



Sfide in cardiologia clinica

10/11 marzo 2017

Mantova MaMu, Centro Congressi Mantova Largo di Porta Pradella, 1

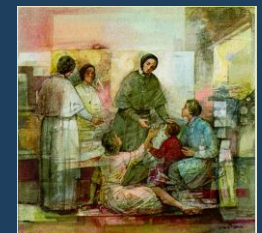


FIBRILLAZIONE ATRIALE E STRATEGIA TERAPEUTICA. IL RUOLO DEI NUOVI ANTICOAGULANTI ORALI E DELL'IMAGING NELLA PREVENZIONE DELLO STROKE ISCHEMICO

G Corrado, MD, FANMCO, FESC
Unità Operativa di Cardiologia
Ospedale Valduce – Como (IT)



H. Valduce 1879





Sfide in cardiologia clinica

10/11 marzo 2017

Mantova MaMu, Centro Congressi Mantova Largo di Porta Pradella, 1

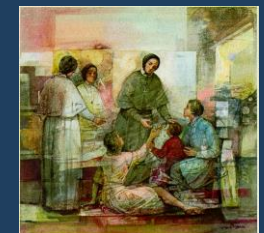


CONFLITTI DI INTERESSE: NESSUNO

G Corrado, MD, FANMCO, FESC
Unità Operativa di Cardiologia
Ospedale Valduce – Como (IT)



H. Valduce 1879



FA: PREVALENZA

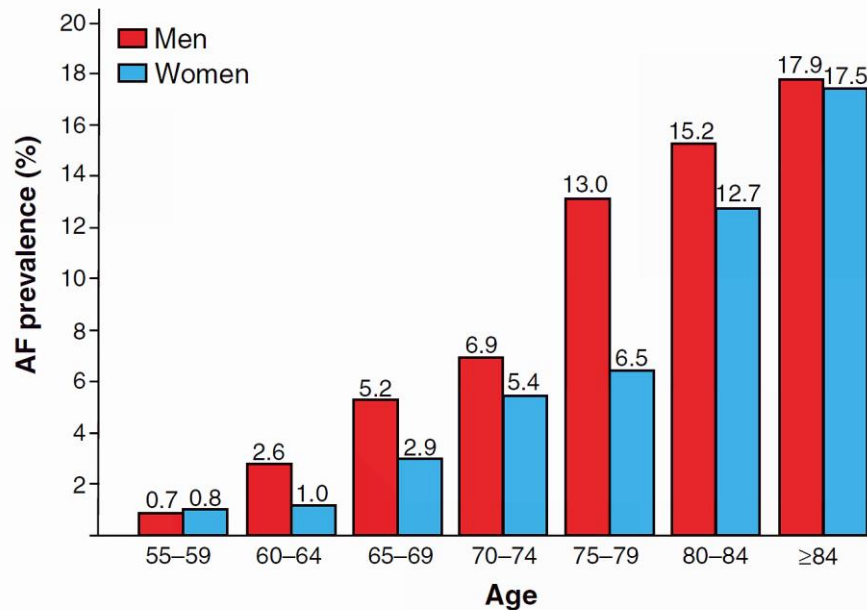


Fig. 1 Prevalence of atrial fibrillation according to age in the Rotterdam study. (adapted from Heeringa et al. [1]).

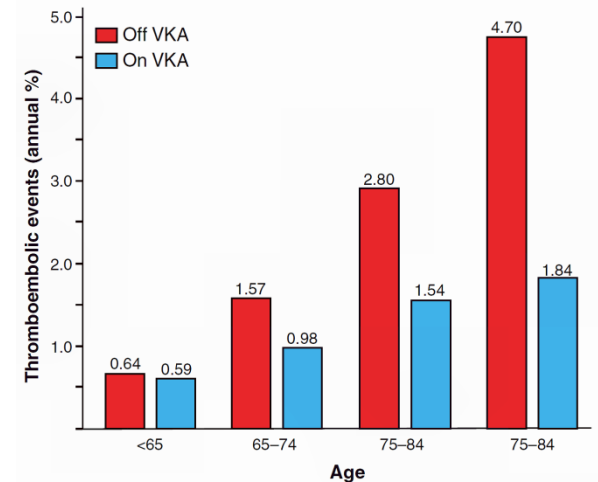


Fig. 2 Rates (annual rate/100) of thromboembolic events per age (adapted from Singer et al. [7]).

Review

Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2011.02464.x

Stroke prevention in elderly patients with atrial fibrillation: challenges for anticoagulation

■ P. R. Sinnaeve¹, M. Brueckmann², A. Clemens², J. Oldgren³, J. Eikelboom⁴ & J. S. Healey⁴

From the ¹Department of Cardiovascular Medicine, University Hospitals Leuven, Leuven, Belgium, ²Boehringer Ingelheim, Global Clinical Development and Medical Affairs, Ingelheim am Rhein, Germany, ³Uppsala Clinical Research Centre and Department of Medical Sciences, Uppsala University, Uppsala, Sweden, and ⁴Population Health Research Institute, Hamilton, Canada



IMPATTO CLINICO

Table 3 Cardiovascular morbidity and mortality associated with atrial fibrillation

Event	Association with AF
Death	Increased mortality, especially cardiovascular mortality due to sudden death, heart failure or stroke.
Stroke	20–30% of all strokes are due to AF. A growing number of patients with stroke are diagnosed with 'silent', paroxysmal AF.
Hospitalizations	10–40% of AF patients are hospitalized every year.
Quality of life	Quality of life is impaired in AF patients independent of other cardiovascular conditions.
Left ventricular dysfunction and heart failure	Left ventricular dysfunction is found in 20–30% of all AF patients. AF causes or aggravates LV dysfunction in many AF patients, while others have completely preserved LV function despite long-standing AF.
Cognitive decline and vascular dementia	Cognitive decline and vascular dementia can develop even in anticoagulated AF patients. Brain white matter lesions are more common in AF patients than in patients without AF.

AF = atrial fibrillation; LV = left ventricular.



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

ESC GUIDELINES

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)

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

Endorsed by the European Stroke Organisation (ESO)

Authors/Task Force Members: Paulus Kirchhof* (Chairperson) (UK/Germany), Stefano Benussi*¹ (Co-Chairperson) (Switzerland), Dipak Kotecha (UK), Anders Ahlsson¹ (Sweden), Dan Atar (Norway), Barbara Casadei (UK), Manuel Castella¹ (Spain), Hans-Christoph Diener² (Germany), Hein Heidbuchel (Belgium), Jeroen Hendriks (The Netherlands), Gerhard Hindricks (Germany), Antonis S. Manolis (Greece), Jonas Oldgren (Sweden), Bogdan Alexandru Popescu (Romania), Ulrich Schotten (The Netherlands), Bart Van Putte¹ (The Netherlands), and Panagiotis Vardas (Greece)

Document Reviewers: Stefan Agewall (CPG Review Co-ordinator) (Norway), John Camm (CPG Review Co-ordinator) (UK), Gonzalo Baron Esquivias (Spain), Werner Budts (Belgium), Scipione Carerj (Italy), Filip Casselman (Belgium), Antonio Coca (Spain), Raffaele De Caterina (Italy), Spiridon Deftereos (Greece), Dobromir Dobrev (Germany), José M. Ferro (Portugal), Gerasimos Filippatos (Greece), Donna Fitzsimons (UK),



FA: COSTI

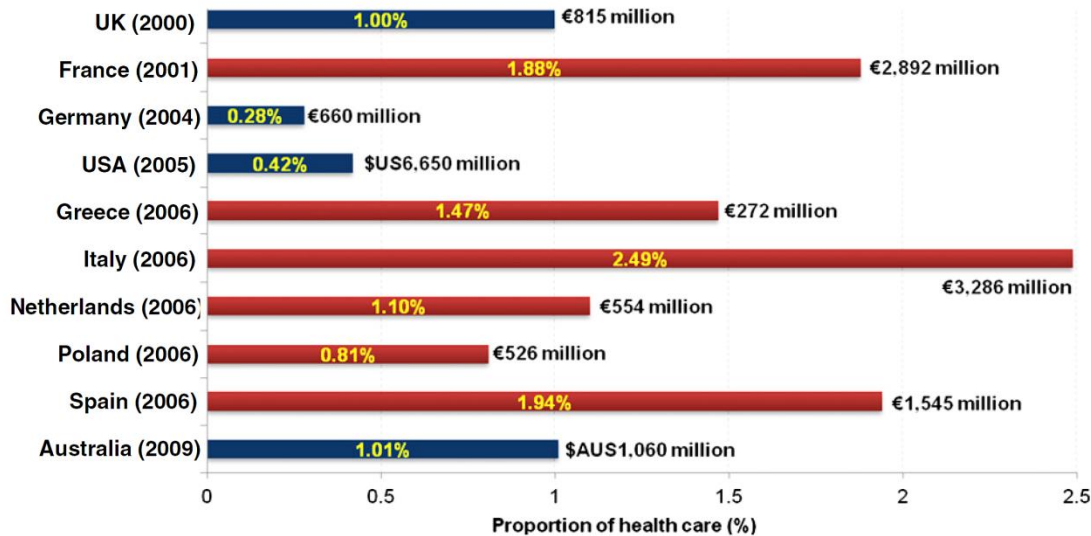


Fig. 6. Estimated health care costs of AF in a range of countries as a proportion of health care spending (■ = direct costs only; ■ = direct and indirect costs) [86–90,93].



Review

Atrial fibrillation: Profile and burden of an evolving epidemic in the 21st century

Jocasta Ball ^{a,b}, Melinda J. Carrington ^{a,b}, John J.V. McMurray ^c, Simon Stewart ^{a,b,*}

