Risk Stratification in the Elderly with Atrial Fibrillation: Therapeutic Implications

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11.2.2015 – Davos

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Prof. Dan Atar
Disclosures

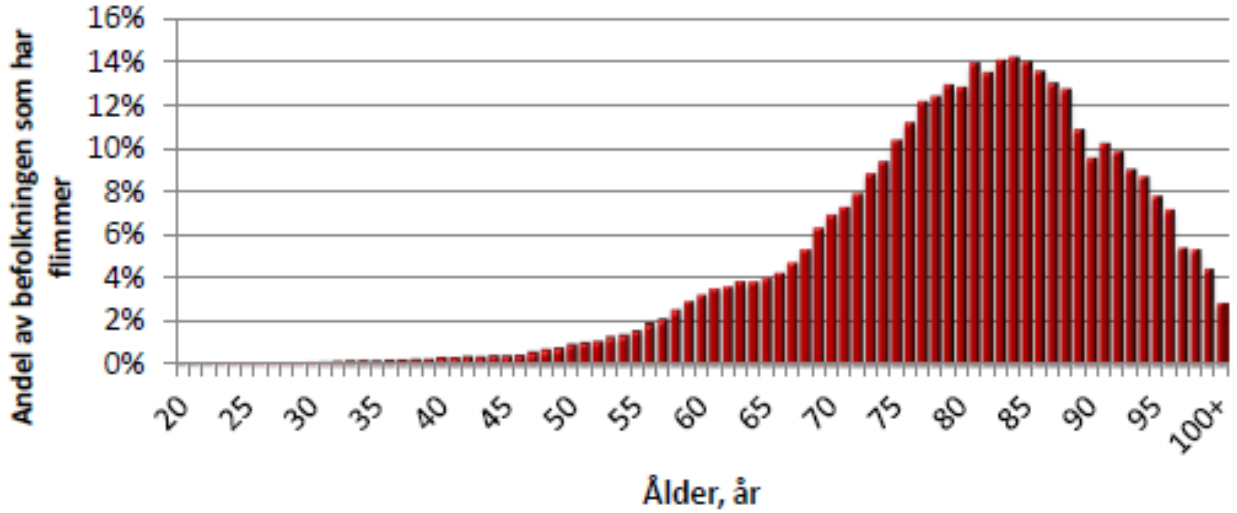
- Co-author of 2010-2012 ESC Guidelines on Atrial Fibrillation and ESC 2012 STEMI Guidelines
- Steering Committee member, National Coordinator for Norway, and Co-author of ACTIVE, ARISTOTLE, AVERROES, GARFIELD, ENGAGE-AF, XANTUS, RE-ALIGN, RE-VERSE, EVOLVE-AF, ARTESIA, PLATO.
- Fees, honoraria from Boehringer- Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Nycomed-Takeda, Cardiome, Astra-Zeneca

Förmaksflimmer i Sverige 2005-2010; förekomst och användning av koagulationshämmande läkemedel

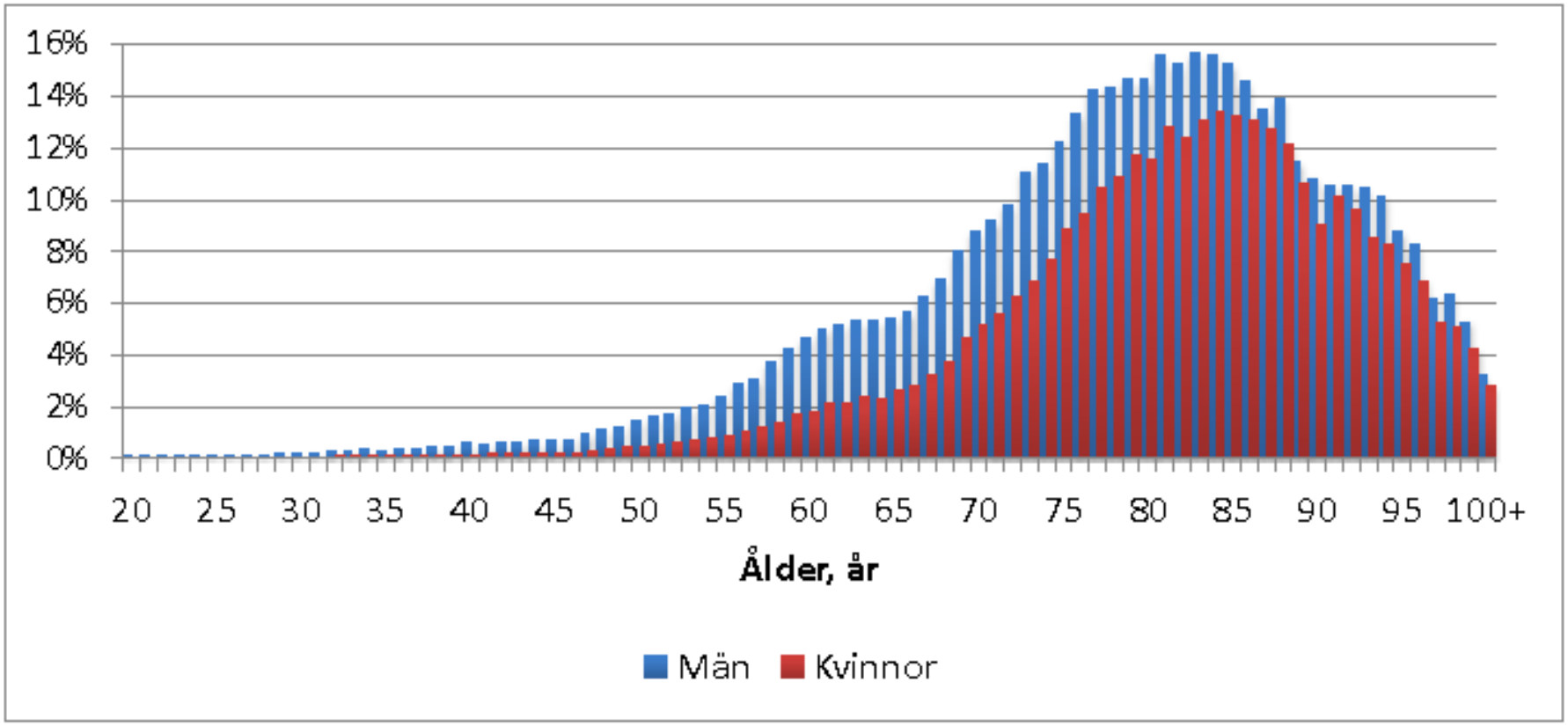
Aktuella svenska data kring kända, diagnostiserade förmaksflimmer

Under tiden 1 juli 2005 till och med 31 december 2010 fick sammanlagt 307 476 vuxna (≥20 år) personer i Sverige diagnoskoden förmaksflimmer (I489) enligt det rikstäckande Patientregistret för sluten- och öppenvård vid svenska sjukhus sedan 1987 (alltså inte inkluderande primärvården). Av dessa avled 98 335 under perioden. Oräknat avlidna fanns vid årsskiftet 2010/2011 således 209 141 personer i Sverige som vid minst ett tillfälle fått diagnosen förmaksflimmer.

