Fibrillazione Atriale

epidemiologia
diagnosi
terapia anticoagulante
casi clinici

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AOU Careggi Firenze

Cremona 20 Settembre 2016

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)

Epidemiologia della Fibrillazione Atriale: l'entità del problema

2010 nei paesi sviluppati — 20.900.000 maschi
12.600.000 femmine

2030 si stimano — 14-17.000.000 di Europei

1 soggetto ogni 4 svilupperà FA

3% della popolazione > 20 anni

Worldwide Epidemiology of Atrial Fibrillation

A Global Burden of Disease 2010 Study

Prevalence of atrial fibrilation and flutter (per 100,000) by region, 2010

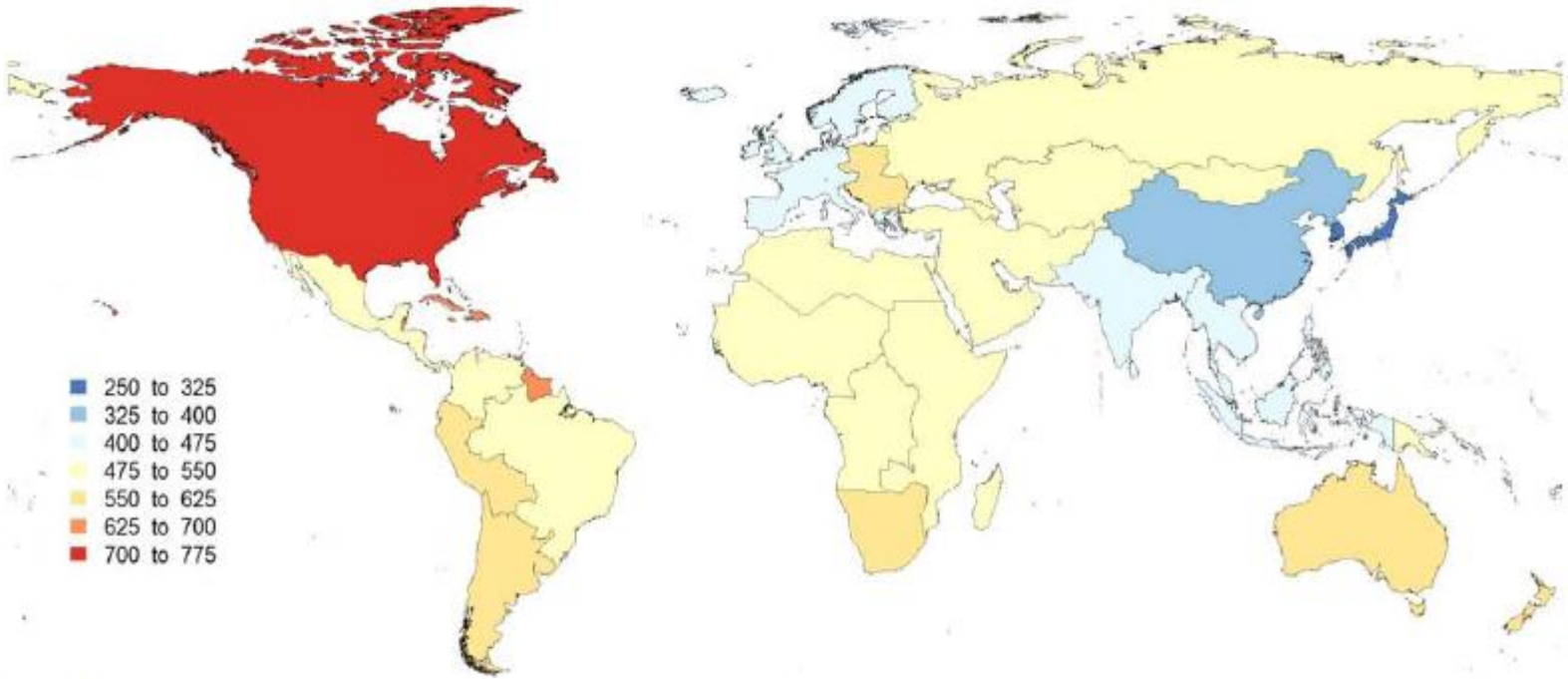

Figure 2. World map showing the age-adjusted prevalence rates (per 100 000 population) of atrial fibrillation in the 21 Global Burden of Disease regions, 2010.

Chug SS et al. Circulation , 2014

Worldwide Epidemiology of Atrial Fibrillation

A Global Burden of Disease 2010 Study

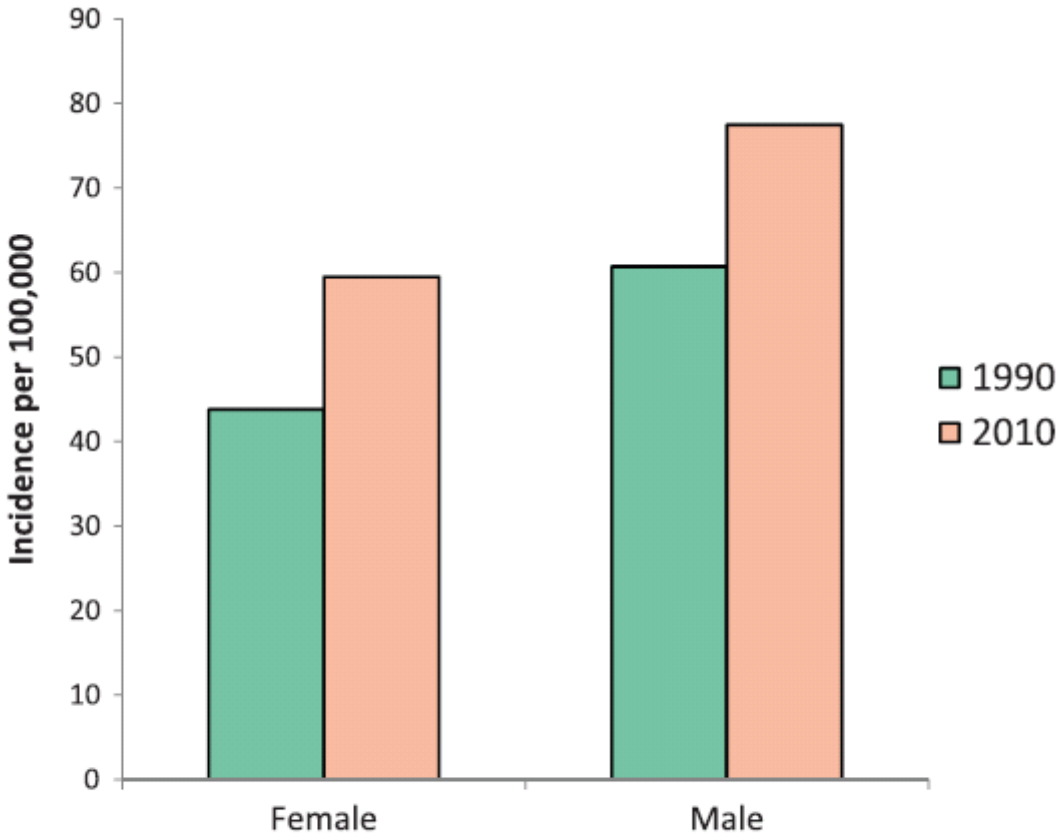

Figure 4. Incidence of atrial fibrillation: 1990 and 2010. Estimated age-adjusted global incidence (per 100 000 person-years) for men and women for 1990 and 2010.

Chug SS et al. Circulation , 2014

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.

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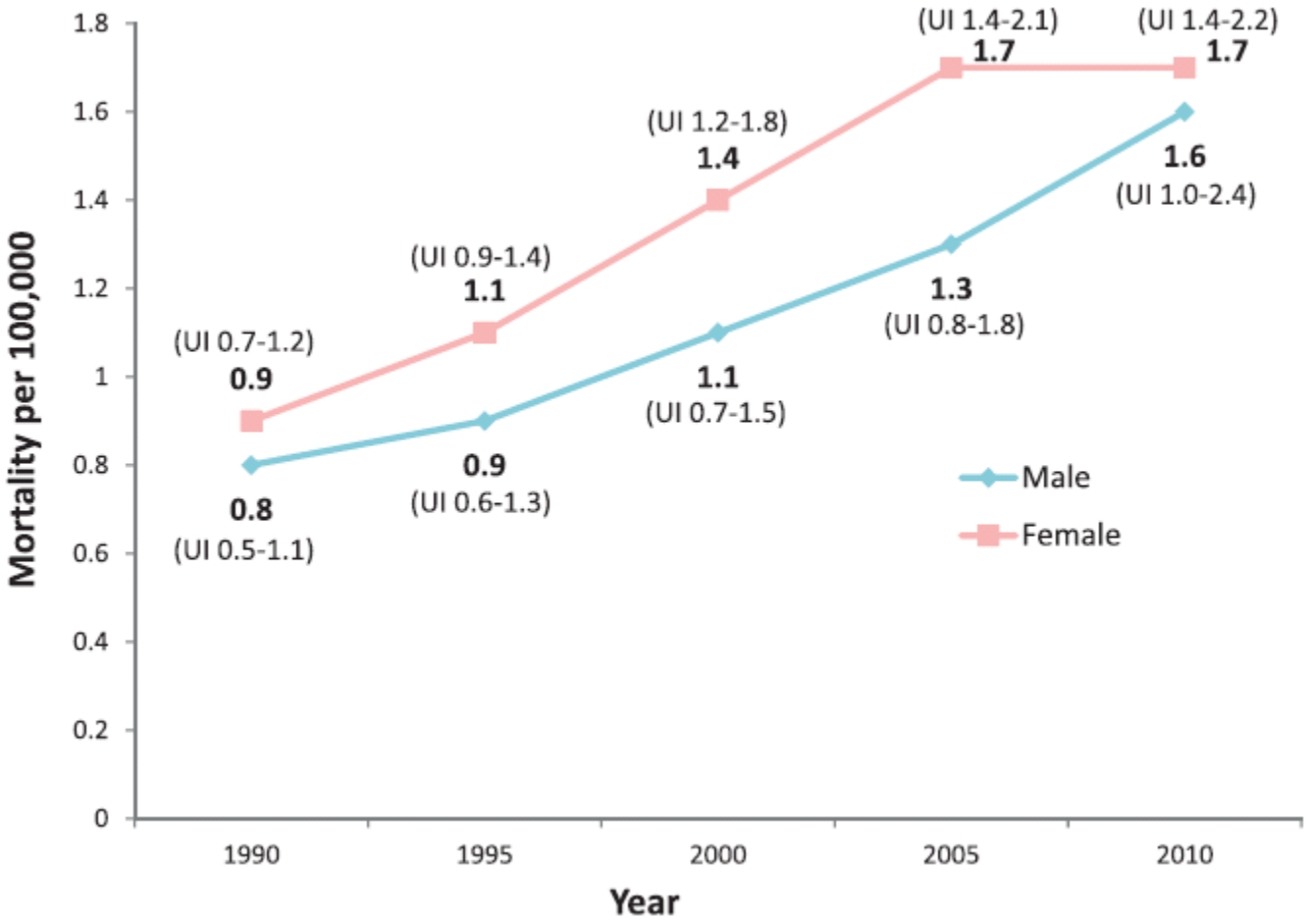
Worldwide Epidemiology of Atrial Fibrillation

