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SPOTLIGHT REVIEW

# Common risk factors for heart failure and cancer

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**Abstract**

Cardiovascular (CV) disease and cancer are the leading causes of death.[1,2] Over the last decades, it has been appreciated that both CV disease and cancer are more common in individuals in whom risk factors for disease development accumulate, and preventative measures have been extremely important in driving down the incidence of disease.[3–6] In general, the field of epidemiology, risk reduction, and preventative trials is divided into health care professionals who have an interest in either CV disease or cancer. As a result, the medical literature and medical practice has largely focused on the one disease, or the other. However, human individuals do not behave according to this dogma. Emerging data clearly suggest that identical risk factors may lead to CV disease in the one individual, but may cause cancer in another, or even both diseases in the same individual. This overlap exists between risk factors that are historically classified as 'CV risk factors' as these factors do equally strong predict cancer development. Therefore, we propose that a holistic approach might better estimate actual risks for CV disease and cancer. In this review, we summarize current insights in common behavioural risk factors for heart failure, being the most progressed and lethal form of CV disease, and cancer.

**Keywords** Cardio-oncology • Heart failure • Risk factors • Cardiovascular risk factors • Hypertension • Lipids • Biomarkers • Inflammation

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## 1. Risk factors for heart failure

The last decades several heart failure (HF) risk scores have been published, mostly from large cohort studies. Although differences between these models exist, most risk models have reported a quite consistent list of risk factors including age, sex, coronary artery disease (CAD), myocardial infarction (MI), hypertension, diabetes mellitus, and obesity as the most important risk factors,[7–12] In turn, some of these endophenotypes, such as CAD and MI, are explained by several established cardiovascular (CV) risk factors, such as diet, sedentary lifestyle, and smoking. Furthermore, genetic risk scores are emerging as a tool to assess the risk of developing HF.[13]

Although numerous studies have shown that risk factor reduction is efficacious, in the Lifelines Study Cohort, in which over 150 000 adult subjects in the Netherlands were enrolled in the period between 2008 and 2012, it was observed that only 25%, 4%, and 59% of patients with hypertension, hypercholesterolaemia, and diabetes received preventive pharmacotherapy.[14] This implicates that there is clear room for improvement, which may further reduce the burden of HF. The 2016 European Society of Cardiology (ESC) guidelines on diagnosis and treatment of HF advocate the use of such drugs, such as statins and angiotensin-converting enzyme (ACE) inhibitors, with the aim to prevent HF.[15] To facilitate case finding, the use of N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) in diagnosis of HF has been proposed. Two recent studies, the STOP-HF and PONTIAC, have shown that targeting apparently healthy subjects with elevated NT-proBNP may reduce the incidence of new onset HF.[16,17]

## 2. Cancer risk factors

As with HF, the last decades have generated numerous articles providing insight in risk factors of cancer in general, and of specific forms of cancer in particular.[5,6] Not quite like HF, the experiences with cancer risk prediction and reduction have been mixed. Challenges in individual risk prediction are many, and include long latency, multiple risk factors, each having a relatively small contribution, and incomplete knowledge of causal cancer pathways. Established risk factors are race, age, sex, genetics, body mass index, family history of cancer, history of tobacco use, lack of physical activity, but again, the causal effect of several of these remains unclear. Identification of risk factors, but mostly the impact of

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individual risk factors, will guide doctors in stratifying subjects in low-risk, medium-risk, and high-risk categories, resulting in preventative strategies.

Patients, generally, have difficulties adhering to recommendations, and many individuals, especially when urbanized, are obese, smoke, and have a lack of physical activity. Preventative strategies largely focus on life style, and supplementation studies, either with drugs, vitamins, or other food components, have been futile with respect to reducing new onset cancer.[18–20]

# 3. The link between heart failure and cancer risk factors

It appears plausible that HF and cancer accompany each other, given the large overlap in risk factors. Indeed, it has been reported that HF and cancer often coincide and evidence emerges of a direct effect between both disease.[21–25] To get a better understanding of the pathological mechanisms behind these diseases, most important risk factors and their entwining are discussed.

