Les complications cardiovasculaires

Les complications cardiaques

Classification

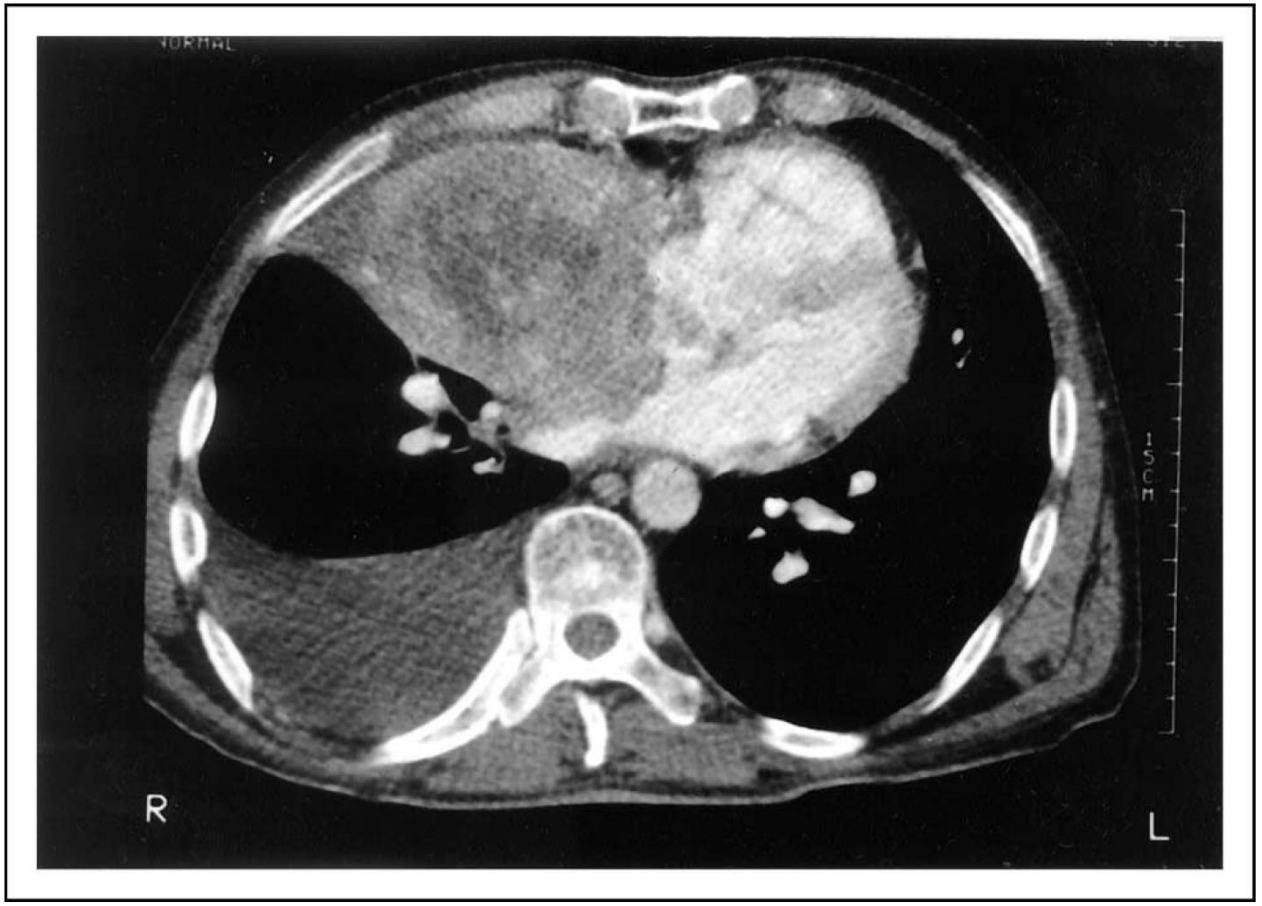
tableau clinique:

- atteinte péricardique
- arythmie
- insuffisance cardiaque
- complication coronaire

facteur causal:

- envahissement néoplasique
- atteinte toxique
- complication infectieuse
- phénomène paranéoplasique

Troubles liés à l'envahissement néoplasique

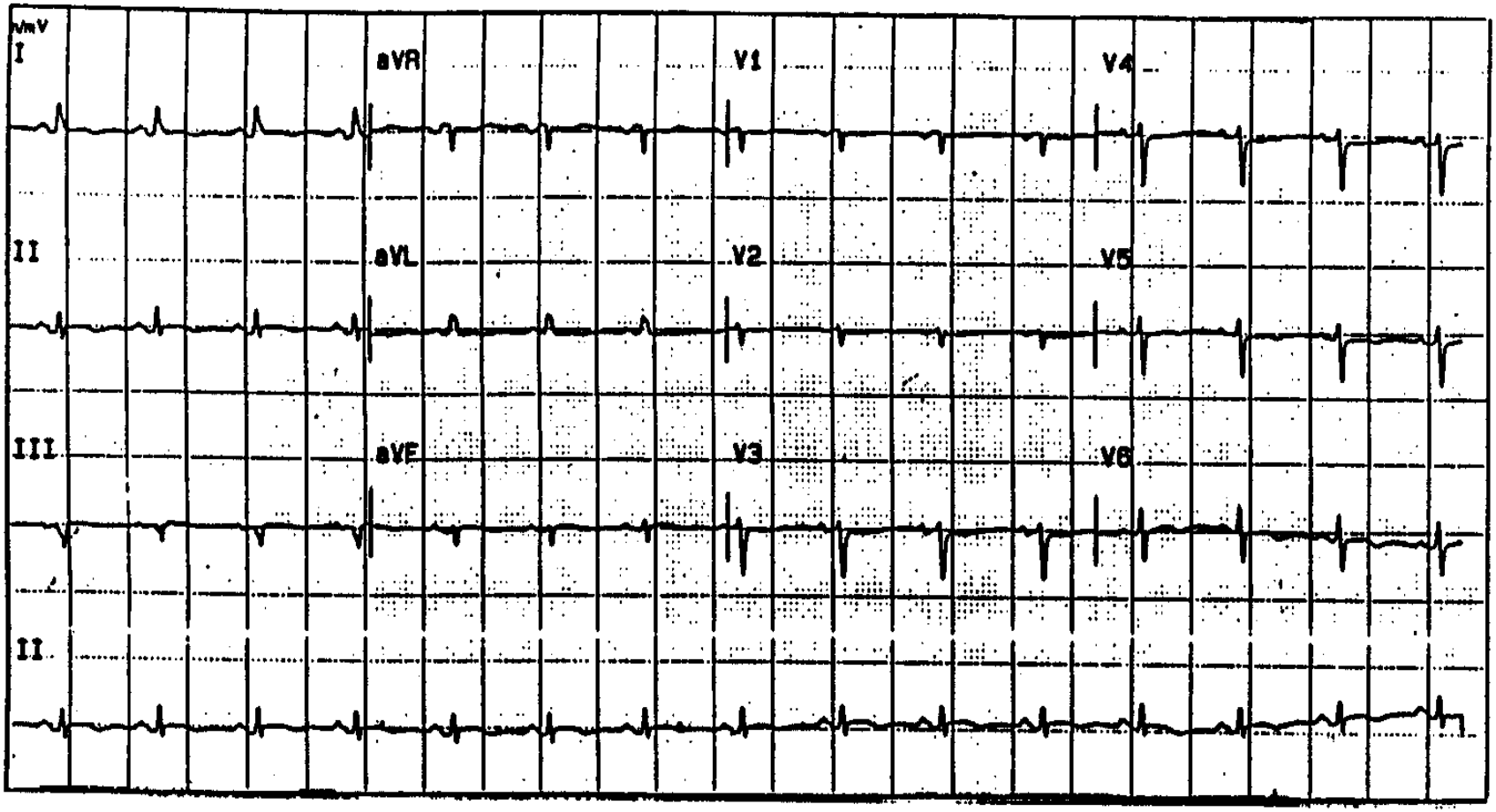


Péricardite maligne

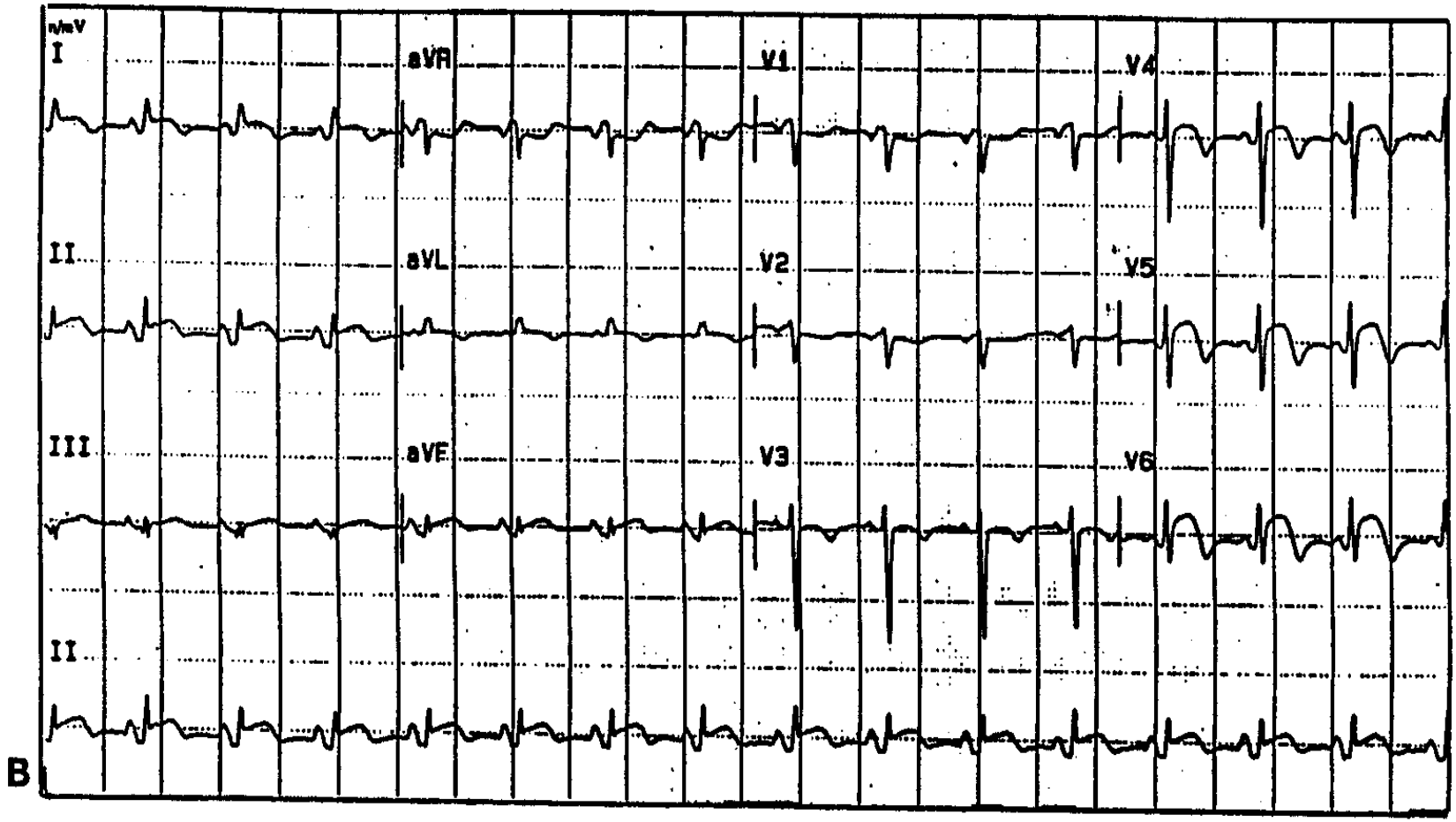
- tableau le plus fréquent
- épanchement évoluant vers la tamponnade
- syndrome obstructif qui, s'il n'est pas diagnostiqué suffisamment tôt, entraînera un état de choc de type obstructif

Métastases myocardiques

- fréquemment retrouvées à l'autopsie atteignant 10 % des cas
- souvent asymptomatiques et non diagnostiquées du vivant du malade
- mises en évidence par échocardiographie et par RMN
- Le piège le plus fréquemment rapporté = apparition de troubles électrocardiographiques simulant un tracé compatible avec un infarctus myocardique



A



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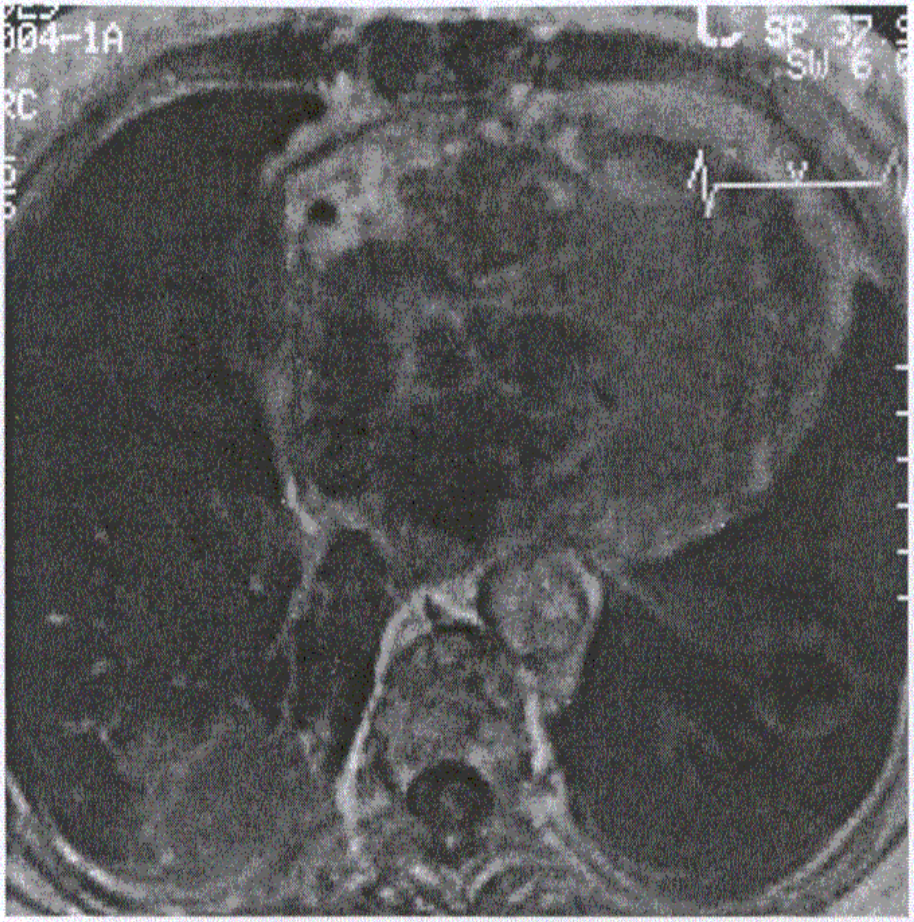


Fig. 2 Transversal T1-weighted image after end-diastolic injection of gadolinium. The primary lung tumour is in the right lobe, and the heart metastasis is located in the wall of the left ventricle, with tumoural infiltration of the pulmonary artery

Cardiotoxicité des traitements

Complications potentielles: nombreuses

- péricardite sèche
- tamponnade péricardique
- arythmies cardiaques
- myocardite toxique
- angor et infarctus myocardique
- insuffisance cardiaque

