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CLINICAL GUIDELINE

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European Neuroendocrine Tumor Society (ENETS) 2022 Guidance Paper for Carcinoid Syndrome and Carcinoid Heart Disease

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1 | MATERIALS AND METHODS

Data regarding the diagnosis, management, and follow-up of carcinoid syndrome (CS) and carcinoid heart disease (CHD) were identified by searches of the MEDLINE database using specific terms in human studies: CS; CHD; screening; epidemiology; diagnosis; treatment; prognosis. The search results were supplemented by manual searching of relevant journals, reference lists in key articles and other appropriate documents, and expert opinion. All recommendations are offered on the basis of the best available evidence, supplemented by the authors' experiences in managing CS and CHD. Each recommendation for treatment will have a level of evidence and grade of recommendation as per the GRADE system (adapted in Infectious Disease society

This first ENETS guidance paper on CS aims to provide practical guidance for NEN specialists in the diagnosis and management of CS, with special emphasis on CHD.

of US Public Health Service grading system)[1] (Tables 1 and 2). A list of abbreviations is provided at the end of the manuscript.

2 | A. INTRODUCTION: GENERAL BACKGROUND

2.1 | a. Definition

Carcinoid syndrome (CS) is the most frequent hormonal complication accompanying neuroendocrine neoplasms (NENs) and is *defined by chronic diarrhoea and/or flushing in the presence of systemic elevated levels of serotonin or its metabolite 5-hydroxyindolacetic acid (5-HIAA)*. Importantly, other causes of these symptoms should be considered and investigated depending on the clinical presentation. CS is predominantly encountered in patients with well-differentiated NENs (neuroendocrine tumours, NETs) of intestinal origin, followed by lung NETs, and only in a minority of patients with pancreatic, ovarian, thymic, or unknown origin (UKO) NETs. The main symptoms defining CS are skin flushing, secretory diarrhoea, bronchospasm, or abdominal pain (in some cases of advanced intestinal NETs) in the presence of systemically elevated levels of serotonin and/or other biologically active amins and peptides. Patients with CS suffer from an impaired quality of life (QoL), which is lower when compared to patients without CS or other types of cancer.[2]

Carcinoid heart disease (CHD) is a rare and complex cardiac complication occurring in patients with advanced NETs and CS, usually manifesting mainly as right-sided heart valves regurgitation/stenosis (*see Section* ***A.*** *d.*) and eventually leading to right heart failure (RHF).

TABLE 1 Level of therapies/intervention for recommendation

Level of evidence for therapies/intervention	Criteria
1a	Systematic review (with homogeneity) of randomised controlled trials (RCTs)
1b	Individual RCT (with narrow confidence interval)
1c	All or none
2a	Systematic review of cohort studies
2b	Individual cohort studies (including low quality RCT, e.g., < 80% follow-up)
2c	Outcomes research: ecological studies
3a	Systematic review (with homogeneity) of case–control studies
3b	Individual case–control study
4	Case series (and poor-quality case–control studies)

Note: Grade of recommendation: A (highest), B, C, D (lowest).

TABLE 2 Level of evidence and grade of recommendation as specified in the GRADE criteria

Level of evidence for studies of diagnostic tests	Criteria
1	An independent, masked comparison with reference standard among an appropriate population of consecutive patients
2	An independent, masked comparison with reference standard among non-consecutive patients or confined to a narrow population of study patients
3	An independent, masked comparison with an appropriate population of patients, but reference standard not applied to all study patients
4	Reference standard not applied independently or masked
5	Expert opinion with no explicit critical appraisal, based on physiology, bench research, or first principles

2.2 | b. Pathophysiology

CS is caused by tumoural secretion of multiple hormonal amines and peptides. Serotonin (5-hydroxytryptamine, 5-HT) is the major secretagogue in CS, with a proposed pathophysiological role in diarrhoea and fibrotic complications; other hormones involved include histamine, tachykinins, kallikrein and prostaglandins.[2] Because tumour-released active hormones are usually inactivated by the liver, CS indicates the presence of (metastatic) tumour sites outside of the portal venous drainage.[3] Liver metastases are present in 87%–100% of patients with CS. However, in 5%–13% of cases, CS may develop in the absence of liver metastases, particularly if the primary tumour arises from the ovary, testis or very rarely lung, or if a large burden of retroperitoneal tumour disease is present.[4,5]

CHD is characterised by plaque-like fibrous deposits on right-sided heart valves and endocardial surfaces, inducing tricuspid valve regurgitation/stenosis and pulmonary valve regurgitation/stenosis, ultimately leading to right ventricular volume overload and right heart failure. Elevated levels of hormones, particularly serotonin, in the right heart are deemed causative for CHD-associated plaque formation. Left-sided valve involvement may occur either in the presence of a patent foramen ovale (PFO), a functioning lung NET, and/or in cases with very high circulating levels of vasoactive substances, overwhelming the hepatic and pulmonary degradative capacity.[6]

2.3 | c. Epidemiology

The prevalence of CS among patients with NETs has varied widely, ranging from 3% to 74% in the past, to 19% to 35% to date, depending on world region and management.[7] Median overall survival in patients with CS is significantly reduced at 4.7 years compared to 7.1 years in NET patients without CS. Tumour burden is a relevant contributor to CS-associated mortality.[4] CHD is present in

TABLE 3 Specific complications of carcinoid syndrome

Complication (Ref.)	Etiology	Symptoms/signs	Diagnosis	Treatment
Carcinoid crisis (2, 10, 14)	Stressor-induced acute release of vasoactive hormones with haemodynamic instability because of distributive shock	Severe flushing, hypertension/ hypotension, severe labial and periocular oedema, severe diarrhoea, shock	Clinical in the appropriate context	Octreotide i.v. (bolus and continuous infusion), i.v. fluids, corticosteroids, vasopressors For prevention: Octreotide s.c. 100–500 μg q 6–8 h or i.v. at a starting dose 50 μg/h, increased to 100–200 μg/h if necessary, 12h pre-operatively and before anaesthesia, continuously throughout the procedure and post-operatively until clinical stability
Niacin deficiency (pellagra) (9)	Shift of tryptophan metabolism from niacin to serotonin	Sun-sensitive dermatitis, diarrhoea, dementia	Plasma vitamin B3 levels	Nicotinamide 200–250 mg
Malnutrition, including vitamins deficiency (vitamin A, D, K, E, B12) (9)	The presence of the tumour itself; the occurrence of diarrhoea; as potential side-effects of systemic anti-tumour therapies	Weight loss, weakness, etc.	Clinical; plasma levels of vitamins, total protein, albumin, lipids	Vitamin replacement, nutritional support

approximately 20%–50% of CS patients and is a major prognostic indicator, with reduced overall survival at 3 years of 31% in patients with CHD, compared to 69% in patients without CHD.[8]

2.4 | d. Carcinoid crisis and other CS complications

Carcinoid crisis is a potentially life-threatening complication of uncontrolled CS caused by the sudden release of high levels of serotonin and other vasoactive substances from a NET, especially in patients with refractory CS (RCS; *see Section* ***C****. b.*). It can occur spontaneously, but more frequently as result of tumour biopsy, surgical manipulation, use of sympathomimetic drugs, anaesthesia or different cytolytic therapies (hepatic embolisation) and sometimes because of peptide receptor radionuclide therapy (PRRT). It is defined by abrupt flushing, severe shifts in blood pressure with haemodynamic instability, profuse diarrhoea, and distressing bronchospasm with wheezing[2] (Table 3). Other specific complications of CS patients are summarised in Table 3.[9]

3 | B. DIAGNOSIS

The presence of CS should be actively scrutinised by history taking, physical examination, and laboratory analysis.

