Terapia con DOAC nel paziente con FA e fenotipo clinico complesso

Le soluzioni

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Disclosure

Speaker fee: BMS, Daichii Sankio, Bayer, Pfizer, Sanofi

Advisory board member: Bayer, Daiichi Sankyo, BMS, Pfizer; Sanofi

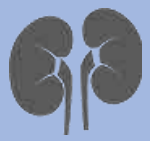
Patients with AF at Moderate or High Risk of Stroke Often Have Co-morbid Diabetes and/or CKD and Are Elderly

Age
Mean 70.2 years

Hypertension
~4 in 5 patients

Stroke
1 in 10 patients

BMI
Mean 27.5 kg/m^2



CKD
(GFR <60 ml/min)
1 in 10 patients

CAD
1 in 5 patients

Smoking
(current/previous)
1 in 3 patients

Diabetes
1 in 5 patients

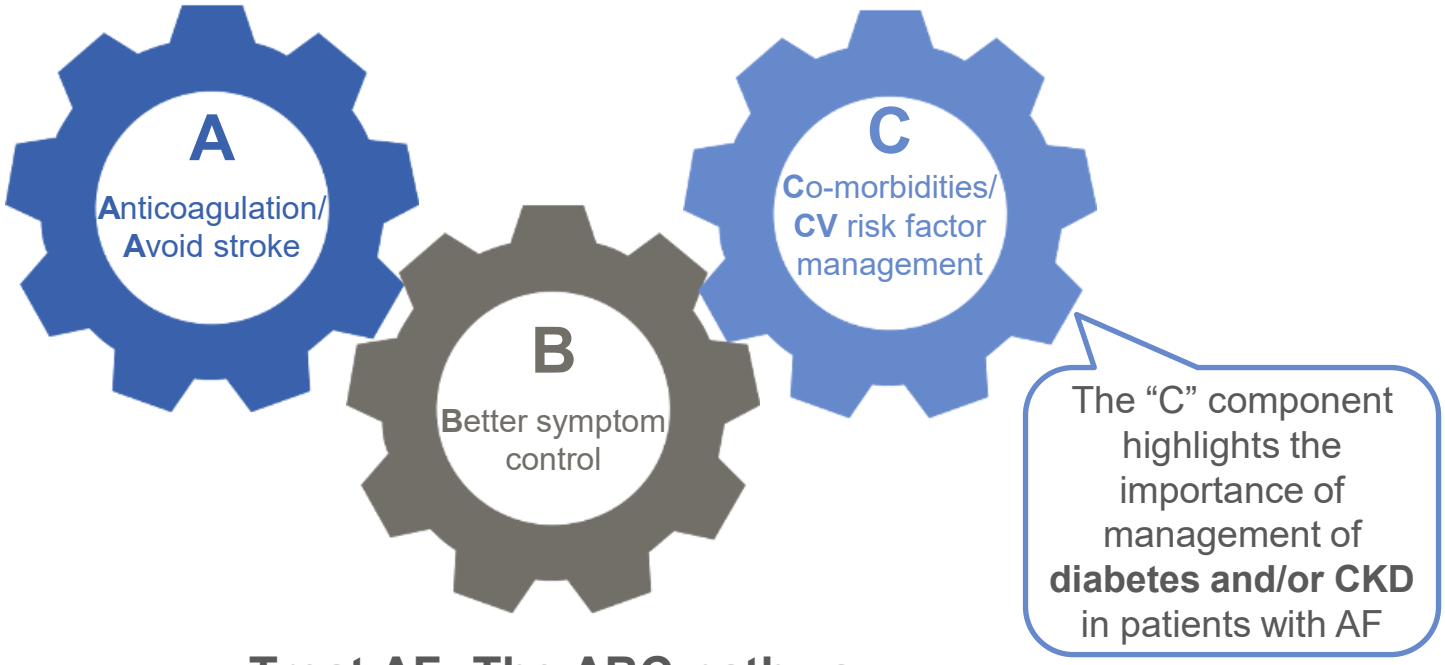
Peripheral vascular disease
~1 in 10 patients

GARFIELD-AF, cohort 1 (n=10,641)

Kakkar AK *et al*. *PLoS One* 2013;8:e63479.

The 2020 ESC Guidelines for the Management of AF Highlight the Importance of Managing Co-morbidities Such as T2D

The Atrial Fibrillation Better Care (ABC) is a holistic approach with the patient at the centre



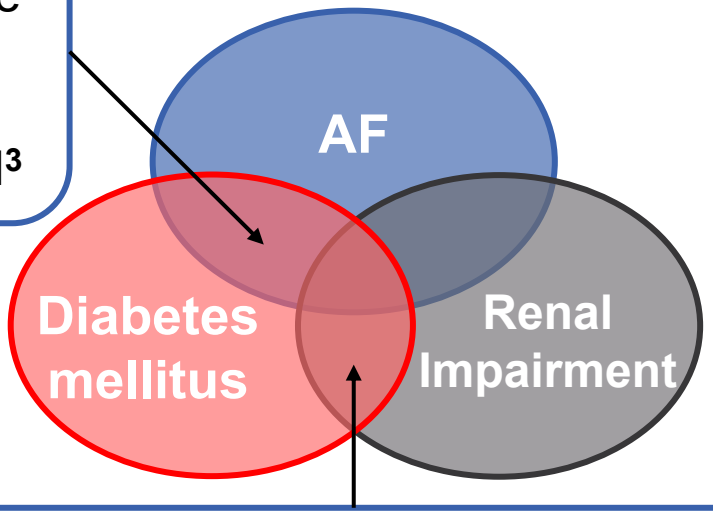
Treat AF: The ABC pathway

Compared with usual care, implementation of the ABC pathway has been significantly associated with lower risk of all cause death, composite outcome of stroke/major bleeding/cardiovascular death lower rates of cardiovascular events and lower health-related costs

Hindricks G *et al*. *Eur Heart J* 2021;42:373–498.

