Repurposing of drugs approved for cardiovascular diseases: opportunity or mirage?

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Abstract

Drug repurposing is a promising way in drug discovery to identify new therapeutic uses -different from the original medical indication- for existing drugs. It has many advantages over traditional approaches to *de novo* drug discovery, since it can significantly reduce healthcare costs and development timeline. In this review, we discuss the possible repurposing of drugs approved for cardiovascular diseases, such as β-blockers, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), statins, aspirin, cardiac glycosides and low-molecular-weight heparins (LMWHs). Indeed, numerous experimental and epidemiological studies have reported promising anti-cancer activities for these drugs. It is worth mentioning, however, that the results of these studies are often controversial and very few data were obtained by controlled prospective clinical trials. Therefore, no final conclusion has yet been reached in this area and no final recommendations can be made. Moreover, β-blockers, ARBs and statins showed promising results in randomised controlled trials (RCTs) where pathological conditions other than cancer were considered. The results obtained have led or may lead to new indications for these drugs.

For each drug or class of drugs, the potential molecular mechanisms of action justifying repurposing, results obtained in vitro and in animal models and data from epidemiological and randomized studies are described.

Keywords

Drug repurposing, statins, β-blockers**,** aspirin**,** RAS inhibitors

1. Introduction

Drug repurposing, using known drugs and compounds for new indications, requires lower costs and shorter approval times than developing a *de novo* drug, as these "old drugs" have already proven safe in humans.

Several experimental studies have suggested repurposing of approved cardiovascular drugs for new indications, in particular for cancer. Indeed, some pleiotropic effects and mechanisms of action of cardiovascular drugs could be effective in blocking tumor cell proliferation, angiogenesis and metastasis. Furthermore, in pathological conditions other than cancer, repurposing of cardiovascular drugs is also expanding.

In this review, we reported the main results of clinical trials and meta-analysis of β-blockers, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), statins, aspirin, cardiac glycosides and low-molecular-weight heparins (LMWHs) in treatment and/or prevention of cancer and other pathological conditions such as Marfan's syndrome, migraine, bacterial and fungal infections, periodontitis, contrast-induced nephropathy and acute kidney injury (AKI) following cardiac surgery.

2. Cardiovascular drugs as new anti-cancers

Cardiovascular diseases and cancer share common epidemiological aspects, including their aging-related nature, and pathophysiological links. Indeed, accumulating clinical and preclinical data suggest the interdependence and biological overlap between cancer and cardiovascular (CV) diseases [1]. Most important traditional risk factors, such as hypertension, type 2 diabetes mellitus (T2DM), obesity and smoke, could explain part of the relationship between CV diseases and

cancer [2]. Several studies have also indicated that progression of either CV diseases or cancer is associated with enhanced tissue inflammation. A relevant evidence of the role of inflammation, as possible link between CV diseases and cancer, has been shown in the CANTOS trial, in which inhibition of interleukin-1 β by canakinumab resulted in an approximately 15% reduction in major adverse CV events, 40% in cancer mortality and 50% in lung cancer incidence [3]. Recently, clonal haematopoiesis has been suggested as exciting novel link between CV disease and cancer [4]. Haematopoietic stem cells in bone marrow may acquire certain mutations in the course of life generating clonal expansion of haematopoietic cells. When clonal haematopoiesis is associated with a mutation in a leukaemia-associated gene, this phenomenon is named clonal haematopoiesis of indeterminate potential (CHIP). CHIP is commonly observed in ageing subjects and has established relation with cancer formation, especially haematological malignancies [5], and more recently with development of CV disease in general [6] and heart failure in particular [7].

In line with these evidences, it has been shown that several biological processes or mediators involved in cancer are targeted by cardiovascular drugs [8]. Catecholamines are believed to play a key role in tumor progression, through the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) pathway [9] and the focal adhesion kinase (FAK) whose activation prevents apoptosis in cancer cells [10]. In cancer cells also the role of local renin-angiotensin system (RAS) [11], which induces VEGF through the angiotensin II type 1 (AT1) receptor and ERK1/2 signaling, leading to increased angiogenesis, tumor growth and tumor invasiveness [12], was largely investigated. Finally, cyclooxygenase [13] and mevalonate pathway,

with subsequent modulations on the RAS-RAF-MEK-ERK [14] or Akt [15] signaling, were shown to be involved in cancer, in particular in glioma.

Consistently, several drugs approved for treatment of cardiovascular diseases including β-blockers, ACE-Is, ARBs, statins, cardiac glycosides, and LMWHs have been found to exert anti-tumor effects, thus suggesting their potential repurposing in oncological adjuvant contexts [16].

2.1 β-blockers and cancer

β-blockers are approved by FDA for the treatment of tachycardia, arrhythmias, hypertension, congestive heart failure, myocardial infarction, coronary artery disease, aortic dissection, portal hypertension, glaucoma, hyperthyroidism, essential tremor, migraine and other conditions.

Strong evidence indicates that endogenous factors, especially various stress-related persistent stimulations, such as β-adrenergic signal amplification, might accelerate cancer progression [10]. Accumulation of catecholamines and increased density of β-adrenergic receptors were shown to promote carcinogenesis in the microenvironment of several breast, pancreas and ovary tumor cells [9,17,18]. Catecholamines could stimulate cell proliferation and survival, inducing cancer growth, via β-adrenergic signaling, which subsequently activates two signal pathways, one protein kinase A (PKA)-dependent and the other (PKA)-independent. PKA mediates multiple signal pathways via phosphorylation of various downstream signal proteins, such as cAMP response element binding protein (CREB), transcription-3 (STAT3), FosB and PI3K/AKT/mTOR/p70S6K/HIF1α. Conversely, the PKA-independent pathway is reported to modulate mitogen activated protein kinase (MAPKs) pathways, NF-κB, activator protein 1 (AP-1) and focal adhesion kinase (FAK) [10].

Many recent studies have investigated the function of β-adrenergic receptor in the progression of cancer metastasis. Catecholamines promote cancer cell invasiveness and angiogenesis by modulating the expression of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs, such as MMP-2, MMP-7 and MMP-9) both in cancer cell lines and in experimental animal models of breast, prostate [10], colon [19] and pancreatic [20] cancers. Norepinephrine plays a critical role in migration and invasion of pancreatic and ovarian cancer through the PKA/STAT3 signaling pathway [20]. The β2-adrenergic antagonists suppressed cancer cell migration and proliferation by inhibiting both cAMP/PKA and Ras, which regulate activation of the MAPK pathway and transcription factors, such as NF-κB, AP-1 and CREB, as well as expression of its target genes, MMPs and VEGF [21,22]. In contrast, β1-adrenergic antagonists suppressed invasion by inhibiting the cAMP/PKA pathway only [18].

In humans, several epidemiological studies have examined the potential effect of β-blockers on the incidence and the outcome of cancer. The results obtained are controversial, suggesting that the anticancer effect of β-blockers is variable and tumor specific. The use of β-blockers was associated with improved overall survival in patients with prostate cancer [23], multiple-myeloma [24], breast, ovarian and non-small-cell lung cancer (NSCLC) [16]. However, other studies showed no clinic benefit with the use of β-blockers in lung cancer [25], colorectal cancer [26], ovarian cancer patients [27]. A recent meta-analysis, including 36 studies and 319,006 patients, demonstrates no association between β-blockers use and cancer prognosis except for cancer-specific survival for ovarian cancer (HR 0.59, 95% CI: 0.36–0.96; p=0.034), pancreatic cancer (HR 0.85, 95% CI: 0.75–0.97; p=0.014), and melanoma (HR 0.81, 95% CI: 0.67–0.97; p=0.026) [28]. Likewise, in a meta-analysis of 27

studies, β-blockers use had no impact on general cancer recurrence, but it improved disease-free survival in melanoma (HR 0.03, 95% CI: 0.01-0.17; p<0.01) and ovarian cancer (HR 0.56, 95% CI: 0.25-1.27; p=0.017) [29]. These results were in contrast with those reported in two previous meta-analysis [30,31]. The same authors suggested that the proposed beneficial effect of β-blockers on cancer survival might be based on immortal time bias, which is increasingly common in cohort studies [32]. The contradictory results could be arisen from the observational design of the studies (retrospective cohort studies or case–control studies), the short follow-up, the population (only patients with cardiovascular diseases) and the multivariable influence factors, including the use of non-selective or selective β1 and β2-blockers.