Q1: How should the clinician assess a patient with suspected CS and CHD at presentation, and during the follow-up?

a. *Clinical evaluation* of these patients is challenging. However, some clinical key findings may help when CS is suspected.[10]

- ***Diarrhoea*** is often the presenting symptom of CS, with a prevalence as high as 60–80% among NET patients with elevated urinary 5-HIAA (u5-HIAA); it is defined as alterations in stool consistency, frequency, volume, and weight. It may be intermittent or continuous, and the coexistence of increased frequency (≥ 3 loose stools) as well as reduced consistency for greater than 4 weeks defines chronic diarrhoea. Personal/family history of chronic/neoplastic gastrointestinal diseases, previous abdominal surgery, and co-existence or history of pancreatic or systemic diseases should also be investigated.[11]
- ***Flushing***, a clinical hallmark of CS, is reported in over 90% of cases (either by the patient and/or by his/her family members); it is an intermittent or persistent sensation of warmth together with skin erythema, usually involving the head, neck, and upper part of the torso, with telangiectasia in longstanding disease. In CS, flushing is usually not associated with sweating ('dry flushing'). It is the result of circulating vasoactive substances, inducing cardiovascular abnormalities (hypo-/hypertension, brady-/tachycardia). Specific flushing features depend on the primary tumour and four different types of flushing have been described in CS[12]:
  - *The first type* is the diffuse, erythematous flush, usually affecting the face, neck, and upper chest. This flush is commonly of short duration, lasting from 1 to 5 min, and is related to the debut of CS.

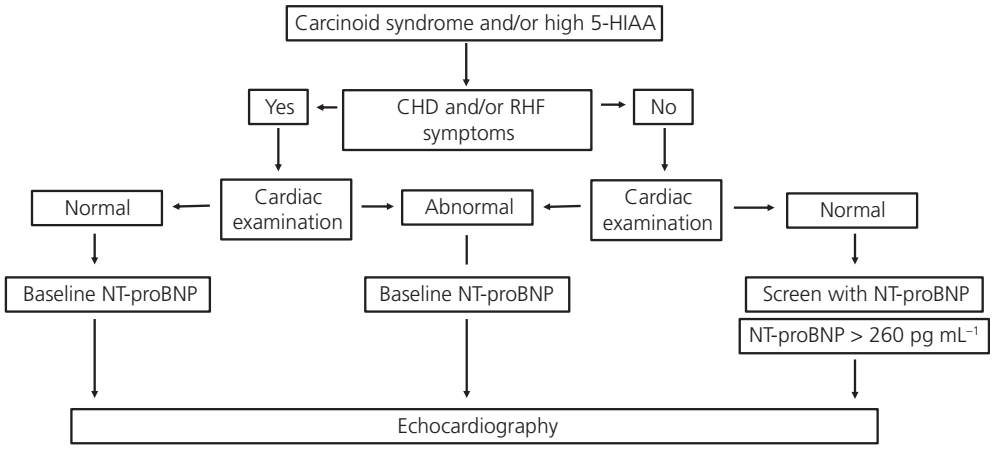

FIGURE 1 Algorithm for CHD investigation in patients with CS and/or high level of 5-HIAA. CS, carcinoid syndrome; CHD, carcinoid heart disease; 5-HIAA, 5-hydroxiindolic acid; NT-proBNP, N-terminal pro-brain natriuretic peptide; RHF, right heart failure

- *The second type* is similar to the first type but is violaceous and may last longer, together with facial telangiectasia, being observed in long-term CS from advanced intestinal NETs and is normally not felt by the patients because they have become adapted to the flushing reaction.
- *The third type* is prolonged, lasting for hours up to several days, sometimes involving the whole body, being associated with profuse lacrimation, swelling of the salivary glands, hypotension, and facial oedema. It is usually associated with lung NETs.
- *The fourth type* (mediated by histamine production), bright red and patchy, may be seen in patients with chronic atrophic gastritis and advanced type 1 gastric NETs. Rarely, type 3 gastric NEN may lead to "***atypical carcinoid syndrome***" in which flushing can be cherry red, patchy, sharply demarcated, serpiginous, and pruritic.

- ***Bronchospasm*** is a rare manifestation of the CS, being reported in approximately 15% of patients, tending to develop concurrently with flushing, sneezing and dyspnoea and linked to histamine and serotonin secretion by the tumour.[10]
- All patients with CS should be questioned and examined for symptoms and physical signs of CHD and consequent RHF including fatigue, dyspnoea, elevated jugular venous pressure, heart murmurs, hepatomegaly, peripheral oedema, and/or ascites. Over 11–27% of patients with moderate to severe tricuspid damage have no or mild symptoms, resulting in delay in diagnosis.[13] Because clinical assessment alone lacks sensitivity to detect CHD, specific biochemical and imaging examinations are required in all patients with CS (Figure 1).
- Early ***malnutrition*** screening should be planned in all patients with CS, and regularly repeated during follow-up.[9]

a. Biochemical evaluation[14]

- *Serotonin or its main metabolite 5-HIAA* should be measured at presentation in all patients with advanced intestinal NETs, in lung/ovary NETs of any stage, in unknown origin (UKO) NETs with liver metastases, and in every NET patient with suspected CS. *4A*
  - *Whole blood serotonin* assay is limited by its saturation in platelets at 40 nmol/10[9] platelets, making it less suitable for CS monitoring.
  - Serotonin is metabolised to 5-HIAA.
    - A *24-h u5-HIAA secretion* above 50 µmol is considered compatible with the diagnosis of CS (u5-HIAA normal range: 2 to 9 mg/24 h or 10.4 to 46.8 µmol/24 h).
    - Because a significant percentage of patients with elevated u5-HIAA is asymptomatic, this screening should occur regardless of CS. *3B*
    - u5-HIAA is significantly higher in patients with than without CHD, and its peak level is a significant predictor of progressive CHD.[15]
    - u5-HIAA > 300 µmol confers a two- to three-fold increase in risk of CHD development/progression.[16]
    - The primary screening of u5-HIAA as a tumour marker is limited by incorrect sampling, serotonin-rich food, or serotoninergic drugs intake, leading to false positive results. *3B*
    - Because of significant variability, u5-HIAA should be preferably analysed in two 24-h urine collections (the ratio of u-5HIAA/creatinine in a spot urine may be used for follow-up of patients with known elevated u5-HIAA levels).[17] *5A*
  - *Plasma 5-HIAA* is an alternative method[18] effectively differentiating CS patients from controls and correlating with the presence of CS and CHD.[19] However its availability is limited. *3B*
- *Chromogranin A (CgA)* has been suggested as a relevant marker for CS and CHD, but levels do not differentiate between NET patients with or without CS. *4D*
- Plasma *N-terminal pro-brain natriuretic peptide (NT-proBNP)* should be evaluated as screening biomarker of CHD in all patients with increased u5-HIAA and/or suspicious symptoms, at baseline and follow-up (Figure 1). NT-pro-BNP belongs to a neurohormone family released by the atria and ventricles in response to the increase in wall stress as a result of volume and pressure overload.[20,21] *4A*
  - *To date*, NT-proBNP is considered the most useful adjunct marker to echocardiography in screening for and monitoring of CHD, as its median levels are significantly higher in patients with than without CHD. *2B*

TABLE 4 Imaging modalities advocated in carcinoid syndrome patients

	Aim	Preferred modality	Timing
1	Determine total tumour burden in whole body as well as in the liver	SSTR PET/CT	Baseline, every 6–12 months
		CT/MRI	Baseline, every 3–6 months
2	Assess somatostatin receptor (SSTR) status	SSTR PET/CT	Baseline and at change of treatment line
3	Evaluate cardiac function including valvular apparatus	Echocardiography	Baseline, every 6–12 months
	CCT, CMRI	As required	
4	Evaluate tumour growth rate	CT/MRI	Baseline, 3 months
5	Evaluate the possibility of locoregional therapy (TAE/TACE/SIRT as well as RFA, MWA, afterloading)	CECT/MRI	–
6	Determine the feasibility of liver directed surgeries	CECT/MRI	–

Abbreviations: CCT, cardiac computed tomography; CECT, contrast enhanced computed tomography; CHD, carcinoid heart disease; CMRI, cardiac magnetic resonance imaging; CT, computed tomography; MRI, magnetic resonance imaging; MWA, microwave ablation; PET, positron emission tomography; RFA, radiofrequency ablation; SIRT, selective internal radiotherapy; SSTR, somatostatin receptor; TAE, trans-arterial embolisation; TACE, trans-arterial chemoembolisation.

