Effects of heart failure pharmacotherapy on cancer: a narrative review of implicated pathways and pre-clinical and clinical evidence

Nabil V. Sayour[1,2,3], Ágnes M. Paál[1], Pietro Ameri[4,5], Wouter C. Meijers[6], Giorgio Minotti[7], Ioanna Andreadou[8], Antonella Lombardo[9,10], Massimiliano Camilli[9,10], Heinz Drexel[11], Erik Lerkevang Grove[12,13], Gheorghe Andrei Dan[14,15], Andreea Ivanescu[14,15], Anne Grete Semb[16], Gianluigi Savarese[17,18], Dobromir Dobrev[19,20,21], Filippo Crea[9,10], Juan-Carlos Kaski[22], Rudolf A. de Boer[6], Péter Ferdinandy[1,23,24#], Zoltán V. Varga[1,2,3#*]

1 - Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary

2 - HCEMM-SU Cardiometabolic Immunology Research Group, Budapest, Hungary

3 - MTA-SE Momentum Cardio-Oncology and Cardioimmunology Research Group, Budapest, Hungary

4 - Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Italian IRCCS Cardiology Network, Genova, Italy

5 - Department of Internal Medicine, University of Genova, Genova, Italy

6 - Department of Cardiology, Thorax Center, Erasmus University Medical Center, Rotterdam, The Netherlands

7 - University Campus Bio-Medico, Rome, Italy

8 - School of Pharmacy, Division of Pharmaceutical Chemistry, Panepistimiopolis-Zografou, Athens, Greece

9 - Department of Cardiovascular and Pulmonary Sciences, Catholic University of the Sacred Heart, Rome, Italy

10 - Department of Cardiovascular Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

11 - Vorarlberg Institut für Vaskuläre Forschung (VIVIT), Feldkirch, Austria

12 - Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

13 - Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark

14 - Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

15 - Cardiology Department, Colentina Clinical Hospital, Bucharest, Romania

16 - Division of Research and Innovation, REMEDY-Centre for treatment of Rheumatic and Musculoskeletal Diseases, Diakonhjemmet hospital, Oslo, Norway

17 - Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

18 - Heart and Vascular and Neuro Theme, Karolinska University Hospital, Stockholm, Sweden

19 - Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Essen, Germany

20 - Department of Medicine and Research Center, Montreal Heart Institute and Université de Montréal, Montréal, Canada

21 - Department of Integrative Physiology, Baylor College of Medicine, Houston, TX, USA

22 - Molecular and Clinical Sciences Research Institute, St. George's University of London, London United Kingdom

23 - Pharmahungary Group, Szeged, Hungary

24 - MTA-SE System Pharmacology Research Group, Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary

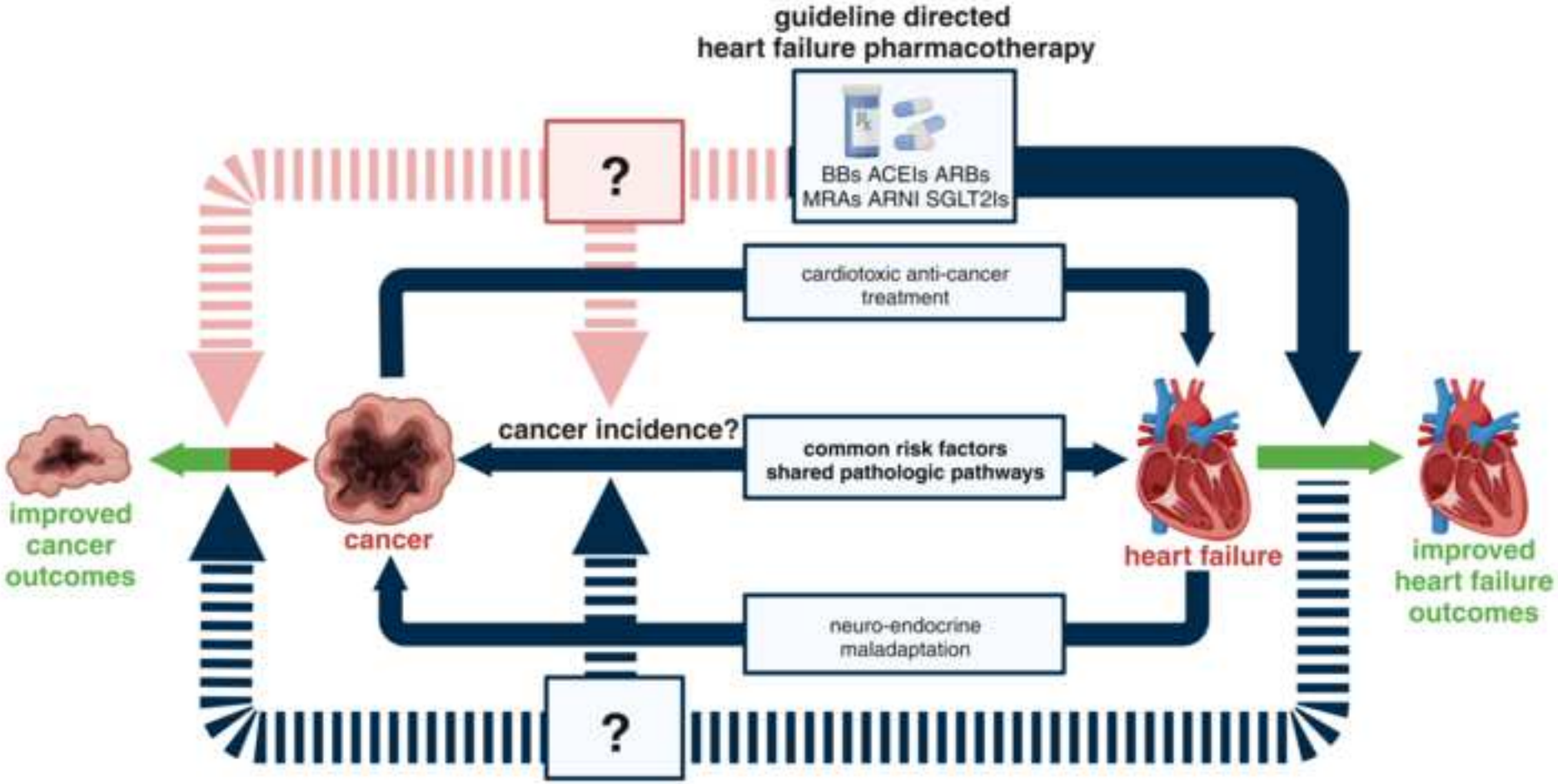
# These authors contributed equally to this work.

* Email: varga.zoltan@med.semmelweis-univ.hu

Abstract

Heart failure (HF) patients have a significantly higher risk of new-onset cancer and cancer-associated mortality, compared to subjects free of HF. While both the prevention and treatment of new-onset HF in patients with cancer have been investigated extensively, less is known about the prevention and treatment of new-onset cancer in patients with HF, and whether and how guideline directed medical therapy (GDMT) for HF should be modified when cancer is diagnosed in HF patients. The purpose of this review is to elaborate and discuss the effects of pillar HF pharmacotherapies, as well as digoxin and diuretics on cancer, and to identify areas for further research and novel therapeutic strategies. To this end, in this review (i) proposed effects and mechanisms of action of guideline-directed HF drugs on cancer derived from pre-clinical data will be described, (ii) the evidence from both observational studies and randomized controlled trials on the effects of GDMT on cancer incidence and cancer-related outcomes, as synthetized by meta-analyses will be reviewed, and (iii) considerations for future pre-clinical and clinical investigations will be provided.

Graphical Abstract



Effects of heart failure pharmacotherapy on cancer: a narrative review of implicated pathways and pre-clinical and clinical evidence

Nabil V. Sayour[1,2,3], Ágnes M. Paál[1], Pietro Ameri[4,5], Wouter C. Meijers[6], Giorgio Minotti[7], Ioanna Andreadou[8], Antonella Lombardo[9,10], Massimiliano Camilli[9,10], Heinz Drexel[11], Erik Lerkevang Grove[12,13], Gheorghe Andrei Dan[14,15], Andreea Ivanescu[14,15], Anne Grete Semb[16], Gianluigi Savarese[17,18], Dobromir Dobrev[19,20,21], Filippo Crea[9,10], Juan-Carlos Kaski[22], Rudolf A. de Boer[6], Péter Ferdinandy[1,23,24#], Zoltán V. Varga[1,2,3#*]

1 - Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary

2 - HCEMM-SU Cardiometabolic Immunology Research Group, Budapest, Hungary

3 - MTA-SE Momentum Cardio-Oncology and Cardioimmunology Research Group, Budapest, Hungary

4 - Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Italian IRCCS Cardiology Network, Genova, Italy

5 - Department of Internal Medicine, University of Genova, Genova, Italy

6 - Department of Cardiology, Thorax Center, Erasmus University Medical Center, Rotterdam, The Netherlands

7 - University Campus Bio-Medico, Rome, Italy

8 - School of Pharmacy, Division of Pharmaceutical Chemistry, Panepistimiopolis-Zografou, Athens, Greece

9 - Department of Cardiovascular and Pulmonary Sciences, Catholic University of the Sacred Heart, Rome, Italy

10 - Department of Cardiovascular Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

11 - Vorarlberg Institut für Vaskuläre Forschung (VIVIT), Feldkirch, Austria

12 - Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

13 - Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark

14 - Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

15 - Cardiology Department, Colentina Clinical Hospital, Bucharest, Romania

16 - Division of Research and Innovation, REMEDY-Centre for treatment of Rheumatic and Musculoskeletal Diseases, Diakonhjemmet hospital, Oslo, Norway

17 - Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

18 - Heart and Vascular and Neuro Theme, Karolinska University Hospital, Stockholm, Sweden

19 - Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Essen, Germany

20 - Department of Medicine and Research Center, Montreal Heart Institute and Université de Montréal, Montréal, Canada

21 - Department of Integrative Physiology, Baylor College of Medicine, Houston, TX, USA

22 - Molecular and Clinical Sciences Research Institute, St. George's University of London, London United Kingdom

23 - Pharmahungary Group, Szeged, Hungary

24 - MTA-SE System Pharmacology Research Group, Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary

# These authors contributed equally to this work.

* Email: varga.zoltan@med.semmelweis-univ.hu

Abstract

Heart failure (HF) patients have a significantly higher risk of new-onset cancer and cancer-associated mortality, compared to subjects free of HF. While both the prevention and treatment of new-onset HF in patients with cancer have been investigated extensively, less is known about the prevention and treatment of new-onset cancer in patients with HF, and whether and how guideline directed medical therapy (GDMT) for HF should be modified when cancer is diagnosed in HF patients. The purpose of this review is to elaborate and discuss the effects of pillar HF pharmacotherapies, as well as digoxin and diuretics on cancer, and to identify areas for further research and novel therapeutic strategies. To this end, in this review (i) proposed effects and mechanisms of action of guideline-directed HF drugs on cancer derived from pre-clinical data will be described, (ii) the evidence from both observational studies and randomized controlled trials on the effects of GDMT on cancer incidence and cancer-related outcomes, as synthetized by meta-analyses will be reviewed, and (iii) considerations for future pre-clinical and clinical investigations will be provided.

Keywords: cardio-oncology, heart failure, cancer, beta-blocker, mineralocorticoid-receptor-antagonist, sodium-glucose-cotransporter-2-inhibitor, angiotensin-receptor-blocker, angiotensin-converting-enzyme-inhibitor, angiotensin receptor neprilysin-inhibitor

1 Introduction

Heart failure (HF) and cancer are leading causes of mortality worldwide[1–6]. Although HF and cancer are conventionally viewed as two separate disease entities, an implicit bidirectional relationship between them has been identified by recent studies[7], as (i) major risk factors and mechanistic pathways overlap in HF and cancer[8–11], (ii) in patients with prevalent cancer, cardiovascular diseases are the leading causes of non-cancer mortality[12–14], (iii) several cancer pharmacotherapies exert cardiotoxic effects[15–18], and (iv) in patients with prevalent HF, majority of observational evidence reported increased cancer incidence and worse cancer outcomes compared with subjects free of HF, irrespective of patients' age, HF etiology, and cancer type[19–25] (*Graphical abstract*). However, an epidemiological study on men with self-reported HF reported no such associations[26], moreover, a Danish nationwide study reported a significant decrease of cancer incidence in patients with prevalent HF after adjusting for multiple variables including co-morbidities and medications[27]. Interestingly, despite major improvements in HF therapies, cancer incidence in HF patients has remained unchanged for the past 20 years, underscoring the importance of cancer in the setting of HF[28,29].

Guideline recommendations exist regarding prevention, screening, monitoring and treatment of new-onset HF in patients receiving cancer therapies[3]. However, no recommendations are available that defines if and how HF treatment should be modified (i) to prevent cancer incidence in HF patients, or (ii) when cancer is diagnosed during the course of HF, and no on-going clinical studies are available addressing these questions. Indeed, based on a systematic search on Clinicaltrials.gov we have found that all of the on-going clinical studies of cardio-oncology are related to prevention or treatment of cancer therapy-related cardiotoxicity (*Supplementary table 1.*).

The purpose of this review is to provide (i) an overview on the effects and proposed mechanisms of action of guideline-directed medical therapy (GDMT) of HF on cancer based on pre-clinical data, and (ii) a balanced interpretation of findings reported in clinical meta-analyses investigating the effects of HF GDMT on cancer incidence and outcomes. Moreover, gaps of knowledge and areas of future pre-clinical and clinical research will also be highlighted.

In this narrative review, we collected evidence from *in vivo* (*Supplementary table 2.*) and *in vitro* (*Supplementary table 3.*) pre-clinical studies, with a special emphasis on drug-type, dosing, cancer type, and endpoints. We also collected information from meta-analyses of clinical studies investigating the effect of HF GDMT on cancer incidence in cancer-free patients, or other cancer-related outcomes (e.g. cancer-specific or recurrence-free survival) in patients with pre-existing cancer at baseline (*Supplementary table 4.*).

2 Effects of beta-blockers on cancer

Beta-adrenoceptor signaling has been suggested to play a contributory role in cancer biology, as it modulates cancer progression mainly via the activation of protein kinase A and the Exchange Protein activated by Adenylyl Cyclase (*Figure 1.*)[30]. Catecholamines regulate beta-adrenoceptors on cancer cells, stromal cells, and tumour-associated macrophages[31], resulting in a procarcinogenic microenvironment. Accordingly, beta-blockers (BBs) may have a potential to decrease cancer incidence or improve cancer outcomes.

2.1 Pre-clinical studies assessing the effects of BBs on cancer

Effects of BBs on cancer have been extensively investigated in the pre-clinical studies, almost unanimously demonstrating potent anti-cancer effects both *in vivo* (*Supplementary table 2.*) and *in vitro* (*Supplementary table 3.*). Most *in vivo* studies tested the non-selective BB propranolol. Propranolol exerted significant anti-cancer effects *in vivo* by inhibiting tumour growth[32–35], reducing metastases[36,37], influencing tumour immuno-microenvironment[38], and by repressing angiogenesis[39]. In contrast, some studies showed that propranolol did not have anti-cancer effects *per se*[40], as it could only enhance the effects of other anti-cancer therapies[38,41–44]. Among *in vivo* studies investigating the anti-cancer effects of non-selective BBs other than propranolol, carvedilol was the most commonly used agent. Most of these studies demonstrated significant anti-cancer effects of carvedilol when used alone in a variety of cancer-types [45–52]. Other BBs, such as the beta1-selective metoprolol[41] and nebivolol[53,54], as well as the non-selective labetalol[33] were also shown to have either anti-cancer effects *per se*, or enhance the anti-cancer effects of other drugs.

Anti-cancer effects of various BBs on several cancer types has been assessed by *in vitro* studies, resulting in variable results. For instance, anti-cancer efficacy of propranolol or beta2-adrenoceptor blockade was reported to be higher compared to beta1-selective BBs by the majority of studies[34,55–58]. Conversely, a study on non-small cell lung cancer cell lines demonstrated no correlation between beta-adrenoceptor selectivity and anti-cancer efficacy of BBs, as both propranolol and the beta1-selective betaxolol significantly decreased colony formation[59]. Of note, metoprolol, the only beta1-selective BB approved for HF that was investigated in this study, was ineffective in such settings. Moreover, superiority of beta1-selective BBs over propranolol has also been demonstrated *in vitro*[60–62], further complicating the picture.

Of note, BB use emerged not only in prevention of cancer development *per se*, but also in prevention of cancer therapy-related cardiotoxicity, as beta-adrenoceptor signaling was shown to share an intricate conundrum with human epidermal growth factor receptor type 2 (ERBB2) in the cardiovascular system, and also in breast cancer[63,64]. As a result, the BB carvedilol was shown to prevent ERBB2-blockade-induced cardiotoxicity[65].

2.2 Clinical studies assessing the effects of BBs on cancer

Intriguingly, contrary to the pre-clinical studies, meta-analyses on clinical observational studies or randomized controlled trials (RCTs) show disparate results regarding effects of BBs on cancer, both in cancer-free patients, and in cancer patients (*Figure 2.*, *Supplementary table 4.*).

2.2.1 Effects of BBs on risk of cancer in cancer-free patients

In a meta-analysis on 9 RCTs, BB use was associated with a non-significant trend toward lower overall risk of any cancer type[66]. Likewise, a network meta-analysis on 70 RCTs showed that the use of BBs was not associated with any change in risk of any cancer type, or cancer mortality[67]. In other meta-analyses, BB use was associated with mixed effects on cancer incidence, varied by cancer types. For instance, two meta-analyses showed no association between BB use and risk of new-onset breast, lung, colon or prostate cancer[68,69]. Other meta-analyses showed that BB use was associated with a significantly increased risk of melanoma[70,71], but of note, the these meta-analyses included the same primary studies. In addition, a meta-analysis resulted in a significantly increased risk of kidney or bladder cancer in BB users[72], while another meta-analysis demonstrated a significantly increased risk for hepatocellular carcinoma in patients with liver cirrhosis using non-selective BBs[73]. Of interest, none of these meta-analyses used HF patients, or HF as an indication for BB use exclusively, according to their study eligibility criteria.

2.2.2 Effects of BBs on cancer outcomes in patients with prevalent cancer

Meta-analyses on breast cancer showed that BB use was associated with either no effect[74–76], or with improved cancer outcomes[77–79] compared to non-users, even when BBs were started after diagnosis of malignancy[79]. Most meta-analyses on lung cancer show no associations of BB use with cancer outcomes[74–76,79]. Still, one meta-analysis reported that (i) non-selective BB use was associated with significantly worse overall survival of lung cancer patients, and that (ii) BB use (not stratified by selectivity) was associated with improved overall survival in stage III patients and in those without surgical cancer treatment[80]. With respect to colorectal cancer, no association has been found between BB use and cancer outcomes[74–76,79]. Regarding malignant melanoma, repeated analyses on the same cohorts hinted towards improved overall survival in patients using BB[74–76]. Conversely, another meta-analysis that included additional cohort studies showed no association of BB use with beneficial cancer outcomes in patients with malignant melanoma[79].

In conclusion, although BBs have been shown to exert significant anti-cancer effects in pre-clinical studies, meta-analyses of clinical studies show inconsistent and sometimes conflicting results regarding the associations of BB use with cancer incidence and outcomes, independently from cancer site and outcome measure. Moreover, there is no consensus on how beta-adrenoceptor selectivity influences the effect of BBs on cancer neither in pre-clinical, nor in clinical studies. It should also be stressed that BBs have no proven effects in HF with preserved ejection fraction, and only minor cardioprotective effects in cancer patients receiving chemotherapy[81]. Nevertheless, as the activation of SNS on cancer outcomes has been well-established in both the pre-clinical studies and the clinical settings[82], there is strong rationale to further investigate the SNS-cancer relationships.

3 Effects of renin-angiotensin-aldosterone system inhibitors on cancer

Many studies have shown that dysregulation of the renin-angiotensin-aldosterone-system (RAAS) may promote cancer, mainly driven by the AT1R-Akt axis (*Figure 1.*)[83]. The idea for investigating effects of RAAS blockade on cancer has first emerged by the retrospective analysis of Lever et al., showing that patients using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) had a reduced risk for developing cancer[84]. This seminal study gave rise to pre-clinical and clinical studies testing the hypothesis that RAAS blockade entails anti-cancer effects, as well as to investigations demonstrating that components of RAAS are expressed in various human cancers and in their microenvironment[83], which are associated with worse outcomes[85,86].

3.1 Pre-clinical studies assessing the effects of RAASIs on cancer

The anti-cancer effects of blocking the RAAS with ACEIs was tested in numerous pre-clinical *in vivo* studies, mostly demonstrating benefits, that could be exerted either alone or in combination with other anti-cancer therapies (*Supplementary table 2.*)[87–91]. Nevertheless, contradictory findings were reported in an early study by Wysocki and colleagues, where captopril did *not* exert significant anti-cancer effects, but was associated with increased mortality in immunocompetent mouse models of renal cancer[92]. However, in a more recent study using a similar immunocompetent cancer model and the same cancer cell line, captopril significantly reduced primary tumour weight and lung metastases. Of note, captopril treatment was started 2 days prior to tumour inoculation, and in a lower dose[93]. The anti-cancer effects of RAAS blockade by ACEIs is further supported by *in vitro* studies, showing a reduction in cell-proliferation, migration and invasion[94–99]. Nevertheless, in contrast to these *in vivo* studies, several *in vitro* studies reported no direct anti-cancer effects of ACEIs[91,100–102], or no synergism with other anti-cancer agents (*Supplementary table 3.*)[103].

Whether findings of these pre-clinical studies is a class effect is not known, as captopril was assessed almost exclusively. Thus, a comprehensive, systematic research strategy to assess the effects of different types of ACEIs is lacking.

ARBs inhibit the AT1R, the key target of angiotensin-II, which is the major effector peptide of the RAAS. In tumour-bearing mice, ARBs exert significant anti-cancer effects by reducing tumour growth and/or fibrosis[104–107], metastases[108,109], tumour neo-angiogenesis[110–112], and influencing tumour immuno-microenvironment (*Supplementary table 2.*)[108,113]. In a seminal study by Rhodes et al., AT1R is overexpressed in 10-20% of breast cancer cases across multiple independent patient cohorts. The study indicated that marked AT1R-overexpression defines a subpopulation of estrogen-receptor-positive, ERBB2-negative breast cancer that may benefit from targeted therapy with ARBs, most particularly losartan. These findings were obtained in both *in vitro* and *in vivo* models AT1R-overexpressing breast cancer, but not in $AT1R^{low}$ cell line[114]. Nevertheless, contradictory results were obtained by a number of *in vitro* and *in vivo* studies demonstrating no or less anti-cancer effects of ARBs, mostly using losartan or irbesartan[115–128] (*Supplementary table 3.*).

Mineralocorticoid receptor antagonists (MRAs) represent a third pillar part of HF GDMT. Only a handful of pre-clinical studies investigated effects of MRAs on cancer currently. Leung and colleagues demonstrated that spironolactone decreased the number of intestinal polyps in APJ^{min} mice (a mouse model of spontaneous intestinal adenoma formation), and inhibited metastases in colorectal carcinoma-implantation studies by pathways that are independent of the mineralocorticoid receptor[129]. Other *in vivo* studies also demonstrated a significant anti-cancer effect of the MRAs by reducing tumour volume[130–132], and/or by inhibiting metastatic spread[133] (*Supplementary table 2.*). Accordingly, majority of *in vitro* studies also show an overall anti-cancer effect of MRAs

either given alone or in combination with other therapeutics (*Supplementary table 3.*)[130,134–138]. Of note, Gold and colleagues reported difference in anti-cancer efficacy of different MRAs, showing superiority of spironolactone over eplerenone[131], a differential effect that needs further elucidation regarding mechanism. Conversely, lack of anti-cancer effects for spironolactone were also found on liver-[132], and pituitary cancer cell lines[139]. Moreover, Aldaz and colleagues demonstrated that spironolactone (either alone, or in combination with dexamethasone) protected the glioblastoma cells against radiation-induced damage[140].

3.2 Clinical studies assessing the effects of RAASIs on cancer

The putative effects of RAAS blockade on malignancy in HF patients was investigated in a seminal meta-analysis by Sipahi and colleagues, in which only RCTs of ARBs were analyzed. Here, a significant association between the use of ARBs and overall cancer risk was reported, mostly attributed to new-onset lung cancer[141]. These results raised doubts about the reliability of this meta-analysis, as adjudication of cancer diagnoses was not uniform among the included studies[142].

3.2.1 Effects of RAASIs on risk of cancer in cancer-free patients

Other meta-analyses of RCTs reported that ARB or ACEI usage was not associated with cancer risk compared to placebo[67,68,143–146]. This lack of association between RAASI use and incident cancer has also been suggested by meta-analyses of cohort studies across multiple cancer types[69–71,147,148]. However, meta-analyses of non-randomized investigations demonstrated a significantly decreased incidence of esophagus[149], colorectal[150], prostate[151], and lung cancer[144], but an increased risk for renal cancer[72,149] and melanoma[149] amongst users of ACEI/ARB compared to non-users. Although a large number of meta-analyses have been conducted to investigate the association between ACEI/ARB use and cancer incidence, only a single recent meta-analysis by

Bommareddy and colleagues assessed the effect of spironolactone on cancer occurrence[152]. This meta-analysis synthesized data from observational studies, showing a significantly decreased risk for prostate cancer, but no effect on other cancer types. Similar to BBLs, effects of RAASIs on cancer incidence were mostly assessed in hypertensive, but not in HF populations by the meta-analyses.

3.2.2 Effects of RAASIs on cancer outcomes in patients with prevalent cancer

In contrast to the disparate effects of RAASIs on cancer incidence, meta-analyses of observational studies demonstrated significantly improved cancer outcomes in patients with digestive system malignancies[153–155], renal cancer[154,156], or all-cause cancer[157] in users of ACEIs or ARBs. Nevertheless, a meta-analysis on RCTs showed neutral effect of RAASIs in cancer patients irrespective of the cancer type[158].

In conclusion, the effect of RAASIs on new-onset cancer risk is conflicting in the current clinical data, varying mostly by cancer types, and also, by primary study design (i.e. RCT or observational). However, in patients with prevalent cancer, majority of meta-analyses either show safety, or even improved cancer-related outcomes when RAASIs are used, compared to non-users. Nevertheless, a major factor that complicates the interpretation of these results is the confounding by indication, that is, most of the clinical data is derived from patients with hypertension, and not with HF, urging for further evidence in the HF populations as well.

4 Effects of angiotensin-receptor-neprilysin-inhibitor on cancer

There is a general lack of pre-clinical and clinical evidence regarding the effect of angiotensin receptor neprilysin inhibitor (ARNI, i.e. sacubitril-valsartan) on cancer, which is another part for HF GDMT [1], a drug that enhances the beneficial cardiovascular effects of endogenous natriuretic peptides (NP)[159,160]. Of note, in the landmark RCT leading to approval of ARNI for treatment of HF with reduced ejection fraction, proportion of cancer deaths was comparable in the ARNI and ACEi arms[161]. Moreover, in a recent cohort study on patients with HF with mildly reduced ejection fraction, ARNI/ACEI/ARB use significantly increased cancer incidence in the primary outcomes within 3 years, although this association was not significant by falsification analysis[162].

NPs have been shown to inhibit tumour growth in several *in vitro* and *in vivo* studies[163–166], nevertheless, these associations should be interpreted with caution, as some malignant cells are also able to produce NPs, questioning generalizability of tumour-inhibitory effects of NPs[167,168]. In addition, it is noteworthy that in principle neprilysin inhibition also increases the availability of factors other than NPs that might influence cancer cell biology[169]. The effects of these substrates should also be considered in future investigations addressing the effects of ARNI on cancer.

5 Effects of sodium-glucose-cotransporter-2 inhibitors on cancer

As glucose is a major substrate required for cancer cell survival and growth, Scafoglio and colleagues hypothesized that the metabolism-shifting effect of SGLT2Is might be protective against malignancy as well[170]. In this seminal investigation, functional expression of SGLT2 on human pancreatic and prostate cancers was demonstrated. In addition, this was the first study providing evidence on SGLT2 inhibitors blocking glucose uptake and reducing tumour growth in a xenograft model of pancreatic

cancer, which led to the conduction of subsequent pre-clinical studies investigating the anti-cancer effects of SGLT2 inhibitors[171].

5.1 Pre-clinical studies assessing the effects of SGLT2Is on cancer

Glucose uptake/metabolism-dependent anti-cancer mechanisms of SGLT2Is have been further demonstrated in cancer-bearing mice, which was attributed to activation of AMPK, and thus, to the inhibition of mTOR[172–174] (*Figure 1., Supplementary table 2.*). Nevertheless, Kaji et al. reported the anti-cancer effect of SGLT2 inhibition to be exerted independently of the systemic glycemic status, although cellular glucose-uptake was not assessed here[175]. Other mechanistic pathways on the anti-cancer effects of SGLT2 blockade were suggested by other studies, showing that SGLT2 inhibition (i) decreases pro-carcinogenic inflammation[176], (ii) activates AMPK, which leads to inactivation of the protooncogene sonic hedgehog[177], (iii) suppresses cancer progression by inhibiting the Hippo signalling pathway through downregulating YAP1 expression[178]. In contrast, however, Korfhage and colleagues reported an increased intestinal adenoma burden in female, but not in male APC^{min} mice, when treated with canagliflozin[179], a result that needs further mechanistic elucidation.

Several *in vitro* studies also indicated that anti-cancer mechanisms of SGLT2Is are mainly attributed to the induction of AMPK[180], which subsequently leads to the inhibition of the Akt/mTOR pathway (*Supplementary table 3.*)[181]. In addition, analyses of metabolomics in SGLT2I-treated cancer cell lines showed that beside the glucose-dependent mechanisms, alteration of other metabolic pathways (e.g. fatty acid metabolism) also contribute to the decrease in cancer cell proliferation[182,183]. Other *in vitro* studies reported that anti-proliferative effects of SGLT2Is are exerted by a significant repression of DNA-synthesis[184], subsequent cell cycle arrest[185], and by blocking aberrant activation of ß-catenin[186]. In the latter study, dapagliflozin and empagliflozin (the

two SGLT2 inhibitors that are currently recommended in HF) exerted non-significant effects, questioning the presence of a class effect.

Of note, in addition to tumour growth studies, SGLT2 inhibitors were also investigated in cancer therapy-related toxicity studies. For instance, dapagliflozin and empagliflozin were shown to revert ponatinib-induced endothelial cell senescence and dysfunction[187].

5.2 Clinical studies assessing the effects of SGLT2Is on cancer

During the safety trials of SGLT2Is in diabetic patients, no significant increase in overall cancer events was observed. Nevertheless, a nominal increase in bladder cancer incidence in men, and breast cancer incidence in women were noted in the SGLT2I-treated arm[188]. These observations have led to systematic investigations of the association between SGLT2I use and cancer, showing inconsistent results (*Supplementary table 4.* & *Figure 4.*).

For instance, a recent meta-analysis of hyperglycaemic patients reported an overall reduced risk of cancer associated with SGLT2I use, and most particularly with dapagliflozin and ertugliflozin vs. placebo[189]. Of note, in this meta-analysis, 2 trials with large sample sizes may have shifted the overall effect size towards benefit by SGLT2Is, whereas the majority of the included studies had large confidence intervals (i.e., small sample sizes) with non-significant effects. Surprisingly, an earlier meta-analysis showed no association of SGLT2I with malignancy, however (i) dapagliflozin significantly increased risk of overall cancer compared to other antidiabetic drugs, and (ii) empagliflozin nominally increased the risk of overall cancer compared to placebo in patients with type 2 diabetes mellitus (T2DM)[190]. Another meta-analysis on T2DM patients showed that risk of overall cancer in obese patients was significantly increased in association with SGLT2I use. This meta-

analysis also showed a tendency towards increased risk of cancer in studies with a follow-up period of >52 months. Moreover, risk of bladder cancer also significantly increased, mainly associated with the use of empagliflozin[191]. In contrast, Dicembrini and colleagues reported a significant risk reduction in bladder cancer associated with dapagliflozin use, although this result was derived from 4 RCTs, one of which might have been overweighed, thus, dominating the overall effect size[192].

Meta-analyses investigating effects of SGLT2Is on outcomes by cancer types show no significant change in the risk of breast cancer[190–192], lung cancer[190–192], prostate cancer[191–193], or melanoma[194], with the latter cancer showing a tendency to increase by SGLT2Is. In addition, similar neutral results were reported regarding renal, pancreatic and hepatocellular cancers as well[192].

As the use of SGLT2I with the indication for HF has only recently been introduced, most meta-analyses synthesize data from studies of patients with diabetes. Nevertheless, the putative association between SGLT2I use and cancer outcomes of HF patients – with or without diabetes – requires investigation in future meta-analyses. Moreover, as the above meta-analyses assessed only the risk of cancer, future studies should also assess the outcomes of patients with prevalent cancer.

6 Effects of digoxin on cancer

Although not considered as a pillar part for HF pharmacotherapy, digoxin is still used in selected HF patients[1]. Effects of digoxin on cancer have been investigated in a variety of *in vitro* studies, mostly showing anti-cancer properties by causing cell-cycle arrest[195–201]. These findings were supported by *in vivo* studies, showing an inhibition of tumour growth[201–203], or reducing distant tumour formation[204]. Despite the appealing pre-clinical data, meta-analyses on clinical studies show rather

contradictory results. For instance, Ahern and colleagues performed an observational study and a meta-analysis showing a significantly increased risk of breast cancer in digoxin users vs. non-users[205]. This finding was further supported by a meta-analysis also reporting significantly increased risk of breast cancer, lung cancer and colorectal cancer, but not prostate cancer in association with digoxin use[206]. In addition, significantly increased all-cause mortality of cancer patients using digoxin was also reported, but no increase in cancer-specific mortality could be detected. It should be emphasized here that these results should be interpreted with caution, as clinical studies may be biased by (i) a higher likelihood of medical contact, and (ii) an intrinsic tendency towards worse outcomes (not only restricted to cancer or cardiovascular outcomes), as patients taking digoxin are on average sicker than those not on this medication.

Overall, there is an apparent discrepancy between the pre-clinical studies (almost unanimously demonstrating anti-cancer effects) and the clinical investigations (showing a tendency towards worse cancer outcomes) regarding effects of digoxin on cancer. This discrepancy highlights the need for increasing the translational value of pre-clinical research, and the reliability of clinical data that are synthesized by meta-analyses.

7 Effects of diuretics on cancer

Loop diuretics (e.g. furosemide) are used in HF patients to reduce symptoms and signs of congestion[1]. The target molecule of furosemide, Na-K-2Cl-transporter has been shown to be expressed on cancer cells, playing a key role in cancer cell growth. Pre-clinical studies have demonstrated anti-cancer effects of furosemide, which was attributed to Na-K-2Cl-transporter

inhibition[207–209], however, no such effects were seen in clinical studies[210]. Although thiazides are not the preferred diuretic agents for decongestion purposes in HF, it should be noted that use of hydrochlorothiazide has been brought in association with increased risk of skin cancer[211], however, a recent meta-analysis has found no such associations[212]. In summary, the interaction between diuretics and malignancy remains inconclusive, especially in HF populations, and further investigations are required to validate the interaction between diuretics and cancer.

8 Future directions for decreasing cancer burden of heart failure

Overall, extensive pre-clinical evidence shows significant anti-cancer effects of all HF GDMT drug classes, nevertheless, no such anti-cancer effects of HF drugs could be confirmed in the clinical reality (*Figure 5.*) – a discrepancy that is not at all restricted to the field of cardio-oncology[213,214]. These findings emphasize the need to conduct pre-clinical studies of higher translational value, and more robust and reliable clinical studies of higher quality, in order to facilitate the formation of recommendations aiming to decrease cancer burden of HF patients (*Figure 6.*).

8.1 Considerations for future pre-clinical studies investigating the effect of HF drugs on cancer

Pre-clinical *in vivo* and *in vitro* studies complement each other, as *in vitro* studies might fail in taking into account the complexity of the systematic effects of a drug, while better exploring the direct effects on cancer.

Another limitation for translation stems from the lack of standardized practice for drug dosing and administration, as there is a high variety of doses of the same drug between cancer studies. Also, HF drug doses in cancer studies do not necessarily correspond to doses used in HF studies.

In addition, there is a difference in the interpretation of studies where (i) administration starts prior to tumour inoculation (i.e. tumour growth inhibition study), or where (ii) administration starts after an established tumour nodule has already formed (i.e. tumour growth delay study).

Another important aspect for increasing translational value could be the use of *in vivo* tumour-models where cardio-metabolic diseases are also induced to better mimic the frequent clinical situation of HF with comorbidities. Although pioneer *in vivo* studies assessing tumour growth in animals with prevalent HF induced by either myocardial infarction or transverse aortic constriction (TAC) have already been published, studies assessing the effect of HF medications either alone or combined in such settings should follow[215–218]. Of note, a TAC model, depending on the severity and length of constriction, could mimic cardiac diseases ranging from non-ischemic HF with reduced or preserved ejection fraction, to aortic stenosis[219], which mimic important sub-populations of HF patients.

Finally, to further enhance translational value, (i) differential effects of HF medications either combined or alone, (ii) different etiologies and stages of prevalent HF, (iii) different cancer types, (iv) effects of age, co-morbidities – e.g. hypertension, atrial fibrillation, obesity –, and co-medications that are present amongst the majority of HF patients, and (v) sex-based differences should be considered when planning future pre-clinical studies to this field.

8.2 Considerations for future clinical investigations on the effect of HF drugs on cancer

Several issues are intrinsic to the study of cardiovascular disease and cancer. First, a major obstacle in the synchronous study of cardiovascular disease and cancer is that, inevitably, successful treatment of the one condition will provide an opportunity for the other condition to progress and become a more important cause of death. For instance, a very powerful HF drug might reduce HF-related outcomes and cardiovascular death, e.g. an MRA. But at the same time, this will provide more opportunity for (latent) cancers to progress and become manifest. This *competing risk* by no means is synonymous to a pro-oncogenic effect of MRA. Vice versa, breast cancer survivors have after 10 years a larger cardiovascular risk than cancer risk[12]. Since these women have survived one potentially lethal condition, they have beaten the cancer risk (at least for some time), while their cardiovascular risk continues and likely has risen due to aggressive cancer treatments. This complex interplay complicates the simultaneous study of CV disease and cancer and is very difficult to adjust.

Second, observational studies are prone to biases, a problem that was touched upon by the meta-analysis of Weberpals and colleagues, where BB use significantly increased overall survival and cancer specific survival of cancer patients. However when observational studies prone to immortal time bias were excluded from the analysis, no significant effects were found for any investigated outcome[74].

