FIBRILLAZIONE ATRIALE E NEOPLASIE

METANALISI DI CONFRONTO TRA ANTICOAGULANTI ORALI DIRETTI E WARFARIN

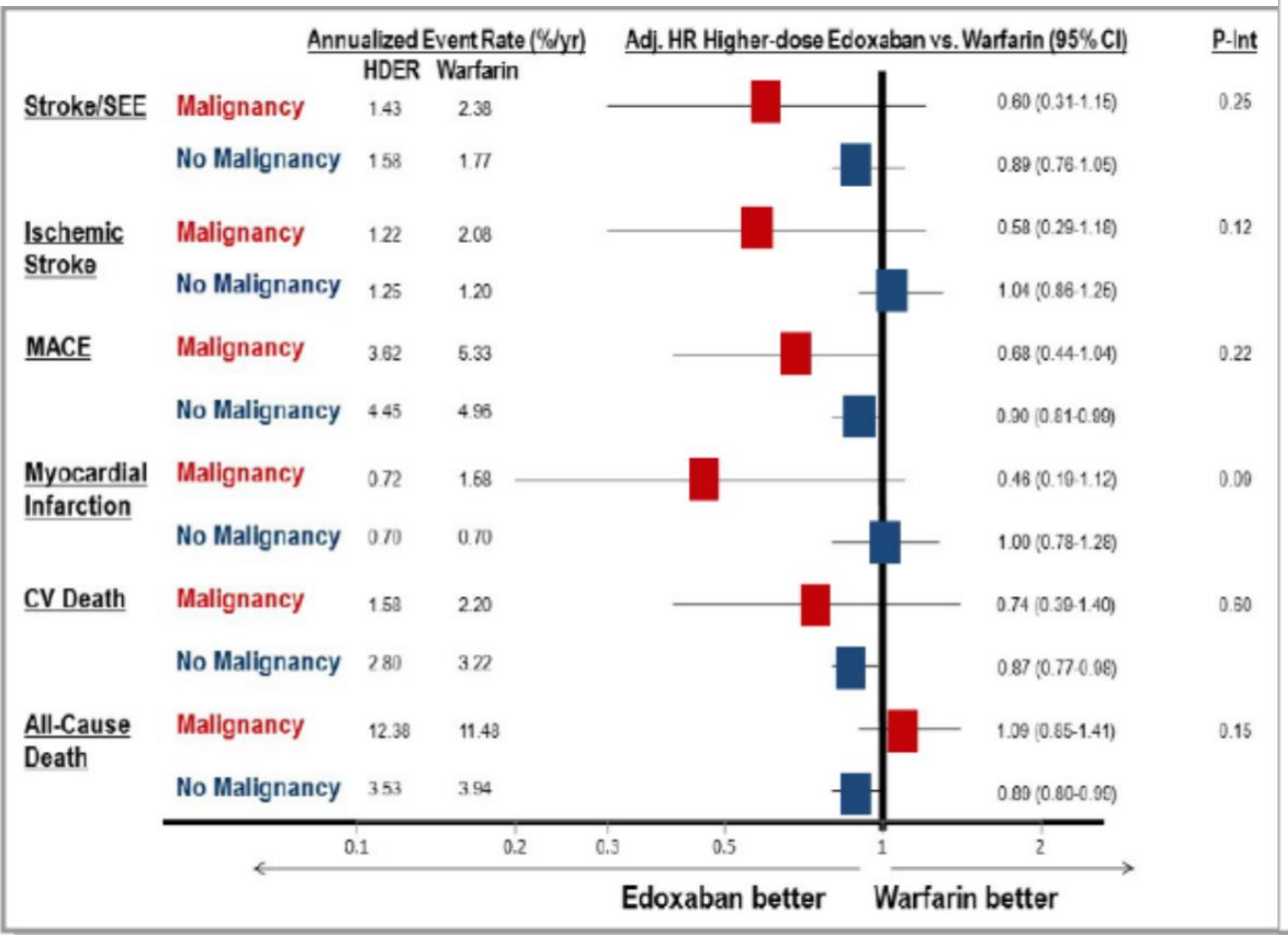
BACKGROUND

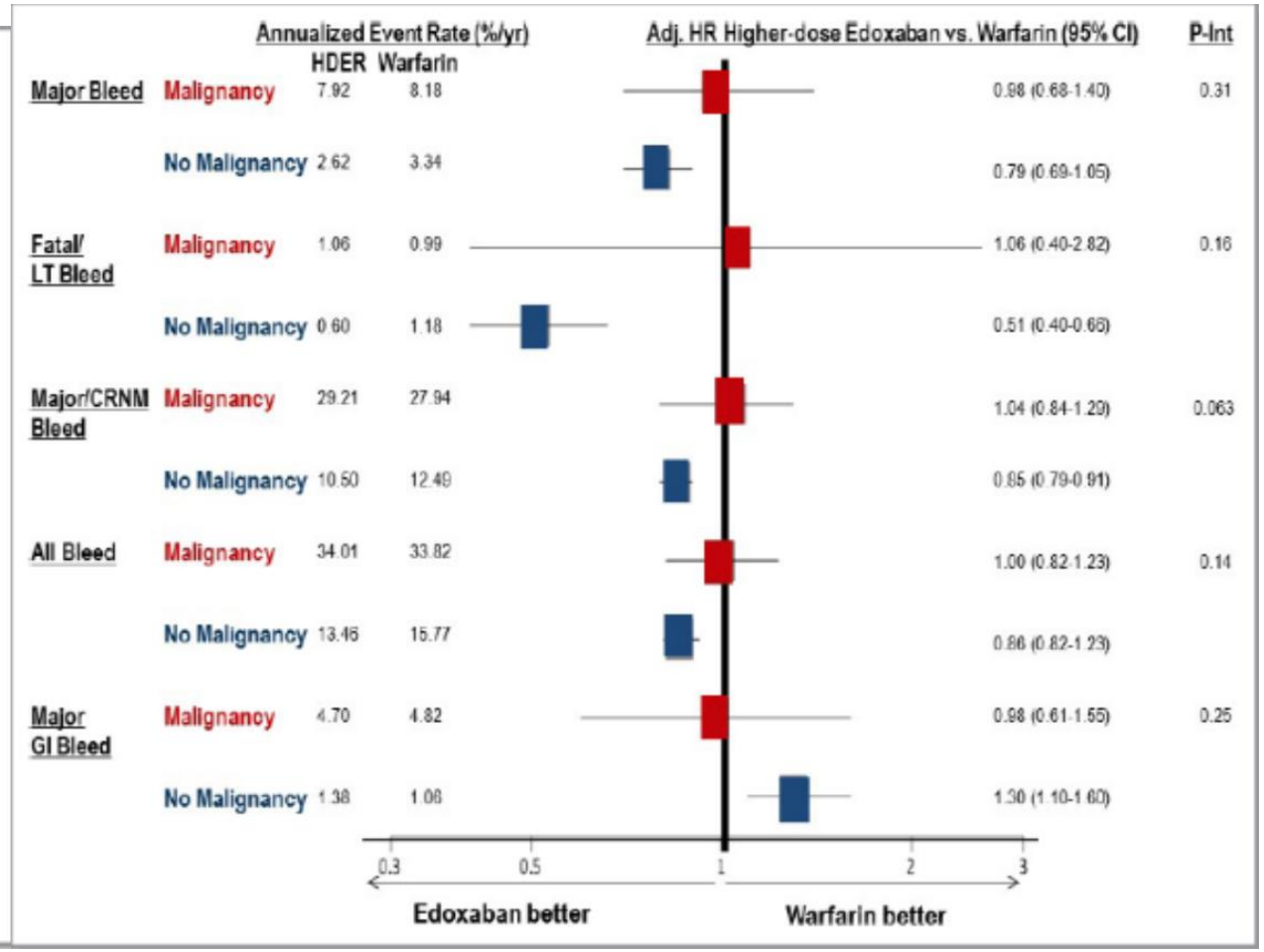
- **Patients with cancer are at higher risk of**
  - Atrial fibrillation
  - Thromboembolic complications (cancer per se, anticancer treatments…)
  - Bleeding (intracranial metastases, thrombocytopenia or actively bleeding high-risk cancer)
- **Warfarin limitations**
  - frequent need for invasive procedures
  - drug-to-drug interactions with antineoplastic agents
  - fluctuations in vitamin K absorption because of common liver function abnormalities, mucositis, diarrhea
  - only 12% of cancer patients treated with warfarin achieve an INR stably in the therapeutic range