- NT-proBNP measurement is highly recommended as a screening tool for identifying patients with high suspicion of CHD in the context of CS. *2B*
- For CHD detection, an NT-proBNP cut-off level of 235–260 pg mL^{-1} (31 pmoL L^{-1}) had shown sensitivity and specificity of 87–92% and 80–91%, respectively (NT-proBNP normal range: men under 70 years: < 100 pg mL^{-1}, women under 70 years: < 150 pg mL^{-1}, 70 years and over: < 300 pg mL^{-1}).
  - It should be noted that Negative Predictive Value of NT-proBNP of < 260 pg mL^{-1} (31 pmoL L^{-1}) is 97%.
  - If NT-proBNP is > 260 pg mL^{-1}, patients should be referred for echocardiography investigation. *2B*
  - If NT-proBNP is < 260 pg mL^{-1}, patients are very unlikely to have CHD.
- NT-proBNP levels positively correlate with the severity of CS, New York Heart Association (NYHA) functional class, and overall mortality. Because CHD can develop and progress rapidly, it is recommended to have a baseline NT-proBNP evaluation at the time of CS diagnosis.[8] *3B*

- *Nutritional assessment* in CS patients should include niacin (vitamin B3) and vitamins A, B12, D, E, and K, in addition to the classic nutritional parameters of cholesterol, triglycerides, albumin, iron, folate, and ferritin.[22] *4B*

a. *Imaging studies* for detailed description on imaging for NETs staging/restaging, please see the European Neuroendocrine Tumor Society (ENETS) consensus guidelines for the standards of care in NETs.[23] In patients with CS the aims of imaging and preferred imaging tools are shown in Table 4.[24]

- Contrast enhanced (CE) computed tomography (CT) including early dynamic phases is a minimal standard for NETs staging/restaging including hepatic tumour load determination as prognostic factor. *2B*
- Liver magnetic resonance imaging (MRI) using diffusion-weighted-imaging and a liver-specific contrast agent is superior for the accurate determination of number and size of lesions, therapy monitoring, or planning possible hepatic surgery or loco-regional treatment. *2B*
- Whole-body staging at initial diagnosis should be preferentially performed using somatostatin receptor imaging (SRI), preferably positron emission tomography (PET) and CECT or, alternatively, somatostatin receptor scintigraphy, although the latter has a significantly lower sensitivity. *2B*
- Quantitative assessment of tumour growth rate on sequential cross sectional imaging studies can provide useful information on tumour activity and prognosis.[25] *3B*
  - In CS patients under consideration for PRRT, especially in lung NETs and G2/3 NETs, presence of somatostatin receptor-negative lesions should be documented and further evaluation with ^{18}F-fluorodeoxyglucose PET/CT should be performed. *4A*
- An increased right-to-left ventricular width ratio on a regular CS patient CECT can indicate the presence of tricuspid valve regurgitation (TR) or pulmonary valve regurgitation (PR) and should be reported as possible sign of CHD (after excluding pulmonary embolism).[26]
- In patients with high degree of suspicion of CS and non-conclusive CECT, MRI and somatostatin receptor (SSTR) PET/CT,^{18}F-DOPA PET/CT may provide additional useful information. *3B*
- See **Q3** for specific imaging to assess CHD.

Q2: What is the differential diagnosis of CS?

The most common symptoms in CS (flushing, diarrhoea, their combination) may represent manifestations of other clinical entities. Also, patients with an established CS, on treatment, can experience deterioration of their symptoms from other causes.[27,28]

- Diarrhoea in CS is always secretory, persists with fasting, may occur during the night and is associated with abdominal discomfort and faecal urgency.

TABLE 5 Differential diagnosis of flushing

Condition	Key characteristics	Associated features
Carcinoid syndrome	Typically, "dry", involves face, neck and upper chest. Reddish brown or bright red. Short lasting.	Diarrhoea, abdominal pain, wheezing, valvular heart disease
Menopause/ hypo-gonadism	Typically, "wet", noted in upper chest and face. Rapidly becoming generalised. Preceded by sudden sensation of heat on the centre of face and upper body	Profuse perspiration
		May associate with palpitations and anxiety
Mastocytosis	Episodic and can be diffuse	Urticaria pigmentosa, Darriers' sign, pruritus, hypotension, tachycardia, abdominal pain and precipitated by opioid analgesics and anaesthesia
Medullary thyroid carcinoma	Facial and upper extremity. Telangiectasia on the same distribution	Associated with hyperthermia and sweating
Anxiety	Hot or cold flushes. Often with sweating	Associated with dyspnoea, palpitations, chest pain, choking, paraesthesia, feelings of unreality, and faintness and trembling

- Sometimes, to prove "secretory" diarrhoea, an estimation of faecal fluid "osmotic gap" is needed, with an "osmotic gap" of < 50 mOsm kg^{-1} being diagnostic for secretory diarrhoea. *4C*
- However, in other NETs (e.g., VIPomas, gastrinomas, medullary thyroid carcinomas [MTC]), as well as in systemic mastocytosis, diarrhoea is also secretory, and the differential diagnosis should be based primarily on laboratory findings.

- Patients with CS treated with somatostatin analogues (SSA) may experience deterioration of previously controlled diarrhoea, or ongoing diarrhoea which never responded to SSA. Other causes of diarrhoea, NET-related (steatorrhoea secondary to SSA, small intestinal bacterial overgrowth, mesenteric ischaemia, bile salt malabsorption or short-bowel syndrome), or NEN-unrelated (colitis, gastroenteritis), need to be excluded. 5A
  - The diagnosis of *steatorrhoea* as a result of SSA-induced pancreatic insufficiency is based on stool features (pale, "oily", difficult to be flushed from the toilet) and may be confirmed by low faecal elastase or pragmatically by a trial of pancreatic enzymes. *5B*
  - Small intestinal *bacterial overgrowth* is noted in patients with mesenteric fibrosis or multiple previous surgery, being associated also with bloating and/or flatulence and its diagnosis is established with an "H2 breath test". *4B*
  - *Mesenteric ischaemia-related diarrhoea* can be suspected by the patient's history and abdominal CECT findings.
  - Patients who have undergone right hemicolectomy may develop *bile salt malabsorption-associated diarrhoea*. This diagnosis is usually based on history and confirmed, when available, with tauroselcholic (selenium-75) acid (SeHCAT) scan, or pragmatically by a trial with bile acid sequestrants. *4B*
  - A *short bowel syndrome*, defined as a length of functional small bowel < 200 cm may occur after extensive intestinal resection.
- Flushing in the context of CS has been described in Section B.
  - Flushing can be noted in other NENs (MTC) as well as in some non-NENs entities (menopause, systemic mastocytosis, anxiety).
  - The key characteristics allowing the distinction of CS-associated flushing from flushing from other causes are summarised in Table 5.

Q3: Which tools are needed to characterise severity of CHD?