A Global Burden of Disease 2010 Study



Chug SS et al. Circulation , 2014

Worldwide Epidemiology of Atrial Fibrillation

A Global Burden of Disease 2010 Study

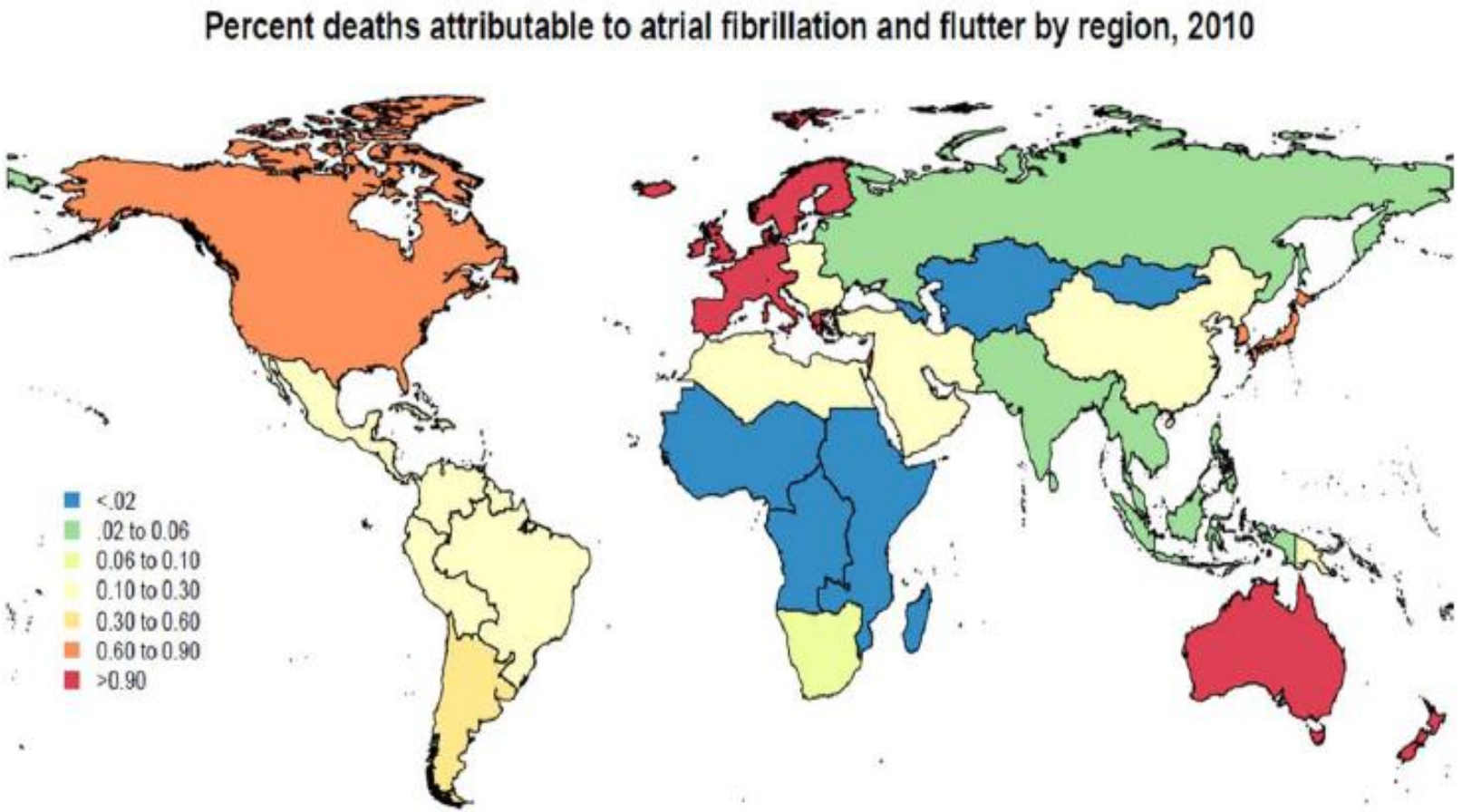


Figure 7. Proportion of global deaths associated with atrial fibrillation in 2010. The map shows color-coded proportions (in percentages) of global deaths in 2010 associated with atrial fibrillation.

Chug SS et al. Circulation , 2014

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The direct costs of AF already amount to approximately 1% of total healthcare spending in the UK, and between 6.0–26.0 billion US dollars in the US for 2008,[36,37] driven by AF-related complications (e.g. stroke) and treatment costs (e.g. hospitalizations). These costs will increase dramatically unless AF is prevented and treated in a timely and effective manner.

Pathophysiology of AF

Genetic aspects

AF, especially early-onset AF, has a strong heritable component that is independent of concomitant cardiovascular disease.

A few young AF patients suffer from inherited cardiomyopathies or channelopathies diseases carry a risk for sudden death.

1/3 of AF patients carry common genetic variants that predispose to AF, albeit with a relatively low added risk.

At least 14 of these common variants are known to increase the risk of prevalent AF in populations.

ESC Guidelines, 2016

Pathophysiology of AF

Remodelling of atrial structure and ion channel function

Activation of fibroblasts
Enhanced connective tissue deposition
Fibrosis
Atrial fatty infiltration
Inflammatory infiltrates
Myocyte hypertrophy,
Necrosis
Amyloidosis

Structural remodelling results in electrical dissociation favouring re-entry and perpetuation of the arrhythmia

ESC Guidelines, 2016

Pathophysiology of AF

Remodelling of atrial structure and ion channel function

The functional and structural changes in atrial myocardium and stasis of blood, especially in the left atrial appendage (LAA), generate a prothrombotic milieu.

Even short episodes of AF lead to atrial myocardial damage and the expression of prothrombotic factors on the atrial endothelial surface,

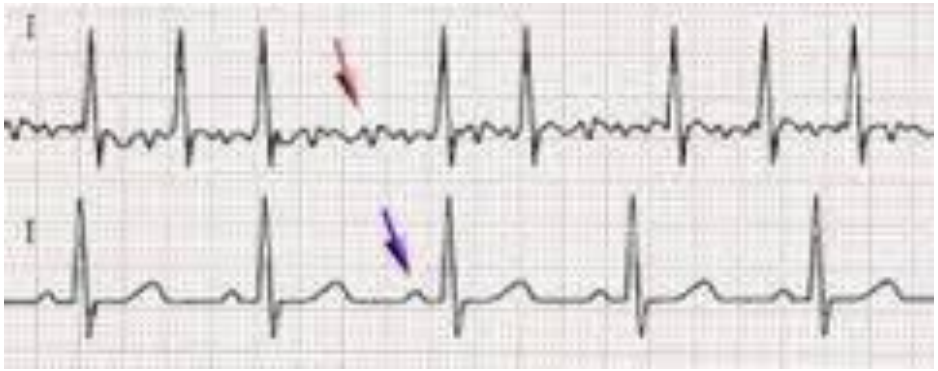
This can partially explain why short episodes of AF convey a long-term stroke risk.

ESC Guidelines, 2016

Clinical presentation

AF is a supra-ventricular arrhythmia that is usually associated with an irregular pulse and this sign at physical examination of patients should always raise the suspicion of AF. To definitely diagnose AF it is necessary a surface ECG recording, where the characteristic findings are irregular R-R intervals without distinct P waves for at least 30 s on a rhythm strip.

DIAGNOSIS OF ATRIAL FIBRILLATION



Absolutely irregular RR intervals and no discernible, distinct P waves.

Clinical presentation

AF usually begins with the paroxysmal form and evolves in the permanent form in about 20% of cases after 5 years.

