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# Radiation-Induced Coronary Artery Disease

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# Cancer Therapies and Vascular Toxicities

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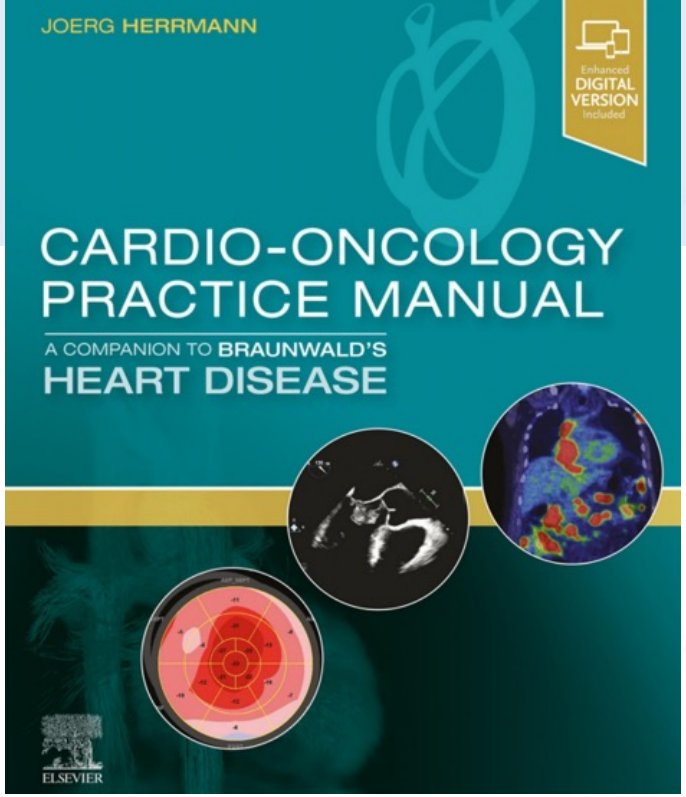


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ESC GUIDELINES

# 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS)

**Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC)**

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Review

# Radiation-induced coronary artery disease: a difficult clinical conundrum

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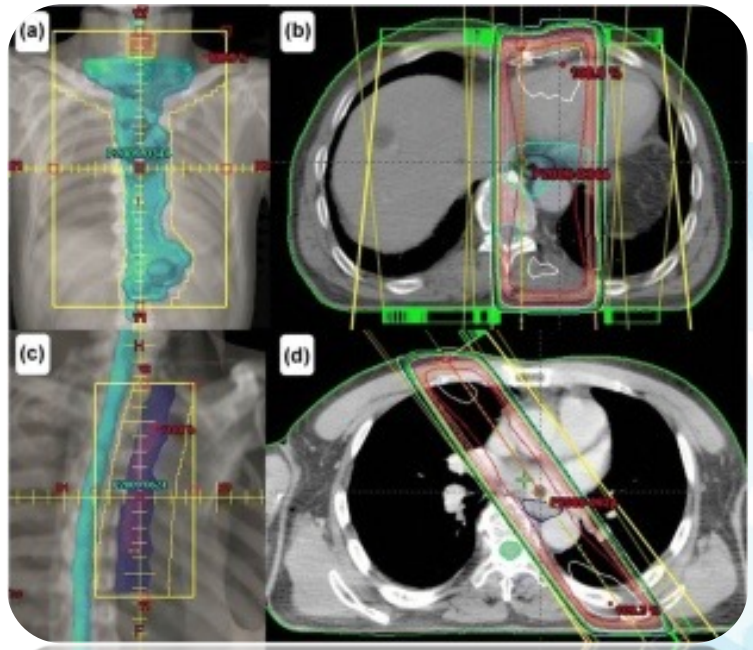
Accelerated coronary artery disease seen following radiation exposure is termed ‘radiation-induced coronary artery disease’ (RICAD) and results from both the direct and indirect effects of radiation exposure.

The incidence of RICAD continues to increase as cancer survival rates improve and it is now the **second most common cause** of morbidity and mortality in patients treated with radiotherapy for breast cancer, Hodgkin’s lymphoma and other mediastinal malignancies.



