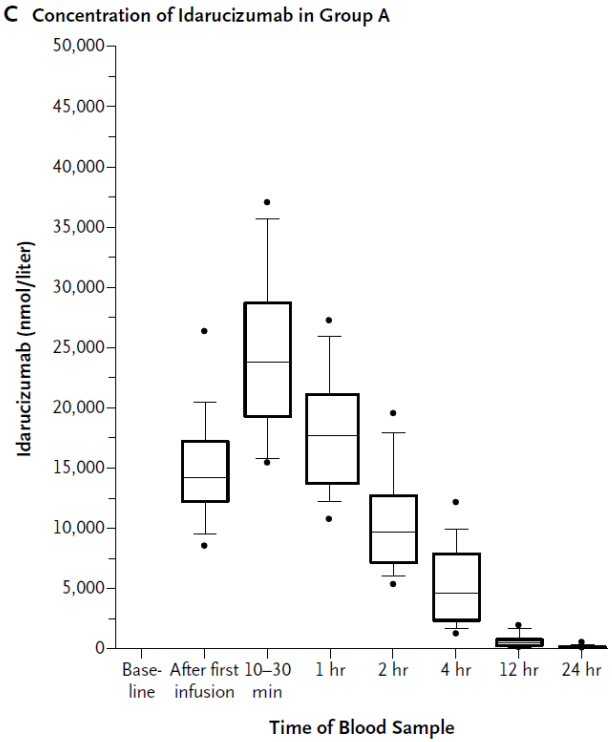
Andexanet

Situations where anticoagulant reversal agents are needed
- in life-threatening or uncontrolled bleeding
- for emergency surgery/urgent procedures

Idarucizumab



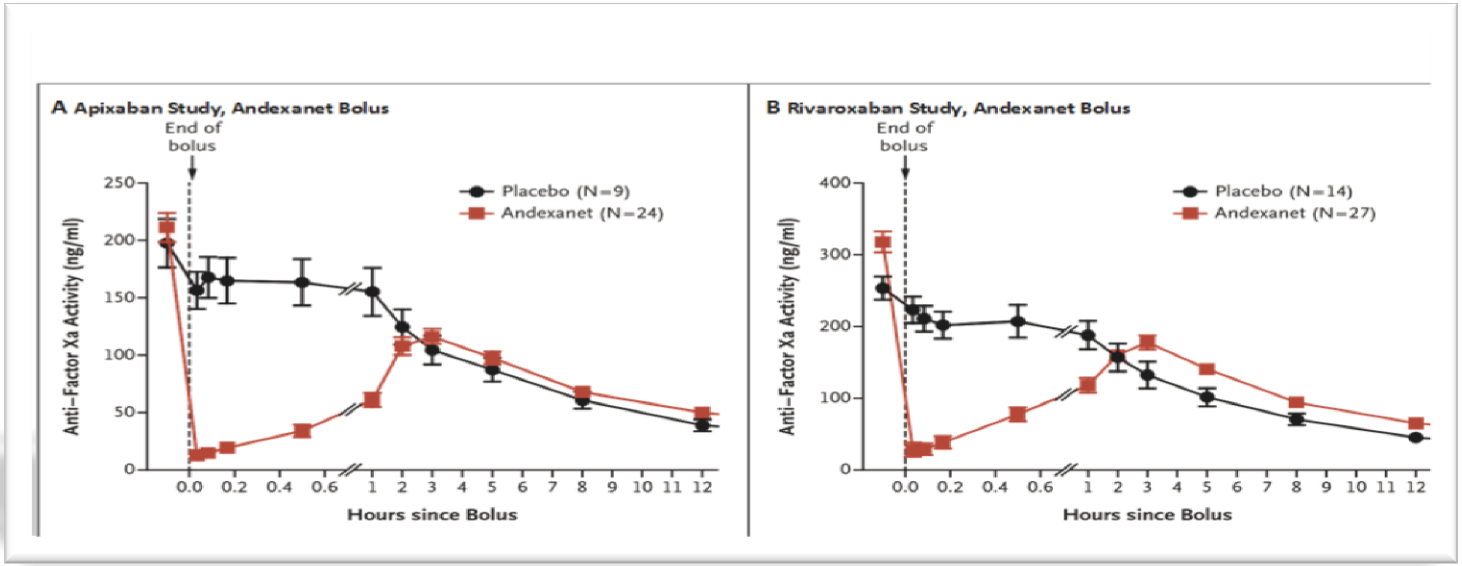




Among 68 patients with an elevated dilute thrombin time and 81 with an elevated ecarin clotting time at baseline, the median maximum percentage reversal was 100%. Idarucizumab normalized the test results in 88 to 98% of the patients, an effect that was evident within minutes. Concentrations of unbound dabigatran remained below 20 ng per milliliter at 24 hours in 79% of the patients.