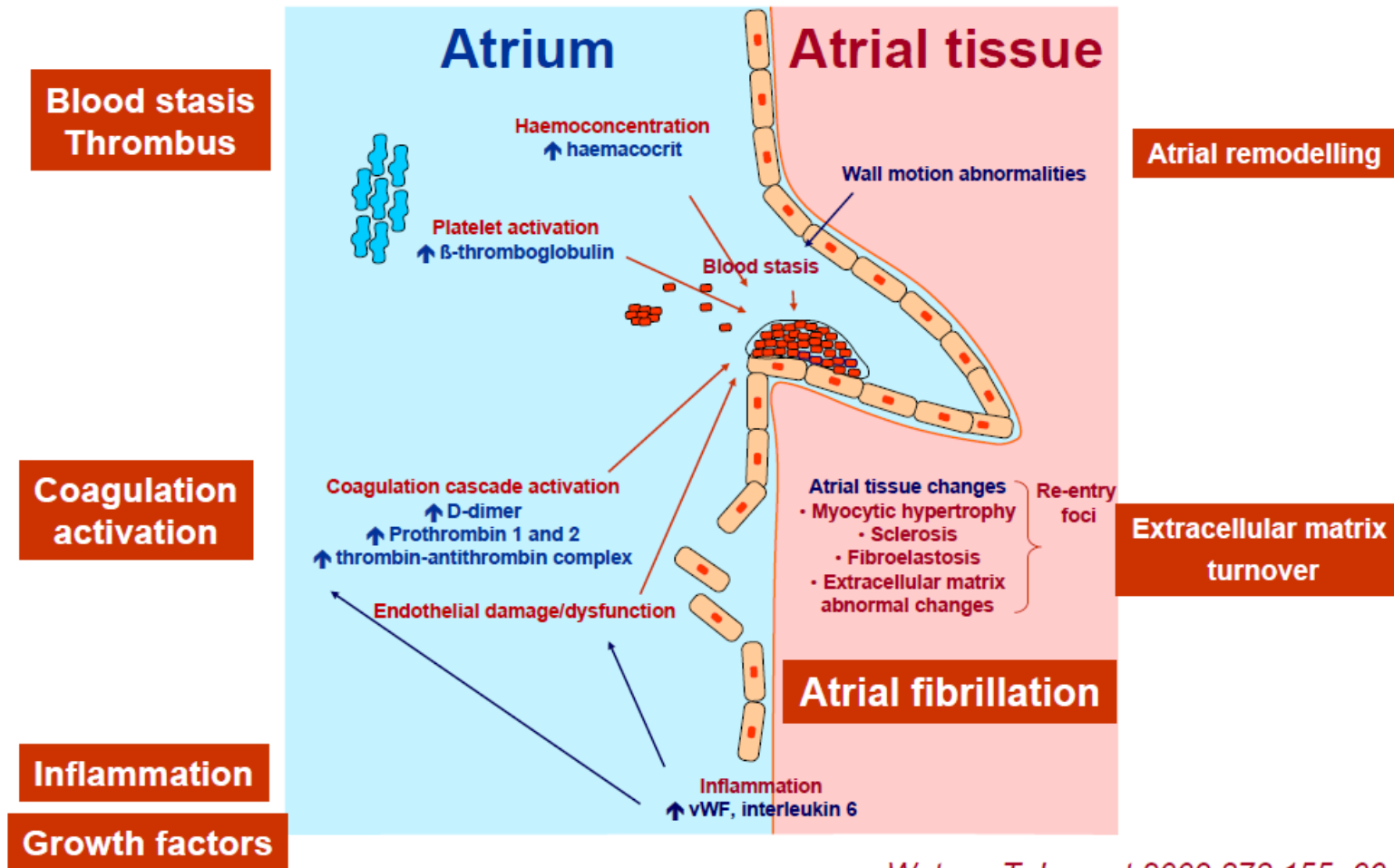
^a Centre of Research Excellence to Reduce Inequality in Heart Disease, Preventative Health, Baker IDI Heart and Diabetes Institute, Melbourne, Australia

^b Department of Epidemiology and Preventative Medicine, Monash University, Melbourne, Australia

^c Institute of Cardiovascular and Medical Sciences, University of Glasgow, Scotland, UK



FISIOPATOLOGIA DELLA TROMBOSI AS IN FA



Watson T. *Lancet* 2009;373:155–66



ITER DELLA FA

- Diagnosticare la fibrillazione atriale
- Stratificare il rischio tromboembolico
- Applicare le linee guida al mondo reale



≠



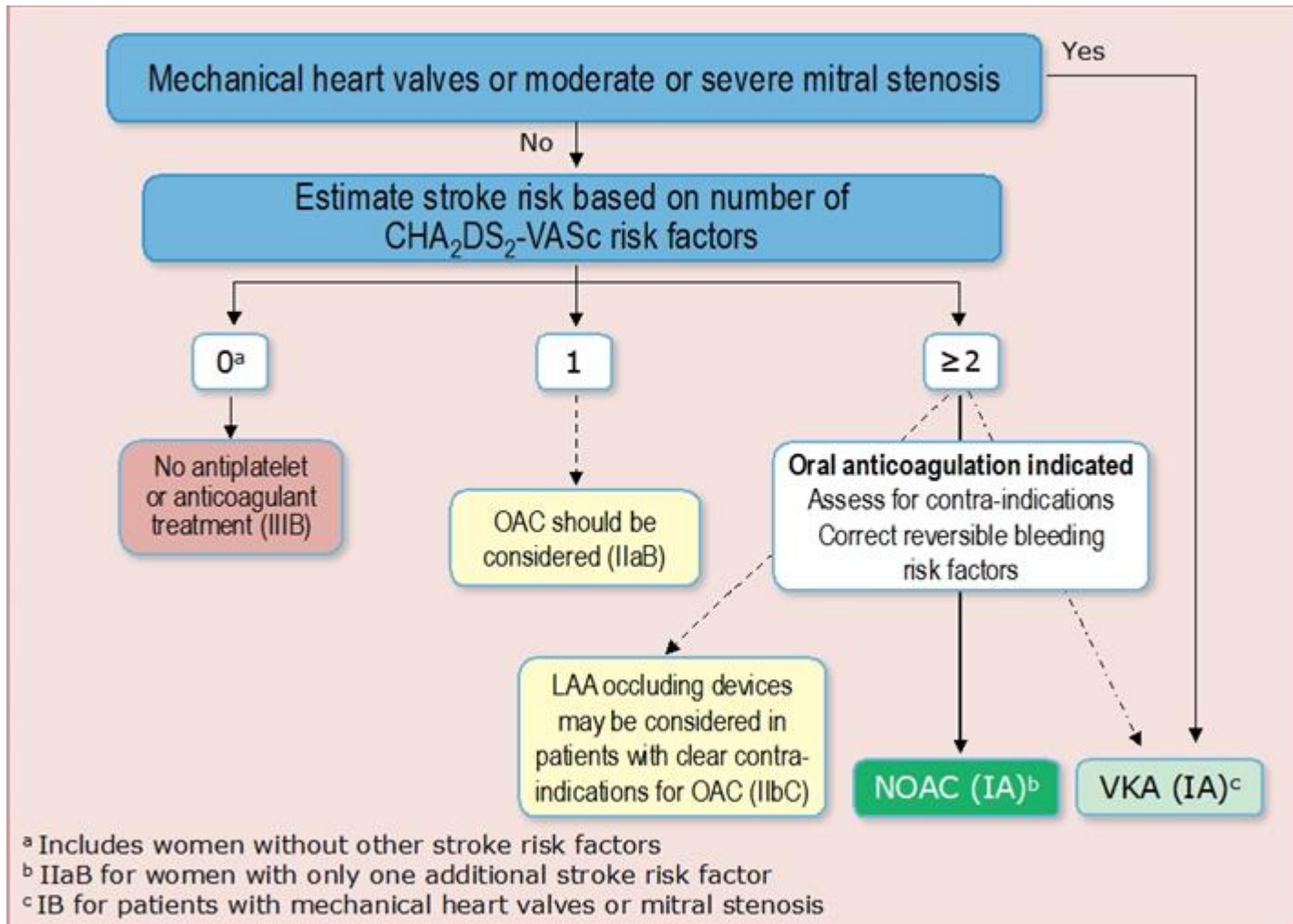
LA STRATIFICAZIONE DEL RISCHIO



The Risk of
Systemic Thromboembolism
in Patients With AF
IS NOT
Homogenous



STROKE PREVENTION IN FA



CHA₂DS₂-VASc



CHA ₂ DS ₂ -VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left-ventricular ejection fraction	1
Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	1
Age 75 years or older	2
Diabetes mellitus Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	1
Previous stroke, transient ischaemic attack, or thromboembolism	2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	1
Age 65–74 years	1
Sex category (female)	1



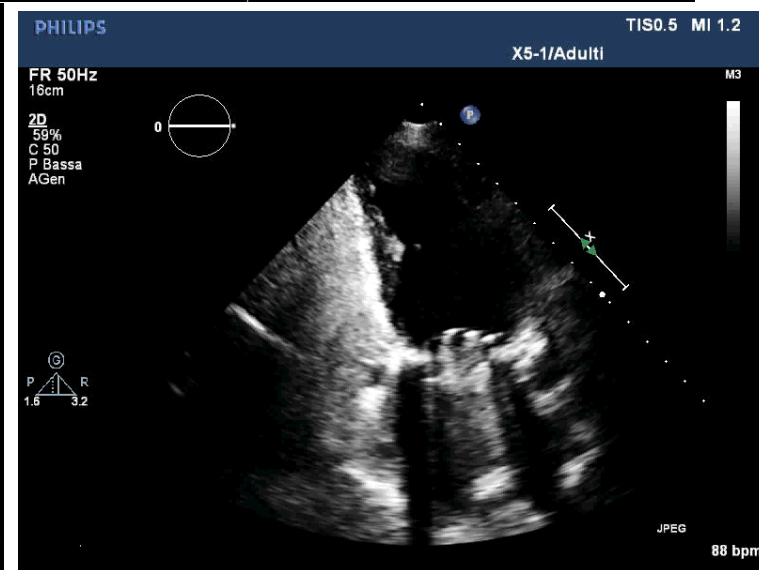
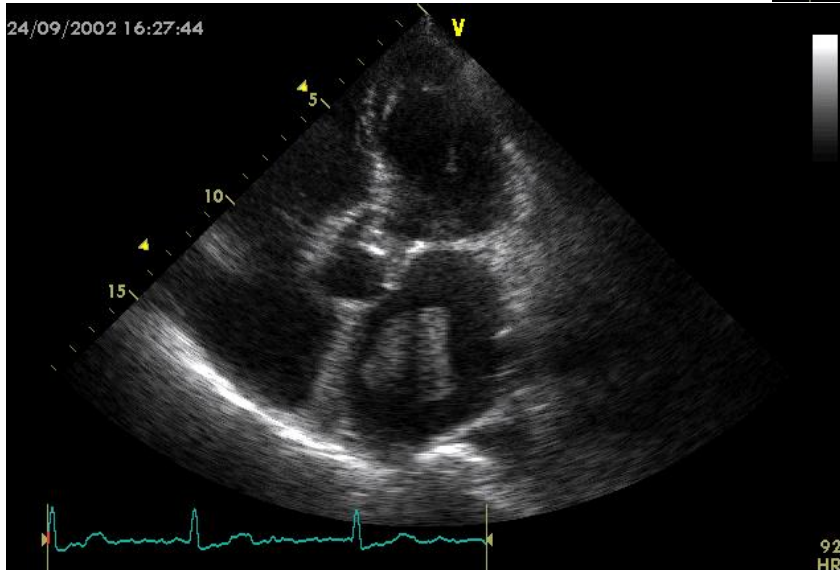
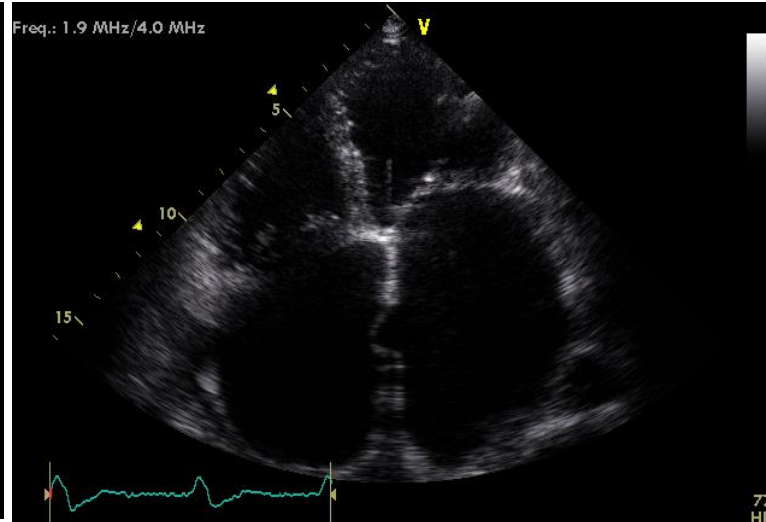
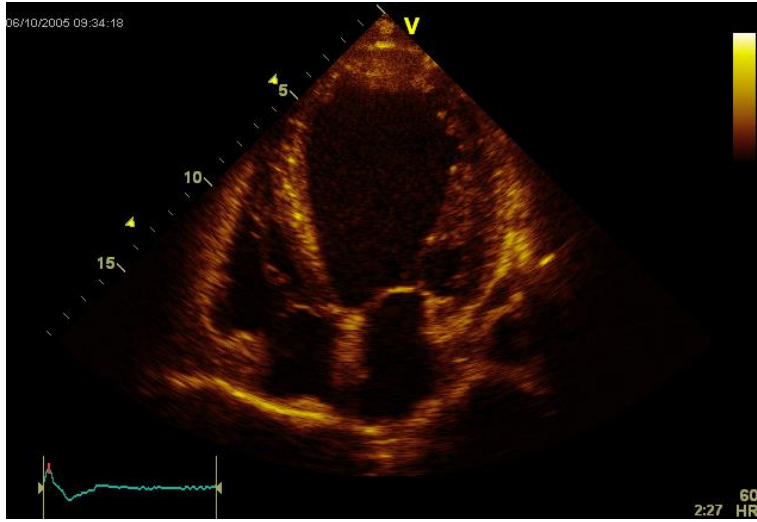
CHA₂DS₂-VASc