Overlapping Comorbidities Increase the Complexity of Stroke Prevention Particularly in AF Patients

- **30% of AF patients have DM[1]**
- DM is an independent risk factor for stroke in patients with AF (RR: 1.7)[2]
- **Risk of death following a stroke is greater for patients with vs without DM[3]**

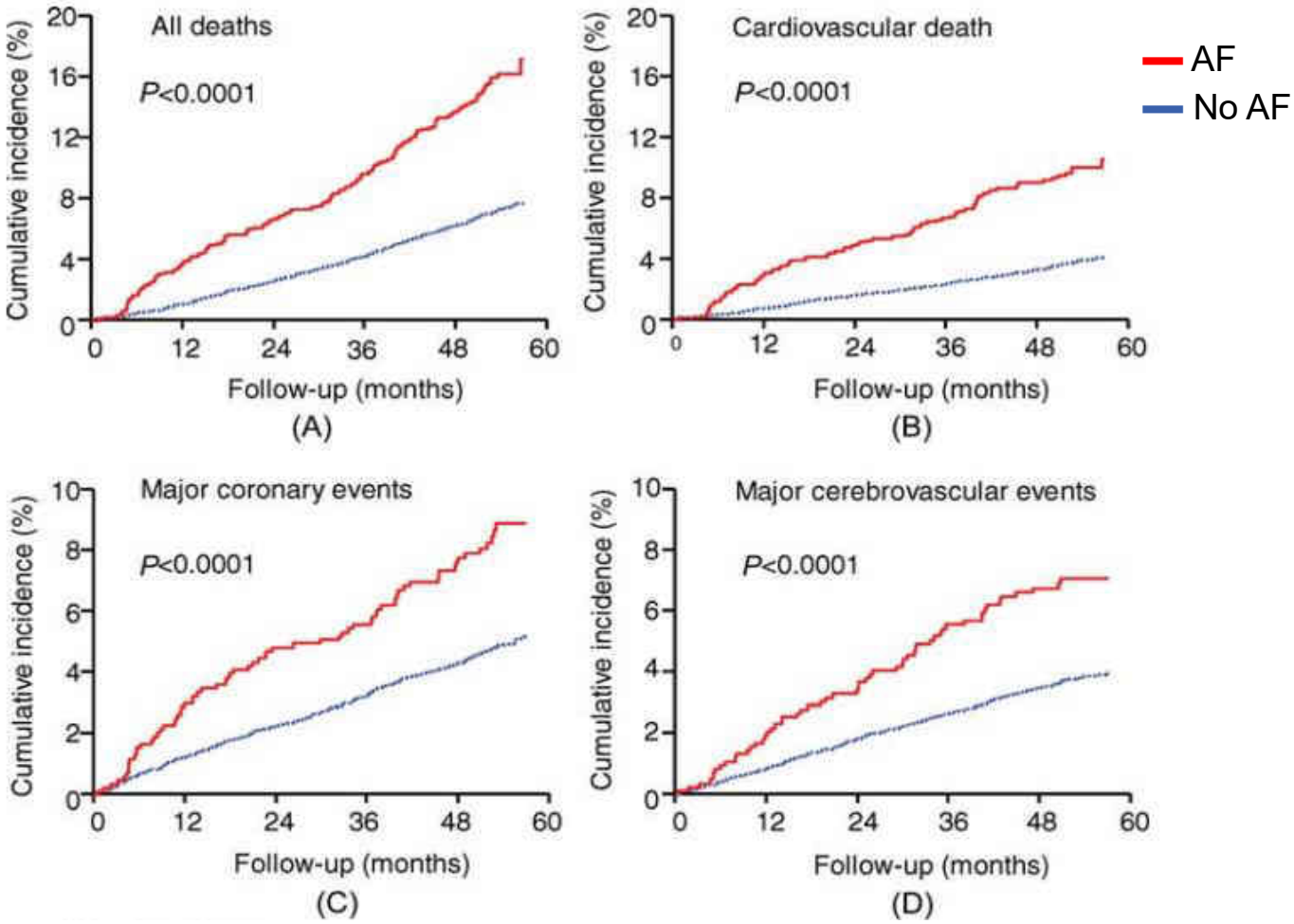


- **Microvascular complications in DM can damage the kidneys[4]**
- The rate of **renal decline in diabetic patients is double** that of patients without diabetes, over 2 years[5]
- **Diabetic kidney disease occurs in around one-third of patients with type 2 DM[6]**

1. Echouffo-Tcheugui JB et al. J Am Coll Cardiol 2017;70:1325-1335.; 2. The Stroke Risk in Atrial Fibrillation Working Group. *Neurology* 2007;69:546–554; 3. Bansilal S et al. *Am Heart J* 2015;170:675–682.e8;
4. Beckman JA et al. *JAMA* 2002;287:2570–2581; 5. Hemmelgarn BR, et al. Kidney Int. 2006;69:2155–2161;
6. Pecoits-Filho P et al. *Diabetol Metab Syndr* 2016;8:50.

AF is Associated with Substantially Increased Risks of Death and Cardiovascular Events in Patients with Type 2 Diabetes

Impact of atrial fibrillation on the risks of serious clinical outcomes in patients with Type 2 Diabetes



Adapted from Du X et al. *Eur Heart J.* 2009 May;30(9):1128-35

Diabetes as Risk Factor for Thromboembolic Events

The 2009 Birmingham Schema expressed as a Point-Based Scoring System, with the Acronym CHA_2DS_2–VASc[1]

Risk Factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65-74 y	1
Sex category (ie female gender)	1

Univariate Predictive Power of Risk Factors for Thromboembolic Events[1]

	Univariate *P* Value	OR[a]
Age > 75	.083	1.46 (0.63-3.35)
Female	.017	2.53 (1.08-5.92)
Stroke/TIA/TE	.023	2.22 (0.78-6.35)
Hypertension	.349	1.01 (0.38-2.66)
Diabetes	.048	1.79 (0.73-4.40)
Heart failure	.967	0.72 (0.27-1.88)
LVEF < 40	.335	0.34 (0.04-2.73)
Vascular disease[b]	.022	2.27 (0.94-5.46)

[a] All results other than LVEF from model without LVEF.
[B] Coronary artery disease, peripheral vascular disease, or a previous thromboembolism other than stroke/TIA.