## 3.1 Hypertension

Hypertension is a prevalent and a well-established risk factor for HF.[8,26] Both clinical and experimental studies demonstrate a causal relationship between hypertension and cardiac remodelling.[27] However, less is known about the association of blood pressure with cancer. This possible association has been addressed in a large pooled European cohort ($n = 577\,799$) in which subjects were followed over a period of 12 years. Every 10 mmHg blood pressure increase was associated with an increased cancer incidence in men [hazard ratio (HR) 1.07, confidence interval (CI) 1.04–1.09], although results were non-significant in women (HR 1.02, CI 1.00–1.05). Nevertheless, in both men and women blood pressure was associated with cancer-related mortality (HR 1.12, CI 1.08–1.15) and (HR 1.06, CI 1.02–1.11), respectively.[28] So, from these data, a small yet significant association between hypertension and cancer may be suspected. To validate a causal role, it is helpful to study the effects of antihypertensive treatment. For renin-angiotensin-aldosterone system (RAAS) inhibitors, a large meta-analysis which included 55 different studies, composed of cancer patients with a variety of tumours focused on the association between RAAS inhibitors and recurrence, metastasis and survival. RAAS inhibitors yielded a beneficial effect on all cancer-endpoints [overall survival (HR 0.82, CI 0.77–0.88), progression-free survival (HR 0.74, CI 0.66–0.84), and disease-free survival (HR 0.80, CI 0.67–0.95)].[29] Blockade of beta adrenergic receptors improves symptoms, reduces hospitalization and enhances survival in patients with HF.[30] A large meta-analysis including over 18 000 subjects demonstrated neutral results regarding the use of β-blockers in breast cancer.[31] In both lung and colorectal cancer patients, no association was observed regarding mortality.[32] Interestingly, β-blocking agents may be of benefit in cancer treatment. Researchers in the field of pancreatic cancer describe that the use of β-blockers suppresses cancer invasion and proliferation.[33] No relationship between cancer incidence and calcium channel blockers (CCB) have been described.[34,35] A very large recent study based upon the United Kingdom population (>850 000 subjects) offered compelling proof that CCB use was not associated with an increased risk of cancer, regardless of the duration of use and type of cancer.[36]

On the other hand, the presence of cancer may have an effect on hypertension, too. In a retrospective cohort in which nearly 30% of 25 000 cancer patients were diagnosed with hypertension,[37] the highest incidence of hypertension was observed in gastric and ovarian cancer. Treatment with chemotherapy (cytotoxic, targeted, or combination) was associated with an average HR between 2-fold and 3.5-fold increase in risk of any degree of hypertension compared with periods of no chemotherapy. In these analyses, a bias for frequent monitoring during therapy has occurred, but nevertheless a large number of patients developed hypertension. Besides the known association of chemotherapy with new onset hypertension, a possible mechanism might be that chemotherapy disrupts angiogenesis, and directly acts on vascular function.[38] A recent review article discusses different chemotherapies and vascular complications, such as hypertension.[39] Besides drug-induced hypertension, physicians also need to be aware of other non-pharmaceutical explanations which could lead to hypertension. Anxiety, known to cause high blood pressure, is a common phenomenon in cancer patients receiving therapy.[40] Prospective studies demonstrate that relaxation therapy reduces anxiety, which also results in lower blood pressure and respiratory rate.[41]

## 3.2 Diabetes mellitus

Patients with diabetes mellitus have an increased risk of developing HF and those with HF are at higher risk for the development of diabetes mellitus. This reciprocal relationship between HF and diabetes mellitus is very strong. Nevertheless, biomarkers that are known to predict incidence HF do not predict diabetes mellitus in a large population-based cohort of nearly 8000 subjects.[42] In this same cohort, it became clear that inflammation-related markers partly explained this strong relation. The presence of diabetes mellitus also influenced adverse outcomes in patients with HF. In the Candesartan in Heart failure-Assessment of Reduction in Mortality and Morbidity (CHARM) trial, the presence of diabetes mellitus was associated with a two-fold increase of either death or the composite outcome of CV death or hospitalization for HF in patients that used insulin therapy, up to an 50% increased risk in non-insulin-treated diabetics.[43]

The presence of diabetes mellitus is also associated with an increased incidence of cancer. Proposed mechanisms include: increased inflammation, increased oxidative stress, direct effects of excess glucose and insulin signalling, and various other factors.[44–46] In a large Italian population cohort, cancer incidence was higher in subjects with diabetes mellitus than in those without diabetes mellitus (HR 1.22, CI 1.15–1.29). Further excess risk was observed in those using insulin therapy (alone or in combination with oral therapies).[47] The relationship between insulin and cancer might be explained by elevation of insulin growth factor (IGF). Meta-analyses have shown an increased risk of several cancers associated with high serum levels of IGF.[48] On the other hand, experimental studies with metformin, the first line oral therapy in diabetes mellitus, suggested antineoplastic effects of metformin. Clearly, these data cannot be directly translated to the real life situation because these results were due to a substantially higher dosages than those indicated for treatment in humans with diabetes mellitus.[49] But meta-analyses of epidemiologic studies have supported the observed association between metformin use and lower incidence of several cancers in patients with diabetes mellitus.[50]

## 3.3 Obesity

The association between HF and obesity has been known for a long time. While the risk of developing HF has been shown to be higher in patients who are obese, a survival advantage exists for overweight/obese patients in comparison to average weight patients. This paradox might

also be similar in patients with cancer.[51] It is speculated that 20% of the incidence of cancer is related to obesity.[52] Overweight and obesity are both associated with an increased relative risk to develop cancer (1.2–1.5 and 1.5–1.8, respectively).[53] It is hypothesized that these effects are due to a state of chronic and low-level inflammation, which may lead to DNA damage and increase in the likelihood of malignant mutations and cancer incidence.[54]

