Come mantenere la sicurezza e l'efficacia delle terapie antitrombotiche nei pazienti complessi

Sicurezza della terapia anticoagulante nei grandi anziani

Daniela Poli

12 Novembre 2016

Epidemiology of atrial fibrillation: European perspective

Prevalence of AF in relation to age and sex

<49 years	0.12%–0.16%
60–70 years	3.7%–4.2%
≥80 years	10.0%–17.0%

male to female ratio of approximately 1.2:1

Despite the greater prevalence in men, women represent the bulk of patients with AF due to their longer lifespan.

Zoni Berisso M et al., 2014

Elderly patients in the START Register

	All patients	AF	VTE
N. patients	9111	5613	2861
>75 years	54.9%	66.6%	36.1%
> 80 years	27.3%	33.5%	17.1%
> 85 years	11.1%	13.6%	7.3%

Incidence and 10-Year Survival of Intracerebral Hemorrhage in a Population-Based Registry

Simona Sacco, MD; Carmine Marini, MD; Danilo Toni, MD;
Luigi Olivieri, MD; Antonio Carolei, MD, FAHA

Table 1. Annual Incidence Rates (Per 100 000) of First-Ever Primary ICH According to Age and Sex

Group	Patient, n	Population at Risk (Person-Years), n	Rate	95% CI
0–44 years	15	843 120	1.78	0.99–2.93
45–54 years	29	180 255	16.09	10.50–23.59
55–64 years	71	169 740	41.83	32.86–52.50
65–74 years	157	160 250	97.97	80.93–116.97
75–84 years	183	104 515	175.09	150.01–203.10
85+ years	94	30 345	309.77	249.37–380.15
All (crude)	549	1 488 225	36.89	33.80–39.97
All (European standardized)			32.94	30.18–35.72
All (world standardized)			15.93	14.41–17.46

Stroke. 2009;40:394-399

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 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

Major Hemorrhage and Tolerability of Warfarin in the First Year of Therapy Among Elderly Patients With Atrial Fibrillation

Elaine M. Hylek, MD, MPH; Carmella Evans-Molina, MD; Carol Shea, RN;
Lori E. Henault, MPH; Susan Regan, PhD