Detta motsvarar en förekomst av 2,9 procent av den vuxna befolkningen (≥20 år) som vid denna tidpunkt utgjordes av 7 232 006 personer.

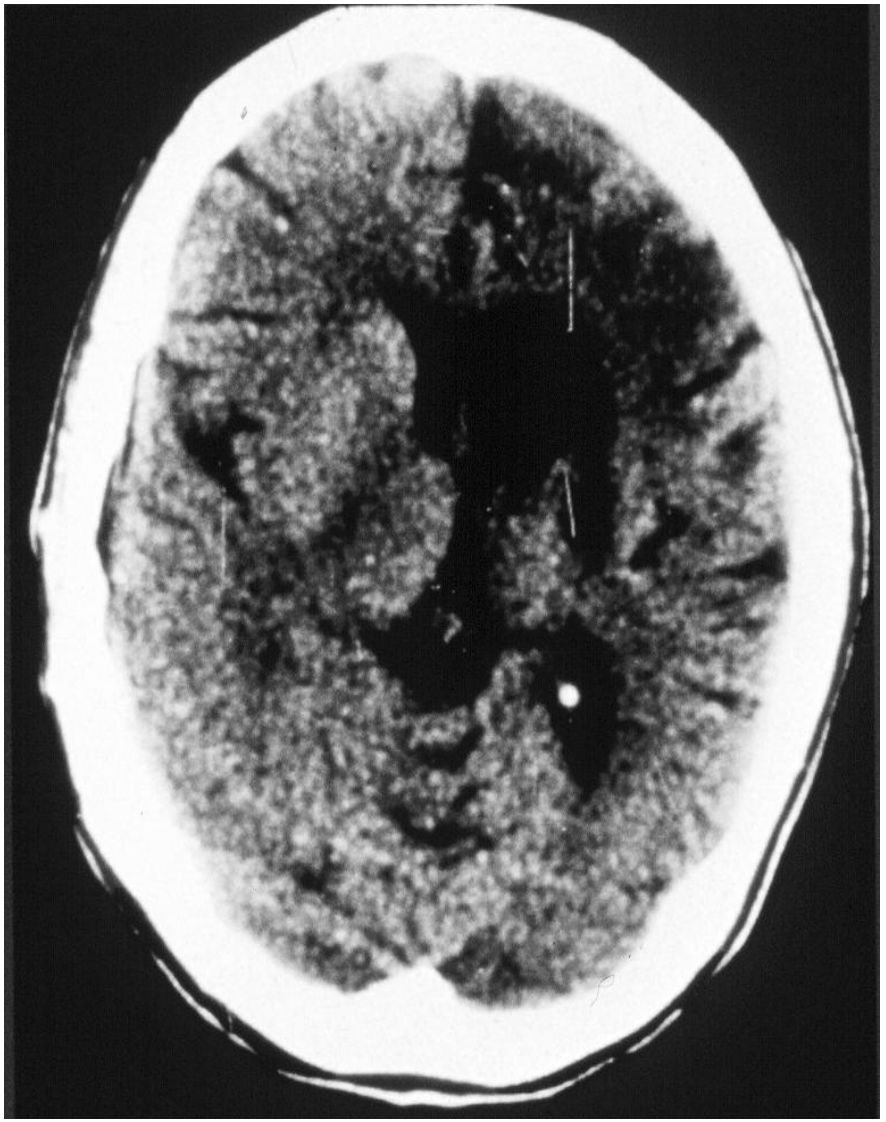


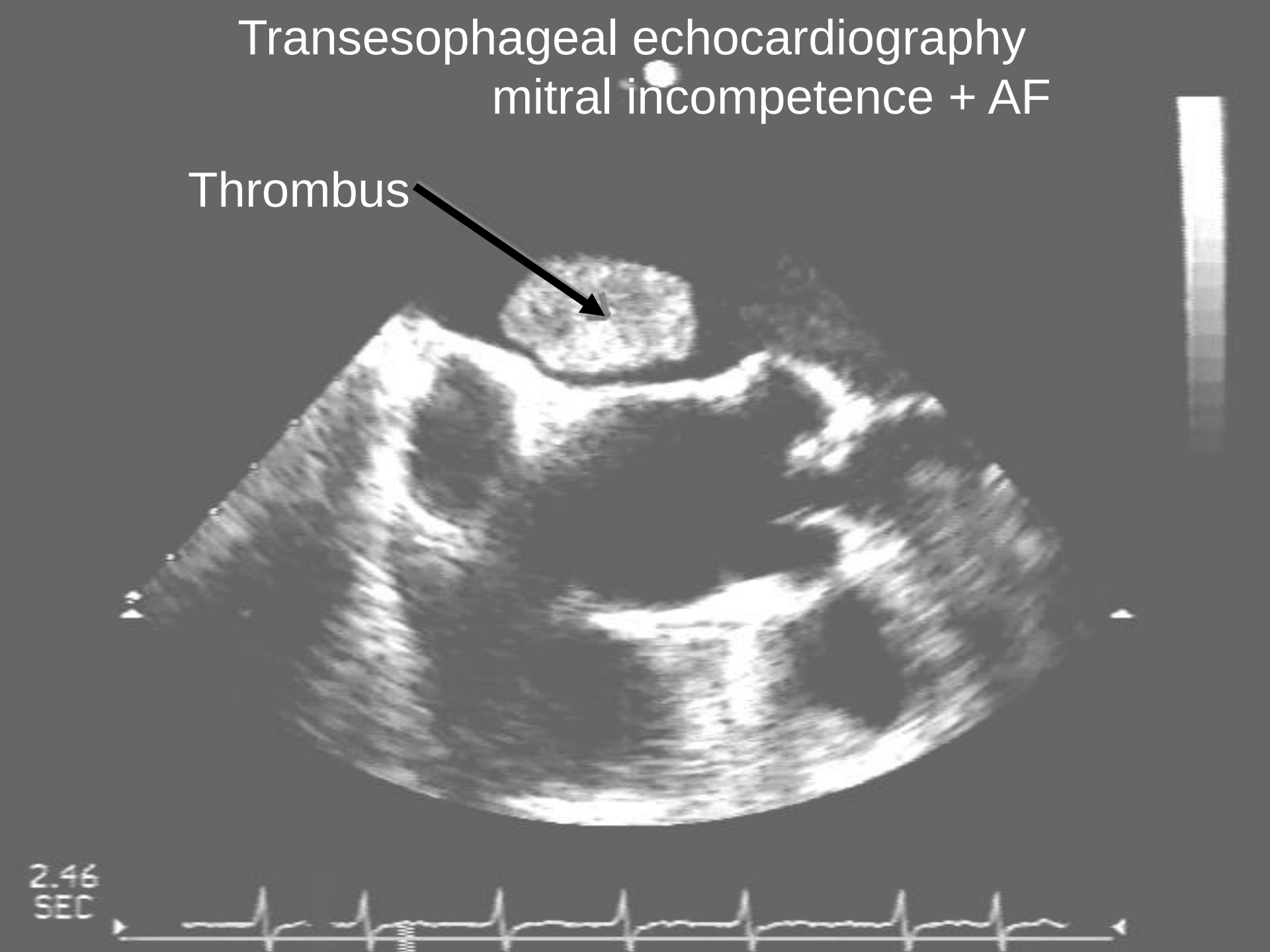
I alla åldersgrupper är förmaksflimmer vanligare bland män än bland kvinnor.