Recommendations	Class	Level
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA ₂ DS ₂ -VASc score of 2 or more.	I	A
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA ₂ DS ₂ -VASc score of 3 or more.	I	A
Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA ₂ DS ₂ -VASc score of 1, considering individual characteristics and patient preferences.	IIa	B
Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA ₂ DS ₂ -VASc score of 2, considering individual characteristics and patient preferences.	IIa	B
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.	I	B
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.	I	A



RUOLO DELL'IMAGING: TTE



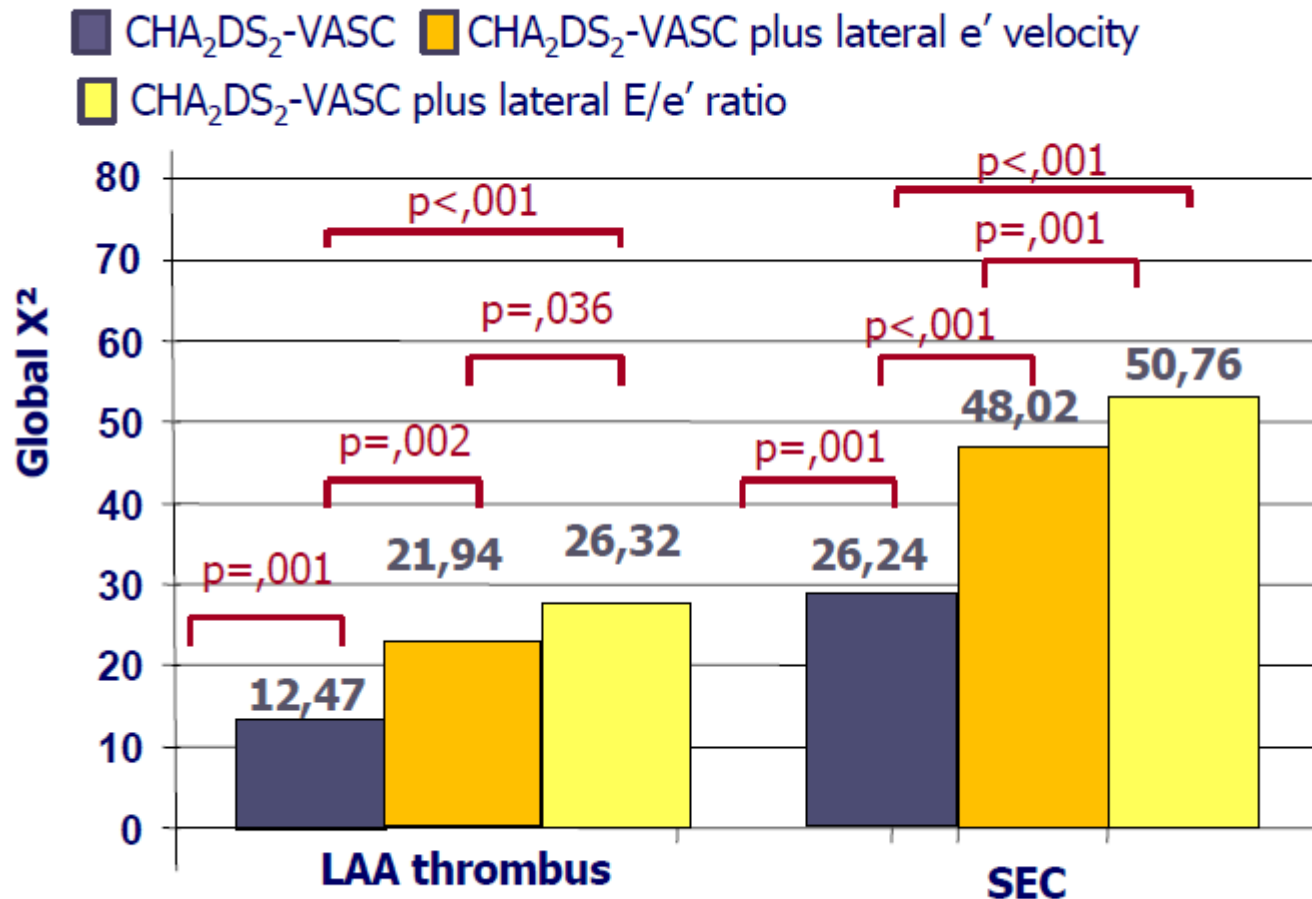
IMAGING E RISCHIO TROMBOEMBOLICO

**L'IMAGING CARDIACO PUO' PERMETTERE
UNA MIGLIORE STRATIFICAZIONE DEL
RISCHIO TROMBOEMBOLICO DELLA FA?**



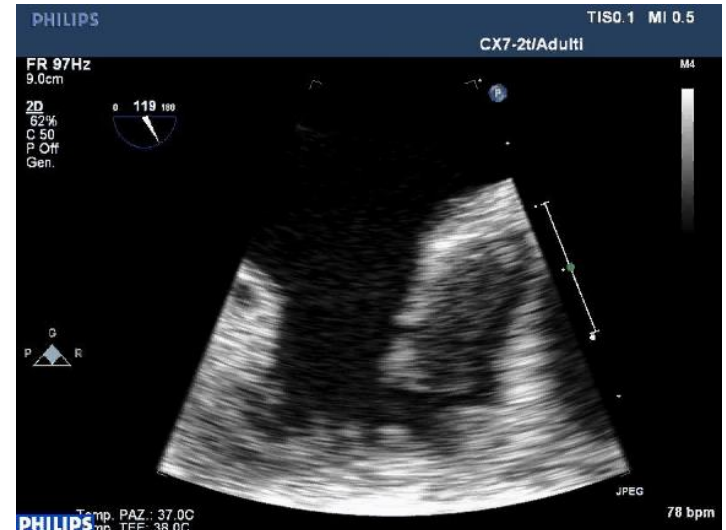
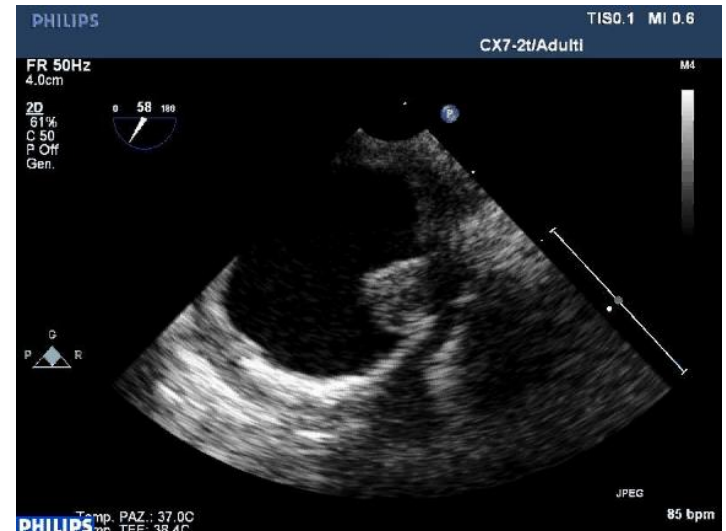
TTE: FUNZIONE DIASTOLICA VS E RISCHIO DI TROMBOSI AUS IN FA NON VALVOLARE

Incremental predictive value of diastolic function parameters beyond the CHA₂DS₂-VASC score



TEE

- Thrombus (RR 2.5; p=0.04)
- Dense smoke (RR 3.7; p<0.001)
- LAA emptying velocity ≤ 20 cm/sec (RR 2.7; p=0.008)
- Complex atheromatous plaque in the thoracic aorta (RR 2.1; p<0.001)



1622

JACC Vol. 31, No. 7
June 1998:1622-6

ATRIAL FIBRILLATION

Transesophageal Echocardiographic Correlates of Clinical Risk of Thromboembolism in Nonvalvular Atrial Fibrillation

MIGUEL ZABALGOITIA, MD, FACC, JONATHAN L. HALPERIN, MD, FACC,*
LESLY A. PEARCE, MS,† JOSEPH L. BLACKSHEAR, MD, FACC,‡
RICHARD W. ASINGER, MD, FACC,§ ROBERT G. HART, MD,

FOR THE STROKE PREVENTION IN ATRIAL FIBRILLATION III INVESTIGATORS

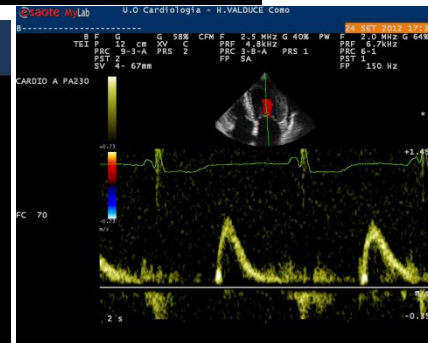
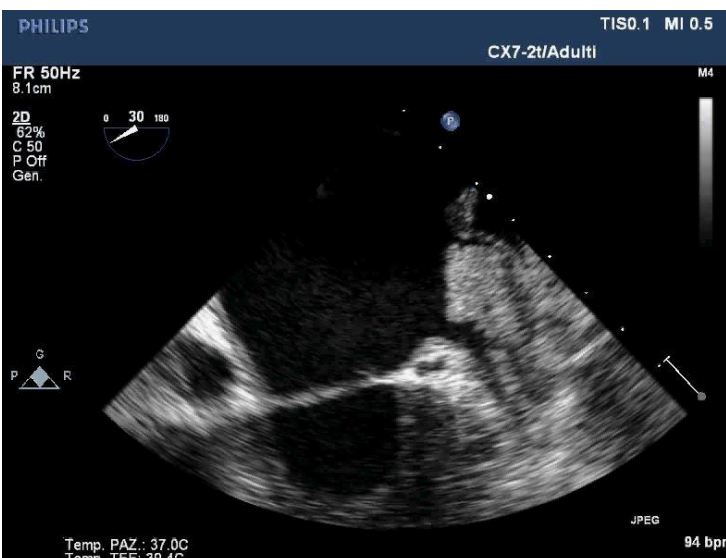
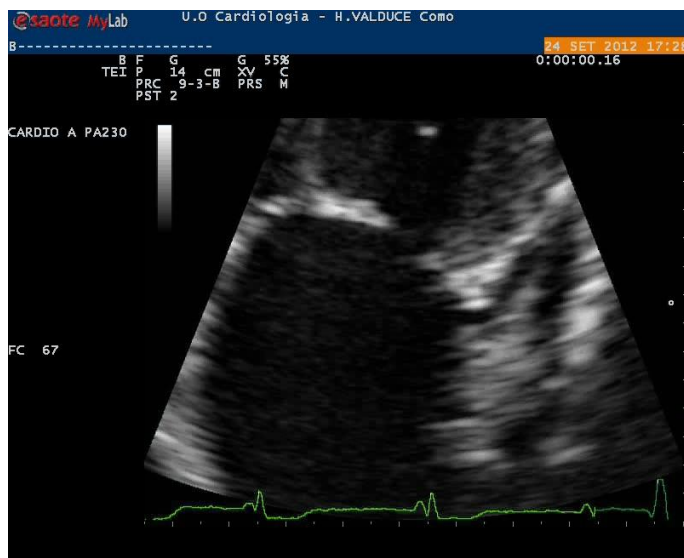
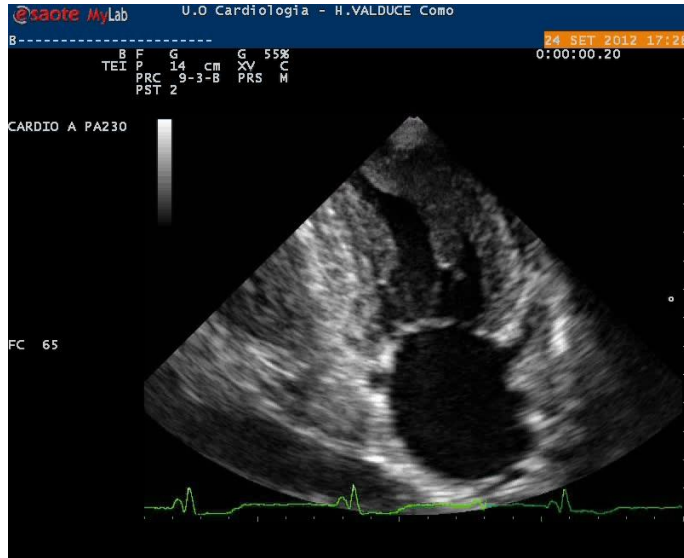
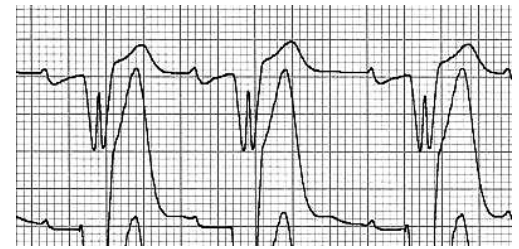
San Antonio, Texas, New York, New York, Seattle, Washington, Jacksonville, Florida, and Minneapolis, Minnesota



