DÉCLARATION DE LIENS D’INTERET AVEC LA PRÉSENTATION

Intervenant : EDERHY, Stephane, Paris

☐ Je n'ai pas de lien d'intérêt à déclarer
Cardio Oncologie :
Une nouvelle Spécialité ?
"Cardiologie interventionnelle et oncologie : problématiques"
16.00-17.30 AUDITORIUM C
SESSION PARALLÈLE 10
En partenariat avec les Intervention’Elles

Modérateur : Estelle VAUTRIN, Grenoble

Stephane Ederhy
Service de cardiologie
Hôpital Saint Antoine
stephane.ederhy@aphp.fr
Cardio Oncology

Cancer patient / Chemotherapy / clinical risk factors

Cardiotoxicity / Prevention / Treatment

Cardiovascular complications of cancer therapy

Strategies for prevention and attenuation of cardiovascular complications of cancer therapy

Onco cardiology

Long-term surveillance programs for cancer survivors
- Myocardial Dysfunction, VHD, CAD,
Cardio Oncology

Cancer patient / Chemotherapy / clinical risk factors

Onco cardiology
Sarcome de haut grade – Oreillette gauche
Cardio Oncology

Cancer patient / Chemotherapy / clinical risk factors

Cardiotoxicity / Prevention / Treatment

Cardiovascular complications of cancer therapy
Cardiovascular complications of Chemotherapy

- Hypertension
- Heart Failure
- Arterial Thrombosis
- QT prolongation

- Pulmonary Hypertension
- PAOD

GRCI 2016
Passion Communication Education
Cardiovascular complications of Chemotherapy

- Hypertension
- Heart Failure
- Arterial Thrombosis
- QT prolongation

- Anthracyclines
- Molecular Targeted Agents
- Immune Checkpoint
Cancer Therapeutics regimens associated with type I and type II Cancer therapeutics related cardiac dysfunction

Cancer

Cancer Therapeutics

Regimen potentially associated with Type 1 Toxicity

Doxorubicin
Epirubicin
Idarubicin
Mitoxantrone

Regimen potentially associated with Type 2 Toxicity

Trastuzumab
Lapatinib
Pertuzumab
Imatinib
Sorafenib
Sunitinib
Bevacizumab
Bortezomib
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type I Myocardial Damage</th>
<th>Type II Myocardial Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Doxorubicin</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Permanent damage and irreversible</td>
<td>High likelihood of recovery in 2-4 months</td>
</tr>
<tr>
<td>Dose Effects</td>
<td>Cumulative, dose related</td>
<td>Not dose related</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Free Radical formation</td>
<td>Blocker ErbB2 signaling</td>
</tr>
<tr>
<td></td>
<td>Oxidative stress/damage</td>
<td></td>
</tr>
<tr>
<td>Ultrastructure</td>
<td>Necrosis</td>
<td>No ultrastructural abnormalities</td>
</tr>
<tr>
<td>Non invasive cardiac testing</td>
<td>Decreased EF</td>
<td>Decreased EF</td>
</tr>
<tr>
<td>Effect of rechallenge</td>
<td>High probability of recurrence</td>
<td>Relative safety of rechallenge</td>
</tr>
</tbody>
</table>

Incidence of Heart Failure with Doxorubicin

Cumulative dose of doxorubicin in mg/m²

30% Asymptomatics
### Incidence of HF episode and molecular targeted agents

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tyrosine Kinase Inhibitors Antibodies</strong></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>1.7 to 3%</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>2 to 28%</td>
</tr>
<tr>
<td><strong>Proteosome inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Bortezomib (Velcade)</td>
<td>2 to 5%</td>
</tr>
<tr>
<td><strong>Tyrosine kinase Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Dasatinib (Sprycel)</td>
<td>2 to 4%</td>
</tr>
<tr>
<td>Imatinib (Gleevec)</td>
<td>0.5 to 1.7%</td>
</tr>
<tr>
<td>Lapatinib (Tykerb)</td>
<td>1.5 to 2.2%</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>2.7 to 11%</td>
</tr>
</tbody>
</table>

