Drug repurposing in cardiovascular diseases: opportunity or hopeless dream?

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Abstract

Cardiovascular disease remains - despite the development of new drugs, devices, and therapeutic strategies- the leading cause of death and disability worldwide.

There is therefore a great need to implement the pharmacological armamentarium, considering also the need to balance the therapeutic and the side effects. Furthermore, the best choice among the drug treatment options and reduction of side effects remain urgent problems for studies of cardiovascular disease.

In this context, drug repurposing could be an innovative way and opportunity to extend and improve pharmacological tools. Indeed, applying well-established drugs and compounds to new indications, drug repurposing has already been proven efficient and safe in humans. Furthermore, this approach generates lower costs and needs shorter time for approval than the development of a de novo drug. In the current review, we discuss the main evidence for the repurposing in cardiovascular diseases of drugs approved and marketed for other pathologies by reviewing their mechanisms of action and the results reported in observational and then in randomized studies.

Keywords

Drug repurposing, cardiovascular diseases

1. Introduction

Drug repurposing (also known as drug repositioning, reprofiling or re-tasking) is a promising field in drug discovery for identifying new therapeutic uses for already studied drugs. These drugs could be either currently approved and marketed for another use or withdrawn because of adverse effects; alternatively, investigational compounds “shelved” due to negative results, when tested in clinical trials, could be repositioned.[1]. In one sentence, drug repositioning can be defined as expanding successful drugs and renewing failed ones [2]. It offers a great opportunity to the traditional de novo drug discovery, since the success rate of developing a new molecular entity is 2.01% only [3] and the number of approved drugs has been declining since the ‘90s. In the last decade, about one-third of the approvals correspond to drug repurposing, and repurposed drugs currently generate around 25% of the annual revenue for the pharmaceutical industry [4]. Drug repurposing is a direct application of polypharmacology, which describes the ability of drugs to act on multiple targets (genes or proteins) or disease pathways. It is known that several drugs can interact with different targets (average 6–13 multiple targets) [5], displaying also off-target effects that could reveal new potential therapeutic applications. These effects are often discovered by serendipitous observations made either in the lab or during clinical studies. For example, the clinical effects of sildenafil on treating erectile dysfunction were observed when it was studied for treating coronary artery disease and pulmonary arterial hypertension [6], whereas the hypertrichosis observed in hypertensive patients led to the development of a topical formulation of minoxidil for promoting hair growth [7]. In some cases, in-depth understanding of the molecular basis of disease and of drug activity have led to successful development of drugs for entirely new therapeutic areas. Azidothymidine is an example of this,

having failed as a chemotherapy drug but having then became a treatment for human immunodeficiency virus, and the same happened with mycophenolate mofetil for lupus nephritis [8]. Furthermore, complex diseases (such as neurodegenerative diseases and cancers) involve networks of multiple mediators or genes, hence necessitate multi-pharmacophores as a part of their therapeutic and system biology-based approaches.

The growing amount and availability of public and open source databases, knowledge, algorithms, and servers let the drug repurposing an increasingly common approach. It has many advantages over traditional de novo drug discovery approaches, since it can significantly reduce the healthcare cost and development timeline [1]. As per an estimate, drug repurposing can potentially make a drug available for use in patients within 3-12 years with a total estimated cost of $40-80 milion versus at least 13-15 years and cost of $2-3 bilion for developing a new drug. [9]. This approach capitalizes on the fact that approved drugs and many abandoned compounds have already been tested in humans and detailed information is available on their pharmacology, formulation and dose [1]. Since repurposed molecules not only have optimized pharmacokinetics, pharmacodynamics, and toxicity profiles, but also are already approved, this approach speeds up the evaluation of drug candidates in clinical trials at the reduced risk of failure [10].

Drug repurposing is also considered as an appropriate method for finding medications for orphan and rare diseases, and is expected to play a major role in this field in the future. Indeed, even though rare diseases collectively affect more than 350 million people worldwide [11], developing de novo therapeutics for their small individual markets is not profitable enough to warrant commercial interest.

In the present review, due to the complexity and the extent of the topic, we will focus only on two aspects of drug repurposing. In the first part, we summarize the most commonly used approaches for drug repurposing, while, in the second part we report the evidence available on the repurposing of approved and marketed drugs in cardiovascular diseases. For each drug or class of drug, the potential underlying molecular mechanisms of action and the results obtained *in vitro* and in animal models are briefly described, while the data of epidemiological and randomized studies are described and discussed more in details.

2. Approaches used for drug repurposing

The main issue in drug repositioning is to identify new drug-disease relationships. The historically unintentional, serendipitous or constrained research effort has been replaced by the need for rational approaches to address this issue. It has stimulated the development of computational methods and mixed approaches alongside the traditional biological experimental approaches [10]. Computational is the process of designing and validating automated workflows that can allow the researcher to generate, evaluate, and prioritize data for several drugs and diseases simultaneously. This technique is particularly useful for orphan diseases, whose pathophysiology is often poorly characterized. Indeed, this approach, used for repurposing, offers a quick way of identifying testable hypotheses that may be translated into the clinic, with large-scale genome-sequencing initiatives contributing to identify the genetic basis of the diseases, and opening up opportunities to rapidly repurpose drugs that target the correspondent protein/s [4].

The computational methods exploit the fact that proteins with similar pockets tend to have similar functions and recognize similar molecules [12]. Compared to biological

experimental approaches, computational approaches greatly reduce the costs and time of drugs discovery, allowing to automatically integrate and analyse vast amounts of data for tens of thousands of drugs and diseases [10]. In the computational drug repurposing strategies, databases play a key role. With the achievement of several technological advances, in particular the high throughput DNA sequencing strategies, and the improvement of data quality and accessibility, various drug and disease knowledge databases, such as DrugBank, ChemBank, OMIM, KEGG, and Pubmed and massive genomic and proteomic databases, such as MIPS, the Protein Data Bank, GEO, and GenBank have been built [10]. Based on data content, the available databases (DBs) can be categorized as: i) RAW data DB (which hold primitive information of drugs and their targets), ii) target-based DB [which hold drugs' targets, including genes along with complement map database (CMAP), RNAs such as long noncoding RNA (lncRNA), mutation information, proteins along with drug-protein connectivity map information, pathways, enzymes, side effects, or a collection of several targets], iii) specific DB (encompass traditional medicine, diseases-specific and geographical data), iv) drug design DB (containing the 3D structure of molecules and molecular replacement information) and v) tool based DB (which consist of tools and web servers for the repurposing usages) [13]. Different DBs can be used to find a new application of the existing drugs.

