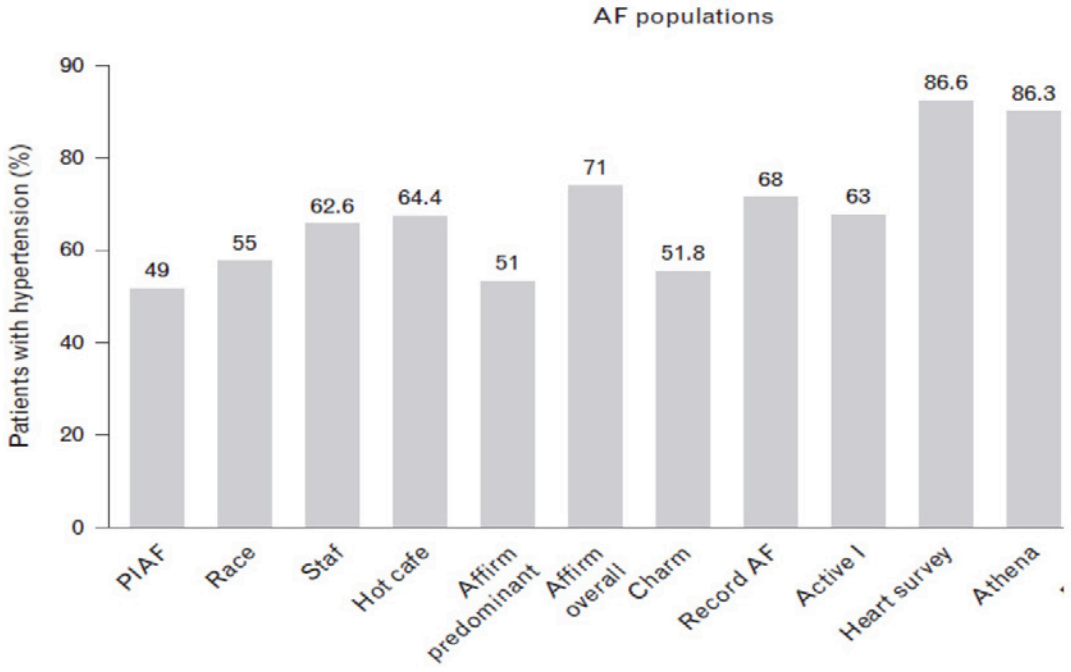
Regione del Veneto
Ospedale Riabilitativo di Alta Specializzazione
O.R.A.S.
Motta di Livenza (Treviso)
Presidente: Prof. Paolo Pauletto

Ipertensione arteriosa e anticoagulazione per via orale

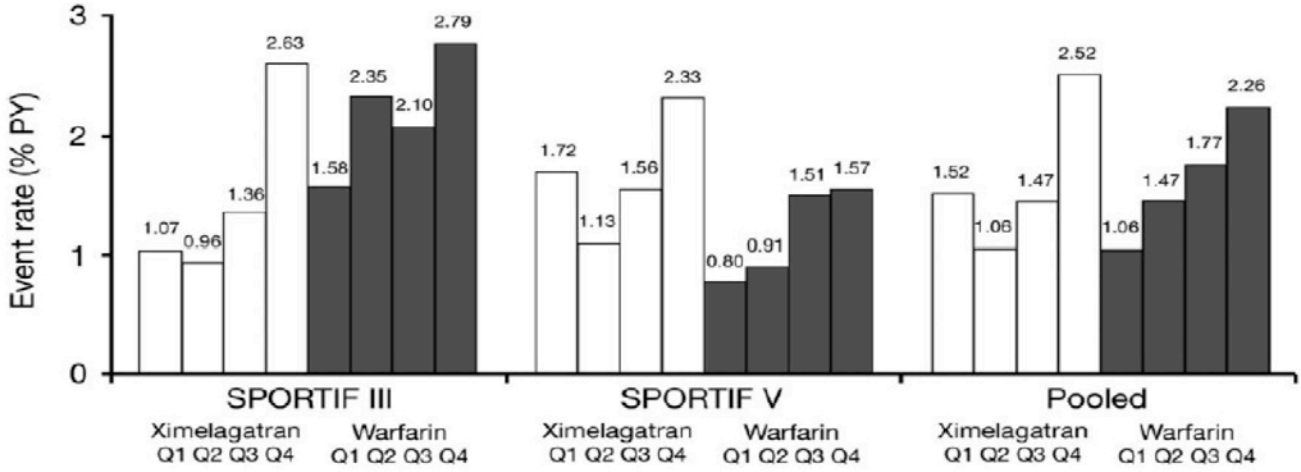
Ipertensione arteriosa, FA e stratificazione del rischio cardioembolico ed emorragico

Prevalence of hypertension in atrial fibrillation trials



Manolis et al, J Hypertens 2011

Rates of stroke/SEE rate in SPORTIF III and V by quartiles of individual patient mean SBP values



SBP quartiles: 84.0–122.6, 122.7–131.3, 131.4–140.7, and 140.8– 191.7 mmHg

European Heart Journal (2007)

Efficacy and safety results by pulse pressure quartiles (mean SBP–mean DBP)