The risk of AF-related complications is not different between short AF episodes and sustained forms of the arrhythmia

lethargy
palpitations
dyspnoea
chest tightness
sleeping difficulties
psychosocial distress
poorer quality of life

Clinical presentation

‘Silent AF’

Previously undiagnosed AF is found in 1.4% of those aged >65 years, suggesting a number needed to screen (NNS) = 70. These findings encourage the further evaluation of systematic AF screening programmes in at-risk populations.

Not rarely AF is firstly detected after an ischaemic stroke or transient ischemic attack (TIA)

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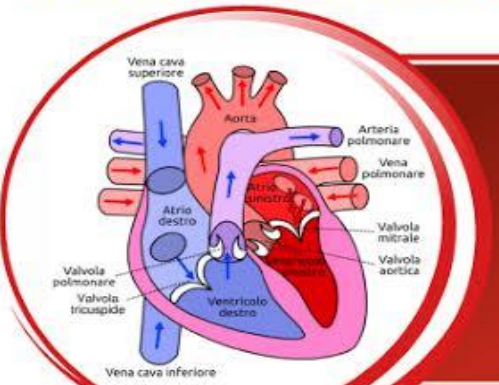
SEZIONE DI FIRENZE

10 SETTEMBRE 2016

FIRENZE, P.ZA DUOMO
SEDE DELLA MISERICORDIA, ORE 10-17

GIORNATA DELLA FIBRILLAZIONE ATRIALE



CONTROLLA IL TUO CUORE!

Misurazione gratuita pressione arteriosa e controllo del ritmo cardiaco

Le aritmie sono alterazioni del ritmo cardiaco che possono nascere in punti diversi del sistema di conduzione del cuore, compromettendo, in modo più o meno severo, la sua funzione di pompa.
La fibrillazione atriale è la forma più diffusa di aritmia cardiaca e si associa ad un alto rischio di **ICTUS CEREBRALE** che si può **PREVENIRE** con la terapia anticoagulante.

Con il patrocinio di:
Feder - A.I.P.A.
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BORGO SAN LORENZO (FI)

140 screenati

4 sospette FA non note

Recommendations for screening for atrial fibrillation

Recommendations	Class[a]	Level[b]	Ref[c]
Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients >65 years of age.	I	B	130, 134, 155
In patients with TIA or ischaemic stroke, screening for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 hours.	I	B	27, 127
It is recommended to interrogate pacemakers and ICDs on a regular basis for atrial high rate episodes (AHRE). Patients with AHRE should undergo further ECG monitoring to document AF before initiating AF therapy.	I	B	141, 156
In stroke patients, additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered to document silent atrial fibrillation.	IIa	B	18, 128
Systematic ECG screening may be considered to detect AF in patients aged >75 years, or those at high stroke risk.	IIb	B	130, 135, 157

ESC Guidelines, 2016

Table 5 Patterns of atrial fibrillation

AF pattern	Definition
First diagnosed AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
Paroxysmal AF	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days.[a] AF episodes that are cardioverted within 7 days should be considered paroxysmal.[a]
Persistent AF	AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more.
Long-standing persistent AF	Continuous AF lasting for ≥1 year when it is decided to adopt a rhythm control strategy.
Permanent AF	AF that is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing persistent AF'.

ESC Guidelines, 2016

Clinical presentation: burden of symptoms of AF

Table 7 **Modified European Heart Rhythm Association symptom scale (modified from Wynn *et al.*[199])**

Modified EHRA score	Symptoms	Description
I	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF[a]
2b	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms[a]
3	Severe	Normal daily activity affected by symptoms related to AF
4	Disabling	Normal daily activity discontinued

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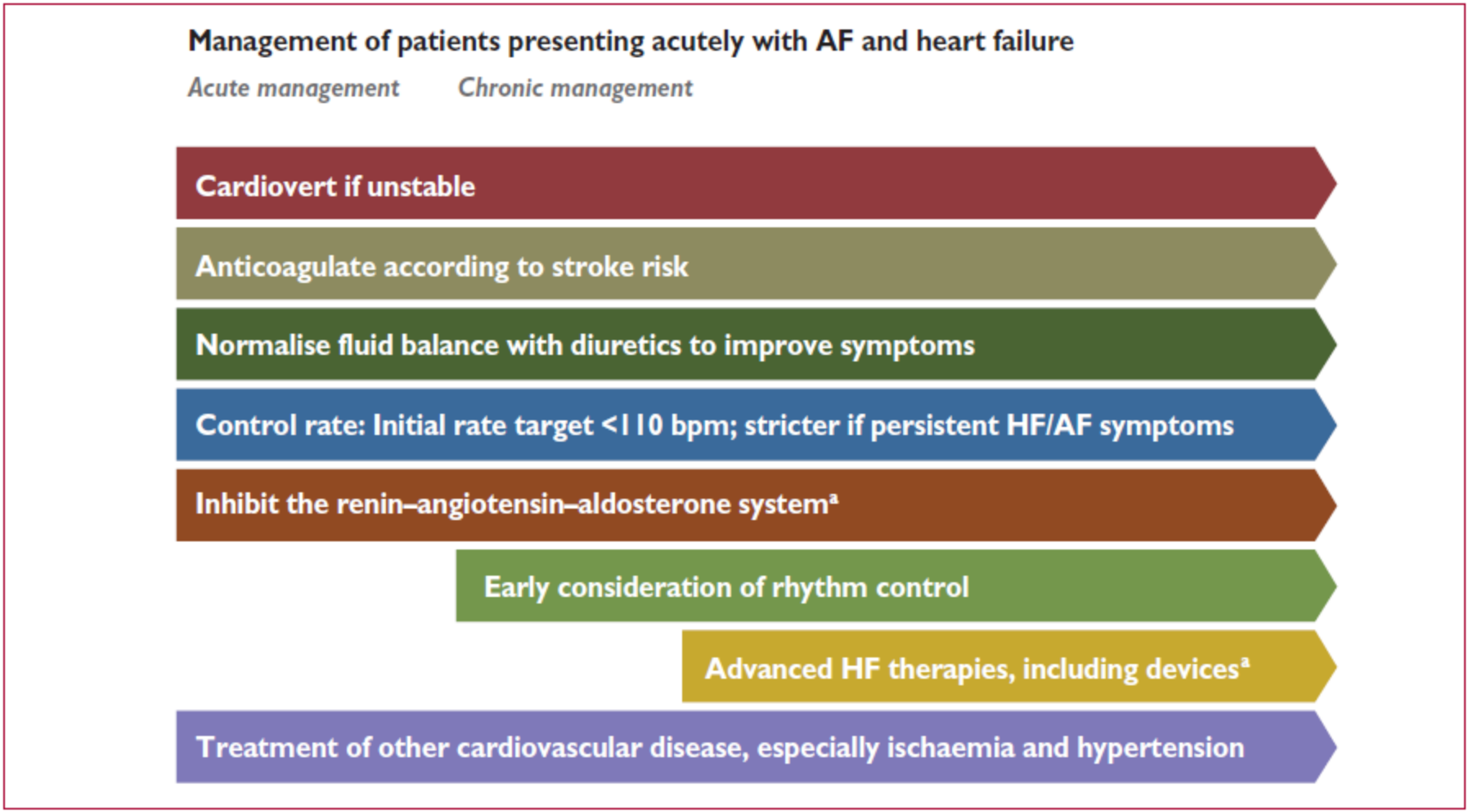

ESC Guidelines, 2016

Clinical presentation

HEART FAILURE

Heart failure and AF can cause and exacerbate each other.

Patients with AF and concomitant heart failure, both with preserved ejection fraction [LV ejection fraction (LVEF) ≥50%] and reduced ejection fraction (LVEF,40%), suffer from a worse prognosis, including increased mortality.

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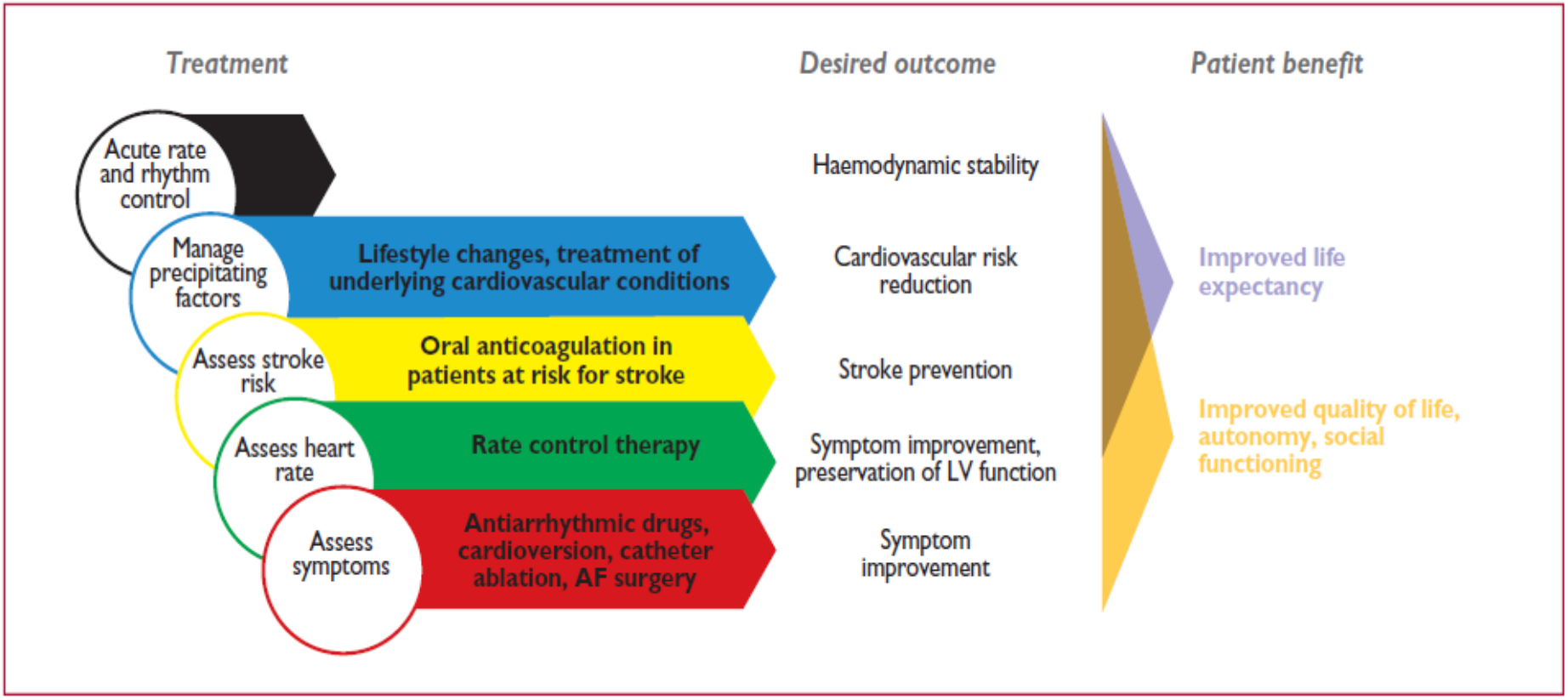
Integrated management of patients with atrial fibrillation



