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SUPPLEMENTARY INFORMATION

In format as provided by the authors

Vascular toxic effects of cancer therapies

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Supplementary Table 1 | **Society guidelines for the management of abnormal vasoreactivity** (peripheral and coronary vasospasm as well as microvascular angina)

Cardio-Oncology perspective	Guideline recommendation
Adopt recommendations	**2017 European Society for Vascular Medicine (ESVM) guidelines – the diagnosis and management of Raynaud's phenomenon[1,a]** • Lifestyle change is an effective means of controlling RP attacks and should include dressing warmly, ceasing smoking, avoiding triggers such as cold, and an occupational therapy assessment for aids if difficulties are reported (*Grade IIa – Level C).* • Calcium channel blockers are the recommended first line drug treatment for RP, if lifestyle modification alone has failed (*Grade I – Level A)* • Nifedipine in slow release form should be used to minimize debilitating vasodilatory side effects and short duration of action. Care should be taken to increase dosage by increments to avoid side effects. If side effects are not severe, patients should be encouraged to tolerate them for two to three weeks as they may subside (*Grade IIa – Level C).*
Adopt recommendations	**2014 AHA/ACC Guideline for the management of patients with non–st-elevation acute coronary syndromes[2,b]** For vasospastic (Prinzmetal) angina • Recommend CCBs alone or in combination with nitrates (class I, LOE B) • Recommend HMG-CoA reductase inhibitor, cessation of tobacco use, and atherosclerosis risk factor modification (class I, LOE B) • Recommend coronary angiography (invasive or noninvasive) for episodic chest pain with transient ST-elevation to detect severe CAD (class I, LOE C) • Provocative testing during invasive coronary angiography may be considered for suspected vaso-spastic angina when clinical criteria and noninvasive assessment fail to determine diagnosis (class IIb, LOE B)
Adopt recommendations	**2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation[3, c]** • In patients with suspected/confirmed vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided (class IIa, LOE B)

Cardio-Oncology perspective	Guideline recommendation
Adopt recommendations	**2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes[4, d]** • An ECG is recommended during angina if possible (class I, LOE C) • Invasive angiography or coronary CTA is recommended in patients with characteristic episodic resting angina and ST-segment changes, which resolve with nitrates and/or calcium antagonists, to determine the extent of underlying coronary disease (class I, LOE C) • Ambulatory ECG recording, preferably monitoring with 12 lead ECG, should be considered in patients with suspected vasospastic angina (class IIa, LOE C) • Ambulatory ST-segment monitoring should be considered to identify ST-segment deviation in the absence of increased heart rate (Class IIa, LOE C) • An intracoronary provocation test should be considered to identify coronary spasm in patients with normal findings or non-obstructive lesions on coronary arteriography and a clinical picture of coronary spasm, to diagnose the site and mode of spasm (class IIa, LOE B)
Adopt recommendations	For Microvascular angina • Guidewire-based CFR and/or microcirculatory resistance measurements should be considered in patients with persistent symptoms, but coronary arteries that are either angiographically normal or have moderate stenoses with preserved iwFR/FFR (class IIa, LOE B) • Intracoronary acetylcholine with ECG monitoring may be considered during angiography, if coronary arteries are either angiographically normal or have moderate stenoses with preserved iwFR/FFR, to assess microvascular vasospasm (class IIb, LOE B) • Transthoracic Doppler of the LAD, CMR, and PET may be considered for non-invasive assessment of CFR (class IIb, LOE B)

[a]Reprinted with permission from REF.[1], Hogrefe/VASA. [b]Reprinted with permission from REF.[2], Elsevier. [c]Reprinted with permission from REF.[3], Oxford University Press. [d]Reprinted with permission from REF.[4], Oxford University Press.

Supplementary Table 2 | **Society guidelines for acute ischemic (thrombotic) events in coronary, carotid, and peripheral arteries**

Cardio-Oncology perspective	Guideline recommendation
	2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation[5, a]
Adopt recommendations if within the goals of care and bleeding risk is not prohibitive	• Reperfusion therapy is indicated in all patients with symptoms of ischaemia of <=12 h duration and persistent ST-segment elevation. I A • If primary PCI cannot be performed in a timely way after STEMI diagnosis, fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications. I A • In asymptomatic patients, routine PCI of an occluded infarct-related artery (IRA) >48 h after onset of STEMI is not indicated. III A
Discussion of DES over BMS (see text)	Primary PCI strategy • Primary PCI of the IRA is indicated. I A • Stenting is recommended (over balloon angioplasty) for primary PCI. I A • Stenting with new-generation DES is recommended over BMS for primary PCI. I A • Radial access is recommended over femoral access if performed by an experienced radial operator. I A • Routine use of thrombus aspiration is not recommended. III A • Routine use of deferred stenting is not recommended. III B
Trials in patients at high bleeding risk have generally used clopidogrel	Antithrombotic therapy • A potent P2Y12 inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. I A • Aspirin oral or i.v. (if unable to swallow) is recommended as soon as possible for all patients without contraindications. I B • Fondaparinux is not recommended for primary PCI. III B

Careful review of contraindications in patients with cancer	Fibrinolytic therapy • When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEMI diagnosis, preferably in the pre-hospital setting.I A • A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended. I B • Oral or i.v. aspirin is indicated. I B • Clopidogrel is indicated in addition to aspirin. I A • Anticoagulation is recommended in patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. I A The anticoagulant can be: • Enoxaparin i.v. followed by s.c. (preferred over UFH). I A • UFH given as a weight-adjusted i.v. bolus followed by infusion. I B • Transfer to a PCI-capable centre following fibrinolysis is indicated in all patients immediately after fibrinolysis. I A • Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock. I A • Rescue PCI is indicated immediately when fibrinolysis has failed (<50% ST-segment resolution at 60–90 min) or at any time in the presence of haemodynamic or electrical instability, or worsening ischaemia. I A • Angiography and PCI of the IRA, if indicated, is recommended between 2–24 h after successful fibrinolysis. I A • Emergency angiography and PCI if needed is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis. I B
Adopt recommendations	Imaging in STEMI patients • Routine echocardiography during hospital stay to assess resting LV and RV function, detect early post-MI mechanical complications, and exclude LV thrombus is recommended in all patients. I B
Adopt recommendations	Behavioural aspects after STEMI • It is recommended to identify smokers and provide repeated advice on stopping, with offers to help with the use of follow-up support, nicotine replacement therapies, varenicline, and bupropion individually or in combination. I A • Participation in a cardiac rehabilitation programme is recommended. I A

Adopt recommendations	Maintenance antithrombotic strategy after STEMI • Antiplatelet therapy with low-dose aspirin (75–100 mg) is indicated. I A • DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contraindicated) is recommended for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding. I A • A PPI in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding. I B
Adopt all of the following recommendations	Routine therapies in the acute, subacute, and long-term phases • Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF <_40% unless contraindicated. I A • Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure, or AV block or severe bradycardia. III B • It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long-term. I A • An LDL-C goal of < 1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8–3.5 mmol/L (70–135 mg/dL) is recommended. I B • ACE inhibitors are recommended, starting within the first 24 h of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes, or an anterior infarct. I A • An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure and/or LV systolic dysfunction, particularly those who are intolerant of ACE inhibitors. I B • MRAs are recommended in patients with an ejection fraction <_40% and heart failure or diabetes, who are already receiving an ACE inhibitor and a beta-blocker, provided there is no renal failure or hyperkalaemia. I B Management of LV dysfunction and acute heart failure in STEMI • ACE inhibitor (or if not tolerated, ARB) therapy is indicated as soon as haemodynamically stable for all patients with evidence of LVEF <_40% and/or heart failure to reduce the risk of hospitalization and death. I A • Beta-blocker therapy is recommended in patients with LVEF <_40% and/or heart failure after stabilization, to reduce the risk of death, recurrent MI, and hospitalization for heart failure. I A

Adopt recommendations if within the goals of care and bleeding risk is not prohibitive	• An MRA is recommended in patients with heart failure and LVEF <_40% with no severe renal failure or hyperkalaemia to reduce the risk of cardiovascular hospitalization and death. I B Management of cardiogenic shock in STEMI • Immediate PCI is indicated for patients with cardiogenic shock if coronary anatomy is suitable. If coronary anatomy is not suitable for PCI, or PCI has failed, emergency CABG is recommended. I B • Routine intra-aortic balloon pumping is not indicated. III B Management of atrial fibrillation • Digoxin is ineffective in converting recent onset AF to sinus rhythm and is not indicated for rhythm control. III A • Calcium channel blockers and beta-blockers including sotalol are ineffective in converting recent onset AF to sinus rhythm. III B • Prophylactic treatment with antiarrhythmic drugs to prevent AF is not indicated. III B Management of ventricular arrhythmias and conduction disturbances in the acute phase • Intravenous beta-blocker treatment is indicated for patients with polymorphic VT and/or VF unless contraindicated. I B • Prophylactic treatment with antiarrhythmic drugs is not indicated and may be harmful. III B • Long-term management of ventricular arrhythmias and risk evaluation for sudden death ICD therapy is recommended to reduce sudden cardiac death in patients with symptomatic heart failure (New York Heart Association class II–III) and LVEF <_35%, despite optimal medical therapy for >3 months and at least 6 weeks after MI, who are expected to survive for at least 1 year with good functional status. I A **2018 ESC/EACTS Guidelines on myocardial revascularization[6, b]** • Early angiography (within 24 h) is recommended if symptoms are completely relieved and ST-segment elevation is completely normalized spontaneously or after nitroglycerin administration (provided there is no recurrence of symptoms or ST-segment elevation) (class I, LOE C) C • In patients with time from symptom onset >12 h, a primary PCI strategy is indicated in the presence of ongoing symptoms suggestive of ischaemia, haemodynamic instability, or life-threatening

Adopt recommendations if within the goals of care and bleeding risk is not prohibitive	arrhythmias.(class I, LOE C) C • A routine primary PCI strategy should be considered in patients presenting late (12–48 h) after symptom onset.(class II, LOE B) • In asymptomatic patients, routine PCI of an occluded IRA >48 h after onset of STEMI is not indicated.(class III, LOE A) **2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction[7, c]** • Primary PCI should be performed in patients with STEMI and ischemic symptoms of less than 12 hours' duration. (*Class I, Level of Evidence: A*) • Primary PCI should be performed in patients with STEMI and ischemic symptoms of less than 12 hours' duration who have contraindications to fibrinolytic therapy, irrespective of the time delay from FMC. (*Class I, Level of Evidence: B*) • Primary PCI should be performed in patients with STEMI and cardiogenic shock or acute severe HF, irrespective of time delay from MI onset. (*Class I, Level of Evidence: B*) • Primary PCI is reasonable in patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia between 12 and 24 hours after symptom onset. (*Class IIa, Level of Evidence: B*) • PCI should not be performed in a noninfarct artery at the time of primary PCI in patients with STEMI who are hemodynamically stable. (*Class III, Level of Evidence: B*)

As noted above, clopidogrel has generally been used in patients at presumed higher bleeding risk	• Aspirin 162 to 325 mg should be given before primary PCI.(*Class I, Level of Evidence: B*)
	• After PCI, aspirin should be continued indefinitely.(*Class I, Level of Evidence: A*)
	• A loading dose of a P2Y12 receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include
	  ○ Clopidogrel 600 mg (*Class I, Level of Evidence: B*); or
	  ○ Prasugrel 60 mg (*Class I, Level of Evidence: B*); or
	  ○ Ticagrelor 180 mg. (*Class I, Level of Evidence: B)*
	• P2Y12 inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (BMS or DES) during primary PCI using the following maintenance doses:
	  ○ Clopidogrel 75 mg daily (*Class I, Level of Evidence: B*); or
	  ○ Prasugrel 10 mg daily (*Class I, Level of Evidence: B*); or
	  ○ Ticagrelor 90 mg twice a day. (*Class I, Level of Evidence: B)*

As above **Fibrinolytic use only after careful review of contraindications and assessed bleeding risks**	• For patients with STEMI undergoing primary PCI, the following supportive anticoagulant regimens are recommended: • UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP IIb/IIIa receptor antagonist has been administered (*Class I, Level of Evidence: C);* or • Bivalirudin with or without prior treatment with UFH (*Class I, Level of Evidence: B*) • Fondaparinux should not be used as the sole anticoagulant to support primary PCI because of the risk of catheter thrombosis. (*Class III, Level of Evidence: B*) • Cardiac catheterization and coronary angiography with intent to perform revascularization should be performed after STEMI in patients with any of the following: • Cardiogenic shock or acute severe HF that develops after initial presentation (*Class I, Level of Evidence: B*); • Intermediate- or high-risk findings on predischarge noninvasive ischemia testing (*Class I, Level of Evidence: B*); or • Myocardial ischemia that is spontaneous or provoked by minimal exertion during hospitalization. (*Class I, Level of Evidence: C*) • PCI is indicated in a noninfarct artery at a time separate from primary PCI in patients who have spontaneous symptoms of myocardial ischemia. (*Class I, Level of Evidence: C*) • In the absence of contraindications, fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of FMC. (*Class I, Level of Evidence: A*) • In the absence of contraindications and when PCI is not available, fibrinolytic therapy is reasonable for patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia within 12 to 24 hours of symptom onset and a large area of myocardium at risk or hemodynamic instability. (*Class IIa, Level of Evidence: C*) • Fibrinolytic therapy should not be administered to patients with ST depression except when a true posterior (inferobasal) MI is suspected or when associated with ST elevation in lead aVR. (*Class III, Level of Evidence: B*)

	• Aspirin (162- to 325-mg loading dose) and clopidogrel (300-mg loading dose for patients <75 years of age, 75-mg dose for patients >75 years of age) should be administered to patients with STEMI who receive fibrinolytic therapy.(*Class I, Level of Evidence: A*) • Aspirin should be continued indefinitely (*Class I, Level of Evidence: A*) and clopidogrel (75 mg daily) should be continued for at least 14 days (*Class I, Level of Evidence: A*) and up to 1 year (*Class I, Level of Evidence: C*) in patients with STEMI who receive fibrinolytic therapy. • PCI of an anatomically significant stenosis in the infarct artery should be performed in patients with suitable anatomy and any of the following: • Cardiogenic shock or acute severe HF (*Class I, Level of Evidence: B*); • Intermediate- or high-risk findings on predischarge noninvasive ischemia testing (*Class I, Level of Evidence: C*); or • Myocardial ischemia that is spontaneous or provoked by minimal exertion during hospitalization. (*Class I, Level of Evidence: C*) • After PCI, aspirin should be continued indefinitely). (*Class I, Level of Evidence: A*) • Clopidogrel should be provided as follows: • A 300-mg loading dose should be given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI within 24 hours of receiving fibrinolytic therapy (*Class I, Level of Evidence: C*); • A 600-mg loading dose should be given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI more than 24 hours after receiving fibrinolytic therapy (*Class I, Level of Evidence:C*); and • A dose of 75 mg daily should be given after PCI. (*Class I, Level of Evidence: C*) • For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with intravenous UFH, additional boluses of intravenous UFH should be administered as needed to support the procedure, taking into account whether GP IIb/IIIa receptor antagonists have been administered. (*Class I, Level of Evidence: C*) • For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with enoxaparin, if the last subcutaneous dose was administered within the prior 8 hours, no additional enoxaparin should be given; if the last subcutaneous dose was administered between 8 and 12 hours earlier, enoxaparin 0.3 mg/kg IV should be given. (*Class I, Level of Evidence: B*)

	Absolute Contraindications to Fibrinolysis ● Any prior ICH ● Known structural cerebral vascular lesion (e.g., arteriovenous malformation) ● Known malignant intracranial neoplasm (primary or metastatic) ● Ischemic stroke within 3 mo ● EXCEPT acute ischemic stroke within 4.5 h ● Suspected aortic dissection ● Active bleeding or bleeding diathesis (excluding menses) ● Significant closed-head or facial trauma within 3 mo ● Intracranial or intraspinal surgery within 2 mo ● Severe uncontrolled hypertension (unresponsive to emergency therapy) ● For streptokinase, prior treatment within the previous 6 months **Relative Contraindications to Fibrinolysis** ● History of chronic, severe, poorly controlled hypertension ● Significant hypertension on presentation (SBP _180 mm Hg or DBP _110 mm Hg) ● History of prior ischemic stroke _3 mo ● Dementia ● Known intracranial pathology not covered in absolute contraindications ● Traumatic or prolonged (_10 min) CPR ● Major surgery (_3 wk) ● Recent (within 2 to 4 wk) internal bleeding ● Noncompressible vascular punctures ● Pregnancy ● Active peptic ulcer ● Oral anticoagulant therapy
Adopt recommendation if within the goals of care	• Urgent CABG is indicated in patients with STEMI and coronary anatomy not amenable to PCI who have ongoing or recurrent ischemia, cardiogenic shock, severe HF, or other high-risk features. (*Class I, Level of Evidence: B*) • CABG is recommended in patients with STEMI at time of operative repair of mechanical defects.