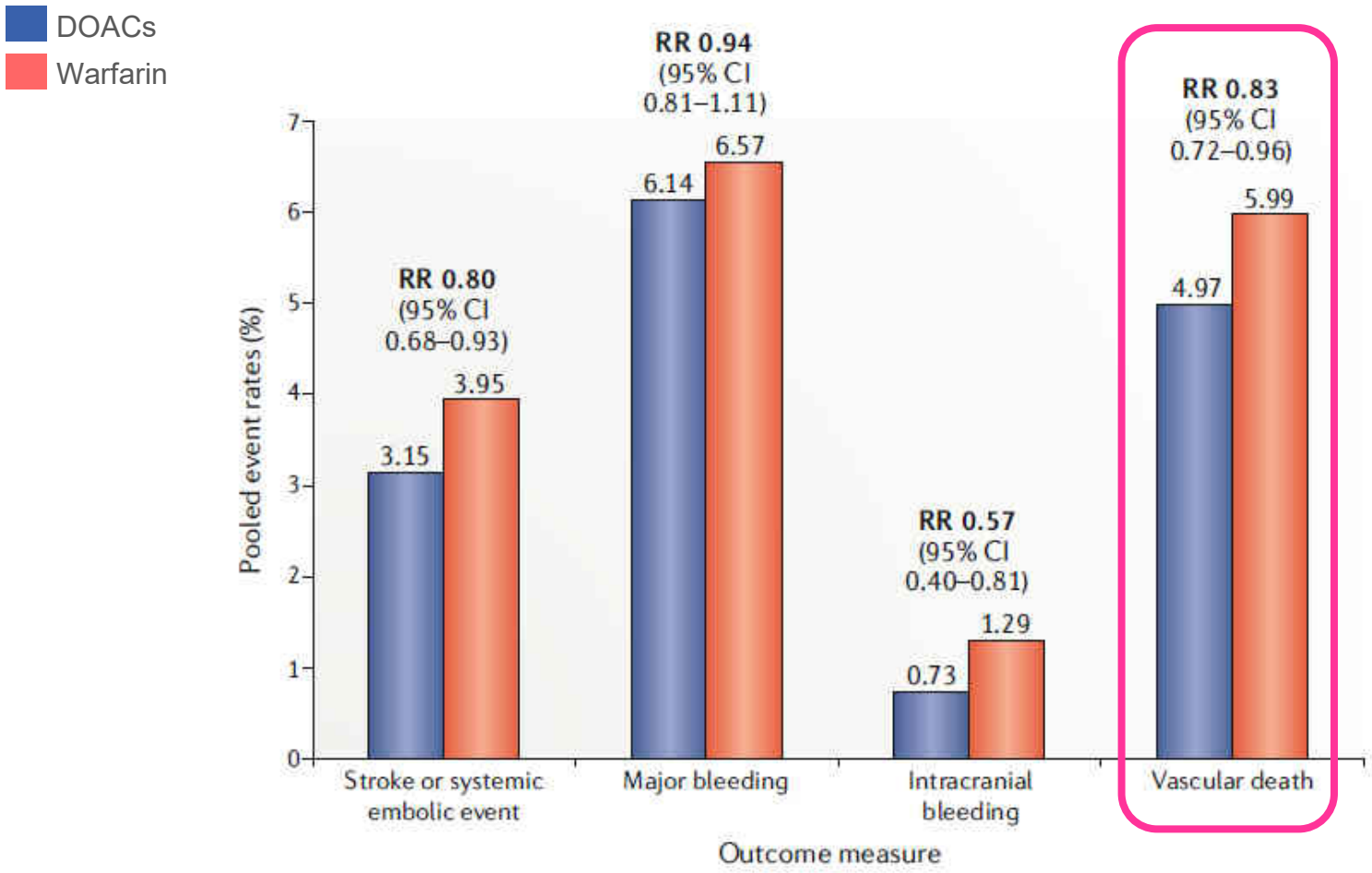
DM independently increases the risk of stroke in patients with AF by 1.7 fold[2]

The duration of diabetes (>3 years) was strongly associated with increased risk of stroke compared to having diabetes for less than 3 years[2]

1. Adapted from Lip GY et al. *Chest* 2010;137(2):263-272;
2 Oladiran O et al. *J Community Hosp Intern Med Perspect*. 2019 Apr;9(2):113–120

The Protection of DOACs in Atrial Fibrillation Patients with Diabetes

Anticoagulation in Patients with Diabetes Mellitus and AF



Pooled event rates of the various outcome measures from DOACs phase III trials.
No interaction between diabetes status and benefits of DOACs was found.

Patti G et al. *Diabetes Metab Res Rev*. 2017;33:e2876; Patti G et al. *Nat Rev Cardiol*. 2019 Feb;16(2):113-130

Decrease of Vascular Death by NOACs Was Significant in Diabetic Patients

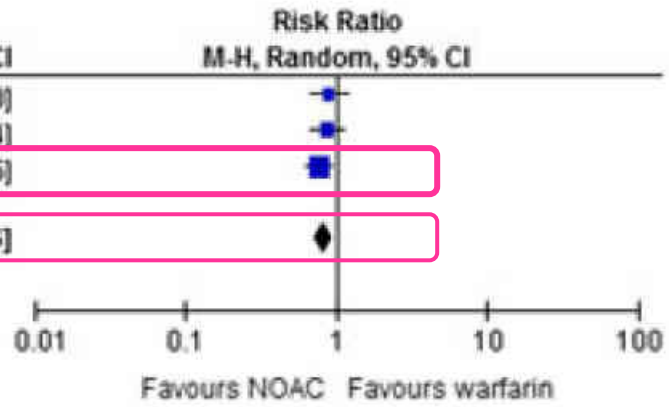
Vascular death

Diabetes

Study	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE	79	2284	88	2263	23.0%	0.89 [0.66, 1.20]
RE-LY	95	1402	109	1410	29.1%	0.88 [0.67, 1.14]
ROCKET-AF	152	2878	192	2817	48.0%	0.77 [0.63, 0.95]
Total (95% CI)		**6564**		**6490**	**100.0%**	**0.83 [0.72, 0.96]**
Total events	326		389			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.80$, df = 2 (P = 0.67); $I^2 = 0\%$

Test for overall effect: Z = 2.57 (P = 0.01)

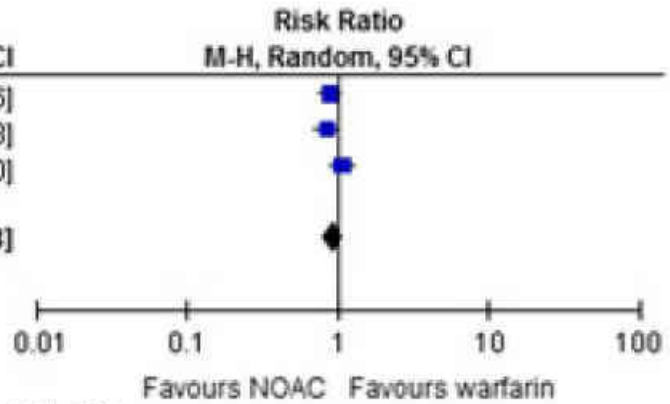


No Diabetes

Study	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE	229	6836	256	6818	35.3%	0.89 [0.75, 1.06]
RE-LY	179	4674	208	4612	31.2%	0.85 [0.70, 1.03]
ROCKET-AF	223	4253	209	4316	33.5%	1.08 [0.90, 1.30]
Total (95% CI)		**15763**		**15746**	**100.0%**	**0.94 [0.81, 1.08]**
Total events	631		673			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.65$, df = 2 (P = 0.16); $I^2 = 45\%$