AF = atrial fibrillation; LV = left ventricular.

ESC Guidelines, 2016

Integrated management of patients with atrial fibrillation

Integrated AF management			
Patient involvement	**Multidisciplinary teams**	**Technology tools**	**Access to all treatment options for AF**
• Central role in care process • Patient education • Encouragement and empowerment for self-management • Advice and education on lifestyle and risk factor management • Shared decision making	• Phycisians (general physicians, cardiology and stroke AF specialists, surgeons) and allied health professionals work in a collaborative practice model • Efficient mix of communication skills, education, and experience	• Information on AF • Clinical decision support • Checklist and communication tools • Used by healthcare professionals and patients • Monitoring of therapy adherence and effectiveness	• Structured support for lifestyle changes • Anticoagulation • Rate control • Antiarrhythmic drugs • Catheter and surgical interventions (ablation, LAA occluder, AF surgery, etc.)
• ***Informed, involved, empowered patient***	• ***Working together in a multidisciplinary chronic AF care team***	• ***Navigation system to support decision making in treatment team***	• ***Complex management decisions underpinned by an AF Heart Team***

AF = atrial fibrillation; LAA = left atrial appendage.

ESC Guidelines, 2016

Framinghan Heart Study
SPAF
ACCP
CHADS2 score

ACCP 2004
AFFIRM 2005

ACCP 2008

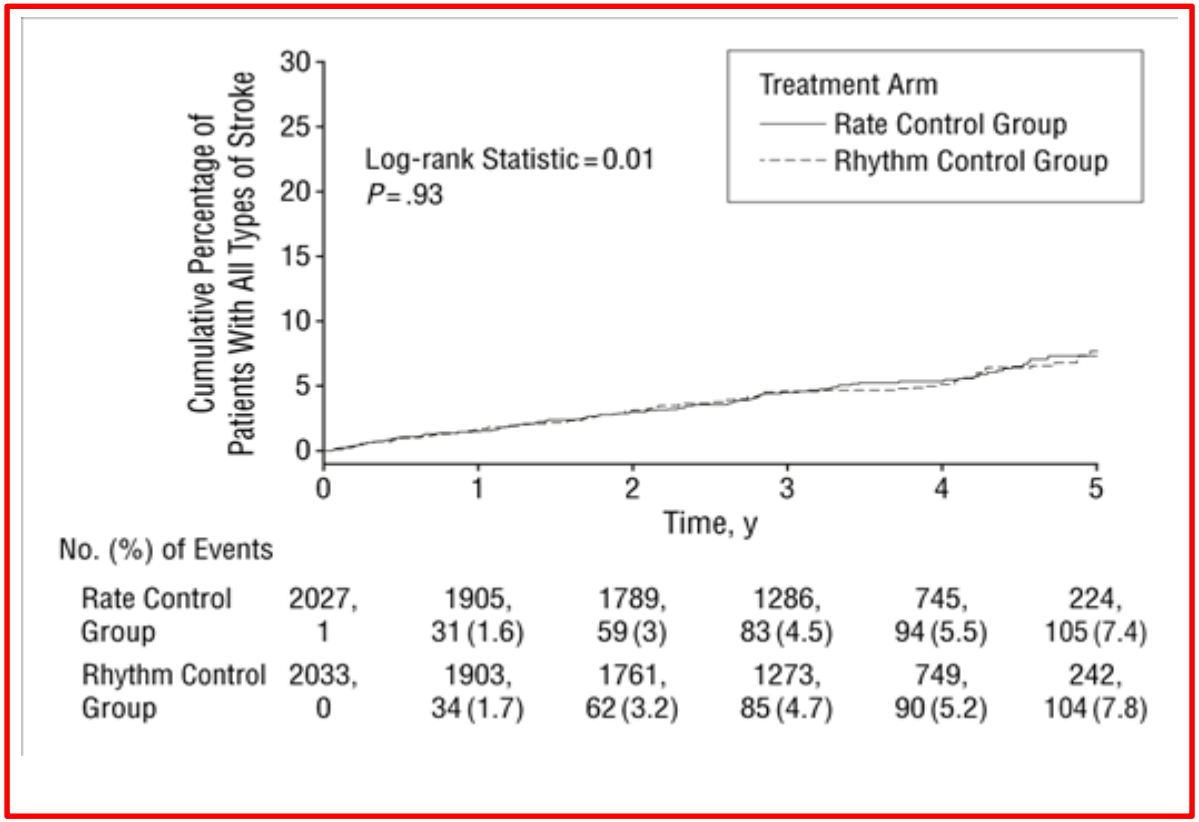
CHA2DS2VASc score

HASBLED score

È tutto chiaro?

Il rischio di stroke nella FA: 20 anni di ricerca clinica

Occurrence and Characteristics of Stroke Events in the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) Study



No. (%) of Events

Rate Control Group	2027, 1	1905, 31 (1.6)	1789, 59 (3)	1286, 83 (4.5)	745, 94 (5.5)	224, 105 (7.4)
Rhythm Control Group	2033, 0	1903, 34 (1.7)	1761, 62 (3.2)	1273, 85 (4.7)	749, 90 (5.2)	242, 104 (7.8)

Sherman DG et al. Arch Intern Med 2005

Risk factors for ischaemic stroke/TIA/systemic embolism in patients with AF: the Swedish Cohort Atrial Fibrillation study

	Multivariate hazard ratios (95% CI)
Age (years) <65 65–74 ≥75	 1.0 (Reference) 2.97 (2.54–3.48) 5.28 (4.57–6.09)
Female sex	1.17 (1.11–1.22)
Previous ischaemic stroke	2.81 (2.68–2.95)
Intracranial bleeding	1.49 (1.33–1.67)
Vascular disease (any) • Myocardial infarction • Previous CABG • Peripheral artery disease	1.14 (1.06–1.23) 1.09 (1.03–1.15) 1.19 (1.06–1.33) 1.22 (1.12–1.32)
Hypertension	1.17 (1.11–1.22)
Heart failure (history)	0.98 (0.93–1.03)
Diabetes mellitus	1.19 (1.13–1.26)
Thyroid disease Thyrotoxicosis	1.00 (0.92–1.09) 1.03 (0.83–1.28)

adapted from Friberg et al Eur Heart J, 2012

Camm J et al, Eur Heart J
doi:10.1093/eurheartj/ehs253

$CHADS_2$ SCORE

Congestive heart failure	1 punto
Hypertension	1 punto
Age >75 years	1 punto
Diabetes Mellitus	1 punto
Stroke/TIA	2 punti

Punteggio 0-6 punti

Basso rischio=0

Rischio moderato=1-2

Alto rischio 3-6

Gage BF, JAMA 2001

Guidelines for the management of atrial fibrillation

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

Table 7 $CHADS_2$ score and stroke rate

$CHADS_2$ score	Patients (n = 1733)	Adjusted stroke rate (%/year)[a] (95% confidence interval)
0	120	1.9 (1.2–3.0)
1	463	2.8 (2.0–3.8)
2	523	4.0 (3.1–5.1)
3	337	5.9 (4.6–7.3)
4	220	8.5 (6.3–11.1)
5	65	12.5 (8.2–17.5)
6	5	18.2 (10.5–27.4)

CHA_2DS_2VASc score and stroke rate

(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**

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Camm J et al Eur Heart Journal 2010

Key Points

The CHA2DS2-VASc score is better at identifying 'truly low-risk' patients with AF and is as good as—and possibly better than—scores such as CHADS2 in identifying patients who develop stroke and thromboembolism.

Camm J et al, Eur Heart J
doi:10.1093/eurheartj/ehs253

The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study.

