III International Workshop on Cardioncology

VI Congresso Nazionale in Cardioncologia

Presidenti del Congresso

Nicola Maurea, Michelino De Laurentiis

Napoli

EUROSTARS HOTEL EXCELSIOR

31 Gennaio - **1** Febbraio **2020**

Edoxaban, atrial fibrillation, elderly and cancer

Nicola Maurea, MD, FACC, FESC

Director of division of Cardiology

National Cancer Institute Fondazione Pascale, Napoli

President of Italian Association of Cardioncology (AICO)

VI Congresso Nazionale in Cardioncologia

III International Workshop on Cardioncology

Napoli, 31 Gennaio – 1 Febbraio 2020

DISCLOSURE INFORMATION

Nicola Maurea

I. Grant/Research Support from the Italian Ministry of Health

II. Advisory Board for Bayer, Daiichi-Sankyo, and Clinigen

III. Speaker for Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo

3,460.025 patients cancer survivors in Italy

	Maschi	Femmine	Maschi e femmine
Tutti i tumori	1.589.119	1.870.906	3.460.025
Vie aerodigestive superiori	36.601	20.587	57.188
Esofago	5.989	1.963	7.951
Stomaco	43.805	37.579	81.384
Colon, retto e ano	250.969	230.749	481.719
Colon	173.948	161.174	335.122
Retto	76.215	63.090	139.305
Fegato	24.504	9.197	33.701
Vie biliari	7.285	8.393	15.677
Pancreas	12.599	10.202	22.801
Laringe	36.135	5.663	41.798
Polmone	69.508	37.407	106.915
Polmone, piccole cellule	10.298	3.649	13.946
Osso	9.042	11.670	20.712
Melanomi della cute	77.189	83.356	160.544
Mesoteliomi	4.245	1.370	5.615
Sarcomi di Kaposi	8.785	2.623	11.408
Tessuti molli	16.156	12.101	28.257
Mammella femminile		815.002	815.002
Utero, Cervice		57.000	57.000
Utero, Corpo		116.772	116.772
Ovaio		50.909	50.909
Prostata	471.108		471.108
Testicolo	55.591		55.591
Rene vie urinarie	84.614	44.607	129.221
Vescica	219.001	58.211	277.212
Encefalo e SNC	26.714	32.422	59.136
Tiroide	47.205	158.447	205.652
Linfomi di Hodgkin	41.849	31.576	73.425
Linfomi non-Hodgkin	76.902	68.895	145.797
Leucemie	47.486	40.128	87.615
SLL/CLL	16.489	15.826	32.315
LNH, DLBC	24.852	19.522	44,374
LNH, follicolari	12.757	14.400	27.157
Leucemie linfoidi acute	15.143	10.858	26.001
Leucemie mieloidi acute	8.922	11.317	20.240
Leucemie mieloidi croniche	8.033	4.480	12.513
Mielomi	18.447	18.354	36.800

TABELLA 23. Numero di persone che vivono dopo una diagnosi di tumore in Italia nel 2019, per tipo di tumore e sesso

Cancer incidence and age

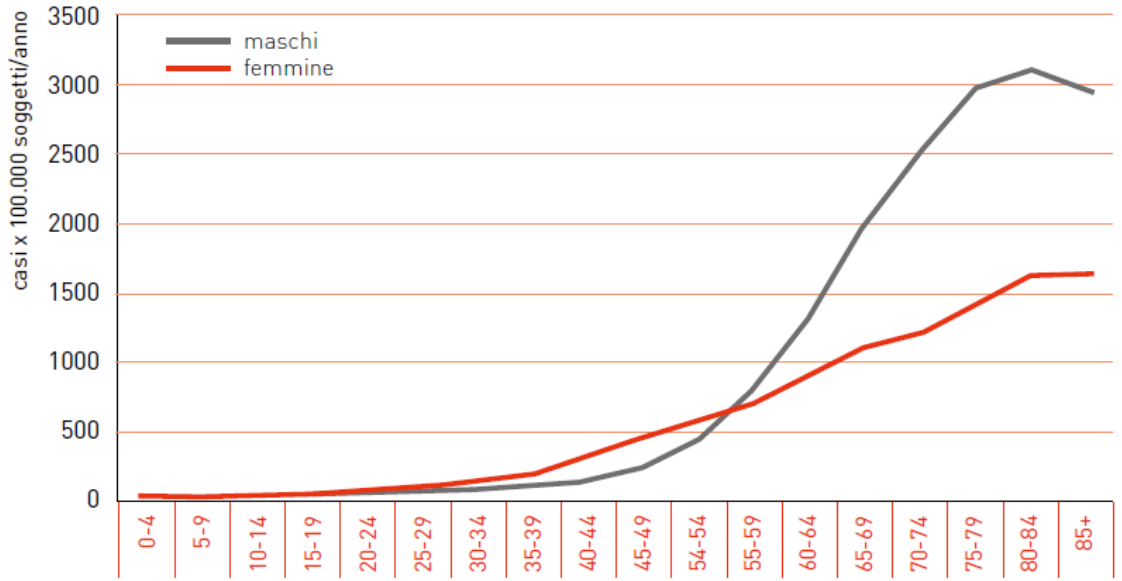


FIGURA 2. **AIRTUM 2010-2015. Incidenza. Tassi età-specifici (x 100.000) per sesso. Tutti i tumori esclusi carcinomi della cute**

Cancer death differentiated for type, range of age and for sex

Rango	Maschi			Femmine		
	Età			Età		
	0-49	50-69	70+	0-49	50-69	70+
Totale (n casi medio/anno)	100% (3.061)	100% (30.947)	100% (77.072)	100% (3.359)	100% (20.794)	100% (57.178)
1°	Polmone (15%)	Polmone (31%)	Polmone (27%)	Mammella (28%)	Mammella (20%)	Mammella (14%)
2°	Sistema nervoso centrale (11%)	Colon-retto (10%)	Colon-retto (10%)	Polmone (9%)	Polmone (15%)	Colon-retto (11%)
3°	Colon-retto (8%)	Fegato (8%)	Prostata (8%)	Colon-retto (7%)	Colon-retto (10%)	Polmone (11%)
4°	Leucemie (7%)	Pancreas (7%)	Fegato (7%)	Sistema nervoso centrale (7%)	Pancreas (7%)	Pancreas (8%)
5°	Stomaco (6%)	Stomaco (6%)	Stomaco (6%)	Utero totale (6%)	Ovaio (6%)	Fegato (6%)

TABELLA 10. Prime cinque cause di morte oncologica e proporzione sul totale dei decessi per tumore per sesso e fascia di età. Pool AIRTUM 2010-2015. 2015 (i dati presentati non sono frutto di stime ma casi reali forniti dai registri per le annate indicate)

5 years survival for type of cancer

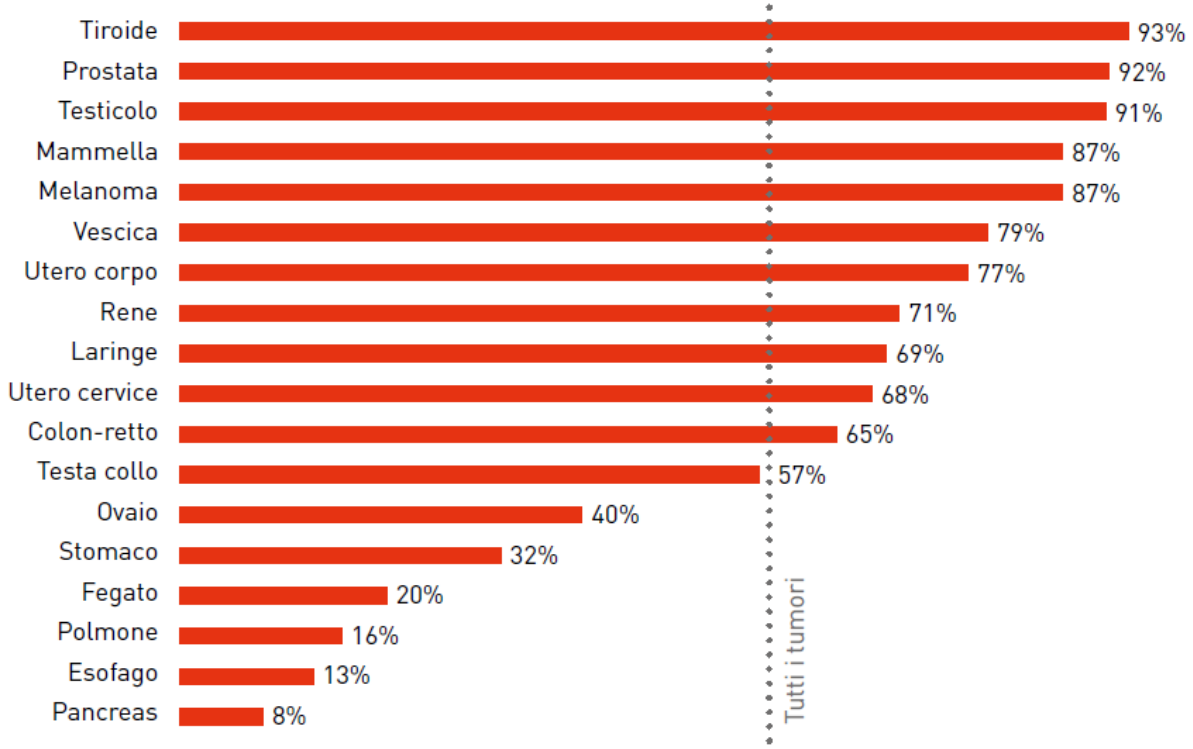
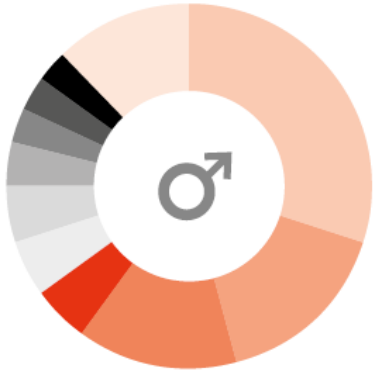


FIGURA 6. **Sopravvivenza netta a 5 anni dalla diagnosi (standardizzata per età) per il periodo di incidenza 2005-2009 (pool AIRTUM), maschi e femmine**

Percentage of cancer survivors differentiated for type of cancer and frequency



Tumore	n.	%
Prostata	471.108	30
Colon-retto-ano	250.969	16
Vescica	219.001	14
Rene	84.614	5
Melanomi, cute	77.189	5
Linfomi non-Hodgkin	76.902	5
Polmone	69.508	4
Testicolo	55.591	3
Leucemie	47.486	3
Tiroide	47.205	3
Altri	189.547	12

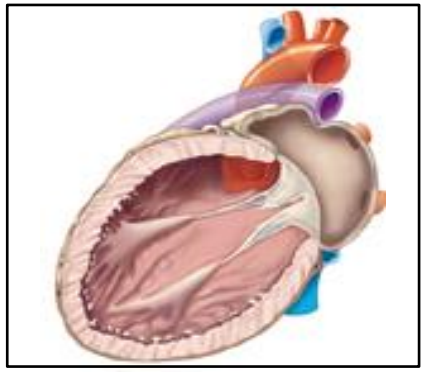
Tumore	n.	%
Mammella	815.002	44
Colon-retto-ano	230.749	12
Tiroide	158.447	8
Utero, corpo	116.772	6
Melanomi, cute	83.356	4
Linfomi non-Hodgkin	68.895	4
Vescica	58.211	3
Utero cervice	57.000	3
Ovaio	50.032	3
Altri	282.473	15

FIGURA 10. Proporzione di persone che vivono dopo una diagnosi di tumore in Italia nel 2019, per i tipi di tumore più frequenti e sesso

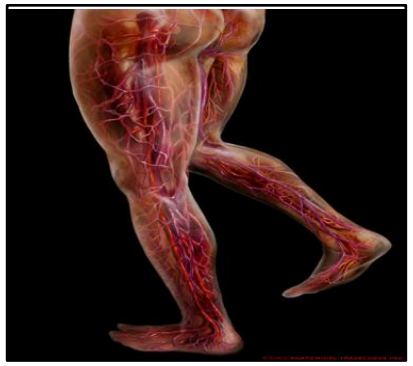
75% of cancer patient have more than 65 years old

Cardiovascular Complications in Cancer Patient

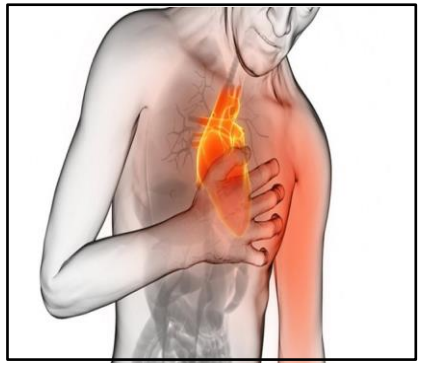
Atrial fibrillation



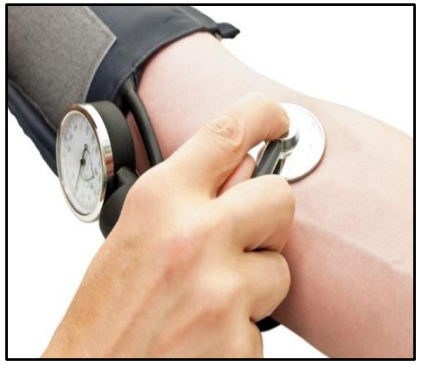
Cardiac Dysfunction
Heart Failure



Thromboembolism



Angina pectoris
Myocardial infarction



Hypertension

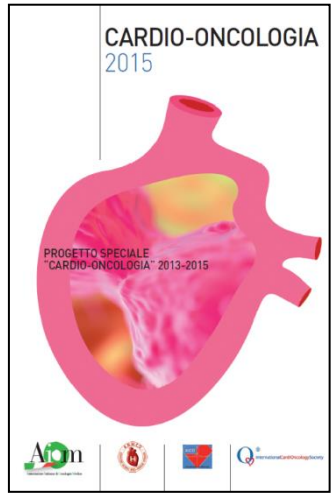
Heart Rhythm, Vol 16, No 3, March 2019

EDITORIAL COMMENTARY

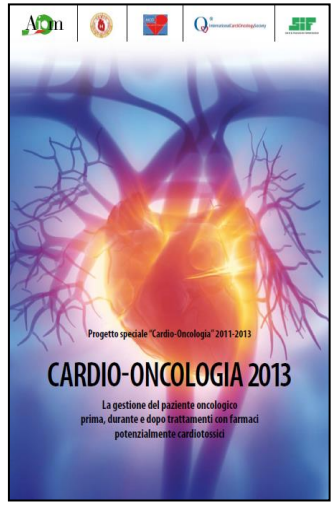
Breast cancer and atrial fibrillation—A malignant combination?