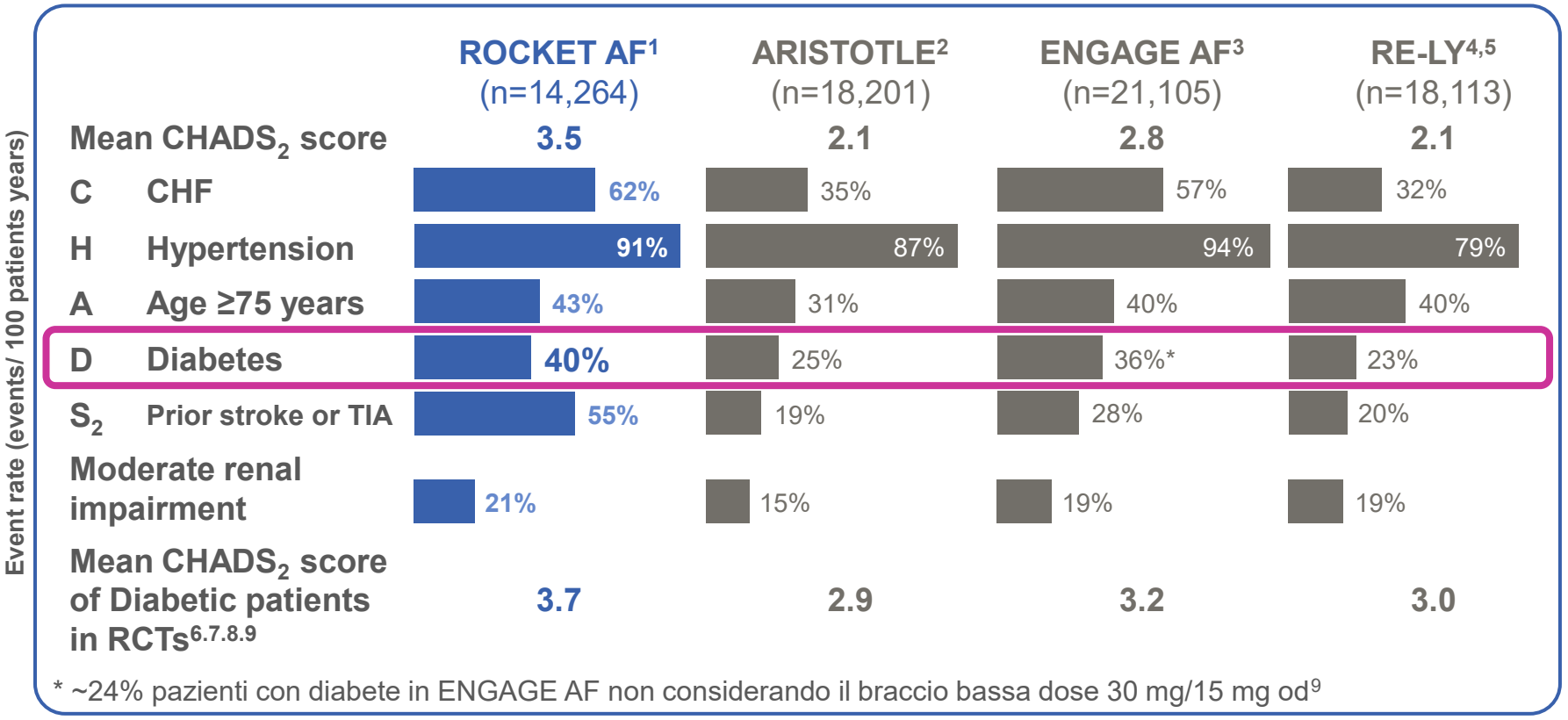
Test for overall effect: Z = 0.88 (P = 0.38)



Test for subgroup differences: $Chi^2 = 1.46$, df = 1 (P = 0.23), $I^2 = 31.4\%$

Patti G et al. *Diabetes Metab Res Rev*. 2017;33:e2876

40% of ROCKET AF Patients Had Diabetes Mellitus with a mean $CHADS_2$ Score of 3.7



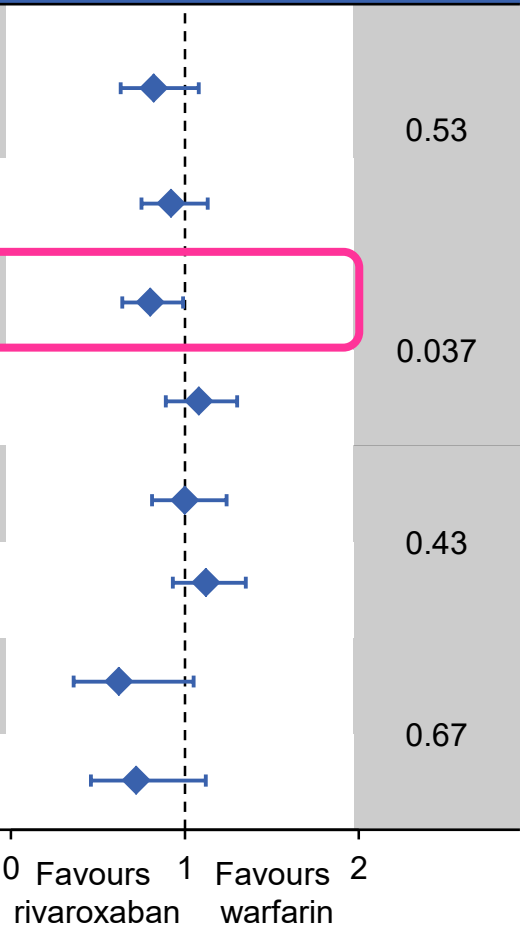
* ~24% pazienti con diabete in ENGAGE AF non considerando il braccio bassa dose 30 mg/15 mg od[9]

AF patients studied in ROCKET AF had a higher risk of stroke than patients in other phase III trials with NOACs

1, Patel MR *et al*, *N Engl J Med* 2011;365:883–891; 2. Granger CB *et al*, *N Engl J Med* 2011;365:981–992;
3. Giugliano RP *et al*, *N Engl J Med* 2013;369:2093–2104; 4. Connolly SJ *et al*, *N Engl J Med* 2009;361:1139–1151;
5. Eikelboom JW *et al*, *Circulation* 2011;123:2363–2372 6. Bansilal S.et al. *Am Heart J*.2015;170(4):675–82.
7. Ezekowitz JA et al, *EHJ* 2015:86-94; 8. Brambatti M. *Int J Cardiol*. 2015;196:127-31;
9. Plitt A et al, *Int J Cardiol*. 2020 Jan 30 pii: S0167-5273(19)35229-5 [Epub ahead of print]

ROCKET AF: Rivaroxaban Showed Consistent Safety & Efficacy Compared with Warfarin in AF Patients with DM