	(*Class I, Level of Evidence: B*) • Aspirin should not be withheld before urgent CABG (*Class I, Level of Evidence: C*) • Clopidogrel or ticagrelor should be discontinued at least 24 hours before urgent on-pump CABG, if possible (*Class I, Level of Evidence: B*) • Short-acting intravenous GP IIb/IIIa receptor antagonists (eptifibatide, tirofiban) should be discontinued at least 2 to 4 hours before urgent CABG (*Class I, Level of Evidence: B*) • Abiximab should be discontinued at least 12 hours before urgent CABG (*Class I, Level of Evidence: B*)
Adopt recommendations **See discussions on DAPT in the text** **Invasive**	**2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation[3, d]** • Early initiation of beta-blocker treatment is recommended in patients with ongoing ischaemic symptoms and without contraindications. I B • It is recommended to continue chronic beta-blocker therapy, unless the patient is in Killip class III or higher. I B • Sublingual or i.v. nitrates are recommended to relieve angina;d i.v. treatment is recommended in patients with recurrent angina, uncontrolled hypertension or signs of heart failure. I C • In patients with suspected/confirmed vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided. IIa B • Aspirin is recommended for all patients without contraindications at an initial oral loading dosed of 150–300 mg (in aspirin-naive patients) and a maintenance dose of 75–100 mg/day long-term regardless of treatment strategy. I A • A P2Y12 inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds. I A • P2Y12 inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk. IIb A • Parenteral anticoagulation is recommended at the time of diagnosis according to both ischaemic and bleeding risks. I B ▪ An immediate invasive strategy (<2 h) is recommended in patients with at least one of the following very-high-risk criteria:

management in keeping with the overall goals of care of the patient	• haemodynamic instability or cardiogenic shock • recurrent or ongoing chest pain refractory to medical treatment • life-threatening arrhythmias or cardiac arrest • mechanical complications of MI • acute heart failure with refractory angina or ST deviation • recurrent dynamic ST- or T-wave changes, particularly with intermittent ST-elevation. I C ▪ An early invasive strategy (<24 h) is recommended in patients with at least one of the following high-risk criteria: • rise or fall in cardiac troponin compatible with MI • dynamic ST- or T-wave changes(symptomatic or silent) • GRACE score .I A ▪ An invasive strategy (<72 h) is recommended in patients with at least one of the following intermediate-risk criteria: • diabetes mellitus • renal insufficiency (eGFR 60 mL/min/1.73 m2) • LVEF ,40% or congestive heart failure • early post-infarction angina • recent PCI • prior CABG • GRACE risk score • or recurrent symptoms or known ischaemia on non-invasive testing. I A
Adopt recommendation	▪ In patients with none of the above mentioned risk criteria and no recurrent symptoms, non-invasive testing for ischaemia (preferably with imaging) is recommended before deciding on an invasive evaluation. I A
Radial access preferred	▪ In centres experienced with radial access, a radial approach is recommended for coronary angiography and PCI. I A
DES use in patients	▪ In patients undergoing PCI, new-generation DESs are recommended. I A ▪ In patients in whom a short DAPT duration (30 days) is planned because of an increased bleeding

with cancer historically lower and subject to discussions **Adopt recommendations**	risk, a new generation DES may be considered over a BMS. IIb B ▪ In patients with multivessel CAD, it is recommended to base the revascularization strategy (e.g. ad hoc culprit-lesion PCI, multivessel PCI, CABG) on the clinical status and comorbidities as well as the disease severity (including distribution, angiographic lesion characteristics, SYNTAX score), according to the local Heart Team protocol. I C ▪ Irrespective of the revascularization strategy, a P2Y12 inhibitor is recommended in addition to aspirin and maintained over 12 months unless there are contraindications such as excessive risk of bleeding events. I A ▪ It is recommended that the Heart Team estimate the individual bleeding and ischaemic risks and guide the timing of CABG as well as management of DAPT. I C ▪ It is recommended to perform CABG without delay in patients with haemodynamic instability, ongoing myocardial ischaemia or very-high-risk coronary anatomy, regardless of antiplatelet treatment. I C ▪ Aspirin is recommended 6–24 h post-CABG in the absence of ongoing bleeding events. I A ▪ It is recommended to continue low-dose aspirin until CABG. I B ▪ It is recommended to tailor antithrombotic treatment according to bodyweight and renal function. I C
Important aspect for patients with cancer	Thrombocytopenia ▪ Immediate interruption of GPIIb/IIIa inhibitor and/or heparin (UFH, LMWH, other heparin products) is recommended in case of thrombocytopenia , 100 000/mL (or >50% relative drop from baseline platelet count) occurring during treatment. I C ▪ In patients treated with GP IIb/IIIa inhibitors, platelet transfusion is recommended in case of major active bleeding events or in the presence of severe (<10 000/mL) asymptomatic thrombocytopenia. I C ▪ Treatment with a non-heparin anticoagulant is recommended in case of documented or suspected HIT.I C ▪ Use of anticoagulants with low or no risk of HIT or brief administration of UFH or LMWH, when

Invasive management in keeping with the overall goals of care of the patient	these are chosen, are recommended to prevent the occurrence of HIT. I C **2018 ESC/EACTS Guidelines on myocardial revascularization[6, b]** ▪ In the absence of ST-segment elevation, a primary PCI strategy is indicated in patients with suspected ongoing ischaemic symptoms suggestive of MI and at least one of the following criteria present: a) haemodynamic instability or cardiogenic shock b) recurrent or ongoing chest pain refractory to medical treatment c) life-threatening arrhythmias or cardiac arrest d) mechanical complications of MI e) acute heart failure f) recurrent dynamic ST-segment or Twave changes, particularly with intermittent T-segment elevation. (class I, LOE C)
Adopt recommendations	**2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes[2, e]** • Administer supplemental oxygen only with oxygen saturation <90%, respiratory distress, or other high-risk features for hypoxemia. I C N/A • Administer sublingual NTG every 5 min _ 3 for continuing ischemic pain and then assess need for IV NTG. I C • Administer IV NTG for persistent ischemia, HF, or hypertension. I B • Initiate oral beta blockers within the first 24 h in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to beta blockade. I A • Use of sustained-release metoprolol succinate, carvedilol, or bisoprolol is recommended for beta-blocker therapy with concomitant NSTE-ACS, stabilized HF, and reduced systolic function. I C N/A • Re-evaluate to determine subsequent eligibility in patients with initial contraindications to beta blockers. I C • Administer initial therapy with nondihydropyridine CCBs with recurrent ischemia and contraindications to beta blockers in the absence of LV dysfunction, increased risk for cardiogenic

	shock, PR interval >0.24 s, or second- or third-degree atrioventricular block without a cardiac pacemaker. I B • Administer oral nondihydropyridine calcium antagonists with recurrent ischemia after use of beta blocker and nitrates in the absence of contraindications. I C N/A • CCBs are recommended for ischemic symptoms when beta blockers are not successful, are contraindicated, or cause unacceptable side effects*. I C N/A • Long-acting CCBs and nitrates are recommended for patients with coronary artery spasm. I C • Initiate or continue high-intensity statin therapy in patients with no contraindications. I A ▪ Non–enteric-coated aspirin to all patients promptly after presentation 162 mg–325 mg. I A ▪ Aspirin maintenance dose continued indefinitely 81 mg/d–325 mg/d. I A ▪ Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin. I B ▪ P2Y12 inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy: o Clopidogrel 300-mg or 600-mg loading dose, then 75 mg/d o Ticagrelor 180-mg loading dose, then 90 mg BID. I B ▪ P2Y12 inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post–PCI patients treated with coronary stents. N/A I B ▪ SC enoxaparin for duration of hospitalization or until PCI is performed, 1 mg/kg SC every 12 h (reduce dose to 1 mg/kg/d SC in patients with CrCl <30 mL/min), Initial 30 mg IV loading dose in selected patients. I A ▪ Bivalirudin until diagnostic angiography or PCI is performed in patients with early invasive strategy only; loading dose 0.10 mg/kg loading dose followed by 0.25 mg/kg/h ▪ Only provisional use of GP IIb/IIIa inhibitor in patients also treated with DAPT. I B ▪ SC fondaparinux for the duration of hospitalization or until PCI is performed; 2.5 mg SC daily. I B ▪ Administer additional anticoagulant with anti-IIa activity if PCI is performed while patient is on fondaparinux. N/A I B ▪ IV UFH for 48 h or until PCI is performed; Initial loading dose 60 IU/kg (max 4,000 IU) with initial infusion 12 IU/kg/h (max 1,000 IU/ h); adjusted to therapeutic aPTT range. I B

Invasive management in keeping with the overall goals of care of the patient	▪ Immediate invasive strategy (within 2 h) o Refractory angina o Signs or symptoms of HF or new or worsening mitral regurgitation o Hemodynamic instability o Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy o Sustained VT or VF ▪ Ischemia-guided strategy o Low-risk score (e.g., TIMI [0 or 1], GRACE [<109]) o Low-risk Tn-negative female patients o Patient or clinician preference in the absence of high-risk features ▪ Early invasive (within 24 h) o None of the above, but GRACE risk score >140 o Temporal change in Tn o New or presumably new ST depression ▪ Delayed invasive (within 25_72 h) o None of the above but diabetes mellitus o Renal insufficiency (GFR <60 mL/min/1.73 m2) o Reduced LV systolic function (EF <0.40) o Early postinfarction angina o PCI within 6 mo o Prior CABG o GRACE risk score 109–140; TIMI score >=2
Important aspects in cardio-oncology patients	▪ NSTE-ACS in older patients o Treat older patients (≥75 y of age) with GDMT, early invasive strategy, and revascularization as appropriate. I A o Individualize pharmacotherapy in older patients, with dose adjusted by weight and/or CrCl to reduce adverse events caused by age-related changes in pharmacokinetics/dynamics,

	volume of distribution, comorbidity, drug interactions, and increased drug sensitivity. I A ○ Undertake patient-centered management for older patients, considering patient preferences/goals, comorbidities, functional and cognitive status, and life expectancy. I B ○ Bivalirudin rather than GP IIb/IIIa inhibitor plus UFH is reasonable for older patients (≥75 y of age), given similar efficacy but less bleeding risk. IIa B ○ It is reasonable to choose CABG over PCI in older patients, particularly those with DM or multivessel disease, because of the potential for improved survival and reduced CVD events. IIa B ▪ Heart failure ○ Treat patients with a history of HF according to the same risk stratification guidelines and recommendations for patients without HF. I B ○ Select a revascularization strategy based on the extent of CAD, associated cardiac lesions, LV dysfunction, and prior revascularization. I B ▪ Cardiogenic shock ○ Recommend early revascularization for cardiogenic shock due to cardiac pump failure. I B ▪ Diabetes mellitus ○ Recommend medical treatment and decisions for testing and revascularization similar to those for patients without DM. I A ▪ Prior CABG ○ Recommend GDMT antiplatelet and anticoagulant therapy and early invasive strategy because of increased risk with prior CABG. I B ▪ Perioperative NSTE-ACS ○ Administer GDMT to perioperative patients with limitations imposed by noncardiac surgery. I C ○ Direct management at underlying cause of perioperative NSTE-ACS. I C ▪ CKD ○ Estimate CrCl and adjust doses of renally cleared medications according to pharmacokinetic data. I B

	○ Administer adequate hydration to patients undergoing coronary and LV angiography. I C N/A ○ Invasive strategy is reasonable in patients with mild (stage 2) and moderate (stage 3) CKD. IIa B ▪ Women ○ Manage women with the same pharmacological therapy as that for men for acute care and secondary prevention, with attention to weight and/or renally calculated doses of antiplatelet and anticoagulant agents to reduce bleeding risk. I B ○ Early invasive strategy is recommended in women with NSTE-ACS and high-risk features (troponin positive). I A ○ Myocardial revascularization is reasonable for pregnant women if ischemia-guided strategy is ineffective for management of life-threatening complications. IIa C ○ Women with low-risk features should not undergo early invasive treatment because of lack of benefit and the possibility of harm. III: No Benefit B ▪ Anemia, bleeding, and transfusion ○ Evaluate all patients for risk of bleeding. I C N/A ○ Recommend that anticoagulant and antiplatelet therapy be weight-based where appropriate and adjusted for CKD to decrease the risk of bleeding. I B ○ There is no benefit of routine blood transfusion in hemodynamically stable patients with hemoglobin levels >8 g/dL. III: No Benefit B ▪ Cocaine and methamphetamine users ○ Manage patients with recent cocaine or methamphetamine use similarly to those without cocaine- or methamphetamine-related NSTE-ACS. The exception is in patients with signs of acute intoxication (e.g., euphoria, tachycardia, and hypertension) and beta-blocker use unless patients are receiving coronary vasodilator therapy. I C N/A ○ It is reasonable to use benzodiazepines alone or in combination with NTG to manage hypertension and tachycardia and signs of acute cocaine or methamphetamine intoxication. IIa C ○ Do not administer beta blockers to patients with recent cocaine or methamphetamine use who have signs of acute intoxication due to risk of potentiating coronary spasm. III: Harm C

Invasive management in keeping with the overall goals of care of the patient	▪ ACS with angiographically normal coronary arteries o Invasive physiological assessment (coronary flow reserve measurement) may be considered with normal coronary arteries if endothelial dysfunction is suspected. IIb B ▪ Stress (Takotsubo) cardiomyopathy o Consider stress-induced cardiomyopathy in patients with apparent ACS and nonobstructive CAD. I C N/A o Perform ventriculography, echocardiography, or MRI to confirm or exclude diagnosis I B o Treat with conventional agents (ACE inhibitors, beta blockers, aspirin, and diuretics) if hemodynamically stable. I C N/A o Administer anticoagulant therapy for LV thrombi. I C N/A o It is reasonable to administer catecholamines for symptomatic hypotension in the absence of LV outflow tract obstruction. IIa C N/A o It is reasonable to use IABP for refractory shock. IIa C N/A o It is reasonable to use beta blockers and alpha-adrenergic agents for LV outflow tract obstruction. IIa C N/A o Prophylactic anticoagulation may be considered to prevent LV thrombi. IIb C N/A **2018 ESC/EACTS Guidelines on myocardial revascularization[6, b]** • In patients with ACS treated with coronary stent implantation, DAPT with a P2Y12 inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as an excessive risk of bleeding (e.g. PRECISEDAPT >=25). I A • In patients with ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT >=25), discontinuation of P2Y12 inhibitor therapy after 6 months should be considered. IIa B • Invasive evaluation and revascularization in NSTE-ACS • An early invasive strategy (<24 h) is recommended in patients with at least one high-risk criterion. I A • An invasive strategy (<72 h after first presentation) is indicated in patients with at least one intermediate-risk criterion or recurrent symptoms. I A • It is recommended that the revascularization strategy (ad hoc culprit-lesion PCI/multivessel