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CHADS2 score 0-1:

CHA2DS2-VASc score 0	**0.84 (95%CI 0.65-1.08)**
CHA2DS2-VASc score 1	**1.79 (95%CI 1.53-2.09)**
CHA2DS2-VASc score 2	**3.67 (95%CI 3.34-4.03)**
CHA2DS2-VASc score 3	**5.75 (95%CI 5.33-6.21)**
CHA2DS2-VASc score 4	**8.18 (95%CI 6.68-10.02)**

CHADS2 score 0:

CHA2DS2-VASc score 0	**0.84 (95%CI 0.65-1.08)**
CHA2DS2-VASc score 1	**1.75 (95%CI 1.46-2.09)**
CHA2DS2-VASc score 2	**2.69 (95%CI 2.19-3.31)**
CHA2DS2-VASc score 3	**3.20 (95%CI 1.60-6.40)**

Olesen JB et al, TH 2012

Antithrombotic Therapy for Atrial Fibrillation

American College of Chest Physicians

Evidence-Based Clinical Practice Guidelines

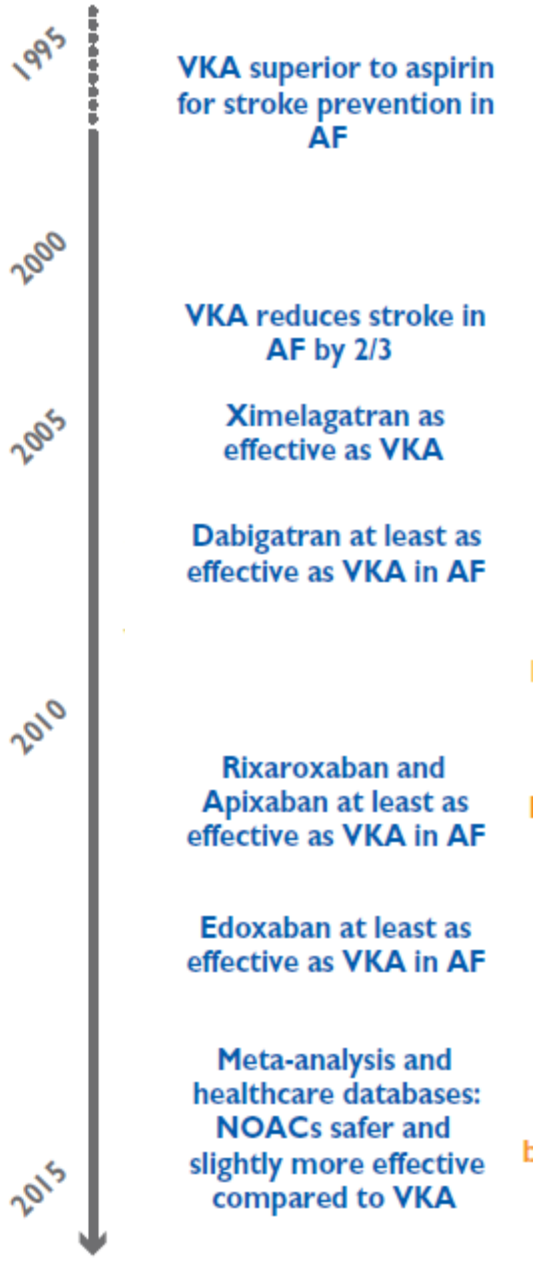
9th Edition - 2012

Methods

…the predictive ability of CHA_2DS_2-VASc is similar to that of the $CHADS_2$ score (C statistics of each risk score is 0.6 across the various studies) and not statistically significantly greater than that of $CHADS_2$.

Because the $CHADS_2$ score has been extensively validated and is easy for clinicians to remember and use, we use the $CHADS_2$ score as the principal approach for our risk-based treatment recommendations..

Singer et al. Chest, 2012



Profilassi dello stroke nella FA: 20 anni di ricerca clinica

ESC Guidelines, 2016

Recommendations for stroke prevention in patients with atrial fibrillation

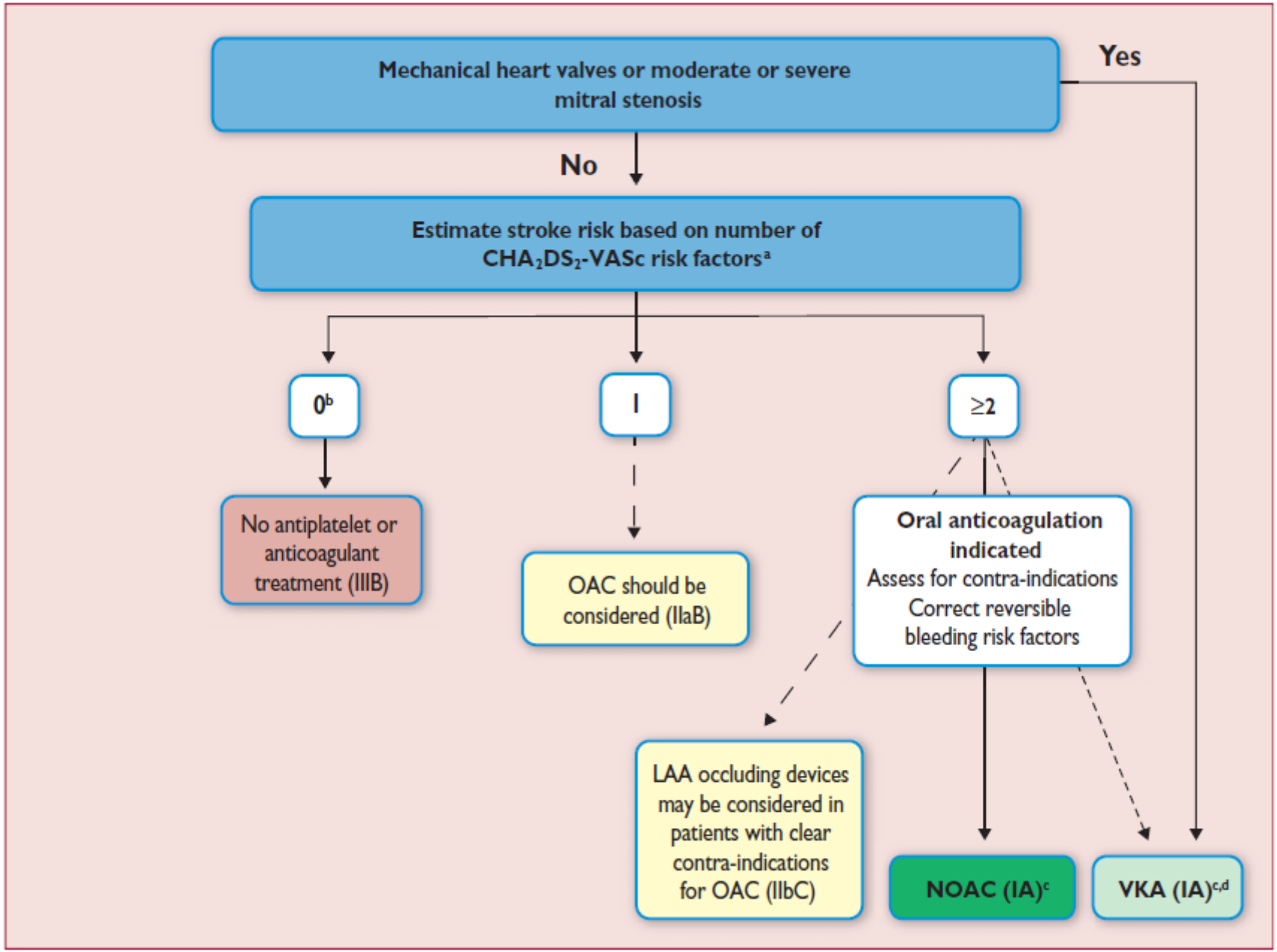
Recommendations	Class[a]	Level[b]	Ref[c]
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA_2DS_2-VASc score of 2 or more.	I	A	38, 318–321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA_2DS_2-VASc score of 3 or more.	I	A	38, 318–321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA_2DS_2-VASc score of 1, considering individual characteristics and patient preferences.	IIa	B	371, 375–377
Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA_2DS_2-VASc score of 2, considering individual characteristics and patient preferences.	IIa	B	371, 376, 377
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	274, 435–440

ESC Guidelines, 2016

Recommendations for stroke prevention in patients with atrial fibrillation

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	39, 318–321, 404
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.	I	A	395, 432, 441-444
AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve).	IIb	A	39, 318, 319, 404, 408
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.	III (harm)	B	429, 445
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.	III (harm)	B	368, 371, 376, 377
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A	38, 429, 430
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).	III (harm)	B C	318–321, 400, 404

ESC Guidelines, 2016



ESC Guidelines, 2016

Key Points

The efficacy of stroke prevention with aspirin is weak, with a potential for harm, since the risk of major bleeding (and ICH) with aspirin is not significantly different to that of OAC, especially in the elderly.

The use of antiplatelet therapy (as aspirin–clopidogrel combination therapy or—less effectively—aspirin monotherapy for those who cannot tolerate aspirin–clopidogrel combination therapy) for stroke prevention in AF should be limited to the few patients who refuse any form of OAC.

Camm J et al, Eur Heart J
doi:10.1093/eurheartj/ehs253

Quale farmaco anticoagulante?