Prior cardiac risk factors

higher radiation dose

younger age at exposure

increase a patient's risk ratio of developing RICAD

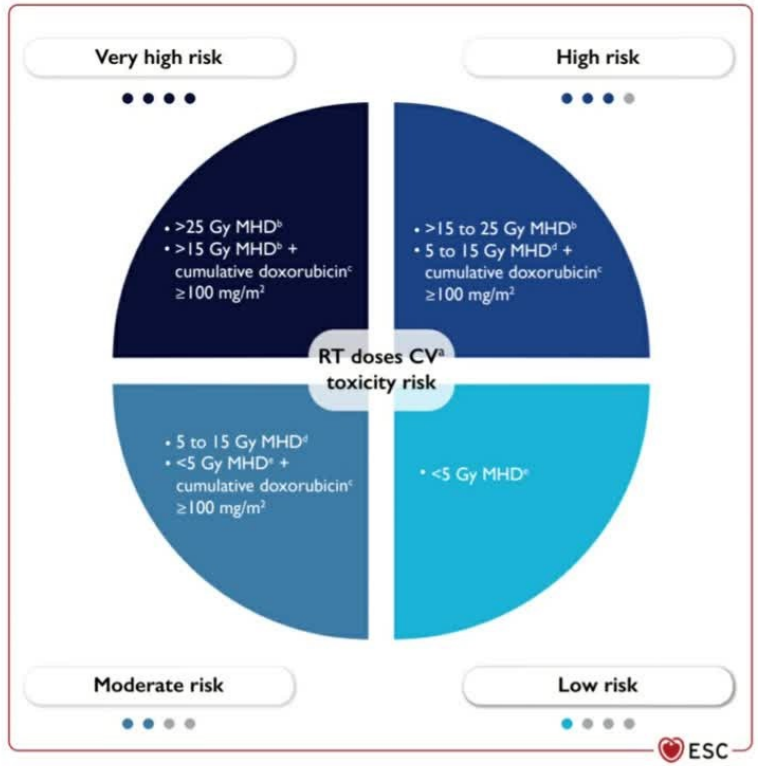



**Figure 23** Radiotherapy mean heart dose and associated cardiovascular toxicity risk. CV, cardiovascular; Gy, Gray; MHD, mean heart dose; RT, radiotherapy. [a]RT risk categorization based on MHD is recommended over categorization based on prescribed dose, which may not accurately reflect cardiac



The incidence of cancer is continually increasing worldwide. In 2018, there were 18.1 million new cancer cases, and this figure is predicted to rise to 29.5 million by 2040. With 50% of oncology patients requiring radiotherapy at some point in their treatment course.

# Cancer treatments that predispose acute coronary syndrome

| | |
|---|---|
| Accelerated atherosclerosis and plaque rupture | ADT (GnRH agonists), ICI, nilotinib, ponatinib, radiation therapy, VEGFi |
| Vasospasm | Bleomycin, fluoropyrimidines, taxanes, VEGFi, vinca alkaloids |
| Coronary thrombosis | Alkylating agents (cisplatin, cyclophosphamide), erlotinib, ICI, IMiD (lenalidomide, thalidomide), monoclonal antibodies (VEGFi, anti-CD20), nilotinib, platinum chemotherapy, PI, ponatinib, VEGFi. |

patients treated for malignancies of the mediastinum, thorax and upper abdomen have been demonstrated to be at an increased risk of cardiovascular disease with a relative risk of greater than 2.4 times that of the general population.

This represents the leading cause of non-malignant tumor-related death, which increases over time for almost all cancer survivors and is an important risk factor to note for the oncologist when offering and consenting patients for radiotherapy treatment.

It is also important for the general medical physician interacting with the patient at multiple stages in their cancer journey and for many years after their successful treatment.

# Manifestations of radiation-induced cardiac toxicity



- Pericardial
- Myocardial
- autonomic
- valvular
- conduction systems
- accelerated CAD ( radiation-induced coronary artery disease)

**generally occurs with a latency period of 15 years post-radiation exposure**

# significant challenges

RICAD can often present silently and requires a high index of clinical suspicion. Therefore, it is no surprise that RICAD is the second most common cause of morbidity and mortality in patients treated with radiotherapy for breast cancer, Hodgkin's lymphoma and other prevalent mediastinal malignancies.

Another challenge is that this cohort of patients has both a possible higher risk of in-stent restenosis as well as a higher risk of adverse surgical outcomes. Challenges to coronary artery bypass grafting (CABG) surgery include an increased risk of mediastinal fibrosis, which can be extensive, as well as damage to the mammary arteries rendering them unsuitable for harvesting. A reduced rate of success of pericardiocentesis for cardiac tamponade has also been observed

# Diagnosis of RICAD



- The presentation of RICAD includes the development of angina, MI and, potentially ischemic heart failure. However, RICAD patients will more frequently present with either atypical or even **'silent'** symptoms compared with their non-irradiated counterparts. This is likely because of multiple factors including autonomic dysfunction following radiation exposure.

The latest ESC guidelines emphasize the critical importance of effective strategies for both prediction and prevention of cardiovascular toxicities for cancer patients.