	PCI/CABG) is based on the patient's clinical status and comorbidities, as well as the disease severity, i.e. distribution and angiographic lesion characteristics (e.g. SYNTAX score), according to the principles for SCAD. I B • In cardiogenic shock, routine revascularization of non-IRA lesions is not recommended during primary PCI. III B
Higher risk of bleeding in certain cancer populations needs to be considered **Adopt recommendations**	**2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS[8, f]** In patients with ACS, ticagrelor (180 mg loading dose, 90 mg b.i.d.) on top of aspirin is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contraindications. I B ▪ In patients with ACS undergoing PCI, prasugrel (60mg loading dose, 10mg o.d.) on top of aspirin is recommended for P2Y12 inhibitor-naıve patients with NSTE-ACS or initially conservatively managed STEMI if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization unless there is a high risk of life-threatening bleeding or other contraindications. I B ▪ Pre-treatment with a P2Y12 inhibitor is generally recommended in patients in whom coronary anatomy is known and the decision to proceed to PCI is made, as well as in patients with STEMI.I A ▪ Clopidogrel (600 mg loading dose, 75 mg o.d.) on top of aspirin is recommended in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive ticagrelor or prasugrel, including those with prior intracranial bleeding or indication for OAC. I A ▪ Clopidogrel (300 mg loading dose in patients aged <_75, 75 mg o.d.) is recommended on top of aspirin in STEMI patients receiving thrombolysis. I A ▪ In NSTE-ACS patients in whom coronary anatomy is not known, it is not recommended to administer prasugrel. III B Measures to minimize bleeding while on dual antiplatelet therapy ▪ Radial over femoral access is recommended for coronary angiography and PCI if performed by an expert radial operator. I A ▪ In patients treated with DAPT, a daily aspirin dose of 75 - 100 mg is recommended. I A ▪ A PPI in combination with DAPT is recommended. I B ▪ Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not

	recommended. III A Switching between oral P2Y12 inhibitors ▪ In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contraindications to ticagrelor exist. I B Dual antiplatelet therapy duration in patients with acute coronary syndrome ▪ In patients with ACS treated with coronary stent implantation, DAPT with a P2Y12 inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding (e.g. PRECISE-DAPT >_25).I A ▪ In patients with ACS who are managed with medical therapy alone and treated with DAPT, it is recommended to continue P2Y12 inhibitor therapy (either ticagrelor or clopidogrel) for 12 months. I A ▪ Ticagrelor is recommended over clopidogrel, unless the bleeding risk outweighs the potential ischaemic benefit. I B ▪ Prasugrel is not recommended in medically managed ACS patients. III B Dual antiplatelet therapy in patients undergoing elective cardiac and non-cardiac surgery ▪ It is recommended to continue aspirin perioperatively if the bleeding risk allows, and to resume the recommended antiplatelet therapy as soon as possible post-operatively. I B ▪ It is not recommended to discontinue DAPT within the first month of treatment in patients undergoing elective non-cardiac surgery. III B Gender considerations ▪ Similar type and duration of DAPT are recommended in male and female patients. I A
Duration of DAPT after either BMS or DES not precisely defined in patients	**2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease[9, g]** ▪ In patients with SIHD treated with DAPT after BMS implantation, P2Y12 inhibitor therapy (clopidogrel) should be given for a minimum of 1 month. I A ▪ In patients with SIHD treated with DAPT after DES implantation, P2Y12 inhibitor therapy (clopidogrel) should be given for at least 6 months. I B-R SR

with cancer and depended on timing of PCI relative to cancer diagnosis and treatment	▪ In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. I B-NR ▪ In patients with SIHD treated with DAPT after BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT with clopidogrel for longer than 1 month in patients treated with BMS or longer than 6 months in patients treated with DES may be reasonable. IIb A SR ▪ In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 3 months may be reasonable. IIb C-LD ▪ In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after BMS or DES implantation, P2Y12 inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months. I B-R ▪ In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. I B-NR ▪ In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y12 inhibitor therapy. IIa B-R ▪ In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance P2Y12 inhibitor therapy. IIa B-R ▪ In patients with ACS (NSTE-ACS or STEMI) treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable. IIb A SR ▪ In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 6 months may be reasonable. IIb C-LD ▪ Prasugrel should not be administered to patients with a prior history of stroke or TIA. III: Harm B-R

Careful review of the goals of care and risk/benefits	**2018 AHA/ASA Guidelines for the Early Management of Patients With Acute Ischemic Stroke[10, h]** • IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who may be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria to determine patient eligibility. I A • IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is also recommended for selected patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well. Physicians should review the criteria outlined in Table 6 determine patient eligibility. I B-R • The potential risks should be discussed during thrombolysis eligibility deliberation and weighed against the anticipated benefits during decision making. I C-EO • In patients undergoing fibrinolytic therapy, physicians should be prepared to treat potential emergent adverse effects, including bleeding complications and angioedema that may cause partial airway obstruction. I B-NR • BP should be maintained <180/105 mm Hg for at least the first 24 hours after IV alteplase treatment. I B-NR • In patients eligible for IV alteplase, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible. I A • Patients eligible for IV alteplase should receive IV alteplase even if EVTs are being considered. I A • Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset. I A • In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended. I A • The technical goal of the thrombectomy procedure should be reperfusion to a modified Thrombolysis in Cerebral Infarction (mTICI) 2b/3 angiographic result to maximize the probability of a good functional clinical outcome. I A • As with IV alteplase, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI grade 2b/3

	should be achieved as early as possible within the therapeutic window. I B-R • Use of stent retrievers is indicated in preference to the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) device. I A • Mechanical thrombectomy with stent retrievers is recommended over intra-arterial thrombolysis as first-line therapy. I C-EO • Administration of aspirin is recommended in patients with AIS within 24 to 48 hours after onset. For those treated with IV alteplase, aspirin administration is generally delayed until 24 hours later but might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk. I A • In patients with AIS, early treatment of hypertension is indicated when required by comorbid conditions (eg, concomitant acute coronary event, acute heart failure, aortic dissection, postthrombolysis sICH, or preeclampsia/eclampsia). Lowering BP initially by 15% is probably safe. I C-EO • Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function.I C-EO • Sources of hyperthermia (temperature >38°C) should be identified and treated. Antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke. I C-EO • Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with AIS. I C-LD
Recommendable if within the goals of care **Adopt recommendations**	**2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)[11, i]** ▪ In the case of neurological deficit, urgent revascularization is indicated. I C ▪ In the absence of neurological deficit, revascularization is indicated within hours after initial imaging in a case-by-case decision. I C ▪ Heparin and analgesics are indicated as soon as possible. I C **2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease[12, j]** ▪ In patients with ALI, systemic anticoagulation with heparin should be administered unless contraindicated. I C-EO ▪ In patients with ALI, the revascularization strategy should be determined by local resources and

	patient factors (e.g., etiology and degree of ischemia) I C-LD ▪ Catheter-based thrombolysis is effective for patients with ALI and a salvageable limb. I A ▪ Patients with ALI should be monitored and treated (e.g., fasciotomy) for compartment syndrome after revascularization. I C-LD ▪ In the patient with ALI, a comprehensive history should be obtained to determine the cause of thrombosis and/or embolization. I C-EO ▪ In addition to identifying a known history of PAD, the history should focus on uncovering clinical evidence of other conditions that can result in ALI through either embolic or thrombotic mechanisms. These conditions include atrial fibrillation, left ventricular thrombus, aortic dissection, trauma, hypercoagulable state, and presence of a limb artery bypass graft. The clinical history should identify the presence or absence of a history of MI, symptoms and signs of left ventricular dysfunction resulting in congestive heart failure, or possible endocarditis. The history should evaluate for possibility of deep vein thrombosis with intracardiac shunt (e.g., patent foramen ovale or other that may result in paradoxical arterial embolism), hypercoagulable state, and family history of thrombosis.

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Supplementary Table 3 | **Society guidelines for stable atherosclerotic disease (coronary, carotid and peripheral**)

Cardio-Oncology perspective	**Guideline recommendation**
Unique, first time recommendations specific to cancer patients	**2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes[4, a]** Cancer patients • Treatment decisions should be based on life expectancy, additional comorbidities such as thrombocytopenia, increased thrombosis propensity, and potential interactions between drugs used in CCS management and antineoplastic agents. I C

	• If revascularization is indicated in highly symptomatic patients with active cancer and increased frailty, the least invasive procedure is recommended. I C
Adopt recommendations	Elderly patients • It is recommended that diagnostic and revascularization decisions are based on symptoms, the extent of ischaemia, frailty, life expectancy, and comorbidities. I C • It is recommended that particular attention is paid to side effects of drugs, intolerance, and overdosing in elderly patients. I C • Radial access is recommended in elderly patients to reduce access-site bleeding complications. I B • The use of DES is recommended in elderly patients. I A
Adopt recommendations, especially in cancer patients with planned therapies that bear vascular toxicity risk	Screening for coronary artery disease in asymptomatic patients • Total risk estimation using a risk-estimation system such as SCORE is recommended for asymptomatic adults >40 years of age without evidence of CVD, diabetes, CKD, or familial hypercholesterolaemia. I C • Assessment of family history of premature CVD (defined as a fatal or non-fatal CVD event, or/and established diagnosis of CVD in first-degree male relatives before 55 years of age or female relatives before 65 years of age) is recommended as part of cardiovascular risk assessment. I C • It is recommended that all individuals aged <50 years with a family history of premature CVD in a first-degree relative (<55 years of age in men or <65 years of age in women) or familial hypercholesterolaemia are screened using a validated clinical score. I B • Assessment of coronary artery calcium score with computed tomography may be considered as a risk modifier in the cardiovascular risk assessment of asymptomatic subjects. IIb B • Atherosclerotic plaque detection by carotid artery ultrasound may be considered as a risk modifier in the cardiovascular risk assessment of asymptomatic subjects. IIb B • ABI may be considered as a risk modifier in cardiovascular risk assessment. IIb B • In high-risk asymptomatic adults (with diabetes, a strong family history of CAD, or when previous risk-assessment tests suggest a high risk of CAD), functional imaging or coronary CTA may be considered for cardiovascular risk assessment. IIb C • In asymptomatic adults (including sedentary adults considering starting a vigorous exercise programme), an exercise ECG may be considered for cardiovascular risk assessment, particularly when attention is paid to non-ECG markers such as exercise capacity. IIb C

Adopt recommendations	Diagnostic management of suspected coronary artery disease • A resting 12 lead ECG is recommended in all patients with chest pain without an obvious non-cardiac cause. I C • A resting 12 lead ECG is recommended in all patients during or immediately after an episode of angina suspected to be indicative of clinical instability of CAD.I C • Ambulatory ECG monitoring is recommended in patients with chest pain and suspected arrhythmias. I C • A resting transthoracic echocardiogram is recommended in all patients for: ▪ Exclusion of alternative causes of angina; (2) Identification of regional wall motion abnormalities suggestive of CAD; (3) Measurement of LVEF for risk stratification; and (4) Evaluation of diastolic function. I B • Chest X-ray is recommended for patients with atypical presentation, signs and symptoms of HF, or suspicion of pulmonary disease. I C • Non-invasive functional imaging for myocardial ischaemia or coronary CTA is recommended as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone. I B • It is recommended that selection of the initial non-invasive diagnostic test is done based on the clinical likelihood of CAD and other patient characteristics that influence test performance, local expertise, and the availability of tests. I C • Functional imaging for myocardial ischaemia is recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic. I B • Invasive coronary angiography is recommended as an alternative test to diagnose CAD in patients with a high clinical likelihood, severe symptoms refractory to medical therapy or typical angina at a low level of exercise, and clinical evaluation that indicates high event risk. Invasive functional assessment must be available and used to evaluate stenoses before revascularization, unless very high grade (>90% diameter stenosis). I B • Invasive coronary angiography with the availability of invasive functional evaluation should be considered for confirmation of the diagnosis of CAD in patients with an uncertain diagnosis on non-invasive testing. IIa B • Coronary CTA should be considered as an alternative to invasive angiography if another non-invasive test is equivocal or non-diagnostic. IIa C

Adopt recommendations	• Coronary CTA is not recommended when extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands, or any other conditions make obtaining good image quality unlikely. III C • Coronary calcium detection by CT is not recommended to identify individuals with obstructive CAD. III C • Exercise ECG is recommended for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk in selected patients. I C Risk assessment • Risk stratification is recommended based on clinical assessment and the result of the diagnostic test initially employed to diagnose CAD.I B • Resting echocardiography is recommended to quantify LV function in all patients with suspected CAD. I C • Risk stratification, preferably using stress imaging or coronary CTA (if permitted by local expertise and availability), or alternatively exercise stress ECG (if significant exercise can be performed and the ECG is amenable to the identification of ischaemic changes), is recommended in patients with suspected or newly diagnosed CAD. I B • In symptomatic patients with a high-risk clinical profile, ICA complemented by invasive physiological guidance (FFR) is recommended for cardiovascular risk stratification, particularly if the symptoms are responding inadequately to medical treatment and revascularization is considered for improvement of prognosis. I A • In patients with mild or no symptoms, ICA complemented by invasive physiological guidance (FFR/iwFR) is recommended for patients on medical treatment, in whom non-invasive risk stratification indicates a high event risk and revascularization is considered for improvement of prognosis. I A • ICA complemented by invasive physiological guidance (FFR) should be considered for risk-stratification purposes in patients with inconclusive or conflicting results from non-invasive testing. IIa B • If coronary CTA is available for event risk stratification, additional stress imaging should be performed before the referral of a patient with few/no symptoms for ICA. IIa B • Echocardiographic assessment of global longitudinal strain provides incremental information to LVEF and may be considered when LVEF is >35%. IIb B

Adopt recommendations	• Intravascular ultrasound may be considered for the risk stratification of patients with intermediate LM stenosis. IIb B Anti-ischemic therapy (angina/ischemia relief) • Medical treatment of symptomatic patients requires one or more drug(s) for angina/ischaemia relief in association with drug(s) for event prevention. I C • It is recommended that patients are educated about the disease, risk factors, and treatment strategy. I C • Timely review of the patient's response to medical therapies (e.g. 2-4 weeks after drug initiation) is recommended. I C • Short-acting nitrates are recommended for immediate relief of effort angina. I B • First-line treatment is indicated with beta-blockers and/or CCBs to control heart rate and symptoms. I A • If angina symptoms are not successfully controlled on a beta-blocker or a CCB, the combination of a beta-blocker with a DHP-CCB should be considered. IIa C • Initial first-line treatment with the combination of a beta-blocker and a DHP-CCB should be considered. IIa B • Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-CCB is contraindicated, poorly tolerated, or inadequate to control angina symptoms. IIa B • When long-acting nitrates are prescribed, a nitrate-free or low-nitrate interval should be considered to reduce tolerance. IIa B • Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates. IIa B • In subjects with baseline low heart rate and low BP, ranolazine or trimetazidine may be considered as a first-line drug to reduce angina frequency and improve exercise tolerance. IIb C • In selected patients, the combination of a beta-blocker or a CCB with second-line drugs (ranolazine, nicorandil, ivabradine, and trimetazidine) may be considered for first-line treatment according to heart rate, BP, and tolerance. IIb B • Nitrates are not recommended in patients with hypertrophic obstructive cardiomyopathy266 or co-

	administration of phosphodiesterase inhibitors. III B • Myocardial revascularization is recommended when angina persists despite treatment with antianginal drugs. I A
Adopt recommendations	Antithrombotic therapy in patients with CCS and in sinus rhythm • Aspirin 75-100 mg daily is recommended in patients with a previous MI or revascularization. I A • Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance. I B • Clopidogrel 75 mg daily may be considered in preference to aspirin in symptomatic or asymptomatic patients, with either PAD or a history of ischaemic stroke or transient ischaemic attack. IIb B • Aspirin 75-100 mg daily may be considered in patients without a history of MI or revascularization, but with definitive evidence of CAD on imaging.IIb C • Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischaemic eventsc and without high bleeding risk.IIa A • Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a moderately increased risk of ischaemic events and without high bleeding risk. IIb A
Adopt recommendations	Antithrombotic therapy post-PCI in patients with CCS and in sinus rhythm • Aspirin 75-100 mg daily is recommended following stenting. I A • Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) is recommended, in addition to aspirin, for 6 months following coronary stenting, irrespective of stent type, unless a shorter duration (1-3 months) is indicated due to risk or the occurrence of life-threatening bleeding. I A • Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) should be considered for 3 months in patients with a higher risk of life-threatening bleeding. IIa A • Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) may be considered for 1 month in patients with very high risk of life-threatening bleeding.284 IIb C • Prasugrel or ticagrelor may be considered, at least as initial therapy, in specific high-risk situations

	of elective stenting (e.g. suboptimal stent deployment or other procedural characteristics associated with high risk of stent thrombosis, complex left main stem, or multivessel stenting) or if DAPT cannot be used because of aspirin intolerance. IIb C
Adopt recommendations	Antithrombotic therapy in patients with CCS and AF • When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC, if a NOAC is recommended in preference to a VKA. I A • Long-term OAC therapy (NOAC or VKA with time in therapeutic range >70%) is recommended in patients with AF and a CHA2DS2-VASc score >_2 in males and >_3 in females. I A • Long-term OAC therapy (NOAC or VKA with time in therapeutic range >70%) should be considered in patients with AF and a CHA2DS2-VASc score of 1 in males and 2 in females. IIa B • Aspirin 75-100 mg daily (or clopidogrel 75 mg daily) may be considered in addition to long-term OAC therapy in patients with AF, history of MI, and at high risk of recurrent ischaemic events who do not have a high bleeding risk. IIb B
Adopt recommendations	Antithrombotic therapy in post-PCI patients with AF or another indication for an OAC • It is recommended that peri-procedural aspirin and clopidogrel are administered to patients undergoing coronary stent implantation. I C • In patients who are eligible for a NOAC, it is recommended that a NOAC (apixaban 5 mg b.i.d., dabigatran 150 mg b.i.d., edoxaban 60 mg o.d., or rivaroxaban 20 mg o.d.) is used in preference to a VKA in combination with antiplatelet therapy. I A • When rivaroxaban is used and concerns about high bleeding riskd prevail over concerns about stent thrombosis or ischaemic stroke, rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant single or dual antiplatelet therapy. IIa B • When dabigatran is used and concerns about high bleeding riskd prevail over concerns about stent thrombosis or ischaemic stroke, dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant single or dual antiplatelet therapy. IIa B • After uncomplicated PCI, early cessation (<_1 week) of aspirin and continuation of dual therapy with an OAC and clopidogrel should be considered if the risk of stent thrombosis is low, or if concerns about bleeding risk prevail over concerns about the risk of stent thrombosis, irrespective of the type of stent used. IIa B • Triple therapy with aspirin, clopidogrel, and an OAC for >_1 month should be considered when the