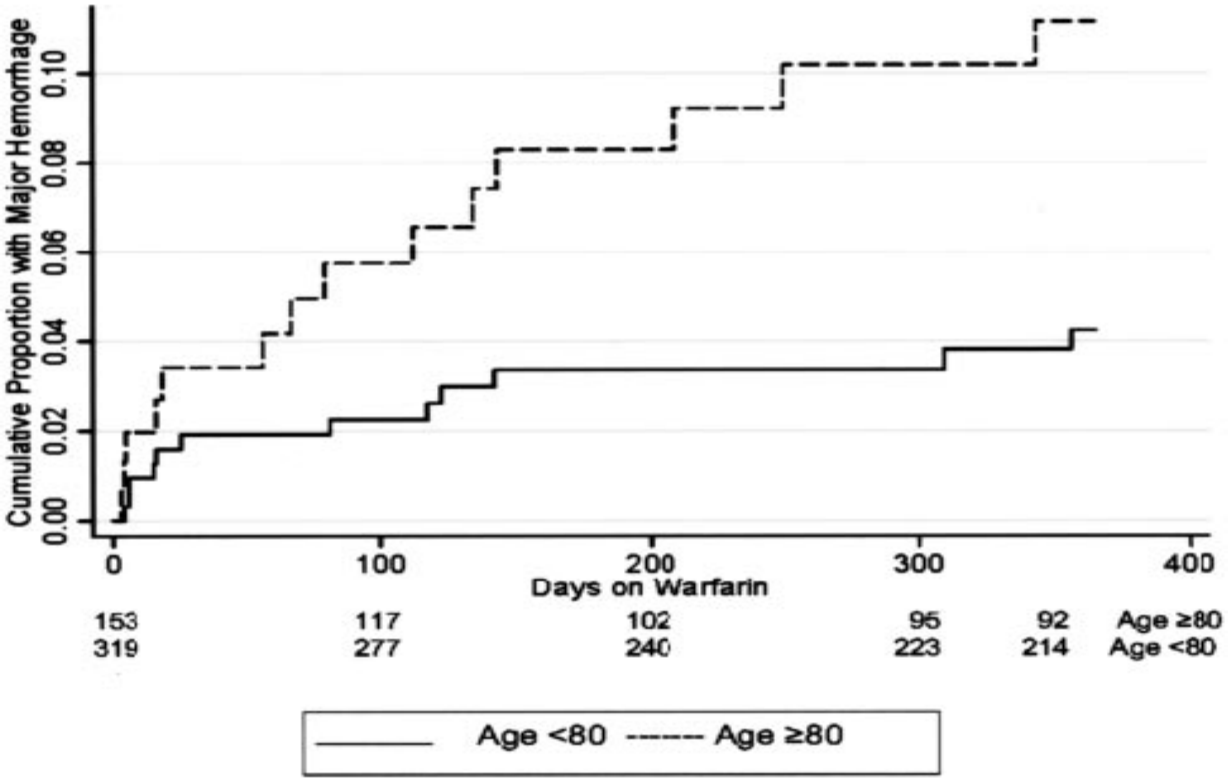

Figure 1. Cumulative incidence of major bleeding among patients aged ≥80 years and <80 years (n=472). Numbers below graph are the number of patients without bleeding who continued on warfarin at that time point (P=0.009, log-rank test).

Circulation. 2007

Major Hemorrhage and Tolerability of Warfarin in the First Year of Therapy Among Elderly Patients With Atrial Fibrillation

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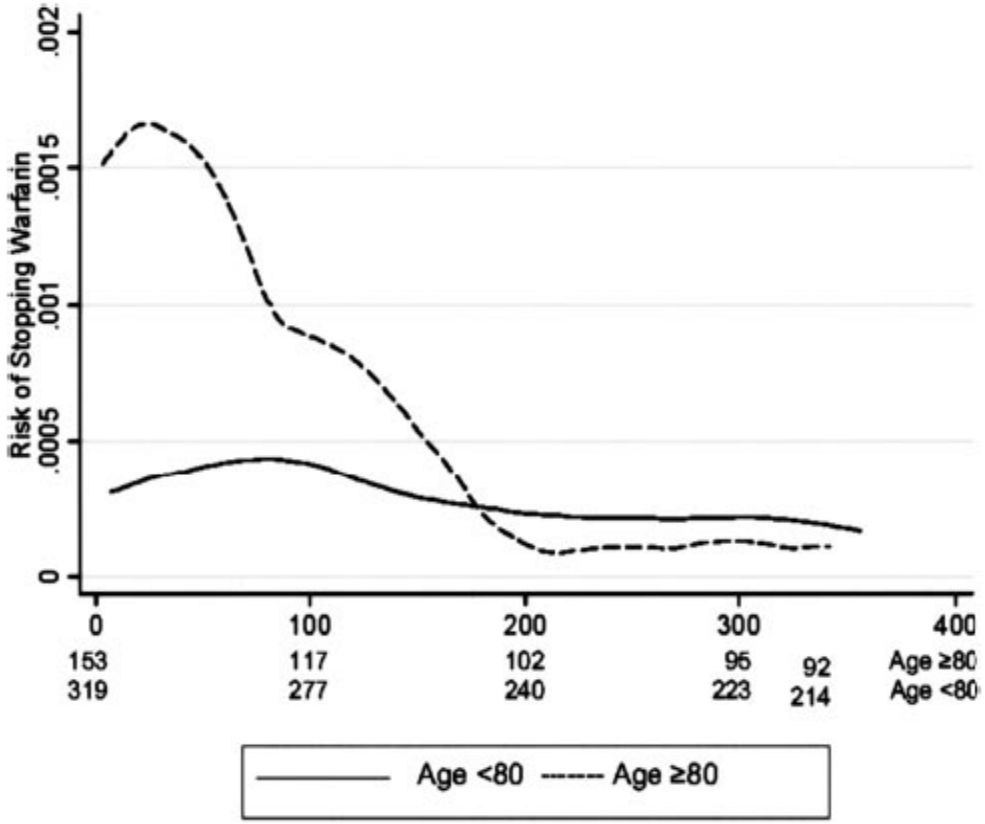

Figure 2. Risk of stopping warfarin in the first year on the basis of perceived safety concerns by age. Numbers below graph are the number of patients on warfarin at that time point ($P<0.001$, log-rank test).