As discussed in previous paragraphs, hypercholesterolaemia is an important risk factor in the development of ischaemic heart disease. Since hypercholesterolaemia is an important player in atherosclerosis, high cholesterol levels can further increase the risk of cancer. Although not verified in human studies, hypercholesterolaemia increases the incidence and pathologic severity of colorectal neoplasia in two independent mouse models.[55] Another experimental study investigating breast cancer models, demonstrates that cholesterol accelerates and enhances tumour formation. In addition, tumours were more aggressive, and tumour angiogenesis was enhanced.[56] Furthermore, treatment of hypercholesterolaemia with diet and/or with ezetimibe suppresses the growth of breast tumours *in vivo*.[57]

## 3.4 Sex

Not so long ago, a typical HF patient was male and had endured a MI. However, the last years, women are catching up: they tend to develop HF at a more advanced age, present more often with HF with preserved ejection fraction, are more symptomatic, and tend to have more comorbidities than men. Although women come to occupy an ever-increasing group of HF patients, European surveys have provided the statistics that men have better odds to receive treatment with ACE inhibitors, β-blockers, and mineralocorticoid receptor antagonists (MRAs) compared with women (odds ratio 1.34, CI 1.22–1.48).[58,59]

Although differences clearly exist between gender, it does not influence mortality in patients with HF. In a Spanish HF cohort of 1252 patients (61.3% males) with a median follow-up of 2.3 years typical differences were observed. Women were older (73.4 ± 10.0 years vs. 66.8 ± 11.9 years; $P < 0.001$), had a higher proportion of preserved systolic function (52.2% vs. 31.9%; $P < 0.001$), and less often suffered from ischaemic cardiomyopathy (44.1% vs. 53.2%; $P < 0.001$). No influence of sex on survival was observed either in the group as a whole or in subgroups with preserved or reduced left ventricular systolic function.[60]

Sex does not only affect HF phenotype and incidence, but gender is also associated with the prevalence of cancer. Men are more likely to be diagnosed with HF at an earlier age, as discussed above, and they are also more frequently diagnosed with cancer. In Europe, there were an estimated 3.9 million new cases of cancer and 1.9 million deaths from cancer in 2018.[2] The cancer burden for men and women varies widely by country. Europe is characterized by striking geographical differences in cancer occurrence. The most common cancer sites were cancers of the female breast, followed by colorectal, lung, and prostate cancer. The most common causes of death from cancer were cancers of the lung, colorectal, breast, and pancreatic origin.[2]

## 3.5 Genetics

Both CV disease and cancer have numerous genetic risk factors, but not many are shared. In this paragraph, we discuss several inherited (germline) genetic mutations and acquired (somatic) genetic mutations. An example in which germ-line mutations play a role is the Wnt/β-catenin pathway. The 'canonical' Wnt/β-catenin signalling pathway is involved in cell proliferation, polarity, migration, and cell fate determination.[61] Aberrant Wnt signalling plays an important role in the pathogenesis of atherosclerosis and also in several cancers.[62,63] Furthermore, mutations in one of the binding proteins of Wnt, LRP6 is involved in both CAD and different forms of cancer.

More acquired mutations that underpin the genetic relation between HF and cancer is for example DYRK1B. DYRK1B is overexpressed in many types of tumours and a gain of function mutation in the DYRK1B gene is linked to CV disease.[64,65] This genetic overlap might represent novel biological shared pathways between cancer development and HF.

A very exciting novel field in with apparent importance to both CV disease and cancer is that of clonal haematopoiesis.[66] Haematopoietic stem cells in bone marrow may acquire certain mutations in the course of life, which may present competitive advantages. Such clonal progeny presents a substantial proportion of the leucocytes and may be measured in the blood. This so-called clonal haematopoiesis of indeterminate potential (CHIP) is a common observation in ageing subjects and has established relation with cancer formation, especially haematological malignancies, although many clones never become malignant.[67] Of interest, recently it was shown that CHIP also appears to be important for development of CV disease in general,[68] and HF in particular.[69] The precise mechanisms underlying this relation are subject to study. This field is rapidly developing, and amongst the gaps in knowledge a central one is if targeting CHIP, or its underpinning genetic variants, could alleviate CV disease.