Adopt recommendations	risk of stent thrombosis outweighs the bleeding risk, with the total duration (<_6 months) decided according to assessment of these risks and clearly specified at hospital discharge. IIa C • In patients with an indication for a VKA in combination with aspirin and/or clopidogrel, the dose intensity of the VKA should be carefully regulated with a target international normalized ratio in the range of 2.02.5 and with time in therapeutic range >70%. IIa B • Dual therapy with an OAC and either ticagrelor or prasugrel may be considered as an alternative to triple therapy with an OAC, aspirin, and clopidogrel in patients with a moderate or high risk of stent thrombosis, irrespective of the type of stent used. IIb C • The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and an OAC. III C Additional therapies • Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or OAC monotherapy who are at high risk of gastrointestinal bleeding. I A • Statins are recommended in all patients with CCS. I A • If a patient's goal is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended. I B • For patients at very high risk who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended. I A • ACE inhibitors (or ARBs) are recommended if a patient has other conditions (e.g. heart failure, hypertension, or diabetes). I A • ACE inhibitors should be considered in CCS patients at very high risk of cardiovascular events. IIa A • Beta-blockers are recommended in patients with LV dysfunction or systolic HF. I A • In patients with a previous STEMI, long-term oral treatment with a beta-blocker should be considered. IIa B • Beta-blockers are recommended as essential components of treatment due to their efficacy in both relieving angina, and reducing morbidity and mortality in HF. I A • ACE inhibitor therapy is recommended in patients with symptomatic HF or asymptomatic LV dysfunction following MI, to improve symptoms and reduce morbidity and mortality. I A • An ARB is recommended as an alternative in patients who do not tolerate ACE inhibition, or an angiotensin receptor-neprilysin inhibitor in patients with persistent symptoms despite optimal medical therapy. I B

Adopt recommendations in the broader scope of goals of care	• An MRA is recommended in patients who remain symptomatic despite adequate treatment with an ACE inhibitor and beta-blocker, to reduce morbidity and mortality. I A • A short-acting oral or transcutaneous nitrate should be considered (effective antianginal treatment, safe in HF). IIa A • Ivabradine should be considered in patients with sinus rhythm, an LVEF <_35% and a resting heart rate >70 b.p.m. who remain symptomatic despite adequate treatment with a beta-blocker, ACE inhibitor, and MRA, to reduce morbidity and mortality. IIa B • Amlodipine may be considered for relief of angina in patients with HF who do not tolerate beta-blockers, and is considered safe in HF. IIb B • Comprehensive risk profiling and multidisciplinary management, including treatment of major comorbidities such as hypertension, hyperlipidaemia, diabetes, anaemia, and obesity, as well as smoking cessation and lifestyle modification, are recommended. I A **2018 ESC/EACTS Guidelines on myocardial revascularization[6, b]** • Revascularization for prognosis: o Left main disease with stenosis >50%. I A o Proximal LAD stenosis >50%. I A o Two- or three-vessel disease with stenosis >50% with impaired LV function (LVEF <_35%). I A o Large area of ischaemia detected by functional testing (>10% LV) or abnormal invasive FFR. I B o Single remaining patent coronary artery with stenosis >50%. I C • Revascularization for symptoms: o Haemodynamically significant coronary stenosisc in the presence of limiting angina or angina equivalent, with insufficient response to optimized medical therapy. • CABG o One vessel disease (class I, LOE A) or two vessel disease (class I, LOE B) vessel disease with proximal LAD o Three vessel or left main with any possible scenario (class I, LOE A)

	• PCI
	  ○ One vessel disease with (class I, LOE A) or without (class I, LOE C) proximal LAD or two vessel disease with or without proximal LAD (class I, LOE C)
	  ○ Three vessel without diabetes mellitus or left main with low SYNTAX score (0-22) (class I, LOE A)
	
	• DES are recommended over BMS for any PCI irrespective of:
	  ○ clinical presentation
	  ○ lesion type
	  ○ planned non-cardiac surgery
	  ○ anticipated duration of DAPT
	  ○ concomitant anticoagulant therapy. I A
	
	• Radial access is recommended as the standard approach, unless there are overriding procedural considerations. I A

Adopt recommendation within the goals of care and a multi-disciplinary team approach **Adopt upon reaching consensus on an individual basis in comparison with the**	**2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease[13, c]** • A Heart Team approach to revascularization is recommended in patients with diabetes mellitus and complex multivessel CAD. (*Class I, Level of Evidence: C)* • CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel CAD for which revascularization is likely to improve survival (3-vessel CAD or complex 2-vessel CAD involving the proximal LAD), particularly if a LIMA graft can be anastomosed to the LAD artery, provided the patient is a good candidate for surgery (*Class I, Level of Evidence: B*) **2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease[14, d]** • Choices about diagnostic and therapeutic options should be made through a process of shared decision making involving the patient and provider, with the provider explaining information about risks, benefits, and costs to the patient. *(Class I, Level of Evidence: C)* • Standard exercise ECG testing is recommended for patients with an intermediate pretest

2019 ESC guidelines	probability of IHD who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidity. *(Level of Evidence: A)* • Exercise stress with nuclear MPI or echocardiography is recommended for patients with an intermediate to high pretest probability of IHD who have an *un*interpretable ECG and at least moderate physical functioning or no disabling comorbidity. *(Class I, Level of Evidence: B)* • Pharmacological stress with nuclear MPI or echocardiography is recommended for patients with an intermediate to high pretest probability of IHD who are incapable of at least moderate physical functioning or have disabling comorbidity. *(Class I, Level of Evidence: B)* • Assessment of resting left ventricular (LV) systolic and diastolic ventricular function and evaluation for abnormalities of myocardium, heart valves, or pericardium are recommended with the use of Doppler echocardiography in patients with known or suspected IHD and a prior MI, pathological Q waves, symptoms or signs suggestive of heart failure, complex ventricular arrhythmias, or an undiagnosed heart murmur). *(Class I, Level of Evidence: B)* • Pharmacological stress with either nuclear MPI or echocardiography is recommended for risk assessment in patients with SIHD who have left bundle-branch block on ECG, regardless of ability to exercise to an adequate workload. *(Class I, Level of Evidence: B*) • Either exercise or pharmacological stress with imaging (nuclear MPI, echocardiography, or CMR) is recommended for risk assessment in patients with SIHD who are being considered for revascularization of known coronary stenosis of unclear physiological significance. *(Class I, Level of Evidence: B)* • Patients with SIHD who have survived sudden cardiac death or potentially life-threatening ventricular arrhythmia should undergo coronary angiography to assess cardiac risk *(Class I, Level of Evidence: B)* • Patients with SIHD who develop symptoms and signs of heart failure should be evaluated to determine whether coronary angiography should be performed for risk assessment *(Class I, Level of Evidence: B)* • Coronary arteriography is recommended for patients with SIHD whose clinical characteristics and results of noninvasive testing indicate a high likelihood of severe IHD and when the benefits are deemed to exceed risk. *(Class I, Level of Evidence: C)*

	Guideline-Directed Medical Therapy • Treatment with aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications in patients with SIHD. (*Class I, Level of Evidence: A*) • Treatment with clopidogrel is reasonable when aspirin is contraindicated in patients with SIHD. (*Class I, Level of Evidence: B*) • Beta-blocker therapy should be started and continued for 3 years in all patients with normal LV function after MI or ACS. *(Class I, Level of Evidence: B)* • Beta-blocker therapy should be used in all patients with LV systolic dysfunction (ejection fraction _40%) with heart failure or prior MI, unless contraindicated. (Use should be limited to carvedilol, metoprolol succinate, or bisoprolol, which have been shown to reduce risk of death.) *(Class I, Level of Evidence: A)* • ACE inhibitors should be prescribed in all patients with SIHD who also have hypertension, diabetes mellitus, LV ejection fraction 40% or less, or chronic kidney disease, unless contraindicated.(*Class I,* Level of Evidence: A) • Angiotensin-receptor blockers are recommended for patients with SIHD who have hypertension, diabetes mellitus, LV systolic dysfunction, or chronic kidney disease and have indications for, but are intolerant of, ACE inhibitors. (*Class I,* Level of Evidence: A) • An annual influenza vaccine is recommended for patients with SIHD. *(Class I, Level of Evidence: B)* Chest pain management • Beta blockers should be prescribed as initial therapy for relief of symptoms in patients with SIHD (*Class I,* Level of Evidence: B) • Calcium channel blockers or long-acting nitrates should be prescribed for relief of symptoms when beta blockers are contraindicated or cause unacceptable side effects in patients with SIHD (*Class I,* Level of Evidence: B) • Calcium channel blockers or long-acting nitrates, in combination with beta blockers, should be prescribed for relief of symptoms when initial treatment with beta blockers is unsuccessful in patients with SIHD (*Class I,* Level of Evidence: B) • Sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with SIHD (*Class I,* Level of Evidence: B)

	Revascularization • A Heart Team approach to revascularization is recommended in patients with unprotected left main or complex CAD. (*Class I,* Level of Evidence: C) • Calculation of the STS and SYNTAX scores is reasonable in patients with unprotected left main and complex CAD (*Class IIa,* Level of Evidence: B) • CABG to improve survival is recommended for patients with significant (_50% diameter stenosis) left main coronary artery stenosis (*Class I,* Level of Evidence: B) • CABG to improve survival is beneficial in patients with significant (_70% diameter) stenoses in 3 major coronary arteries (with or without involvement of the proximal LAD artery or in the proximal ○ LAD artery plus 1 other major coronary artery *(Class I, Level of Evidence: B)* • CABG or PCI to improve survival is beneficial in survivors of sudden cardiac death with presumed ischemia-mediated ventricular tachycardia caused by significant (_70% diameter) stenosis in a major coronary artery. (*Class I,* CABG Level of Evidence: B; PCI Level of Evidence: C) • CABG or PCI to improve symptoms is beneficial in patients with 1 or more significant (_70% diameter) coronary artery stenoses amenable to revascularization and unacceptable angina despite GDMT (*Class I,* Level of Evidence: A) • PCI with coronary stenting (bare-metal stent or drug-eluting stent) should not be performed if the patient is not likely to be able to tolerate and comply with dual antiplatelet therapy for the appropriate duration of treatment based on the type of stent implanted). *(Class III, Level of Evidence: B)* Follow-up • Patients with SIHD should receive periodic follow-up, at least annually, that includes all of the following *(Class I, Level of Evidence: C)*: • Assessment of symptoms and clinical function; • Surveillance for complications of SIHD, including heart failure and arrhythmias; • Monitoring of cardiac risk factors; and • Assessment of the adequacy of and adherence to recommended lifestyle changes and medical therapy. • Assessment of LV ejection fraction and segmental wall motion by echocardiography or radionuclide imaging is recommended in patients with new or worsening heart failure or evidence of intervening MI by history or ECG. *(Class I, Level of Evidence: C)*

	• Standard exercise ECG testing is recommended in patients with known SIHD who have new or worsening symptoms not consistent with UA and who have a) at least moderate physical functioning and no disabling comorbidity and b) an interpretable ECG.(*Class I,* Level of Evidence: B) • Exercise with nuclear MPI or echocardiography is recommended in patients with known SIHD who have new or worsening symptoms not consistent with UA and who have a) at least moderate physical functioning or no disabling comorbidity but b) an uninterpretable ECG. (*Class I,* Level of Evidence: B)
Adopt recommendations as in line with the goals of care of the patient	**2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)[11, e]** • In 'average surgical risk' patients with an asymptomatic 60–99% stenosis, CEA should be considered in the presence of clinical and/or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is > 5 years. IIa B • In asymptomatic patients who have been deemed 'high risk for CEA' and who have an asymptomatic 60–99% stenosis in the presence of clinical and/or imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, CAS should be considered, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is > 5 years. IIa B • In 'average surgical risk' patients with an asymptomatic 60–99% stenosis in the presence of clinical and/or imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, CAS may be an alternative to CEA provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is > 5 years. IIb B • CEA is recommended in symptomatic patients with 70–99% carotid stenoses, provided the documented procedural death/stroke rate is < 6%. I A • CEA should be considered in symptomatic patients with 50–69% carotid stenoses, provided the documented procedural death/stroke rate is < 6%. IIa A • In recently symptomatic patients with a 50–99% stenosis who present with adverse anatomical features or medical comorbidities that are considered to make them 'high risk for CEA', CAS should be considered, provided the documented procedural death/stroke rate is < 6%. IIa B • When revascularization is indicated in 'average surgical risk' patients with symptomatic carotid

	disease, CAS may be considered as an alternative to surgery, provided the documented procedural death/stroke rate is < 6%. IIb B • When decided, it is recommended to perform revascularization of symptomatic 50–99% carotid stenoses as soon as possible, preferably within 14 days of symptom onset. I A • Revascularization is not recommended in patients with a < 50% carotid stenosis.138 III A • In patients with asymptomatic >50% carotid artery stenosis, long-term antiplatelet therapy (commonly low-dose aspirin) should be considered when the bleeding risk is low. IIa C • In patients with symptomatic carotid stenosis, long-term SAPT is recommended (87). I A • DAPT with aspirin and clopidogrel is recommended for at least 1 month after CAS (60). I B
Adopt recommendations	**2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)[11, e]** • Measurement of the ABI is indicated as a first-line non-invasive test for screening and diagnosis of LEAD. I C • In the case of incompressible ankle arteries or ABI >1.40, alternative methods such as the toe-brachial index, Doppler waveform analysis or pulse volume recording are indicated. I C • DUS is indicated as a first-line imaging method to confirm LEAD lesions. I C • DUS and/or CTA and/or MRA are indicated for anatomical characterization of LEAD lesions and guidance for optimal revascularization strategy. I C • The data from an anatomical imaging test should always be analysed in conjunction with symptoms and haemodynamic tests prior to a treatment decision. I C • Smoking cessation is recommended in all patients with PADs. • Healthy diet and physical activity are recommended for all patients with PADs. I C • Statins are recommended in all patients with PADs. I A • In patients with PADs, it is recommended to reduce LDL-C to < 1.8 mmol/L (70 mg/dL) or decrease it by >_ 50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL). I C • In diabetic patients with PADs, strict glycaemic control is recommended. I C • Antiplatelet therapy is recommended in patients with symptomatic PADs. I C • In patients with PADs and hypertension, it is recommended to control blood pressure at < 140/90 mmHg. I A • ACEIs or ARBs should be considered as first-line therapyc in patients with PADs and hypertension.