Ankur A. Karnik, MD, FHRS, FACC,* Emelia J. Benjamin, MD, ScM, FACC, FAHA,*†‡
Ludovic Trinquart, PhD‡§


CARDIO-
ONCOLOGIA
2019
RACCOMANDAZIONI
PRATICHE
SIAARTI

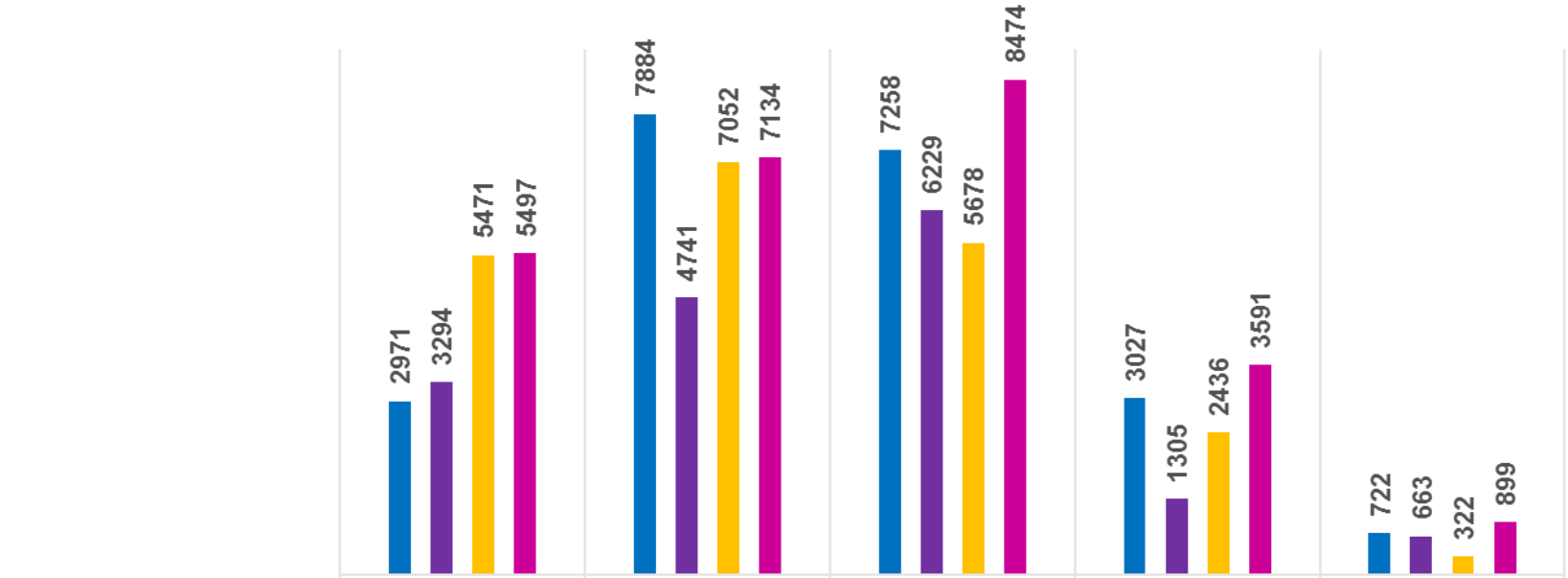

CARDIO-ONCOLOGIA
2015
PROGETTO SPECIALE
"CARDIO-ONCOLOGIA" 2013-2015


CARDIO-
ONCOLOGIA
2017
PROGETTO SPECIALE
"CARDIO-ONCOLOGIA" 2015-2017


Progetto speciale "Cardio-Oncologia" 2011-2013
CARDIO-ONCOLOGIA 2013
La gestione del paziente oncologico
prima, durante e dopo trattamenti con farmaci
potenzialmente cardiotossici


CARDIO-
ONCOLOGIA
2018
PROGETTO SPECIALE
"CARDIO-ONCOLOGIA 2018"

Old patients in registrative DOACS trials

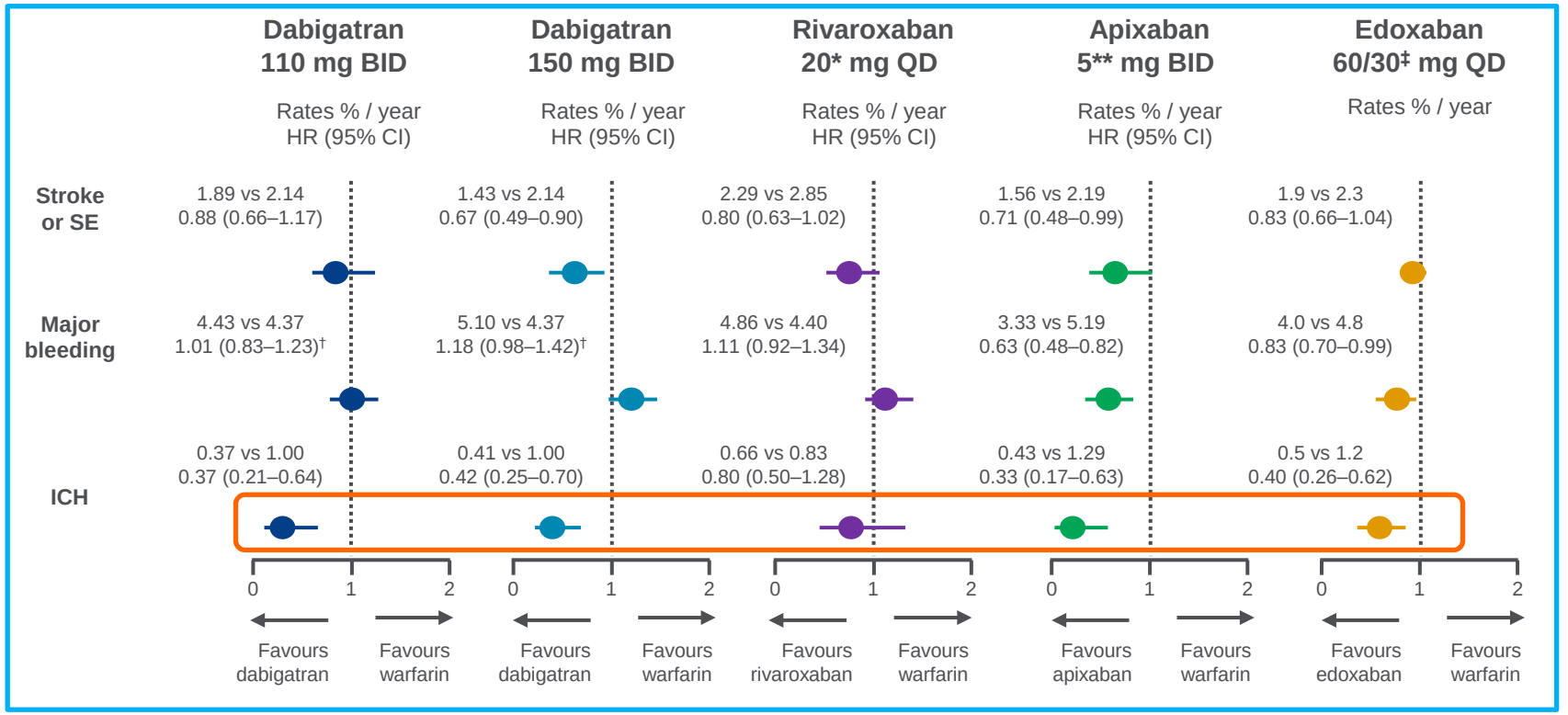


	< 65 anni	65-74 anni	≥ 75 anni	≥ 80 anni	≥85 anni
RELY	2971	7884	7258	3027	722
ROCKET-AF	3294	4741	6229	1305	663
ARISTOTLE	5471	7052	5678	2436	322
ENGAGE AF-TIMI 48	5497	7134	8474	3591	899

Adapted form Kato et al. Ageing Reasearch Reviews (2019) 49; 115-124 https://doi.org/10.1016/j.arr.2018.10.006

Pazienti anziani nei trial registrativi per la FANV

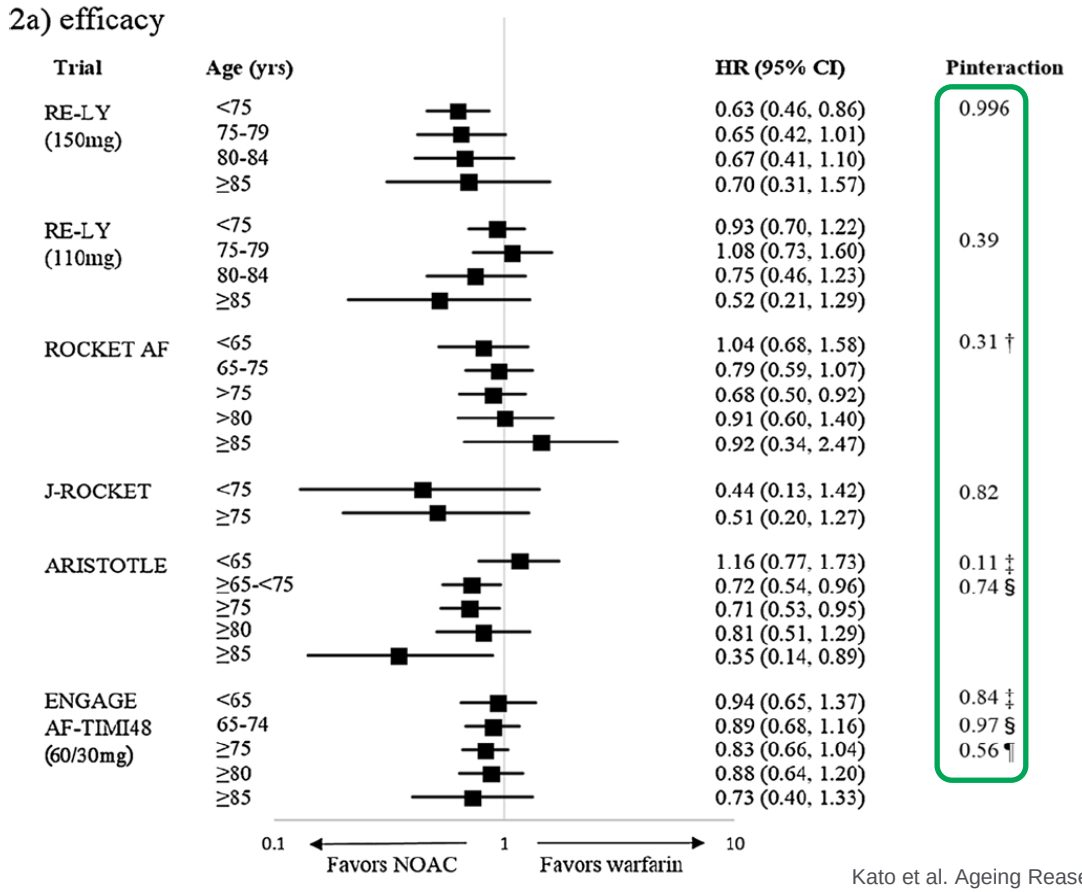
Efficacy and safety of DOACs vs Warfarin in patients ≥75 years old



*Reduced to 15 mg if CrCl 30–49 mL/min
**Reduced to 2.5 mg twice-daily if at least two of the following criteria were present: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dl
†P<0.001 vs warfarin
‡Reduced dose as per the SmPC
BID, twice daily; ICH, intracranial haemorrhage; QD, once daily

Modified from Capranzano P, et al. Expert Rev Cardiovasc Ther 2013;11:959–73;
Kato ET, et al. J Am Heart Assoc 2016;5:e003432