New more high-quality studies, such as RCTs, and differentiation of β-blockers subclasses -according to their pharmacodynamic properties- to be tested in dedicated clinical trials are needed to overcome these limitations and to confirm or reject the possible use of β-blockers for treating cancers in humans.

Currently, there are several on-going trials evaluating the feasibility, tolerability or effectiveness of β-blockers as anti-cancer drugs. The details are reported in Table 1.

2.2 Statins and cancer

Statin are a class of drugs that are approved by FDA for the treatment of hypercholesterolemia and atherosclerotic coronary artery disease. Statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the mevalonate biosynthesis pathway, leading to a decreased biosynthesis of the downstream products of mevalonate, such as farnesyl pyrophosphate and geranyl-geranyl phosphate. These metabolites are essential for the biological activation of small G proteins, including Ras, Rac and Rho, whereas

their deficiency significantly disturbs the conjugated transduction pathways regulating proliferation, migration, cytoskeleton function, and death. Interestingly, deregulated or elevated activity of HMG-CoA reductase has been shown in several cancers, such as hepatocellular carcinoma, leukemia, lymphoma, colorectal and lung adenocarcinoma [33]. Likewise, high-dose statin treatment has been shown to directly cause apoptosis and block tumour cell growth, invasion and metastatic potential in multiple human cancer cell lines [16,33].

Statins can induce apoptosis of cancer cells through multiple molecular mechanisms, decreasing the protein levels of anti-apoptotic proteins such as Bcl-2 and Bcl-xL, up-regulating the activation of pro-apoptotic molecules such as Bax, Bad, and caspases 3, 8, and 9, decreasing phosphorylation and degradation of Bim, up-regulating the activity of p38 MAPK, iNOS and JNK [34,35]. Statins inhibit cancer cell growth and survival inducing G(1)/S cell cycle arrest with up-regulation of the cell cycle kinase inhibitors p21, p27 or p53, decreasing Akt phosphorylation, and inhibiting Rho-mediated cell proliferation [35,36]. Furthermore, statins could inhibit proliferation of tumor cells, as observed for other cell lines, such as human airway smooth muscle cells [37], by blocking the functioning of the G protein beta/gamma dimer through inhibition of its association to the plasma membrane [38]. This effect leads an inhibition of the Src-dependent pathway and, thus, of RAS activation [39]. Several experimental evidence also suggest that statins impair the metastatic potential of tumor cells by inhibiting cell migration, attachment to the extracellular matrix and invasion of the basement membrane through disorganization of actin cytoskeleton and reduction of endothelial leukocyte adhesion molecule (such as E-selectin), MMP-2 and MMP-9, urokinase and epithelial growth factor [33,34]. In animal models of cancers, statins alone decrease tumor load of breast cancer, colon cancer, acute

myelogenous leukemia, melanoma, hepatoma, pancreatic, lung and neuroblastoma. Of note, statins were also shown to potentiate the activity of anti-cancer drugs, such as doxorubicin [33,40]. Based on these data, the prophylactic activity of statins was postulated and then investigated in pharmacoepidemiological studies.

Findings of meta-analysis showed that statin use is associated with a reduced risk of gastric cancer [26 RCTs and 8 observational studies; relative ratio (RR) 0.73, 95% CI: 0.58-0.93] and esophageal cancer (13 studies; OR^{adj} 0.72, 95% CI: 0.60-0.86), particularly in patients with barrett's esophagus (11 studies; OR 0.57, 95% CI: 0.43-0.75) [35,40]. In a case-control study of glioma cases (n=517) and controls (n=400), treatment with lipophilic statins as simvastatin and lovastatin decreased the risk of glioma (OR 0.49, 95% CI: 0.30-0.81 and OR 0.47, 95% CI: 0.24-0.93, respectively) [40]. A decreased risk of cancer mortality was also reported for prostate, ovarian and uterine cancer in patients who used statins prior to diagnosis [35,40,41]. Statins use is associated with a reduced risk of liver cancer, most strongly in Asian, but also in western populations, and in absence of a duration-risk relationship [40]. No association between cancer risk and statins use was instead reported in colorectal, breast, bladder, kidney, lung, pancreatic, skin, and mixed malignancies [34,35,40].

The results obtained by observational and retrospective studies are controversial, suggesting that the anti-cancer activity of statins could be cancer-dependent and that lipophilic statins could be more effective in reducing cancer mortality and recurrence risk compared to hydrophilic statins [36]. Although statins do not affect the incidence of most cancers, they exert significant benefits on recurrence and survival in many cancer types, including liver and breast cancer [34].

However, only few controlled prospective clinical trials have investigated the therapeutic use of statins as monotherapy or as combination for cancer treatment. In

phase II studies, atorvastatin was shown to be ineffective on colorectal cancer, whereas simvastatin in combination with chemotherapeutic agents, such as irinotecan, 5-fluorouracil and leucovorin, showed promising anticancer activity, as suggested by the overall response rate (ORR 46.9%, 95% CI: 31.0-58.8, n=49 patients) [40]. However, this effect was not observed on progression-free survival in a larger phase III trial (n=269 patients) [42] and in a selected population of colorectal cancer patients (n=52) with a KRAS mutation in tumour tissue [43]. Similarly to colorectal cancer, the promising improved response rate (RR 38.5%, 95% CI: 25.3-51.7), observed in non-adenocarcinomatous non-small-cell lung cancer (NA-NSCLC) patients (n=52) treated with simvastatin in combination with the chemotherapeutic agent gefitinib [40], was not confirmed in another phase II trial (n=68 patients) [44]. Pravastatin plus chemoembolization significantly improved survival of patients with advanced hepatocellular carcinoma (18 months *vs* 9 months; p=0.006) [40]. In a phase II trial (n=36 patients), high dose pravastatin administered with the chemotherapeutic agents idarubicin and cytarabine significantly improved the response rate (RR 75%, 95% CI: 58-88%) of patients with high-risk acute myeloid leukemia (AML) [45], but not of those with poor-risk (p=0.062) [46]. Also in patients with small-cell lung cancer (SCLC) pravastatin combined with standard SCLC therapy, although safe, does not improve the overall survival rate (HR 1.01, 95% CI: 0.88-1.16; p=0.90) [47].

In gastric and pancreatic cancer patients, simvastatin, pravastatin and lovastatin did not improve outcome in phase II studies [40,48]. Thus, despite a robust preclinical data and some encouraging clinical studies, most prospective studies have been disappointing. A recent review stated the poor and inadequate design of clinical trials for the lack effect of statins. The authors pointed out the dosing schedule, the choice

of statin and diet as crucial factors to consider in designing cancer clinical trials [49]. Moreover, genetic factors may also contribute to the inter-individual variation in statin response. It will be important to discover possible predictive biomarkers that identify the patients most likely to respond to statins, such as TP53, whose gain-of-function mutations can increase the expression of HMGCR [50], a key mediator of statin resistance [51].

On-going trials evaluating the effects of statins on cancer are detailed in Table 1.

2.3 ACE-Is, ARBs and cancer

Angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) are two classes of drugs that target the renin–angiotensin system (RAS), inhibiting the activity of ACE and blocking AT1 receptor, respectively. These drugs are approved by FDA and widely used for the treatment of hypertension, heart failure, left ventricular dysfunction after myocardial infarction, acute myocardial infarction and diabetic nephropathy.

Components of renin-angiotensin system (RAS) are expressed in cells of various human cancers and in many cell types of tumor microenvironments [52]. RAS signaling in these cells promotes angiogenesis, cell growth and migration, invasion, metastasis, apoptosis, cancer-associated inflammation and the onset of an immunosuppressive microenvironment [16,35,53].