Yeh et al. J Am Coll Cardiol 2009;24,2231-2247
Cardio Oncology

Cancer patient / Chemotherapy / clinical risk factors

Cardiotoxicity / Prevention / Treatment

Strategies for prevention and attenuation of cardiovascular complications of cancer therapy
Primary vs Secondary prevention

Cardiotoxic chemotherapy

Prevention strategy

Primary prevention
All pts already treated with cardiotoxic chemo

Secondary prevention
Preclinical signs?
Biomarker increase?
Echo parameters?
Which strategy for primary prevention

- Cardiotoxic chemotherapy

Primary prevention

- Beta blockers
- MRA
- ARBs
- Combination Therapy
- Statins
Angiotensin II-receptor inhibition with candesartan to prevent trastuzumab related cardiotoxic effects in patients with early breast cancer

Cumulative 2-year incidences of cardiac events for the patients assigned to candesartan and those assigned to placebo

Boekhout A JAMA Oncology 2016;2:1030-1307
Initiation of regiment potentially associated with type I toxicity

Baseline LVEF
3DE (preferred) / 2 DE (consider contrast)
GLS, Troponin

LVEF < 53%
GLS < LLN
+ Troponin > 0
Consider CMR
Cardiology Consultation

LVEF > 53%
GLS > LLN
+ Troponin < 0
F/U at completion and 6 months later
Initiation of regiment potentially associated with type I toxicity

Baseline LVEF
3DE (prefered) / 2 DE (consider contrast)
GLS, Troponin

LVEF < 53% GLS < LLN + Troponins > 0
Consider CMR
Cardiology Consultation

LVEF > 53% GLS > LLN + Troponins < 0
F/U at completion and 6 months later

Treat? (ESC 2016) ACE i, BB, ARB, MRA
Targeting the VEGF Pathway

- Anti-VEGF (Bev)
- Anti-VEGFR-2
- VEGF Receptor
- VEGF Trap
- Kinase Inhibitors
- Aptamer
Mécanismes Hypertension Artérielle

Voie Du NO

A

- VEGF-A
- VEGF receptor 2
- Anti-VEGF antibody
- Tyrosine kinase inhibitor
- Endothelin(ET)-1
- ET_A receptor

Smooth muscle cell
Endothelial cell

PI3K-AKT eNOS NO
GMP sGC

Vasodilation
Hypertension

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Mécanismes Hypertension Arterielle
Raréfaction Capillaire

B

Capillary beds

Capillary rarefaction

Hypertension

VEGF-A

VEGF receptor 2

Anti-VEGF antibody

Tyrosine kinase inhibitor

Endothelin(ET)-1

$\text{ET}_\text{A}$ receptor

Smooth muscle cell

Endothelial cell
<table>
<thead>
<tr>
<th>Chimiotherapie</th>
<th>Incidence HTA Tous Grades</th>
<th>Incidence grade &gt; 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercet</td>
<td>46 %</td>
<td>18 %</td>
</tr>
<tr>
<td>Axitinib</td>
<td>30 %</td>
<td>5 %</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>22 %</td>
<td>11 %</td>
</tr>
<tr>
<td>Cediranib</td>
<td>72 %</td>
<td>33 %</td>
</tr>
<tr>
<td>Motesanib</td>
<td>56 %</td>
<td>25 %</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>37 %</td>
<td>8 %</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>17 %</td>
<td>4 %</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>24 %</td>
<td>8 %</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>21 %</td>
<td>2 %</td>
</tr>
</tbody>
</table>
## Prise en charge de la HTA sous Therapie ciblée
### Principe généraux

<table>
<thead>
<tr>
<th>NCI CTCAE v 4</th>
<th>Therapie Ciblée</th>
<th>Modification Dose</th>
<th>Dose Cycle suivant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0-2</td>
<td>Poursuivre</td>
<td>Non</td>
<td>Pas de chgt</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Retarder jusqu'à grade ≤ 2</td>
<td>Réduire d'un pallier</td>
<td>Tox ≤G2 discuter augmentation dose</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Retarde jusqu'à grade ≤ 2</td>
<td>Réduire d'un pallier Envisager interruption définitive</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose 0</th>
<th>Dose 1</th>
<th>Dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>160 mg</td>
<td>120 mg</td>
<td>80 mg</td>
</tr>
</tbody>
</table>