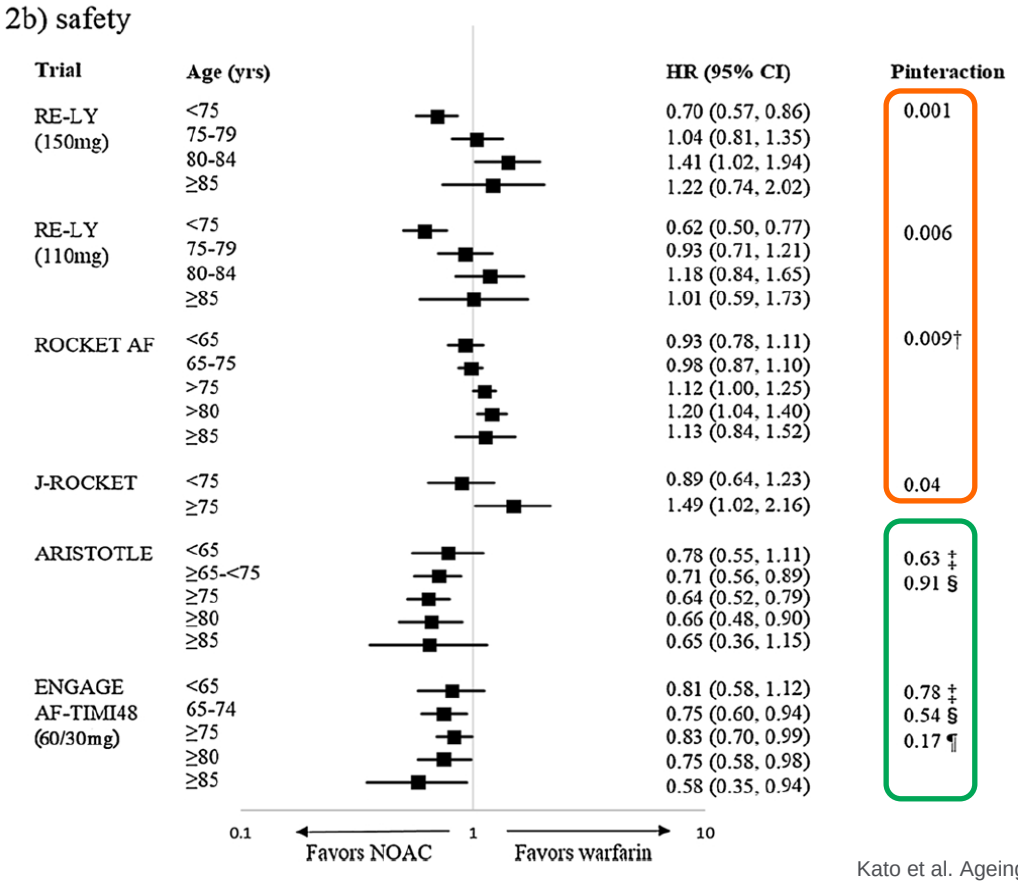
DOACs vs AVK in AF patients:
Primary endpoint of efficacy for range of age



There is no significative interaction for all NOACS between age and risk of stroke/SEE (efficacy end-point) (Kato 2019)

Kato et al. Ageing Reasearch Reviews (2019) 49; 115-124 https://doi.org/10.1016/j.arr.2018.10.006

DOACs vs AVK in AF patients:
Primary endpoint of safety for range of age



There is significative interaction only between dabigatran and rivaroxaban between age and risk of bleeding (safety end-point) (Kato 2019)

Kato et al. Ageing Reasearch Reviews (2019) 49; 115-124 https://doi.org/10.1016/j.arr.2018.10.006

AGS Beers Criteria for Potentially Inappropriate Medications: Warning for older patients

Table 4. 2019 American Geriatrics Society Beers Criteria® for Potentially Inappropriate Medications: Drugs To Be Used With Caution in Older Adults[a]

Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Aspirin for primary prevention of cardiovascular disease and colorectal cancer	Risk of major bleeding from aspirin increases markedly in older age. Several studies suggest lack of net benefit when used for primary prevention in older adult with cardiovascular risk factors, but evidence is not conclusive. Aspirin is generally indicated for secondary prevention in older adults with established cardiovascular disease	Use with caution in adults ≥70 years	Moderate	Strong
Dabigatran Rivaroxaban	Increased risk of gastrointestinal bleeding compared with warfarin and reported rates with other direct oral anticoagulants when used for long-term treatment of VTE or atrial fibrillation in adults >75 years	Use with caution for treatment of VTE or atrial fibrillation in adults >75 years	Moderate	Strong
Prasugrel	Increased risk of bleeding in older adults; benefit in highest-risk older adults (eg, those with prior myocardial infarction or diabetes mellitus) may offset risk when used for its approved indication of acute coronary syndrome to be managed with percutaneous coronary intervention.	Use with caution in adults ≥75 years	Moderate	Weak
Antipsychotics Carbamazepine Diuretics Mirtazapine Oxcarbazepine SNRIs SSRIs TCAs Tramadol	May exacerbate or cause SIADH or hyponatremia; monitor sodium level closely when starting or changing dosages in older adults	Use with caution	Moderate	Strong

American Geriatrics Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults
*By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel**

ENGAGE-AF: Baseline demographic characteristics for age groups

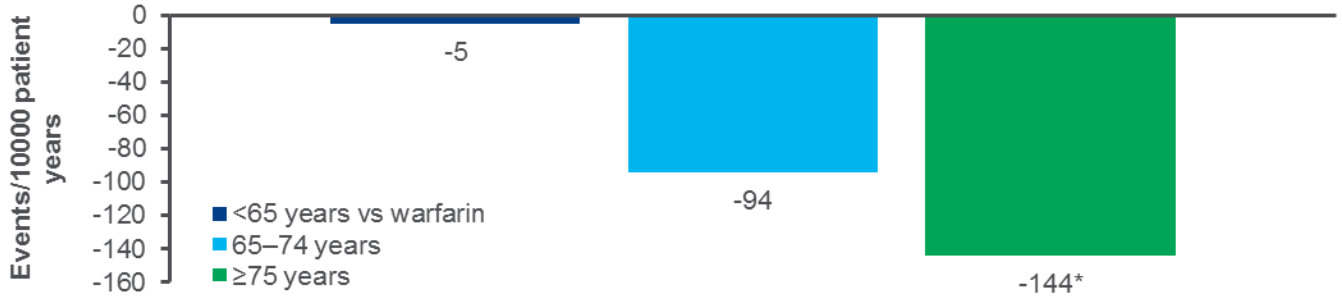
Caratteristica	<65 anni (N = 5497)	65 – 74 anni (N = 7134)	≥75 anni (N = 8474)
Weight (kg) median (IQR)	91 (78–106)	83 (71–96)	**76** (66–87)
CrCl (mL/min) median (IQR)[a]	98 (79–123)	74 (60–90)	**56** (45–69)
$CHADS_2$ mean (SD)	2.6 (0.8)	2.7 (0.8)	**3.2** (1.1)
HAS-BLED score ≥3, n (%)	894 (16)	4129 (58)	**4779** (56)
TTR (%) median (IQR)[b]	67 (56–76)	68 (57–77)	**70** (57–78)
Dose reduced, n (%)[a]	571 (10%)	1297 (18%)	**3488 (41%)**

[a]At randomization; [b]Includes only patients randomized to warfarin.
$CHADS_2$ = Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, and prior Stroke or TIA or thromboembolism; HAS-BLED = Hypertension, Abnormal renal and liver function, Stroke, Bleeding history or disposition, Labile INR, Elderly, Drugs or alcohol; CrCl = creatinine clearance; IQR = interquartile range; SD = standard deviation; TIA = transient ischemic attack; TTR = time in therapeutic range.

Kato et al. J Am Heart Assoc (2016) 5:e003432

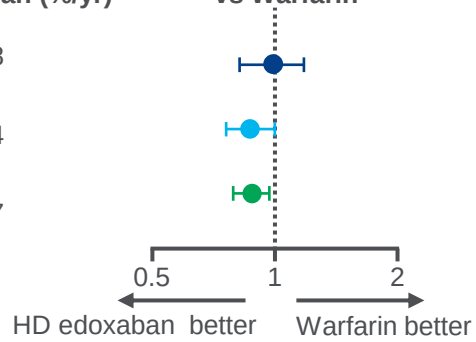
ENGAGE-AF: Clinical benefit in age group (efficacy +safety)

Absolute Risk Difference (HD Edoxaban vs Warfarin)



Hazard Ratio

	Warfarin (%/yr)	HD Edoxaban (%/yr)	HD Edoxaban vs Warfarin	HR (95% CI)	P_{int}
<65 years (n = 5497)	4.9	4.8		0.99 (0.82–1.18)	0.48
65-74 years (n = 7134)	7.3	6.4		0.87 (0.76–1.00)	
≥75 years (n = 8474)	11.2	9.7		0.88 (0.79–0.97)	

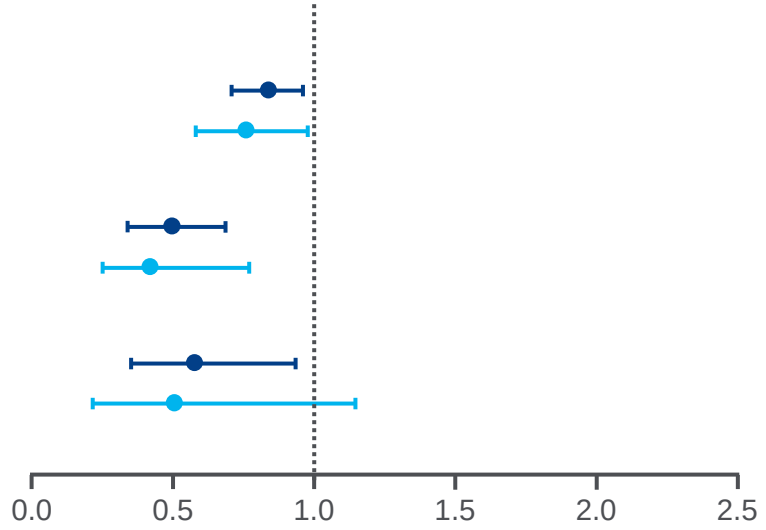


*P <0.05 vs warfarin
CI = confidence interval; HD edoxaban = higher-dose edoxaban regimen (60/30 mg once-daily); HR = hazard ratio; yr = year.

Kato et al. J Am Heart Assoc (2016) 5:e003432

ENGAGE-AF: Safety outcome in patients ≥80 years old

Endpoint	Event Rate (%/year) Warfarin	Edoxaban 60/30 mg	Edox 60/30 mg vs Warfarin HR (95% CI)	P-int
Major Bleeding				
<80 years	3.0	2.5	0.83 (0.71–0.96)	0.54
≥80 years	6.2	4.6	0.75 (0.58–0.98)	
ICH				
<80 years	0.7	0.4	0.49 (0.34–0.69)	0.64
≥80 years	1.6	0.6	0.41 (0.22–0.77)	
Fatal Bleeding				
<80 years	0.3	0.2	0.57 (0.35–0.94)	0.79
≥80 years	0.8	0.4	0.50 (0.21–1.15)	

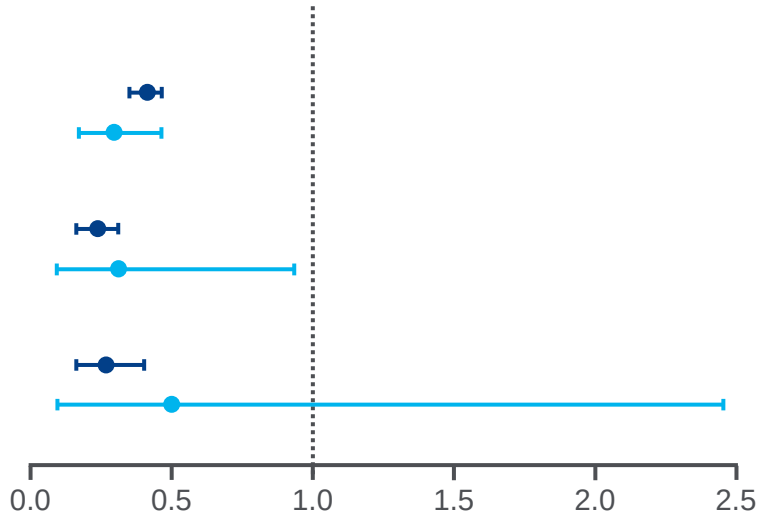


CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial hemorrhage

Kato et al. J Am Heart Assoc (2016) 5:e003432

ENGAGE-AF: Safety outcome in patients ≥85 years old

Endpoint	Event Rate (%/year) Warfarin	Edoxaban 60/30 mg	Edox 60/30 mg vs Warfarin HR (95% CI)	P-int
Major Bleeding				
<85 years	3.3	2.7	0.82 (0.72–0.94)	0.17
≥85 years	8.8	5.0	0.58 (0.35–0.94)	
ICH				
<85 years	0.8	0.4	0.46 (0.33–0.62)	0.62
≥85 years	1.6	0.9	0.61 (0.20–1.88)	
Fatal Bleeding				
<85 years	0.4	0.2	0.52 (0.33–0.82)	0.45
≥85 years	0.6	0.6	0.99 (0.20–4.91)	



CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial hemorrhage

Kato et al. J Am Heart Assoc (2016) 5:e003432

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

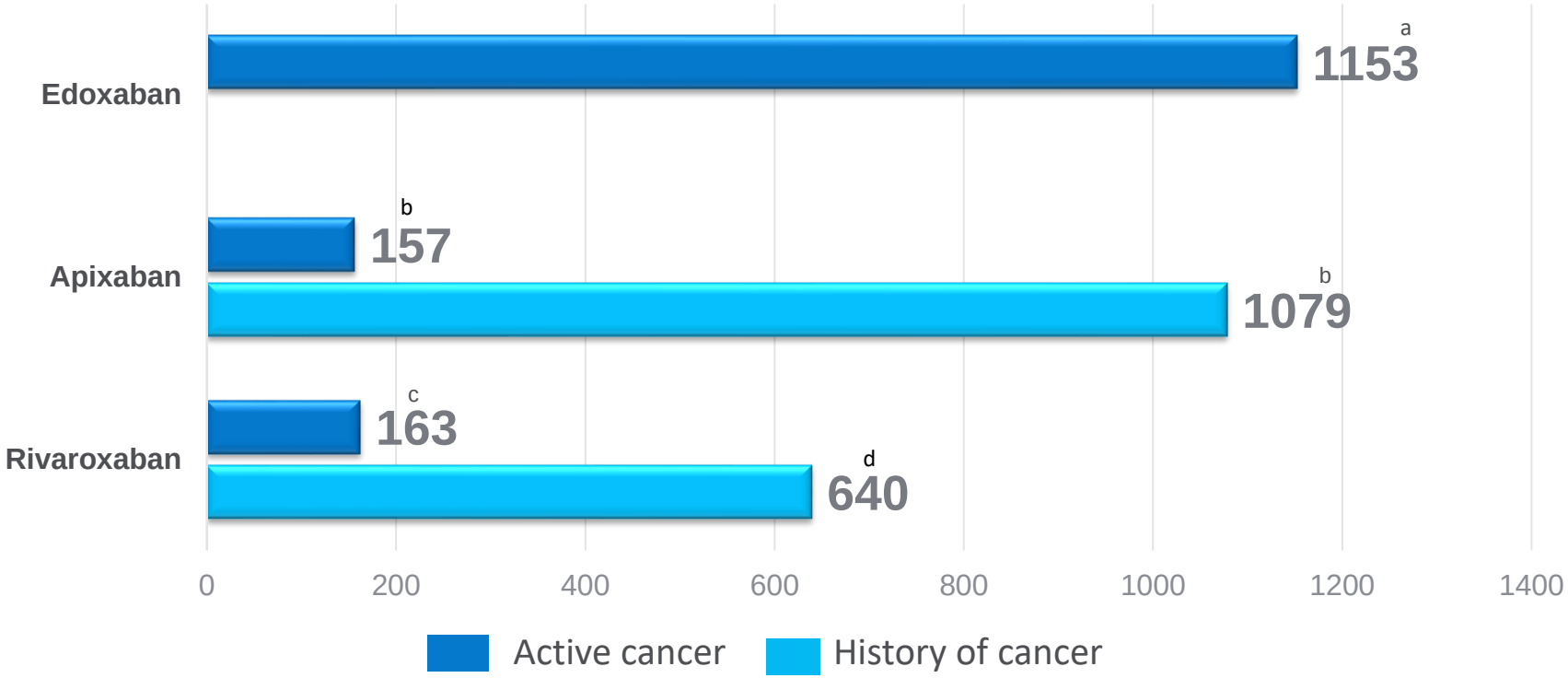
Efficacy and Safety of Edoxaban in Patients With Active Malignancy and Atrial Fibrillation: Analysis of the ENGAGE AF-TIMI 48 Trial

Christina L. Fanola, MD, MSc; Christian T. Ruff, MD, MPH; Sabina A. Murphy, MPH; James Jin, PhD; Anil Duggal, MD; Noe A. Babilonia, MD; Piyamitr Sritara, MD; Michele F. Mercuri, MD, PhD; Pieter W. Kamphuisen, MD; Elliott M. Antman, MD, Eugene Braunwald, MD; Robert P. Giugliano, MD, SM

- **1153 (5,5%) patients developed cancer (new diagnosis or recurrence of remote cancer) with the most common sites GI, prostate and lung.**
- Efficacy and safety of edoxaban vs. warfarin were preserved.
- In patients with cancer, edoxaban was effective in the prevention of stroke/systemic embolic event vs. warfarin and had a similar risk of major bleeding.

Fanola et al. JACC 2017; 2017: 69(11) Suppl. ACC 2017

AF and Cancer: number of DOACS patients/active cancer and history of cancer



a: sottonalisi ENGAGE-AF – Fanola et al. JACC 2017; 2017: 69(11) Suppl. ACC 2017
b: sottoanalisi ARISTOTLE - Melloni et al. Am J Med 2017;130:1440-1448
c: Studio osservazionale monocentico – Laube et al. Am J Cardiol 2017;120:213-217
d: sottoanalisi ROCKET-AF - Chen et al. Eur Heart J Qual Care Clin Outcomes 2019;5(2):145-152

Edoxaban: Data in patients with FA and Cancer

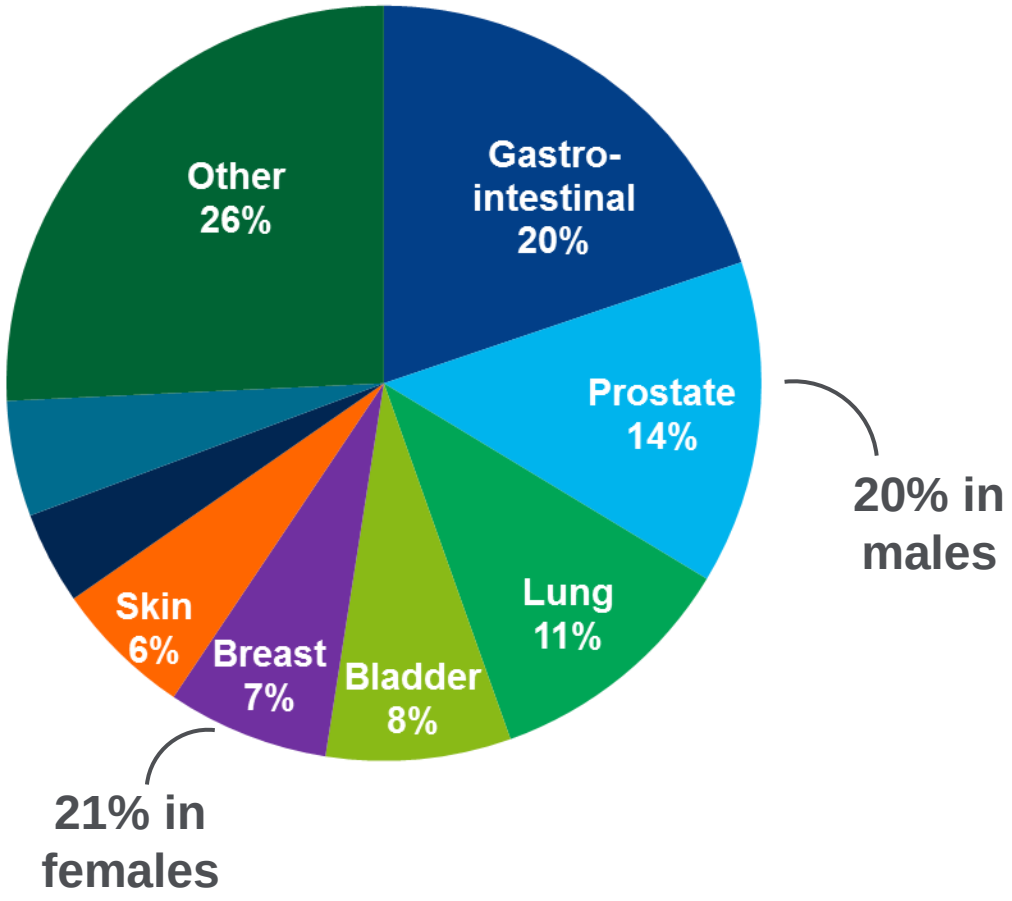
ENGAGE AF–TIMI 48: Baseline characteristics in patients with a new diagnosis or cancer recurrence

Characteristic	Cancer (N=1153, 5.5%)	NO Cancer (N=19952, 94.5%)	p
Age, yrs (median)	75	72	<0.001
Male sex	69%	62%	<0.001
White race	86%	81%	<0.001
N America / W Europe	50%	37%	<0.001
BMI (median)	29	29	0.84
Prior malignancy	14%	6%	<0.001
CHA_2DS_2-VASc (mean)	4.4	4.3	0.01
Prior Stroke or TIA	25%	29%	0.004
Diabetes mellitus	39%	36%	0.07
Hypertension	95%	94%	0.14
Heart failure	52%	58%	<0.001
Coronary artery disease	37%	33%	0.017
Prior VKA experience	66%	59%	<0.001
Current smoking	8.9%	7.3%	0.034
Prior bleeding	13%	10%	<0.001
Dose-reduction at randomization	27%	25%	0.20

BMI, body mass index, VKA, vitamin K antagonist

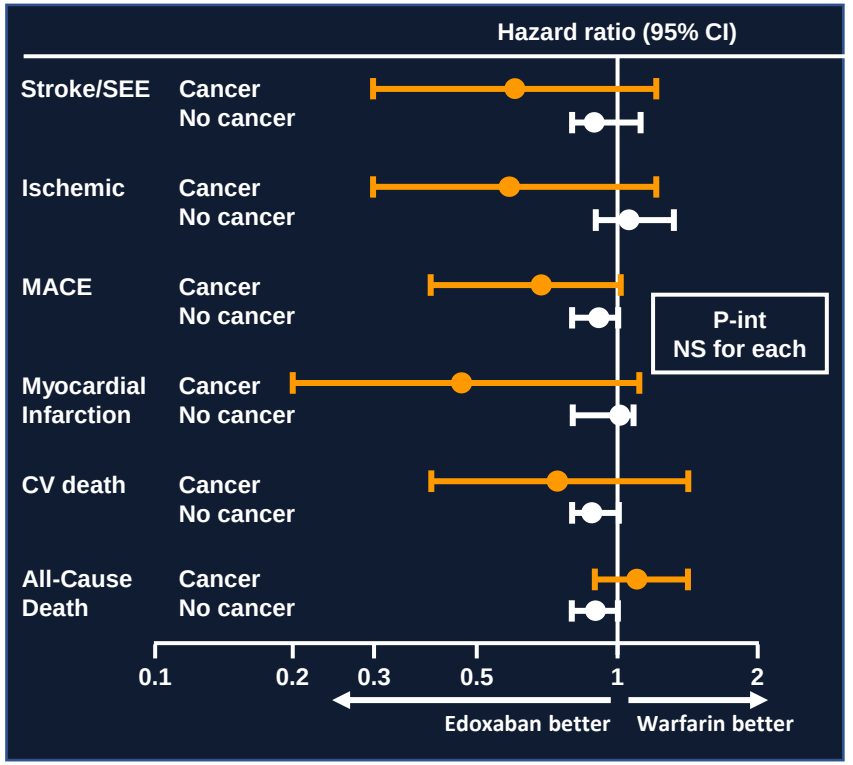
Fanola et al. JACC 2017; 2017: 69(11) Suppl. ACC 2017

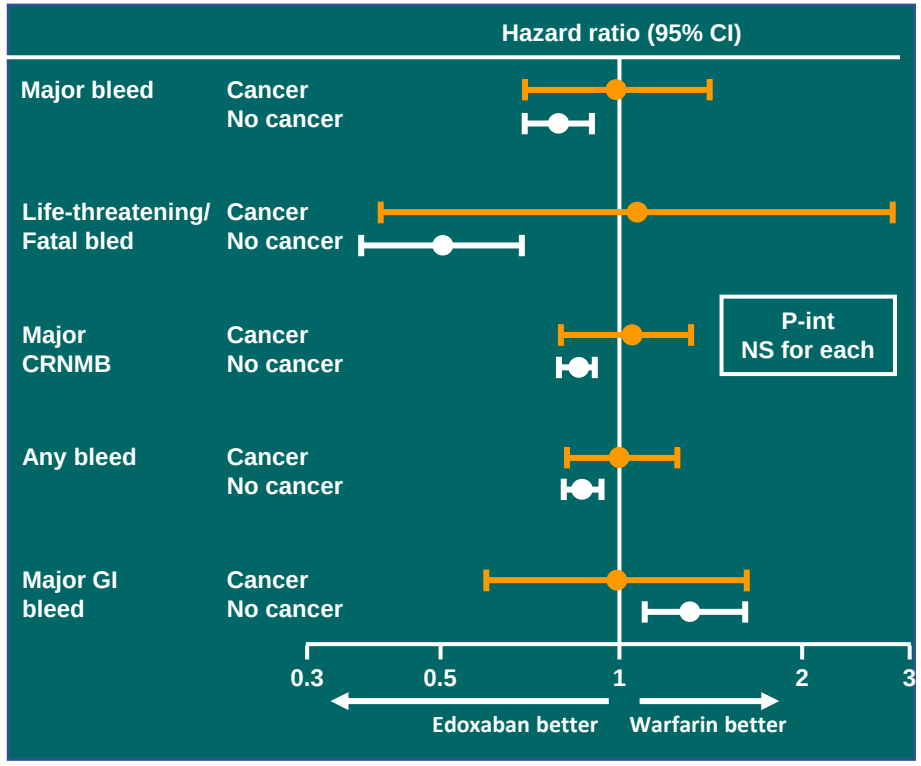
Types of cancer in ENGAGE sub-analysis



Fanola CL et al. JAHA 2018;7:e008987. DOI: 10.1161/HAHA.118.008987

ENGAGE-AF SUB-ANALYSIS:Efficacy and safety endpoints by malignancy status in Edoxaban 60/30 mg vs Warfarin