## 3.6 Smoking

Smoking is a well-known and amendable risk factor for both CAD and cancer, especially for lung and bladder cancer.[70,71] There is massive evidence on the unequivocal relation between smoking and cancer. The effect of smoking and cancer incidence has also been studied in patients who suffered a MI prior to cancer development. A reassuring observation in this study was the reduction of new-onset cancer in patients that stopped (or reduced) smoking. A study with 1486 patients with a follow-up of more than 20 years, demonstrated that the excess risk for incidence cancer among persistent smokers was HR 1.75 (95% CI 1.22–2.50), whereas the risk of those who quit smoking was HR 1.14 (95% CI 0.80–1.62).[72]

## 3.7 Myocardial infarction

All these above described risk factors may eventually result in acute cardiac events, such as MI. Even though identification and treatment of patients with MI has improved significantly the past decade, it still remains the most important risk factor for incident HF.[73] In recent years, the association between MI and cancer has also been established. Two prospective cohort studies describe the future risk of incident cancer in patients with MI. The first study was a large population-based study ($n = 28\,763$) and included participants without a previous history of MI or cancer and had a follow-up period of more than 15 years.[74] A total of 1747 subjects endured a MI, of which 146 suffered from subsequent cancer. Patients with a MI had an increased risk of 46% (HR 1.46, 95% CI 1.21–1.77) to develop cancer compared with those without MI. This increased risk persisted even 6 months after the initial event. Women seemed more prone to develop cancer, as the incidence rates were higher in women than in men. Another study reported on 1081 subjects with a MI and a mean follow-up of nearly 5 years.[75] The authors demonstrated that those who developed HF had a higher incidence of cancer compared with those without HF (HR 2.16, CI 1.39–3.35). These studies demonstrate that patients suffering a MI have an increased risk of cancer,

even after a significant time period after the actual event. This risk is even higher in patients who also develop HF after the event.

The mechanism behind a MI is the blockage of the blood supply to a certain region of the myocardium due to rupture of an atherosclerotic plaque in a coronary artery, which immediately declares the association with several HF and cancer risk factors. Hypercholesterolaemia and smoking are only two of several risk factors for this ischaemic process. Hypercholesterolaemia is discussed in the obesity paragraph above.

Interestingly, a reduced mortality rate after acute MI has been described in certain cancer patients treated with anti-neoplastic pads. These pads, contain sodium nitroprusside, demonstrated improved outcome after MI (with pad: 12.3% mortality vs. without pad: 29.9%).[76] It is thought that systemic restoration of impaired nitric oxide explains these observations.

# 4. Cardiovascular drug and the risk of cancer

## 4.1 Diuretics

Fluid retention and congestion are hallmarks of HF and are associated both with severe symptoms and poor outcomes.[77] Millions of people worldwide use diuretics, therefore, even a small increase in the cancer incidence rate would have a significant public impact. Fortunately, the results regarding diuretic use are neutral (although mixed) and no clear suspicion of increased cancer risk exists.[78,79] A recent article from the Danish Cancer Registry described an increased risk for skin cancer with hydrochlorothiazide, which was ascribed to enhanced photosensitivity of the skin due to thiazide intake.[80]

## 4.2 Statins

One of the most prescribed drugs in CV disease, reduce CV-related morbidity and mortality. The use of a statin is not associated with reduced cancer incidence (short-term effect for cancer risk) and the evidence is inconclusive.[81] Researchers have hypothesized that statins may also have potent anti-inflammatory properties that could have protective effects against cancer, but this is yet to be proven. Nevertheless, only conflicting data have been published regarding cholesterol levels and/or statins treatment, as can be read in another review.[82]

## 4.3 Aspirin

Being an established treatment in preventing adverse events in patients with CV disease, aspirin is often considered a primary prevention, although the net value for this therapy is uncertain.[83] Evidence is beginning to emerge regarding low-dose aspirin and cancer prevention. In eight CV trials, patients randomized to either aspirin or placebo were pooled and cancer occurrence was monitored. Aspirin treatment was associated with a 21% lower risk of death from any cancer during the in-trial follow-up period (HR 0.79, CI 0.68–0.92).[84] The recent published ARRIVE trial, which investigated low-dose aspirin and vascular events in a low-medium risk population did not demonstrate a lower incidence of cancer. It has to be noted that this population also demonstrated less than expected CV endpoints.[85] The mechanism behind the beneficial effects of aspirin in both diseases might be different. In CV disease, it owes to antiplatelet effects, whereas in cancer it may be due to cyclooxygenase (COX)-dependent and COX-independent mechanisms.[86]

## 4.4 Oral antidiabetic drugs

A strong relationship exists between diabetes mellitus, CV disease, and cancer. Metformin is the most commonly prescribed drug for Type II diabetes mellitus, as it prevents microvascular and macrovascular complications.[87] It is believed that the systemic effect of metformin, manifested in reduced circulating levels of insulin and IGF-1, might be associated with anticancer action.[88] Several meta-analyses and epidemiological studies have described a diminished cancer incidence of 30–50% in metformin users relative to either insulin or sulfonylureas.[89–91] New treatment modalities in diabetes mellitus such as SGLT2 inhibitors, as well as their risk of cancer, remain uncertain. In a recent systematic review and meta-analysis, no association with either increased or reduced risk for cancer incidence was observed amongst those receiving SGLT2.[92]

## 4.5 Medical radiation

The risk associated with CAD itself, and especially the procedure of coronary angiography are relatively high in comparison with the hypothetical additional lifetime risk of malignancy in patients undergoing different radiological cardiac diagnostic procedures.[93] Awareness should be raised for those receiving high-dose radiation, or younger patients.