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Patients with renal impairment and on dialysis

First choice	Patients with AF and stage III CKD (creatinine clearance 30–49 mL/min) may be treated with apixaban 5 mg twice daily (apixaban 2.5 mg twice a day if ≥1 additional criteria: age ≥80 years, body weight ≤60 kg, serum creatinine ≥ 1.5 mg/dL (133 μmol/L are present), rivaroxaban 15 mg daily, or edoxaban 30 mg once daily
Second choice	Dabigatran 110 mg twice daily
Not recommended	Dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily

Diener HC. Eur Heart J 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Patients with renal impairment and on dialysis

First choice	For patients with AF on haemodialysis, no anticoagulation or VKA therapy is appropriate
Not recommended	Dabigatran, rivaroxaban, apixaban*, or edoxaban

First choice	Patients with AF and creatinine clearance of >95 mL/min may be treated with dabigatran 150 twice daily, rivaroxaban 20 mg once daily or apixaban 5 mg twice daily. No preference for NOACS over VKAs
Second choice	Edoxaban 60 mg once daily (not recommended in USA based on FDA indication approval)

Diener HC. Eur Heart J 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Patients with a high risk of gastrointestinal bleeding

Diener HC. Eur Heart J 2016

First choice	For patients with a high risk of gastrointestinal bleeding, apixaban 5 mg twice daily or dabigatran 110 mg twice daily may be used
Second choice	Dabigatran 150 mg twice daily, edoxaban 60 mg once daily, or rivaroxaban 20 mg once daily
Comments	Gastrointestinal bleeding, even in the setting of anticoagulation, does usually not cause death or permanent major disability. Thus, the choice of OAC should be driven mainly by stroke prevention considerations. The label 'high risk of gastrointestinal bleeding' is imprecise. For example, patients with *H. pylori*-related ulcer haemorrhage may no longer be at high risk of bleeding once the infection has been eradicated. The gastrointestinal bleeding risk associated with any anticoagulant is increased by concurrent use of antiplatelet agents, including aspirin.[41]

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Non-vitamin K oral anticoagulants and age

First choice	In patients older than 75 years, we suggest apixaban 5 mg twice daily [2.5 mg if ≥2 of the following: age ≥80 years, body weight ≤60 kg, or creatinine ≥1.5 mg/dL (133 μmol/L)]
Second choice	Dabigatran 110 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily

Diener HC. Eur Heart J 2016

Combination therapy with oral anticoagulants and antiplatelets

The addition of a NOAC increased the bleeding risk by 79–134%, while reducing recurrent ischaemic events only marginally in patients without AF.

OAC monotherapy is recommended in AF patients with stable CAD but without an ACS and/or coronary intervention in the previous 12 months.

In patients treated for ACS, and in those receiving a coronary stent, short-term triple combination therapy of OAC, clopidogrel, and aspirin seems warranted.

ESC Guidelines, 2016

Fibrillazione Atriale:

Il rischio emorragico

EUROPEAN SOCIETY OF CARDIOLOGY®

Europace (2011) **13**, 723–746
doi:10.1093/europace/eur126

EHRA POSITION PAPER

Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis

Gregory Y.H. Lip (Chair)[1*†], Felicita Andreotti[2†‡], Laurent Fauchier[3†], Kurt Huber[4*†], Elaine Hylek[5†], Eve Knight[6†], Deirdre A. Lane[1†], Marcel Levi[7†], Francisco Marin[8†], Gualtiero Palareti[9†], and Paulus Kirchhof (Co-chair)[10†]

Table 1 Annual rates of major haemorrhage among patients taking warfarin

Study	Year published	Population (*n*)	Major haemorrhage, % per year	ICH % per year	New to warfarin, %	Age, mean
Randomised trials						
AFI[18]	1994	AF ($n = 3691$)	1.3	0.3	100	69
SPAF II[19] (2 age strata)	1994	AF ($n = 715$)	1.7	0.5	100	NR
		AF ($n = 385$)	4.2	1.8	100	80
AFFIRM[20]	2002	AF ($n = 4060$)	2.0	0.6	NR	70
SPORTIF III[21]	2003	AF ($n = 3407$)	2.2	0.4	27	70
SPORTIF V[22]	2005	AF ($n = 3422$)	3.4	0.1	15	72
ACTIVE W[23]	2006	AF ($n = 6706$)	2.2	NR	23	71
RE-LY[24]	2009	AF ($n = 18006$)	3.4	0.74	51	72
ROCKET-AF[25]	Presented 2010	AF ($n = 14264$)	3.5	0.7	37	73
Inception cohort						
Landefeld and Goldman[26]	1989	All ($n = 565$)	7.4	1.3	100	61
Steffensen *et al.*[27]	1997	All ($n = 682$)	6.0	1.3	100	59F/66M
Beyth *et al.*[28]	1998	All ($n = 264$)	5.0	0.9	100	60
Pengo *et al.*[29]	2001	AF ($n = 433$)	Age $\geq$ 75: 5.1	NA	100	68
			Age $<$ 75: 1.0			
Hylek *et al.*[30]	2007	AF ($n = 472$)	7.2	2.5	100	77
Non-inception cohort (prevalent warfarin use)						
Van der Meer *et al.*[31]	1993	All ($n = 6814$)	2.7	1.3	NR	66
Fihn *et al.*[32]	1996	All ($n = 928$)	1.0	1.3	NR	58
ATRIA[33]	2003	AF ($n = 6320$)	1.52	0.46	NR	71
Poli *et al.*[34]	2009	AF ($n = 783$)	1.4	2.5	NR	75
Rose *et al.*[35]	2009	AF ($n = 3396$)	1.9	NA	5	74

Lip G et al. Europace 2011

Bleeding risk in very old patients on VKA treatment: results of a prospective collaborative study.

On the behalf of FCSA

	Atrial Fibrillation
Number	3015
Males (%)	1361 (45.1)
Median Age (IQR)	83 (80-102)
Follow-up period (years)	7620
Time in Therapeutic Range(IQR)	63 (50-75)
N. of major bleedings (rate x100 pt-yrs)	132 (1.73)
ICH	42 (0.55)
GI	51 (0.67)

Table 4 Factors affecting bleeding risk when using oral anticoagulant therapy

Intensity of anticoagulation
Management modality
• Usual care vs. dedicated anticoagulation clinic or increased monitoring frequency or self management
Patient characteristics
• Age
• Genetics (may also be assessed by the INR response in the initial period of VKA therapy initiation)
• Prior stroke
• History of bleeding
• Anaemia
• Co-morbidity (hypertension, renal insufficiency, liver disease)
Use of concomitant medication or alcohol
• Antiplatelet agents
• NSAIDs
• Medication that affects the intensity of anticoagulation
• Alcohol abuse

Lip G et al. Europace 2011

Bleeding risk stratification models

1998 OBRI Outpatients bleeding risk index

2006 HEMORR$_2$HAGE
2006 Shireman et al

2009 HASBLED

2010 Fang et al

Bleeding risk stratification models

HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

Low risk = 0-1
Intermediate risk = 2
High risk = ≥ 3

Pisters et al 2009

American College of Chest Physicians

Antithrombotic Therapy for Atrial Fibrillation

9th Edition - 2012

Bleeding Risk Assessment

We have not made separate recommendations depending on patients bleeding risk because there are *insufficient data* to estimate reliably the absolute bleeding rates for patients in different categories of bleeding risk on different antithrombotic regimens.

Singer et al. Chest, 2012

Performance of the HEMORR$_2$HAGES, ATRIA, and HAS-BLED Bleeding Risk–Prediction Scores in Patients With Atrial Fibrillation Undergoing Anticoagulation

The AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) Study

Table 3 AUCs (or C-Indexes) for HEMORR$_2$HAGES, ATRIA, and HAS-BLED Scores

	Any Clinically Relevant Bleeding			Major Bleeding			Death		
AUC Analysis	AUC	95% CI	SE	AUC	95% CI	SE	AUC	95%CI	SE
HEMORR$_2$HAGES	0.55	0.51–0.59	0.019	0.60	0.51–0.69	0.046	0.57	0.50–0.65	0.033
HAS-BLED	0.60	0.56–0.63	0.019	0.65	0.56–0.73	0.043	0.67	0.60–0.73	0.035
ATRIA	0.50	0.46–0.54	0.020	0.61	0.51–0.70	0.048	0.63	0.56–0.69	0.037

AUC = area under the curve; CI = confidence interval; SE = standard error; other abbreviations as in Table 2.

Conclusions:

All 3 tested bleeding risk–prediction scores demonstrated *only modest* performance in predicting any clinically relevant bleeding…

Apostolakis S et al, JACC 2012

Which Risk Factors Are More Associated With Ischemic Stroke Than Intracerebral Hemorrhage in Patients With Atrial Fibrillation?

Emer R. McGrath, MB; Moira K. Kapral, MD; Jiming Fang, PhD; John W. Eikelboom, MD; Aengus ó Conghaile, MB; Michelle Canavan, MB; Martin J. O'Donnell, MB; on behalf of the Investigators of the Registry of the Canadian Stroke Network

Key risk factors for ischemic stroke are also risk factors for major bleeding, including ICH. Some of these "shared" risk factors (eg, age, hypertension, diabetes mellitus, and renal impairment) are included in clinical prediction rules for both ischemic stroke and major bleeding. Without knowledge of their comparative importance for predicting ischemic stroke and ICH, it is unclear how these "shared" risk factors should influence therapeutic decisions.

McGrath E et al, Stroke 2012

Which Risk Factors Are More Associated With Ischemic Stroke Than Intracerebral Hemorrhage in Patients With Atrial Fibrillation?