Pollack CV Jr et al, N Engl J Med. 2015 6;373(6):511-20

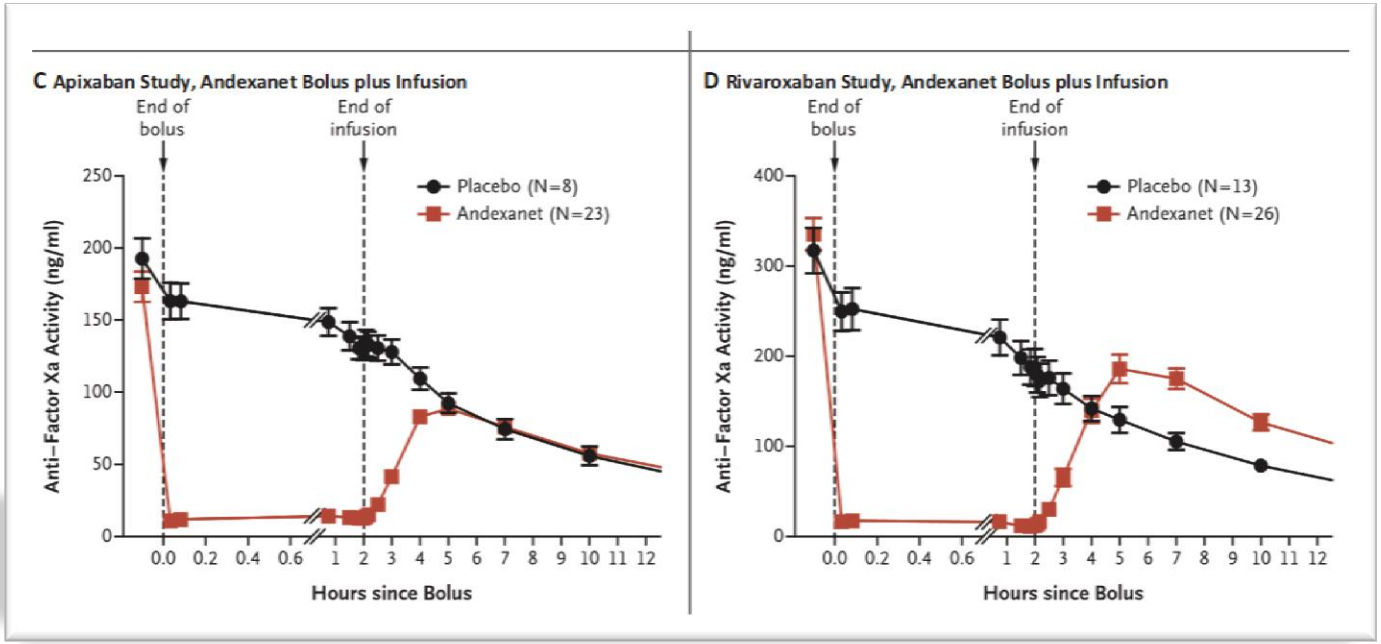
Andexanet-alfa
ANNEXA-A and ANNEXA-R
Results of Phase III (first part)



Attività anti-Xa tra le persone che avevano ricevuto il trattamento anticoagulante con apixaban o rivaroxaban misurata prima e dopo la somministrazione di andexanet o placebo al giorno 4. al termine della somministrazione del bolo. ***Pannello A*** mostra i dati dai partecipanti allo studio apixaban con un bolo endovenoso di 400 mg o placebo; ***Pannello B*** mostra i dati dei partecipanti allo studio rivaroxaban (ALLEGATO A, con un bolo endovenoso di 800 mg o placebo

