Plonger dans l'interaction du trio Cancer – FA – Anticoagulants 18/11/2023

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Déclarations de liens d'intérêts (5 dernières années)

- Lecture : Abbvie, Amgen, Astellas, Boehringer Ingelheim/Lilly, Bristol Myers Squibb, Janssen-Cilag, Medtronic, MSD, Organon, Pfizer, Takeda

- Conseil scientifique : Amgen, Astra-Zeneca, Bayer Healthcare, Organon

- Invitation en congrès : Amgen, Boehringer Ingelheim/Lilly, MSD, Servier

Plonger dans l'interaction du trio Cancer – FA – Anticoagulant
Bienvenu à la table des négociations

Yalta
4-11/02/1945

W Churchill
FD Roosevelt
J Staline

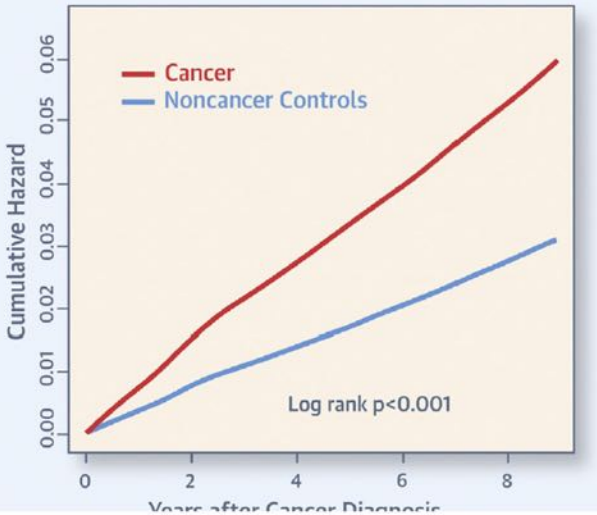
1- Le lien cancer – traitement anticancéreux - FA

Cancer et FA : Pour quel type de cancer ? Hémopathie, digestif, urologique, SNC et ORL

Etude cas contrôle : Matching âge / genre

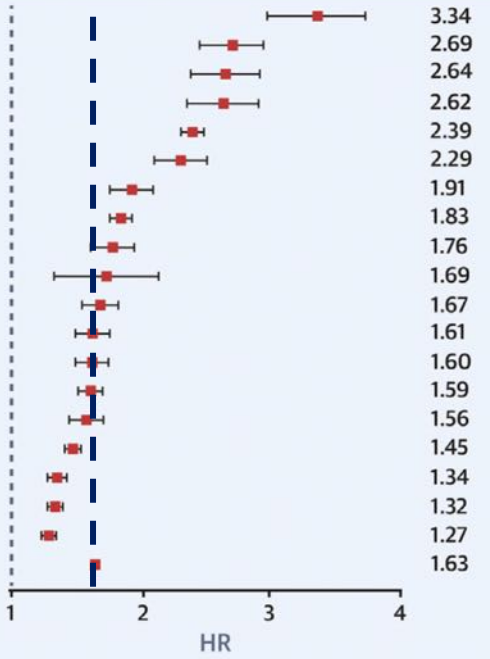
Patients diagnosed with cancer (n=816,811)
compared with
1:2 age and sex matched control (n=1,633,663)

Cancer associated with increased risk of AF
Adjusted subdistribution HR 1.63, 95% CI 1.61-1.66



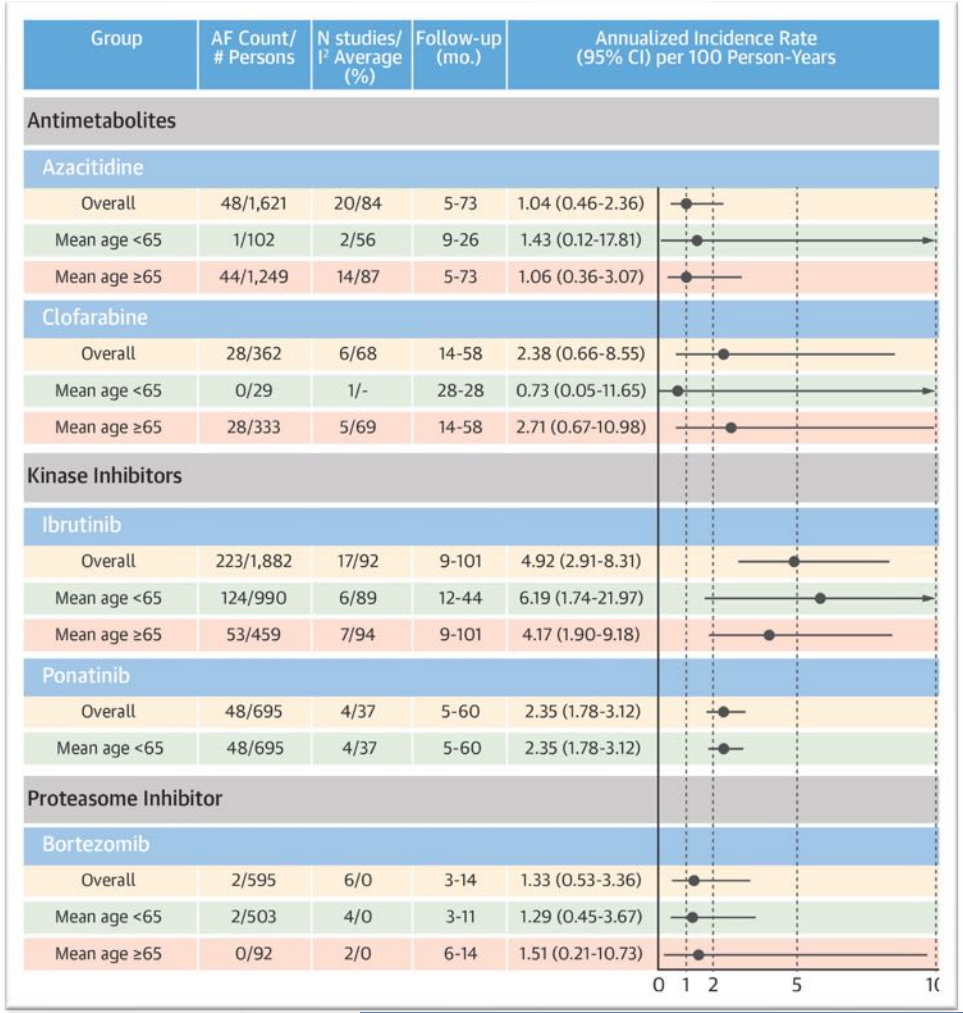
Increased AF risk according to malignancy type