Therefore, targeting RAS with ACE-Is and angiotensin II receptor blockers (ARBs) has received considerable attention as a promising strategy for anticancer intervention.

In several *in vitro* and animal studies anti-RAS strategies have been reported to be effective in multiple anti-cancer mechanisms. In particular, ACE-Is and ARBs could

modulate cancer-associated inflammation, decreasing activation of NF-kB and infiltration of tumor-associated macrophages by MCP-1 inhibition. They could downregulate the activity of MMPs (MMP-2 and MMP-9), and reduce VEGF levels, decrease microvessel density and angiogenesis, tumor inflammatory environment overall leading to tumor growth regression [35,52,54]. In experimental studies, anti-RAS agents displayed pro-apoptotic and anti-proliferatory effects, which could be mediated by inactivation of PI3-kinase/Akt pathway, MAPK and p38, down-regulation of CyclinD1, Bcl-xL and GSK3β, up-regulation of p27, and activation of caspases [55,56]. Finally, anti-RAS strategies are also likely to effectively reduce tumor desmoplasia, reducing active TGF-beta and collagen I expression, and thereby decreasing solid stress, increasing tumor perfusion, reducing hypoxia, enhancing T cell infiltration and antitumor immunity [53]. All these experimental evidence have suggested ACE-Is or ARBs as repurposed drugs in oncology.

Several observational and retrospective studies have examined the association between RAS inhibitors and cancer survival. The results have remained conflicting even in studies where the same type of cancer was considered. Indeed, some studies showed no association between RAS inhibitors and prostate, esophageal, hepatic and gastric cancer occurrence [35] and with survival in patients with NSCLC [57].

Other studies, however, showed that RAS inhibitors were associated with decreased incidence of esophageal, pancreatic, and colon cancer [35] and with improved survival in patients with NSCLC [57]. Furthermore, the use of RAS inhibitors were associated with better survival in patients with metastatic renal cell carcinoma, metastatic colorectal cancer, glioblastoma and advanced hepatocellular carcinoma who received VEGF-targeted therapies or platinum-based chemotherapy [53]. These

results could be explained by observation in preclinical studies that AT1R signaling regulates proliferation and migration of cancer cells through transactivation of the EGFR by metalloproteinase-dependent shedding of EGF ligands. Thus, these evidences suggest the need for future prospective studies to evaluate the possible use of RAS inhibitors into adjuvant regimens, for the treatment of either cancers vulnerable to anti-angiogenic therapies or tumors resistant to platinum- or anti-EGFR-based chemotherapeutic schemes.

Interestingly, a recent meta-analysis of 55 studies suggests that RAS inhibitors could improve the survival of cancer patients, depending on cancer type and types of RAS inhibitors [57]. In this context, ARBs were proposed to produce better clinical results compared with ACE-Is [57] since some peptides that are involved into the RAS pathway, such as angiotensin- (1-7) and bradykinin, could influence the anti-tumor effects of ARBs or ACE-Is [54].

The prospective clinical trials available so far are very few and not conclusive yet. A recent single-arm phase II clinical trial (n=49 patients) showed that total neoadjuvant therapy with FOLFIRINOX (5-fluorouracil, irinotecan and oxaliplatin), losartan, and chemoradiotherapy provides downstaging of locally advanced pancreatic ductal adenocarcinoma and is associated with an improved margin-negative resection rate (69%; 95% CI: 55%-82%) [58]. Candesartan in addition to gemcitabine, however, failed to demonstrate activity against advanced pancreatic cancer [59].

Currently, five on-going studies are now expected to clarify the role of RAS- inhibitors in the treatment of cancer in the following setting: losartan and hypo-fractionated radiation after chemotherapy in borderline resectable or locally advanced unresectable pancreatic cancer (http://www.ClinicalTrials.gov NCT04106856); losartan with FOLFIRINOX followed by accelerated short course radiation therapy

with capecitabine in locally advanced pancreatic cancer (NCT01821729); losartan with nivolumab in combination with FOLFIRINOX and stereotactic body radiation therapy (SBRT) in localized pancreatic cancer (NCT03563248); losartan with sunitinib in relapsed or refractory osteosarcoma in pediatric and adult (NCT03900793); ramipril in addition to chemoradiation in glioblastoma (NCT03475186).

2.4 Cardiac glycosides and cancer

Cardiac glycosides are a family of compounds that inhibit the activity of Na^+-K^+-ATPase pump, leading to accumulation of intracellular Na^+ and a subsequent increase of intracellular Ca^{2+}. These drugs are approved by FDA for the treatment of congestive heart failure, atrial fibrillation and atrial flutter with rapid ventricular response.

The expression of Na^+-K^+-ATPase was found increased in several cancer models, such as gastric, bladder, colorectal and NSCLC [16,35]. Experimental studies showed that cardiac glycosides mediated inhibitory effect on the proliferation and induced apoptosis of certain cancer cells, increasing intracellular Ca^{2+} and Na^+ [16] and changing intracellular Bax/ Bcl-2 proportion [60]. Other studies found that cardiac glycosides modulated Src kinase, reducing PI3-kinase, Akt, EGFR and STAT3 activity, and enhanced Cdk5/p25 pathways [61,62]. In experimental studies it was found that cardiac glycosides increased the susceptibility of cancer cells to radiotherapy, especially in breast, lung, cervical, and prostate cancer cells [35].

When tested in observational studies however cardiac glycosides provided inconsistent results in several cancers such as colorectal, male breast and prostate cancer.

A recent meta-analysis including 14 case-control studies and 15 cohort studies showed that not only cardiac glycosides did not provide any beneficial clinical effects in lowering cancer risk or improving cancer survival, but rather suggested that the estrogen-like activity of cardiac glycosides could increase the risk of certain types of tumors, such as uterus and breast cancer [63].

To the best of our knowledge, only one prospective clinical trial has been concluded so far. In this phase IB study (n=20 patients), combination of digoxin and trametinib, a BRAF and MEK inhibitor, induces partial responses in patients with BRAF wild-type metastatic melanomas compared to those treated with trametinib alone (50% and 10%, respectively) [64]. This result is in line with experimental evidence suggesting that cardiac glycosides are not enough to induce the regression of patient-derived xenografts, but they synergize with MAPK pathway inhibitors to induce regression.

Currently, three ongoing studies are investigating the role of digoxin in the treatment of cancer in the following setting: digoxin in breast cancer (http://www.ClinicalTrials.gov NCT01763931) and in advanced or metastatic breast cancer (NCT03928210); association of digoxin, simvastatin and metformin in advanced pancreatic cancer and other advanced solid tumors (NCT03889795).

2.5 Aspirin and cancer

Aspirin, also known as acetylsalicylic acid, irreversibly inhibits the activity of cyclooxygenase-1 (COX-1), reducing the production of prostaglandins and thromboxane. However, it also exerts an inhibitory effect on COX-2, the mechanism of which is considered partly a result of salicylation. Aspirin is approved for several pathological conditions in which inflammation and pain are present. In particular, aspirin is mainly utilized to treat headache, toothache, migraine, neuralgia, sore

throat, dysmenorrhoea, symptomatic relief of influenza, feverishness, rheumatic pains, sciatica, lumbago, fibrositis, muscular aches and pains. It also has an antithrombotic action, mediated through inhibition of platelet activation, which has been shown to be useful in secondary prophylaxis following myocardial infarction, and in patients with unstable angina and cerebral transient ischaemic attacks.

Early theories indicated that the block of inflammatory factors, in the inflammatory microenvironment of the tumor, could directly expose the tumor cells to immune cells that orchestrate their elimination. Recent studies corroborated this hypothesis, demonstrating that over-expression of prostaglandin E2 (PGE2) could attenuate the immune system's normal response to diseased cells and lead cancer from escaping immune surveillance [65]. In addition, platelets could also help tumor cells to escape the immune system [66], promoting tumor cell proliferation and enhancing their ability to migrate [67].