BACKGROUND

- **Advantages of direct oral anticoagulants (DOACs)**
  - more predictable dose–response relationship
  - shorter half-life
  - fewer drug and food interactions

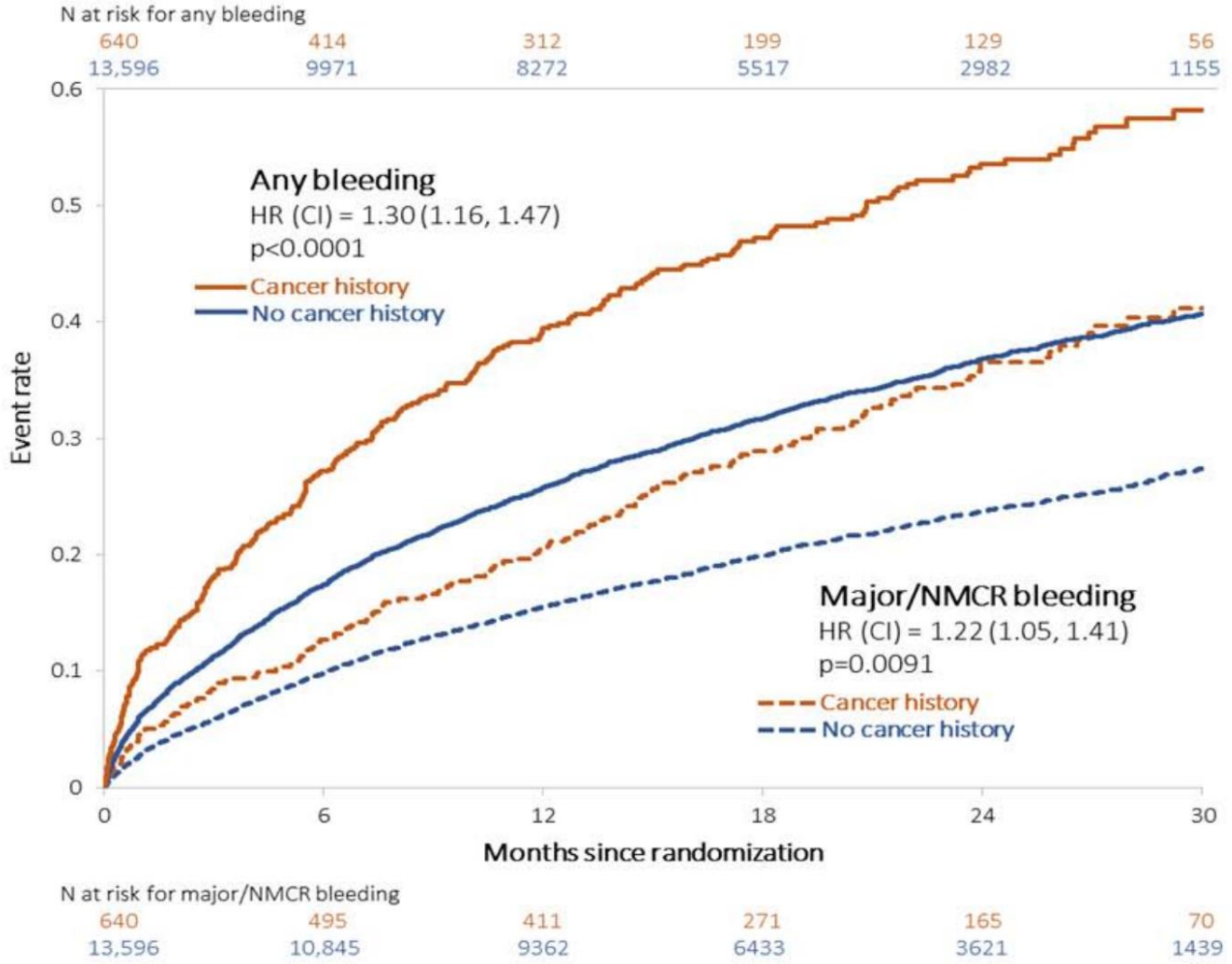
EDOXABAN





Fanola et al, J Am Heart Assoc. 2018

RIVAROXABAN



Chen et al. Eur Heart J Quale care Clin Outcomes, 2019

APIXABAN

	Active/Treated			No Cancer			p-value*
	Apixaban	Warfarin	HR (95% CI)	Apixaban	Warfarin	HR (95% CI)	
Efficacy endpoints							
Stroke or SE	0 (0%)	5 (6.2%)	0 (0–infinity)	196 (2.3%)	251 (3.0%)	0.77 (0.64–0.93)	0.9469
Overall death	5 (6.6%)	11 (13.6%)	0.45 (0.16–1.29)	548 (6.5%)	626 (7.4%)	0.87 (0.77–0.97)	0.2209
Ischemic stroke	0 (0%)	3 (3.7%)	0 (0–infinity)	147 (1.7%)	166 (2.0%)	0.88 (0.70–1.10)	0.9556
MI	0 (0%)	1 (1.2%)	0 (0–infinity)	78 (0.9%)	90 (1.1%)	0.86 (0.63–1.16)	0.9668
VTE: PE/DVT	0 (0%)	1 (1.2%)	0 (0–infinity)	27 (0.3%)	33 (0.4%)	0.81 (0.49–1.35)	0.9775
Safety endpoints							
ISTH major bleeding	1 (1.3%)	5 (6.2%)	0.19 (0.02–1.59)	303 (3.6%)	430 (5.1%)	0.69 (0.59–0.80)	0.2339
Major or CRNM bleeding	6 (7.9%)	10 (12.4%)	0.56 (0.20–1.54)	560 (6.6%)	810 (9.6%)	0.67 (0.60–0.75)	0.7253
Any bleeding	27 (35.5%)	30 (37.0%)	0.93 (0.55–1.56)	2149 (25.3%)	2815 (33.3%)	0.71 (0.67–0.75)	0.3089
Intracranial bleeding	0 (0%)	2 (2.5%)	0 (0–infinity)	52 (0.6%)	113 (1.3%)	0.45 (0.32–0.63)	0.9701
Net composite endpoint							
Composite efficacy endpoint†	5 (6.6%)	16 (19.8%)	0.30 (0.11–0.83)	734 (8.6%)	841 (10.0%)	0.86 (0.78–0.95)	0.0421