**Si Arrêt nécessaire du TMC > 4 semaine, stop prescription**
Molecular targeted agents and QT prolongation

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HDAC inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Vorinostat (Zolinza)</td>
<td>3.5 to 6 %</td>
</tr>
<tr>
<td><strong>Tyrosine kinase Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Dasatinib (Sprycel)</td>
<td>&lt; 1-3 %</td>
</tr>
<tr>
<td>Lapatinib (Tykerb)</td>
<td>16 %</td>
</tr>
<tr>
<td>Nilotinib (Tasigna)</td>
<td>1 to 10 %</td>
</tr>
</tbody>
</table>

Yeh et al. J Am Coll Cardiol 2009;24,2231-2247
Torsades de pointes - ECG
Initiation traitement
Examen clinique : Asymptomatique ?
HTA ?, ICA ?, DT ?
Ordonnance ?
Inhibiteur CYP3A4 ?
ECG : QT m / QTc F
métabolisme : K+ / Mg 2+ Fonction hépatique

Suivi
Examen clinique : Asymptomatique ?
ECG : D7, périodique, après changement dose
surveillance K+ / Mg 2+

Stop Nilotinib
Si Symptomatique
Si QTcF > 480 msec
Ponatinib et événement cardio vasculaire

- SCA: 12%
- AVC: 6%
- AOMI: 8%
- MVTE: 5%
Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial

<table>
<thead>
<tr>
<th></th>
<th>Nilotinib 300 mg x 2 N=279 N(%)</th>
<th>Nilotinib 400 mg x 2 N=277 N(%)</th>
<th>Imatinib 400 mg N=280 N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
<td>Any grade</td>
</tr>
<tr>
<td>HTN</td>
<td>29 (10.4)</td>
<td>4 (1.4)</td>
<td>23 (8.3)</td>
</tr>
<tr>
<td>Symp QTc prolongation</td>
<td>5 (1.8)</td>
<td>2 (0.7)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>11 (3.9)</td>
<td>6 (2.2)</td>
<td>24 (8.7)</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>4 (1.4)</td>
<td>3 (1.1)</td>
<td>9 (3.2)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>7 (2.5)</td>
<td>4 (1.4)</td>
<td>7 (2.5)</td>
</tr>
</tbody>
</table>
Gestion du risque d'événements cardiovasculaire sous Nilotinib au cours des LMC

<table>
<thead>
<tr>
<th>LMC-PC Diagnostic</th>
<th>Risque CV</th>
<th>Options thérapeutiques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokal : Faible / intermédiaire Et pas d’ACA</td>
<td>Faible / Moyen</td>
<td>Imatinib ou Nilotinib</td>
</tr>
<tr>
<td>Sokal : Faible / intermédiaire Et pas d’ACA</td>
<td>Elevé / Très Elevé</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Sokal : Elevé ou Présence d’ACA</td>
<td>Faible / Moyen</td>
<td>Nilotinib ou Imatinib</td>
</tr>
<tr>
<td>Sokal : Elevé ou Présence d’ACA</td>
<td>Elevé / Très élevé</td>
<td>Imatinib ou discuter Nilotinib</td>
</tr>
</tbody>
</table>
Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation
1279 HL pts treated with mediastinal irradiation, Median FU = 14.7 y,
636 cardiac events in 187 pts