Third, indication for the use of HF drugs was not always attributed to HF exclusively in current observational studies, but rather to hypertension (for ACEIs/ARBs) or diabetes (for SGLT2Is), causing confounding by indication. Therefore, to generate evidence whether and how HF treatment should be modified to improve (or at least not to worsen) cancer-related outcomes in cohorts of HF patients with prevalent cancer is of paramount importance.

Fourth, crucially, cancer outcomes generally are poorly adjudicated in most cardiovascular RCTs, which intrinsically flaws the outputs of any meta-analysis. Systematic assessment of new-onset

cancer risk in future HF RCTs is essential to collect valuable information with potential clinical implications, that may require longer follow-up after termination for cardiovascular end-points[220,221]. On the other hand, systematic assessment of cardiovascular outcomes in future cancer trials is equally important. For instance, the latest RCT with immune checkpoint inhibitors (ICI) did not systematically collect troponin values, while we know that ICI-mediated myocarditis is a potentially lethal side-effect of immunotherapy, that occurs in 2-5% of all patients[222].

In general, stratifying patients in clinical investigations based on (i) type and length of use of HF pharmacotherapy of different combinations, (ii) etiology and clinical stage of HF, (iii) cancer type, (iv) age, co-morbidities, and co-medications, is essential because individual patients with co-morbidities may require other types of drugs than HF medications, and importantly (v) based on sex, may more clearly show how HF medications affect cancer incidence, progression and outcomes, being of paramount importance for clinical decision-making. For instance, the differential sex-related effects of HF medications were addressed by Stolfo and colleagues who showed that female HF patients were more likely to receive BBs, diuretics, and digoxin. Of note, digoxin use was associated with an increased risk of death in females[223], but females were less likely to receive RAASIs compared to male HF patients[224].

Overall, definitive answers would be obtained from proof-of-concept phase II RCTs that directly assess the effects of HF drugs on cancer in HF patients, therefore, such investigations are eagerly waited to be conducted in the future. Of note, although direct effects of HF drugs on cancer, or the effects of successfully reversed HF on cancer may be hard to dissect in future studies, if the outcome is definitive, this question should be addressed by further mechanistic investigations (*Graphical abstract*).

Besides guideline-directed pharmacotherapies of HF, investigating other therapeutic options would also facilitate solving this issue. For instance, the interleukin-1beta inhibitor canakinumab has been shown to reduce HF-related hospitalization and mortality[225,226], and cumulative incidence of lung cancer in atherosclerotic patients[227], raising the question whether targeting inflammation, a shared pathomechanistic pathway of both HF and cancer, could mean a solution for decreasing cancer burden of HF patients.

In conclusion, translatability of pre-clinical studies, and reliability of clinical investigations should be improved to facilitate decision-making on whether and how HF treatment should be modified to decrease cancer incidence and improve cancer outcomes of HF patients.

9 Author Contributions

ZVV and PF conceived the review, and provided overall supervision and funding. NVS wrote the manuscript. ÁMP and NVS collected and analysed data regarding in vivo and in vitro studies. NVS collected and analysed data regarding clinical meta-analyses. NVS made the figures. All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data. All authors drafted or revised the manuscript critically for important intellectual content, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

10 Acknowledgments

Figures were in part created with *Biorender.com*.

References

1. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure: Developed by the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) With the Special Contributio. *Eur. Heart J.* **2021**, *42*, 3599–3726, doi:10.1093/eurheartj/ehab368.

2. Heidenreich, P.A.; Bozkurt, B.; Aguilar, D.; Allen, L.A.; Byun, J.J.; Colvin, M.M.; et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **2022**, *79*, e263–e421, doi:https://doi.org/10.1016/j.jacc.2021.12.012.

3. Lyon, A.R.; López-Fernández, T.; Couch, L.S.; Asteggiano, R.; Aznar, M.C.; Bergler-Klein, J.; et al. 2022 ESC Guidelines on Cardio-Oncology Developed in Collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the T. *Eur. Heart J.* **2022**, *43*, 4229–4361, doi:10.1093/eurheartj/ehac244.

4. James, S.L.; Abate, D.; Abate, K.H.; Abay, S.M.; Abbafati, C.; Abbasi, N.; et al. Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 354 Diseases and Injuries for 195 Countries and Territories, 1990–2017: A Systematic Analysis for the Global Burden of Disease Study 2017. *Lancet* **2018**, *392*, 1789–1858, doi:https://doi.org/10.1016/S0140-6736(18)32279-7.

5. Savarese, G.; Becher, P.M.; Lund, L.H.; Seferovic, P.; Rosano, G.M.C.; Coats, A.J.S. Global Burden of Heart Failure: A Comprehensive and Updated Review of Epidemiology. *Cardiovasc. Res.* **2022**, cvac013, doi:10.1093/cvr/cvac013.

6. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; et al. Global Cancer

Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA. Cancer J. Clin.* **2021**, *71*, 209–249, doi:10.3322/caac.21660.

7. Aboumsallem, J.P.; Moslehi, J.; de Boer, R.A. Reverse Cardio-Oncology: Cancer Development in Patients With Cardiovascular Disease. *J. Am. Heart Assoc.* **2020**, *9*, e013754, doi:10.1161/JAHA.119.013754.

8. de Boer, R.A.; Hulot, J.-S.; Tocchetti, C.G.; Aboumsallem, J.P.; Ameri, P.; Anker, S.D.; et al. Common Mechanistic Pathways in Cancer and Heart Failure. A Scientific Roadmap on Behalf of the Translational Research Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur. J. Heart Fail.* **2020**, *22*, 2272–2289, doi:https://doi.org/10.1002/ejhf.2029.

9. Bertero, E.; Canepa, M.; Maack, C.; Ameri, P. Linking Heart Failure to Cancer. *Circulation* **2018**, *138*, 735–742, doi:10.1161/CIRCULATIONAHA.118.033603.

10. Lau, E.S.; Paniagua, S.M.; Liu, E.; Jovani, M.; Li, S.X.; Takvorian, K.; et al. Cardiovascular Risk Factors Are Associated With Future Cancer. *JACC CardioOncology* **2021**, *3*, 48–58, doi:https://doi.org/10.1016/j.jaccao.2020.12.003.

11. Narayan, V.; Thompson, E.W.; Demissei, B.; Ho, J.E.; Januzzi, J.L.; Ky, B. Mechanistic Biomarkers Informative of Both Cancer and Cardiovascular Disease: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **2020**, *75*, 2726–2737, doi:https://doi.org/10.1016/j.jacc.2020.03.067.

12. Sturgeon, K.M.; Deng, L.; Bluethmann, S.M.; Zhou, S.; Trifiletti, D.M.; Jiang, C.; et al. A Population-Based Study of Cardiovascular Disease Mortality Risk in US Cancer Patients. *Eur. Heart J.* **2019**, *40*, 3889–3897, doi:10.1093/eurheartj/ehz766.

13. Zaorsky, N.G.; Churilla, T.M.; Egleston, B.L.; Fisher, S.G.; Ridge, J.A.; Horwitz, E.M.; et al. Causes of Death among Cancer Patients. *Ann. Oncol.* **2017**, *28*, 400–407, doi:https://doi.org/10.1093/annonc/mdw604.

14. Mehta, L.S.; Watson, K.E.; Barac, A.; Beckie, T.M.; Bittner, V.; Cruz-Flores, S.; et al. Cardiovascular Disease and Breast Cancer: Where These Entities Intersect: A Scientific Statement From the American Heart Association. *Circulation* **2018**, *137*, e30–e66, doi:10.1161/CIR.0000000000000556.

15. Zamorano, J.L.; Gottfridsson, C.; Asteggiano, R.; Atar, D.; Badimon, L.; Bax, J.J.; et al. The Cancer Patient and Cardiology. *Eur. J. Heart Fail.* **2020**, *22*, 2290–2309, doi:https://doi.org/10.1002/ejhf.1985.

16. Tocchetti, C.G.; Ameri, P.; de Boer, R.A.; D'Alessandra, Y.; Russo, M.; Sorriento, D.; et al. Cardiac Dysfunction in Cancer Patients: Beyond Direct Cardiomyocyte Damage of Anticancer Drugs: Novel Cardio-Oncology Insights from the Joint 2019 Meeting of the ESC Working Groups of Myocardial Function and Cellular Biology of the Heart. *Cardiovasc. Res.* **2020**, *116*, 1820–1834, doi:10.1093/cvr/cvaa222.

17. Efentakis, P.; Andreadou, I.; Iliodromitis, K.E.; Triposkiadis, F.; Ferdinandy, P.; Schulz, R.; et al. Myocardial Protection and Current Cancer Therapy: Two Opposite Targets with Inevitable Cost. *Int. J. Mol. Sci.* 2022, *23*.

18. Gergely, T.G.; Kucsera, D.; Tóth, V.E.; Kovács, T.; Sayour, N. V; Drobni, Z.D.; et al. Characterization of Immune Checkpoint Inhibitor-Induced Cardiotoxicity Reveals Interleukin-17A as a Driver of Cardiac Dysfunction after Anti-PD-1 Treatment. *Br. J. Pharmacol.* **2023**, *180*, 740–761, doi:https://doi.org/10.1111/bph.15984.

19. Banke, A.; Schou, M.; Videbæk, L.; Møller, J.E.; Torp-Pedersen, C.; Gustafsson, F.; et al. Incidence of Cancer in Patients with Chronic Heart Failure: A Long-Term Follow-up Study. *Eur. J. Heart Fail.* **2016**, *18*, 260–266, doi:https://doi.org/10.1002/ejhf.472.

20. Hasin, T.; Gerber, Y.; Weston, S.A.; Jiang, R.; Killian, J.M.; Manemann, S.M.; et al. Heart Failure After Myocardial Infarction Is Associated With Increased Risk of Cancer. *J. Am. Coll. Cardiol.* **2016**, *68*, 265–271, doi:https://doi.org/10.1016/j.jacc.2016.04.053.

21. Luca, B.N.M.; A., W.C.; Michael, S.; Mark, de B.; John, D.; Clive, W.; et al. Prevalence of Cardiovascular Disease in Patients With Potentially Curable Malignancies. *JACC CardioOncology* **2022**, *4*, 238–253, doi:10.1016/j.jaccao.2022.03.004.

22. Leedy, D.J.; Reding, K.W.; Vasbinder, A.L.; Anderson, G.L.; Barac, A.; Wactawski-Wende, J.; et al. The Association between Heart Failure and Incident Cancer in Women: An Analysis of the Women's Health Initiative. *Eur. J. Heart Fail.* **2021**, *23*, 1712–1721, doi:https://doi.org/10.1002/ejhf.2207.

23. Roderburg, C.; Loosen, S.H.; Jahn, J.K.; Gänsbacher, J.; Luedde, T.; Kostev, K.; et al. Heart Failure Is Associated with an Increased Incidence of Cancer Diagnoses. *ESC Hear. Fail.* **2021**, *8*, 3628–3633, doi:10.1002/ehf2.13421.

24. Edoardo, B.; Fabio, R.; Eliana, R.; Antonio, D.; Lucia, B.; Lidia, S.; et al. Cancer Incidence and Mortality According to Pre-Existing Heart Failure in a Community-Based Cohort. *JACC CardioOncology* **2022**, *4*, 98–109, doi:10.1016/j.jaccao.2021.11.007.

25. Camilli, M.; Chiabrando, J.G.; Lombardi, M.; Del Buono, M.G.; Montone, R.A.; Lombardo, A.; et al. Cancer Incidence and Mortality in Patients Diagnosed with Heart Failure: Results from an Updated Systematic Review and Meta-Analysis. *Cardio-Oncology* **2023**, *9*, 8, doi:10.1186/s40959-023-00158-1.

26. Selvaraj, S.; Bhatt, D.L.; Claggett, B.; Djoussé, L.; Shah, S.J.; Chen, J.; et al. Lack of Association Between Heart Failure and Incident Cancer. *J. Am. Coll. Cardiol.* **2018**, *71*, 1501–1510, doi:https://doi.org/10.1016/j.jacc.2018.01.069.

27. Schwartz, B.; Schou, M.; Gislason, G.H.; Køber, L.; Torp-Pedersen, C.; Andersson, C. Prevalence and Incidence of Various Cancer Subtypes in Patients with Heart Failure vs Matched Controls. *Int. J. Cardiol.* **2020**, *316*, 209–213, doi:10.1016/j.ijcard.2020.05.035.

28. Bruhn, J.; Malmborg, M.; Garred, C.H.; Ravn, P.; Zahir, D.; Andersson, C.; et al. Temporal Trends in the Incidence of Malignancy in Heart Failure: A Nationwide Danish Study. *Eur. Heart J.* **2023**, *44*, 1124–

1132, doi:10.1093/eurheartj/ehac797.

29. Ameri, P.; Bertero, E.; Meijers, W.C. Cancer Is a Comorbidity of Heart Failure. *Eur. Heart J.* **2023**, *44*, 1133–1135, doi:10.1093/eurheartj/ehac710.

30. Cole, S.W.; Sood, A.K. Molecular Pathways: Beta-Adrenergic Signaling in Cancer. *Clin. Cancer Res.* **2012**, *18*, 1201–1206, doi:10.1158/1078-0432.CCR-11-0641.

31. Sloan, E.K.; Priceman, S.J.; Cox, B.F.; Yu, S.; Pimentel, M.A.; Tangkanangnukul, V.; et al. The Sympathetic Nervous System Induces a Metastatic Switch in Primary Breast Cancer. *Cancer Res.* **2010**, *70*, 7042–7052, doi:10.1158/0008-5472.CAN-10-0522.

32. Zhou, C.; Chen, X.; Zeng, W.; Peng, C.; Huang, G.; Li, X.; et al. Propranolol Induced G0/G1/S Phase Arrest and Apoptosis in Melanoma Cells via AKT/MAPK Pathway. *Oncotarget* **2016**, *7*, 68314–68327, doi:10.18632/oncotarget.11599.

33. Partecke, L.I.; Speerforck, S.; Käding, A.; Seubert, F.; Kühn, S.; Lorenz, E.; et al. Chronic Stress Increases Experimental Pancreatic Cancer Growth, Reduces Survival and Can Be Antagonised by Beta-Adrenergic Receptor Blockade. *Pancreatology* **2016**, *16*, 423–433, doi:10.1016/j.pan.2016.03.005.

34. Wei, W.-J.; Shen, C.-T.; Song, H.-J.; Qiu, Z.-L.; Luo, Q.-Y. Propranolol Sensitizes Thyroid Cancer Cells to Cytotoxic Effect of Vemurafenib. *Oncol. Rep.* **2016**, *36*, 1576–1584, doi:10.3892/or.2016.4918.

35. Maccari, S.; Buoncervello, M.; Rampin, A.; Spada, M.; Macchia, D.; Giordani, L.; et al. Biphasic Effects of Propranolol on Tumour Growth in B16F10 Melanoma-Bearing Mice. *Br. J. Pharmacol.* **2017**, *174*, 139–149, doi:10.1111/bph.13662.

36. Wrobel, L.J.; Le Gal, F.A. Inhibition of Human Melanoma Growth by a Non-Cardioselective β-Blocker. *J. Invest. Dermatol.* **2015**, *135*, 525–531, doi:https://doi.org/10.1038/jid.2014.373.

37. Sorski, L.; Melamed, R.; Matzner, P.; Lavon, H.; Shaashua, L.; Rosenne, E.; et al. Reducing Liver

Metastases of Colon Cancer in the Context of Extensive and Minor Surgeries through β-Adrenoceptors Blockade and COX2 Inhibition. *Brain Behav. Immun.* **2016**, *58*, 91–98, doi:10.1016/j.bbi.2016.05.017.

38. Kuang, X.; Qi, M.; Peng, C.; Zhou, C.; Su, J.; Zeng, W.; et al. Propranolol Enhanced the Anti-Tumor Effect of Sunitinib by Inhibiting Proliferation and Inducing G0/G1/S Phase Arrest in Malignant Melanoma. *Oncotarget* **2018**, *9*, 802–811, doi:10.18632/oncotarget.22696.

39. Pasquier, E.; Street, J.; Pouchy, C.; Carre, M.; Gifford, A.J.; Murray, J.; et al. β-Blockers Increase Response to Chemotherapy via Direct Antitumour and Anti-Angiogenic Mechanisms in Neuroblastoma. *Br. J. Cancer* **2013**, *108*, 2485–2494, doi:10.1038/bjc.2013.205.

40. Palm, D.; Lang, K.; Niggemann, B.; Drell IV, T.L.; Masur, K.; Zaenker, K.S.; et al. The Norepinephrine-Driven Metastasis Development of PC-3 Human Prostate Cancer Cells in BALB/c Nude Mice Is Inhibited by β-Blockers. *Int. J. Cancer* **2006**, *118*, 2744–2749, doi:https://doi.org/10.1002/ijc.21723.

41. Kokolus, K.M.; Zhang, Y.; Sivik, J.M.; Schmeck, C.; Zhu, J.; Repasky, E.A.; et al. Beta Blocker Use Correlates with Better Overall Survival in Metastatic Melanoma Patients and Improves the Efficacy of Immunotherapies in Mice. *Oncoimmunology* **2018**, *7*, e1405205, doi:10.1080/2162402X.2017.1405205.

42. Fjæstad, K.Y.; Rømer, A.M.A.; Goitea, V.; Johansen, A.Z.; Thorseth, M.-L.; Carretta, M.; et al. Blockade of Beta-Adrenergic Receptors Reduces Cancer Growth and Enhances the Response to Anti-CTLA4 Therapy by Modulating the Tumor Microenvironment. *Oncogene* **2022**, *41*, 1364–1375, doi:10.1038/s41388-021-02170-0.

43. Moisan, F.; Oucherif, S.; Kaulanjan-Checkmodine, P.; Prey, S.; Rousseau, B.; Bonneu, M.; et al. Critical Role of Aquaporin-1 and Telocytes in Infantile Hemangioma Response to Propranolol Beta Blockade. *Proc. Natl. Acad. Sci. U. S. A.* **2021**, *118*, e2018690118, doi:10.1073/pnas.2018690118.

44. MacDonald, C.R.; Bucsek, M.J.; Qiao, G.; Chen, M.; Evans, L.; Greenberg, D.J.; et al. Adrenergic

Receptor Signaling Regulates the Response of Tumors to Ionizing Radiation. *Radiat. Res.* **2019**, *191*, 585–589, doi:10.1667/RR15193.1.

45. Acheampong, D.O.; Baffour, I.K.; Atsu Barku, V.Y.; Addo, J.K.; Essuman, M.A.; Boye, A. Zanthoxylum Zanthoxyloides Alkaloidal Extract Improves CCl4-Induced Hepatocellular Carcinoma-like Phenotypes in Rats. *Evid. Based. Complement. Altern. Med.* **2021**, *2021*, 3804379, doi:10.1155/2021/3804379.

46. Balaha, M.; Kandeel, S.; Barakat, W. Carvedilol Suppresses Circulating and Hepatic IL-6 Responsible for Hepatocarcinogenesis of Chronically Damaged Liver in Rats. *Toxicol. Appl. Pharmacol.* **2016**, *311*, 1–11, doi:10.1016/j.taap.2016.10.012.

47. Cleveland, K.H.; Yeung, S.; Huang, K.M.; Liang, S.; Andresen, B.T.; Huang, Y. Phosphoproteome Profiling Provides Insight into the Mechanism of Action for Carvedilol-Mediated Cancer Prevention. *Mol. Carcinog.* **2018**, *57*, 997–1007, doi:10.1002/mc.22820.

48. Gillis, R.D.; Botteri, E.; Chang, A.; Ziegler, A.I.; Chung, N.-C.; Pon, C.K.; et al. Carvedilol Blocks Neural Regulation of Breast Cancer Progression in Vivo and Is Associated with Reduced Breast Cancer Mortality in Patients. *Eur. J. Cancer* **2021**, *147*, 106–116, doi:10.1016/j.ejca.2021.01.029.

49. Abdullah Shamim, M.; Yeung, S.; Shahid, A.; Chen, M.; Wang, J.; Desai, P.; et al. Topical Carvedilol Delivery Prevents UV-Induced Skin Cancer with Negligible Systemic Absorption. *Int. J. Pharm.* **2022**, *611*, 121302, doi:10.1016/j.ijpharm.2021.121302.

50. Chang, A.; Yeung, S.; Thakkar, A.; Huang, K.M.; Liu, M.M.; Kanassatega, R.-S.; et al. Prevention of Skin Carcinogenesis by the β-Blocker Carvedilol. *Cancer Prev. Res.* **2015**, *8*, 27–36, doi:10.1158/1940-6207.CAPR-14-0193.

51. Hoare, J.I.; Osmani, B.; O'Sullivan, E.A.; Browne, A.; Campbell, N.; Metcalf, S.; et al. Carvedilol Targets β-Arrestins to Rewire Innate Immunity and Improve Oncolytic Adenoviral Therapy. *Commun. Biol.* **2022**, *5*, 106, doi:10.1038/s42003-022-03041-4.

52. Huang, K.M.; Liang, S.; Yeung, S.; Oiyemhonlan, E.; Cleveland, K.H.; Parsa, C.; et al. Topically Applied Carvedilol Attenuates Solar Ultraviolet Radiation Induced Skin Carcinogenesis. *Cancer Prev. Res.* **2017**, *10*, 598–606, doi:10.1158/1940-6207.capr-17-0132.

53. Chen, Q.; Jiang, H.; Wang, Z.; Cai, L.-Y.; Jiang, Y.-C.; Xie, L.; et al. Adrenergic Blockade by Nebivolol to Suppress Oral Squamous Cell Carcinoma Growth via Endoplasmic Reticulum Stress and Mitochondria Dysfunction. *Front. Pharmacol.* **2021**, *12*, 691998, doi:10.3389/fphar.2021.691998.

54. Niu, M.; Xu, J.; Liu, Y.; Li, Y.; He, T.; Ding, L.; et al. FBXL2 Counteracts Grp94 to Destabilize EGFR and Inhibit EGFR-Driven NSCLC Growth. *Nat. Commun.* **2021**, *12*, 5919, doi:10.1038/s41467-021-26222-x.

55. Zhang, D.; Yong Ma, Q.; Hu, H.-T.; Zhang, M. B2-Adrenergic Antagonists Suppress Pancreatic Cancer Cell Invasion by Inhibiting CREB, NF-KB and AP-1. *Cancer Biol. Ther.* **2010**, *10*, 19–29, doi:10.4161/cbt.10.1.11944.

56. Xie, W.; He, R.; Zhang, J.; He, Y.; Wan, Z.; Zhou, C.; et al. B‐blockers Inhibit the Viability of Breast Cancer Cells by Regulating the ERK/COX‐2 Signaling Pathway and the Drug Response Is Affected by ADRB2 Single‐nucleotide Polymorphisms. *Oncol Rep* **2019**, *41*, 341–350, doi:10.3892/or.2018.6830.

57. Szewczyk, M.; Richter, C.; Briese, V.; Richter, D.-U. A Retrospective in Vitro Study of the Impact of Anti-Diabetics and Cardioselective Pharmaceuticals on Breast Cancer. *Anticancer Res.* **2012**, *32*, 2133–2138.

58. Koh, M.; Takahashi, T.; Kurokawa, Y.; Kobayashi, T.; Saito, T.; Ishida, T.; et al. Propranolol Suppresses Gastric Cancer Cell Growth by Regulating Proliferation and Apoptosis. *Gastric cancer Off. J. Int. Gastric Cancer Assoc. Japanese Gastric Cancer Assoc.* **2021**, *24*, 1037–1049, doi:10.1007/s10120-021-01184-7.

59. Sidorova, M.; Petrikaitė, V. The Effect of Beta Adrenoreceptor Blockers on Viability and Cell Colony Formation of Non-Small Cell Lung Cancer Cell Lines A549 and H1299. *Molecules* 2022, *27*.

60. Farhoumand, L.S.; Fiorentzis, M.; Kraemer, M.M.; Sak, A.; Stuschke, M.; Rassaf, T.; et al. The Adrenergic Receptor Antagonist Carvedilol Elicits Anti-Tumor Responses in Uveal Melanoma 3D Tumor Spheroids and May Serve as Co-Adjuvant Therapy with Radiation. *Cancers (Basel).* 2022, *14*.

61. Duckett, M.M.; Phung, S.K.; Nguyen, L.; Khammanivong, A.; Dickerson, E.; Dusenbery, K.; et al. The Adrenergic Receptor Antagonists Propranolol and Carvedilol Decrease Bone Sarcoma Cell Viability and Sustained Carvedilol Reduces Clonogenic Survival and Increases Radiosensitivity in Canine Osteosarcoma Cells. *Vet. Comp. Oncol.* **2020**, *18*, 128–140, doi:https://doi.org/10.1111/vco.12560.

62. Zhang, D.; Ma, Q.; Shen, S.; Hu, H. Inhibition of Pancreatic Cancer Cell Proliferation by Propranolol Occurs through Apoptosis Induction: The Study of Beta-Adrenoceptor Antagonist's Anticancer Effect in Pancreatic Cancer Cell. *Pancreas* **2009**, *38*, 94–100, doi:10.1097/MPA.0b013e318184f50c.

63. Negro, A.; Brar, B.K.; Gu, Y.; Peterson, K.L.; Vale, W.; Lee, K.-F. ErbB2 Is Required for G Protein-Coupled Receptor Signaling in the Heart. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 15889–15893, doi:10.1073/pnas.0607499103.

64. Sysa-Shah, P.; Tocchetti, C.G.; Gupta, M.; Rainer, P.P.; Shen, X.; Kang, B.-H.; et al. Bidirectional Cross-Regulation between ErbB2 and β-Adrenergic Signalling Pathways. *Cardiovasc. Res.* **2016**, *109*, 358–373, doi:10.1093/cvr/cvv274.

65. Guglin, M.; Krischer, J.; Tamura, R.; Fink, A.; Bello-Matricaria, L.; McCaskill-Stevens, W.; et al. Randomized Trial of Lisinopril Versus Carvedilol to Prevent Trastuzumab Cardiotoxicity in Patients With Breast Cancer. *J. Am. Coll. Cardiol.* **2019**, *73*, 2859–2868, doi:10.1016/j.jacc.2019.03.495.

66. Monami, M.; Filippi, L.; Ungar, A.; Sgrilli, F.; Antenore, A.; Dicembrini, I.; et al. Further Data on Beta-Blockers and Cancer Risk: Observational Study and Meta-Analysis of Randomized Clinical Trials. *Curr. Med. Res. Opin.* **2013**, *29*, 369–378, doi:10.1185/03007995.2013.772505.

67. Bangalore, S.; Kumar, S.; Kjeldsen, S.E.; Makani, H.; Grossman, E.; Wetterslev, J.; et al. Antihypertensive Drugs and Risk of Cancer: Network Meta-Analyses and Trial Sequential Analyses of 324 168 Participants from Randomised Trials. *Lancet Oncol.* **2011**, *12*, 65–82, doi:https://doi.org/10.1016/S1470-2045(10)70260-6.

68. Copland, E.; Canoy, D.; Nazarzadeh, M.; Bidel, Z.; Ramakrishnan, R.; Woodward, M.; et al. Antihypertensive Treatment and Risk of Cancer: An Individual Participant Data Meta-Analysis. *Lancet Oncol.* **2021**, *22*, 558–570, doi:10.1016/S1470-2045(21)00033-4.

69. Qi, J.; An, R.; Bhatti, P.; Spinelli, J.J.; Murphy, R.A. Anti-Hypertensive Medications and Risk of Colorectal Cancer: A Systematic Review and Meta-Analysis. *Cancer causes & Control CCC* **2022**, *33*, 801–812, doi:10.1007/s10552-022-01570-1.

70. Gandini, S.; Palli, D.; Spadola, G.; Bendinelli, B.; Cocorocchio, E.; Stanganelli, I.; et al. Anti-Hypertensive Drugs and Skin Cancer Risk: A Review of the Literature and Meta-Analysis. *Crit. Rev. Oncol. Hematol.* **2018**, *122*, 1–9, doi:https://doi.org/10.1016/j.critrevonc.2017.12.003.

71. Tang, H.; Fu, S.; Zhai, S.; Song, Y.; Han, J. Use of Antihypertensive Drugs and Risk of Malignant Melanoma: A Meta-Analysis of Observational Studies. *Drug Saf.* **2018**, *41*, 161–169, doi:10.1007/s40264-017-0599-x.

72. Xie, Y.; Xu, P.; Wang, M.; Zheng, Y.; Tian, T.; Yang, S.; et al. Antihypertensive Medications Are Associated with the Risk of Kidney and Bladder Cancer: A Systematic Review and Meta-Analysis. *Aging (Albany. NY).* **2020**, *12*, 1545–1562, doi:10.18632/aging.102699.

73. Thiele, M.; Albillos, A.; Abazi, R.; Wiest, R.; Gluud, L.L.; Krag, A. Non-Selective Beta-Blockers May Reduce Risk of Hepatocellular Carcinoma: A Meta-Analysis of Randomized Trials. *Liver Int.* **2015**, *35*, 2009–2016, doi:https://doi.org/10.1111/liv.12782.

74. Weberpals, J.; Jansen, L.; Carr, P.R.; Hoffmeister, M.; Brenner, H. Beta Blockers and Cancer Prognosis –

The Role of Immortal Time Bias: A Systematic Review and Meta-Analysis. *Cancer Treat. Rev.* **2016**, *47*, 1–11, doi:https://doi.org/10.1016/j.ctrv.2016.04.004.

75. Na, Z.; Qiao, X.; Hao, X.; Fan, L.; Xiao, Y.; Shao, Y.; et al. The Effects of Beta-Blocker Use on Cancer Prognosis: A Meta-Analysis Based on 319,006 Patients. *Onco. Targets. Ther.* **2018**, *11*, 4913–4944, doi:10.2147/OTT.S167422.

76. Yap, A.; Lopez-Olivo, M.A.; Dubowitz, J.; Pratt, G.; Hiller, J.; Gottumukkala, V.; et al. Effect of Beta-Blockers on Cancer Recurrence and Survival: A Meta-Analysis of Epidemiological and Perioperative Studies. *Br. J. Anaesth.* **2018**, *121*, 45–57, doi:https://doi.org/10.1016/j.bja.2018.03.024.

77. Childers, W.K.; Hollenbeak, C.S.; Cheriyath, P. β-Blockers Reduce Breast Cancer Recurrence and Breast Cancer Death: A Meta-Analysis. *Clin. Breast Cancer* **2015**, *15*, 426–431, doi:10.1016/j.clbc.2015.07.001.

78. Raimondi, S.; Botteri, E.; Munzone, E.; Cipolla, C.; Rotmensz, N.; DeCensi, A.; et al. Use of Beta-Blockers, Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers and Breast Cancer Survival: Systematic Review and Meta-Analysis. *Int. J. Cancer* **2016**, *139*, 212–219, doi:https://doi.org/10.1002/ijc.30062.

79. Zhong, S.; Yu, D.; Zhang, X.; Chen, X.; Yang, S.; Tang, J.; et al. β-Blocker Use and Mortality in Cancer Patients: Systematic Review and Meta-Analysis of Observational Studies. *Eur. J. cancer Prev. Off. J. Eur. Cancer Prev. Organ.* **2016**, *25*, 440–448, doi:10.1097/CEJ.0000000000000192.

80. Lei, Z.; Yang, W.; Zuo, Y. Beta-Blocker and Survival in Patients with Lung Cancer: A Meta-Analysis. *PLoS One* **2021**, *16*, e0245773.

81. Vaduganathan, M.; Hirji, S.A.; Qamar, A.; Bajaj, N.; Gupta, A.; Zaha, V.G.; et al. Efficacy of Neurohormonal Therapies in Preventing Cardiotoxicity in Patients With Cancer Undergoing Chemotherapy. *JACC CardioOncology* **2019**, *1*, 54–65,

doi:https://doi.org/10.1016/j.jaccao.2019.08.006.

82. Cole, S.W.; Nagaraja, A.S.; Lutgendorf, S.K.; Green, P.A.; Sood, A.K. Sympathetic Nervous System Regulation of the Tumour Microenvironment. *Nat. Rev. Cancer* **2015**, *15*, 563–572, doi:10.1038/nrc3978.

83. George, A.J.; Thomas, W.G.; Hannan, R.D. The Renin–Angiotensin System and Cancer: Old Dog, New Tricks. *Nat. Rev. Cancer* **2010**, *10*, 745–759, doi:10.1038/nrc2945.

84. Lever, A.F.; Hole, D.J.; Gillis, C.R.; McCallum, I.R.; McInnes, G.T.; MacKinnon, P.L.; et al. Do Inhibitors of Angiotensin-I-Converting Enzyme Protect against Risk of Cancer? *Lancet* **1998**, *352*, 179–184, doi:https://doi.org/10.1016/S0140-6736(98)03228-0.

85. Ino, K.; Shibata, K.; Kajiyama, H.; Yamamoto, E.; Nagasaka, T.; Nawa, A.; et al. Angiotensin II Type 1 Receptor Expression in Ovarian Cancer and Its Correlation with Tumour Angiogenesis and Patient Survival. *Br. J. Cancer* **2006**, *94*, 552–560, doi:10.1038/sj.bjc.6602961.

86. Arrieta, O.; Villarreal-Garza, C.; Vizcaíno, G.; Pineda, B.; Hernández-Pedro, N.; Guevara-Salazar, P.; et al. Association between AT1 and AT2 Angiotensin II Receptor Expression with Cell Proliferation and Angiogenesis in Operable Breast Cancer. *Tumour Biol. J. Int. Soc. Oncodevelopmental Biol. Med.* **2015**, *36*, 5627–5634, doi:10.1007/s13277-015-3235-3.

87. Nakaya, K.; Otsuka, H.; Kondo, K.; Otani, T.; Nagata, M. Tumor Growth-Inhibitory Effect of an Angiotensin-Converting Enzyme Inhibitor (Captopril) in a Lung Cancer Xenograft Model Analyzed Using 18F-FDG-PET/CT. *Nucl. Med. Commun.* **2016**, *37*.

88. Fujita, M.; Hayashi, I.; Yamashina, S.; Fukamizu, A.; Itoman, M.; Majima, M. Angiotensin Type 1a Receptor Signaling-Dependent Induction of Vascular Endothelial Growth Factor in Stroma Is Relevant to Tumor-Associated Angiogenesis and Tumor Growth. *Carcinogenesis* **2005**, *26*, 271–279, doi:10.1093/carcin/bgh324.

89. Attoub, S.; Gaben, A.M.; Al-Salam, S.; Al Sultan, M.A.H.; John, A.; Nicholls, M.G.; et al. Captopril as a Potential Inhibitor of Lung Tumor Growth and Metastasis. *Ann. N. Y. Acad. Sci.* **2008**, *1138*, 65–72, doi:https://doi.org/10.1196/annals.1414.011.

90. Jordan, B.F.; Peeterbroeck, J.; Karroum, O.; Diepart, C.; Magat, J.; Grégoire, V.; et al. Captopril and S-Nitrosocaptopril as Potent Radiosensitizers: Comparative Study and Underlying Mechanisms. *Cancer Lett.* **2010**, *293*, 213–219, doi:https://doi.org/10.1016/j.canlet.2010.01.016.

91. Yang, Y.; Ma, L.; Xu, Y.; Liu, Y.; Li, W.; Cai, J.; et al. Enalapril Overcomes Chemoresistance and Potentiates Antitumor Efficacy of 5-FU in Colorectal Cancer by Suppressing Proliferation, Angiogenesis, and NF-KB/STAT3-Regulated Proteins. *Cell Death Dis.* **2020**, *11*, 477, doi:10.1038/s41419-020-2675-x.

92. Wysocki, P.J.; Kwiatkowska, E.P.; Kazimierczak, U.; Suchorska, W.; Kowalczyk, D.W.; Mackiewicz, A. Captopril, an Angiotensin-Converting Enzyme Inhibitor, Promotes Growth of Immunogenic Tumors in Mice. *Clin. Cancer Res.* **2006**, *12*, 4095–4102, doi:10.1158/1078-0432.CCR-05-2489.

93. Araújo, W.F.; Naves, M.A.; Ravanini, J.N.; Schor, N.; Teixeira, V.P.C. Renin-Angiotensin System (RAS) Blockade Attenuates Growth and Metastatic Potential of Renal Cell Carcinoma in Mice. *Urol. Oncol. Semin. Orig. Investig.* **2015**, *33*, 389.e1-389.e7, doi:https://doi.org/10.1016/j.urolonc.2014.11.022.

94. Brown, R.E.; Lun, M.; Prichard, J.W.; Blasick, T.M.; Zhang, P.L. Morphoproteomic and Pharmacoproteomic Correlates in Hormone-Receptor-Negative Breast Carcinoma Cell Lines. *Ann. Clin. Lab. Sci.* **2004**, *34*, 251–262.

95. Rooprai, H.K.; Kandanearatchi, A.; Maidment, S.L.; Christidou, M.; Trillo-Pazos, G.; Dexter, D.T.; et al. Evaluation of the Effects of Swainsonine, Captopril, Tangeretin and Nobiletin on the Biological Behaviour of Brain Tumour Cells in Vitro. *Neuropathol. Appl. Neurobiol.* **2001**, *27*, 29–39, doi:10.1046/j.0305-1846.2000.00298.x.

96. Williams, R.N.; Parsons, S.L.; Morris, T.M.; Rowlands, B.J.; Watson, S.A. Inhibition of Matrix Metalloproteinase Activity and Growth of Gastric Adenocarcinoma Cells by an Angiotensin Converting Enzyme Inhibitor in in Vitro and Murine Models. *Eur. J. Surg. Oncol.* **2005**, *31*, 1042–1050, doi:10.1016/j.ejso.2005.04.003.

97. De la Iglesia Iñigo, S.; López-Jorge, C.E.; Gómez-Casares, M.T.; Lemes Castellano, A.; Martín Cabrera, P.; López Brito, J.; et al. Induction of Apoptosis in Leukemic Cell Lines Treated with Captopril, Trandolapril and Losartan: A New Role in the Treatment of Leukaemia for These Agents. *Leuk. Res.* **2009**, *33*, 810–816, doi:10.1016/j.leukres.2008.09.029.

98. Fendrich, V.; Lopez, C.L.; Manoharan, J.; Maschuw, K.; Wichmann, S.; Baier, A.; et al. Enalapril and ASS Inhibit Tumor Growth in a Transgenic Mouse Model of Islet Cell Tumors. *Endocr. Relat. Cancer* **2014**, *21*, 813–824, doi:10.1530/ERC-14-0175.

99. Chen, Y.-H.; Huang, C.-H.; Lu, H.-I.; Chen, C.-H.; Huang, W.-T.; Hsieh, M.-J.; et al. Prognostic Impact of Renin-Angiotensin System Blockade in Esophageal Squamous Cell Carcinoma. *J. Renin Angiotensin Aldosterone Syst.* **2015**, *16*, 1185–1192, doi:10.1177/1470320314535275.