Efficacy outcome		Rivaroxaban events/100 PY (total events) n=7131	Warfarin events/100 PY (total events) n=7133	HR (95% CI)	HR (95% CI)	*p*-value (intx)
Primary efficacy outcome: Stroke or SE	DM	1.74 (95)	2.14 (114)	0.82 (0.63–1.08)		0.53
	No DM	2.12 (174)	2.32 (192)	0.92 (0.75–1.13)		
Vascular death	DM	2.83 (152)	3.65 (192)	0.80 (0.64–0.99)		0.037
	No DM	2.73 (223)	2.53 (209)	1.08 (0.89–1.30)		
Major bleeding	DM	3.79 (165)	3.90 (169)	1.00 (0.81–1.24)		0.43
	No DM	3.47 (230)	3.17 (217)	1.12 (0.93–1.35)		
ICH	DM	0.50 (22)	0.82 (36)	0.62 (0.36–1.05)		0.67
	No DM	0.49 (33)	0.69 (48)	0.72 (0.46–1.12)		

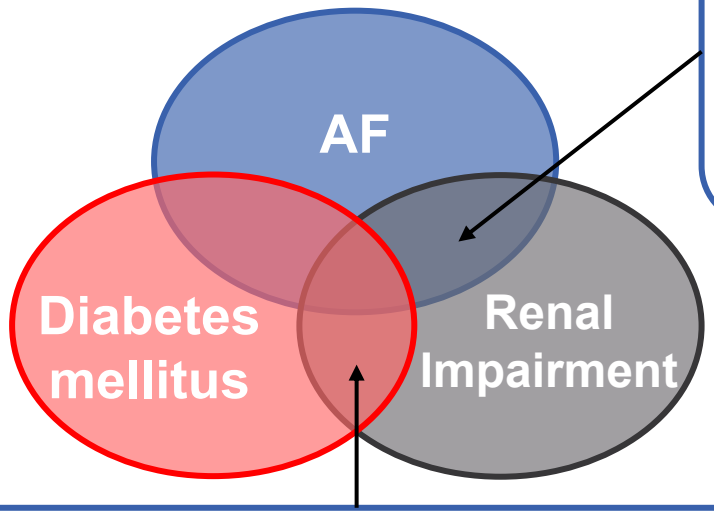


*Results for vascular death are from post hoc analysis
Mean baseline $CHADS_2$ score 3.7 for diabetic and 3.3 for non-diabetic patients.

Bansilal S.et al. *Am Heart J*.2015;170(4):675–82

AF, Renal Impairment and anticoagulant drugs

Overlapping Comorbidities Increase the Complexity of Stroke Prevention Particularly in AF Patients



- **65%** of patients with **AF** have **renal impairment**[1]
- CKD is associated with an increased risk of developing AF and *vice versa*[2], as well as bleeding[3,4]

- **Microvascular complications in DM can damage the kidneys**[5]
- The rate of **renal decline in diabetic patients is double** that of patients without diabetes, over 2 years[6]
- **Diabetic kidney disease occurs in around one-third of patients with type 2 DM**[7]

1. Boriani G et al. *Sci Rep* 2016;6:30271; 2. Boriani G et al. *Europace* 2015;17:1169–1196; 3. Kirchhof P et al. *Eur Heart J* 2016;37;2893–2962; 4. Olesen JB et al. *N Engl J Med* 2012;367:625–635; 5. Beckman JA et al. *JAMA* 2002;287:2570–2581; 6. Hemmelgarn BR, et al. Kidney Int. 2006;69:2155–2161;
7. Pecoits-Filho P et al. *Diabetol Metab Syndr* 2016;8:50.

There is limited data regarding warfarin use in CKD as prior studies did not quantify CKD patients or only included low numbers of them. Warfarin use in end-stage renal disease (ESRD) is especially controversial due to conflicting evidence

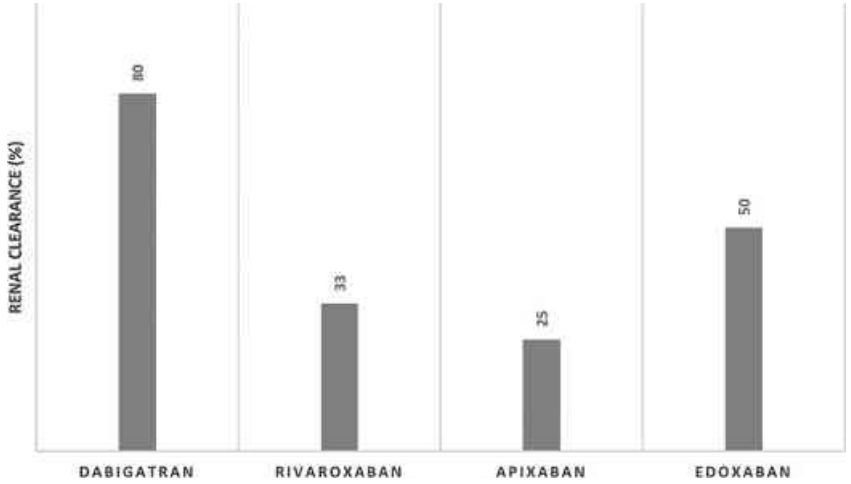
Major trials supporting the use of DOACs excluded patients with severe CKD or ESRD. In addition, patients with CKD have been shown to be at especially increased risk of off-label dosing of DOACs, with overdosing associated with increased mortality, and underdosing associated with increased cardiovascular hospitalizations

Bhatia HS et al. *Clinical Cardiology 2018*;41:1395–1402.

Options for therapeutic anticoagulation to reduce thromboembolism risk in pts with AF and CKD

In pts **on dialysis** warfarin was not beneficial for stroke prevention, with a 44% increased risk of bleeding.
This is prtobably due to:

- Impaired heamostasis and comorbidities
- Use of heparin during dialysis
- Decreased Vit K-dependend inhibitors of calcification with accelerated vascular calcium deposition
- Lower TTR



CKD stage	Warfarin	DOACs
Mild to moderate Stages 2-3 (eGFR 30-90 mL/min/1.73 m^2)	Primarily observational data supporting use	High quality data support use, may be superior to warfarin
Severe Stage 4 (eGFR 15-29 mL/min/1.73 m^2)	Limited data supports use	Pharmacologic studies allow for use with dose reductions, lack patient data
End stage renal disease Stage 5 (eGFR <15 mL/min/1.73 m^2 or on hemodialysis)	Majority of studies suggest lack of benefit and possible harm	*Dabigatran* removed by dialysis *Rivaroxaban* has safe drug levels based on modeling, but lacks patient data *Apixaban* safe and effective based on modeling and retrospective data, prospective data needed

Abbreviations: AF, atrial fibrillation; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate.

Bhatia HS et al. *Clinical Cardiology 2018*;41:1395–1402.

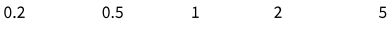
Cochrane Database of Systematic Reviews 2017
Art. No.: CD011373. DOI: 10.1002/14651858.CD011373.pub2

[Intervention Review]

Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease

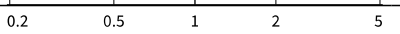
Analysis 2.1. Comparison 2 Direct oral anticoagulants versus warfarin: subgroup analysis for participants with CrCl 30 to 50 mL/min, Outcome 1 All strokes and systemic embolic events.

Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE Study 2010	28/1365	34/1382		20.21%	0.83[0.51,1.37]
ENGAGE AF-TIMI 48 Study 2013	31/1309	35/1311		21.7%	0.89[0.55,1.43]
J-ROCKET AF Study 2012	4/141	5/143		2.95%	0.81[0.22,2.96]
RE-LY Study 2009	47/2428	30/1126		24.14%	0.73[0.46,1.14]
ROCKET AF Study 2010	43/1474	51/1476		31%	0.84[0.57,1.26]
Total (95% CI)	**6717**	**5438**		**100%**	**0.82[0.66,1.02]**



Analysis 2.2. Comparison 2 Direct oral anticoagulants versus warfarin: subgroup analysis for participants with CrCl 30 to 50 mL/min, Outcome 2 Major bleeding.

Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE Study 2010	43/1357	83/1380		22.14%	0.53[0.37,0.76]
ENGAGE AF-TIMI 48 Study 2013	50/1302	66/1305		22.2%	0.76[0.53,1.09]
J-ROCKET AF Study 2012	7/141	8/143		5.66%	0.89[0.33,2.38]
RE-LY Study 2009	133/2428	62/1126		26.11%	0.99[0.74,1.33]
ROCKET AF Study 2010	66/1474	69/1476		23.89%	0.96[0.69,1.33]
Total (95% CI)	**6702**	**5430**		**100%**	**0.8[0.62,1.03]**
Total events: 299 (DOAC), 288 (Warfarin)					
Heterogeneity: Tau^2=0.04; Chi^2=8.51, df=4(P=0.07); I^2=52.99%					
Test for overall effect: Z=1.71(P=0.09)					

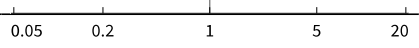


[Intervention Review]

Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease

Analysis 3.1. Comparison 3 Direct oral anticoagulants versus warfarin: subgroup analysis for participants with CrCl 15 to 30 mL/min, Outcome 1 All strokes and systemic embolic events.

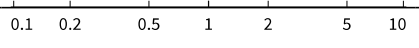
Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE Study 2010	4/137	7/133		79.5%	0.55[0.17,1.85]
ENGAGE AF-TIMI 48 Study 2013	2/68	1/52		20.5%	1.53[0.14,16.41]
Total (95% CI)	**205**	**185**		**100%**	**0.68[0.23,2]**
Total events: 6 (DOAC), 8 (Warfarin)					
Heterogeneity: Tau^2=0; Chi^2=0.56, df=1(P=0.46); I^2=0%					
Test for overall effect: Z=0.7(P=0.49)					



Less with DOAC — Less with warfarin

Analysis 3.2. Comparison 3 Direct oral anticoagulants versus warfarin: subgroup analysis for participants with CrCl 15 to 30 mL/min, Outcome 2 Major bleeding.

Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE Study 2010	5/136	16/132		100%	0.3[0.11,0.8]
Total (95% CI)	**136**	**132**		**100%**	**0.3[0.11,0.8]**
Total events: 5 (DOAC), 16 (Warfarin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.4(P=0.02)					



Less with DOAC — Less with warfarin

Bleeding risk and efficacy of apixaban vs warfarin in patients with advanced CKD or ESRD

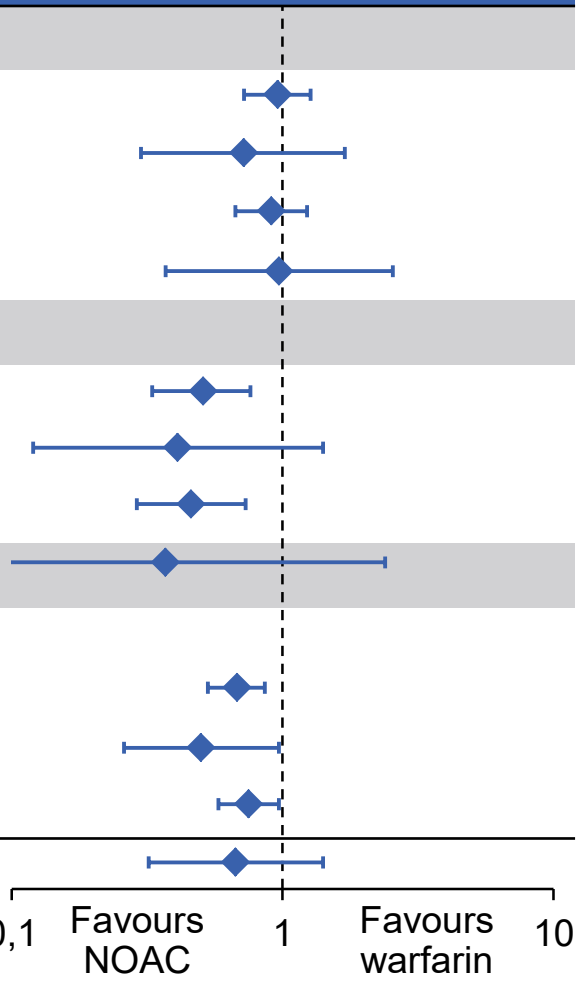
- ✓ **Siontis**: Retrospective administrative study using the US Renal Data System reflecting Medicare patients
- ✓ **Reed**: retrospective small observational study (warfarin group had a higher rate of associated SAPT/DAPT)
- ✓ **Chokesuwattanaskul**: a meta-analysis of 5 trials

	Siontis 2018	Reed 2018	Chokesuwattanaskul 2018
Number in study	25 523	124	43 850
OR of major bleed with apixaban	0.72 (CI 0.59-0.87)	0.25(CI: 0.07-0.82)	0.42 (CI: 0.28-0.61)
OR of stroke/ embolism with apixaban	0.88 (CI: 0.69-1.12)	NA	OR = 0.56 (CI: 0.23-1.39)
Bleeding risk	Favors apixaban	Favors apixaban	Favors apixaban
Efficacy	No significant difference	No significant difference	No significant difference

Weber J et al. *Europen J Haemtology 2019; 102: 312-318.*

1 yy Renal Function deterioration in AF Patients Receiving DOACs

Renal outcome	Event rate/100 PYs	HR	HR (95% CI)
Apixaban			
≥30% decline in eGFR	24.58	0.96	
Doubling of creatinine	3.00	0.72	
Acute kidney injury	13.68	0.91	
Kidney failure	1.93	0.97	
Dabigatran			
≥30% decline in eGFR	12.30	0.51	
Doubling of creatinine	1.7	0.41	
Acute kidney injury	6.49	0.46	
Kidney failure	0.67	0.37	
Rivaroxaban			
≥30% decline in eGFR	17.25	0.68	
Doubling of creatinine	2.11	0.5	
Acute kidney injury	11.07	0.75	
Kidney failure	1.3	0.67	



With diabetes at baseline (n=4,333)

Not intended for direct comparison

Yao X et al. *J Am Coll Cardiol* 2017;70:2621–2632.