Current computational drug-repositioning strategies can be categorized as drug-based, disease-based and profile-based. Drug-based approaches are often based on pharmacophore modelling and pharmacological data, and take advantage from chemical structure, side effects and other drug characteristics to determine the drug similarity. This approach was used to propose the repurposing of ethambutol and metaraminol for the treatment of African sleeping sickness [14]. Disease-based

approaches predict new drug indications exploiting disease-disease similarity that is often calculated using disease phenotype, disease genetic and genomic data. Thus, drug-based and disease-based approaches exploit drug–drug or disease–disease similarity and existing drug-treatment knowledge to infer new disease–drug associations [15]. Unlike the drug-based and disease-based strategy, the profile-based approaches do not depend on existing drug-treatment knowledge and may have increased ability to discover new drug-disease associations. Indeed, the profile-based drug-repositioning approaches mainly exploit the gene expression profiles of diseases and their changes upon drug treatment. The profile-based repositioning strategies have successfully found new drug candidates for inflammatory bowel disease [16] and small cell lung cancer [17].

3. Repurposing drugs in cardiovascular diseases

3.1 Anti-cytokine drugs

It is widely recognized that atherosclerosis is not only a disorder of lipoprotein accumulation in the arterial wall, but also a disease of chronic inflammation [18]. A complex cocktail of pro-inflammatory cytokines, chemokines, bioactive lipids, and adhesion molecules mediates atherosclerosis-related inflammation. Cysteinyl leukotrienes (CysLTs) have been hypothesized to play a crucial role in the pathogenesis of atherosclerosis, as suggested by encouraging results obtained with montelukast, a CysLT1 receptor antagonists, as a cardiovascular protective drug in animal models and in still limited human clinical trials [19–21] and, limited to animal study, also on cerebrovascular diseases [22]. Several large-scale prospective cohort studies have also strongly suggested a role of cytokines in atherogenesis and cardiovascular diseases [23,24], and this was also corroborated by data obtained in

animal studies [18]. A comprehensive review of these studies indicated that only for a few cytokines there are consistent data to classify them as typically pro-atherogenic (i.e. IL-1, IFN-γ, TNF-α, and M-CSF) or anti-atherogenic (IL-10), and that some cytokines (IL-4, IL-6 and GM-CSF) can exert pro- or anti-atherogenic effects depending on the experimental conditions [18]. The finding that some immune-mediated inflammatory diseases (i.e. systemic lupus erythematous, rheumatoid arthritis, and psoriasis) are associated with increased risk of cardiovascular diseases [25] further highlight the relevance of inflammation in this clinical setting.

Thus, all these evidence suggested that pharmacological block of cytokines could lead to clinical benefit for patients with atherosclerosis, even in the absence of lipid lowering. The availability of monoclonal antibody-based immunotherapies targeting cytokines, which are just approved for several immune-mediated inflammatory diseases [26], provides opportunities to address this issue (Figure 1).

3.1.1 Anti-TNF-α drugs

From almost 20 years, anti-TNF-α therapy, based on anti-TNF-α monoclonal antibodies (infliximab, adalimumab, certolizumab pegol, and golimumab) or soluble TNF receptor fusion proteins (etanercept), is used for the treatment of rheumatic diseases.

A recent meta-analysis of 13 cohort studies of rheumatoid arthritis (RA) patients (n=106,202) showed that anti-TNF-α therapy was associated with a reduced risk for all cardiovascular events [pooled adjusted relative risk (RR) 0.46; 95% CI: 0.28-0.77], myocardial infarction (MI) (pooled adjusted RR 0.81; 95% CI: 0.68-0.96), and cerebrovascular accident (CVA) (pooled adjusted RR 0.69; 95% CI: 0.53-0.89) [27]. Notably, RA patients who responded positively to anti-TNF-α treatment, as assessed

by reduced joint symptoms, showed a reduced risk of acute coronary syndrome (ACS) [28]. In psoriatic arthritis patients, the use of anti-TNF-α monoclonal antibodies was associated with a decreased development of carotid atherosclerotic plaques in non-randomized observations [29]. The latter result was confirmed by a randomized controlled trial (RCT) (n=40 RA patients), which showed that the use of infliximab on top of methotrexate for 6 months improved the pulse wave velocity (PWV) compared to methotrexate alone (p=0.044) [30]. Similarly, in a RCT enrolling 41 RA patients, golimumab prevented the progression of the mean intima-media thickness (IMT) and PWV, compared to patients treated with placebo [31].

Although preclinical data have suggested that TNF-α blocking could favourably modify the evolution and progression of heart failure (HF) [32], this effect was not confirmed in prospective clinical trials. In the first small-randomized trials evaluating TNF-α blocking (n=18 patients), etanercept treatment (1, 4, or 10 mg/m^2 by single intravenous infusion) in patients with advanced heart failure (HF) resulted in a significant dose-dependent improvement in left ventricular (LV) structure and function [33]. Similarly, etanercept (5 or 12 mg/m^2 biweekly subcutaneously) for 3 months led to a significant dose-dependent improvement in LV ejection fraction (EF) and LV remodelling in 47 patients with advanced HF [34]. However, the following larger trials did not confirm these beneficial effects in patients with moderate-to-severe chronic HF. In the ATTACH study (n=150 patients), the short-term TNF-α antagonism with infliximab failed to improve the clinical condition, and at high doses it exacerbated the risk of death and of re-hospitalization [35]. Similar negative results were obtained in the RENEWAL study, which analyzed the data of two studies evaluating etanercept in HF patients with LVEF ≤ 0.30, in the RECOVER study (n=1,123 patients; etanercept 25 mg once or twice per week subcutaneously) and in the

RENAISSANCE study (n=925 patients; etanercept 25 mg 2 or 3 times per week subcutaneously). Etanercept had no effect on clinical status in RECOVER (p=0.34) or RENAISSANCE (p=0.17) and had no effect on the death or chronic HF hospitalization end point in RENEWAL (RR 1.1, 95% CI: 0.91-1.33; p=0.33) compared to placebo [36]. The reason for lack of clinical benefit of TNF-α blocking is not clear. However, one possible explanation is that TNF-α has dual and ambivalent effect leading to either a beneficial or a deleterious action in chronic HF [37].