Recent studies showed that COX-2 is up-regulated in several cancer cells, such as carcinoma in situ, breast, colorectal and NSCLC [65], and induces tumor growth and anti-apoptotic effects by increasing the expression of c-Jun-dependent transcription factors and bcl-2, respectively [68]. In addition, COX-2 and PGE2 overexpression is thought to induce neovascularization and to provide nutrition for tumor survival and proliferation [16]. Finally, COX-2 can affect up-regulation of MMP-2 expression, which then promotes tumor invasion and metastasis [68].

Therefore, targeting COX has largely investigated as new anticancer strategy. Several experimental studies showed that aspirin effectively inhibit a variety of tumor cell growth through multiple mechanisms. Aspirin can induce cell cancer apoptosis, downregulating bcl-2 expression and upregulating Bax and p53 [68], arrest cell cycle [69], disrupt abnormal collagen deposition, inhibiting NF-κB/P4HA2 axis and LMCD1-

AS1/let-7g/P4HA2 axis [70], promote DNA self-healing, inducing high expression of DNA mismatch repair proteins hMLH1, hMSH2, hMSH6 and hPMS2 [71], and reduce tumor cell invasion, downregulating MMP-2 expression and platelet activity [67,72].

The results obtained by large epidemiological studies have shown that regular aspirin use significantly reduced risk of several cancers, including colorectal, esophageal, gastric, breast and prostate cancer [73,74]. A recent analysis of systematic reviews, reporting on specific sites or long-term aspirin use, showed consistent evidence that long-term use of aspirin is necessary to achieve a cancer prevention benefit [75]. The effects of aspirin on cancer are not evident until at least 3 years after initiation of use, but cancer incidence was reduced after 3 years of treatment, and mortality was reduced from 5 years for as long as follow-up was available. In this analysis, the daily dose of 75 mg seems to be as effective as the higher dose (325 mg), but with lower risk of gastrointestinal bleeding.

However, in a 10-year observational follow-up study (n=2,536 patients), the efficacy of low-dose aspirin in cancer chemoprevention was not observed in patients with diabetes (HR 0.92, 95% CI: 0.73–1.14; p=0.4) [76]. In line, a meta-analysis involving a lower number of patients and studies did not find evidence for the role of aspirin as chemopreventive for colorectal cancer [77].

Overall, the lack of prospective clinical trials does not allow to confirm these promising data. However, a multicentre, randomised, placebo-controlled trial in 709 individuals with sporadic colorectal neoplasia, showed that, although aspirin did not reduce colorectal adenoma risk (RR 0.99, 95% CI: 0.87-1.12), it was effective in reducing the total number of colorectal adenomas per participant [78].

On-going trials, investigating aspirin as an adjuvant agent, for treatment and prevention of colorectal cancer are detailed in Table 1.

2.6 Low-molecular-weight heparins (LMWHs) and cancer

LMWHs are a class of antithrombotic agents derived from unfractionated heparin that inhibit coagulation by activating anti-thrombin III and subsequently inhibiting factor Xa. These drugs are approved for prophylaxis of venous thromboembolic disease (VTE) and for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).

LMWHs are currently the first-line prophylaxis and treatment of choice for venous thromboembolism in cancer patients. Beyond their anticoagulant action, several experimental evidences have suggested that LMWH could have potential benefits in cancer through multiple mechanisms [79]. Indeed, LMVHs were shown to inhibit CXCL12-mediated cell migration, angiogenesis (by interfering with VEGF, TF-FVIIa activation, fibrin and thrombin), P- and L-selectin-mediated cell adhesion, cell proliferation, tumour invasion, tumour growth and metastasis [79,80].

Studies in patients with cancer showed that LMWH treatment was associated with improvement of VTE recurrence and also with decreased mortality. The earliest evidences were provided by two meta-analyses of the ‘90s. The first, including randomized studies published between 1980 and 1994, showed a reduced RR for mortality (0.33, 95% CI: 0.1-0.8; p=0.01) in cancer patients treated with LMWH [81]. Then, as reported in a systematic review of nine studies for treatment of VTE, treatment with LMWH was associated with improved 3-month mortality (OR 0.61, 95% CI: 0.40-0.93) [82]. A post-hoc analysis of the CLOT trial for the prevention of recurrent VTE in patients with cancer (n=602) showed that dalteparin improved the risk of death at 1 year (HR 0.50, 95% CI: 0.27-0.95; p=0.03) in patients without metastasis, but not in patients with metastasis [83]. A more recent post-hoc analysis

of the PROTECHT study on thromboembolic prophylaxis in patients with advanced cancer (n=1150) showed that nadroparin improved the estimated 1-year survival rate (83%, 95% CI: 79%-87%) compared to placebo (76%, 95% CI: 70%-83%) only in patients with disease control [84].

The anti-cancer effect was also investigated in patients without VTE. In the FAMOUS study, where patients with advanced malignancy (n=385) were enrolled, subcutaneous injection of dalteparin (5,000 IU) failed to improve the median survival compared to placebo (10.8 *vs* 9.14 months; p=0.19). However, in a subgroup of patients (dalteparin, n =55; and placebo, n=47) with a better prognosis and who were alive 17 months after randomization, estimated survival at 2 and 3 years from randomization was significantly improved for patients receiving dalteparin versus placebo (78% *vs* 55% and 60% *vs* 36%, respectively; p=0.03) [85]. Patients with advanced solid cancers (n=302) enrolled in the MALT study, nadroparin favourably influences the survival rate (HR of mortality 0.75, 95% CI: 0.59-0.96; p=0.021). As for the FAMOUS study, a better HR (0.64, 95% CI: 0.45-0.90) and overall survival (15.4 *vs* 9.4 months of placebo group) were observed in those patients with a higher life expectancy (more than 6 months) [86]. In a meta-analysis of five randomized trials, including the FAMOUS and the MALT studies, patients with limited SCLC experienced a clear survival benefit (HR 0.56, 95% CI: 0.38–0.83; p=0.004). The survival benefit was not statistically significant for either patients with extensive small cell lung cancer (HR 0.80, 95% CI: 0.60–1.06; p=0.12) or patients with advanced cancer (HR 0.84, 95% CI: 0.68–1.03; p=0.08) [87]. All these evidences support the hypothesis that patients with a better prognosis benefit the most from the effect of heparin. In line with this, the ABEL study, enrolling 38 patients with newly-diagnosed, limited-stage SCLC, showed that bemiparin improved the median progression-free

survival (HR 2.58, 95% CI: 1.15-5.80; p=0.022) and overall survival (HR 2.96, 95% CI: 1.22-7.21; p=0.017) [88].

However, a recent meta-analysis of nine studies, published from 2004 to 2013, and 5,987 patients, 98.4% of whom had advanced-stage disease (III and IV), did not confirm the survival benefit of LMWH. The results of this meta-analysis suggest that the use of prophylactic LMWH does not have a discernible effect on overall survival in patients with solid malignancy without VTE [(pooled OR for overall 1-year mortality 0.87, 95% CI: 0.70–1.08; p=0.21) (pooled RR 0.94, 95% CI: 0.86–1.04; p=0.24)] [89]. This conclusion is consistent with those of four recent prospective trials. In CONKO-004 pilot trial enrolling 312 patients with inoperable pancreatic cancer, subcutaneous enoxaparin (40 mg/day) was not effective in progression-free (HR 1.06, 95% CI: 0.84-1.32; p=0.64) and overall survival (HR 1.01, 95% CI: 0.87-1.38; p=0.44) [90]. In the FRAGMATIC trial, conducted in 2,202 patients with newly-diagnosed lung cancer of any stage and histology, prophylactic dose of dalteparin lead a significant reduction in VTE, but failed to improve overall survival (HR 1.01, 95% CI: 0.93-1.10; p=0.814) or metastasis-free survival (HR 0.99, 95% CI: 0.91-1.08; p=0.864) [91]. In the RASTEN trial, a randomized phase III study, enrolling SCLC patients (n=390), enoxaparin at a supra-prophylactic dose (1 mg/kg/day by subcutaneous injection) did not improve overall survival (HR 1.11, 95% CI: 0.89–1.38; p=0.36) and progression-free survival (HR 1.18, 95% CI: 0.95–1.46; p= 0.14) [92]. In the TILT trial, conducted in 549 patients with resected NSCLC, tinzaparin failed to improve overall survival (HR 1.24, 95% CI: 0.92–1.68; p=0.17) and the cumulative incidence of recurrence (subdistribution HR 0.94, 95% CI: 0.68–1.30; p=0.70) [93].