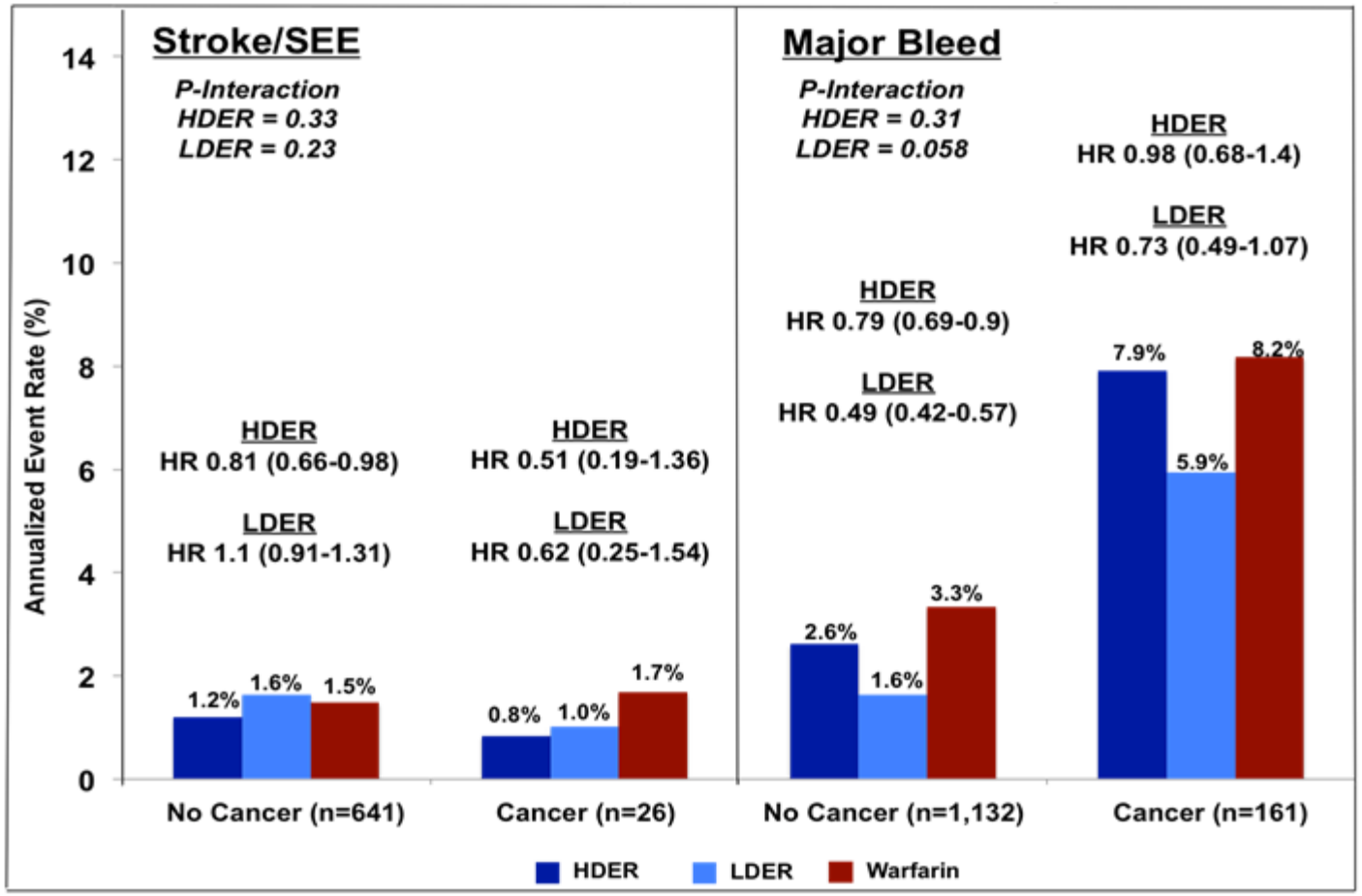
Included malignant tumours (major organ system), hematologic cancer, metastases (primary unknown), recurrence of remote cancer, melanoma, non-melanoma skin cancer (metastatic).

Fanola et al. JACC March 21, 2017 Volume 69, Issue 11

J Am Heart Assoc. 2018

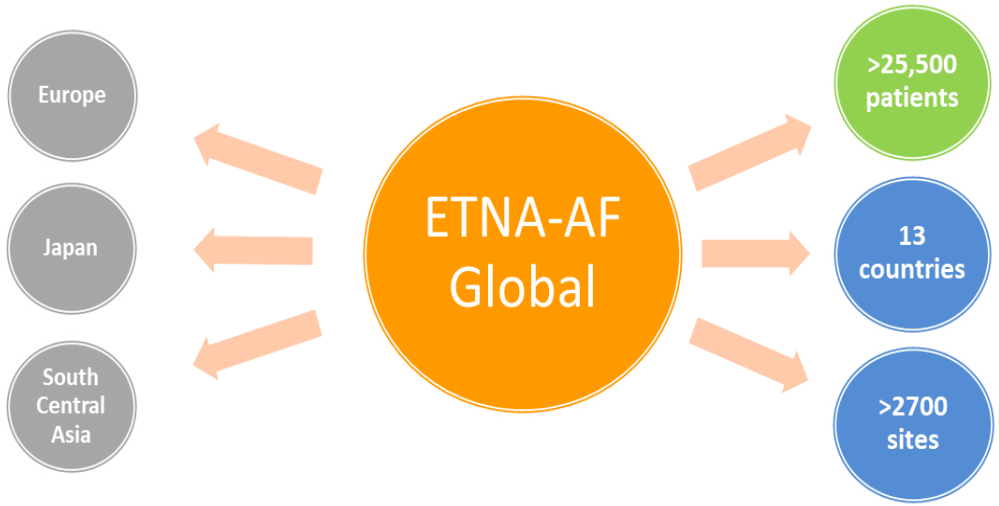
Efficacy and Safety of Edoxaban in Patients With Active Malignancy and Atrial Fibrillation: Analysis of the ENGAGE AF-TIMI 48 Trial

Christina L. Fanola, MD, MSc; Christian T. Ruff, MD, MPH; Sabina A. Murphy, MPH; James Jin, PhD; Anil Duggal, MD; Noe A. Babilonia, MD; Piyamitr Sritara, MD; Michele F. Mercuri, MD, PhD; Pieter W. Kamphuisen, MD; Elliott M. Antman, MD, Eugene Braunwald, MD; Robert P. Giugliano, MD, SM



[a] SEE, systemic embolic event; HDER, higher dose edoxaban regimen; LDER, lower dose edoxaban regimen

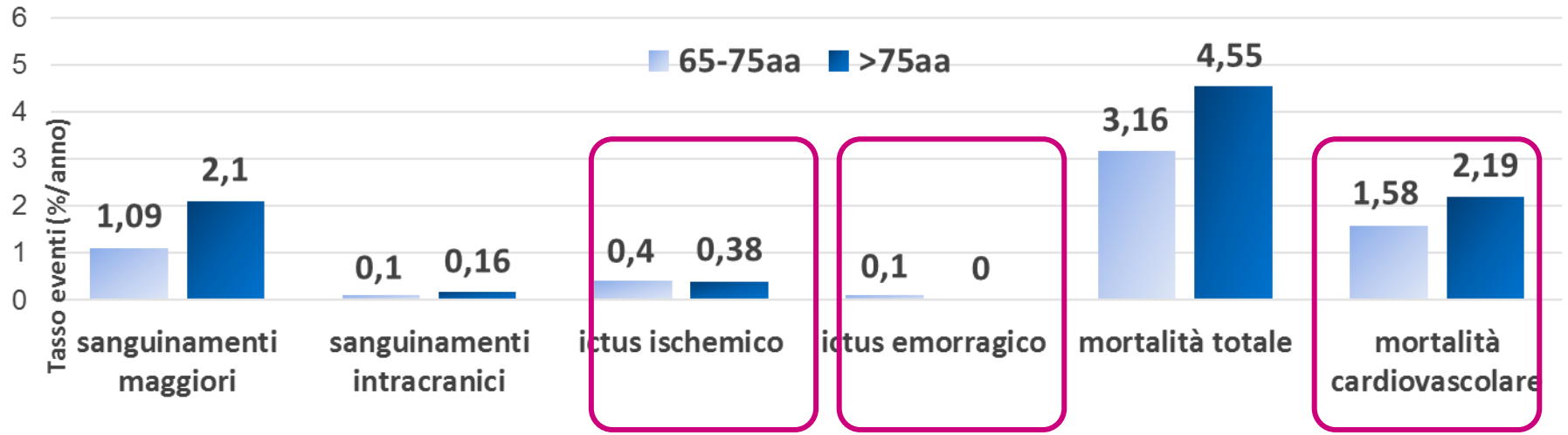
ETNA-AF Programme: the register *Edoxaban Treatment in routine clinical practice for patients with nonvalvular Atrial Fibrillation Europe* (ETNA-AF Europe).



FA: Fibrillazione Atriale
PASS: Post-authorization Safety Study
EMA: European Medicines Agency

1. Ameri P et al Giornale Italiano di Cardiologia 2020.....
Figura tratta da De Caterina R et al. JCM 2019;20:97–104

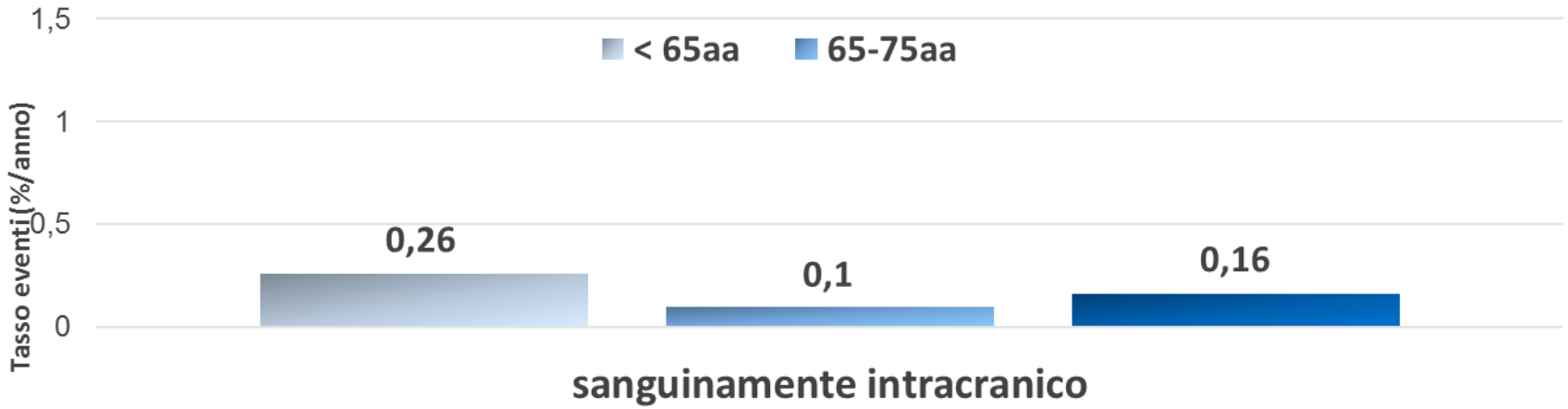
ETNA-AF Italy: Results for age



- Age is a powerful risk factor for emorragic and ischemic events
- It is relevant the balance between safety and efficacy od edoxaban in the group of patient of ≥ 75 years old
- Gli eventi ischemici, in questo gruppo di pazienti, sono occorsi con frequenza comparabile a quella rilevata nelle fasce d'età più basse The frequency of ischemic events in group > 75 years old are occured with a frequency comparable to that relevated in the group of 65-75 years old

Ameri P et al Giornale Italiano di Cardiologia 2020.....

ETNA-AF Italia: Sanguinamenti intracranici per età



- **Il dato di particolare interesse, e in controtendenza, è il non aumento delle emorragie intracraniche osservato nella fascia di età più avanzata, a conferma della sicurezza di edoxaban**

Ameri P et al Giornale Italiano di Cardiologia 2020……

BOOKLET

LA FIBRILLAZIONE ATRIALE NEL PAZIENTE ONCOLOGICO

Nicola Maurea

Iris Parrini

ANMCO – Task Force Cardioncologia 2017

Meccanismi patogenetici potenziali che collegano cancro e fibrillazione atriale

Farmakis, JACC 2014

10 La gestione della fibrillazione atriale nel paziente oncologico

Nicola Maurea[1], Enrico Barbieri[2]