SPAF III JACC 1998



TROMBOSI IN RS



TEE AND CV OF AF

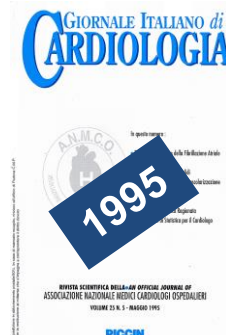
- ◆ Initial studies: if thrombus excluded on TEE → CV without OAC
- ◆ Post CV thromboembolic events described in Pts after a TEE negative for thrombus

Black IW et al. Exclusion of atrial thrombus by transesophageal echocardiography does not preclude embolism after cardioversion of atrial fibrillation. *Circulation* 1994;89:2509 - 2513

- ◆ A thrombogenic milieu may be created as a result of CV from AF no NSR (LA/LAA stunning)

Role of TEE

- ◆ enable early CV without prolonged preCV OAC in low risk pts
- ◆ to identify high risk pts with thrombi in whom CV should be postponed.



LAVORI ORIGINALI - ORIGINAL CONTRIBUTIONS

G Ital Cardiol 1995; 25: 543-552

L'ECOCARDIOGRAFIA TRANSESOFAGEA NEI PAZIENTI IN FIBRILLAZIONE ATRIALE CANDIDATI A CARDIOVERSIONE: UTILITÀ E LIMITI

EMANUELE ANTONIELLI (*) - ALFREDO PIZZUTI (*) - NICOLA GANDOLFO (**)
MASSIMILIANO BOSCO (***) - MARIAGRAZIA SCLAVO (***) - MASSIMO MAGNACCA (****)
GIOVANNI LEONARDI (*) - BALDASSARRE DORONZO (*) - GIORGIO BARALIS (*)
MARGHERITA DI LEO (*)

Transesophageal echocardiography before cardioversion in patients with atrial fibrillation: usefulness and limits



CV ETE-GUIDATA DI FA: STUDI CLINICI

Strategia della CV ETE-guidata: ricerca di trombi pre-esistenti e scoagulazione al momento dell'ETE e per 4 settimane dopo la CV. Nei pz. con trombosi atriale mantenimento della TAO \geq 4 settimane e successivo ETE di controllo.

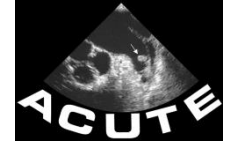
Study	Reference Number	n	Atrial Thrombi	Embolic Events
Orsinelli (1993)	103	39	9 (23%)	1 (2.56%)
Stoddard (1995)	113	206	37 (18%)	0
Klein (1997)	4	126	7 (13%)	0
Weigner (1998)	114	466	64 (13.9%)	1 (0.21%)
Grimm (1998)	115	417	28 (7%)	0
Corrado (1999)	116	123	11 (9%)	0
ACUTE (2000)	16	619	79 (13.6%)	5 (0.81%)
Total		1,996	235 (11.8%)	7 (0.35%)

Klein AL et al.,
JACC 2001;37:691.

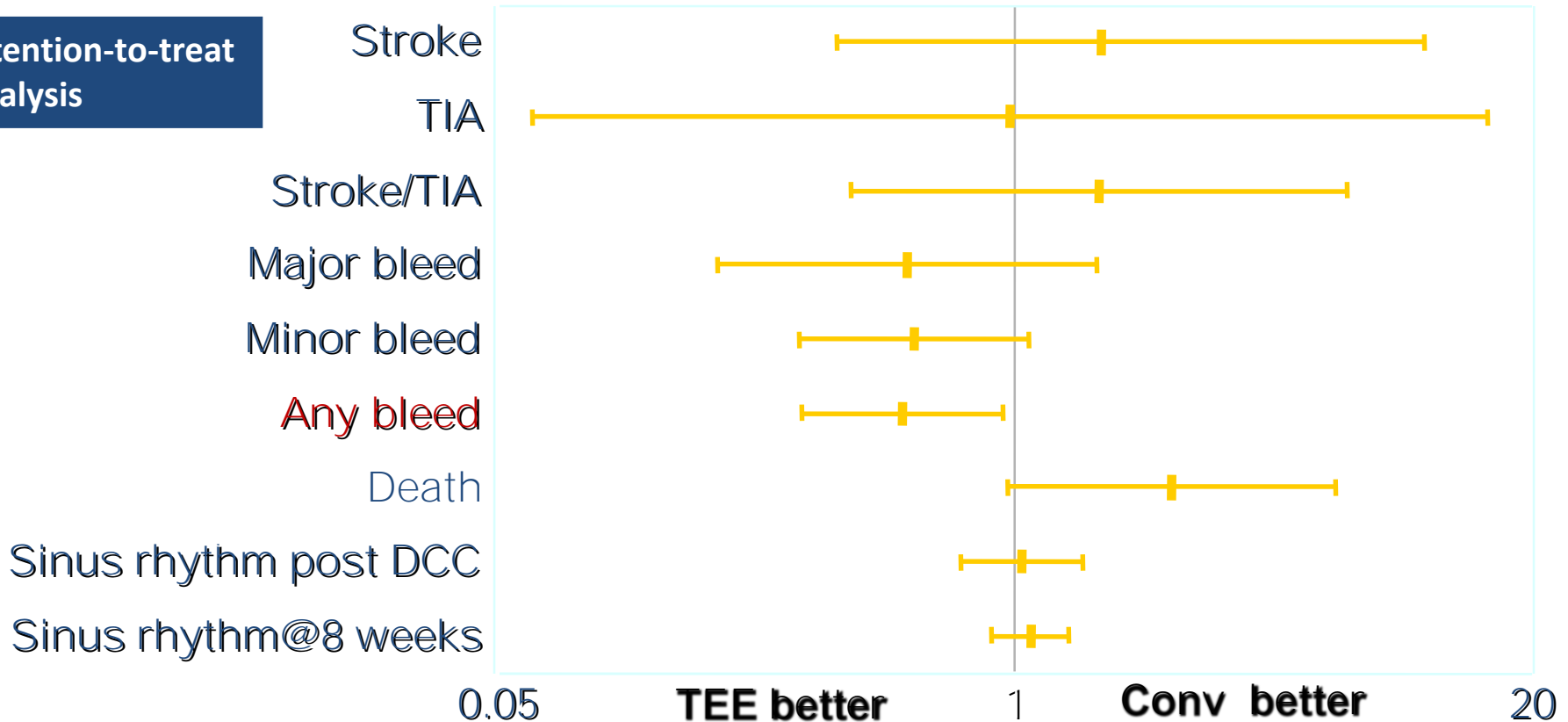
ACUTE = Assessment of Cardioversion Using Transesophageal Echocardiography.



ENDPOINT PRIMARI E SECONDARI - OR (95% CI)



Intention-to-treat
analysis



DATI AGGREGATI PER ENTRAMBI I BRACCI

- eventi embolici: 0,7% (< dell'attesa)
- eventi emorragici: 4,2% (> dell'attesa)



PREVALENCE OF THROMBI IN PATIENTS ON CHRONIC OAC WITH SUBTHERAPEUTIC INRs

Table 1 Patients' characteristics

	No LAA thrombi	LAA thrombi	p Value
Number of patients	37 (90.2%)	4 (9.8%)	
Age (years)	64.35 (\pm 10.28)	66.25 (\pm 0.96)	NS
Male gender	23 (62%)	2 (50%)	NS
Hypertension	20 (54%)	2 (50%)	NS
Digitalis use	13 (35%)	3 (75%)	NS
Structural heart disease	20 (54%)	3 (75%)	NS
Atrial fibrillation	32 (86%)	4 (100%)	NS
Atrial flutter	5 (14%)	0	NS
INR minimum value	1.72 (\pm 0.20)	1.45 (\pm 0.09)	0.0068
LVEF (%)	54.91 (\pm 10)	55.5 (\pm 16.4)	NS
LVFS (%)	33.95 (\pm 9.7)	35 (\pm 8.8)	NS
LA diameter (mm)	43.57 (\pm 8.2)	42.75 (\pm 10.4)	NS
LAA emptying velocity (cm/s)	25.86 (\pm 12.4)	13.75 (\pm 4.5)	0.0313
LAA filling velocity (cm/s)	28.42 (\pm 14.9)	13.75 (\pm 10.4)	0.0326
LA/LAA echo-contrast	14/37 (38%)	4/4 (100%)	0.030

Eur J Echocardiogr (2004) 5, 257-261



CLINICAL/ORIGINAL PAPERS

Prevalence of atrial thrombi in patients with atrial fibrillation/flutter and subtherapeutic anticoagulation prior to cardioversion

G. Corrado^{a,*}, S. Beretta^b, L. Sormani^a, G. Tadeo^a, G. Foglia-Manzillo^a, L.M. Tagliagambe^a, M. Santarone^a

^aUnità Operativa di Cardiologia, Ospedale Valduce, Como, Italy

^bUnità Operativa di Neurologia, AO Ospedale Civile di Vimercate, Italy

Prevalence of LAA thrombus in a similar population: 9.9%

Shen X et al. Prevalence of intra-atrial thrombi in atrial fibrillation patients with subtherapeutic INRs while taking conventional anticoagulation. *Am J Cardiol* 2002;90:660-662



TEE AND CLINICAL RISK FACTORS FOR THROMBOEMBOLISM IN AF

CARDIOVASCULAR MEDICINE

Atrial fibrillation: relation between clinical risk factors and transoesophageal echocardiographic risk factors for thromboembolism

S Illien, S Maroto-Järvinen, G von der Recke, C Hammerstingl, H Schmidt, S Kuntz-Hehner, B Lüderitz, H Omran

Heart 2003;89:165-168

Objective: To correlate clinical risk factors for thromboembolism with transoesophageal echocardiography (TOE) markers of a thrombogenic milieu.