100. Rasha, F.; Ramalingam, L.; Menikdiwela, K.; Hernandez, A.; Moussa, H.; Gollahon, L.; et al. Renin Angiotensin System Inhibition Attenuates Adipocyte-Breast Cancer Cell Interactions. *Exp. Cell Res.* **2020**, *394*, 112114, doi:10.1016/j.yexcr.2020.112114.

101. Lu, Y.; Lian, S.; Ye, Y.; Yu, T.; Liang, H.; Cheng, Y.; et al. S-Nitrosocaptopril Prevents Cancer Metastasis in Vivo by Creating the Hostile Bloodstream Microenvironment against Circulating Tumor Cells. *Pharmacol. Res.* **2019**, *139*, 535–549, doi:10.1016/j.phrs.2018.10.020.

102. Carl-McGrath, S.; Ebert, M.P.A.; Lendeckel, U.; Röcken, C. Expression of the Local Angiotensin II System in Gastric Cancer May Facilitate Lymphatic Invasion and Nodal Spread. *Cancer Biol. Ther.* **2007**, *6*, 1218–1226, doi:10.4161/cbt.6.8.4412.

103. SMITH, T.I.M.A.D.; PHYU, S.U.M.; AKABUOGU, E.U. Effects of Administered Cardioprotective Drugs on Treatment Response of Breast Cancer Cells. *Anticancer Res.* **2016**, *36*, 87 LP – 93.

104. Okazaki, M.; Fushida, S.; Harada, S.; Tsukada, T.; Kinoshita, J.; Oyama, K.; et al. The Angiotensin II Type 1 Receptor Blocker Candesartan Suppresses Proliferation and Fibrosis in Gastric Cancer. *Cancer Lett.* **2014**, *355*, 46–53, doi:10.1016/j.canlet.2014.09.019.

105. Takagi, H.; Kaji, K.; Nishimura, N.; Ishida, K.; Ogawa, H.; Takaya, H.; et al. The Angiotensin II Receptor Blocker Losartan Sensitizes Human Liver Cancer Cells to Lenvatinib-Mediated Cytostatic and Angiostatic Effects. *Cells* **2021**, *10*, 575, doi:10.3390/cells10030575.

106. Mainetti, L.E.; Rico, M.J.; Kaufman, C.D.; Grillo, M.C.; Guercetti, J.; Baglioni, M.V.; et al. Losartan Improves the Therapeutic Effect of Metronomic Cyclophosphamide in Triple Negative Mammary Cancer Models. *Oncotarget* **2020**, *11*, 3048–3060, doi:10.18632/oncotarget.27694.

107. Li, W.; Li, S.; Chen, I.X.; Liu, Y.; Ramjiawan, R.R.; Leung, C.-H.; et al. Combining Losartan with Radiotherapy Increases Tumor Control and Inhibits Lung Metastases from a HER2/Neu-Positive Orthotopic Breast Cancer Model. *Radiat. Oncol.* **2021**, *16*, 48, doi:10.1186/s13014-021-01775-9.

108. Regan, D.P.; Coy, J.W.; Chahal, K.K.; Chow, L.; Kurihara, J.N.; Guth, A.M.; et al. The Angiotensin Receptor Blocker Losartan Suppresses Growth of Pulmonary Metastases via AT1R-Independent Inhibition of CCR2 Signaling and Monocyte Recruitment. *J. Immunol.* **2019**, *202*, 3087–3102, doi:10.4049/jimmunol.1800619.

109. Cai, X.-J.; Wang, Z.; Xu, Y.-Y.; Yang, G.-Y.; Zhang, R.-Y.; Wang, Y. Candesartan Treatment Enhances Liposome Penetration and Anti-Tumor Effect via Depletion of Tumor Stroma and Normalization of Tumor Vessel. *Drug Deliv. Transl. Res.* **2021**, *11*, 1186–1197, doi:10.1007/s13346-020-00842-0.

110. Ruderman, S.; Eshein, A.; Valuckaite, V.; Dougherty, U.; Almoghrabi, A.; Gomes, A.; et al. Early Increase in Blood Supply (EIBS) Is Associated with Tumor Risk in the Azoxymethane Model of Colon

Cancer. *BMC Cancer* **2018**, *18*, 814, doi:10.1186/s12885-018-4709-7.

111. Hashemzehi, M.; Rahmani, F.; Khoshakhlagh, M.; Avan, A.; Asgharzadeh, F.; Barneh, F.; et al. Angiotensin Receptor Blocker Losartan Inhibits Tumor Growth of Colorectal Cancer. *EXCLI J.* **2021**, *20*, 506–521, doi:10.17179/excli2020-3083.

112. Oh, E.; Kim, J.Y.; Cho, Y.; An, H.; Lee, N.; Jo, H.; et al. Overexpression of Angiotensin II Type 1 Receptor in Breast Cancer Cells Induces Epithelial-Mesenchymal Transition and Promotes Tumor Growth and Angiogenesis. *Biochim. Biophys. Acta* **2016**, *1863*, 1071–1081, doi:10.1016/j.bbamcr.2016.03.010.

113. Saber, S.; Mahmoud, A.A.A.; Goda, R.; Helal, N.S.; El-Ahwany, E.; Abdelghany, R.H. Perindopril, Fosinopril and Losartan Inhibited the Progression of Diethylnitrosamine-Induced Hepatocellular Carcinoma in Mice via the Inactivation of Nuclear Transcription Factor Kappa-B. *Toxicol. Lett.* **2018**, *295*, 32–40, doi:10.1016/j.toxlet.2018.05.036.

114. Rhodes, D.R.; Ateeq, B.; Cao, Q.; Tomlins, S.A.; Mehra, R.; Laxman, B.; et al. AGTR1 Overexpression Defines a Subset of Breast Cancer and Confers Sensitivity to Losartan, an AGTR1 Antagonist. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 10284–10289, doi:10.1073/pnas.0900351106.

115. Xia, T.; He, Q.; Shi, K.; Wang, Y.; Yu, Q.; Zhang, L.; et al. Losartan Loaded Liposomes Improve the Antitumor Efficacy of Liposomal Paclitaxel Modified with PH Sensitive Peptides by Inhibition of Collagen in Breast Cancer. *Pharm. Dev. Technol.* **2018**, *23*, 13–21, doi:10.1080/10837450.2016.1265553.

116. Hu, C.; Liu, X.; Ran, W.; Meng, J.; Zhai, Y.; Zhang, P.; et al. Regulating Cancer Associated Fibroblasts with Losartan-Loaded Injectable Peptide Hydrogel to Potentiate Chemotherapy in Inhibiting Growth and Lung Metastasis of Triple Negative Breast Cancer. *Biomaterials* **2017**, *144*, 60–72, doi:https://doi.org/10.1016/j.biomaterials.2017.08.009.

117. Chen, Y.-H.; Huang, C.-H.; Lu, H.-I.; Chen, C.-H.; Huang, W.-T.; Hsieh, M.-J.; et al. Prognostic Impact of

Renin-Angiotensin System Blockade in Esophageal Squamous Cell Carcinoma. *J. Renin-Angiotensin-Aldosterone Syst.* **2014**, *16*, 1185–1192, doi:10.1177/1470320314535275.

118. Oura, K.; Tadokoro, T.; Fujihara, S.; Morishita, A.; Chiyo, T.; Samukawa, E.; et al. Telmisartan Inhibits Hepatocellular Carcinoma Cell Proliferation in Vitro by Inducing Cell Cycle Arrest. *Oncol Rep* **2017**, *38*, 2825–2835, doi:10.3892/or.2017.5977.

119. Kobara, H.; Fujihara, S.; Iwama, H.; Matsui, T.; Fujimori, A.; Chiyo, T.; et al. Antihypertensive Drug Telmisartan Inhibits Cell Proliferation of Gastrointestinal Stromal Tumor Cells in Vitro. *Mol Med Rep* **2020**, *22*, 1063–1071, doi:10.3892/mmr.2020.11144.

120. Woo, Y.; Jung, Y. Angiotensin II Receptor Blockers Induce Autophagy in Prostate Cancer Cells. *Oncol Lett* **2017**, *13*, 3579–3585, doi:10.3892/ol.2017.5872.

121. Redondo-Müller, M.A.; Stevanovic-Walker, M.; Barker, S.; Puddefoot, J.R.; Vinson, G.P. Anti-Cancer Actions of a Recombinant Antibody (R6313/G2) against the Angiotensin II AT1 Receptor. *Endocr. Relat. Cancer* **2008**, *15*, 277–288, doi:10.1677/ERC-07-0068.

122. Kosugi, M.; Miyajima, A.; Kikuchi, E.; Horiguchi, Y.; Murai, M. Angiotensin II Type 1 Receptor Antagonist Candesartan as an Angiogenic Inhibitor in a Xenograft Model of Bladder Cancer. *Clin. Cancer Res.* **2006**, *12*, 2888–2893, doi:10.1158/1078-0432.CCR-05-2213.

123. Kosugi, M.; Miyajima, A.; Kikuchi, E.; Kosaka, T.; Horiguchi, Y.; Murai, M. Effect of Angiotensin II Type 1 Receptor Antagonist on Tumor Growth and Angiogenesis in a Xenograft Model of Human Bladder Cancer. *Hum. Cell* **2007**, *20*, 1–9, doi:10.1111/j.1749-0774.2007.00025.x.

124. Wilisch-Neumann, A.; Pachow, D.; Wallesch, M.; Petermann, A.; Böhmer, F.D.; Kirches, E.; et al. Re-Evaluation of Cytostatic Therapies for Meningiomas in Vitro. *J. Cancer Res. Clin. Oncol.* **2014**, *140*, 1343–1352, doi:10.1007/s00432-014-1683-6.

125. Funao, K.; Matsuyama, M.; Kawahito, Y.; Sano, H.; Chargui, J.; Touraine, J.-L.; et al. Telmisartan as a

Peroxisome Proliferator-Activated Receptor-γ Ligand Is a New Target in the Treatment of Human Renal Cell Carcinoma. *Mol. Med. Rep.* **2009**, *2*, 193–198, doi:10.3892/mmr_00000083.

126. Olschewski, D.N.; Hofschröer, V.; Nielsen, N.; Seidler, D.G.; Schwab, A.; Stock, C. The Angiotensin II Type 1 Receptor Antagonist Losartan Affects NHE1-Dependent Melanoma Cell Behavior. *Cell. Physiol. Biochem.* **2018**, *45*, 2560–2576, doi:10.1159/000488274.

127. Martínez, V.R.; Aguirre, M. V; Todaro, J.S.; Piro, O.E.; Echeverría, G.A.; Naso, L.G.; et al. Interaction of Zn with Losartan. Activation of Intrinsic Apoptotic Signaling Pathway in Lung Cancer Cells and Effects on Alkaline and Acid Phosphatases. *Biol. Trace Elem. Res.* **2018**, *186*, 413–429, doi:10.1007/s12011-018-1334-x.

128. Fujihara, S.; Morishita, A.; Ogawa, K.; Tadokoro, T.; Chiyo, T.; Kato, K.; et al. The Angiotensin II Type 1 Receptor Antagonist Telmisartan Inhibits Cell Proliferation and Tumor Growth of Esophageal Adenocarcinoma via the AMPKα/MTOR Pathway in Vitro and in Vivo. *Oncotarget* **2017**, *8*, 8536–8549, doi:10.18632/oncotarget.14345.

129. Leung, W.-H.; Vong, Q.P.; Lin, W.; Janke, L.; Chen, T.; Leung, W. Modulation of NKG2D Ligand Expression and Metastasis in Tumors by Spironolactone via RXRγ Activation. *J. Exp. Med.* **2013**, *210*, 2675–2692, doi:10.1084/jem.20122292.

130. Shahar, O.D.; Kalousi, A.; Eini, L.; Fisher, B.; Weiss, A.; Darr, J.; et al. A High-Throughput Chemical Screen with FDA Approved Drugs Reveals That the Antihypertensive Drug Spironolactone Impairs Cancer Cell Survival by Inhibiting Homology Directed Repair. *Nucleic Acids Res.* **2014**, *42*, 5689–5701, doi:10.1093/nar/gku217.

131. Gold, A.; Eini, L.; Nissim-Rafinia, M.; Viner, R.; Ezer, S.; Erez, K.; et al. Spironolactone Inhibits the Growth of Cancer Stem Cells by Impairing DNA Damage Response. *Oncogene* **2019**, *38*, 3103–3118, doi:10.1038/s41388-018-0654-9.

132. Kaji, K.; Yoshiji, H.; Kitade, M.; Ikenaka, Y.; Noguchi, R.; Shirai, Y.; et al. Selective Aldosterone Blocker, Eplerenone, Attenuates Hepatocellular Carcinoma Growth and Angiogenesis in Mice. *Hepatol. Res.* **2010**, *40*, 540–549, doi:10.1111/j.1872-034X.2010.00636.x.

133. Feldman, R.D.; Ding, Q.; Hussain, Y.; Limbird, L.E.; Pickering, J.G.; Gros, R. Aldosterone Mediates Metastatic Spread of Renal Cancer via the G Protein-Coupled Estrogen Receptor (GPER). *FASEB J.* **2016**, *30*, 2086–2096, doi:https://doi.org/10.1096/fj.15-275552.

134. Isobe, A.; Takeda, T.; Wakabayashi, A.; Tsuiji, K.; Li, B.; Sakata, M.; et al. Aldosterone Stimulates the Proliferation of Uterine Leiomyoma Cells. *Gynecol. Endocrinol.* **2010**, *26*, 372–377, doi:10.3109/09513590903511521.

135. Lee, H.J.; Rho, J.; Gui, S.R.; Kim, M.K.; Lee, Y.K.; Lee, Y.S.; et al. Effect of Aldosterone on the Amplification of Oncolytic Vaccinia Virus in Human Cancer Lines. *Korean J. Hepatol.* **2011**, *17*, 213–219, doi:10.3350/kjhep.2011.17.3.213.

136. King, S.; Bray, S.; Galbraith, S.; Christie, L.; Fleming, S. Evidence for Aldosterone-Dependent Growth of Renal Cell Carcinoma. *Int. J. Exp. Pathol.* **2014**, *95*, 244–250, doi:10.1111/iep.12074.

137. Fidrus, E.; Hegedűs, C.; Janka, E.A.; Paragh, G.; Emri, G.; Remenyik, É. Inhibitors of Nucleotide Excision Repair Decrease UVB-Induced Mutagenesis-an in Vitro Study. *Int. J. Mol. Sci.* **2021**, *22*, 1638, doi:10.3390/ijms22041638.

138. Sanomachi, T.; Suzuki, S.; Togashi, K.; Sugai, A.; Seino, S.; Okada, M.; et al. Spironolactone, a Classic Potassium-Sparing Diuretic, Reduces Survivin Expression and Chemosensitizes Cancer Cells to Non-DNA-Damaging Anticancer Drugs. *Cancers (Basel)* **2019**, *11*, 1550, doi:10.3390/cancers11101550.

139. Nogami, H.; Hiraoka, Y.; Aiso, S. Estradiol and Corticosterone Stimulate the Proliferation of a GH Cell Line, MtT/S: Proliferation of Growth Hormone Cells. *Growth Horm. IGF Res.* **2016**, *29*, 33–38, doi:https://doi.org/10.1016/j.ghir.2016.03.006.

140. Aldaz, P.; Fernández-Celis, A.; López-Andrés, N.; Arozarena, I. Novel Insights into the Role of the Mineralocorticoid Receptor in Human Glioblastoma. *Int. J. Mol. Sci.* 2021, *22*.

141. Sipahi, I.; Debanne, S.M.; Rowland, D.Y.; Simon, D.I.; Fang, J.C. Angiotensin-Receptor Blockade and Risk of Cancer: Meta-Analysis of Randomised Controlled Trials. *Lancet Oncol.* **2010**, *11*, 627–636, doi:https://doi.org/10.1016/S1470-2045(10)70106-6.

142. Pasternak, B.; Svanström, H.; Callréus, T.; Melbye, M.; Hviid, A. Use of Angiotensin Receptor Blockers and the Risk of Cancer. *Circulation* **2011**, *123*, 1729–1736, doi:10.1161/CIRCULATIONAHA.110.007336.

143. Datzmann, T.; Fuchs, S.; Andree, D.; Hohenstein, B.; Schmitt, J.; Schindler, C. Systematic Review and Meta-Analysis of Randomised Controlled Clinical Trial Evidence Refutes Relationship between Pharmacotherapy with Angiotensin-Receptor Blockers and an Increased Risk of Cancer. *Eur. J. Intern. Med.* **2019**, *64*, 1–9, doi:10.1016/j.ejim.2019.04.019.

144. Shen, J.; Huang, Y.-M.; Wang, M.; Hong, X.-Z.; Song, X.-N.; Zou, X.; et al. Renin-Angiotensin System Blockade for the Risk of Cancer and Death. *J. Renin. Angiotensin. Aldosterone. Syst.* **2016**, *17*, doi:10.1177/1470320316656679.

145. Sipahi, I.; Chou, J.; Mishra, P.; Debanne, S.M.; Simon, D.I.; Fang, J.C. Meta-Analysis of Randomized Controlled Trials on Effect of Angiotensin-Converting Enzyme Inhibitors on Cancer Risk. *Am. J. Cardiol.* **2011**, *108*, 294–301, doi:https://doi.org/10.1016/j.amjcard.2011.03.038.

146. Coleman, C.I.; Baker, W.L.; Kluger, J.; White, C.M. Antihypertensive Medication and Their Impact on Cancer Incidence: A Mixed Treatment Comparison Meta-Analysis of Randomized Controlled Trials. *J. Hypertens.* **2008**, *26*.

147. Cao, L.; Zhang, S.; Jia, C.-M.; He, W.; Wu, L.-T.; Li, Y.-Q.; et al. Antihypertensive Drugs Use and the Risk of Prostate Cancer: A Meta-Analysis of 21 Observational Studies. *BMC Urol.* **2018**, *18*, 17, doi:10.1186/s12894-018-0318-7.

148. Batais, M.; Almigbal, T.; Alotaibi, K.; Alodhayani, A.; Alkhushail, A.; Altheaby, A.; et al. Angiotensin Converting Enzyme Inhibitors and Risk of Lung Cancer: A Systematic Review and Meta-Analysis. *Medicine (Baltimore).* **2021**, *100*, e25714, doi:10.1097/MD.0000000000025714.

149. Yoon, C.; Yang, H.-S.; Jeon, I.; Chang, Y.; Park, S.M. Use of Angiotensin-Converting-Enzyme Inhibitors or Angiotensin-Receptor Blockers and Cancer Risk: A Meta-Analysis of Observational Studies. *CMAJ* **2011**, *183*, E1073-84, doi:10.1503/cmaj.101497.

150. Dai, Y.-N.; Wang, J.-H.; Zhu, J.-Z.; Lin, J.-Q.; Yu, C.-H.; Li, Y.-M. Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers Therapy and Colorectal Cancer: A Systematic Review and Meta-Analysis. *Cancer Causes Control* **2015**, *26*, 1245–1255, doi:10.1007/s10552-015-0617-1.

151. Mao, Y.; Xu, X.; Wang, X.; Zheng, X.; Xie, L. Is Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers Therapy Protective against Prostate Cancer? *Oncotarget* **2016**, *7*, 6765–6773, doi:10.18632/oncotarget.6837.

152. Bommareddy, K.; Hamade, H.; Lopez-Olivo, M.A.; Wehner, M.; Tosh, T.; Barbieri, J.S. Association of Spironolactone Use With Risk of Cancer: A Systematic Review and Meta-Analysis. *JAMA dermatology* **2022**, *158*, 275–282, doi:10.1001/jamadermatol.2021.5866.

153. Zhou, Q.; Chen, D.-S.; Xin, L.; Zhou, L.-Q.; Zhang, H.-T.; Liu, L.; et al. The Renin-Angiotensin System Blockers and Survival in Digestive System Malignancies: A Systematic Review and Meta-Analysis. *Medicine (Baltimore).* **2020**, *99*, e19075, doi:10.1097/MD.0000000000019075.

154. Sun, H.; Li, T.; Zhuang, R.; Cai, W.; Zheng, Y. Do Renin–Angiotensin System Inhibitors Influence the Recurrence, Metastasis, and Survival in Cancer Patients? *Med.* **2017**, *96*, e6394, doi:10.1097/md.0000000000006394.

155. Chen, X.; Yi, C.-H.; Ya, K.-G. Renin-Angiotensin System Inhibitor Use and Colorectal Cancer Risk and Mortality: A Dose-Response Meta Analysis. *J. Renin. Angiotensin. Aldosterone. Syst.* **2020**, *21*,

1470320319895646, doi:10.1177/1470320319895646.

156. Asgharzadeh, F.; Hashemzehi, M.; Moradi-Marjaneh, R.; Hassanian, S.M.; Ferns, G.A.; Khazaei, M.; et al. Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers as Therapeutic Options in the Treatment of Renal Cancer: A Meta-Analysis. *Life Sci.* **2020**, *242*, 117181, doi:10.1016/j.lfs.2019.117181.

157. Song, T.; Choi, C.H.; Kim, M.K.; Kim, M.-L.; Yun, B.S.; Seong, S.J. The Effect of Angiotensin System Inhibitors (Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers) on Cancer Recurrence and Survival: A Meta-Analysis. *Eur. J. cancer Prev. Off. J. Eur. Cancer Prev. Organ.* **2017**, *26*, 78–85, doi:10.1097/CEJ.0000000000000269.

158. Zhao, Y.-T.; Li, P.-Y.; Zhang, J.-Q.; Wang, L.; Yi, Z. Angiotensin II Receptor Blockers and Cancer Risk: A Meta-Analysis of Randomized Controlled Trials. *Medicine (Baltimore).* **2016**, *95*, e3600, doi:10.1097/MD.0000000000003600.

159. Myhre, P.L.; Vaduganathan, M.; Claggett, B.; Packer, M.; Desai, A.S.; Rouleau, J.L.; et al. B-Type Natriuretic Peptide During Treatment With Sacubitril/Valsartan: The PARADIGM-HF Trial. *J. Am. Coll. Cardiol.* **2019**, *73*, 1264–1272, doi:https://doi.org/10.1016/j.jacc.2019.01.018.

160. P., M.S.; F., P.M.; Alexander, C.; R., I.S.; S., M.A.; Michael, F.G.; et al. Atrial Natriuretic Peptide and Treatment With Sacubitril/Valsartan in Heart Failure With Reduced Ejection Fraction. *JACC Hear. Fail.* **2021**, *9*, 127–136, doi:10.1016/j.jchf.2020.09.013.

161. Desai, A.S.; McMurray, J.J. V; Packer, M.; Swedberg, K.; Rouleau, J.L.; Chen, F.; et al. Effect of the Angiotensin-Receptor-Neprilysin Inhibitor LCZ696 Compared with Enalapril on Mode of Death in Heart Failure Patients. *Eur. Heart J.* **2015**, *36*, 1990–1997, doi:10.1093/eurheartj/ehv186.

162. Stolfo, D.; Lund, L.H.; Sinagra, G.; Lindberg, F.; Dahlström, U.; Rosano, G.; et al. Heart Failure Pharmacological Treatments and Outcomes in Heart Failure with Mildly Reduced Ejection Fraction.

Eur. Hear. J. - Cardiovasc. Pharmacother. **2023**, pvad036, doi:10.1093/ehjcvp/pvad036.

163. Vesely, B.A.; McAfee, Q.; Gower Jr, W.R.; Vesely, D.L. Four Peptides Decrease the Number of Human Pancreatic Adenocarcinoma Cells. *Eur. J. Clin. Invest.* **2003**, *33*, 998–1005, doi:10.1046/j.1365-2362.2003.01262.x.

164. Vesely, B.A.; Fitz, S.R.; Gower Jr, W.R.; Vesely, D.L. Vessel Dilator: Most Potent of the Atrial Natriuretic Peptides in Decreasing the Number and DNA Synthesis of Human Squamous Lung Cancer Cells. *Cancer Lett.* **2006**, *233*, 226–231, doi:10.1016/j.canlet.2005.03.024.

165. Vesely, B.A.; Song, S.; Sanchez-Ramos, J.; Fitz, S.R.; Alli, A.A.; Solivan, S.M.; et al. Five Cardiac Hormones Decrease the Number of Human Small-Cell Lung Cancer Cells. *Eur. J. Clin. Invest.* **2005**, *35*, 388–398, doi:10.1111/j.1365-2362.2005.01501.x.

166. Vesely, D.L.; Clark, L.C.; Garces, A.H.; McAfee, Q.W.; Soto, J.; Gower Jr, W.R. Novel Therapeutic Approach for Cancer Using Four Cardiovascular Hormones. *Eur. J. Clin. Invest.* **2004**, *34*, 674–682, doi:https://doi.org/10.1111/j.1365-2362.2004.01402.x.

167. Ohsaki, Y.; Gross, A.J.; Le, P.T.; Oie, H.; Johnson, B.E. Human Small Cell Lung Cancer Cells Produce Brain Natriuretic Peptide. *Oncology* **1999**, *56*, 155–159, doi:10.1159/000011957.

168. Wigle, D.A.; Campling, B.G.; Sarda, I.R.; Shin, S.H.; Watson, J.D.; Frater, Y.; et al. ANP Secretion from Small Cell Lung Cancer Cell Lines: A Potential Model of ANP Release. *Am. J. Physiol. Circ. Physiol.* **1995**, *268*, H1869–H1874, doi:10.1152/ajpheart.1995.268.5.H1869.

169. Pavo, N.; Prausmüller, S.; Bartko, P.; Goliasch, G.; Hülsmann, M. Neprilysin as a Biomarker: Challenges and Opportunities. *Card. Fail. Rev.* **2020**, *6*, doi:10.15420/cfr.2019.21.

170. Scafoglio, C.; Hirayama, B.A.; Kepe, V.; Liu, J.; Ghezzi, C.; Satyamurthy, N.; et al. Functional Expression of Sodium-Glucose Transporters in Cancer. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, E4111-9, doi:10.1073/pnas.1511698112.

171. Dutka, M.; Bobiński, R.; Francuz, T.; Garczorz, W.; Zimmer, K.; Ilczak, T.; et al. SGLT-2 Inhibitors in Cancer Treatment—Mechanisms of Action and Emerging New Perspectives. *Cancers (Basel).* 2022, *14*.

172. Zhou, J.; Zhu, J.; Yu, S.-J.; Ma, H.-L.; Chen, J.; Ding, X.-F.; et al. Sodium-Glucose Co-Transporter-2 (SGLT-2) Inhibition Reduces Glucose Uptake to Induce Breast Cancer Cell Growth Arrest through AMPK/MTOR Pathway. *Biomed. Pharmacother.* **2020**, *132*, 110821, doi:https://doi.org/10.1016/j.biopha.2020.110821.

173. Nasiri, A.R.; Rodrigues, M.R.; Li, Z.; Leitner, B.P.; Perry, R.J. SGLT2 Inhibition Slows Tumor Growth in Mice by Reversing Hyperinsulinemia. *Cancer Metab.* **2019**, *7*, 10, doi:10.1186/s40170-019-0203-1.

174. Villani, L.A.; Smith, B.K.; Marcinko, K.; Ford, R.J.; Broadfield, L.A.; Green, A.E.; et al. The Diabetes Medication Canagliflozin Reduces Cancer Cell Proliferation by Inhibiting Mitochondrial Complex-I Supported Respiration. *Mol. Metab.* **2016**, *5*, 1048–1056, doi:https://doi.org/10.1016/j.molmet.2016.08.014.

175. Kaji, K.; Nishimura, N.; Seki, K.; Sato, S.; Saikawa, S.; Nakanishi, K.; et al. Sodium Glucose Cotransporter 2 Inhibitor Canagliflozin Attenuates Liver Cancer Cell Growth and Angiogenic Activity by Inhibiting Glucose Uptake. *Int. J. Cancer* **2018**, *142*, 1712–1722, doi:https://doi.org/10.1002/ijc.31193.

176. Kabel, A.M.; Arab, H.H.; Abd Elmaaboud, M.A. Effect of Dapagliflozin and/or L-Arginine on Solid Tumor Model in Mice: The Interaction between Nitric Oxide, Transforming Growth Factor-Beta 1, Autophagy, and Apoptosis. *Fundam. Clin. Pharmacol.* **2021**, *35*, 968–978, doi:https://doi.org/10.1111/fcp.12661.

177. Xie, Z.; Wang, F.; Lin, L.; Duan, S.; Liu, X.; Li, X.; et al. An SGLT2 Inhibitor Modulates SHH Expression by Activating AMPK to Inhibit the Migration and Induce the Apoptosis of Cervical Carcinoma Cells. *Cancer Lett.* **2020**, *495*, 200–210, doi:https://doi.org/10.1016/j.canlet.2020.09.005.

178. Ren, D.; Sun, Y.; Zhang, D.; Li, D.; Liu, Z.; Jin, X.; et al. SGLT2 Promotes Pancreatic Cancer Progression

by Activating the Hippo Signaling Pathway via the HnRNPK-YAP1 Axis. *Cancer Lett.* **2021**, *519*, 277–288, doi:https://doi.org/10.1016/j.canlet.2021.07.035.

179. Korfhage, J.; Skinner, M.E.; Basu, J.; Greenson, J.K.; Miller, R.A.; Lombard, D.B. Canagliflozin Increases Intestinal Adenoma Burden in Female ApcMin/+ Mice. *J. Gerontol. A. Biol. Sci. Med. Sci.* **2022**, *77*, 215–220, doi:10.1093/gerona/glab254.

180. Shoda, K.; Tsuji, S.; Nakamura, S.; Egashira, Y.; Enomoto, Y.; Nakayama, N.; et al. Canagliflozin Inhibits Glioblastoma Growth and Proliferation by Activating AMPK. *Cell. Mol. Neurobiol.* **2022**, doi:10.1007/s10571-022-01221-8.

181. Xu, D.; Zhou, Y.; Xie, X.; He, L.; Ding, J.; Pang, S.; et al. Inhibitory Effects of Canagliflozin on Pancreatic Cancer Are Mediated via the Downregulation of Glucose Transporter‐1 and Lactate Dehydrogenase A. *Int. J. Oncol.* **2020**, *57*, 1223–1233, doi:10.3892/ijo.2020.5120.

182. Nakano, D.; Kawaguchi, T.; Iwamoto, H.; Hayakawa, M.; Koga, H.; Torimura, T. Effects of Canagliflozin on Growth and Metabolic Reprograming in Hepatocellular Carcinoma Cells: Multi-Omics Analysis of Metabolomics and Absolute Quantification Proteomics (IMPAQT). *PLoS One* **2020**, *15*, e0232283, doi:10.1371/journal.pone.0232283.

183. Papadopoli, D.; Uchenunu, O.; Palia, R.; Chekkal, N.; Hulea, L.; Topisirovic, I.; et al. Perturbations of Cancer Cell Metabolism by the Antidiabetic Drug Canagliflozin. *Neoplasia* **2021**, *23*, 391–399, doi:10.1016/j.neo.2021.02.003.

184. Yamamoto, L.; Yamashita, S.; Nomiyama, T.; Kawanami, T.; Hamaguchi, Y.; Shigeoka, T.; et al. Sodium-Glucose Cotransporter 2 Inhibitor Canagliflozin Attenuates Lung Cancer Cell Proliferation in Vitro. *Diabetol. Int.* **2021**, *12*, 389–398, doi:10.1007/s13340-021-00494-6.

185. Wang, L.; Liu, M.; Yin, F.; Wang, Y.; Li, X.; Wu, Y.; et al. Trilobatin, a Novel SGLT1/2 Inhibitor, Selectively Induces the Proliferation of Human Hepatoblastoma Cells. *Molecules* **2019**, *24*,

doi:10.3390/molecules24183390.

186. Hung, M.-H.; Chen, Y.-L.; Chen, L.-J.; Chu, P.-Y.; Hsieh, F.-S.; Tsai, M.-H.; et al. Canagliflozin Inhibits Growth of Hepatocellular Carcinoma via Blocking Glucose-Influx-Induced β-Catenin Activation. *Cell Death Dis.* **2019**, *10*, 420, doi:10.1038/s41419-019-1646-6.

187. Madonna, R.; Barachini, S.; Moscato, S.; Ippolito, C.; Mattii, L.; Lenzi, C.; et al. Sodium-Glucose Cotransporter Type 2 Inhibitors Prevent Ponatinib-Induced Endothelial Senescence and Disfunction: A Potential Rescue Strategy. *Vascul. Pharmacol.* **2022**, *142*, 106949, doi:https://doi.org/10.1016/j.vph.2021.106949.

188. Lin, H.-W.; Tseng, C.-H. A Review on the Relationship between SGLT2 Inhibitors and Cancer. *Int. J. Endocrinol.* **2014**, *2014*, 719578, doi:10.1155/2014/719578.

189. Benedetti, R.; Benincasa, G.; Glass, K.; Chianese, U.; Vietri, M.T.; Congi, R.; et al. Effects of Novel SGLT2 Inhibitors on Cancer Incidence in Hyperglycemic Patients: A Meta-Analysis of Randomized Clinical Trials. *Pharmacol. Res.* **2022**, *175*, 106039, doi:10.1016/j.phrs.2021.106039.

190. Shi, N.; Shi, Y.; Xu, J.; Si, Y.; Yang, T.; Zhang, M.; et al. SGLT-2i and Risk of Malignancy in Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials . *Front. Public Heal.* 2021, *9*.

191. Tang, H.; Dai, Q.; Shi, W.; Zhai, S.; Song, Y.; Han, J. SGLT2 Inhibitors and Risk of Cancer in Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Diabetologia* **2017**, *60*, 1862–1872, doi:10.1007/s00125-017-4370-8.

192. Dicembrini, I.; Nreu, B.; Mannucci, E.; Monami, M. Sodium-Glucose Co-Transporter-2 (SGLT-2) Inhibitors and Cancer: A Meta-Analysis of Randomized Controlled Trials. *Diabetes. Obes. Metab.* **2019**, *21*, 1871–1877, doi:10.1111/dom.13745.

193. Cui, H.; Wang, Y.; Yang, S.; He, G.; Jiang, Z.; Gang, X.; et al. Antidiabetic Medications and the Risk of Prostate Cancer in Patients with Diabetes Mellitus: A Systematic Review and Meta-Analysis.

Pharmacol. Res. **2022**, *177*, 106094, doi:10.1016/j.phrs.2022.106094.

194. Tang, H.; Yang, K.; Song, Y.; Han, J. Meta-Analysis of the Association between Sodium-Glucose Co-Transporter-2 Inhibitors and Risk of Skin Cancer among Patients with Type 2 Diabetes. *Diabetes. Obes. Metab.* **2018**, *20*, 2919–2924, doi:10.1111/dom.13474.

195. Chou, J.-C.; Li, J.-H.; Chen, C.-C.; Chen, C.-W.; Lin, H.; Wang, P.S. Inhibitory Effects of Digoxin and Digitoxin on Cell Growth in Human Ovarian Cancer Cell Line SKOV-3. *Integr. Cancer Ther.* **2021**, *20*, 15347354211002662, doi:10.1177/15347354211002662.

196. Hou, Y.-Q.; Wang, Y.-Y.; Wang, X.-C.; Liu, Y.; Zhang, C.-Z.; Chen, Z.-S.; et al. Multifaceted Anti-Colorectal Tumor Effect of Digoxin on HCT8 and SW620 Cells in Vitro. *Gastroenterol. Rep.* **2020**, *8*, 465–475, doi:10.1093/gastro/goaa076.

197. Deng, K.; Shen, J.; Wang, W.; Li, M.; Li, H.; Chen, C.; et al. Sodium Chloride (NaCl) Potentiates Digoxin-Induced Anti-Tumor Activity in Small Cell Lung Cancer. *Cancer Biol. Ther.* **2019**, *20*, 52–64, doi:10.1080/15384047.2018.1504723.

198. Joseph, J. V; Conroy, S.; Pavlov, K.; Sontakke, P.; Tomar, T.; Eggens-Meijer, E.; et al. Hypoxia Enhances Migration and Invasion in Glioblastoma by Promoting a Mesenchymal Shift Mediated by the HIF1α-ZEB1 Axis. *Cancer Lett.* **2015**, *359*, 107–116, doi:10.1016/j.canlet.2015.01.010.

199. Zhang, X.-H.; Wang, X.-Y.; Zhou, Z.-W.; Bai, H.; Shi, L.; Yang, Y.-X.; et al. The Combination of Digoxin and GSK2606414 Exerts Synergistic Anticancer Activity against Leukemia in Vitro and in Vivo. *BioFactors* **2017**, *43*, 812–820, doi:https://doi.org/10.1002/biof.1380.

200. Wang, Z.; Zheng, M.; Li, Z.; Li, R.; Jia, L.; Xiong, X.; et al. Cardiac Glycosides Inhibit P53 Synthesis by a Mechanism Relieved by Src or MAPK Inhibition. *Cancer Res.* **2009**, *69*, 6556–6564, doi:10.1158/0008-5472.CAN-09-0891.

201. Wang, Y.; Ma, Q.; Zhang, S.; Liu, H.; Zhao, B.; Du, B.; et al. Digoxin Enhances the Anticancer Effect on

Non-Small Cell Lung Cancer While Reducing the Cardiotoxicity of Adriamycin. *Front. Pharmacol.* **2020**, *11*, 186, doi:10.3389/fphar.2020.00186.

202. Glass, O.K.; Bowie, M.; Fuller, J.; Darr, D.; Usary, J.; Boss, K.; et al. Differential Response to Exercise in Claudin-Low Breast Cancer. *Oncotarget* **2017**, *8*, 100989–101004, doi:10.18632/oncotarget.21054.

203. Crezee, T.; Tesselaar, M.H.; Nagarajah, J.; Corver, W.E.; Morreau, J.; Pritchard, C.; et al. Digoxin Treatment Reactivates in Vivo Radioactive Iodide Uptake and Correlates with Favorable Clinical Outcome in Non-Medullary Thyroid Cancer. *Cell. Oncol.* **2021**, *44*, 611–625, doi:10.1007/s13402-021-00588-y.

204. Beheshti Zavareh, R.; Lau, K.S.; Hurren, R.; Datti, A.; Ashline, D.J.; Gronda, M.; et al. Inhibition of the Sodium/Potassium ATPase Impairs N-Glycan Expression and Function. *Cancer Res.* **2008**, *68*, 6688–6697, doi:10.1158/0008-5472.CAN-07-6833.

205. Ahern, T.P.; Tamimi, R.M.; Rosner, B.A.; Hankinson, S.E. Digoxin Use and Risk of Invasive Breast Cancer: Evidence from the Nurses' Health Study and Meta-Analysis. *Breast Cancer Res. Treat.* **2014**, *144*, 427–435, doi:10.1007/s10549-014-2886-x.

206. Osman, M.H.; Farrag, E.; Selim, M.; Osman, M.S.; Hasanine, A.; Selim, A. Cardiac Glycosides Use and the Risk and Mortality of Cancer; Systematic Review and Meta-Analysis of Observational Studies. *PLoS One* **2017**, *12*, e0178611.