Composite endpoint‡	6 (7.9%)	18 (22.2%)	0.32 (0.13–0.81)	948 (11.2%)	1124 (13.3%)	0.83 (0.76–0.90)	0.0441

Melloni et al,
Am J Med 2017

Direct oral Xa inhibitors versus warfarin in patients with cancer and atrial fibrillation: a meta-analysis

Matteo Casula[a,b], Federico Fortuni[a,b], Francesca Fabris[a,b], Sergio Leonardi[a,b], Massimiliano Gnecchi[a,b], Antonio Sanzo[a], Alessandra Greco[c] and Roberto Rordorf[a]

Casula et a., Journal of Cardiovascular Medicine 2020

STUDY CHARACTERISTICS

Table 1 Study characteristics

First author	Year of publication	Original trial	Number of patients with cancer	Treatment	Control	Primary efficacy outcome	Primary safety outcome	Active cancer definition	Median follow-up (years)
Chen	2019	ROCKET AF	640	Rivaroxaban (20 mg or 15 mg OD)	Warfarin	All-cause stroke or SE	Major or CRNMB	'Actively treated cancer' (if receiving cancer treatment with hormonal or ChT agents)	1.9
Melloni	2017	ARISTOTLE	1236	Apixaban (5 mg or 2.5 mg b.i.d.)	Warfarin	Stroke or SE	MB (ISTH)	'Active (or recent) cancer' (active or treated within the past 1 year)	1.8
Fanola	2018	ENGAGE AF-TIMI 48	1153	Edoxaban (60 mg or 30 mg OD)	Warfarin	Time to 1st stroke or SE	MB (ISTH)	Postrandomization 'new or recurrent malignancy'	2.8

b.i.d., bis in die; ChT, chemotherapy; CRNMB, clinically relevant nonmajor bleeding; ISHT, international society of thrombosis and haemostasis; MB, major bleeding; OD, once a day; SE, systemic embolism.