Design: Clinical risk factors for thromboembolism and TOE markers of a thrombogenic milieu were assessed in consecutive patients with non-rheumatic atrial fibrillation. The following TOE parameters were assessed: presence of spontaneous echo contrast, thrombi, and left atrial appendage blood flow velocities. A history of hypertension, diabetes mellitus, or thromboembolic events, patient age > 65 years, and chronic heart failure were considered to be clinical risk factors for thromboembolism.

Setting: Tertiary cardiac care centre.

Patients: 301 consecutive patients with non-rheumatic atrial fibrillation scheduled for TOE.

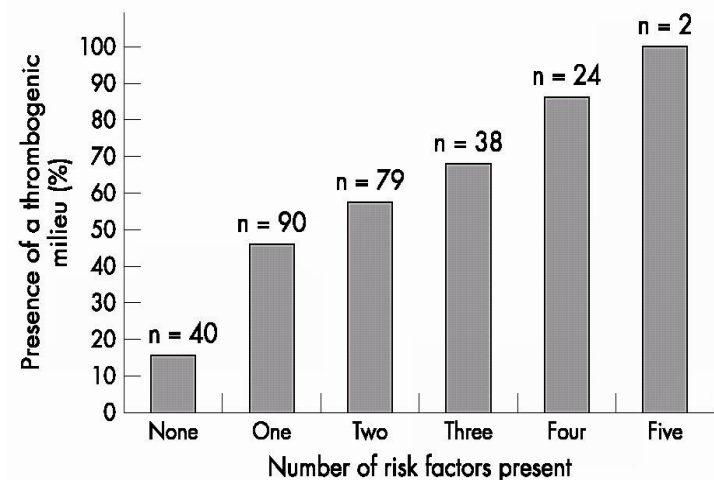
Results: 255 patients presented with clinical risk factors. 158 patients had reduced left atrial blood flow velocities, dense spontaneous echo contrast, or both. Logistic regression analysis showed that a reduced left ventricular ejection fraction and age > 65 years were the only independent predictors of a thrombogenic milieu (both $p < 0.0001$). The probability of having a thrombogenic milieu increased with the number of clinical risk factors present ($p < 0.0001$). 17.4% of the patients without clinical risk factors had a thrombogenic milieu whereas 41.2% of the patients presenting one or more clinical risk factors had none.

Conclusion: There is a close relation between clinical risk factors and TOE markers of a thrombogenic milieu. In addition, TOE examination allows for the identification of patients with a thrombogenic milieu without clinical risk factors.

See end of article for authors' affiliations

Correspondence to: Dr H Omran, Department of Medicine-Cardiology, University of Bonn, Sigmund-Freud-Strasse 25, D-53105 Bonn, Germany; omran@uni-bonn.de

Accepted 2 October 2002



- There is a close relation between clinical risk factors and TEE markers of a thrombogenic milieu.

Nevertheless.....

- TEE allows for the identification of patients with a thrombogenic milieu without clinical risk factors (17%).



TEE AND CLINICAL RISK FACTORS FOR THROMBOEMBOLISM IN AF

Utility of Transesophageal Echocardiography in Identification of Thrombogenic Milieu in Patients With Atrial Fibrillation (an ACUTE Ancillary Study)

Senthil K. Thambidorai, MD^a, R. Daniel Murray, PhD^a, Kapil Parakh, MD^a, Tushar K. Shah, MD^a, Ian W. Black, MD^c, Susan E. Jasper, RN, BSN^a, Jianbo Li, PhD^b, Carolyn Apperson-Hansen, Mstat^b, Craig R. Asher, MD^a, Richard A. Grimm, DO^a and Allan L. Klein, MD^{a,*}, for the ACUTE Investigators[†]

TEE performed at 70 centers in 571 patients
Predictors of TE analyzed

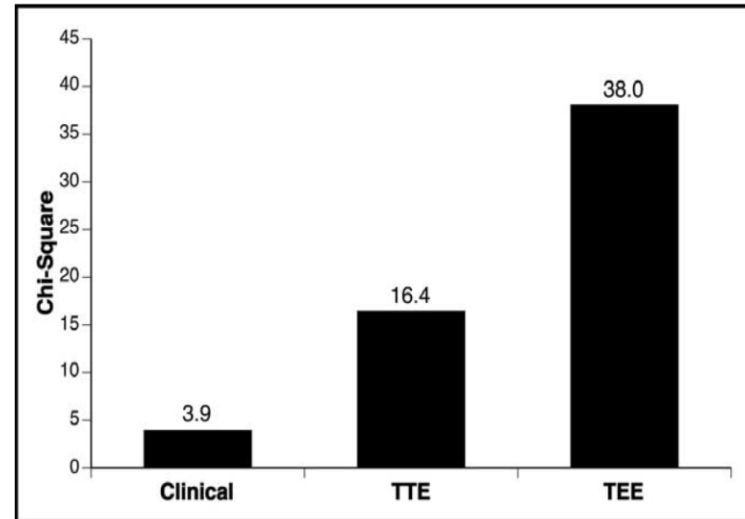


Figure 2. Chi-square and incremental value of clinical examination ($p > 0.05$), transthoracic echocardiography (TTE) ($p < 0.01$), and TEE ($p < 0.001$) from the full model show that TEE had the most significant incremental value in predicting a thromboembolic milieu (patients who had thrombi and a patient who had an embolic event, $n = 85$).

- Clinical, TTE, and TEE RF contributed significantly to the prediction of composite thrombus/embolism.
- However, TEE thromboembolic RF were the strongest predictors of TE and provided statistically significant incremental value (chi-square 38.0, $p < 0.001$) for identification of risk.



TEE AND CLINICAL RISK FACTORS FOR THROMBOEMBOLISM IN AF: LONE AF

- TEE in 82 LAF pts and in 289 non-LAF pts.
- LAA abnorm: LAA area $> 5 \text{ cm}^2$, LAA velocities $< 25 \text{ cm/sec}$, LA/LAA SEC/Thr
- LA/LAA SEC: LAF 29,3%, non-LAF 49,8% ($p < 0.001$)
- Prevalence of LAA SEC in LAF pts: 17.9% ≤ 60 yrs
39.5% > 60 yrs ($p < 0.005$)
- Prevalence of LAA SEC in LAF pts: 5.9% in
paroxysmal LAF 45.8% in persistent LAF ($p < 0.005$)

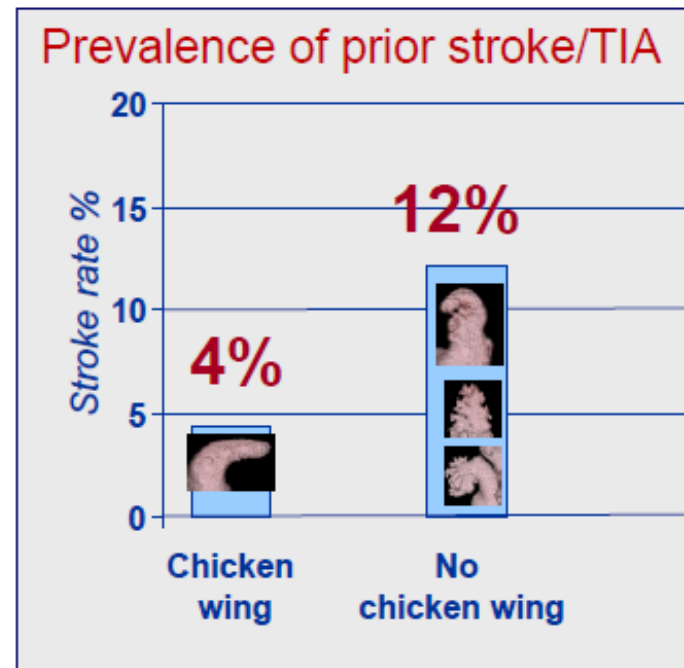
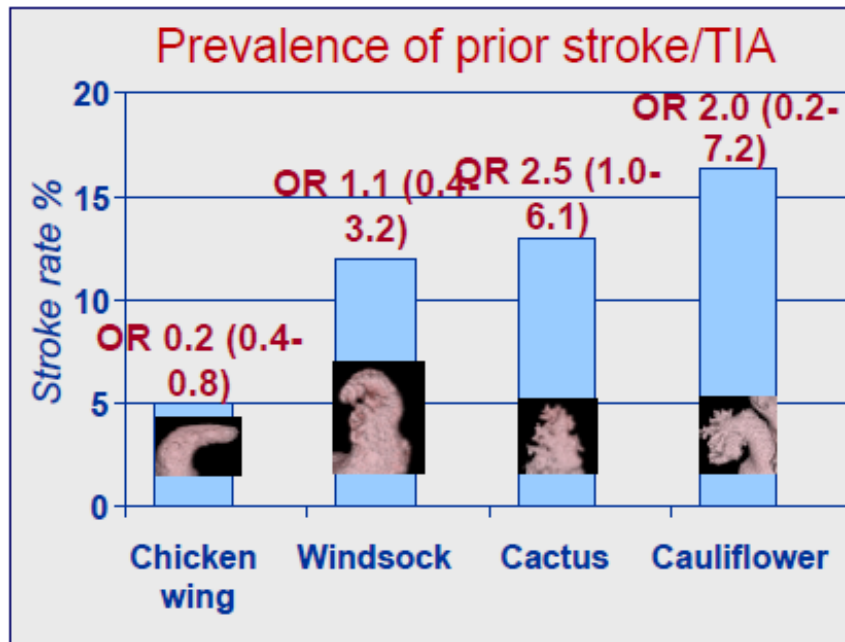


Di Angelantonio E et al *Am J Cardiol* 2005;95:592



MORFOLOGIA DELL'AUS E RISCHIO TE

Prevalence of prior stroke/TIA according to different LAA morphologies and in chicken wing versus non-chicken wing morphologies