Mean pulse pressure: quartile	Event rate[a] (per PY)			
	Stroke/SEE	Mortality	Major bleed	ALAT >3 × ULN[b]
10.0–46.7	36/2801 = 1.29%	105/2825 = 3.72%	49/2509 = 1.95%	78/943 = 8.3%
46.8–53.4	39/2816 = 1.38%	97/2842 = 3.41%	45/2530 = 1.78%	47/939 = 5.0%
53.5–60.7	36/2828 = 1.27%	90/2847 = 3.16%	57/2491 = 2.29%	50/872 = 5.7%
60.8–110.0	73/2788 = 2.62%	104/2832 = 3.67%	66/2424 = 2.72%	49/910 = 5.4%

[a]Pooled analysis over treatments (except for ALAT) and studies SPORTIF III and V.
[b]Ximelagatran patients only; rates per patient (not per year).

European Heart Journal (2007)

$CHADS_2$ e CHA_2DS_2VASc score

CHADS2 Risk	Score
CHF	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2
TOTAL	6

CHA2DS2-VASc Risk	Score
CHF or or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease	1
Age 65-74 y	1
Sex category	1
TOTAL	10

HAS-BLED Score

Hypertension	1
Abnormal renal or liver function	1 (each)
Stroke history	1
Bleeding history	1
Labile INR	1
Elderly (> 65 years)	1
Drugs or alcohol	1 (each)
TOTAL	9

The HAS-BLED indicates the risk of bleeding
per se it does not containdicate anticoagulation

Journal of Thrombosis and Haemostasis, **9**: 39–48 DOI: 10.1111/j.1538-7836.2010.04085.x

A comparison of risk stratification schemes for stroke in 79 884 atrial fibrillation patients in general practice

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Highlight

The CHA_2DS_2-VASc does not replace $CHADS_2$, it does complement it:

- Where patients have a $CHADS_2 \geq 2$ the decision is to anticoagulate
- Where patients have a $CHADS_2$ of 0-1, the CHA_2DS_2-VASc may help to discriminate
  (i.e., CHA_2DS_2-VASc scores 0 do not need anticoagulation;
  CHA_2DS_2-VASc scores ≥ 1 may need anticoagulation)
- The scheme's predictive ability is poor, with a C statistic of 0.606

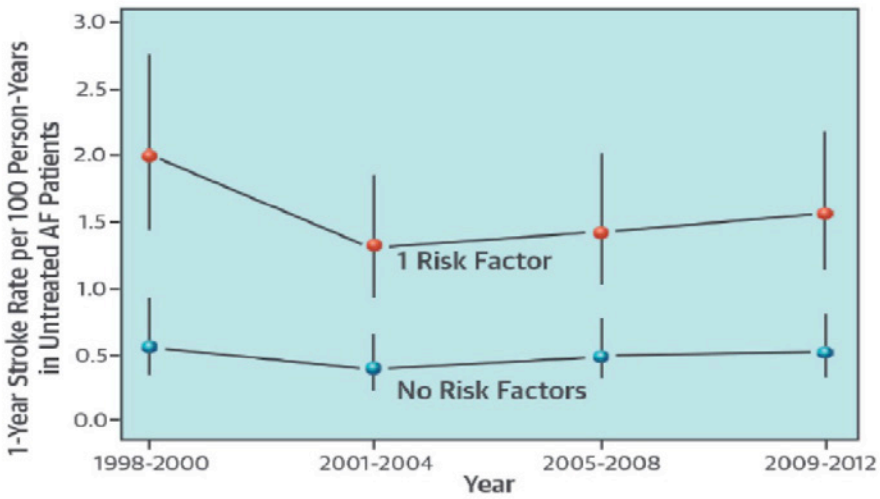
No consensus on how best to treat these patients

Low-risk patients
(CHA_2DS_2VASc = 0 [male], 1 [female])

vs

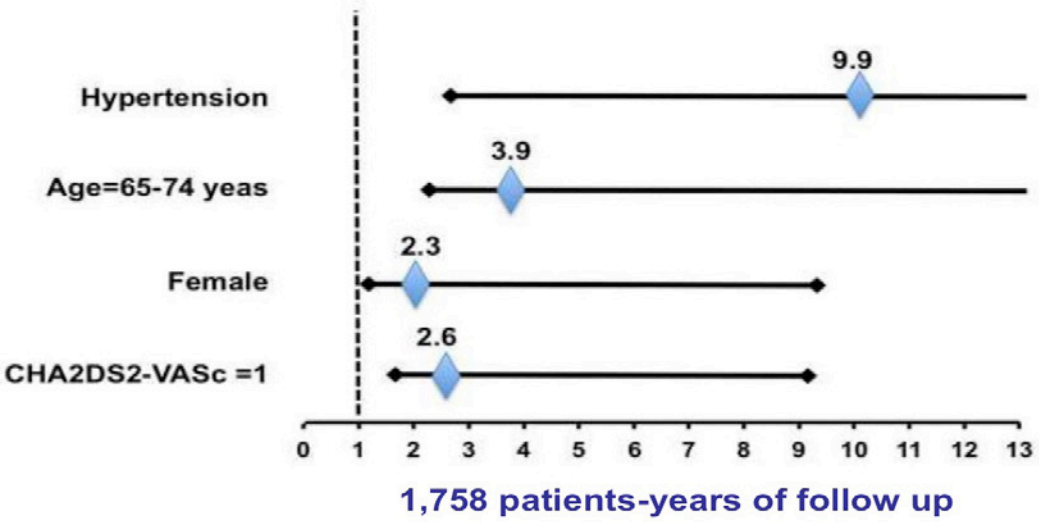
1 additional stroke risk factor
(CHA_2DS_2VASc = 1 [male], = 2 [female])