Overall, the incongruity of the data obtained in clinical trials does not support the use of LMWH in cancer treatment, which is currently limited to primary prophylaxis in

patients at high risk of VTE, in patients diagnosed with VTE, and as secondary prophylaxis [94]. However, future clinical trials are needed to identify the group of patients eligible for anticoagulant therapy, focusing on those with a better prognosis and without metastatic disease. Currently, there are several trials investigating LMWH for VTE prevention in cancer patients, but only one in patients without risk of VTE. This study will evaluate whether the extended peri-operative tinzaparin improve disease-free survival in patients with resectable colorectal cancer (http://www.ClinicalTrials.gov NCT01455831).

3. Cardiovascular drugs in non-cancer pathologies

3.1 β-blockers and ARBS in Marfan's syndrome (MFS)

Marfan's syndrome is an autosomal dominant disorder of connective tissue, caused by mutations in the gene encoding fibrillin-1 (FBN1) and excessive TGFβ activation. It is characterized by several cardiovascular manifestations, the major morbidity and mortality factors being progressive aortic-root dilatation and dissection that require clinical management.

Several experimental studies in animal models showed that the ARB losartan and the β-blocker propranolol preserved aortic-wall architecture and inhibited aortic dilatation, root growth and wall thickness [95].

In a meta-analysis including 5 non-randomized follow-up studies and 1 prospective randomized trial (n=802 patients), the β-blocker therapy (mainly atenolol, propranolol, nadolol and metoprolol) failed however to improve clinical output, measured as aortic dissection or rupture, cardiovascular surgery, or death [odds ratio (OR) 1.54, 95% CI: 0.99-2.40] [96]. By contrast, a meta-analysis of 5 non-randomized studies, enrolling children and adolescent patients (n=392), showed that β-blocker therapy (mainly

atenolol or propranolol) significantly decreased the rate of aortic dilatation [standard mean difference (SMD) -1.30, 95% CI: -2.11 to -0.49; p=0.002]. A tendency of beneficial clinical outcome was observed in the β-blocker treatment group when compared with no β-blocker treatment group (OR 0.87, 95% CI: 0.37-2.04). No significant difference was reported for clinically important endpoints, such as death, cardiovascular surgery, or aortic dissection or rupture [97].

In a recent review, data from all the randomised controlled trials available until 28 June 2017, with at least 1 year in duration, assessing the effects of β-blocker monotherapy compared with placebo, no treatment or surveillance, were analyzed [98]. It was found only one randomised controlled trial comparing long-term propranolol to no treatment. In this open-label, randomised, single-centre trial including 70 MFS patients, long-term propranolol treatment reduced the mean slope of the regression line for the aortic-root dimensions (0.023 *vs* 0.084 per year, p<0.001), but it did not reduce the incidence of all-cause mortality (RR 0.24, 95% CI: 0.01-4.75), of aortic dissection (RR 0.59, 95% CI: 0.12-3.03), aortic regurgitation (RR 1.19, 95% CI: 0.18-7.96), congestive heart failure (RR 1.19, 95% CI: 0.18-7.96) or cardiovascular surgery (RR 0.59, 95% CI: 0.12-3.03) compared to no treatment. The others retrospective and prospective studies of the efficacy of β-blocker in MFS reported in this review showed mixed results. Despite this, most of the authors suggested that β-blocker therapy might decrease the rate of aortic root dilatation in MFS and recommend β-blocker treatment as soon as the diagnosis is made.

ARBs (mainly losartan and irbesartan) effectiveness was evaluated in several clinical trials, combined with baseline therapy versus no additional therapy. The studies comparing the cardiovascular-protective effects of losartan and β-blocker showed variable results. In a retrospective single center study conducted on 90 MFS patients

undergoing aortic root replacement, RAS blockade (ARBs or ACE-Is) plus β-blocker improved survival free from major aortic events (p=0.008), risk of major aortic events [hazard ratio (HR) 0.38, 95% CI: 0.30-0.43; p=0.002] and mean diameter change in descending thoracic (0.9±0.7 mm/year *vs* 2.5±1.0 mm/year; p<0.001) and supra-renal abdominal aorta compared with β-blocker alone [99].

In the COMPARE study, a multicentre, open-label, RCT, enrolling MFS patients (n=233), 3-year treatment with losartan reduced the aortic root dilatation rate (0.77±1.36 *vs* 1.35±1.55 mm; p=0.014) compared to control (i.e. β-blocker and calcium channel blocker therapy). This effect was also present in patients with prior aortic root replacement (0.50±1.26 *vs* 1.01±1.31 mm; p=0.033). However, no effect was observed in the composite end point (aortic dissection, elective aortic surgery, or cardiovascular death) [100]. Using the same cohort of patients, Franken and colleagues found that patients with haplo-insufficient FBN1 mutations (n=38) seemed to be more responsive to losartan therapy than patients with dominant negative FBN1 mutations, since 3 years of losartan treatment reduced aortic root dilatation rate (0.5±0.8 mm *vs* 1.8±1.5 mm; p=0.001), biventricular end diastolic volume (EDV) and stroke volume (SV) only in these patients and not in dominant negative patients [101,102].

In a double-blind, randomized, multicentre, placebo-controlled, add-on trial enrolling 299 patients with a median follow-up of 3.5 years, losartan (50-100 mg daily) combined with standard therapy (86% received β-blocker therapy, mainly atenolol) does not significantly alter the aortic root dilatation rate, despite slight but significant decrease in both systolic and diastolic blood pressure. The authors suggest that β-blocker therapy alone should therefore remain the standard first line therapy in these patients [103].

Several RCTs were designed to compare the effects of β-blocker and ARBs, without a placebo group. A multicentre RCT, enrolling 608 children and young adults MFS patients treated for 3-years with atenolol (maximum daily dose 250 mg) or losartan (maximum daily dose 100 mg), showed no significant difference in the baseline-adjusted rate of change in the aortic root z score between treatment groups (-0.139 ± 0.013 units per year for atenolol and -0.107 ± 0.013 for losartan; p=0.08) and in the average annual rate of change in the absolute diameter of the aortic root (0.069 ± 0.004 cm for atenolol and 0.075 ± 0.004 cm for losartan; p=0.20). Relevantly, younger subjects showed a greater decrease in the aortic root z score over time (p< 0.001 for atenolol, p= 0.002 for losartan), without a significant difference between the treatment groups (p=0.38 for interaction) [104].

In randomized, double blind pilot study in MFS and Loeys–Dietz syndrome patients (n=17) treated with atenolol (25–50 mg daily) or losartan (25 mg daily), the percent changes at 12-months compared to baseline in several echocardiographic-doppler measures of the vascular properties of the aorta [i.e., characteristic impedance (Zc), input impedance (Zi), elastic modulus (Ep), total arterial compliance (TAC), stiffness indexes] were well above the 10% threshold favouring the losartan group, suggesting a beneficial effect on the vascular properties of the central aorta. However, the hydraulic power seems to be more beneficially affected by atenolol. Thus, atenolol and losartan might improve vascular function and stiffness via distinct mechanisms of action [105]. Similar hypothesis was formulated by the authors of a double-blind trial in MFS adults (n=34) treated for 6 months with losartan (100 mg QD) or atenolol (50 mg QD). Indeed, pulse wave velocity (PWV) decreased in atenolol group (–1.15 ± 1.68 m/s; p=0.01), but not in losartan group (–0.22 ± 0.59 m/s; p=0.15; between-group difference p=0.04). In contrast, central augmentation index (AIx) decreased in

the losartan group (–9.6 ± 8.6%; p<0.001) but not in the atenolol group (0.9 ± 6.2%, p=0.57; between-group difference p<0.001) [106].

