Il Ruolo dei DOAC nella fibrillazione atriale nel paziente oncologico

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Fibrillazione atriale e cancro

- L’aritmia più frequente
- Interessa 1.5% - 2% della popolazione generale
- La prevalenza aumenta con l’età: 10% a 80 anni – 18% a 85 anni
- Comorbidità predisponenti: ipertensione,insufficienza cardiaca, valvulopatie,BPCO, diabete, tireopatie, nefropatie croniche , disrurbi elettrolitici
- Dato l’aumento di cancro con l’età e la presenza di altre condizioni predisponenti alla FA l’associazione fra cancro e FA è ampiamente possibile.
- La FA aumenta di 5 volte il rischio di stroke , triplica il rischio di insufficienza cardiaca,raddoppia la mortalità

JACC Farmakis et al. 2014

20-year incident malignancy inpatients with new-onset AF has been reportedly low at 10%,incident AF may occur in up to 30% of patients with certain types of malignancy (eg, thoracic).

Fenola JAHA 2018

AF in patients with malignancy may independently double the risk of venous or arterial thromboembolism compared with either condition alone

Hu Int J Cardiol 2013

Some malignancies may also inherently increase the risk for major bleeding in patients with AF (eg, hematologic cancer), which is potentiated further with anticoagulant therapy

Fenola JAHA 2018

Table I Baseline characteristics in AF patients with and without history of cancer

Baseline characteristics (%)	No cancer (*N* = 7431)	History of cancer (*N* = 2318)	*P*-value
Medical history			
Peripheral vascular disease	12.6	16.0	<0.0001
Congestive heart failure	32.4	34.4	0.07
Prior myocardial infarction	15.4	18.1	0.002
Stroke/transient ischaemic attack	14.4	17.6	0.0001
Prior gastrointestinal bleed	8.1	12.7	<0.0001
CHADS2 risk score ≥ 2	69.6	80.1	<0.0001
CHADS VASC score ≥ 2	89.5	96.2	<0.0001
ORBIT risk score			<0.0001
0–2	54.8	45.3	
3	16.1	17.6	
≥3	21.2	32.1	
AF type			<0.0001
New onset	5.0	2.7	
Paroxysmal	51.2	49.0	
Persistent/ permanent AF	43.7	48.3	
Current AF management			<.0001
Rate control	67.2	71.7	
Rhythm control	32.8	28.3	
Prior cardioversions	31.1	27.1	0.0003
Prior catheter ablation	6.1	4.0	0.0001

Melloni : Orbit – AF registry EHJ Qual Care Clin Outcomes 2017

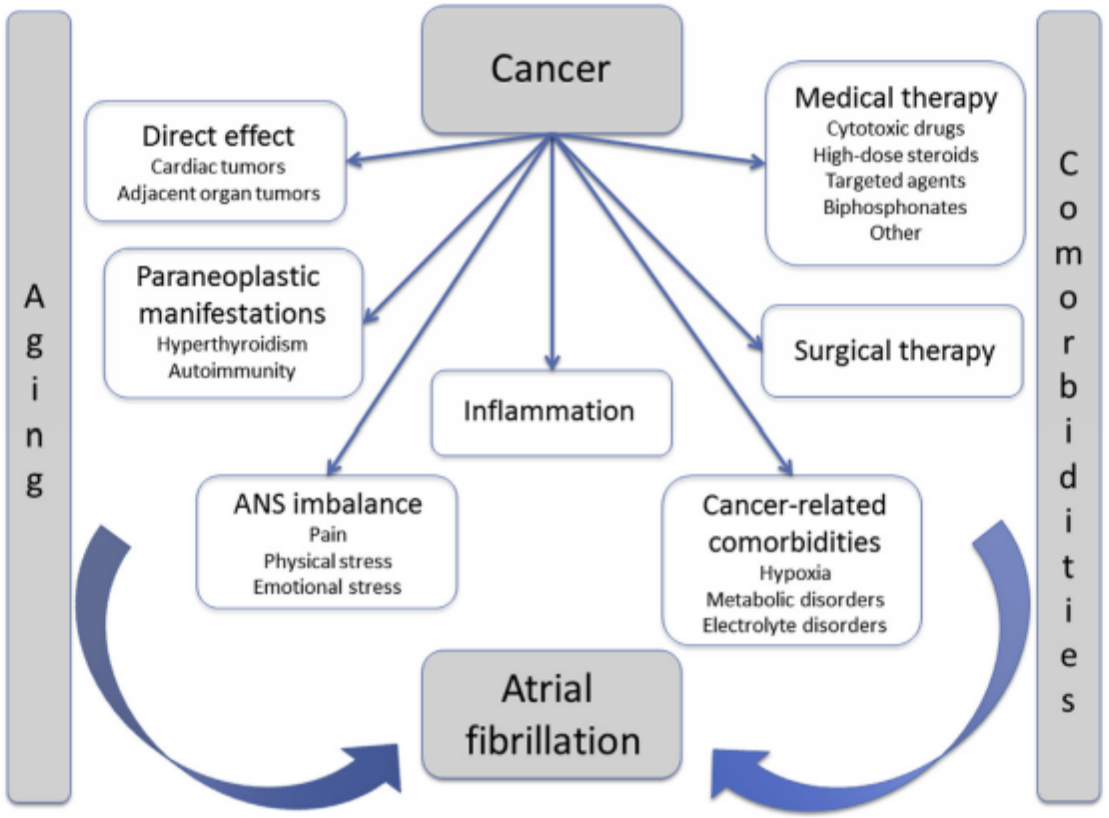

Figure 1 **An Overview of the Potential Pathogenetic Mechanisms Linking Cancer With Atrial Fibrillation**

Cancer may cause atrial fibrillation, rarely by direct invasion of the heart and more commonly by chemotherapy and supportive therapies, surgery, chronic inflammation, autonomous nervous system (ANS) imbalance, paraneoplastic manifestation, and metabolic, electrolyte, and other abnormalities. In addition, aging and coexisting comorbid conditions may predispose both to cancer and to atrial fibrillation.

JACC Farmakis et al. 2014

Farmaci chemioterapici che possono provocare fibrillazione atriale

Agenti alchilanti (cisplatino, ciclofosfamide, ifosfamide, melfalan)
Antracicline
Antimetaboliti (capecitabina, 5-fluorouracile, gemcitabina)
Interleuchina-2
Interferoni
Rituximab
Romidepsina
Inibitori delle tirosinchinasi (ponatinib, sorafenib, sunitinib, ibrutinib)
Inibitori della topoisomerasi II (amsacrina, etoposide)
Taxani
Alcaloidi della vinca

Ibrutinib

Table 1 Epidemiological Evidence of AF in Patients With Cancer

First Author, Year (Ref. #)	No. of Patients	Condition	AF Prevalence
Hu et al., 2012 (3)	24,125	Various types of cancer	2.4% at cancer diagnosis plus 1.8% after cancer diagnosis (new onset)
Erichsen et al., 2012 (4)	28,333 with AF and 28,3260 without AF	Colorectal cancer	Colorectal cancer: 0.59% in AF vs. 0.05% in non-AF
Guzzetti et al., 2008 (5)	1,317	Colorectal or breast cancer	3.6%
Guzzetti et al., 2002 (6)	456	Colorectal cancer	5.2%
Onaitis et al., 2010 (8)	13,906	Pulmonary resection for lung cancer	12.6%
Imperatori et al., 2012 (9)	454	Pulmonary resection for lung cancer	9.9%
Cardinale et al., 2007 (10)	400	Pulmonary resection for lung cancer	18%
Roselli et al., 2005 (11)	604	Pulmonary resection for lung cancer	19%
Nojiri et al., 2011 (13)	553	Pulmonary resection for lung cancer	5.6%
Salvatici et al., 2010 (14)	400	Pulmonary resection for lung cancer	18%
Cardinale et al., 1999 (15)	233	Pulmonary resection for lung cancer	12%
Nojiri et al., 2010 (16)	126	Pulmonary resection for lung cancer	23%
Nojiri et al., 2010 (50)	80	Pulmonary resection for lung cancer	28%
Ciszewski et al., 2013 (65)	117	Pulmonary resection for lung cancer	16%
Siu et al., 2005 (18)	563	Colectomy for colorectal cancer	4.4%
Walsh et al., 2004 (24)	174	Colectomy for colorectal cancer	5.4% (pre- and post-operatively)
Ojima et al., 2013 (66)	207	Esophagectomy for esophageal cancer	9.2%
Erichsen et al., 2011 (28)	11,887	Cancer ± bisphosphonates	3.2% in bisphosphonate group vs. 2.4% in controls
Wilkinson et al., 2010 (29)	20,571	Cancer ± bisphosphonates	18.0% in bisphosphonate group vs. 12.7% in controls
Arslan et al., 2011 (67)	124	Cancer + bisphosphonate	0%
Abonowara et al., 2012 (68)	136	TSH suppression for thyroid cancer	10.3%