Table 1. Cardiotoxicity of Antineoplastic Agents

Antitumor Class/Drug	Toxicity	Comment
Antitumor antibiotics		
Anthracyclines		
Daunorubicin	Cardiomyopathy	Mechanism: oxidative damage via lipid peroxidation; increased risk of cardiotoxicity with cumulative dosing > 400 mg/m^2; dexrazoxane or liposomal formulation can reduce toxicity
Doxorubicin	Myopericarditis	
Epirubicin	SVT	
Idarubicin	Ventricular ectopy	
Anthraquinones	CHF	Increased risk with cumulative dose > 160 mg/m^2
Mitoxantrone	Arrhythmias	
Bleomycin	Pericarditis; myocardial ischemia/infarction	
Mitomycin	CHF	Increased risk with cumulative dose > 30 mg/m^2
Topoisomerase inhibitors		
Etoposide	Vasospasm	Case reports only
	Myocardial ischemia/infarction	
Alkylating agents		
Cyclophosphamide	Heart block	Mechanism: endothelial capillary damage; observed at doses > 120-170 mg/kg; cardiac failure usually resolves over 3-4 weeks and is treated with supportive care
	Tachyarrythmias	
	CHF	
	Hemorrhagic myopericarditis	
Ifosfamide	Atrial ectopy	Observed at doses > 6.25-10 g/m^2
	Bradycardia	
	CHF	
Cisplatin	Arrhythmias	Mechanism may be related to drug-induced electrolyte abnormalities; von Willebrand's factor concentration can predict arterial occlusive events; vast majority of cardiac toxicity is seen in combination chemotherapy
	Heart block	
	CHF	
	Myocardial ischemia/infarction	
Busulfan	Endocardial fibrosis	Single autopsy finding
Microtubule-targeting drugs		
Vinca alkaloids	Myocardial ischemia/infarction	Mechanism: vasoconstriction
Taxanes	Bradycardia/AV block	Typically reversible; may potentiate anthracycline toxicity
	Atrial and ventricular arrythmias	
	CHF	
	Myocardial ischemia	
Antimetabolites		
Fluorouracil	Cardiac failure	Likely mechanism is coronary vasospasm; ischemic events more common when used in combination with cisplatin; β blocker, calcium channel blocker, or nitrates may decrease risk
	Atrial or ventricular ectopy	
	Myocardial ischemia/infarction	
Capecitabine	Same as above	Not as well studied as infusional fluorouracil
Methotrexate	Arrhythmias	Case reports only
	Myocardial ischemia/infarction	
Fludarabine	Hypotension	
	Angina	
Cytarabine	Angina	Corticosteroids seem to be beneficial for pericarditis
	Pericarditis with effusion	

J Clin Oncol 23:7685-7696. © 2005

CHIMIOTHÉRAPIE ANTICANCÉREUSE ET RISQUE DE DYSFONCTION SYSTOLIQUE DU VENTRICULE GAUCHE/INSUFFISANCE CARDIAQUE	
Agents	**Incidence (%)**
Anthracyclines	
Doxorubicine	3-26
Épirubicine	0,9-3,3
Idarubicine	5-18
Cyclophosphamide	7-28
Ifosfamide	17
Décitabine	5
Docétaxel	2,3-8
Thérapies moléculaires ciblées	
Trastuzumab	2-28
Pazopanib	0,6-11
Ponatinib	3-15
Sorafénib	1,9-11
Dabrafénib	8-9
Sunitinib	1-27
Dasatinib	8-9
Lapatinib	0,9-4,9
Tramétinib	7-11
Carfilzomib	7
Bortézomib	2-5
Immunothérapie	0,29

Tableau 1.

Cardiomyopathie aux anthracyclines

- Adriamycine (doxorubicine), épirubicine
- 3 tableaux cliniques:
  - aigu/subaigu: rare (arythmies, troubles ECG, péricardite, décompensation cardiaque)
  - chronique: tachycardie puis insuffisance cardiaque congestive (dont OPH)
  - tardive: décompensation cardiaque très progressive dans les années suivant la fin du traitement

Cardiotoxicité chronique aux anthracyclines

- liée à la dose cumulative
- facteurs prédisposants: irradiation médiastinale, comorbidité cardiaque, hypertension artérielle, âge, sexe féminin
- détection par FEVG (isotopique, échographique): suboptimale
- dosage et suivi de la troponine
- le traztuzumab (AC antiHER2) peut révéler ou majorer cette cardiotoxicité

Table 1. Anthracycline Cardiotoxicity

Agent	Conversion Factor	Level of 5% Incidence of Cardiotoxicity
Doxorubicin	1	450 mg
Daunorubicin	0.5	900 mg
Epirubicin	0.5	935 mg
Idarubicin	2	225 mg
Mitoxantrone	2.2	200 mg

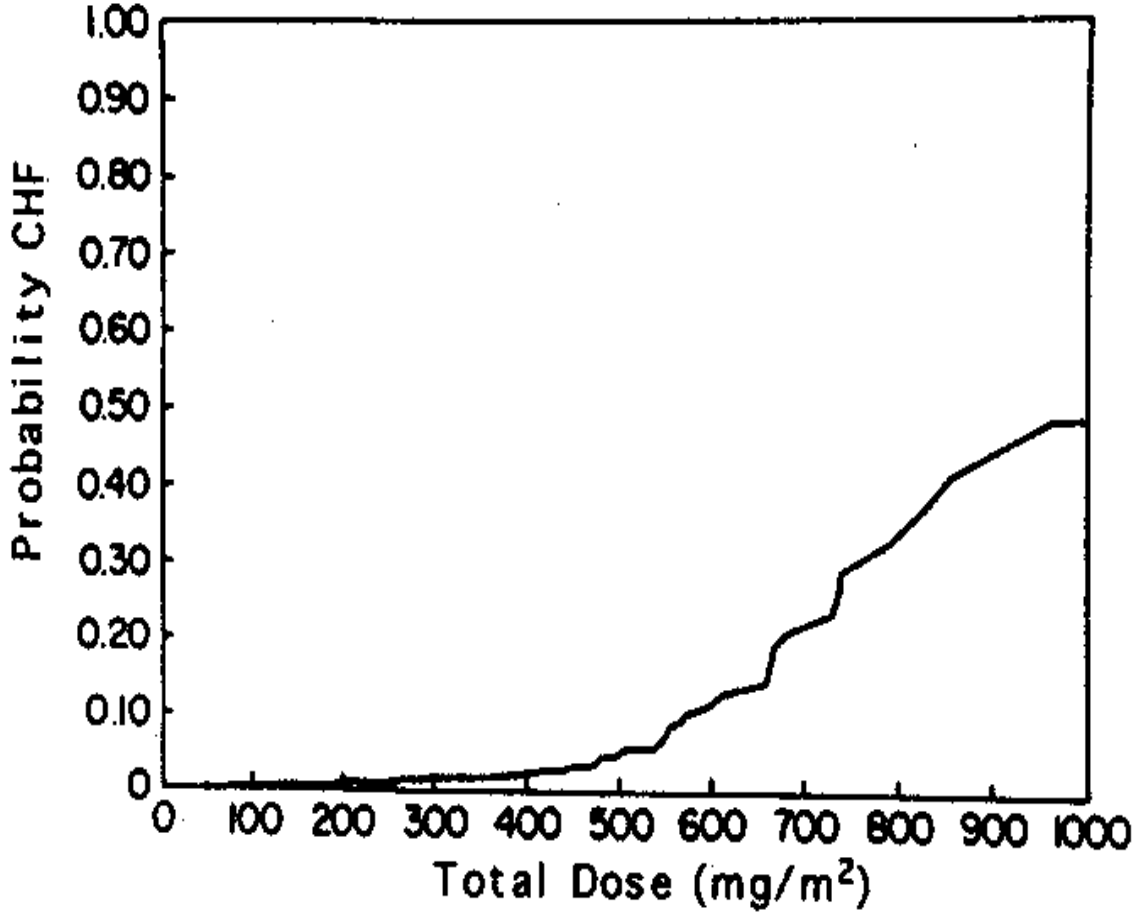
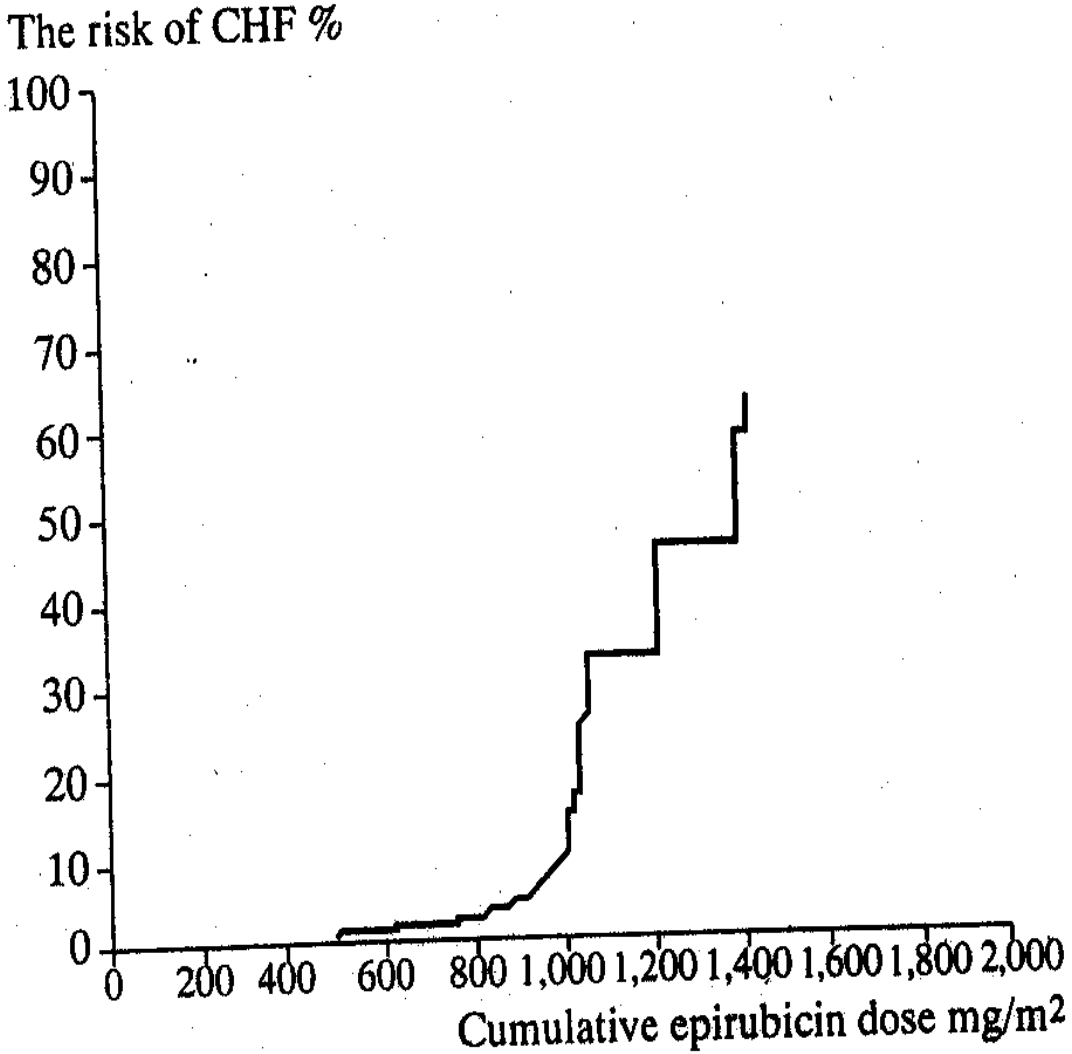


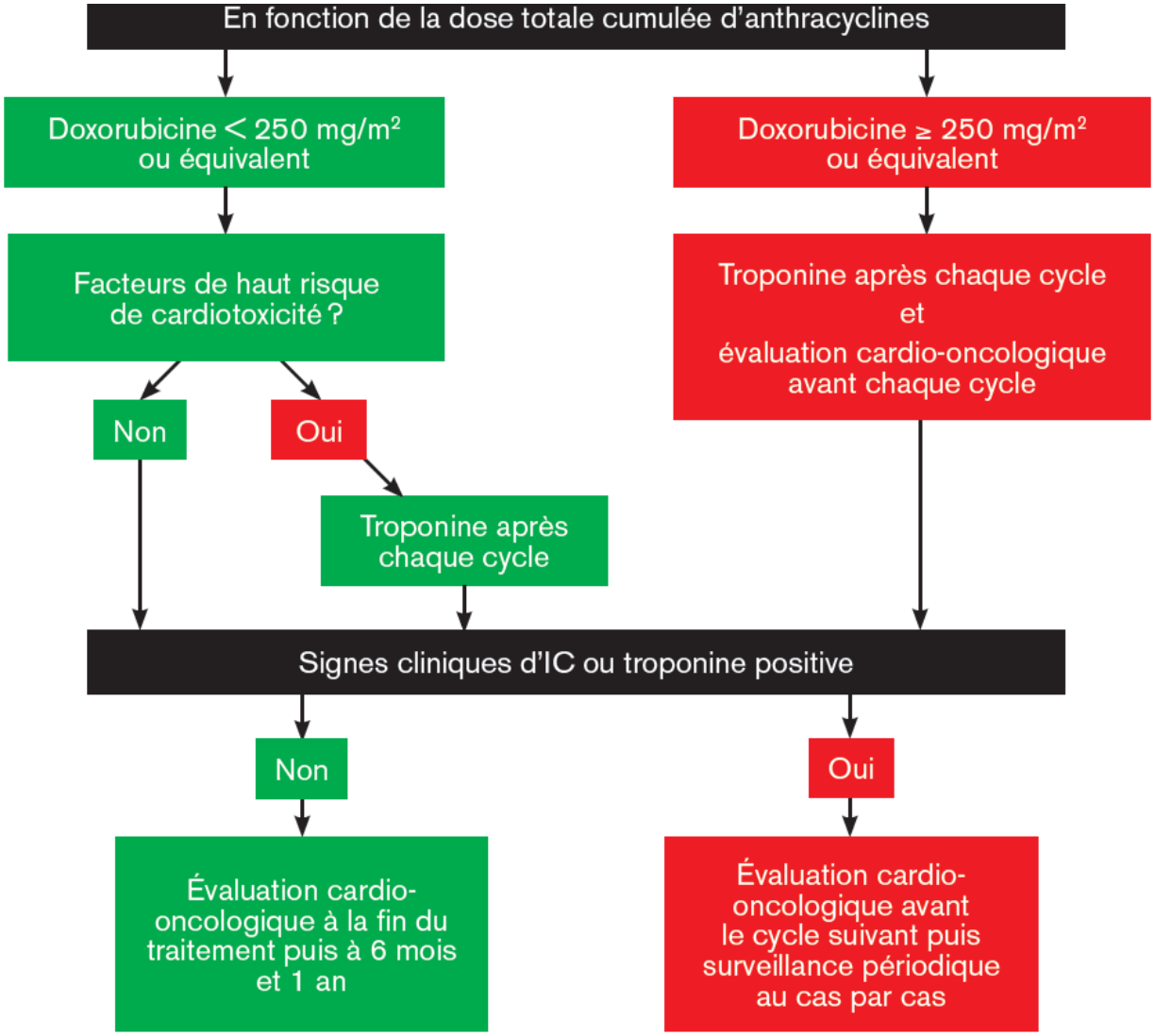
Figure 1. Cumulative probability of developing doxorubicin-induced congestive heart failure (*CHF*) plotted against total cumulative dose of doxorubicin in all patients receiving the drug (3941 patients; 88 cases of congestive heart failure). Reproduced from Von Hoff and colleagues (6) with permission of *Annals of Internal Medicine*.