No significant differences were found in aortic size changes between the losartan (50-100 mg daily) and atenolol (50-100 mg daily) groups in the LOAT study, a phase IIIb, randomized, parallel, double-blind trial, conducted in 140 MFS patients. After 3 years of follow-up, no difference was observed in the absolute difference of aortic root diameter (-0.3 mm, 95% CI: -1.1 to 0.4; p=0.382) and indexed by body surface area (BSA) (-0.5 mm/m^2, 95% CI: -1.2 to 0.1; p=0.092) between losartan and atenolol groups. Also, the difference of ascending aorta diameter indexed by BSA (-0.3 mm/m^2, 95% CI: -0.8 to 0.3; p=0.326) was similar between losartan and atenolol [107].

In a recent systematic review and meta-analysis, including the last 7 RCTs reported above [100,103–107] plus another study, and involving 1381 patients who received only β-blocker and ARB-related therapies, no difference were observed in changes of aortic root diameter (SMD 0.04, 95% CI: -0.11 to 0.19; p=0.63), aortic dissection (Peto OR 1.67, 95% CI: 0.42-6.72; p=0.47), aortic surgery (risk ratio = 0.97, 95% CI: 0.66-1.41, p=0.86) and death (Peto OR = 2.78, 95% CI: 0.39-19.82; p=0.31). In addition, a subgroup analysis considering patients treated with ARBs plus β-blocker and β-blocker alone, the double drug therapy improved, although not significantly, aortic root diameter (SMD 0.11, 95% CI: -0.22 to 0.45; p=0.52), ascending aorta diameter (SMD 0.10, 95% CI: -0.07 to 0.27; p=0.26) and aortic surgery (Peto OR 1.10, 95% CI: 0.75-1.61; p=0.62). The authors suggested that ARB therapy is not inferior to β-blocker therapy, and that co-treatment with ARB seemed to be favourable to those of only β-blocker therapy [108].

An open-label extension of the LOAT study (n=128 patients), with a follow-up of a mean of 6.7 years, showed no difference between losartan and atenolol in aortic root diameter increase, aortic dilation progression (-0.0 mm/year, 95% CI: -0.25 to 0.17; p=0.754), combined endpoint of aortic surgery, aortic dissection, or death (p=0.462) or combined endpoint of acute aortic syndrome or death (p=0.305) [109].

The effectiveness of losartan in combination with β-blocker was reported in isolated case-report also in neonatal MFS (nMFS), which is characterized by rapidly progressive multi-valvular cardiac disease and death from congestive heart failure, typically within the first year of life. The five nMFS patients with combined β-blocker and losartan treatment lived at least 2 years, suggesting that this strategy should be considered for nMFS patients to prevent rapidly progressive aortic root dilatation [110].

In conclusion, patients with Marfan's syndrome and aortic root dilation should receive β-blocker or ARB therapy. However, RCTs with large sample sizes are needed to clarify drug-related effects and relevant factors in the future. In particular, individual's characteristics, including tolerance, age, aortic size, family history of aortic dissection, genetic mutation, and other risk factors should be considered in the study design.

3.2 β-blockers and migraine

Migraine is considered not only as a central nervous system (CNS) disorder but also a systemic metabolic disorder, in which release of serotonin from platelet appears to be highly involved. The use of β-blockers for the treatment of migraine began in the late '60's. Several mechanisms of action of β-blockers in the prophylactic treatment

of migraine have been suggested, such as inhibition of cerebral arterial dilatation and modulation of serotonin release from platelets.

The 2012 American Academy of Neurology guideline recommends β-blockers, specifically propranolol and metoprolol, as first line therapy for preventing migraine [111].

In a systematic review and meta-analysis, including 108 RCTs (50 placebo-controlled and 58 comparative effectiveness trials), propranolol (n=74 trials) and metoprolol (n=21 trials) were the most commonly evaluated β-blockers. In episodic migraine, among β-blockers, only propranolol showed high-quality evidence in reducing the rate of migraines than placebo at 8 and 12 weeks [(8 weeks: -1.5 headaches/month, 95% CI: -2.3 to -0.65) (12 weeks: -1.2 headaches/month, 95% CI: -1.8 to -0.60)], headache index (8 weeks: SMD -0.48, 95% CI: -0.75 to -0.22 and 12 weeks: -0.41, 95% CI: -0.65 to -0.17), headache severity (8 weeks: SMD -0.51, 95% CI: -0.76 to -0.26) and headache duration (8 weeks: -6.1 hours, 95% CI: -16.2 to -0.39). Propranolol also showed improvement of headaches at 12 weeks [RR 1.4, 95% CI: 1.1-1.8; number needed to treat (NNT) 4.5, 95% CI: 2.8-12.9]. Although with lower quality evidence, metoprolol, and in same case also bisoprolol and timolol, were also effective. Very few RCTs evaluated the effectiveness of β-blockers in chronic migraine and tension-type headache. In these trials propranolol was no better than valproic acid or flunarizine, and the combinations (propranolol plus topiramate and propranolol plus flunarizine) were no better than topiramate and flunarizine alone [112].

In conclusion, almost all trials evaluated the effectiveness of β-blockers within 12 weeks; this is an important limitation since migraine is a chronic condition. Thus, whether treatment benefit persists, increases or decreases is unknown and deserves

further studies. Furthermore, future trials might define the effectiveness of β-blockers in migraine prophylaxis in comparison to other classes of medication, not only in episodic migraine, but also in chronic migraine and tension-type headache.

3.3 Statins and bacteria-related diseases

Several *in vitro* and *in vivo* experimental studies have suggested a possible therapeutic use of statins to treat bacterial infections in humans [113,114]. However, the mechanisms by which this antibacterial effect occurs have yet to be fully clarified. Currently, the hypothesized mechanisms include the inhibition of Rho GTPase activity and cholesterol production, which could explain the pleiotropic effects of statins repressing cell growth or reducing biofilm viability and production. Statins may also bind to bacterial cell surface structures and/or surface proteins, and reduce the production of a protective membrane-stabilising metabolite in the mevalonate pathway, resulting in decreased bacteria proliferation and virulence [114]. Furthermore, statins could decrease invasion and survival within host-cells through inhibition of lipid raft formation and suppress the production of toxins [113].

Statins have shown positive effects in particular in respiratory tract infections. Simvastatin, but not fluvastatin and pravastatin, showed *in vitro* antibacterial activity against respiratory pathogens such as *Moraxella catarrhalis* and *Streptococcus pneumoniae.* Thus, a likely mechanism is that the hydrophobic character of simvastatin perturbs the bacterial membrane in a ‘‘soap-like’’ manner, with the result of release of the autolytic enzyme LytA and subsequent degradation of cell wall peptidoglycan (PGN) and autolysis. The antibacterial effect of simvastatin against *Streptococcus pneumoniae* is independently of HMG-CoA reductase blockade. In mouse models of lung infection, simvastatin protected against *Streptococcus*

pneumoniae and *Staphylococcus aureus*, by enhancing bacterial clearance, dampening inflammatory response and modulating coagulation [115,116]. By contrast, simvastatin is ineffective against *Haemophilus influenzae* [117].

Numerous retrospective and observational studies, and systematic reviews with meta-analysis suggest that individuals using statins have a reduced risk of death due to bacteremia, sepsis, or pneumonia [118,119]. However, these studies, with the inherent likelihood of selection, heterogeneity or ascertainment bias, provide relatively weak support for "off-label" use of statins as prophylaxis against infection.

Thus, RCTs in uniform patient populations, distinguishing de novo from continued statin therapy, are needed.