JACC Farmakis et al. 2014

Vedovati patients with cancer and atrial fibrillation **treated with DOACS**: A prospective cohort study Int J Cardiol 2018 (2300 pts)

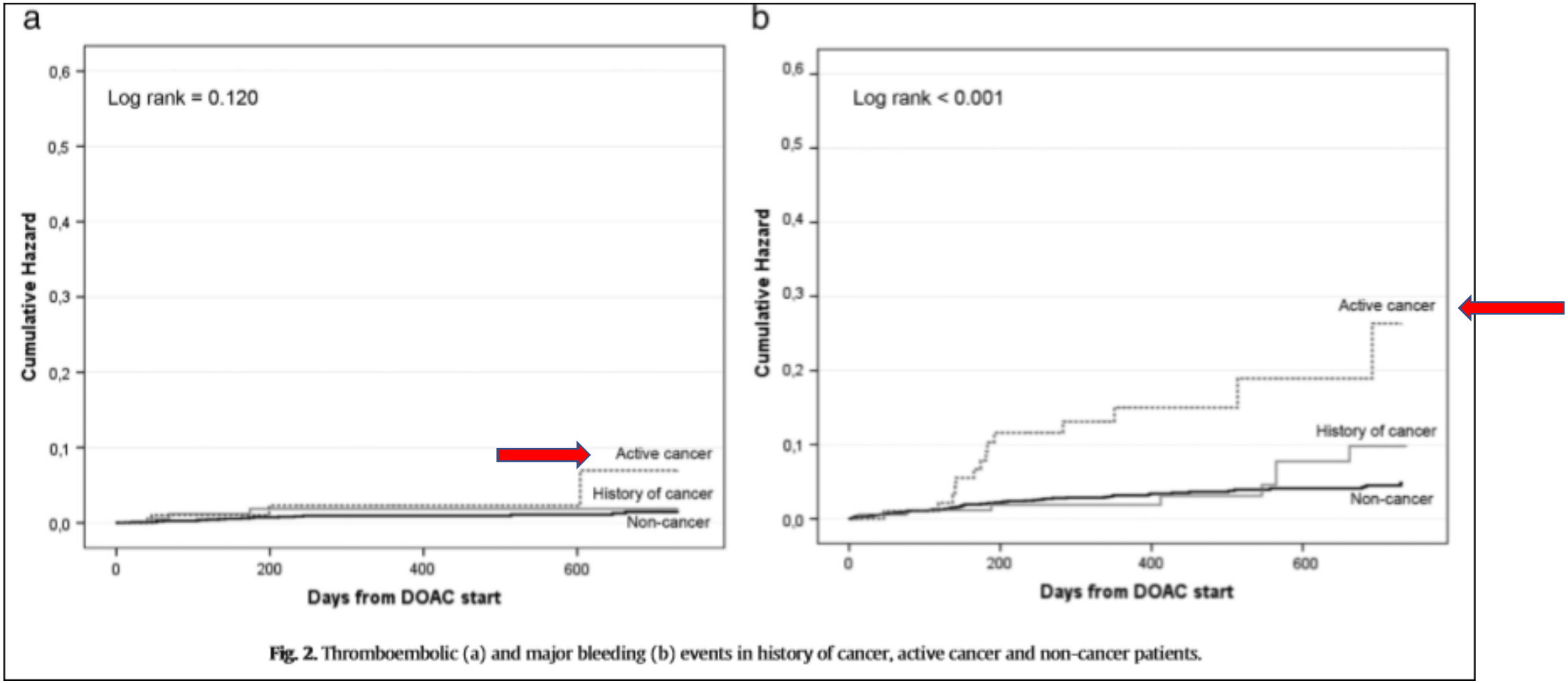

Fig. 2. Thromboembolic (a) and major bleeding (b) events in history of cancer, active cancer and non-cancer patients.

Gestione pratica della terapia anticoagulante del paziente con cancro e FA

- Algoritmo
- Indici di rischio
- Terapia con eparina
- Warfarin e DOAC
- Valutazione del paziente e interazioni chemioterapici

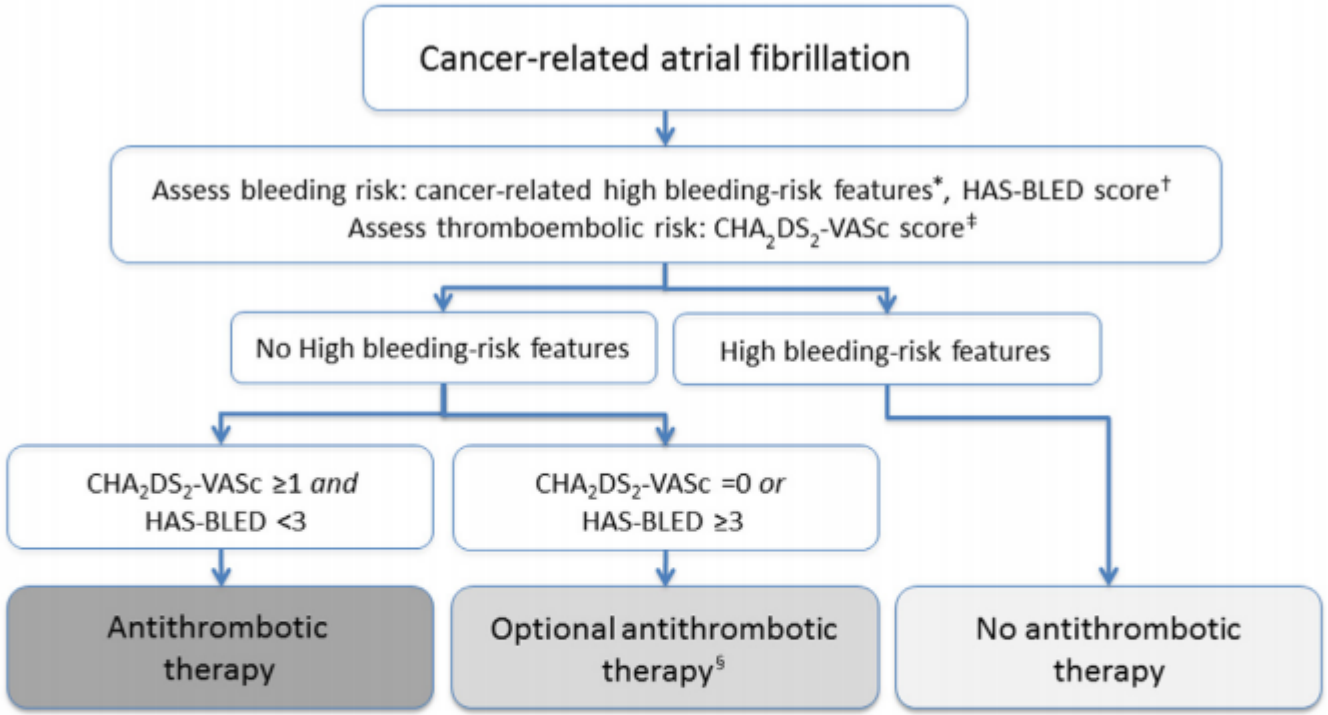

Figure 2 **Algorithm for Antithrombotic Therapy in Cancer-Related Atrial Fibrillation**

A practical algorithm for antithrombotic therapy in cancer-related atrial fibrillation. *Intracranial tumor, hematologic malignancies with coagulation defects, cancer therapy-induced thrombocytopenia, severe metastatic hepatic disease etc. †HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly ‡CHA_2DS_2-VASc = Congestive heart failure or left ventricular dysfunction Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex (female) §Antithrombotic therapy may be considered in high thromboembolic risk associated with certain cancers (e.g., pancreatic, ovarian, lung, primary hepatic) or cancer therapies (e.g., cisplatin, gemcitabine, 5-fluorouracil, erythropoietin, granulocyte colony stimulating factors).