207. Panet, R.; Marcus, M.; Atlan, H. Overexpression of the Na+/K+/Cl− Cotransporter Gene Induces Cell Proliferation and Phenotypic Transformation in Mouse Fibroblasts. *J. Cell. Physiol.* **2000**, *182*, 109–118, doi:https://doi.org/10.1002/(SICI)1097-4652(200001)182:1<109::AID-JCP12>3.0.CO;2-A.

208. Iwamoto, L.M.; Fujiwara, N.; Nakamura, K.T.; Wada, R.K. Na-K-2Cl Cotransporter Inhibition Impairs Human Lung Cellular Proliferation. *Am. J. Physiol. Cell. Mol. Physiol.* **2004**, *287*, L510–L514, doi:10.1152/ajplung.00021.2004.

209. Shiozaki, A.; Nako, Y.; Ichikawa, D.; Konishi, H.; Komatsu, S.; Kubota, T.; et al. Role of the $Na^+/K^+/2Cl^-$ Cotransporter NKCC1 in Cell Cycle Progression in Human Esophageal Squamous Cell Carcinoma. *World J. Gastroenterol.* **2014**, *20*, 6844–6859, doi:10.3748/wjg.v20.i22.6844.

210. Liu, P.; McMenamin, Ú.C.; Spence, A.D.; Johnston, B.T.; Coleman, H.G.; Cardwell, C.R. Furosemide Use and Survival in Patients with Esophageal or Gastric Cancer: A Population-Based Cohort Study. *BMC Cancer* **2019**, *19*, 1017, doi:10.1186/s12885-019-6242-8.

211. Shin, D.; Lee, E.S.; Kim, J.; Guerra, L.; Naik, D.; Prida, X. Association Between the Use of Thiazide Diuretics and the Risk of Skin Cancers: A Meta-Analysis of Observational Studies. *J. Clin. Med. Res.* **2019**, *11*, 247–255, doi:10.14740/jocmr3744.

212. Heisel, A.G.U.; Vuurboom, M.D.; Daams, J.G.; de Rie, M.A.; Vogt, L.; van den Born, B.-J.H.; et al. The Use of Specific Antihypertensive Medication and Skin Cancer Risk: A Systematic Review of the Literature and Meta-Analysis. *Vascul. Pharmacol.* **2023**, *150*, 107173, doi:https://doi.org/10.1016/j.vph.2023.107173.

213. Sayour, N. V; Brenner, G.B.; Makkos, A.; Kiss, B.; Kovácsházi, C.; Gergely, T.G.; et al. Cardioprotective Efficacy of Limb Remote Ischaemic Preconditioning in Rats: Discrepancy between a Meta-Analysis and a Three-Centre in Vivo Study. *Cardiovasc. Res.* **2023**, *119*, 1336–1351, doi:10.1093/cvr/cvad024.

214. Begley, C.G.; Ioannidis, J.P.A. Reproducibility in Science. *Circ. Res.* **2015**, *116*, 116–126, doi:10.1161/CIRCRESAHA.114.303819.

215. Avraham, S.; Abu-Sharki, S.; Shofti, R.; Haas, T.; Korin, B.; Kalfon, R.; et al. Early Cardiac Remodeling Promotes Tumor Growth and Metastasis. *Circulation* **2020**, *142*, 670–683, doi:10.1161/CIRCULATIONAHA.120.046471.

216. Meijers, W.C.; Maglione, M.; Bakker, S.J.L.; Oberhuber, R.; Kieneker, L.M.; de Jong, S.; et al. Heart Failure Stimulates Tumor Growth by Circulating Factors. *Circulation* **2018**, *138*, 678–691,

doi:10.1161/CIRCULATIONAHA.117.030816.

217. Koelwyn, G.J.; Newman, A.A.C.; Afonso, M.S.; van Solingen, C.; Corr, E.M.; Brown, E.J.; et al. Myocardial Infarction Accelerates Breast Cancer via Innate Immune Reprogramming. *Nat. Med.* **2020**, *26*, 1452–1458, doi:10.1038/s41591-020-0964-7.

218. de Wit, S.; Aboumsallem, J.P.; Shi, C.; Schouten, E.M.; Bracun, V.; Meijers, W.C.; et al. Pressure Overload–Induced Cardiac Hypertrophy Stimulates Tumor Growth in Tumor-Prone ApcMin Mice. *Circ. Hear. Fail.* **2023**, *0*, e010740, doi:10.1161/CIRCHEARTFAILURE.123.010740.

219. Sayour, N. V; Tóth, V.É.; Nagy, R.N.; Vörös, I.; Gergely, T.G.; Onódi, Z.; et al. Droplet Digital PCR Is a Novel Screening Method Identifying Potential Cardiac G-Protein-Coupled Receptors as Candidate Pharmacological Targets in a Rat Model of Pressure-Overload-Induced Cardiac Dysfunction. *Int. J. Mol. Sci.* 2023, *24*.

220. Dobbin, S.J.H.; Shen, L.; Petrie, M.C.; Packer, M.; Solomon, S.D.; McMurray, J.J. V; et al. Characteristics and Outcomes of Patients with a History of Cancer Recruited to Heart Failure Trials. *Eur. J. Heart Fail.* **2023**, *25*, 488–496, doi:https://doi.org/10.1002/ejhf.2818.

221. Tini, G.; Bertero, E.; Signori, A.; Sormani, M.P.; Maack, C.; De Boer, R.A.; et al. Cancer Mortality in Trials of Heart Failure With Reduced Ejection Fraction: A Systematic Review and Meta-Analysis. *J. Am. Heart Assoc.* **2020**, *9*, e016309, doi:10.1161/JAHA.119.016309.

222. Lehmann, L.H.; Heckmann, M.B.; Bailly, G.; Finke, D.; Procureur, A.; Power, J.R.; et al. Cardiomuscular Biomarkers in the Diagnosis and Prognostication of Immune Checkpoint Inhibitor Myocarditis. *Circulation* **2023**, *0*, doi:10.1161/CIRCULATIONAHA.123.062405.

223. Rathore, S.S.; Wang, Y.; Krumholz, H.M. Sex-Based Differences in the Effect of Digoxin for the Treatment of Heart Failure. *N. Engl. J. Med.* **2002**, *347*, 1403–1411, doi:10.1056/NEJMoa021266.

224. Davide, S.; Alicia, U.; Ola, V.; Anna, S.; Ljung, F.U.; M.C., R.G.; et al. Sex-Based Differences in

Heart Failure Across the Ejection Fraction Spectrum. *JACC Hear. Fail.* **2019**, *7*, 505–515, doi:10.1016/j.jchf.2019.03.011.

225. Ridker, P.M.; Everett, B.M.; Thuren, T.; MacFadyen, J.G.; Chang, W.H.; Ballantyne, C.; et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N. Engl. J. Med.* **2017**, *377*, 1119–1131, doi:10.1056/NEJMoa1707914.

226. Everett, B.M.; Cornel, J.H.; Lainscak, M.; Anker, S.D.; Abbate, A.; Thuren, T.; et al. Anti-Inflammatory Therapy With Canakinumab for the Prevention of Hospitalization for Heart Failure. *Circulation* **2019**, *139*, 1289–1299, doi:10.1161/CIRCULATIONAHA.118.038010.

227. Ridker, P.M.; MacFadyen, J.G.; Thuren, T.; Everett, B.M.; Libby, P.; Glynn, R.J.; et al. Effect of Interleukin-1β Inhibition with Canakinumab on Incident Lung Cancer in Patients with Atherosclerosis: Exploratory Results from a Randomised, Double-Blind, Placebo-Controlled Trial. *Lancet* **2017**, *390*, 1833–1842, doi:10.1016/S0140-6736(17)32247-X.

.

11 Figure & Table legends

Graphical abstract: The risk factors and pathophysiological pathways of both heart failure and cancer are common. The discipline of cardio-oncology investigates how heart failure and cancer progression are connected: on one hand, the cardiac effects of anti-cancer medications or cancer-derived metabolic byproducts are investigated, whereas on the other hand, the possible effects of heart failure on cancer progression are examined, such as those mediated by maladaptive neuroendocrine activation and factors secreted from the failing heart. Nevertheless, there is a lack of systematic knowledge on how HF pharmacotherapies affect new-onset cancer incidence or prevalent cancer outcomes, and whether these effects are mediated through the improvement in cardiac functions.

Figure 1.: Suggested mechanism of action of the different HF pharmacotherapies on cancer cells. **A:** adrenaline, **NA:** noradrenaline, **Ang:** angiotensinogen, **Ang1:** angiotensin-I, **Ang2:** angiotensin-II, **ACE:** angiotensin-converting enzyme, **Aldo:** aldosterone, **ARB:** angiotensin receptor blocker, **ACEI:** angiotensin-converting enzyme inhibitor, **BB:** β-blocker, **SGLT2I:** sodium-glucose-cotransporter-2 inhibitor, **ß-AR:** ß-adrenergic receptor, **AT_1-R:** angiotensin-II-receptor type 1, **SGLT2:** sodium-glucose-cotransporter-2, **MC-R:** mineralocorticoid receptor, **MRA:** mineralocorticoid receptor antagonist, **cAMP:** cyclic adenosine-monophosphate, **EPAC:** exchange protein directly activated by cAMP, **PKA:** protein-kinase A, **IP_3:** inositol-triphosphate, **Akt:** protein-kinase B, **mTOR:** mammalian target of rapamycin, **Gluc:** glucose, **AMPK:** adenosine monophosphate-activated protein kinase, **TF:** transcription factors.

Figure 2.: Meta-analyses of clinical studies on the effect of BBs on cancer incidence or outcomes. Black letters: neutral or no effect on cancer incidence or outcomes; green letters: improvement of cancer incidence or outcomes; red letters: worsening of cancer incidence or outcomes. The number

of studies used for overall effect size estimation are marked (*n*). **OS:** overall survival, **CSS:** cancer specific survival, **CR:** cancer recurrence, **DFS:** disease-free survival, **Obs:** observational studies, **RCTs:** randomized controlled trials. The meta-analyses are referenced in the text.

Figure 3.: Meta-analyses of clinical studies on the effect of RAAS-inhibitors (ARBs, ACEIs or MRAs) on cancer incidence or outcomes. Black letters: neutral or no effect on cancer incidence or outcomes; green letters: improvement of cancer incidence or outcomes; red letters: worsening of cancer incidence or outcomes. The number of studies used for overall effect size estimation are marked (*n*). **OS:** overall survival, **CSS:** cancer specific survival, **CR:** cancer recurrence, **DFS:** disease-free survival, **Obs:** observational studies, **RCTs:** randomized controlled trials. The meta-analyses are referenced in the text.

Figure 4.: Meta-analyses of clinical studies on the effect of SGLT2Is on cancer incidence or outcomes. Black letters: neutral or no effect on cancer incidence or outcomes; green letters: improvement of cancer incidence or outcomes; red letters: worsening of cancer incidence or outcomes. The number of studies used for overall effect size estimation are marked (*n*). **OS:** overall survival, **CSS:** cancer specific survival, **CR:** cancer recurrence, **DFS:** disease-free survival, **Obs:** observational studies, **RCTs:** randomized controlled trials. The meta-analyses are referenced in the text.

Figure 5.: A graphical summary for both the pre-clinical and the clinical evidence on the effect of different HF pharmacotherapies on cancer. The terms were defined as follows: *beneficial:* decreases cancer incidence, or improves any patient outcome; *neutral:* no effect on cancer incidence, or no effect on any patient outcome; *harmful:* increased incidence or worsening of any patient outcome; *conflicting:* there are studies showing either benefit or harm on cancer incidence or outcomes.

Figure 6.: A graphical summary of future directions for decreasing cancer burden of heart failure from pre-clinical studies to clinical investigations and their meta-analyses. HF: heart failure; RCT: randomized controlled trial.

Graphical abstract

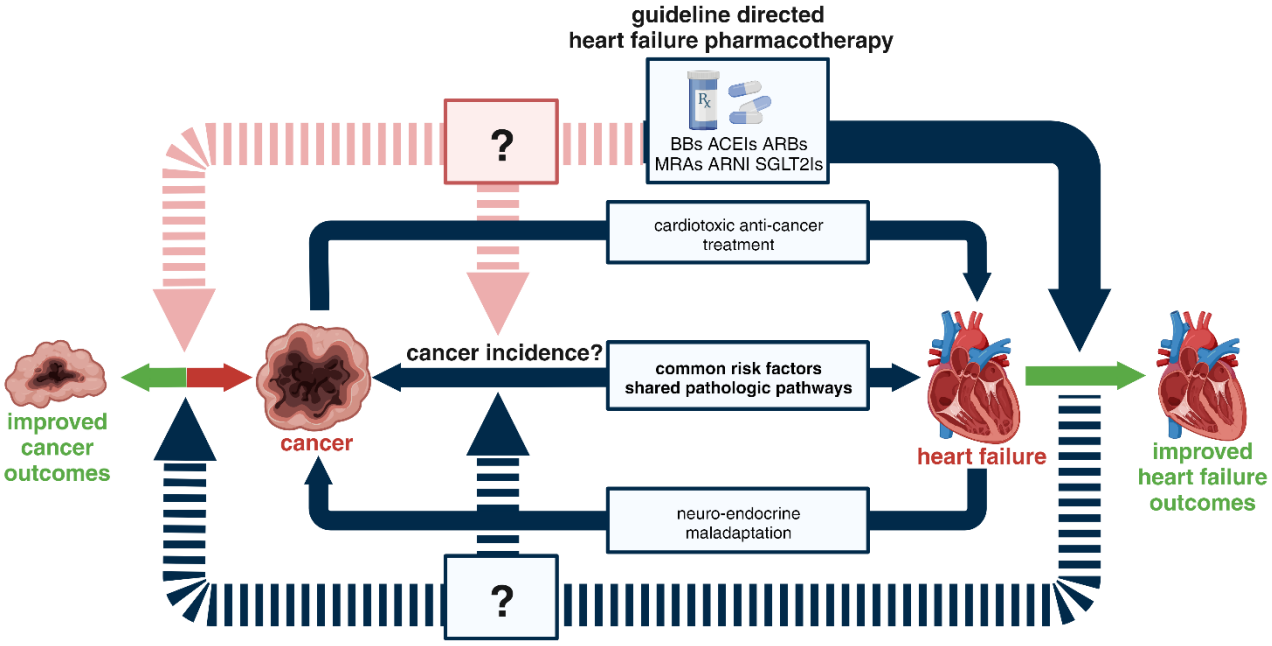


Figure 1:

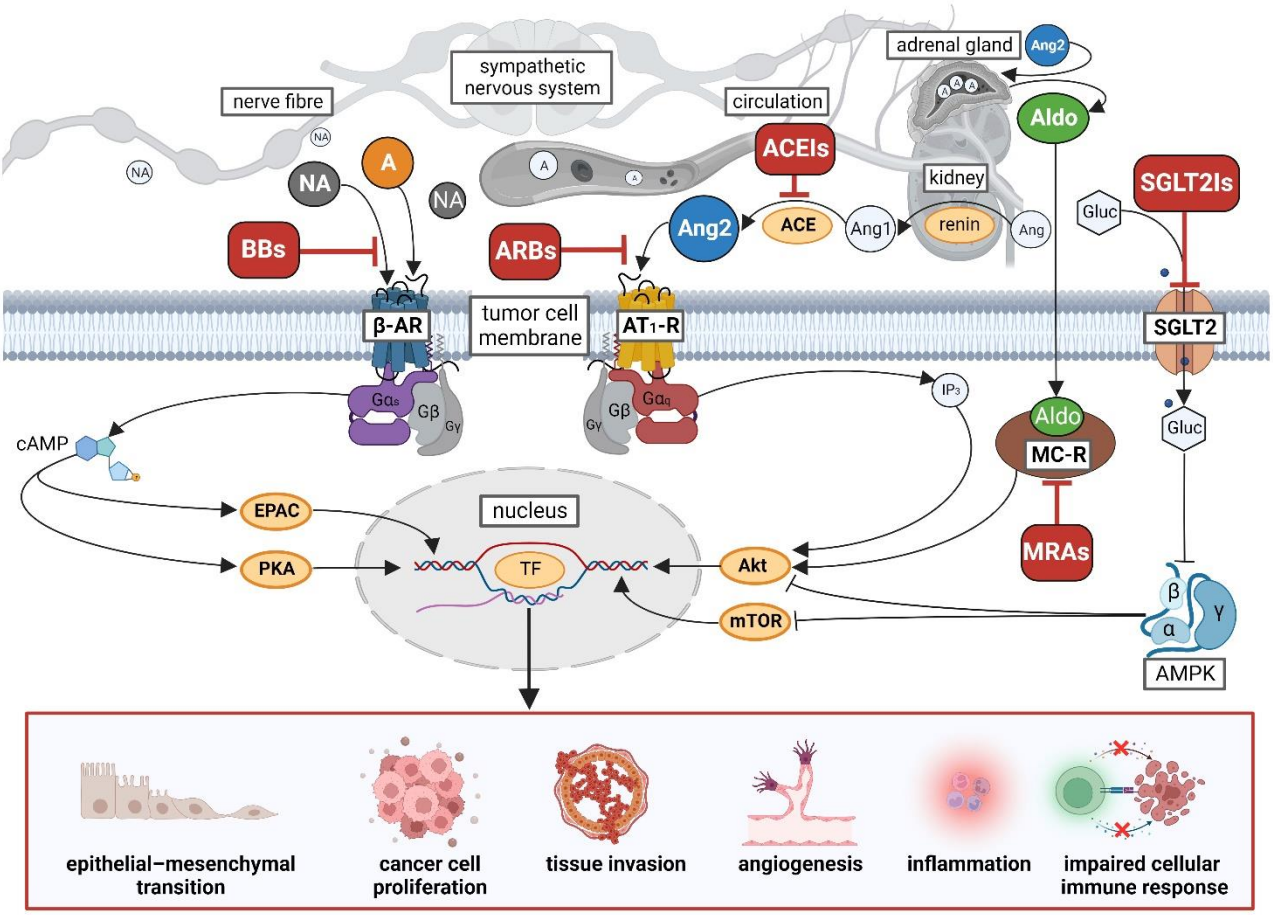

sympathetic nervous system
nerve fibre
circulation
adrenal gland
Ang2
Aldo
ACEIs
kidney
SGLT2Is
NA
A
BBs
ARBs
Ang2
ACE
Ang1
renin
Ang
Gluc
β-AR
tumor cell membrane
AT1-R
SGLT2
Gαs
Gβ
Gγ
Gαq
IP3
cAMP
Aldo
MC-R
Gluc
EPAC
nucleus
PKA
TF
Akt
MRAs
mTOR
β
γ
α
AMPK
epithelial–mesenchymal transition
cancer cell proliferation
tissue invasion
angiogenesis
inflammation
impaired cellular immune response

Figure 2:

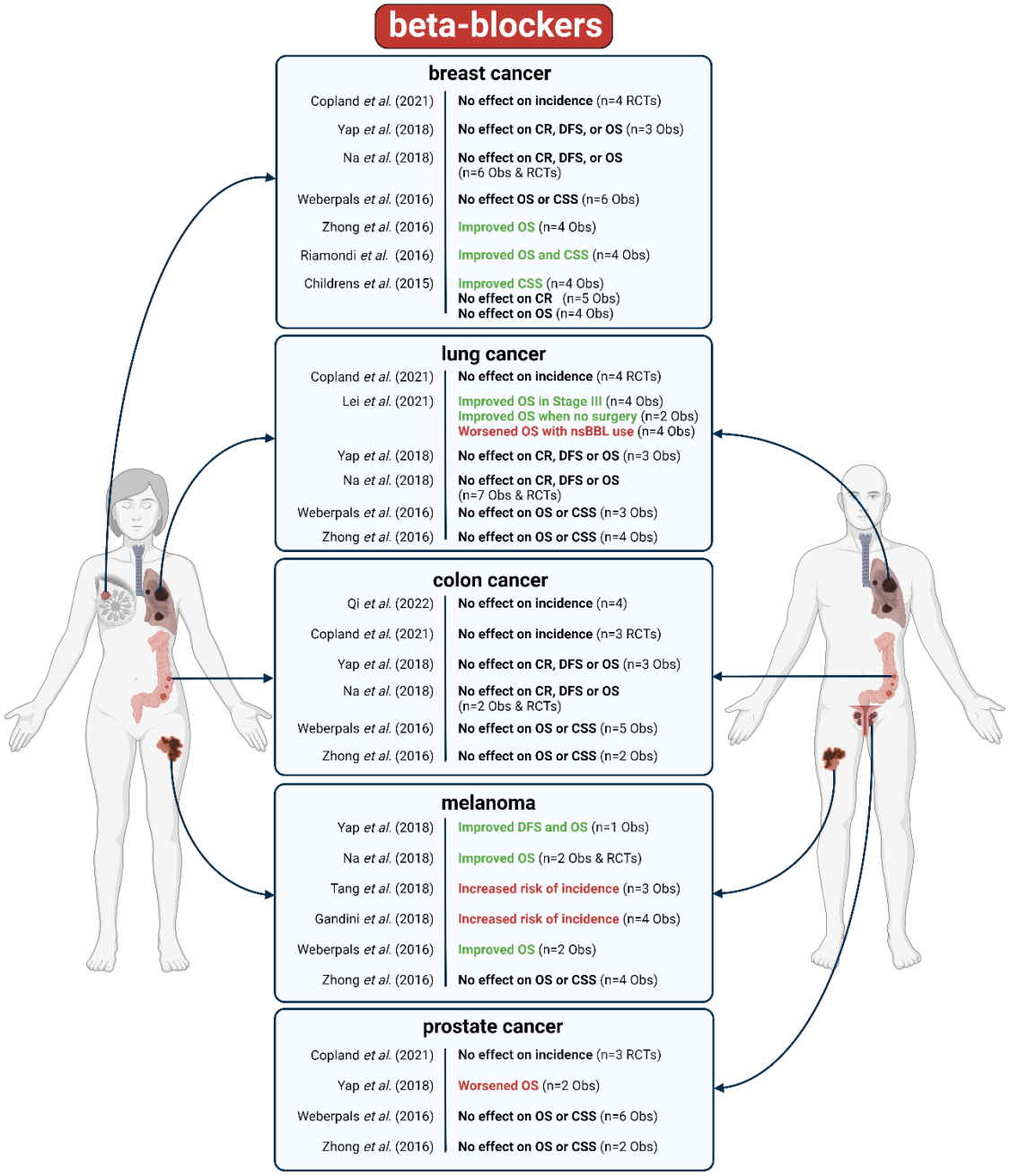

beta-blockers
breast cancer
Copland et al. (2021) No effect on incidence (n=4 RCTs)
Yap et al. (2018) No effect on CR, DFS, or OS (n=3 Obs)
Na et al. (2018) No effect on CR, DFS, or OS (n=6 Obs & RCTs)
Weberpals et al. (2016) No effect OS or CSS (n=6 Obs)
Zhong et al. (2016) Improved OS (n=4 Obs)
Riamondi et al. (2016) Improved OS and CSS (n=4 Obs)
Childrens et al. (2015) Improved CSS (n=4 Obs)
No effect on CR (n=5 Obs)
No effect on OS (n=4 Obs)
lung cancer
Copland et al. (2021) No effect on incidence (n=4 RCTs)
Lei et al. (2021) Improved OS in Stage III (n=4 Obs)
Improved OS when no surgery (n=2 Obs)
Worsened OS with nsBBL use (n=4 Obs)
Yap et al. (2018) No effect on CR, DFS or OS (n=3 Obs)
Na et al. (2018) No effect on CR, DFS or OS (n=7 Obs & RCTs)
Weberpals et al. (2016) No effect on OS or CSS (n=3 Obs)
Zhong et al. (2016) No effect on OS or CSS (n=4 Obs)
colon cancer
Qi et al. (2022) No effect on incidence (n=4)
Copland et al. (2021) No effect on incidence (n=3 RCTs)
Yap et al. (2018) No effect on CR, DFS or OS (n=3 Obs)
Na et al. (2018) No effect on CR, DFS or OS (n=2 Obs & RCTs)
Weberpals et al. (2016) No effect on OS or CSS (n=5 Obs)
Zhong et al. (2016) No effect on OS or CSS (n=2 Obs)
melanoma
Yap et al. (2018) Improved DFS and OS (n=1 Obs)
Na et al. (2018) Improved OS (n=2 Obs & RCTs)
Tang et al. (2018) Increased risk of incidence (n=3 Obs)
Gandini et al. (2018) Increased risk of incidence (n=4 Obs)
Weberpals et al. (2016) Improved OS (n=2 Obs)
Zhong et al. (2016) No effect on OS or CSS (n=4 Obs)
prostate cancer
Copland et al. (2021) No effect on incidence (n=3 RCTs)
Yap et al. (2018) Worsened OS (n=2 Obs)
Weberpals et al. (2016) No effect on OS or CSS (n=6 Obs)
Zhong et al. (2016) No effect on OS or CSS (n=2 Obs)

Figure 3:

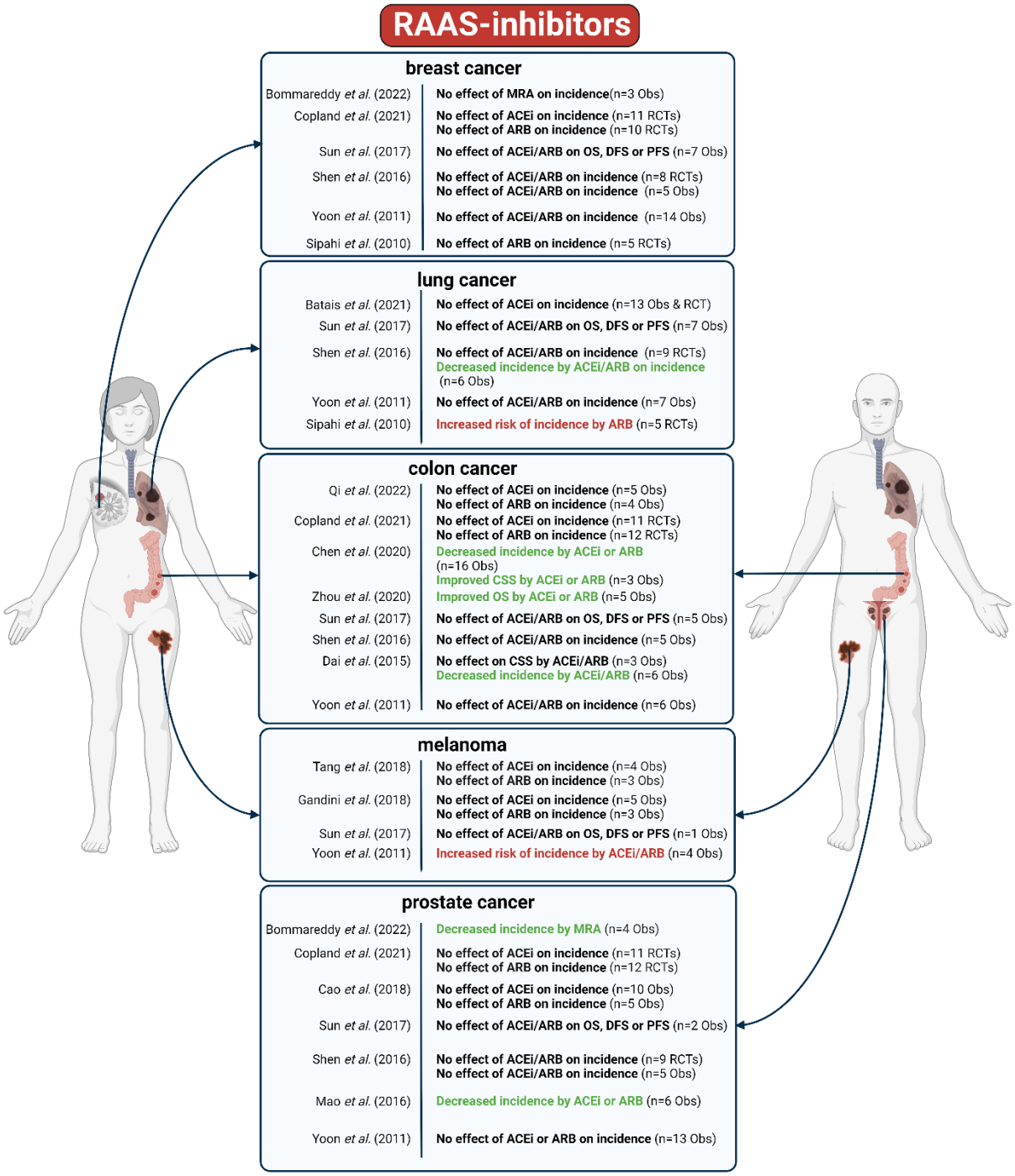

RAAS-inhibitors
breast cancer
Bommareddy et al. (2022) No effect of MRA on incidence(n=3 Obs)
Copland et al. (2021) No effect of ACEi on incidence (n=11 RCTs)
No effect of ARB on incidence (n=10 RCTs)
Sun et al. (2017) No effect of ACEi/ARB on OS, DFS or PFS (n=7 Obs)
Shen et al. (2016) No effect of ACEi/ARB on incidence (n=8 RCTs)
No effect of ACEi/ARB on incidence (n=5 Obs)
Yoon et al. (2011) No effect of ACEi/ARB on incidence (n=14 Obs)
Sipahi et al. (2010) No effect of ARB on incidence (n=5 RCTs)
lung cancer
Batais et al. (2021) No effect of ACEi on incidence (n=13 Obs & RCT)
Sun et al. (2017) No effect of ACEi/ARB on OS, DFS or PFS (n=7 Obs)
Shen et al. (2016) No effect of ACEi/ARB on incidence (n=9 RCTs)
Decreased incidence by ACEi/ARB on incidence (n=6 Obs)
Yoon et al. (2011) No effect of ACEi/ARB on incidence (n=7 Obs)
Sipahi et al. (2010) Increased risk of incidence by ARB (n=5 RCTs)
colon cancer
Qi et al. (2022) No effect of ACEi on incidence (n=5 Obs)
No effect of ARB on incidence (n=4 Obs)
Copland et al. (2021) No effect of ACEi on incidence (n=11 RCTs)
No effect of ARB on incidence (n=12 RCTs)
Chen et al. (2020) Decreased incidence by ACEi or ARB (n=16 Obs)
Improved CSS by ACEi or ARB (n=3 Obs)
Zhou et al. (2020) Improved OS by ACEi or ARB (n=5 Obs)
Sun et al. (2017) No effect of ACEi/ARB on OS, DFS or PFS (n=5 Obs)
Shen et al. (2016) No effect of ACEi/ARB on incidence (n=5 Obs)
Dai et al. (2015) No effect on CSS by ACEi/ARB (n=3 Obs)
Decreased incidence by ACEi/ARB (n=6 Obs)
Yoon et al. (2011) No effect of ACEi/ARB on incidence (n=6 Obs)
melanoma
Tang et al. (2018) No effect of ACEi on incidence (n=4 Obs)
No effect of ARB on incidence (n=3 Obs)
Gandini et al. (2018) No effect of ACEi on incidence (n=5 Obs)
No effect of ARB on incidence (n=3 Obs)
Sun et al. (2017) No effect of ACEi/ARB on OS, DFS or PFS (n=1 Obs)
Yoon et al. (2011) Increased risk of incidence by ACEi/ARB (n=4 Obs)
prostate cancer
Bommareddy et al. (2022) Decreased incidence by MRA (n=4 Obs)
Copland et al. (2021) No effect of ACEi on incidence (n=11 RCTs)
No effect of ARB on incidence (n=12 RCTs)
Cao et al. (2018) No effect of ACEi on incidence (n=10 Obs)
No effect of ARB on incidence (n=5 Obs)
Sun et al. (2017) No effect of ACEi/ARB on OS, DFS or PFS (n=2 Obs)
Shen et al. (2016) No effect of ACEi/ARB on incidence (n=9 RCTs)
No effect of ACEi/ARB on incidence (n=5 Obs)
Mao et al. (2016) Decreased incidence by ACEi or ARB (n=6 Obs)
Yoon et al. (2011) No effect of ACEi or ARB on incidence (n=13 Obs)

Figure 4:

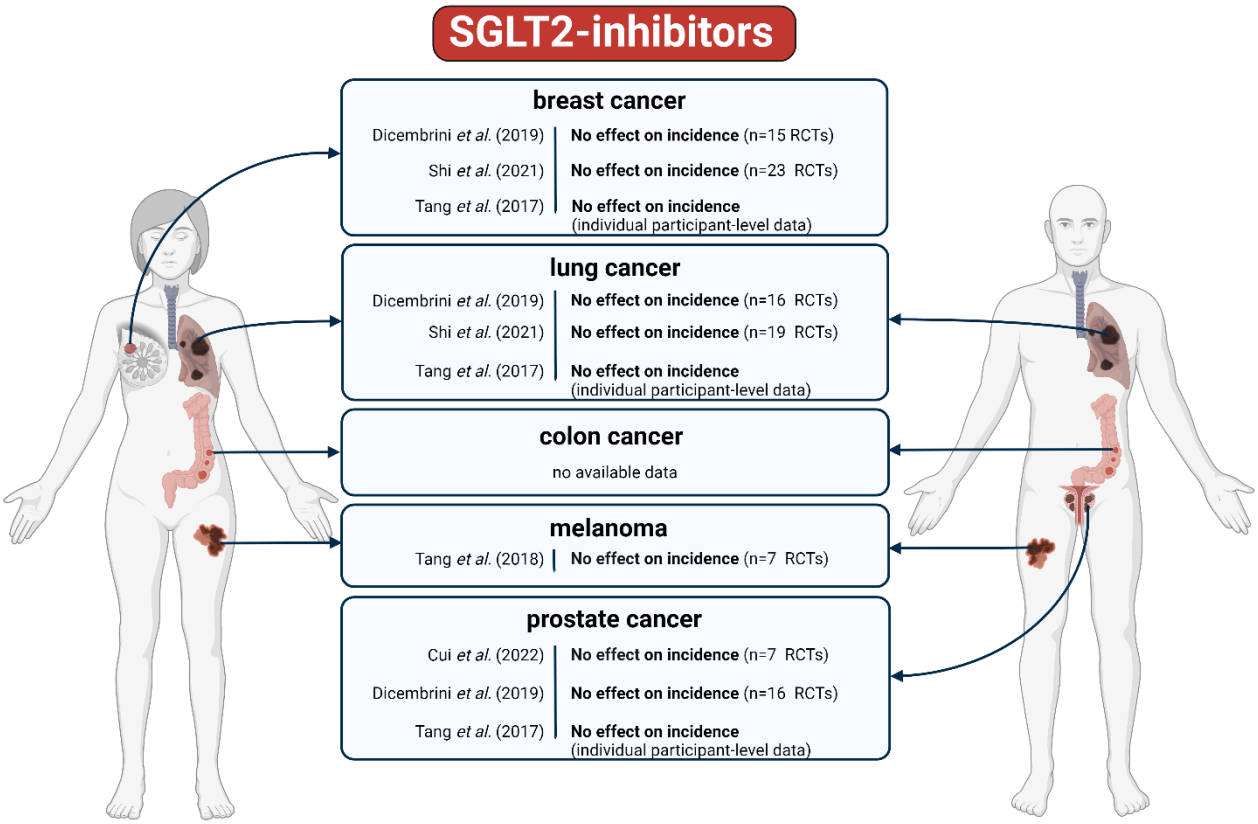


Figure 5:

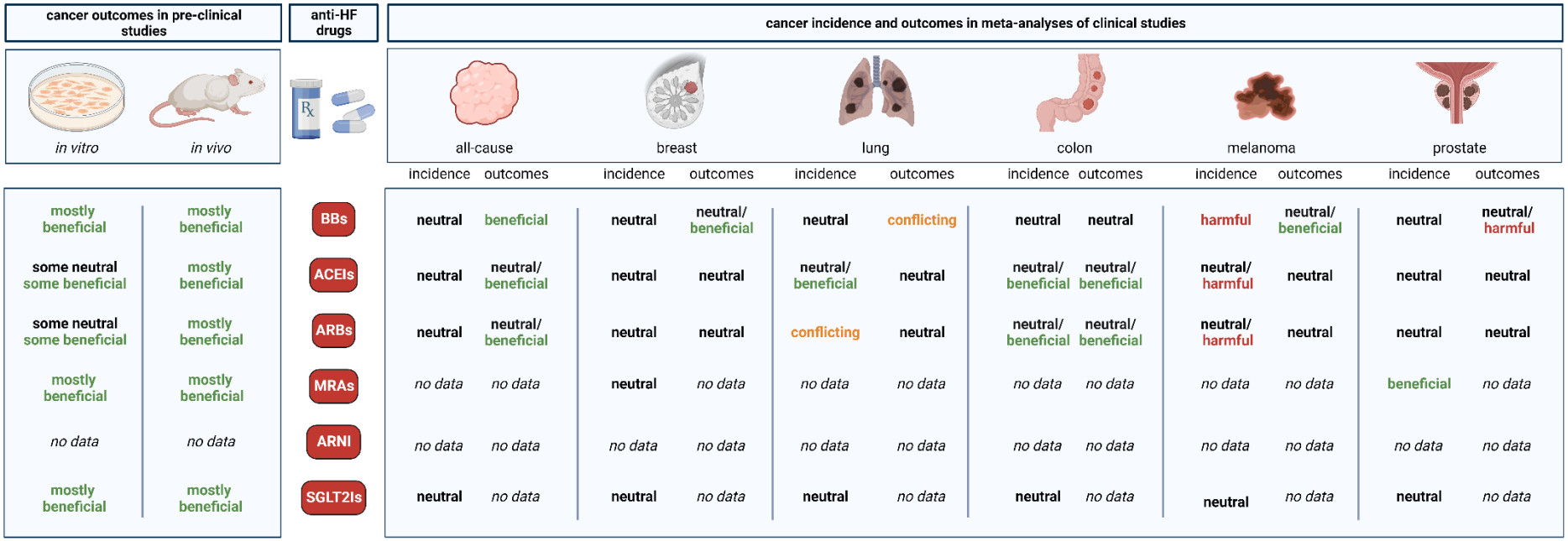

cancer outcomes in pre-clinical studies
anti-HF drugs
cancer incidence and outcomes in meta-analyses of clinical studies
in vitro
in vivo
all-cause
breast
lung
colon
melanoma
prostate
incidence outcomes incidence outcomes incidence outcomes incidence outcomes incidence outcomes incidence outcomes
mostly beneficial | mostly beneficial | BBs | neutral | beneficial | neutral | neutral/ beneficial | neutral | conflicting | neutral | neutral | harmful | neutral/ beneficial | neutral | neutral/ harmful
some neutral some beneficial | mostly beneficial | ACEIs | neutral | neutral/ beneficial | neutral | neutral | neutral/ beneficial | neutral | neutral/ beneficial | neutral/ beneficial | neutral/ harmful | neutral | neutral | neutral
some neutral some beneficial | mostly beneficial | ARBs | neutral | neutral/ beneficial | neutral | neutral | conflicting | neutral | neutral/ beneficial | neutral/ beneficial | neutral/ harmful | neutral | neutral | neutral
mostly beneficial | mostly beneficial | MRAs | no data | no data | neutral | no data | no data | no data | no data | no data | no data | no data | beneficial | no data
no data | no data | ARNI | no data | no data | no data | no data | no data | no data | no data | no data | no data | no data | no data | no data
mostly beneficial | mostly beneficial | SGLT2Is | neutral | no data | neutral | no data | neutral | no data | neutral | no data | neutral | no data | neutral | no data

Figure 6.