In a single centre phase II randomized placebo-controlled trial enrolling patients with sepsis (n=100), atorvastatin (40 mg daily) improved the conversion rate to severe sepsis compared to placebo (4% *vs* 24%; p=0.007) [120]. This result was confirmed in 250 patients, stratified by site and prior statin use, enrolled in a phase II, multicenter, randomized, placebo-controlled trial. Prolonged therapy with atorvastatin (20 mg per day) in previous statin users was associated with an improvement in mortality at 28 days [adjusted Odds Ratio (OR^{adj}) 0.17, 95% CI: 0.03-0.85; p=0.03]. The difference was not statistically significant at 90 days (OR^{adj} 0.33, 95% CI: 0.09-1.22; p=0.10). De novo therapy, however, was not associated with a statistically significant difference in mortality [121].

Atorvastatin exerts also positive effects in patients with bronchiectasis. In a proof-of-concept randomized placebo-controlled trial in patients with bronchiectasis (n=60), atorvastatin reduced cough measured by the Leicester Cough Questionnaire (LCQ) (MD=2.2, 95% CI: 0.5–3.9; p=0.01) compared to placebo from baseline to 6 months. However, with respect to systemic inflammation, atorvastatin had no effect on the

amounts of IL1β, IL6, IL10 and TNFα, leucocyte count, total neutrophil count, and the erythrocyte sedimentation rate [122]. In a double-blind cross-over RCT enrolling 27 patients with bronchiectasis infected with *Pseudomonas aeruginosa*, high-dose atorvastatin (80 mg) for 3 months failed to reduce cough severity (LCQ score), but it improved the St. Georges Respiratory Questionnaire (SGRQ) (MD -5.62, 95% CI: -10.13 to -1.13; p=0.016) and serum levels of CXCL8 (p=0.04), TNF (p=0.01), and ICAM1 (p=0.04) compared to placebo [123]. However, in a randomized placebo-controlled in intensive care unit (ICU) patients with ventilator-associated pneumonia (VAP) (n=300), simvastatin (60 mg daily) did not improve 28-day survival [124].

In addition to antibacterial effect, anti-inflammatory effects of statins are suggested as adjuvant benefits in *Helicobacter pylori* eradication rate. In a randomised placebo-controlled trial enrolling 113 patients with *Helicobacter pylori* infection treated with triple eradication regimen, simvastatin (20 mg twice daily for 1 week) improved the eradication rate (86% *vs* 69%; p<0.04) [125].

Overall, the results of clinical studies assessing the repurposing of statins as antimicrobials have been inconclusive, in particular when infections were treated with de novo statins. Robust conclusions might be reached by prospective RCTs focusing on statin and pathogen specificity, bacterial virulence, combinatorial therapy, and/or means of drug administration.

Currently, there are two trials investigating the antibacterial effect of pravastatin against *Mycobacterium tuberculosis* as adjunctive therapy (http://www.ClinicalTrials.gov NCT03456102 and NCT03882177).

In conclusion, although the results are promising, multi-centre studies are needed to verify these findings, investigating the doses, the specific anti-pathogen activity and the prior statin use.

3.4 Statins and fungal infection

Several *in vitro* studies have indicated antifungal effects of statins with the exception of cerivastatin and pitavastatin, which have no reports documenting their antifungal activity [126]. The capacity of statin to modulate biosynthetic pathway of important isoprenoids (as farnesyl pyrophosphate and geranylgeranyl pyrophosphate), through the inhibition of HMG-CoA reductase, is proposed as mechanism underlying the antifungal activity of statins. Indeed, it was shown that statins decrease the biosynthesis of ergosterol in fungal cells, resulting in a decreased membrane fluidity [126], and that supplementation with ergosterol or cholesterol in aerobic fungal culture led to partial recovery from statin-mediated growth inhibition [127]. Statins are also able to block the biosynthesis of some fungal siderophores such as fusarinine, and through this mechanism, they induce iron starvation [128]. Furthermore, inhibiting biosynthesis of farnesyl pyrophosphate, statins could block isoprenylation of different fungal proteins, such as heme A, which causes the decrease of cytochrome C biosynthesis and dysfunctional respiration of fungal cells [126]. The statin-induced disruption of Ras protein prenylation has been described affecting biofilm production, fungal cell morphogenesis and ability of some fungal spores to germinate [129]. Finally, statins were shown to induce damage to mitochondrial functions, DNA fragmentation and cytoplasm condensation by altering the processing of MRas1 protein, blocking the accumulation of MRas3 protein, and disrupting the MRas1/p20 protein complex [130].

These antifungal effects were also observed in animal models of fungal infections, such as candidemia, keratitis, pythiosis and mucormycosis [126]. Although the data indicate that statins could potentially be efficacious in the treatment of fungal

infections, additional animal studies are required to confirm their effectiveness since the low number of studies.

Up-to-date, there are few studies regarding the antifungal activity of statins in human. The first evidence was reported in a retrospective cohort study on intra-abdominal solid-organ transplanted patients with bloodstream infections (n=311), of which 9% (n=30) had fungal infections. Overall, statins use was associated with a lower risk of mortality (OR 0.18, 95% CI: 0.04–0.78; p=0.008) [131]. Then, three studies have supported the efficacy of statins in candidemia. A single small case-matched candidemia study showed lower mortality (OD 0.09, 95% CI: 0.11–0.75; p=0.03) among 15 statin-users compared to 30 matched controls [132]. A retrospective cohort study in patients with T2DM who underwent gastrointestinal surgery (n=1019) indicated that the use of statins during the 6 months before hospitalization is positively correlated with a decreased incidence of cultures positive for candidiasis (OR 0.60, 95% CI: 0.38–0.96; p=0.03) and with a statistically significant prolonged time to event (p=0.01) [133]. Similarly, results of another multicenter cohort study of hospitalized adults with candidemia (n=326) documented that statin use 7 days prior to hospitalization was independently associated with a decrease in early 5 day case-fatality (OR^{adj} 0.17, 95% CI: 0.03–0.93; p=0.041), but not 14 days, and overall (30 days) case-fatality [134]. On the contrary, in two other retrospective studies statin use was ineffective in patients with fungal infections. In the first, a review of 124 candidemia episodes, statin use during candidemia did not alter mortality, length of stay, or intensive care requirement [135]. In the second, a case-controlled study including 238 patients, statin use within 3 months of index date was not an independent variable for prevention or development of invasive infections by zygomycetes and aspergillus spp [136].

Overall, considering the high bias risk in retrospective and observational studies, additional randomized, controlled, double-blinded clinical trials are needed.

3.5 Statins and periodontitis

The well documented anti-inflammatory effects of statins, together with actions on MMPs, osteoclasts and osteoblasts [137,138] have provided the rationale for the their possible use for treating periodontitis. A retrospective study of 100 periodontitis patients showed that systemic statins treatment was associated with a 37% reduction in the number of pathological periodontal pockets ($p=0.00043$) and a 40% smaller periodontal inflammatory burden index (PIBI) ($p=0.00069$) compared to patients without statin [139].

Thus, several randomized, placebo-controlled trials, enrolling patients with chronic periodontitis, were performed to evaluate the effect of locally delivered statins. A recent systematic review and meta-analysis, evaluating 8 randomized, controlled trials and 2 prospective studies including a total of 576 patients, showed that statins treatment (simvastatin, atorvastatin and rosuvastatin) induced a better change from baseline of defect fill (weighted MD 1.37 mm, 95% CI: 0.96-1.77; $p<0.0001$), probing depth (PD) reduction (WMD 1.76 mm, 95% CI: 1.04-2.47; $p<0.0001$), and clinical attachment level (CAL) gain (WMD 1.58 mm, 95% CI: 0.89-2.28; $p<0.0001$) [140]. One randomized, controlled trial (n=90 patients) included in this meta-analysis, showed that rosuvastatin (1.2% subgingivally delivered) improved significantly better modified sulcus bleeding index (mSBI), PD, CAL, and IBD depth than atorvastatin (1.2% subgingivally delivered) or placebo gels at 6 and 9 months [141]. The authors suggested that the significance of the greater clinical benefits might be explained by the stronger anti-inflammatory action of rosuvastatin compared to that of atorvastatin.