JACC Farmakis et al. 2014

Rischio emorragico in relazione al cancro

- **Tipo di neoplasia:** per esempio neoplasia cerebrale, neoplasie ematologiche con difetti della coagulazione, trombocitopenia indotta da terapia oncologica o malattia epatica metastatica. Se sono presenti, non si può prescrivere la terapia antitrombotica. Se, invece, non sono presenti si possono applicare gli score di rischio.
- **Score di rischio :**
    - se il CHA2DS2-VASc è ≥2 e l'HAS-BLED è <3 si procede con la terapia antitrombotica;
- se **Has Bleed ≥3** terapia antitrombotica diventa opzionale e considerata solo in associazione a **cancro associato ad alto rischio tromboembolico** (pancreas, ovaio, polmone fegato) **o a terapie oncologiche particolari** (cisplatino, 5 – fluoracile, gemcitabina, eritropoietina).
- schede dell'Agenzia Italiana del Farmaco (AIFA),:per tutti e quattro gli anticoagulanti orali diretti (direct oral anticoagulants, DOAC), le controindicazioni relative alla neoplasie riguardano solo l'alto rischio di sanguinamento
- "Importantly, however, **a high bleeding risk in itself should not automatically result in the decision not to anticoagulate as stroke risk tracks along with bleeding risk** (2018 EHRA Practical Guide on NOACs in AF)"

2. RACCOMANDAZIONI PER LA TERAPIA CON I NAO

2.1 Pazienti naive al trattamento con anticoagulanti

Per i pazienti naive agli anticoagulanti senza i fattori di rischio trombotico ed emorragico previsti dal criterio 1 del Piano terapeutico AIFA[14], considerando il miglior profilo costo/beneficio, va considerata la possibilità di intraprendere un trattamento con AVK per almeno 6 mesi, dopo il quale può essere valutato l'eventuale passaggio ai NAO qualora la qualità della terapia dovesse risultare insoddisfacente.

2.2 Paziente che inizia la terapia con NAO

Si aggiorna la "*Scheda informativa per il prescrittore*" con i criteri previsti per edoxaban (vedasi pagg. 8-9).
La scheda è strutturata nel rispetto dei punteggi CHA2DS2-VASc e HAS-BLED previsti per ciascun principio attivo dai rispettivi PT AIFA. **La valutazione di entrambi i punteggi si rende necessaria ai fini dell'eleggibilità del paziente e della prescrizione a carico del SSN** ma appare corretto precisare che la valutazione dell'HAS-BLED si discosta da quanto indicato dalle più recenti linee guida ESC[1] le quali raccomandano la valutazione clinica del rischio emorragico nei pazienti in trattamento con anticoagulanti orali al solo fine di identificare i fattori di rischio modificabili (forza della raccomandazione: classe IIa, livello B) e non come strumento per escludere o includere i pazienti al trattamento anticoagulante.
Si riportano in **tabella 4** i dosaggi raccomandati, da scheda tecnica, per la FANV.

Decreto Regione Veneto 98: Linee guida impiego NAO nella regione Veneto . Aggiornamento 2017

Sulla base di quanto sopra, **gli assistibili sono stati classificati:**

-

“con” un adeguato controllo dell’INR in presenza di un valore di TTR superiore o uguale al 70%;

-

“senza” un adeguato controllo dell’INR in presenza di un va lore di TTR inferiore al 70%;

-

“con” un’alterazione del rischio trombotico o emorragico in presenza di un punteggio calcolato di CHA2DS2-VASc ≥1 e di HAS-BLED > 3 oppure di un valore di TTR < 70%;

-

“senza” un’alterazione del rischio trombotico o emorragico se presentavano un punteggio calcolato di CHA2DS2-VASc < 1 o di HAS-BLED ≤ 3 e di un valore di TTR ≥ 70%.

Patients in atrial fibrillation treated with NOAC: quale indice di rischio?

- **Because stroke and bleeding risks are closely related**
- Stroke risk scores could also be used to identify patients with high bleeding risks
- **Compare the performance of 2 stroke risk scores CHA2DS2-VASc and CHADS 2 and 3 bleeding risk scores HAS-BLED,ORBIT, and ATRIA in predicting major and intracranial bleeding.**
- Stroke risk scores had similar performance to the bleeding risk scores, likely because the stroke and bleeding risks factors overlap.
- **The strongest predictor of major bleeding was age (CHA2DS2-VASc assigns 2 points to ≥ 75 years)**
- Careful assessment and active management of bleeding risk factors in patients on NOACs who have high stroke risk scores, not just those with high bleeding risk scores,no incremental benefit of any bleeding score in comparison with stroke risk scores. A high bleeding risk score should generally not result in withholding oral anticoagulation.
- The 2 stroke risk scores (CHA2DS2-VASc and CHADS2) and 3 bleeding risk scores (HAS-BLED, ORBIT, and ATRIA) had similar, albeit modest, performance in predicting major bleeding and intracranial bleeding in patients with AF treated with NOACs. **A single stroke risk score appears to be a convenient tool in identifying low-risk patients who may not require anticoagulation therapy, whereas at the same time highlights patients at elevated bleeding risk for closer followup**. Careful assessment and active management of bleeding risk factors may be warranted in all patients on NOACs who have high CHA2DS2-VASc or CHADS2scores.

Yao : Am J Cardiol 2017

Gestione pratica della terapia anticoagulante del paziente con cancro e FA

- Algoritmo
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- Warfarin e DOAC
- Valutazione del paziente e interazioni chemioterapici

Terapia della fibrillazione atriale in pazienti con cancro

La terapia con Eparina a basso peso molecolare (LMWH) è associata ad una miglior sopravvivenza rispetto agli antagonisi della Vit K in pazienti con tumori solidi non metastatici e TEV . L'effetto è imputabile ad un potenziale effetto antitumorale ed antimetastatico della LMWH.

Tuttavia il ruolo della LMWH nella terapia anticoagulante a lungo termine nei pazienti con cancro e fibrillazione atriale deve essere provato

JACC Farmakis et al. 2014

In cancer patients who develop incident AF, VKAs, or LMWH have been traditionally preferred over NOACs, based on greater clinical experience with these drugs, possibility for loser monitoring and availability of 'reversal' options. **However, evidence for stroke prevention with LMWH in AF is lacking and LMWH is contraindicated in secondary prevention in the setting of acute stroke.**