A meta-analysis published in 2019 including 5 trials of pediatric patients with Kawasaki disease (KD) (n=494) suggests that TNFα blockers could instead have beneficial effects on treatment resistance (RR 0.57, 95% CI: 0.38-0.86; low-certainty evidence) and have low adverse effect 'infusion reaction' after treatment initiation for KD (RR 0.06, 95% CI: 0.01-0.45; low-certainty evidence) when compared with no treatment or additional treatment with intravenous immunoglobulin [38].

Overall, the data of large RCTs don't support the use of TNF-α blockers in chronic HF patients. However, small RCTs suggest beneficial effects in subclinical atherosclerosis, artery stiffness and KD.

Currently, two on-going studies are investigating the role of anti-TNF-α therapy in coronary function. The first one evaluates the effect of certolizumab on coronary flow reserve (CFR) in RA patients (http://www.ClinicalTrials.gov NCT02714881), whereas the second one assesses the impact of etanercept treatment in children with KD on the rate of coronary artery dilation and disease (CAD) and on the levels of C-reactive Protein (http://www.ClinicalTrials.gov NCT00841789).

3.1.2 Anti-IL-1 drugs

Pharmacological agents targeting IL-1β have been approved for the treatment of

cryopyrin-associated periodic syndromes (CAPS) and other rare auto-inflammatory diseases (canakinumab, rilonacept), and for rheumatoid arthritis and neonatal-onset multisystem inflammatory disease (anakinra). Canakinumab is a selective monoclonal antibody that directly targets IL-1β, rilonocept is an IL-1 trap that further inhibits the IL-1 receptor, whereas anakinra is a recombinant human IL-1 competitive receptor antagonist that inhibits both IL-1α and IL-1β.

The first evidence that IL-1β blocking could lead to a cardiovascular benefit was obtained in a placebo-controlled trial, in which the acute and chronic administration of anakinra (150 mg subcutaneously) in RA patients (n=23 for both conditions) improved parameters of myocardial contractility and relaxation, coronary flow reserve, and endothelial function [39].

Small RCTs with anakinra showed promising but controversial results in HF patients. Treatment with anakinra (100 mg) for 12 weeks improved the peak Vo_2, a parameter of cardiorespiratory fitness, from 14.5 (10.5-16.6) mL/kg/min to 16.1 (13.2-18.6) mL/kg/min (p=0.009) in patients with recently decompensated systolic HF and elevated C-reactive Protein (CRP) levels (>2 mg/L) (n=60) [40]. This effect is controversial in patients with heart failure with preserved ejection fraction (HFpEF). Indeed, in a crossover RCT (n=12 patient with HFpEF), anakinra (100 mg for 14 days) led to a statistically significant improvement in Vo_2 (+1.2 ml/kg/min; p=0.009) [41], whereas in a subsequent study (n=31 patients) published in 2018 no positive effects on peak Vo_2 or V_E/Vco_2 slope were reported [42]. However, anakinra showed favourable reduction of about 50% for NT-proBNP and about 60-70% for high-sensitivity CRP (hs-CRP) in patients with HF [41–43]. Anakinra treatment (100 mg) for 2 weeks reduced hs-CRP [geometric mean (GM) ratio 0.38, 95% CI: 0.24-0.61; p=0.0001] and IL-6 (GM ratio 0.66, 95% CI: 0.46-0.94; p=0.022) levels also in non-

ST elevation ACS (NSTE-ACS) patients (n=182), but showed little or worse long-term benefit [44]. Similarly, in a randomized controlled phase 2 trial published in 2018 enrolling patients with acute stroke (n=80), anakinra (100 mg twice daily for 3 days) significantly reduced IL-6 and hs-CRP plasma levels, but it was not associated with a favourable outcome on modified Rankin Scale [45].

The cardiovascular effects of canakinumab were largely evaluated by the CANTOS Investigative Group. In a phase IIb trial on patients with diabetes mellitus at high cardiovascular risk (n=556), canakinumab (5, 15, 50, or 150 mg monthly) showed benefits on inflammation, with decrease plasma level exceeding 50% for CRP and IL-6 [46]. The results of phase III CANTOS study published in 2019 enrolling patients with previous MI and high CRP levels (n=10,061) show that inflammation inhibition by canakinumab was associated with a significant dose-dependent trend in reduced rates of hospitalization for HF and the composite of hospitalization for HF or HF-related mortality [47]. The results of the CANTOS study represent the first large-scale evidence indicating that IL-1-targeted therapy may have a role in HF. Furthermore, a secondary analyses of patients with greater than average levels of hs-CRP inhibition had substantially greater clinical benefits with 31% reductions in cardiovascular [adjusted hazard ratio (HR^{adj}) =0.69, 95% CI: 0.56-0.85; p=0.0004] and all-cause mortality (HR^{adj}=0.69, 0.58-0.81; p<0.0001) [48]. Thus, CANTOS provided the first proof in humans that targeting inflammation can reduce cardiovascular event rates independently of lipid lowering. However, the cost-effectiveness of canakinumab might prevent it from become part of routine care.

In a meta-analysis published in 2019 including 8 RCTs (5 for anakinra and 3 for canakinumab) and involving 15,647 participants, IL-1 blockade treatment was associated with a significantly decreased risk of overall major adverse cardiovascular

events (MACE) (RR 0.88, 95% CI: 0.82-0.94), unstable angina (RR 0.80, 95% CI: 0.66-0.98), breakthrough or recurrence of heart failure (RR 0.44, 95% CI: 0.22-0.87) and level of CRP [standardized mean difference (SMD) -0.30, 95% CI: -0.51 to -0.09]. However, no association was found between IL-1 blockade treatment and acute MI as well as death from all causes [49]. Although the increase of infection-related deaths was not observed, this aspect must be taken into consideration, and long-term survival effect after IL-1 blockade treatment still needs further clinical studies.

Anakinra is still effective in recurrent pericarditis. In a small withdrawal RCT (open label with anakinra followed by a double-blind withdrawal step with anakinra or placebo until recurrent pericarditis occurred), anakinra (2 mg/kg per day, up to 100 mg) reduced the risk of recurrent pericarditis with the incidence rate difference of -1.95% (95% CI: -3.3% to -0.6%) [50].