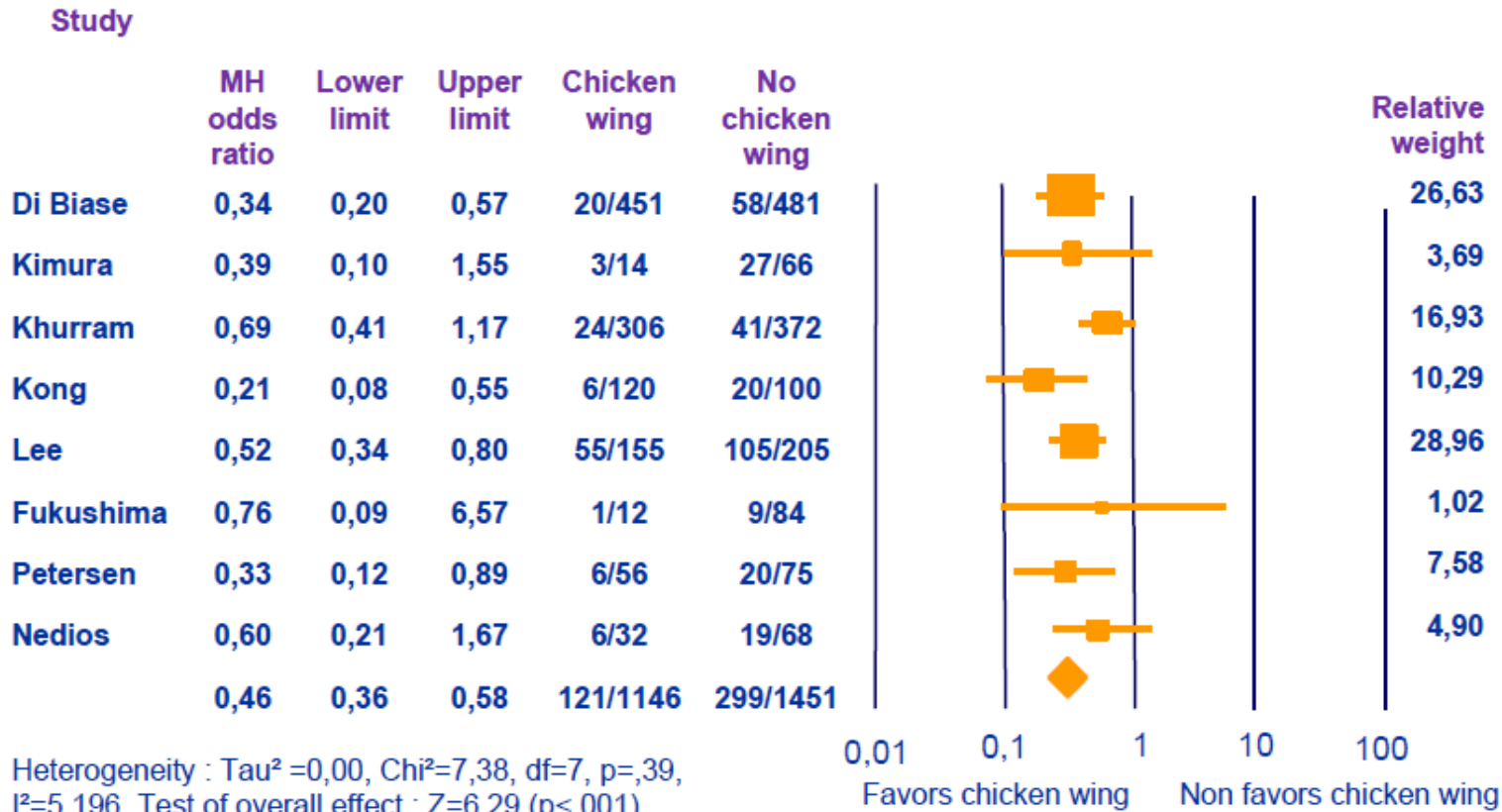


Non-Chicken Wing: independent predictor of stroke with an OR of 2.95 (95% CI: 1.75 to 4.99, p = 0.041).



MORFOLOGIA DELL'AUS E RISCHIO TE

Forest plot : "Chicken wing" vs "non-chicken wing" and stroke risk



Lupercio, F. Heart Rhythm. 2016 : 13; 1402-9



FLUTTER ATRIALE

Thromboembolic risk in atrial flutter

The FLASIEC (FLutter Atriale Società Italiana di Ecografia Cardiovascolare) multicentre study

G. Corrado¹, A. Sgalambro², A. Mantero³, F. Gentile⁴, M. Gasparini⁵, R. Bufalino⁶, A. Morabito⁷, G. Trocino⁷, R. Schiavina⁷, S. Mandorla⁸, R. Mangia⁹, D. Tovena¹⁰, K. Savino¹¹, F. Jacopi¹², E. M. Pellegrino¹³, F. Agostini¹⁴, G. Centonze¹⁵, F. Bovenzi¹⁶, E. Caprino¹⁷, G. Tadeo¹ and M. Santarone¹ for the FLASIEC Investigators

¹Unità Operativa di Cardiologia, Ospedale Generale Valtice, Como, Italy; ²Servizio di Diagnostica Policardiografica con Unità Coronarica, Ospedale Civico, Cologno, Italy; ³Servizio Centrale di Cardiologia, Ospedale Niguarda, Milano, Italy; ⁴Divisione di Cardiologia, Ospedale Bassini, Cinisello Balsamo, Italy; ⁵Dipartimento di Cardiologia, Istituto Clinico Humanitas, Rozzano, Italy; ⁶Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Italy; ⁷Divisione di Cardiologia, Ospedale San Gerardo dei Tintori, Monza, Italy; ⁸Divisione di Cardiologia, Ospedale Silvestrini, Perugia, Italy; ⁹Divisione di Cardiologia, Ospedale Cardinale Panico, Tricase, Italy; ¹⁰Divisione di Cardiologia, Ospedale Maggiore, Crema, Italy; ¹¹Cattedra di Cardiologia, Università degli Studi di Perugia, Italy; ¹²Dipartimento di Cardiologia, Ravenna-Faenza-Lugo, Sede di Faenza, Italy; ¹³Divisione di Cardiologia, Ospedale Sacro Cuore di Gesù, Gallipoli, Italy; ¹⁴Ospedale Carlo Poma, Mantova, Italy; ¹⁵Servizio Autonomo di Cardiologia, Ospedale di Matera, Italy; ¹⁶Divisione di Cardiologia, Policlinico di Bari, Italy; ¹⁷Divisione di Cardiologia, Ospedale Civile, Vigevano, Italy

Aims Patients with atrial flutter are believed to be at lower risk of thromboembolism than patients with atrial fibrillation. However, the incidence of atrial thrombi and the need for anticoagulation in patients with atrial flutter is not well established.

Methods and Results A prospective observational multicentre study was undertaken to assess the frequency of atrial thrombi and spontaneous echoccontrast and the prevalence for aortic complex atherosclerotic lesions in a cohort of unsynchronized patients with atrial flutter. We evaluated 134 patients (102 male, aged 70 ± 9 years); exclusion criteria were history of atrial fibrillation, rheumatic mitral valve disease and mitral mechanical prosthesis. The median of atrial flutter duration was 33 days. Twelve patients had been taking warfarin for more than 7 days. One hundred and twenty-four patients (93%) underwent a transoesophageal echocardiogram, which revealed left atrial appendage thrombi in two patients (1.6%) and right atrial thrombi in one patient (1%). At least moderate left

atrial echoccontrast was found in 16/124 patients (13%). Complex atherosclerotic aortic plaques were detected in 10 patients (8%). Atrial flutter conversion was attempted in 93/134 patients (69%). At the 1-month follow-up, two patients experienced a thromboembolic event following restoration of sinus rhythm.

Conclusions Atrial thrombi and echoccontrast, and complex aortic atherosclerotic plaques are relatively uncommon in patients with atrial flutter. Post-cardioversion embolism was observed in two patients in our study population. (Eur Heart J 2001; 22: 1042-1051, doi:10.1053/euhj.2001.2427)

© 2001 The European Society of Cardiology

Key Words: Atrial flutter, echocardiography, thromboembolism.

See page 984 for the Editorial comment on this article

- 134 pz. con FLA isolato provenienti da 13 strutture ospedaliere italiane.
- ETE in 124/134 → trombosi Aus in 2 pz. (1,6%), trombosi AD in 1 pz. (1%), ECS moderato/denso in 16 pz. (13%), placche Ao complesse in 10 pz. (8%)
- CV in 93/134 pz.; 2 eventi embolici nel FU post CV



Eur Heart J 2001;22:1042-45



FLUTTER ATRIALE

Investigators	TEEs with A Flutter	Prevalence of LA thrombus (%)	Prevalence of SEC (%)
Santiago et al	17	0%	6%
Corrado et al	124	1.6% (pure AFL)	13% (pure AFL)
Omran et al	20 (9, pure AFL)	0%	20% (11%, pure AFL)
Schmidt et al	202	1%	28%
Parikh et al.	455 (270, pure AFL)	5.3% (5.2%, pure AFL)	25.9% (23.7%, pure AFL)
Grönefeld et al	62	6.5 %	22.6%
Irani et al	47	11%	32%
Gaibazzi et al	106	14% (3% with pure AFL)	32%
Black et al	7	14%	43%



IMAGING E RISCHIO TROMBOEMBOLICO

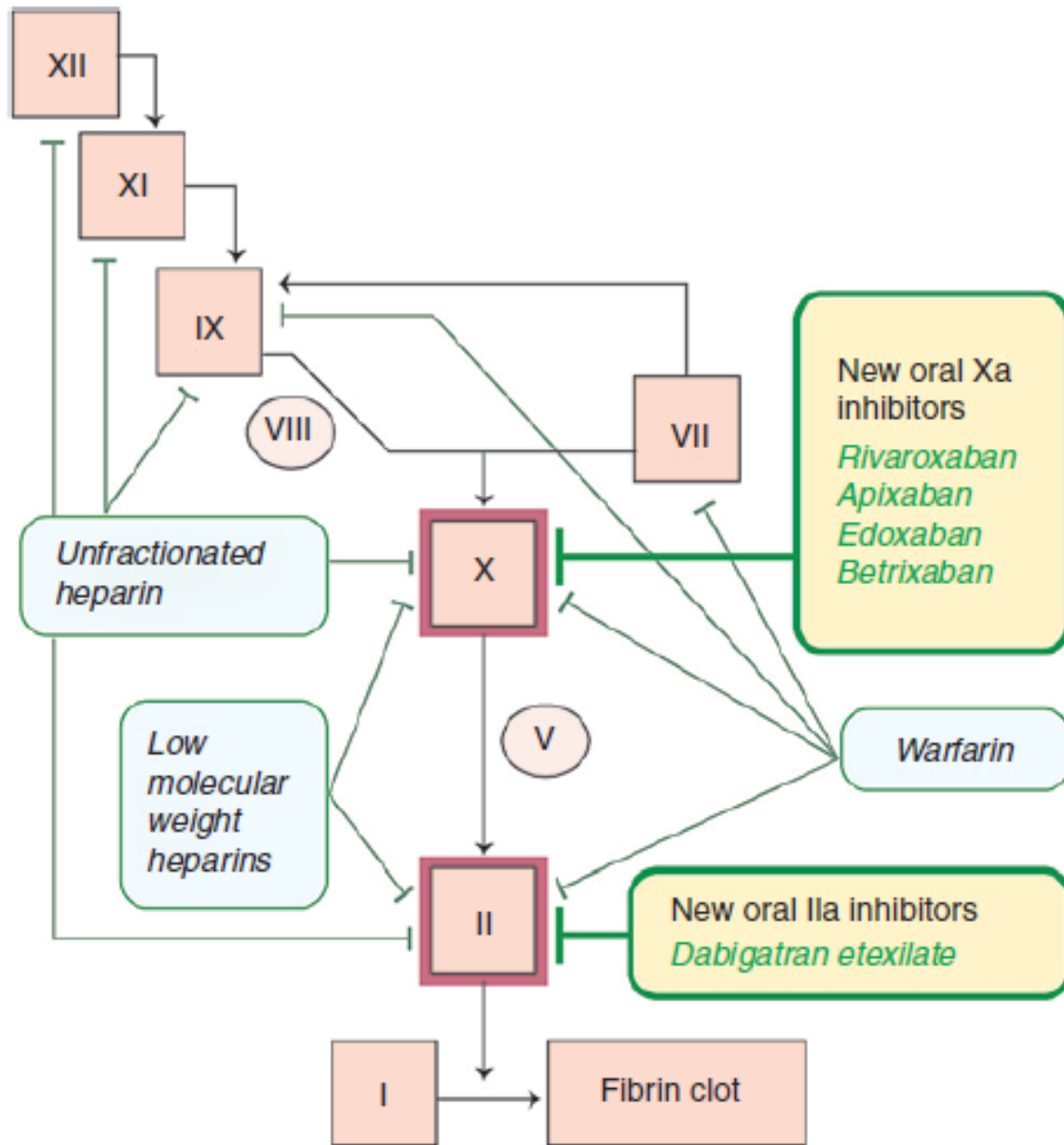
L'IMAGING CARDIACO PUO' PERMETTERE UNA MIGLIORE STRATIFICAZIONE DEL RISCHIO TROMBOEMBOLICO DELLA FA?