# 5. Heart failure therapy influenced by cancer

The treatment strategy for patients who develop cancer may be altered due to HF as an important comorbidity, and a diagnosis of cancer might also influence how HF patients should be treated.[94]

Up titration is a key element used for treating patients with HF and is necessary to achieve an optimal medical therapy that leads to improved outcomes.[95] It includes high doses of a β-blocker with either ACE inhibitors, angiotensin-receptor blockers (ARB), or angiotensin receptor/neprilysin inhibitors (ARNi), as well as a MRAs.[15] It is possible that optimal HF treatment is unable to be maintained in patients diagnosed with cancer. In daily practice, this treatment regimen is altered due to health status deterioration from malignancy or when anti-tumour drugs are administered.

For example, patients with a history of CV disease and who are diagnosed with malignancies tend to present themselves at the emergency department with either the signs or symptoms related to cancer progression or the side effects of chemotherapy. These signs generally include hypotension, electrolyte depletion, and acutely worsening renal function caused by fluid loss (less intake/vomiting/diarrhoea). The physicians who treat these patients automatically withdraw drugs targeting the neuro-hormonal or sympathetic system. Careful up titration at a later stage is often neglected. We recommend that these patients are also consulted by a cardiologist, who along with an oncologist can determine the point at which certain therapies should be withheld or restarted.

# 6. Going from individual risk factors to shared pathophysiological pathways

Besides (and in part in response to) shared risk factors as discussed, several pathophysiological pathways are shared between both HF and cancer. Examples are increased oxidative stress, activated neuro-hormonal

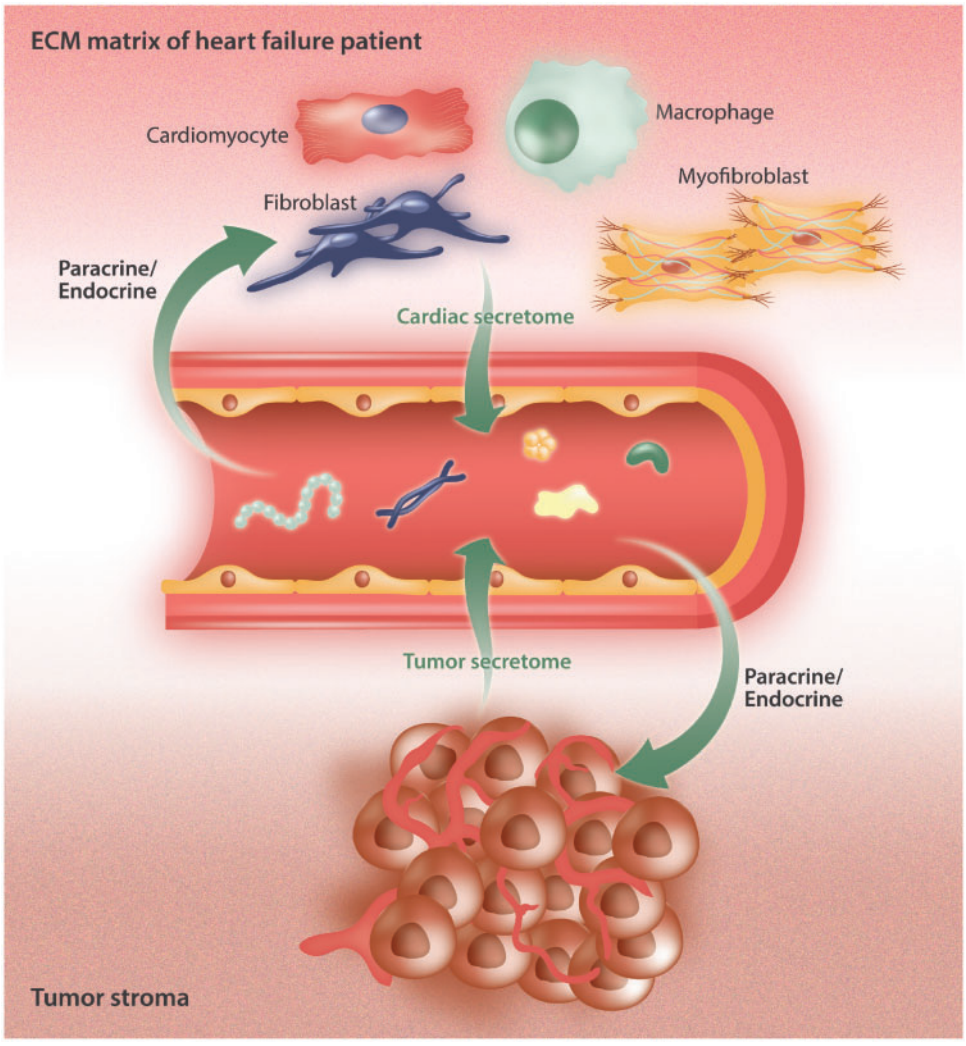


**Figure 1** Hypothetical depiction of the 'cardiac and tumour secretomes', each affecting the cardiac extracellular matrix and the tumour stroma via paracrine and endocrine signalling.