1-year stroke rates per 100 person-years in untreated AF patients and 0 or 1 stroke risk factors: data from 39,400 patients from Danish cohorts



G.Y.H. Lip et al., JACC 2015

Ischemic stroke in 9,727 AF patients and no antithrombotic therapy: individual components of CHA_2DS_2VASc 1



Duo Huang, PACE (2014; 37:1442-1447)

Oral Anticoagulation, Aspirin, or No Therapy in Patients With Nonvalvular AF With 0 or 1 Stroke Risk Factor Based on the CHA_2DS_2-VASc Score

Gregory Y.H. Lip, MD,*† Flemming Skjøth, MSc, PhD,*‡ Lars Hvilsted Rasmussen, MD, PhD,* Torben Bjerregaard Larsen, MD, PhD*‡

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Should Atrial Fibrillation Patients With Only 1 Nongender-Related CHA_2DS_2-VASc Risk Factor Be Anticoagulated?

Laurent Fauchier, MD, PhD; Nicolas Clementy, MD; Arnaud Bisson, MD; Fabrice Ivanes, MD, PhD; Denis Angoulvant, MD, PhD; Dominique Babuty, MD, PhD; Gregory Y.H. Lip, MD

(*Stroke*. 2016;47:1831-1836. DOI: 10.1161/STROKEAHA.116.013253.)

Refinement of Ischemic Stroke Risk in Patients with Atrial Fibrillation and CHA_2DS_2-VASc Score of 1

DUO HUANG, M.B.B.S.,*,† LUO ANGUO, M.B.B.S.,*,‡ WEN-SHENG YUE, B.Sc.,*,† LIXUE YIN, M.D.,‡ HUNG-FAT TSE, M.D., PH.D.,* and CHUNG-WAH SIU, M.D.*
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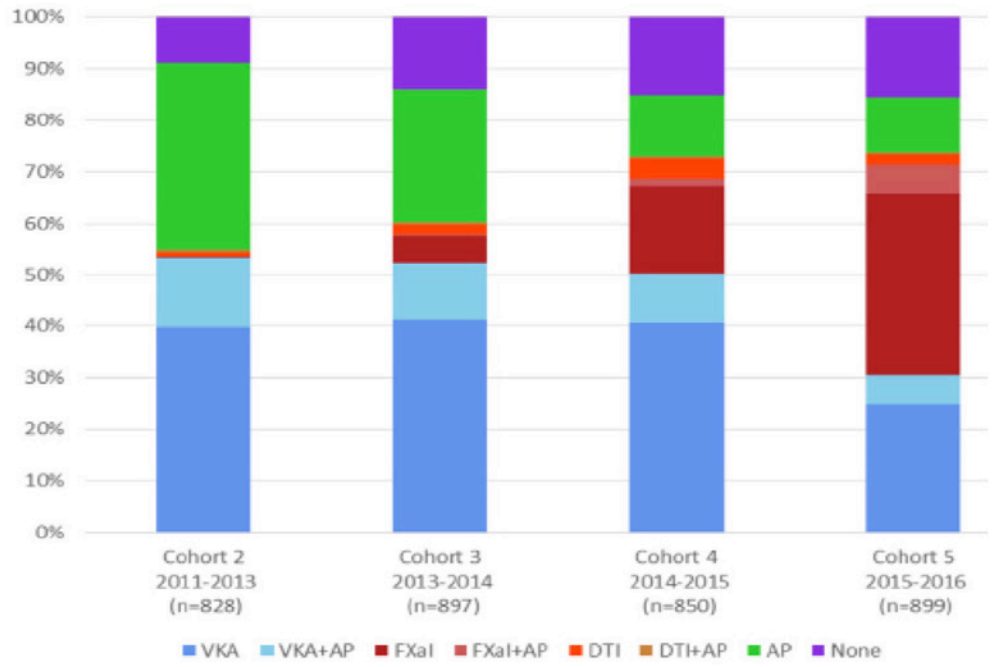
PACE (2014; 37:1442-1447)

