L'utilizzo dei DOACs nella pratica clinica

Prof . Riccardo Raddino

Dipartimento di Specialità medico-chirurgiche, scienze radiologiche e sanità pubblica
Università degli Studi di Brescia
Cattedra e U.O. Cardiologia
Spedali Civili di Brescia

La lettura dei dati attraverso le linee guida ESC

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ESC GUIDELINES

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

An update of the 2010 ESC Guidelines for the management of atrial fibrillation
Developed with the special contribution of the European Heart Rhythm Association

Table 4 Summary of the clinical trials involving novel anticoagulants vs. warfarin for stroke prevention in non-valvular AF

	Dabigatran (RE-LY)[70,71]			Rivaroxaban (ROCKET-AF)[3]		Apixaban (ARISTOTLE)[4]	
Study characteristics							
Study design	Randomized, open-label			Randomized, double-blind		Randomized, double-blind	
Outcomes (% per year)							
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban
	(*n* = 6022)	(*n* = 6076)	(*n* = 6015)	(*n* = 7133)	(*n* = 7131)	(*n* = 9081)	(*n* = 9120)
		(RR, 95% CI; *P* value)	(RR, 95% CI; *P* value)		(HR, 95% CI; *P* value)		(HR, 95% CI; *P* value)
Stroke/systemic embolism	1.69	1.11 (0.66, 0.53–0.82; *P* for superiority <0.001)	1.53 (0.91, 0.74–1.11; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12) (ITT)	1.6	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)
Ischaemic stroke	1.2	0.92 (0.76, 0.60–0.98; *P* = 0.03)	1.34 (1.11, 0.89–1.40; *P* = 0.35)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* =0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)
Major bleeding	3.36	3.11 (0.93, 0.81–1.07; *P* = 0.31)	2.71 (0.80, 0.69–0.93; *P* = 0.003)	3.4	3.6 (*P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)
Intracranial bleeding	0.74	0.30 (0.40, 0.27–0.60; *P* <0.001)	0.23 (0.31, 0.20–0.47; *P* <0.001)	0.7	0.5 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)
Extracranial bleeding	2.67	2.84 (1.07, 0.92–1.25; *P* = 0.38)	2.51 (0.94, 0.80–1.10; *P* = 0.45)	–	–	–	–

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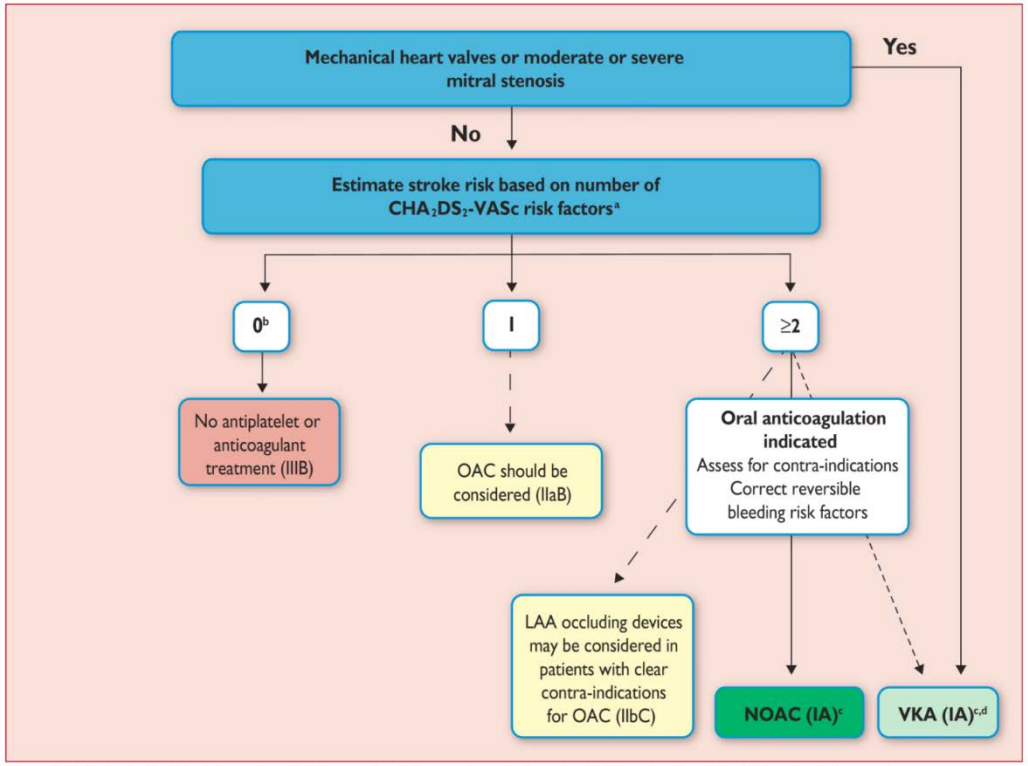
2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)



AF = atrial fibrillation; LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist.
[a]Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, prior Sstroke/TIA/embolus (2 points), Vascular disease, age 65–74 years, female Sex.
[b]Includes women without other stroke risk factors.
[c]IIaB for women with only one additional stroke risk factor.
[d]IB for patients with mechanical heart valves or mitral stenosis.

Figure 8 Stroke prevention in atrial fibrillation.

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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
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

AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; TTR = time in therapeutic range; VKA = vitamin K antagonist.

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

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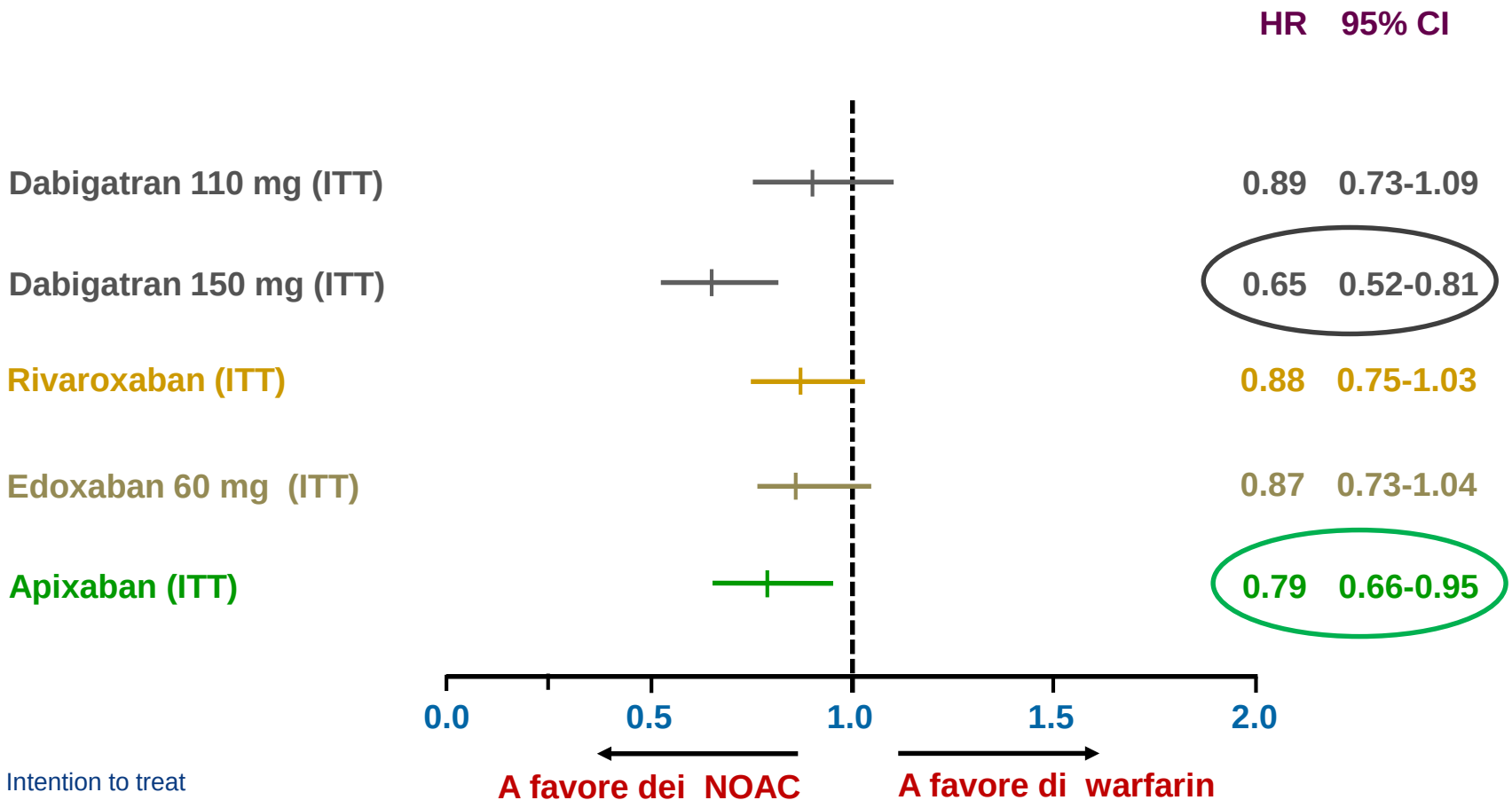
Table 13 Characteristics of approved Non-vitamin K antagonist oral anticoagulants compared

	Dabigatran (RE-LY)			Rivaroxaban (ROCKET-AF)		Apixaban (ARISTOTLE)		Edoxaban (ENGAGE AF-TIMI 48)		
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60	Edoxaban 30
	n = 6022	*n* = 6076	*n* = 6015	*n* = 7133	*n* = 7131	*n* = 9081	*n* = 9120	*n* = 7036	n = 7035	*n* = 7034
	Event rate, %/year	Event rate, %/year (RR vs. warfarin)	Event rate, %/year (RR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; *P* for non-inferiority and superiority <0.001)	1.54 (0.89, 0.73–1.09; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; *P* <0.001 for non-inferiority, *P* = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; *P* = 0.005 for non-inferiority, *P* = 0.10 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P* <0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)	0.47	0.26 (0.54, 0.38–0.77; *P* <0.001)	0.16 (0.33, 0.22–0.50; *P* <0.001)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; *P* = 0.41)	2.92 (0.80, 0.70–0.93; *P* = 0.003)	3.45	3.60 (1.04; 0.90-2.30; *P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)	3.43	2.75 (0.80, 0.71–0.91; *P* <0.001)	1.61 (0.47, 0.41–0.55; *P* <0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P* <0.001)	0.23 (0.29 0.19–0.45; *P* <0.001)	0.74	0.49 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)	0.85	0.39 (0.47, 0.34–0.63; *P* <0.001)	0.26 (0.30, 0.21–0.43; *P* <0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P* <0.001)	1.13 (1.04, 0.82–1.33; *P* = 0.74)	1.24	2.00 (1.61; 1.30-1.99; *P* < 0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P* <0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; *P* = 0.12)	0.82 (1.29, 0.96-1.75; *P* = 0.09)	1.12	0.91 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)	0.75	0.70 (0.94, 0.74–1.19; *P* = 0.60)	0.89 (1.19, 0.95–1.49; *P* = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.21	1.87 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; *P* = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

NOAC *vs.* warfarin: Ictus e ES



ITT Intention to treat

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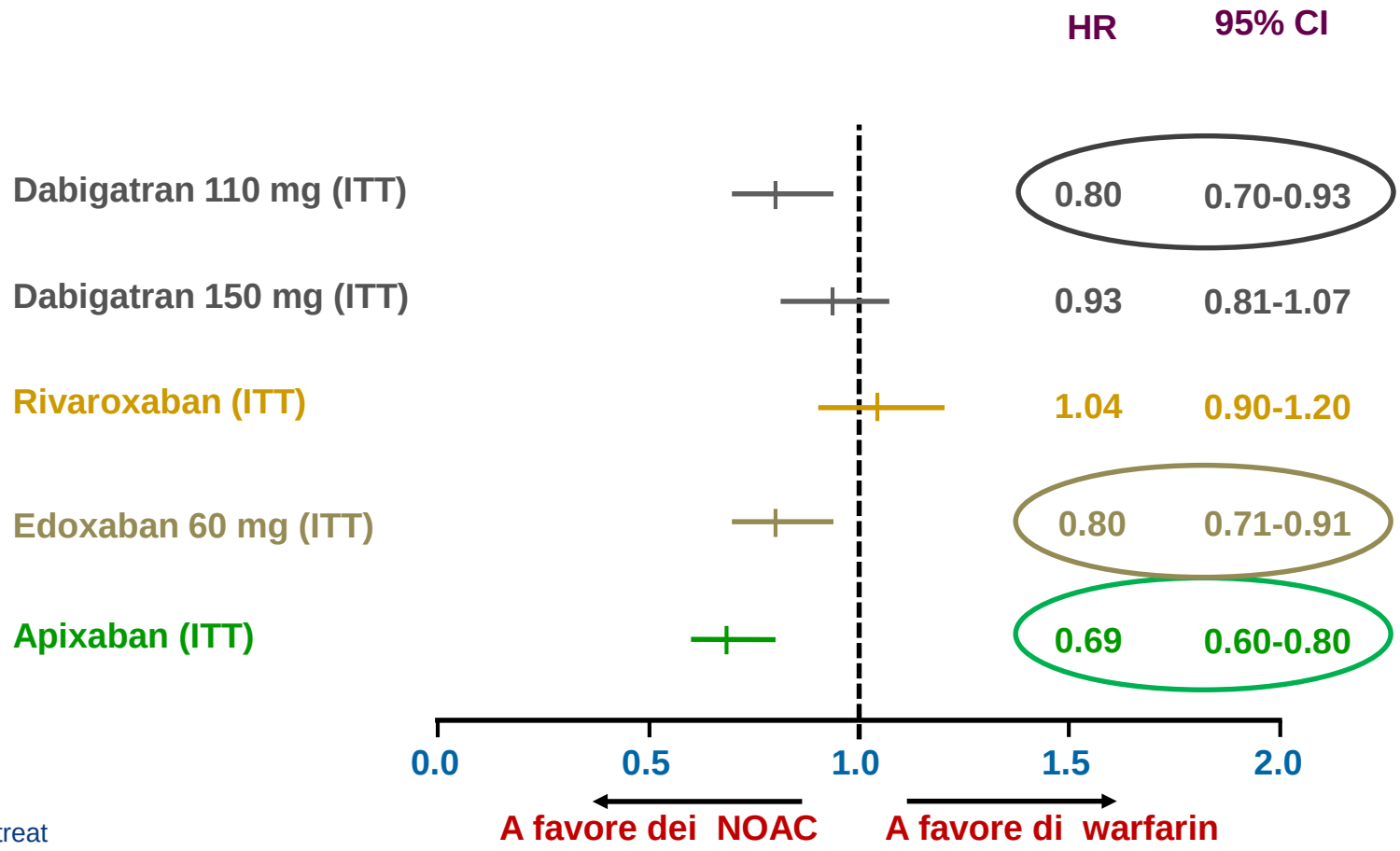
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60	Edoxaban 30
	n = 6022	*n* = 6076	*n* = 6015	*n* = 7133	*n* = 7131	*n* = 9081	*n* = 9120	*n* = 7036	n = 7035	*n* = 7034
	Event rate, %/year	Event rate, %/year (RR vs. warfarin)	Event rate, %/ year (RR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; *P* for non-inferiority and superiority <0.001)	1.54 (0.89, 0.73–1.09; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; *P* <0.001 for non-inferiority, *P* = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; *P* = 0.005 for non-inferiority, *P* = 0.10 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P* <0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)	0.47	0.26 (0.54, 0.38–0.77; *P* <0.001)	0.16 (0.33, 0.22–0.50; *P* <0.001)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; *P* = 0.41)	2.92 (0.80, 0.70–0.93; *P* = 0.003)	3.45	3.60 (1.04; 0.90-2.30; *P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)	3.43	2.75 (0.80, 0.71–0.91; *P* <0.001)	1.61 (0.47, 0.41–0.55; *P* <0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P* <0.001)	0.23 (0.29 0.19–0.45; *P* <0.001)	0.74	0.49 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)	0.85	0.39 (0.47, 0.34–0.63; *P* <0.001)	0.26 (0.30, 0.21–0.43; *P* <0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P* <0.001)	1.13 (1.04, 0.82–1.33; *P* = 0.74)	1.24	2.00 (1.61; 1.30-1.99; *P* < 0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P* <0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; *P* = 0.12)	0.82 (1.29, 0.96-1.75; *P* = 0.09)	1.12	0.91 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)	0.75	0.70 (0.94, 0.74–1.19; *P* = 0.60)	0.89 (1.19, 0.95–1.49; *P* = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.21	1.87 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; *P* = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