Circulation. 2007

Rischio emorragico di pazienti molto anziani in trattamento con farmaci antiVitamina K:risultati dello studio EPICA

Condotto nei Centri aderenti a FCSA

Numero dei pazienti arruolati: 4093

	X 100 anni di trattamento
Emorragie maggiori	1.87
cerebrali	0.55
gastrointestinali	0.68
altre	0.67

Risk Factors Associated With Bleeding Events: Univariate Analysis

	Incidence Rate Ratio	95% CI	*P*
Male sex	1.41	1.04–1.92	0.02
Previous TIA/stroke	1.33	0.92–1.90	0.10
Age >85 y	1.30	1.01–1.65	0.05
VTE vs AF	1.40	1.02–1.85	0.03
Hypertension	1.40	0.97–2.06	0.06
History of bleeding	5.41	3.29–8.50	<0.0001
Prior gastrointestinal bleeding	5.77	3.08–9.96	<0.0001
Prior cerebral bleeding	3.29	0.67–9.79	0.08
Renal failure (serum creatinine ≥1.5 mg/dL)	1.67	1.04–2.60	0.02
Poor TTR control	1.25	0.91–1.70	0.14
Active cancer	2.81	1.80–4.25	<0.0001
Antiplatelet use	1.32	0.77–2.14	0.25
History of falls	2.95	1.79–4.66	<0.0001
Comedications (≥3 drugs)	1.43	1.01–2.05	0.04
Creatinine clearance ≤30 mL/min	1.95	1.2–3.3	0.011

CI indicates confidence interval; TIA, transient ischemic attack; VTE, venous thromboembolism; AF, atrial fibrillation; and TTR, time in the therapeutic range.

Poli D et al. Circulation, 2011

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

Twelve-month outcomes and predictors of very stable INR control in prevalent warfarin users

D. M. WITT,*†‡ T. DELATE,†‡ N. P. CLARK,*† C. MARTELL,† T. TRAN,† M. A. CROWTHER,§ D. A. GARCIA,¶ W. AGENO** and E. M. HYLEK†† ON BEHALF OF THE WARPED CONSORTIUM[1]

Table 3 Predictors of stable INR control status (c-statistic = 0.69)

Predictor	Adjusted odds ratio	95% CI
Age		
>70 years	1.93	1.56–2.38
≤70 years	–	–
Sex		
Female	–	–
Male	1.44	1.16–1.78
INR target		
2.0	2.80	1.83–4.28
2.5	–	–
≥3.0	0.28	0.17–0.47

JTH, 2010

Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall

Brian F. Gage, MD, MSc,[a] Elena Birman–Deych, MS,[a] Roger Kerzner, MD,[b] Martha J. Radford, MD,[c] David S. Nilasena, MD, MSPH, MS,[d] Michael W. Rich, MD[b]

Table 2 Rates of intracranial hemorrhage, stratified by cohort

	Intracranial hemorrhage rate (95% CI) per 100 patient-years	
Intracranial hemorrhage type	High-fall-risk patients (n = 1245)	Other patients (n = 18 261)
Traumatic	2.0 (1.3–3.1)*	0.34 (0.27–0.45)
Nontraumatic	0.7 (0.4–1.5)	0.8 (0.7–0.9)
Total*	2.8 (1.9–4.1)†	1.1 (1.0–1.3)

*$P < 0.0001$ High-fall vs other patients.
†$P = 0.0005$ High-fall vs other patients.

Am J Med, 2005

Original Investigation

Incidence and Determinants of Traumatic Intracranial Bleeding Among Older Veterans Receiving Warfarin for Atrial Fibrillation

John A. Dodson, MD, MPH; Andrew Petrone, MPH; David R. Gagnon, MD, MPH, PhD; Mary E. Tinetti, MD; Harlan M. Krumholz, MD, MS; J. Michael Gaziano, MD, MPH