systems, and a dysregulated immune system. Furthermore, inflammation is a crucial pathophysiological phenomenon, which is shared between HF and cancer. Several studies have provided evidence that progression of either HF or cancer is linked to enhanced tissue inflammation.[96,97] Several players have been recognized, including (but not limited to) dysregulated T-cells,[98,99] a switch in the macrophage population from M1 to M2 macrophages,[100,101] and influx of various other inflammatory cells (neutrophils, monocytes, and mast cells).[102,103] All of these cells are responsible for a sequelae of events and are able to drive a specific programme, involving a complex set of paracrine and endocrine signals, attracting other cells, production and excretion of pro-inflammatory factors (cytokines), and bringing to expression receptors or factors receptive for additional signals. Given this extremely complex process, it comes to little surprise that up until now, the direct interplay between pro-inflammatory cytokines or cells released from either cardiac or tumour tissue on the other organs remains unclear, if any of such exist. Compelling evidence has recently been presented, underscoring the importance of inflammation for both diseases. The interleukin-1β blocker canakinumab, studied in the CANTOS trial, resulted in an approximately 15% reduction in major adverse CV events in comparison placebo in patients with vascular disease.[104] But in addition, canakinumub also reduced cancer mortality by approximately 40% and incident lung cancer, by >50%.[105] Although of circumstantial nature, these observations clearly bolster the hypothesis that inflammation connects HF and cancer.

## 7. Cardiac extracellular matrix vs. tumour stroma

In studying HF, the primary source cells of interest generally are cardiomyocytes that may undergo structural changes (cardiomyocyte hypertrophy), and functional changes (sarcomeric changes and disturbed calcium handling). However, the heart contains substantial amounts of connective tissue and it is in fact increasingly recognized that the majority of cardiac cells are not cardiomyocytes, but rather fibroblasts, endothelial cells, and inflammatory cells. Several of such cells produce extracellular matrix (ECM) proteins that constitute the ECM. Increased apposition of ECM is more and more recognized as a main culprit in HF

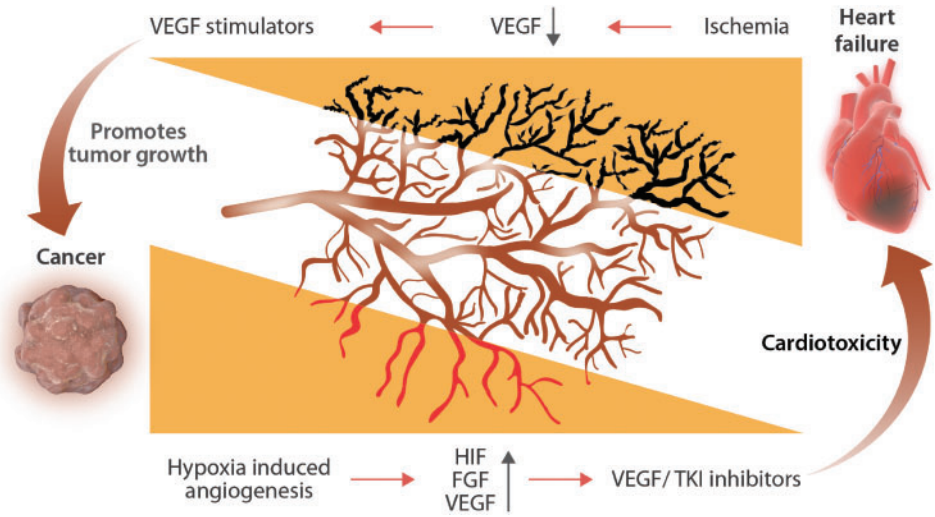


**Figure 2** Graphical presentation of the contradictory dynamics and effects of angiogenesis between heart failure and cancer, and the possible interaction of drugs affecting angiogenesis on heart failure and cancer. FGF, fibroblast growth factor; HIF, hypoxia induced factor; TKI tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

development.[106–108] Cardiac fibroblasts respond to various triggers by exhibiting a specific programme, where they turn from quiescent fibroblasts into matrix secreting myofibroblasts, initiating changes that have profound implications for the structure and function of the connective tissue.[108] It is becoming apparent that connective tissue need to be considered as a living tissue, and not a static scar that produces multiple factors that act as paracrine and endocrine factors, and many of them in fact are secreted in the blood stream and may act on peripheral organs, possibly on (latent) cancers as well.[25]

On the other hand, in cancer, the principle cells being studied are the malignant cells from the originating tumour organ. However, as in HF, there is more and more recognition that the supporting tissue, in cancer often being referred to as tumour stroma, plays a crucial role in cancer development, growth, but also treatment response or insensitivity.[109] There is increasing awareness that the microenvironment of tumours, as in HF, has very important roles in signalling, in promoting or reducing cell growth stimulation or arrest, in angiogenesis, and in the dynamics of the molecular programme of tumours, as depicted in *Figure 1*.[109] The tumour micro-environment may respond to specific triggers, such as obesity, which has been shown to increase myofibroblast content, the inflammasome, and several other elements of the stroma.[110]

Future research should address if factors of the cardiac ECM and the tumour stroma respond identically to certain triggers such as obesity or diabetes, and if they present a line of communication between the two distant organs.