CHD quantification requires careful clinical, biochemical, echocardiographic, and radiological assessment.[29,30]

- Clinical examination for signs of CHD and related RHF is notoriously unreliable and should be looked for, but not relied upon, as an adequate screening tool.
- NT-proBNP is the most sensitive biomarker to date for the presence and severity of CHD and should be measured in all patients with elevated u5-HIAA, regardless of CS (*see also Section on biochemical investigation, Q1*). *4A*
- CHD diagnosis and monitoring by severity quantification is challenging and focusses on functional imaging of the left and right chambers of the heart.
  - Transthoracic echocardiography (TTE) is the key investigation for CHD diagnosis and monitoring by using the ENETS CHD TF Echo synoptic score.[31] This should be ideally undertaken by an experienced professional in CHD. Additional experienced TTE imaging of the pulmonary valve involvement provides information needed to determine degree of valve disease. *2B*
  - TTE should include an 'agitated saline contrast study' to identify a PFO. *2B*
  - Stress echocardiography does not provide any additional information. Cardiopulmonary exercise may play a role in assessment of asymptomatic and minimally symptomatic patients with CHD who have enlarged RV with impaired right ventricular (RV) function.
  - Advanced ultrasound techniques, such as 3D TTE or 3D transoesophageal echocardiography (TOE), may be helpful in

TABLE 6 Indications for cardiac CT or MRI for evaluation of CHD severity

	Cardiac CT, for assessment of:	Cardiac MRI, for identification and assessment of:
Indications	• Valvular pathology, especially of pulmonary valve • Coronary arteries • Relationship of cardiac metastasis (if present) to coronary arteries • Right ventricular volume and function • Extra-cardiac involvement • Valvular sizing	• Right ventricle size and function • Valvular pathology when echocardiography images are inadequate • Extra-cardiac involvement

Abbreviations: CHD, carcinoid heart disease; CT, computed tomography; MRI, magnetic resonance imaging.

identifying and assessing valve pathology. 3D TTE could be valuable in the assessment of right ventricular size and function. *3C*

- Cardiac magnetic resonance imaging (CMRI) and cardiac CT (CCT) are useful additional modalities, used when TTE images are inadequate or in pre-operative planning (Table 6).[32] *3B*
- At the same time, it should be noted that assessment of severity of pulmonary vein (PV) involvement with echocardiography can be difficult and misleading, and functional assessment of pulmonary regurgitation with MRI should also be measured and interpreted with care.
- Full cardiac CT (requiring a high-pitch or high-volume CT scanner) allows excellent anatomical visualisation of the pulmonary valve. In addition, it allows assessment of coronary arteries, relationship of cardiac metastases (if present) with regard to coronary arteries, and RV function assessment being mostly utilised in pre-operative planning.[33] *3B*

4 | C. THERAPY

Q4: Which are the principles/aims of treatment in a patient with CS?[34,35]

Patients with untreated CS often present with debilitating symptoms (diarrhoea, flushing, bronchoconstriction, abdominal pain, niacin deficiency-related symptoms) and may develop long-term complications, such as CHD, with a major negative impact on patient's health-related quality of life (HRQoL). All patients with CS should be promptly treated aiming:

- To achieve maximal symptom control and ideally normal u5-HIAA levels. *2bA*
- To control or reduce tumour burden. *1bA*
- To prevent the appearance/progression/recurrence of CHD.*3bA*
- In patients with CHD, to anticipate the development of irreversible ventricular dysfunction and to avoid any delay in valvular treatment. *3bA*
- To improve patients' nutritional status and HRQoL.*1b*ACS treatment is challenging. The availability of multiple therapeutic options favours a personalised approach. NET-specific therapies are addressed in dedicated ENETS guidelines.

Q5: How to manage CS?

a. First line management

- SSA, octreotide or lanreotide, are the mainstay of CS treatment.[34,36] SSA bind to SSTR which are expressed by most NET cells, the presence of which is confirmed by increased tumour uptake on SRI. SSA inhibit the secretion of several hormones and vasoactive substances, improving symptoms in up to 70% and decreasing u5-HIAA levels in approximately 46% of CS patients. *2aA*
- It is not mandatory, but strongly recommended, to have a positive SRI to start therapy with SSA (Consensus opinion). *2B*
- Octreotide is available as a short-acting subcutaneous/intravenous or a long-acting release (octreotide LAR) formulations, the latter being administered intramuscularly 30 mg/4 weeks. Because drug concentration reaches a plateau at 14 days from injection, patients with mild CS can start with octreotide LAR 30 mg alone. *2bA*
- Lanreotide Autogel® is available as a depot formulation of 60 mg, 90 mg and 120 mg and administered s.c. at a dose of 120 mg/4 weeks; drug concentration reaches a steady state in the first day, dispensing the need for concomitant short-acting octreotide.
- When CS symptoms are moderate/severe, administration of the long-acting SSA (octreotide LAR or lanreotide Autogel®) should be combined with short-acting octreotide 100 μg to 500 μg every 6–8 h, for up to 2 weeks or as a rescue therapy when CS is not controlled. *3bA*
- SSA are safe and well-tolerated, with only 1 to 11% of patients requiring discontinuation as a result of adverse events.
- Short-term adverse events are mild, including pain/engorgement at injection site, nausea, diarrhoea, abdominal cramps, flatulence, and hyperglycaemia.
- Long-term adverse events include fibrotic nodules at injection sites, cholelithiasis and exocrine pancreatic insufficiency, occurring in 5%–15% of cases; diabetic patients need close follow-up, as anti-glycaemic treatment intensification may be needed.
  - Prophylactic cholecystectomy to avoid cholelithiasis should be considered cautiously during resection of primary small bowel NETs because it may worsen diarrhoea in patients with previous small bowel resection.[37]

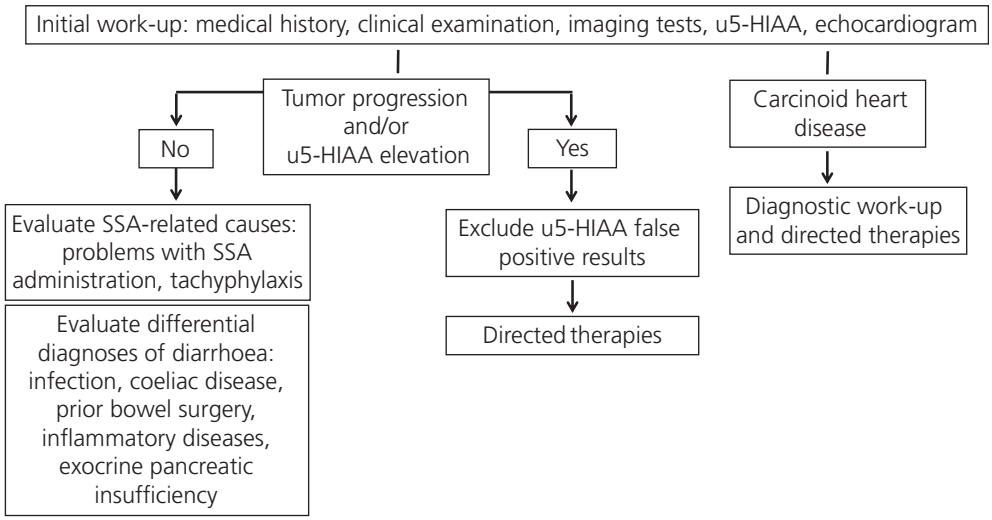

FIGURE 2 Refractory carcinoid syndrome work-up. u5-HIAA, urinary 5-hydroxiindolic acid; SSA, somatostatin analogues

- Exocrine pancreatic insufficiency (steatorrhoea) develops in almost one-quarter of patients receiving SSA, with more than 90% occurring after 6–24 months of treatment; it can be treated with oral pancreatic enzymes supplements.[38,39]
- Dose reduction of octreotide LAR from 30 mg to 20 mg and lanreotide Autogel® from 120 mg to 90 mg can be offered to patients who are intolerant of higher dosages. Alternatively, the injection frequency can be reduced beyond every 4 weeks.
- Although there are no randomised controlled trials powered to directly compare SSA for CS, octreotide and lanreotide are similarly safe and effective in managing CS and tumour growth. *3bA*

a. *Second and further lines of management — **refractory CS (RCS)***[40–42]

RCS is defined by recurring or persisting CS symptoms and increasing or persistently high u5-HIAA levels despite the use of maximum label doses of SSA. RCS may be divided into either **non-aggressive** or **aggressive**, based on symptoms burden (< or ≥ 4 BM/day, and/or < or ≥ 5 flushing episodes/day, respectively) together with disease stability (stable or progressive), hepatic burden (< or ≥ 50% liver involvement), and/or the presence of CHD.