**Recommendation Table 21 — Recommendations for baseline risk assessment of patients before radiotherapy to a volume including the heart**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Baseline CV risk assessment[c] and estimation of 10-year fatal and non-fatal CVD risk with SCORE2 or SCORE2-OP[d] is recommended.[19,389] | I | B |
| Baseline echocardiography should be considered in patients with previous CVD before RT to a volume including the heart. | IIa | C |

# SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions.

| | Men | | Women | |
|---|---|---|---|---|
| | Coefficients (95% CI) | Subdistribution hazard ratios | Coefficients (95% CI) | Subdistribution hazard ratios |
| Age (per year) | 0.063 (0.055 to 0.071) | 1.07 | 0.079 (0.070 to 0.087) | 1.08 |
| History of diabetes | 0.425 (0.305 to 0.544) | 1.50 | 0.601 (0.465 to 0.737) | 1.80 |
| History of diabetes × age (per year) | -0.017 (-0.040 to 0.005) | | -0.011 (-0.032 to 0.011) | |
| Current smoking | 0.352 (0.279 to 0.426) | 1.39 | 0.492 (0.398 to 0.587) | 1.59 |
| Current smoking × age (per year) | -0.025 (-0.040 to -0.009) | | -0.026 (-0.043 to -0.008) | |
| SBP (per 10 mmHg) | 0.094 (0.079 to 0.109) | 1.09 | 0.102 (0.085 to 0.119) | 1.10 |
| SBP (per 10 mmHg) × age (per year) | -0.005 (-0.008 to -0.002) | | -0.004 (-0.007 to -0.002) | |
| Total cholesterol (per 1 mmol/L) | 0.085 (0.054 to 0.116) | 1.10 | 0.060 (0.027 to 0.094) | 1.06 |
| Total cholesterol (per 1 mmol/L) × age (per year) | 0.007 (0.002 to 0.013) | | -0.001 (-0.056 to 0.004) | |
| HDL cholesterol (per 1 mmol/L) | -0.356 (-0.445 to -0.268) | 0.71 | -0.304 (-0.403 to -0.205) | 0.75 |
| HDL cholesterol (per 1 mmol/L) × age (per year) | 0.009 (-0.009 to 0.027) | | 0.015 (0.0002 to 0.031) | |

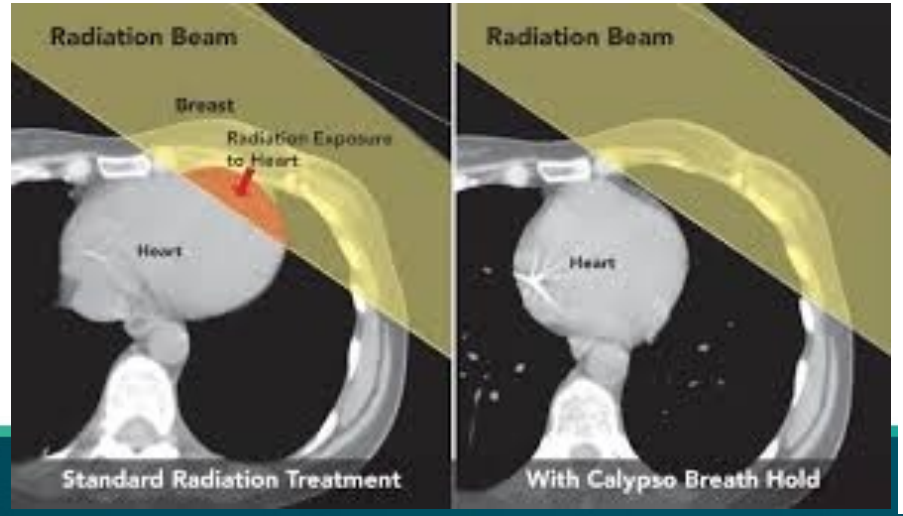
Sex-specific coefficients and subdistribution hazard ratios (SHRs) from Fine and Gray models predicted the risk of fatal and non-fatal CVD events as derived in the CONOR study. The SHRs are shown for age centred at 73 years, systolic blood pressure at 150 mmHg, total cholesterol at 6 mmol/L, and HDL cholesterol at 1.4 mmol/L. These SHRs are relevant for risk estimation only and have no aetiological interpretation.

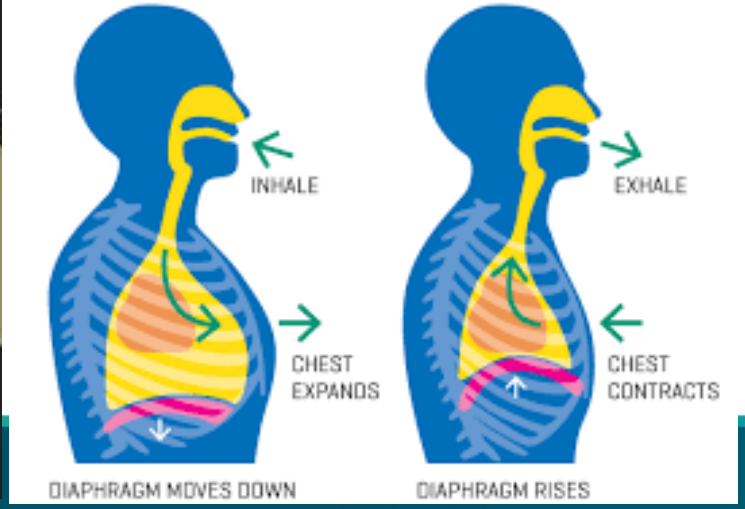
CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; SBP, systolic blood pressure.