## 8. Angiogenesis

Formation of new blood vessels, a physiological process, is clearly essential for growing structures such as tumours and metastases. Most rapid proliferating tissues are characterized by insufficient and disproportionate blood vessel formation, and the ensuing ischaemia is a trigger for the production of hypoxia sensing pathways, including hypoxia-inducible factor (HIF), and growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor, but also nitric oxide, angiopoietins, and many more factors. It is now generally accepted that there is an angiogenic switch that either tips towards a net absence of angiogenesis, or tips towards enhanced angiogenesis, where neovascularization is active and supports tumour growth.[111]

Recent advances in the understanding of angiogenic mechanisms have resulted in the development of anti-angiogenic agents that effectively block tumour growth and metastases.[112] There are multiple anti-angiogenic drugs to treat angiogenesis-dependent cancers and metastases, but most prominent are VEGF inhibitors such as bevacizumab and tyrosine kinase inhibitors (TKIs).

In HF, on the other hand, tissue hypoxia and ischaemia is generally not accompanied by proportionate vessel growth.[113] It has been observed that insufficient production of pro-angiogenic factors in dilated cardiomyopathy and other forms of HF are present,[114,115] and this may contribute to the progression of HF. Some have advocated the use of pro-angiogenic factors to combat HF.[116]

Given the importance of angiogenesis to normal cardiac physiology, it comes as little surprise that anti-angiogenic drugs have cardiac side-effects.[117] The incidence of VEGF and TKI-associated CV toxicity is substantial. Many patients suffer from acute rises in blood pressure, and a substantial proportion develop hypertension. Their use is associated with the development of left ventricular dysfunction, HF but also myocardial ischaemia.

Where angiogenesis is lagging behind and much needed in HF, it rather contributes to cancer and metastases progression. Future research should delineate tissue-specific switches in angiogenesis and ideally, these should be targeted in HF and cancer to their benefit, while leaving the process unaffected in the other condition. Clearly, this represents a challenging task. *Figure 2* displays the contradictory dynamics and effects of angiogenesis between cardiac and tumour tissue.