Casula et a., Journal of Cardiovascular Medicine 2020

POPULATION CHARACTERISTICS

Table 2 Population characteristics

Original trial	Age (years)	Female (%)	BMI (kg/m^2)	Prior stroke, TIA or SE (%)	Hypertension (%)	Heart failure (%)	Prior use of VKA (%)	ASA (%)	PAF (%)	$CHADS_2$	CHA_2DS_2-VASc	HAS-BLED
ROCKET AF	72.2	39.7	28.2	54.7	90.5	62.5	62.4	36.5	17.6	3.5	–	2.8
ARISTOTLE	70.3	35.2	–	19.5	87.5	35.4	57.2	30.9	–	2.1	3.4	1.7
ENGAGE AF-TIMI 48	72.1	37.6	28.7	28.3	93.6	57.4	59.0	–	25.4	2.8	4.3	2.5

ACEi, ACE inhibitors; ARBs, angiotensin receptor blockers; ASA, aspirin; BB, beta blockers; PAF, paroxysmal atrial fibrillation; SE, systemic embolism; TIA, transient ischemic attack; VKA, vitamin K antagonists.

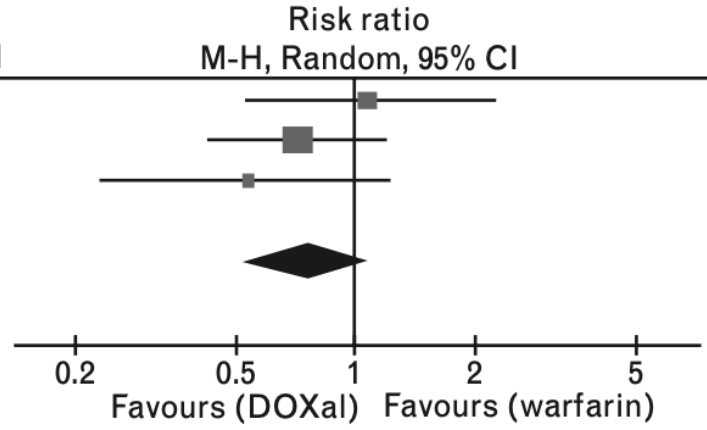
Casula et a., Journal of Cardiovascular Medicine 2020

STROKE OR SYSTEMIC EMBOLISM AND MAJOR BLEEDING IN PATIENTS WITH CANCER

– Stroke or SE

Study or subgroup	DOXal Events	DOXal Total	warfarin Events	warfarin Total	Weight	Risk ratio M-H, Random, 95% CI
ARISTOTLE	15	615	14	621	26.9%	1.08 (0.53, 2.22)
ENGAGE AF-TIMI 48	33	758	24	395	53.2%	0.72 (0.43, 1.20)
ROCKET AF	8	307	16	329	20.0%	0.54 (0.23, 1.23)
Total (95% CI)		1680		1345	100.0%	0.76 (0.52, 1.10)
Total events	56		54			

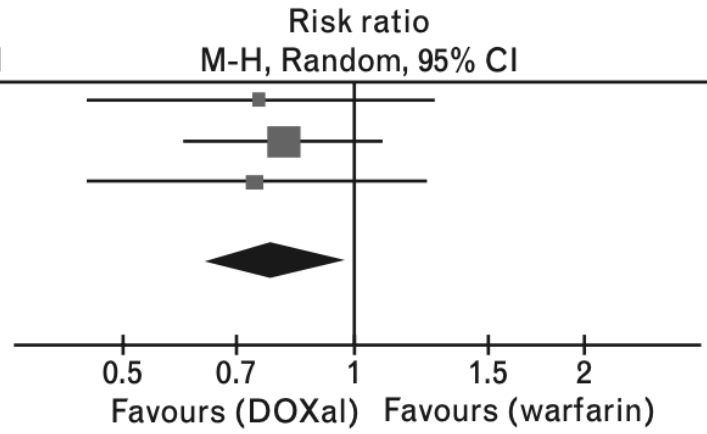
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.65$, df = 2 ($P = 0.44$); $I^2 = 0\%$
Test for overall effect: $Z = 1.48$ ($P = 0.14$)