Currently, an on-going study will test the hypothesis that anakinra improves cardiorespiratory fitness, diastolic dysfunction, and elevated inflammation in patients with HFpEF (http://www.ClinicalTrials.gov NCT02173548).

3.1.3 Anti-IL-6 drugs

Tocilizumab, a humanized monoclonal antibody against the interleukin-6 (IL-6) receptor, has been approved for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis and giant cell arteritis.

In a multi-data-base cohort study of RA patients (n=28,028) published in 2017, tocilizumab was as effective as the anti–TNF-α antibody, abatacept or tofacitinib, on the incidence of the major adverse cardiovascular event (combined HR 0.84, 95% CI: 0.56-1.26) [51]. Recent small RCTs suggest that a single dose of tocilizumab might

be used as additional therapy for MI. In fact, in NSTEMI patients undergoing percutaneous coronary intervention (PCI) (n=117), tocilizumab (280 mg by intravenous infusion) reduced peri-procedural myocardial injury in terms of less serum high-sensitive Troponin-T (159 *vs* 234 ng/L/h; p=0.007) and CRP (2.0 *vs* 4.2 mg/L/h; p<0.001) [52], whereas tocilizumab (162 mg subcutaneously) was free of adverse events in patients with MI [53].

Tocilizumab might be useful also for treating arteritis. Indeed, in a small RCT recruiting patients (n=30) with new-onset or relapsing giant-cell arteritis, tocilizumab (8 mg/kg intravenously, for a total of 13 infusions every 4 weeks until week 52) improved complete remission at 52 weeks (risk difference 65%, 95% CI: 36–94; p=0.0010) [54]. These data have been confirmed in another RCT enrolling patients with giant-cell arteritis, tocilizumab treatment (162 mg subcutaneously, weekly or every 2 weeks for 52 weeks) improved sustained remission (p<0.001) and the cumulative median prednisone dose (p<0.001) [55]. Furthermore, in a RCT enrolling patients with giant-cell arteritis (n=30) published in 2019, 52-week treatment with tocilizumab induces a lasting remission that persists in half of the patients after treatment stop. Indeed, more than 50% of patients with complete remission (n=17) remained in lasting clinical and serological remission for a mean of 29.3 months after discontinuation of tocilizumab therapy [56]. In the same year, a recent case-report of a man treated with PCI for acute MI suggests a beneficial effect in Takayasu arteritis (TA), reducing serum pentraxin-3 (PTX3) level, a marker of TA activity. Notably, tocilizumab also reduced N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level and reversed LV remodelling [57].

Currently, there are several on-going studies evaluating the effects of tocilizumab in cardiovascular area, such as cardiac arrest, myocardial infarction and giant-cell

arteritis. In particular, these studies investigate the effect of tocilizumab on markers of cardiac injury and inflammation, cardiac function and survival in patients with out-of-hospital cardiac arrest (http://www.ClinicalTrials.gov NCT03863015), on myocardial salvage index and markers of cardiac injury in patients with ACS (http://www.ClinicalTrials.gov NCT03004703) and on partial or complete remission of giant cell arteritis (http://www.ClinicalTrials.gov NCT04049071, NCT03745586 and NCT03726749).

3.1.4 Anti-IL-17 drugs

Treatment with secukinumab (10 mg/kg intravenously every 2 weeks for 1 month and then 150 mg or 75 mg subcutaneously every 4 weeks), a monoclonal antibody anti-IL-17, approved for arthritis or psoriasis, did not show any improvement in the incidence of the major adverse cardiovascular event in two placebo-controlled study in patients with psoriatic arthritis (n=606) [58] or with ankylosing spondylitis (n=454) [59].

In a RCT published in 2019 enrolling 150 patients with psoriasis, after 12 months of treatment, secukinumab improved the myocardial function parameters, such as global longitudinal strain (GLS) (increase of 14% *vs* 2% with cyclosporine and *vs* 4% with methotrexate), GLS rate at early diastole (increase of 41% *vs* 4% *vs* 9%, respectively) and LV twisting (increase of 28% *vs* 8% *vs* 6%, respectively) ($p<0.05$). Secukinumab also resulted in a greater improvement of coronary flow reserve (CFR) and PWV ($p<0.05$) [60]. In the same year, the results of the CARIMA study (n=151 patients with plaque-type psoriasis) have been published. Twelve weeks of secukinumab treatment (150 or 300 mg weekly for 4 weeks, and then every 4 weeks) resulted only in a slight increase in baseline-adjusted mean flow-mediated dilation

(FMD) of the brachial artery (+1.2% and +0.76% for 300-mg group and 150-mg group; p=0.223 and p=0.403 respectively, compared to placebo). However, FMD was significantly higher than baseline in patients receiving the label dose of 300 mg secukinumab for 52 weeks (+2.1%, 95% CI: 0.8-3.3; p=0.0022). No clinically relevant changes in augmentation index and PWV, parameters of arterial stiffness, and in the total plaque burden in the carotid artery and the aorta were observed [61]. In line, in a small RCT published in 2020 enrolling patients with psoriatic disease (n=15), 6 months of treatment with secukinumab (300 mg weekly for the first 4 weeks and then every 4 weeks), ustekinumab (a monoclonal antibody anti-IL-12/IL-23) or ixekizumab (another monoclonal antibody anti-IL-17) failed to improve IMT (0.53 ± 0.9 mm *vs* 0.54 ± 0.9 mm; p=0.737) and PWV values (8.89 ± 2.02 mm vs 8.59 ± 1.96 mm; p=0.163) compared to baseline [62]. Thus, to date, there is no definitive information on the cardiovascular safety of anti-IL-17 immunotherapies.

Currently, there is only one on-going study evaluating the effects of secukinumab in giant cell arteritis in terms of remission of the disease and normalization of CRP level (http://www.ClinicalTrials.gov NCT03765788).