Type of cancer	Number	Events	Time to event	Incidence*	HR (95% CI)†
Multiple myeloma	4,058	299	1.74	19.76	3.34
Esophagus	6,587	481	1.45	19.59	2.69
Leukemia	8,563	384	1.75	12.37	2.64
CNS	8,241	360	1.5	10.91	2.62
Lung	49,435	3,017	1.57	17.59	2.39
Non-Hodgkin lymphoma	12,166	502	1.79	9.43	2.29
Renal	14,608	520	1.64	7.35	1.91
Liver	46,601	1,896	1.63	11.30	1.83
Head & neck	11,638	442	1.74	8.32	1.76
Melanoma	1,964	70	2.11	8.00	1.69
Biliary	12,125	546	1.55	12.77	1.67
Pancreatic	15,020	578	1.47	14.06	1.61
Bladder	14,039	650	1.97	9.27	1.60
Breast	81,066	1,212	1.76	3.04	1.59
Gynecologic	31,474	566	1.89	3.72	1.56
Colorectal	101,603	3,356	1.8	6.64	1.45
Prostate	29,010	1,349	2.07	8.80	1.34
Thyroid	153,923	1,949	1.95	2.27	1.32
Stomach	124,740	3,691	1.81	5.96	1.27
All	816,811	25,356	1.72	6.65	1.63



Yun JP et al. *J Am Coll Cardiol CardioOnc* 2021;3:221-32

Cancer et FA : Sous quel traitement ? Ibrutinib, Clofarabine, Ponatinib



Group	AF Count/ # Persons	N studies/ I² Average (%)	Follow-up (mo.)	Annualized Incidence Rate (95% CI) per 100 Person-Years
Antimetabolites				
Azacitidine				
Overall	48/1,621	20/84	5-73	1.04 (0.46-2.36)
Mean age <65	1/102	2/56	9-26	1.43 (0.12-17.81)
Mean age ≥65	44/1,249	14/87	5-73	1.06 (0.36-3.07)
Clofarabine				
Overall	28/362	6/68	14-58	2.38 (0.66-8.55)
Mean age <65	0/29	1/-	28-28	0.73 (0.05-11.65)
Mean age ≥65	28/333	5/69	14-58	2.71 (0.67-10.98)
Kinase Inhibitors				
Ibrutinib				
Overall	223/1,882	17/92	9-101	4.92 (2.91-8.31)
Mean age <65	124/990	6/89	12-44	6.19 (1.74-21.97)
Mean age ≥65	53/459	7/94	9-101	4.17 (1.90-9.18)
Ponatinib				
Overall	48/695	4/37	5-60	2.35 (1.78-3.12)
Mean age <65	48/695	4/37	5-60	2.35 (1.78-3.12)
Proteasome Inhibitor				
Bortezomib				
Overall	2/595	6/0	3-14	1.33 (0.53-3.36)
Mean age <65	2/503	4/0	3-11	1.29 (0.45-3.67)
Mean age ≥65	0/92	2/0	6-14	1.51 (0.21-10.73)

Meta-analyse de 191 études cliniques randomisées

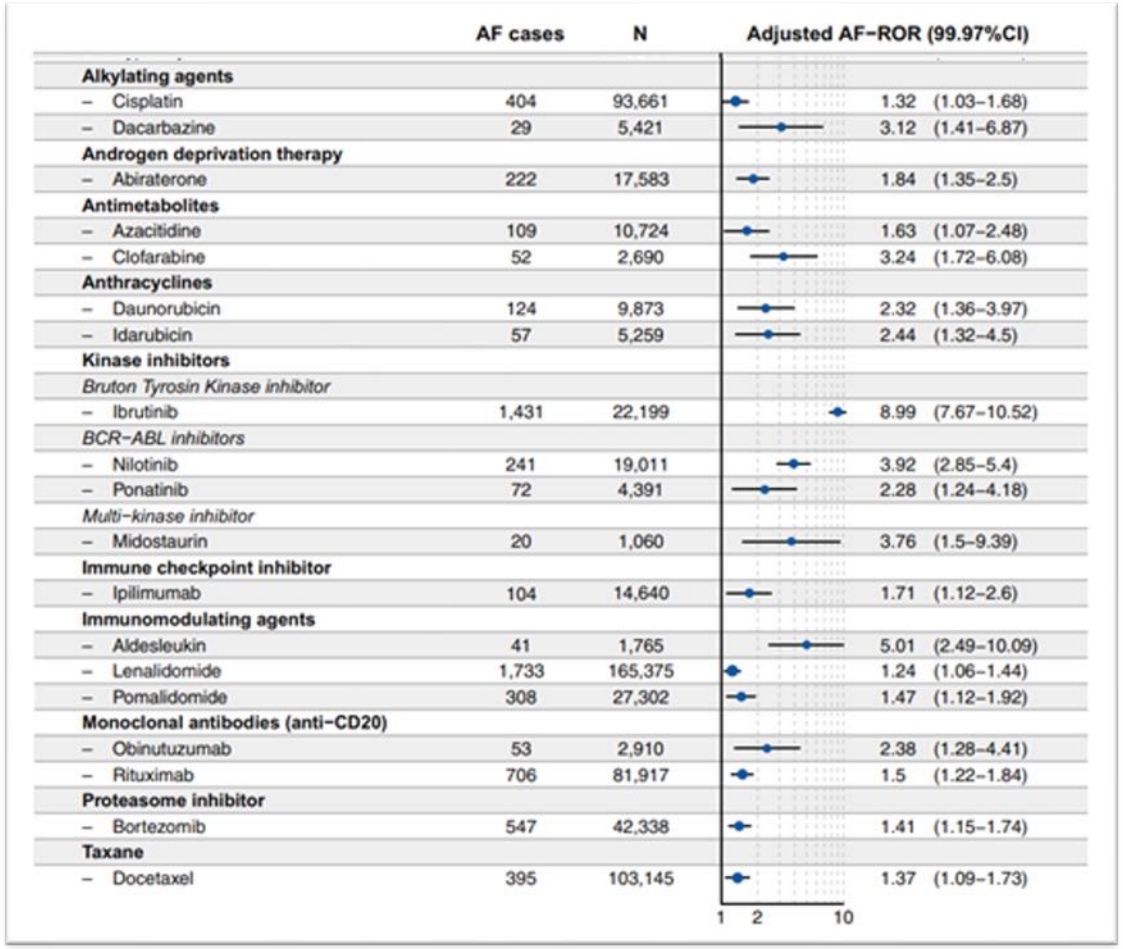
1) **Ibrutinib :** LLC, Lymphomes (manteau, zone marginale)
2) **Clofarabine** : Leucémie aiguë lymphoïde
3) **Ponatinib :** LMC, leucémie aiguë lymphoblastique
4) Bortezomib : myélome multiple
5) Azacitidine : LAM, LMMC, syndrome myélodysplasique

Mais limites études cliniques randomisées :

1) Nombre de patients
2) Durée d'exposition
3) Comorbidités non représentatives de la population

Alexandre J et al. *J Am Coll Cardiol CardioOnc* 2023;5:216-226

Cancer et FA : Sous quel traitement ?