Cardiac diagnoses adjusted for competing risk of death

Algorithm for patient management after chest radiotherapy

1. Baseline pre radiation Echocardiography
2. Chest Radiation Exposure
3. Yearly clinical history and physical examination
   - Screen for modifiable risk factors
     - Correct risk factors
4. Search for signs and symptoms suggestive of:
   - Pericardial effusion/constriction
   - VHD
   - LVSD/HF
   - CAD
   - Conduction system disease
   - Carotid artery disease
5. Echocardiography
   - CMR/CT if constriction
6. Carotid US
7. Asymptomatic
   - Screening Echocardiography 5 years after exposure in high risk patients
   - 10 year after exposure in the others
8. Functional non invasive stress test for CAD (5 to 10 years after exposure in high risk patients)
9. Re-assess every 5 years
Cardio Oncology

Cancer patient / Chemotherapy / clinical risk factors

Cardiotoxicity / Prevention / Treatment

Long-term surveillance programs for cancer survivors.
Myocardial Dysfunction, VHD, CAD.
Shared Risk factors in cardiovascular disease and cancer
Cardiac mortality among 200,000 five-year survivors of cancer diagnosed at 15 to 39 years of age:

Cumulative mortality from cardiac disease among 5-year survivors of Hodgkin lymphoma according to attained age by age at cancer diagnosis.

Cancer patients with cardiovascular disease have survival rates comparable to patients within the age-cohort of 10 years older without cardiovascular morbidity.

Crude survival according to the presence of cardiovascular disease and age.

Janssen-Heijnen critical Reviews in oncology/hematology 2009
Short- and Long-term cause of death in patients treated with primary PCI for STEMI

Kaplan Meier curves showing all cause mortality, non cardiac mortality and cardiac mortality. Long-term mortality of patients with STEMI after PCI.

Pedersen J Am Coll Cardiol 2014; 64: 2101-8
## Cardiotoxicity and coronary artery disease

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanisms</th>
<th>Risk of CAD and ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoropyrimides (5FU, Capecitabine, Gemcitabine)</td>
<td>Endothelial injury Vasospasm</td>
<td>Up to 18% manifest myocardial ischemia Up to 7-10% silent myocardial ischemia</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Procoagulant status Arterial thrombosis</td>
<td>20 year absolute risk of up to 8% after testicular cancer 2% risk of arterial thrombosis</td>
</tr>
<tr>
<td>VEGF inhibitors (Bevacizumab, Sorafenib, Sunitinib)</td>
<td>Procoagulant status Arterial thrombosis Endothelial injury</td>
<td>Risk of arterial thrombosis; bevacizumab 3.8%, Sorafenib 1.7%, Sunitinib 0.4%</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Endothelail injury Plaque rupture Thrombosis</td>
<td>2-7 increase RR of AMI Cumulative 30 year coronary events incidence of 10% in HLS Risk proportional to irradiation dose</td>
</tr>
</tbody>
</table>
Outcomes after PCI in cancer patients

A. CV mortality, 31.4% vs. 27.7%, p=0.31
B. CV mortality, ML, or repeat revascularisation, 51.1% vs. 55.8%, p=0.37
C. CV mortality, 26.0% vs. 27.7%, p=0.19
D. CV mortality, ML, or repeat revascularisation, 45.5% vs. 55.7%, p=0.40
Outcome after ST elevation myocardial infarction in patients with cancer treated with PCI

Velders Am J Cardiol 2013; 112: 1867 - 1872
In-hospital outcomes and 5-year cause-specific mortality of cancer patients admitted for an acute myocardial infarction.
The French Registry on Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) 2005 Cohort

Cardiovascular death

Whole AMI population
No History of cancer
History of cancer
Adjusted HR : 1.09, 0.81-1.47, P<0.05

STEMI population
No History of cancer
History of cancer
Adjusted HR : 1.11, 0.69-1.78, P=0.67

Non Cardiovascular death

Whole AMI population
No History of cancer
History of cancer
Adjusted HR : 2.47, 1.73-3.52, P<0.001

NSTEMI population
No History of cancer
History of cancer
Adjusted HR : 1.72, 1.06-2.78, P=0.03

STEMI population
No History of cancer
History of cancer
Adjusted HR : 4.02, 2.33-6.94, P<0.001

A history of cancer per se does not appear to be a risk factor for increased in hospital mortality, or long-term cardiovascular mortality in patients admitted for acute myocardial infarction.