Figur 2 *Andel män och kvinnor i Sverige som har förmaksflimmer. Källa: Patientregistret*

Thromboembolic stroke in AF




Transesophageal echocardiography
mitral incompetence + AF
Thrombus
2.46
SEC

Risk Stratification in the Elderly with Atrial Fibrillation:Therapeutic Implications

1. According to the ESC guidelines 2010 / 2012

2. According to the EHRA practice guide 2013

3. According to EHRA/EAPCI consensus document 2014

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

	RE-LY[5]			ROCKET-AF[6]		ARISTOTLE[7]		ENGAGE AF-TIMI 48[8]		
	Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (n=6015)	Warfarin (n=6022)	Rivaroxaban (n=7131)	Warfarin (n=7133)	Apixaban (n=9120)	Warfarin (n=9081)	Edoxaban 60 mg (n=7035)	Edoxaban 30 mg (n=7034)	Warfarin (n=7036)
Age (years)	71·5 (8·8)	71·4 (8·6)	71·6 (8·6)	73 (65–78)	73 (65–78)	70 (63–76)	70 (63–76)	72 (64–68)	72 (64–78)	72 (64–78)
≥75 years	40%	38%	39%	43%	43%	31%	31%	41%	40%	40%

Ruff CT et al., Lancet. 2014;383:955-62

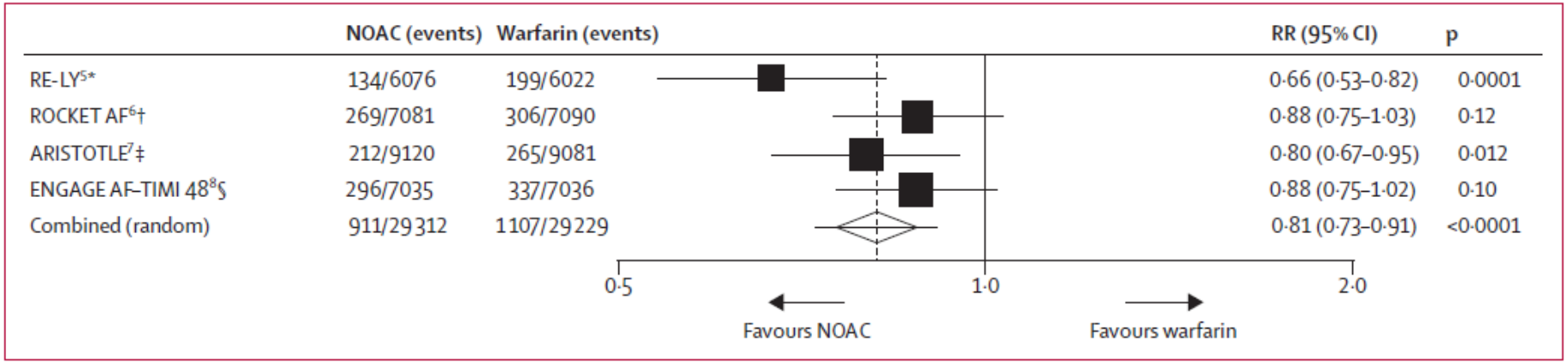


Figure 1: Stroke or systemic embolic events

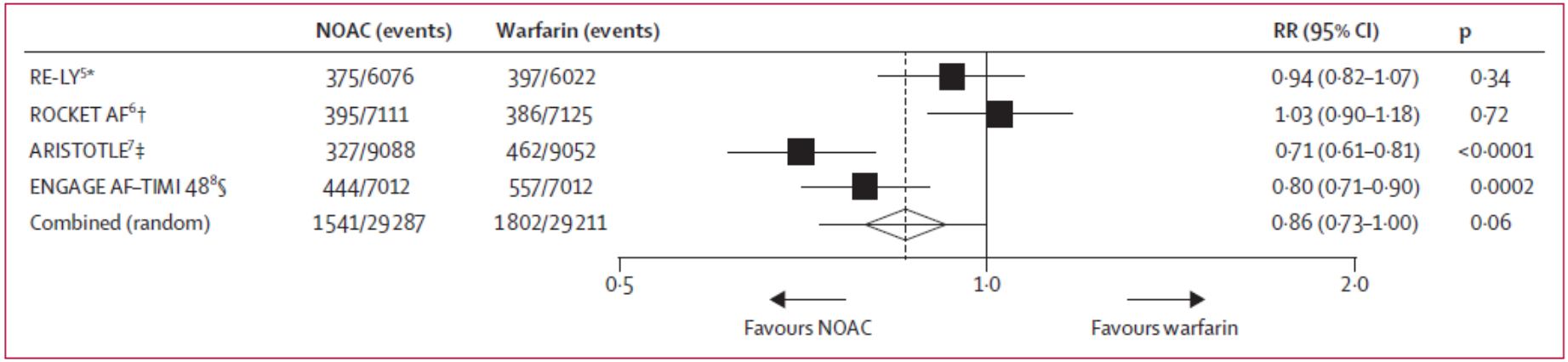


Figure 3: Major bleeding

Ruff CT et al., Lancet. 2014;383:955-62

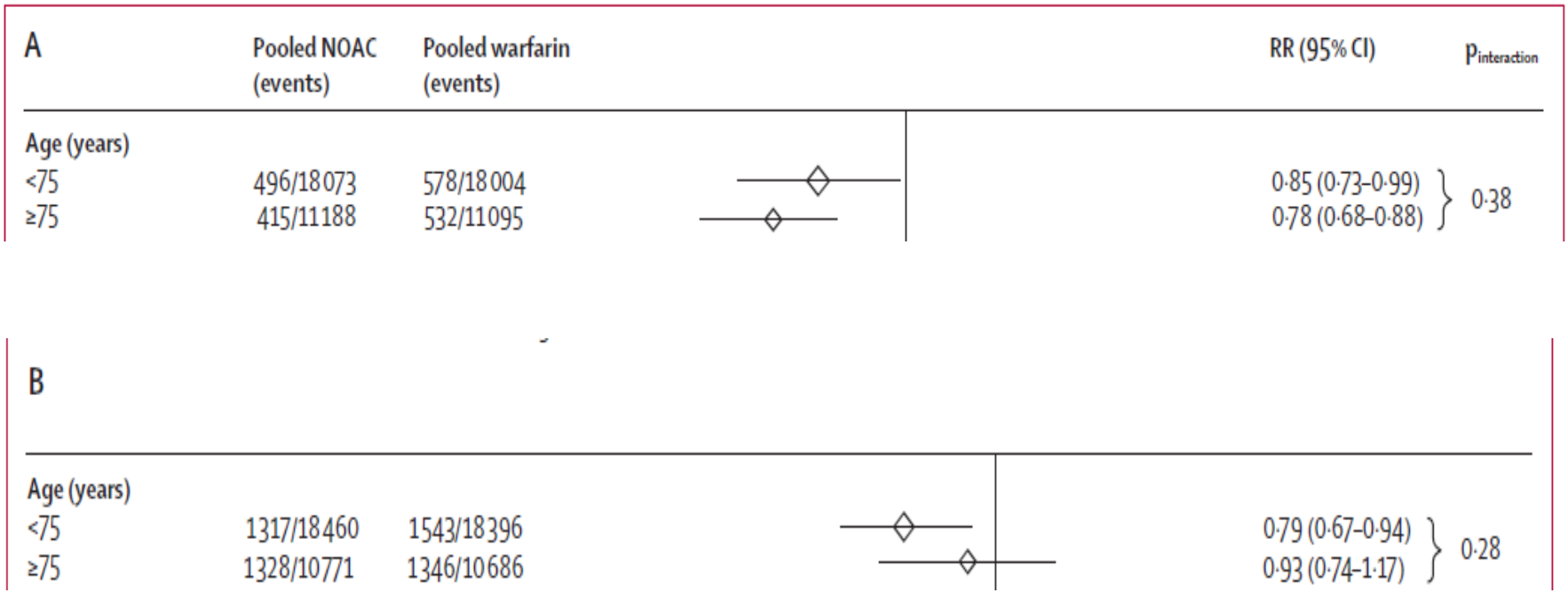


Figure 4: Stroke or systemic embolic events subgroups (A) and major bleeding subgroups (B)

Ruff CT et al., Lancet. 2014;383:955-62

European Heart Journal
doi:10.1093/eurheartj/ehq278

ESC GUIDELINES

Guidelines for the management of atrial fibrillation

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA)†

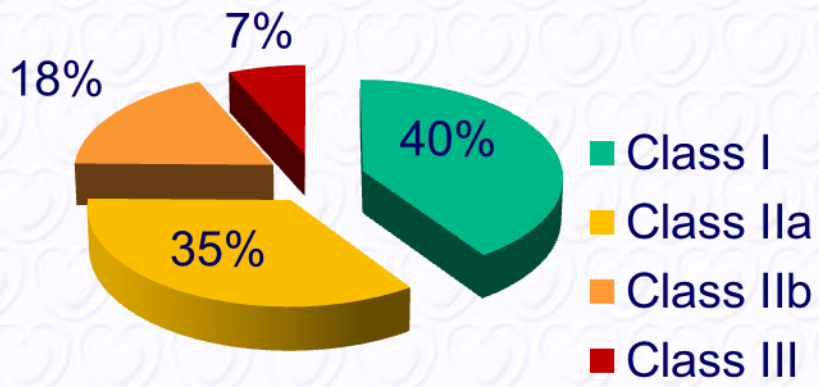
Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

European Heart Journal

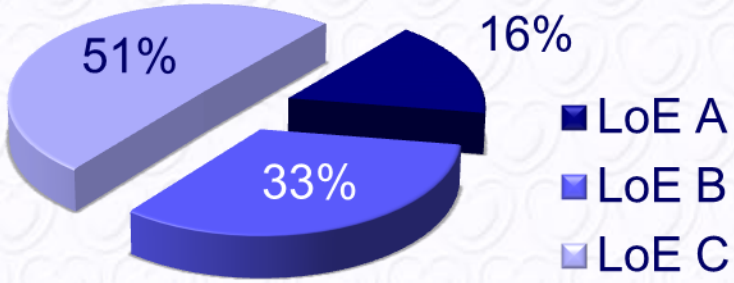
http://eurheartj.oxfordjournals.org/

Recommendations
Total = 210

Class of Recommendation



Level of Evidence



- I: is recommended
- IIa: should be considered
- IIb: may be considered
- III: should not…

ESC Pocket Guidelines

Management of Patients with Atrial Fibrillation

Guidelines Update Task Force

John Camm (Chairperson) *(UK)*; Gregory Y.H. Lip *(UK)*; Raffaele De Caterina *(Italy)*; Irene Savelieva *(UK)*; Dan Atar *(Norway)*; Stefan Hohnloser *(Germany)*; Gerhard Hindricks *(Germany)*; Paulus Kirchhof *(UK)*

2012 focussed update of the ESC Guidelines for the Management of Atrial Fibrillation

An update of the 2010 ESC Guidelines for the Management of Atrial Fibrillation

●Since 2010, further validation of the CHA_2DS_2-VASc score

Lip GY. *J Thromb Haemost* 2011;**9** Suppl 1:344–351.
Potpara TS, et al. *Circ Arrhythm Electrophysiol* 2012;**5**:319–326.
Olesen JB, et al. *Thromb Haemost* 2012;**107**:1172–1179
Van Staa TP, et al. *J Thromb Haemost* 2011;**9**:39–48.
Abu-Assi E, et al. *Int J Cardiol.* 2011

Recommendations for prevention of thromboembolism in non-valvular AF - general		
Recommendations	**Class**	**Level**
The CHA_2DS_2-VASc score is recommended as a means of assessing stroke risk in non-valvular AF.	I	A

www.escardio.org/guidelines

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

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Courtesy Prof. R. de Caterina