	AF cases	N	Adjusted AF-ROR (99.97%CI)
Alkylating agents			
– Cisplatin	404	93,661	1.32 (1.03–1.68)
– Dacarbazine	29	5,421	3.12 (1.41–6.87)
Androgen deprivation therapy			
– Abiraterone	222	17,583	1.84 (1.35–2.5)
Antimetabolites			
– Azacitidine	109	10,724	1.63 (1.07–2.48)
– Clofarabine	52	2,690	3.24 (1.72–6.08)
Anthracyclines			
– Daunorubicin	124	9,873	2.32 (1.36–3.97)
– Idarubicin	57	5,259	2.44 (1.32–4.5)
Kinase inhibitors			
Bruton Tyrosin Kinase inhibitor			
– Ibrutinib	1,431	22,199	8.99 (7.67–10.52)
BCR-ABL inhibitors			
– Nilotinib	241	19,011	3.92 (2.85–5.4)
– Ponatinib	72	4,391	2.28 (1.24–4.18)
Multi-kinase inhibitor			
– Midostaurin	20	1,060	3.76 (1.5–9.39)
Immune checkpoint inhibitor			
– Ipilimumab	104	14,640	1.71 (1.12–2.6)
Immunomodulating agents			
– Aldesleukin	41	1,765	5.01 (2.49–10.09)
– Lenalidomide	1,733	165,375	1.24 (1.06–1.44)
– Pomalidomide	308	27,302	1.47 (1.12–1.92)
Monoclonal antibodies (anti-CD20)			
– Obinutuzumab	53	2,910	2.38 (1.28–4.41)
– Rituximab	706	81,917	1.5 (1.22–1.84)
Proteasome inhibitor			
– Bortezomib	547	42,338	1.41 (1.15–1.74)
Taxane			
– Docetaxel	395	103,145	1.37 (1.09–1.73)

Données en concordance avec la Vigibase

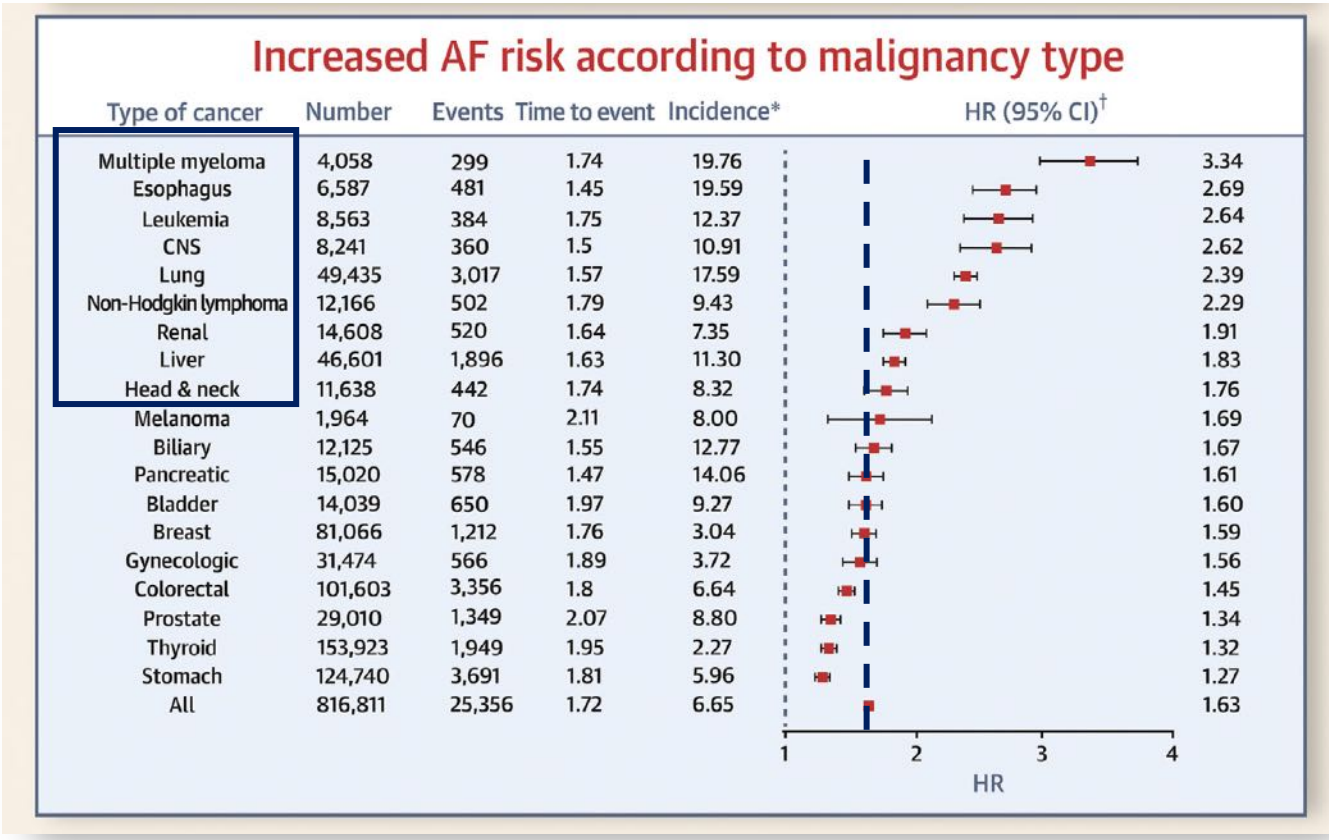
1) **Ibrutinib :** LLC, lymphomes (manteau, zone marginale)
2) **Clofarabine** : leucémie aiguë lymphoïde
3) **Ponatinib :** LMC, leucémie aiguë lymphoblastique
4) **Bortezomib** : myélome multiple
5) **Azacitidine** : LAM, LMMC, syndrome myélodysplasique

Données supplémentaires avec la Vigibase

1) **Akylants :** poumon, ovaire
2) **Abiraterone** : prostate
3) **Anthracyclines :** hémopathie, sein
4) **Nilotinib** : LMC
5) **Immunothérapie** : mélanome, poumon, rein, CHC, etc…
6) **Immunomodulateurs** : myélome
7) **Anti CD 20** : LLC, lymphome
8) **Taxanes** : sein, prostate, ORL, poumon, gastrique

Alexandre J et al. *EHJ – Cardiovascular Pharmacotherapy* 2021;7:312-320

Cancer et FA : Sous quel traitement ?
Ne pas négliger le terrain, les spécificités de la tumeur



Meta-analyse de 191 études cliniques randomisées
Données de la Vigibase

1) **Ibrutinib :** LLC, Lymphomes (manteau, zone marginale)
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5) **Azacitidine** : LAM, LMMC, syndrome myélodysplasique

Autres éléments explicatifs ?