# Preventing the development of RICAD

- Computed tomography (CT) simulation
- 3D conformal radiotherapy (3DCRT) planning
- intensity-modulated radiotherapy (IMRT)
- volumetric modulated arc therapy (VMAT) techniques
- deep-inspiratory breath hold (DIBH) technique

| TECHNIQUE | CARDIAC-SPARING MECHANISM |
|---|---|
| Breath hold | With inspiration, distance from chest wall to the heart increases |
| Prone position | Breast falls away from chest wall Increases distance from the heart to radiation therapy (RT) beam |
| Intensity modulated RT | Computerized leaves and dose planning algorithms allow for shaping of radiation field to limit cardiac dose |
| Proton beam irradiation | Utilizes difference in properties of protons compared with photons to allow for reduced dose fall off |
| Accelerated partial breast irradiation | Smaller target volume allows for possible decreased dose to the heart |
| Intraoperative RT | Smaller target volume and, in some cases. lower energy reduced dose to the heart |



(1) Modification of the dose and volume of RT treatments where possible. RT protocols should target the minimum volume required to the minimum dose needed to obtain the desired clinical benefit.

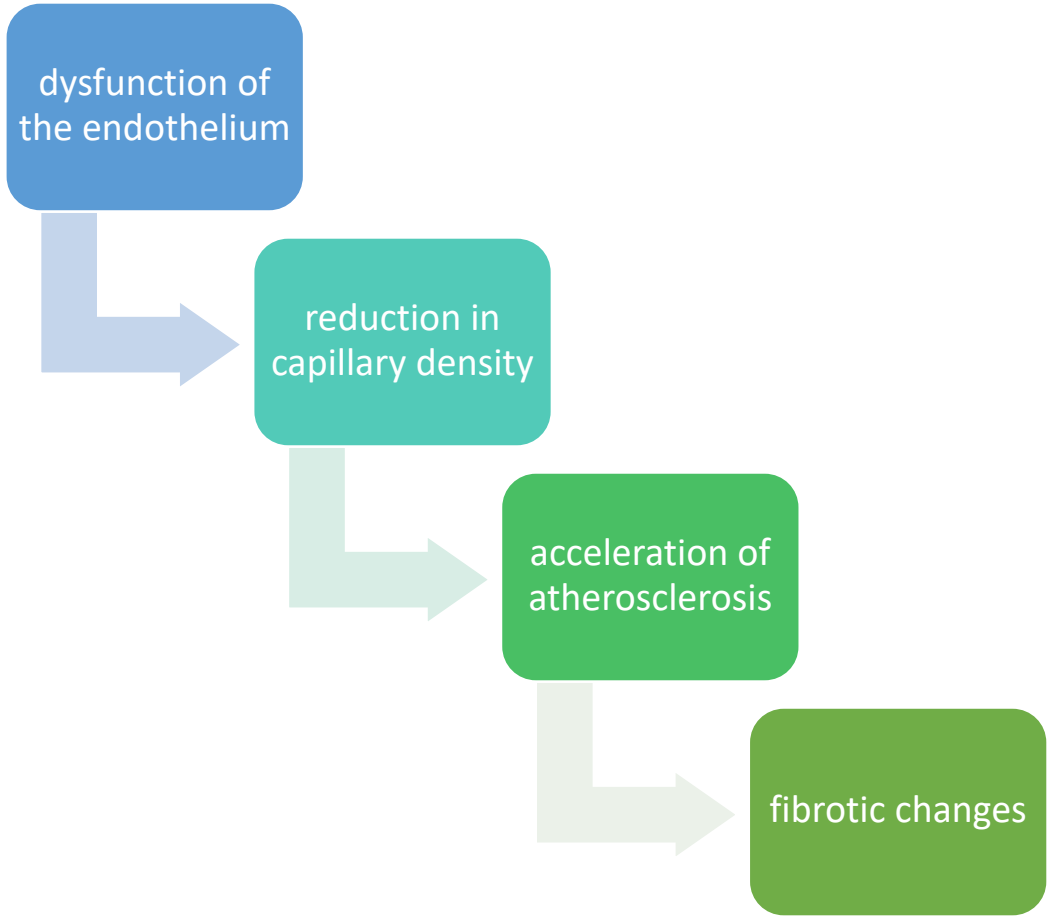
(2) Modification of delivery techniques to reduce cardiac radiation exposure should lead to a considerable reduction in risk. Modern heart-sparing RT strategies include: the optimal use of modern intensity-modulated photon RT technologies; the use of deep inspiration breath-hold or respiratory-gated techniques in BC, lymphoma and lung cancer; or the use of image guided RT to ensure accuracy of delivery and proton beam therapy.