NUMEROSI DATI DELLA LETTERATURA
INDICANO CHE QUESTO E' POSSIBILE.

TUTTAVIA IL RUOLO DELL'IMAGING NELLA
STRATIFICAZIONE DEL RISCHIO TE,
ECCEPTE CHE PER LA CV, NON HA
TUTT'ORA UN RUOLO SIGNIFICATIVO
NELLE LINEE GUIDA E NELLA PRATICA
CLINICA



ACs



Mantha, S., Cabral, K. and Ansell, J. (2013), New Avenues for Anticoagulation in Atrial Fibrillation. *Clinical Pharmacology & Therapeutics*, 93: 68–77. doi: 10.1038/clpt.2012.197



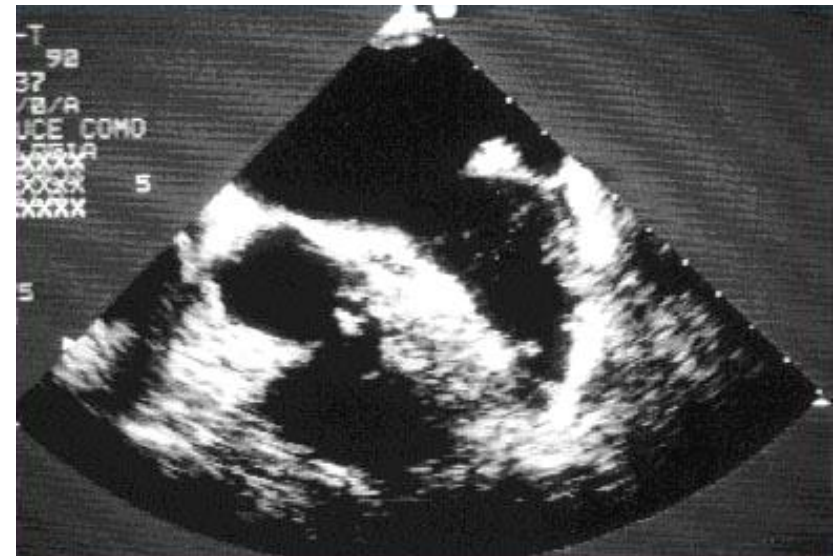
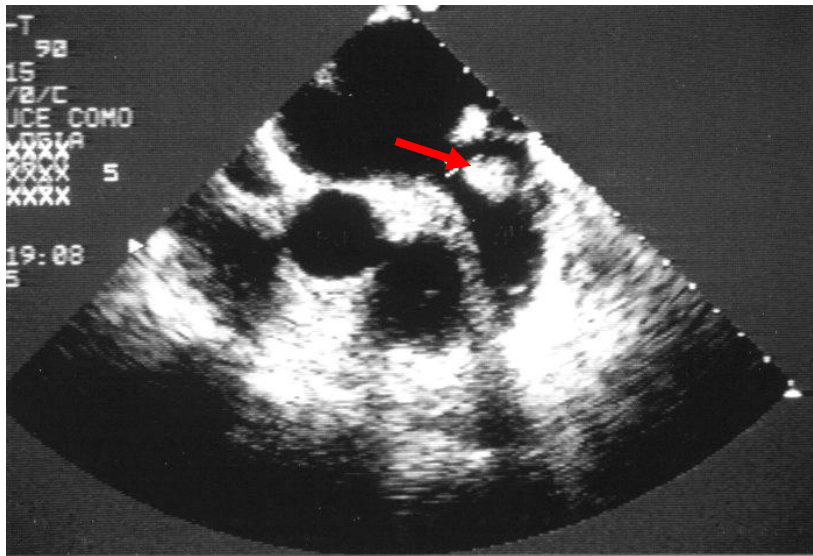
FA ED EFFETTO PROTETTIVO DEGLI ANTI VIT K

FAVORISCONO LA LISI ENDOGENA,
PREVENGONO LA SOVRAPPOSIZIONE TROMBOTICA

**Atrial Thrombi Resolution After
Prolonged Anticoagulation in Patients
With Atrial Fibrillation***

A Transesophageal Echocardiographic Study

*Giovanni Corrado, MD; Giorgio Tadeo, MD; Sandro Beretta, MD;
Luca Mario Tagliagambe, MD; Giovanni Foglia Manzillo, MD;
Manuela Spata, MD; and Mauro Santarone, MD*



TEE con sonda monoplana.

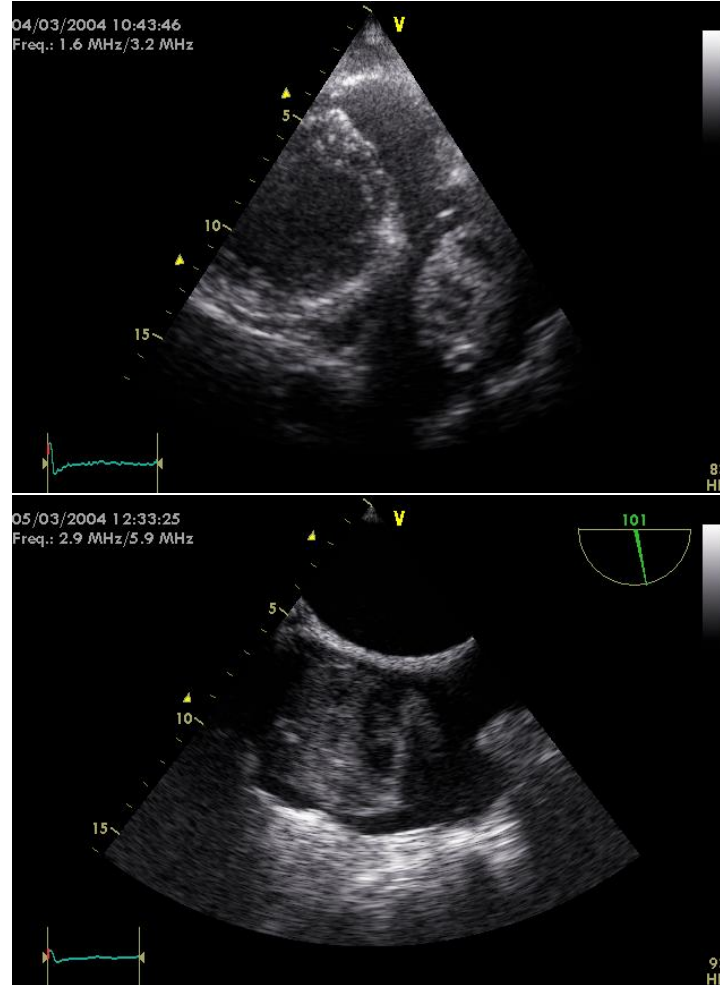
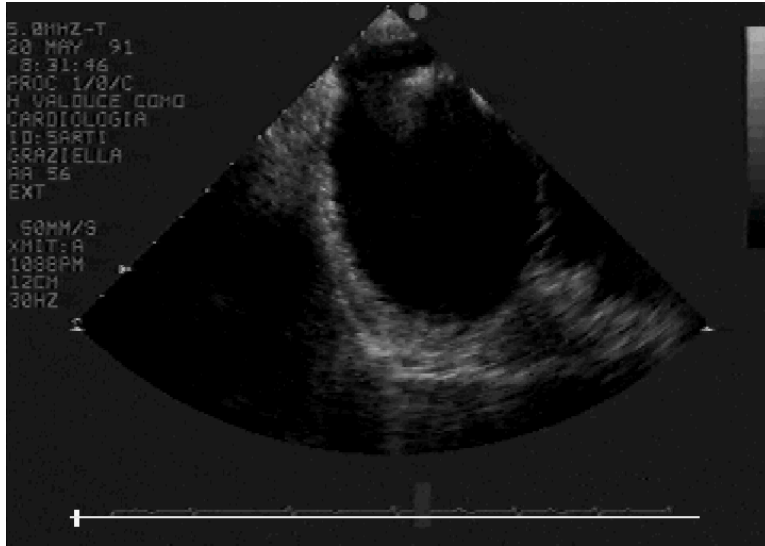
Fig. A: Trombo peduncolato all'imbocco della AuS (freccia)

Fig. B: stessa paziente dopo 4 sett di TAO. Regressione del trombo



ANTI VIT K. NON SEMPRE...

FAVORISCONO LA LISI
ENDOGENA,
PREVENGONO LA
SOVRAPPOSIZIONE
TROMBOTICA



EFFETTI DELLA TERAPIA ANTICOAGULANTE SULLA TROMBOSI AS/AuS

Supplementary Table I. Published studies on LA/LAA thrombus on echocardiography and resolution with anticoagulation

Study	Anticoagulant	Findings
Akdeniz et al ⁵³ (observational)	Warfarin (target INR 2.0-3.0)	<ul style="list-style-type: none"> Thrombus was observed in 32 (15.4%) of 208 patients after 4-6 wk of warfarin therapy Of the 11 patients who underwent a control TEE, 7 (63.6%) exhibited thrombus resolution
Collins et al ¹⁵ (observational)	Warfarin (target INR 2.0-2.8)	<ul style="list-style-type: none"> Thrombus resolution in 86% of patients with AF after 4 wk of warfarin therapy
Seidl et al ¹⁷ (single-center observational)	Warfarin (target INR 2.0-3.0)	<ul style="list-style-type: none"> Thrombus was observed in the left atrium of 55 (7.7%) of the 719 patients in the TEE-guided group All 55 patients had their INR increased to 3-3.5 for 4 wk, and resolution of the LA thrombus was detected on TEE in 55% of patients Low resolution rate explained partially by the inclusion of patients with valvular AF (nearly one-third of study population)
Corrado et al ⁴ (observational)	Warfarin (target INR ≥ 2)	<ul style="list-style-type: none"> Resolution of atrial thrombi after 4 wk of warfarin therapy in 9 (81.8%) of 11 patients (95% CI 48.2-97.7%)
Jaber et al ¹⁶ (observational)	Warfarin (mean INR 2.2) or heparin	<ul style="list-style-type: none"> 174 patients with thrombi in LAC and LAA. 161 patients received anticoagulant therapy for 47 \pm 18 d 80% success in resolving LAC and LAA thrombi as demonstrated by follow-up TEE. Better success in resolving LAA thrombi (82.5%) vs LAC thrombi (53.3%)
Fukuda et al ⁵⁴ (observational)	Warfarin (target INR ≥ 2)	<ul style="list-style-type: none"> 148 patients on warfarin therapy for >3 wk with subtherapeutic anticoagulation (INR 1.9 \pm 0.7) LA thrombus was observed on TEE in 13 (8.8%) patients with nonvalvular AF LA thrombus was observed in 3 (3.6%) of 83 patients with sufficient anticoagulation (>3 wk)
Nagarakanti et al ⁵ (RE-LY, post hoc analysis)	Dabigatran 110 mg bid (D110); dabigatran 150 mg bid (D150); warfarin	<ul style="list-style-type: none"> 165 patients on D110 therapy, 162 patients on D150 therapy, and 88 patients on warfarin therapy were assessed using TEE 1.8% of D110 patients, 1.2% of D150 patients, and 1.1% of warfarin patients were positive for LA thrombi Thrombus resolution not reported
Vidal et al ²² (case study)	Dabigatran 150 mg bid	<ul style="list-style-type: none"> 59-year-old White woman had LAA thrombus detected by TEE Unable to achieve therapeutic INR with warfarin therapy so switched to dabigatran Resolution of thrombus achieved after 7 wk of dabigatran treatment
Hammerstingl et al ²⁴ (case study)	Rivaroxaban 15 mg od	<ul style="list-style-type: none"> 64-year-old man with LAA thrombus detected by TEE 4 wk of treatment with rivaroxaban was associated with decrease in thrombus size Complete thrombus resolution was identified after 6 wk of therapy
Takasugi et al ²⁵ (case study)	Rivaroxaban 10 mg od	<ul style="list-style-type: none"> 3 patients (2 males, 1 female) had presence of LAA thrombi detected by TEE Treatment with rivaroxaban led to resolution of thrombus within 8-33 d 2 patients had resolution after 8 d of therapy, with the other patient showing a reduction in thrombus size after 21 d and resolution after 33 d of therapy
Kawakami et al ²⁶ (case study)	Apixaban 5 mg bid	<ul style="list-style-type: none"> 72-year-old man with LAA thrombus identified by TEE 16 d of apixaban treatment led to complete thrombus resolution
Dobashi et al ²⁷ (case study)	Apixaban 2.5 mg bid	<ul style="list-style-type: none"> 86-year-old man with LA thrombus detected through TEE 11 wk of apixaban treatment resulted in almost complete thrombus resolution

Abbreviations: *bid*, twice daily; *od*, once daily; LAC, left atrial cavity.