– Major bleeding

Study or subgroup	DOXal Events	DOXal Total	warfarin Events	warfarin Total	Weight	Risk ratio M-H, Random, 95% CI
ARISTOTLE	24	615	32	621	19.4%	0.76 (0.45, 1.27)
ENGAGE AF-TIMI 48	98	758	63	395	60.7%	0.81 (0.61, 1.09)
ROCKET AF	23	309	33	331	20.0%	0.75 (0.45, 1.24)
Total (95% CI)		1682		1347	100.0%	0.79 (0.63, 0.99)
Total events	145		128			

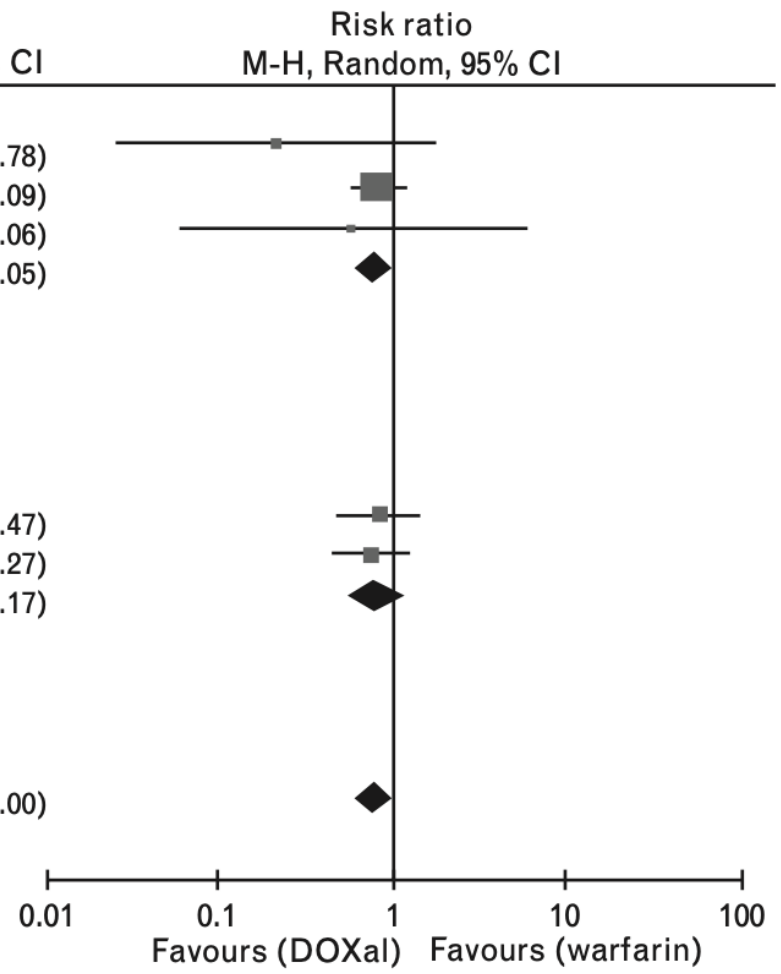
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.10$, df = 2 ($P = 0.95$); $I^2 = 0\%$
Test for overall effect: $Z = 2.06$ ($P = 0.04$)