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

ESC 2010 AF Guidelines

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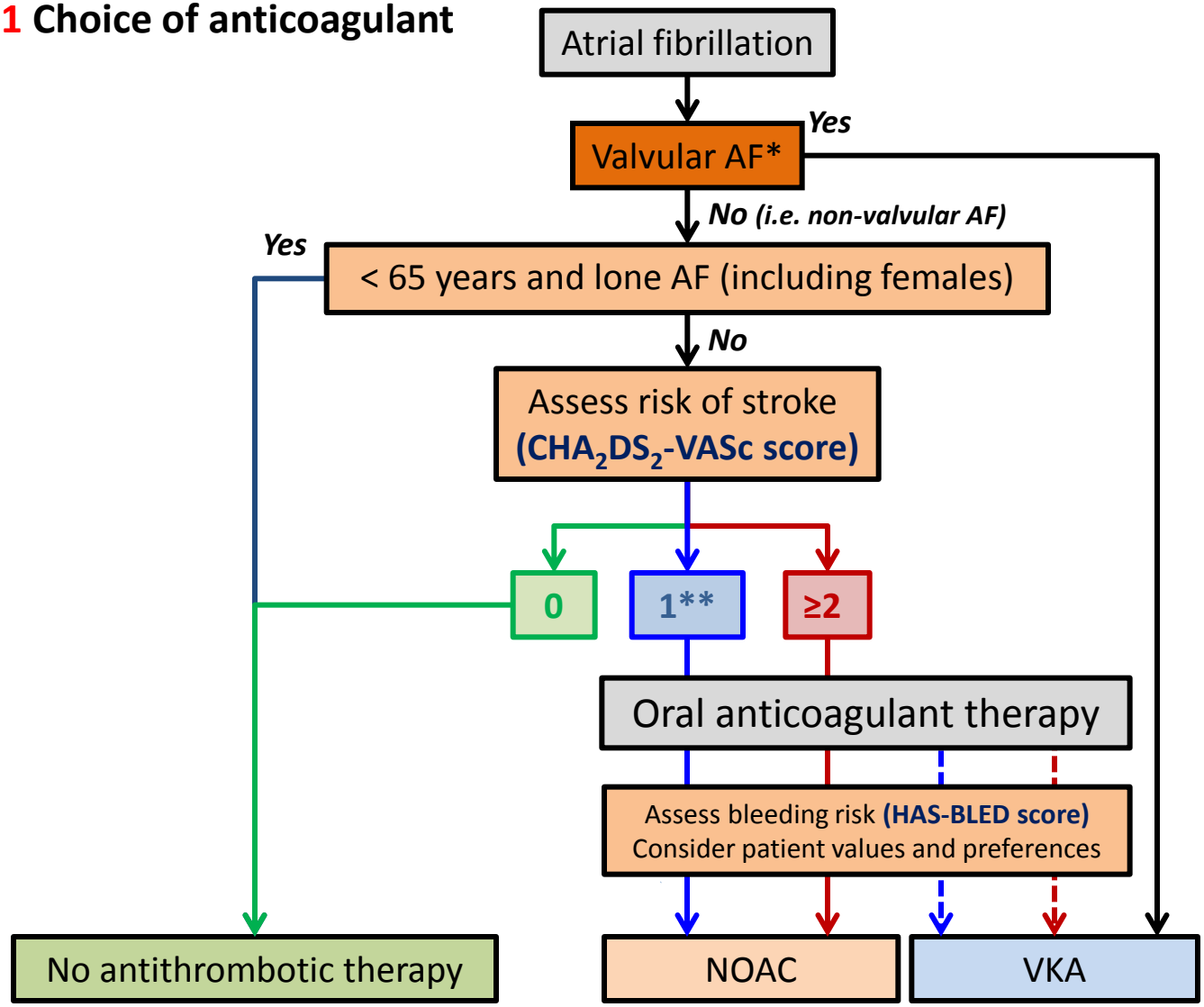
European Heart Journal (2010) **31**, 2369–2429
doi:10.1093/eurheartj/ehq278

Figure 1 Choice of anticoagulant



* Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

** Antiplatelet therapy with aspirin plus clopidogrel, or – less effectively – aspirin only, may be considered in patients who refuse any OAC.

Colour: CHA_2DS_2-VASc score; green = 1, blue = 2, red = ≤2. Line: Solid: best option; Dashed: alternative option.

If absolute contraindications to any OAC or anti-platelet therapy, left atrial appendage closure device can be considered.

AF = atrial fibrillation; CHA_2DS_2-VASc = see text; HAS-BLED = see text; NOAC = novel anticoagulants; VKA = vitamin K antagonist.

Risk Stratification in the Elderly with Atrial Fibrillation:Therapeutic Implications

1. According to the ESC guidelines 2010/12:
   The elderly have a particular therapeutic implication based on their distinct CHADS-VASc score: indication for OAC

1. According to the EHRA practice guide 2013

2. According to EHRA/EAPCI consensus document 2014

Risk Stratification in the Elderly with Atrial Fibrillation:Therapeutic Implications

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EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1], M.D., Ph.D., Peter Verhamme[1], M.D., Ph.D., Marco Alings[2], M.D., Ph.D., Matthias Antz[3], M.D., Werner Hacke[4], M.D., Jonas Oldgren[5], M.D., Ph.D., Peter Sinnaeve[1], M.D., Ph.D., A. John Camm[6], M.D., Paulus Kirchhof[7], M.D., Ph.D.

1. Department of Cardiovascular Medicine, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium; 2. Department of Cardiology, Amphia Ziekenhuis, Breda, Netherlands; 3. Department of Cardiology, Klinikum Oldenburg, Oldenburg, Germany; 4. Department of Neurology, Ruprecht Karls Universität, Heidelberg, Germany; 5. Uppsala Clinical Research Center and Dept of Medical Sciences, Uppsala University, Uppsala, Sweden; 6. Clinical Cardiology, St George's University, London, United Kingdom; 7. University of Birmingham Centre for Cardiovascular Sciences, Birmingham, UK, and Department of Cardiology and Angiology, University of Münster, Germany

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A Registered Branch of the ESC

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EHRA guide

- Practical guidance on how to utilize the NOAC's

- The focus is on typical situations and challenges faced in clinical practice, such as
  - drug-drug interactions (concomitant med.)
  - bleeding events
  - need for surgery
  - concomitant CHD
  - stroke despite adequate SPAF therapy

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

Action to be taken in case of DDIs

Three levels of alert:

- Red – contraindicated/not recommended for use
- Orange – adapt NOAC dose
  - dabigatran: 150 mg to 110 mg BID
  - rivaroxaban: 20 mg to 15 mg QD
  - apixaban: 5 mg to 2.5 mg BID
- Yellow – consider dose reduction if two concomitant yellow interactions
- Where no data available, NOACs not recommended yet

Heidbuchel et al, Europace 2013;15:625-651; Heidbuchel et al, Eur Heart J 2013;34:2094-106