Patients with RCS may suffer from an incapacitating burden of symptoms, as well as CS-related complications such as CHD.

- The ***initial work-up of suspected RCS*** consists of a thorough investigation of the differential diagnosis of worsening CS symptoms, measurement of u5-HIAA and appropriate tumour imaging.
- The ***causes of RCS*** remain obscure, but radiological and/or biochemical tumour progression should be differentiated from the differential diagnoses of worsening CS.
- ***Differential diagnosis of RCS*** (Figure 2) includes problems with SSA administration, SSA tachyphylaxis, SSA-induced exocrine pancreatic insufficiency, infectious/inflammatory diarrhoea, mesenteric fibrosis, and worsening of diarrhoea in patients whose primary small bowel NET was surgically removed.
  - Clinicians should be aware of causes of false positive elevations of u5-HIAA, such as serotonin-reuptake receptor inhibitors, acetaminophen, and consumption of serotonin-rich foods (e.g., bananas, pineapple, tomatoes, plums, eggplant, avocado, kiwi, fruits in general, nuts) prior to the urinary test.
  - Decreased SSA absorption consequent to fibrosis at the injection sites may develop in patients receiving long-term SSA.
  - Worsening of CS 2–3 weeks after SSA injection may imply tachyphylaxis; more frequent doses (octreotide LAR 30 mg/2–3 weeks or lanreotide Autogel® 120 mg/2 weeks), [2bA] increased octreotide LAR dosage to 60 mg every 4 weeks or switching to the alternative SSA can be considered. *3bA*

    Overall, SSA dose-escalation offers symptom improvement in nearly 80% of cases, whereas only 29% of patients show further reduction in u5-HIAA levels.[42]
- It is important to re-assess all patients with RCS for CHD with an echocardiogram and NT-proBNP (see CHD work-up session).Once administration problems and differential diagnoses are excluded, NET-directed therapies should be added to SSA, aiming at tumour control that also improve CS (dose-escalation of SSA, loco-regional therapies, PRRT, everolimus and interferon-alpha) or direct hormone secretion control (telotristat ethyl).

The best therapeutic sequence for RCS has not been yet determined by randomised trials, and it should be decided based on severity of RCS and tumour status[37] (Figure 3). Importantly, SSA should be continued throughout all treatment lines of CS.

- ***Treatment of RCS with radiologically stable NET or indolent progression and low symptom/tumour burden***
  - *SSA* should be continued, with their dosage being optimised. *4A*
  - *Hepatic resection* should be applied with curative intent (R0 resection of metastatic lesions) or considered for symptom relief as cytoreductive (debulking) surgery, based on tumour operability/metastatic type.[38] *3bB*

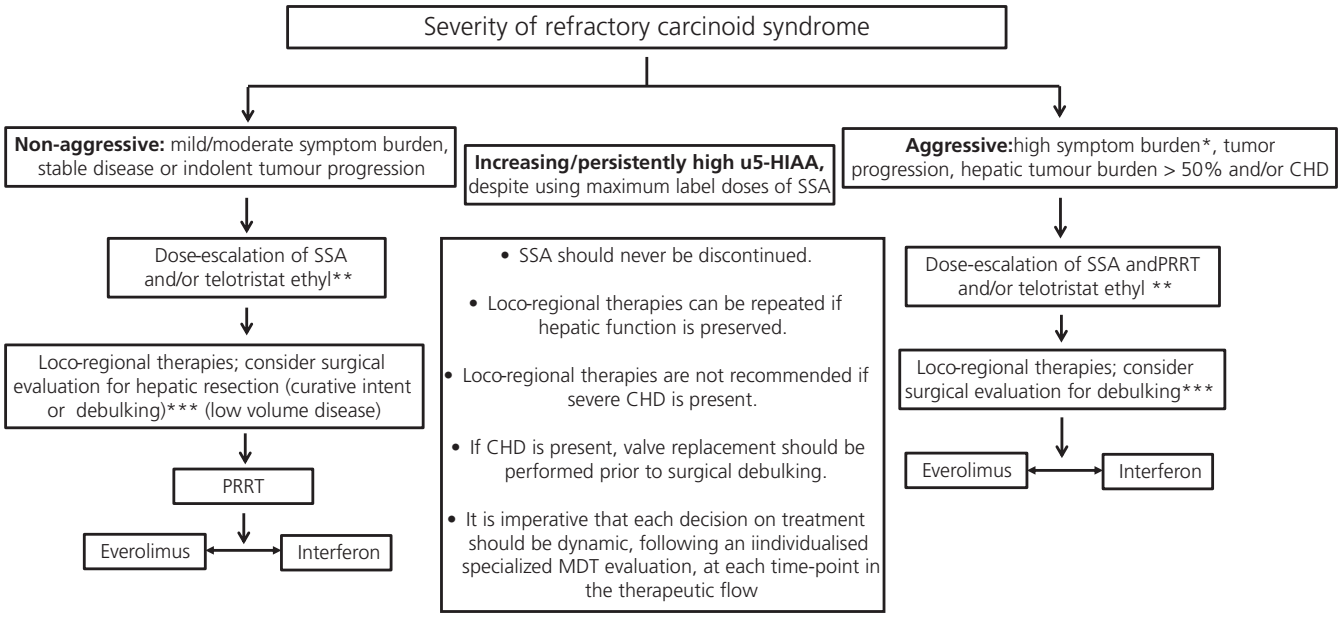

FIGURE 3 Refractory carcinoid syndrome: proposed treatment sequence. *Aggressive CS: more than four bowel movements (BM)/day and/or more than five flushing episodes/day. **When available, and when CS-related diarrhoea is predominant. ***Surgical debulking can be considered earlier, if possible, in highly selected cases, based on the type of liver metastasis (Type I or Type II) and weighing up severity of CHD and the impact of debulking on CHD. CS, carcinoid syndrome; CHD, carcinoid heart disease; MDT, multidisciplinary team; PRRT, peptide receptor radioligand, therapy; SSA, somatostatin analogues; u5-HIAA, urinary 5-hydroxiindolic acid

Importantly, in the presence of CHD, the optimal sequence of cardiac and liver surgery must be determined in an individual fashion based on the severity and symptoms of CHD and on multidisciplinary team (MDT) discussion.[42] There is limited evidence from retrospective studies that hepatic resection can reduce progression of CHD and improve prognosis significantly in eligible patients. By contrast, upfront valve replacement should be considered prior to hepatic surgery, in the presence of already progressive/significant CHD, to prevent complications because of a "pulsatile" liver and enable curative/cytoreductive surgical strategies. Small retrospective series revealed similar survival after hepatic resection in patients with or without CHD, thus suggesting an important role for valve replacement and interval hepatic resection. It is worthwhile mentioning that precise evidence-based criteria for the above have not been published.

- *Loco-regional therapies* may be considered for patients with predominant liver inoperable metastases, requiring CS control. *3aA*

Hepatic trans-arterial embolisation (TAE), trans-arterial chemoembolisation (TACE) or trans-arterial radioembolisation/selective internal radiotherapy (TARE/SIRT) controls CS symptoms in up to 75% cases and can be repeated if there is preserved liver function.[43,44] For patients with CS and G1 intestinal NET, where chemotherapy offers little benefit, bland hepatic embolisation is preferred. *3aB*.