Siegal DM et al, N Engl J Med. 2015 Dec 17;373(25):2413-24

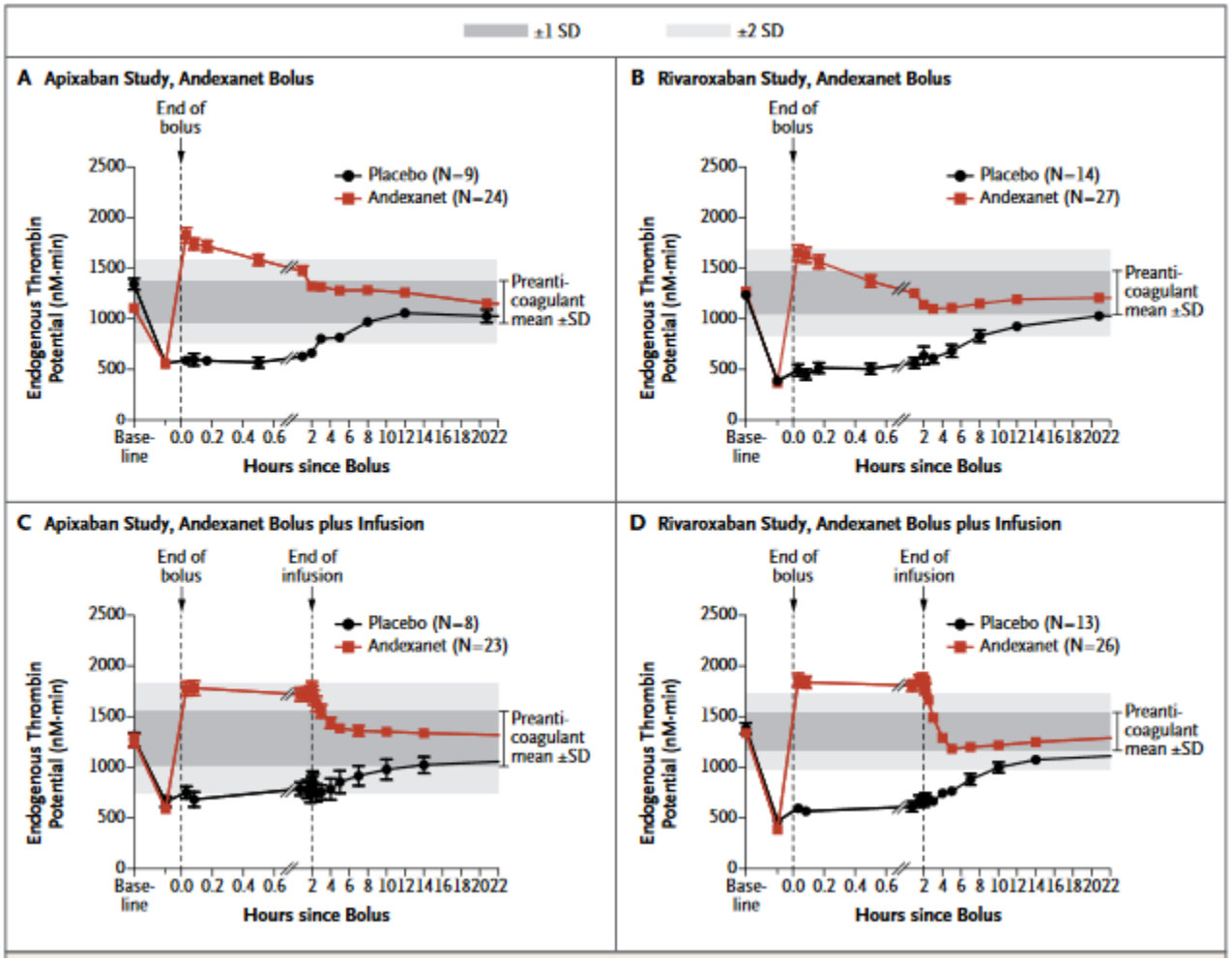
Andexanet-alfa
ANNEXA-A and ANNEXA-R
Results of Phase III (second part)



Attività anti-Xa tra le persone che avevano ricevuto il trattamento anticoagulante con apixaban o rivaroxaban misurata dopo la somministrazione di andexanet o placebo al termine della somministrazione dell'infusione. ***Pannello C*** partecipanti allo studio che hanno ricevuto apixaban+andexanet, come bolo endovenoso di 400 mg più un'infusione di 4 mg-per-minuto per 120 minuti o placebo; e ***Pannello D*** partecipanti allo studio che hanno ricevuto rivaroxaban+andexanet, come bolo endovenoso 800 mg più un'infusione a 8-mg-per-minuto per 120 minuti o placebo.

Siegal DM et al, N Engl J Med. 2015 Dec 17;373(25):2413-24

Time Courses of Thrombin Generation before and after the Administration of Andexanet



Reduction in tissue factor pathway inhibitor (TFPI) activity, an endogenous, reversible fXaI

Increase in prothrombin fragments F1 and F2

Siegal DM et al. N Engl J Med 2015;373:2413-24.