2018 EHRA Practical Guide on NOACs in AF

kcj 2018 Korean Circulation Journal

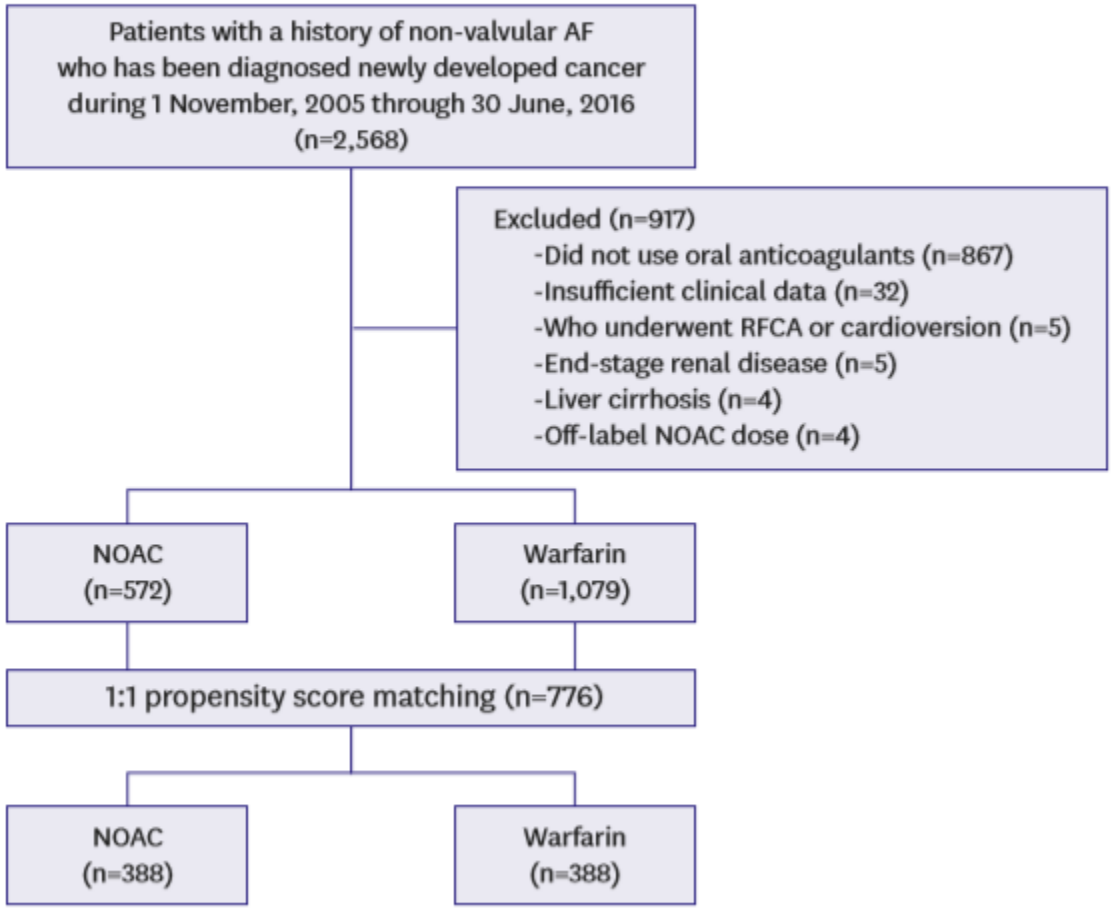

Figure 1. Flowchart of patients participating in this study.
AF = atrial fibrillation; NOAC = non-vitamin K antagonist oral anticoagulant; RFCA = radiofrequency catheter ablation.

Studio retrospettivo non randomizzato

Table 2. Clinical outcomes according to anticoagulation strategies (PS-matched populations)

Event	NOAC (n=388)		Warfarin (n=388)		p value	Full NOAC (n=109)		Reduced NOAC (n=279)		p value	Dabigatran (n=140)		Apixaban (n=138)		Rivaroxaban (n=110)		p value
	Number	Rate	Number	Rate		Number	Rate	Number	Rate		Number	Rate	Number	Rate	Number	Rate	
Ischemic stroke/SE	9	1.3	40	5.9	<0.001	2	0.9	7	1.4	0.98	2	0.7	4	1.8	3	1.6	0.53
Ischemic stroke	9	1.3	39	5.5	<0.001	2	0.9	7	1.4	0.63	2	0.7	4	1.8	3	1.6	0.53
SE	0	0	1	0.4	0.27	0	0	0	0	NA	0	0	0	0	0	0	NA
Major bleeding	8	1.2	36	5.1	<0.001	2	0.9	6	1.2	0.74	3	1.0	3	1.3	2	1.0	0.93
Intracranial	1	0.2	8	1.1	0.02	0	0	1	0.2	0.51	0	0	1	0.4	0	0	0.33
Gastrointestinal	7	1.0	25	3.5	0.001	2	0.9	5	1.0	0.90	3	1.0	2	0.9	2	1.0	>0.999
Other sites	0	0	4	0.6	0.20	0	0	0	0	NA	0	0	0	0	0	0	NA
All-cause death	41	6.1	93	13.3	<0.001	10	4.8	31	6.6	0.45	13	4.4	14	6.7	14	8.1	0.28

Event rate was described as event per 100-patient years.
NA = not applicable; NOAC = non-vitamin K antagonist oral anticoagulant; PS = propensity score; SE = systemic embolism.

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Korean Circulation Journal

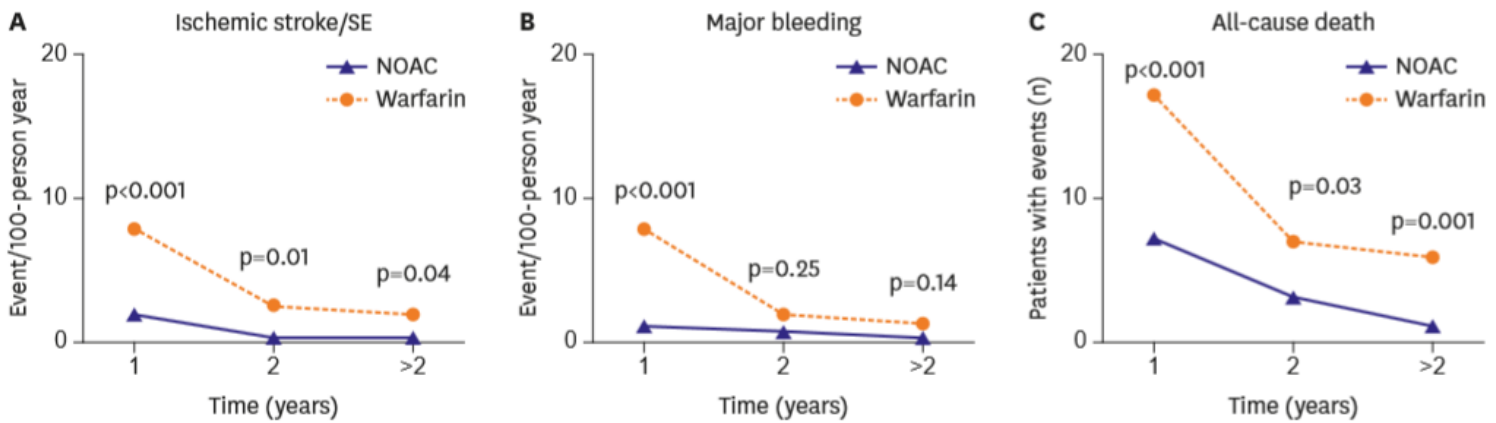


Figure 3. Proportion of patients with events according to the duration after cancer diagnosis in the PS matched NOAC and warfarin groups.
NOAC = non-vitamin K antagonist oral anticoagulant; PS = propensity score; SE = systemic embolism.

Nel I° anno in terapia (operazioni, chemio e radioterapia) un INR ottimale (2 – 3) fu raggiunto solo nel 12% dei pazienti