TACE/SIRT may be reserved for G2 intestinal or non-intestinal NET. *3bB* In the absence of conclusive data on which trans-arterial treatment is most efficient, the selection should be made based on individual factors such as tumour load, topography of metastases, and arterial anatomy.

- *PRRT* with ^{177}Lutetium-DOTATATE represents an effective option for NET patients.

with positive SRI and RCS, with significant decrease in diarrhoea, pain, fatigue, and flushing, and > 30% decrease in u5-HIAA in 56% of patients.[45,46] *3bB*

- A small series demonstrated that *everolimus* combined with octreotide LAR led to symptom relief in RCS.[46,47] In the RADIANT 2 phase III trial, more pronounced reduction in u5-HIAA favored everolimus and octreotide compared with octreotide alone.[48] Despite its low evidence as an anti-secretory agent, everolimus has proven antitumour activity in NET and can be considered in RCS patients. *4C*
- The anti-secretory effects of *interferon alpha* (IFN-α) may be useful in RCS patients. *2bB*

In several single-arm prospective series, the response rates to IFN-α have been up to 90% for clinical and 80% for biochemical control. A multicentre randomised study combining IFN-α with SSA did not demonstrate a significant beneficial effect versus SSA alone for symptom control. The recommended dose of IFN-α is 3–9 MU s.c. every other day. A slow-release formulation of 50–100 μg PEGylated IFN-α is given s.c. once a week. However, the low tolerability of the drug has limited its use.[49]

- *Chemotherapy or tyrosine kinases inhibitors* are rarely used in clinical practice in CS, being considered mainly as an anti-tumour option for lung/pancreatic/thymic NENs. *3bD*

Most data on chemotherapy for RCS are old and inconsistently describe CS-specific outcomes, restricted only to a 5-HIAA response rates of approximately 31%. Therefore, their role in symptom control in CS is limited. *4D*

- *All the upper mentioned therapeutic options, and specifically liver-related procedures, should be discussed within an MDT with a high degree of caution* and defined as contra-indicated in patients with limited liver residual function, in the presence of moderate/severe ascites and/or concomitant physical/echocardiographic signs of severe right heart failure, and/or when patient performance status is low.
- *Telotristat ethyl* (an oral inhibitor of tryptophan hydroxylase, the rate-limiting enzyme of serotonin synthesis), significantly reduced RCS-associated diarrhoea and u5-HIAA in clinical trials and in real-world patients.[50,51] The recommended dose is 250 mg TID; side effects include mild abdominal pain and nausea. *1bB*

- ***Treatment of RCS with radiologically progressive NET and/ or high symptom burden***
  - *SSA* should be continued, with their dosage being optimised.
  - *Telotristat ethyl* should be added to SSA, where available, for control of RCS-associated diarrhoea. *1bB*
  - *PRRT* in the setting of very high tumour burden and progressive liver disease together with RCS and/or CHD is a matter of debate. Hepatic tumour burden per se prior to PRRT does not appear to be associated with an increased risk of liver toxicity[52]; however, liver failure is possible in patients with massive tumour bulk and RCS. Therefore, careful individualised decisions, taken within an MDT, and consideration of reducing the dosages of PRRT and alternating them with possible valve-replacement, are recommended in these severely-ill patients. *3bB*
  - *Hepatic resection/loco-regional therapies* are effective for CS, as mentioned earlier, but not recommended if severe CHD is present; in this situation, valve replacement should be performed prior to surgical debulking/loco-regional interventions. *3aB*
  - The other therapeutic options listed for patients with RCS and stable/indolent disease and/or mild symptom burden also apply to more aggressive RCS, preferably after treatment with PRRT.

a. *Treatment of carcinoid crisis*

- We recommend prophylactic short-acting octreotide prior to and during invasive procedures—to be tapered down afterwards, or continuous infusions when major surgical/loco-regional interventions are considered or when there is concurrent CHD. *3b*
  - We propose doses of s.c. octreotide of 100–500 μg every 6–8 h or i.v. octreotide infused at a starting dose of 50 μg h^{-1}, increased to 100–200 μg h^{-1} if necessary, 12 h pre-operatively and before anaesthesia, continuously throughout the procedure and post-operatively until the patient is clinically stable.[37,53,54] *3bA*
- For patients starting PRRT and using short-acting SSA, this should be continued up to 8–24 h prior to administration and restarted 8–24 h after PRRT.[55] *4A*
- Despite prophylactic measures, carcinoid crisis is not entirely preventable and requires prompt recognition intraoperatively and aggressive treatment including intravenous fluids, corticosteroids, and vasopressors.
- Sympathomimetics can precipitate hormonal release by the tumour paradoxically leading to distributive shock and should be used cautiously in patient with CS. However, if a CS patient needs to be on sympathomimetics (e.g., patients in an intensive care unit on hypovolemic or septic shock), a simultaneous i.v. octreotide infusion to prevent carcinoid crisis is recommended and the selective alpha$_1$-agonist phenylephrine and vasopressin are the preferred vasopressors in this context. *4A*

a. *Supportive therapeutic strategies*

- *Nutrition counselling* is recommended to improve nutrition status, control diarrhoea, and avoid foods that trigger carcinoid symptoms. *4A*In patients with short bowel syndrome, anti-diarrhoeal agents, such as loperamide, may be useful. Patients with niacin deficiency or pellagra should be started on niacin or nicotinamide 200–250 mg PO once daily with further treatment tailored to circulating levels. *4A*.

Ultimately, all patients develop symptomatic progression of CS when on an SSA. Therefore, once CS treatment is initiated, physicians should actively monitor the patient's status for a clinical, biochemical, and radiological response. Symptom relief should be monitored monthly in the first 2–3 months and, once achieved, at intervals of 4–6 months. Biochemical and imaging tests can be evaluated every 4–6 months. *4B*.

Q6: What are the general recommendations for the initial management of CHD?[56]

All patients diagnosed with CHD should be managed by a MDT (*see also Q11*).[57] *2A*

- The two main goals of management are *aggressive reduction of hormonal secretion by the tumour* and *management of CHD and RHF*, when present. A holistic approach must be taken, with consideration of NET status, CHD severity/symptoms, and nutritional and general performance status of the patient.[58,59]
  - For tumour and CS control (*see also Q5*).
  - In patients with symptomatic RHF, standard treatments, including loop/thiazide diuretics, aldosterone antagonist therapy and cautious fluid and salt restriction, can improve patient's symptoms but must be used judiciously to avoid a paradoxical worsening of symptoms because of a reduction in cardiac output. The doses depend on the individual context, patients' blood pressure, renal function, other co-morbidities, or medications.
  - Patients with CHD require lifelong clinical, biochemical, and echocardiographic monitoring to facilitate early identification of disease progression. It is important to note that CHD can progress rapidly, and patients should have regular NT-proBNP and echocardiograms at intervals of 6–12 months.[60] *4A*

Q7: Do's and don'ts in CS/severe CHD

Do's:

- Echocardiograms should thoroughly describe each affected valve including leaflet thickening, mobility, degree of regurgitation and stenosis, and assessment of right ventricular size and function. *3A*
- During CECT/MRI for NET staging, the contrast flow rate must be lowered in patients with severe cardiac impairment, and one should be aware of the longer circulation time when timing contrast phases and interpreting the images. *5B*
- Guidelines for the fluid and amino-acid infusion (volume, rate), as well as the flow rate of ^{177}Lutetium-DOTATATE in the presence of CHD, are unavailable. However, based on clinical experience, some leading centres will extend the duration of infusion of amino-acid (LysArg) by decreasing the infusion rate from 250 mL h^{-1} to 175–200 mL h^{-1} and decrease the total volume to 50%–75%; alternatively, other expert centres recommend regular amino-acid infusion rate at 250 mL h^{-1}, directly followed by a single injection of furosemide 40 mg, particularly in patients with severe CHD and elevated jugular venous pressure or peripheral oedema (the total volume and rate of infusion should be titrated to the cardiac function and coordinated with the MDT cardiologist) (Consensus opinion). *5B*