It is important to appreciate that post-radiotherapy patients represent a comorbid population. Studies of cancer survivors beyond 5 years post-diagnosis have demonstrated a 1.7-to-18.5- fold increased incidence of cardiovascular disease risk factors including HTN, DM and dyslipidemia when compared with age-matched counterparts without a history of cancer

# primary prevention of RICAD



# Pathophysiology and inflammatory pathways associated with RICAD




key mechanism causing vascular damage.

formation of a large proportion of reactive oxygen species

release of monocyte chemotactic factor, tumor necrosis factor, and interleukins (IL) 1, 6 and 8

atherosclerotic process

primary prevention

statins, colchicine, clopidogrel , aspirin, ACE inhibitors and antioxidants

the primary prevention of CAD should continue as per general guidance with reference to the patient's overall risk of CAD.

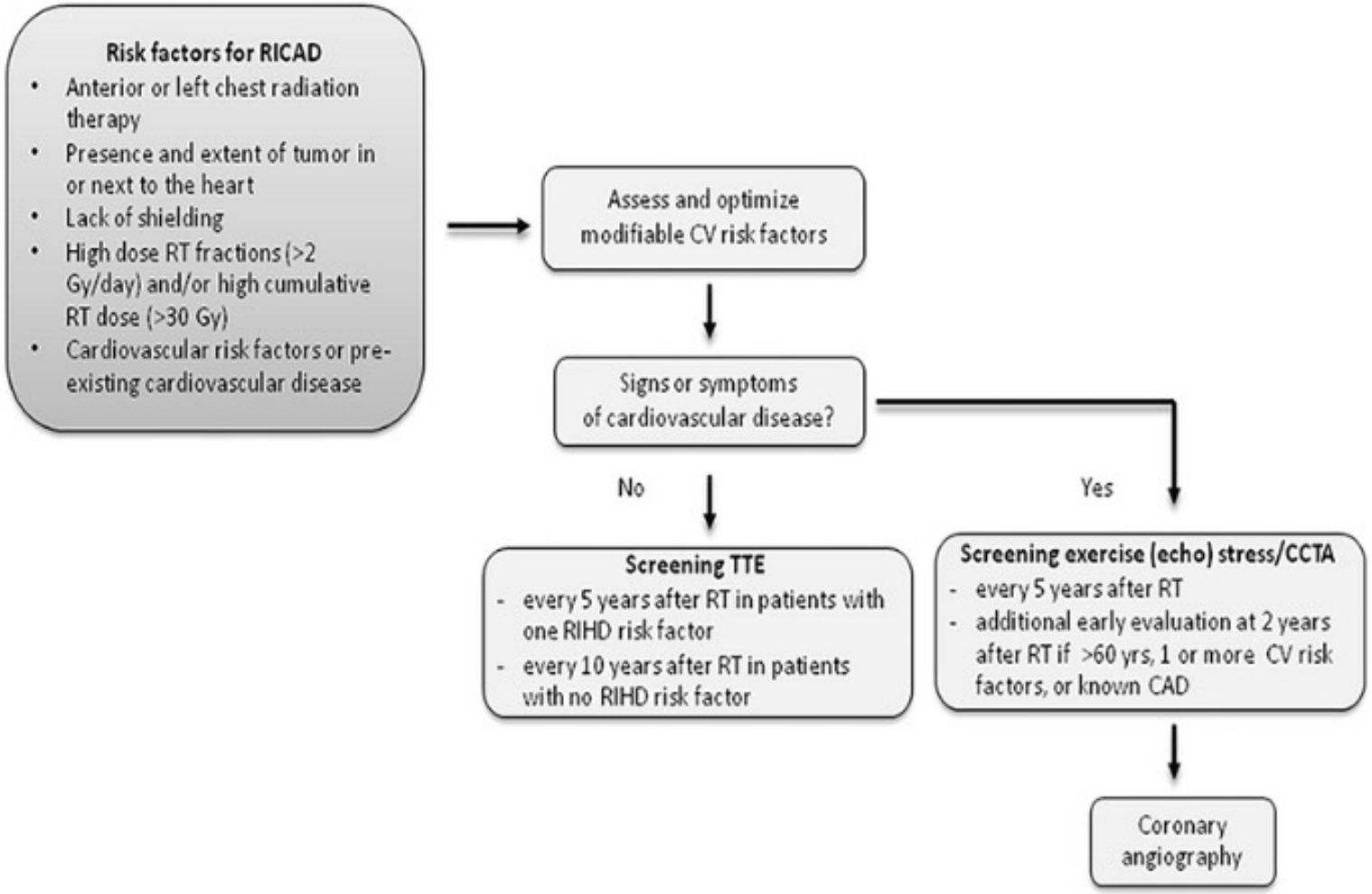
best choice

minimal radiation exposure with maximal clinical information

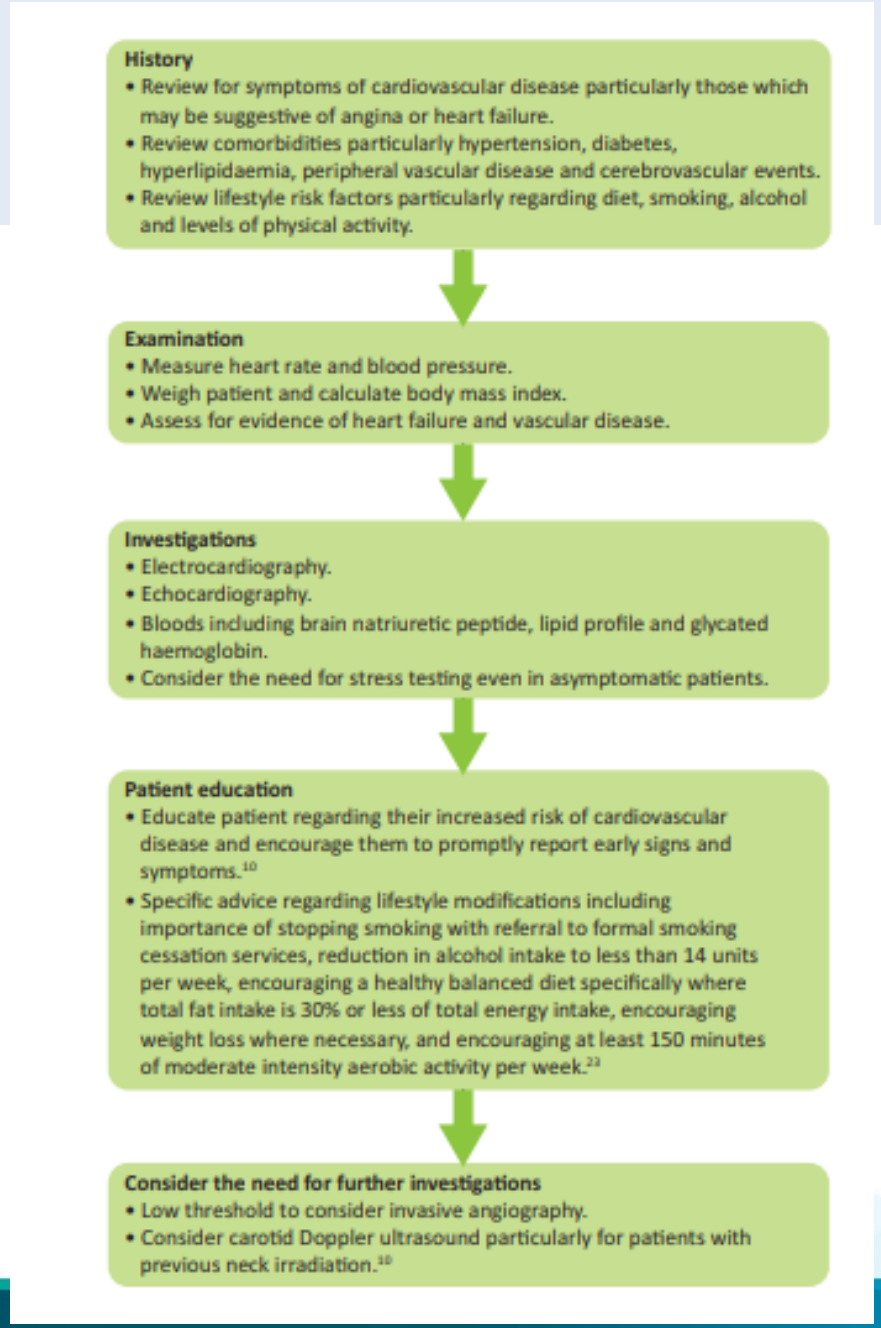
**screen for RICAD**

- myocardial perfusion imaging using technetium-99m tetrofosmin
- stress echocardiography
- cardiovascular magnetic resonance with stress perfusion
- CT coronary angiography with or without coronary artery calcium scoring