	IIa B • Long-term SAPT is recommended in symptomatic patients. I A • Long-term SAPT is recommended in all patients who have undergone revascularization. I C • SAPT is recommended after infra-inguinal bypass surgery. I A • Because of the lack of proven benefit, antiplatelet therapy is not routinely indicated in patients with isolated asymptomatic LEAD. III A • In patients with PADs and AF, OAC is recommended when the CHA2DS2-VASc score is >_2. I A • On top of general prevention, statins are indicated to improve walking distance. I A • In patients with intermittent claudication: o supervised exercise training is recommended. I A o unsupervised exercise training is recommended when supervised exercise training is not feasible or available. I C • When daily life activities are compromised despite exercise therapy, revascularization should be considered. IIa C • When daily life activities are is severely compromised, revascularization should be considered in association with exercise therapy. IIa B • An endovascular-first strategy is recommended for short (i.e. <5 cm) occlusive aorto-iliac lesions. I C • An endovascular-first strategy is recommended in short (i.e. <25 cm) femoral-popliteal lesions. I C • In patients who are not at high risk for surgery, bypass surgery is indicated for long (i.e. >_25 cm) superficial femoral artery lesions when an autologous vein is available and life expectancy is > 2 years. I B • The autologous saphenous vein is the conduit of choice for femoro-popliteal bypass. I A • In the case of chronic limb threatening ischemia, infra-popliteal revascularization is indicated for limb salvage. I C • For revascularization of infra-popliteal arteries: o bypass using the great saphenous vein is indicated. I A o endovascular therapy should be considered. IIa B

Adopt recommendations as in line with the goals of care of the patient	Chronic limb threatening ischemia • Early recognition of tissue loss and/or infection and referral to the vascular team is mandatory to improve limb salvage. I C • In patients with CLTI, assessment of the risk of amputation is indicated. I C • In patients with CLTI and diabetes, optimal glycaemic control is recommended. I C • For limb salvage, revascularization is indicated whenever feasible. I B
Adopt recommendations	**2016 AHA/ACC Guidelines on the Management of Patients with Lower Extremity Peripheral Artery Disease[12, f]** • In patients with history or physical examination findings suggestive of PAD, the resting ABI, with or without segmental pressures and waveforms, is recommended to establish the diagnosis. I B • Resting ABI results should be reported as abnormal (ABI £0.90), borderline (ABI 0.91–0.99), normal (1.00–1.40), or noncompressible (ABI >1.40). I C • Toe-brachial index (TBI) should be measured to diagnose patients with suspected PAD when the ABI is greater than 1.40. I B • Patients with exertional non–joint-related leg symptoms and normal or borderline resting ABI (>0.90 and <=1.40) should undergo exercise treadmill ABI testing to evaluate for PAD. I B • Duplex ultrasound, computed tomography angiography (CTA), or magnetic resonance angiography (MRA) of the lower extremities is useful to diagnose anatomic location and severity of stenosis for patients with symptomatic PAD in whom revascularization is considered. IB • Invasive angiography is useful for patients with CLI in whom revascularization is considered. I C • Antiplatelet therapy with aspirin alone (range 75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD. I A • Treatment with a statin medication is indicated for all patients with PAD. I A • Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death. I A • Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit. I A • Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication. I A • In patients with claudication, a supervised exercise program is recommended to improve functional

	status and QoL and to reduce leg symptoms. I A • A supervised exercise program should be discussed as a treatment option for claudication before possible revascularization. I B • Endovascular procedures are effective as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant aortoiliac occlusive disease. I A • When surgical revascularization is performed, bypass to the popliteal artery with autogenous vein is recommended in preference to prosthetic graft material. I A • In patients with CLI, revascularization should be performed when possible to minimize tissue loss . I B • Endovascular procedures are recommended to establish in-line blood flow to the foot in patients with nonhealing wounds or gangrene. I B • When surgery is performed for CLI, bypass to the popliteal or infrapopliteal arteries (i.e., tibial, pedal) should be constructed with suitable autogenous vein. I A • Surgical procedures are recommended to establish in-line blood flow to the foot in patients with nonhealing wounds or gangrene. I C • Patients with PAD should be followed up with periodic clinical evaluation, including assessment of cardiovascular risk factors, limb symptoms, and functional status. I C • Patients with PAD who have undergone lower extremity revascularization (surgical and/or endovascular) should be followed up with periodic clinical evaluation and ABI measurement. • In addition to the clinical evaluation of cardiovascular risk factors, functional status, and adherence to medical therapy and smoking cessation, patients with PAD who have previously undergone lower extremity revascularization (surgical and/or endovascular) require additional ongoing assessment and care. I C • Follow-up visits after revascularization should include reassessment of the patient's limb symptoms and interval change in functional status, as well as participation in a structured exercise program. Pulse examination and ABI are included in the assessment. A change in ABI of 0.15 is considered clinically significant

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Supplementary Table 4 | **Society guidelines for venous thromboembolism**

Cardio-Oncology perspective	Guideline recommendation
These are specific guidelines for patients with cancer and as such pertain to the cardio-oncology patient population	**2016 ITAC-CME consensus recommendations[15, a]** Initial treatment of established venous thromboembolism (VTE): first 10 days of anticoagulation 1. Low-molecular-weight heparin (LMWH) is recommended for the initial treatment of established VTE in patients with cancer (grade 1B). 2. Fondaparinux and unfractionated heparin can also be used for the initial treatment of established VTE in patients with cancer (grade 2D). 3. Thrombolysis in patients with cancer with established VTE should only be considered on a case-by-case basis, with specific attention paid to contraindications, especially bleeding risk—eg, specifically if brain metastasis (guidance, based on evidence of very low quality and the high bleeding risk of thrombolytic therapy). 4. In the initial treatment of VTE, inferior vena cava filters can be considered in the case of contraindication for anticoagulant treatment or in the case of pulmonary embolism recurrence under optimal anticoagulation. Periodic reassessment of contraindications for anticoagulation is recommended, and anticoagulation should be resumed when safe. Early maintenance (10 days to 3 months) and long-term (beyond 3 months) 1. LMWHs are preferred over vitamin K antagonists (VKAs) for the treatment of VTE in patients with cancer (grade 1A). 2. LMWH should be used for a minimum of 3 months to treat established VTE in patients with cancer (grade 1A). 3. Direct oral anticoagulants can be considered for VTE treatment of patients with stable cancer not receiving systemic anticancer therapy, and in cases where VKA is an acceptable, but not an available, treatment choice (guidance). 4. After 3–6 months, termination or continuation of anticoagulation (LMWH, VKA, or direct oral anticoagulants) should be based on individual assessment of the benefit-to-risk ratio, tolerability, drug availability, patient preference, and cancer activity (guidance, in the absence of data).

	Treatment of VTE recurrence in patients with cancer given anticoagulant treatment, three options can be considered: a) increase in LMWH dose (by 20–25%) in patients treated with LMWH b) switch from VKA to LMWH in patients treated with VKA; and c) inferior vena cava filter insertion—with continued anticoagulant therapy, unless contraindicated Treatment of established catheter-related thrombosis 1. For the treatment of symptomatic catheter-related thrombosis in patients with cancer, anticoagulant treatment is recommended for a minimum of 3 months; in this setting, LMWHs are suggested. Direct comparisons between LMWHs and VKAs have not been made in this setting. 2. The central venous catheter can be kept in place if it is functional, well positioned, and non-infected with good resolution of symptoms under close surveillance; irrespective of whether the central venous catheter is kept or removed, no standard approach in terms of duration of anticoagulation is established (guidance). Prophylaxis of venous thromboembolism (VTE) in surgically treated patients with cancer 1. Use of low-molecular-weight heparin (LMWH) once per day or low-dose unfractionated heparin (UFH) three times per day is recommended to prevent postoperative VTE in patients with cancer; pharmacological prophylaxis should be started 12–2 h preoperatively and continued for at least 7–10 days; no data are available to allow conclusions regarding the superiority of one type of LMWH over another (grade 1A). 2. Evidence to support fondaparinux as an alternative to LMWH for the prophylaxis of postoperative VTE in patients with cancer is insufficient (grade 2C). 3. Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in patients with cancer is recommended (grade 1A). 4. Extended prophylaxis (4 weeks) with LMWH to prevent postoperative VTE after major laparotomy in patients with cancer is indicated in patients with a high VTE risk and low bleeding risk (grade 1B). 5. Extended prophylaxis (4 weeks) with LMWH for the prevention of VTE in patients with cancer undergoing laparoscopic surgery is recommended in the same way as for laparotomy (grade 2C). 6. Mechanical methods are not recommended as monotherapy, except when pharmacological methods are contraindicated (grade 2B). 7. Inferior vena cava filters are not recommended for routine prophylaxis (grade 1A).

	Prophylaxis of VTE in medically treated patients with cancer 1. We recommend prophylaxis with LMWH, UFH, or fondaparinux in medically treated patients with cancer and reduced mobility who are admitted to hospital (grade 1B). In this setting, direct oral anticoagulants are not recommended routinely (guidance). 2. Primary prophylaxis with LMWH, vitamin K antagonists, or direct oral anticoagulants in patients receiving systemic anticancer therapy is not recommended routinely (grade 1B). 3. Primary pharmacological prophylaxis of VTE with LMWH is indicated in patients with locally advanced or metastatic pancreatic cancer treated with systemic anticancer therapy and who have a low bleeding risk (grade 1B). 4. Primary pharmacological prophylaxis of VTE might be indicated in patients with locally advanced or metastatic lung cancer treated with systemic anticancer therapy and who have a low bleeding risk (grade 2C). 5. In patients treated with thalidomide and lenalidomide combined with steroids or other systemic anticancer therapies, or both, VTE primary pharmacological prophylaxis is recommended (grade 1A); in this setting, vitamin K antagonists at low or therapeutic doses, LMWH at prophylactic doses, and low-dose aspirin can be used and have shown similar effects with regard to preventing VTE (grade 2C). Prophylaxis of catheter-related thrombosis 1. Use of anticoagulation for routine prophylaxis of CRT is not recommended (grade 1A). 2. Catheters should be inserted on the right side, in the jugular vein, and the distal extremity of the central catheter should be located at the junction of the superior vena cava and the right atrium (grade 1B). VTE treatment in unique situations 1. A brain tumour per se is not a contraindication for anticoagulation for established venous thromboembolism (VTE; grade 2C). 2. For the treatment of established VTE in patients with cancer with a brain tumour, we prefer low-molecular-weight heparin (LMWH; guidance). 3. We recommend the use of LMWH or unfractionated heparin (UFH) started postoperatively for the prevention of VTE in patients with cancer undergoing neurosurgery (grade 1A). 4. Primary prophylaxis of VTE in medically treated patients with cancer and with brain tumour who

	are not undergoing neurosurgery is not recommended (grade 1B). 5. In the presence of severe renal failure (creatinine clearance <30 mL/min), we suggest using UFH followed by early vitamin K antagonists (possible from day 1) or LMWH adjusted to anti-Xa level for the treatment of established VTE (guidance, in the absence of data and an unknown balance between desirable and undesirable effects). 6. In patients with severe renal failure (creatinine clearance <30 mL/min), an external compression device can be applied, and pharmacological prophylaxis should be considered on a case-by-case basis; in patients with severe renal failure (creatinine clearance <30 mL/min), UFH can be used on a case-by-case basis (guidance, in the absence of data and a balance between desirable and undesirable effects depending on the level of VTE risk). 7. In patients with cancer and thrombocytopenia, full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is >50 g/L and bleeding is not evident; for patients with a platelet count <50 g/L, decisions on treatment and dose should be made on a case-by-case basis with the utmost caution (guidance, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk vs VTE risk). 8. In patients with cancer with mild thrombocytopenia, a platelet count >80 g/L, pharmacological prophylaxis might be used; if the platelet count is <80 g/L, pharmacological prophylaxis should only be considered on a case-by-case basis and careful monitoring is recommended (guidance, in the absence of data and a balance between desirable and undesirable eff ects depending on the bleeding risk vs VTE risk). 9. In pregnant patients with cancer, standard treatment for established VTE and standard prophylaxis should be implemented (guidance, in the absence of data and based on the contraindication of vitamin K antagonists during pregnancy). **International Society of Thrombosis and Haemostasis Guidance Statements** **2018 Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH[16, b]** 1. We recommend individualized treatment regimens after shared decision-making with patients. 2. We suggest the use of specific DOACs for cancer patients with an acute diagnosis of VTE, a low risk of bleeding, and no drug–drug interactions with current systemic therapy. LMWHs constitute an acceptable alternative. Currently, edoxaban and rivaroxaban are the only DOACs that have been compared with LMWH in RCTs in cancer populations. A final treatment recommendation should be made after shared decision-making with patients regarding a potential reduction in recurrence but

	higher bleeding rates with specific DOACs, incorporating patient preferences and values. 3. We suggest the use of LMWHs for cancer patients with an acute diagnosis of VTE and a high risk of bleeding, including patients with luminal gastrointestinal cancers with an intact primary, patients with cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes, or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis, or colitis. Specific DOACs (edoxaban and rivaroxaban) are acceptable alternatives if there are no drug–drug interactions with current systemic therapy. A final treatment recommendation should be made after shared decision-making with patients regarding a potential reduction in recurrence but higher bleeding rates with specific DOACs, incorporating patient preferences and values. **2015 Diagnosis and treatment of the incidental venous thrombosis in cancer patients**[17, c] 1. In cancer patients with a diagnosis of incidental VTE, we recommend a careful review of the history to exclude symptomatic VTE. 2. In patients with incidental PE involving the main, lobar, segmental or multiple subsegmental pulmonary arteries, we suggest that no further testing is required to confirm the diagnosis. 3. In patients with isolated SSPE, we recommend careful review of the images by radiologists, and suggest that compression ultrasonography of the lower limbs be performed to detect concomitant incidental DVT. 4. In patients with incidental ileofemoral DVT on CT of the abdomen and pelvis, we suggest confirming the diagnosis with Doppler ultrasonography of the pelvis and compression ultrasonography of the lower limbs. 5. In cancer patients with incidental VTE, we recommend standard anticoagulation with LMWH in those with symptoms compatible with VTE. 6. In patients with incidental proximal DVT, or PE of the main, lobar, segmental or multiple subsegmental pulmonary arteries, we recommend therapeutic anticoagulation for at least 6 months. 7. In patients with isolated SSPE with proximal DVT, we recommend therapeutic anticoagulation for at least 6 months. 8. In patients with isolated SSPE with distal DVT or without DVT, we suggest that the decision to provide anticoagulation be made on a case-by-case basis, considering the risk of bleeding, the presence of risk factors for recurrent thrombosis, the performance status of the patient, and patient preference. If the decision is not to anticoagulate, we suggest clinical monitoring and serial bilateral

	compression ultrasonography after 1 week in those with distal DVT, to detect thrombus extension. 9. In patients with incidental splanchnic vein thrombosis, we suggest anticoagulant therapy in patients with thrombosis that appears to be acute, or that shows progression or extension over time, and in those who are neither actively bleeding nor have a very high risk of bleeding. 10. In cancer patients with evidence of disease or ongoing systemic or locoregional therapy, we suggest periodic re-evaluation of the risks of bleeding and VTE recurrence, as well as patient preferences, to guide the decision of whether to extend LMWH beyond 6 months. **2014 Prevention of Venous Thromboembolism in Cancer Outpatients**[18, d] 1. We recommend that cancer outpatients be assessed for the risk of cancer-associated VTE at the time of initiation of systemic therapy and periodically, for as long as systemic therapy is ongoing. Risk assessment may be utilized as an opportunity to educate patients about the warning signs and symptoms of VTE. 2. We recommend against routine thromboprophylaxis in cancer outpatients, i.e. without risk assessment, and against its use in low-risk patients as defined by the Khorana Score. 3. We recommend that patients be considered for enrollment in RCTs of outpatient prophylaxis to strengthen the evidence base. 4. We suggest that, in the absence of available clinical trials, cancer patients with solid tumors and a Khorana Score of ≥ 3 or advanced pancreatic cancer starting or receiving systemic therapy should be prescribed outpatient thromboprophylaxis, except for those with contraindications to anticoagulation or a diagnosis of primary brain tumor. 5. We recommend that patients with myeloma receiving thalidomide-based or lenalidomide-based combination regimens be prescribed outpatient thromboprophylaxis, except for those with contraindications to anticoagulation. 6. We suggest that, when outpatient thromboprophylaxis is indicated in patients with solid tumors as previously discussed, LMWHs should be used. 7. We recommend that either LMWHs or aspirin be used for outpatient thromboprophylaxis in patients with myeloma receiving thalidomide-based or lenalidomide-based combination regimens. We suggest that LMWHs should be preferred in this setting for patients with additional risk factors, such as a prior history of thromboembolism. 8. We suggest that LMWHs should be used as monotherapy at routine prophylaxis doses for outpatient thromboprophylaxis in patients with solid tumors and myeloma for a period of 12 weeks after the initiation of a new systemic therapy regimen. We suggest higher doses (dalteparin

	200 IU kg^{-1} daily for 4 weeks and 150 IU kg^{-1} daily thereafter or enoxaparin 1 mg kg^{-1} daily) in patients with advanced pancreatic cancer who are not otherwise considered to be at high risk for bleeding. 9. We suggest that if, in patients with myeloma, aspirin monotherapy is selected for prophylaxis, the dose of 100 mg daily (or the closest available formulation) should be used for the duration of thalidomide-based or lenalidomide-based combination regimens. **2014 Prevention of venous thromboembolism in hospitalized medical cancer patients**[19, e] 1. In patients with active cancer hospitalized for an acute medical illness, we recommend the use of pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications. 2. In patients admitted for minor procedures or short-term chemotherapy infusion, we suggest not using pharmacologic thromboprophylaxis. 3. In patients with active cancer hospitalized for an acute medical illness, we recommend the use of heparins throughout hospitalization, and suggest the use of LMWH rather than UFH. 4. In medical hospitalized cancer patients, we recommend not using the new oral anticoagulants for VTE thromboprophylaxis. 5. In patients with active cancer hospitalized for an acute medical illness, we suggest mechanical prophylaxis with pneumatic compression devices in patients with concomitant bleeding or a high risk of bleeding. 6. We recommend initiating or resuming pharmacologic thromboprophylaxis once bleeding resolves. 7. In patients with active cancer hospitalized for an acute medical illness, we recommend pharmacologic thromboprophylaxis if the platelet count is ≥ 50 × 10^9 L^{-1} in the absence of other contraindications. 8. If the platelet count is between 25 × 10^9 L^{-1} and 50 × 10^9 L^{-1}, we suggest an individualized 'case-by-case' approach. 9. We suggest not using pharmacologic prophylaxis in patients with a platelet count of < 25 × 10^9 L^{-1}. 10. In hospitalized medical cancer patients with a creatinine clearance rate (Cockcroft–Gault) of ≥ 30 mL min^{-1}, we recommend standard prophylactic doses of LMWH in the absence of other contraindications. 11. In cancer patients with a creatinine clearance below 30 mL min^{-1}, we suggest LMWH with a low degree of bioaccumulation or UFH.