TABELLA 35. Agenti dei farmaci tumorali associati con la fibrillazione atriale

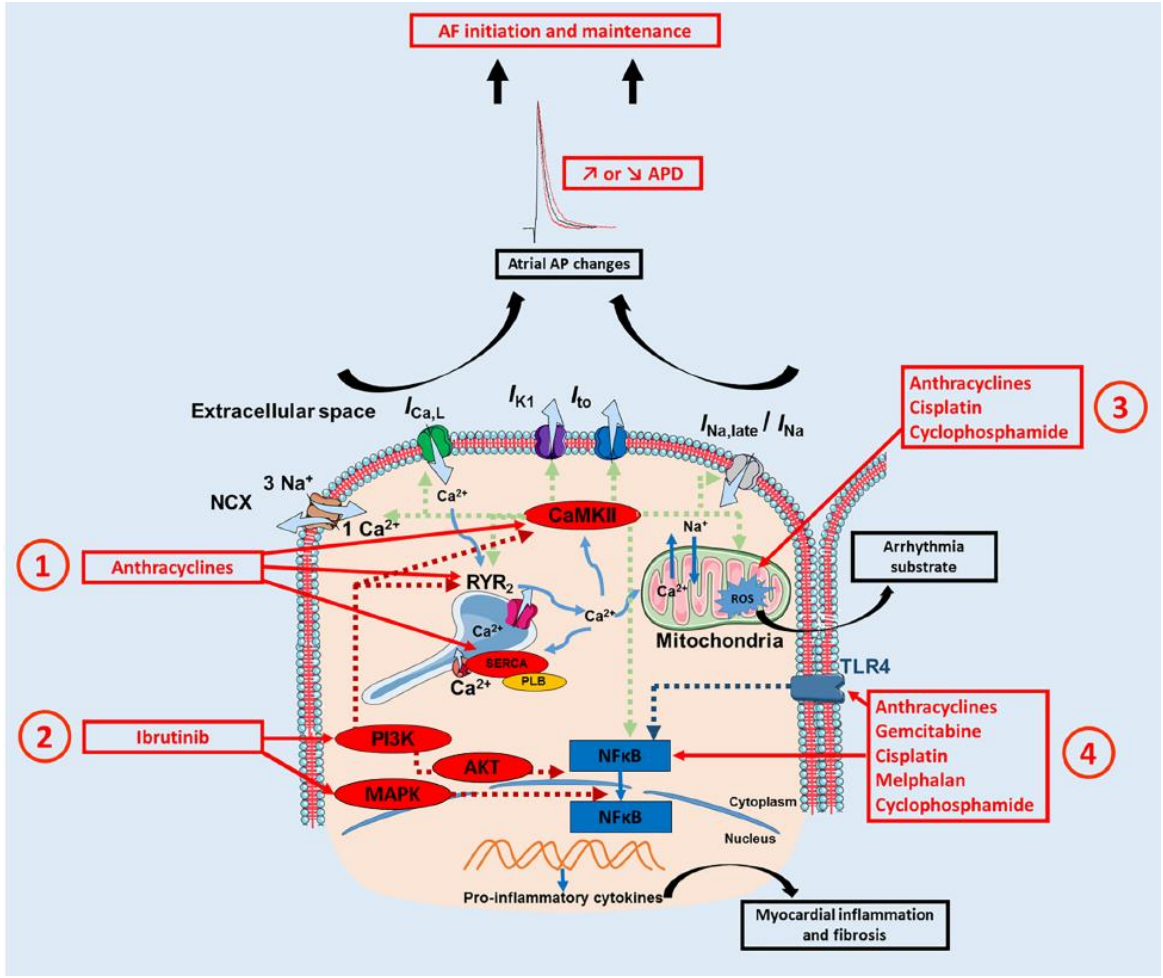
Tipi di aritmia	Farmaci che la causano
Fibrillazione Atriale	Agenti alchilanti (cisplatino, ciclofosfamide, ifosfamide melfalan), antracicline, antimetaboliti (capecitabina, 5-FU, gemcitabina), IL-2, interferoni, rituximab, romidepsin alchilanti, piccola molecola TKI (ponatinib, sorafenib, sunitinib, ibrutinib), topoisomerasi II inibitori (amsacrina, etoposide), taxani, alcaloide della vinca.

Select Cancer Therapies Associated With Atrial Arrhythmias and Thrombotic Adverse Events

Class	Anti-Cancer Mechanism	Select Drug Examples	Mechanism of Cardiovascular Toxicity
Cancer therapies associated with atrial arrhythmias			
Anthracyclines	Inhibition of DNA/RNA synthesis via topoisomerase inhibition	Doxorubicin Daunorubicin Idarubicin Epirubicin	? Direct cardiotoxicity
Alkylating agents	Inhibition of DNA/RNA synthesis via formation of carbonium ions	Melphalan	Unknown
Anti-metabolites	Inhibition of DNA/RNA synthesis via acting as a pyrimidine analog	Fluorouracil	? Ischemia
Interleukins	Immunotherapy	Il-2	Inflammation
Bruton's tyrosine kinase TKIs	Inhibition of Bruton's tyrosine kinase	Ibrutinib Acalabrutinib	? Direct kinase inhibition
Immune checkpoint inhibitors	Activation of immune system	Ipilimumab Nivolumab Pembrolizumab	Cardiac inflammation; myocarditis, pericarditis, vasculitis

Mosarla RC et al. JACC 2019

Potential mechanisms involved in anticancer drug-induced atrial fibrillation



Alexandre J et al, Pharmacology & Therapeutics 2018

Management and outcomes of patients with atrial fibrillation and *a history of* cancer: the ORBIT-AF registry

9749 pazienti:
- Cancro: 2318
- No cancro: 7431

Table 2 CV outcomes in AF patients with and without history of cancer

Outcomes	No cancer[a]	History of cancer[a]	Adjusted HR (95% CI)	*P*-values
All-cause death	4.92	7.75	1.26 (1.11–1.42)	0.0003
CV death	2.07	2.89	1.10 (0.90–1.34)	0.35
Non-CV death	2.42	4.24	1.35 (1.14–1.60)	0.0004 ←
First stroke, non-CNS embolism, or TIA	1.48	1.96	1.04 (0.82–1.32)	0.74
First major bleed	3.45	5.13	1.21 (1.04–1.40)	0.02 ←
New onset HF diagnosis (*N* = 6545)	1.53	1.73	0.90 (0.66–1.21)	0.47

CV, cardiovascular; CNS, central nervous system; TIA, transient ischaemic attack; HF, heart failure; HR, hazard ratio; CI, confidence interval.
[a]Event rate per 100 patient-years follow-up.

Conclusion A history of cancer is common among AF patients with up to one in four patients having both. Antithrombotic therapy, rates of cerebrovascular accident, other thrombotic events and cardiac death were similar in AF patients with or without a history of cancer. Patients with cancer, however, were at higher risk of major bleeding and non-CV death.

Melloni et al. European Heart Journal – Quality of Care and Clinical Outcomes 2017

Effectiveness of Warfarin among Patients with Cancer

Adam J. Rose, MD[1,2,5], Jeff P. Sharman, MD[3], Al Ozonoff, PhD[4], Lori E. Henault, MPH[1], and Elaine M. Hylek, MD, MPH[1]

Patients with cancer may experience especially erratic control of the international normalized ratio (INR).[1] Contributing factors may include drug interactions, fluctuations in dietary vitamin K intake, therapy interruptions, hepatic dysfunction, mucositis, and diarrhea and the hypercoagulable state induced by the cancer itself.[2–10]

CONCLUSIONS: Compared to matched controls, cancer patients receiving warfarin spend less time in the target INR range, have more variable INR values, and have more thrombotic events. These effects are not dependent on whether the patient is anticoagulated for VTE or another indication.

J Gen Intern Med. 2007 Jul;22(7):997-1002

International Journal of Cardiology 203 (2016) 372–378

Contents lists available at ScienceDirect

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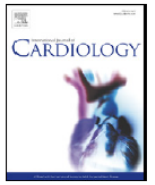
journal homepage: www.elsevier.com/locate/ijcard



Bleeding risk and major adverse events in patients with cancer on oral anticoagulation therapy

2168 consecutive non-valvular AF patients with newly diagnosed malignancies.

The **optimal INR** (2.0 to 3.0) level was achieved in **only 12% of patients**.

However, **1 year after cancer diagnosis**, only OAT+ patients **with the target therapeutic range of ≥ 60%** demonstrated **better cumulative survival free of composite end point*** than OAT−patients (p = 0.026).

Conclusion: During the first year after the cancer diagnosis, **OAT did not improve the composite end point because of poor INR control caused by cancer treatment**.

OAT: oral anticoagulant therapy

****Major adverse cardiac events (MACEs) and major bleeding***

Lee et al.

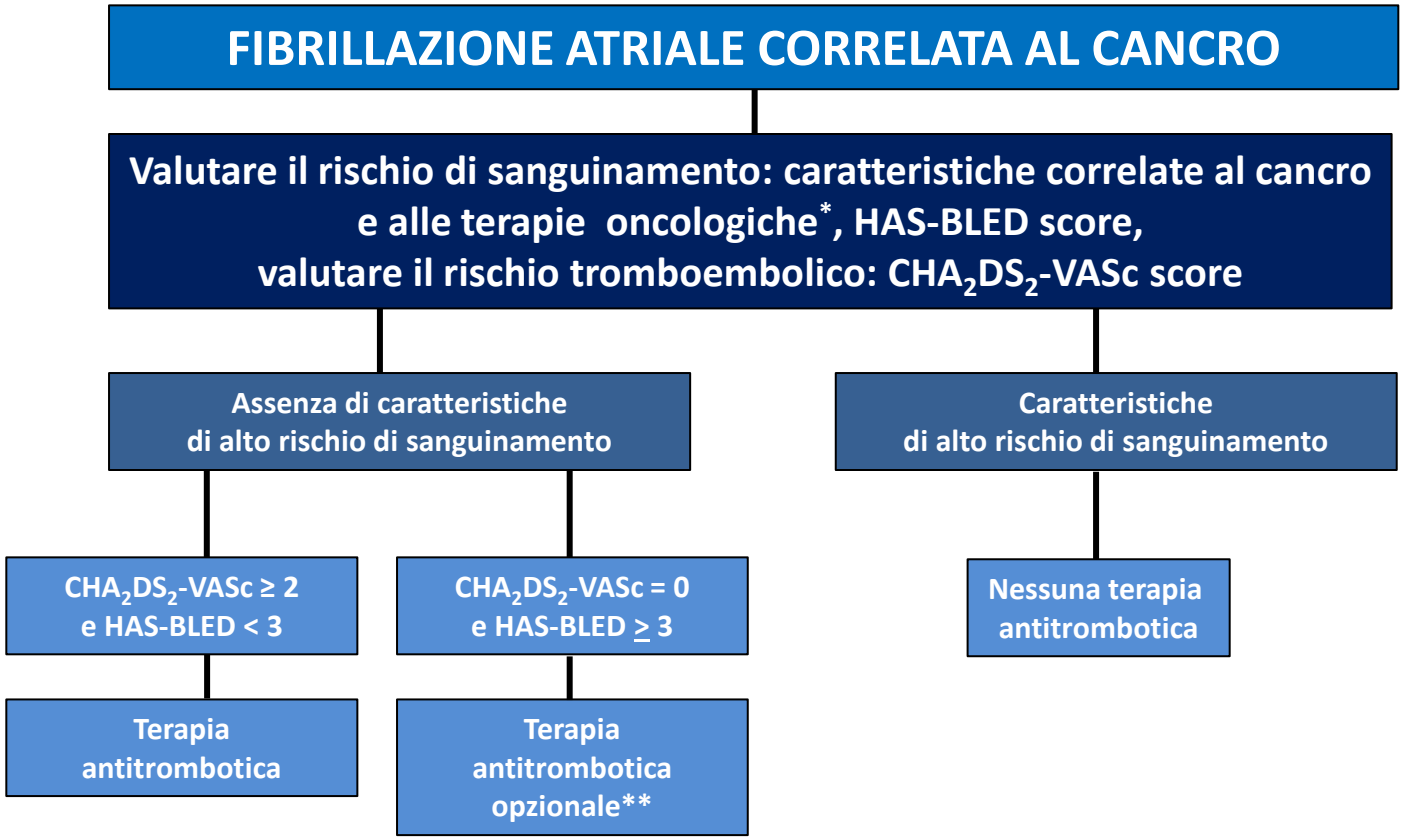
The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

19. Anticoagulation in atrial fibrillation patients with a malignancy

However, evidence for stroke prevention with LMWH in AF is lacking and LMWH is contraindicated in secondary prevention in the setting of acute stroke.

Steffel J et al. European Heart Journal 2018

Algoritmo per la terapia antitrombotica nella fibrillazione atriale correlata al cancro



*Tumore intracranico, neoplasie ematologiche con difetti della coagulazione, trombocitopenia indotta dalla terapia, grave malattia epatica metastatica, terapie oncologiche a rischio di sanguinamento. **La terapia antitrombotica può essere considerata in alcuni cancri associati ad alto rischio tromboembolico (ad esempio pancreas, ovaie, polmone, fegato) o a terapie oncologiche (ad esempio cisplatino, gemcitabina, 5-fluorouracile, eritropoietina, fattori di crescita dei granulociti)

Anticancer therapies associated with gastrointestinal (GI) toxicity

Drug class	Agent or agents	Types of toxicity
Alkylating agent (in high doses)[21]	Cyclophosphamide, bendamustine, busulfan, ifosfamide, melphalan	Stomatitis
Antimetabolite[21]	5-Fluorouracil, cytarabine, floxuridine, methotrexate	Diarrhea, stomatitis
Antimitotic agent[21]	Vinblastine, vincristine	Stomatitis, constipation
Checkpoint inhibitor[22]	Ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab	Colitis, diarrhea
EGFR inhibitor[22]	Cetuximab	Diarrhea
	Erlotinib, afatinib, gefitinib	Diarrhea, GI bleeding or perforation
Immunomodulating agent[21]	Interleukin 2	Stomatitis, colitis
MEK inhibitor[22]	Trametinib	Diarrhea
Nitrosourea[21]	Carmustine, lomustine	Diarrhea
PI3K inhibitor[22]	Idelalisib	Colitis
Topoisomerase inhibitor[21]	Etoposide	Stomatitis
	Irinotecan	Diarrhea, stomatitis
VEGF or VEGFR inhibitor[22]	Axitinib, bevacizumab	GI bleeding or perforation

[a] The list of therapies in the table is incomplete; agents are provided as examples.
EGFR = epidermal growth factor receptor; MEK = mitogen-activated protein kinase kinase; PI3K = phosphatidylinositol-4,5-bisphosphate 3-kinase; VEGF(R) = vascular endothelial growth factor (receptor).