NOAC *vs.* warfarin: sanguinamenti maggiori



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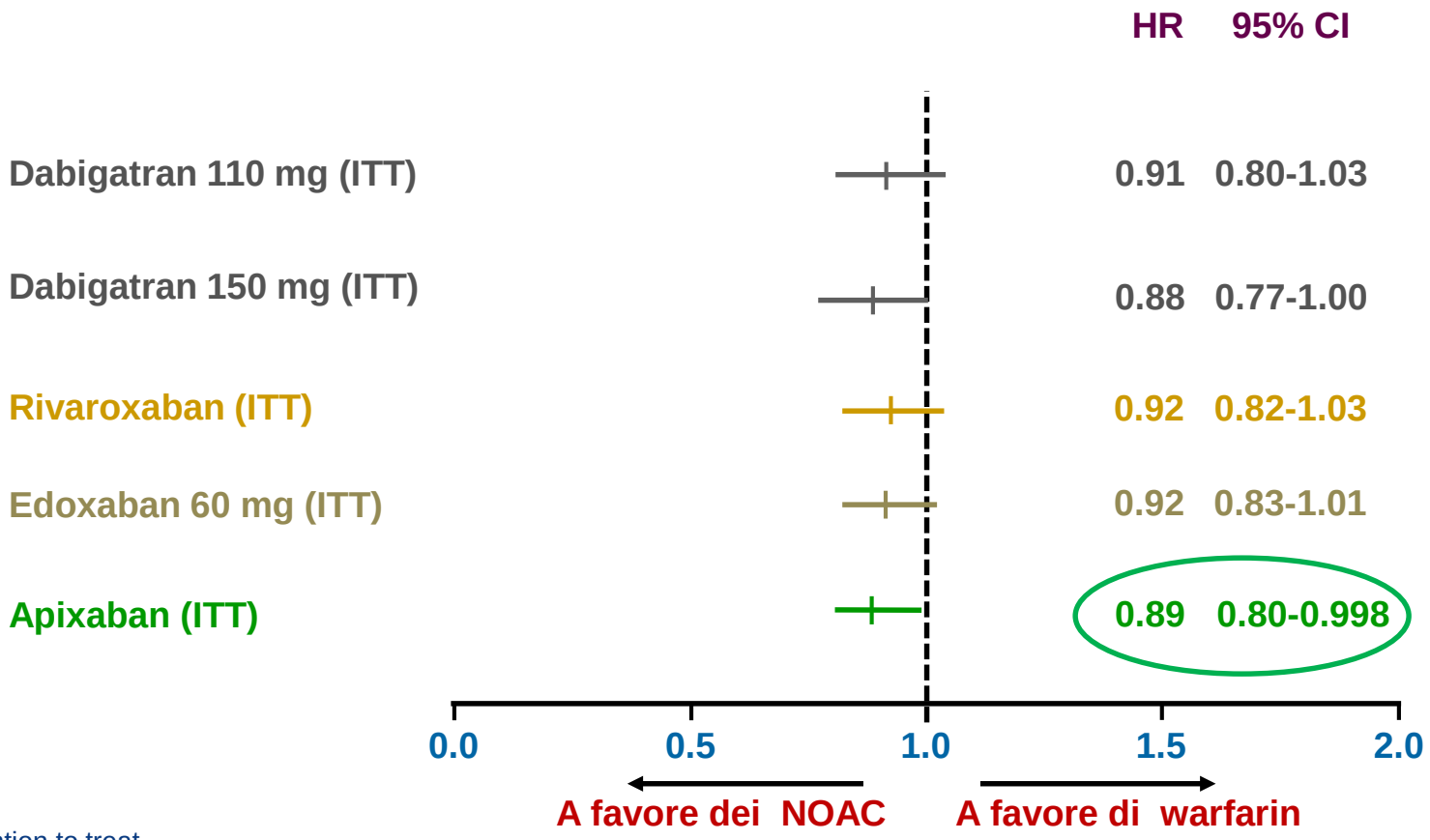
	Event rate, %/year	Event rate, %/year (RR vs. warfarin)	Event rate, %/ year (RR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; *P* for non-inferiority and superiority <0.001)	1.54 (0.89, 0.73–1.09; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; *P* <0.001 for non-inferiority, *P* = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; *P* = 0.005 for non-inferiority, *P* = 0.10 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P* <0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)	0.47	0.26 (0.54, 0.38–0.77; *P* <0.001)	0.16 (0.33, 0.22–0.50; *P* <0.001)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; *P* = 0.41)	2.92 (0.80, 0.70–0.93; *P* = 0.003)	3.45	3.60 (1.04; 0.90-2.30; *P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)	3.43	2.75 (0.80, 0.71–0.91; *P* <0.001)	1.61 (0.47, 0.41–0.55; *P* <0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P* <0.001)	0.23 (0.29 0.19–0.45; *P* <0.001)	0.74	0.49 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)	0.85	0.39 (0.47, 0.34–0.63; *P* <0.001)	0.26 (0.30, 0.21–0.43; *P* <0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P* <0.001)	1.13 (1.04, 0.82–1.33; *P* = 0.74)	1.24	2.00 (1.61; 1.30-1.99; *P* < 0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P* <0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; *P* = 0.12)	0.82 (1.29, 0.96-1.75; *P* = 0.09)	1.12	0.91 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)	0.75	0.70 (0.94, 0.74–1.19; *P* = 0.60)	0.89 (1.19, 0.95–1.49; *P* = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.21	1.87 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; *P* = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

NOAC *vs.* warfarin: mortalità da tutte le cause



ITT Intention to treat

1. Connolly et al. NEJM 2010;363:1875-6, suppl app.
2. Patel et al. NEJM 2011;365:883-91,suppl app.
3. Granger et al. NEJM 2011;365:981-92.

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Table 13 Characteristics of approved Non-vitamin K antagonist oral anticoagulants compared

	Dabigatran (RE-LY)			Rivaroxaban (ROCKET-AF)		Apixaban (ARISTOTLE)		Edoxaban (ENGAGE AF-TIMI 48)		
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60	Edoxaban 30
	n = 6022	*n* = 6076	*n* = 6015	*n* = 7133	*n* = 7131	*n* = 9081	*n* = 9120	*n* = 7036	n = 7035	*n* = 7034
	Event rate, %/year	Event rate, %/year (RR vs. warfarin)	Event rate, %/ year (RR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; *P* for non-inferiority and superiority <0.001)	1.54 (0.89, 0.73–1.09; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; *P* <0.001 for non-inferiority, *P* = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; *P* = 0.005 for non-inferiority, *P* = 0.10 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P* <0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)	0.47	0.26 (0.54, 0.38–0.77; *P* <0.001)	0.16 (0.33, 0.22–0.50; *P* <0.001)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; *P* = 0.41)	2.92 (0.80, 0.70–0.93; *P* = 0.003)	3.45	3.60 (1.04; 0.90-2.30; *P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)	3.43	2.75 (0.80, 0.71–0.91; *P* <0.001)	1.61 (0.47, 0.41–0.55; *P* <0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P* <0.001)	0.23 (0.29 0.19–0.45; *P* <0.001)	0.74	0.49 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)	0.85	0.39 (0.47, 0.34–0.63; *P* <0.001)	0.26 (0.30, 0.21–0.43; *P* <0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P* <0.001)	1.13 (1.04, 0.82–1.33; *P* = 0.74)	1.24	2.00 (1.61; 1.30-1.99; *P* < 0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P* <0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; *P* = 0.12)	0.82 (1.29, 0.96-1.75; *P* = 0.09)	1.12	0.91 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)	0.75	0.70 (0.94, 0.74–1.19; *P* = 0.60)	0.89 (1.19, 0.95–1.49; *P* = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.21	1.87 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; *P* = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

NOAC *vs.* warfarin: Infarto miocardico

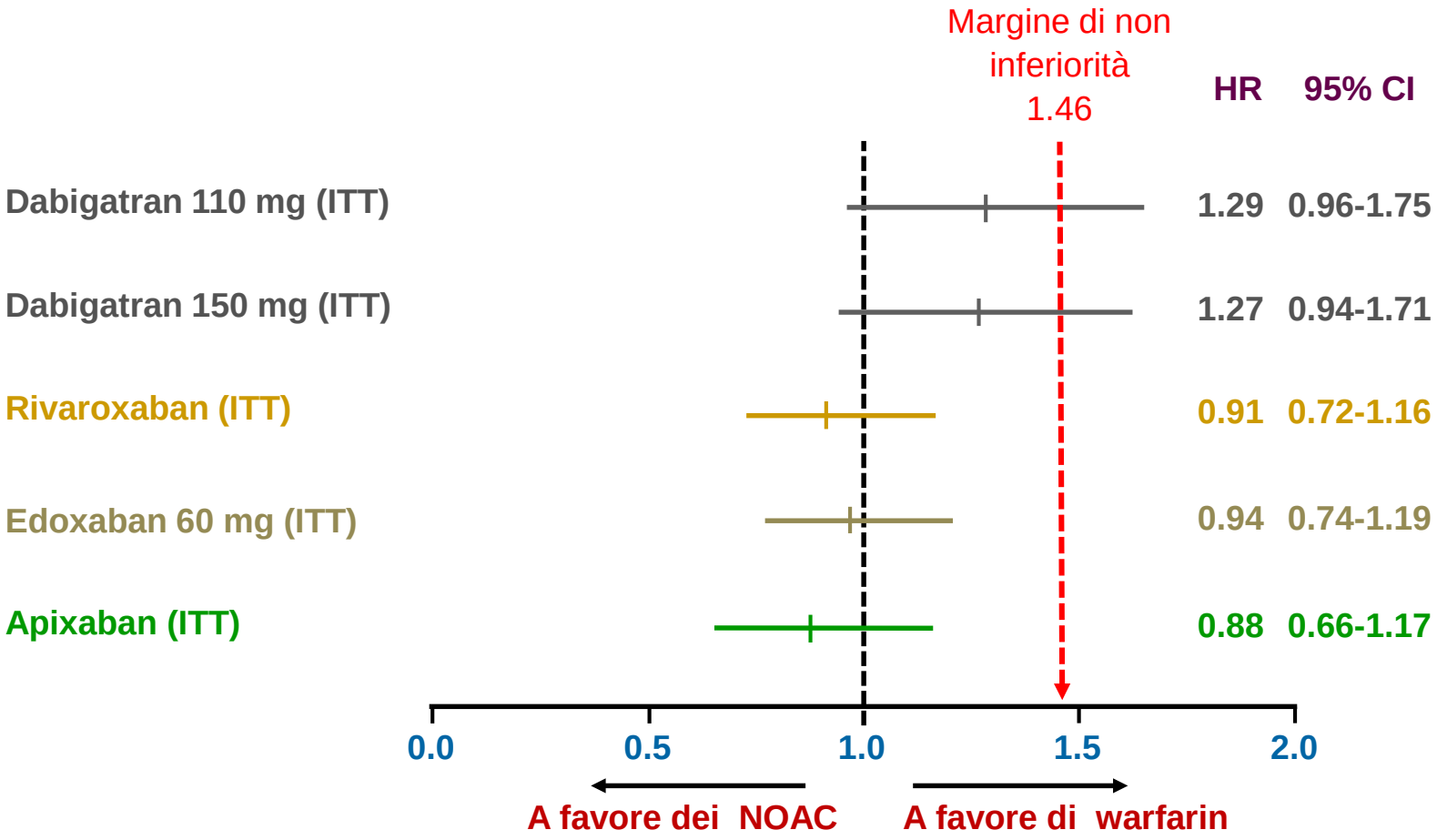

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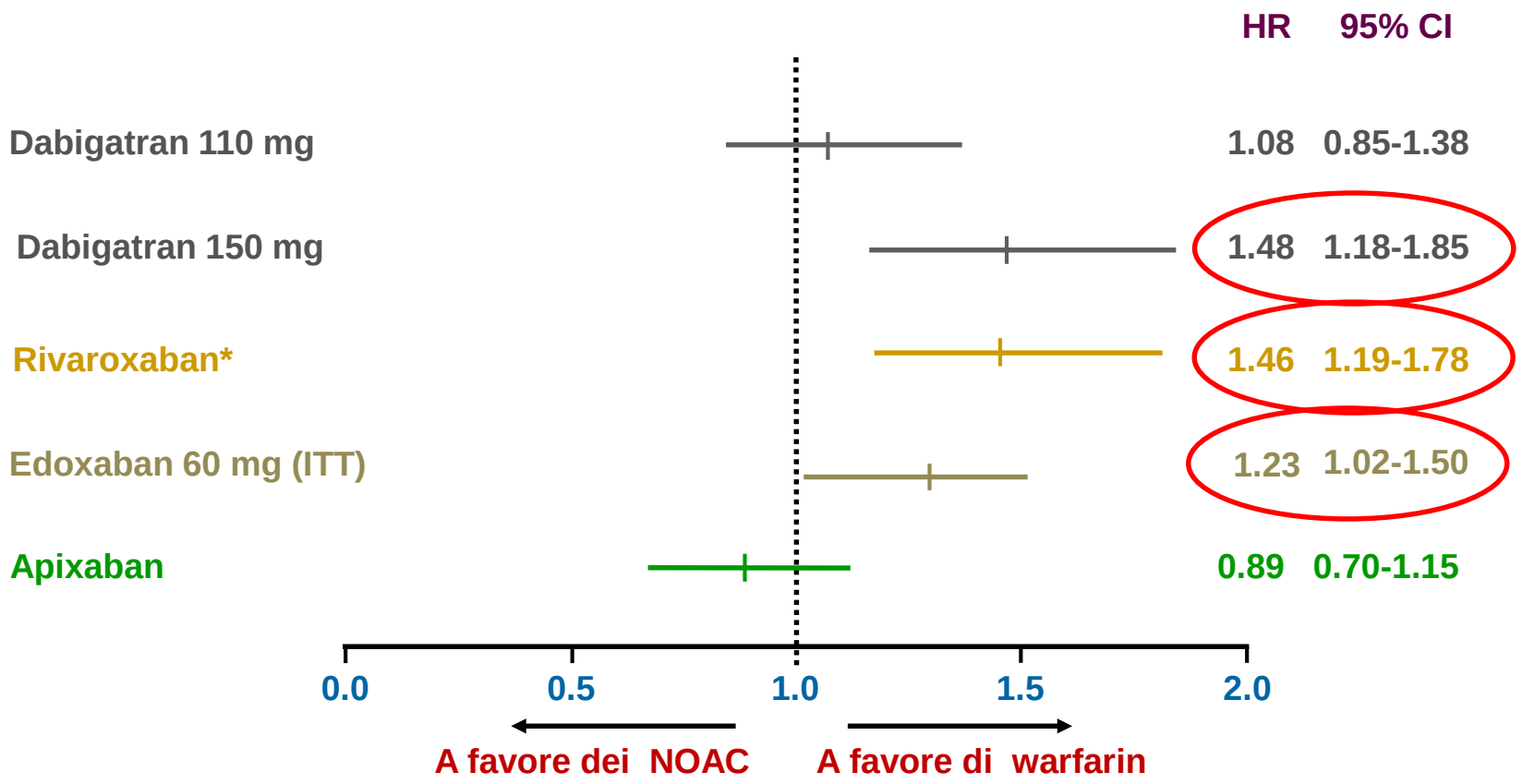
Table 13 Characteristics of approved Non-vitamin K antagonist oral anticoagulants compared