	2014 Catheter-associated deep vein thrombosis of the upper extremity in cancer patients[20, f] 1. We recommend ultrasonography as the initial test of choice for the diagnosis of suspected upper extremity thrombosis. 2. We recommend against the utilization of D-dimer to exclude the diagnosis of suspected catheter-associated upper extremity deep vein thrombosis. 3. We suggest evaluation of deep vein thrombosis by standard contrast venography in cases of high clinical suspicion and negative (or non-diagnostic) ultrasound testing. Less invasive radiographic methods such as CT venography or MRI venography can be considered if contrast venography is not available or practical. 4. We suggest anticoagulation with low-molecular-weight heparin without removal of the catheter if the central venous catheter is functional and required for ongoing therapy. 5. We recommend removal of a non-functional, infected or incorrectly positioned catheter and suggest anticoagulation with low-molecular-weight heparin. 6. We suggest a short duration of anticoagulation (3–5 days), if clinically practical, prior to removal of a central venous catheter. 7. We suggest removal of a central venous catheter without anticoagulation if therapeutic anticoagulation cannot be safely administered due to the active risk of hemorrhage. 8. We suggest anticoagulation over no anticoagulation for an incidental catheter-associated DVT. Alternative strategies such as serial ultrasound and/or catheter removal can be considered. 9. We recommend anticoagulation over thrombolysis for the acute management of catheter-associated thrombosis. Consideration of clot-directed thrombolysis should be reserved for cases of massive clot burden and/or refractory thrombosis. 10. In cases of thrombocytopenia without bleeding, the decision to anticoagulate or withhold anticoagulation should be made on an individual basis. 11. We suggest 3–6 months of anticoagulation for a symptomatic, catheter-associated upper extremity deep vein thrombosis. 12. We suggest the long-term administration of low-molecular-weight heparin over warfarin in cancer patients. 13. We suggest anticoagulation for the duration the catheter remains in place for individuals with ongoing risk factors, such as persistent central venous catheter.

	2013 Management of challenging cases of patient with cancer-associated thrombosis including recurrent thrombosis and bleeding[21, g] 1. We recommend that cancer patients with symptomatic recurrent VTE despite therapeutic anticoagulation with VKAs be switched to therapeutic weight-adjusted doses of LMWH. 2. We suggest that cancer patients with symptomatic recurrent VTE despite anticoagulation with LMWH continue with LMWH at a higher dose, starting at an increase of ~ 25% of the current dose or increasing it back up to the therapeutic weight-adjusted dose if they are receiving non-therapeutic dosing. 3. We recommend that all cancer patients with recurrent VTE despite anticoagulation be reassessed 5–7 days after a dose escalation of their anticoagulant therapy. Patients with symptomatic improvement should continue with the same dose of LMWH and resume their usual follow-up. In patients without symptomatic improvement, we suggest using the peak anti-FXa level to estimate the dose of the next escalation. 4. We recommend giving full therapeutic doses of anticoagulation without platelet transfusion in patients with CAT and a platelet count of ≥ $50 \times 10^9\ L^{-1}$. 5. For acute CAT and thrombocytopenia (< $50 \times 10^9\ L^{-1}$): a) We recommend full therapeutic doses of anticoagulation with platelet transfusion to maintain a platelet count of ≥ $50 \times 10^9\ L^{-1}$. b) If platelet transfusion is not possible or is contraindicated, we suggest insertion of a retrievable filter and removal of the filter when the platelet count recovers and anticoagulation can be resumed. 6. For subacute or chronic CAT and thrombocytopenia (< $50 \times 10^9\ L^{-1}$): a) We suggest reducing the dose of LMWH to 50% of the therapeutic dose or using a prophylactic dose of LMWH in patients with a platelet count of 25–$50 \times 10^9\ L^{-1}$. b) We suggest discontinuing anticoagulation in patients with a platelet count of < $25 \times 10^9\ L^{-1}$. 7. We recommend careful and thorough assessment of each bleeding episode, including identification of the source, its severity or impact, and reversibility. 8. We recommend usual supportive care with transfusion and surgical intervention to stop the bleeding, whenever indicated and possible. 9. We recommend withholding anticoagulation in patients who have a major or life-threatening bleeding episode. 10. We suggest IVC filter insertion in patients with acute CAT or subacute CAT who are having a major

	or life-threatening bleeding episode. 11. We recommend against IVC filter insertion in patients with chronic CAT. 12. We recommend initiating or resuming anticoagulation and removing the retrievable IVC filter (if inserted) once the bleeding resolves. 13. We recommend against IVC filter insertion in the absence of contraindications to anticoagulation. 14. We suggest IVC filter insertion in cancer patients with contraindications to anticoagulation and a high risk of potentially fatal PE. 15. We recommend resuming anticoagulation with LMWH and removing the retrievable filter in cancer patients when the contraindication has resolved. **2014 American Society of Clinical Oncology Clinical Practice Guideline Update 2014: Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer[22, h]** ● Most hospitalized patients with active cancer require thromboprophylaxis throughout hospitalization. Data are inadequate to support routine thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusion. ● Routine thromboprophylaxis is not recommended for ambulatory patients with cancer. It may be considered for highly select high-risk patients. ● Patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy and/or dexamethasone should receive prophylaxis with either low–molecular weight heparin (LMWH) or low-dose aspirin to prevent venous thromboembolism (VTE). ● Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days. ● Extending postoperative prophylaxis up to 4 weeks should be considered in those undergoing major abdominal or pelvic surgery with high-risk features. ● LMWH is recommended for the initial 5 to 10 days of treatment of established deep vein thrombosis and pulmonary embolism as well as for long-term secondary prophylaxis for at least 6 months. ● Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE. ● Anticoagulation should not be used to extend survival of patients with cancer in the absence of other indications. ● Patients with cancer should be periodically assessed for VTE risk. ● Oncology professionals should educate patients about the signs and symptoms of VTE.

	2019 NCCN Guidelines on Cancer-Associated Venous Thromboembolic Disease[23, i] Anticoagulation for VTE • Monotherapy a) LWMH: Dalteparin 200 U/kg SC daily for 30 days, then 150 U/kg once daily for 2-6 months (category 1), enoxaparin (category 2A) b) Rivaroxaban 15 mg BID for 21 days, then 20 mg daily (category 2A) c) Fondaprarunux 5, 75., 10 mg [<50, 50-100, and >100 kg] (category 2A) d) UFH (categpry 2B) e) UFH IV then SC (category 2A) f) UFH SC (category 2A) g) For patients who refuse or have compelling reasons to avoid LMWH: Apixaban (category 2A) • Combination therapy with edoxaban a) LMWH (dalteparin 200 U/kg SC daily or enoxaparin 1 mg/kg SC BID) (category 1) or UFH IV or SC for 5-10 days, then edoxaban 60 mg daily (or 30 mg if CrCl 30-50 mL or <60 kg weight or concomitant p-glycoprotein inhibitors or inducers) for at least 6 months • Combination therapy with warfarin a) LMWH (as above), fondaparinux, or UFH IV or SC for 5-10 days, then warfarin with INR 2-3 for at least 6 months • Combination therapy with dabigatran a) LMWH (dalteparin 200 U/kg SC daily or enoxaparin 1 mg/kg SC BID) (category 1) or UFH IV or SC for 5-10 days, then dabigatran 150 mg BID (as long as CrCl >30 mL/min) for at least 6 months • Duration a) Minimum of 3 months b) For non-catheter-associated DVT/PE indefinite while cancer is active, under treatment or risk factors for recurrence persist c) For catheter-asscoiated thrombosis, anticoagulation as long as catheter is in place, recommended at least 3 months

	2016 ACCP Guidelines[24, j] • In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C). • In patients with DVT of the leg or PE who receive extended therapy, we suggest that there is no need to change the choice of anticoagulant after the first 3 months (Grade 2C). • In patients with DVT of the leg or PE and active cancer ("cancer-associated thrombosis") and who (i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B), or (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B). • In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE (Grade 2B). • In patients with acute DVT or PE who are treated with anticoagulants, we recommend against the use of an inferior vena cava (IVC) filter (Grade 1B). • In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS (Grade 2B).

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Supplementary Table 5 | **Society guidelines for pulmonary hypertension**

Cardio-Oncology perspective	Guideline recommendation
Adopt recommendations	**2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension[25, a]** • Vasoreactivity testing is recommended in patients with PAH associated with drugs use to detect patients who can be treated with high doses of a CCB • A positive response to vasoreactivity testing is defined as a reduction of mean PAP ≥10 mmHg to

Adopt recommendations	reach an absolute value of mean PAP ≤40 mmHg with an increased or unchanged cardiac output • Nitric oxide is recommended for performing vasoreactivity testing • Intravenous epoprostenol is recommended for performing vasoreactivity testing as an alternative • High doses of CCBs are recommended in patients with IPAH, HPAH and DPAH who are responders to acute vasoreactivity testing • Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) is • recommended in patients with IPAH, HPAH and DPAH treated by high doses of CCBs • Continuation of high doses of CCBs is recommended in patients with IPAH, HPAH and DPAH in WHO-FC I or II with marked haemodynamic improvement (near normalization) • Initiation of specific PAH therapy is recommended in patients in WHO-FC III or IV or those without marked haemodynamic improvement (near normalization) after high doses of CCBs • For patients with WHC FC II and III, the endothelin receptor antagonists ambrisentan, bosentan, • Macitentan, or the phosphodiesterase type 5 inhibitors Sildenafil, Tadalafil, Vardenafil, or the • Guanylate cyclase stimulators Riociguat , or combination therapy with Ambrisentan +tadalafil, or sequential therapy with Macitentan added to sildenafil • Riociguat added to bosentan Selexipage added to ERA and/or PDE-5i • For patients with WHC FC II and III, Epoprostenol Intravenous **American College of Chest Physicians (CHEST): Guideline and expert panel report on pharmacologic therapy for pulmonary arterial hypertension in adults (2014)[26, b]** • We suggest that the severity of a pulmonary arterial hypertension (PAH) patient's disease be evaluated in a systematic and consistent manner, using a combination of World Health Organization (WHO) functional class (FC), exercise capacity, echocardiographic, laboratory and hemodynamic variables in order to inform therapeutic decisions (Grade CB). • We suggest that, whenever possible, all PAH patients be evaluated promptly at a center with expertise in the diagnosis of PAH, ideally prior to the initiation of therapy (Grade CB). • We suggest collaborative and closely coordinated care of PAH patients involving the expertise of both local physicians and those with expertise in PAH care (Grade CB). • For treatment naive PAH patients with WHO FC I symptoms, we suggest continued monitoring for the development of symptoms that would signal disease progression and warrant the initiation of pharmacotherapy (Grade CB).

	• We suggest that patients at risk for the development of PAH (eg, patients with systemic sclerosis or the presence of a known mutation placing the patient at risk for PAH) be monitored for the development of symptoms of PAH (Grade CB). • We suggest also that contributing causes of PH (eg, sleep apnea and systemic hypertension) in patients with PAH be treated aggressively (Grade CB). • We suggest that patients with PAH, in the absence of contraindications, should undergo acute vasoreactivity testing using a short-acting agent at a center with experience in the performance and interpretation of vasoreactivity testing (Grade CB). • We suggest that patients with PAH who, in the absence of right-heart failure or contraindications to CCB therapy, demonstrate acute vasoreactivity according to consensus definition, should be considered candidates for a trial of therapy with an oral CCB blocker (Grade CB). • We suggest that CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity (Grade CB). • PAH-Specific Pharmacotherapies Patients With WHO FC II Symptoms: For treatment naive PAH patients with WHO FC II symptoms who are not candidates for, or who have failed CCB therapy, we advise monotherapy be initiated with a currently approved endothelin receptor antagonist (ETRA), phosphodiesterase-5 (PDE5) inhibitor, or the soluble guanylate cyclase stimulator riociguat. • Patients with WHO FC III Symptoms: For treatment-naive PAH patients with WHO FC III symptoms who are not candidates for, or who have failed CCB therapy, we advise monotherapy be initiated with a currently approved ETRA, a PDE5 inhibitor, or the soluble guanylate cyclase stimulator riociguat. • Patients with WHO FC IV Symptoms: For treatment naive PAH patients in WHO FC IV, we advise initiation of monotherapy with a parenteral prostanoid agent. • PAH Patients on Established PAH-Specific Therapy: In PAH patients initiating therapy with IV epoprostenol, we suggest against the routine simultaneous initiation of bosentan (Grade CB). • For WHO FC III or IV PAH patients with unacceptable clinical status despite established PAH-specific monotherapy, we advise addition of a second class of PAH therapy to improve exercise capacity. Such patients are ideally evaluated at centers with expertise in the evaluation and treatment of complex patients with PAH.

[a]Reprinted from REF.[25] with permission of the © 2019 European Society of Cardiology & European Respiratory Society. *European Respiratory Journal* **46** (4) 903–975; https://doi.org/10.1183/13993003.01032-2015, published 30 September 2015. [b]Reprinted with permission from REF.[26], Elsevier.

Supplementary Table 6 | **Guideline recommendations for cardiovascular complications of immunotherapies**

Recommendation	Strength	Level of evidence
2018 American Society of Clinical Oncology Clinical Practice Guideline: Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy[27] • Patient and family caregivers should receive timely and up-to-date education about immunotherapies, their mechanism of action, and the clinical profile of possible irAEs prior to initiating therapy and throughout treatment and survivorship. • There should be a high level of suspicion that new symptoms are treatment related. • In general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities. • Hold ICPis for most grade 2 toxicities and consider resuming when symptoms and/or laboratory values revert to grade 1 or less. Corticosteroids (initial dose of 0.5 to 1 mg/kg/d of prednisone or equivalent) may be administered. • Hold ICPis for grade 3 toxicities and initiate high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone IV 1 to 2 mg/kg/d). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. If symptoms do not improve with 48 to 72 hours of high-dose corticosteroid, infliximab may be offered for some toxicities. • When symptoms and/or laboratory values revert to grade 1 or less, rechallenging with ICPis may be offered; however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended. • In general, grade 4 toxicities warrant permanent discontinuation of ICPis, with the exception of endocrinopathies that have been controlled by hormone replacement. • Diagnostic work-up • Evaluation of signs and symptoms of PE or DVT may include • Clinical prediction rule to stratify patients with suspected venous thromboembolism • Venous ultrasound for suspected DVT • CTPA for suspected PE	Moderate	Expert consensus

• Can also consider D-dimer for low-risk patients based on risk stratification by clinical prediction rule for DVT/PE when CT or Doppler are not available or appropriate
• Ventilation/perfusion scan is also an option when CTPA is not appropriate
• Consider other testing, including ECG, CXR, BNP and troponin levels, and arterial blood gas
 	
• G1: Venous thrombosis (eg, superficial thrombosis)
  ○ Continue ICPi
  ○ Warm compress
  ○ Clinical surveillance
 	
• G2: Venous thrombosis (eg, uncomplicated DVT)
  ○ Medical intervention indicated
  ○ Continue ICPi
 	
• G3: Thrombosis (eg, uncomplicated PE [venous], nonembolic, cardiac mural [arterial] thrombus)
  ○ medical intervention indicated
  ○ Management according to CHEST, ACC, and/or AHA guidelines and consider consult from cardiology or other relevant specialties
  ○ LMWH is suggested over VKA, dabigatran, rivaroxaban apixaban, or edoxaban for initial and long-term treatment
  ○ IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term
 	
• G4: Life-threatening (eg, PE, cerebrovascular event, arterial insufficiency), hemodynamic or neurologic instability,
 	
  ○ Urgent intervention indicated
  ○ Permanently discontinue ICPi
  ○ Admit patient and management according to CHEST, ACC, and/or AHA		

guidelines and with guidance from cardiology ○ Respiratory and hemodynamic support ○ LMWH is suggested over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment ○ IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term ○ Further clinical management as indicated based on symptoms • Additional considerations ○ While it may be impossible to determine the etiology of thromboembolic disease in patients with advanced cancer and the role, if any, that ICPi treatment plays, it is reasonable to remove the potential inciting agents given the severity and life-threatening potential of G4 complications. Clinicians are to use clinical judgment and take into account the risks and benefits when deciding whether to discontinue ICPi treatment. ○ Anticoagulant therapy duration should continue for a minimum of 9-12 months to indefinitely in the setting of active cancer unless patient is asymptomatic, doing well, or in remission.		