Carrier et al, Curr Oncol 2018

10 La gestione della fibrillazione atriale nel paziente oncologico

Nicola Maurea[1], Enrico Barbieri[2]

Tabella 36. Criteri di utilizzo dei NAO nei pazienti oncologici

Valutazione dei pazienti
Fattori di rischio per sanguinamento Nessun evento di sanguinamento maggiore nei due mesi precedenti. Assenza di tumori intracranici o viscerali ad alto rischio di sanguinamenti maggiori
Piastrine Numero di piastrine >50,000 per µl. Nessuna previsione di riduzione dovuta alla chemioterapia
Studio di coagulazione PT, PPT e fibrinogeno normali
Test funzionali del fegato Nessuna insufficienza epatica significativa (es. Child Pugh B o C, cirrosi)
Funzione renale CrCl >30ml/min. Nessuna previsione di riduzione dovuta a chemioterapia nefrotossica
Farmaci Assenza di uso concomitante di farmaci con un forte effetto sul citocromo P450 3A4 e sulla glicoproteina P. Considerare la lista di farmaci chemioterapici, biologici, ormonali o di supporto che modulano il citocromo P450 3A4 e/o la glicoproteina P. Buona compliance.

10 La gestione della fibrillazione atriale nel paziente oncologico

Nicola Maurea[1], Enrico Barbieri[2]

	Dabigatran[1]	Rivaroxaban[1,2]	Apixaban[1,3]	Edoxaban[4-9]
Target	IIa (trombina)	Xa	Xa	Xa
Ore al Cmax	1,25–3	2–4	1–3	1–2
Metabolismo del CYP	Nessuno	32%	~25%	<10%
Biodisponibilità	6%	80%	66%	62%
Trasportatori	P-gp	P-gp/BCRP	P-gp/BCRP	P-gp
Legame proteico	35%	93%	87%	50%
Emivita	12-14 h	5-9 h	8-15 h	10-14 h
Eliminazione renale	80%*	33%#	25%#	35%*

* Della sostanza assorbita

Della sostanza data

BCRP = proteina di resistenza del carcinoma mammario
CYP = citocroma P450
P-gp = P-glicoproteina

Anticipated Drug-Drug Interaction Between Common Anticancer Drug Classes and DOACs

	P-Glycoprotein Interaction (All DOACs Affected)	CYP3A4 Interaction (Strongly Affects Rivaroxaban and Apixaban)
Inhibition	• Immune-modulating agents (e.g., tacrolimus; strong to moderate to competition to none) • Tyrosine kinase inhibitors (e.g., imatinib; strong to moderate to competition to none) • Hormonal agents (e.g., abiraterone; strong to competition to none)	• Immune modulating agents (e.g., cyclosporine; moderate to mild to competition) • Tyrosine kinase inhibitors (e.g., nilotinib; moderate to mild to competition) • Hormonal agents (e.g., bicalutamide; moderate to mild to competition to none) • Topoisomerase inhibitors (e.g., etoposide; mild to competition to none) • Anthracyclines (e.g., idarubicin; mild to competition to none) • Alkylating agents (e.g., cyclophosphamide; mild to competition to none)
Induction	• Anthracyclines (e.g., doxorubicin; strong to competition to none) • Antimitotic agents (e.g., vinblastine; strong to competition) • Immune-modulating agents (e.g., dexamethasone; strong to competition to none)	• Immune-modulating agents (e.g., dexamethasone; strong to moderate to competition) • Antimitotic agents (e.g., paclitaxel; moderate to mild to competition) • Tyrosine kinase inhibitors (e.g., vemurafenib; moderate to competition) • Hormonal agents (e.g., enzalutamide; strong to competition to none)
Minimal to no Interaction	• Alkylating agents (e.g., bendamustine; competition to none) • Antimetabolites (e.g., methotrexate; competition to none) • Monoclonal antibodies (e.g., rituximab; none) • Platinum based agents (e.g., cisplatin; none) • Intercalating agents (e.g., bleomycin; none)	• Monoclonal antibodies (e.g., brentuximab; competition to none) • Antimetabolites (e.g., pemetrexed; none) • Platinum based agents (e.g., oxaliplatin; none) • Intercalating agents (e.g., mitomycin C; none)

Anticipated interactions are offered within anticancer drug classes as no interaction, competition, or potential interaction (mild, moderate, or strong). Intraclass differences exist in inhibition/induction and presence and strength of interaction. Table 4 of the 2018 European Heart Rhythm Association practical guide (3) offers more detailed drug–drug interactions and anticipated effects on DOAC drug levels.

CYP3A4 = Cytochrome P450 3A4; DOAC = direct oral anticoagulants.

Mosarla RC et al. JACC 2019

Common drug-drug interactions with direct factor Xa inhibitors

Drug class and name	Interaction effect		
	Edoxaban[a]	Rivaroxaban[b]	Apixaban[b]
Antimitotic agents			
Vinblastine	↓	↓	↓
Anti-mycotic agents			
Azithromycin	↑	↑	↑
Clarithromycin	↑	↑	↑
Erythromycin	↑	↑	↑
Itroconazole	↑	↑	↑
Ketoconazole	↑	↑	↑
Posaconazole	—	↑	↑
Voriconazole	—	↑	↑
Anthracyclines			
Doxorubicin	↓	↓	↓
Hormonal agents			
Tamoxifen	↑	↑	↑
Immune-modulating agents			
Cyclosporine	↑	↑	↑
Dexamethasone	↓	↓	↓
Tacrolimus	↑	↑	↑
Protease inhibitors			
Indinavir	↑	↑	↑
Nelfinavir	↑	↑	↑
Ritonavir	↑	↑	↑
Saquinavir	↑	↑	↑
Tyrosine kinase inhibitors			
Imatinib	—	↓	↓
Lapatinib	↑	↑	↑
Nilotinib	↑	↑	↑
Sunitinib	↑	↑	↑

[a] Substrate of P-glycoprotein.
[b] Substrate of P-glycoprotein and CYP3A4 (cytochrome P450 3A4).
↑ = increases plasma factor Xa through P-glycoprotein or CYP3A4 inhibition; ↓ = decreases plasma factor Xa through P-glycoprotein or CYP3A4 induction; — = no effect on plasma factor Xa.

[a] Substrate of P-glycoprotein.
[b] Substrate of P-glycoprotein and CYP3A4 (cytochrome P450 3A4).
↑ = increases plasma factor Xa through P-glycoprotein or CYP3A4 inhibition; ↓ = decreases plasma factor Xa through P-glycoprotein or CYP3A4 induction; — = no effect on plasma factor Xa.

10 La gestione della fibrillazione atriale nel paziente oncologico

Nicola Maurea[1], Enrico Barbieri[2]

TABELLA 37. Lista dei farmaci concomitanti forti inibitori e induttori della glicoproteina P e del citocromo P450 3A4

Inibitori			
Antimicotici	**Inibitori delle proteasi**	**Immunosoppressori***	**Altri**
Chetoconazolo	Ritonavir	Ciclosporine	Claritromicina
Itraconazolo	Lopinavir/ritronavir	Tacrolimus	Conivaptan
Voriconazolo	Indinavir/ritronavir		
Posaconazolo			
Fluconazolo			

Induttori	
Anti-epilettici	**Altri**
Fenitoina	Claritromicina
Carbamazepina	Conivaptan

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Interazioni con i farmaci concomitanti forti inibitori e induttori della glicoproteina P e del citocromo P450 3A4

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Antibiotics					
Clarithromycin; Erythromycin	Moderate P-gp competition and strong CYP3A4 inhibition	+15 to 20%	+60% AUC +30% C_{max}	+90%[SmPC]	+34% (Erythromycin)/ +54% (Clarithromycin) [SmPC129]
Rifampicin	P-gp/BCRP and CYP3A4/ CYP2J2 inducers	Minus 66%[SmPC]	Minus 54%[138]	Minus 35%, but with compensatory increase of active metabolites	Up to minus 50%[SmPc]
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[129]
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[SmPC]
Itraconazole; Ketoconazole; Voriconazole	potent P-gp and BCRP competition; CYP3A4 inhibition	+140 to 150% (US: 2 x 75 mg if CrCl 30–50 mL/min)	+100%[136]	+87 to 95%[132] (reduce NOAC dose by 50%)	Up to +160%[SmPc]
Posaconasole	Mild to moderate P-gp inhibition	SmPC	SmPC		SmPC

Steffel J et al. European Heart Journal 2018

NOACs e Interazioni: Farmaci Antineoplastici (1/9)

	Via[142]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		**Yes**	**Yes**	**Yes**	**Yes**
CYP3A4 substrate		**No**	**Yes (≈25%)**	**No (<4%)**	**Yes (≈18%)**
Antimitotic agents					
Paclitaxel	Moderate CYP3A4 induction; CYP3A4/P-gp competition				
Vinblastine	Strong P-gp induction; CYP3A4/P-gp competition				
Docetaxel, Vincristine	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Vinorelbine	Mild CYP3A4 induction; CYP3A4/P-gp competition				

- Nessuna interazione rilevante
- Controindicato/ non raccomandato
- Cautela nelle politerapie o se ≥ 2 fattori rischio per sang.
- Considerare rid. dosaggio o diverso NOAC
- Controindicato/ non raccomandato
- Cautela, evitare se possibile
- No dati clinici o di PK, ma solo RCP o expert opinion

Steffel; European Heart Journal (2018) 00, 1–64; doi:10.1093/eurheartj/ehy136

NOACs e Interazioni: Farmaci Antineoplastici (2/9)

	Via[142]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		**Yes**	**Yes**	**Yes**	**Yes**
CYP3A4 substrate		**No**	**Yes (≈25%)**	**No (<4%)**	**Yes (≈18%)**
Antimetabolites					
Metotrexate	P-gp competition; no relevant interaction anticipated				
Pemetrexed, Purine analogs, Pyrimidine analogs	No relevant interaction anticipated				
Topoisomerase inhibitors					
Topotecan	No relevant interaction anticipated				
Irinotecan	CYP3A4/P-gp competition; No relevant interaction anticipated				
Etoposide	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				

- Nessuna interazione rilevante
- Controindicato/ non raccomandato
- Cautela nelle politerapie o se ≥ 2 fattori rischio per sang.
- Considerare rid. dosaggio o diverso NOAC
- Controindicato/ non raccomandato
- Cautela, evitare se possibile
- No dati clinici o di PK, ma solo RCP o expert opinion

Steffel; European Heart Journal (2018) 00, 1–64; doi:10.1093/eurheartj/ehy136

NOACs e Interazioni: Farmaci Antineoplastici (3/9)

	Via[142]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		**Yes**	**Yes**	**Yes**	**Yes**
CYP3A4 substrate		**No**	**Yes (≈25%)**	**No (<4%)**	**Yes (≈18%)**
Anthracyclines/Anthracenediones					
Doxorubicin	Strong P-gp induction, mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Idarubicin	Mild CYP3A4 inhibition; P-gp competition				
Daunorubicin	P-gp competition; No relevant interaction anticipated				
Mitoxantrone	No relevant interaction anticipated				

- Nessuna interazione rilevante
- Controindicato/ non raccomandato
- Cautela nelle politerapie o se ≥ 2 fattori rischio per sang.
- Considerare rid. dosaggio o diverso NOAC
- Controindicato/ non raccomandato
- Cautela, evitare se possibile

No dati clinici o di PK, ma solo RCP o expert opinion

Steffel; European Heart Journal (2018) 00, 1–64; doi:10.1093/eurheartj/ehy136

NOACs e Interazioni: Farmaci Antineoplastici (4/9)

	Via[142]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		**Yes**	**Yes**	**Yes**	**Yes**
CYP3A4 substrate		**No**	**Yes (≈25%)**	**No (<4%)**	**Yes (≈18%)**
Alkylating agents					
Ifosfamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Ciclophosphamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Lomustine	Mild CYP3A4 inhibition				
Busulfan	CYP3A4 competition; No relevant interaction anticipated				
Bendamustine	P-gp competition; No relevant interaction anticipated				
Chlorambucil, Melphalan, Carmustine, Procarbazine, Dacarbazine, Temozolomide	No relevant interaction anticipated				

- Nessuna interazione rilevante
- Controindicato/ non raccomandato
- Cautela nelle politerapie o se ≥ 2 fattori rischio per sang.
- Considerare rid. dosaggio o diverso NOAC
- Controindicato/ non raccomandato
- Cautela, evitare se possibile
- No dati clinici o di PK, ma solo RCP o expert opinion

Steffel; European Heart Journal (2018) 00, 1–64; doi:10.1093/eurheartj/ehy136

NOACs e Interazioni: Farmaci Antineoplastici (5/9)

	Via[142]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		**Yes**	**Yes**	**Yes**	**Yes**
CYP3A4 substrate		**No**	**Yes (≈25%)**	**No (<4%)**	**Yes (≈18%)**
Platinum-based agents					
Cisplatin, Carboplatin, Oxaliplatin	No relevant interaction anticipated				
Intercalating agents					
Bleomycin, Dactinomycin	No relevant interaction anticipated				
Mitomycin C	No relevant interaction anticipated				

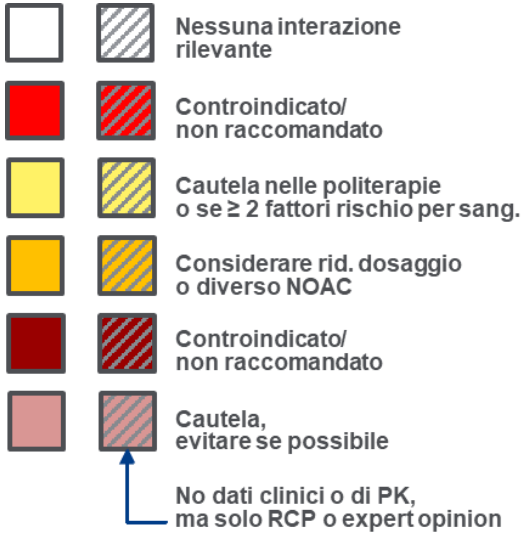
- Nessuna interazione rilevante
- Controindicato/ non raccomandato
- Cautela nelle politerapie o se ≥ 2 fattori rischio per sang.
- Considerare rid. dosaggio o diverso NOAC
- Controindicato/ non raccomandato
- Cautela, evitare se possibile