Ederhy S, Simon T, Danchin N on behalf the FAST MI 2005 investigators
Cardio Oncology

Prevention and Life style Interventions

- Epidemiology and registry research (cancer survivors)
- Educational and training of cardiology and oncology health team

CV burden
- CV health and CVRF
- Host and cancer treatment

Guidelines and clinical practice standards

Basic translational and clinical research (Imaging, Biomarkers)

Oncology clinical trial With comprehensive CV safety Data

Adapted from Barac J Am Coll Cardiol 2015; 65: 2739 - 46
An Invitation from the Editors of Cardio-Oncology

Steven E. Lipshultz,1,2 Giorgio Minotti,3 Joseph Caver4 and Vivian I. Franco1

Advances in cancer treatments have brought hope to patients with these diseases once thought to be incurable. However, these same treatments can inadvertently harm healthy cells and affect systems unrelated to the cancer, especially the cardiovascular system [1]. A precise definition of cardiotoxicity is still lacking [2]. However, an overwhelming body of evidence has established that patients exposed to antineumor therapies have several laboratory or clinical indices of cardiovascular dysfunction and that become more evident as patients live longer. As a result, patients with cancer who have or who are at risk of cardiovascular toxicity are now being treated collaboratively by oncologists-hematologists, radiation therapists, and cardiologists, which has led to a new interdisciplinary field, cardio-oncology.

The journal Cardio-Oncology is a dedicated forum for oncologists, cardiologists, researchers, and other health care providers who care for patients who have survived or who are being treated for cancer. It also provides the opportunity for the latest and highest quality evidence in this emerging field to be widely shared in the medical community. The mission of Cardio-Oncology is to publish research that addresses the balance between curing cancer and limiting the adverse cardiovascular effects of cancer treatment. To achieve this mission, we welcome a broad range of original research and review articles addressing many questions in this complex field from a multidisciplinary approach. Cardio-oncology has many areas of research. Here, we highlight some of the more pressing issues in the field and invite authors to submit for publication their work on these and other issues.

First, we have to better understand the risks of cardiovascular toxicity to establish effective prevention and surveillance protocols. A lack of awareness or underestimating the cardiovascular risks of cancer treatment among clinicians can inadvertently harm the patient in the long term. Many risk factors for cardiovascular toxicity have been identified in cancer patients during and after treatment. These factors include a cumulative dose of anthracycline (≥400 mg/m² for adults ≥18 years old) and ≥300 mg/m² for children ≤18 years old) [3], concurrent radiation therapy, younger or older age at diagnosis, female sex, black race, and the presence of other cardiovascular comorbidities.

However, the differences between patients who do and do not develop cardiotoxicity are substantial, even if they have some of the same risk factors. To explain these differences, investigators have explored possible genetic involvement. For example, hereditary hemochromatosis is a genetic disorder of iron metabolism that leads to iron overload-associated tissue injury. In this disorder, gene mutations in the C282Y allele are associated with myocardial injury in anthracycline-treated survivors of childhood acute lymphoblastic leukemia [4]. This mutation might cause excess iron accumulation in cardiac cells and increase the heart's vulnerability to damage from free radicals formed by the divalent-cation iron complexes, but the actual mechanisms are not known. Another study found an increased risk of cardiomyopathy in patients exposed to low-to-moderate doses of anthracyclines. These patients were homozygous for the G allele in the carnitine palmitoyltransferase 3 gene and presumably formed higher levels of a toxic anthracycline metabolite [5].

Although additional studies are needed to validate these genetic risk factors, behavioral risks, such as smoking, physical inactivity, excess body weight, and alcohol consumption, also deserve further exploration and are becoming increasingly important as survival increases in number and in age.

