What do patients with heart failure die from?
A single assassin or a conspiracy?

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Globally, non-communicable diseases now account for most deaths, with cardiovascular disease and cancer at the top of this unfortunate league table. In 2017, in Western Europe, 29% of deaths were attributed to cancer and 33% to cardiovascular diseases[1]; in the USA, 21% were attributed to cancer and 23% to heart disease[2]. Unfortunately, many people get both cardiovascular disease and cancer. Most people who die from cardiovascular disease will first develop heart failure even if it is not recorded as the cause of death[3] and amongst incident cases of heart failure, 25% will already have a history of cancer[4] and 15% may subsequently die of cancer[5].

Heart failure and cancer share many common risk factors (e.g. obesity and smoking), many common symptoms (dyspnoea, fatigue, oedema, weight loss) and many similar complications, including depression, anaemia, iron deficiency and cachexia[6]. Cancer and its treatment may cause heart failure or aggravate pre-existing cardiac dysfunction. There may also be biological mechanisms by which heart failure enhances tumour growth[7], whilst clonal haematopoiesis of indeterminate

potential (CHIP) provides a common stem for the development of heart failure and cancer[7].

The two largest studies investigating a potential epidemiological link between heart failure and the subsequent development of cancer, have shown contradictory results. An analysis of hospital administrative records in Denmark[8] identified 9,307 patients with heart failure who were not known to have cancer at the time of diagnosis. Of these, 975 developed cancer during a mean follow-up of 4.5 years (SD ±2.3 years). Compared to patients without heart failure, the incidence rate ratio for developing any type of cancer was 1.24 (95% CI 1.15–1.33) after adjusting for age and sex, but not for other common risk factors for heart failure and cancer. In contrast, an analysis of data from 28,341 participants in the Physicians' Health Studies programme[9], comprising two randomized controlled trials testing aspirin and vitamin supplements, identified 1,420 new cases of heart failure and 7,363 new cases of cancer during a median follow-up of 20 years but found no association (crude HR 0.92; 95%CI 0.80–1.08).

In this issue, Bayés-Genís et al[10] report mortality and cause of death amongst 1,876 patients with heart failure and a left ventricular ejection fraction <50% at a single clinic in a tertiary cardiac centre in Spain. Median follow-up, censored for death (a statistical convention that clinicians should not necessarily adopt), was 4.2 years. During this time, 935 patients died. Although most deaths were cardiovascular, 138 (15%) people died of cancer, a similar proportion to that reported in the UK from a similar clinic[11] and a large administrative data-base[5]. This is a much lower proportion than die with cancer in the general population, which is not surprising given the high mortality related to cardiorespiratory disease in patients with heart failure. The authors go on to suggest that the proportion of deaths due to non-cardiovascular causes has risen over the last 20 years from less than 20% to more than 60% and that the proportion due to cancer has risen from less than 5% to more than 20%. However, in the period with the most robust data (2010-17) there was little evidence of a change in the mode of death. Adjudications in earlier periods might have been less robust before the clinical service, data-acquisition and adjudication procedures were fully mature. Conrad et al[5], using administrative data from primary and secondary care in the UK, identified 86,833 incident cases of heart failure

between 2002 and 2013. In this period, the proportion of deaths within one year of diagnosis that were cardiovascular fell from 52% to 43%, the proportion of deaths due to cancer was stable (14% to 15%) but deaths due to infection and/or respiratory disease rose from 18% to 25%. For those aged 80 years or less, all-cause mortality at one year fell by 21% due to a marked decline in cardiovascular mortality with little change in non-cardiovascular deaths. In contrast, all-cause mortality at one year was unchanged in older people, despite a 26% reduction in cardiovascular mortality, because it was offset by a rise in non-cardiovascular deaths, suggesting that current treatments for heart failure might modify how older patients die but do not prolong their lives.

Clinical trials of patients with heart failure and a reduced left ventricular ejection fraction (HFrEF) suggest that about 80% of deaths are cardiovascular, although perhaps only 25% die ‘of’ heart failure. Fewer than 10% of deaths are attributed to cancer, with little evidence of a change in the last 20 years (Figure 1). However, by design, clinical trials select patient-characteristics in order to enrich the population for the sorts of events that the intervention is designed to influence.

Clinical trials of heart failure with a preserved left ventricular ejection fraction (HFpEF) report a higher proportion of non-cardiovascular deaths (Figure 1), which may be one reason why so many have failed to show that treatments targeting cardiovascular disease improve outcome. Data from a clinic in the UK[11], similar to that described by Bayés-Genís et al[10], suggests a similarly higher proportion of deaths for non-cardiovascular reasons amongst people with HFrEF or HFpEF than observed in clinical trials (Figure 1). From a clinical trialists perspective, it is important to select patients who might benefit from the intervention being studied, whether it is for cancer or for heart disease. Older patients are more likely to have or develop multiple diseases that may confound the interpretation of trials aimed at a specific therapeutic target. Although treatments that are effective in younger patients with few comorbidities cannot be assumed to improve outcome in older people, younger patients should not be denied effective treatments just because trials conducted in older multi-morbid patients failed to show benefit.

Classification of clinical events, including death, is an evolving art that does not have a sound scientific basis. Classification depends heavily on the interpretation

of small words such as “of”, “from” and “with”. Oncologists are often uncertain about the cause of death in their patients; many will die “with” cancer but not “of” cancer. Indeed, analysis of 816 autopsies on patients who died whilst being treated for cancer found a cardiovascular cause for death in 194 (24%) cases (Figure 2)[12]. Deaths due to myocardial infarction, stroke or pulmonary embolism might appear unrelated to cancer[13] but inflammation may cause vascular damage and activate coagulation pathways leading to fatal thrombotic events. Other causes of death in patients with cancer include infection, renal failure and suicide. Many patients who have incurable cancer will not actually die of cancer. All of these considerations also hold true for heart failure. Most patients with heart failure don’t die of heart failure; they die suddenly, or they get respiratory or urinary infections with septicaemia and multi-organ failure, or they have myocardial infarctions and strokes, or they get old and develop dementia; some will die “of” heart failure but many more will die “with” heart failure. As treatments for heart failure extend life, it is inevitable that more patients with heart failure will get cancer. Similarly, discovery of more effective treatments for cancer will lead to more people developing heart failure. Ultimately, most people now die due to a conspiracy of diseases and not a single lethal problem.

Newer approaches to adjudication reflect this and no longer just report the primary cause of events but include other factors that conspire to produce an adverse outcome.

Treating heart failure and cancer, two malignant diseases, at the same time is challenging for both oncologists and cardiologists.[14,15,16] Many centres of excellence have established cardio-oncology services to evaluate the risk of cardiotoxicity, monitor the effects of therapy on cardiac function, ensure that curative treatment for cancer is not inappropriately withheld and manage patients who develop cardiac dysfunction and heart failure whilst being treated for cancer[17,18]. We must hope that all patients with heart failure have access to similar resources for their care when needed and not just those with two malignant diseases rather than just one.

In conclusion, an increase in the number of people developing cancer is an unfortunate consequence of the success in delaying the onset of heart failure into older age and greater longevity after heart failure has developed. Successful prevention and treatment of cancer is likely to have the same effect on the number of

people developing heart failure. Those unfortunate enough to develop multiple, debilitating, incurable conditions may become reluctantly reconciled to dying but perhaps, for some, death may be postponed too long[7]?

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