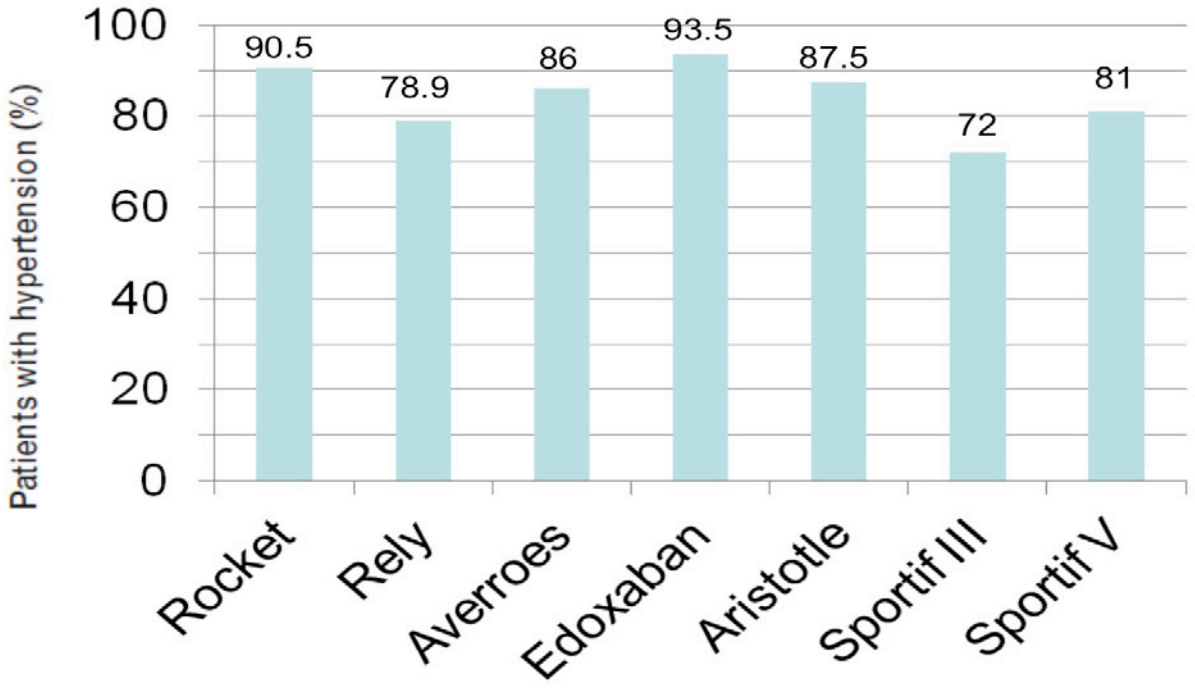
Trattamento con DOACs nei pazienti ipertesi: cosa emerge dai trials clinici ?

Antithrombotic treatment at diagnosis by Cohort
C2=2011-2013, C3=2013-2014, C4=2014-2015, C5=2015-2016



Apenteng PN, et al. BMJ 2018 – The GARFIELD-AF Registry

Trials testing DOACs in atrial fibrillation: focus on blood pressure



Comparison of Characteristics and Outcomes of *Dabigatran* Versus *Warfarin* in Hypertensive Patients With Atrial Fibrillation (from the RE-LY Trial)

Rangadham Nagarakanti, MD[a,b], Lars Wallentin, MD, PhD[c], Herbert Noack, PhD[d], Martina Brueckmann, MD[d,e], Paul Reilly, PhD[f], Andreas Clemens, MD[d,g], Stuart J. Connolly, MD[h], Salim Yusuf, MD, DPhil[h], and Michael D. Ezekowitz, MBChB, DPhil[i,j,*]