3.2 Colchicine

Colchicine is currently approved for prophylaxis and treatment of acute gout flares, other crystal diseases and familial Mediterranean fever (FMF). In addition to its commonly known uses, colchicine has potential benefits in a wide range of other conditions, including cardiovascular diseases, because of its broad anti-inflammatory effect. These effects are mainly related to disruption of microtubules [63] and downstream cellular functions of leucocytes [64]. Indeed, colchicine blocks neutrophil adhesion to endothelium by modulating the distribution of adhesion molecules on the

endothelial cells [65], and suppressing the release of the chemotactic agent leukotriene B4, as well as altering neutrophil deformability [64]. Furthermore, colchicine inhibits NALP3 inflammasome-driven caspase-1 activation, IL-1β processing and release, production of superoxides and release of various cytokines and pyrogens [66,67]. Interestingly, colchicine was also shown to suppress smooth muscle cell proliferation and increase cell apoptosis [64].

In the last two decades, colchicine has been largely used for the treatment of pericarditis and post-pericardiotomy syndrome (PPS) [68], and from 2015, the European Society of Cardiology recommends colchicine as first-line therapy for acute and recurrent pericarditis, as well as for the acute treatment of PPS [69]. In line, an updated meta-analysis published in 2019 including ten RCTs (n=1,981 patients) confirms that colchicine reduced the overall risk of pericardial effusion in pericarditis and recurrent pericarditis, and in PPS compared with placebo (RR 0.57, 95% CI: 0.44-0.74) [70]. In details, colchicine reduced the risk of recurrence both in patients with a first acute pericarditis (2 studies; RR 0.40, 95% CI: 0.24-0.66) as well as in patients with recurrent pericarditis (3 studies; RR 0.48, 95% CI: 0.36-0.63). It also reduced the need for re-hospitalization (5 studies; RR 0.31, 95% CI: 0.16-0.60) and the number of patients with persistent symptoms after 72 hours (5 studies; RR 0.43, 95% CI: 0.34-0.54) in patients with pericarditis. On the contrary, colchicine was ineffective in patients after heart surgery. The authors suggested that the clinical use of colchicine for the setting of PPS and postoperative PE after heart surgery should be investigated in further multicenter RCTs.

The effects of colchicine in other cardiovascular areas, such as stable coronary artery disease (CAD), percutaneous coronary intervention, STEMI and stable chronic HF, have been also investigated.

In a large retrospective, cross-sectional study of patients with gout (n=1,288), colchicine significantly decreased the prevalence of MI (RR 0.46; p=0.03), with fewer deaths and lower CRP levels, although these did not achieve statistical significance [71]. However, this study has some critical limitations, since no adjustment for any potential confounders was performed and duration of colchicine use was unclear. In a more recent cohort study of patients with gout (n=1,002) with a median follow-up of 16.5 months, colchicine use was associated with a 49% lower risk in a composite primary outcome of MI, stroke and transient ischaemic attack (HR^{adj} 0.51, 95% CI: 0.30-0.88; p=0.016), as well as a 73% lower risk in all-cause mortality (HR^{adj} 0.27, 95% CI: 0.17-0.43; p<0.0001) compared to patients who did not use colchicine [72].

Colchicine may confer lower risk for a second cardiovascular event in the general population, as shown by several prospective trials. In patients with stable CAD, the addition of colchicine 0.5 mg daily to optimal medical therapy (aspirin and/or clopidogrel, statin) was associated with a 60% relative decrease of hs-CRP (95% CI: 54%-67%) [73] and a decreased composite primary outcome of cardiovascular death, non-cardioembolic stroke, acute coronary syndrome, and out-of-hospital cardiac arrest (HR 0.33; 95% CI: 0.18-0.59; p<0.001) compared with patients who did not use colchicine [74].

Colchicine may also prevent re-stenosis after coronary angioplasty in manner dependent on the angioplasty method used. Indeed, colchicine (0.6 mg twice daily) was ineffective in preventing restenosis in patients undergoing balloon angioplasty (n=197) [75], whereas colchicine (0.5 mg twice daily) was associated with less in-stent lumen area loss (1.6 mm^2 *vs* 2.9 mm^2; p=0.002) and a decreased in-stent restenosis rate (odds ratio 0.38, 95% CI: 0.18-0.79; p=0.007) when administered to diabetic patients after PCI with a bare-metal stent [76]. Furthermore, in patients with

ACS, colchicine treatment reduced transcoronary inflammation. Although in a study published in 2012 in patients with ACS or acute ischemic stroke (n=80), colchicine did not significantly reduce absolute or relative hs-CRP levels at 30 days [77], two subsequent studies showed that, within 24 hours of administration, colchicine treatment (1.5 mg) markedly reduced transcoronary gradients of IL-1β, IL-18, and IL-6 by 40% to 88% (p=0.028, 0.032, and 0.032, respectively) [78], and transcoronary levels of chemokine ligand 2 and 5 (CCL2 and CCL5) and C-X3-C motif chemokine ligand 1 (CX3CL1) ($p<0.05$) [79]. A prospective non-randomized observational study published in 2018 showed that these cytokine changes might translate into favourable plaque modification. In patients with recent ACS (<1 month), colchicine treatment (0.5mg/day for 1 year) significantly reduced the low attenuation plaque volume (LAPV) (40.9% *vs* 17.0%; p=0.008), a marker of plaque instability, and hs-CRP (37.3% *vs* 14.6%; $p<0.001$) compared to controls [80].

A potential benefit of colchicine was also reported for STEMI patients. In a trial of 151 patients, colchicine (2mg loading dose followed by 0.5mg twice daily for 5 days) significantly reduced the area under the curve of creatine kinase-MB concentration, a marker of infarct size, and the median maximum troponin-T value. Notably, also the absolute infarct volume, measured by cardiac MRI with late gadolinium enhancement 6 to 9 days after the index STEMI, was significantly lower in patients treated with colchicine [81]. However, in a study of 44 STEMI patients treated for one month with colchicine 1 mg/day no effect on the mean peak CRP value was observed [82]. In the COLCOT study, a RCT published in 2019, involving patients (n=4,745) recruited within 30 days after a MI, low-dose colchicine (0.5 mg once daily) reduced the composite risk of death from cardiovascular causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization (HR

0.77, 95% CI: 0.61-0.96; p=0.02). In detail, it reduced the risk for death from cardiovascular causes (HR 0.83, 95% CI: 0.25 to 2.73), for resuscitated cardiac arrest (HR 0.91, 95% CI: 0.68-1.21) for myocardial infarction (HR 0.26, 95% CI: 0.10-0.70) and for urgent hospitalization for angina leading to coronary revascularization (HR 0.50, 95% CI: 0.31-0.81) [83].