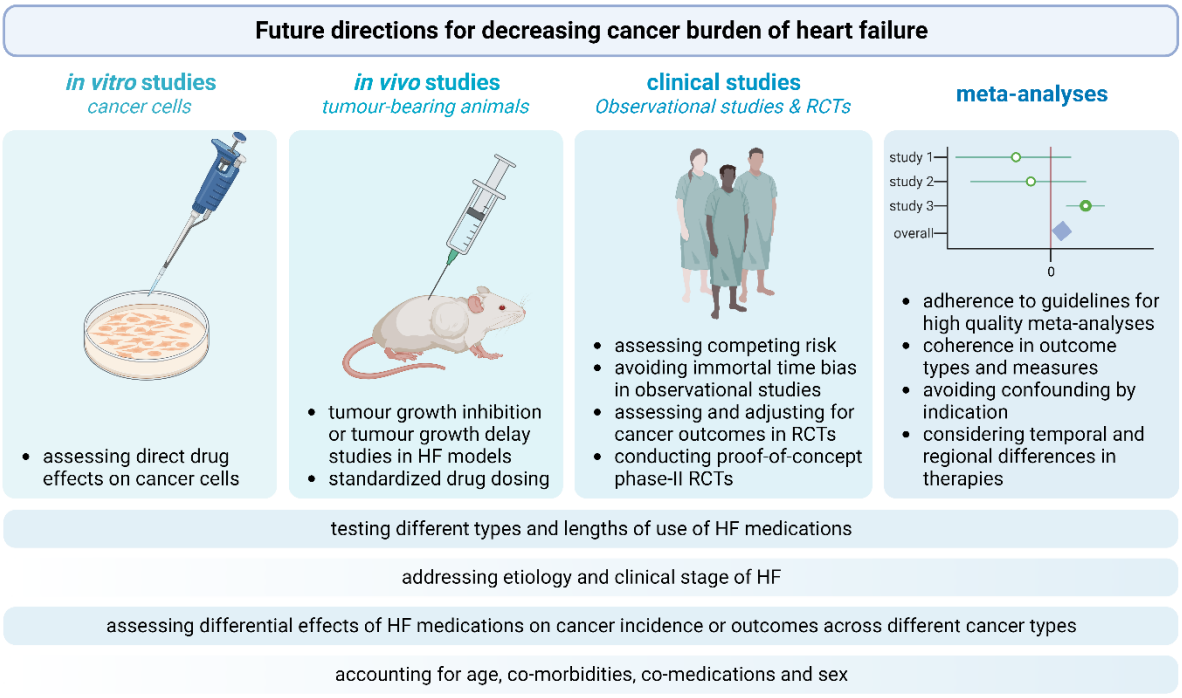


Figure 1

Click here to access/download;Figure;Figure_1.jpeg

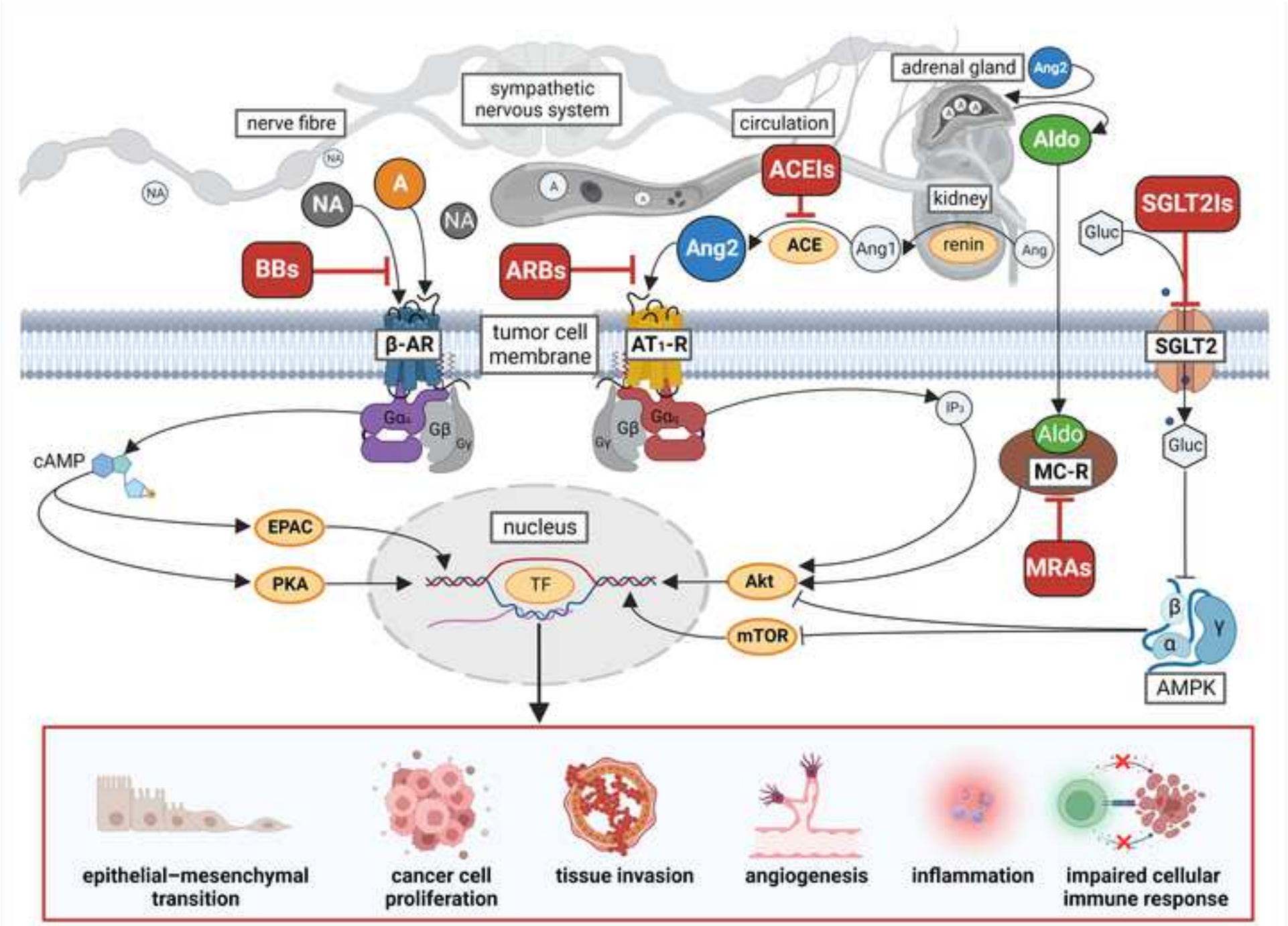


Figure 2

Click here to access/download;Figure;Figure_2.png

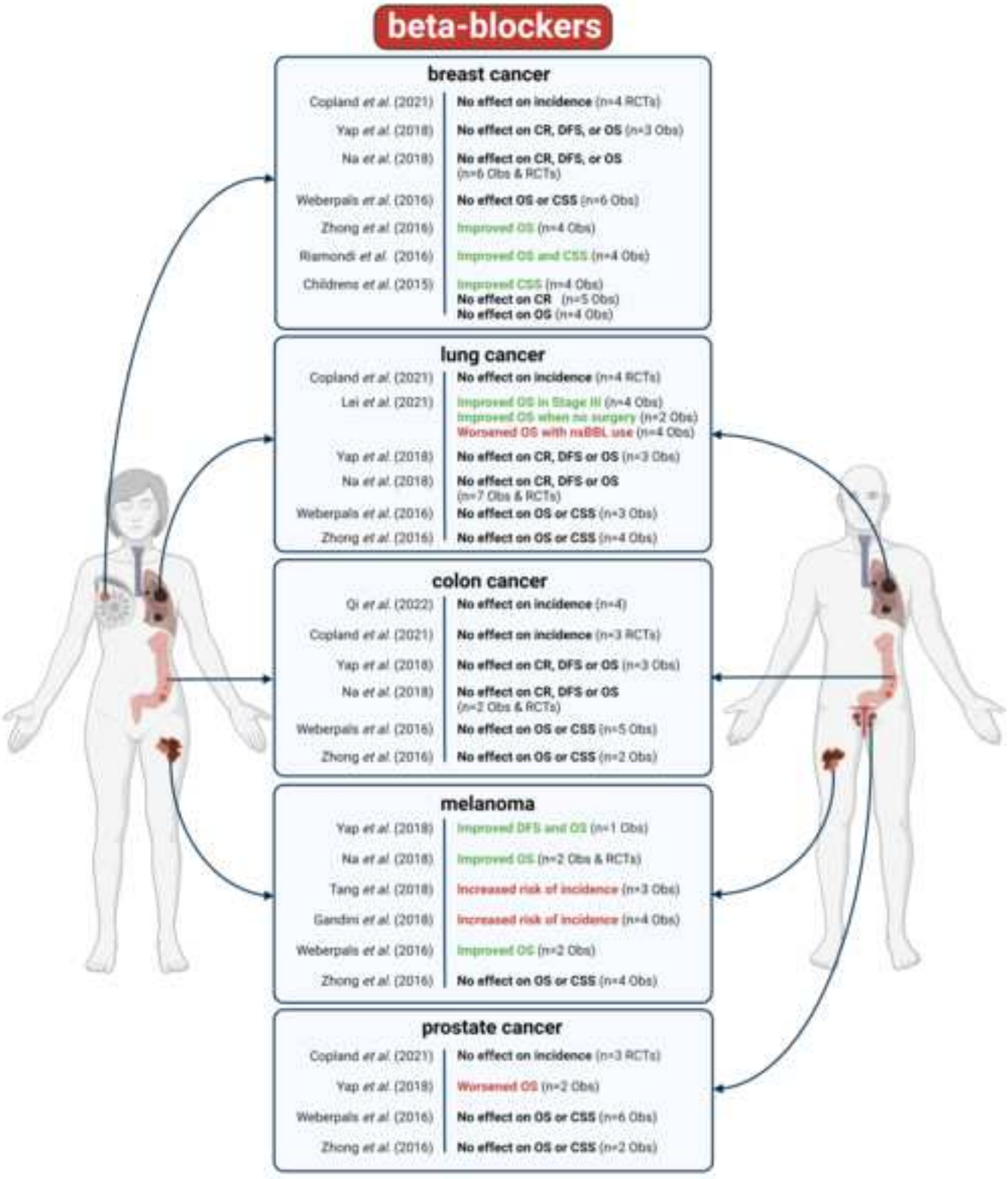


Figure 3

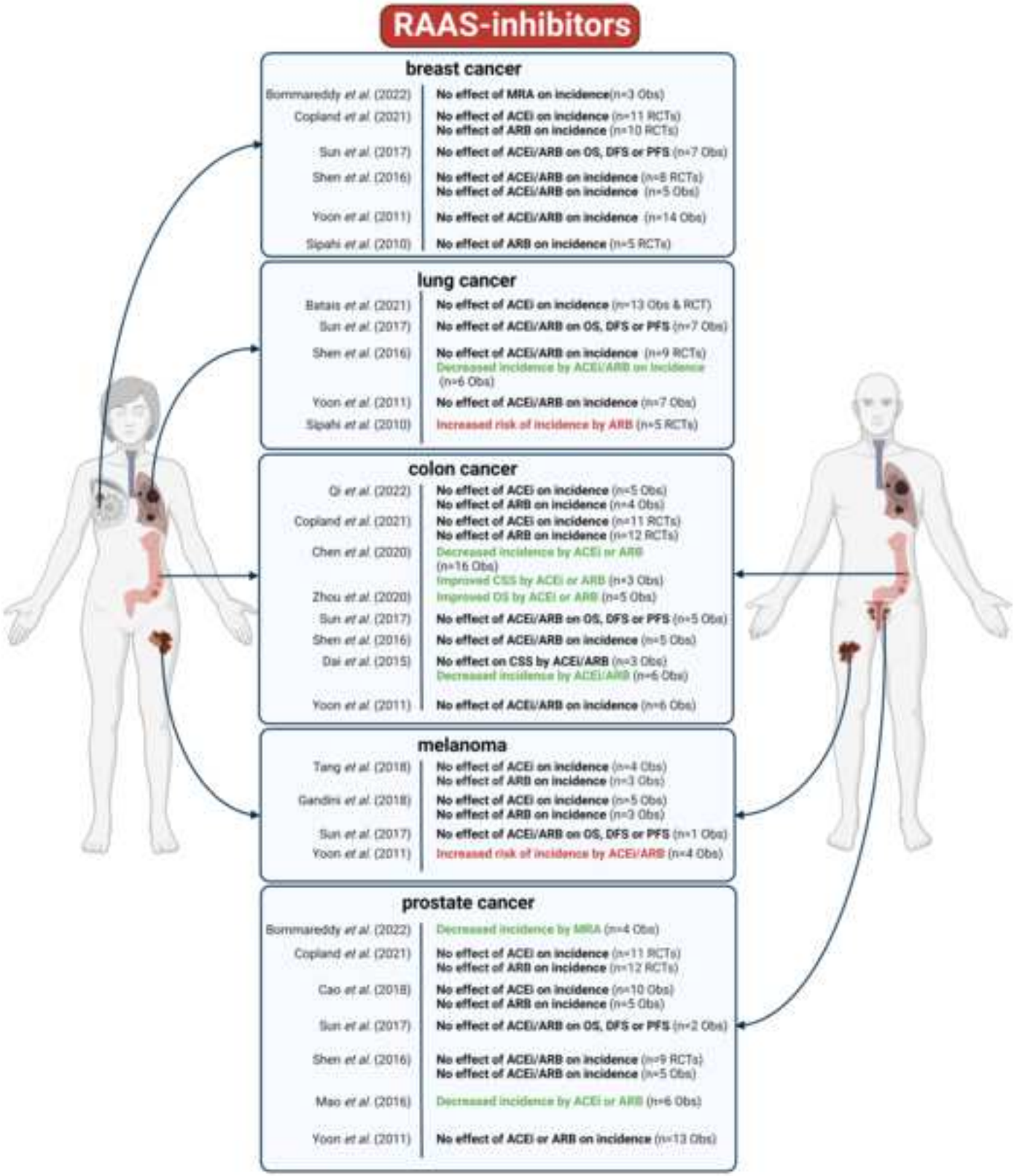


Figure 4

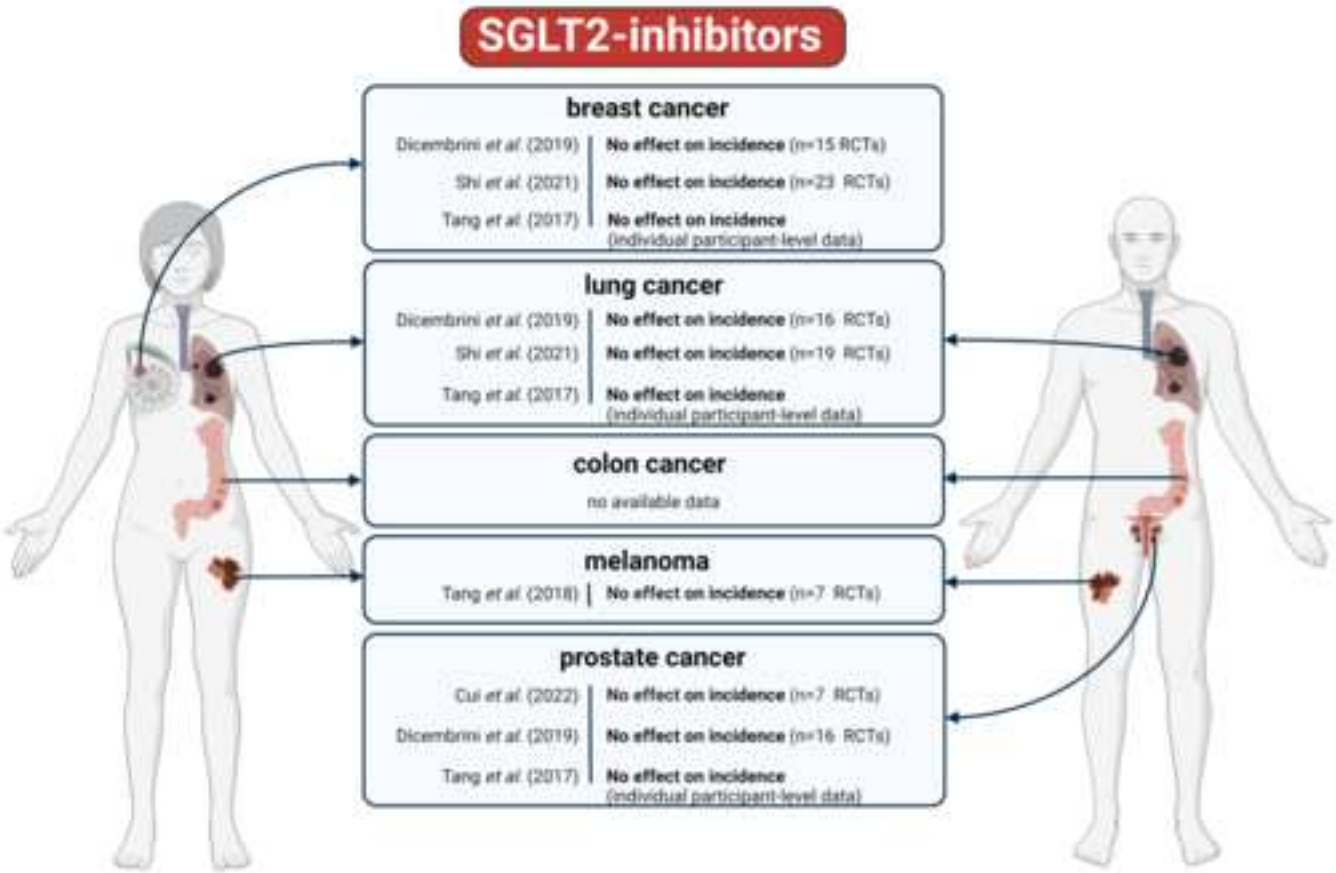


Figure 5

Click here to access/download;Figure;Figure_5.png

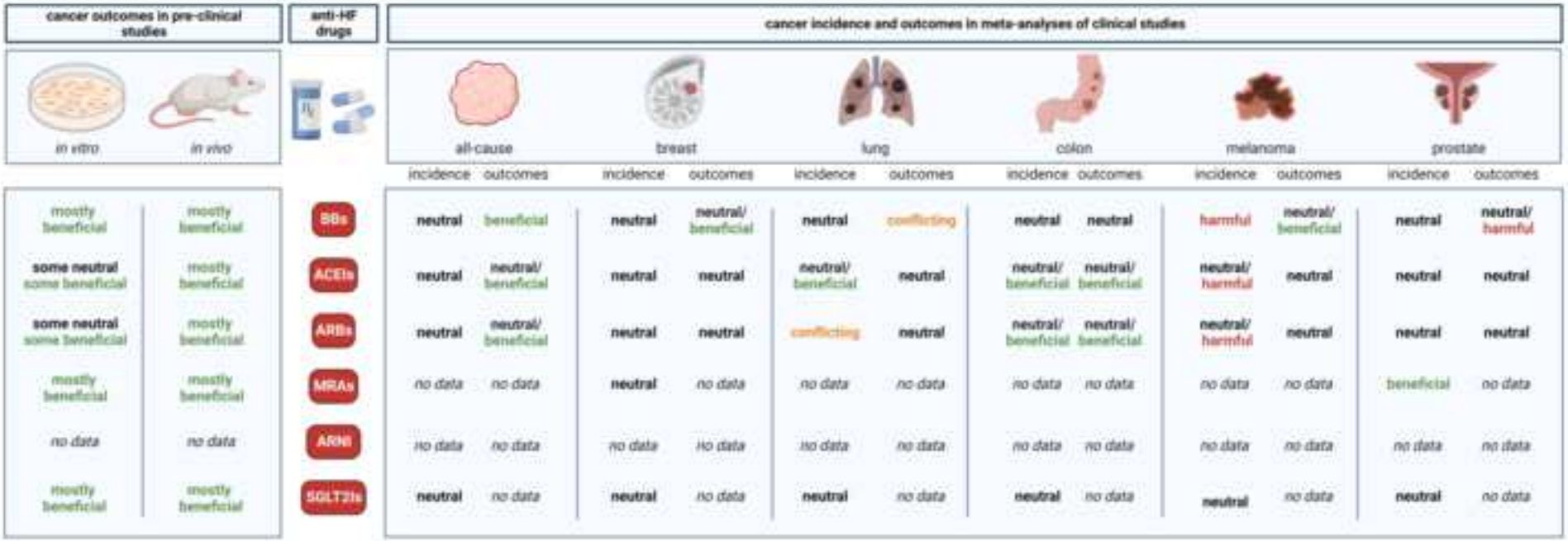


Figure 6

Future directions for decreasing cancer burden of heart failure

in vitro studies
cancer cells

- assessing direct drug effects on cancer cells

in vivo studies
tumour-bearing animals

- tumour growth inhibition or tumour growth delay studies in HF models
- standardized drug dosing

clinical studies
Observational studies & RCTs

- assessing competing risk
- avoiding immortal time bias in observational studies
- assessing and adjusting for cancer outcomes in RCTs
- conducting proof-of-concept phase-II RCTs

meta-analyses

- adherence to guidelines for high quality meta-analyses
- coherence in outcome types and measures
- avoiding confounding by indication
- considering temporal and regional differences in therapies

testing different types and lengths of use of HF medications

addressing etiology and clinical stage of HF

assessing differential effects of HF medications on cancer incidence or outcomes across different cancer types

accounting for age, co-morbidities, co-medications and sex

Supplementary table 1

NCT number	Status	Study design	Population	Intervention	Comparator	Outcome (primary)
NCT04962711	recruiting	prospective, randomized, controlled	cancer survivors >65 years old with chemotherapy >10 years ago	cardio-oncology disease management plan (optimization of pharmacotherapy, exercise intervention)	usual care	change in exercise capacity
NCT04598646	not yet recruiting	prospective, randomized, controlled	pediatric, adolescent and young adult (aya) cancer survivors	cario-oncology rehabilitation	behavioral support only	patient access and recruitment; testing- and intervention-related serious adverse events; patient exercise adherence
NCT03882580	recruiting	prospective, cohort	cancer patients who were evaluated within a cardio-oncology program	-	-	number of patients having a benefit after this specific cardio-oncology check up and follow up
NCT05194111	recruiting	prospective, randomized, single blinded, phase 1&2	cancer survivors diagnosed at ≤39 years of age who have stage b heart failure	sacubitril-valsartan	valsartan	evaluating the eligibility requirements and determining the tolerability of treatment with sacubitril-valsartan
NCT02943590	active, not recruiting	prospective, randomized, double blinded, phase 2	patients ≥18 years of age with newly diagnosed nhl and hl scheduled to receive anthracycline-based therapy	atorvastatin	placebo	left ventricular ejection fraction (lvef)
NCT05921279	recruiting	prospective, cohort	adult female patients diagnosed with stage i-iii breast cancer receiving chemotherapy	-	-	number of participants with successful application of guideline-directed cardio-oncology assessments and surveillance
NCT02818517	recruiting	prospective, cohort	all oncologic patients who were evaluated in the cardio-oncology clinic	ace inhibitors and beta blockers	N/A	echo-global strain; troponin; ace inhibitor and beta blocker treatment effect; bnp
NCT04680442	recruiting	prospective, randomized, double blinded, phase 2	patients with stage i-iii her-2 positive breast cancer receiving adjuvant or neoadjuvant therapy with trastuzumab, pertuzumab, or trastuzumab-emtansine, with evidence of left ventricular dysfunction	review by a cardiologist and receiving acei/arb and/or bb, and for dose titration	continuing or holding anti-cancer therapy guided by an adaptation of the 2008 canadian recommendations	the proportion of participants completing trastuzumab, pertuzumab, or trastuzumab-emtansine (t-dm1) as planned at its initiation; co-primary safety outcomes as lvef at the close-out visit, and the composite of nyha class iii or iv heart failure or cardiovascular death
NCT03760588	active, not recruiting	prospective, randomized, double blinded, phase 2	women with histological evidence of invasive early breast cancer scheduled for adjuvant therapy with anti-cancer regimens that include anthracyclines	sacubitril-valsartan	placebo	change in left ventricular ejection fraction by cardiovascular magnetic resonance

NCT03186404	active, not recruiting	prospective, randomized, double blinded, phase 2	patients with malignancies requiring anthracycline based chemotherapy with a curative intent: (breast cancer; aggressive lymphomas; leukemia; sarcoma) and with high cardiovascular risk	atorvastatin	placebo	cardiac mri measured lvef within 4 weeks of anthracycline completion
NCT02717507	active, not recruiting	prospective, randomized, double blinded, phase 2	cancer diagnosis < 22 years of age that completed cancer treatment ≥2 years prior enrollment, lifetime cumulative anthracycline dose of ≥250 mg/m^2 doxorubicin equivalent	carvedilol	placebo	left ventricular thickness-dimension ratio derived from echocardiogram
NCT04262830	recruiting	prospective, cohort	long-term childhood cancer survivors treated with anthracyline therap	-	-	left ventricular ejection fraction
NCT05851053	recruiting	cross-sectional, cohort	breast cancer survivors matched with women of the same age (±1 year), but who had no history of cancer or cancer treatment (chemotherapy or radiotherapy)	-	-	left ventricular systolic dysfunction
NCT04055636	recruiting	prospective, cohort	male and female more than 18 years old with verified cancer or with non-toxic dilated cardiomyopathy (control group)	-	-	all-cause mortality; heart transplantation; cardioverter-defibrillator implantation; hospitalization with heart failure decompensation
NCT05298072	not yet recruiting	cohort	initial diagnosis of breast cancer; planned anthracycline-based therapy; first-line chemotherapy; first visit before initiation of chemotherapy	N/A	N/A	cardiotoxicity during observational period

NCT06005259	not yet recruiting	prospective, randomized, triple masked, phase 4	patients of >18 years of age diagnosed with cancer indicated for anthracycline chemotherapy treatment	spironolactone	placebo	incidence of cardiotoxicity, defined as: a decrease in ejection fraction by 10% or more to lvef < 50%, as seen on transthoracic echocardiogram; or relative drop in global longitudinal strain greater than 15% compared to baseline, observed on transthoracic echocardiogram; new increase in cardiac biomarkers
NCT05892146	recruiting	prospective, randomized, quadruple masked	patients of 20-65 years of age who are newly diagnosed with breast cancer or lymphoma and never accepted anti-cancer therapy	sacubitril-valsartan	conventional therapy	change in absolute global longitudinal strain value measured by left ventricular global peak systolic longitudinal strain
NCT05607017	not yet recruiting	phase 1, single group, open label	patients who are receiving radiation therapy as part of standard of care treatment for breast cancer	losartan	-	extracellular volume of myocardial fibrosis measured by cardiac mri
NCT04737265	recruiting	prospective, randomized, open label, phase 1&2	patients of ≥18 years of age diagnosed with breast cancer or lymphoma (any subtype), planned to receive an anthracycline based chemotherapy regimen	biomarker guided intervention	usual care	recruitment rate; retention rate; adherence rate; compliance rate; maximum tolerated dose; incidence of adverse events
NCT02962661	recruiting	prospective, randomized, open label, phase 1	patients with lvef ≤40% with nyha class i, ii and iii, documented from treatment with anthracyclines for any malignancy at any dose at any time without evidence of other causes of cardiomyopathy; for patients who have received trastuzumab: persistent lv dysfunction must be present 90 days after discontinuation of trastuzumab; treated with appropriate maximal medical therapy for heart failure.	intravenous or transendocardial implantation of human mesenchymal stem cells	usual care	incidence of adverse events, change in left ventricular ejection fraction

NCT05732051	recruiting	prospective, randomized, triple masked, phase 2	women with metastatic breast cancer (stage iv breast cancer) scheduled for anthracycline-containing chemotherapy	nicotinamide riboside	placebo	reduction in left ventricular systolic function measured by cardiovascular magnetic resonance
NCT04023110	active, not recruiting	prospective, randomized, open label, phase 1	females of at least 18 years old diagnosed with stage i-iii breast cancer with treatment plan to include therapy with anthracyclines and/or trastuzumab in the adjuvant or neo-adjuvant setting	carvedilol	usual care	left ventricular ejection fraction; treatment adherence; adverse events
NCT05880160	not yet recruiting	randomized, open label	adult patients with prior diagnosis of human epidermal growth factor receptor 2 - targeted therapy related cardiac dysfunction, who currently receive standard heart failure/cardioprotective medications	cancer treatment withdrawal	cancer treatment continuation	number of participants with relapse in cardiotoxicity, defined based on international cardio-oncology society 2021 guidelines
NCT05507879	recruiting	prospective, cohort	patients with breast cancer who have previously received chemotherapy or are about to be treated with chemotherapy	-	-	significance oftrpc6 coding sequencing
NCT02610426	recruiting	retrospective, case-control	patients with breast cancer enrolled on e5103 with or without congestive heart failure	-	-	identification of rare coding variants of large effect that predict the risk of chf
NCT05377320	not yet recruiting	prospective, cohort	cancer survivors at intermediate, high, or very high risk for developing cardiovascular disease will pursue a cardio-oncology visit	clinical decision aid	usual care	medication use, imaging surveillance

NCT05465031	not yet recruiting	prospective, randomized, double blinded, phase 4	female patients of ≥18 years of age with histologically confirmed breast cancer and complete assessment of tumor phenotype gradin ia-iiic or oligometastatic grade iv with a plan of using systemic treatment (preoperative, postoperative or combined) with anthracyclines and/or anti-her2 drugs	sacubitril-valsartan	placebo	decrease in left ventricular ejection fraction ≥ 5%

Supplementary table 1.: On-going clinical studies of cardio-oncology. The following search string was used on ClinicalTrials.gov (accessed: 2023.09.18): 'heart failure' as condition or disease, AND 'cancer' as other term. Search was restricted to either 'recruiting', or 'active, not recruiting', or 'not yet recruiting'. A total of 98 registered trials was screened for eligibility, of which 27 on-going studies were related to cardio-oncology. Most of the studies were designed to assess interventions that may decrease cancer therapy-related cardiovascular diseases, with some them testing the effects of HF medications compared to placebo/usual care.

Supplementary table 2

Effects of BBs on cancer assessed *in vivo*								
Cancer type	**Study**	**Cell line**	**Animal model**	**Treatment**	**Tumor volume measurement**	**Major outcomes for treatment**	**Suggested mechanism of action**	**Synergism**
Breast cancer	**R. D. Gillis et al. (2021)**[1]	MDA-MB-231	orthotopic xenograft tumour implantation in mice	carvedilol (2 mg/kg/day)	bioluminescence	carvedilol reduced primary tumour growth and metastsis only in SN activation	-	-
Breast cancer	**M. Tibensky et al. (2021)**[2]	-	N-methyl-N-nitrosourea-induced breas cancer in rats	propranolol (20 mg/kg five times a week)	caliper	propranolol prolonged time of first palpable tumor detection, reduced tumor incidence	increased Caspase-3 gene expression	-
Breast cancer	**R. P. Dawes et al. (2020)**[3]	-	MMTV-PyMT mice, spontaneous	nadolol (1.5 mg in s.c. 60-day continuous release pellet)	terminal primary tumour weight, metastasis histology	nadolol increased primary tumour weight and metastases	increased exosomal TGFß2	-
Breast cancer	**D. Liu et al. (2015)**[4]	MCF-7/Her2	17β-estradiol containing pellets plus orthotopic xenograft tumour implantation in mice	propranolol (2 mg/kg i.p. twice a week)	caliper	propranolol alone did not affect cancer growth	inhibition of Akt, ERK and mTOR phosphorylation	propranolol reversed trastuzumab-resitence of cancer: propranolol+trastuzumab decreased tumour volume
Breast cancer	**D. M. Lamkin et al. (2015)**[5]	MDA-MB-231HM	orthotopic xenograft tumour implantation in mice	propranolol (2 mg/kg/day s.c.)	caliper, bioluminescence	propranolol alone did not affect cancer growth, but inhibited phentolamine-induced tumour growth and metastases	-	-

Breast cancer	**J. P. Campbell et al. (2012)**[6]	MDA-MB-231	heterotopic xenograft tumour implantation in Foxn1^{nu} BALB/c mice	propranolol (0.5 g/L in drinking water ad libitum)	caliper	propranolol inhibited sympathetic activation-induced tumour growth and metastastic bone colonization	-	-
Lung cancer	**D. Hu et al. (2021)**[7]	LLC	heterotopic syngraft tumour implantation in mice	propranolol (0.5 g/L in drinking water ad libitum)	caliper	propranolol alone inhibited tumour growth	increased NK cell cytotoxicity	grain-sized moxibustion ± propranolol combination: no difference in anti-cancer efficacy
Lung cancer	**M. Niu et al. (2021)**[8]	H1975 or PC-9 or PC-9/AZDR	heterotopic xenograft tumour implantation in mice	nebivolol (10 mg/kg i.p. six times a week)	caliper	nebivolol alone inhibited tumor growth and cell proliferation	nebivolol upregulated FBXL2 expression which inhibits EGFR-driven tumour growth	nebivolol + osimertinib/Grp94-inhibitor-1: strong inhibitory effects on osimertinib-resistant cells
Lung cancer	**A. Chang et al. (2015)**[9]	A549	heterotopic xenograft tumour implantation in mice	carvedilol (26 mg/kg/day, p.o.)	caliper	carvedilol alone reduced tumor volume	-	-
Colorectal cancer	**K. Y. Fjæstad et al. (2022)**[10]	MC38	heterotopic syngraft tumour implantation in mice	propranolol (0.5 g/L in drinking water ad libitum)	caliper	propranolol alone decreased tumour growth	anti-angionetic effect by decreasing intratumoral Vegfa gene expression	proranolol increased anti-cancer efficacy of anti-CTLA4 therapy
Colorectal cancer	**C. R. MacDonald et al. (2019)**[11]	CT26.CL25	heterotopic syngraft tumour implantation in mice	propranolol (10 mg/kg/day i.p.)	caliper	propranolol was used only in combination with radiation	higher expression of granzyme-B in tumour microenvironment	propranolol improved anti-cancer efficacy of radiation
Colorectal cancer	**L. Sorski et al. (2016)**[12]	CT26	syngraft tumour injection to spleen or portal vein in mice	propranolol 5 mg/kg subcutaneously in a single dose	number of surface hepatic metastases, liver weight	propranolol alone did not affect metastasis	NK cell activaiton	etodolac+propranolol combination: improved host resistance to metastasis
Melanoma	**F. Moisan et al. (2021)**[13]	A375	orthotopic xenograft tumour implantation in mice	propranolol (2 mg/kg/day)	caliper	propranolol was used only in combination with bevacizumab	no significant anti-cancer activity	bevacizumab+propranolol combination: no significant anti-cancer effect

Melanoma	**K. H. Cleveland et al. (2018)**[14]	A375 with $BRAF^{V600E}$ mutation	orthotopic xenograft tumour implantation in mice	carvedilol 600 ug/day p.o.	caliper	carvedilol decreased tumour growth	-	-
Melanoma	**X. Kuang et al. (2017)**[15]	A375	orthotopic xenograft tumour implantation in mice	propranolol 2mg/kg/day p.o.	caliper	propranolol alone did not affect tumour growth	-	propranolol enhanced anti-tumour effect of low dose sunitinib
Melanoma	**K. M. Kokolus et al. (2017)**[16]	B16-F10	orthotopic syngraft tumour implantation	metoprolol (10 mg/kg/day i.p.)	caliper	metoprolol alone did not affect tumour growth	-	metoprolol did not enhance anti-tumour effects of αPD-1+IL-2 combination
Melanoma	**K. M. Kokolus et al. (2017)**[16]	B16-F10	orthotopic syngraft tumour implantation	propranolol (10 mg/kg/day i.p.)	caliper	propranolol alone decreased tumor growth	-	propranolol enhanced anti-tumour effects of αPD-1, αPD-1+IL-2 combination, but not IL-2
Melanoma	**S. Maccari et al. (2017)**[17]	B16-F10	orthotopic syngraft tumour implantation	propranolol (10, 20, 30, 40 mg/kg/day i.p.)	caliper	propranolol decreased tumour growth in a biphasic dose (10 and 40 mg/kg/day)	influencing systemic vascular resistance	-
Melanoma	**L. J. Wrobel et al. (2016)**[18]	-	MT/ret mice, spontaneous	propranolol (0.5 g/L in drinking water ad libitum)	primary tumor occurrence (primary tumour-free survival), metastases	propranolol prolonged primary tomour-free survival, and delayed formation of metastases	reduced myeloid infiltration, increased granzyme-B-expressing lymphid cells in primary tumours, increased NK and cytotoxic T-cells in metastases	-

Melanoma	**C. Zhou et al. (2016)**[19]	A375 or human patient derived melanoma	orthotopic xenograft tumour implantation	propranolol (2 or 10 mg/kg/day i.p.)	caliper	propranolol decreased tumour growth (lower dose was more effective)	inhibited proliferation, induced apoptosis and promoted cell necrosis in tumors	-
Melanoma	**L. J. Wrobel et al. (2015)**[20]	human patient derived melanoma	orthotopic xenograft tumour implantation	propranolol (0.5 g/L in drinking water ad libitum)	caliper	propranolol decreased tumour growth and metastases	inhibited proliferation and angiogenesis, induced apoptosis through upregulation of TP53 and downregulation of Akt3 and HIF1a	-
Melanoma	**G-H. Deng et al. (2014)**[21]	B16-F1	orthotopic syngraft tumour implantation	propranolol (1 µmol/100 g/day by microosmotic pumps)	caliper	propranolol alone did not affect tumour growth, but inhibited tumor growth promoting effect of norepinephrine	-	-
Prostate cancer	**D. Palm et al. (2006)**[22]	PC-3	heterotopic xenograft tumour implantation in mice	propranolol (1 µmol/100 g bw s.c. by microosmotic pumps)	bioluminescence	significantly decreased lymph-node metastases and inhibited norepinephrine-induced tumour growth	-	-