The risk of CHF %
100
90
80
70
60
50
40
30
20
10
0
0
200
400
600
800
1,000
1,200
1,400
1,600
1,800
2,000
Cumulative epirubicin dose mg/m2

Traitement

- décompensation: symptomatique
- inhibiteurs enzyme de conversion
- + β-bloquants au long terme après recompensation

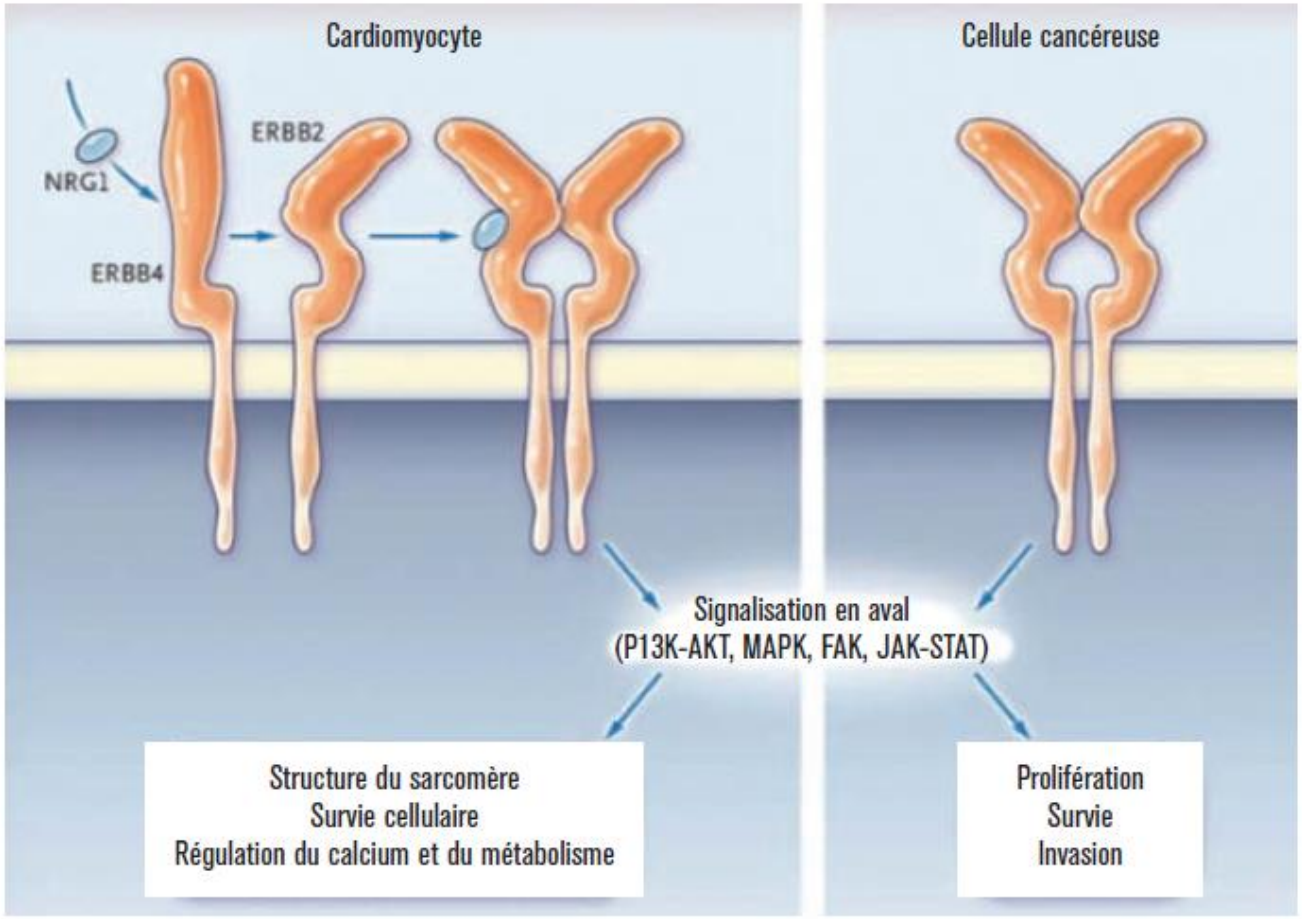
- tout est dans la prévention !


En fonction de la dose totale cumulée d'anthracyclines
Doxorubicine < 250 mg/m² ou équivalent
Doxorubicine ≥ 250 mg/m² ou équivalent
Facteurs de haut risque de cardiotoxicité ?
Troponine après chaque cycle et évaluation cardio-oncologique avant chaque cycle
Non
Oui
Troponine après chaque cycle
Signes cliniques d'IC ou troponine positive
Non
Oui
Évaluation cardio-oncologique à la fin du traitement puis à 6 mois et 1 an
Évaluation cardio-oncologique avant le cycle suivant puis surveillance périodique au cas par cas

Traztuzumab (Herceptine^{R})

- Indication: cancers du sein exprimant la protéine HER2/neu (20 à 40 % des cas)
- Mécanisme : anticorps monoclonal bloquant le récepteur HER2 à l'EGF, médiant une cytotoxicité cellulaire anticorps-dépendante

Figure 1. Voie de signalisation ErbB2 impliquée dans le cœur et la cellule tumorale.
D'après la réf. 2.



Insuffisance cardiaque

- insuffisance cardiaque chez 1 à 4 % des patients
- diminution de la fonction cardiaque : 10 % des patients
- surtout si exposition aux anthracyclines
- mécanisme : inhibition de l'activation des récepteurs ErbB2-ErbB4 déclenchant des voies de survie des myocytes lors de l'activation de signaux de stress aigu (due à l'exposition aux anthracyclines)
- répond au traitement médical et à l'arrêt de l'administration du trastuzumab mais pas certain qu'elle soit irréversible

Table 1. Chemotherapy-Related Cardiac Dysfunction

	Type I (myocardial damage)	Type II (myocardial dysfunction)
Characteristic agent	Doxorubicin	Trastuzumab
Clinical course, response to CRCD therapy	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2-4 months (reversible)
Dose effects	Cumulative, dose related	Not dose related
Mechanism	Free radical formation, oxidative stress/damage	Blocked ErbB2 signaling
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultra structural abnormalities
Noninvasive cardiac testing	Decreased ejection fraction by ultrasound or nuclear determination: global decrease in wall motion	Decreased ejection fraction by ultrasound or nuclear determination: global decrease in wall motion
Effect of rechallenge	High probability of recurrent dysfunction that is progressive, may result in intractable heart failure and death	Increasing evidence for the relative safety of rechallenge; additional data needed
Effect of late sequential stress	High likelihood of sequential stress related cardiac dysfunction	Low likelihood of sequential stress-related cardiac dysfunction

Abbreviation: CRCD, chemotherapy-related cardiac dysfunction.

Journal of Clinical Oncology, Vol 23, No 13 (May 1), 2005: pp 2900-2902

Cyclophosphamide et ifosfamide

- Nécrose myocardique à mégadose:
  - cyclophosphamide:
    - 240 mg/kg = léthal
    - 120 à 200 mg/kg: cas sporadiques (en fait limite semble = 1550 mg/m²/j x 4j)
  - ifosfamide: pour des doses de 10 à 18 g/m²
- Tableau clinique: péricardite, décompensation cardiaque, nécrose diffuse du cœur

5-fluorouracile

- cardiotoxicité importante: angor, arythmie, mort subite, décompensation cardiaque, infarctus myocardique, choc cardiogénique
- tableau clinique brutal
- facteurs favorisants: radiothérapie médiastinale, cisplatine
- pourrait être liée à un problème de formulation

Annals of Oncology **1**: 409–414, 1990.

Review

5-Fluorouracil cardiotoxicity: A critical review

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Summary. 5-Fluorouracil is a commonly administered chemotherapy agent that has infrequently been associated with cardiotoxicity. This review highlights the clinical features of this syndrome as described in reports from the medical literature. Clinical and laboratory evidence supporting proposed underlying mechanisms are reviewed.

Key words: 5-Fluorouracil, toxicity, angina, thrombosis, myocardial infarction, coronary spasm

Introduction

5-Fluorouracil (5-FU) is among the most commonly used chemotherapy drugs in clinical oncologic practice. It has become useful in the treatment of a variety of human malignancies including gastrointestinal cancer, breast cancer, and head and neck cancer. 5-FU has shown antitumor activity as single agent therapy and synergistically with other antitumor agents, and a mul-

Table 2. Cardiac manifestations reported with 5-FU administration.

Angina
Supraventricular tachycardia
Ventricular tachycardia
Congestive heart failure
Reversible cardiomyopathy
Myocardial infarction
Sudden death

Les thérapies ciblées

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Cardiovascular Toxic Effects of Targeted Cancer Therapies

Javid J. Moslehi, M.D.

N Engl J Med 2016;375:1457-67.
DOI: 10.1056/NEJMra1100265

Targeted cancer therapies

HER2 inhibitors			
HER2 monoclonal antibody	Trastuzumab	HER2	Decline in LVEF, congestive heart failure
Newer HER2 inhibitors	Pertuzumab, trastuzumab emtansine, lapatinib	HER2	Decline in LVEF, congestive heart failure
VEGF signaling pathway inhibitors		VEGF signaling pathway	Hypertension, venous or arterial thromboembolic events, proteinuria, cardiomyopathy
VEGFA monoclonal antibody	Bevacizumab		
VEGF trap	Aflibercept		
VEGFR2 monoclonal antibody	Ramucirumab		
Tyrosine kinase inhibitor with anti-VEGF activity	Sunitinib, sorafenib, pazopanib, axitinib, vandetanib, regorafenib, cabozantinib, lenvatinib	VEGF receptors (mainly VEGFR2) and other kinases; PDGFR	
Multitargeted tyrosine kinase inhibitors	Dasatinib	ABL, ABL mutants (except T315I), and other kinases; SRC, KIT, PDGFR, EGFR, BRAF, DDR1, DDR2, ephrin receptors	Pulmonary hypertension, vascular events, prolongation of QT interval corrected for heart rate
	Nilotinib	ABL, ABL mutants (except T315I), and other kinases; ABL2 (also called ARG), KIT, DDR1, NQO2	Coronary, cerebral, and peripheral vascular events, hyperglycemia, prolongation of QT interval corrected for heart rate
	Ponatinib	ABL, ABL mutants (including T315I), and other kinases; FGFR, VEGFR, PDGFR, ephrin receptors, SRC, KIT, RET, TEK (also called TIE2), FLT3	Coronary, cerebral, and peripheral vascular events

Other multitargeted tyrosine kinase inhibitors			
Anaplastic lymphoma kinase inhibitors	Crizotinib, ceritinib	Anaplastic lymphoma kinase	Bradycardia, prolongation of QT interval corrected for heart rate
PI3K–AKT–mTOR inhibitors†	Everolimus, temsirolimus	PI3K–AKT–mTOR signaling pathway	Cardiometabolic toxic effects, including hypercholesterolemia, hypertriglyceridemia, hyperglycemia
Bruton's tyrosine kinase inhibitors	Ibrutinib	Bruton's tyrosine kinase	Atrial fibrillation, other arrhythmias
MEK inhibitors	Trametinib	MEK1, MEK2	Cardiomyopathy
Immunomodulatory drugs	Thalidomide, lenalidomide, pomalidomide	Lymphoid transcription factors IKZF1 and IZKF3	Venous or arterial thromboembolic events
Proteasome inhibitors	Bortezomib, carfilzomib	Ubiquitin–proteasome system	Cardiomyopathy, hypertension, venous or arterial thromboembolic events, arrhythmia
Immune checkpoint inhibitors	Pembrolizumab, nivolumab	Programmed cell death 1	Myocarditis
	Ipilimumab	CTLA4	Myocarditis

Les inhibiteurs de point de contrôle immunitaire

Table 1. Cardiovascular Adverse Events Reported in Phase 3 Trials of Immune Checkpoint Inhibitors.*

Study and Year	Tumor Type	Drug	Exposed Patients	Reported Cases of Cardiovascular Toxicity
			no.	*no. (%)*
All studies			5347	10 (0.19)
Hodi et al., 2010	Melanoma	Ipilimumab	511	0
Robert et al., 2011	Melanoma	Ipilimumab	247	0
Weber et al., 2015	Melanoma	Nivolumab	268	0
Robert et al., 2015	Melanoma	Nivolumab	206	1 case of hypotension (0.49)
Robert et al., 2015	Melanoma	Pembrolizumab or ipilimumab	811	1 cardiac arrest associated with metabolic imbalances from ipilimumab-induced diarrhea; 4 cases of hypertension (0.62)
Larkin et al., 2015	Melanoma	Nivolumab, ipilimumab, or nivolumab plus ipilimumab	937	0
Eggermont et al., 2015 and 2016	Melanoma (adjuvant)	Ipilimumab	471	1 case of myocarditis (0.21)
Borghaei et al., 2015	Non-squamous non–small-cell lung cancer	Nivolumab	287	1 case of cardiac tamponade; 1 case of pericardial effusion (0.70)
Brahmer et al., 2015	Squamous non–small-cell lung cancer	Nivolumab	131	0
Reck et al., 2016	Non–small-cell lung cancer	Pembrolizumab	154	0
Herbst et al., 2016	Non–small-cell lung cancer	Pembrolizumab	682	1 case of myocardial infarction (0.15)
Motzer et al., 2015	Renal-cell carcinoma	Nivolumab	406	0
Ferris et al., 2016	Head and neck squamous-cell carcinoma	Nivolumab	236	0

DOI: 10.1056/NEJMc1615251

VigiBase (OMS)

	ICSRs reported for ICIs (n=31 321)	ICSRs reported in full database (n=16 343 451)	IC (IC_{025})
Myocarditis	122 (0·39%)	5515 (0·03%)	3·47 (3·20)
Pericardial diseases	95 (0·30%)	12 800 (0·08%)	1·93 (1·63)
Cardiac supraventricular arrhythmias	222 (0·71%)	68 597 (0·42%)	0·75 (0·56)
Vasculitis	82 (0·26%)	33 289 (0·20%)	0·36 (0·03)
Temporal arteritis	18 (0·06%)	696 (<0·01%)	3·33 (2·59)
Polymyalgia rheumatica	16 (0·05%)	1709 (0·01%)	2·12 (1·33)
Heart failure	225 (0·72%)	142 502 (0·87%)	−0·28 (−0·47)
Cerebral haemorrhage	250 (0·80%)	179 621 (1·10%)	−0·46 (−0·65)
Endocardial disorders	8 (0·03%)	3149 (0·02%)	0·38 (−0·79)
Haemorrhage (clinical events)	1023 (3·27%)	875 398 (5·36%)	−0·71 (−0·80)
Cerebral arterial ischaemia	195 (0·62%)	161 618 (0·99%)	−0·67 (−0·88)
Cardiac conductive disorders	37 (0·12%)	26 008 (0·16%)	−0·42 (−0·93)
Myocardial infarction	167 (0·53%)	163 908 (1·00%)	−0·91 (−1·14)
Biological haemostatic disorders favouring haemorrhage	135 (0·43%)	136 474 (0·84%)	−0·95 (−1·21)
Arterial systemic ischaemia	203 (0·65%)	215 741 (1·32%)	−1·02 (−1·23)
Cardiac death or shock	136 (0·43%)	144 825 (0·89%)	−1·03 (−1·28)
Hypertension and related end-organ damages	198 (0·63%)	239 232 (1·46%)	−1·2 (−1·42)
Vascular neoplasm	4 (0·01%)	2687 (0·02%)	−0·33 (−2·06)
Torsade de pointes or long-QT syndrome	22 (0·07%)	31 642 (0·19%)	−1·44 (−2·11)
Cardiac ventricular arrhythmias	22 (0·07%)	33 504 (0·20%)	−1·52 (−2·19)
Pulmonary hypertension and related cardiac involvement	17 (0·05%)	30 718 (0·19%)	−1·76 (−2·53)
Cardiac valve disorders	2 (0·01%)	25 500 (0·16%)	−4·3 (−6·89)
Dyslipidaemia	20 (0·06%)	64 555 (0·39%)	−2·6 (−3·30)

Data are n (%) unless otherwise stated. ICIs refers to any ICSRs reported for treatment with nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, or tremelimumab. A positive IC_{025} value (>0) is the traditional threshold used in statistical signal detection with VigiBase. ICSRs=individual case safety reports. ICIs=immune checkpoint inhibitors. IC=information component. IC_{025}=lower end of a 95% credibility interval for the IC.