Casula et a., Journal of Cardiovascular Medicine 2020

MAJOR BLEEDING IN SUBGROUPS

Study or subgroup	DOXal Events	DOXal Total	warfarin Events	warfarin Total	Weight	Risk ratio M-H, Random, 95% CI
3.1.1 Active cancer						
ARISTOTLE	1	76	5	81	1.2%	0.21 (0.03, 1.78)
ENGAGE AF-TIMI 48	98	758	63	395	61.1%	0.81 (0.61, 1.09)
ROCKET AF	1	23	2	27	1.0%	0.59 (0.06, 6.06)
Subtotal (95% CI)		857		503	63.2%	0.79 (0.59, 1.05)
Total events	100		70			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.57$, df = 2 ($P = 0.46$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.63$ ($P = 0.10$)						
3.1.2 History of cancer						
ARISTOTLE	23	539	27	540	17.7%	0.85 (0.50, 1.47)
ROCKET AF	22	286	31	304	19.1%	0.75 (0.45, 1.27)
Subtotal (95% CI)		825		844	36.8%	0.80 (0.55, 1.17)
Total events	45		58			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.10$, df = 1 ($P = 0.75$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.16$ ($P = 0.25$)						
Total (95% CI)		1682		1347	100.0%	0.79 (0.63, 1.00)
Total events	145		128			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.67$, df = 4 ($P = 0.80$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.00$ ($P = 0.05$)						
Test for subgroup differences: $Chi^2 = 0.00$. df = 1 ($P = 0.95$). $I^2 = 0\%$						



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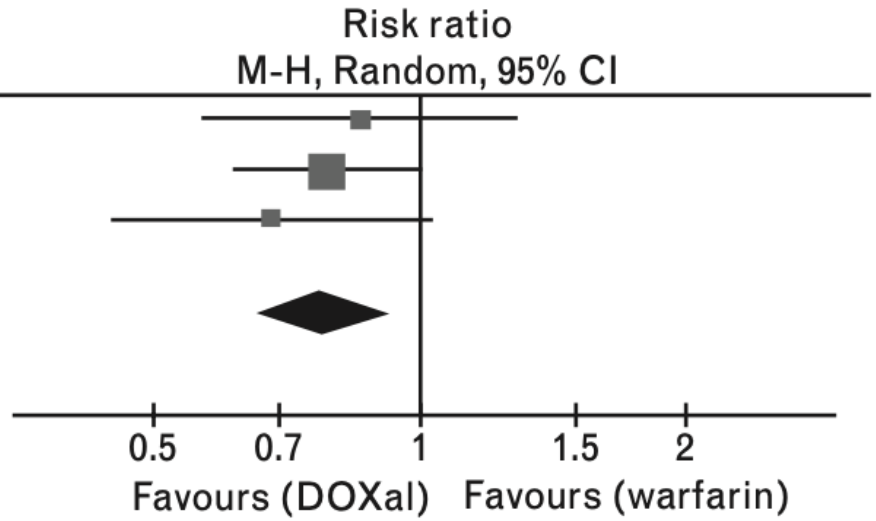
NET CLINICAL BENEFIT

Study or subgroup	DOXal Events	DOXal Total	warfarin Events	warfarin Total	Weight	Risk ratio M-H, Random, 95% CI
ARISTOTLE	39	615	46	621	20.7%	0.86 (0.57, 1.29)
ENGAGE AF-TIMI 48	131	758	87	395	59.7%	0.78 (0.62, 1.00)
ROCKET AF	31	309	49	331	19.6%	0.68 (0.44, 1.03)
Total (95% CI)		1682		1347	100.0%	0.78 (0.64, 0.94)
Total events	201		182			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.62$, df = 2 ($P = 0.73$); $I^2 = 0\%$

Test for overall effect: $Z = 2.65$ ($P = 0.008$)



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LIMITATIONS

- Only data from RCTs
  - post hoc analysis of the ROCKET AF trial: pts with a life expectancy < 2 years excluded
  - the overall consistence of the results in the active cancer population (i.e. patients who mostly developed cancer after their enrollment in the RCT) can mitigate this limitation
- No access to the individual patient data
- Patients across the included studies were heterogeneous
  - no subgroup analysis to evaluate outcomes in different types of cancer, drugs and doses.
- No data available on the use of dabigatran for patients with AF and cancer

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CONCLUSIONS

- In patients with cancer and atrial fibrillation, direct oral Xa inhibitors have similar efficacy and may be safer compared with warfarin.
- These results are consistent both in patients with active cancer and history of cancer.
- No data fulfilling the inclusion criteria were available on the use of dabigatran in patients with cancer and atrial fibrillation.

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