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What do we know about Carcinoid Heart Disease? A systematic literature review

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Introduction

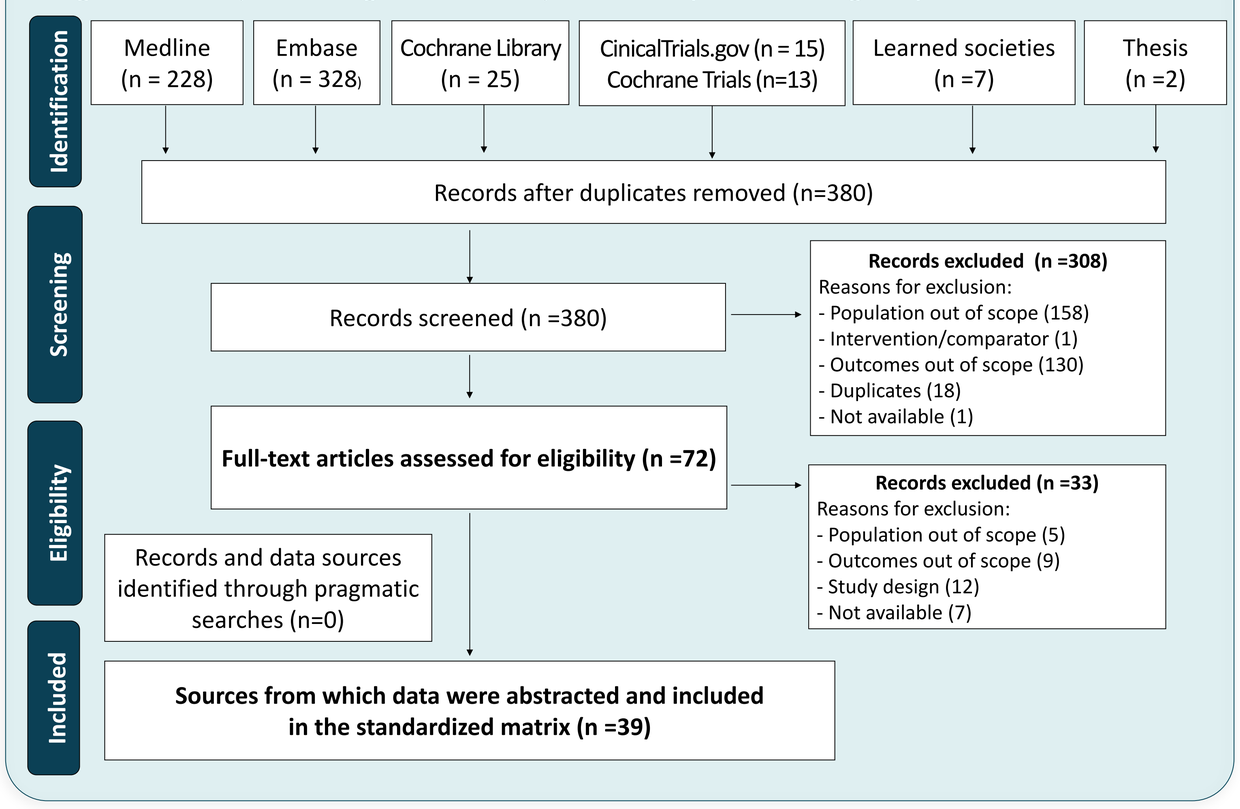
- Patients with advanced neuroendocrine tumours may develop carcinoid syndrome (CS), which consists of a constellation of symptoms that arise as a result of a massive release of serotonin and neuropeptides directly into the systemic circulation. CS is characterised by diarrhoea, flushing, wheezing/bronchospasm, and palpitations/cardiac damage.
- Carcinoid Heart Disease (CHD) is a life-threatening complication, which develops in 20-70% of patients, with CS. It is associated with 30–50% reduction in the expected survival of those patients. Elevated levels of Serotonin, represented by high levels of 5HIAA, are thought to be the key mediator of the development of CHD. However, NT-proBNP is a better biomarker of the presence and severity of CHD in patients with CS [1].
- The aim of this systematic literature review (SLR) was to review general and epidemiology published findings for CHD.
- This poster reports the general outcomes among CS patients with CHD.

Methods

Search, screening and study identification

- A systematic literature search using a predefined search strategy was performed on August 1, 2016 in Ovid (Medline, Medline in Process, EMBASE and Cochrane CENTRAL), ClinicalTrials.gov and key learned scientific society websites. No time restrictions were applied but language was limited to English, French and German.
- Searched terms included “Hedinger syndrome”, “Carcinoid Heart Disease”, as well as “carcinoid” combined with “cardiac”, “cardiopathy” “cardiovascular”, “heart”, “valve”, “valvular”, “valvulopathy”, “myocardial”.
- Abstract and full-text screening was performed against a pre-determined eligibility criteria for PICOS. Letters, editorials, reviews without original research data were excluded. Study type, patient characteristics and epidemiological outcomes were collected.
- A total of 618 records were identified. After de-duplication, 380 records were retrieved and screened. 72 records were included for full-text review against the eligibility criteria.
- Nevertheless, 50 excluded records reported drug-induced fibrotic valvular heart disease. Drug inducing valvular heart disease include some drugs from classes such as ergot derivatives, antidepressants, antidiabetics, appetite suppressants, cathecolaminergic agents, dopamine agonists and recreational drug ecstasy.
- 39 records, published between 1985 and 2016, were selected for data extraction (Figure1).