Finally, in a prospective randomized study of patients with stable chronic HF (n=267), colchicine (0.5 mg twice daily) for 6 months decreased CRP and IL-6 (-5.1 mg/l and -4.8 pg/ml, respectively; p<0.001 for both) compared with control, but it was ineffective on achieving at least one-grade improvement in NYHA functional status classification and the rate of the composite of death or hospital stay for HF [84]. Overall, colchicine was effective in improving cardiovascular outcomes in patients with CAD, ACS or STEMI, suggesting possible new indications for these pathological conditions, although larger RCTs are needed to confirm these results.

Currently, there are several on-going studies evaluating the effects of colchicine in cardiovascular area, such as atrial fibrillation (AF), percutaneous coronary intervention and STEMI. In particular, these studies will evaluate the effects of colchicine in preventing AF in patients undergoing elective cardiac surgery (http://www.ClinicalTrials.gov NCT03015831), and peri-procedural myocardial necrosis and infarction, all-cause mortality, non-fatal MI, or target vessel revascularization (http://www.ClinicalTrials.gov NCT02594111) and inflammation biomarkers (http://www.ClinicalTrials.gov NCT01709981) in PCI patients. In patients with STEMI undergone primary PCI, the effects of colchicine will be evaluated as changes in LV remodelling, inflammation biomarkers, incidence of major adverse cardiovascular events and composite of cardiovascular events (http://www.ClinicalTrials.gov NCT03156816 and NCT03048825). Furthermore, in

this patient population, the effect of a loading dose of colchicine on the occurrence of periprocedural myocardial infarction will be also investigated (http://www.ClinicalTrials.gov NCT03735134). Finally, a trial will investigate the effects of colchicine administration for acute pericardial effusion after radiofrequency catheter ablation of AF on the recurrences of arrhythmia (http://www.ClinicalTrials.gov NCT02260206), whereas another study will evaluate coronary segment endothelial function and inflammation biomarkers in patients with CAD (http://www.ClinicalTrials.gov NCT02366091).

3.3 Methotrexate

Methotrexate, an analogue of the B-vitamin folic acid, has been approved for over 50 years and is widely used for the treatment of a variety of cancers and autoimmune diseases, including rheumatoid arthritis and psoriasis.

Several *in vitro* and *in vivo* animal studies suggest that methotrexate might provide cardioprotection through its anti-inflammatory and immunomodulatory activity. The putative mechanisms mediating these effects could be ascribed to inhibition of dihydrofolate reductase (DHFR), leading to a reduced synthesis or methylation of DNA and RNA, and inhibition of aminoimidazole carboxamidoribonucleotide (AICAR) transformylase with subsequent activation of the adenosine A_{2A} receptor [85]. Methotrexate was shown to reduce the expression of some pro-inflammatory cytokines (IL-1, IL-6 and TNF-α) and cell adhesion molecules (ICAM-1 and VCAM-1) on endothelial cells, and to reduce the formation of free radicals, malondialdehyde and acetaldehyde protein adducts [85].

Epidemiological studies have shown that methotrexate might also exert protective effects against atherosclerotic cardiovascular disease. In a meta-analysis of 10

observational studies of patients with rheumatoid arthritis, psoriasis or polyarthritis, methotrexate was associated with a 21% lower risk of total CVD (95% CI: 0.73-0.87; p<0.001) and a 18% lower risk of MI (n=5 studies; 95% CI: 0.71-0.96; p=0.01) [86]. This beneficial effect was confirmed by a more recent meta-analysis of 10 observational and randomised controlled trials on rheumatoid arthritis patients. Here, methotrexate was associated with a 28% lower risk for total CVD (95% CI: 0.57-0.91; p=0.007) and a 19% lower risk for MI (n=3 studies; 95% CI: 0.68-0.96; p=0.01) [87].

However, the chance of methotrexate repurposing for the management of patients with atherosclerotic cardiovascular disease has been disappointed by prospective trials. In a small RCT published in 2017 including 84 STEMI patients, methotrexate (0.05 mg/kg intravenous bolus followed by 0.05 mg/kg/hour for 6 hours) administered before PCI did not reduce reinfarction, mortality rates and plasma level of hs-CRP, creatine kinase- myocardial band (CK-MB), BNP and troponin. Furthermore, at 3 months, LVEF was lower in patients who received methotrexate (49.0% ± 14.1%) than in the placebo group (56.4% ± 10.0%; p=0.01) [88]. Negative results were also obtained in a larger randomized trial published in 2019, which enrolled 4,786 patients with previous MI, or multivessel coronary disease with either type 2 diabetes or the metabolic syndrome treated with low-dose methotrexate (at a target dose of 15 to 20 mg weekly). Methotrexate did not result in lower IL-1β, IL-6, or CRP levels, and in lower risk for composite of nonfatal MI, nonfatal stroke, CV death or hospitalization for unstable angina (HR 0.96; 95% CI: 0.79-1.16; p=0.67) [89].

Currently, the few data of RCTs don’t support the repurposing of methotrexate as cardioprotective agent. However, only after the results of on-going RCTs, the exact effectiveness of methotrexate will be established. Indeed, there are several on-going studies evaluating the effects of methotrexate in cardiovascular area, such as CAD,

STEMI and giant cell arteritis. In particular, these studies will evaluate the effects of methotrexate on LV remodelling, inflammation biomarkers and BNP levels in STEMI patients (http://www.ClinicalTrials.gov NCT03516903), coronary segment endothelial function and inflammation biomarkers in patients with CAD (http://www.ClinicalTrials.gov NCT02366091), coronary vasoreactivity, endothelial function, tissue perfusion and LV function in stable CAD patients with type 2 diabetes or metabolic syndrome (http://www.ClinicalTrials.gov NCT02786134), and rate of relapse in giant cell arteritis patients (http://www.ClinicalTrials.gov NCT03892785).