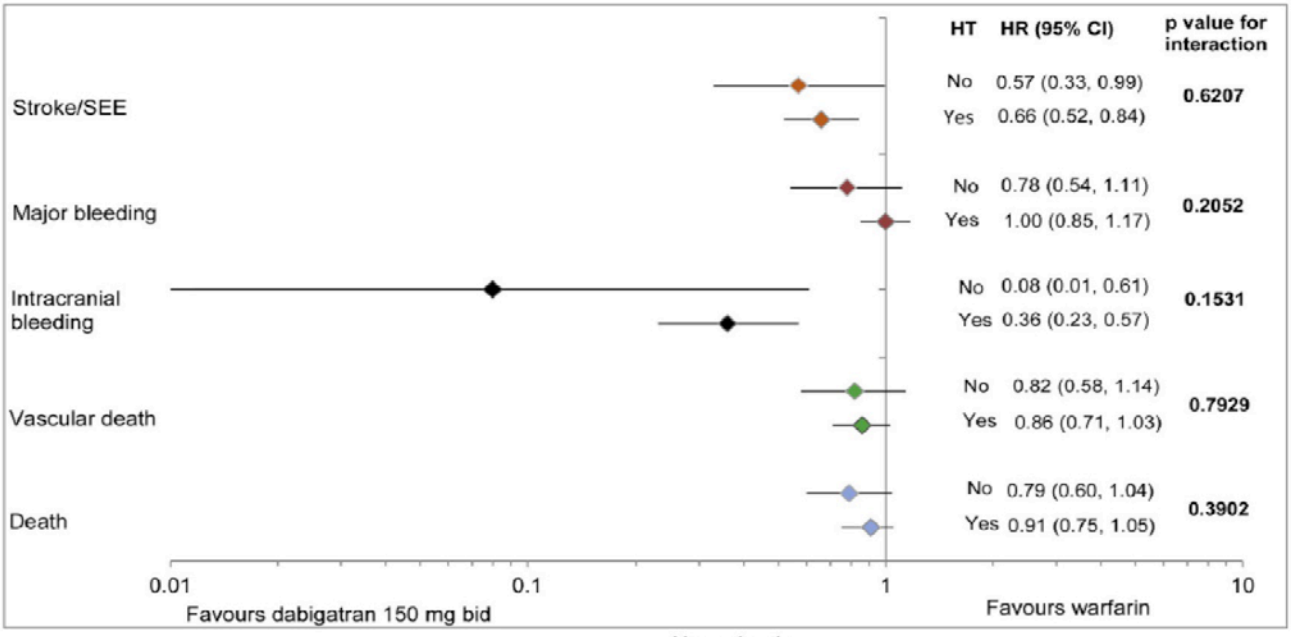
Hypertension is frequent in patients with atrial fibrillation (AF) and is an independent risk factor for stroke. The Randomized Evaluation of Long Term Anticoagulant TherapY (RE-LY) trial found dabigatran 110 mg (D110) and 150 mg twice daily (D150) noninferior or superior to warfarin for stroke reduction in patients with AF, with either a reduction (D110) or similar rates (D150) of major bleeding. Baseline characteristics and outcomes were compared in patients with and without hypertension. The quality of blood pressure control was also assessed. In RE-LY, 14,283 patients (78.9%) had hypertension. The mean blood pressure at baseline was 132.6 ± 17.6/77.7 ± 10.6 and 124.8 ± 16.7/74.6 ± 10.0 mm Hg for patients with and without hypertension, respectively. More patients with hypertension were diabetic (25.6% vs 14.8%, p <0.001), women (38.6% vs 28.3%, p <0.001), and had greater $CHADS_2$ (2.3 vs 1.4, p <0.001) and CHA_2DS_2-VASc scores (3.8 vs 2.8, p <0.001). Mean blood pressure in all treatment arms in hypertensive patients was similar (130 ± 18/76 ± 11 mm Hg) during the trial. The efficacy and safety of D110 and D150 compared to warfarin were similar (p = nonsignificant) in hypertensive (stroke/systemic embolism rate of 1.47%, 1.20%, and 1.81% and major bleed rate of 2.89%, 3.70%, and 3.69% in the D110, D150, and W, respectively) and normotensive patients (stroke/systemic embolism rate of 1.79%, 0.78%, and 1.36% and major bleed rate of 2.84%, 2.37%, and 3.03% per year in the D110, D150, and W, respectively). Hypertensive patients had more major bleeds (3.39% vs 2.76%; p = 0.007). Intracranial bleeds were similar (0.47% vs 0.31%; p = 0.12). In conclusion, patients with hypertension in RE-LY were more likely female, diabetic, with a greater $CHADS_2$ and CHA_2DS_2-VASc scores. Blood pressure control in RE-LY was excellent. The benefits of dabigatran over warfarin, including a substantial reduction of intracranial hemorrhage, were similar in both hypertensive and non-hypertensive patients. (Am J Cardiol 2015;116:1204–1209)

RE-LY: baseline characteristics in patients with or without hypertension

	Hypertension†		p value
	Present n=14,283 (78.9%)	Absent n =3830 (21.1%)	
Mean (SD) age (years)	71.6 (8.1)	70.9 (10.5)	ns
Diabetes mellitus	25.6%	14.8%	< 0.001
Sex, % Female	38.6	28.3	<0.001
AF type			
Persistent	4545 (31.8%)	1244 (32.5%)	
Paroxysmal	4767 (33.4%)	1176 (30.7%)	
Permanent	4968 (34.8%)	1407 (36.7%)	
Mean (SD) blood pressure (mmHg)			
Systolic	132.6 (17.6)	124.8 (16.7)	<0.001
Diastolic	77.7 (10.6)	74.6 (10.0)	<0.001
Median CrCl,(mL/min)	68.5	67.5	ns
Mean (SD) baseline $CHADS_2$*	2.3 (1.1)	1.4 (0.9)	<0.001
Mean (SD) baseline CHA_2DS_2-VASc*	3.8 (1.4)	2.8 (1.2)	<0.001
Mean (SD) baseline HASBLED	1.3 (1.0)	1.3 (1.0)	ns
Heart failure	30.7%	36.9%	<0.001
Prior stroke/SEE/TIA, %	21.2	24.3	<0.001