	Dabigatran (RE-LY)			Rivaroxaban (ROCKET-AF)		Apixaban (ARISTOTLE)		Edoxaban (ENGAGE AF-TIMI 48)		
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60	Edoxaban 30
	n = 6022	*n* = 6076	*n* = 6015	*n* = 7133	*n* = 7131	*n* = 9081	*n* = 9120	*n* = 7036	n = 7035	*n* = 7034
	Event rate, %/year	Event rate, %/year (RR vs. warfarin)	Event rate, %/year (RR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; *P* for non-inferiority and superiority <0.001)	1.54 (0.89, 0.73–1.09; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; *P* <0.001 for non-inferiority, *P* = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; *P* = 0.005 for non-inferiority, *P* = 0.10 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P* <0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)	0.47	0.26 (0.54, 0.38–0.77; *P* <0.001)	0.16 (0.33, 0.22–0.50; *P* <0.001)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; *P* = 0.41)	2.92 (0.80, 0.70–0.93; *P* = 0.003)	3.45	3.60 (1.04; 0.90-2.30; *P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)	3.43	2.75 (0.80, 0.71–0.91; *P* <0.001)	1.61 (0.47, 0.41–0.55; *P* <0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P* <0.001)	0.23 (0.29 0.19–0.45; *P* <0.001)	0.74	0.49 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)	0.85	0.39 (0.47, 0.34–0.63; *P* <0.001)	0.26 (0.30, 0.21–0.43; *P* <0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P* <0.001)	1.13 (1.04, 0.82–1.33; *P* = 0.74)	1.24	2.00 (1.61; 1.30-1.99; *P* < 0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P* <0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; *P* = 0.12)	0.82 (1.29, 0.96-1.75; *P* = 0.09)	1.12	0.91 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)	0.75	0.70 (0.94, 0.74–1.19; *P* = 0.60)	0.89 (1.19, 0.95–1.49; *P* = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.21	1.87 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; *P* = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

NOAC *vs.* warfarin: sanguinamenti maggiori gastrointestinali



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	n = 6022	*n* = 6076	*n* = 6015	*n* = 7133	*n* = 7131	*n* = 9081	*n* = 9120	*n* = 7036	n = 7035	*n* = 7034
	Event rate, %/year	Event rate, %/year (RR vs. warfarin)	Event rate, %/year (RR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; *P* for non-inferiority and superiority <0.001)	1.54 (0.89, 0.73–1.09; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; *P* <0.001 for non-inferiority, *P* = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; *P* = 0.005 for non-inferiority, *P* = 0.10 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P* <0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)	0.47	0.26 (0.54, 0.38–0.77; *P* <0.001)	0.16 (0.33, 0.22–0.50; *P* <0.001)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; *P* = 0.41)	2.92 (0.80, 0.70–0.93; *P* = 0.003)	3.45	3.60 (1.04; 0.90-2.30; *P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)	3.43	2.75 (0.80, 0.71–0.91; *P* <0.001)	1.61 (0.47, 0.41–0.55; *P* <0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P* <0.001)	0.23 (0.29 0.19–0.45; *P* <0.001)	0.74	0.49 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)	0.85	0.39 (0.47, 0.34–0.63; *P* <0.001)	0.26 (0.30, 0.21–0.43; *P* <0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P* <0.001)	1.13 (1.04, 0.82–1.33; *P* = 0.74)	1.24	2.00 (1.61; 1.30-1.99; *P* < 0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P* <0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; *P* = 0.12)	0.82 (1.29, 0.96-1.75; *P* = 0.09)	1.12	0.91 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)	0.75	0.70 (0.94, 0.74–1.19; *P* = 0.60)	0.89 (1.19, 0.95–1.49; *P* = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.21	1.87 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; *P* = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

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Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P* <0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)	0.47	0.26 (0.54, 0.38–0.77; *P* <0.001)	0.16 (0.33, 0.22–0.50; *P* <0.001)
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Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P* <0.001)	0.23 (0.29 0.19–0.45; *P* <0.001)	0.74	0.49 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)	0.85	0.39 (0.47, 0.34–0.63; *P* <0.001)	0.26 (0.30, 0.21–0.43; *P* <0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P* <0.001)	1.13 (1.04, 0.82–1.33; *P* = 0.74)	1.24	2.00 (1.61; 1.30-1.99; *P* < 0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P* <0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; *P* = 0.12)	0.82 (1.29, 0.96-1.75; *P* = 0.09)	1.12	0.91 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)	0.75	0.70 (0.94, 0.74–1.19; *P* = 0.60)	0.89 (1.19, 0.95–1.49; *P* = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.21	1.87 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; *P* = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

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	Dabigatran (RE-LY)			Rivaroxaban (ROCKET-AF)		Apixaban (ARISTOTLE)		Edoxaban (ENGAGE AF-TIMI 48)		
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60	Edoxaban 30
	n = 6022	*n* = 6076	*n* = 6015	*n* = 7133	*n* = 7131	*n* = 9081	*n* = 9120	*n* = 7036	n = 7035	*n* = 7034
	Event rate, %/year	Event rate, %/year (RR vs. warfarin)	Event rate, %/year (RR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; *P* for non-inferiority and superiority <0.001)	1.54 (0.89, 0.73–1.09; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; *P* <0.001 for non-inferiority, *P* = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; *P* = 0.005 for non-inferiority, *P* = 0.10 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P* <0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)	0.47	0.26 (0.54, 0.38–0.77; *P* <0.001)	0.16 (0.33, 0.22–0.50; *P* <0.001)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; *P* = 0.41)	2.92 (0.80, 0.70–0.93; *P* = 0.003)	3.45	3.60 (1.04; 0.90-2.30; *P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)	3.43	2.75 (0.80, 0.71–0.91; *P* <0.001)	1.61 (0.47, 0.41–0.55; *P* <0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P* <0.001)	0.23 (0.29 0.19–0.45; *P* <0.001)	0.74	0.49 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)	0.85	0.39 (0.47, 0.34–0.63; *P* <0.001)	0.26 (0.30, 0.21–0.43; *P* <0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P* <0.001)	1.13 (1.04, 0.82–1.33; *P* = 0.74)	1.24	2.00 (1.61; 1.30-1.99; *P* < 0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P* <0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; *P* = 0.12)	0.82 (1.29, 0.96-1.75; *P* = 0.09)	1.12	0.91 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)	0.75	0.70 (0.94, 0.74–1.19; *P* = 0.60)	0.89 (1.19, 0.95–1.49; *P* = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.21	1.87 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; *P* = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

QUALE NOAC PER QUALE PAZIENTE?
ANALISI IN PAZIENTI PARTICOLARI

NEI PAZIENTI a MAGGIOR RISCHIO

$CHADS_2 => 3$

Original Article

Comparative Efficacy and Safety of New Oral Anticoagulants in Patients With Atrial Fibrillation

Circulation

Metanalisi sui pz con CHADS2 > 3 nei rispettivi trial

WHAT IS KNOWN?

- Dabigatran, an oral thrombin inhibitor, and rivaroxaban and apixaban, oral factor Xa inhibitors, have been found to be safe and effective in reducing stroke risk in patients with atrial fibrillation compared with warfarin.
- In the absence of data from direct comparisons of these new anticoagulants, adjusted indirect comparison can be used to compare treatment effects using warfarin as a common comparator group.

WHAT THIS STUDY ADDS

- Patients in 3 major warfarin-controlled randomized trials were comparable when limited to those with a $CHADS_2$ score of ≥3.
- We found no statistically significant differences among the 3 drugs in their efficacy in preventing stroke and systemic embolism, although apixaban and dabigatran were numerically superior to rivaroxaban.
- Apixaban produced statistically significant fewer major hemorrhages than dabigatran and rivaroxaban.

(*Circulation Cardiovasc Qual Outcomes.* 2012;5:00-00.)

Comparative Efficacy and Safety of New Oral Anticoagulants in Patients With Atrial Fibrillation

Table 3. Primary Efficacy and Safety in Subgroups of Trial Patients With CHADS2 Score ≥3

	New Anticoagulant			Warfarin			
	Subjects	Events	Event Rate per 100 Person-Years	Subjects	Events	Event Rate (95% CI) per 100 Person-Years*	Hazard Ratio (95% CI)
Primary efficacy end point: stroke or systemic embolism (intention-to-treat analysis)							
Apixaban (ARISTOTLE)	2758	94	1.9†	2744	132	2.8† (2.35–3.31)	0.68 (0.52–0.88)
Dabigatran 110 mg (RE-LY)‡	1968	82‡	2.12	1933	101§	2.68 (2.19–3.24)	0.79 (0.59, 1.05)‖
Dabigatran 150 mg (RE-LY)‡	1981	74‡	1.88	1933	101§	2.68 (2.19–3.24)	0.70 (0.52, 0.95)‖
Rivaroxaban (ROCKET-AF)¶	6156	239	2.25	6155	270	2.56 (2.27–2.88)	0.88 (0.74, 1.05)
Major Hemorrhage (on-treatment analysis)							
Apixaban (ARISTOTLE)	NR#	126	2.9†	NR#	173	4.2† (3.61–4.86)	0.69 (0.55–0.87)
Dabigatran 110 mg (RE-LY) approximated**	1966	147	3.80	1931	172	4.61 (3.96–5.34)	0.82 (0.66–1.03)‖
Dabigatran 150 mg (RE-LY) approximated**	1979	188	4.86	1931	172	4.61 (3.96–5.34)	1.05 (0.86–1.30)‖
Rivaroxaban (ROCKET-AF)††	6187	337	3.64	6191	337	3.60 (3.23–4.00)	1.01 (0.87–1.18)

(*Circulation Cardiovasc Qual Outcomes.* 2012;5:00-00.)

NEI PAZIENTI ANZIANI

European Heart Journal Advance Access published February 20, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu046

CLINICAL RESEARCH
Atrial fibrillation

Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial

Patients	N. (%)
patients enrolled	18.201
< 65 year	5.471
65 to <75 year	7.052
≥ 75 year	5.678

≥ 80 year 2.352

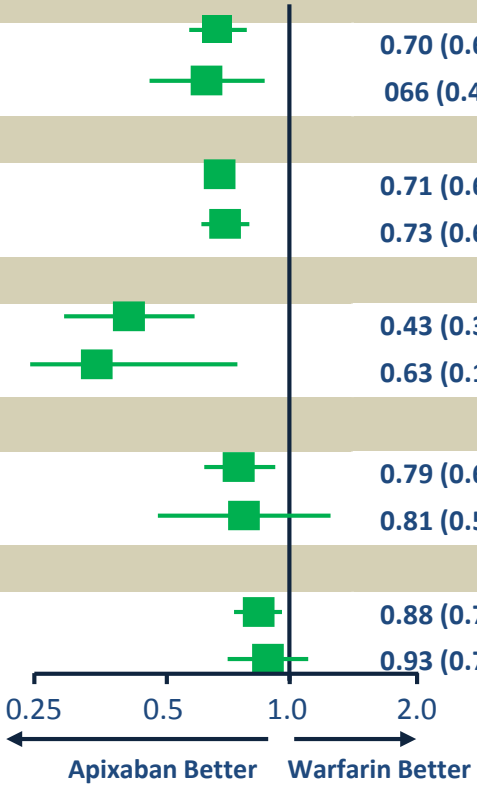
≥ 90 year 84

In ARISTOTLE la popolazione anziana era ben rappresentata

ARISTOTLE: Efficacia e sicurezza di apixaban vs. warfarin erano confermate nei pazienti ≥ 80 anni

2352 patients (13%) were ≥80 years of age in ARISTOTLE

	Apixaban	Warfarin	HR (95% CI)	Interaction *P* value
Major Bleeding				0.7404
Age <80	260 (1.93)	366 (2.78)	0.70 (0.60, 0.82)	
Age ≥80	67 (3.55)	96 (5.41)	066 (0.48, 0.90)	
All Bleeding				0.8332
Age <80	1964 (17.0)	2558 (24.4)	0.71 (0.67, 0.76)	
Age ≥80	392 (26.4)	502 (37.4)	0.73 (0.64, 0.83)	
Intracranial Bleeding				0.6656
Age <80	43 (0.32)	98 (0.73)	0.43 (0.30, 0.62)	
Age ≥80	9 (0.47)	24 (1.32)	0.63 (0.17, 0.77)	
Stroke/Systemic Embolism				0.9080
Age <80	179 (1.23)	225 (1.55)	0.79 (0.65, 0.96)	
Age ≥80	33 (1.53)	40 (1.90)	0.81 (0.51, 1.29)	
All-cause Mortality				0.7259
Age <80	452 (3.03)	507 (3.42)	0.88 (0.78, 1.00)	
Age ≥80	151 (6.86)	162 (7.44)	0.93 (0.74, 1.16)	



HR, hazard ratio; CI, confidence interval

Adapted from Halvorsen S et al. ACC Congress; March 9-11, 2013; San Francisco, CA.