Summary and conclusions

1 - NOACs are life-saving drugs

2 - The term nonvalvular is misleading

3 - OAC in low thromboembolic risk patients is debated, but I favor its use

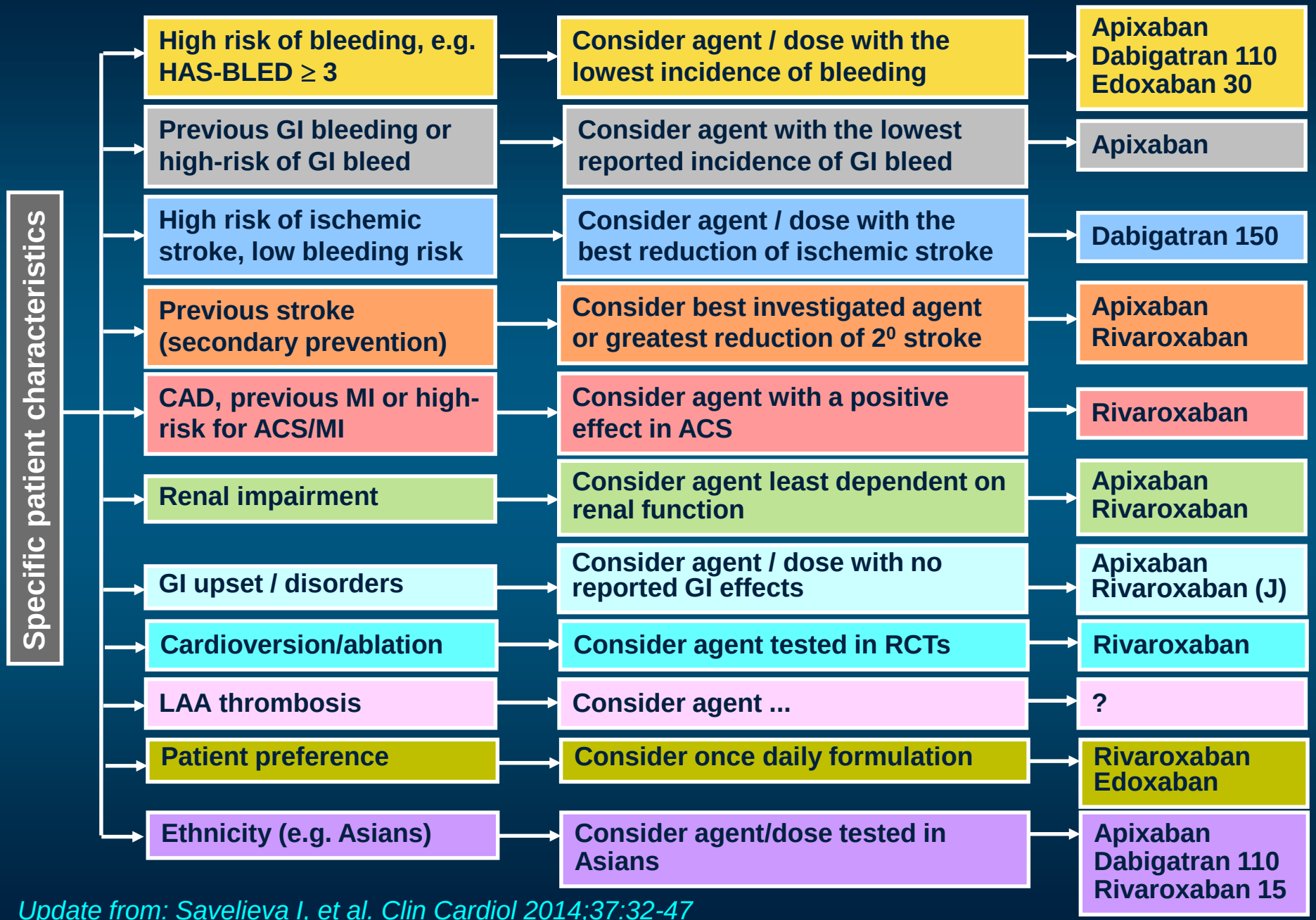
4 - The elderly benefit from NOACs (vs warfarin and ASA)

5 - Registries and Subgroup data are reassuring

6 - Approved dosing may differ from trial protocols

7 - Antidotes for NOACs have been developed and one of them, idarucizumab, is already available

Pointers Towards Which NOAC to Choose



Update from: Savelieva I, et al. Clin Cardiol 2014;37:32-47

Thanks!