# Recommended screening for patients with RICAD



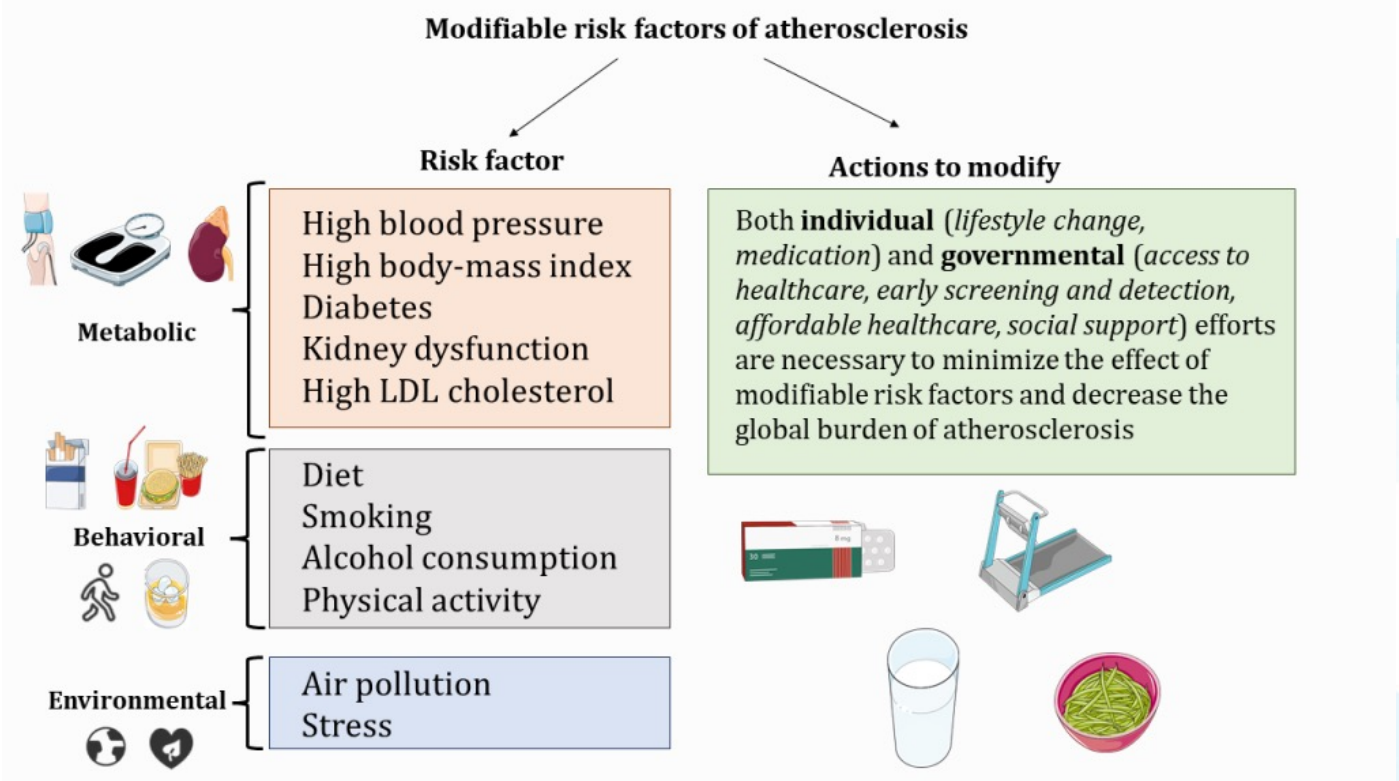
# Suggested process for surveillance of patients following radiotherapy