1) **Œsophage / Poumon / Foie / ORL :** OH / CMI ?
2) **SNC** : influence du SNA ?
3) **Myélome :** anémie, maladie rénale, amylose AL ?
4) **Œsophage / Poumon** : inflammation locale ? Post-op ?

Alexandre J et al. *J Am Coll Cardiol CardioOnc* 2023;5:216-226 / Yun JP et al. *J Am Coll Cardiol CardioOnc* 2021;3:221-32

2- La balance bénéfice risque cancer – FA – traitement anticoagulant

Les patients ayant un cancer sont moins souvent traités par anticoagulant (10-15%)

CENTRAL ILLUSTRATION Association of Cancer History With Prevalence of Cardiology Involvement and Anticoagulant Prescription Fills in Patients With Nonvalvular Atrial Fibrillation

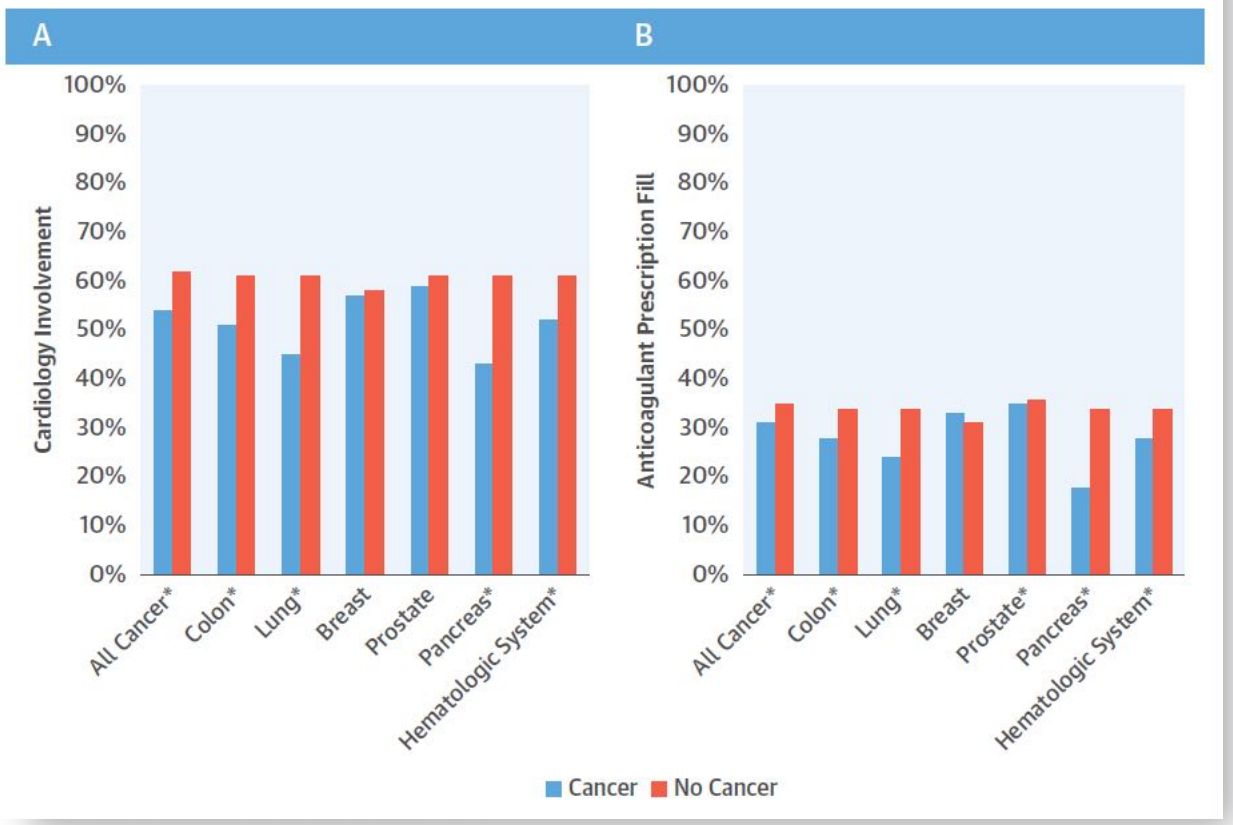


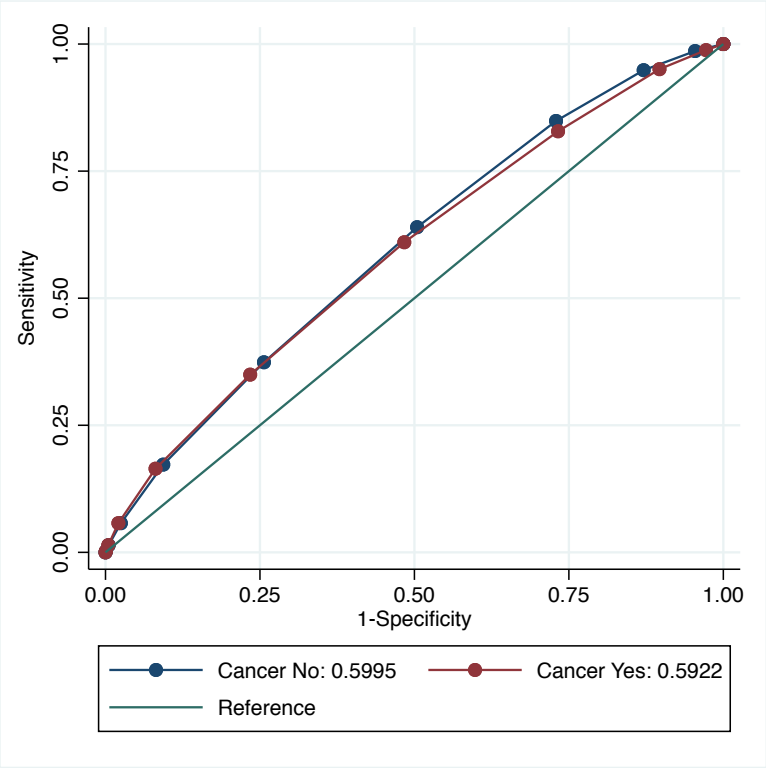
TABLE 2 Association of Cancer History With Prevalence of Anticoagulant Prescription Fills in Patients With Nonvalvular Atrial Fibrillation: MarketScan 2009 to 2014 (N = 388,045)