Cardiol Ther (2013) 2:135–149
DOI 10.1007/s40119-013-0019-y

REVIEW

Anticoagulation in Patients Aged ≥75 years with Atrial Fibrillation: Role of Novel Oral Anticoagulants

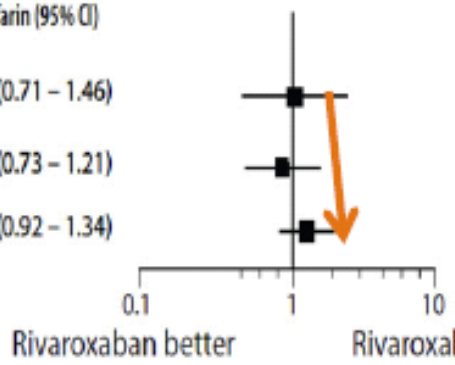
Kuan H. Ng · Robert G. Hart · John W. Eikelboom

Table 3 Comparison of novel oral anticoagulants in patients ≥75 years

Novel agent	Trial	Intervention versus warfarin unless specified	Number of participants ≥75 years	Hazard Ratio for Stroke Risk	Hazard Ratio for major Hemorrhage
Dabigatran	RE-LY [10]	Dabigatran 110 mg bid	7,258	0.88 (0.66–1.17)	1.01 (0.83–1.23)
		Dabigatran 150 mg bid		0.67 (0.49–0.90)	1.18 (0.98–1.42)
Rivaroxaban	ROCKET-AF [11]	Rivaroxaban 20 mg bid (15 mg od if eCrCl 30–49 ml/min)	6,229	0.88 (0.75–1.03)[a]	1.04 (0.90–1.20)[a]
Apixaban	ARISTOTLE [12]	Apixaban 5 mg bid	5,678	0.79 (0.65–0.95)[b]	0.69 (0.60–0.80)[b]

RELAZIONE
SANGUINAMENTO MAGGIORE - ETA'

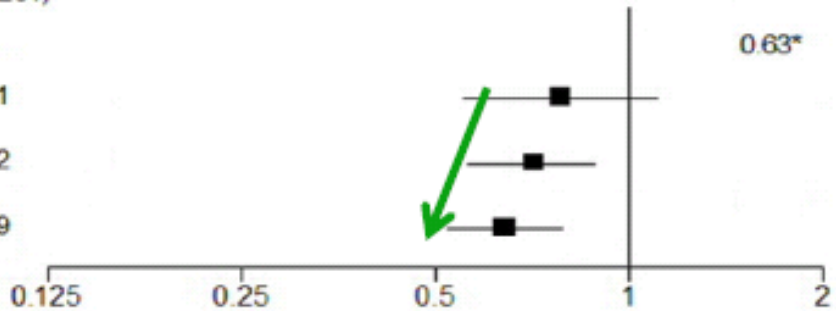
		Rivaroxaban no. of events (%/yr)	Warfarin	Warfarin (95% CI)	Interaction
Age	< 65	59 (2.21)	59 (2.16)	1.02 (0.71 – 1.46)	0.5914
	65 to 74	113 (3.03)	123 (3.24)	0.94 (0.73 – 1.21)	
	≥ 75	223 (4.86)	204 (4.40)	1.11 (0.92 – 1.34)	



S.G Goodman et al. *Journal of the American College of Cardiology* DOI: 10.1016/j.jacc.2013.11.013

A vs W, HR 0.77
A vs W, HR 0.71
A vs W, HR 0.64

	Apixaban %/year	Warfarin %/year	Interaction p value
Primary Efficacy Outcome (n=18201)			
Major Bleeding (n=18140)			0.63*
< 65	1.17	1.51	
65 – <75	1.99	2.82	
≥ 75	3.33	5.19	

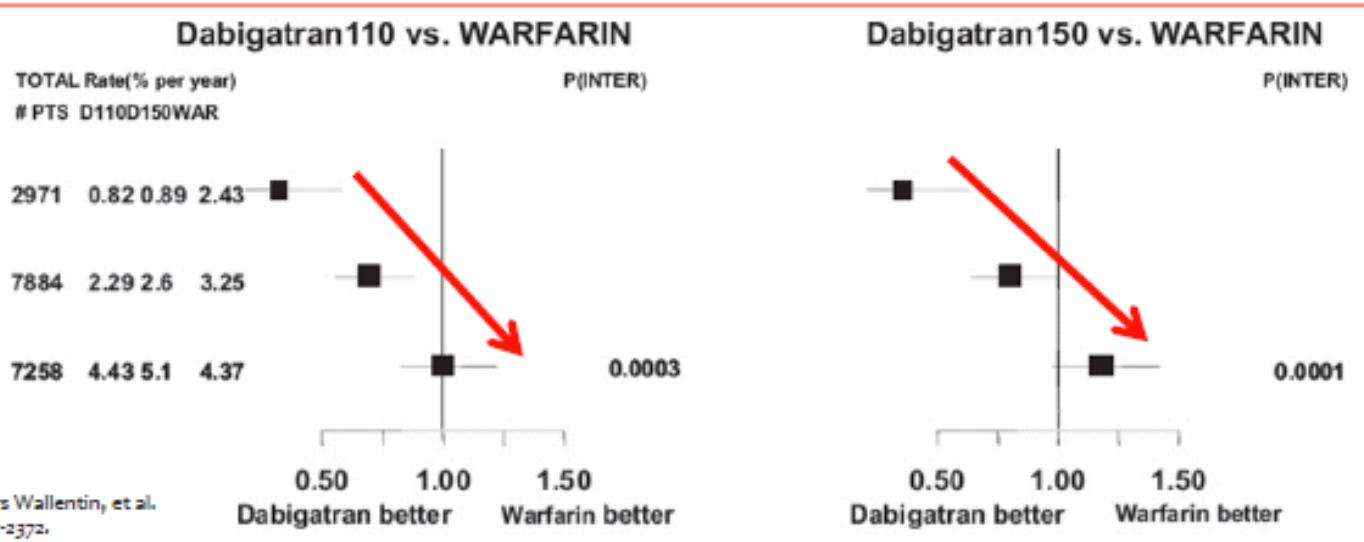


Sigrun Halvorsen, Lars Wallentin et al. abstract data presented at ACC 2013

D 110 vs W, HR 0.37
D 150 vs W, HR 0.37

D 110 vs W, HR 0.71
D 150 vs W, HR 0.80

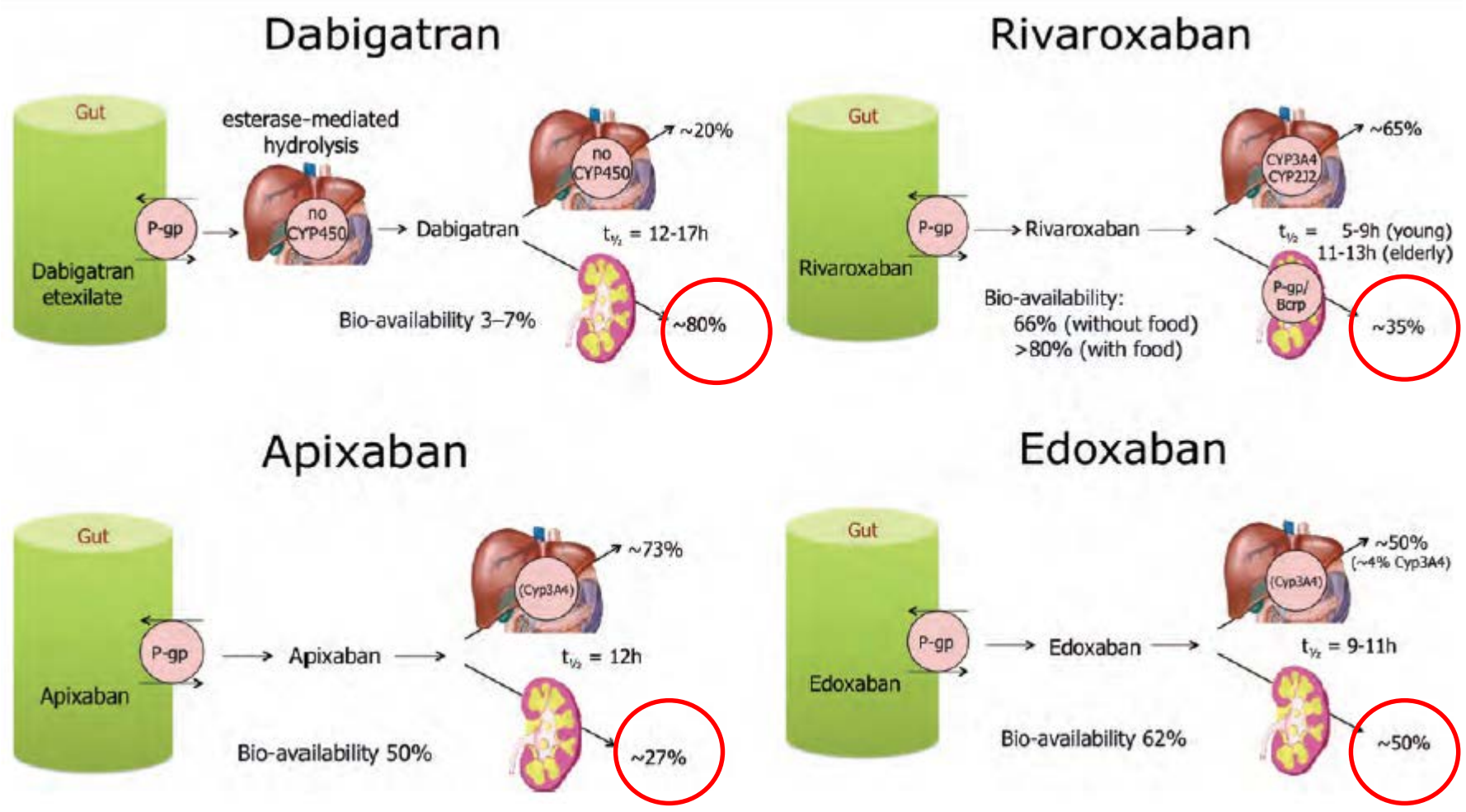
D 110 vs W, HR 1.01
D 150 vs W, HR 1.16



John W. Eikelboom , Lars Wallentin, et al. *Circulation*. 2011;123:2363-2372.

NEI PAZIENTI CON FUNZIONE RENALE ALTERATA

Farmacologia clinica di dabigatran, edoxaban, rivaroxaban e apixaban



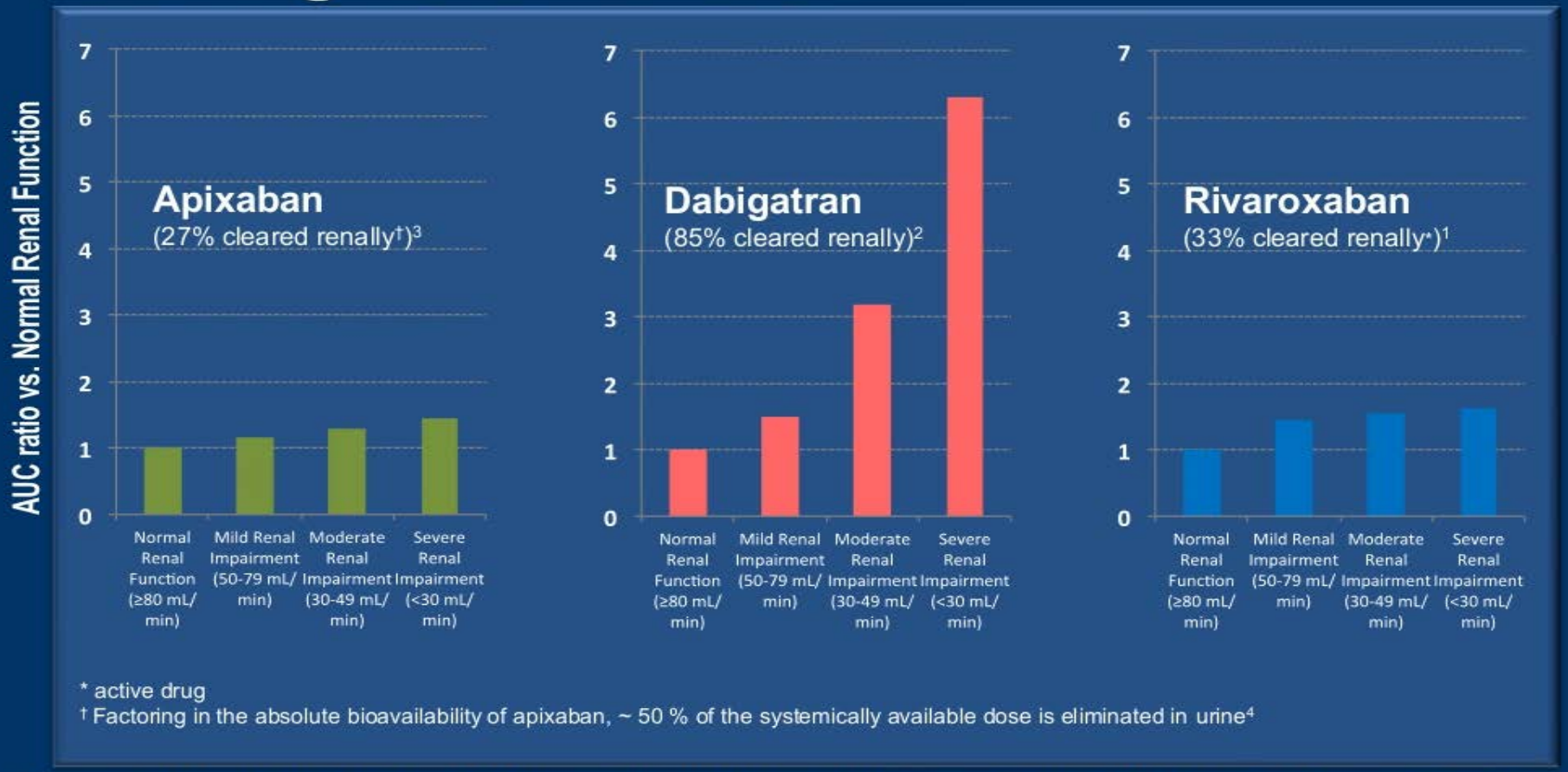
ELSEVIER

Canadian Journal of Cardiology 29 (2013) S24–S33

Review

Importance of Pharmacokinetic Profile and Variability as Determinants of Dose and Response to Dabigatran, Rivaroxaban, and Apixaban

New OACs: Total Drug Exposure (AUC) with Declining Renal Function



* active drug

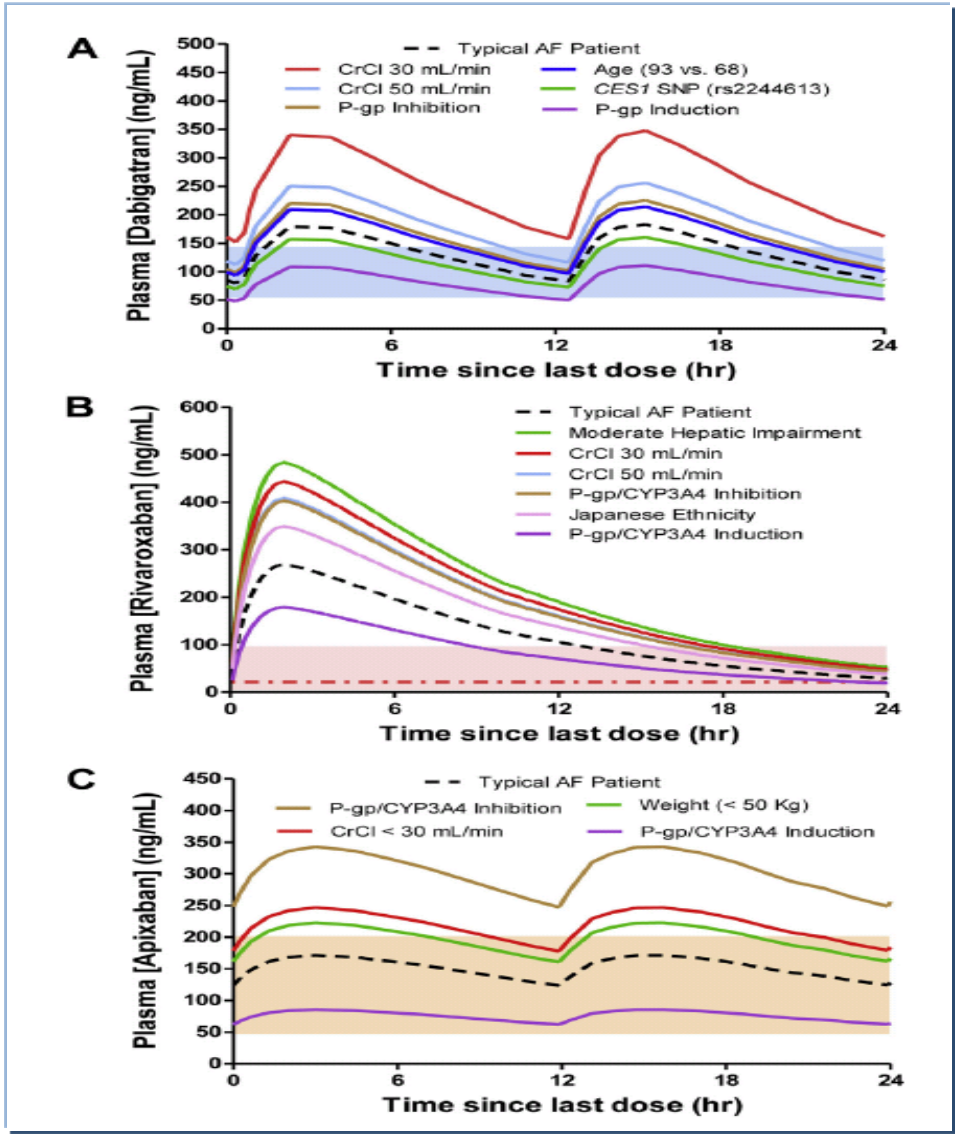
† Factoring in the absolute bioavailability of apixaban, ~ 50 % of the systemically available dose is eliminated in urine[4]