Possible drug–drug interactions – Effect on NOAC plasma levels, part 1

		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Atorvastatin	P-gp/ CYP3A4	+18%		no effect	no effect
Digoxin	P-gp	no effect		no effect	no effect
Verapamil	P-gp/wk CYP3A4	+12–180%		+ 53% (slow release)	
Diltiazem	P-gp/wk CYP3A4	no effect	+40%		
Quinidine	P-gp	+50%		+80%	+50%
Amiodarone	P-gp	+12–60%		no effect	
Dronedarone	P-gp/CYP3A4	+70–100%			
Ketoconazole; itraconazole; voriconazole; posaconazole;	P-gp and BCRP/ CYP3A4	+140–150%	+100%		up to +160%

Red – contraindicated; orange – reduce dose; yellow – consider dose reduction if another yellow factor present; hatching – no data available; recommendation made from pharmacokinetic considerations

Heidbuchel et al, Europace 2013;15:625-651; Heidbuchel et al, Eur Heart J 2013;34:2094-106

Possible drug–drug interactions – Effect on NOAC plasma levels, part 2

	Interaction	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fluconazole	CYP3A4	no data	no data	no data	+42%
Cyclosporin; tacrolimus	P-gp	no data	no data	no data	+50%
Clarithromycin; erythromycin	P-gp/CYP3A4	+15–20%	no data	no data	+30–54%
HIV protease inhibitors	P-gp and BCRP/ CYP3A4	no data	strong increase	no data	up to +153%
Rifampicin; St John's wort; carbamezepine; phenytoin; phenobarbital	P-gp and BCRP/ CYP3A4/CYP2J2	-66%	-54%	-35%	up to -50%
Antacids	GI absorption	-12-30%	no data	no effect	no effect

Red – contraindicated; orange – reduce dose; yellow – consider dose reduction if another yellow factor present; hatching – no data available; recommendation made from pharmacokinetic considerations

Heidbuchel et al, Europace 2013;15:625-651; Heidbuchel et al, Eur Heart J 2013;34:2094-106

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- Practical guidance on how to utilize the NOAC's

- The focus is on typical situations and challenges faced in clinical practice, such as
  - renal dysfunction
  - bleeding events
  - need for surgery
  - concomitant CHD
  - stroke despite adequate SPAF therapy

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

Patients with chronic kidney disease

Estimated $t_{½}$ and AUC NOAC plasma concentrations compared to healthy controls

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
CrCl ≥60 ml/min CKD Stage I & II	~14 h[1]	~14.6 h[4] (+16%)	~8.6 h[2]	~8.5 h[3] (+44%)
CrCl 30–60 ml/min CKD Stage III	~18 h[1]	~17.6 h (+29%)	~9.4 h[2]	~9 h[3] (+52%)
CrCl 15–30 ml/min CKD Stage IV	~28 h[1]	~17.3 h (+44%)	~16.9 h[2]	~9.5 h[3] (+64%)
CrCl ≤15 ml/min CKD Stage V	no data	-	no data	no data

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1. Stangier et al, Clinical pharmacokinetics 2010;49:259-68
2. Ridout et al, J Clin Pharmacol 2009:49:1124
3. Kubitza et al, Br J Clin Pharmacol 2010:70:703-2
4. Chang et al,, abstract
   Heidbuchel et al, Europace 2013;15:625-651
   Heidbuchel et al, Eur Heart J 2013;34:2094-106

NOACs in renal dysfunction – Practical recommendations for dosing in chronic kidney disease

Dabigatran	Apixaban	Edoxaban *	Rivaroxaban
When CrCl 30–49 ml/min, 150 mg BID is possible (SmPC) but 110 mg BID if 'high risk of bleeding' (SmPC) or 'recommended' (GL update)[1] Note: 75 mg BID approved in US only[#] -If CrCl 15–30 ml/min -If CrCl 30–49 ml/min -And other orange factor (e.g. verapamil)	CrCl 15–29 ml/min: 2.5 mg BID is possible Serum creatinine ≥1.5 mg/dl in combination with age ≥80 years or weight ≤60 kg (SmPC) or with other 'yellow' factor: 2.5 mg BID	not available	15 mg OD when CrCl 15–49 ml/min

*No EMA approval yet. Needs update after finalisation of SmPC; [#]No EMA indication. FDA recommendation based on pharmacokinetics. Carefully consider benefits and risks of this approach. Note that 75 mg capsules are not available in Europe for AF indication; [‡] Australian prescribing information

Disclaimer: All NOACS should always be used in accordance with local prescribing authorization, which may or may not be the same as in Europe and the US

1. Camm et al, Eur Heart J 2012;33:2719-47; Heidbuchel et al, Europace 2013;15:625-651; Heidbuchel et al, Eur Heart J 2013;34:2094-106

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NOACs in chronic kidney disease – Practical suggestions

- Dabigatran may not be first choice as primarily cleared renally but may be used in stable patients.
- FXa inhibitors have 25–50% renal clearance therefore may be preferred
- Consider dose reductions in patients with CrCl <50 ml/min: apixaban 2.5 mg BID,[1] rivaroxaban 15 mg/day[2]
- Avoid NOACs in AF patients on haemodialysis: consider VKAs

1. Fox et al, Eur Heart J 2011;32:2387-94; 2. Connolly et al N Engl J Med 2011; 364:806-17; Heidbuchel et al, Europace 2013;15:625-651; Heidbuchel et al, Eur Heart J 2013;34:2094-106

NOACs in chronic kidney disease – Practical suggestions

- Monitor renal function regularly and adapt the dose accordingly
- Monitor renal function at the following intervals:

yearly	stage I–II (CrCl ≥60 ml/min)
6-monthly	stage III, elderly (>75 yrs) or frail patients on dabigatran (CrCl 30–60 ml/min)
3-monthly	stage IV (CrCl ≤30 ml/min)

Heidbuchel et al, Europace 2013;15:625-651; Heidbuchel et al, Eur Heart J 2013;34:2094-106

EHRA guide

- **Practical guidance on how to utilize the NOAC's**

- **The focus is on typical situations and challenges faced in clinical practice, such as**
  - **drug-drug interactions (concomitant med.)**
  - **bleeding events**
  - **need for surgery**
  - **concomitant CHD**
  - **stroke despite adequate SPAF therapy**

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

When to stop NOACs before a planned surgical intervention

Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban *		Rivaroxaban	
	No important bleeding risk and/or local haemostasis possible: perform at trough level (i.e. ≥12h or 24h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24h	≥48h	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 50–80 ml/min	≥36h	≥72h	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 30–50 ml/min §	≥48h	≥96h	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 15–30 ml/min §	not indicated	not indicated	≥36h	≥48h	no data yet	no data yet	≥36h	≥48h
CrCl <15 ml/min	no official indication for use							

*no EMA approval yet.; Low risk: surgery with low risk of bleeding. High risk: surgery with high risk of bleeding § many of these patients may be on the lower dose of dabigatran (i.e. 2x110 mg/d) or apixaban (i.e. 2x2.5 mg/d), or have to be on the lower dose of rivaroxaban (15 mg/d).