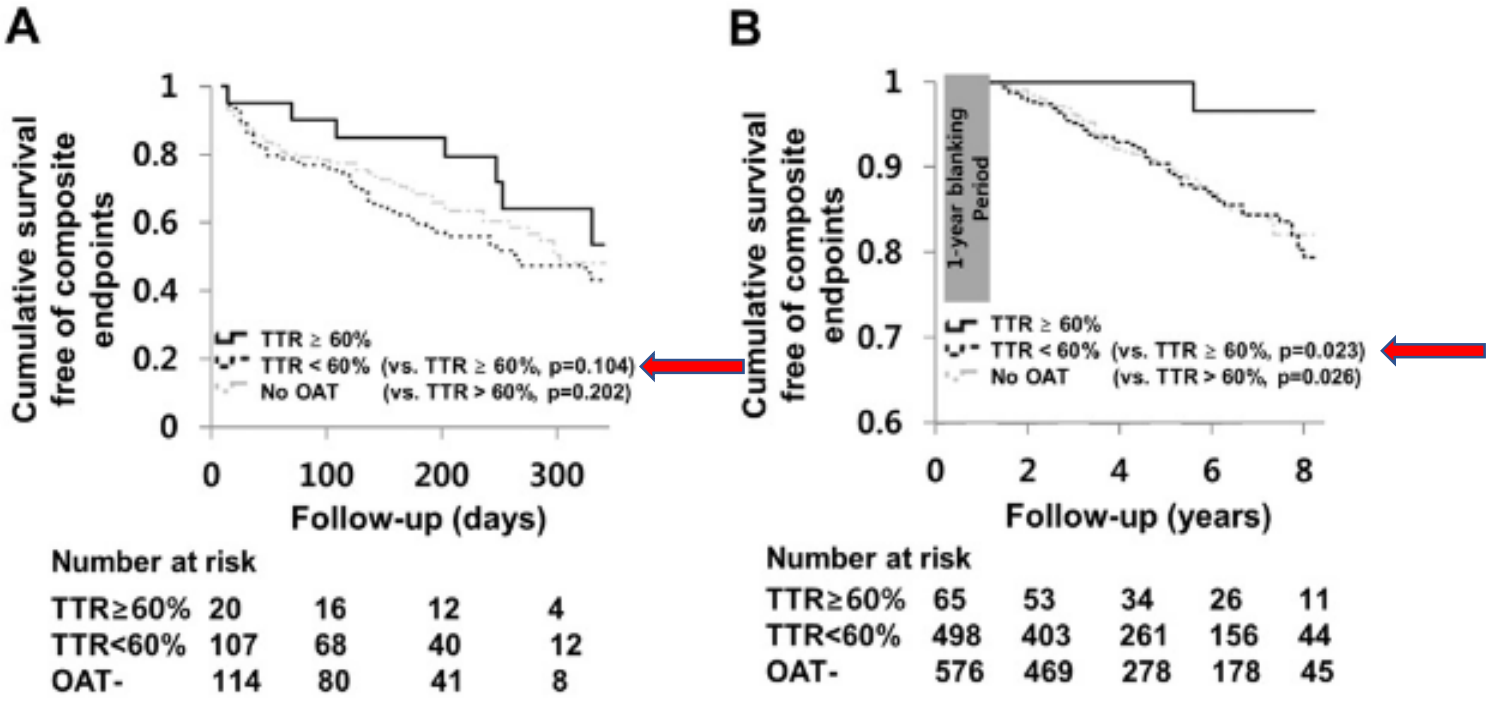


Fig. 6. Kaplan–Meier survival curves for the composite end point in matched population according to TTR and time duration after cancer diagnosis. (A) Within 1 year of cancer diagnosis. OAT + patients with TTR ≥60% had no significant difference for the cumulative survival free of composite endpoint with OAT − patients ($p = 0.202$) and those with TTR <60% ($p = 0.104$). (B) After 1 year of cancer diagnosis. OAT + patients with TTR ≥60% had higher cumulative survival free of the composite end point than OAT − patients ($p = 0.026$) and those with TTR < 60% ($p = 0.023$).

Lee Int J Cardiol 2016

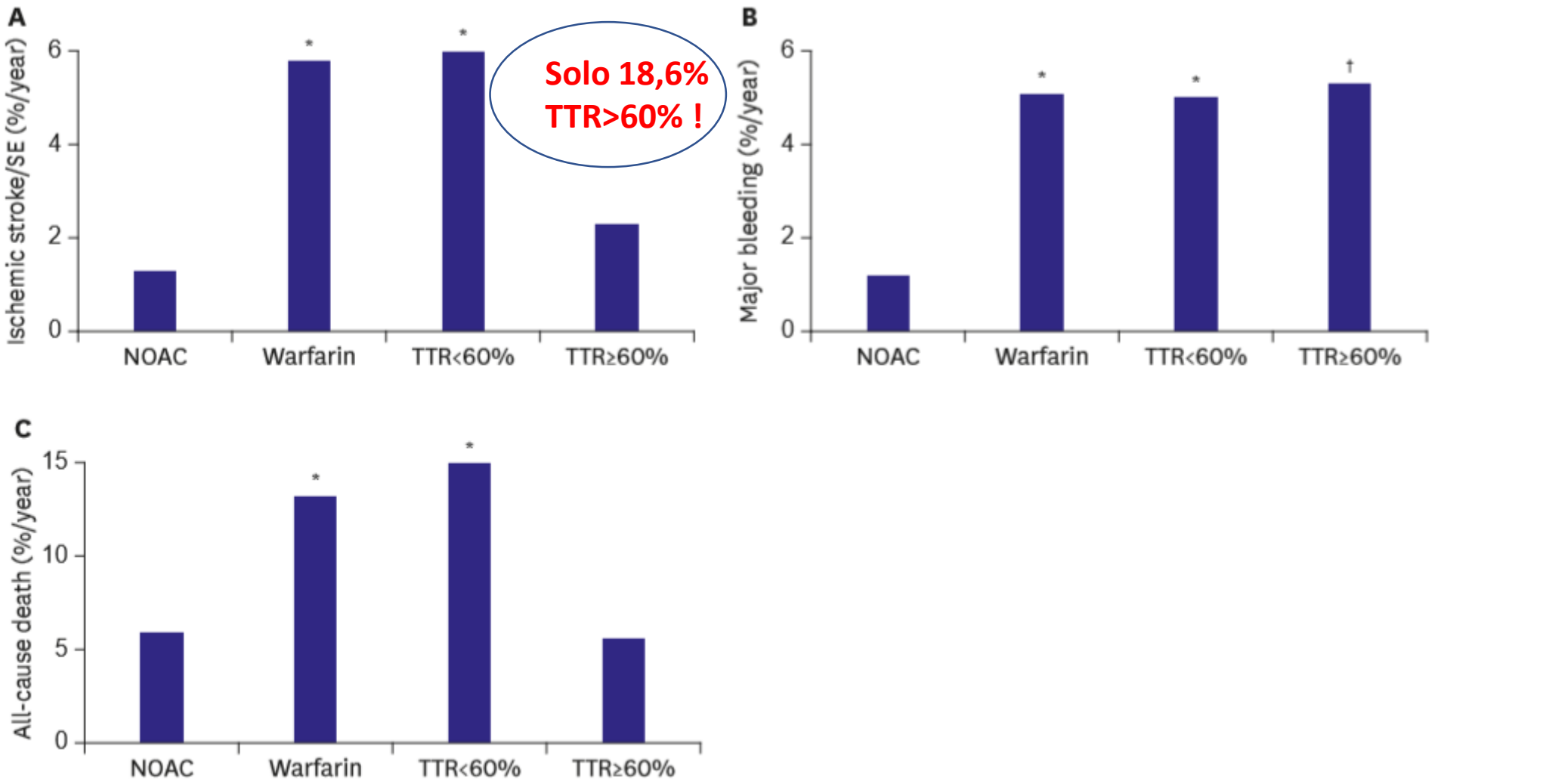


Figure 4. Cumulative incidence rates of all clinical events according to anticoagulation strategy. (A) Ischemic stroke/SE, (B) major bleeding, (C) all-cause death. NOAC = non-vitamin K antagonist oral anticoagulant; SE = systemic embolism; TTR = target therapeutic range.
*Warfarin and TTR <60% groups showed significantly higher rates of all clinical events than NOAC group, †TTR ≥60% group showed significantly higher rates of major bleeding than NOAC group.