1. Xarelto® PM, July 18, 2012 ; 2. Pradaxa ® PM November 12, 2012; 3. Eliquis® PM November 27, 2012; 4. FDA Eliquis Drug Approval Package, Clinical Pharmacology/Biopharmaceutics Review

Canadian Journal of Cardiology 29 (2013) S24–S33

Review

Importance of Pharmacokinetic Profile and Variability as Determinants of Dose and Response to Dabigatran, Rivaroxaban, and Apixaban



Anticoagulants in atrial fibrillation patients with chronic kidney disease

Robert G. Hart, John W. Eikelboom, Alistair J. Ingram and Charles A. Herzog

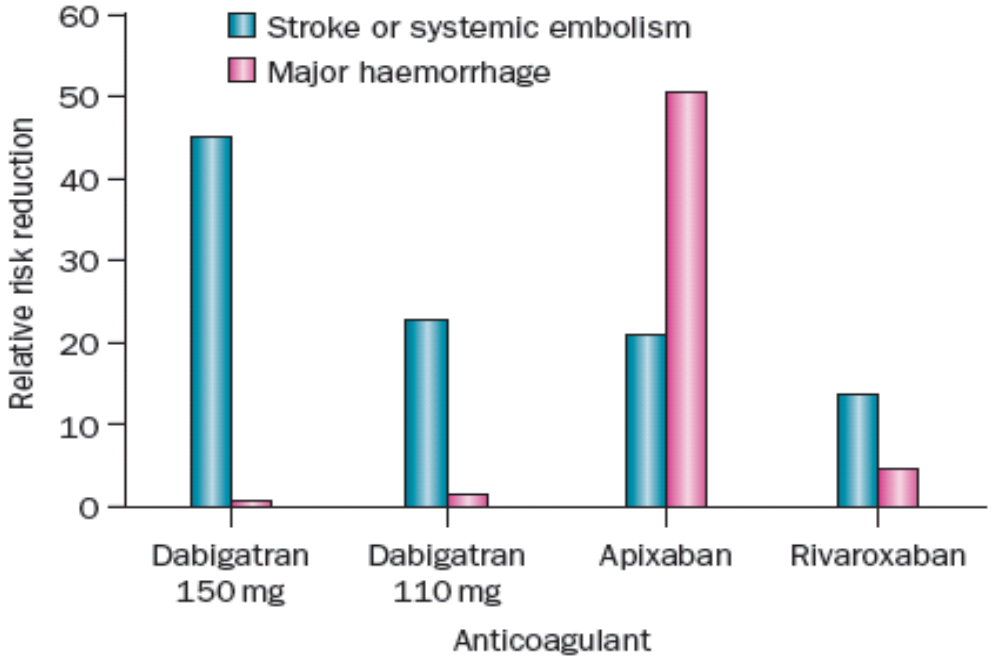
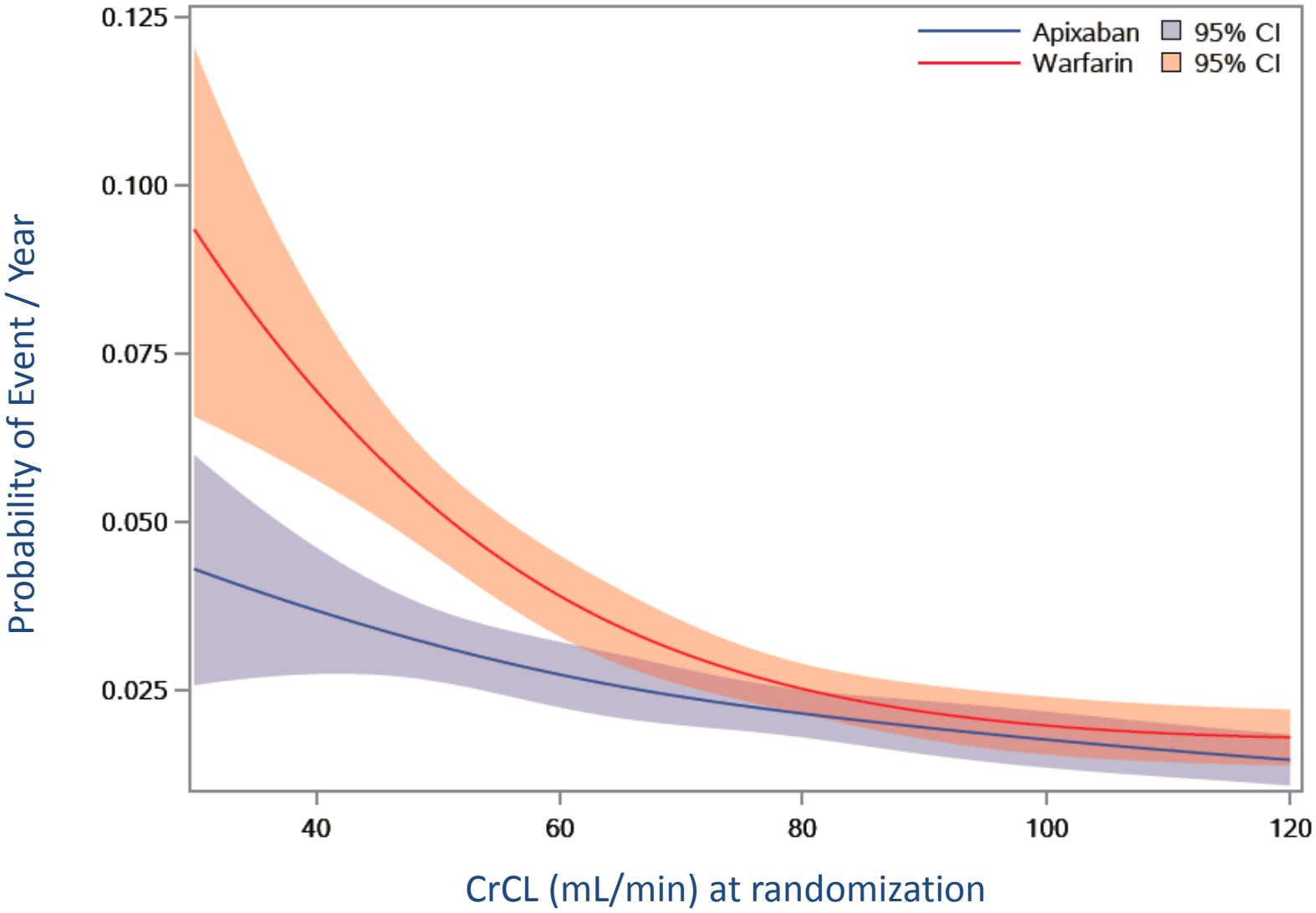


Figure 1 | Relative risk reductions in stroke or systemic embolism and major haemorrhage by novel oral anticoagulants versus warfarin in patients with moderate CKD.[9,12,25] Patients with CKD had estimated creatinine clearances of 30–49 ml/min, except for those treated with apixaban (25–50 ml/min). Risk reductions were statistically significant for dabigatran 150 mg on stroke and for apixaban on major haemorrhage. Abbreviation: CKD, chronic kidney disease.

Major Bleeding by Creatinine Clearance

5 mg Twice Daily Only



Alexander et al. Poster presentation at ESC Aug/Sept 2015; London, UK Poster/oral poster no.2032

CrCL, creatinine clearance

NEI PAZIENTI CON PRECEDENTE ICTUS O TIA

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Walter N. Kernan, Bruce Ovbiagele, Henry R. Black, Dawn M. Bravata, Marc I. Chimowitz, Michael D. Ezekowitz, Margaret C. Fang, Marc Fisher, Karen L. Furie, Donald V. Heck, S. Claiborne (Clay) Johnston, Scott E. Kasner, Steven J. Kittner, Pamela H. Mitchell, Michael W. Rich, DeJuran Richardson, Lee H. Schwamm and John A. Wilson

Stroke. published online May 1, 2014;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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AF Recommendations

1. **For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event *(Class IIa; Level of Evidence C)*.** (New recommendation)
2. **VKA therapy *(Class I; Level of Evidence A)*, apixaban *(Class I; Level of Evidence A)*, and dabigatran *(Class I; Level of Evidence B)* are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in INR therapeutic range if the patient has been taking VKA therapy.** (Revised recommendation)
3. **Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF *(Class IIa; Level of Evidence B)*.** (New recommendation)

PAZIENTI IN AMIODARONE e Xa

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ORIGINAL INVESTIGATIONS

Amiodarone, Anticoagulation, and Clinical Events in Patients With Atrial Fibrillation

Insights From the ARISTOTLE Trial

Greg Flaker, MD,* Renato D. Lopes, MD, PhD,† Elaine Hylek, MD, MPH,‡ Daniel M. Wojdyla, MS,†
Laine Thomas, PhD,† Sana M. Al-Khatib, MD, MHS,† Renee M. Sullivan, MD,* Stefan H. Hohnloser, MD,§
David Garcia, MD,|| Michael Hanna, MD,¶ John Amerena, MBBS,# Veli-Pekka Harjola, MD, PhD,** Paul Dorian, MD,††
Alvaro Avezum, MD, PhD,‡‡ Matyas Keltai, MD, DSc,§§ Lars Wallentin, MD, PhD,|||| Christopher B. Granger, MD,†
for the ARISTOTLE Committees and Investigators

AMIODARONE 2051 pazienti

Use and outcomes of antiarrhythmic therapy in patients with atrial fibrillation receiving oral anticoagulation: Results from the ROCKET AF trial

Benjamin A. Steinberg, MD,[*] Anne S. Hellkamp, MS,[*] Yuliya Lokhnygina, PhD,[*]
Jonathan L. Halperin, MD,[†] Günter Breithardt, MD,[‡] Rod Passman, MD,[§]
Graeme J. Hankey, MD,[‖] Manesh R. Patel, MD,[*] Richard C. Becker, MD,[¶]
Daniel E. Singer, MD,[#] Werner Hacke, MD, PhD,[**] Scott D. Berkowitz, MD,[††]
Christopher C. Nessel, MD,[‡‡] Kenneth W. Mahaffey, MD,[§§]
Keith A.A. Fox, MBChB,[‖‖] Robert M. Califf, MD,[¶¶] Jonathan P. Piccini, MD, MHS, FHRS,[*]
on behalf of the ROCKET AF Steering Committee and Investigators

AMIODARONE 1144 pazienti

RIVAROXABAN

Table 4 Adjusted outcomes of rivaroxaban vs warfarin stratified by amiodarone use at baseline

	Amiodarone			No AAD			
Outcome	Rivaroxaban, events per 100 patient-years (total events)	Warfarin, events per 100 patient-years (total events)	Rivaroxaban vs warfarin, HR (95% CI)	Rivaroxaban, events per 100 patient-years (total events)	Warfarin, events per 100 patient-years (total events)	Rivaroxaban vs warfarin, HR (95% CI)	Interaction *P* (amiodarone and treatment)
Stroke or non-CNS embolism	2.14 (19)	1.74 (15)	1.71 (0.80–3.65)	2.16 (237)	2.54 (279)	**0.82 (0.68–0.98)**	.063
Bleeding							
Major or NMCR bleeding	15.90 (108)	13.82 (92)	1.35 (0.94–1.92)	15.00 (1284)	14.53 (1261)	**1.12 (1.00–1.25)**	.33
Major bleeding	3.84 (29)	1.88 (14)	2.20 (0.98–4.91)	3.61 (343)	3.58 (347)	1.05 (0.90–1.24)	.078
ICH	0.52 (4)	0.27 (2)	2.42 (0.37–16.0)	0.50 (48)	0.78 (77)	**0.61 (0.42–0.88)**	.16
GI	1.70 (13)	0.40 (3)	4.58 (0.92–22.8)	1.75 (168)	1.14 (112)	**1.68 (1.30–2.18)**	.23
Fatal	0.13 (1)	0.40 (3)	0.48 (0.06–3.83)	0.25 (24)	0.50 (49)	**0.49 (0.30–0.80)**	.98
NMCR bleeding	12.28 (85)	12.03 (81)	1.24 (0.84–1.83)	11.92 (1035)	11.28 (993)	**1.15 (1.01–1.31)**	.71

AAD = antiarrhythmic drug; CI = confidence interval; CNS = central nervous system; GI = gastrointestinal; HR = hazard ratio; ICH = intracranial hemorrhage; NMCR = nonmajor clinically relevant.