Table 1: **Cardiovascular immune-related adverse events reported with ICIs versus those reported in the full database from VigiBase, from Nov 14, 1967, to Jan 2, 2018**

	ICSRs reported with ICIs (n=31 321)			ICSRs reported in full database (starting 2008*; n=12 455 401)	ROR (95% CI) anti-PD-1 or anti-PD-L1 *vs* anti-CTLA-4 monotherapy	ROR (95% CI) combination ICIs *vs* monotherapy	ROR (95% CI) ICIs *vs* full database
	Anti-PD-1 or anti-PD-L1 monotherapy (n=20 643)	Anti-CTLA-4 monotherapy (n=8266)	Combination ICIs (n=2412)				
Myocarditis	84 (0·41%)	6 (0·07%)	32 (1·33%)	4454 (0·04%)	5·62 (2·46–12·88)†	4·31 (2·86–6·38)†	11·21 (9·36–13·43)†
Pericardial diseases	74 (0·36%)	13 (0·16%)	8 (0·33%)	10 009 (0·08%)	2·28 (1·27–4·12)†	1·10 (0·53–2·24)	3·80 (3·08–4·62)†
Vasculitis	56 (0·27%)	18 (0·22%)	8 (0·33%)	20 987 (0·17%)	1·25 (0·73–2·12)	1·30 (0·62–2·67)	1·56 (1·25–1·94)†
Temporal arteritis	7 (0·03%)	10 (0·12%)	1 (0·04%)	568 (<0·01%)	0·28 (0·11–0·74)†	0·71 (0·07–3·94)	12·99 (8·12–20·77)†
Polymyalgia rheumatica	14 (0·07%)	1 (0·01%)	1 (0·04%)	1254 (0·01%)	5·61 (0·74–42·66)	0·80 (0·08–4·62)	5·13 (3·13–8·40)†

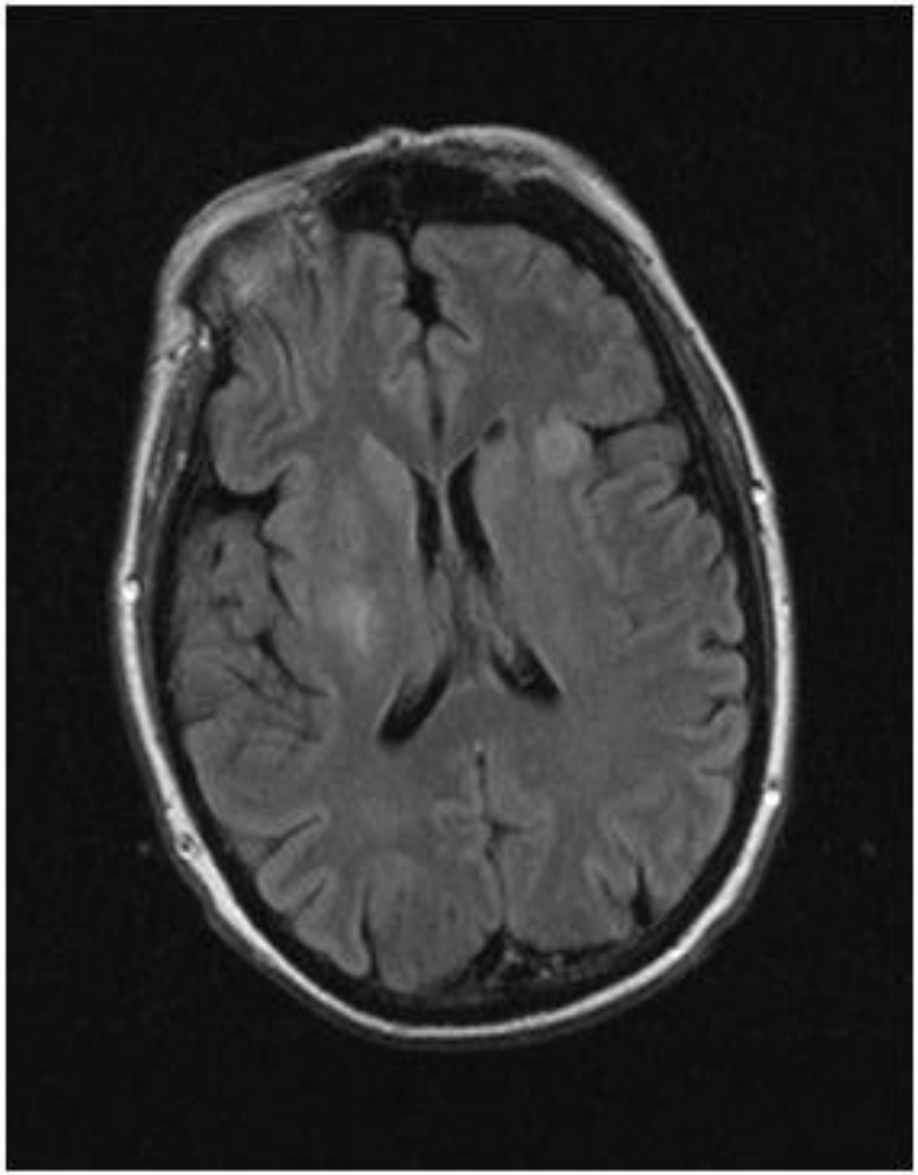
Data are n (%) unless otherwise stated. ICIs refers to any ICSR reported for treatment with nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, or tremelimumab. Anti-PD-1 or anti-PD-L1 monotherapy refers to any ICSR associated with any of the following five drugs only when used alone: nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab. Anti-CTLA-4 monotherapy refers to any ICSR associated with ipilimumab or tremelimumab alone. Combination ICIs refers to any ICSR reported with at least one anti-PD-1 or anti-PD-L1 drug combined with an anti-CTLA-4 drug. ICSRs=individual case safety reports. ICIs=immune checkpoint inhibitors. ROR=reporting odds ratio. *First reports of ICSRs associated with ICIs started in 2008. †Significant over-reporting after Bonferroni adjustment for multiple tests within immunotherapy subgroups [p≤(0·05/10 tests)=p≤0·005].

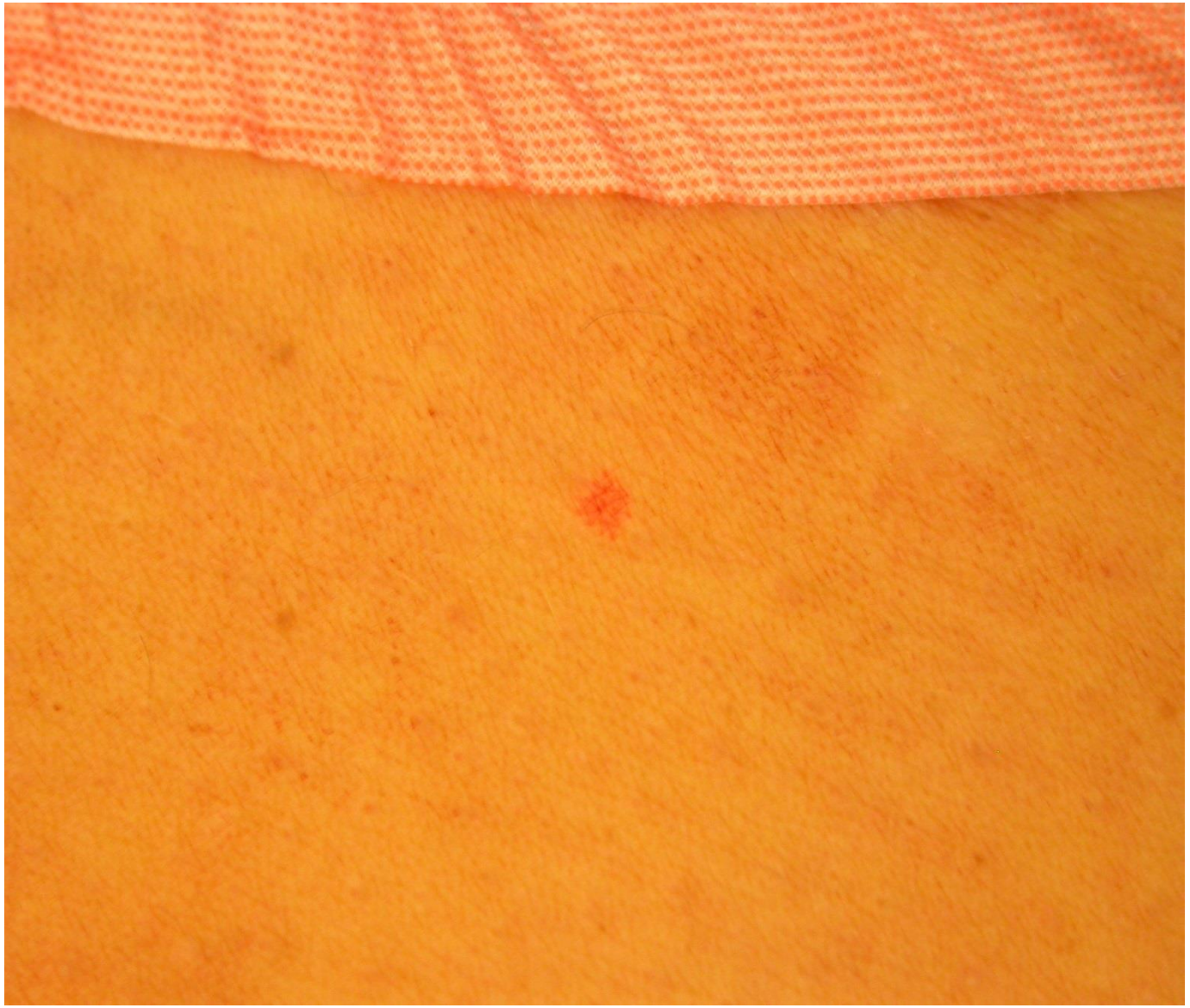
***Table 2*: Selected cardiovascular adverse events (detected as signals) reported for ICIs versus the full database from VigiBase, from Jan 1, 2008, to Jan 2, 2018**

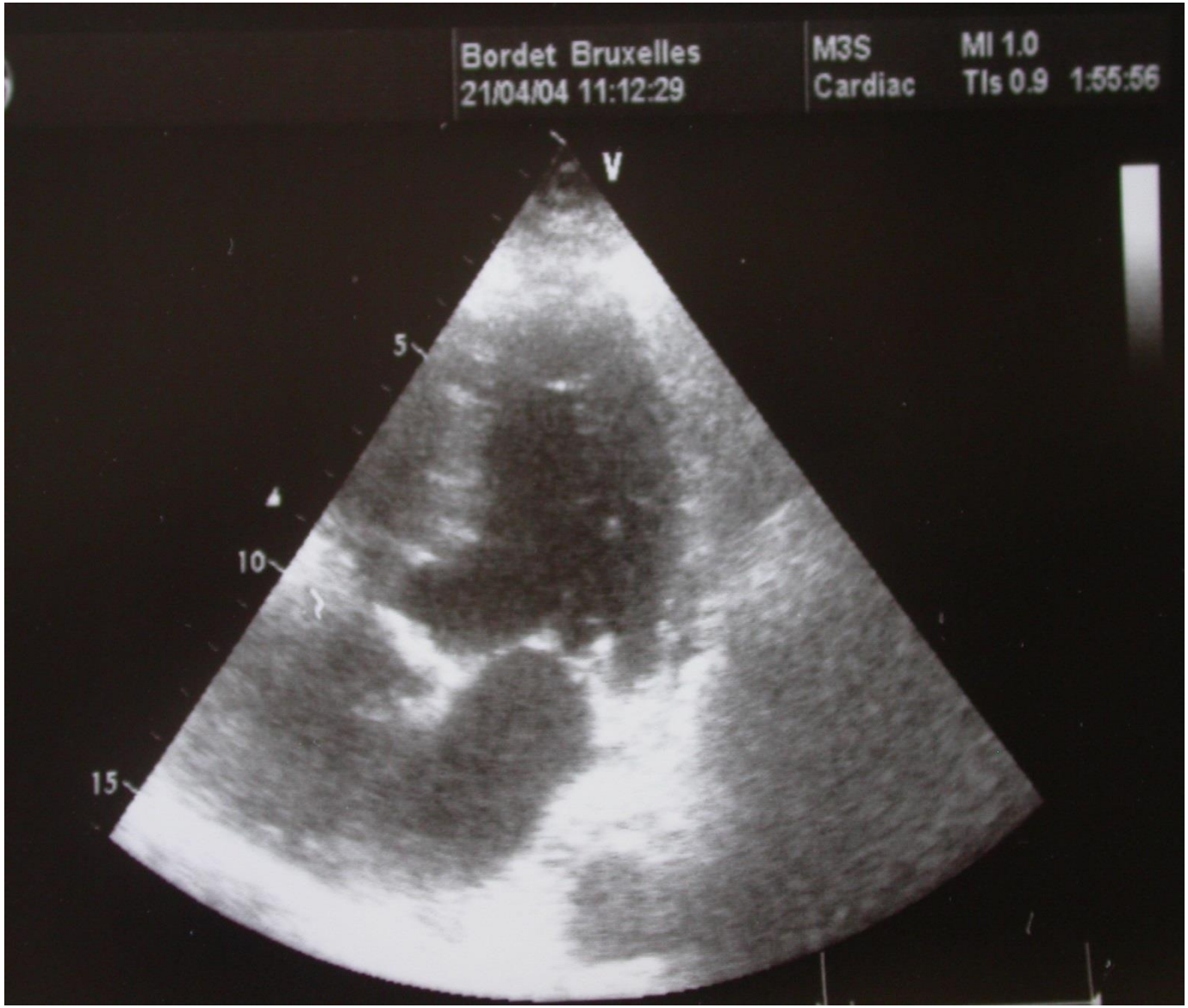
Les effets secondaires cardiovasculaires étaient sévères dans la majorité des cas (> 80%), avec la mort dans 61 (50%) des 122 cas de myocardite, 20 (21%) des 95 cas de maladie péricardique et cinq (6%) des 82 cas de vascularite.

Le traitement optimal des myocardites reste à déterminer.