3.4 Metformin

Metformin is approved as anti-diabetic drug since 1957, and it remains one of the first medications prescribed for type 2 diabetes mellitus (T2DM). Besides having few adverse effects, metformin possesses several additional properties beyond glycemic control. *In vitro* and *in vivo* studies showed that metformin reduces inflammation (i.e. hs-CRP, s-ICAM, s-VCAM, PAI-1, NF-kB), oxidative stress (i.e. by inhibiting PARP1 and complex 1 of the respiratory chain and by increasing the expression of antioxidant genes activating transcription factor SKN-1/Nrf2), fibrosis, endothelial apoptosis (i.e. by down-regulation of FOXO3 and caspase-3) and vascular remodeling [90]. Furthermore, metformin attenuates mitochondrial dysfunction, through the eNOS/SIRT1/p53 and SIRT1/FOXO pathway, the degradation of CHOP and the closure of mitochondrial permeability transition pore (mPTP), and increases mitochondrial biogenesis by enhancing PGC1-α [90,91]. Metformin also attenuates cell hypertrophy through the suppression of phosphorylation of Akt/protein kinase B (AKT) and mammalian target of rapamycin (mTOR) [92]. These molecular and cellular effects could explain the cardiovascular protection observed in several

experimental studies. In this respect, metformin has been shown to reduce pulmonary pressure, vascular remodelling, cardiac ischemia-reperfusion injury, cardiac hypertrophy and development of heart failure [90,91].

Despite the well-documented cardioprotection observed in diabetic patients, acute administration of metformin, during or soon after an ischemic event, yields no cardioprotection in non-diabetic subjects. In the GIPS-III RCT, which enrolled 380 patients with STEMI, metformin treatment (500 mg bid) initiated immediately after PCI did not show any clear beneficial effect on NT-proBNP levels or LVEF at 4 months [93]. Similarly, in a small RCT in 173 patients with coronary heart disease, metformin treatment (850 mg bid) had little or no effect on several surrogate markers of cardiovascular disease (such as total cholesterol, HDL-cholesterol, non-HDL-cholesterol, triglycerides and hs-CRP) [94]. In patients who underwent coronary artery bypass graft (CABG) surgery (n=57), metformin pre-treatment for 3 days (500 mg three times per day) was not effective in reducing peri-procedural myocardial injury [95]. On the contrary, in a RCT in 152 patients with metabolic syndrome undergoing PCI, metformin pre-treatment for 7 days (250 mg three times per day) reduced the peak level of CK-MB (2.70 ± 4.30 *vs* 6.29 ± 8.03 ng/ml; p<0.001) and troponin I (0.02 ± 0.05 *vs* 0.07 ± 0.10 ng/ml; p=0.001). Interestingly, at 1 year follow-up, metformin was associated with a reduced risk of death from any cause, MI after PCI, MI after PCI hospitalization or ischemia-driven target lesion revascularization (HR 0.25, 95% CI: 0.10-0.62; log rank p=0.001) [96].

The effect of metformin was also evaluated in HF patients without T2DM. In the TAYSIDE trial treatment of insulin resistant HF patient (n= 62) with metformin (2 g/day) for 4 months improved the secondary outcome of V_E/V_{CO2} slope, a prognostic measure of exercise capacity, from 32.9 ± 15.9 to 28.1 ± 8.8 (p=0.034) [97]. Of note,

the recent randomized controlled MET-REMODEL trial published in 2019 enrolling non-diabetic patients with a history of CAD, left ventricular hypertrophy, and ischemia-reperfusion and/or pre-diabetes (n=68), showed that 12-month of metformin (prolonged release, 1000 mg twice daily) significantly reduced the left ventricular mass indexed to height (LVMI) compared with placebo group [mean difference (MD) -1.37, 95% CI: -2.63 to -0.12; p=0.033] [98]. In the same year, a RCT enrolling patients (n=162) with T2DM and hypertension without overt HF showed that 1-year treatment with metformin (500 mg/day and titrated up to 2250 mg/day) failed to improve LV mass index, BNP levels, or E/e (early diastolic transmitral flow velocity/early diastolic mitral annular velocity, an indicator of LV diastolic function) compared to other hypoglycemic agents [99].

The effects of metformin in preventing and improving cardiovascular disease were investigated by a systematic review and meta-analysis published in 2019 including 40 studies (15 RCTs, 22 retrospective cohort studies and 3 case-control studies) in T2DM patients with CAD. Metformin reduces the risk of cardiovascular mortality (HR^{adj} 0.81, 95% CI: 0.79-0.84; p<0.00001), all-cause mortality (HR^{adj} 0.67, 95% CI: 0.60-0.75; p<0.00001) and incidence of CV events (HR^{adj} 0.83, 95% CI: 0.78-0.89; p<0.00001). Subgroup analysis showed that metformin reduced all-cause mortality in MI (HR^{adj} 0.79, 95% CI: 0.68-0.92; p=0.003) and HF patients (HR^{adj} 0.84, 95% CI: 0.81-0.87; p<0.00001), the incidence of CV events in HF (HR^{adj} 0.83, 95% CI: 0.70-0.98; p=0.03) and T2DM patients (HR^{adj} 0.83, 95% CI: 0.77-0.88; p<0.00001), but had no significant effect on MI (HR^{adj} 0.87, 95% CI: 0.72-1.04; p=0.13). However, the non-T2DM subgroup analysis revealed that metformin failed to reduce the risk of CV events (HR^{adj} = 0.92, 95% CI: 0.28-3.00; p=0.89) in non-diabetic patients [100].

In conclusion, metformin showed to have potential effectiveness to be used for treatment of CVD irrespective of diabetes status. However, RCTs are needed to provide evidence for recommending metformin in patients with CAD without T2DM.

Currently, there are several on-going studies evaluating the effects of metformin in cardiovascular area, such as heart failure and CAD, in patients without T2DM. In particular, these studies will evaluate the effects of metformin on change in LV function, V_E/V_{CO2} slope and BNP level in HF patients (http://www.ClinicalTrials.gov NCT03331861), pulmonary artery pressure in HF with preserved ejection fraction patients (http://www.ClinicalTrials.gov NCT03629340), plaque volume or tissue component percentage change in CAD pre-diabetic patients (http://www.ClinicalTrials.gov NCT02744976) and markers of atherosclerosis, systemic inflammation, oxidative stress, endothelial dysfunction in obese patients with moderate chronic kidney disease (http://www.ClinicalTrials.gov NCT02252081). Furthermore, the effect of metformin on survival or cardiovascular hospitalization in insulin resistance/T2DM patients with moderate to severe HF will be also investigated (http://www.ClinicalTrials.gov NCT03514108).