Effects of ACEIs on cancer assessed *in vivo*								
Lung cancer	**K. Nakaya et al. (2016)**[23]	A549	heterotopic xenograft tumour implantation in severe combined immunodeficiency mice	captopril (3 mg/mouse/day)	18F-FDG-PET/CT imaging	captopril reduced tumor volume and metabolic tumor volume	-	-
Lung cancer	**S. Attoub et al. (2008)**[24]	LMN35	heterotopic xenograft tumour implantation in mice	captopril (2.8 mg/kg i.p. 6 days a week)	caliper	captopril reduced primary tumor volume and angiogenesis, tendentially reduced lymph node metastasis	-	-
Lung cancer	**R. R. Kohl et al. (2007)**[25]	A549	heterotopic xenograft tumour implantation	ramipril (2.5 mg/kg/day in drinking water ad libitum)	caliper	ramipril did not affect tumor response to radiation, but reduced radiation injury of normal tissue	-	-
Colorectal cancer	**Y. Yang et al. (2020)**[26]	SW620	heterotopic xenograft tumour implantation in mice	enalapril (0.6 mg/kg/day p.o.)	caliper	enalapril alone did not affect tumour growth	enalapril + 5-FU: EMT suppression, NF-κB/STAT3 suppression, MMP-9 and MMP-2 suppression	enalapril+5-FU combination: reduced tumour growth, proliferation, angiogenisis, metastasis
Colorectal cancer	**S. L. Koh et al. (2014)**[27] **G. E. Riddiough et al. (2021)**[28]	mouse colorectal cancer cells, developed via dimethyl-hydrazine induction of colon carcinoma in CBA mice	intrasplenic injeciton of cancer cells	captopril (250 mg/kg/day i.p.)	stereometric tumour burden analysis	captopril decreased metastasis burden of regenerating liver remnant	captopril increased PD-1 expression in T-cells, modulates myeloid-derived suppressor cell populaitons	-

Colorectal cancer	**D. L. V. Ardila et al. (2020)**[29]	mouse colorectal cancer cells, developed via dimethyl-hydrazine induction of colon carcinoma in CBA mice	intrasplenic injeciton of cancer cells	captopril (750 mg/kg/day i.p.)	stereometric tumour burden analysis	captopril reduced metastatic growth and tumor viability, modulates spatio-temporal infiltration of lymphocytes into tumour	-	-
Colorectal cancer	**T. Kochi et al. (2014)**[30]	-	azoxymethane-induced colonic premalignant lesions in diabetic and hypertensive rats	captopril (8 mg/kg/day in drinking water ad libitum)	aberrant cryptic foci size and density	captopril inhibits early size and density of aberrant cryptic foci	reduced colonic epithelial expression of AT1R, ACE, TNF-alpha, IL-18, MCP-1, iNOS and VEGF mRNA expression	-
Colorectal cancer	**S. Wen Wen et al. (2013)**[31]	mouse colorectal cancer cells, developed via dimethyl-hydrazine induction of colon carcinoma in CBA mice	intrasplenic injeciton of cancer cells	captopril (750 mg/kg/day i.p.)	stereometric tumour burden analysis	captopril decreased tumor load	increased number of liver AT1R-positive Kuppfer cells	-
Melanoma	**P. J. Wysock et al. (2006)**[32]	B78-H1	heterotopic syngraft tumour implantation	captopril (25, or 60 mg/kg/day)	caliper	captopril did not affect tumour growth	-	-

Effects of ARBs on cancer assessed *in vivo*								
Breast cancer	**W. Li et al. (2021)**[33]	MCa-M3C	orthotopic syngraft tumour implantation in mice	losartan (40 mg/kg/day p.o.)	caliper	losartan alone did not affect tumour growth	-	losartan enhanced tumour response to radiation therapy
Breast cancer	**L. E. Mainetti et al. (2020)**[34]	M-234p or M-406	heterotopic syngraft tumour implantation	losartan (150-200 mg/kg/day p.o.)	caliper	losartan alone did not affect tumour growth	-	losartan enhanced tumour response to cyclophosphamide: increased number of TUNEL+ and Foxp3+ cells, decreased number of HIF1-α positive cells, lower % of αSMA+ positive cells
Breast cancer	**X-J. Cai et al. (2021)**[35]	NIH 3T3 & 4T1 (3:1)	heterotopic syngraft tumour implantation	candesartan (20 mg/kg/day p.o.)	caliper	candesartan decreased tumour growth and metastasis	tumor vessel normalization and depletion of ECM, inhibition of metastasis by eliminating collagen-I	candesartan + pegylated liposome–encapsulated zoledronic acid combination: stronger decrease in active TGF-β1 but no significant improvement over single treatment
Breast cancer	**T. Takiguchi et al. (2021)**[36]	4T1-Luc	orthotopic syngraft tumour implantation	valsartan (60 mg/kg/day p.o.)	micro-computed tomography imaging	valsartan attenuates tumour growth and metastases induced by angiotensin-II	attenuated upregulation of protein expressions caused by Ang II (c-Myc, cyclin D1, fibronectin, vimentin, αSMA and Snail)	-
Breast cancer	**Y. Ma et al. (2019)**[37]	MDA-MB-231, or 4T1	orthotopic xenograft tumour implantation	losartan (40 mg/kg/day p.o.)	caliper, bioluminescence imaging	losartan reduces tumor growth and lymph node metastasis	reduced CXCR4/SDF-1α expression	-

Breast cancer	**R. Coulson et al. (2017)**[38]	-	MPA+DMBA-induced breast cancer	losartan (600 mg/L in drinking water ad libitum)	timet o first tumour incidence	losartan delayed tumor onset, inhibited progression	decreased cytokine production, decreased TGFβ1, integrin β3, connective tissue growth factor	-
Breast cancer	**T. Xia et al. (2018)**[39]	4T1	heterotopic syngraft tumour implantation	losartan (2.5, or 10 mg/kg/day i.v.)	caliper	losartan did not affect tumour growth	-	-
Breast cancer	**E. Oh et al. (2016)**[40]	MCF7, or AGTR1-overexpressing MCF7	heterotopic xenograft tumour implantation	losartan (90 mg/kg i.p. three times a week)	caliper	losartan inhibited tumor growth and angiogenesis upregulated by AGTR1 overexpression	increasing mesenchymal markers and decreasing E-cadherin levels	-
Breast cancer	**D. R. Rhodes (2009)**[41]	MCF7-AGTR1	orthotopic xenograft tumour implantation	losartan (90 mg/kg/day)	caliper	losartan reduced early and late tumor growth	-	-
		MCF7-Gus	orthotopic xenograft tumour implantation	losartan (90 mg/kg/day)	caliper	no effect on tumor growth	-	-
Lung cancer	**D. Volonte et al. (2021)**[42]	-	K-RasLA2-G12D mice	losartan (50 mg/kg/day i.p.)	number of surface lung tumors	losartan inhibits lung tumor formation	downregulation of phospho(Tyr705)-STAT3, upregulated AGT and HMGA1 mRNAs	-
Lung cancer	**D. P. Regan et al. (2019)**	4T1-luc, or CT26-luc, or CT26-GFP	heterotopic syngraft tumour implantation	losartan (60mg/kg/day i.p.)	bioluminescence imaging	losartan supressed pulmonary metastasis growth	sustained blockade of inflammatory monocyte recruitment	not performed
Colorectal cancer	**E. Tabatabai et al. (2021)**[43]	CT-26	heterotopic syngraft tumour implantation	candesartan (6.5 mg/kg/day i.p.)	caliper	candesartan inhibited tumour growth	decreasing collagen content, inducing tumor necrosis and changing the oxidant/antioxidant balance in tumor tissue	candesartan enhanced the anti-tumor effects of 5-FU

Colorectal cancer	**M. Hashemzehi et al. (2021)**[44]	HT-29	heterotopic xenograft tumour implantation	losartan (90 mg/kg/day i.p.)	caliper	losartan inhibited tumor growth	inhibiting angiogenesis and changing the oxidant/anti-oxidant balance in tumor tissue	losartan enhanced the anti-tumor effects of 5-FU
Colorectal cancer	**U. Dougherty et al. (2019)**[45]	-	$Apc^{+/LoxP}$; Cdx2P-Cre mice	losartan (160 mg/L in drinking water ad libitum)	colonoscopy	losartan decreased cancer incidence and tumour size	reduced pAKT and pERK	losartan+vitamin D combination: tumor multiplicity was numerically less, reduced β-catenin expression and ADAM17 from VD single treatment was not observed in the combination treatment
Colorectal cancer	**F. Asgharzadeh et al. (2022)**[46]	CT-26	heterotopic syngraft tumour implantation in mice	valsartan (40 mg/kg/day p.o.)	caliper	valsartan reduced tumour growth	induction of apoptosis via inhibiting RAS pathway	valsartan increased the anti-cancer efficacy of 5-FU
Colorectal cancer	**S. C. W. Stevens et al. (2015)**[47]	C26	heterotopic syngraft tumour implantation in mice	losartan (10 mg/kg in drinking water ad libitum)	terminal tomour weight	losartan reduced tumor weight	reduction in adenocarcinoma cell proliferation	-
Melanoma	**S. Ishikane et al. (2018)**[48]	B16-F10	syngraft lung metastasis model (tail vein injection)	valsartan (10, or 20, or 40 mg/kg/day in drinking water ad libitum)	nodule counting	valsartan alone did not affect metastases, but inhibited angiotensin-II-induced metastatic colony formation	-	-
Melanoma	**A. H. Otake et al. (2010)**[49]	B16-F10	orthotopic syngraft tumour implantation	losartan (75 mg/kg/day doubled every 3 days until 300 mg/kg/day p.o.)	caliper	losartan decreased tumor volume, no decrease in metastasis	lower new vessel formation in tumors	-
Prostate cancer	**A. Alhusban et al. (2014)**[50]	PC3	heterotopic xenograft tumour implantation	candesartan (6.5 mg/kg/day i.p.)	caliper	candesartan inhibited tumour growth	inhibited VEGF mRNA expression Independent of AT2-R activation	-

Prostate cancer	**S. Takahashi et al. (2012)**[51]	-	TRAP rats, spontaneous	telmisartan or candesartan (2 or 10 mg/kg/day in drinking water ad libitum)	counting total acini in each prostatic lobe	both doses of candesartan or telmisartan attenuated prostate carcinogenesis	activation of caspases, inactivated p38 MAPK, down-regulated androgen receptors	-

Effects of MRAs on cancer assessed *in vivo*								
Colorectal cancer	**W-H. Leung et al. (2013)**[52]	-	C57BL/6J-APCMin/J mice	spironolactone (1.25 mg/mouse i.p. twice a week)	polyp counting	spironolactone decreased number of polyps	increased the expression of Raet1 ligand in the polyps, up-regulation of NKG2DL expression independent of the MR pathway	-
		HT29, or HCT116	heterotopic xenograft tumour implantation in mice	spironolactone (1.25 mg/mouse i.p. twice a week)	bioluminescence imaging	spironolactone inhibits tumor metastasis	antimetastatic effect is independent of MR but activation of the ATM–ATR pathway requires the activation of RXRγ	-

Effects of SGLT2Is on cancer assessed *in vivo*								
Breast cancer	**J. Zhou et al. (2020)**[53]	MCF-7	heterotopic xenograft tumour implantation	dapagliflozin (100 mg/kg/day p.o.)	caliper	dapagliflozin delayed tumor growth	-	-
Breast cancer	**A. R. Nasiri et al. (2019)**[54]	E0771	heterotopic syngraft tumour implantation in obese and non-obese mice	dapagliflozin 2.5 mg/kg/day in drinking water ad libitum	caliper	dapagliflozin slows tumor growth in insulin-dependent manner	reversing hyperinsulinemia	-
Colorectal cancer	**A. R. Nasiri et al. (2019)**[54]	MC38	heterotopic syngraft tumour implantation in obese and non-obese mice	dapagliflozin 2.5 mg/kg/day in drinking water ad libitum	caliper	dapagliflozin slows tumor growth in insulin-dependent manner	reversing hyperinsulinemia	-
Colorectal cancer	**J. Korfhage et al. (2022)**[55]	-	C57BL/6J-Apc^{min} mice, spontaneous	chow containing 180 parts per million canagliflozin for 30-72 days	intestinal section imaging	canagliflozin increased intestinal adenoma burden in female mice	-	-
Prostate cancer	**C. Scafoglio et al. (2015)**[56]	PC3	heterotopic xenograft tumour implantation	canagliflozin (30 mg/kg/day p.o.)	microPET/CT imaging	canagliflozin reduced tumor growth	increased central necrotic area	canagliflozin+gemcitabine combination: higher reduction in tumor growth

Supplementary table 2.: *In vivo* studies investigating the effect of guideline-directed HF pharmacotherapies on cancer.

References:

1. Gillis, R. D. *et al.* Carvedilol blocks neural regulation of breast cancer progression in vivo and is associated with reduced breast cancer mortality in patients. *Eur. J. Cancer* **147**, 106–116 (2021).
2. Tibensky, M. *et al.* Chronic propranolol treatment moderately attenuated development of N-methyl-N-nitrosourea-induced mammary carcinoma in female rats. *Anticancer. Drugs* **32**, 1011–1018 (2021).
3. Dawes, R. P. *et al.* Chronic Stress Exposure Suppresses Mammary Tumor Growth and Reduces Circulating Exosome TGF-β Content via β-Adrenergic Receptor Signaling in MMTV-PyMT Mice. *Breast Cancer (Auckl).* **14**, 1178223420931511 (2020).
4. Liu, D. *et al.* β2-AR signaling controls trastuzumab resistance-dependent pathway. *Oncogene* **35**, 47–58 (2016).
5. Lamkin, D. M. *et al.* α2-Adrenergic blockade mimics the enhancing effect of chronic stress on breast cancer progression. *Psychoneuroendocrinology* **51**, 262–270 (2015).
6. Campbell, J. P. *et al.* Stimulation of host bone marrow stromal cells by sympathetic nerves promotes breast cancer bone metastasis in mice. *PLoS Biol.* **10**, e1001363 (2012).
7. Hu, D. *et al.* Grain-sized moxibustion promotes NK cell antitumour immunity by inhibiting adrenergic signalling in non–small cell lung cancer. *J. Cell. Mol. Med.* **25**, 2900–2908 (2021).
8. Niu, M. *et al.* FBXL2 counteracts Grp94 to destabilize EGFR and inhibit EGFR-driven NSCLC growth. *Nat. Commun.* **12**, 5919 (2021).
9. Chang, A. *et al.* Prevention of skin carcinogenesis by the β-blocker carvedilol. *Cancer Prev. Res.* **8**, 27–36 (2015).
10. Fjæstad, K. Y. *et al.* Blockade of beta-adrenergic receptors reduces cancer growth and enhances the response to anti-CTLA4 therapy by modulating the tumor microenvironment. *Oncogene* **41**, 1364–1375 (2022).
11. MacDonald, C. R. *et al.* Adrenergic receptor signaling regulates the response of tumors to ionizing radiation. *Radiat. Res.* **191**, 585–589 (2019).
12. Sorski, L. *et al.* Reducing liver metastases of colon cancer in the context of extensive and minor surgeries through β-adrenoceptors blockade and COX2 inhibition. *Brain Behav. Immun.* **58**, 91–98 (2016).
13. Moisan, F. *et al.* Critical role of Aquaporin-1 and telocytes in infantile hemangioma response to propranolol beta blockade. *Proc. Natl. Acad. Sci. U. S. A.* **118**, e2018690118 (2021).
14. Cleveland, K. H. *et al.* Phosphoproteome profiling provides insight into the mechanism of action for carvedilol-mediated cancer prevention. *Mol. Carcinog.* **57**, 997–1007 (2018).
15. Kuang, X. *et al.* Propranolol enhanced the anti-tumor effect of sunitinib by inhibiting proliferation and inducing G0/G1/S phase arrest in malignant melanoma. *Oncotarget* **9**, 802–811 (2018).
16. Kokolus, K. M. *et al.* Beta blocker use correlates with better overall survival in metastatic melanoma patients and improves the efficacy of immunotherapies in mice. *Oncoimmunology* **7**, e1405205 (2018).
17. Maccari, S. *et al.* Biphasic effects of propranolol on tumour growth in B16F10 melanoma-bearing mice. *Br. J. Pharmacol.* **174**, 139–149 (2017).
18. Jean Wrobel, L. *et al.* Propranolol induces a favourable shift of anti-tumor immunity in a murine spontaneous model of melanoma. *Oncotarget* **7**, 77825–77837 (2016).
19. Zhou, C. *et al.* Propranolol induced G0/G1/S phase arrest and apoptosis in melanoma cells via AKT/MAPK pathway. *Oncotarget* **7**, 68314–68327 (2016).
20. Wrobel, L. J. & Le Gal, F. A. Inhibition of Human Melanoma Growth by a Non-Cardioselective β-Blocker. *J. Invest. Dermatol.* **135**, 525–531 (2015).
21. Deng, G.-H. *et al.* Exogenous norepinephrine attenuates the efficacy of sunitinib in a mouse cancer model. *J. Exp. Clin. Cancer Res.* **33**, 21 (2014).
22. Palm, D. *et al.* The norepinephrine-driven metastasis development of PC-3 human prostate cancer cells in BALB/c nude mice is inhibited by β-blockers. *Int. J. Cancer* **118**, 2744–2749 (2006).
23. Nakaya, K., Otsuka, H., Kondo, K., Otani, T. & Nagata, M. Tumor growth-inhibitory effect of an angiotensin-converting enzyme inhibitor (captopril) in a lung cancer xenograft model analyzed using 18F-FDG-PET/CT. *Nucl. Med. Commun.* **37**, (2016).

24. Attoub, S. *et al.* Captopril as a Potential Inhibitor of Lung Tumor Growth and Metastasis. *Ann. N. Y. Acad. Sci.* **1138**, 65–72 (2008).

25. Kohl, R. R., Kolozsvary, A., Brown, S. L., Zhu, G. & Kim, J. H. Differential Radiation Effect in Tumor and Normal Tissue after Treatment with Ramipril, an Angiotensin-Converting Enzyme Inhibitor. *Radiat. Res.* **168**, 440–445 (2007).

26. Yang, Y. *et al.* Enalapril overcomes chemoresistance and potentiates antitumor efficacy of 5-FU in colorectal cancer by suppressing proliferation, angiogenesis, and NF-κB/STAT3-regulated proteins. *Cell Death Dis.* **11**, 477 (2020).

27. Koh, S. L. *et al.* Blockade of the renin–angiotensin system inhibits growth of colorectal cancer liver metastases in the regenerating liver. *Clin. Exp. Metastasis* **31**, 395–405 (2014).

28. Riddiough, G. E. *et al.* Captopril, a Renin–Angiotensin System Inhibitor, Attenuates Tumour Progression in the Regenerating Liver Following Partial Hepatectomy. *International Journal of Molecular Sciences* vol. 23 at https://doi.org/10.3390/ijms23095281 (2022).

29. Vallejo Ardila, D. L. *et al.* Immunomodulatory effects of renin-angiotensin system inhibitors on T lymphocytes in mice with colorectal liver metastases. *J. Immunother. cancer* **8**, (2020).

30. Kochi, T. *et al.* Preventive effects of the angiotensin-converting enzyme inhibitor, captopril, on the development of azoxymethane-induced colonic preneoplastic lesions in diabetic and hypertensive rats. *Oncol. Lett.* **8**, 223–229 (2014).

31. Wen, S. W., Ager, E. I., Neo, J. & Christophi, C. The renin angiotensin system regulates Kupffer cells in colorectal liver metastases. *Cancer Biol. Ther.* **14**, 720–727 (2013).

32. Wysocki, P. J. *et al.* Captopril, an Angiotensin-Converting Enzyme Inhibitor, Promotes Growth of Immunogenic Tumors in Mice. *Clin. Cancer Res.* **12**, 4095–4102 (2006).

33. Li, W. *et al.* Combining losartan with radiotherapy increases tumor control and inhibits lung metastases from a HER2/neu-positive orthotopic breast cancer model. *Radiat. Oncol.* **16**, 48 (2021).

34. Mainetti, L. E. *et al.* Losartan improves the therapeutic effect of metronomic cyclophosphamide in triple negative mammary cancer models. *Oncotarget* **11**, 3048–3060 (2020).

35. Cai, X.-J. *et al.* Candesartan treatment enhances liposome penetration and anti-tumor effect via depletion of tumor stroma and normalization of tumor vessel. *Drug Deliv. Transl. Res.* **11**, 1186–1197 (2021).

36. Takiguchi, T. *et al.* Angiotensin II promotes primary tumor growth and metastasis formation of murine TNBC 4T1 cells through the fibroblasts around cancer cells. *Eur. J. Pharmacol.* **909**, 174415 (2021).

37. Ma, Y. *et al.* AGTR1 promotes lymph node metastasis in breast cancer by upregulating CXCR4/SDF-1α and inducing cell migration and invasion. *Aging (Albany. NY).* **11**, 3969–3992 (2019).

38. Coulson, R. *et al.* The angiotensin receptor blocker, Losartan, inhibits mammary tumor development and progression to invasive carcinoma. *Oncotarget* **8**, 18640–18656 (2017).

39. Xia, T. *et al.* Losartan loaded liposomes improve the antitumor efficacy of liposomal paclitaxel modified with pH sensitive peptides by inhibition of collagen in breast cancer. *Pharm. Dev. Technol.* **23**, 13–21 (2018).

40. Oh, E. *et al.* Overexpression of angiotensin II type 1 receptor in breast cancer cells induces epithelial-mesenchymal transition and promotes tumor growth and angiogenesis. *Biochim. Biophys. Acta* **1863**, 1071–1081 (2016).

41. Rhodes, D. R. *et al.* AGTR1 overexpression defines a subset of breast cancer and confers sensitivity to losartan, an AGTR1 antagonist. *Proc. Natl. Acad. Sci. U. S. A.* **106**, 10284–10289 (2009).

42. Volonte, D., Sedorovitz, M., Cespedes, V. E., Beecher, M. L. & Galbiati, F. Cell autonomous angiotensin II signaling controls the pleiotropic functions of oncogenic K-Ras. *J. Biol. Chem.* **296**, (2021).

43. Tabatabai, E. *et al.* Inhibition of angiotensin II type 1 receptor by candesartan reduces tumor growth and ameliorates fibrosis in colorectal cancer. *EXCLI J.* **20**, 863–878 (2021).

44. Hashemzehi, M. *et al.* Angiotensin receptor blocker Losartan inhibits tumor growth of colorectal cancer. *EXCLI J.* **20**, 506–521 (2021).

45. Dougherty, U. *et al.* Losartan and Vitamin D Inhibit Colonic Tumor Development in a Conditional Apc-Deleted Mouse Model of Sporadic Colon Cancer. *Cancer Prev. Res.* **12**, 433–448 (2019).

46. Asgharzadeh, F. *et al.* Inhibition of angiotensin pathway via valsartan reduces tumor growth in models of colorectal cancer. *Toxicol. Appl. Pharmacol.* **440**, 115951 (2022).

47. Stevens, S. C. W. *et al.* Losartan treatment attenuates tumor-induced myocardial dysfunction. *J. Mol. Cell. Cardiol.* **85**, 37–47 (2015).

48. Ishikane, S. *et al.* Angiotensin II promotes pulmonary metastasis of melanoma through the activation of adhesion molecules in vascular endothelial cells. *Biochem. Pharmacol.* **154**, 136–147 (2018).

49. Otake, A. H. *et al.* Inhibition of angiotensin II receptor 1 limits tumor-associated angiogenesis and attenuates growth of murine melanoma. *Cancer Chemother. Pharmacol.* **66**, 79–87 (2010).

50. Alhusban, A. *et al.* Clinically relevant doses of candesartan inhibit growth of prostate tumor xenografts in vivo through modulation of tumor angiogenesis. *J. Pharmacol. Exp. Ther.* **350**, 635–645 (2014).

51. Takahashi, S. *et al.* Therapeutic targeting of angiotensin II receptor type 1 to regulate androgen receptor in prostate cancer. *Prostate* **72**, 1559–1572 (2012).

52. Leung, W.-H. *et al.* Modulation of NKG2D ligand expression and metastasis in tumors by spironolactone via RXRγ activation. *J. Exp. Med.* **210**, 2675–2692 (2013).

53. Zhou, J. *et al.* Sodium-glucose co-transporter-2 (SGLT-2) inhibition reduces glucose uptake to induce breast cancer cell growth arrest through AMPK/mTOR pathway. *Biomed. Pharmacother.* **132**, 110821 (2020).

54. Nasiri, A. R., Rodrigues, M. R., Li, Z., Leitner, B. P. & Perry, R. J. SGLT2 inhibition slows tumor growth in mice by reversing hyperinsulinemia. *Cancer Metab.* **7**, 10 (2019).

55. Korfhage, J. *et al.* Canagliflozin Increases Intestinal Adenoma Burden in Female ApcMin/+ Mice. *J. Gerontol. A. Biol. Sci. Med. Sci.* **77**, 215–220 (2022).

56. Scafoglio, C. *et al.* Functional expression of sodium-glucose transporters in cancer. *Proc. Natl. Acad. Sci. U. S. A.* **112**, E4111-9 (2015).

Supplementary table 3

Effects of BBs on cancer assessed *in vitro*							
Cancer type	**Study**	**Cell line**	**Treatment**	**Tumor growth measurement**	**Major outcomes by BB**	**Suggested mechanism of action**	**Synergism**
Breast cancer	**S. Jdeed et al. (2022)**[1]	MCF10DCIS.com	carvedilol 100 nmol/L for 4 days	fluorescent cell counting with DAPI, clonigenic assay	enhanced antiproliferative effect	normalized ARIDA1A levels	bex +carvedilol combination: markedly stronger inhibition of proliferation
		MCF-7	carvedilol 100 nmol/L for 5 days	fluorescent cell counting with DAPI, clonigenic assay	modestly suppressed growth	enriched ARID1A genomic occupancy at regulatory regions of the IGF-1 pathway	bex + carvedilol combination: markedly stronger inhibition of proliferation
Breast cancer	**R. D. Gillis et al. (2021)**[2]	4T1.2	carvedilol 10 pM-1 µM for 10 min	cyclic adenosine monophosphate assay	prevents tumour cell invasion	-	isoprenaline+carvedilol combination: antagonised isoprenaline-induced cAMP production, isoprenaline-stimulated MMP2 expression and CRE activation
		MDA-MB-231	carvedilol 10 pM-1 µM for 10 min	cyclic adenosine monophosphate assay	prevents tumour cell invasion	-	isoprenaline+carvedilol combination: antagonised isoprenaline-induced cAMP production, isoprenaline-stimulated MMP2 expression and CRE activation
Breast cancer	**W-Y. Xie et al. (2019)**[3]	MDA-MB-231	propranolol 100, 200 and 400 µM for for 24, 48 and 72 h	Alamar Blue assay, annexin V-FITC apoptosis assay	inhibited cell viability	increased number of in G0/G1 phase and induced apoptosis	-
		MDA-MB-231	metoprolol 100, 200 and 400 µM for for 24, 48 and 72 h	alamar blue assay, annexin V-FITC apoptosis assay	no notable effect	-	-
Breast cancer	**Z. Ma et al. (2019)**[4]	MCF-10A	carvedilol 0.5-10 µmol/l for 48h	determination of intracellular ROS levels, single cell gel electrophoresis (comet assay)	BB was used only in combination with BaP	-	BaP+carvedilol combination: inhibits BaP-induced change in MDM2 and p53 expression levels MDM2, DNA damage and ROS production by PI3K/AKT signaling pathway
Breast cancer	**A. Montoya et al. (2017)**[5]	SKBR3	propranolol 10-200 µM for 48h	alamar blue assay	disrupted cell proliferation	decreased phosphorylation MAPKs and CREB and increased phosphorylation of AKT, GSK3 and p53	-
		SKBR3	carvedilol 10-200 µM for 48h	alamar blue assay	reduces proliferative index	-	-
		SKBR3	esmolol 10-200 µM for 48h	alamar blue assay	reduces proliferative index	less effective then non-selective β-blockers	esmolol+butaxamine and esmolol+ICI-118,551 combination: failed to produce synergy
		SKBR3	nebivolol 10-200 µM for 48h	alamar blue assay	reduces proliferative index	more effective then selective β-blockers	-
		SKBR3	atenolol 10-200 µM for 48h	alamar blue assay	reduces proliferative index	less effective then non-selective β-blockers	atenolol+butaxamine and atenolol+ICI-118,551 combination: failed to produce synergy

		AU565	propranolol 10-200 µM for 48h	alamar blue assay	reduces proliferative index	-	-
		BTS549	propranolol 10-200 µM for 48h	alamar blue assay	reduces proliferative index	-	-
		HCC38	propranolol 10-200 µM for 48h	alamar blue assay	reduces proliferative index	-	-
		HCC70	propranolol 10-200 µM for 48h	alamar blue assay	reduces proliferative index	-	-
		MDA-MB-231	propranolol 10-200 µM for 48h	alamar blue assay	reduces proliferative index	-	-
		MDA-MB-361	propranolol 10-200 µM for 48h	alamar blue assay	reduces proliferative index	-	-
		MDA-MB-175	propranolol 10-200 µM for 48h	alamar blue assay	reduces proliferative index	-	-
Breast cancer	**C. Choy et al. (2016)**[6]	MDA-MB-231	propranolol 33.3 µM for 5 days	cell counting	decreased the rate of cell proliferation	-	propranolol+terbutaline sulfate combination: eliminated increased proliferation effect
		MDA-MB-231Br	propranolol 33.3 µM for 5 days	cell counting	decreased the rate of cell proliferation	-	propranolol+terbutaline sulfate combination: eliminated increased proliferation effect
Breast cancer	**G. Talarico et al. (2016)**[7]	MDA-MB-436	atenolol 500 µM for 48 and 72h	7-AAD flow cytometry apoptosis assay	not or marginally increased apoptotic frequency	-	-
		ZR-75-1	atenolol 500 µM for 48 and 72h	7-AAD flow cytometry apoptosis assay	not or marginally increased apoptotic frequency	-	metformin+atenolol combination: mediated activation of AMPK
Breast cancer	**T. A. D. Smith et al. (2016)**[8]	SKBR3	carvedilol 25 ng/ml for 72 h	MTT assay	BB was used only in combination with doxorubicin and with or without trastuzumab	-	doxorubicin+carvedilol and doxorubicin+carvedilol+trastuzumab: not interfere growth-inhibitory effect
		BT474	carvedilol 25 ng/ml for 72 h	MTT assay	BB was used only in combination with doxorubicin and with or without trastuzumab	-	doxorubicin+carvedilol and doxorubicin+carvedilol+trastuzumab: not interfere growth-inhibitory effect
Breast cancer	**J. M. Wilson et al. (2015)**[9]	MDA-MB-231	propranolol 10, 25, 50 µM for 72 hours	thymidine proliferation assay	no significant differences in cell proliferation	-	-
Breast cancer	**G. Dezong et al. (2014)**[10]	MCF-7	carvedilol 0.1, 1.0, and 5.0 µmol/L for 48h + NE	migration and invasion assay (membrane invasion culture system)	BB was used only in combination with norepinephrine	decreased potential of migration and invasion	norepinephrine+carvedilol combination: inhibited mainly PKCδ-Src pathway also cAMP/PKA-Src pathway
		MDA-MB-231	carvedilol 0.1, 1.0, and 5.0 µmol/L for 48h + NE	migration and invasion assay (membrane invasion culture system)	BB was used only in combination with norepinephrine	decreased potential of migration and invasion	norepinephrine+carvedilol combination: inhibited cAMP/PKA-Src pathway

Breast cancer	**M. Szewczyk et al. (2012)**[11]	MCF-7	bisoprolol for 24h	BrDU assay, LDH assay	low cytotoxic impact and no influenced cell growth+	-	-
		BT20	bisoprolol for 24h	BrDU assay, LDH assay	low cytotoxic impact with decreased cell growth	-	-
		MCF-7	propranolol for 24h	BrDU assay, LDH assay	highly cytotoxic impact with strong decrease of cell proliferation	-	-
		BT20	propranolol for 24h	BrDU assay, LDH assay	highly cytotoxic impact with strong decrease of cell proliferation	-	-
Colorectal cancer	**J. Hu et al. (2021)**[12]	HCT116	propranolol (20, 40, 60, 80, 100, 120, and 160 μM; 25, 50, 100, 150, 200, 250, and 300 μM) for 48h	CCK-8 assay	inhibition of proliferation, apoptosis induction	-	T1012G+propranolol combination: enhanced inhibition of cell viability
		Widr	propranolol (20, 40, 60, 80, 100, 120, and 160 μM; 25, 50, 100, 150, 200, 250, and 300 μM) for 48h	CCK-8 assay	inhibition of proliferation, apoptosis induction	-	T1012G+propranolol combination: enhanced inhibition of cell viability
		MC38	propranolol (20, 40, 60, 80, 100, 120, and 160 μM; 25, 50, 100, 150, 200, 250, and 300 μM) for 48h	CCK-8 assay	inhibition of proliferation, apoptosis induction	-	T1012G+propranolol combination: enhanced inhibition of cell viability
		CT26WT	propranolol (20, 40, 60, 80, 100, 120, and 160 μM; 25, 50, 100, 150, 200, 250, and 300 μM) for 48h	CCK-8 assay	inhibition of proliferation, apoptosis induction	-	T1012G+propranolol combination: enhanced inhibition of cell viability
Colorectal cancer	**M. Coelho et al. (2015)**[13]	HT-29	propranolol 0.1-100 μM for for 12 or 24h	MTS assay, MTT assay	decreased cell proliferation	-	adrenaline+propranolol combination: reduced AD-induced cell proliferation, isoprenalin+propranolol combination: decreased cell proliferation stimulated by ISO
		HT-29	carvedilol 0.1-100 μM for for 12 or 24h	MTS assay, MTT assay	no significant decrease in cell proliferation	-	carvedilol+adrenaline and carvedilol+isoprenaline combination: reversing the proliferative effects of AD and ISO

		HT-29	atenolol 0.1-100 µM for for 12 or 24h	MTS assay, MTT assay	decreased cell proliferation	-	atenolol+adrenaline and atenolol+isoprenaline combination: blocked AD- and ISO-induced cell proliferation
Lung cancer	**M. Sidorova et al. (2022)**[14]	A549	atenolol 500 µM for 72h	MTT assay, colony formation assay	reduced cell viability	induced apoptosis	-
		H1299	atenolol 500 µM for 72h	MTT assay, colony formation assay	reduced cell viability, no reduction in number of colonies	induced both apoptosis and necrosis	-
		A549	betaxolol 500 µM for 72h	MTT assay, colony formation assay	strongly reduced cell viability, strongest completely suppressed colony formation ability	induced apoptosis	-
		H1299	betaxolol 500 µM for 72h	MTT assay, colony formation assay	strongly reduced cell viability, completely suppressed colony formation ability	induced both apoptosis and necrosis	-
		A549	esmolol 500 µM for 72h	MTT assay, colony formation assay	reduced cell viability, slightly stronger inhibited growth of cell colonies	induced apoptosis	-
		H1299	esmolol 500 µM for 72h	MTT assay, colony formation assay	reduced cell viability, slightly stronger inhibited growth of cell colonies	induced both apoptosis and necrosis	-
		A549	metoprolol 500 µM for 72h	MTT assay, colony formation assay	slightly stronger reduced cell viability, slightly stronger inhibited growth of cell colonies	induced apoptosis	-
		H1299	metoprolol 500 µM for 72h	MTT assay, colony formation assay	reduced cell viability, slightly stronger inhibited growth of cell colonies	induced both apoptosis and necrosis	-
		A549	pindolol 500 µM for 72h	MTT assay, colony formation assay	reduced cell viability, inhibited growth of cell colonies	induced apoptosis	-
		H1299	pindolol 500 µM for 72h	MTT assay, colony formation assay	reduced cell viability, inhibited growth of cell colonies	induced both apoptosis and necrosis	-

		A549	propranolol 500 µM for 72h	MTT assay, colony formation assay	strongly reduced cell viability, completely suppressed colony formation ability	induced apoptosis	-
		H1299	propranolol 500 µM for 72h	MTT assay, colony formation assay	most reduced cell viability, completely suppressed colony formation ability	induced both apoptosis and necrosis	-
		A549	timolol 500 µM for 72h	MTT assay, colony formation assay	reduced cell viability, inhibited growth of cell colonies	induced apoptosis	-
		H1299	timolol 500 µM for 72h	MTT assay, colony formation assay	reduced cell viability, inhibited growth of cell colonies	induced both apoptosis and necrosis	-
Lung cancer	**M. Niu et al. (2021)**[15]	H1975	nebivolol	MTS assay	strongly inhibited cell viability	upregulated FBXL2 and downregulated EGFR expression	-
		PC-9	nebivolol 10 µM for 48h	MTS assay	strongly inhibited cell viability	upregulated FBXL2 and downregulated EGFR expression	-
Lung cancer	**K. R. Chaudhary et al. (2019)**[16]	PC-9	propranolol 50 µM + radiation	clonigenic assay	decreased clonogenic survival	downregulates p-PKA, sensitizes to direct cytotoxic effects of radiation	propranolol+cisplatin combination: further decrease of clonogenic survival
		A549	propranolol 50 µM + radiation	clonigenic assay	decreased clonogenic survival	downregulates p-PKA, sensitizes to direct cytotoxic effects of radiation	propranolol+cisplatin combination: further decrease of clonogenic survival
		PC9	propranolol 1 µM + radiation	clonigenic assay	no significant impact on clonogenic survival	-	-

		A549	propranolol 1 µM + radiation	clonigenic assay	no significant impact on clonogenic survival	-	-
Lung cancer	**M. B. Nilsson et al. (2017)**[17]	HCC827	propranolol 1 µM one hour before NE + erlotinib for 24h	MTS assay	BB was used only in combination with norepinephrine	blocked effect on EGFR TKI resistance	norepinephrine+propranolol combination: abrogated NE-induced inactivation of LKB1 and blocked IL-6
Lung cancer	**A. Chang et al. (2015)**[18]	A549	carvedilol 1, 10, 30 µM	anchorage-independent growth assay in soft agar, SRB assay	inhibited colony formation at high concentrations	decreased viability and cell mobility	-
Lung cancer	**G-H. Deng et al. (2014)**[19]	A549	propranolol 10 µM 30 minutes before adding NE for 6h	ELISA	blocked NE-induced upregulation of VEGF, IL-8, and IL-6 protein levels	-	-
Melanoma	**L. S. Farhoumand et al. (2022)**[20]	Mel270	sotalol for 7days	spheroid viability assay (ATP luminescence assay)	no effect on spheroid viability	-	-
		Mel270	timolol for 7days	spheroid viability assay (ATP luminescence assay)	no effect on spheroid viability	-	-
		Mel270	pindolol for 7days	spheroid viability assay (ATP luminescence assay)	no effect on spheroid viability	-	-
		Mel270	propranolol 150 µM for 7days	spheroid viability assay (ATP luminescence assay)	decreased spheroid viability in a concentration-dependent manner	-	-
		Mel270	labetolol 150 µM for 7days	spheroid viability assay (ATP luminescence assay)	decreased spheroid viability in a concentration-dependent manner	main anti-tumor mechanism due to α receptor blocking	-
		Mel270	carvedilolol 10-50 µM µM for 48h and 7days	spheroid viability assay (ATP luminescence assay), cell viability assay	most potently decreased spheroid viability in a concentration-dependent manner	main anti-tumor mechanism due to α receptor blocking by inducing apoptotic pathways	-
		92-1	carvedilolol 10-50 µM for 7days	spheroid viability assay (ATP luminescence assay)	reduced spheroid viability	higher concectration needed because of lower penetration of larger tumors	-
		UPMD2	carvedilolol 10-50 µM µM for 7days	spheroid viability assay (ATP luminescence assay)	blocked spheroid viability	-	-