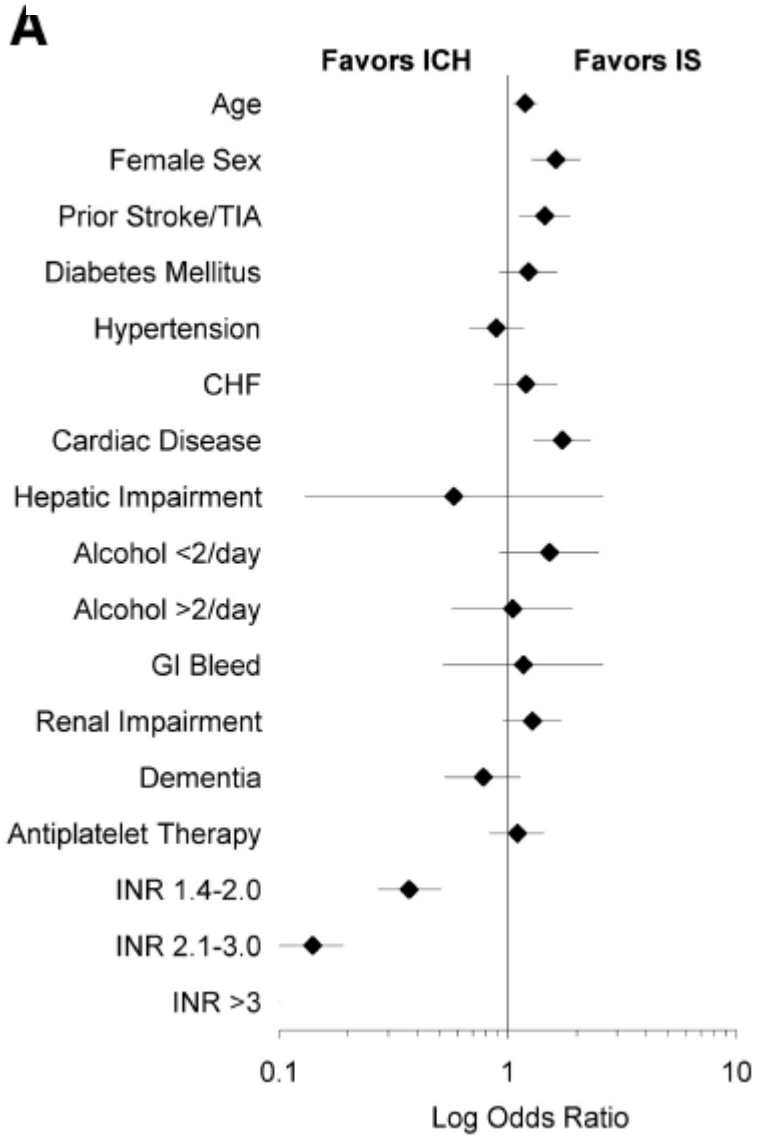
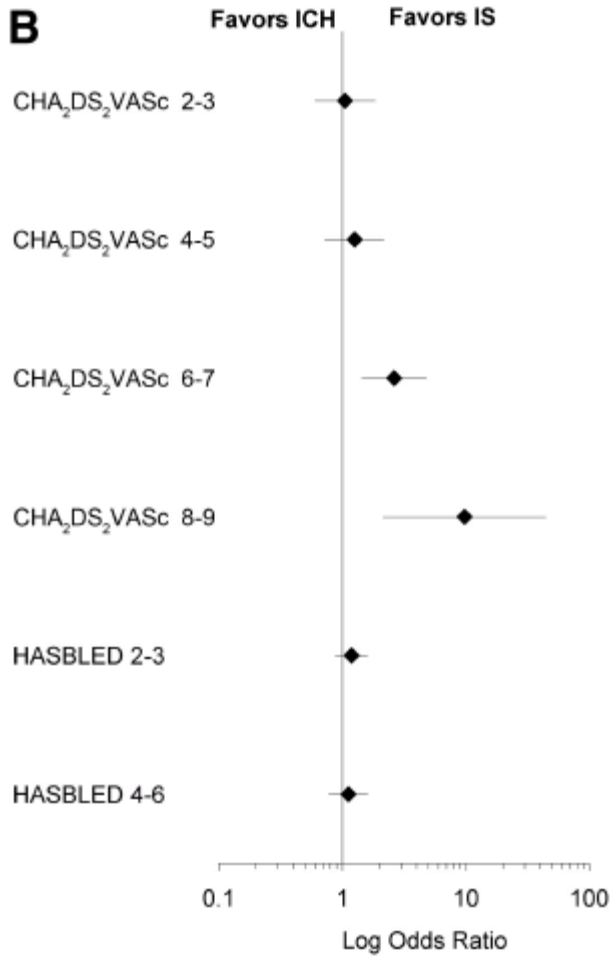


Figure. A, Forest plot of risk factors for ischemic stroke relative to ICH in patients with atrial fibrillation.

McGrath E et al, Stroke 2012

Which Risk Factors Are More Associated With Ischemic Stroke Than Intracerebral Hemorrhage in Patients With Atrial Fibrillation?



Forest plot of risk factors for ischemic stroke relative to ICH in patients with atrial fibrillation—CHA_2DS_2VASc and HAS-BLED scores. ICH indicates intracerebral hemorrhage; CHA_2DS_2VASc, Cardiac Failure, Hypertension, Age ≥75, Diabetes Mellitus, Stroke, Vascular Disease, Age 65–74 and Sex Category (female); HAS-BLED, Hypertension, Abnormal Renal/ Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol.

McGrath E et al, Stroke 2012

Similar performance of HASBLED, CHADS2 and CHA2DS2VASc scores in bleeding risk prediction of Atrial Fibrillation patients: the refined HAS-BED score.

Results from the START REGISTER

Distribution and rate of major bleedings in relation to the scores (categorized)

	Low risk (n-rate x100 pt-yrs)	High risk (n-rate x100 pt-yrs)	RR (95% CI)	p
HAS-BLED	45 (1.1)	70 (2.3)	2.0 (1.4-3.0)	0.002
HAS-BED	57 (1.2)	58 (2.4)	1.9 (1.3-2.8)	0.0006
CHADS2	29 (1.2)	86 (1.9)	1.5 (1.0-2.4)	0.05
CH2DS2VASc	8 (1.4)	107 (1.7)	1.1 (0.6-2.8)	0.6

Submitted

Similar performance of HASBLED, CHADS2 and CHA2DS2VASc scores in bleeding risk prediction of Atrial Fibrillation patients: the refined HAS-BED score. Results from the START REGISTER

Predictive ability for hemorrhage of the scores (continuous)

	c statistic	p value	95% CI
HAS-BLED	0.61	0.000	0.560-0.667
HAS-BED	0.58	0.002	0.530-0.639
$CHADS_2$	0.58	0.002	0.531-0.638
CHA_2DS_2VASc	0.56	0.021	0.509-0.618

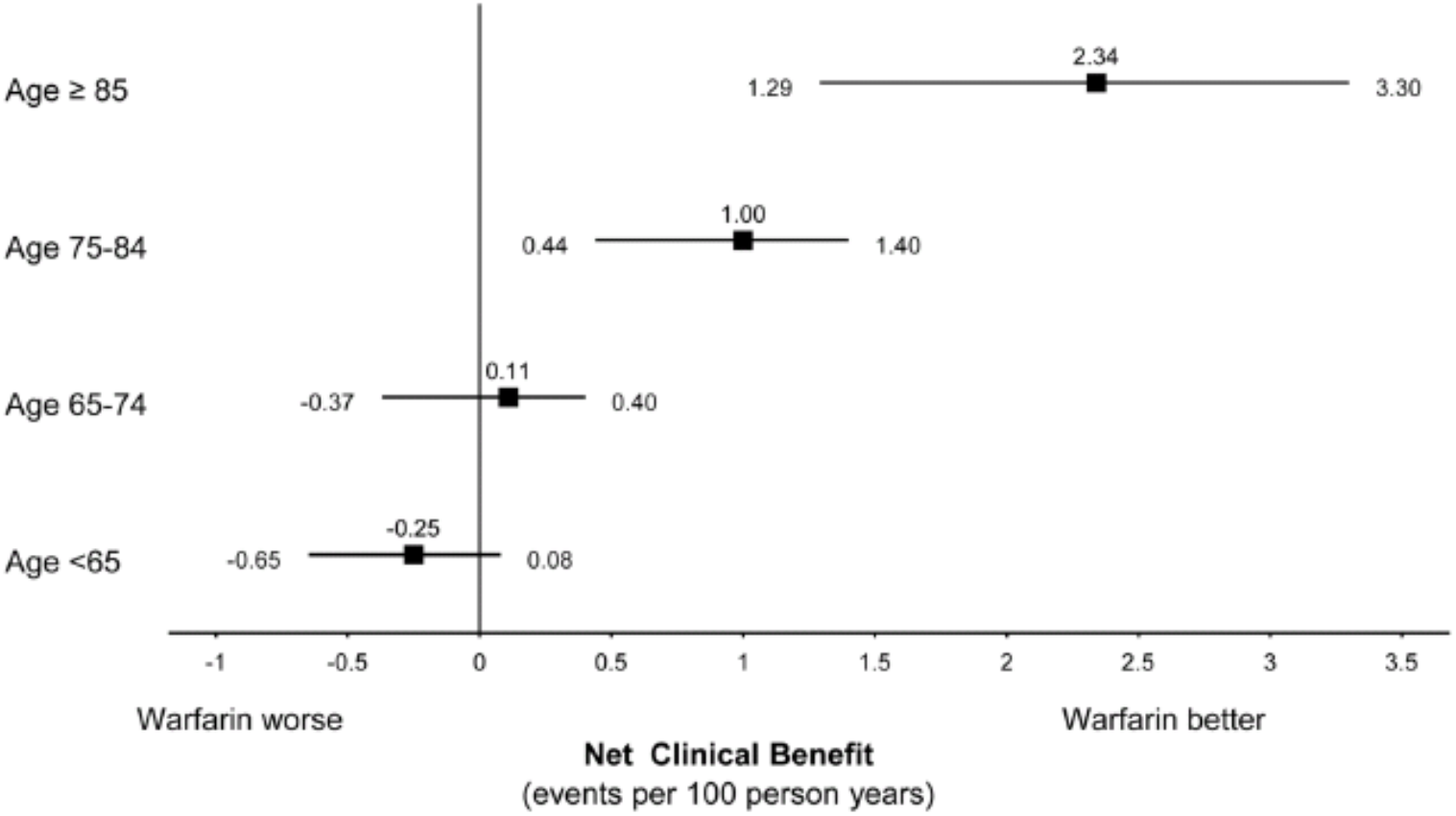
Predictive ability for hemorrhage of the scores (categorized)