No dati clinici o di PK, ma solo RCP o expert opinion

Steffel; European Heart Journal (2018) 00, 1–64; doi:10.1093/eurheartj/ehy136

NOACs e Interazioni: Farmaci Antineoplastici (6/9)

Tyrosine kinase inhibitors		
Imatinib, Crizotinib	Strong P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition	
Nilotinib, Lapatinib	Moderate-to-strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition	
Vemurafenib	Moderate CYP3A4 induction; CYP3A4/P-gp competition	
Dasatinib	Mild CYP3A4 inhibition; CYP3A4/P-gp competition	
Vandetanib, Sunitinib	Strong P-gp induction; CYP3A4 competition	
Erlotinib, Gefitinib	CYP3A4 competition; No relevant interaction anticipated	



Steffel; European Heart Journal (2018) 00, 1–64; doi:10.1093/eurheartj/ehy136

NOACs e Interazioni: Farmaci Antineoplastici (7/9)

	Via[142]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		**Yes**	**Yes**	**Yes**	**Yes**
CYP3A4 substrate		**No**	**Yes (≈25%)**	**No (<4%)**	**Yes (≈18%)**
Monoclonal antibodies					
Brentuximab	CYP3A4 competition; No relevant interaction anticipated				
Rituximab, Alemtuzumab, Cetuximab, Trastuzumab, Bevacizumab	No relevant interaction assumed				

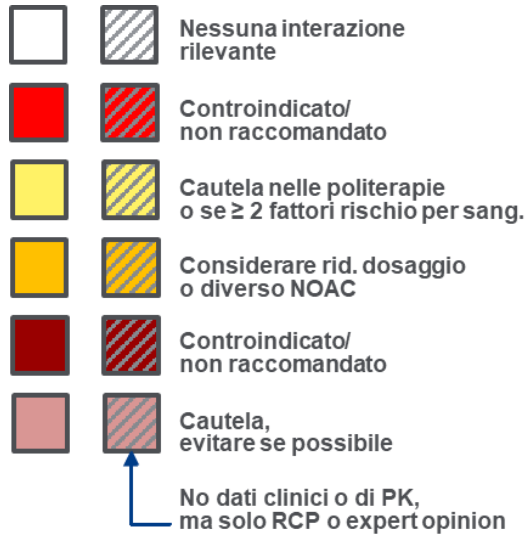
- Nessuna interazione rilevante
- Controindicato/ non raccomandato
- Cautela nelle politerapie o se ≥ 2 fattori rischio per sang.
- Considerare rid. dosaggio o diverso NOAC
- Controindicato/ non raccomandato
- Cautela, evitare se possibile

No dati clinici o di PK, ma solo RCP o expert opinion

Steffel; European Heart Journal (2018) 00, 1–64; doi:10.1093/eurheartj/ehy136

NOACs e Interazioni: Farmaci Antineoplastici (8/9)

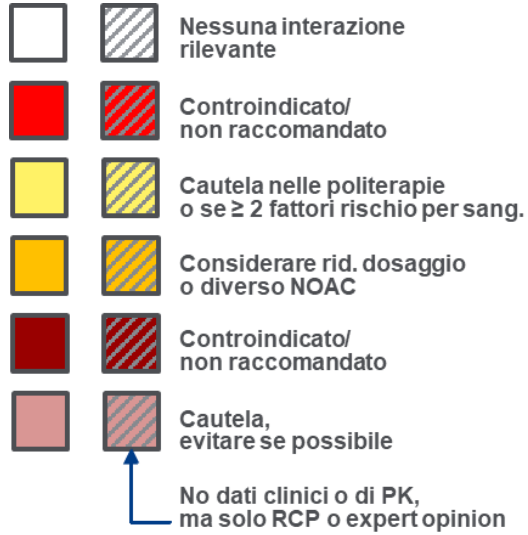
Hormonal agents					
Abiraterone	Moderate CYP3A4 inhibition, strong P-gp inhibition; CYP3A4/P-gp competition				
Enzalutamide	Strong CYP3A4 induction, strong P-gp inhibition; CYP3A4/P-gp competition				
Bicalutamide	Moderate CYP3A4 inhibition				
Tamoxifen	Strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4 competition				
Anastrozole	Mild CYP3A4 inhibition				
Flutamide	CYP3A4 competition; No relevant interaction anticipated				
Letrozole, Fulvestrant	CYP3A4 competition; No relevant interaction anticipated				
Raloxifene, Leuprolide, Mitotane	No relevant interaction anticipated				



Steffel; European Heart Journal (2018) 00, 1–64; doi:10.1093/eurheartj/ehy136

NOACs e Interazioni: Farmaci Antineoplastici (9/9)

Immune-modulating agents					
Cyclosporine	Strong-to-moderate P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC	SmPC	+73%[143]	
Dexamethasone	Strong CYP3A4/P-gp induction; CYP3A4/P-gp competition				
Tacrolimus	Strong-to-moderate P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC			
Prednisone	Moderate CYP3A4 induction; CYP3A4 competition				
Temsirolimus, Sirolimus	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Everolimus	CYP3A4 competition; No relevant interaction anticipated				



Steffel; European Heart Journal (2018) 00, 1–64; doi:10.1093/eurheartj/ehy136

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Antimitotic agents						
Vinca alkaloids						
Vinblastine	+++		+	●	●	
Vincristine	+++		+	●		
Vinorelbine	+++		+			
Taxanes						
Docetaxel	+++		+	●		
Paclitaxel	**+++**	**++**		●		
Antimetabolites						
Antifolates						
Methotrexate				●		
Pemetrexed						
Purine analogs						
Mercaptopurine						
Thioguanine						
Pentostatin						
Cladribine						
Clofarabine						
Fludarabine						
Pyrimidine analogs						
Fluorouracil						
Capecitabine						
Cytarabine						
Gemcitabine						
Azacitadine						
Decitabine						

[a] +++, strong interaction; ++, moderate interaction; +, weak interaction.
[b] Data for strength of P-glycoprotein interactions are limited. ●, indicates that an interaction has been documented.
[c] Bold indicates the drug is either a strong or a moderate inhibitor of CYP3A4 (with or without P-glycoprotein interaction). These drugs have increased risk for interactions with the new oral anticoagulants that are metabolized by CYP3A4.

Short, The Oncologist 2014

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Topoisomerase inhibitors						
Topotecan						
Irinotecan	+++			●		
Etoposide	+++		+	●		
Anthracyclines/ anthracenediones						
Doxorubicin	+++		+	●	●	
Daunorubicin				●		
Idarubicin			+	●		
Mitoxantrone						
Alkylating agents						
Cyclophosphamide	+		+			
Ifosfamide	+++		+			
Chlorambucil						
Melphalan						
Bendamustine				●		
Carmustine						
Lomustine			+			
Busulfan	+++					
Procarbazine						
Dacarbazine						
Temozolomide						

[a] +++, strong interaction; ++, moderate interaction; +, weak interaction.
[b] Data for strength of P-glycoprotein interactions are limited. ●, indicates that an interaction has been documented.
[c] Bold indicates the drug is either a strong or a moderate inhibitor of CYP3A4 (with or without P-glycoprotein interaction). These drugs have increased risk for interactions with the new oral anticoagulants that are metabolized by CYP3A4.

Short, The Oncologist 2014

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Platinum-based agents						
Cisplatin						
Carboplatin						
Oxaliplatin						
Intercalating agents						
Bleomycin						
Mitomycin C				●		
Dactinomycin						
Tyrosine kinase inhibitors						
Imatinib	+++		++	●		●
Dasatinib	+++		+			
Nilotinib	+++		+	●		●
Erlotinib	+++					
Gefitinib	+++					
Lapatinib	+++		+	●		●
Sunitinib	+++					●
Sorafenib	+					
Crizotinib	+++		++	●		●
Vemurafenib	+	++		●		
Vandetanib	+++					●
Monoclonal antibodies						
Rituximab						
Brentuximab	+++					
Alemtuzumab						
Cetuximab						
Trastuzumab						
Bevacizumab						

[a] +++, strong interaction; ++, moderate interaction; +, weak interaction.
[b] Data for strength of P-glycoprotein interactions are limited. ●, indicates that an interaction has been documented.
[c] Bold indicates the drug is either a strong or a moderate inhibitor of CYP3A4 (with or without P-glycoprotein interaction). These drugs have increased risk for interactions with the new oral anticoagulants that are metabolized by CYP3A4.

Short, The Oncologist 2014

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Hormonal agents						
Tamoxifen	+++		+			●
Raloxifene						
Anastrozole			+			
Letrozole	+					
Fulvestrant	+					
Leuprolide						
Flutamide	+++					
Bicalutamide			++			
Enzalutamide	+++	+++				●
Abiraterone	+++		++			●
Mitotane						
Immune-modulating agents						
Cyclosporine	+++		++	●		●
Sirolimus	+++		+	●		
Everolimus	+++			●		
Temsirolimus	+++		+	●		
Tacrolimus	+++		+	●		●
Dexamethasone	+++	+++		●	●	●
Prednisone	+	++				

[a] +++, strong interaction; ++, moderate interaction; +, weak interaction.
[b] Data for strength of P-glycoprotein interactions are limited. ●, indicates that an interaction has been documented.
[c] Bold indicates the drug is either a strong or a moderate inhibitor of CYP3A4 (with or without P-glycoprotein interaction). These drugs have increased risk for interactions with the new oral anticoagulants that are metabolized by CYP3A4.

Short, The Oncologist 2014

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Miscellaneous						
Lenalidomide				●		
Bortezomib	+++		+			
Bexarotene	+	++				
Supportive care						
Prochlorperazine						
Ondansetron	+++			●		
Palonosetron	+					
Metoclopramide						
Aprepitant	+++	++	++			
Fosaprepitant	+++	++	++			
Oxycodone	+++					
Hydromorphone						
Morphine						
Fentanyl	+++		+			
Methadone	+++		+			
Acetaminophen	+		+			
Lorazepam						
Clonazepam	+++					
Filgrastim						
Epoetin alfa						
Darbepoetin alfa						

[a] +++, strong interaction; ++, moderate interaction; +, weak interaction.
[b] Data for strength of P-glycoprotein interactions are limited. ●, indicates that an interaction has been documented.
[c] Bold indicates the drug is either a strong or a moderate inhibitor of CYP3A4 (with or without P-glycoprotein interaction). These drugs have increased risk for interactions with the new oral anticoagulants that are metabolized by CYP3A4.

Short, The Oncologist 2014

Anticoagulation of cancer patients with non- valvular atrial fibrillation receiving chemotherapy: guidance from the SSC of the ISTH

Guidance Statements

- We recommended **individualized anticoagulation regimens** after **shared decision-making** with patients, based wherever possible on risk of stroke, bleeding and patients values.

- In cancer patients **on chemotherapy with newly diagnosed NVAF**, with **exception** of patients with **luminal gastrointestinal cancers** with no surgery or patients with **active gastrointestinal mucosal abnormalities** such as duodenal ulcers, gastritis, esophagitis or colitis we suggest the **use of a DOAC over a VKA** or LMWH as anticoagulant therapy if no clinically relevant drug-to-drug interactions are expected

Delluc A et al, J Tromb Haemost 2019

Anticoagulation of cancer patients with non- valvular atrial fibrillation receiving chemotherapy: guidance from the SSC of the ISTH

Guidance Statements

- In cancer patients with **NVAF already on an anticoagulant** regimen before starting chemotherapy, we recommended continuing **the same anticoagulation regimen** unless there are clinically relevant drug-to-drug interaction

  a) In cancer patients on chemotherapies with **clinically relevant VKA interactions**, we suggest considering a DOAC if no additional drug-drug interaction with DOAC or close monitoring of VKA (target INR between 2 and 3)

  b) In cancer patients on chemotherapies **unable to tolerate an oral route** of admininistration (e.g. nausea and vomiting), we suggest the **use of parenteral anticoagulation** with therapeutic dosing of LMWH **with resumption of oral** anticoagulation as soon as possible.

Delluc A et al, J Tromb Haemost 2019

Conclusions

- DOACs are a **more practical alternative to warfarin**, with comparable clinical efficacy and safety
- **Rapid onset** (1-2 hours) **and shorter half-life** of DOACs (6-12 hours) compared with warfarin (40 hours) offer **additional practical advantages** over VKAs in cancer patients **who undergo frequent medication changes and invasive procedures.**
- As for cancer-associated VTE, **carefully consider**:
  - Bleeding risks (e.g. tumor type)
  - (Clinically revelant) drug-drug interactions
  - Thrombocytopenia ($< 50 \times 10^9\ L^{-1}$)
  - Renal and hepatic function
  - Patients preferences and values
- **Anticoagulant therapy** regularly reassessed as patient's cancer status and **management change over time**

Conclusioni

- Necessari algoritmi dedicati che valutino prima le caratteristiche di alto rischio di sanguinamento e di trombofilia del tipo di tumore e poi gli score di rischio.

- L'Edoxaban alla luce dei risultati della sottoanalisi dell'ENGAGE AF-Timi 48 garantisce sicurezza ed efficacia nel paziente con fibrillazione atriale e cancro.

- Le linee guida EHRA 2018 hanno aperto all'uso del NAO in oncologia.

- L'Edoxaban per il suo profilo metabolico (scarsa interazione con citocromo) garantisce una maggiore facilità d'uso.