Inapppetenza,vomito, difficolta' ad alimentarsi, mucositi diarrea, fluttuazioni assorbimento vit K
Alterazioni nella funzione epatica e/o renale
Interazioni chemioterapici tramite CYP3A4 and P-glycoproteina, interruzioni terapia

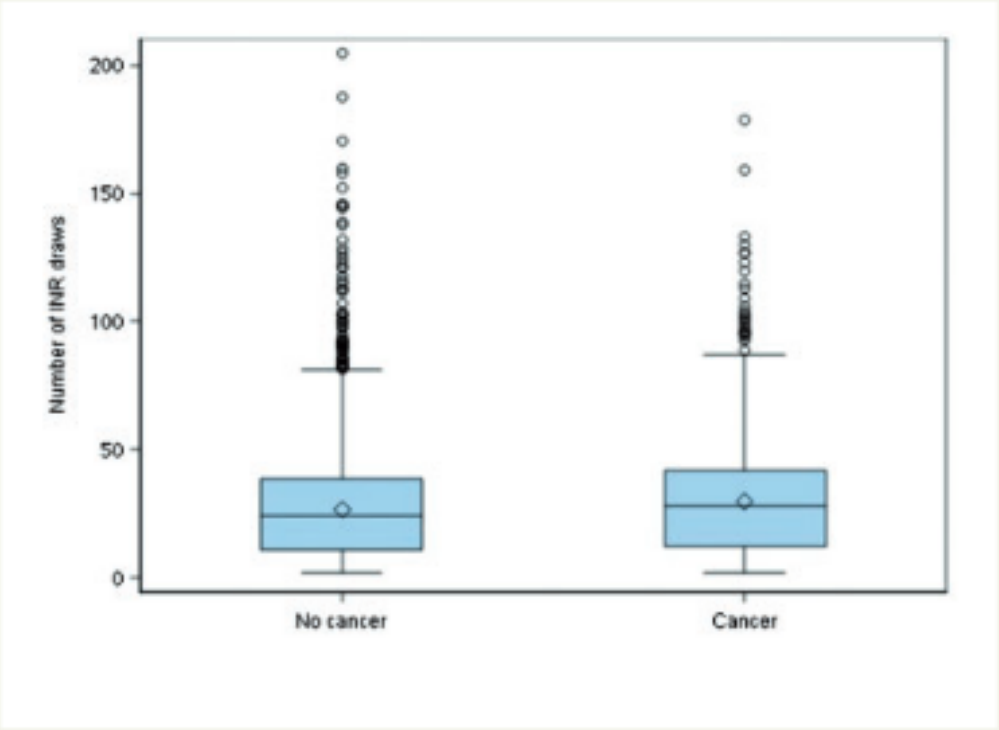


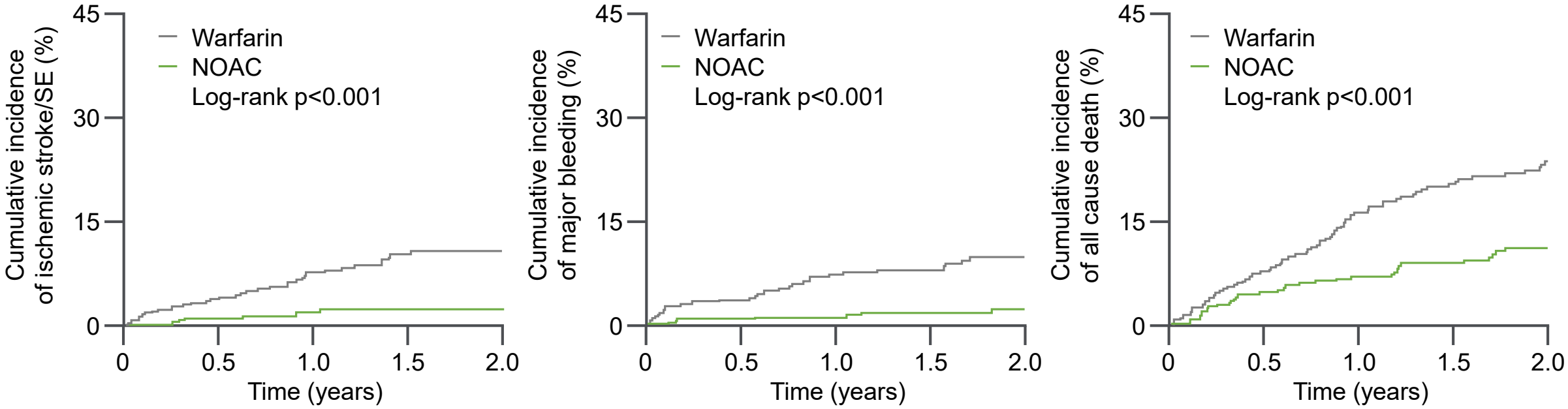
Figure 1 Number of INR checks in AF patients with and without history of cancer. INR, International Normalized Ratio; AF, atrial fibrillation.

Esclusi pazienti con aspettativa vita < 6 mesi

Melloni : Orbit – AF registry EHJ Qual Care Clin Outcomes 2017

NOAC Use in AF patients With Cancer

- NOACs have significantly lower incidences of ischemic stroke/systemic embolism (p<0.001), major bleeding (p<0.001), and all-cause death (p<0.001) than warfarin
  - The incidence of major bleeding was particularly lower within 1 year after cancer diagnosis
  - The incidences of all clinical events were significantly lower in the NOAC group vs warfarin group



Kim et al. Korean Circ J. 2018;48:406–17.

DOACS in Patients with NVAF and Active Cancer

Methods

- MarketScan databases (Truven Health MarketScan Commercial Claims and Encounters Database and the Medicare supplemental and Coordination of Benefits Database (Truven Health Analytics, Inc, Ann Arbor, MI)
- **16 096** AF patients (mean age, 74 years) initiating oral anticoagulant and being actively treated for cancer between 2010 and 2014.
- Objective: determine the effectiveness and associated risks of DOACs vs warfarin in a large population of cancer patients with AF. We also explored the outcomes in specific cancer types, and the outcomes for head-to head comparisons of DOACs

Shah et al. Blood Advances 2017

Table 2. Adjusted HRs (95% CIs) comparing the safety and effectiveness of oral anticoagulant users to matched warfarin users for the treatment of nonvalvular AF in active cancer patients, MarketScan, 2010-2014

	No. of events	Person-years	No. of events	Person-years	HR (95% CI)	*P*
	Rivaroxaban user (n = 2808)		Matched warfarin user (n = 5673)			
Ischemic stroke	16	2277	59	5 279	0.74 (0.40, 1.39)	.35
Severe bleeding	68	2245	181	5 207	1.09 (0.79, 1.50)	.59
Other bleeding	50	2213	177	5 031	0.79 (0.55, 1.13)	.2
VTE*	124	2046	472	3 903	0.51 (0.41, 0.63)	<.0001
Asthma (control outcome)	41	2259	91	5 253	0.99 (0.64, 1.51)	.94
	Dabigatran user (n = 2189)		Matched warfarin user (n = 8339)			
Ischemic stroke	26	3310	127	10 878	0.89 (0.56, 1.42)	.63
Severe bleeding	70	3273	329	10 706	0.96 (0.72, 1.27)	.75
Other bleeding	40	3236	306	10 376	0.58 (0.41, 0.84)	.003
VTE*	49	3199	743	8 206	0.28 (0.21, 0.38)	<.0001
Asthma (control outcome)	38	3302	183	10 825	0.75 (0.51, 1.10)	.14
	Apixaban user (n = 1078)		Matched warfarin user (n = 2775)			
Ischemic stroke	4	550	18	1 773	0.71 (0.19, 2.60)	.6
Severe bleeding	10	551	84	1 744	0.37 (0.17, 0.79)	.01
Other bleeding	9	538	72	1 699	0.58 (0.25, 1.31)	.19
VTE*	7	540	218	1 325	0.14 (0.07, 0.32)	<.0001
Asthma (control outcome)	13	549	40	1 760	0.99 (0.53, 2.22)	.98

Adjusted for age, sex, CHA_2DS_2-VASc score, prior history of the outcome, and HDPS.
*Patients with prevalent VTE excluded from the analysis.