(*)	*c statistic*	p value	95% CI
HAS-BLED	0.59	0.001	0.539-0.643
HAS-BED	0.52	0.4	0.468-0.579
$CHADS_2$	0.54	0.1	0.494-0.596
CHA_2DS_2VASc	0.51	0.8	0.455-0.561

(submitted)

The Net Clinical Benefit of Warfarin Anticoagulation in Atrial Fibrillation

Daniel E. Singer, MD, **Yuchiao Chang, PhD**, **Margaret C. Fang, MD, MPH**, **Leila H. Borowsky, MPH**, **Niela K. Pomernacki, RD**, **Natalia Udaltsova, PhD**, and **Alan S. Go, MD**



The net clinical benefit of warfarin by age group

Ann Intern Med. 2009

A national survey of the management of atrial fibrillation with antithrombotic drugs in Italian primary care

Giampiero Mazzaglia[1]; Alessandro Filippi[2]; Marianna Alacqua[3]; Warren Cowell[4]; Annabelle Shakespeare[4]; Lorenzo G. Mantovani[5]; Cosetta Bianchi[6]; Claudio Cricelli[2]

[1]Health Search, Italian College of General Practitioners, Florence, Italy; [2]Italian College of General Practitioners, Florence, Italy; [3]IRCCS Centro Neurolesi 'Bonino-Pulejo', Messina, Italy; [4]Bayer HealthCare, Uxbridge, UK; [5]CIRFF – Center of Pharmacoeconomics, Federico II University of Naples, Naples, Italy; [6]Bayer HealthCare, Milan, Italy

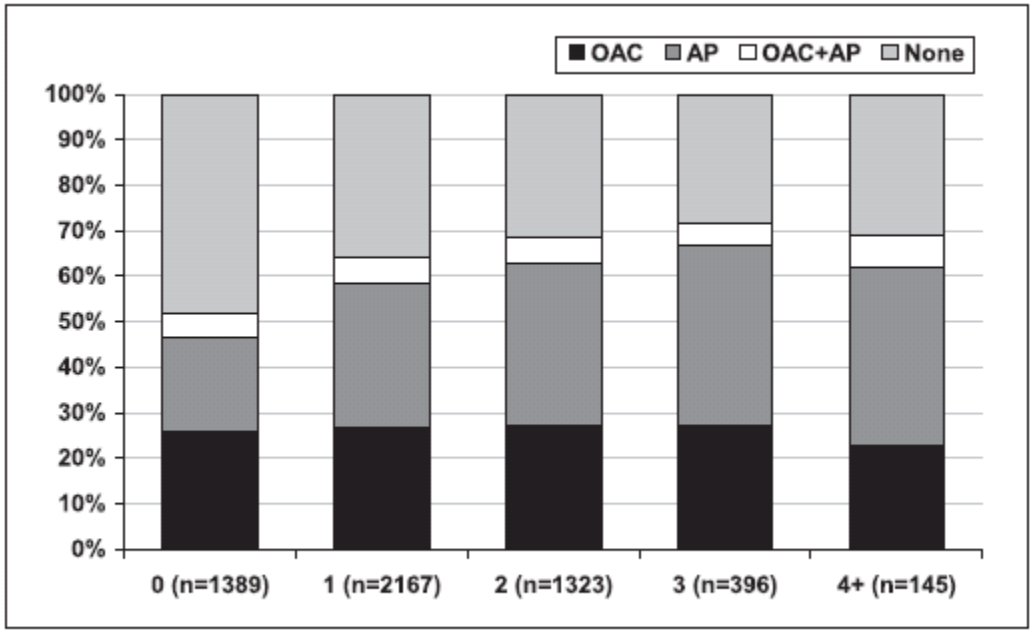


Figure 3: Antithrombotic drug prescription per risk category according to the CHADS2 score. Correlation between worsening stroke risk and change in AT prescription; P-values: OAC, 0.7683; AP, <0.0001; OAC+AP, 0.7417.

Mazzaglia G et al. Thromb Haemost 2010

Risk of stroke and oral anticoagulant use in atrial fibrillation:

a cross-sectional survey

Holt T et al, Br J Gen Pract 2012

Table 3. Trends in prescribing of anticoagulants in those with $CHADS_2$ ≥2 and CHA_2DS_2-VASc ≥2, 2007–2010[a]

	2007	2008	2009	2010
Size of sample with atrial fibrillation	62 146	64 524	63 533	59 804
Number identified with $CHADS_2$ ≥2	34 827	36 394	35 948	34 041
Percentage with $CHADS_2$ ≥2	56.0	56.4	56.6	56.9
Proportion, %				
Anticoagulant	49.7	50.3	51.2	53.0
Antiplatelet	43.9	43.8	43.4	42.2
Both	6.0	6.3	6.5	6.5
Neither	12.4	12.1	11.9	11.3
Number identified with CHA_2DS_2VASc ≥2	52 668	54 526	53 781	50 547
Percentage with CHA_2DS_2-VASc ≥2	84.7	84.5	84.7	84.5
Proportion, %				
Anticoagulant	48.0	48.7	49.3	50.7
Antiplatelet	42.9	43.2	42.9	42.0
Both	5.7	6.0	6.2	6.1
Neither	14.7	14.1	13.9	13.4

[a]Changes in the proportions treated with anticoagulants were all significant at the P<0.01 level.

BN, femmina, 90 aa

Ipertesa, non altri fattori di rischio per stroke
Connettivite indifferenziata in trattamento steroideo
Insufficienza renale cronica moderata (creatinina 1.5)
6 anni fa etp mammaria

Indicazione alla TAO:
fibrillazione atriale, in TAO con warfarin da molti anni ben condotta senza complicazioni

BN, femmina, 90 aa

CHADS2 score = 2
CHA2DS2VASc= 4

Da qualche tempo sindrome vertiginosa, è caduta 2 volte senza complicazioni e una 3° volta con ematoma del capo e della coscia: inviata in PS. Non fratture, non anemizzazione Warfarin sospeso per l'ampia estensione degli ematomi

BN, femmina, 90 aa

HASBLED score= 4

E' indicata la ripresa della terapia anticoagulante?
Quale farmaco?

BN, femmina, 90 aa

Si decidere di proseguire con ASA 100 mg in attesa di valutare l'evoluzione della s. vertiginosa e il rischio di cadute.

Dopo 5 giorni ricovero in PS per disartria durata circa 20'
Riprende warfarin (INR 2.0-3.0)

DGT, M anni 89 – Kg 65

1996 Sindrome bradi-tachi impianto pace maker
episodi di FAP non databili
3/2014 TVP/EP spontanea in paz con eterozigosi per fattore V Leiden.
Inizia TAO ben condotta
IRC creatinina 1.7 eGFR 27 ml/min

05/4/2016 emorragia talamica sx e del braccio posteriore della capsula interna 30/3 INR 3.77

dopo la fase acuta, buon recupero funzionale con minimi esiti (RANKIN scale=1)

DGT, M anni 89 – Kg 65

CHA2DS2VASc =2 (età) rischio stimato 2-3% anno

rischio di recidiva di emorragia cerebrale 5 volte superiore rispetto a paz in TAO che non abbiano avuto pregresse emorragie cerebrali

DGT, M anni 89 – Kg 65

Che fare?

Nessuna profilassi antitrombotica

warfarin 1.5-2.0

apixaban 2.5x2

dabigatran 110x2

edoxaban 30 mg

rivaroxaban 15 mg

DGT, M anni 89 – Kg 65

Cosa abbiamo deciso

apixaban 2.5x2
sta bene al follow-up del 2° mese

CT, F anni 86 – Kg 65

APP:
indicazione alla TAO: FAC di recente riscontro ad insorgenza non databile
APR:
2012 NSTEMI VCG negativa per lesioni stenosanti, ipertrofia concentrica del V sx con FE 51%
2013 AOP trattata con PTCA bilaterale delle a. femorali
in trattamento con ASA 100 mg e Clopidogrel 75
Atrovastatina, Bisoprololo, Furosemide,

CT, F anni 86

Hb 12.2
Plt 340.000
creatinina 1.23 eGFR 34 ml/min

quale terapia anticoagulante?
Prosegue l'antiaggregante in associazione?

COSA ABBIAMO DECISO

CT, F anni 86

Si inizia warfarin (INR 2.0-3.0)
Si consiglia la sospensione di entrambi gli antiaggreganti

Dopo 6 mesi prosegue warfarin, non complicazioni