31951 pt ≥ 75 years on VKA for atrial fibrillation

98.1% males

Mean age 81.1 years

TTR<60% 55.9% of patients

JAMA Cardiol, 2016

Table 2. Unadjusted and Adjusted Models

Variable	Hazard Ratio (95% CI)	
	Unadjusted	Adjusted[a]
Dementia	2.11 (1.53-2.92)[b]	1.76 (1.26-2.46)[b]
Arthritis	0.98 (0.81-1.18)	0.91 (0.75-1.10)
Fall within the past year	1.72 (1.21-2.44)[b]	1.32 (0.88-1.98)
Visual impairment	1.09 (0.92-1.30)	1.03 (0.86-1.23)
Anemia	1.35 (1.10-1.65)[b]	1.23 (1.00-1.52)[c]
Dizziness	1.43 (0.93-2.19)	1.22 (0.79-1.87)
Diabetes mellitus	1.04 (0.87-1.24)	0.98 (0.81-1.18)
Depression	1.49 (1.22-1.82)[b]	1.30 (1.05-1.61)[c]
Body mass index <20[d]	1.07 (0.63-1.83)	1.12 (0.67-1.88)
Hypertension	1.17 (0.94-1.46)	1.16 (0.92-1.46)
Abnormal renal or liver function	1.42 (1.00-2.01)	1.32 (0.93-1.89)
Prior stroke	1.24 (0.96-1.60)	1.11 (0.86-1.44)
Prior bleed	0.93 (0.54-1.61)	0.80 (0.46-1.39)
Problem drug or alcohol use	0.48 (0.18-1.29)	0.45 (0.17-1.20)
Polypharmacy, ≥4 medications	1.15 (0.90-1.47)	0.98 (0.75-1.29)
Anxiolytic use	1.33 (1.04-1.70)[c]	1.24 (0.96-1.60)
Antipsychotic use	0.76 (0.48-1.18)	1.02 (0.64-1.61)
Anticonvulsant use	1.30 (1.01-1.69)[c]	1.35 (1.04-1.75)[c]
Antihypertensive use	2.63 (2.06-3.35)[b]	1.15 (0.89-1.49)
INR control		
Moderate	1.02 (0.78-1.34)	1.00 (0.77-1.32)
Labile	1.40 (1.10-1.80)[b]	1.33 (1.04-1.72)[c]

risk factors for traumatic intracranial bleeding

JAMA Cardiol, 2016

Original Investigation

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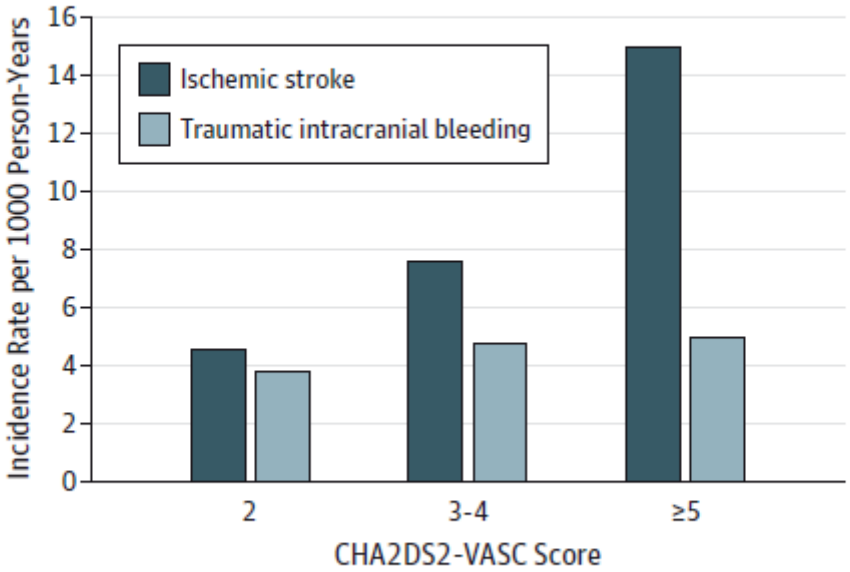
Figure 3. Rate of Traumatic Intracranial Bleeding and Stroke, Stratified by CHA2DS2-VASc Score



JAMA Cardiol, 2016

Original Investigation

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The incidence rate of any intracranial bleeding (traumatic or nontraumatic) was14.58 per1000 pt-yrs.

More than half (57.2%) of the intracranial bleeding events were non traumatic.

Among the 1317 patients who experienced any intracranial bleeding event, 407 (30.9%) had more than 1 episode.

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JAMA Cardiol, 2016

Recurrence of ICH after resumption of anticoagulation with VK antagonists

CHIRONE Study

Table 4 Type of recurrent ICH in relation to the type of index ICH

	Spontaneous recurrent ICH (%)	Posttraumatic recurrent ICH (%)
Spontaneous index ICH (n = 99)	8 (88)[a]	1 (12)
Posttraumatic index ICH (n = 157)	5 (45)	6 (55)
Total	13 (65)	7 (35)

Abbreviation: ICH = intracranial hemorrhage.
[a] $p = 0.07$.