Figure 1. Study flow diagram for study selection (PRISMA diagram)[2]



Results

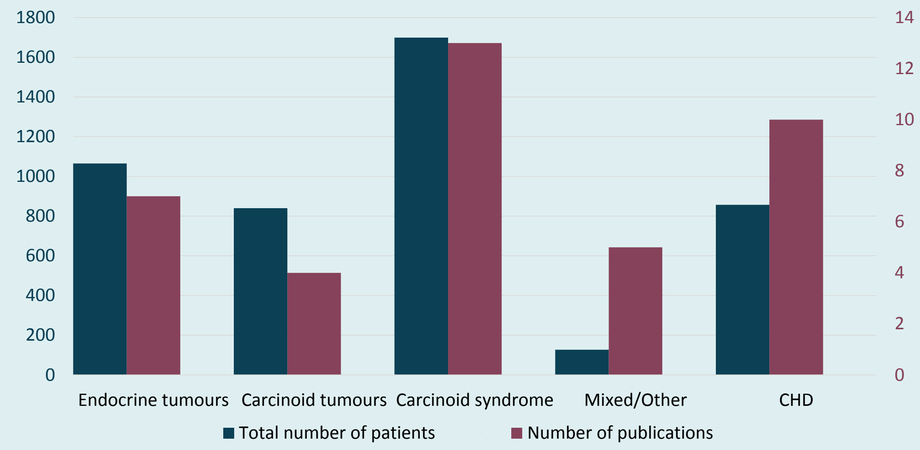
Study characteristics and design

- 54% of publications were from Europe and 46% from USA.
- Only 2 out 39 papers reflected an international collaboration (each limited to two countries).
- The most active hubs of clinicians interested in CS and CHD work at the Mayo Clinic (USA), University Hospital Ambroise Paré (France) and Royal Free Hospital (UK).
- Authors’ (n=219) specialty affiliations were mainly cardiology (28%), surgery (17%) and gastroenterology (13%).
- Most studies (36/39) were retrospective/prospective observational reporting between 7 and 265 CHD patients (median US 65, EU 27). Study periods varied from 1 to 28 years (median US 20 years EU 5 years).
- Other publications included two clinical studies [3-4] and a necropsy study [5]. No CHD-specific randomized clinical trials were found.
- No registry was identified. Most authors worked with data extracted from hospital departments’ medical records.

Population

- Observed populations were heterogeneous: studies analysed CHD patients (total 857 patients) or screened them from CS (1,699 patients), carcinoid (840) or endocrine tumours (1,065) (Figure 2).
- Mean aged varied from 43 to 65 year old with a minimum of 27 years old. The gender distribution varied from 39% to 64% being male.

Figure 2. Initial (baseline) population and number of publications



Diagnosis, biomarkers and progression assessment

- Time between the diagnosis of CS and the diagnosis of CHD varied from 1 month to 12 years. Majority of patients in selected studies received at least one echocardiography to confirm diagnosis.
- There are several echocardiographic scoring systems developed; however, there is a lack of standardized criteria for quantifying CHD progression. There might be considerable heterogeneity across a country in multiple aspects of screening and management of carcinoid heart disease [6].
- Compared to no-CHD patients, CHD patients have significantly higher levels of Chromogranin-A (CgA; 745±1,097 vs. 86±90ng/ml, p<0.0001) [7], NT-proBNP CHD (894 ng l^{-1} vs. 89 ng l^{-1}, p<0.001) [8] and urinary 5-hydroxyindoleacetic acid (5-HIAA): on average 2-4 fold higher [5, 9-17].
- Peak 5-HIAA levels are linked to CHD progression (odds ratio, 1.08 for each increase of 25 mg per 24 hours [95%CI 1.03 to 1.13]; P=0.009) [18].
- Patients diagnosed with CHD during 1995-2000 were characterized by lower peak 5-HIAA and greater use of treatment with somatostatin analogues and hepatic artery embolization than among patients diagnosed between 1981 and 1995 (p<0.001) [19].

CHD management

- The treatment of CHD includes general measures for the treatment of heart failure (salt and water restriction, use of diuretics, compression stockings), medical therapy (somatostatin analogues), tumour debulking surgery (hepatic resection) and cardiac surgery.
- The proportion of patients receiving valvular surgery varies between 31% and 47% in large series (n>65) [1, 18-20].
- Most of reviewed publications did not report eligibility criteria to receive surgery. Despite high perioperative mortality, surgical outcome has been improved potentially due to earlier patient referral and better perioperative management: survivors benefit from better functional capacity and improved congestive heart failure CHD outcomes have improved over time with greater use of somatostatin analogues, hepatic artery embolization, better perioperative management and surgery outcomes.
- As elevated concentrations of serotonin plays a key role in the pathogenesis and the progression of CHD, it is advocated that all patients with raised plasma/serum/urine 5-HIAA concentrations are at risk of cardiac involvement and warrant inclusion in a carcinoid cardiac surveillance programme. A proposed therapeutic strategy to lessen the development of CHD is to decrease 5-HIAA.

Conclusions

- This is a first CHD systematic literature review that aimed to provide a general overview of the disease, clinical and epidemiological outcomes.
- As CHD is a rare disease, reporting of CHD outcomes are inconsistent, and visibility is low. Research faces limitations: lack of large clinical studies, poor feasibility of randomised trials, lack of standardized criteria for quantifying CHD progression.
- More international collaboration is needed.

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