A single-center RCT also evaluated the effectiveness of atorvastatin (1.2% subgingivally delivered) in patients with chronic periodontitis and T2DM, in which the periodontal tissue destruction is more severe. Atorvastatin significantly induced greater mSBI and PD reduction as well as relative attachment level (RAL) gain at 3, 6, and 9 months than the placebo group [142].

Currently, there is only one trial investigating the effectiveness of simvastatin in periodontitis, in particular the effect of locally-applied simvastatin on clinical attachment level and alveolar bone in periodontal maintenance patients (http://www.ClinicalTrials.gov NCT03452891).

However, due to the relatively small sample sizes of the included studies, there is need for future multicenter RCTs confirm the advantages of using statins in combination with non-surgical periodontal treatment for patients with periodontitis.

3.6 Statins and contrast-induced nephropathy

Contrast-induced nephropathy (CIN) is an acute kidney injury that might occur after the intravascular use of iodinated contrast media (CM) during diagnostic coronary angiography (CAG) or percutaneous coronary intervention (PCI). Of note, the risk of CIN is higher in acute myocardial infarction, T2DM, congestive heart failure, advanced age, and hypertension. There are currently limited strategies to prevent CIN, such as intravenous pre- and post-hydration with 0.9% sodium chloride plus N-acetylcysteine or $NaHCO_3$ [143].

Several *in vitro* and *in vivo* experimental studies have shown the ability of statins to attenuate CIN, mainly by modulating oxidative stress (i.e. decrease of lipid hydroperoxides and myeloperoxidase, increase of glutathione levels), inflammatory responses (through the regulation of JNK/p38/Hsp2 and TLR4/MyD88 signaling

pathways) and apoptosis (through the up-regulation of Hsp27) [144–147]. Moreover, statins may reduce the reabsorption of contrast agents in renal tubules, thereby reducing toxicity within them [148].

A meta-analysis of 21 RCTs (12 using atorvastatin, 6 rosuvastatin and 3 simvastatin), involving 7,746 patients undergoing CAG or PCI, showed that the risk of acute CIN, also named CI-AKI (contrast-induced acute kidney injury), was reduced by short-term statin therapy compared with the control (RR 0.57, 95% CI: 0.47–0.69; p<0.00001). The results remained significant regardless of whether patients received or not hydration or N-acetylcysteine or the type of contrast agent and statin used. The decreased risk of CI-AKI remained significant analysing patients with chronic kidney disease (CKD), T2DM or congestive heart failure. Interestingly, a sub-group analysis showed that the risk incidence of CI-AKI was lower in the high-dose versus lower-dose statin group (RR 0.31, 95 %CI: 0.17–0.56; p<0.0001) [149].

A recent meta-analysis of 9 RCTs (4 not included in the previous meta-analysis) comparing the lipophilic statin-atorvastatin pre-treatment with placebo for prevention of CI-AKI, in patients undergoing CAG (n=2,270), showed that atorvastatin reduces the risk of CI-AKI (OR 0.46, 95% CI: 0.27–0.79; p=0.004) compared with the control group. A sub-analysis obtained similar results with high-dose atorvastatin (≥ 80 mg daily) reducing the risk of CI-AKI (OR 0.45, 95% CI: 0.21–0.95; p=0.04) [150].

Some authors hypothesize that rosuvastatin, thanks to its hydrophilic characteristics, may have a better tendency to prevent CIN than others, probably due to a longer plasma half-life and a stronger anti-inflammatory effect. In a recent meta-analysis of 15 RCTs with a total of 2,673 patients undergoing CAG or PCI, short-term moderate or high-dose rosuvastatin treatment (20 or ≥40 mg daily) showed a 55% lower risk of CIN compared with low-dose rosuvastatin pre-treatment (≤10 mg daily) or placebo

group (RR 0.45, 95% CI: 0.35–0.58; p<0.0001). Furthermore, moderate or high-dose rosuvastatin treatment significantly reduced the incidence of CIN compared with the control [(RR 0.39, 95% CI: 0.29–0.54; p<0.0001) and (RR 0.56, 95% CI: 0.37–0.85; p=0.006) respectively]. A subgroup analysis showed that moderate or high-dose rosuvastatin pre-treatment could decrease the incidence of CIN in patients with CKD (RR 0.53, 95% CI: 0.30–0.93; p=0.03), T2DM (RR 0.51, 95% CI: 0.31–0.86; p=0.01) or acute coronary syndrome patients undergoing PCI (RR 0.52, 95% CI: 0.35–0.76; p=0.0009) [151].

Overall, the results of these meta-analyses suggest that short-term statin therapy, initiated before invasive procedures, prevents the development of CI-AKI. Furthermore, the preventive effect of statins on CIN showed also advantages in patients with CKD, T2DM, congestive heart failure or acute coronary syndrome undergoing PCI.

Currently, there is only one trial investigating the effective of atorvastatin in combination with ascorbic acid for prevention of contrast-induced nephropathy (http://www.ClinicalTrials.gov NCT03391830).

3.7 Statins and acute kidney injury (AKI) following cardiac surgery

Cardiac surgery with cardiopulmonary bypass may lead to *acute kidney injury* (AKI) through decreased renal perfusion, bursts of inflammatory mediators or emboli [152]. As for contrast-induced nephropathy, pleiotropic effects of statins could protect kidney also in this clinical condition.

In two recent observational studies, pre-surgical statin therapy is associated with a reduction in AKI risk after cardiac surgery [153,154]. In a cohort of 17,000 cardiac surgery patients, a 22% relative risk reduction of AKI was observed in statin-treated

patients (RR 0.78, 95% CI: 0.63-0.96) [154], while a lower effect was reported in a cohort of 3,704 patients (RR 0.86, 95% CI: 0.74-0.98) [153]. In contrast, a retrospective study of 10,648 consecutive patients undergoing coronary artery bypass grafting, statin therapy was not associated with a reduced risk of AKI (OR 0.97, 95% CI: 0.84-1.12; p=0.68) [155]. Thus, the results of retrospective studies remain inconclusive.

A recent meta-analysis of 8 RCTs, evaluating data from 3,204 patients undergoing cardiac surgery and treated with statin therapy or placebo/no intervention, showed that perioperative statin therapy was not associated with decreased risk of postoperative AKI (RR 1.02, 95% CI: 0.82-1.28; p=0.85). Furthermore, the authors stated that sufficient evidence has accumulated to reject the possibility that perioperative statin therapy can significantly improve the incidence of AKI [156].

In conclusion, although the negative results do not support the use of statin therapy to prevent AKI after cardiac surgery, the renal effects of perioperative statin therapy should be further investigated by analysing specific statin regimens and selected groups of patients.

4. Conclusion

Data from several experimental studies, also confirmed by observational and retrospective evidence, have suggested anti-cancer effects of β-blockers, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), statins, NSAIDs, cardiac glycosides and Low-molecular-weight heparins (LMWHs). Retrospective studies have however several limitations including a low level of evidence, the retrospective nature of the registry, the frequent lack of data on covariates, treatment duration and dose and the low sample size in subgroups, which

may have led to false positive results. The results of large-scale RCTs were often inconclusive or in contrast with those obtained in pilot studies. Therefore, no definitive conclusion has been drawn from the clinical studies and no definitive recommendations can be made.

With regard to treatment and/or prevention of other pathological conditions, β-blockers, ARBs and statins have shown promising results in RCTs and this has led, or may lead in the near future, to new indications for these drugs. Indeed, β-blockers as well as ARBs showed significant effectiveness in migraine and in Marfan's syndrome. Statin in combination with non-surgical periodontal treatment exerted additional benefits in patients with periodontitis, whereas short-term statin therapy initiated before invasive procedures prevented the development of CI-AKI.

Disclosure

None

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Figure Legends

Figure 1. The main anti-cancer effects and related mechanisms of action for repurposed cardiovascular drugs.

Figure 2. The direct antibacterial effects of statins. Bacterial growth and virulence are modulated by statins mainly by enhancing degradation of bacterial wall peptidoglycan and autolysis and by reducing bacterial growth, attachment, lipid raft formation, invasion, biofilm formation and dampening the impact of toxins on host cells.