Subgroup	Prescription Fill (%)		Primary Analysis RR (95% CI)*†	Propensity Score-Matched RR (95% CI)*‡
	Cancer	No Cancer		
All cancer	(n = 64,016)	(n = 324,029)		
Any	31	35	0.89 (0.88-0.90)	0.89 (0.88-0.90)
Colon	28	34	0.86 (0.83-0.89)	0.87 (0.84-0.90)
Lung	24	34	0.73 (0.71-0.76)	0.75 (0.72-0.77)
Breast§	33	31	1.02 (0.99-1.05)	1.03 (1.01-1.06)
Prostate‖	35	36	0.95 (0.93-0.97)	0.96 (0.94-0.98)
Pancreas	18	34	0.60 (0.52-0.68)	0.61 (0.53-0.69)
Hematologic	28	34	0.85 (0.83-0.88)	0.87 (0.84-0.90)
Active cancer	(n = 26,450)	(n = 324,029)		
Any	29	35	0.85 (0.83-0.86)	0.85 (0.83-0.87)
Colon	26	34	0.80 (0.76-0.84)	0.81 (0.77-0.85)
Lung	23	34	0.72 (0.69-0.75)	0.73 (0.69-0.76)
Breast§	32	31	1.02 (0.98-1.06)	1.03 (0.99-1.07)
Prostate‖	32	36	0.89 (0.86-0.92)	0.91 (0.87-0.94)
Pancreas	19	34	0.59 (0.50-0.70)	0.60 (0.51-0.72)
Hematologic	26	34	0.78 (0.75-0.82)	0.80 (0.76-0.84)
Remote cancer	(n = 37,556)	(n = 324,029)		
Any	32	35	0.91 (0.90-0.92)	0.91 (0.90-0.93)
Colon	31	35	0.89 (0.85-0.93)	0.90 (0.86-0.95)
Lung	25	35	0.74 (0.70-0.78)	0.75 (0.71-0.79)
Breast§	33	31	1.00 (0.97-1.04)	1.02 (0.98-1.05)
Prostate‖	36	37	0.96 (0.94-0.99)	0.97 (0.94-0.99)
Pancreas	18	34	0.58 (0.47-0.70)	0.58 (0.48-0.71)
Hematologic	31	35	0.91 (0.87-0.94)	0.92 (0.88-0.96)

O'Neal WT et al *J Am Coll Cardiol* 2018;72:1913-22

Cancer et FA : Evaluation du risque cardio-embolique CHA2DS2VASc 0-1 : sous estimation !

CHA2DS2VASc



Pastori D et al. *Cancer* 2021;127:2122-2129

Patient group	(*n*)	IR [95% CI]	HR [95% CI]
Thromboembolism			
CHA_2DS_2-VASc score 2–9 and recent cancer	608	72.0 [66.5–77.9]	10.0 [7.9, 12.6]
CHA_2DS_2-VASc score 2–9 no recent cancer	8176	81.7 [80.0–83.5]	12.3 [9.8, 15.3]
CHA_2DS_2-VASc score 1 and recent cancer	35	29.0 [20.8–40.4]	4.1 [2.8, 6.1]
CHA_2DS_2-VASc score 1 - no recent cancer	169	9.8 [8.4–11.4]	1.6 [1.2, 2.1]
CHA_2DS_2-VASc score 0 and recent cancer	7	14.7 [7.0–30.9]	2.1 [1.0, 4.6]
CHA_2DS_2-VASc score 0 - no recent cancer	79	6.1 [4.9–7.6]	1.0 [1.0, 1.0]
Bleeding			
CHA_2DS_2-VASc score 2–9 and recent cancer	582	69.6 [64.2–75.5]	6.7 [5.5, 8.2]
CHA_2DS_2-VASc score 2–9 - no recent cancer	4611	46.0 [44.7–47.4]	4.7 [3.9, 5.7]
CHA_2DS_2-VASc score 1 and recent cancer	48	40.2 [30.2–53.2]	3.9 [2.8, 5.5]
CHA_2DS_2-VASc score 1 - no recent cancer	271	15.9 [14.1–17.9]	1.7 [1.4, 2.1]
CHA_2DS_2-VASc score 0 and recent cancer	20	42.2 [27.2–65.5]	4.2 [2.6, 6.8]
CHA_2DS_2-VASc score 0 - no recent cancer	117	9.1 [7.6–10.9]	1.0 [1.0, 1.0]

D'Souza M et al. *Eur J Prev Cardiol* 2018;25:651-8.

Cancer et FA
Comment évaluer le risque hémorragique ?

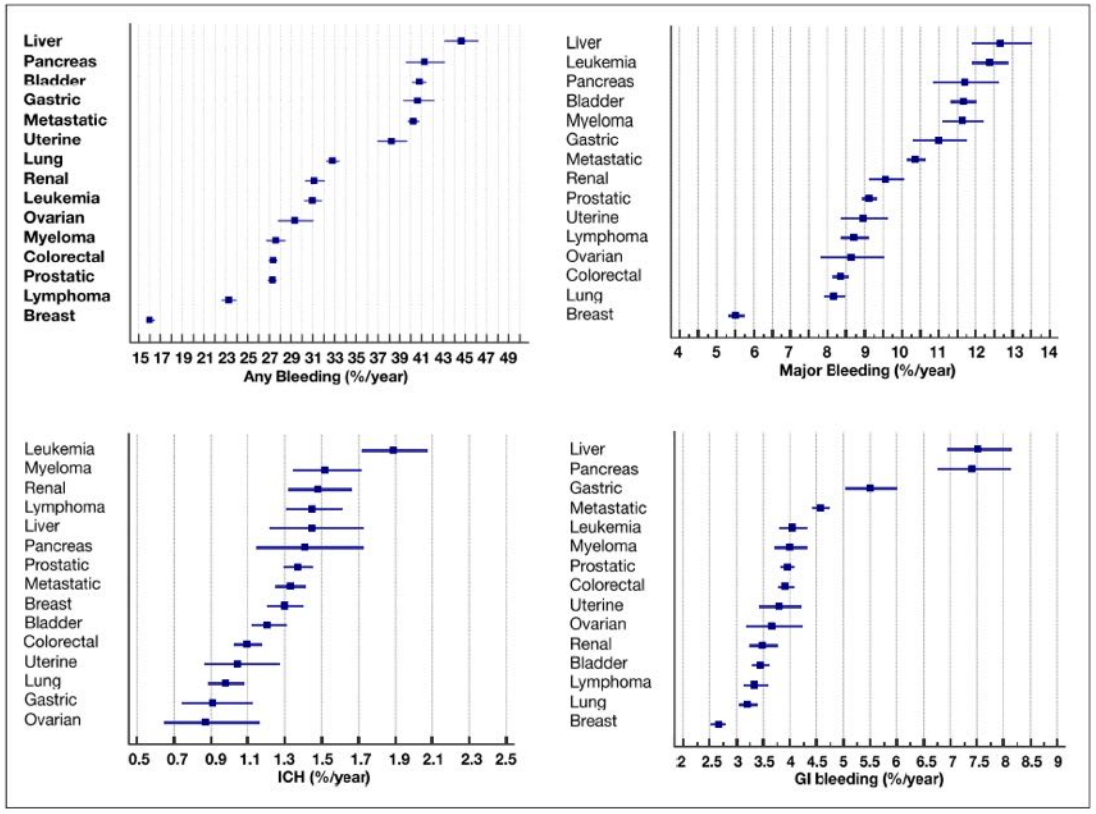


Figure 1. Incidence rates (and 95% CIs) of any bleeding (left top panel), major bleeding (right top panel), GI bleeding (right lower panel), and ICH (left lower panel), according to the cancer site. GI indicates gastrointestinal; and ICH, intracranial hemorrhage.