		UPMM3	carvedilolol 10–50 µM for 7days	spheroid viability assay (ATP luminescence assay)	most blocked viability	-	carvedilol+radiation combination: completely blocked repopulation of spreading spheroid
Melanoma	**P. Bustamante (2019)**[21]	MEL270	propranolol 12.5-200 µL for 24h	trypan blue exclusion assay, CCK-8 assay	decreased cell viability in a dose-dependent manner	reduction in metabolic activity by reduced dehydrogenase activity by 50%, induction of apoptosis and cell cycle arrest (TUNEL assay)	-
		OMM2.5	propranolol 12.5-200 µL for 24h	trypan blue exclusion assay, CCK-8 assay	decreased cell viability in a dose-dependent manner	reduction in metabolic activity by reduced dehydrogenase activity by 50%	-
		MP41	propranolol 12.5-200 µL for 24h	trypan blue exclusion assay, CCK-8 assay	decreased cell viability in a dose-dependent manner	reduction in metabolic activity by reduced dehydrogenase activity by 50%, induction of apoptosis and cell cycle arrest (TUNEL assay)	-
		MP46	propranolol 12.5-200 µL for 24h	trypan blue exclusion assay, CCK-8 assay	decreased cell viability in a dose-dependent manner	reduction in metabolic activity by reduced dehydrogenase activity by 50%	-
		WM266.4	propranolol 12.5-200 µL for 24h	trypan blue exclusion assay, CCK-8 assay	decreased cell viability in a dose-dependent manner	reduction in metabolic activity by reduced dehydrogenase activity by 50%, induction of apoptosis and cell cycle arrest (TUNEL assay)	-
Melanoma	**S. Maccari et al. (2017)**[22]	B16F10	propranolol 0,01-10 µM for 24, 48 and 72 h	MTS assay	does not affect cell proliferation	-	-
Melanoma	**C. Zhou et al. (2016)**[23]	A375	propranolol 25-400 µM for 24h, 48h and 72h	alamar blue assay	reduced cell proliferation	induced cell cycle arrest, activated mitochondria-mediated apoptosis pathway and inhibited MAPK pathway	-
		P-3 (acral human patient)	propranolol 25-400 µM for 24h, 48h and 72h	alamar blue assay	reduced cell proliferation	-	-
Prostate cancer	**D. Palm et al. (2006)**[24]	PC-3-luc cells	propranolol 10 µM for 4 days	cell counting	no measurable influence on the proliferation	-	propranolol+norepinephrine combination: inhibited NE-induced increase of migratory activity

Effects of ACEIs on cancer assessed *in vitro*							
Cancer type	**Study**	**Cell line**	**Treatment**	**Tumor growth measurement**	**Major outcomes by BB**	**Suggested mechanism of action**	**Synergism**
Breast cancer	**F. Rasha et al. (2020)**[25]	MCF-7	captopril 100 µM for 24–72h	MTT assay	did not alter markers of cancer cell growth	-	-
		MDA-MB-231	captopril 100 µM for 24–72h	MTT assay	did not alter markers of cancer cell growth	reduced markers of inflammation	-
Breast cancer	**T. A. D. Smith at el. (2016)**[8]	SKBR3	enalapril 5 µM, 25 ng/ml, 250 ng/ml and 5 µg/ml for 72h	MTT assay	ACEI was used only in combination with doxorubicin and with or without trastuzumab	-	doxorubicin+enalapril and doxorubicin+trastuzumab+enalapril combination: did not interfere with the growth-inhibitory effect of doxorubicin alone nor in combination with trastuzumab
		BT474	enalapril 5 µM, 25 ng/ml, 250 ng/ml and 5 µg/ml for 72h	MTT assay	ACEI was used only in combination with doxorubicin and with or without trastuzumab	-	doxorubicin+enalapril and doxorubicin+trastuzumab+enalapril combination: did not interfere with the growth-inhibitory effect of doxorubicin alone nor in combination with trastuzumab
Breast cancer	**S. Namazi et al. (2014)**[26]	MCF-7	medium containing either 100 µmol/L captopril + 1 µmol/L TAM for 96h	MTT assay	reduced number of viable	-	captopril+losartan combination: increased inhibitory effect of TAM
		TAM-R	medium containing either 100 µmol/L captopril + 1 µmol/L TAM	MTT assay	MTT could not be performed	led to cell death	captopril+losartan combination: led to cell death
Breast cancer	**E. Napoleone et al. (2012)**[27]	MDA-MB-231	captopril 10 µg/ml for 6h	MTT assay	no cytotoxic effect	dose-dependent inhibition of TF activity	-
Breast cancer	**R. E. Brown et al. (2004)**[28]	SKBR-3	captopril 3 and 9 mM for 4days	MTS assay	inhibitory effects on cell growth in a dose-dependant manner	decrease in p-ERK1/2 and p-JNK	-
		MDA-175	captopril 3 and 9 mM for 4days	MTS assay	strongest inhibitory effects on cell growth in a dose-dependant manner	decrease in p-Akt and an increase in p-ERK1/2 and p-JNK	-
		MDA-231	captopril 3 and 9 mM for 4days	MTS assay	inhibitory effects on cell growth in a dose-dependant manner	decrease in p-JNK	-
Colorectal cancer	**Y. Yang et al. (2020)**[29]	SW620	enalapril 0-2000 µM for 48 or 72 h	MTT assay, Annexin V/PI apopotosis assay	not significantly affect cell viability	no significant effect on cell apoptosis	5-FU+enalaprilcombination: extremely decreased cell viability and more profound apoptosis

		HCT116	enalapril 0-2000 μM for 48 or 72 h	MTT assay, Annexin V/PI apopotosis assay	not significantly affect cell viability	no significant effect on cell apoptosis	5-FU+enalaprilcombination: extremely decreased cell viability and more profound apoptosis
		P1 (median 5-FU-resistant)	enalapril 0-2000 μM for 48 or 72 h	MTT assay, Annexin V/PI apopotosis assay	-	-	5-FU+enalaprilcombination: extremely suppressed cell growth
		P2 (5-FU-resistant)	enalapril 0-2000 μM for 48 or 72 h	MTT assay, Annexin V/PI apopotosis assay	-	-	5-FU+enalaprilcombination: extremely suppressed cell growth
		P3 (5-FU-resistant)	enalapril 0-2000 μM for 48 or 72 h	MTT assay, Annexin V/PI apopotosis assay	-	-	5-FU+enalaprilcombination: extremely suppressed cell growth
Colorectal cancer	**Y. Lu et al. (2019)**[30]	HT-29	S-nitrosocaptopril 0.1-1000 μM for 24h	MTT assay	no statistically significant changes in cell viability	indicating that IC50 was greater than 1000 μM	-
Colorectal cancer	**Y. Lu et al. (2014)**[31]	HT-29	S-nitrosocaptopril 0.1-1000 μM for 24h	MTT assay	could not reach the inhibitory IC50 values	indicating that the IC50 was greater than 1000 μM	-
Melanoma	**Y. Lu et al. (2019)**[30]	B16F10	S-nitrosocaptopril 0.1-1000 μM for 24h	MTT assay	no statistically significant changes in cell viability	indicating that IC50 was greater than 1000 μM	-

Effects of ARBs on cancer assessed *in vitro*							
Cancer type	**Study**	**Cell line**	**Treatment**	**Tumor growth measurement**	**Major outcomes by BB**	**Suggested mechanism of action**	**Synergism**
Breast cancer	**F. Rasha et al. (2020)**[25]	MCF-7	telmisartan 10 µM for 24-72h	MTT assay	ARB was used only in combination with angiotensin2	-	angiotensin2+telmisartan combination: blocked Ang2 effects by reducing IL-6 secretion
		MDA-MB-231	telmisartan 10 µM for 24-72h	MTT assay	ARB was used only in combination with angiotensin2	-	angiotensin2+telmisartan combination: blocked Ang2 effects by reducing IL-6 secretion
Breast cancer	**S. Ni et al. (2020)**[32]	T-47D	candesartan cilexetic 5 µM, 10 µM, 15 µM, and 20 µM for 48 h or 10 days	cell proliferation (CCK-8 assay) and cell clonogenic assay	decreased proliferation	inhibiting effect related to unique structure and irrelevant to A2T1R antagonistic effect	-
		MCF-7	candesartan cilexetic 5 µM, 10 µM, 15 µM, and 20 µM for 48 h or 10 days	cell proliferation (CCK-8 assay) and cell clonogenic assay, apoptosis assay (Annexin-V/PI assay)	decreased proliferation	inhibiting effect related to unique structure and irrelevant to A2T1R antagonistic effect	-
Breast cancer	**M. A. Redondo-Müller et al. (2008)**[33]	MCF7	losartan 0.005-25 µM for 48h	XTT assay	no inhibitory effect	-	-
		MDA-MB-231	losartan 0.005-25 µM for 48h	XTT assay	no inhibitory effect	-	-
		T47D	losartan 0.005-25 µM for 48h	XTT assay	43% inhibition at 25 µM	-	-
Breast cancer	**S. Namazi et al. (2014)**[26]	MCF-7	losartan 10 µM	MTT assay	reversal of tamoxifen resistance in combination with captopril	-	captopril+losartan+tamoxifen combination: led to cell death and reversal of tamoxifen resistance
Breast cancer	**N. Du et al. (2012)**[34]	MCF-7	irbesartan 0.1-100 µM for 30 min before Ang2 for 24h	MTT assay	inhibition of angiotensin II mediated proliferation	greatest inhibition of Ang2-mediated cell proliferation in a dose-dependent manner	angiotensin2+irbesartan combination: suppression of ANG II effects on proliferation and cell cycle

		MCF-7	losartan 0.1-100 µM for 30 min before Ang2 for 24h	MTT assay	inhibition of angiotensin II mediated proliferation	inhibited Ang2-mediated cell proliferation in a dose-dependent manner	angiotensin2+losartan combination: suppression of ANG II effects on proliferation and cell cycle
		MCF-7	valsartan 0.1-100 µM for 30 min before Ang2 for 24h	MTT assay	inhibition of angiotensin II mediated proliferation	inhibited Ang2-mediated cell proliferation in a dose-dependent manner	angiotensin2+valsartan combination: suppression of ANG II effects on proliferation and cell cycle
		MCF-7	candesartan 0.1-100 µM for 30 min before Ang2 for 24h	MTT assay	inhibition of angiotensin II mediated proliferation	inhibited Ang2-mediated cell proliferation in a dose-dependent manner	angiotensin2+candesartan combination: suppression of ANG II effects on proliferation and cell cycle
Colorectal cancer	**F. Asgharzadeh et al. (2022)**[35]	CT26	valsartan 1 nM-10 mM for 24h	MTT assay, cell scratch assay	dose-dependently inhibited cell proliferation and migration	modulates ROS formation and oxidative stress	5-FU+valsartan combination: decreased the IC50 value of 5-FU
Colorectal cancer	**E. Tabatabai et al. (2021)**[36]	CT-26	candesartan 0-1000 µM for 24h	growth inhibition (MTT) assay	inhibited cell viability in dose-dependent manner	induced cell death, decreased MMP-3 and MMP-9 expression and increased E-cadherin expression	-
		SW-480	candesartan 0-1000 µM for 24h	growth inhibition (MTT) assay	inhibited cell viability in dose-dependent manner	induced cell death, decreased MMP-3 and MMP-9 expression and increased E-cadherin expression	-
Colorectal cancer	**M. Hashemzehi et al. (2021)**[37]	CT-26	Losartan 0-1000 µM for 24h	MTT assay	decreased cell viability in a concentration-dependent manner, decreased spheroid size and induced tumor shrinkage	induced cell toxicity and apoptosis by upregulating mRNA levels of key pro-apoptotic genes including P53 and BAX, downregulated PI3K, AKT and cyclin D1 expression in a time-dependent manner	-

Lung cancer	**S. Ni et al. (2020)**[32]	A549	candesartan cilexetic 5 μM, 10 μM, 15 μM, and 20 μM for 48 h or 10 days	CCK-8 assay, cell clonogenic assay	inhibited cell proliferation and clonogenic survival in a dose-dependent manner	neddylation inhibition, induced cancer cell apoptosis by increasing total numbers of early and late apoptotic and cleaved-PARP	-
		EKVX	candesartan cilexetic 5 μM, 10 μM, 15 μM, and 20 μM for 48 h or 10 days	CCK-8 assay, cell clonogenic assay	decreased proliferation	inhibiting effect related to unique structure and irrelevant to A2T1R antagonistic effect	-
		H1299	candesartan cilexetic 5 μM, 10 μM, 15 μM, and 20 μM for 48 h or 10 days	CCK-8 assay, cell clonogenic assay	decreased proliferation	inhibiting effect related to unique structure and irrelevant to A2T1R antagonistic effect	-
Lung cancer	**V. R. Martínez et al. (2018)**[38]	A549	losartan 2.5, 5, 10, 25, 50, 75, 100, 250, and 500 μM for 24 h	MTT assay	no siginificant effect	-	ZnLos combination: declined cell proliferation in a dose-dependent manner
Lung cancer	**M. Rasheduzzaman et al. (2018)**[39]	A549	candesartan 2.5, 5, 10 μM for 12h	cell viability test, Annexin V assay	ARB was used only in combination with TRAIL	-	TRAIL+candesartan combination: increased observation of apoptotic cell morphologies, induced apoptosis in a dose-dependent manner, decreased cell viability
		HCC-15	candesartan 2.5, 5, 10 μM for 12h	cell viability test, Annexin V assay	ARB was used only in combination with TRAIL	-	TRAIL+candesartan combination: increased observation of apoptotic cell morphologies, induced apoptosis in a dose-dependent manner, decreased cell viability
Melanoma	**D. N. Olschewski et al. (2018)**[40]	MV3	losartan 0.7 μmol/l for 24h	cell counting	no significant effect	-	ATII+losartan combination: no significant effect
Prostate cancer	**Y. Woo et al. (2017)**[41]	PC3	fimasartan 100, 200 and 400 μM for 48 and 72h	WST-1 assay	reduced cell viability with greatest cytotoxicity	induced autophagy by increased LC3-II ecxpression, induced anti-migratory activity	-
		DU145	fimasartan 100, 200 and 400 μM for 48 and 72h	WST-1 assay	reduced cell viability with greatest cytotoxicity	induced anti-migratory activity	-

		LNCap-LN3	fimasartan 100, 200 and 400 µM for 48 and 72h	WST-1 assay	reduced cell viability with greatest cytotoxicity	-	-
		PC3	losartan 100, 200 and 400 µM for 48 and 72h	WST-1 assay	reduced cell viability	induced autophagy by increased LC3-II ecxpression	-
		DU145	losartan 100, 200 and 400 µM for 48 and 72h	WST-1 assay	reduced cell viability	-	-
		LNCap-LN3	losartan 100, 200 and 400 µM for 48 and 72h	WST-1 assay	reduced cell viability	-	-
		PC3	eprosartan 100, 200 and 400 µM for 48 and 72h	WST-1 assay	reduced cell viability	induced autophagy by increased LC3-II ecxpression	-
		DU145	eprosartan 100, 200 and 400 µM for 48 and 72h	WST-1 assay	reduced cell viability	-	-
		LNCap-LN3	eprosartan 100, 200 and 400 µM for 48 and 72h	WST-1 assay	reduced cell viability	-	-
		PC3	valsartan 100, 200 and 400 µM for 48 and 72h	WST-1 assay	reduced cell viability withlowest anti-proliferative activity	induced autophagy by increased LC3-II ecxpression	-
		DU145	valsartan 100, 200 and 400 µM for 48 and 72h	WST-1 assay	reduced cell viability withlowest anti-proliferative activity	-	-
		LNCap-LN3	valsartan 100, 200 and 400 µM for 48 and 72h	WST-1 assay	reduced cell viability withlowest anti-proliferative activity	-	-
Prostate cancer	**M. S. Islas et al. (2016)**[42]	LNCaP	irbesartan 25, 50 and 100 µM for 24h	MTT assay	decreased cell viability	-	-
		DU145	irbesartan 25, 50 and 100 µM for 24h	MTT assay	decreased cell viability	-	-

Prostate cancer	**A. Alhusban et al. (2014)**[43]	PC3	candesartan 0.5, 5, 10, 25, and 200 μM for 24h and 72h	BrdU assay, MTT assay, ELISA-based apoptosis assay	induced dose-dependent antiapoptotic effect, did not have effect on the proliferation or viability	inhibited VEGF mRNA expression	-
		DU145	candesartan 0.5, 5, 10, 25, and 200 μM for 24h and 72h	na	na	inhibited VEGF mRNA expression	-
Prostate cancer	**Y-J. Da et al. (2012)**[44]	LNCap	losartan 10 μM for 24h	MTT assay	no significant effect	-	angiotensin2+losartan combination: no significant effect
Prostate cancer	**J-i. Teranishi et al. (2008)**[45]	LNCaP	olmesartan 10 μM for 30 min before Ang3 treatment for 5 days	cell counter	ARB was used only in combination with angiotensin3	suppressed cell growth induced by Ang3 treatment	angiotensin3+olmesartan combination: inhibited phosphorylation of MAPK activated by Ang3
		DU145	olmesartan 10 μM for 30 min before AngIII treatment for 5 days	cell counter	ARB was used only in combination with angiotensin3	suppressed cell growth induced by Ang3 treatment	angiotensin3+olmesartan combination: inhibited phosphorylation of MAPK activated by Ang3
Prostate cancer	**H. Ishiguro et al. (2007)**[46]	LNCaP	telmisartan 1 and 10 mM for 30 min before Ang2 treatment	MTT assay	inhibited cell growth	-	DHT+telmisartan combination: downregulated PSA expression
		DU145	telmisartan 1 and 10 mM for 30 min before Ang2 treatment	MTT assay	inhibited cell growth	attenuated phosphorylation of MAPK	DHT+telmisartan combination: downregulated PSA expression, GW9662+telmisartan combination: cell growth was also inhibited
Prostate cancer	**H. Uemura et al. (2005**[47]**)**	PC-3	losartan 10 μM for 30 min before Ang2 or EGF treatment for 5 days	cell growth analysis	no significant effect	-	-

Effects of MRAs on cancer assessed *in vitro*							
Cancer type	**Study**	**Cell line**	**Treatment**	**Tumor growth measurement**	**Major outcomes by MRAs**	**Suggested mechanism of action**	**Synergism**
Colorectal cancer	**W-H. Leung et al. (2013)**[49]	HCT116	spironolactone 56 μM for 24h	comet assay	decrease in DNA breakage	induced ATM–ATR pathways and NKG2DL expression requiring RXRγ activation	-
		HCT116	spironolactone 56 μM for 5 days	cytotoxicity assay	not affecting cell viability	upregulated NKG2DLs, increased ULBP2 expression in a dose-dependent manner	-
		SW480	spironolactone 56 μM for 5 days	cytotoxicity assay	not affecting cell viability	increased ULBP2 and ULBP1 expression in a dose-dependent manner, enhanced primary NK cell-mediated lysis	-
		HT29	spironolactone 56 μM for 5 days	cytotoxicity assay	not affecting cell viability	increased ULBP2 expression in a dose-dependent manner, enhanced primary NK cell-mediated lysis	-
		HCT15	spironolactone 56 μM for 5 days	cytotoxicity assay	not affecting cell viability	increased ULBP2 and ULBP1 expression in a dose-dependent manner	-
Lung cancer	**T. Sanomachi et al. (2019)**[50]	A549	spironolactone 25, 50 and 100 μM for 3 days	Trypan blue exclusion assay	induced cell death and inhibited cell growth	-	gemcitabine+spironolactone and osimertinib+spironolactone combination: spironolactone reversed resistance
		PC-9	spironolactone 25, 50 and 100 μM for 3 days	Trypan blue exclusion assay	induced cell death and inhibited cell growth	-	gemcitabine+spironolactone and osimertinib+spironolactone combination: spironolactone reversed resistance
		PC-9-(osimertinib resistant)	spironolactone 25, 50 and 100 μM for 3 days	Trypan blue exclusion assay	induced cell death and inhibited cell growth	-	gemcitabine+spironolactone and osimertinib+spironolactone combination: spironolactone reversed resistance
		A549 cancer stem cell line	spironolactone 25, 50 and 100 μM for 3 days	Trypan blue exclusion assay	induced cell death and inhibited cell growth	-	-

Melanoma	**S. Sayedyahossein et al. (2021)**[51]	131/4-5B1	spironolactone 10 µM for 72h	immunoprecipitation	reduced cytoplasmic levels of both PANX1 and β-catenin	-	-
Prostate cancer	**A. Dovio et al. (2009)**[48]	LNCaP	eplerenone 1 µM for 24h	na	blocking cortisol's inhibitiory effect on IL-1β-inducible osteoprtegerin release	-	cortisol+eplerenone combination: completely reverted the effect of cortisol

Effects of SGLT2Is on cancer assessed *in vitro*							
Cancer type	**Study**	**Cell line**	**Treatment**	**Tumor growth measurement**	**Major outcomes by MRAs**	**Suggested mechanism of action**	**Synergism**
Breast cancer	**D. Papadopoli et al. (2021)**[52]	SKBR3	canagliflozin 50 μM for 24h	automated TC10 cell counting, trypan blue exclusion assay	inhibited cell proliferation	interfere with glutamine-mediated anaplerosis and inhibits glutamine metabolism largely independent of SGLT2 inhibition	-
		BT474	canagliflozin 50 μM for 24h	automated TC10 cell counting, trypan blue exclusion assay	inhibited cell proliferation	largely independent of SGLT2 inhibition	-
		NT2196	canagliflozin 50 μM for 24h	automated TC10 cell counting, trypan blue exclusion assay	modest suppression of cell proliferation	-	-
		NT2197	canagliflozin 50 μM for 24h	automated TC10 cell counting, trypan blue exclusion assay	modest suppression of cell proliferation	-	-
		SKBR3	dapagliflozin 50 μM for 24h	automated TC10 cell counting, trypan blue exclusion assay	inhibited cell proliferation	largely independent of SGLT2 inhibition	-
		BT474	dapagliflozin 50 μM for 24h	automated TC10 cell counting, trypan blue exclusion assay	inhibited cell proliferation	-	-
Breast cancer	**S. G. Eliaa et al. (2020)**[53]	MDA-MB-231	empagliflozin 0,1-100 uM/l for 24 h	MTT assay, Annexin V-FITC apoptosis assay	inhibited cell growth, increase in the percent of apoptotic	clear decline in the cell population at the S phase, interfering mTOR pathway and inhibited calmodulin	doxorubicin+empagliflozin combination: greater cell growth inhibition in a dose-dependent manner
Breast cancer	**V. Quagliariello et al. (2020)**[54]	MCF-7	empagliflozin 500 nM for 72h	MTT assay, Annexin V-FITC apopotosis assay	SGLT2I was used only in combination with ipilimumab or anti CTLA-4 antibody	-	ipilimumab+digoxin combination: ameliorated cell responsiveness to ipilimumab, anti CTLA-4+digoxin combination: increased anticancer efficacy of anti CTLA-4 antibody
		MDA-MB-231	empagliflozin 500 nM for 72h	MTT assay, Annexin V-FITC apopotosis assay	SGLT2I was used only in combination with ipilimumab or anti CTLA-4 antibody	-	ipilimumab+digoxin combination: ameliorated cell responsiveness to ipilimumab, anti CTLA-4+digoxin combination: increased anticancer efficacy of anti CTLA-4 antibody
Breast cancer	**J. Zhou et al. (2020)**[55]	MCF-7	dapagliflozin 3.67, 11, 33, 100, 300 μM for 24h and72h	MTT assay, colony formation assay	blocked cell proliferation and growth and inhibit	induced G1/G0 cell cycle arrest, inhibition of mTOR	-

					the clonogenic survival	pathway via AMPK activation	
		MCF-7	canagliflozin 3.67, 11, 33, 100, 300 µM for 72h	MTT assay	blocked cell proliferation	inhibition of mTOR pathway via AMPK activation	-
		MCF-7	canagliflozin 40 µM for 48h	MTT assay	SGLT2I was used only in combination with doxorubicin	-	doxorubicin+canagliflozin combination: increased cytotoxic activity of DOX
Breast cancer	**S. Komatsu et al. (2020)**[56]	MCF-7	ipragliflozin 0-50 µM for 0-4 days	manual cell counting, BrDU incorporation assay	decreased cell number in a dose-dependent manner	through SGLT2 inhibition, inhibited DNA synthesis	-
Lung cancer	**L. Yamamoto et al. (2021)**[57]	A549	canagliflozin 1-50 µM for 0-3 days	manual cell counting, BrDU incorporation assay	decreased cell number in a dose-dependent manner	inhibited DNA synthesis in a dose-dependent manner, attenuated cell cycle progression	-
		H520	canagliflozin 1-50 µM for 0-3 days	manual cell counting, BrDU incorporation assay	attenuated cell proliferation	-	-
		H1975	canagliflozin 1-50 µM for 0-3 days	manual cell counting, BrDU incorporation assay	attenuated cell proliferation	-	-

Supplementary table 3.: *In vitro* studies investigating the effect of guideline-directed HF pharmacotherapies on cancer.

References:

1. Jdeed, S., Erdős, E., Bálint, B. L. & Uray, I. P. The Role of ARID1A in the Nonestrogenic Modulation of IGF-1 Signaling. *Mol. Cancer Res.* **20**, 1071–1082 (2022).

2. Gillis, R. D. *et al.* Carvedilol blocks neural regulation of breast cancer progression in vivo and is associated with reduced breast cancer mortality in patients. *Eur. J. Cancer* **147**, 106–116 (2021).

3. Xie, W.-Y. *et al.* β‐blockers inhibit the viability of breast cancer by regulating the ERK/COX‐2 signaling pathway and the drug response is affected by ADRB2 single‐nucleotide polymorphisms. *Oncol. Rep.* **41**, 341–350 (2019).

4. Ma, Z., Liu, X., Zhang, Q., Yu, Z. & Gao, D. Carvedilol suppresses malignant proliferation of mammary epithelial through inhibition of the ROS‐mediated PI3K/AKT signaling pathway. *Oncol. Rep.* **41**, 811–818 (2019).

5. Montoya, A. *et al.* Use of non-selective β-blockers is associated with decreased tumor proliferative indices in early stage breast cancer. *Oncotarget* **8**, 6446–6460 (2017).

6. Choy, C. *et al.* Inhibition of β2-adrenergic receptor reduces triple-negative breast cancer brain metastases: The potential benefit of perioperative β-blockade. *Oncol. Rep.* **35**, 3135–3142 (2016).

7. Talarico, G. *et al.* Aspirin and atenolol enhance metformin activity against breast cancer by targeting both neoplastic and microenvironment. *Sci. Rep.* **6**, 18673 (2016).

8. Smith, T. A. D., Phyu, S. M. & Akabuogu, E. U. Effects of Administered Cardioprotective Drugs on Treatment Response of Breast Cancer. *Anticancer Res.* **36**, 87–93 (2016).

9. Wilson, J. M., Lorimer, E., Tyburski, M. D. & Williams, C. L. β-Adrenergic receptors suppress Rap1B prenylation and promote the metastatic phenotype in breast cancer. *Cancer Biol. Ther.* **16**, 1364–1374 (2015).

10. Dezong, G., Zhongbing, M., Qinye, F. & Zhigang, Y. Carvedilol suppresses migration and invasion of malignant breast by inactivating Src involving cAMP/PKA and PKCδ signaling pathway. *J. Cancer Res. Ther.* **10**, 998–1003 (2014).

11. Szewczyk, M., Richter, C., Briese, V. & Richter, D.-U. A retrospective in vitro study of the impact of anti-diabetics and cardioselective pharmaceuticals on breast cancer. *Anticancer Res.* **32**, 2133–2138 (2012).

12. Hu, J. *et al.* β-Adrenergic Receptor Inhibitor and Oncolytic Herpesvirus Combination Therapy Shows Enhanced Antitumoral and Antiangiogenic Effects on Colorectal Cancer. *Front. Pharmacol.* **12**, 735278 (2021).

13. Coelho, M. *et al.* Antiproliferative effects of β-blockers on human colorectal cancer. *Oncol. Rep.* **33**, 2513–2520 (2015).

14. Sidorova, M. & Petrikaitė, V. The Effect of Beta Adrenoreceptor Blockers on Viability and Cell Colony Formation of Non-Small Cell Lung Cancer Cell Lines A549 and H1299. *Molecules* **27**, (2022).

15. Niu, M. *et al.* FBXL2 counteracts Grp94 to destabilize EGFR and inhibit EGFR-driven NSCLC growth. *Nat. Commun.* **12**, 5919 (2021).

16. Chaudhary, K. R. *et al.* Effects of β-Adrenergic Antagonists on Chemoradiation Therapy for Locally Advanced Non-Small Cell Lung Cancer. *J. Clin. Med.* **8**, (2019).

17. Nilsson, M. B. *et al.* Stress hormones promote EGFR inhibitor resistance in NSCLC: Implications for combinations with β-blockers. *Sci. Transl. Med.* **9**, (2017).

18. Chang, A. *et al.* Prevention of skin carcinogenesis by the β-blocker carvedilol. *Cancer Prev. Res. (Phila).* **8**, 27–36 (2015).

19. Deng, G.-H. *et al.* Exogenous norepinephrine attenuates the efficacy of sunitinib in a mouse cancer model. *J. Exp. Clin. Cancer Res.* **33**, 21 (2014).

20. Farhoumand, L. S. *et al.* The Adrenergic Receptor Antagonist Carvedilol Elicits Anti-Tumor Responses in Uveal Melanoma 3D Tumor Spheroids and May Serve as Co-Adjuvant Therapy with Radiation. *Cancers (Basel).* **14**, (2022).

21. Bustamante, P. *et al.* Beta-blockers exert potent anti-tumor effects in cutaneous and uveal melanoma. *Cancer Med.* **8**, 7265–7277 (2019).

22. Maccari, S. *et al.* Biphasic effects of propranolol on tumour growth in B16F10 melanoma-bearing mice. *Br. J. Pharmacol.* **174**, 139–149 (2017).

23. Zhou, C. *et al.* Propranolol induced G0/G1/S phase arrest and apoptosis in melanoma via AKT/MAPK pathway. *Oncotarget* **7**, 68314–68327 (2016).

24. Palm, D. *et al.* The norepinephrine-driven metastasis development of PC-3 human prostate cancer in BALB/c nude mice is inhibited by beta-blockers. *Int. J. cancer* **118**, 2744–2749 (2006).

25. Rasha, F. *et al.* Renin angiotensin system inhibition attenuates adipocyte-breast cancer cell interactions. *Exp. Cell Res.* **394**, 112114 (2020).

26. Namazi, S. *et al.* The role of captopril and losartan in prevention and regression of tamoxifen-induced resistance of breast cancer cell line MCF-7: An in vitro study. *Biomed. Pharmacother.* **68**, 565–571 (2014).

27. Napoleone, E. *et al.* Inhibition of the renin-angiotensin system downregulates tissue factor and vascular endothelial growth factor in human breast carcinoma. *Thromb. Res.* **129**, 736–742 (2012).

28. Brown, R. E., Lun, M., Prichard, J. W., Blasick, T. M. & Zhang, P. L. Morphoproteomic and pharmacoproteomic correlates in hormone-receptor-negative breast carcinoma cell lines. *Ann. Clin. Lab. Sci.* **34**, 251–262 (2004).

29. Yang, Y. *et al.* Enalapril overcomes chemoresistance and potentiates antitumor efficacy of 5-FU in colorectal cancer by suppressing proliferation, angiogenesis, and NF-κB/STAT3-regulated proteins. *Cell Death Dis.* **11**, 477 (2020).

30. Lu, Y. *et al.* S-Nitrosocaptopril prevents cancer metastasis in vivo by creating the hostile bloodstream microenvironment against circulating tumor. *Pharmacol. Res.* **139**, 535–549 (2019).

31. Lu, Y. *et al.* Nitric oxide inhibits hetero-adhesion of cancer to endothelial: restraining circulating tumor from initiating metastatic cascade. *Sci. Rep.* **4**, 4344 (2014).

32. Ni, S. *et al.* Discovery of candesartan cilexetic as a novel neddylation inhibitor for suppressing tumor growth. *Eur. J. Med. Chem.* **185**, 111848 (2020).

33. Redondo-Müller, M. A., Stevanovic-Walker, M., Barker, S., Puddefoot, J. R. & Vinson, G. P. Anti-cancer actions of a recombinant antibody (R6313/G2) against the angiotensin II AT1 receptor. *Endocr. Relat. Cancer* **15**, 277–288 (2008).

34. Du, N. *et al.* Angiotensin II receptor type 1 blockers suppress the cell proliferation effects of angiotensin II in breast cancer by inhibiting AT1R signaling. *Oncol. Rep.* **27**, 1893–1903 (2012).

35. Asgharzadeh, F. *et al.* Inhibition of angiotensin pathway via valsartan reduces tumor growth in models of colorectal cancer. *Toxicol. Appl. Pharmacol.* **440**, 115951 (2022).

36. Tabatabai, E. *et al.* Inhibition of angiotensin II type 1 receptor by candesartan reduces tumor growth and ameliorates fibrosis in colorectal cancer. *EXCLI J.* **20**, 863–878 (2021).

37. Hashemzehi, M. *et al.* Angiotensin receptor blocker Losartan inhibits tumor growth of colorectal cancer. *EXCLI J.* **20**, 506–521 (2021).

38. Martínez, V. R. *et al.* Interaction of Zn with Losartan. Activation of Intrinsic Apoptotic Signaling Pathway in Lung Cancer and Effects on Alkaline and Acid Phosphatases. *Biol. Trace Elem. Res.* **186**, 413–429 (2018).

39. Rasheduzzaman, M., Jeong, J.-K. & Park, S.-Y. Resveratrol sensitizes lung cancer cell to TRAIL by p53 independent and suppression of Akt/NF-κB signaling. *Life Sci.* **208**, 208–220 (2018).

40. Olschewski, D. N. *et al.* The Angiotensin II Type 1 Receptor Antagonist Losartan Affects NHE1-Dependent Melanoma Cell Behavior. *Cell. Physiol. Biochem. Int. J. Exp. Cell. Physiol. Biochem. Pharmacol.* **45**, 2560–2576 (2018).

41. Woo, Y. & Jung, Y. Angiotensin II receptor blockers induce autophagy in prostate cancer. *Oncol Lett* **13**, 3579–3585 (2017).

42. Islas, M. S. *et al.* Experimental and DFT characterization, antioxidant and anticancer activities of a Cu(II)-irbesartan complex: structure-antihypertensive activity relationships in Cu(II)-sartan complexes. *J. Biol. Inorg. Chem. JBIC a Publ. Soc. Biol. Inorg. Chem.* **21**, 851–863 (2016).

43. Alhusban, A. *et al.* Clinically relevant doses of candesartan inhibit growth of prostate tumor xenografts in vivo through modulation of tumor angiogenesis. *J. Pharmacol. Exp. Ther.* **350**, 635–645 (2014).

44. Da, Y. *et al.* Synthesis and biological evaluation of new fluorine substituted derivatives as angiotensin II receptor antagonists with anti-hypertension and anti-tumor effects. *Bioorg. Med. Chem.* **20**, 7101–7111 (2012).

45. Teranishi, J. *et al.* Evaluation of role of angiotensin III and aminopeptidases in prostate cancer . *Prostate* **68**, 1666–1673 (2008).

46. Ishiguro, H., Ishiguro, Y., Kubota, Y. & Uemura, H. Regulation of prostate cancer cell growth and PSA expression by angiotensin II receptor blocker with peroxisome proliferator-activated receptor gamma ligand like action. *Prostate* **67**, 924–932 (2007).

47. Uemura, H. *et al.* Antiproliferative activity of angiotensin II receptor blocker through cross-talk between stromal and epithelial prostate cancer. *Mol. Cancer Ther.* **4**, 1699–1709 (2005).

48. Dovio, A. *et al.* Differential expression of determinants of glucocorticoid sensitivity in androgen-dependent and androgen-independent human prostate cancer cell lines. *J. Steroid Biochem. Mol. Biol.* **116**, 29–36 (2009).

49. Leung, W.-H. *et al.* Modulation of NKG2D ligand expression and metastasis in tumors by spironolactone via RXRγ activation. *J. Exp. Med.* **210**, 2675–2692 (2013).

50. Sanomachi, T. *et al.* Spironolactone, a Classic Potassium-Sparing Diuretic, Reduces Survivin Expression and Chemosensitizes Cancer to Non-DNA-Damaging Anticancer Drugs. *Cancers (Basel).* **11**, (2019).

51. Sayedyahossein, S. *et al.* Pannexin 1 binds β-catenin to modulate melanoma cell growth and metabolism. *J. Biol. Chem.* **296**, 100478 (2021).

52. Papadopoli, D. *et al.* Perturbations of cancer cell metabolism by the antidiabetic drug canagliflozin. *Neoplasia* **23**, 391–399 (2021).

53. Eliaa, S. G., Al-Karmalawy, A. A., Saleh, R. M. & Elshal, M. F. Empagliflozin and Doxorubicin Synergistically Inhibit the Survival of Triple-Negative Breast Cancer via Interfering with the mTOR Pathway and Inhibition of Calmodulin: In Vitro and Molecular Docking Studies. *ACS Pharmacol. Transl. Sci.* **3**, 1330–1338 (2020).

54. Quagliariello, V. *et al.* NLRP3 as Putative Marker of Ipilimumab-Induced Cardiotoxicity in the Presence of Hyperglycemia in Estrogen-Responsive and Triple-Negative Breast Cancer. *Int. J. Mol. Sci.* **21**, (2020).

55. Zhou, J. *et al.* Sodium-glucose co-transporter-2 (SGLT-2) inhibition reduces glucose uptake to induce breast cancer cell growth arrest through AMPK/mTOR pathway. *Biomed. Pharmacother.* **132**, 110821 (2020).