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Results Rivaroxaban vs Warfarin users

- similar rates of ischemic stroke and severe bleeding
- rate of incident VTE was half in rivaroxaban users

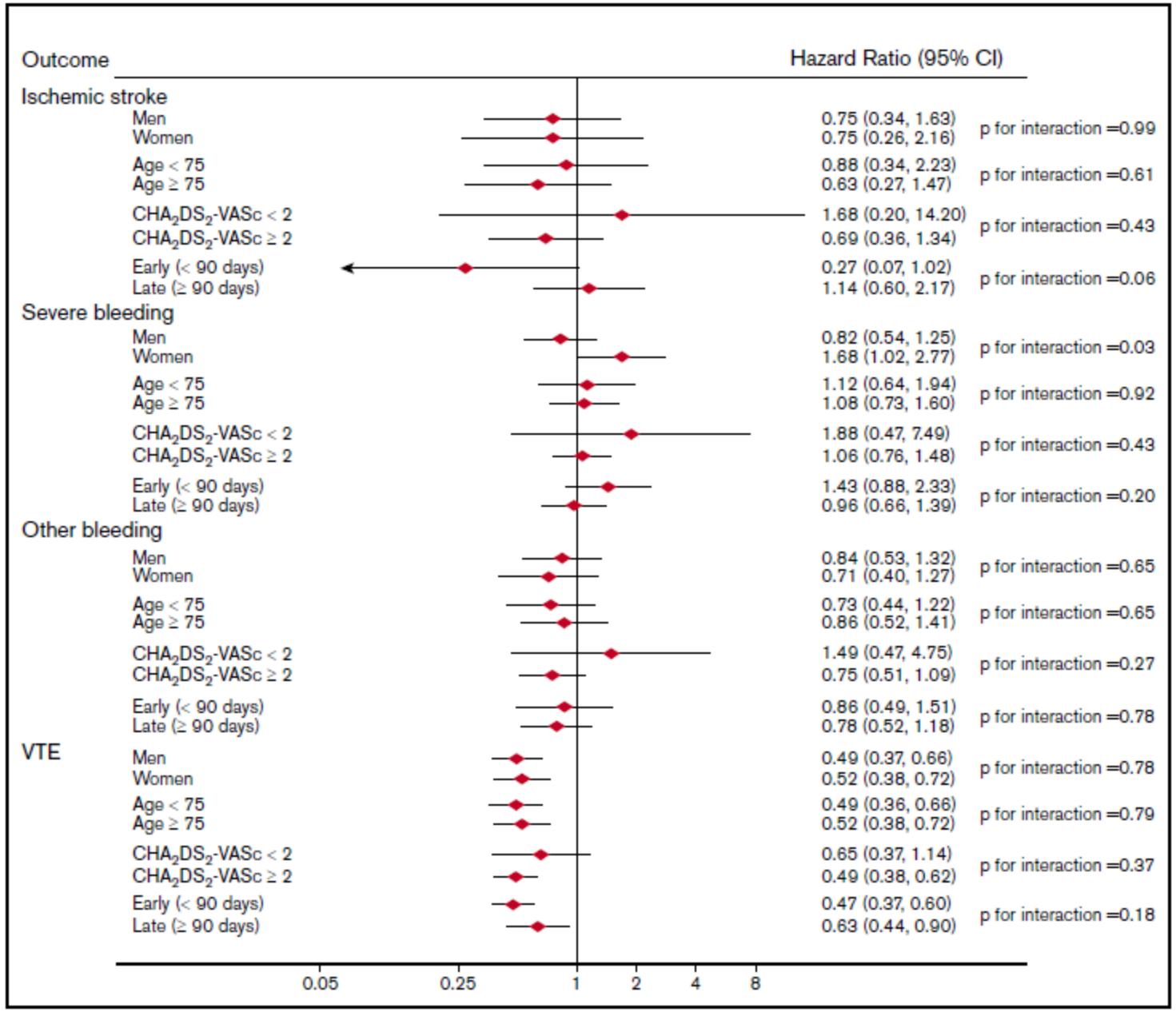

Figure 1. Adjusted HRs (95% CIs) of outcomes among anticoagulant users, stratified by subgroups: rivaroxaban vs warfarin users.

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- **Results Dabigatran vs Warfarin users**

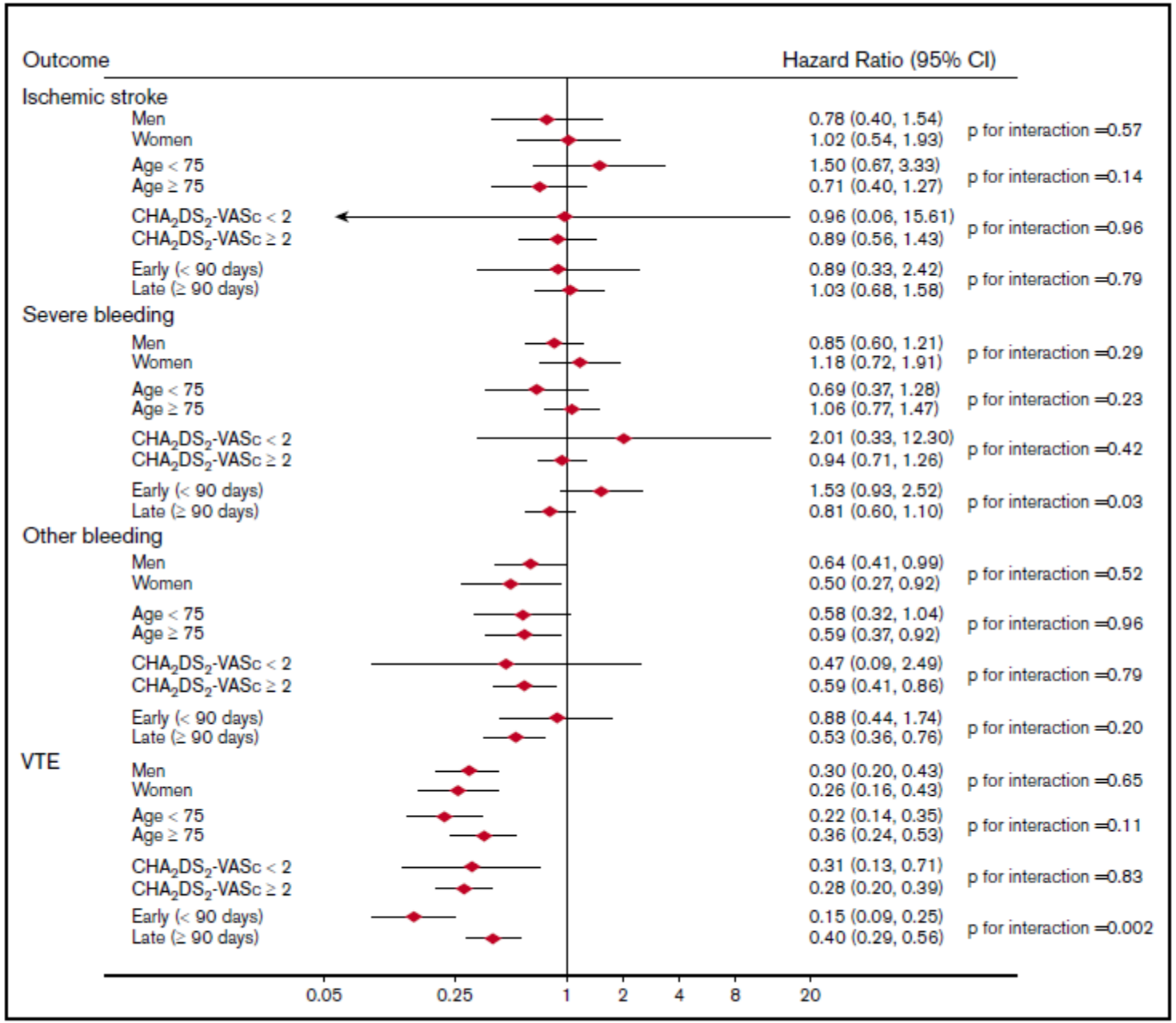

Figure 2. Adjusted HRs (95% CIs) of outcomes among anticoagulant users, stratified by subgroups: dabigatran vs warfarin users.