R. Nagarakanti et al, Am J Cardiol 2015

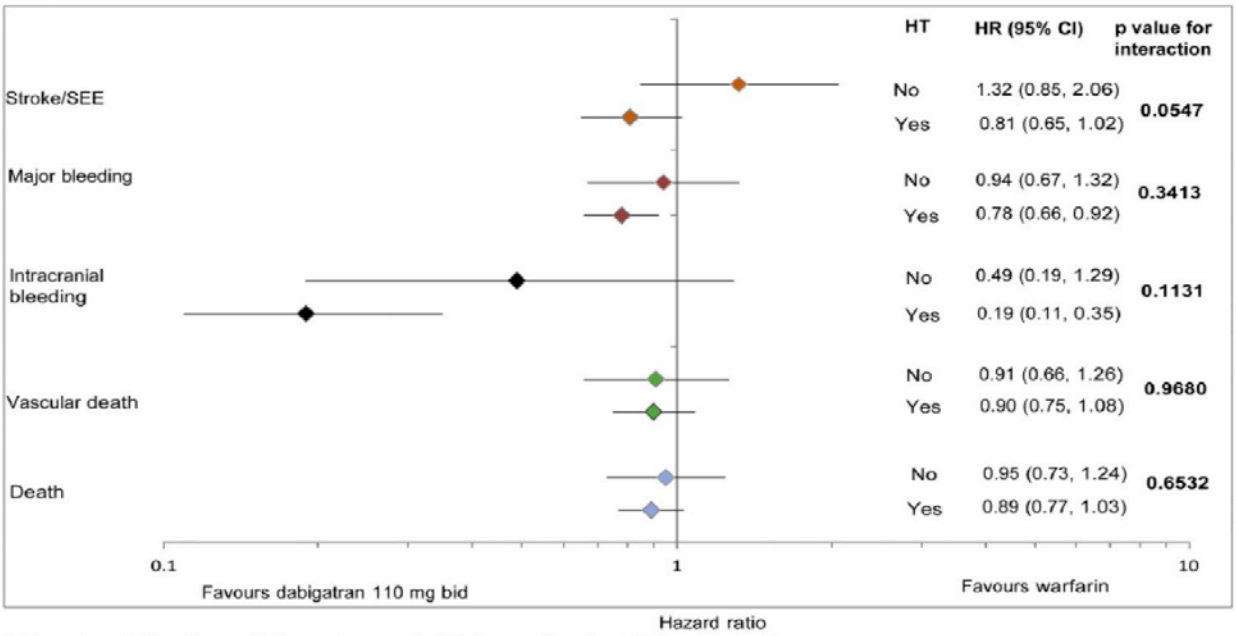
RE-LY: HR of efficacy and safety for Dabigatran 150 mg b.i.d. versus warfarin in patients with or without hypertension



bid, twice daily; CI, confidence interval; HR, hazard ratio; HT, hypertension.

R. Nagarakanti et al, Am J Cardiol 2015

RE-LY: HR of efficacy and safety for Dabigatran 110 mg b.i.d. versus warfarin in patients with or without hypertension



bid, twice daily; CI, confidence interval; HR, hazard ratio; HT, hypertension.

Major bleeding and ICH based on safety interval (from the first to last dose þ 6 days), all other end points based on ITT interval (from randomization until study end).

R. Nagarakanti et al, Am J Cardiol 2015

Blood Pressure Control and Risk of Stroke or Systemic Embolism in Patients With Atrial Fibrillation: Results From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial

Meena P. Rao, MD, MPH; Sigrun Halvorsen, MD, PhD; Daniel Wojdyla, MS; Laine Thomas, PhD; John H. Alexander, MD, MHS; Elaine M. Hylek, MD, MPH; Michael Hanna, MD; M. Cecilia Bahit, MD; Renato D. Lopes, MD, PhD; Raffaele De Caterina, MD, PhD; Cetin Erol, MD; Shinya Goto, MD, PhD; Fernando Lanas, MD; Basil S. Lewis, MD; Steen Husted, MD, DSc; Bernard J. Gersh, MB, ChB, DPhil; Lars Wallentin, MD, PhD; Christopher B. Granger, MD; on behalf of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Steering Committee and Investigators

Background—Patients with atrial fibrillation (AF) and hypertension are at high risk for stroke. Previous studies have shown elevated risk of stroke in patients with AF who have a history of hypertension (regardless of blood pressure [BP] control) and in patients with elevated BP. We assessed the association of hypertension and BP control on clinical outcomes.

Methods and Results—In ARISTOTLE (n=18 201), BP was evaluated as history of hypertension requiring treatment and elevated BP (systolic ≥140 and/or diastolic ≥90 mm Hg) at study entry and any point during the trial. Hazard ratios (HRs) were derived from Cox proportional hazards models including BP as a time-dependent covariate. A total of 15 916 (87.5%) patients had a history of hypertension requiring treatment. In patients with elevated BP measurement at any point during the trial, the rate of stroke or systemic embolism was significantly higher (HR, 1.53; 95% confidence interval [CI], 1.25–1.86), as was hemorrhagic stroke (HR 1.85; 95% CI, 1.26–2.72) and ischemic stroke (HR, 1.50; 95% CI, 1.18–1.90). Rates of major bleeding were lower in patients with a history of hypertension (HR, 0.80; 95% CI, 0.66–0.98) and nonsignificantly lower in patients with elevated BP at study entry (HR, 0.89; 95% CI, 0.77–1.03). The benefit of apixaban versus warfarin on preventing stroke or systemic embolism was consistent among patients with and without a history of hypertension (*P* interaction=0.27), BP control at baseline (*P* interaction=0.43), and BP control during the trial (*P* interaction=0.97).

Conclusions—High BP measurement at any point during the trial was independently associated with a substantially higher risk of stroke or systemic embolism. These results strongly support efforts to treat elevated BP as an important strategy to optimally lower risk of stroke in patients with AF.