When to restart NOACs after a planned surgical intervention

Procedures with immediate and complete haemostasis: Atraumatic spinal/epidural anethesia Clean lumbar puncture	Resume 6–8 h after surgery
Procedures associated with immobilization: Procedures with post-operative risk of bleeding:	Initiate reduced venous or intermediate dose of LMWH 6–8 h after surgery if haemostasis achieved. Restart NOACs 48–72h after surgery upon complete haemostasis Thromboprophylaxis (e.g. with LMWH) can be initiated 6-8 h after surgery

Risk Stratification in the Elderly with Atrial Fibrillation:Therapeutic Implications

1. According to the ESC guidelines 2010 / 2012

1. According to the EHRA practice guide 2013:
   The elderly have multiple particular therapeutic implications based on factors such as frailty, organ-function, concomitant medications and comorbidities

1. According to EHRA/EAPCI consensus document 2014

EHRA guide

- **Practical guidance on how to utilize the NOAC's**

- **The focus is on typical situations and challenges faced in clinical practice, such as**
  - **renal insufficiency**
  - **bleeding events**
  - **need for surgery**
  - **concomitant CHD / ACS**
  - **stroke despite adequate SPAF therapy**

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

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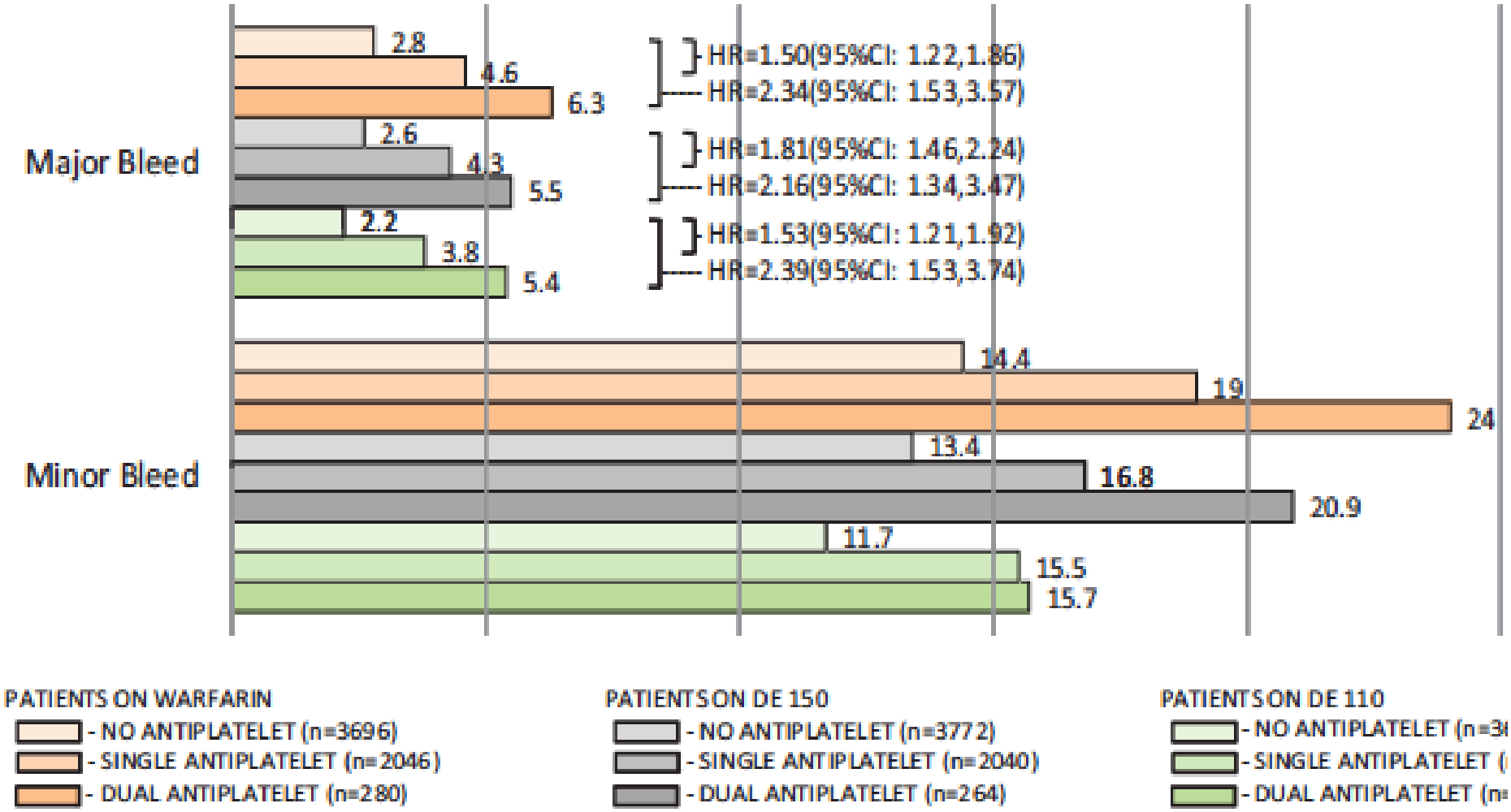
Dabigatran vs warfarin and bleeding risk in AF patients recieving antiplatelets