APIXABAN

TABLE 2 Observed Rates and Number of Events for Efficacy and Safety Endpoints in Patients With Amiodarone and No Amiodarone at Randomization and by Study Drug Assignment

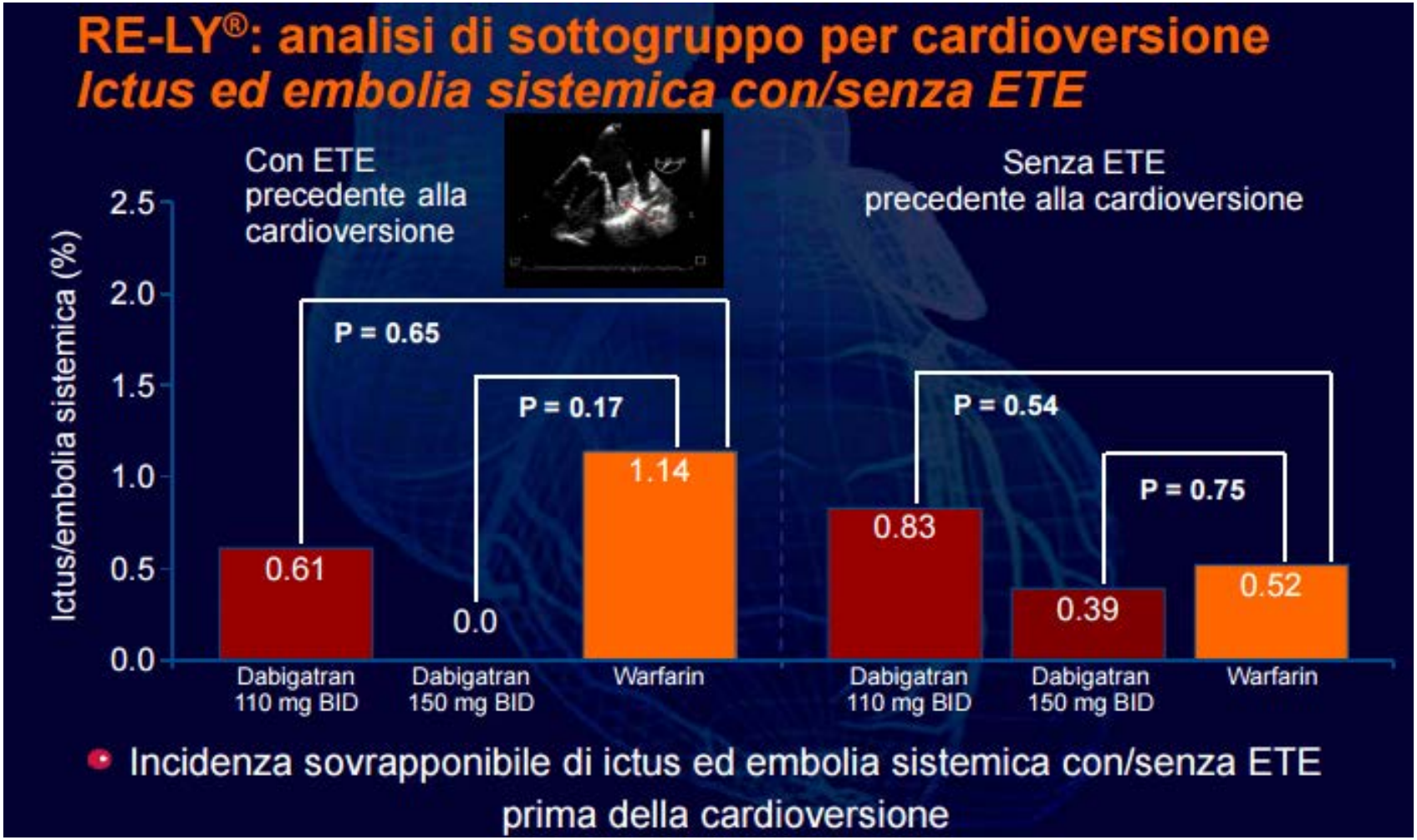
	Amiodarone				No Amiodarone				
Event	Overall	Apixaban	Warfarin	HR (95% CI)*	Overall	Apixaban	Warfarin	HR (95% CI)*	Interaction p Value
Efficacy endpoints									
Stroke or SE	1.55 (58)	1.24 (23)	1.85 (35)	0.68 (0.40-1.15)	1.43 (416)	1.29 (189)	1.57 (227)	0.82 (0.68-1.00)	0.4776
All-cause death	4.91 (187)	4.15 (78)	5.65 (109)	0.74 (0.55-0.98)	3.56 (1060)	3.43 (514)	3.68 (546)	0.93 (0.83-1.05)	0.1366
CV death	2.63 (100)	2.34 (44)	2.90 (56)	0.81 (0.54-1.20)	1.82 (541)	1.74 (260)	1.90 (281)	0.92 (0.77-1.09)	0.5611
Non-CV death	1.58 (60)	1.38 (26)	1.76 (34)	0.79 (0.47-1.31)	1.13 (335)	1.10 (165)	1.15 (170)	0.96 (0.78-1.19)	0.4728
MI	0.27 (10)	0.21 (4)	0.32 (6)	0.68 (0.19-2.41)	0.61(179)	0.58 (85)	0.65 (94)	0.90 (0.90-1.20)	0.6790
Safety endpoints									
Major bleeding	2.46 (82)	1.86 (31)	3.06 (51)	0.61 (0.39-0.96)	2.60 (690)	2.18 (293)	3.03 (397)	0.72 (0.62-0.84)	0.4894
Major/CRNM bleeding	5.12 (167)	3.92 (64)	6.31 (103)	0.63 (0.46-0.86)	4.99 (1298)	4.10 (542)	5.92 (756)	0.70 (0.62-0.78)	0.5226
Intracranial bleeding	0.74 (25)	0.30 (5)	1.19 (20)	0.25 (0.10-0.67)	0.54 (146)	0.35 (47)	0.74 (99)	0.46 (0.33-0.66)	0.2456

Values are %/year (n). *Hazard ratios are apixaban versus warfarin.

CI = confidence interval; CRNM = clinically relevant non-major; CV = cardiovascular; HR = hazard ratio; other abbreviations as in Table 1.

Peri-cardioversione?

Cardioversione: dabigatran



Cardioversione: apixaban

ARISTOTLE trial – post-hoc analysis

- 18 201 patients randomised in the trial:
  - 743 cardioversions performed in 540 patients
- Transoesophageal echocardiographic (TEE) data were available in 171 patients (203 cardioversions) None of the patients had evidence of a left atrial thrombus
  - 4 patients had evidence of spontaneous echo contrast (1 assigned to Apixaban, 3 assigned to warfarin)

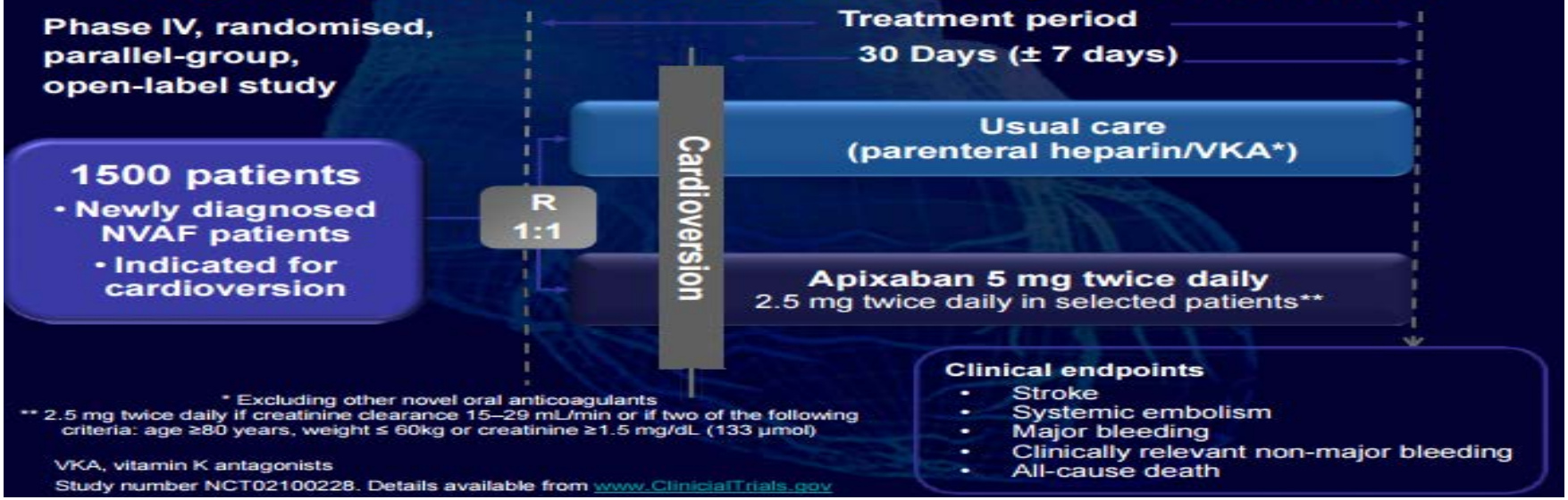
Clinical Outcomes Within 30 Days After Cardioversion (ITT analysis)

Outcome	Warfarin (n=412)	Apixaban (n=331)	Total (N=743)
Stroke or SE	0	0	0
MI	1 (0.2)	1 (0.3)	2 (0.2)
Major bleeding	1 (0.2)	1 (0.3)	2 (0.2)
Death	2 (0.5)	2 (0.6)	4 (0.5)

Values are n, number of cardioversions (%).
MI, myocardial infarction; SE, systemic embolism.

Flaker G et alJ Am Coll Cardiol 2014;63:1082–7

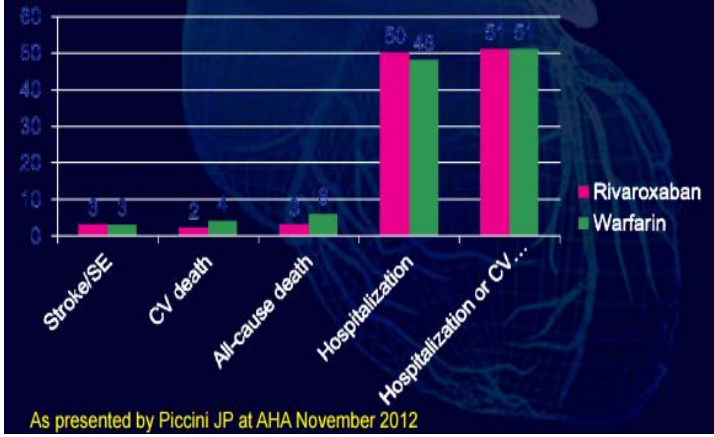
EMANATE trial: Apixaban in patients with newly diagnosed NVAF indicated for early cardioversion



Cardioversione: rivaroxaban

Risultati dei pazienti sottoposti a ECV/PCV/Ablazione nello studio ROCKET AF

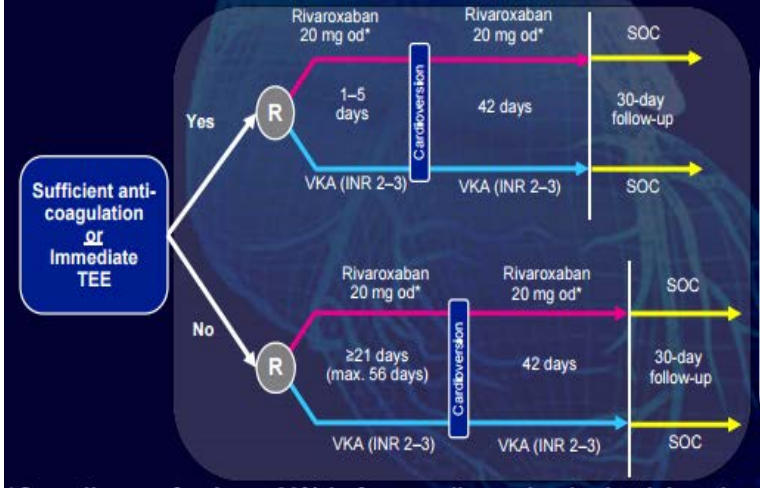
- 143 pazienti sono stati sottoposti a Cardioversione Elettrica
- 142 pazienti sono stati sottoposti a Cardioversione Farmacologica
- 79 pazienti sono stati sottoposti ad Ablazione



As presented by Piccini JP at AHA November 2012

X-VeRT

Studio in aperto, randomizzato



*Compliance of at least 80% before cardioversion in the delayed cardioversion group

Cappato R *et al. Eur Heart J* 2014: doi: 10.1093/eurheartj/ehu367

X-VeRT: primary efficacy endpoints

	Rivaroxaban (N=978)		VKA (N=492)		Risk ratio (95% CI)
	%	n*	%	n*	
Primary efficacy endpoint	**0.51**	**5**	**1.02**	**5**	**0.50 (0.15–1.73)**
Stroke	0.20	2	0.41	2	
Haemorrhagic stroke	0.20	2		0	
Ischaemic stroke		0	0.41	2	
TIA		0		0	
Non-CNS SE		0	0.20	1	
MI	0.10	1	0.20	1	
Cardiovascular death	0.41	4	0.41	2	

*Number of patients with events; patients may have experienced more than one primary efficacy event mITT population

Cappato R *et al. Eur Heart J* 2014: doi: 10.1093/eurheartj/ehu367

X-VeRT: primary safety endpoints

	Rivaroxaban (N=988)		VKA (N=499)		Risk ratio (95% CI)
	%	n*	%	n*	
Major bleeding	**0.61**	**6**	**0.80**	**4**	**0.76 (0.21–2.67)**
Fatal	0.1	1	0.4	2	
Critical-site bleeding	0.2	2	0.6	3	
Intracranial haemorrhage	0.2	2	0.2	1	
Hb decrease ≥2 g/dl	0.4	4	0.2	1	
Transfusion of ≥2 units of packed RBCs or whole blood	0.3	3	0.2	1	

*Number of patients with events; patients may have experienced more than one primary safety event Safety population

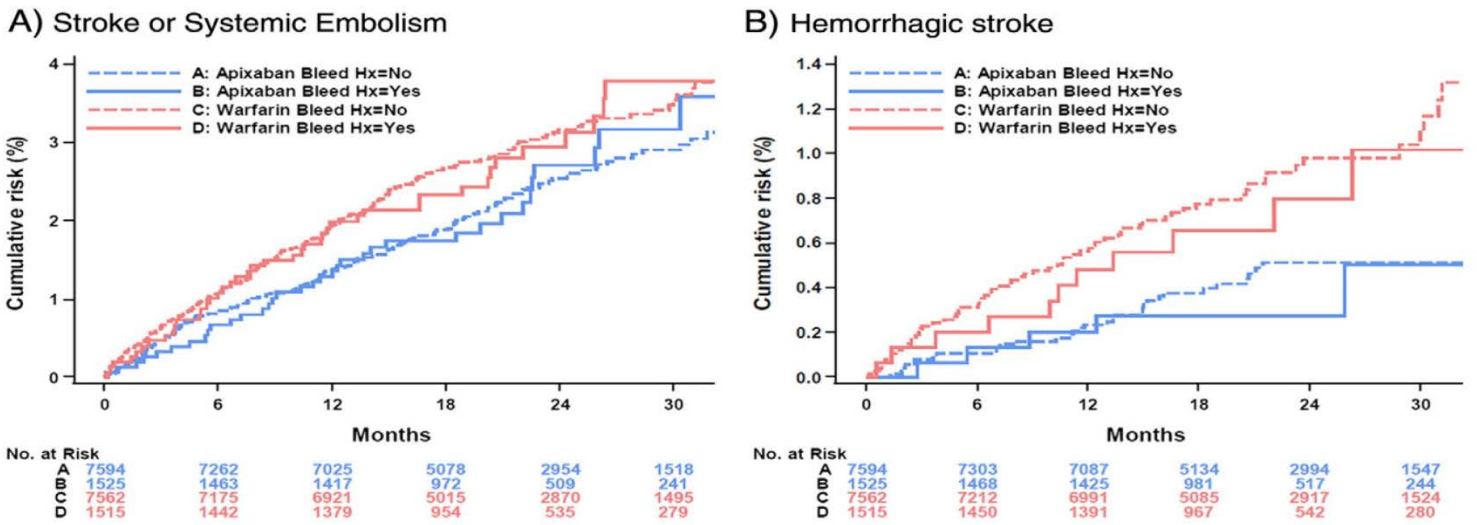
Cappato R *et al. Eur Heart J* 2014: doi: 10.1093/eurheartj/ehu367

Pazienti con storia di sanguinamenti

American Heart Journal
May 2016

History of bleeding and outcomes with apixaban versus warfarin in patients with atrial fibrillation in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial

Raffaele De Caterina, MD, PhD, [a] Ulrika Andersson, MSc, [b] John H. Alexander, MD, MHS, [c] Sana M. Al-Khatib, MD, MHS, [c] M. Cecilia Bahit, MD, [d] Shinya Goto, MD, PhD, [e] Michael Hanna, MD, [f] Claes Held, [b,g] Stefan Hohnloser, MD, [h] Elaine M. Hylek, MD, MPH, [i] Fernando Lanas, MD, [j] Renato D. Lopes, MD, PhD, [c] José López-Sendón, MD, PhD, FESC, [k] Giulia Renda, MD, [a] John Horowitz, MD, PhD, [l] Christopher B. Granger, MD, [c] and Lars Wallentin, MD, PhD [b,g], on behalf of the ARISTOTLE Investigators *Chieti, Italy; Uppsala, Sweden; Durham, NC; Santa Fe, Argentina; Isehara, Japan; Princeton, NJ; Frankfurt, Germany; Boston, MA; Temuco, Chile; IdiPaz Madrid, Spain; and Adelaide, Australia*

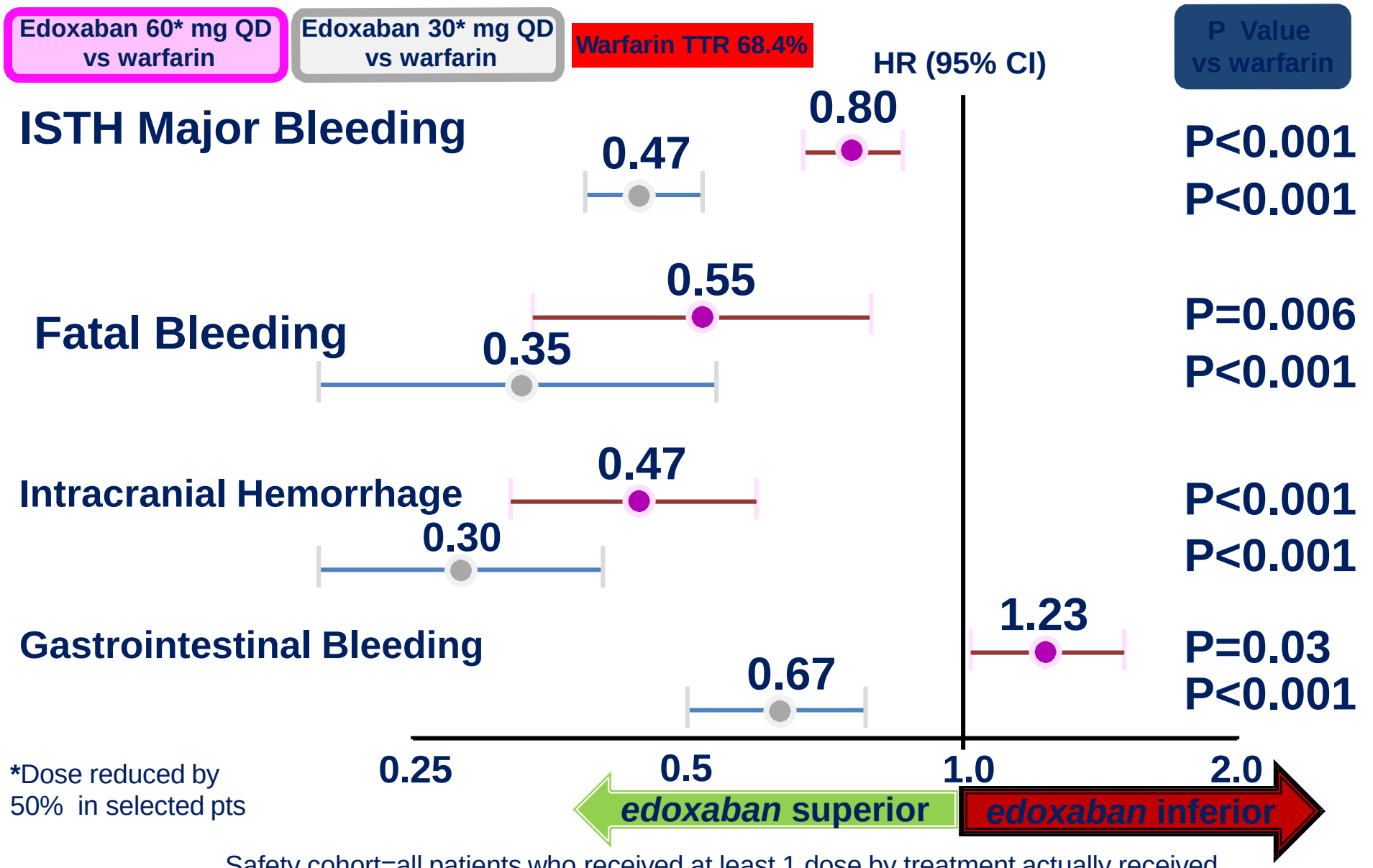


Kaplan-Meier curves depicting the accumulation of events as a function of time, divided according to the presence (continuous line) or absence of a history of bleeding (dotted line) and of the randomized treatment (apixaban in blue) or warfarin (red). **A**, Stroke and SE. **B**, Hemorrhagic stroke. **C**, Death. **D**, Major bleeding.

L'effetto favorevole di apixaban vs warfarin per stroke, stroke emorragico, sanguinamenti maggiori e morte rimane consistente nonostante la storia di pregressi sanguinamenti.

Main Safety Results

- Safety Cohort on Treatment -



*Dose reduced by 50% in selected pts

Safety cohort=all patients who received at least 1 dose by treatment actually received

In confronto a warfarin la monosomministrazione di edoxaban:

Non inferiore su stroke/SEE (entrambe le dosi)

- Alta dose ↓stroke/see (trend ITT)

Entrambe le dosi riducono significativamente:

- Sanguinamenti maggiori (20%/53%)
- Emorragie intracraniche (53%/70%)
- Stroke emorragico(46%/67%)
- Morte CV (14%/15%)

Superiore outcomes clinico

<u>No</u> eccesso di stroke o sanguinamento nella fase di transizione da o verso warfarin al termine del trial

Il mondo reale

European Heart Journal Advance Access published September 1, 2015

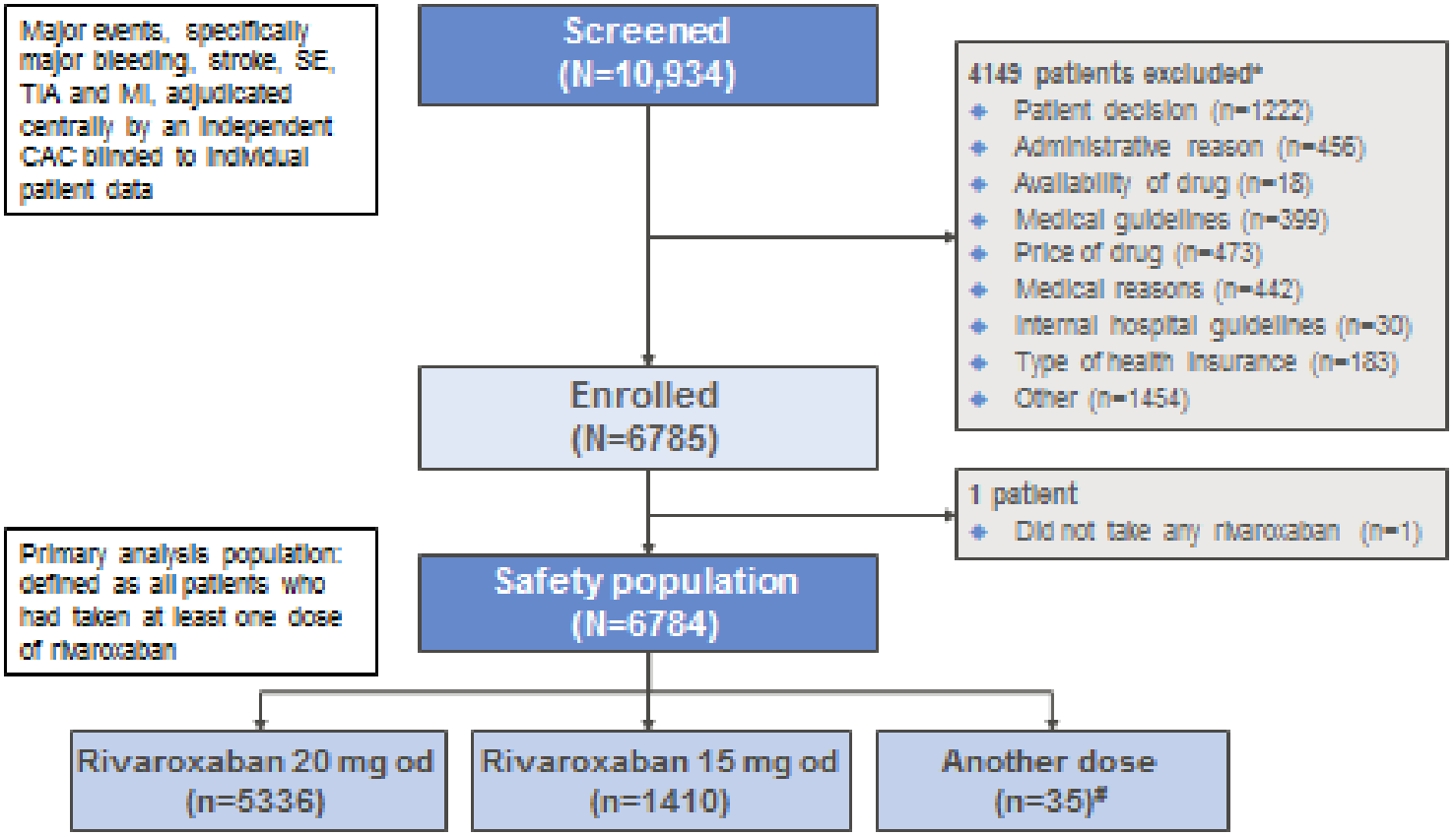
European Heart Journal
doi:10.1093/eurheartj/ehv466

FASTTRACK
ESC Clinical Registry

XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation

A. John Camm[1]*, Pierre Amarenco[2], Sylvia Haas[3], Susanne Hess[4], Paulus Kirchhof[5,6], Silvia Kuhls[7], Martin van Eickels[4], and Alexander G.G. Turpie[8], on behalf of the XANTUS Investigators

XANTUS: Patient Flow



*Reasons for not continuing in the study included, but were not limited to, patient decision, administrative or medical reasons. Some patients could have more than one reason for exclusion; #other dose includes any initial daily rivaroxaban dose besides 15/20 mg od (excluding missing information, n=3)

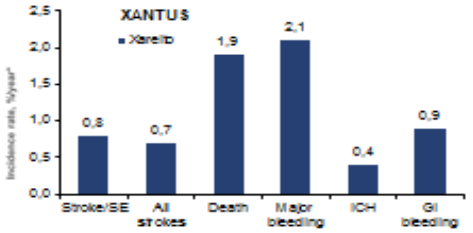
Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

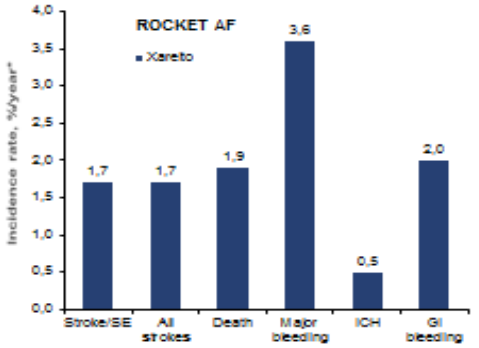
XANTUS

XANTUS è il primo studio internazionale prospettico che descrive l'utilizzo di rivaroxaban in un ampia popolazione con NVAF

Comparison of Main Outcomes: XANTUS versus ROCKET AF

	$CHADS_2$	Prior stroke[a]
ROCKET AF[1]	3.5	55%
XANTUS[2]	2.0	19%





*Includes prior stroke, SE or TIA; †Events per 100 patient-years

1. Patel MR *et al*, *N Engl J Med* 2011;365:883–891; 2. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS

I pazienti erano a rischio globale inferiore rispetto allo studio di fase III ROCKET AF trial

In XANTUS dimostrazione di bassi tassi di stroke/SE e sanguinamenti maggiori compresi gli intracranici e GI
L'incidenza di questi outcomes generalmente incrementa con l'aumentare degli indici di rischio di stroke I

Sanguinamenti maggiori sono stati generalmente gestiti con terapia conservativa

La persistenza in trattamento e la soddisfazione del paziente era alta

- 80% persitenza in rivaroxaban
- 75% soddisfatti a 1 anno

Real Life

XANTUS: Treatment-Emergent Thromboembolic Events and All-Cause Death

	Rivaroxaban (N=6784)	
	Incidence proportion, n (%)	Incidence rate, %/year (95% CI)*
All-cause death	118 (1.7)	1.9 (1.6–2.3)
Thromboembolic events (stroke, SE, TIA, and MI)	108 (1.6)	1.8 (1.5–2.1)
Stroke/SE	51 (0.8)	0.8 (0.6–1.1)
Stroke	43 (0.6)	0.7 (0.5–0.9)
Primary haemorrhagic	11 (0.2)	
Primary ischaemic	32 (0.5)	
SE	8 (0.1)	0.1 (0.1–0.3)
TIA	32 (0.5)	0.5 (0.4–0.7)
MI	27 (0.4)	0.4 (0.3–0.6)

*Events per 100 patient-years

Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS

XANTUS: Treatment-Emergent Bleeding Events

	Rivaroxaban (N=6784)	
	Incidence proportion, n (%)	Incidence rate, %/year (95% CI)*
Major bleeding	128 (1.9)	2.1 (1.8–2.5)
Fatal	12 (0.2)	0.2 (0.1–0.3)
Critical organ bleeding	43 (0.6)	0.7 (0.5–0.9)
Intracranial haemorrhage	26 (0.4)	0.4 (0.3–0.6)
Mucosal bleeding#	60 (0.9)	1.0 (0.7–1.3)
Gastrointestinal	52 (0.8)	0.9 (0.6–1.1)
Haemoglobin decrease ≥2 g/dl‡	52 (0.8)	0.9 (0.6–1.1)
Transfusion of ≥2 units of packed RBCs or whole blood‡	53 (0.8)	0.9 (0.6–1.1)
Non-major bleeding events	878 (12.9)	15.4 (14.4–16.5)

Patients could experience multiple bleeding events in different categories. *Events per 100 patient-years; †numbers are for major mucosal and gastrointestinal bleeding events; ‡representing major bleeding

Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS

Sanguinamenti maggiori nell'1.9% dei pazienti (n=128) [1]

Trattati prevalentemente con terapia conservativa[1]

0.8% dei pazienti (n=53) hanno ricevuto trasfusioni di ≥2 unità

Basso utilizzo di agenti di inversione dell'effetto– come prothrombin complex concentrate (PCC) [1]Utilizzo di PCC in 2 pazienti