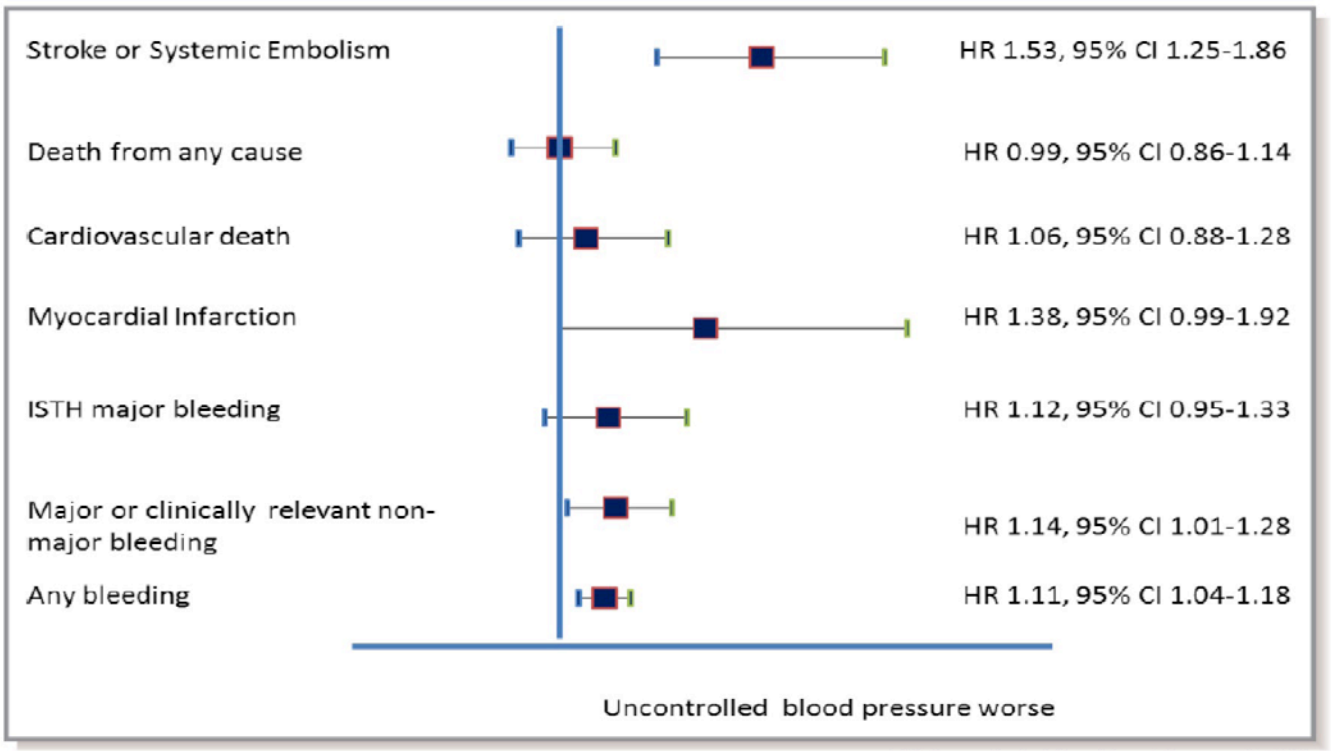
Clinical Trial Registration—URL: https://ClinicalTrials.gov/. Unique identifier: NCT00412984. (***J Am Heart Assoc.*** **2015;4: e002015 doi: 10.1161/JAHA.115.002015)**

ARISTOTLE: Baseline Characteristics According to History of HTN at Study Entry

	History of HTN (n=15 916)	No History of HTN (n=2285)	*P* Value*
CHA_2DS_2-VASc, mean (SD)	3.5 (1.52)	2.7 (1.24)	<0.0001
CHA_2DS_2-VASc score, no. (%)			<0.0001
0–2	4288 (26.9)	1087 (47.6)	
3–5	9940 (62.5)	1152 (50.4)	
>5	1688 (10.6)	46 (2.0)	
HAS-BLED, mean (SD)	1.8 (1.05)	1.7 (1.05)	0.2401

MP Rao et al, J Am Heart Assoc. 2015

ARISTOTLE: adjusted HRs for the association between elevated blood pressure at any point during the trial and efficacy and safety endpoints



MP Rao et al, J Am Heart Assoc. (2015)

ARISTOTLE: Apixaban 5 mg b.i.d. vs Warfarin and outcomes by history of hypertension at baseline

	History of Hypertension			No History of Hypertension			Interaction *P* Value
	Apixaban Rate* (n)	Warfarin Rate* (n)	HR (95% CI)	Apixaban Rate* (n)	Warfarin Rate* (n)	HR (95% CI)	
Efficacy endpoints							
Stroke/SE	1.31 (191)	1.59 (231)	0.82 (0.68–0.10)	0.99 (21)	1.67 (34)	0.60 (0.35–1.02)	0.27
Ischemic/uncertain type of stroke	1.00 (146)	1.04 (151)	0.96 (0.77–1.21)	0.75 (16)	1.17 (24)	0.64 (0.34–1.21)	0.24
Hemorrhagic stroke	0.24 (36)	0.48 (70)	0.51 (0.34–0.76)	0.19 (4)	0.39 (8)	0.49 (0.15–1.61)	0.93
Death from any cause	3.38 (505)	3.77 (562)	0.90 (0.79–1.01)	4.53 (98)	5.09 (107)	0.89 (0.67–1.17)	0.96
CV death	1.75 (262)	1.91 (285)	0.92 (0.77–1.08)	2.13 (46)	2.81 (59)	0.76 (0.51–1.11)	0.38
MI	0.51 (75)	0.66 (96)	0.78 (0.57–1.05)	0.71 (15)	0.29 (6)	2.44 (0.95–6.28)	0.02
Safety endpoints							
ISTH major bleeding	2.07 (277)	3.00 (394)	0.69 (0.59–0.80)	2.60 (50)	3.73 (68)	0.70 (0.48–1.00)	0.96
Major or CRNM bleeding	4.00 (527)	5.94 (761)	0.68 (0.61–0.76)	4.54 (86)	6.50 (116)	0.70 (0.53–0.93)	0.82
Any bleeding	17.91 (2042)	25.76 (2680)	0.71 (0.67–0.75)	19.29 (314)	26.31 (380)	0.75 (0.64–0.87)	0.55