Rationale and design of a study exploring the efficacy of once-daily oral rivaroxaban (X-TRA) on the outcome of left atrial/left atrial appendage thrombus in nonvalvular atrial fibrillation or atrial flutter and a retrospective observational registry providing baseline data (CLOT-AF)



Gregory Y. H. Lip, MD,^a Christoph Hammerstingl, MD,^b Francisco Marin, MD,^c Riccardo Cappato, MD,^d Isabelle Ling Meng, MD, PhD,^e Bodo Kirsch, MSc,^f Eolo Morandi, MD,^g Martin van Eickels, MD,^h and Ariel Cohen, MD, PhD^b Birmingham, United Kingdom; Bonn, Berlin, Germany; Murcia, Spain; Milan, Italy; São Paulo, Brazil; and Paris, France



Left atrial thrombus resolution in atrial fibrillation or flutter: Results of a prospective study with rivaroxaban (X-TRA) and a retrospective observational registry providing baseline data (CLOT-AF)



Gregory Y. H. Lip, MD,^{1,2} Christoph Hammerstingl, MD,³ Francesco Martin, MD,⁴ Riccardo Cappato, MD,⁵ Isabelle Ling Meng, MD,⁶ Hodo Kirsch, MSc,⁷ Martin van Riecke, MD,⁸ and Axel Cohen, MD,⁹ on behalf of the X-TRA study and CLOT-AF registry investigators¹ Birmingham, United Kingdom; ²Amberg, Denmark; ³Bonn, Germany; ⁴Marcia, Spain; ⁵Rozzano, Italy; ⁶Berlin, Germany; and ⁷Paris, France

Background Data on left atrial/left atrial appendage (LA/LAA) thrombus resolution after non-vitamin K antagonist (VKA) oral anticoagulant treatment are scarce. The primary objective of X-TRA was to explore the use of rivaroxaban for the resolution of LA/LAA thrombi in patients with nonvalvular atrial fibrillation (AF) or atrial flutter, with the CLOT-AF registry providing retrospective data after standard-of-care therapy in this setting.

Methods X-TRA was a prospective, single-arm, open-label, multicenter study that investigated rivaroxaban treatment for 6 weeks for LA/LAA thrombus resolution in patients with nonvalvular AF or atrial flutter and LA/LAA thrombus confirmed at baseline on a transesophageal echocardiogram (TEE). CLOT-AF retrospectively collected thrombus-related patient outcome data after standard-of-care anticoagulant treatment for 2 to 12 weeks in patients with nonvalvular AF or atrial flutter who had LA/LAA thrombi on TEE recorded in their medical file.

Results In X-TRA, patients were predominantly (95.0%) from Eastern European countries. The adjudicated thrombus resolution rate was 41.5% (22/53 modified intention-to-treat [mITT] patients; 95% CI 28.1%-55.9%) based on central TEE assessments. Resolved or reduced thrombus was evident in 60.4% (32/53 mITT patients; 95% CI 46.0%-73.6%) of patients. In CLOT-AF, the reported thrombus resolution rate was 62.5% (60/96 mITT patients; 95% CI 52.0%-72.2%) and appeared better in Western European countries (34/50; 68.0%) than in Eastern European countries (26/46; 56.5%).

Conclusion X-TRA is the first prospective, multicenter study examining LA/LAA thrombus resolution with a non-VKA oral anticoagulant in VKA-naïve patients or in patients with suboptimal VKA therapy. Rivaroxaban could be a potential option for the treatment of LA/LAA thrombi. (Am Heart J 2016;178:126-34.)

APIXABAN AND LA/LAA THR. RESOLUTION

Table II. Resolution rates of LA/LAA thrombi

	Evaluation set	Total n	Thrombus resolution		
			n thrombus resolved	%	95% CI
Prospective X-TRA study					
Complete thrombus resolution (assessed by blinded adjudicators)*	mITT	53	22	41.5	28.1-55.9
Complete thrombus resolution (assessed by blinded adjudicators), worst-case scenario considering subjects without EOT TEE as nonresolved	ITT	60	22	36.7	24.6-50.1
Resolved or reduced thrombus (assessed by blinded adjudicators)†	mITT	53	32	60.4	46.0-73.6
Retrospective CLOT-AF registry					
Complete thrombus resolution	mITT	96	60	62.5	52.0-72.2
Complete thrombus resolution by region					
Eastern Europe	mITT	46	26	56.5	41.1-71.1
Western Europe	mITT	50	34	68.0	53.3-80.5
Complete thrombus resolution, worst-case scenario considering subjects without EOT TEE as nonresolved	ITT	156	60	38.5	30.8-46.6
Complete thrombus resolution, best-case scenario considering subjects without EOT TEE as resolved	ITT	156	120	76.9	69.5-83.3

* This includes 2 patients who had 2 thrombi each. Both thrombi were resolved in each case.

† In 12 patients (22.6%), thrombi were larger, and in another 9 patients (17.0%), thrombi were found unchanged (blinded central assessment); no patients had a new thrombus.



NOACs



Frank R. Kolassa, Christopher G. Garg

In patients with non-valvular atrial fibrillation, oral anticoagulation with vitamin K antagonists reduces the risk of stroke by more than 60%. But vitamin K antagonists have limitations, including requiring routine blood testing and an increased haemorrhage and fatality risk. Novel oral anticoagulants, in part related to these limitations, are now used to treat about half of patients who should be treated according to guideline recommendations. In the past decade, oral agents have been developed that directly block the activity of Factor IIa, as well as drugs that directly inhibit activated Factor X (the active site for the first protein in the final common pathway in the activation of thrombin). These novel non-vitamin K antagonist oral anticoagulants (NOACs) have been shown to be at least as good as warfarin for stroke prevention in atrial fibrillation and are now preferred to have better safety profiles. Their oral advantages is underpinned by significantly lower adverse events compared with warfarin in large clinical trials. Because of these features and their ease of use, they are recommended for stroke prevention in atrial fibrillation. They have also had a great effect on rates, but they currently lack specific antidotes. This paper addresses the role of anticoagulation for stroke prevention in atrial fibrillation in the era of NOACs, with a focus on special situations including management in the event of bleeding and across the issue of procedures including catheter ablation, cardiac ablation, and device implantation. Also there are insights with concomitant coronary artery disease, with advanced age, with chronic kidney disease, or with valvular heart disease, all of them discussed as well as the interaction of NOACs with other cardiac medications, and switching between anticoagulants.

Received 2015 09 03
Accepted 2015 11 12
© 2016 Elsevier Ltd
http://dx.doi.org/10.1016/j.ijic.2015.11.002

	RE-LY ⁵	ROCKET-AF ⁶	ARISTOTLE ⁷	ENGAGE-AF ⁸
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Drug target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Renal clearance	~80%	~35%	~25%	~50%
Drug dosing	150 mg twice a day; 110 mg twice a day	20 mg once a day (15 mg for creatinine clearance <50 mL/min)	5 mg twice a day (2.5 mg when two of three following criteria are met: age ≥80 years, weight ≤60 kg, creatinine ≥1.5 mg/dL [133 µmol/L])	60 mg once a day (30 mg for creatinine clearance 30–50 mL/min, weight ≤60 kg, or strong P-glycoprotein inhibitor)
Drug metabolism	P-glycoprotein	P-glycoprotein and CYP3A4	P-glycoprotein and CYP3A4	P-glycoprotein
Mean CHADS ₂ score	2.1	3.5	2.1	2.8
Design	Open label (dabigatran vs warfarin)	Blinded	Blinded	Blinded

Table 1: The four large trials comparing non-vitamin K antagonist oral anticoagulants with warfarin for stroke prevention in atrial fibrillation

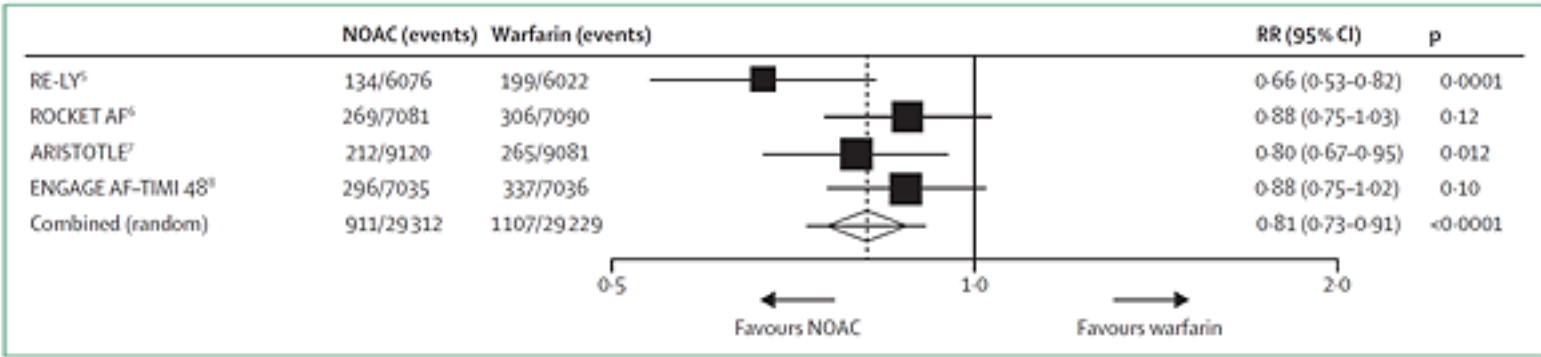


Figure 1: Stroke or systemic embolism in the four trials comparing non-vitamin K antagonist oral anticoagulants (NOACs) to warfarin in patients with atrial fibrillation¹²
RR=risk ratio. Reproduced from reference 12, by permission of Elsevier.





Sfide in cardiologia clinica

10/11 marzo 2017

Mantova MaMu, Centro Congressi Mantova Largo di Porta Pradella, 1



FIBRILLAZIONE ATRIALE E STRATEGIA TERAPEUTICA. IL RUOLO DEI **NUOVI ANTICOAGULANTI ORALI** E DELL'IMAGING NELLA PREVENZIONE DELLO STROKE ISCHEMICO

G Corrado, MD, FANMCO, FESC
Unità Operativa di Cardiologia
Ospedale Valduce – Como (IT)



H. Valduce 1879