Complications infectieuses



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Cardiac
MI 1.0
TIs 0.9
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10
15

rares et rarement diagnostiquées

- myocardite
- abcès cardiaque
- péricardite infectieuse
- seules fréquentes: les endocardites des valves droites en rapport avec un cathéter à chambre

Phénomènes paranéoplasiques

Endocardite thrombotique non bactérienne

= endocardite marastique

- Cause des lésions allant d'agrégats plaquettaires microscopiques à de grosses végétations sur les valves cardiaques (surtout aortique et mitrale)
- Survient le plus souvent dans des cancers avancés
  - Souvent adénocarcinomes
  - Peut atteindre des taux de 75% dans les autopsies
  - Cancer bronchique : 7%
- À l'origine d'infarctus par emboles systémiques: splénique, rénaux, distaux mais surtout cérébraux et coronaires
- Diagnostic souvent difficile: souffle cardiaque fugace, petites lésions non visibles en échographie

Cardiac Valvular Vegetations in Cancer Patients: A Prospective Echocardiographic Study of 200 Patients

Yeouda Edoute, MD, PhD, Nissim Haim, MD, Diana Rinkevich, MD, Benjamin Brenner, MD, Shimon A. Reisner, MD, *Haifa, Israel*

PURPOSE: Nonbacterial thrombotic endocarditis can complicate various malignancies and may cause morbidity and mortality mainly as a result of systemic embolism. The antemortem diagnosis of nonbacterial thrombotic endocarditis is rare. The purpose of our study was to assess the frequency, echocardiographic characteristics, and clinical correlation of nonbacterial thrombotic endocarditis in cancer patients.

PATIENTS AND METHODS: A prospective echocardiographic screening of 200 nonselected ambulatory patients with solid tumors was performed. Patients were evaluated for evidence of thromboembolic events and for plasma D-dimer levels. A cohort of 100 consecutive patients without overt heart disease referred to echocardiography for the detection of an occult arterial embolic source served as a control group. It consisted of 52 males and 48 accidents, and 4 "silent" segmental left ventricular wall motion abnormalities on echocardiography). Thromboembolism was noticed in 9 of 38 patients (24%) with vegetations compared with 13 of 162 patients without vegetations (8%; $P = 0.013$). Plasma D-dimer level was examined in a subgroup of 170 patients. D-dimer level was increased in 19 of 21 patients (90%) with thromboembolism compared with 76 of 149 patients without thromboembolism (51%; $P = 0.001$).

CONCLUSIONS: This study demonstrated a high prevalence of cardiac valvular lesions in patients with solid tumors. Vegetations were associated with thromboembolism. Plasma D-dimer level was significantly increased in patients with thromboembolism. *Am J Med.* 1997;102:252–258.

Traitement

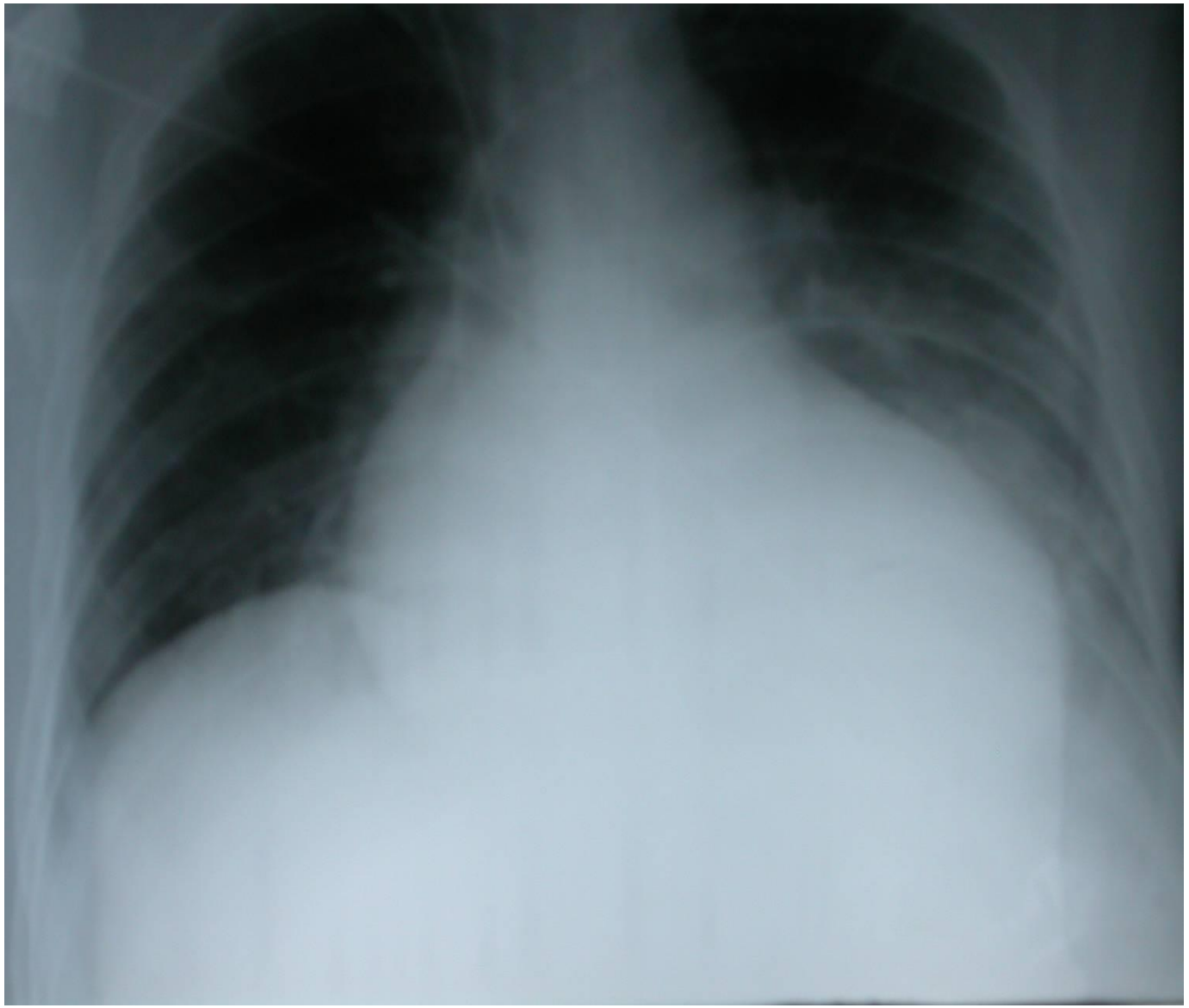
Héparine: en cas de

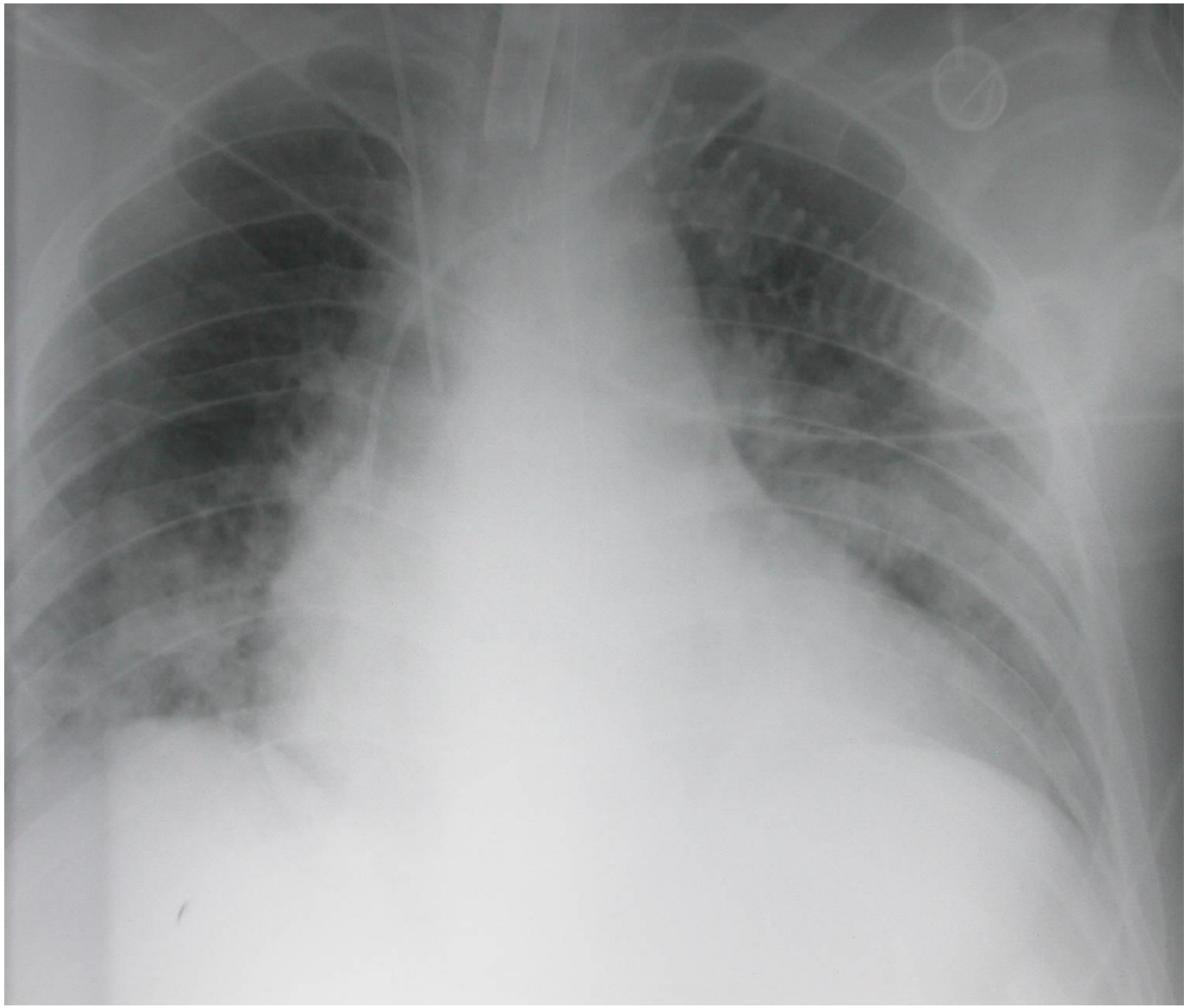
- Embolies systémiques ou pulmonaires
- Végétations visibles à l'échographie

Efficacité non établie

Tumeurs carcinoïdes

- entraînent une atteinte de l'endocarde et des valves cardiaques
- le plus souvent insuffisance cardiaque droite avec insuffisance tricuspidienne





Phéochromocytome

- cardiomyopathie aux cathécolamines, réversible avec le contrôle de la tumeur
- dépression myocardique avec choc cardiogénique avec cardiomyopathie dilatée à l'échocardiographie
- infarctus myocardique à coronaire saine

Les complications vasculaires

Variées!

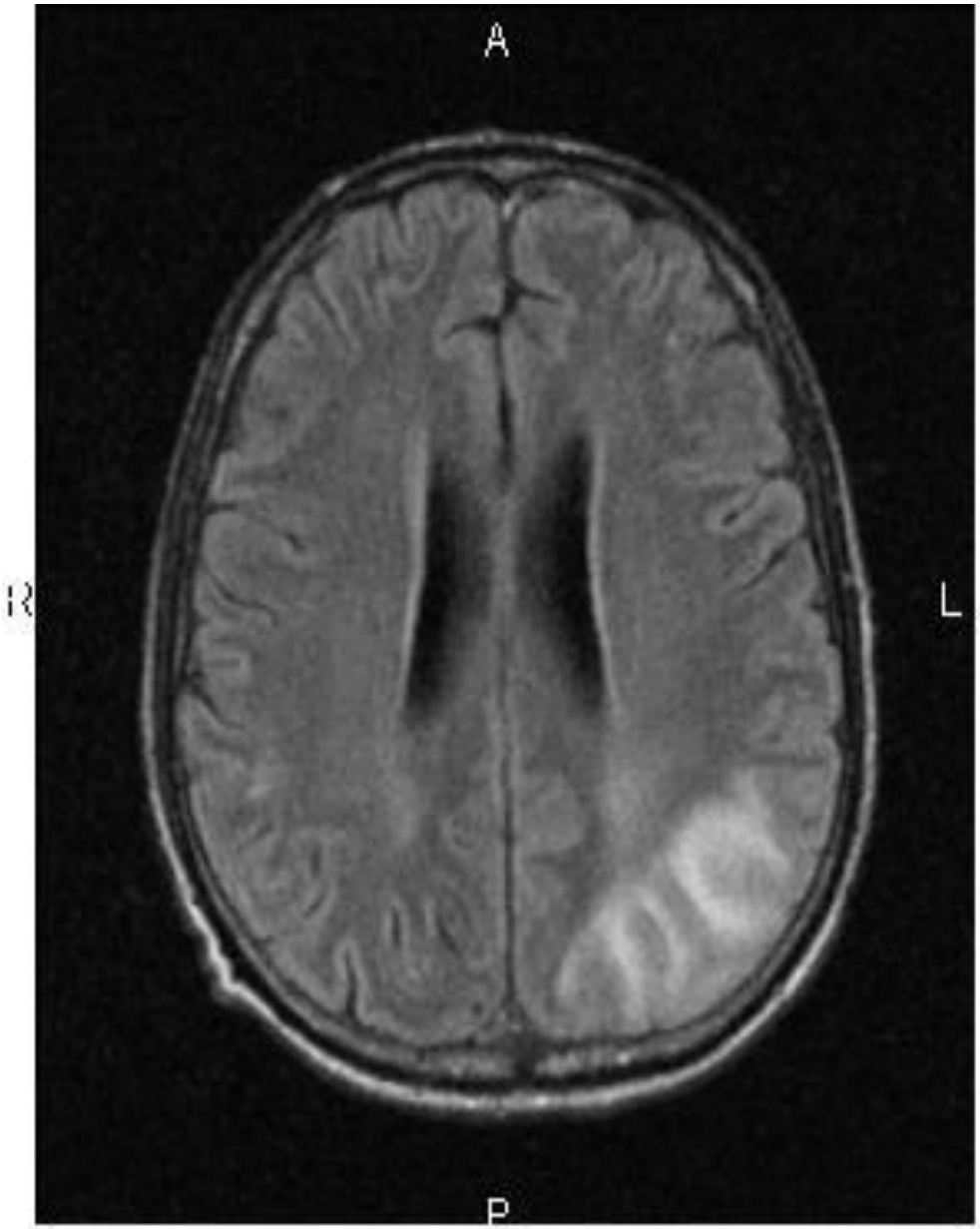
- syndrome de Trousseau
- thrombophlébites superficielles (migrantes)
- thromboses veineuses profondes avec embolies pulmonaire et paradoxale
- thrombose artérielle
- embolies sur endocardite thrombotique non bactérienne
- thrombose cardiaque
- embolie néoplasique
- vasculites paranéoplasiques
- thrombose sur phénomènes autoimmuns paranéoplasiques
- aggravation pathologie vasculaire préexistante.