Pastori D et al. *JAHA* 2022;11:e026388.

Les situations à risque

1. **Formes métastatiques**
2. **Tumeur en place** : rein, vessie, intestin, estomac, pancréas
3. **Troubles la coagulation :** Leucémie, foie
4. **Thrombopathie** : myélome multiple, foie

Cancer et FA
Comment évaluer le risque hémorragique

Table 3. ROC Curves for Different Outcomes in Patients With AF and Cancer

Area under the curve (95% CI)				
Variable	Any bleeding	Major bleeding	ICH	GB
HAS-BLED score (continuous)	0.809 (0.808–0.810)	0.774 (0.772–0.776)	0.744 (0.740–0.748)	0.752 (0.749–0.755)
HAS-BLED score ≥3	0.753 (0.751–0.754)	0.716 (0.714–0.718)	0.698 (0.694–0.702)	0.702 (0.699–0.704)
ATRIA score (continuous)	0.768 (0.766–0.769)	0.777 (0.774–0.779)	0.635 (0.629–0.641)	0.728 (0.725–0.731)
ATRIA score ≥5	0.678 (0.676–0.680)	0.700 (0.698–0.702)	0.563 (0.557–0.568)	0.662 (0.659–0.665)
ORBIT score (continuous)	0.918 (0.917–0.918)	0.870 (0.869–0.871)	0.742 (0.738–0.745)	0.825 (0.822–0.827)
ORBIT score ≥4	0.813 (0.811–0.814)	0.805 (0.804–0.807)	0.641 (0.635–0.646)	0.756 (0.753–0.758)

AF indicates atrial fibrillation; ATRIA, anemia, severe renal disease (eg, dialysis), age ≥75 years, prior bleeding, and hypertension; GB, gastrointestinal bleeding; HAS-BLED, uncontrolled hypertension (systolic blood pressure >160 mm Hg), abnormal kidney (dialysis or transplant)/liver function (ie, cirrhosis), previous stroke, bleeding history or predisposition, elderly age (≥65 years), and drug (antiplatelet, nonsteroidal anti-inflammatory drugs)/alcohol abuse; ICH, intracranial hemorrhage; ORBIT, older age ≥75 years, anemia, bleeding history, chronic kidney disease, and treatment with antiplatelet drugs; and ROC, receiver operating characteristic.

Pastori D et al. *JAHA* 2022;11:e026388.

3- Le choix du traitement anticoagulant cancer – FA

Cancer et FA
Quel choix d'anticoagulant ?

Table 4 Drug-drug interactions and predicted plasma levels of oral anticoagulants and targeted cancer therapies

		Oral Anticoagulants				
		Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Tyrosine Kinase Inhibitors	Afatinib					
	Axitinib					
	Bosutinib					
	Cabozantinib					
	Ceritinib	↑*OAC levels*		↑*OAC levels*	↑*OAC levels*	
	Crizotinib	↑OAC levels	↑*OAC levels**	↑*OAC levels**	↑OAC levels*	↑*OAC levels**
	Dasatinib	↑OAC levels & effect	↑OAC effect	↑OAC levels & effect	↑OAC levels & effect	↑OAC effect
	Erlotinib	↑OAC levels				
	Gefitinib	↑OAC effect				
	Ibrutinib	↑OAC effect	↑*OAC levels & effect**	↑OAC levels & effect*	↑OAC levels & effect*	↑*OAC levels & effect**
	Imatinib	↑*OAC levels & effect*		↑OAC levels	↑OAC levels	
	Lapatinib		↑*OAC levels**	↑OAC levels*	↑OAC levels*	↑*OAC levels**
	Lenvatinib					

Nombreux Inhibiteurs de Tyrosine Kinase augmentent l'effets des AVK et des AOD

Asnani et al. *Cardiology* 2017

Cancer et FA
Quel choix d'anticoagulant ? Pas les HBPM…

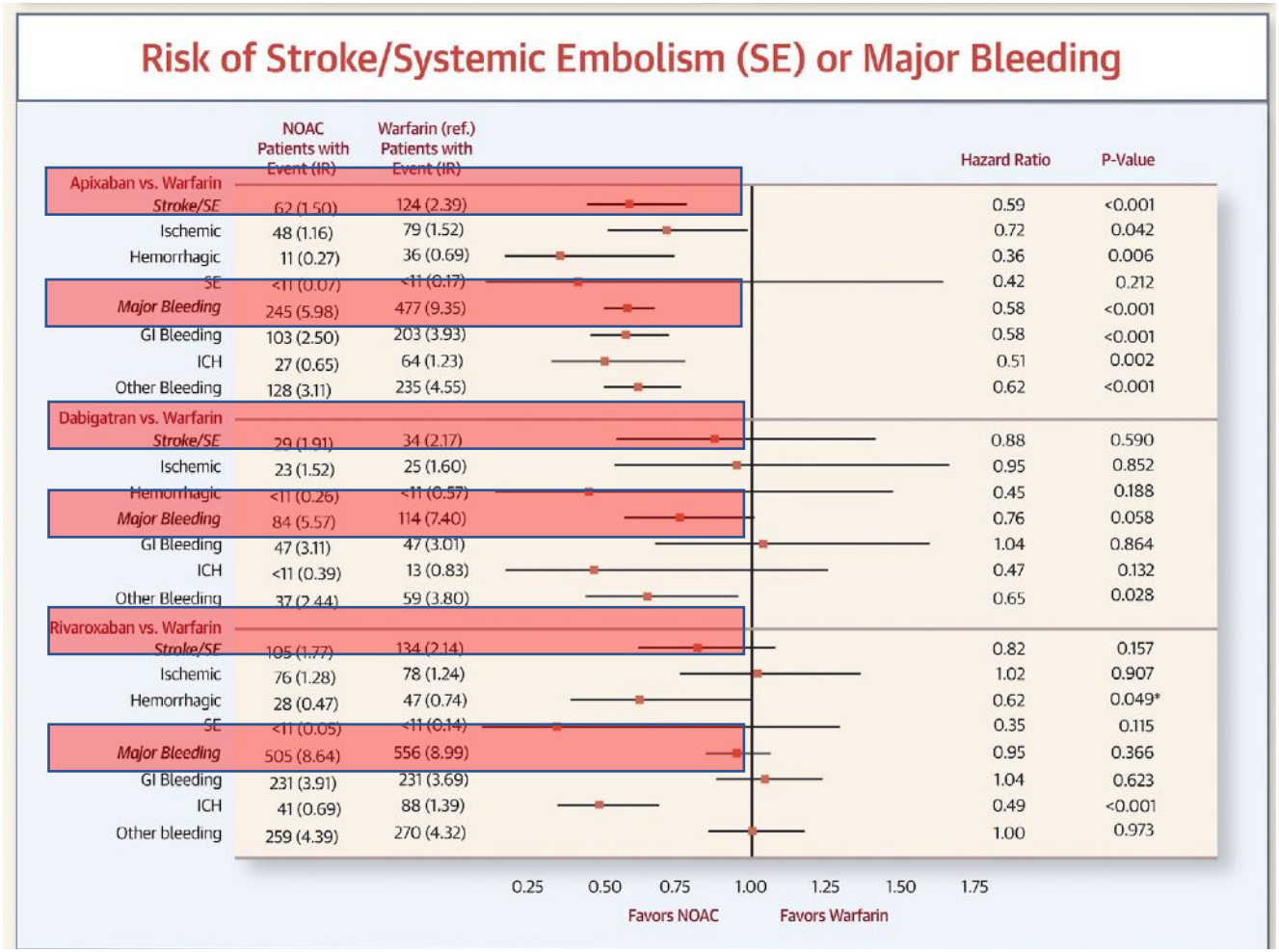
Figure 1. Pattern of anticoagulant use in cancer patients with atrial fibrillation. Group 1 patients who did not received anticoagulant, group 2 patients who received warfarin before cancer diagnosis, group 3 patients who received DOACs before cancer diagnosis and group 4 patients who received LMWH/UFH before cancer diagnosis. *NO AC* no anticoagulant, *DOAC* direct oral anticoagulant, *LMWH* low-molecular-weight heparin, *UFH* unfractionated heparin.