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Supplementary Table 7 | **Consensus recommendations for cardiac catheterization aspects for patients with cancer by the Society for Cardiovascular Angiography and Interventions (SCAI)**[28]

Listing of recommendations (no grading of the strength of recommendation or supporting level of evidence)
• Cardiovascular screening recommendations for cancer survivors Referral to a survivorship center/cardio-oncology program is recommended for cancer survivors who are not being actively followed by hematology/oncologist.
• Medical record documentation of the patient's chemotherapy and radiotherapy treatment course with cumulative doses should be retrieved.
• Transthoracic echocardiography (TTE) should be performed on patients with a history of significant anthracycline dose exposure (>240 mg/m2) or chest radiation exposure (>30 Gy) starting no later than 2 years after completion of

therapy, at 5 years after diagnosis and continued every 5 years thereafter.
• In high-risk groups (known coronary artery disease, age >60, one or more CV risk factors) screening after chest radiation therapy should be initiated 2 years after radiation therapy.
• Coronary angiography is indicated for symptomatic patients with a history of radiotherapy, risk factors for RIHD, and noninvasive testing (i.e., stress MPI/echo/MRI, CCTA) that suggest a high likelihood of severe ischemic heart disease.
• Coronary angiography is reasonable to consider for the evaluation of LV systolic dysfunction after chest radiation and to evaluate for radiation-induced ischemic heart disease.
• Right and left heart catheterization is reasonable to evaluate the presence of pericardial constriction and restrictive cardiomyopathy if noninvasive imaging (echocardiography, CT, MR) is insufficient to provide a diagnosis.
• Right and/or left heart catheterization and coronary angiography is reasonable to perform as per ACC/AHA guidelines for preoperative planning for patients with severe RIHD.
• There is a known association between accelerated coronary artery disease and elevated cardiovascular events and mortality after chest radiation, particularly in high-risk populations such as those with Hodgkin's lymphoma who have undergone mantle field radiation. For these patients, functional imaging and/or CAC/CCTA is reasonable to perform ≥5 years post-radiotherapy, and further workups (e.g., coronary angiography, functional testing) is indicated for risk stratification if there is concern for severe ischemic heart disease.
Special considerations for patients with cancer with thrombocytopenia undergoing cardiac catheterization
• Prophylactic platelet transfusion is not recommended in patients undergoing cardiac catheterization with thrombocytopenia, unless recommended by the oncology/hematology team for one of the following indications:
○ Platelet count <20,000/mL and one of the following: (a) high fever, (b) leukocytosis, (c) rapid fall in platelet count, (d) other coagulation abnormality
○ Platelet count <20,000/mL in solid tumor patients receiving therapy for bladder, gynecologic, or colorectal tumors, melanoma, or necrotic tumors
○ Therapeutic platelet transfusions are recommended in thrombocytopenic patients who develop bleeding during or after cardiac catheterization. Repeat platelet counts are recommended after platelet transfusions.
○ 30–50 U/kg unfractionated heparin is the initial recommended dose for thrombocytopenic patients undergoing PCI who have platelets <50,000/mL. ACT should be monitored.
○ For platelet counts <30,000/mL, revascularization and DAPT should be decided after a preliminary multidisciplinary evaluation (interventional cardiology/oncology/hematology) and a risk/benefit analysis.
○ Aspirin administration may be used when platelet counts are >10,000/mL.

○ DAPT with clopidogrel may be used when platelet counts 30,000–50,000/mL. Prasugrel, ticagrelor and IIB-IIIA inhibitors should not be used in patients with platelet counts <50,000.
○ If platelet counts are <50,000, the duration of DAPT may be restricted to 2 weeks following PTCA alone, 4 weeks after bare-metal stent (BMS), and 6 months after second or third generation drug-eluting stents (DES) if optimal stent expansion was confirmed by IVUS or OCT.
○ There is no minimum platelet count to perform a diagnostic coronary angiogram.
Access considerations for patients with cancer undergoing cardiac catheterization
• For cancer patients who are excellent candidates for both access types, the radial artery is preferred. Femoral access is the preferred approach for cancer patients on hemodialysis, those with abnormal Allen's tests in both arms, multiple radial procedures or a-lines, bilateral mastectomy or when a complex intervention is anticipated.
• The use of smaller sheath sizes, prompt removal of sheaths and early ambulation is recommended.
• A lower dose of intra-arterial or intravenous unfractionated heparin at a dose of 50 U/kg or 3.000 units is recommended for patients with cancer with thrombocytopenia and platelet count <50k undergoing cardiac catheterization via radial access.
• A femoral angiogram is recommended after transfemoral access to promptly identify and address potential access complications.
Special considerations for patients with cancer undergoing cardiac catheterization for CAD
• Decision-making regarding revascularization in patients with active cancer must take into consideration the overall prognosis of the patient.
• For patients with cancer with an acceptable prognosis, the general revascularization criteria for appropriate use must be carefully evaluated and only the most appropriate indications (scores 7 and above) should be considered [225].
• For patients with cancer with an expected survival <1 year, percutaneous revascularization may be considered for patients with acute STEMI and high-risk NSTEMI. For patients with stable angina, every effort must be made to maximally optimize medical therapy before resorting to an invasive strategy. This approach must include addressing other cancer-related comorbidities that potentially exacerbate ischemia, such as anemia, infection, hypoxia, etc. Should the patient continue to experience persistently severe angina (CCS Class III or IV), consideration may be given to percutaneous revascularization as a palliative option.
• FFR is recommended before non-urgent PCI to justify the need for revascularization.
• When invasive approach is indicated:

○ Balloon angioplasty should be considered for patients with cancer who are not candidates for DAPT (Platelets <30,000/mL) or when a non-cardiac procedure or surgery is necessary as soon as possible.
○ BMS should be considered for patients with platelet counts >30,000/mL who need a non-cardiac procedure, surgery or chemotherapy which can be postponed for >4 weeks.
○ Newer generation DES should be considered for patients with platelet counts >30,000/mL who are not in immediate need for a non-cardiac procedure, surgery or chemotherapy.
○ Bivalirudin and/or radial approach should be considered to minimize the risk of bleeding.
• Post intervention:
• Intravascular imaging such as IVUS or optical coherence tomography (OCT) is recommended after stent placement to ensure optimal expansion and an absence of complications given the potential for early DAPT interruption.

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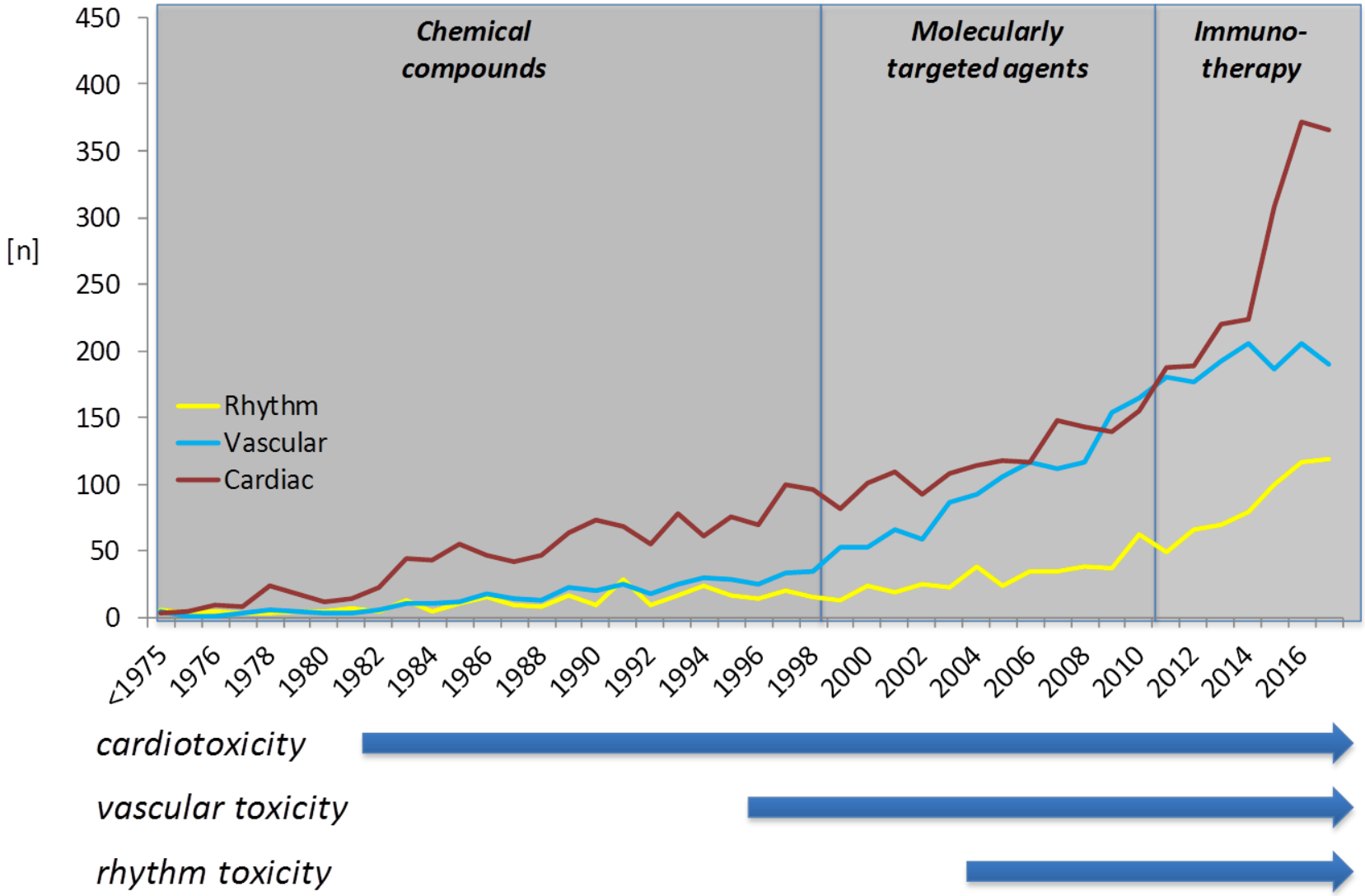
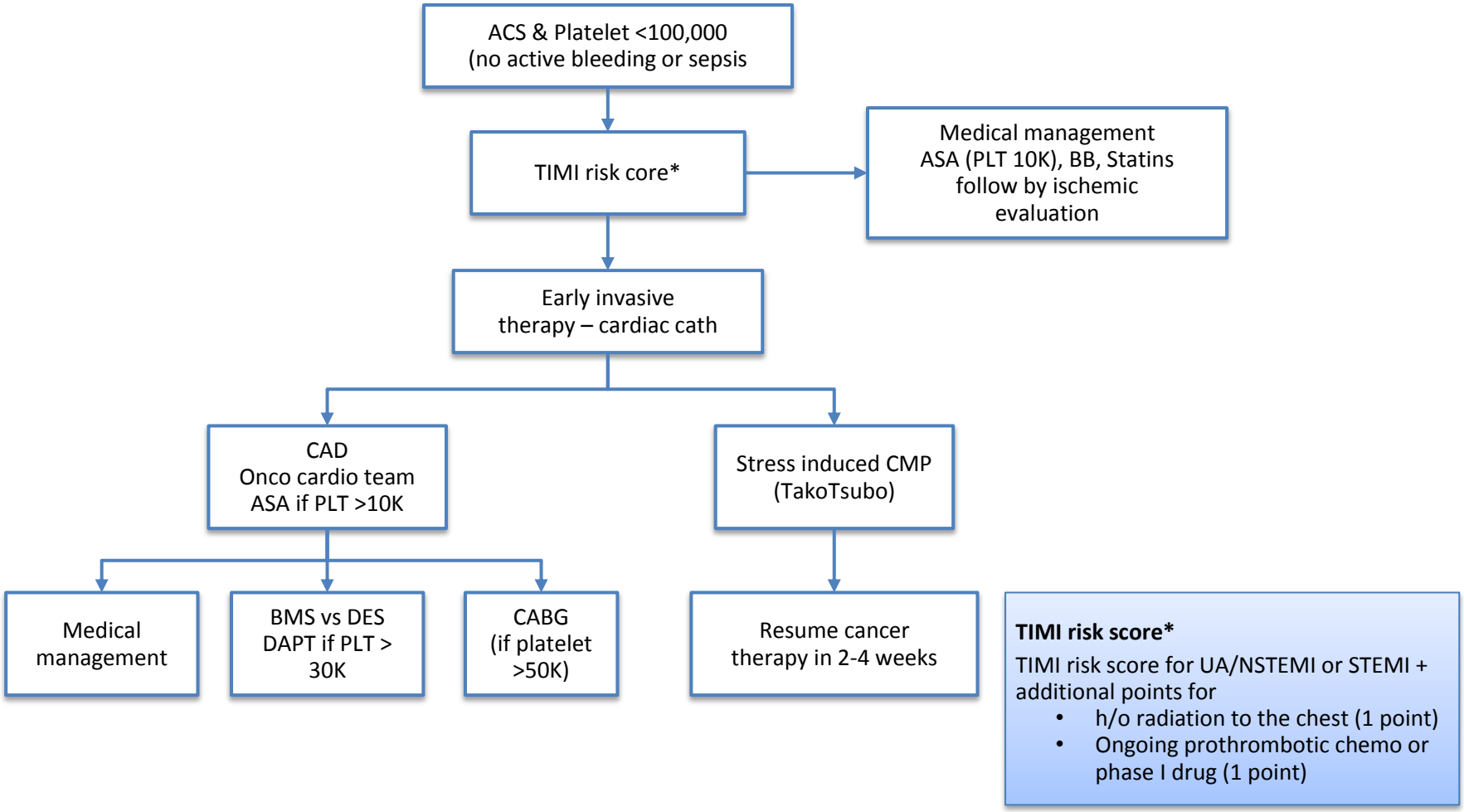
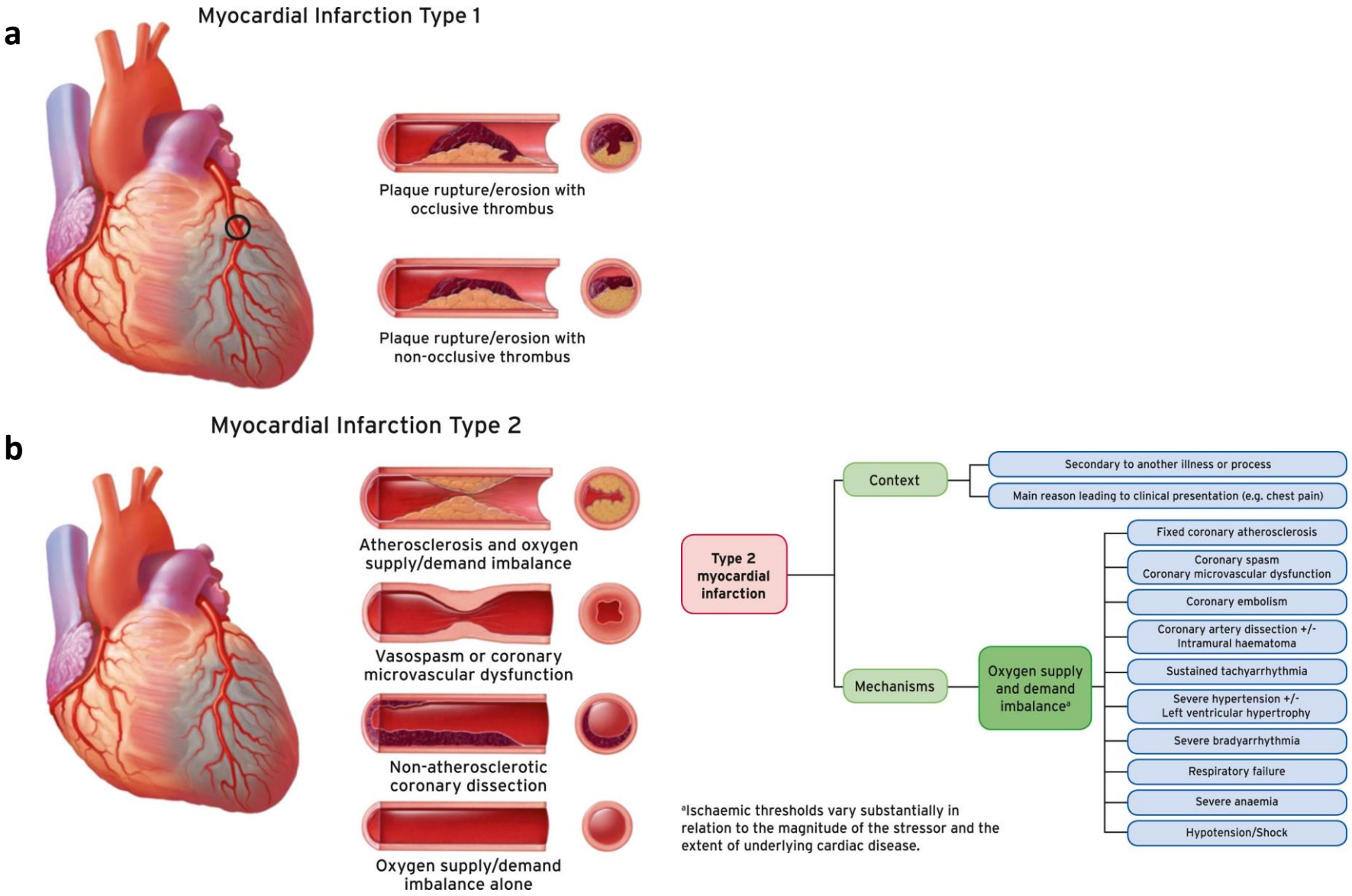