Neurology® 2014;82:1-7

Antithrombotic Treatments for Stroke Prevention in Elderly Patients With Nonvalvular Atrial Fibrillation: Drugs and Doses

Risk of fall

Available data suggest that risk of fall should non be a barrier to use OACs.

Data on outcomes in patients at high risk of fall are insufficient.

There is no standard definition of high risk of fall.

The decision of using OACs should be individualized.

Kilickpap M et al. Canadian J of Cardiol, 2016

Summary of evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation Report of the Guideline Development Subcommittee of the American Academy of Neurology

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Cognitive impairment and risk of fall

D2. Clinicians might offer oral anticoagulation to patients with NVAF who have dementia or occasional falls. However, clinicians should counsel patients or their families that the risk–benefit ratio of oral anticoagulants is uncertain in patients with NVAF who have moderate to severe dementia or very frequent falls (Level B).

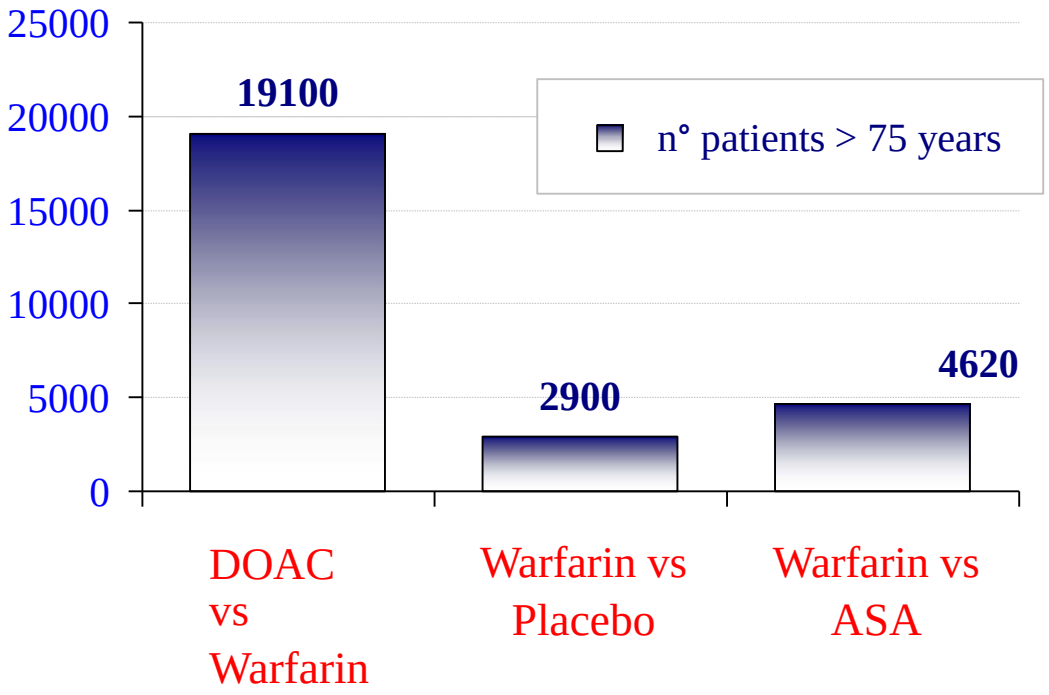
Culebras A et al. Neurology® 2014;82:716–724.

I nuovi anticoagulanti orali

Median age and percentage of patients aged ≥75 years in the trials with new anticoagulants