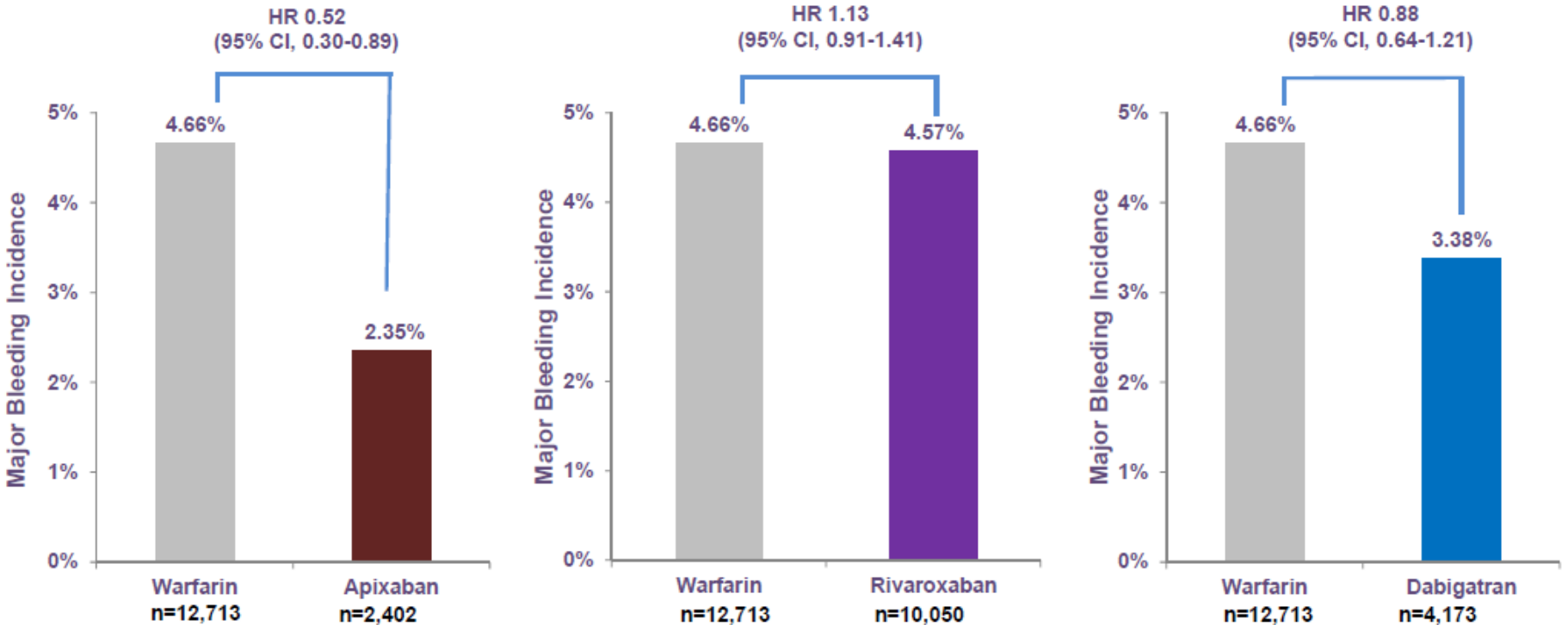
Utilizzo acido tranexamico in 3 pazienti

Utilizzo di etamsylate in 1 paziente

Valori in linea con i dati di ROCKET AF [2] e del registro di Dresda[3]

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466; 2. Piccini JP *et al, Eur Heart J* 2014; 35(28):1873-80;
3. Beyer-Westendorf J *et al, Blood* 2014; 124(6):955-62

Lip G.Y.H et al: comparazione nel mondo reale del rischio di sanguinamenti maggiori In pazienti con NVAF e nuovo inizio di terapia con apixaban, dabigatran, rivaroxaban o warfarin (per 100 person-year)

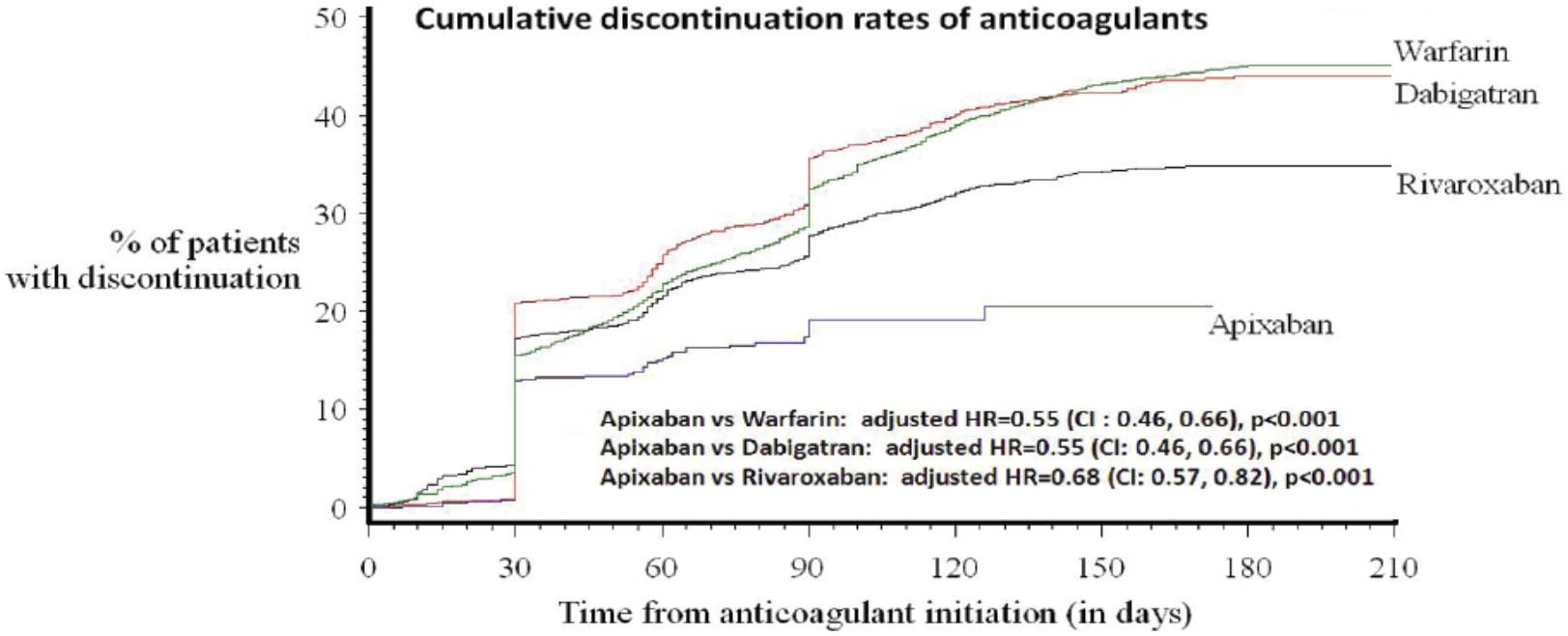


ACC.14
TCT@ACC-i2 | Innovation in Intervention

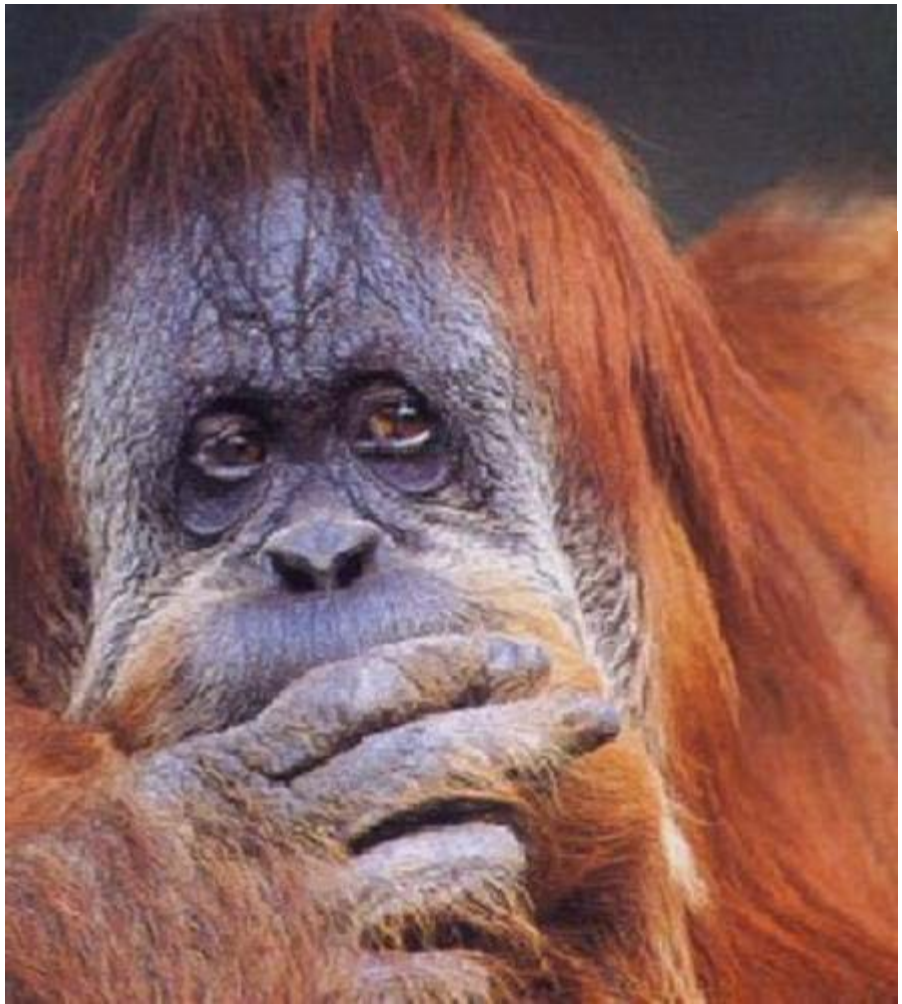
A415
JACC April 1, 2014
Volume 63, Issue 12

Arrhythmias and Clinical EP

REAL WORLD DISCONTINUATION RATES WITH APIXABAN VERSUS WARFARIN, DABIGATRAN, OR RIVAROXABAN AMONG ATRIAL FIBRILLATION PATIENTS NEWLY INITIATED ON ANTICOAGULATION THERAPY: EARLY FINDINGS



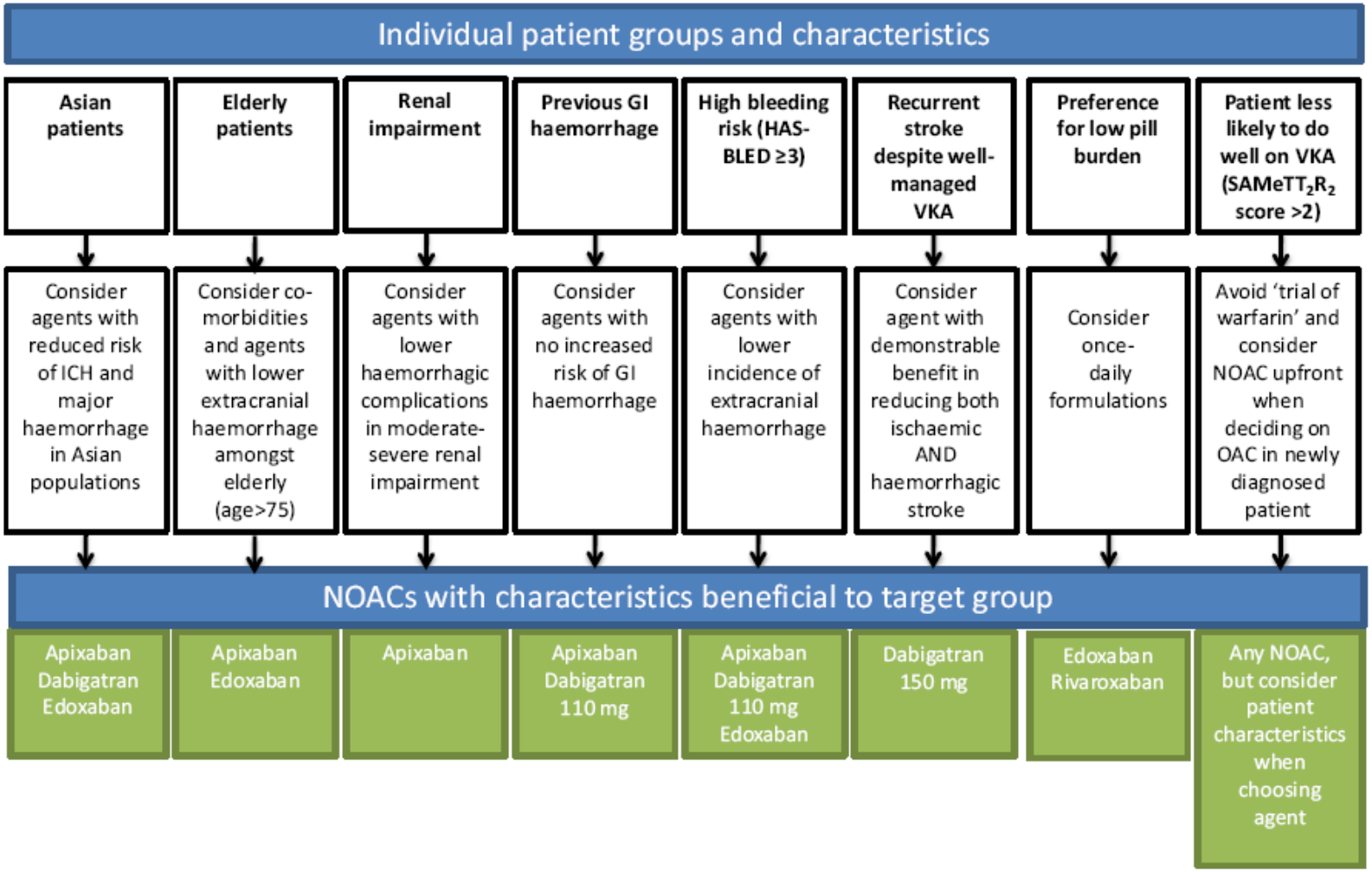
Tassi di interruzione della terapia significativamente inferiori



Per anni abbiamo atteso una soluzione alternativa ai dicumarolici….

Dagli studi clinici emergono numerosi dati, indicazioni e numerose certezze… ma noi lavoriamo nella realtà e questo adesso non ci preoccupa più…

DOAC e caratteristiche dei pazienti



Shields AM and Lip GYH. J Intern Med 2015, march 15

Non capita spesso in Medicina di ottenere risultati in studi clinici come quelli ottenuti nell'ambito della classe di NUOVI ANTICOAGULANTI, classe di farmaci con indiscussa efficacia e sicurezza.

La ricerca farmacologica dei trial si è concretizzata nella realtà , come dimostrato in registri osservazionali.

Il clinico ha la possibilità di scegliere tra diverse opzioni terapeutiche tutte efficaci e sicure, SELEZIONANDO ALCUNE PREFERENZE PER PARTICOLARI CARATTERISTICHE DI PAZIENTI.

Rispetto al passato assume ulteriore importanza la COMPLIANCE del paziente.

Il problema dell'antidoto è in via di soluzione…

Con i dati di cui disponiamo attualmente l'unica limitazione nella pratica clinica all'impiego dei NOAC nel trattamento della FA non valvolare è rappresentata dalla procedura di prescrizione (numero di medici prescrittori e piano terapeutico).

Cattedra e Unità Operativa di Cardiologia
Dipartimento Specialità Medico Chirurgiche Scienze Radiologiche e Sanità Pubblica
Università degli Studi di Brescia
Azienda Spedali Civili di Brescia

Grazie

Prof. RICCARDO RADDINO