Mécanismes

État hypercoagulable dû au cancer:

- Expression anormale de facteur tissulaire par les cellules néoplasiques
- Facteur procoagulant du cancer
- Stimulation de cellules normales à avoir une activité procoagulante
- Syndrome d'hyperviscosité
- Auto-anticorps: anticardiolipine (anti-phospholipides), anti-IL8

- Facteurs de comorbidité :
  - Compression vasculaire
  - Immobilisation
  - Dysfonction hépatique
  - Sepsis
  - Pathologies vasculaires sous-jacentes
- Traitements anticancéreux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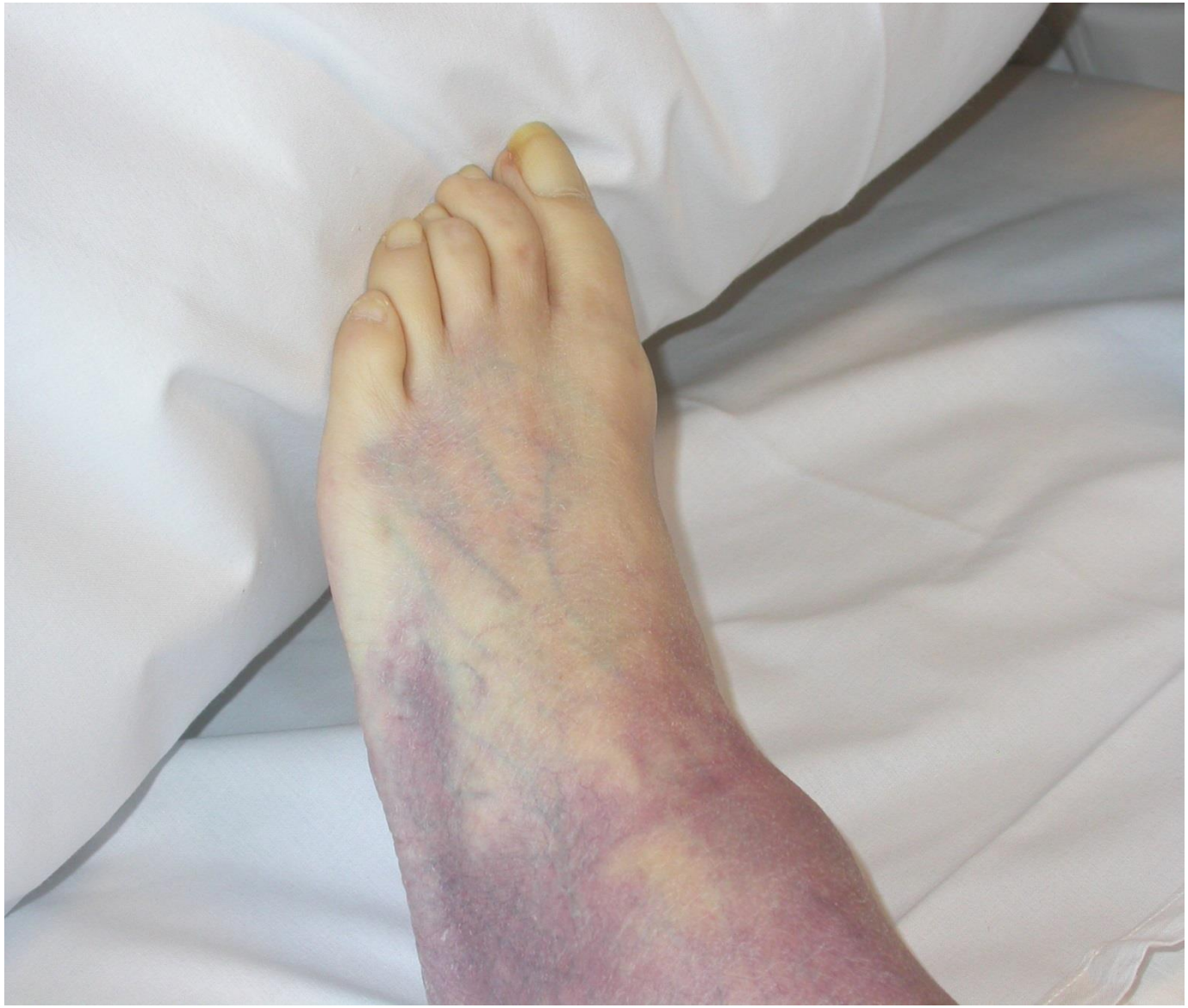
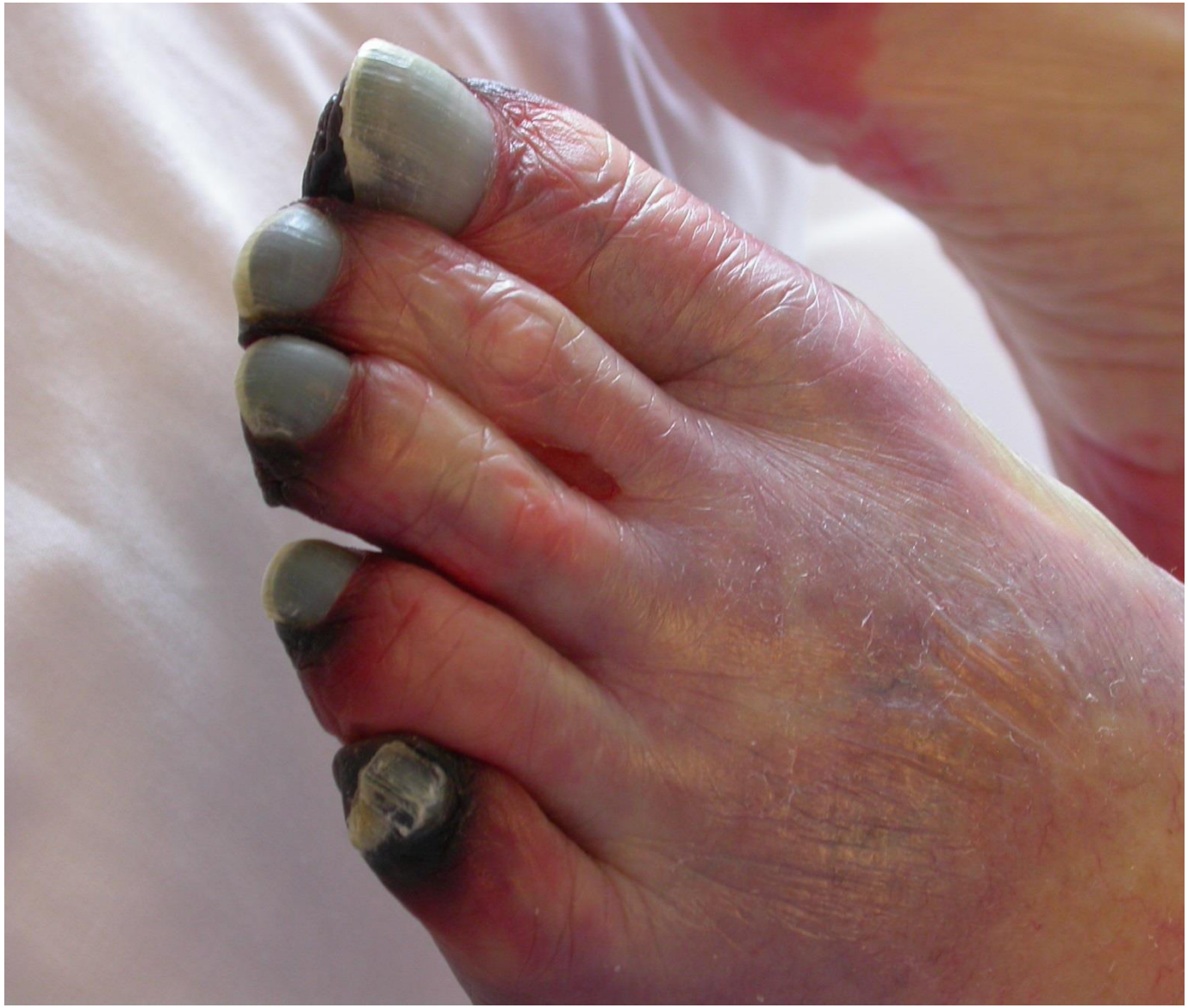
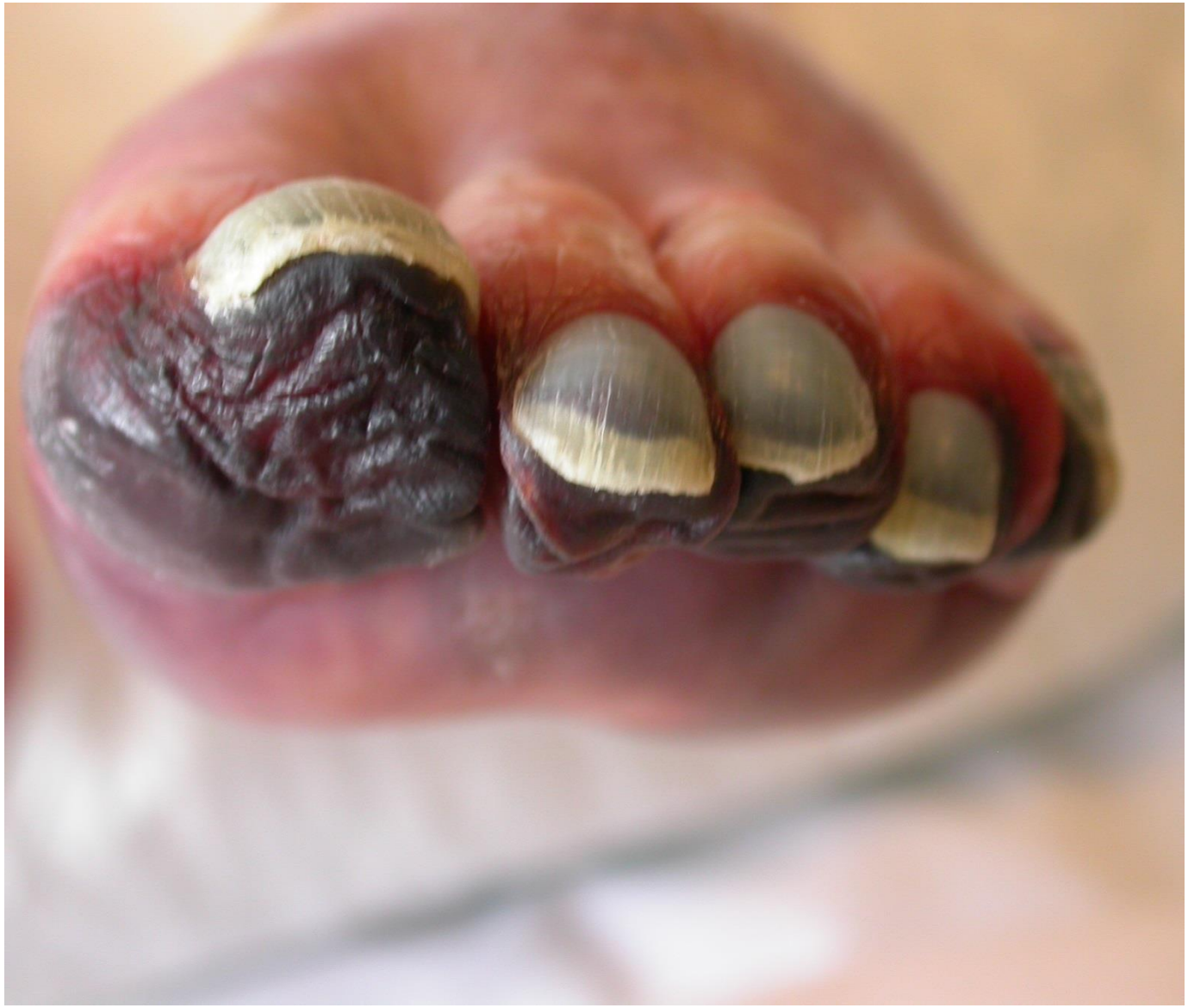
Les thromboses artérielles

Tableau clinique

- Angor et infarctus myocardique
- AVC ischémique
- Infarctus rénaux
- Infarctus mésentérique
- Artériopathie périphérique avec ischémie distale (membres):
  - chimiothérapie à base de cisplatine







En cause

- agents anticancéreux (5FU, cisplatine, bévacizumab, sunitinib, sorafenib, inhibiteurs de point de contact immunitaires …)
- radiothérapie
- CIVD
- endocardite thrombosante non bactérienne (marastique)
- embolies tumorales et le lymphome malin endovasculaire
- rupture artère carotide (ligature)
- syndromes myéloprolifératifs

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

High Incidence of Thromboembolic Events in Patients Treated With Cisplatin-Based Chemotherapy: A Large Retrospective Analysis

Russell A. Moore, Nelly Adel, Elyn Riedel, Manisha Bhutani, Darren R. Feldman, Nour Elise Tabbara, Gerald Soff, Rekha Parameswaran, and Hani Hassoun

Table 2. Overall Incidence of Thromboembolic Events (N = 932)

Thromboembolic Event	No. of Patients	%
Thrombosis	169	18.1
Types of thromboses (n = 169)		
DVT alone	84	49.7
PE alone	43	25.4
DVT + PE	23	13.6
Arterial thrombosis alone	14	8.3
DVT + arterial thrombosis	5	3.0
Subtypes of DVTs (n = 112)		
Proximal lower extremity	22	19.6
Proximal lower and distal lower extremity	18	16.1
Proximal lower extremity and central*	5	4.4
Proximal lower extremity and central* and distal lower extremity	1	0.9
Proximal upper extremity	2	1.8
Proximal upper and distal upper extremity	3	2.7
Proximal upper and internal jugular vein and distal upper extremity	4	3.6
Internal jugular vein	5	4.4
Internal jugular vein and distal upper extremity	1	0.9
Central*	27	24.1
Distal lower extremity	20	17.9
Distal lower and distal upper extremity	1	0.9
Distal upper extremity	3	2.7
Subtypes of arterial events (n = 19)		
Central†	6	31.6
Myocardial infarction	2	10.5
Cerebrovascular accident	10	52.6
Transient ischemic attack	1	5.3
Symptomatic or incidental event (n = 169)		
Symptomatic	95	56.2
Incidental	74	43.8

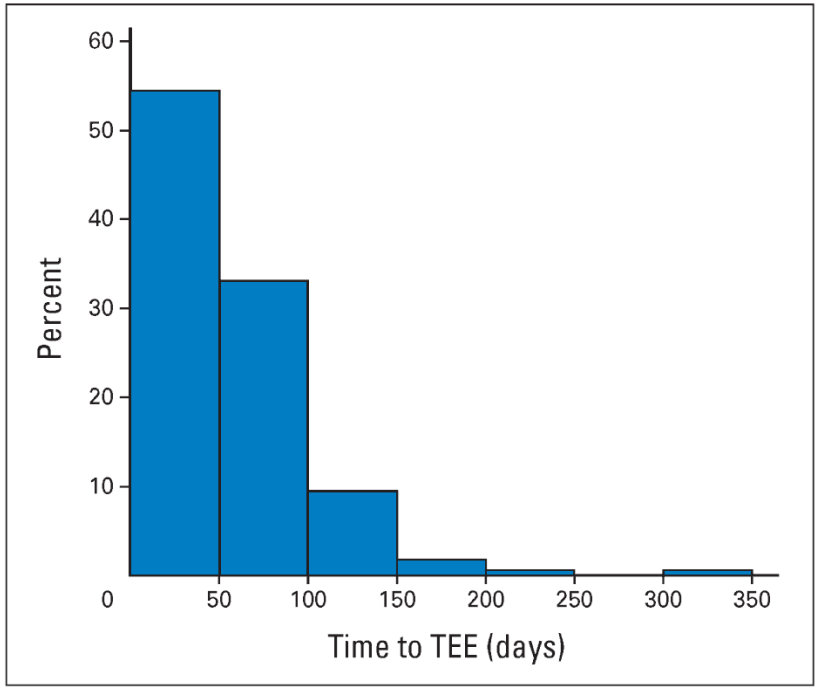


Fig 1. Time to thrombosis in patients who developed a thromboembolic event (TEE).