Don'ts:

- Besides SSA, do not administer systemic/loco-regional therapies before assessing cardiac status as carcinoid crisis may occur inducing cardiac decompensation (high grade of caution is needed).
- Cessation of SSA before SRI or PRRT is not recommended (use rescue s.c. or i.v. octreotide or adjust date of SRI/PRRT to be at the end of SSA monthly administration) in uncontrolled CS/CHD patients. *3bB*
- Do not start second-line therapies without a proper evaluation of the differential diagnosis of RCS. *3bB*

Q8: What is the appropriate surgical management of CHD?[61,62,63]

a. *Methods*

- Surgical valve replacement is the established CHD treatment.[64] *3bA*
- Minimally invasive cardiac surgery has a limited role in CHD, as a full sternotomy is required to access both the pulmonary valve (PV) and tricuspid valve (TV) in the same procedure.[65] *4D*
- Percutaneous valve-in-valve procedures are feasible in degenerative surgical valves in CHD, which is a further argument for using bio-prostheses as the primary option in valvular replacement surgery (*see also Q10*). *4B*
- Percutaneous pulmonary and tricuspid valves are available, but data on placement in patients with CHD are currently lacking.[65] *4D*

a. *Indications for cardiac surgery*

- Severe symptomatic CHD (e.g., fatigue, dyspnoea, oedema, ascites) with at least 12 months of anticipated post-operative NET-related survival. *3bA*
- *RV dilatation should not represent, per se, an indication for surgery in asymptomatic NET patients*.
  - A close cardiologic follow-up is required, not to delay surgery as soon as the first symptoms are present and to avoid escalation of medical treatment.
  - Asymptomatic patients with severe RV enlargement and reduced RV systolic function and normal exercise capacity are unlikely to derive symptomatic benefit from surgery. The overall prognosis of these patients depends on multiple factors with the major determinant being the underlying NET status and prognosis. Those cases should be discussed in detail by the CHD MDT, as well as with the patient, and a decision should be made on a case-by-case basis. *3bA*

a. *Timing of surgery*

- The optimal timing of valve replacement should be individualised and decided when the patient has a clear indication (see above), under optimal treatment following MDT assessment and has provided informed consent.[66] *3aA*
- In a large cohort of 240 operated patients from the Mayo Clinic, survival was significantly better in patients with any lower pre-operative NYHA class. At the same time, valve operation in asymptomatic patients was not associated with survival benefit.[67]
- By consensus, following MDT discussion, patients referred for cardiac surgery should have evidence of symptomatic RHF, with at least 12 months of anticipated post-operative survival from their NET disease. *4B*
- Be mindful when it is too late for cardiac surgery (e.g., severe uncontrolled CS and RHF in a patient with high tumour burden and limited hepatic/cardiac/performance status reserve).

a. *Pre-operative assessment*

- Assess the presence of PFO with a baseline "bubble" contrast TTE or intraoperative TOE imaging; it should be closed at the time of valve surgery. *4B*
- Assess coronary status by coronary angiography (CA) or coronary computerized tomography (CCT). *4B*
- Assess valves by TTE (if necessary, TOE) and CMR for evaluating the valves, both ventricle's volume and function. Be aware that, with severe TR, PV involvement degree could be underestimated and that functional assessment of PR severity either with echocardiography or MRI could be misleading.[68] *4B*
- Assessment of valve size can be achieved using CCT.[32] *4B*
- Assess liver/renal/coagulation tests and perform carotid Doppler. *4B*

- Consider cardiopulmonary exercise testing in patients with CHD without cardiac symptoms and enlarging RV to establish functional status. *4B*

a. *Pre-operative management (see also Q5)*

- Admission of a patient ≥ 48 h before surgery if patient nutritional status is good. *5B*
- Commence an octreotide infusion 12 h prior to operation, continue perioperatively and post-operatively until the patient is haemodynamically stable (see *Q4 c*).
- Be aware of the danger related to the use of catecholamines.
- Be aware of perioperative anaesthetic complications and the need for an experienced anaesthetist in dealing with CHD patients (within the MDT).

a. *Surgical management of CHD*

- Cardiac surgery, which primarily consists of valve replacement, is the most effective treatment option for advanced CHD. *3bA*
  - In patients with severe cardiac involvement and well-controlled systemic disease, valve replacement surgery is an effective treatment modality that can markedly improve symptoms and contribute to an improved outcome.[67,68]
  - In a study of 240 patients operated on at the Mayo Clinic, the overall survival estimates at 1, 3, and 5 years were 69%, 48%, and 34%.[69]
  - Short-term survival is improved with surgery[70]: in a study by Edwards et al.,[71] 1- and 2-year survival rates after surgery were 75% and 69% versus 45% and 15% on medical treatment only, when 32 patients with CHD were operated on versus 15 who were deemed unsuitable for intervention.
- 30-day mortality post-surgery has markedly declined over time[37,38] with increasing volume of patients operated on in selected institutions.[69]
- There is marked symptomatic improvement after valve replacement surgery in CHD patients, with majority of patients being re-classified as NYHA class I post-operatively[67,72,73]
- Patients undergoing combined tricuspid valve replacement (TVR) and pulmonary valve replacement (PVR) had significantly higher survival compared to operations without PVR, when involvement of PV into CHD led to more than mild PR.[71]
- The feasibility of quadruple valve replacement leading to marked functional improvement has also been reported by several groups.[66]
- In a recent metanalysis[74] consisting of 416 pre-operative patients, 97% had moderate or severe TR, 72% moderate or severe PR, and 33% with PS with or without regurgitation. Left heart characteristics included mitral valve regurgitation (MR) in 24% and aortic valve regurgitation (AR) in 18% of patients.
  - TR is usually the predominant lesion in CHD, and all patients with severe TR are candidates for TVR unless surgery is contraindicated.
  - PVR with patch enlargement of the right ventricular outflow tract is performed for management of PR and to facilitate implantation of the PV prosthesis of optimal size.[74]
  - Mitral valve replacement (MVR) may be performed, depending on the severity of mitral valve (MV) involvement.
  - Aurtic valve replacement (AVR) is the option for CHD involvement of the aortic valve (AV).
- Additional procedures include PFO closure and removal of intramyocardial metastasis.
  - The presence of a PFO should always be researched during surgery (and closed if present) even if not diagnosed during the pre-operative assessment.
- Because of increased risk of development of high-degree AV block post TV replacement, it is common practice to implant RV epicardial and right atrial (if in sinus rhythm prior to surgery and for possibility of A-V sequential pacing) pacing wires.[75] This should be considered in patients undergoing cardiac reoperation.