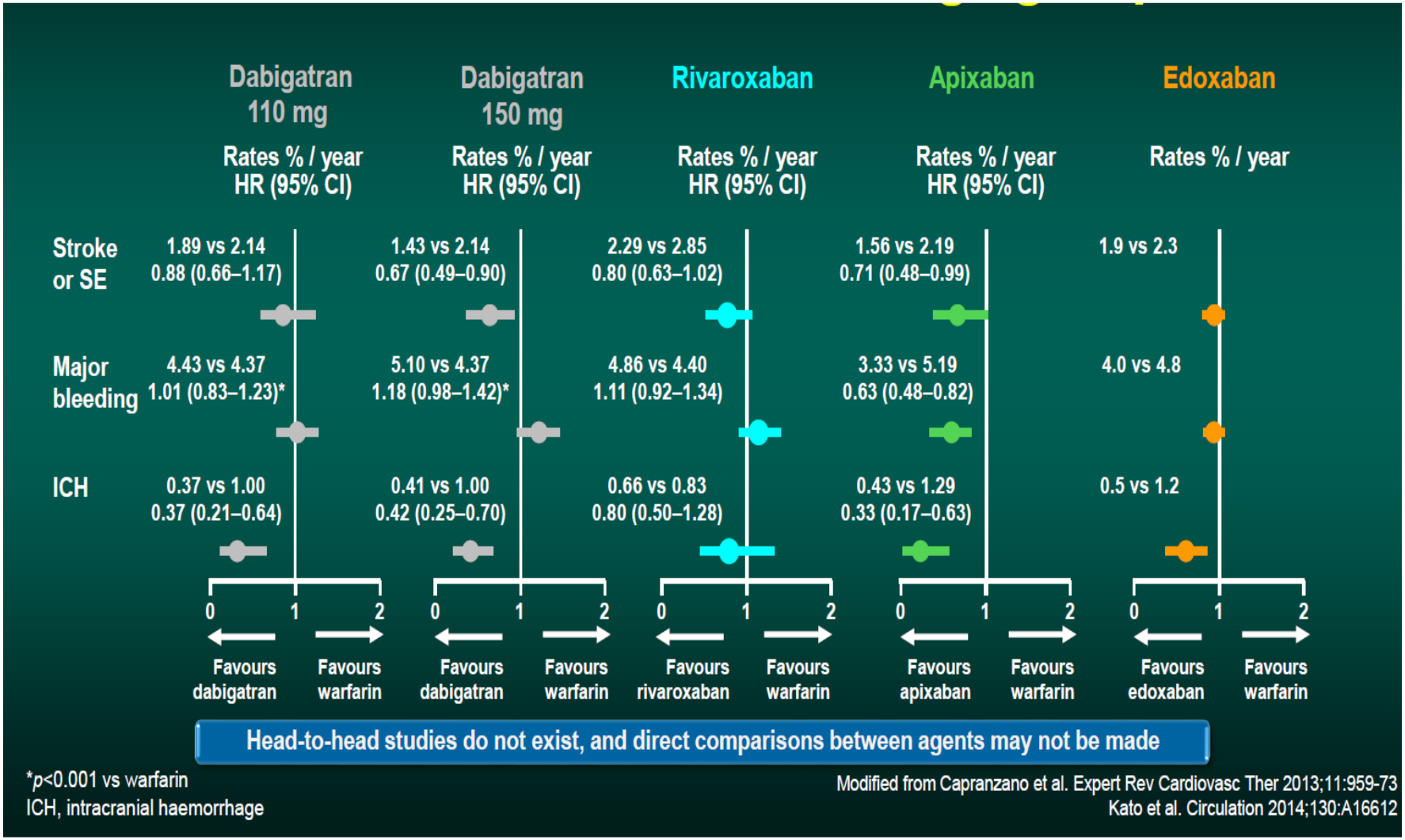
	Tested drug	comparator	Median age (IQR)	% of patiens ≥75 years	Mean $CHADS_2$ score
Re-ly (1)	dabigatran	warfarin	72 (22-97)	40.1	2.1
Rocket AF (2)	rivaroxaban	warfarin	73 (65-78)	43.1	3.5
Aristotle (3)	apixaban	warfarin	70 (63-76)	31.2	2.1
Averroes (4)	Apixaban	aspirin	70±9 (mean±SD)	33.9	2.1

Elderly patients in phase III trials of Atrial Fibrillation



Coppens M et al. CMAJ 2013; 185: 1479-80

Efficacy and safety of NOACs versus warfarin in the ≥75 age group



*p<0.001 vs warfarin
ICH, intracranial haemorrhage

Modified from Capranzano et al. Expert Rev Cardiovasc Ther 2013;11:959-73
Kato et al. Circulation 2014;130:A16612

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

- All of the AF trials confirmed the increased risk of major bleeding among older adults compared with younger.
- The risks of both bleeding and stroke increase with age.
- Older age is the reason often given for not prescribing anticoagulants for individuals aged over 80 years.
- Given the high risk for ischaemic stroke, anticoagulant therapy offers net clinical benefit for older adults, including those at risk of falls.
- Compared with VKAs, all of the NOACs reduced the incidence of ICH.