Chimiothérapie (et hormonothérapie)

Cancer du sein

- Toujours pendant la chimiothérapie (jamais après)

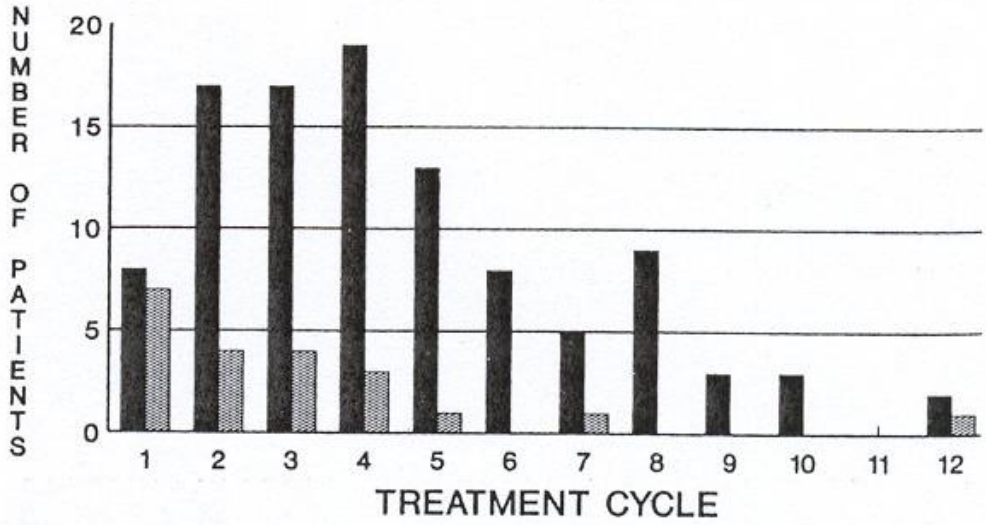


Fig 1. The 125 vascular complications that occurred during cyclic therapy. Complications on tamoxifen (three) or observation (five) were not included. (■) Venous, (▨) arterial.

Table 5. Vascular Complications Observed

	Adjuvant Therapy Patients (n = 2,352)	Observation Patients (n = 321)	Total
Venous events			
Deep venous thrombosis	73	1	74
Pulmonary emboli	31	0	31
Retinal vein thrombosis	1	0	1
Mesenteric vein thrombosis	1	0	1
Total venous events	106	1	107
Arterial events			
Cerebral vascular accidents	10	4	14
Emboli/thrombi to an extremity	11	0	11
Mesenteric artery thrombosis	1	0	1
Total arterial events	22	4	26
Total thrombotic events	128	5	133

European Journal of Cancer 120 (2019) 122–131

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Acute vascular events as a possibly related adverse event of immunotherapy: a single-institute retrospective study☆

Jair Bar [a,b,*], Gal Markel [b,c], Teodor Gottfried [a], Ruth Percik [a,b,d], Raya Leibowitz-Amit [a,b], Raanan Berger [a,b], Talia Golan [a,b], Sameh Daher [a], Alisa Taliansky [a], Elizabeth Dudnik [e], Katerina Shulman [f], Damien Urban [a,b], Amir Onn [g]

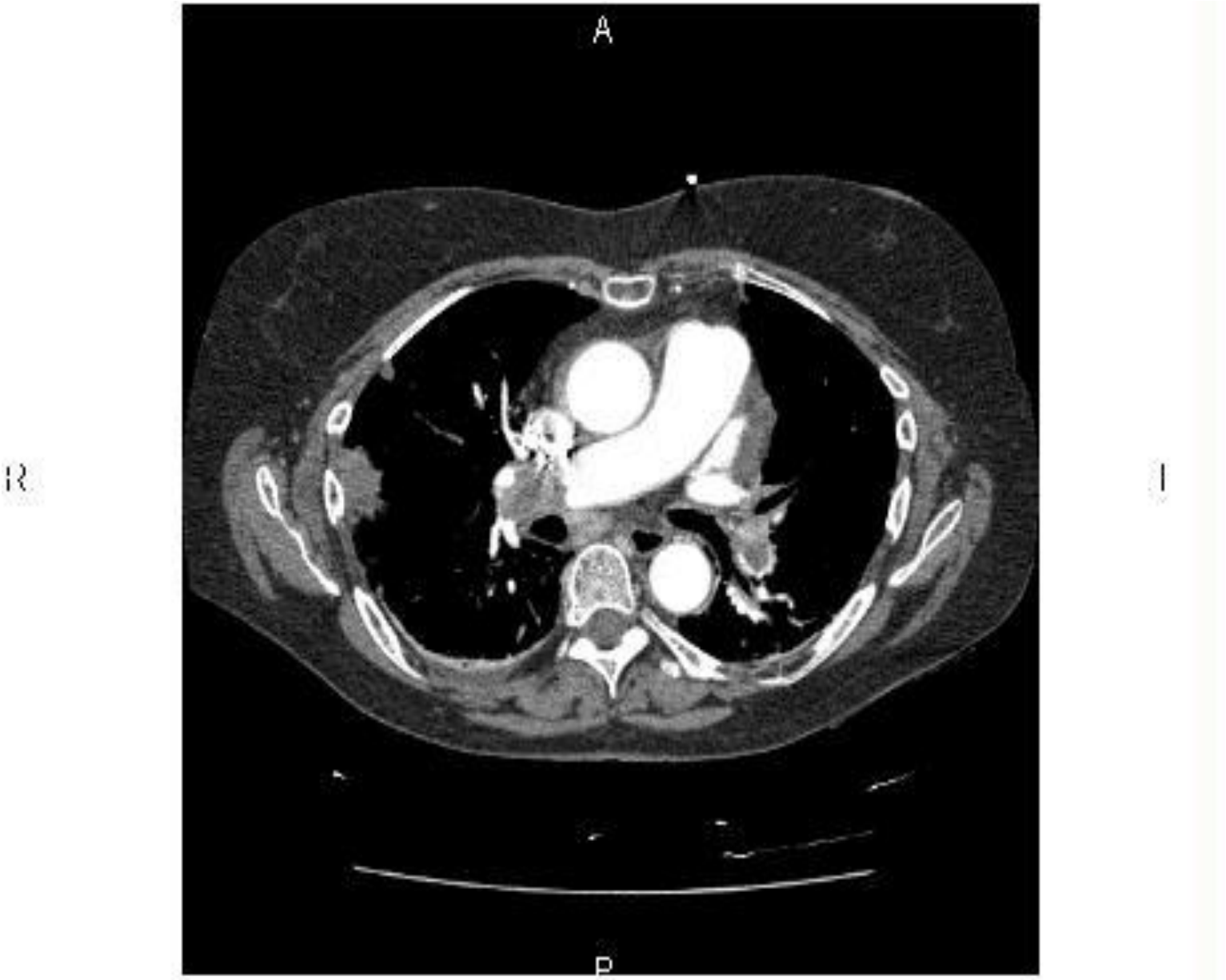
Traitement des lésions artérielles

- Attitude préventive
  - Bilan vasculaire avant traitement du cancer et traitement des lésions significatives
  - Si facteurs de risque : héparine (aspirine ?)
- Traitement
  - Interventionnel ou anticoagulation si thrombose
  - Vasodilatateurs si spasme

Attitude envers pathologie coronaire coexistante

- Une intervention précoce réduit le risque
  - Ne retarde que de deux – trois semaines le traitement du cancer
- Tenir compte des contre-indications éventuelles à thrombolyse, anti-agrégation et anti-coagulation

Les thromboses veineuses et l'embolie pulmonaire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Traitement : l'héparine de bas PM est le traitement le plus utilisé

	Meyer 2002			Lee 2003		
	HBPM	**AVK**	**p**	**HBPM**	**AVK**	**p**
N pts	71	75		338	338	
TVP				4,1 %	10,9 %	0,002
Embolie non fatale			0,04	2,4 %	2,7 %	
Embolie fatale				1,5 %	2,1 %	
Hh majeure	7 %	16 %	0,09	6 %	4 %	0,27
Hh fatale	0	8 %	0,03	0,2 %	0	
Mortalité à 6 mois	31 %	38,7 %	0,25	39 %	41 %	0,53

Research

Original Investigation

Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer
A Randomized Clinical Trial

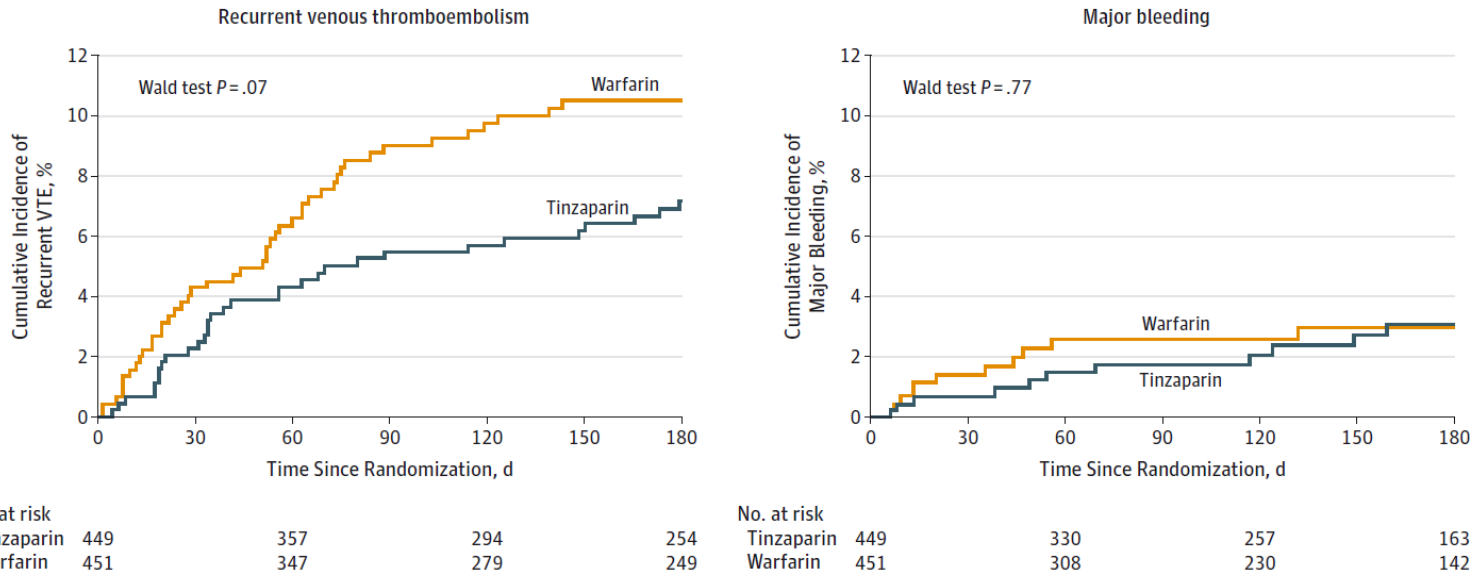
Agnes Y. Y. Lee, MD, MSc; Pieter W. Kamphuisen, MD, PhD; Guy Meyer, MD; Rupert Bauersachs, MD; Mette S. Janas, MD, PhD; Mikala F. Jarner, MSc; Alok A. Khorana, MD; for the CATCH Investigators

JAMA. 2015;314(7):677-686. doi:10.1001/jama.2015.9243

Table 1. Baseline Characteristics of Patients in the CATCH Trial

	No. (%)	
	Tinzaparin (n = 449)	Warfarin (n = 451)
Age, mean (SD), y	59.7 (12.7)	58.8 (12.5)
Sex		
Women	262 (58.4)	273 (60.5)
Men	187 (41.6)	178 (39.5)
Location		
Asia and Middle East	196 (43.7)	195 (43.2)
Eastern Europe	94 (20.9)	96 (21.3)
Western Europe and North America	75 (16.7)	75 (16.6)
Central and South America	84 (18.7)	85 (18.8)
Weight, mean (SD), kg	67.3 (17.3)	67.1 (16.3)
Creatinine clearance, mL/min/1.73 m^2		
<30	8 (1.8)	2 (0.4)
30-<60	59 (13.1)	60 (13.3)
≥60	355 (79.1)	378 (83.8)
Noncalculable due to missing data	27 (6.0)	11 (2.4)
Primary tumor site		
Gynecologic	101 (22.5)	102 (22.6)
Colorectal	66 (14.7)	53 (11.8)
Upper gastrointestinal	56 (12.5)	49 (10.9)
Lung	48 (10.7)	56 (12.4)
Genitourinary	53 (11.8)	41 (9.1)
Hematologic	44 (9.8)	50 (11.1)
Breast	37 (8.2)	47 (10.4)
Other	44 (9.8)	53 (11.8)
Known metastases	247 (55.0)	245 (54.3)
Cancer therapy[a]	228 (50.8)	248 (55.0)
Systemic medical therapy[b]	189 (42.1)	193 (42.8)
Radiation	51 (11.4)	41 (9.1)
Surgery	24 (5.3)	38 (8.4)
Hospitalization 3 d or longer[c]	140 (31.2)	146 (32.4)
Immobility[c]	33 (7.3)	45 (10.0)
ECOG performance status		
0 or 1	343 (76.4)	348 (77.2)
2	106 (23.6)	103 (22.8)
Previous history of VTE	27 (6.0)	30 (6.7)
Qualifying thrombotic event		
Symptomatic DVT	252 (56.1)	259 (57.4)
Symptomatic DVT with incidental PE	82 (18.3)	90 (20.0)
Symptomatic PE	48 (10.7)	44 (9.8)
Symptomatic PE with incidental DVT	11 (2.4)	11 (2.4)
Symptomatic PE and symptomatic DVT	48 (10.7)	32 (7.1)
No qualifying VTE	8 (1.8)	15 (3.3)

Figure 2. Cumulative Incidence Among Patients With Active Cancer According to Treatment With Tinzaparin vs Warfarin

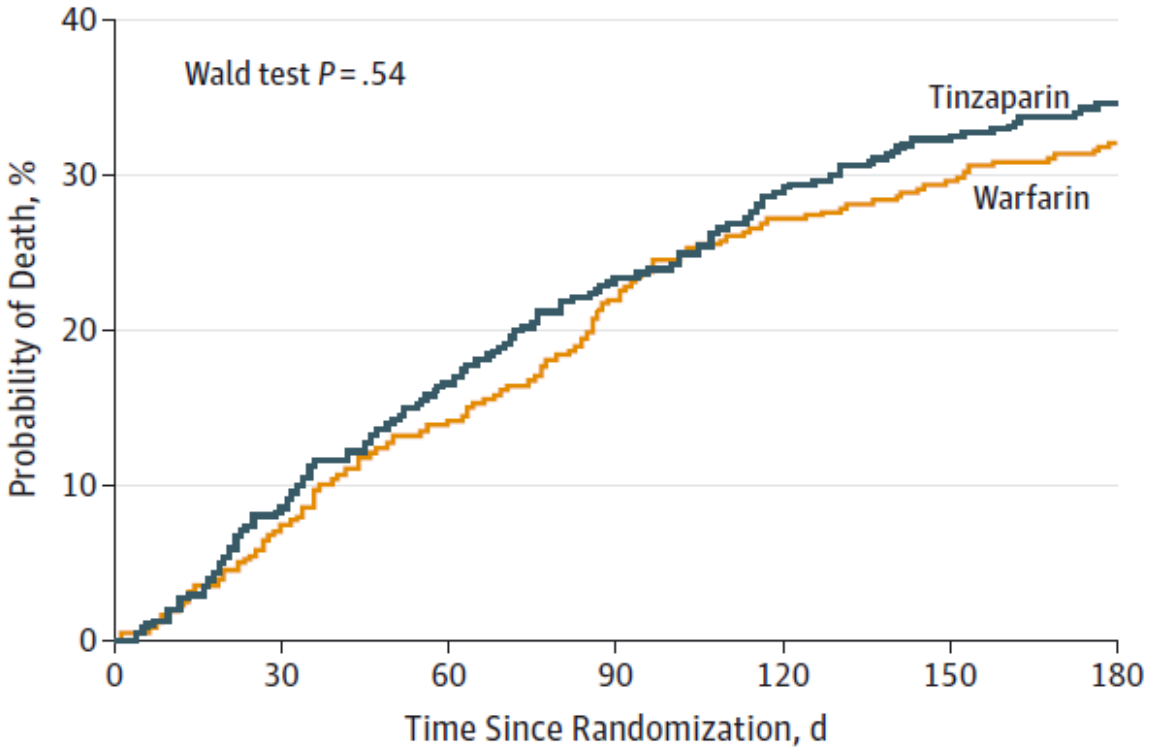


VTE indicates venous thromboembolism. Source: The left panel of Figure 2 was reproduced with permission from the American Society of Hematology.[24]