2019 ESC-EASD Guidelines on Diabetes, Pre-diabetes and CVD

Recommendations for the management of arrhythmias in patients with diabetes

Recommendations	Class[a]	Level[b]
Oral anticoagulation with a NOAC, which is preferred over a VKA, is recommended in patients with DM aged >65 years with AF and a CHA_2DS_2-VASc score ≥2, if not contraindicated.[503]	I	A

ESC European Society of Cardiology

When DM and AF coexist, there is a substantially higher risk of all cause death, **CV death**, stroke, and HF

These findings suggest that AF identifies subjects with DM who are likely to obtain greater benefits from aggressive management of cardiovascular risk factors

Cosentino F et al, *Eur Heart J* 2020 Jan 7;41(2):255-323

Recent Guidelines Recommend NOACs in Patients with AF to Reduce Risk of Renal Outcomes

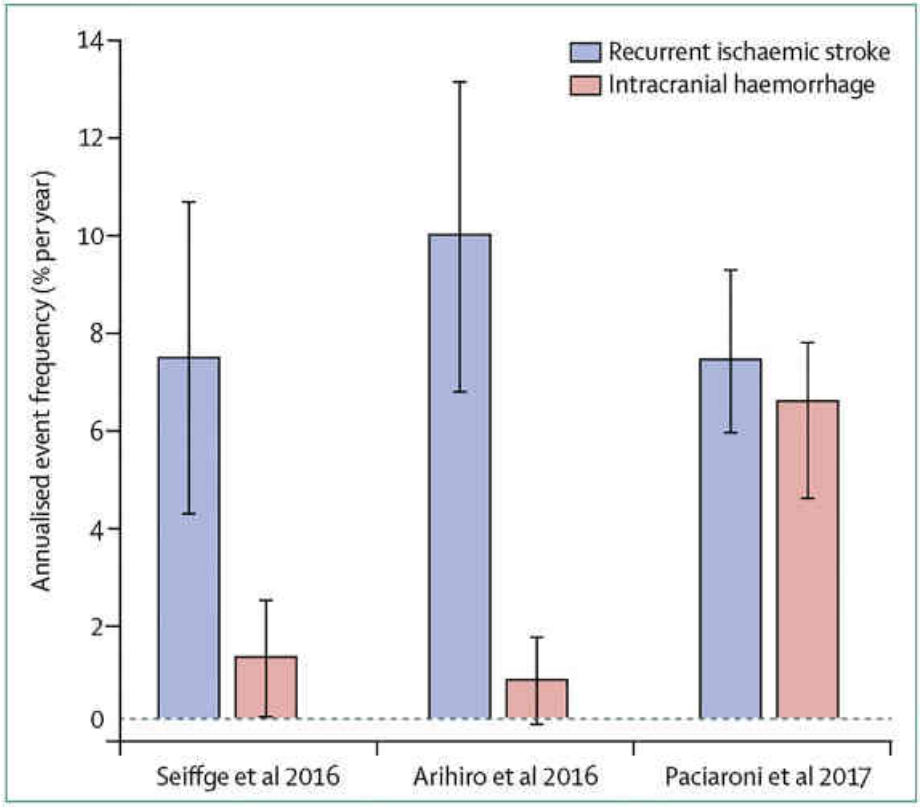
CKD stage	AHA/ACC/HRS	ESC	CCS
Mild to moderate Stages 2-3 (eGFR 30-90 mL/min/1.73 m^2)	Warfarin (class 1, LOE A) DOACs (class 1, LOE B) with dose adjustment for moderate CKD (class IIb, LOE C)	DOACs recommended in general (mild to moderate CKD not mentioned)	DOACs recommended in general (mild to moderate CKD not mentioned)
Severe Stage 4 (eGFR 15-29 mL/min/1.73 m^2)	Warfarin recommended, DOACs may be considered (class IIb, LOE C)	Anticoagulation may safely be given (specific drugs not mentioned)	Warfarin recommended
End stage renal disease Stage 5 (eGFR <15 mL/min/1.73 m^2 or on hemodialysis)	Warfarin recommended (class IIa, LOE B), recommend against dabigatran and rivaroxaban (class III, LOE C)	No specific recommendation given	Cannot recommend routine anticoagulation for dialysis patients due to lack of data

Abbreviations: ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Associated; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; LOE, level of evidence.

Bhatia HS et al. *Clinical Cardiology 2018*;41:1395–1402.

How and when to treat NVAF patients after a cerebrovascular event?

Risk of recurrent ischemic strokeand intracranial haemorrhage in patients with AF and a recent ischemic stroke