56. Komatsu, S. *et al.* SGLT2 inhibitor ipragliflozin attenuates breast cancer cell proliferation. *Endocr. J.* **67**, 99–106 (2020).

57. Yamamoto, L. *et al.* Sodium-glucose cotransporter 2 inhibitor canagliflozin attenuates lung cancer cell proliferation in vitro. *Diabetol. Int.* **12**, 389–398 (2021).

Supplementary table 4

Effects of BBs on cancer assessed by meta-analyses of clinical studies											
ID	**PRISMA or MOOSE guidelines**	**Baseline cancer status**	**Main aim**	**Number of included studies (study type)**	**Main outcomes**	**Outcomes by cancer types (number of studies)**					
						Breast cancer	**Lung cancer**	**Colorectal cancer**	**Melanoma**	**Prostate**	**Other cancers**
M. Monami et al. (2013)[1]	Followed	Cancer-free patients	To investigate the relationship between BB treatment and the incidence of cancer in diabetic and non-diabetic patients.	9 (RCT)	**BB use is associated with non-significant trend toward lower risk of cancer.**	Outcome was not broken down to cancer types					
A. Yap et al. (2018)[2]	Followed	Cancer patients	To investigate the association between BB use and cancer recurrence (CR), disease-free survival (DFS), and overall survival (OS).	27 (observational)	BB use has no effect on CR, and has mixed effects on different cancer types.	**No effect** (3)	**No effect** (3)	**No effect** (3)	**Improved DFS and OS** (1)	**Worsened OS** (2)	**Ovarian: no effect** (6) **Endometrial: no effect on DFS, worsened OS** (1) **Head & Neck: no effect on DFS, worsened OS** (1) **Renal: no effect** (1) **Esophagus: no effect** (1) **Pancreatic: no effect** (2) **Stomach: no effect** (1)
Z. Na et al. (2018)[3]	Followed	Cancer patients	To investigate the relationship between BB exposure and survival outcomes of various cancers.	36 (observational and RCT)	BB use is associated with **significant increase of CSS**, but has no effect on OS, ACM, DFS, PFS, RFS.	**No effect** (6)	**No effect** (7)	**No effect** (2)	**Improved OS** (2)	N/A	**Ovarian: improved OS** (5) **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic: Improved OS** (2) **Stomach:** N/A

C. Choi et al. (2014)[4]	Followed	Cancer patients	To assess whether adding beta blockers to the treatment regimen of patients with various types of cancer had an impact on survival.	18 (observational)	BB use is associated with **significant increase of OS and DFS.**	Outcome was not broken down to cancer types					
J. Weberpals et al. (2016)[5]	Followed	Cancer patients	To summarize evidence on the association between pre- and post-diagnostic beta blocker exposure and cancer survival.	30 (observational)	BB use is associated with **significant increase of OS and CSS,** mainly driven by post-diagnostic BB use. No associations between selectivity of BB and OS or CSS.	**No effect** (6)	**No effect** (3)	**No effect** (5)	**Improved OS** (2)	**No effect** (6)	**Ovarian: no effect** (2) **Endometrial:** N/A **Head & Neck:** N/A **Renal: no effect** (1) **Esophagus: no effect** (1) **Pancreatic: no effect** (2) **Stomach: no effect** (1)
S. Zhong et al. (2016)[6]	Followed	Cancer patients	To assess the relationship between postdiagnostic and prediagnostic β-blocker use and the survival of cancer patients for both all-cause mortality and cancer-specific mortality.	24 (observational)	Prediagnostic BB use showed no benefit, but **postdiagnostic BB use improved all-cause mortality or cancer specific mortality**.	**Improved all cause mortality** (3)	**No effect** (4)	**No effect** (2)	**No effect** (4)	**No effect** (2)	**Ovarian: improved all cause mortality** (1) **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A
S. Riamondi et al. (2016)[7]	Followed	Cancer patients	To shed light on possible role of the use of antihypertensive drugs in breast cancer development and survival.	10 (observational)	BB use is associated with **significant improvement in OS and CSS**, and borderline improvement in DFS.	**Improved OS and CSS** (8)	N/A	N/A	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A

Z. Y. Wen et al. (2021)[8]	Followed	Cancer patients	To further identify the correlation between post-diagnostic BB usage and ovarian cancer prognosis.	11 (observational)	Post-diagnostic BB use is not associated with ovarian cancer prognosis.	N/A	N/A	N/A	N/A	N/A	**Ovarian: no effect** (11) **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A
Z. Lei et al. (2021)[9]	Followed	Cancer patients	To provide a systematic evaluation of the association between BB use and survival of lung cancer.	10 (observational)	BB use was not associated with significantly affected OS in lung cancer.	N/A	**Improved OS in Stage III** (4) **Improved OS when no surgery was performed** (2) **nsBBs significantly worsened OS** (4)	N/A	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A
A. Majidi et al. (2020)[10]	Not followed	Cancer patients	To review the evidence for a possible relation between common chronic disease medications and survival among women with ovarian cancer	11 (observational)	**BB use has no effect on OS of women with ovarian cancer.**	N/A	N/A	N/A	N/A	N/A	**Ovarian: No effect** (11) **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A
H. Tang et al. (2018)[11]	Not followed	Cancer-free patients	To quantify the association between use of antihypertensive drugs and malignant melanoma risk	8 (observational	**BB significantly increases risk of melanoma.**	N/A	N/A	N/A	**Increased risk of cancer** (n=3)	N/A	**Ovarian:** No effect (11) **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A

W. K. Childrens et al. (2015)[12]	Not followed	Cancer patients	To perform a systematic review and meta-analysis of the effect of β-blockers on breast cancer outcomes	7 (observational)	**BB use has no effect on breast CR or all cause mortality, but significantly decreases cancer death.**	**No effect on CR** (n=5) **significantly decreased cancer death** (n=4) **No effect on all cause mortality** (n=4)	N/A	N/A	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A
M. Thiele et al. (2015)[13]	Followed	Cancer-free patients	To evaluate the effect of nsBB on HCC.	12 (RCT)	**nsBB use decrease risk of HCC.**	N/A	N/A	N/A	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A
S. Gandini et al. (2018)[14]	Followed	Cancer-free patients	To investigate the association between use of anti-hypertensive drugs and the risk of cutaneous melanoma and non-melanoma skin cancer	19 (observational)	**BB significantly increases risk of skin cancer.**	N/A	N/A	N/A	**Increased risk of cancer** (n=4)	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
S. Bangalore et al. (2011)[15]	Followed	Cancer-free patients	To assess the association between antihypertensive drugs and the risk of cancer in a comprehensive analysis of data from randomised clinical trials.	70 (RCT)	**BB has no effect on risk of cancer or cancer mortality.**	Outcome was not broken down to cancer types					

Y. Xie et al. (2019)[16]	Followed	Cancer-free patients	To investigate how the use of antihypertensive medications may influence the incidence of bladder/kidney cancer	31 (observational)	**BB significantly increases kidney cancer risk.**	N/A	N/A	N/A	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** **increased risk** (n=12) **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
E. Copland et al. (2021)[17]	Followed	Cancer-free patients	To investigate the association between antihypertensive medication and cancer in a large individual patient data meta-analysis of randomised clinical trials	33 (RCT)	**BB use has no effect on risk of cancer or cancer mortality.**	**No effect on cacer risk** (n=4)	**No effect on cacer risk** (n=4)	**No effect on cancer risk** (n=3)	N/A	**No effect on cacer risk** (n=3)	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal: N/A** **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
J. Qi et al. (2022)[18]	Followed	Cancer-free patients	To investigate associations associations between colorectal cancer risk and antihypertensive medications: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs), and diuretics.	13 (observational)	**BB use has no effect on colorectal cacer risk.**	N/A	N/A	**No effect on cancer risk** (n=4)	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A

Effects of RAASIs (ACEIs, ARBs, MRAs) on cancer assessed by meta-analyses of clinical studies											
ID	**PRISMA or MOOSE guidelines**	**Baseline cancer status**	**Main aim**	**number of included studies (study type)**	**Main outcomes**	**Outcomes by cancer types (number of studies)**					
						Breast cancer	**Lung cancer**	**Colorectal cancer**	**Melanoma**	**Prostate**	**Other cancers**
C. I. Coleman et al. (2008)[19]	Not followed	Cancer-free patients	To determine the association between commonly used antihypertensive agents and the incidence of cancer.	27 (RCT)	Neither ARBs, nor ACEis had significant effects on incidence of cancer.	Outcome was not broken down to cancer types					
I. Sipahi et al. (2010)[20]	Not followed	Cancer-free patients	To examine the effect of ARBs on occurrence of new cancers.	9 (RCT)	**ARBs significantly increased risk of new cancer compared to placebo. ARBs significantly increased the occurrence of new cancer in patients with ACEi background therapy, compared to ACEi alone.** No significant effect on cancer death.	No effect (5)	**Increased risk** (5)	N/A	N/A	No effect (5)	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A

S. Bangalore et al. (2011)[15]	Followed	Cancer-free patients	To assess the association between antihypertensive drugs and the risk of cancer in randomised clinical trials.	70 (RCT)	ARBs or ACEis had no significant effect on cancer risk, or cancer related deaths, compared to placebo. **The combination of ARBs and ACEis significantly increased cancer risk,** but not cancer deaths.	Outcome was not broken down to cancer types					
I. Sipahi et al. (2011)[21]	Followed	Cancer-free patients	To determine the effect of ACE inhibitors on cancer occurrence and cancer death, and on occurrence of gastrointestinal cancers given previous concerns of increased risk.	14 (RCT)	ACEis have no significant effect on cancer risk, cancer deaths, or gastrointestinal cancers.	No effect (14)	N/A	N/A	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
C. Yoon et al. (2011)[22]	Not followed	Cancer-free patients	To assess the association between use of ACEis or ARBs and cancer risk.	28 (observational)	No significant association between the use of ACEis or ARBs and the risk of cancer in all of the studies. **Beneficial effect of ACEis or ARBs on risk of cancer in Cohort studies, Nested case-control studies, and studies with long-term follow-up. ACEis or ARBs marginally increased the risk of cancer in Conventional case-control studies.**	No effect (6, 8)	No effect (4, 3)	No effect (4, 2)	**Increased risk** (3, 1)	No effect (8, 5)	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** **increased risk** (6, 2) **Esophagus:** **decreased risk** (2, 2) **Pancreatic:** N/A **Stomach:** no effect (2, 2) **Hepatocellular:** N/A

Y. Dai et al. (2015)[23]	Followed	Both cancer-free and cancer patients	To investigate the association between ACEi or ARB therapy and colorectal cancer.	11 (observational)	ACEi or ARB use **significantly decreases colorectal cancer incidence**, but have no significant effect on CSS. No significant dose-reponse relationship was found.	N/A	N/A	**Decreased incidence** (6) **No effect on CSS** (3)	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
Y. Mao et al. (2016)[24]	Followed	Cancer-free patients	To summarize and to quantity the existing evidence on the relationship between RAS inhibitors and prostate cancer based on all relevant cohort studies.	9 (observational)	ACEi or ARB use **significantly decreases risk for prostate cancer**.	N/A	N/A	N/A	N/A	**Decreased incidence** (6)	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
J. Shen et al. (2016)[25]	Followed	Both cancer-free and cancer patients	To assess the association between ACEI/ARB use and risk of cancer and death.	31 (17 observational, 14 RCT)	**ACEI/ARB users had a lower incidence of cancer in the observational studies but not in the RCTs** **Mortality reduction with ARB/ACEI was marginally signifcant in the observational studies but not in the RCTs** **Incidence reduction was not significantly different with the duration of the follow-up**	**No effect on incidence** (n=5 observational) **No effect on incidence** (n=8 RCT)	**Decreased incidence** (n=6 observational) **No effect on incidence** (n=9 RCT)	**No effect on incidence** (n=5 observational)	N/A	**No effect on incidence** (n=5 observational) **No effect on incidence** (n=9 RCT)	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A

T. Song et al. (2017)[26]	Followed	Cancer patients	To assess the current evidence on the potential benefit of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) on cancer recurrence and survival.	11 (observational)	**The use of ACEIs or ARBs in cancer patients can lead to a 40 and 25% reduction in the risk of cancer recurrence and mortality.**	Outcome was not broken down to cancer types					
Y. Zhao et al. (2016)[27]	Not followed	Cancer patients	To investigate the risk of cancer associated with ARB at different background ACEI levels.	17 (RCT)	**No significant differences in cancer incidence when compared ARB alone with placebo alone, ARB alone with ACEI alone, ARB plus partial use of ACEI with placebo plus partial use of ACEI, or ARB plus ACEI combination with ACEI**	Outcome was not broken down to cancer types					
H. Sun et al. (2017)[28]	Not followed	Cancer patients	To evaluate the effect of RAS inhibitors on recurrence, metastasis, and survival in cancer patients.	55 (observational)	**Mixed effect on OS depending on cancer types. Overall OS, DFS and PFS show significant improvement mainly driven by ARBs, but not ACEis**	No effect on OS (n=7)	**No effect on OS** (n=7)	**No effect on OS** (n=5)	**No effect on OS** (n=1)	**No effect on OS** (n=2)	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck: no effect on OS** (n=1) **Renal: improved OS** (n=7) **Esophagus: no effect on OS** (n=2) **Pancreatic: improved OS** (n=2) **Stomach: improved OS** (n=2) **Hepatocellular: improved OS** (n=2)

S. Gandini et al. (2018)[14]	Followed	Cancer-free patients	To investigate the association between use of anti-hypertensive drugs and the risk of cutaneous melanoma and non-melanoma skin cancer.	19 (observational)	**ACEi and ARB have no effect on risk of skin cancer, including melanoma**	N/A	N/A	N/A	**No effect on risk of cancer** (n=5 for ACEi, n=3 for ARB)	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
L. Cao et al. (2018)[29]	Followed	Cancer-free patients	To investigate the relationship between antihypertensive drugs use and the risk of prostate cancer.	21 (observational)	**ACEi and ARB have no effect on risk of prostate cancer neither in cohort, nor in case control studies**	N/A	N/A	N/A	N/A	**No effect on risk of cancer** (n=10 for ACEi, n=5 for ARB)	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
T. Datzmann et al. (2019)[30]	Followed	Cancer-free patients	To investigate the available randomised and observational study data on ARBs and carcinogenesis.	12 (7 RCT, 5 observational)	**Risk of cancer was elevated in case-constrol studies, but not in RCTs or in cohort studies. No effect on tumour specific mortality.**	**No effect on tumor specific mortality** (n=6)	**No effect on tumor specific mortality** (n=5)	N/A	N/A	**No effect on tumor specific mortality** (n=3)	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A

Q. Zhou et al. (2020)[31]	Followed	Cancer patients	To investigate the effect of long-term oral RAS-blockade (ACEi or ARB) on digestive system malignancies.	13 (observational)	**RAS blockade improves CSS, OS and RFS of digestive system malignancies, which is mainly driven by ARBs**	N/A	N/A	**Improved OS** (n=5)	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic: improved OS** (n=3) **Stomach:** N/A **Hepatocellular: improved OS** (n=2)
X. Chen et al. (2020)[32]	Not followed	Cancer patients	To determine whether use of the renin–angiotensin system (RAS) inhibitors would increase colorectal cancer morbidity and mortality.	16 (observational)	**RAS blockade improves risk of colorectal cancer and CSS**	N/A	N/A	**Improved risk of cancer** (n=16) **Improved CSS** (n=3)	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
F. Asgharzadeh et al. (2020)[33]	Not followed	Cancer patients	To explore the potential clinical impact of ACEI/ARB in renal cancer.	9 (observational)	**RAS blockade improves RCC mortality, mainly driven by ARBs.**	N/A	N/A	N/A	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal: improved mortality** (n=3) **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A

Y. Xie et al. (2019)[16]	Followed	Cancer-free patients	To investigate how the use of antihypertensive medications may influence the incidence of bladder/kidney cancer	31 (observational)	**ARB and ACEi significantly increases kidney cancer risk. ARB siggnificantly increase bladder cancer risk.**	N/A	N/A	N/A	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal: increased risk** (n=4 for ARB, n=10 for ACEi) **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
M. Batais et al. (2021)[34]	Followed	Cancer-free patients	To investigate relationship between the use of angiotensin converting enzyme inhibitors (ACEIs) and the risk of lung cancer	13 (1 RCT, 12 observational)	**ACEI use has no effect on lung cancer risk.**	N/A	**No effect on cancer risk** (n=13)	N/A	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
E. Copland et al. (2021)[17]	Possibly followed	Cancer-free patients	To investigate the association between antihypertensive medication and cancer in a large individual patient data meta-analysis of randomised clinical trials.	33 (RCT)	**ARB or ACEI use have no effect on cacer risk or cancer mortality.**	**No effect on cacer risk for ARB** (n=10) **or ACEI** (n=11)	**No effect on cacer risk for ARB** (n=12) **or ACEI** (n=13)	**No effect on cacer risk for ARB** (n=12) **or ACEI** (n=11)	N/A	**No effect on cacer risk for ARB** (n=12) **or ACEI** (n=11)	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A

J. Qi et al. (2022)[18]	Followed	Cancer-free patients	To investigate associations associations between colorectal cancer risk and antihypertensive medications: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs), and diuretics.	13 (observational)	**ARB or ACEI use have no effect on colorectal cacer risk.**	N/A	N/A	No effect on cancer risk for ACEI (n=5) or ARB (n=4)	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
H. Tang et al. (2018)[11]	Not followed	Cancer-free patients	To quantify the association between use of antihypertensive drugs and malignant melanoma risk.	8 (observational)	**ACEI or ARB has no effect on risk of melanoma**	N/A	N/A	N/A	**No effect risk of cancer for ARB** (n=3) **or ACEI** (n=4)	N/A	**Ovarian: No effect** (n=11) **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A
K. Bommareddy et al. (2022)[35]	Followed	Cancer-free patients	To determine the pooled occurrence of cancers, in particular breast and prostate cancers, among those who were ever treated with spironolactone.	7 (observational)	**Spironolacton use significantly decreased risk of prostate cancer**, but had no effect on other cancer types	No effect (3)	N/A	N/A	N/A	**Decreased risk of cancer** (n=4)	**Ovarian:** no effect (n=2) **Endometrial:** N/A **Head & Neck:** N/A **Renal:** no effect (n=3) **Esophagus:** no effect (n=2) **Pancreatic:** N/A **Stomach:** no effect (n=2) **Hepatocellular:** N/A

Effects of SGLT2Is on cancer assessed by meta-analyses of clinical studies											
ID	**PRISMA or MOOSE guidelines**	**Baseline cancer status**	**Main aim**	**number of included studies (study type)**	**Main outcomes**	**Outcomes by cancer types (number of studies)**					
						Breast cancer	**Lung cancer**	**Colorectal cancer**	**Melanoma**	**Prostate**	**Other cancers**
H. Cui et al. (2022)[35]	Followed	Cancer-free patients	To assess the effects of antidiabetic medications on pancreatic cancer in patients with diabetes mellitus.	47 (RCTs & Observational)	**Observational studies show no effect of metformin/TZD/SU/INS /DPP4i on prostate cancer. RCTs show significant decrease in prostatce cancer risk by TZDs/GLP-1RAs, but not with SGLT2is.**	N/A	N/A	N/A	N/A	**No effect** (n=7)	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
R. Benedetti et al. (2022)[35]	Followed	Cancer-free patients	To assess the effects of SGLT2i on all cause cancer incidence in patients with hyperglycaemia.	20 (RCTs)	**Overall reduced risk of cancer compared to placebo particularly by dapagliflozin and ertugliflozin. 2 big trials shift the overall effect size to benefitial effect of SGLT2is, overall big CIs (small studies) with no effect, EMPA shows increased risk in 3 big trials but had no effect on overall effect size**	Outcome was not broken down to cancer types					
I. Dicembrini et al. (2019)[36]	Followed	Cancer-free patients	To assess the effects of SGLT2i on all cause cancer incidence.	27 (RCTs)	**No effect of SGLT2is on incidence of overall cancer**	**No effect** (n=15)	**No effect** (n=16)	N/A	N/A	**No effect** (n=16)	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N**o effect** (n=7) **Esophagus:** N/A **Pancreatic:** N**o effect** (n=8) **Stomach:** N/A **Hepatocellular: No effect** (n=5)

H. Tang et al. (2018)[37]	Not followed	Cancer-free patients	To assess the effect of SGLT2i on skin cancer.	21 (RCTs)	**Almost (but not significantly) increased melanoma risk, almost (but not significantly) decreased non-melanoma skin cancer risk**	N/A	N/A	N/A	**No effect (n=7)**	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
H. Tang et al. (2017)[38]	Followed	Cancer-free patients	To assess the effect of SGLT2i on all cause cancer risk in T2DM patients.	46 (RCTs)	**Risk of bladder cancer might be increased with SGLT2 inhibitors, especially empagliflozin. Canagliflozin might be protective against gastrointestinal cancers.**	**No effect**	**No effect**	N/A	N/A	**No effect**	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** no effect **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A
N. Shi et al. (2021)[39]	Followed	Cancer-free patients	To determine the relationship between SGLT-2i and malignancy risk in T2DM patients.	84 (RCTs)	**DAPA significantly increased risk of overall cancer compared to other antidiabetic drugs. EMPA significantly increases risk of overall cancer compared to placebo (n=15). EMPA significantly increases digestive system malignancies compared to placebo (n=8).**	**No effect** (n=23)	**No effect** (n=19)	N/A	N/A	N/A	**Ovarian:** N/A **Endometrial:** N/A **Head & Neck:** N/A **Renal:** N/A **Esophagus:** N/A **Pancreatic:** N/A **Stomach:** N/A **Hepatocellular:** N/A

Supplementary table 4.: Meta-analyses of observational studies or randomized controlled trials investigating the effect of guideline-directed HF pharmacotherapies on cancer.

References

1. Monami, M.; Filippi, L.; Ungar, A.; Sgrilli, F.; Antenore, A.; Dicembrini, I.; et al. Further Data on Beta-Blockers and Cancer Risk: Observational Study and Meta-Analysis of Randomized Clinical Trials. *Curr. Med. Res. Opin.* **2013**, *29*, 369–378, doi:10.1185/03007995.2013.772505.
2. Yap, A.; Lopez-Olivo, M.A.; Dubowitz, J.; Pratt, G.; Hiller, J.; Gottumukkala, V.; et al. Effect of Beta-Blockers on Cancer Recurrence and Survival: A Meta-Analysis of Epidemiological and Perioperative Studies. *Br. J. Anaesth.* **2018**, *121*, 45–57, doi:https://doi.org/10.1016/j.bja.2018.03.024.
3. Na, Z.; Qiao, X.; Hao, X.; Fan, L.; Xiao, Y.; Shao, Y.; et al. The Effects of Beta-Blocker Use on Cancer Prognosis: A Meta-Analysis Based on 319,006 Patients. *Onco. Targets. Ther.* **2018**, *11*, 4913–4944, doi:10.2147/OTT.S167422.
4. Choi, C.H.; Song, T.; Kim, T.H.; Choi, J.K.; Park, J.-Y.; Yoon, A.; et al. Meta-Analysis of the Effects of Beta Blocker on Survival Time in Cancer Patients. *J. Cancer Res. Clin. Oncol.* **2014**, *140*, 1179–1188, doi:10.1007/s00432-014-1658-7.
5. Weberpals, J.; Jansen, L.; Carr, P.R.; Hoffmeister, M.; Brenner, H. Beta Blockers and Cancer Prognosis – The Role of Immortal Time Bias: A Systematic Review and Meta-Analysis. *Cancer Treat. Rev.* **2016**, *47*, 1–11, doi:https://doi.org/10.1016/j.ctrv.2016.04.004.
6. Zhong, S.; Yu, D.; Zhang, X.; Chen, X.; Yang, S.; Tang, J.; et al. β-Blocker Use and Mortality in Cancer Patients: Systematic Review and Meta-Analysis of Observational Studies. *Eur. J. cancer Prev. Off. J. Eur. Cancer Prev. Organ.* **2016**, *25*, 440–448, doi:10.1097/CEJ.0000000000000192.
7. Raimondi, S.; Botteri, E.; Munzone, E.; Cipolla, C.; Rotmensz, N.; DeCensi, A.; et al. Use of Beta-Blockers, Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers and Breast Cancer Survival: Systematic Review and Meta-Analysis. *Int. J. Cancer* **2016**, *139*, 212–219, doi:https://doi.org/10.1002/ijc.30062.
8. Wen, Z.-Y.; Gao, S.; Gong, T.-T.; Jiang, Y.-T.; Zhang, J.-Y.; Zhao, Y.-H.; et al. Post-Diagnostic Beta Blocker Use and Prognosis of Ovarian Cancer: A Systematic Review and Meta-Analysis of 11 Cohort Studies With 20,274 Patients . *Front. Oncol.* 2021, *11*.
9. Lei, Z.; Yang, W.; Zuo, Y. Beta-Blocker and Survival in Patients with Lung Cancer: A Meta-Analysis. *PLoS One* **2021**, *16*, e0245773.
10. Majidi, A.; Na, R.; Dixon-Suen, S.; Jordan, S.J.; Webb, P.M. Common Medications and Survival in Women with Ovarian Cancer: A Systematic Review and Meta-Analysis. *Gynecol. Oncol.* **2020**, *157*, 678–685, doi:https://doi.org/10.1016/j.ygyno.2020.03.028.
11. Tang, H.; Fu, S.; Zhai, S.; Song, Y.; Han, J. Use of Antihypertensive Drugs and Risk of Malignant Melanoma: A Meta-Analysis of Observational Studies. *Drug Saf.* **2018**, *41*, 161–169, doi:10.1007/s40264-017-0599-x.
12. Childers, W.K.; Hollenbeak, C.S.; Cheriyath, P. β-Blockers Reduce Breast Cancer Recurrence and Breast Cancer Death: A Meta-Analysis. *Clin. Breast Cancer* **2015**, *15*, 426–431, doi:10.1016/j.clbc.2015.07.001.
13. Thiele, M.; Albillos, A.; Abazi, R.; Wiest, R.; Gluud, L.L.; Krag, A. Non-Selective Beta-Blockers May Reduce Risk of Hepatocellular Carcinoma: A Meta-Analysis of Randomized Trials. *Liver Int.* **2015**, *35*, 2009–2016, doi:https://doi.org/10.1111/liv.12782.
14. Gandini, S.; Palli, D.; Spadola, G.; Bendinelli, B.; Cocorocchio, E.; Stanganelli, I.; et al. Anti-Hypertensive Drugs and Skin Cancer Risk: A Review of the Literature and Meta-Analysis. *Crit. Rev. Oncol. Hematol.* **2018**, *122*, 1–9, doi:https://doi.org/10.1016/j.critrevonc.2017.12.003.
15. Bangalore, S.; Kumar, S.; Kjeldsen, S.E.; Makani, H.; Grossman, E.; Wetterslev, J.; et al. Antihypertensive Drugs and Risk of Cancer: Network Meta-Analyses and Trial Sequential Analyses of 324 168 Participants from Randomised Trials. *Lancet Oncol.* **2011**, *12*, 65–82, doi:https://doi.org/10.1016/S1470-2045(10)70260-6.
16. Xie, Y.; Xu, P.; Wang, M.; Zheng, Y.; Tian, T.; Yang, S.; et al. Antihypertensive Medications Are Associated with the Risk of Kidney and Bladder Cancer: A Systematic Review and Meta-Analysis. *Aging (Albany. NY).* **2020**, *12*, 1545–1562, doi:10.18632/aging.102699.
17. Copland, E.; Canoy, D.; Nazarzadeh, M.; Bidel, Z.; Ramakrishnan, R.; Woodward, M.; et al. Antihypertensive Treatment and Risk of Cancer: An Individual Participant Data Meta-Analysis. *Lancet Oncol.* **2021**, *22*, 558–570, doi:10.1016/S1470-2045(21)00033-4.
18. Qi, J.; An, R.; Bhatti, P.; Spinelli, J.J.; Murphy, R.A. Anti-Hypertensive Medications and Risk of Colorectal Cancer: A Systematic Review and Meta-Analysis. *Cancer causes & Control CCC* **2022**, *33*, 801–812, doi:10.1007/s10552-022-01570-1.
19. Coleman, C.I.; Baker, W.L.; Kluger, J.; White, C.M. Antihypertensive Medication and Their Impact on Cancer Incidence: A Mixed Treatment Comparison Meta-Analysis of Randomized Controlled Trials. *J. Hypertens.* **2008**, *26*.
20. Sipahi, I.; Debanne, S.M.; Rowland, D.Y.; Simon, D.I.; Fang, J.C. Angiotensin-Receptor Blockade and Risk of Cancer: Meta-Analysis of Randomised Controlled Trials. *Lancet Oncol.* **2010**, *11*, 627–636, doi:https://doi.org/10.1016/S1470-2045(10)70106-6.

21. Sipahi, I.; Chou, J.; Mishra, P.; Debanne, S.M.; Simon, D.I.; Fang, J.C. Meta-Analysis of Randomized Controlled Trials on Effect of Angiotensin-Converting Enzyme Inhibitors on Cancer Risk. *Am. J. Cardiol.* **2011**, *108*, 294–301, doi:https://doi.org/10.1016/j.amjcard.2011.03.038.

22. Yoon, C.; Yang, H.-S.; Jeon, I.; Chang, Y.; Park, S.M. Use of Angiotensin-Converting-Enzyme Inhibitors or Angiotensin-Receptor Blockers and Cancer Risk: A Meta-Analysis of Observational Studies. *CMAJ* **2011**, *183*, E1073-84, doi:10.1503/cmaj.101497.

23. Dai, Y.-N.; Wang, J.-H.; Zhu, J.-Z.; Lin, J.-Q.; Yu, C.-H.; Li, Y.-M. Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers Therapy and Colorectal Cancer: A Systematic Review and Meta-Analysis. *Cancer Causes Control* **2015**, *26*, 1245–1255, doi:10.1007/s10552-015-0617-1.

24. Mao, Y.; Xu, X.; Wang, X.; Zheng, X.; Xie, L. Is Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers Therapy Protective against Prostate Cancer? *Oncotarget* **2016**, *7*, 6765–6773, doi:10.18632/oncotarget.6837.

25. Shen, J.; Huang, Y.-M.; Wang, M.; Hong, X.-Z.; Song, X.-N.; Zou, X.; et al. Renin-Angiotensin System Blockade for the Risk of Cancer and Death. *J. Renin. Angiotensin. Aldosterone. Syst.* **2016**, *17*, doi:10.1177/1470320316656679.

26. Song, T.; Choi, C.H.; Kim, M.K.; Kim, M.-L.; Yun, B.S.; Seong, S.J. The Effect of Angiotensin System Inhibitors (Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers) on Cancer Recurrence and Survival: A Meta-Analysis. *Eur. J. cancer Prev. Off. J. Eur. Cancer Prev. Organ.* **2017**, *26*, 78–85, doi:10.1097/CEJ.0000000000000269.

27. Zhao, Y.-T.; Li, P.-Y.; Zhang, J.-Q.; Wang, L.; Yi, Z. Angiotensin II Receptor Blockers and Cancer Risk: A Meta-Analysis of Randomized Controlled Trials. *Medicine (Baltimore).* **2016**, *95*, e3600, doi:10.1097/MD.0000000000003600.

28. Sun, H.; Li, T.; Zhuang, R.; Cai, W.; Zheng, Y. Do Renin–Angiotensin System Inhibitors Influence the Recurrence, Metastasis, and Survival in Cancer Patients? *Med.* **2017**, *96*, e6394, doi:10.1097/md.0000000000006394.

29. Cao, L.; Zhang, S.; Jia, C.-M.; He, W.; Wu, L.-T.; Li, Y.-Q.; et al. Antihypertensive Drugs Use and the Risk of Prostate Cancer: A Meta-Analysis of 21 Observational Studies. *BMC Urol.* **2018**, *18*, 17, doi:10.1186/s12894-018-0318-7.

30. Datzmann, T.; Fuchs, S.; Andree, D.; Hohenstein, B.; Schmitt, J.; Schindler, C. Systematic Review and Meta-Analysis of Randomised Controlled Clinical Trial Evidence Refutes Relationship between Pharmacotherapy with Angiotensin-Receptor Blockers and an Increased Risk of Cancer. *Eur. J. Intern. Med.* **2019**, *64*, 1–9, doi:10.1016/j.ejim.2019.04.019.

31. Zhou, Q.; Chen, D.-S.; Xin, L.; Zhou, L.-Q.; Zhang, H.-T.; Liu, L.; et al. The Renin-Angiotensin System Blockers and Survival in Digestive System Malignancies: A Systematic Review and Meta-Analysis. *Medicine (Baltimore).* **2020**, *99*, e19075, doi:10.1097/MD.0000000000019075.

32. Chen, X.; Yi, C.-H.; Ya, K.-G. Renin-Angiotensin System Inhibitor Use and Colorectal Cancer Risk and Mortality: A Dose-Response Meta Analysis. *J. Renin. Angiotensin. Aldosterone. Syst.* **2020**, *21*, 1470320319895646, doi:10.1177/1470320319895646.

33. Asgharzadeh, F.; Hashemzehi, M.; Moradi-Marjaneh, R.; Hassanian, S.M.; Ferns, G.A.; Khazaei, M.; et al. Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers as Therapeutic Options in the Treatment of Renal Cancer: A Meta-Analysis. *Life Sci.* **2020**, *242*, 117181, doi:10.1016/j.lfs.2019.117181.

34. Batais, M.; Almigbal, T.; Alotaibi, K.; Alodhayani, A.; Alkhushail, A.; Altheaby, A.; et al. Angiotensin Converting Enzyme Inhibitors and Risk of Lung Cancer: A Systematic Review and Meta-Analysis. *Medicine (Baltimore).* **2021**, *100*, e25714, doi:10.1097/MD.0000000000025714.

35. Bommareddy, K.; Hamade, H.; Lopez-Olivo, M.A.; Wehner, M.; Tosh, T.; Barbieri, J.S. Association of Spironolactone Use With Risk of Cancer: A Systematic Review and Meta-Analysis. *JAMA dermatology* **2022**, *158*, 275–282, doi:10.1001/jamadermatol.2021.5866.

36. Dicembrini, I.; Nreu, B.; Mannucci, E.; Monami, M. Sodium-Glucose Co-Transporter-2 (SGLT-2) Inhibitors and Cancer: A Meta-Analysis of Randomized Controlled Trials. *Diabetes. Obes. Metab.* **2019**, *21*, 1871–1877, doi:10.1111/dom.13745.

37. Tang, H.; Yang, K.; Song, Y.; Han, J. Meta-Analysis of the Association between Sodium-Glucose Co-Transporter-2 Inhibitors and Risk of Skin Cancer among Patients with Type 2 Diabetes. *Diabetes. Obes. Metab.* **2018**, *20*, 2919–2924, doi:10.1111/dom.13474.

38. Tang, H.; Dai, Q.; Shi, W.; Zhai, S.; Song, Y.; Han, J. SGLT2 Inhibitors and Risk of Cancer in Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Diabetologia* **2017**, *60*, 1862–1872, doi:10.1007/s00125-017-4370-8.

39. Shi, N.; Shi, Y.; Xu, J.; Si, Y.; Yang, T.; Zhang, M.; et al. SGLT-2i and Risk of Malignancy in Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials . *Front. Public Heal.* 2021, *9*.

Third-party permissions statement

The authors do hereby declare that all illustrations and figures in the manuscript (MS # EURHEARTJ-D-23-02316) are original and not require reprint permission. All figures were made using Biorender.com.

European Heart Journal

Declarations

Conflict of interest

PF is the founder and CEO of Pharmahungary Group, a group of R&D companies. GS reports grants and personal fees from Vifor, grants from Boehringer Ingelheim, personal fees from Societa´ Prodotti Antibiotici, grants and personal fees from AstraZeneca, personal fees from Roche, personal fees from Servier, grants and personal fees from Novartis, personal fees from GENESIS, grants and personal fees from Cytokinetics, personal fees from Medtronic, grants from Boston Scientific, grants and personal fees from PHARMACOSMOS, grants from Merck, grants from Bayer, personal fees from TEVA, outside the submitted work. PA reports speaker and/or advisor fees from Astra Zeneca, Boehringer Ingelheim, Bayer, Novartis, Daiichi Sankyo, Amgen, Janssen and MSD, all outside the submitted work. ELG has received speaker honoraria or consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers SquiBB, Pfizer, MSD, Novo Nordisk, Lundbeck Pharma and Organon. He is investigator in clinical studies sponsored by AstraZeneca, Idorsia or Bayer and has received unrestricted research grants from Boehringer Ingelheim. DD obtained honoraria for educational lectures from Novartis, Sanofi and Daiichi Sankyo, all unrelated to this work. RAdB has received research grants and/or fees from AstraZeneca, ABBott, Boehringer Ingelheim, Cardior Pharmaceuticals GmbH, Ionis Pharmaceuticals, Inc., Novo Nordisk, and Roche; and has had speaker engagements with ABBott, AstraZeneca, Bayer, Bristol Myers SquiBB, Novartis, and Roche. AGS has received speakers honoraria from Merck/Schering-Plough, BMS, UCB, Pfizer/Wyeth, Sanofi, Novartis, Pfizer, Lilly and Women's College Hospital, Toronto, Canada. Other authors have nothing to declare.

Data availability

No data were generated or analysed for or in support of this paper.

Funding

The work was supported by the European Union's Horizon 2020 Research and Innovation Programme under grant agreement no. 739593 and by a Momentum Research Grant from the Hungarian Academy of Sciences (LP-2021-14 to Z.V.V.). This project was additionally supported by grants from the National Research, Development and Innovation Office (NKFIH) of Hungary (FK134751 to Z.V.V.). The Ministry for Innovation and Technology in Hungary provided funding to this study under the Thematic Excellence Programme (2020-4.1.1.-TKP2020), the 2020-1.1.5-GYORSÍTÓSÁV call programme (2020-1.1.5-GYORSÍTÓSÁV-2021-00011), the TKP2021- EGA funding scheme (TKP2021-EGA-23), and the Research Excellence Programme (TKP/ITM/NKFIH). This study was also supported by the National Heart Laboratory Project no. RRF-2.3.1-21-2022-00003 implemented with the support provided by the European Union. N.V.S. was supported by the Semmelweis 250+ Excellence PhD Scholarship (EFOP-3.6.3-VEKOP-16-2017-00009), and by the Gedeon Richter Excellence PhD Scholarship. PA was supported by the Italian Ministry of Health (GR-2018-12365661 - CHANGE Study; Ricerca Corrente 2018-2020 IRCCS Ospedale Policlinico San Martino). DD was supported by National Institutes of Health grants (RO1HL131517, RO1HL136389, RO1HL089598, RO1HL163277, and RO1HL160992) and the European Union (large-scale integrative project MAESTRIA, No. 965286). WCM and RAdB are supported by the European Research Council (ERC CoG 818715).