Table 2. Primary and Secondary Efficacy and Safety Outcomes in the CATCH Trial

	No. (%)			
	Tinzaparin (n = 449)	Warfarin (n = 451)	HR (95% CI)	*P* Value
Primary Efficacy Outcome				
Recurrent VTE	31 (6.9)[a]	45 (10.0)	0.65 (0.41-1.03)	.07
Secondary Efficacy Outcomes				
Symptomatic DVT[b]	12 (2.7)	24 (5.3)	0.48 (0.24-0.96)	.04
Symptomatic nonfatal PE	3 (0.7)	2 (0.4)	NA	
Fatal PE[c]	17 (3.8)	17 (3.8)	0.96 (0.49-1.88)	.89
Incidental proximal DVT	0	1 (0.2)	NA	
Incidental PE	0	1 (0.2)	NA	
Recurrent VTE, per protocol, No./total patients (%)	29/351 (8.3)	39/307 (12.7)	0.62 (0.38-1.00)	.05

Figure 3. All-Cause Mortality Among Patients With Active Cancer According to Treatment With Tinzaparin vs Warfarin



No. at risk				
Tinzaparin	449	364	303	268
Warfarin	451	371	305	273

Les NACO: apparaissent dans l'arsenal thérapeutique

JOURNAL OF CLINICAL ONCOLOGY | RAPID COMMUNICATION

Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)

Annie M. Young, Andrea Marshall, Jenny Thirlwall, Oliver Chapman, Anand Lokare, Catherine Hill, Danielle Hale, Janet A. Dunn, Gary H. Lyman, Charles Hutchinson, Peter MacCallum, Ajay Kakkar, F.D. Richard Hobbs, Stavros Petrou, Jeremy Dale, Christopher J. Poole, Anthony Maraveyas, and Mark Levine

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on May 10, 2018.

Processed as a Rapid Communication manuscript.

Written on behalf of the SELECT-D Collaborative Group

A B S T R A C T

Purpose

Venous thromboembolism (VTE) is common in patients with cancer. Long-term daily subcutaneous low molecular weight heparin has been standard treatment for such patients. The purpose of this study was to assess if an oral factor Xa inhibitor, rivaroxaban, would offer an alternative treatment for VTE in patients with cancer.

Le rivaroxaban est associé à une récurrence relativement plus faible de la maladie TEV mais à un risque d'hémorragie plus élevé par rapport à la daltéparine.

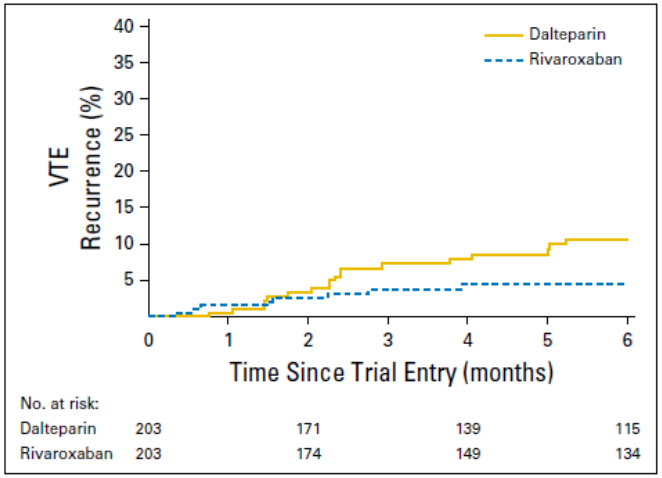


Fig 2. Time to venous thromboembolism (VTE) recurrence within 6 months.

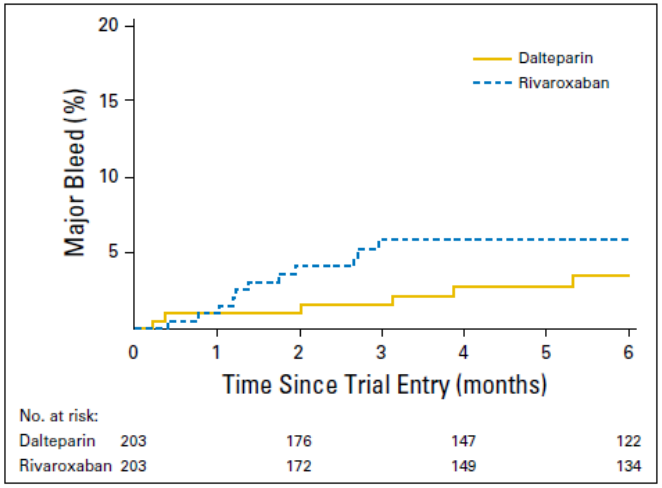


Fig 3. Time to major bleed within 6 months.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D., for the Hokusai VTE Cancer Investigators*

N Engl J Med 2018;378:615-24.
DOI: 10.1056/NEJMoa1711948

L'édoxaban par voie orale était non inférieur à la daltéparine sous-cutanée en ce qui concerne l'issue composite d'une thromboembolie veineuse récurrente ou d'un saignement important.

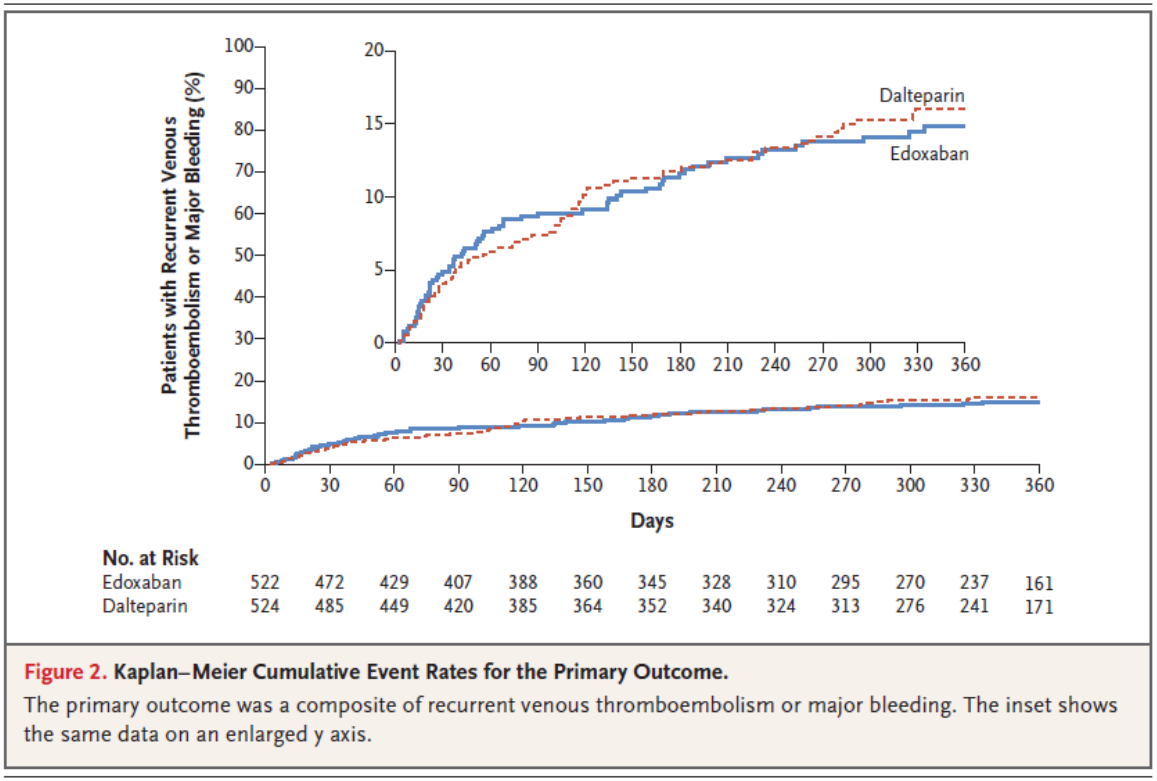


Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary Outcome.
The primary outcome was a composite of recurrent venous thromboembolism or major bleeding. The inset shows the same data on an enlarged y axis.

Le taux de thromboembolie veineuse récurrente était plus faible, mais le taux de saignements majeurs était plus élevé avec l'édoxaban qu'avec la daltéparine.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer

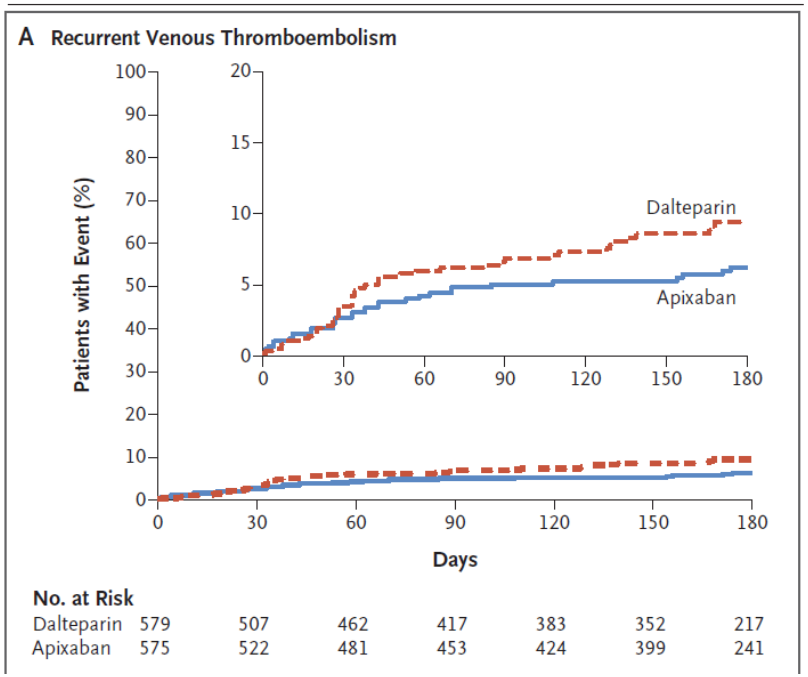
Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Guy Meyer, M.D., Andres Muñoz, M.D., Menno V. Huisman, M.D., Jean M. Connors, M.D., Alexander Cohen, M.D., Rupert Bauersachs, M.D., Benjamin Brenner, M.D., Adam Torbicki, M.D., Maria R. Sueiro, M.D., Catherine Lambert, M.D., Gualberto Gussoni, M.D., Mauro Campanini, M.D., Andrea Fontanella, M.D., Giorgio Vescovo, M.D., and Melina Verso, M.D., for the Caravaggio Investigators*

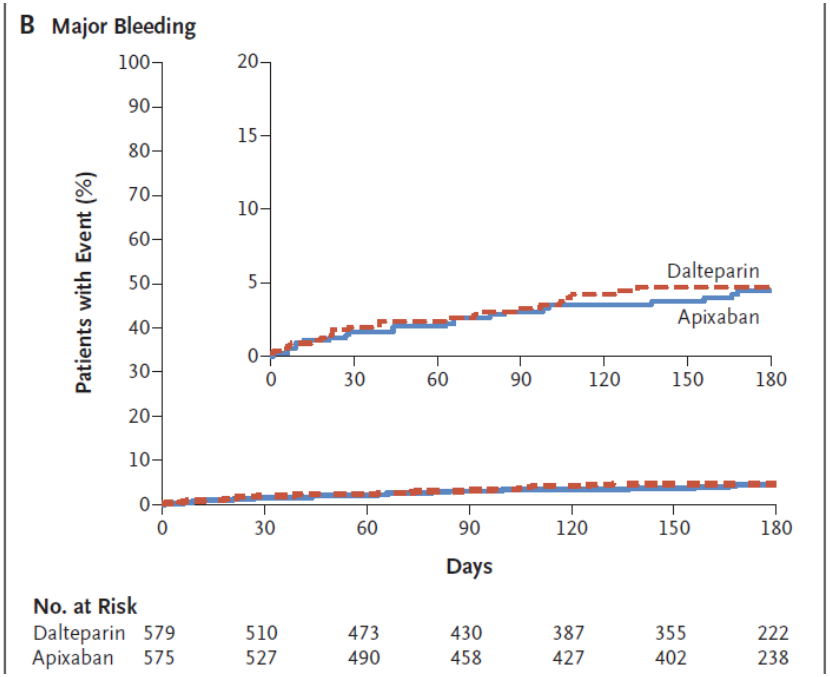
DOI: 10.1056/NEJMoa1915103

Table 2. Clinical Outcomes during the Trial Period.*

Outcome	Apixaban (N=576)	Dalteparin (N=579)	Hazard Ratio (95% CI)	P Value
Primary efficacy outcome — no. (%)†				
Recurrent venous thromboembolism‡	32 (5.6)	46 (7.9)	0.63 (0.37–1.07)	<0.001 for noninferiority; 0.09 for superiority
Recurrent deep-vein thrombosis	13 (2.3)	15 (2.6)	0.87 (0.34–2.21)	
Recurrent pulmonary embolism	19 (3.3)	32 (5.5)	0.54 (0.29–1.03)	
Fatal pulmonary embolism§	4 (0.7)	3 (0.5)	1.93 (0.40–9.41)	
Primary safety outcome — no. (%)				
Major bleeding¶	22 (3.8)	23 (4.0)	0.82 (0.40–1.69)	0.60
Major gastrointestinal bleeding	11 (1.9)	10 (1.7)	1.05 (0.44–2.50)	
Major nongastrointestinal bleeding	11 (1.9)	13 (2.2)	0.68 (0.21–2.20)	
Secondary outcomes — no. (%)				
Recurrent venous thromboembolism or major bleeding	51 (8.9)	66 (11.4)	0.70 (0.45–1.07)	
Clinically relevant nonmajor bleeding	52 (9.0)	35 (6.0)	1.42 (0.88–2.30)	
Major or clinically relevant nonmajor bleeding‖	70 (12.2)	56 (9.7)	1.16 (0.77–1.75)	
Death from any cause**	135 (23.4)	153 (26.4)	0.82 (0.62–1.09)	
Event-free survival††	422 (73.3)	397 (68.6)	1.36 (1.05–1.76)	

L'apixaban oral n’est pas inférieur à la daltéparine sous-cutanée pour le traitement de la thromboembolie veineuse associée au cancer sans risque accru d'hémorragie majeure.





Quelle durée et quand arrêter ?

- Durée : 3 à 6 mois
  - Jusqu'au contrôle du cancer? fin de la chimiothérapie ?
- Si récidive :
  - Cancer actif : jusqu'à résolution de la maladie
  - Si récidive sous AVK : avoir un PTT correct, sinon HBPM
  - Si récidive sous NACO: HBPM
  - Si récidive sous HBPM à dose réduite : HBMP à dose pleine
- Filtre cave
  - Contre-indication aux anticoagulants
  - Récidive sous anticoagulation bien conduite