It is also necessary to understand the pathophysiology and mechanisms of cardiotoxicity in both old and new treatment regimens. Multiple mechanisms of cardiotoxicity have been proposed for anthracyclines, but less is known about other chemotherapeutics or the new generation of "targeted" drugs. Lessons from treatment...
11.6 Cancer

Certain chemotherapeutic agents can cause (or aggravate) LV systolic dysfunction and HF. The best recognized of these are the anthracyclines (e.g. doxorubicin) and trastuzumab. Dexrazoxane may confer some cardioprotection in patients receiving anthracyclines. Pre- and post-evaluation of EF is essential in patients receiving cardiotoxic chemotherapy, as detailed elsewhere. Patients developing LV systolic dysfunction should not receive further chemotherapy and should receive standard treatment for HF-REF. Mediastinal irradiation can also lead to a variety of long-term cardiac complications, although the less frequent use of high-dose, wide-field radiotherapy has led to a decline in these problems.
Patients with malignancies are at increased risk for thrombo-embolic events.

Many forms of cancer interact directly or indirectly with the coagulation system. Some tumours directly secrete pro-thrombotic factors, while others induce inflammatory reactions either through humoral or direct interaction with the immune system. The increased risk for thromboembolism justifies consideration of established anticoagulant therapy.

Cancer therapy inflicts bleeding risks.

Every form of cancer therapy, be it surgery, irradiation, or chemotherapy, may induce a bleeding through local wounds (surgery).
had diabetes mellitus, previous MI or prior PCI. Thirty-day death or MI was less frequent among patients with non-obstructive CAD (2.2%) vs. obstructive CAD (13.3%) [adjusted OR 0.15 (95% CI 0.11, 0.20)]. Thirty-day death or MI and 1-month mortality were also lower among patients with non-obstructive CAD [adjusted OR 0.19 (95% CI 0.14, 0.25) and adjusted OR 0.37 (95% CI 0.28, 0.49), respectively]. \(^{332}\) While invasive evaluation and, if appropriate and feasible, revascularization is indicated in patients at high ischemic risk, in a proportion of them this strategy is not offered because of the perception that patients might not benefit in terms of event reduction—due to the estimated increased risk related to coronary angiography and/or revascularization—or quality of life. Patients in whom an invasive strategy may be withheld by the treating physicians may include very elderly or frail patients (section 5.8.1); patients with comorbidities such as dementia, severe chronic renal insufficiency (section 5.8.3) or cancer and patients at high risk of bleeding complications (section 4.3). Usually these patient categories have been excluded from RCTs.

With respect to oral antplatelet therapy in the context of medically managed NSTE-ACS, the CURE study randomized 12,562 patients to clopidogrel or placebo in addition to aspirin for 3–12 months (mean duration of treatment 9 months). The majority of patients were treated conservatively, while <40% underwent coronary revascularization during the study period. The primary outcome, a composite of death from CV causes, non-fatal MI or stroke at 1 year, occurred in 9.3% of the patients in the clopidogrel group and 11.4% of the patients in the placebo group [RR 0.80 (95% CI 0.72, 0.90), P < 0.001]. There were significantly more patients with major bleeds in the clopidogrel group than in the placebo group [3.7% vs. 2.7%: RR 1.38 (95% CI 1.13, 1.67), P = 0.001]. \(^{337}\) A registry looked (95% CI 0.61, 0.93), P = 0.01). The incidence of non-CAE major bleeds was numerically higher in the ticagrelor-treated patients [2.8% vs. 2.2%; HR 1.33 (95% CI 0.91, 1.94), P = 0.142]. \(^{332}\)

5.6.4.1.2 CAD not amenable to revascularization. Data regarding patients with ACS who are not amenable to revascularization due to severe/diffuse CAD are sparse. The available observational studies included mainly patients with stable CAD and refractory angina.\(^{336,337}\) Although the prognosis differs according to patient characteristics (e.g., age, prior CABG or PCI, LV dysfunction, congestive heart failure), overall, patients not amenable to revascularization have higher mortality compared with patients who are revascularized.\(^{8,39}\) The main objective of pharmacological treatment is relief from refractory angina, as detailed in the 2013 ESC guidelines on the management of stable CAD.\(^{63}\)