	Patient-years	Number of event	Event rate (event/100 PY)	Unadjusted HR (95% CI)	aHR-MSM (95% CI)
Stroke					
Warfarin	1353	19	1.4 (0.9–2.2)	Reference	Reference
DOAC	471	9	2.7 (1.0–3.7)	1.3 (0.6–3.0)	0.8 (0.2–2.7)
LMWH/UFH	319	16	5.0 (3.1–8.2)	3.1 (1.6–6.0)	2.4 (1.0–5.6)
GI-bleeding					
Warfarin	1217	47	3.8 (2.9–5.1)	Reference	Reference
DOAC	434	24	5.5 (3.7–8.2)	1.4 (0.8–2.3)	1.5 (0.9–2.6)
LMWH/UFH	276	23	8.3 (5.5–12.5)	1.9 (1.2–3.2)	1.2 (0.6–2.4)
Intracranial bleeding					
Warfarin	1370	22	1.6 (1.0–2.4)	Reference	Reference
DOAC	492	6	1.2 (0.5–2.7)	0.7 (0.3–1.8)	0.8 (0.3–2.5)
LMWH/UFH	333	10	3.0 (1.6–5.6)	1.7 (0.8–3.5)	1.1 (0.4–3.1)
Overall -bleeding					
Warfarin	973	112	11.5 (9.5–13.8)	Reference	Reference
DOAC	316	45	14.2 (10.6–19.0)	1.2 (0.8–1.7)	1.1 (0.7–1.6)
LMWH/UFH	197	49	24.8 (18.8–32.9)	2.0 (1.4–2.8)	1.1 (0.6–1.7)
Death					
Warfarin	1419	57	4.0 (3.1–5.2)	Reference	Reference
DOAC	516	28	5.4 (3.7–7.8)	1.4 (0.9–2.2)	1.2 (0.7–2.2)
LMWH/UFH	349	50	14.3 (10.8–18.9)	4.1 (2.7–6.1)	4.5 (2.8–7.2)

Table 2. Clinical outcomes in atrial fibrillation patients who had active cancer. *GI* gastrointestinal, *DOAC* direct oral anticoagulant, *LMWH* low-molecular-weight heparin, *UFH* unfractionated heparin, *PY* patient-years, *HR* hazard ratio, *aHR* adjusted subdistribution hazard ratio, *CI* confidence interval.

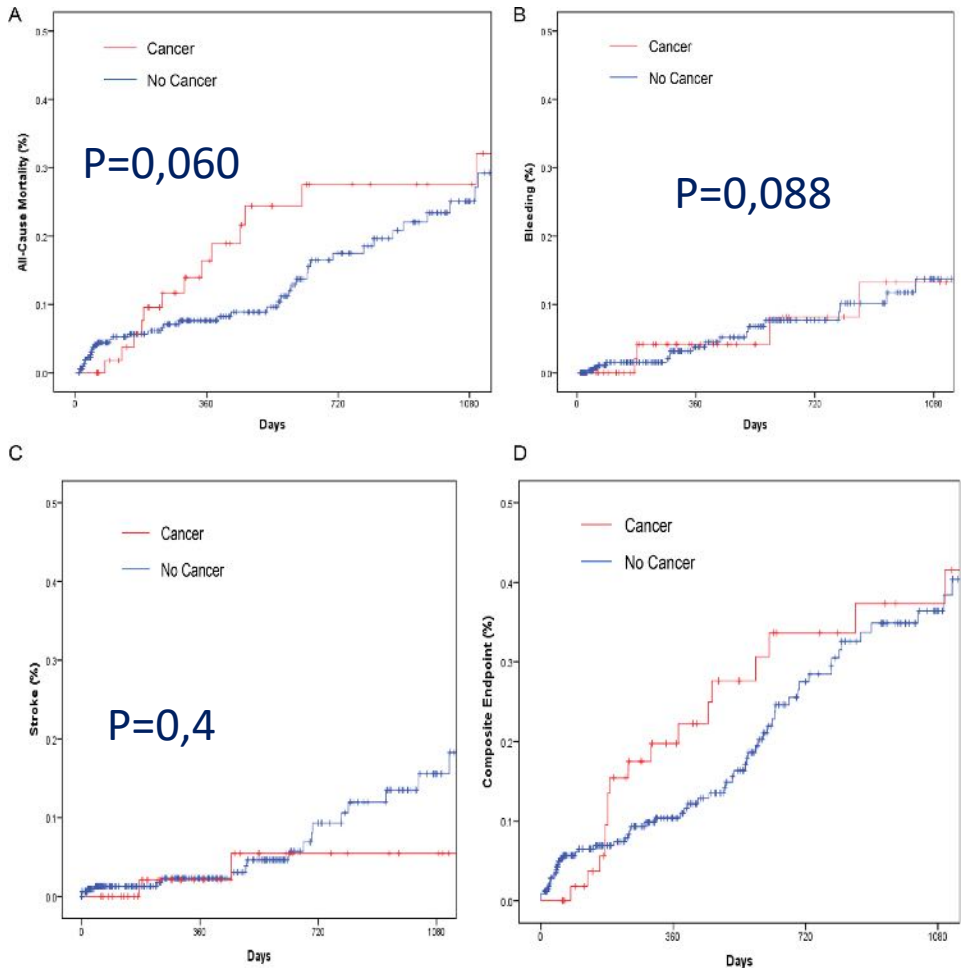
Chai-Adisaksopha C et al. Sci Rep 2023;13:10937

Cancer et FA
Quel choix d'anticoagulant ? AOD ≥ AVK



Deitelzweig S et al. JACC CardioOncol 2021

Cancer et FA
Contre-indication anticoagulants : FAG ?