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- **Results Apixaban vs Warfarin users**

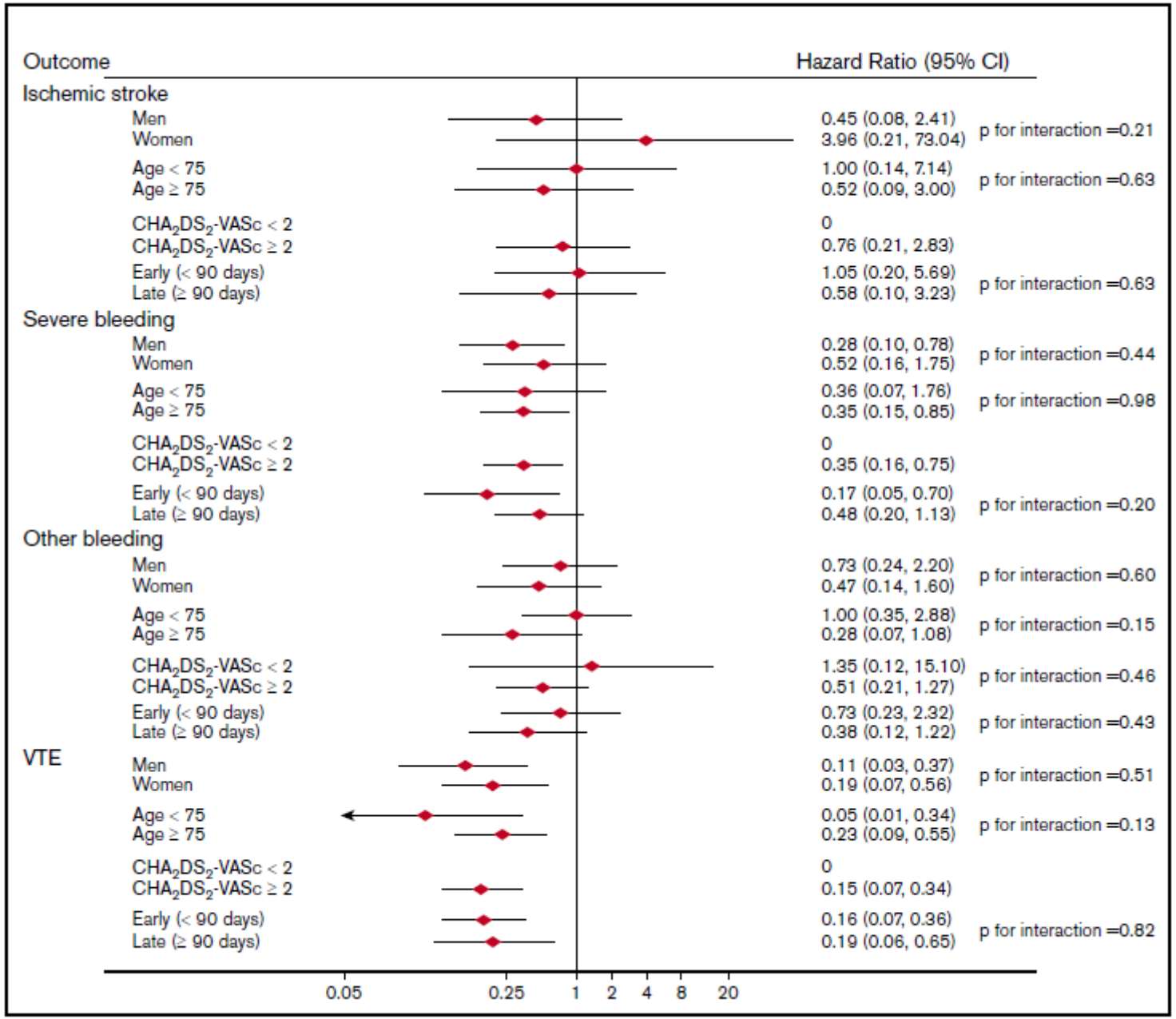

Figure 3. Adjusted HRs (95% CIs) of outcomes among anticoagulant users, stratified by subgroups: apixaban vs warfarin users.

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Comparative effectiveness of DOAC and Warfarin in patients with cancer and atrial fibrillation using MarketScan databases*

1 Sicuri ed efficaci come il Warfarin per prevenzione ischemic stroke

2 Probabile miglior profilo di sanguinamento, simile a quello dei pazienti senza cancro

3 Con tutti i DOAC riduzione del 50% – 85% nell'incidenza di VTE rispetto al Warfarin

*Studio USA retrospettivo;CHA2DS2-VASc 4.6 (WARF) – 4.2 (DOAC); FU 12 mesi

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Gestione pratica della terapia anticoagulante del paziente con cancro e FA

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- Terapia con eparina
- Warfarin e DOAC
- Valutazione del paziente e interazioni chemioterapici

Patient assessment
Risk factors for bleeding No major bleeding events in the past 2 months Absence of intracranial or visceral tumor at high risk for major bleeding
Platelets Platelet count >50,000 per μL No anticipated decrease due to disease or chemotherapy
Coagulation studies Normal PT, PTT, and fibrinogen
Liver function tests No significant hepatic impairment (e.g., Child-Pugh B or C, cirrhosis)
Renal function CrCl >30 mL/min (rivaroxaban) CrCl >15 mL/min (dabigatran and apixaban) No anticipated fluctuations due to nephrotoxic chemotherapy or other drugs
Medications No concomitant use of drugs with strong effect on CYP3A4 and/or P-glycoprotein

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Table 5 Absorption and metabolism of the different NOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	3 to 7%	50%	62%[51]	66% without food. Almost 100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose (if normal renal function; see also 'Patients with chronic kidney disease' section)[a]	20%/80%	73%/27%[52–55]	50%/50%[36,51,56]	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination, moderate contribution)[57]	Minimal (<4% of elimination)	Yes (elimination, moderate contribution)
Absorption with food	No effect	No effect	6–22% more; minimal effect on exposure[58]	+39% more[59]
Intake with food recommended?	No	No	No	Mandatory
Absorption with H2B/PPI	−12 to 30% (not clinically relevant)[60–62]	No effect[63]	No effect	No effect[59,64]
Asian ethnicity	+25%[62]	No effect	No effect[58]	No effect
GI tolerability	Dyspepsia 5 to 10%	No problem	No problem	No problem
Elimination half-life	12 to 17 h[61]	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)

H2B, H2-blocker; PPI, proton pump inhibitor; GI, Gastrointestinal.
[a]For clarity, data are presented as single values, which are the mid-point of ranges as determined in different studies.

EHRA 2015

Interazioni chemioterapici tramite CYP3A4 and P-glycoproteina

Tabella 2. Farmaci oncologici che interagiscono con il citocromo CYP3A4.

Substrato	Induttore	Inibitore
Abiraterone, acetaminofene, aprepitant, bexarotene, bortezomib, brentuximab, busulfan, ciclofosfamide, ciclosporina, clonazepam, crizotinib, dasatinib, desametasone, docetaxel, doxorubicina, enzalutamide, erlotinib, etoposide, everolimus, fentanil, fosaprepitant, flutamibe, fulvestrant, gefitinib, ifosfamide, imatinib, irinotecan, lapatinib, letrozolo, metadone, nilotinib, ondansetron, ossicodone, paclitaxel, palonosetron, prednisone, sirolimus, sorafenib, sunitinib, tacrolimus, tamoxifene, temsirolimus, vandetanib, vemurafenib, vinblastina, vincristina, vinorelbina	Aprepitant, bexarotene, desametasone, enzalutamide, fosaprepitant, paclitaxel, prednisone, vemurafenib	Abiraterone, acetaminofene, anastrozole, aprepitant, bicalutamide, bortezomib, ciclofosfamide, ciclosporina, crizotinib, dasatinib, docetaxel, doxorubicina, etoposide, fentanil, fosaprepitant, idarubicina, ifosfamide, imatinib, lapatinib, lomustine, metadone, nilotinib, sirolimus, tacrolimus, tamoxifene, temsirolimus, vinblastina, vincristina, vinorelbina

Tabella 3. Farmaci oncologici che interagiscono con la P-glicoproteina.

Substrato	Induttore	Inibitore
Bendamustina, ciclosporina, crizotinib, daunorubicina, desametasone, docetaxel, doxorubicina, etoposide, everolimus, idarubicina, imatinib, irinotecan, lapatinib, lenalidomide, methotrexate, mitomicina C, nilotinib, ondansetrone, paclitaxel, sirolimus, tacrolimus, temsirolimus, vemurafenib, vinblastina, vincristina	Desametasone, doxorubicina, vinblastina	Abiraterone, ciclosporina, crizotinib, desametasone, enzalutamide, imatinib, lapatinib, nilotinib, sunitinib, tacrolimus, tamoxifene, vandetanib

Tabella 1. Farmaci forti inibitori o induttori della P-glicoproteina e del citocromo CYP3A4, spesso usati in associazione agli anti-tumorali.

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