a. *Choice of valve prosthesis*

- The decision on the type of prosthesis should be individualised based on the risk of bleeding, the specific tumour-related life expectancy, and possible future therapeutic interventions.[75]
- The use of *mechanical valves* should be discouraged having several disadvantages:
  - The need for anticoagulation therapy, which may be problematic in a patient with liver metastases.
  - The increased risk of thrombosis of mechanical prostheses in the tricuspid and pulmonic position.
- *Bioprosthetic valves* are the recommended option[73] because of the inherent increased risk of bleeding in patients with advanced high-volume liver disease and hepatic dysfunction from NET, the increased likelihood of invasive procedures requiring temporary discontinuation of anticoagulant agents, and, to a lesser extent, the risk of right-sided mechanical valve thrombosis.
  - If new NET-associated structural valve deterioration occurs in biological prostheses, it can likely be treated with catheter-based valve-in-valve re-replacement. *4A*
- Optimisation of CS treatment after cardiac surgery may protect bioprosthetic valves from the adverse effects of increased NET vasoactive and hormonal products. The prosthesis dysfunction related to carcinoid rate eventually is reduced by the aggressive normalisation of 5-HIAA under SSA therapy with potential additive therapy (Figure 2). *3bA*

a. *Post-operative care and follow-up should include*

- Perform u5-HIAA/NT-proBNP regularly every 3–6 months aiming for their near/normalisation (u5-HIAA at least < 300 μmol/24 h), to prevent CHD recurrence which may be rapid in patients with RCS. *5B*
- Assess patient's QoL improvement, as well as optimal management of symptoms. *5B*

- Perform echocardiography post-operatively, then 3 months after stopping vitamin K antagonist (VKA) to confirm normal prosthetic valve function, and then 6–12 months later, and review every 6–12 months, based on patient's condition. *5B*
- Post-operatively, following bioprosthetic valve replacement, either VKA or novel oral anticoagulants are recommended for 3–6 months, with a preference for VKA albeit not supported by randomised trials (Consensus opinion). *5B*
  - Bioprosthetic valve function should be reassessed 1–3 months following initiation of anticoagulation to reassess prosthesis function. *5B*
  - Additional imaging with CT or TOE can be considered when bioprosthetic valve dysfunction is identified and TTE imaging is suboptimal. *5B*
- Causes for bioprosthetic valve dysfunction should be considered such as thrombosis, infection or plaque formation related to CHD. *5B* If bioprosthetic valve gradients increase by 50%, there is new abnormal leaflet thickening, abnormal leaflet mobility or prosthetic regurgitation following anticoagulation cessation, anticoagulation should be restarted and bioprosthetic valves reassessed in 1–3 months.[76] *5B*
- If early (< 3 years) bioprosthetic valve deterioration occurs, thrombus should be considered and evaluation with TOE or CCT should be performed.[77,78]

Q9: "Nonsurgical" interventional options for CHD[8]

- The experience with minimally invasive options (percutaneous catheter-based interventions, valve-in-valve replacements) is limited; however, this approach will play a growing role in the future, as:
  - Valve-in-valve replacement is feasible in degenerated surgical bioprosthesis, and should be the first choice in CHD patients.[79]
    - The mechanism of degeneration should be evaluated and if there are features of bioprosthetic valve thrombosis, VKA should be tried initially if the patient is clinically stable
    - Endocarditis should be excluded as a cause for bioprosthetic valve degeneration prior to considering valve-in-valve treatment.
  - For first-time procedures, percutaneous valve implantation has been reported for the pulmonary valve in CHD in selected patients.
  - Conversely to the left side, the risk of outflow tract obstruction, para-valvular leaks, and haemolysis is low.
  - The expected valve durability in this low-pressure environment is probably better but valve thrombosis remains a concern in transcatheter valves.
- A study (TRICAR), evaluating whether valved stent graft implant reduces TR and improves the symptoms and QoL in CHD patients who are unable to have a new valve via a surgical procedure, is ongoing (ClinicalTrials.gov Identifier: NCT05064514).

Q10: What are the advantages of MDT approach in improving the overall management of CS and CHD patients?

Decisions for optimal management of patients with moderate to severe CHD, as part of advanced NEN and CS, are complex and require a "holistic" approach as well as close collaboration between *NEN Physicians* and *Cardiac Specialists*. A dedicated CHD MDT will facilitate the optimal patient's medical treatment and define the appropriate type, as well as optimal timing for cardiac intervention (surgical/catheter based).

The CHD MDT, which can run separately or be a part of the main NEN MDT, will discuss patients with significant (moderate/severe or progressing) CHD who have been assessed in the cardiology/CHD clinic and fulfil the echocardiogram and/or clinical criteria for cardiac intervention. If the CHD MDT runs separately, all referred patients need to have been previously discussed at the main NEN MDT meeting, where decisions about control of hormonal secretion and tumour growth should have been made.

CHD MDT mandatory members include NEN physician(s), cardiologist(s) with expertise in CHD (preferable), cardio-thoracic surgeon(s), cardiac anesthetist, NEN and cardiology specialist nurses, and a dedicated nutritionist.

Several factors associated to the heart, NEN disease and patient' status and preferences need to be considered. Cardiovascular symptoms (NYHA class), RV function, tricuspid and left-sided cardiac valves (through echocardiography) and pulmonary valve (through TTE/TOE, CCT/CMRI) need to be thoroughly reviewed alongside NEN disease status (stable/progressing) and tumour burden, as well as patient-related factors including comorbidities, major organ function, and nutritional status.

CHD MDT members need to:

- Evaluate the risk of heart intervention as opposed to the patient's anticipated outcome if no interventional cardiac treatment is offered.
- Evaluate NET status (stable or progressing) and the oncological prognosis in relation to cardiosurgical risk.
- Assess the effect of CHD on the management of NEN disease overall.
- Determine whether a cardiac intervention in asymptomatic patients could facilitate future NEN treatments.
- Assess major organ function (liver and kidney).
- Assess patient's nutritional and overall performance status.
- Decisions need to be made about the type of intervention and timeframe.Following the CHD MDT outcome, the patient should be informed for the final treatment decision through an informed consent. The NET patient needs to accept the acute risk related to cardiac surgery as opposed to long-term risk of congestive heart failure, alongside the overall prognosis of NET disease.

5 | D. WHAT DO WE NOT KNOW IN CS AND CHD?

There are many other *unmet needs* to be fulfilled in these complex patients, such as:

- ***CS related unmet needs:***
  - Elucidate specific hormonal contributors to CS symptoms in individual patients.
  - Discover diagnostic biomarkers that more completely encompass the full clinical spectrum of CS.
  - Further develop and implement blood-based assays for serotonin and/or 5-HIAA in the diagnosis and follow-up of CS.
  - Develop and validate prognostic markers of survival outcome and predictive factors for QoL improvement and response to therapy in CS.
  - Understand the biological mechanisms of resistance of CS-directed therapies.
  - Unravel the biological drivers of CS, paving the way towards the discovery of novel drug targets.
  - Optimal treatment sequencing across the spectrum of CS, in the presence or absence of progressive disease and with the aim to prevent CS-related complications.
  - Invest in the design and execution of multicentre clinical trials specifically for CS patients, using well-defined and validated criteria for patient inclusion and definition of clinically relevant therapeutic endpoints.
- ***CHD related unmet needs:***
  - Elucidate the role of catheter-based cardiovascular therapies in selected group of patients.
  - Unravel the right time for the cardiac intervention (when patient is symptomatic or when is asymptomatic/minimally symptomatic but with progressive dilatation of RV size and deterioration of RV function).
  - Asses the role of functional assessment using cardiopulmonary exercise testing for optimal timing of intervention.
  - In terms of heart surgery, evaluate prognostic indicators in CHD patients versus in patients with CHD-unrelated valvular heart disease.
  - Evaluate how accurate is the overall prognosis of patients with NET, when determining a surgical intervention.
  - Assess the impact of cardiac intervention on the course of disease.
  - Biological prognostic markers of more aggressive CS and CHD are needed.
  - The biological drivers of CHD need to be unravelled.

6 | E. SUMMARY

This ENETS guidance paper, developed by a multidisciplinary consensus task force, provides up-to-date and practical advice on the diagnosis and management of CS and CHD, based on recent developments and using the recent ENETS Echo synoptic report in CHD patients.[31] Hopefully, these recommendations will pave the road for more standardised care for our CS and CHD patients resulting in improved outcomes. Upcoming studies aimed to fulfill the gap will allow us to focus on many unmet needs in this field.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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