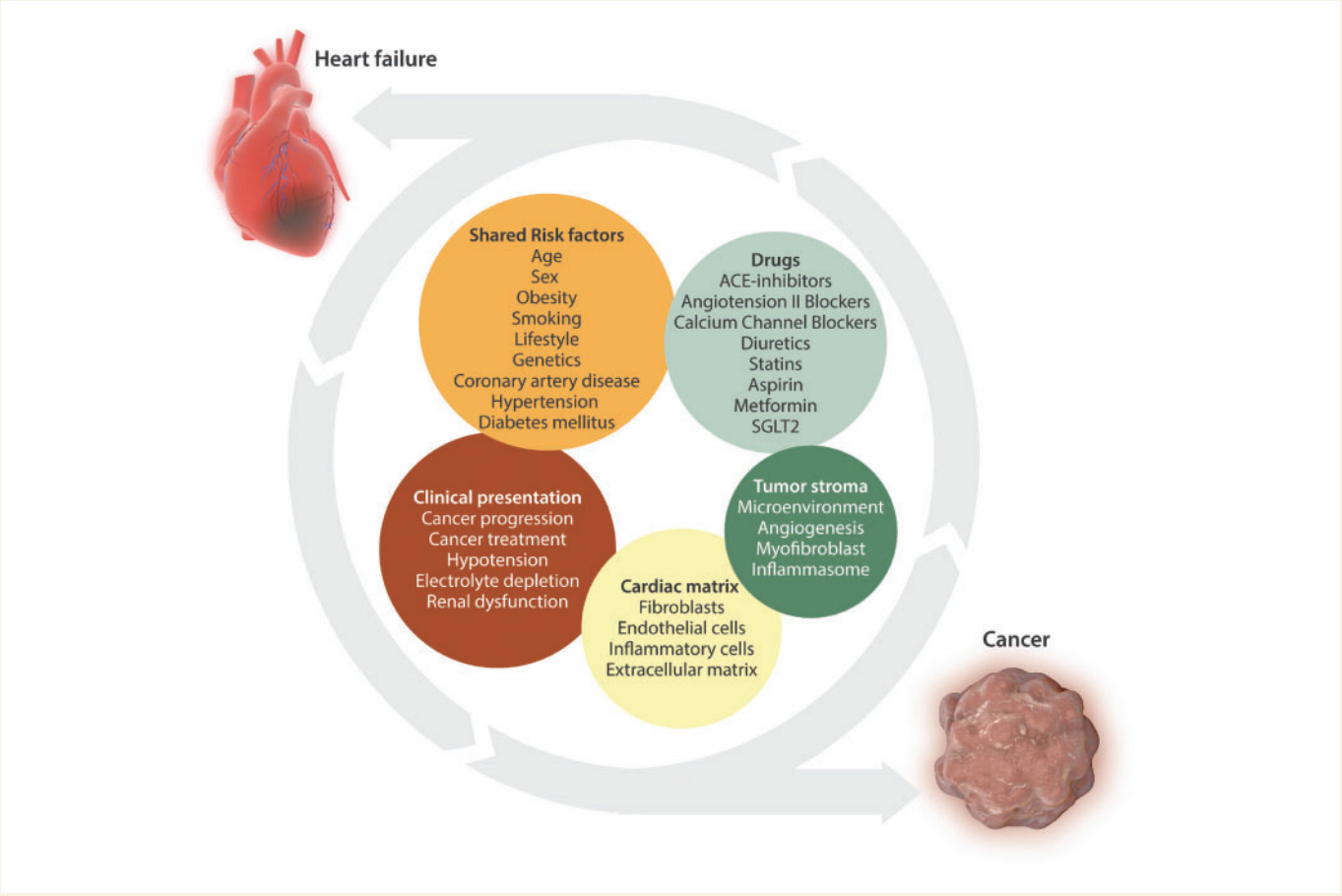


**Figure 3** Proposed schedule of the complex interplay between heart failure and cancer.

## 9. Immunology

In the last decades is has become increasingly evident that innate immune and inflammatory signalling processes play essential roles in cardiac remodelling.[118,119] The central molecules and receptors of the innate immune system are expressed in both cardiomyocytes and fibroblasts in the heart. Further, an activation of the adaptive immune system,[120,121] requiring specific cooperation between antigen-presenting cells and distinct antigen specific receptors on T cells, also plays an important role in infarct healing and cardiac remodelling. A profound and sustained immunological and inflammatory response has been observed in HF, and this may have strong repercussion for the physiology of distant organs, including tumours.[122]

A dramatic change is the landscape of anti-cancer therapy has occurred in the last years due to the discovery of immune therapy with different immune checkpoint inhibitors.[123] Nevertheless, a fatal cardiac complication also emerged with the use of these drugs. An 'over-active' immune system can cause auto-immune like diseases such as fulminant myocarditis with a mortality rate of nearly 50%.[124] Because immune therapy benefits many cancer patients and indication is rapidly expanding, these detrimental complications unfortunately will become a new clinical entity.

In the same vein, cancer development relies on several phenomena that are driven by immunological derailment.[125,126] In particular, during the of cancer formation, which often lasts several years, tumour cells interact with the tumour stroma and microenvironment, characterized by escaping the detection of the immune system. Several factors pertinent to HF such as growth factors (VEGF, PDGF), interleukins (IL-1, IL6, TNF-alpha), and further involvement of cells such as leucocytes and macrophages drive tumour formation as they drive adverse cardiac remodelling.

## 10. Summary

CV disease in general, and HF in particular, appear strongly related to cancer. The one condition is more often associated with the other than could be expected based on coincidence. The intimate connections and the almost obligatory consistency in risk factors suggest that these conditions may have much more in common than previously believed. Classical risk factors explain part of this relationship, and combatting smoking, sedentary lifestyle, and obesity will inevitably reduce both HF and cancer. Cardio-oncology has mostly focused on the consequences for the heart of cancer treatment, especially chemotherapy and radiotherapy. In this review, we aimed to draw attention for the fact that many risk factors are shared between CV disease and cancer. Oncologists will score risk factors as cancer risk factors, whereas cardiologists will score similar factors as CV risk factors. Clearly, appreciation that most risk factors may contribute to both disease will help organ or disease specialists realizing that patients with such risk factors are prone to more diseases at the same time. We also have put forward several more connections that may seem less straightforward, but that we

believe might be important in the connection and understanding of either disease. Particularly, we discussed the effects several (CV) drugs may have. Further, genetic background may play a role and clonal haematopoiesis, which has been established as a risk factor for cancer, now also has been studied in CV disease. In addition, specific changes in diseased tissue, in the connective tissue, the vasculature and in immune cells, may contribute to both diseases, and exert effects that far outplay the local situation. The overlap is abundant and complex, and several pathways and cross-talk needs to be elucidated as indicated in *Figure 3*. Ongoing studies in these fields likely will elucidate several more shared factors and pathways, which we believe, will help to better understand and treat both lethal diseases.

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