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

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

E il paziente >90 anni?

JAMA Internal Medicine | Original Investigation

Risk of Bleeding and Thrombosis in Patients 70 Years or Older Using Vitamin K Antagonists

Hilde A. M. Kooistra, PhD; Agneta H. Calf, MD; Margriet Piersma-Wichers, MD; Hanneke C. Kluin-Nelemans, PhD; Gerbrand J. Izaks, PhD; Nic J. G. M. Veeger, PhD; Karina Meijer, PhD

Table 2. Clinical End Points

Characteristic	70-79 Years			80-89 Years			≥90 Years		
	Inception Cohort	Long-Term Cohort	Event Rate[a]	Inception Cohort	Long-Term Cohort	Event Rate[a]	Inception Cohort	Long-Term Cohort	Event Rate[a]
Patients, No.	385	719		385	715		385	724	
Observation-years	424	1962		432	1832		365	1404	
Total bleeding events, No. (major bleeding events, No.)	90 (6)	263 (16)	14.8 (0.9)	87 (9)	290 (13)	16.7 (1.0)	93 (4)	227 (16)	18.1 (1.1)
Intracranial	2 (2)	9 (9)	0.5	2 (2)	8 (8)	0.4	1 (1)	4 (4)	0.3

JAMA, August 2016

JAMA Internal Medicine | Original Investigation

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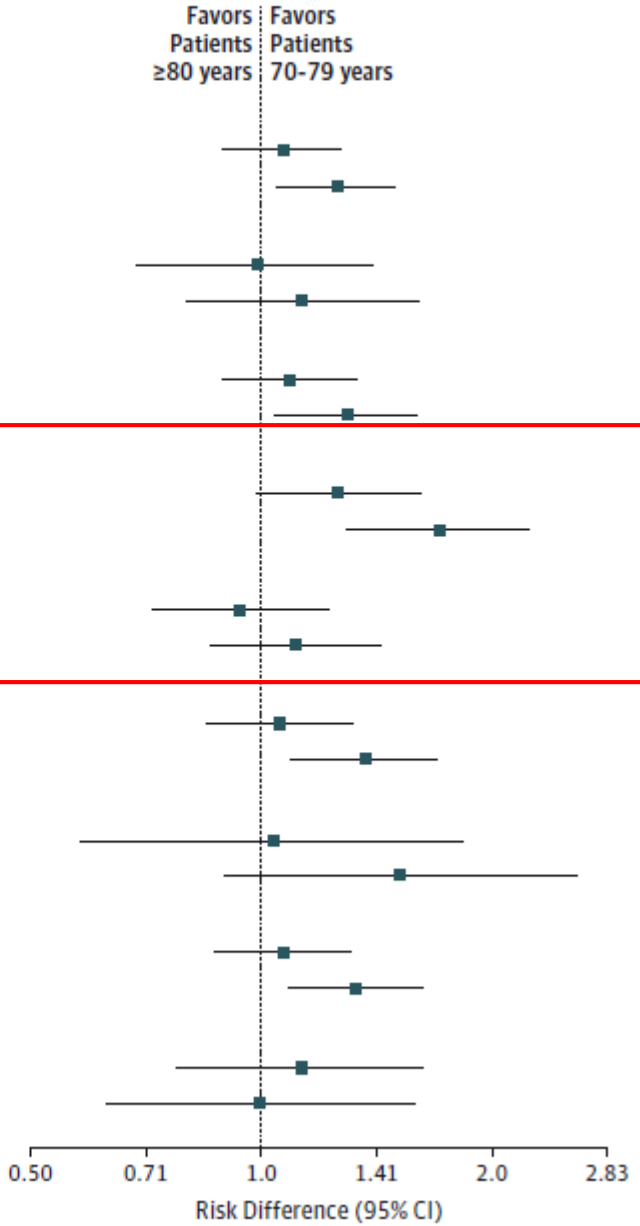
Table 3. Comparison of VKA Control Among Age Groups

Characteristic	Age, y			*P* Value
	70-79	80-89	≥90	
Mean iTTR, %	73.5	71.1	66.4	<.001
Mean time above the therapeutic INR range, %	14.5	15.1	17.4	<.001
Mean time below the therapeutic INR range, %	12.0	13.7	16.2	<.001
Mean INR	2.93	2.90	2.93	.32
Median variability of the INR	0.61	0.78	1.01	<.001
Mean time between INR measurements, wk	2.6	2.5	2.3	<.001
Mean No. of VKA tablets per day	2.3	1.9	1.6	<.001