MP Rao et al, J Am Heart Assoc. (2015)

European Heart Journal (2017) **38**, 860–868
doi:10.1093/eurheartj/ehw069

REVIEW

Prevention

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

Hans-Christoph Diener[1]*, James Aisenberg[2], Jack Ansell[3], Dan Atar[4], Günter Breithardt[5], John Eikelboom[6], Michael D. Ezekowitz[7,8,9], Christopher B. Granger[10], Jonathan L. Halperin[11], Stefan H. Hohnloser[12], Elaine M. Hylek[13], Paulus Kirchhof[14,15], Deirdre A. Lane[16], Freek W.A. Verheugt[17], Roland Veltkamp[18], and Gregory Y.H. Lip[19,20]

Stroke or systemic embolism (% per year) in relation to the presence or absence of hypertension in the four trials comparing DOACs with warfarin

Trial	Drug and dose	Hypertension	No. of patients	NOAC	Warfarin	HR (95% CI)	P-interaction
RE-LY[1]	Dabigatran 110 mg twice daily	Yes	9488	1.46	1.78	0.82[a]	
		No	2549	1.79	1.36	1.31[a]	0.06
	Dabigatran 150 mg twice daily	Yes	9545	1.20	1.78	0.64[a]	
		No	2453	0.78	1.36	0.57[a]	0.58
ROCKET AF[3]	Rivaroxaban 20 mg once daily	Yes	12 801	2.73	3.47	0.79 (0.65–0.97)	
		No	1342	2.18	3.06	0.71 (0.74–1.45)	0.85
ARISTOTLE[2]	Apixaban 5 mg twice daily	Yes	15 916	1.31	1.59	0.82 (0.68–1.00)	
		No	2285	0.99	1.67	0.60 (0.35–1.02)	0.27
ENGAGE AF[4]	Edoxaban 60 mg once daily[b]	Yes	19 754	1.51	1.80	0.84*	
		No	1351	2.49	1.79	1.38*	0.09

HC Diener et al, European Heart Journal 2017

Major bleedings (% per year)* in relation to the presence or absence of hypertension in trials comparing DOACs with Warfarin treatment

Trial	Drug and dose	Hypertension	No. of patients	NOAC	Warfarin	HR (95% CI)	P-interaction
ARISTOTLE[2]	Apixaban 5 mg twice daily[b]	Yes	15 916	2.07	3.00	0.69 (0.59–0.80)	
		No	2285	2.60	3.73	0.70 (0.48–1.00)	0.96
ENGAGE AF[4]	Edoxaban 60 mg once daily[b]	Yes	19 754	2.72	3.42	0.80[a]	
		No	1351	3.17	3.42	0.93[a]	0.68

***defined according to the International Society of Thrombosis and Hemostasis**

HC Diener et al, European Heart Journal 2017

European Heart Journal (2017) **38**, 860–868
doi:10.1093/eurheartj/ehw069

REVIEW

Prevention

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Hans-Christoph Diener[1]*, James Aisenberg[2], Jack Ansell[3], Dan Atar[4], Günter Breithardt[5], John Eikelboom[6], Michael D. Ezekowitz[7,8,9], Christopher B. Granger[10], Jonathan L. Halperin[11], Stefan H. Hohnloser[12], Elaine M. Hylek[13], Paulus Kirchhof[14,15], Deirdre A. Lane[16], Freek W.A. Verheugt[17], Roland Veltkamp[18], and Gregory Y.H. Lip[19,20]

Treatment Suggestions:
Hypertension: no preference for a particular DOAC
CHA_2DS_2VASc = 1 [male], = 2 [female]: Dabigatran/Apixaban

CONCLUSIONI

- L' ipertensione è un fattore di rischio maggiore per insorgenza di FA
- L' ipertensione di per se si accompagna a un aumentato rischio di ictus ischemico ed emorragico
- Fra i pazienti con FA, quelli ipertesi hanno un outcome più sfavorevole
- La presenza di ipertensione in soggetti CHA_2DS_2VASc = 1 [male], = 2 [female] fa propendere per il trattamento anticoagulante
- Gli anticoagulanti diretti (DOACs) offrono vantaggi rispetto alla warfarina
- Non vi sono dati di confronto attendibili su efficacia/sicurezza dei vari DOACs nei pazienti ipertesi