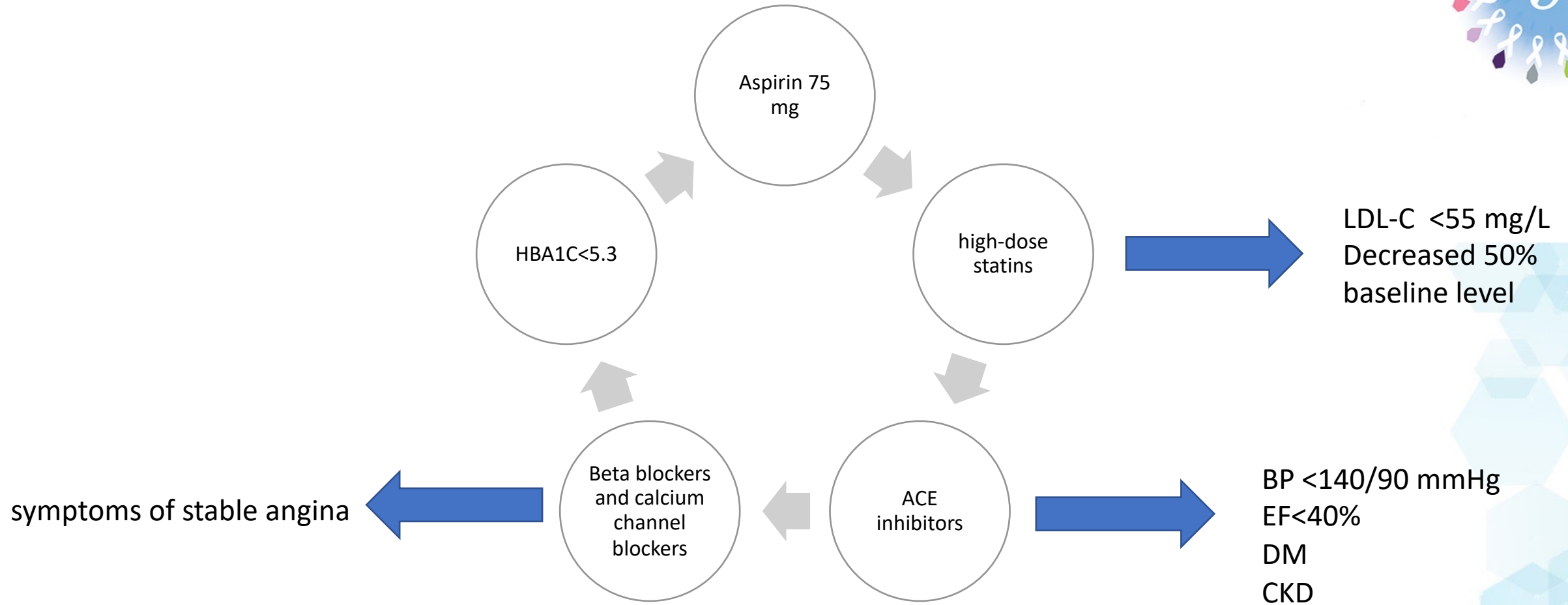
# Management of RICAD

Aggressive secondary prevention including controlling medical and lifestyle factors such as smoking, obesity, hypercholesterolemia, hyperglycemia and hypertension is mandatory as these factors act synergistically with radiation exposure to increase the lifetime risk for major coronary events from 2% to 7%

Medical management of known CAD is key for control of symptoms, halting progression of atherosclerosis



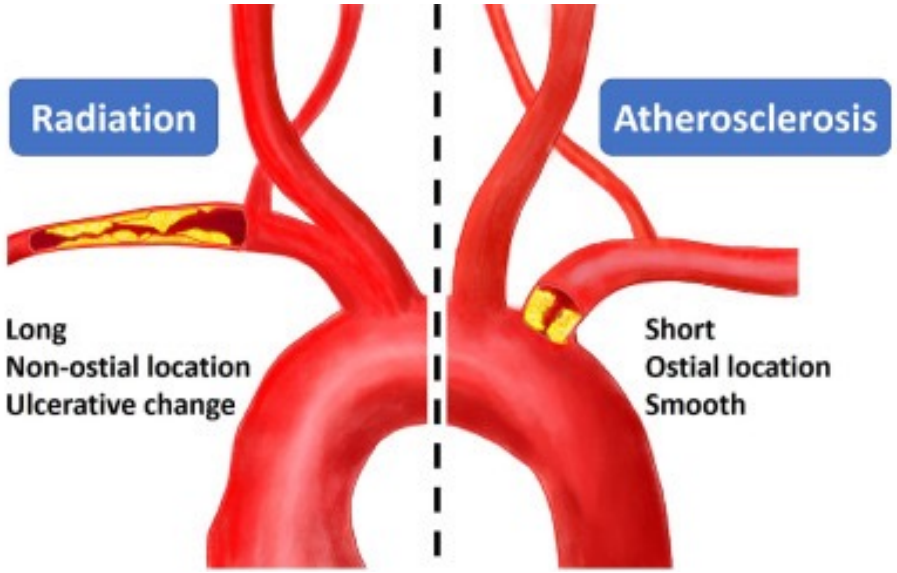
# All patients with CAD should be initiated on



# European Society of Cardiology recommendations for medical management of coronary artery disease and relevant treatment targets

| Recommendations for medical management of coronary artery disease | Relevant treatment targets |
|---|---|
| All patients with coronary artery disease should be initiated on high-dose statin treatment, such as atorvastatin 80 mg once nightly, irrespective of their formal lipid profile results. | Aim to decrease LDL-C by at least 50% of the patient's baseline with an overall target for total LDL-C of <1.4 mmol/L.[11,24] |
| Angiotensin-converting enzyme inhibitors are recommended for all patients with co-existing diabetes, chronic kidney disease or heart failure with an ejection fraction <40%. | Aim to target blood pressure of <140/90 mmHg or ideally <130/80 mmHg if the patient is able to tolerate this.[11,24] |
| All patients with co-existing diabetics should have their diabetic control optimised. | Aim to target glycated haemoglobin <53 mmol/mol, however, more stringent goals may be chosen for selected patients.[24] |

LDL-C = low-density lipoprotein cholesterol.




if a patient only requires coronary revascularization, it may be reasonable to consider PCI as a first line therapy, but this should be an individualized decision based on the specific sites of the patient’s disease.

# Home massage

- RICAD continues to increase as cancer survival rates improve and it is now the **second most common cause** of morbidity and mortality in patients treated with radiotherapy of mediastinum.
- For prevention we can recommend Modification of the dose and volume of RT treatments where possible. RT protocols should target the minimum volume required to the minimum dose needed to obtain the desired clinical benefit.
- For primary prevention some treatments like statin and ASA are at trials and should continue as per general guidance with reference to the patient's overall risk of CAD.
- We should educate patients that they has increased cardiovascular risk and screening every 5 years.
- patients with RICAD had a higher rate of restenosis of bypassed vessels compared with the general population and , it may be reasonable to consider PCI as a first line therapy

Thank You!