Seiffge et al →205 pts, 79 yy, median treatment time 5 dd post stroke

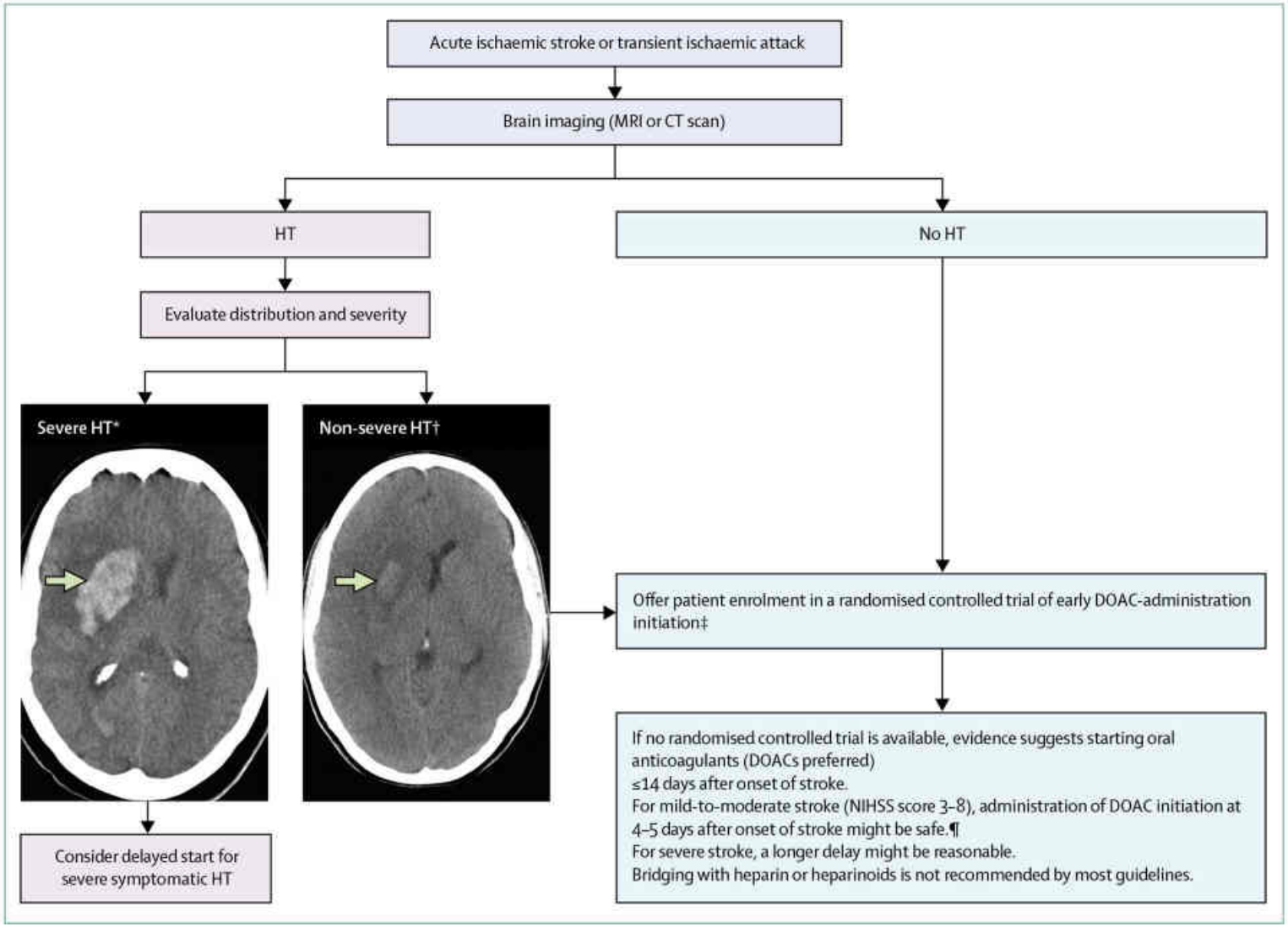
Arihiro et al →1192 pts, 78 yy, 5 days

Paciaroni et al →1127 pts, 76yy, 8 days for dabigatran/rivaroxaban, 7 days for apixaban, stroke piu' gravi

Prospective observational studies reported that early DOAC treatment was associated with a low frequency of clinical symptomatic HT, wheras later DOAC administration initiation (> 7 dd or > 14 dd) was associated with ↑ rate of recurrent ischemic stroke

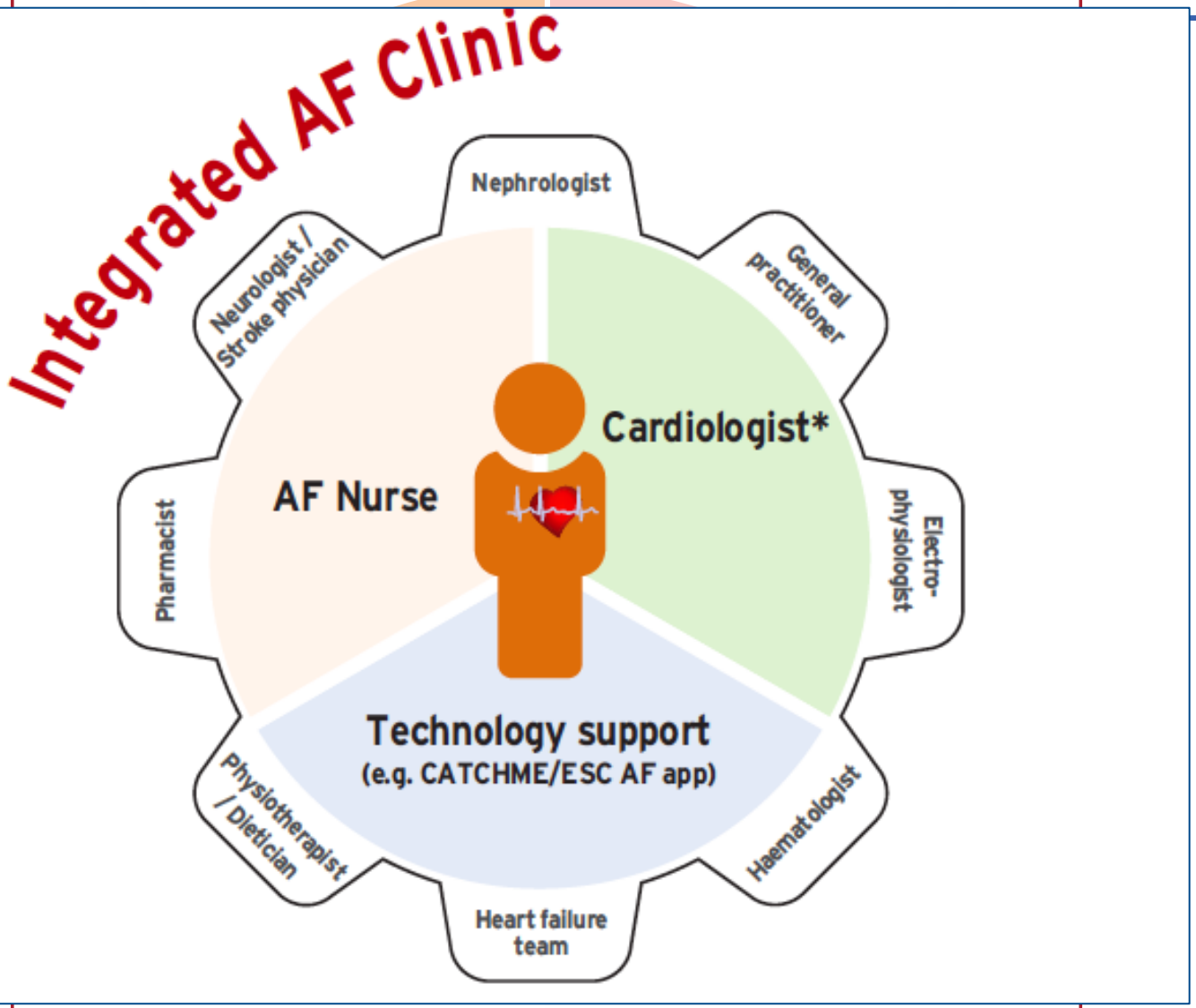
Bhatia HS et al. *Clinical Cardiology 2018*;41:1395–1402.

Timing for initiation of direct anticoagulant administration



Seiffge DJ et al. *Lancet Neurology 2019*;18(1):117-126.

Integrated AF management team



ESC guidelines FA 2020