Patients sans cancer N=332

Patients avec ATCD de cancer N=39

Patients avec cancer en cours de traitement N=16

Kumar S et al. Am J Cardiol 2023;202:176-81

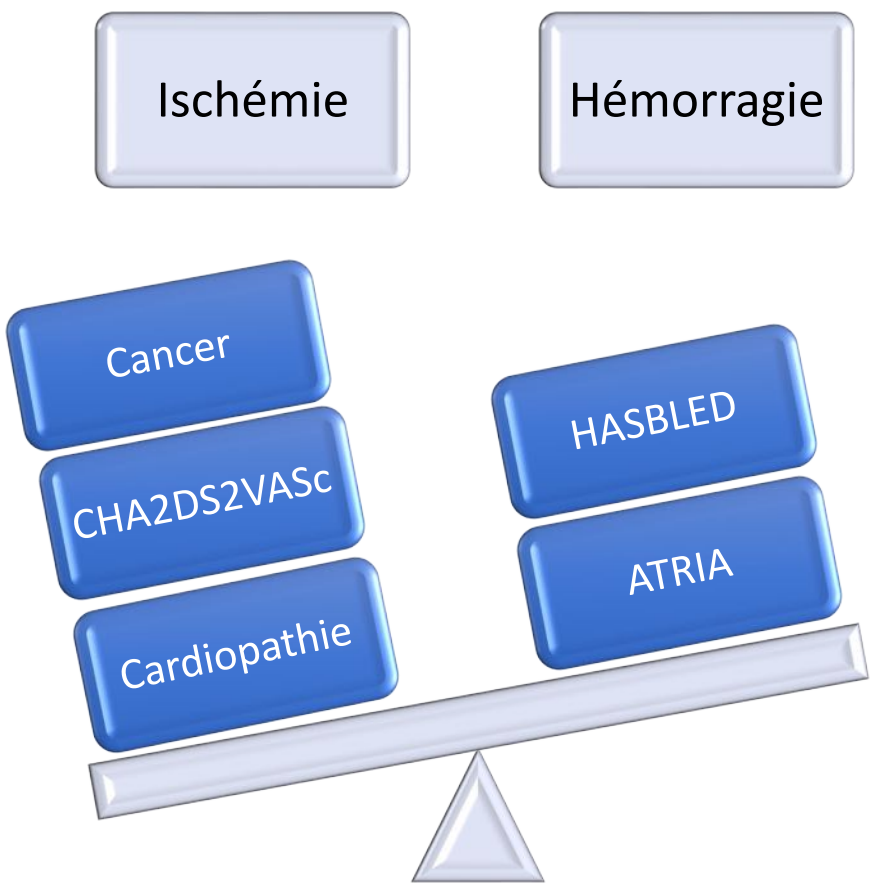
4- Conclusion
Plonger dans l'interaction du trio Cancer – FA – Anticoagulants

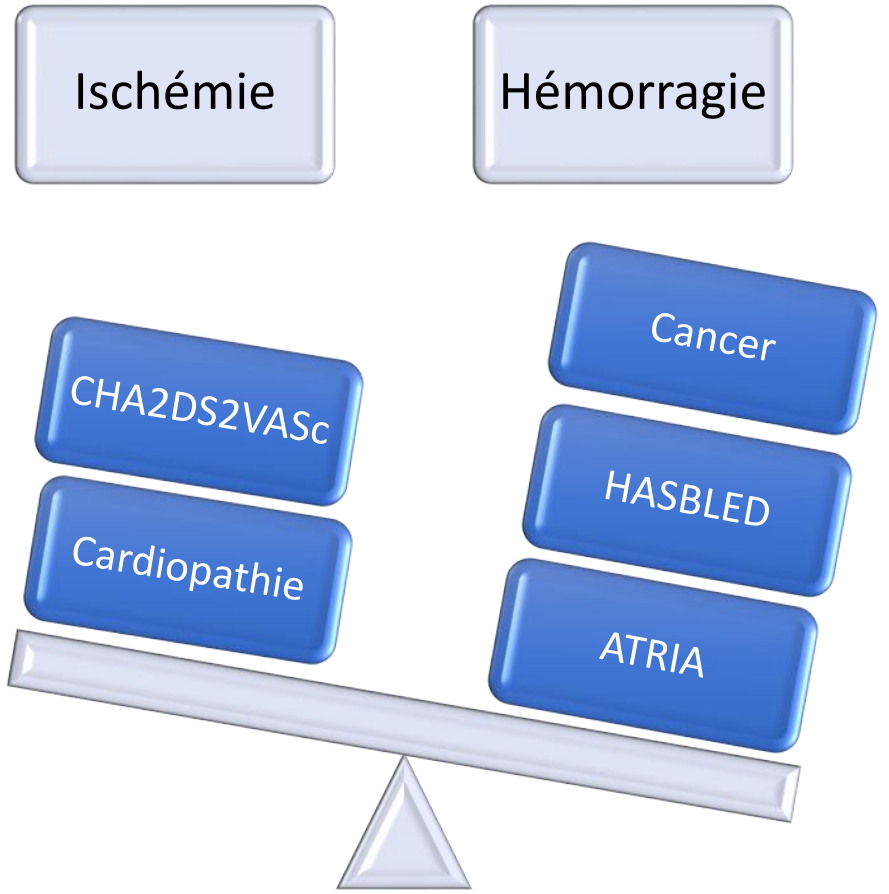
Plonger dans l'interaction du trio Cancer – FA – Anticoagulant
Résultats des négociations

Yalta
4-11/02/1945

W Churchill
FD Roosevelt
J Staline

Le dilemme pour le cardiologue : cancer





Plonger dans l'interaction du trio Cancer – FA – Anticoagulant

- Le cancer et son traitement peuvent augmenter la fréquence la FA

- Risque cardio-embolique en cas de cancer ≥ en l'absence de cancer :

Attention au score de CHA2DS2VASc 0-1

- Risque hémorragique : digestif, urologique, SNC, hémato

- Choix de l'anticoagulant : AOD ≥ AVK > HBPM mais attention aux interactions