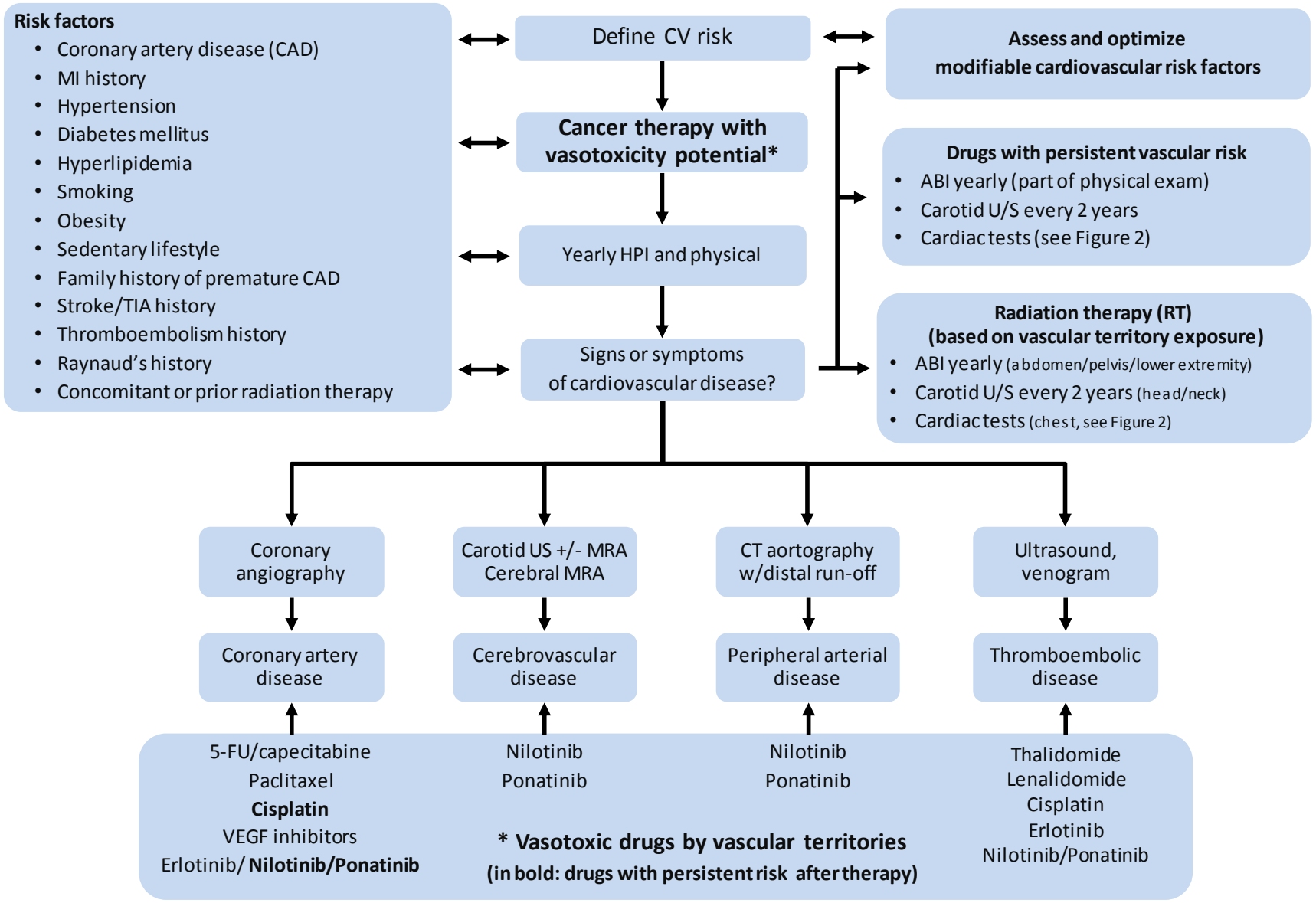
Supplementary Figure 1 | Number of articles published on cancer therapeutics and the three specified cardiovascular toxicities: cardiac, vascular, and arrhythmia.



Supplementary Figure 2 | Revascularization approach for patients with cancer, as outlined in the Society for Cardiovascular Angiography and Interventions (SCAI) expert consensus statement on the evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory. Reproduced with permission from REF.[28], Wiley-VCH.

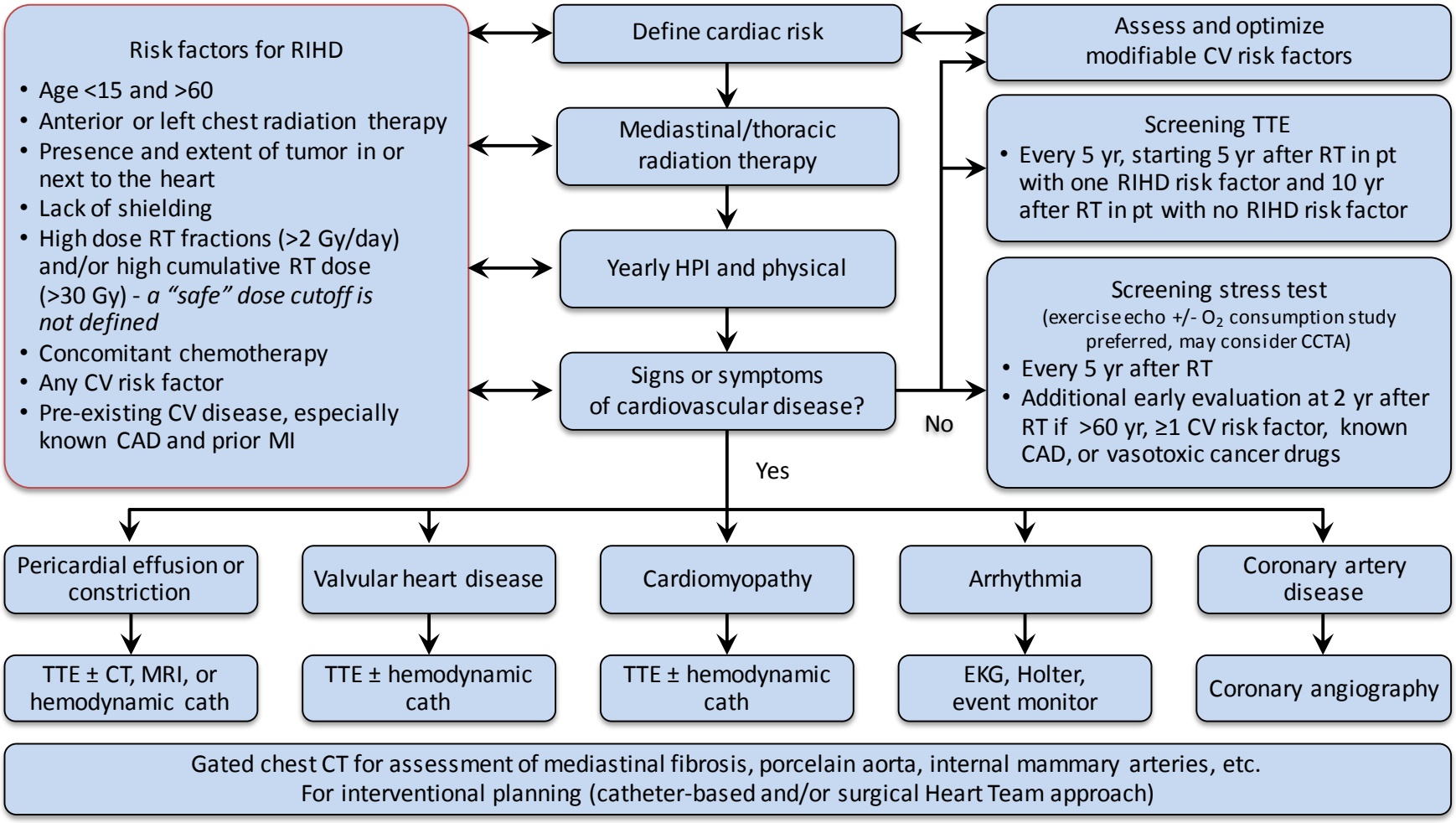


Supplementary Figure 3 | Illustration of type 1 (a) and type 2 (b) myocardial infarction, as per the Fourth Universal Definition of Myocardial Infarction[29]. Reproduced with permission from REF.[29], Elsevier.



Supplementary Figure 4 | Suggested SCAI algorithm for the cardiovascular screening of patients on chemotherapy. HPI, history of present illness; TIA, transient ischemic attack; ABI, ankle–brachial index; U/S, Ultrasound; CCTA, cardiac computed tomography angiography. *Pivotal to the sequence is the determination of baseline cardiac risk, including presence of ischemic heart disease, history of

myocardial infarction, cardiovascular risk factor profile, and calculated atherosclerotic cardiovascular disease risk, for example, AHA/ACC ASCVD risk calculator, Framingham risk score, or ESC Score. Reproduced with permission from REF.[28], Wiley-VCH.



Supplementary Figure 5 | Suggested SCAI algorithm for the cardiovascular screening of patients on radiation therapy. RIHD, radiation-induced heart disease; HPI, history of present illness; TTE, transthoracic echocardiogram; CCTA, cardiac computed tomography angiography; EKG, electrocardiogram; RT, radiation therapy. *Pivotal to the sequence is the determination of baseline cardiac risk, including presence of ischemic heart disease, history of myocardial infarction, cardiovascular risk factor profile, and calculated 10 year atherosclerotic cardiovascular disease (ASCVD) risk (http://tools.cardiosource.org/ASCVD-Risk-Estimator), which remain the cohorts at highest risk for overall and early (<5 years) presentation of acute coronary events during follow-up; if established IHD/CAD or 10-year ASCVD risk ≥5.0% and/or patient aged >60 years, consider further testing and treatment (moderate–high intensity statin) to define the burden of disease prior

to radiation therapy. **Potential sequelae of radiation therapy to the head/neck, abdomen/pelvis should also be assessed. Reproduced with permission from REF.[28], Wiley-VCH.

References

1. Belch, J. *et al.* ESVM guidelines - the diagnosis and management of Raynaud's phenomenon. *Vasa* **46**, 413-423 (2017).
2. Amsterdam, E. A. *et al.* 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol.* **64**, e139-e228 (2014).
3. Roffi, M. *et al.* 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur. Heart J* **37**, 267-315 (2016).
4. Knuuti J, Wijns W, Saraste A, *et al.* ESC Scientific Document Group .2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur. Heart J.* **41**, 407-477(2019).
5. Ibanez, B. *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur. Heart J.* **39**, 119-177 (2018).
6. Neumann, F. J. *et al.* 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur. Heart J.* **40**, 87-165 (2019).
7. O'Gara, P. T. *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol.* **61**, e78-140 (2013).
8. Valgimigli, M. *et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur. Heart J.* **39**, 213-260 (2018).
9. Levine, G. N. *et al.* 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *J. Am. Coll. Cardiol.* **68**, 1082–115 (2016).
10. Powers, W. J. *et al.* 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* **49**, e46-e110 (2018).
11. Aboyans, V. *et al.* 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur. Heart J.* **39**, 763-816 (2018).

12. Gerhard-Herman, M. D. *et al.* 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **69**, e71-e126 (2017).
13. Fihn, S. D. *et al.* 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J. Am. Coll. Cardiol.* **64**, 1929-1949 (2014).
14. Fihn, S. D. *et al.* 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* **126**, e354-471 (2012).
15. Farge, D. *et al.* International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol.* **17**, e452-e466 (2016).
16. Khorana, A. A. *et al.* Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. *J Thromb Haemost* **16**, 1891-1894, doi:10.1111/jth.14219 (2018).
17. Di Nisio, M. *et al.* Diagnosis and treatment of incidental venous thromboembolism in cancer patients: guidance from the SSC of the ISTH. *J. Thromb. Haemost.* **13**, 880-883 (2015).
18. Khorana, A. A. *et al.* Prevention of venous thromboembolism in cancer outpatients: guidance from the SSC of the ISTH. *J. Thromb. Haemost.* **12**, 1928-1931 (2014).
19. Di Nisio, M. *et al.* Prevention of venous thromboembolism in hospitalized medical cancer patients: guidance from the SSC of the ISTH. *J. Throm.b Haemost.* **12**, 1746-1749 (2014).
20. Zwicker, J. I., Connolly, G., Carrier, M., Kamphuisen, P. W. & Lee, A. Y. Catheter-associated deep vein thrombosis of the upper extremity in cancer patients: guidance from the SSC of the ISTH. *J. Thromb. Haemost.* **12**, 796-800 (2014).
21. Carrier, M. *et al.* Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH. *J. Thromb. Haemost.* **11**, 1760-1765 (2013).
22. Lyman, G. H. *et al.* Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014. *J. Clin. Onco.l* **33**, 654-656 (2015).
23. Streiff, M. B. *et al.* NCCN Guidelines Insights: Cancer-Associated Venous Thromboembolic Disease, Version 2.2018. *J. Natl Compr. Canc. Netw.* **16**, 1289-1303 (2018).
24. Kearon, C. *et al.* Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest* **149**, 315-352 (2016).
25. Galie, N. *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society

(ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur. Heart J.* **37**, 67-119 (2016).

26. Taichman, D. B. *et al.* Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. *Chest* **146**, 449-475 (2014).
27. Brahmer, J. R. *et al.* Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J.Clin. Oncol.* **36**, 1714-1768 (2018).
28. Iliescu, C. *et al.* SCAI expert consensus statement: Evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory (Endorsed by the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencionista). *Catheter Cardiovasc. Interv.* **87**, 895-899 (2016).
29. Thygesen, K. *et al.* Fourth Universal Definition of Myocardial Infarction (2018). *J. Am. Coll. Cardiol.* **72**, 2231-2264 (2018).