JAMA, August 2016

Figure 2. Subgroup Analysis of Relative Risk of Bleeding for Patients Aged 80 to 89 Years and 90 Years or Older vs Patients Aged 70 to 79 Years

		No. of Bleeding Events	HR (95% CI)
Total cohort	70-79 y	239	Reference
	80-89 y	242	1.07 (0.89-1.27)
	≥90 y	232	1.26 (1.05-1.50)
Inception cohort	70-79 y	62	Reference
	80-89 y	63	0.99 (0.69-1.40)
	≥90 y	63	1.13 (0.80-1.61)
Long-term cohort	70-79 y	177	Reference
	80-89 y	179	1.09 (0.89-1.34)
	≥90 y	169	1.30 (1.05-1.60)
Male	70-79 y	144	Reference
	80-89 y	115	1.26 (0.99-1.61)
	≥90 y	81	1.71 (1.30-2.24)
Female	70-79 y	95	Reference
	80-89 y	127	0.94 (0.72-1.23)
	≥90 y	151	1.11 (0.86-1.43)
Atrial fibrillation	70-79 y	151	Reference
	80-89 y	173	1.06 (0.85-1.32)
	≥90 y	177	1.37 (1.10-1.70)
Venous embolism	70-79 y	26	Reference
	80-89 y	21	1.04 (0.58-1.84)
	≥90 y	31	1.52 (0.90-2.57)
Therapeutic INR range 2.0-3.5	70-79 y	174	Reference
	80-89 y	190	1.07 (0.87-1.31)
	≥90 y	208	1.33 (1.09-1.63)
Therapeutic INR range 2.5-4.0	70-79 y	65	Reference
	80-89 y	52	1.13 (0.78-1.63)
	≥90 y	24	1.00 (0.63-1.59)



JAMA, August 2016

Gender differences of bleeding and stroke risk in very Old atrial fibrillation patients on VKA treatment
Results of the EPICA study on the behalf of FCSA (Italian Federation of Anticoagulation Clinics)

Daniela Poli [a,*], Emilia Antonucci [b], Sophie Testa [c], Walter Ageno [d], Gualtiero Palareti [e] and on the behalf of FCSA (Italian Federation of Anticoagulation Clinics) [1]

Table 3
Distribution of adverse events in relation to gender.

	Males N (x100 pt-years)	Females N(x100 pt-years)	RR (95%CI)	p value
Major bleedings	75 (2.2)	57 (1.4)	1.6 (1.1–2.3)	0.001
Cerebral bleedings	23 (0.7)	19 (0.5)	1.4 (0.7–2.8)	0.2
GI bleeding	30 (0.9)	21 (0.5)	1.7 (0.9–3.1)	0.06
Fatal Bleedings	13 (0.4)	12 (0.3)	1.3 (0.5–3.1)	0.5
Stroke/TIA	45 (1.3)	67 (1.6)	1.2 (0.8–1.8)	0.25
Death for all causes	125 (3.6)	157 (3.8)	1.0 (0.8–1.3)	0.7

TIA = transient ischemic attack.

VKA treatment and bleeding rate of patients aged older than 90 years.

Results from a prospective multicentre START REGISTER study.

START REGISTER cohort 1

4579 AF patients naïve to anticoagulation.

196 patients aged ≥90 yrs (97 starting treatment a≥90 yrs,

99 patients became ≥90 yrs during follow-up)

Females 125 (63.8%)

Follow-up 187 pt-years

VKA treatment and bleeding rate of patients aged older than 90 years. Results from a prospective multicentre START REGISTER study.

Major Bleedings	7 (rate 4.37 x100 pt/yrs)
ICH	3 (rate 1.64 x100 pt/yrs)
Patients on VKAs	5 (rate 4.42x100 pt/yrs)
	2 ICH
Patients on DOACs	2 (rate 4.24x100 pt/yrs)
	1 ICH

VKA treatment and bleeding rate of patients aged older than 90 years.

Results from a prospective multicentre START REGISTER study.

	N.	Major Bleeding	Rate x 100 pt-yrs
males	67	4	5.5
females	122	3	2.6

Grazie per l'attenzione