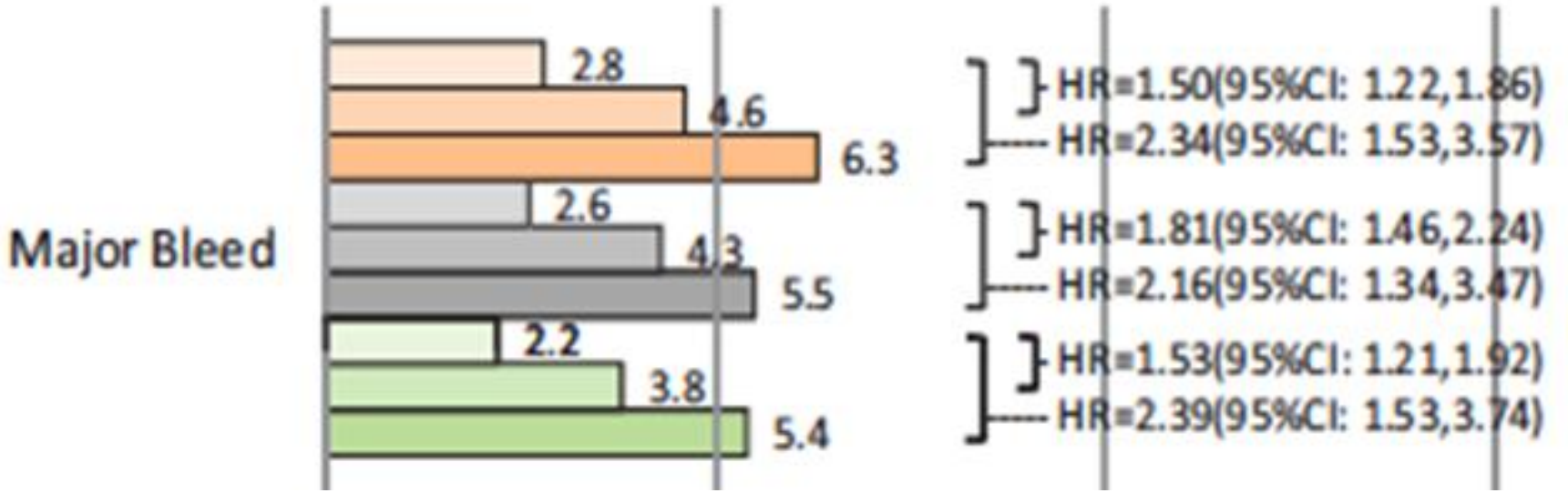
Post-hoc analysis from RE-LY



Dans AL et al *Circulation*. 2013;127:634-640

Dabigatran vs warfarin and bleeding risk in AF patients recieving antiplatelets

Post-hoc analysis from RE-LY



Characteristic	D 110 mg	D 150 mg	Warfarin	P-value 110 vs. W	P-value 150 vs. W
Number of patients (n)	6015	6076	6022		
Major bleeding	2.71	3.11	3.36	0.003	0.31

Dans AL et al *Circulation*. 2013;127:634-640

European Heart Journal Advance Access published August 25, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu298

CURRENT OPINION

Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS)

Task Force Members: Gregory Y.H. Lip* (UK, Chairman), Stephan Windecker (Switzerland)†, Kurt Huber (Austria)†, Paulus Kirchhof (UK)†, Francisco Marin (Spain), Jurriën M. Ten Berg (Netherlands), Karl Georg Haeusler (Germany), Giuseppe Boriani (Italy), Davide Capodanno (Italy), Martine Gilard (France), Uwe Zeymer (Germany), Deirdre Lane (UK, Patient Representative).

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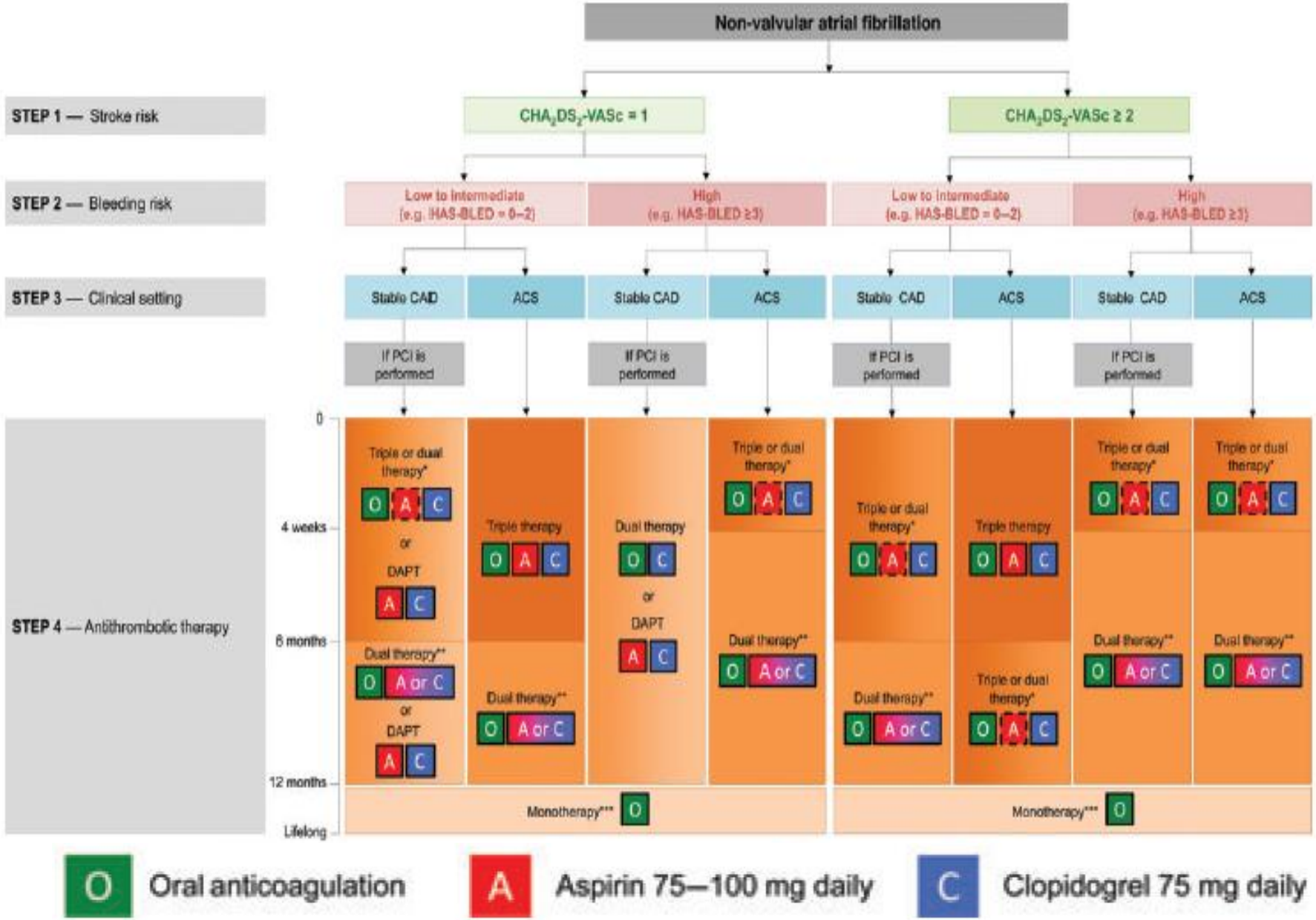
CURRENT OPINION



Risk Stratification in the Elderly with Atrial Fibrillation:Therapeutic Implications

1. According to the ESC guidelines 2010 / 2012

2. According to the EHRA practice guide 2013

3. According to EHRA/EAPCI consensus document 2014: Triple and even dual antiplatelet therapy together with OAC as short as possible, stratified according to risk.

Thank you for your attention

Oslo University Hospital