5.6.4.2 In patients with normal coronary angiogram (see Web addenda) Tako-Tscho cardiomyopathy, non-CAD-associated coronary thrombosis, vasospasm and microvascular disease may all cause NSTE-ACS. While these conditions have been extensively covered in the 2013 ESC guidelines on the management of stable CAD, the most relevant features are summarised in the Web addenda.\(^{63}\)

5.6.5 Percutaneous coronary intervention

5.6.5.1 Technical aspects and challenges

Although suspected or confirmed NSTE-ACS represents the most frequent indication for coronary angiography and PCI worldwide, few studies focus on the technical aspects of PCI in this setting. Hence information on PCI techniques and outcomes has to be derived largely from observational studies and registries.
2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

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2.12 Oncology and the heart
Objectives26,27

- To develop knowledge of the manifestations of primary, benign and malignant, and metastatic cardiac tumours;
- To evaluate cardiovascular effects of malignancies and cancer therapies (chemotherapy, radiotherapy, and cancer surgery);
- To participate in the management of patients with tumors involving the heart and with cardiovascular complications associated with the treatment of non-cardiac malignancies.

Knowledge

- Symptoms and signs of cardiac tumours, including systemic and embolic manifestations;
- Classification, diagnosis, and therapy of primary and metastatic cardiac tumours;
- Effects of tumours on coagulation and the occurrence of thromboembolism;
- Obstruction to blood flow induced by proliferative processes (e.g. vena cava syndrome, atrial myxoma, pulmonary artery compression);
- Effects of thoracic radiotherapy on the pericardium, myocardium, conducting system, and coronary arteries;
- Cardiac toxicity associated with cancer therapy: e.g. anthracyclines, trastuzumab, and protein kinase targeted therapeutics;
- Other adverse effects of chemotherapeutic drugs: myocardial ischaemia; thrombosis, and embolism; altered BP; rhythm and conduction disturbances: bradycardia and heart block, tachycardia, arrhythmias;
- Complications of permanent venous access devices;
- Strategies for preventing adverse effects of chemotherapeutic drugs (e.g. statins).

Skills

The ability to:

- use appropriate imaging modalities for diagnosing primary and metastatic tumours and for differentiating tumours from non-neoplastic cardiac masses such as thrombi or vegetations, or aberrant variants of normal structures;
- evaluate the cardiovascular system of patients prior to cancer therapy;
- evaluate the cardiovascular system of patients during and after cancer therapy;
- follow-up and treat oncologic patients with cardiovascular complications.

Behaviours and attitudes

- Team working with general practitioners, oncologists, oncological nurses, radiologists, and surgeons;
- Willingness to refer the oncological patient for invasive cardiac evaluation and cardiac biopsy when indicated;
- Empathetic and supportive approach towards the psychologically vulnerable oncological patient.
Torsades de pointes - ECG
### Classification ESC 2012 du risque de mortalité cardiovasculaire globale à 10 ans

<table>
<thead>
<tr>
<th>Groupe de risque</th>
<th>Au moins 1 des items suivants</th>
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| Très élevé       | Maladie cardiovasculaire documentée  
                  | Infarctus du myocarde  
                  | Syndrome coronarien  
                  | Accident vasculaire cérébral ischémique  
                  | Artériopathie périphérique  
                  | Revascularisation artérielle  
                  | Diabète avec au moins 1 autre facteur de risque cardiovasculaire majeur ou atteinte microvasculaire  
                  | Insuffisance rénale chronique sévère  
                  | SCORE<sup>a</sup> ≥ 10 % |
| Élevé            | Un facteur de risque majeur très élevé  
                  | (HTA sévère, dyslipidémie familiale)  
                  | Diabète sans autre facteur de risque cardiovasculaire majeur et sans atteinte microvasculaire  
                  | Insuffisance rénale chronique modérée  
                  | SCORE<sup>a</sup> ≥ 5 % et ≤ 10 % |
| Moyen            | SCORE<sup>a</sup> ≥ 1 % et ≤ 5 % |
| Faible           | SCORE<sup>a</sup> ≤ 1 % |