3.5 Incretin mimetics or GLP-1 receptor agonists (GLP-1 RAs)

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) (exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide and semaglutide) are currently available as treatment options for T2DM.

However, in cellular and animal models of atherosclerosis, hypertension and MI, GLP-1 RAs have been largely demonstrated to exert several extra-glycemic effects, providing additional benefits that could possibly improve CV risk. Indeed, GLP-1 RAs increased eNOS, improved endothelial function, cardiac output, exercise capacity

and respiratory efficiency, reduced endothelial adhesion molecules, arterial wall accumulation of monocyte/macrophage, systolic blood pressure, and MI size, and activated pro-survival kinases and cytoprotective genes, reducing apoptosis of cardiomyocytes [101].

Clinical studies in patients with T2DM suggest that GLP-1 RAs protect against non-glycemic CV risk factors compared with placebo and most standard anti-diabetes agents. Indeed, in retrospective and pooled analyses, exenatide reduced likelihood of having a CV event (HR 0.81, 95% CI: 0.68-0.91; p=0.01) [102] or enhance the percentage to be free of a primary major adverse cardiovascular events (MACE) over 1 year (p<0.0001) [103] compared with other glucose-lowering therapies.

Thus, small clinical trials were performed to verify this cardioprotective effect in non-diabetic patients. In randomized, double-blind, placebo-controlled trials, incretin mimetics were shown to be effective in STEMI patients undergoing primary PCI, regardless of the presence of diabetes. In patients undergoing PCI (n=172), exenatide, infused for 6 hours after revascularization, increased the salvage index (0.71±0.13 *vs* 0.62±0.16; p=0.003) and reduced infarct size (0.30±0.15 *vs* 0.39±0.15; p=0.003) compared to placebo at 3 months follow-up [104]. Furthermore, in another study with the same clinical setting, pharmacological treatment and follow-up, exenatide increased salvage index, compared to placebo, both among patients with normoglycemia (0.68±0.17 *vs* 0.62±0.12; p=0.08) and hyperglycemia (0.73±0.11 *vs* 0.64±0.15; p=0.017) at hospital admission [105]. However, a post hoc analysis published in 2016 involving 334 patients with a first STEMI followed-up for 5.2 years, exenatide as an adjunct to primary PCI reduced the incidence of admission for heart failure (11% *vs* 20%, HR 0.53; p=0.042) compared to the placebo, but it failed to reduce the primary composite endpoint (24% *vs* 27%, HR 0.80; p=0.35) or the

secondary endpoint of all-cause-mortality (14% *vs* 9%, HR 1.45; p=0.20) [106]. Exenatide subcutaneously injected was also effective as reported in a study despite the small sample size (n=58 patients). Indeed, exenatide was associated with reduction of infarct size (12.8±11.7 *vs* 26.4±11.6 g; p=0.006) at about 1 month and improvement of left ventricular function [(mean value of EF %: 58.8±1.3 *vs* 56.8±0.9; p<0.05) and (mean of E/E' ratio: 11.9±1.3 *vs* 15.0±0.9; p<0.05)] at 6 months [107].

In a study enrolling 92 patients, liraglutide administered for 7 days in PCI-treated patients increases LVEF (MD 4.1%, 95% CI: 1.1%-6.9%; p<0.001) and stroke volume (MD 6.8 mL; p=0.006) compared to placebo at 3 months follow-up. These cardioprotective effects were associated with better anti-inflammatory conditions (MD in serum hs-CRP levels -0.27 mg/dL, 95% CI: -0.55 to -0.02; p<0.001) and amelioration of endothelial dysfunction [(MD of NO synthase activity 1.02; p<0.001) and (MD of serum NO levels 7.9 µmol/L; p<0.001)] [108]. In another study published in 2016 enrolling 96 patients, liraglutide for 7 days improves myocardial salvage (0.66±0.14 *vs* 0.55±0.15; p=0.001) and infarct size (15±12 *vs* 21±15 g; p=0.05) at 3 months from PCI. These cardioprotective effects were associated with reduced serum hs-CRP levels (MD -0.24 mg/dL, 95% CI: -0.38 to -0.09; p<0.001) and improved endothelial dysfunction [(MD of NO synthase activity 1.75; 95% CI: 0.89-2.37; p<0.001) and (MD of serum NO levels 14.5 µmol/L, 95% CI: 8.5-19.5; p<0.001)] [109].

A RCT published in 2016 showed that liraglutide treatment for 7 days was also effective in NSTEMI patients. At 3 months, liraglutide increased LVEF (MD 4.7%, 95% CI: 0.7%-9.2%; p=0.009), ameliorated inflammation (MD of hs-CRP levels -0.22 mg/dL, 95 % CI: -0.42 to -0.02; p=0.02) and reduced oxidative stress (MD serum of SOD level 11.2 U/mL, 95 % CI: 5.1-16.1; p<0.001) compared to placebo [110].

Although these promising results, larger RCTs are needed to confirm incretin mimetics as potential adjuvant therapy for STEMI and NSTEMI patients treated with PCI.

Currently, there are several on-going studies evaluating the effects of GLP-1 RAs in cardiovascular area, such as STEMI, heart surgery and atrial fibrillation (AF), in patients without T2DM. In particular, these studies will evaluate the effects of exenatide on change in myocardial infarct size, myocardial salvage index and major adverse cardiovascular events (MACE) in STEMI patients (http://www.ClinicalTrials.gov NCT02404376), and death from any cause, adverse events or hospitalization for heart failure in patients undergoing open heart surgery (http://www.ClinicalTrials.gov NCT02673931). The effect of liraglutide on changes in size of left atrial epicardial adipose tissue and atrial function will be studied in AF patients undergoing catheter ablation (http://www.ClinicalTrials.gov NCT02673931).

3.6 PDE Inhibitors

Phosphodiesterase 5 inhibitors (PDE5is) were originally developed for the treatment of coronary artery disease and for pulmonary arterial hypertension (PAH), but they are currently approved for treating erectile dysfunction (sildenafil, tadalafil, vardenafil and avanafil).

However, numerous experimental evidences support the use of PDE5is also in heart failure (HF) patients. PDE5is have shown anti-apoptotic effects in cardiomyocytes, by activating PKG through up-regulation of NOS proteins and by increasing the Bcl-2 to Bax ratio, and cardiac anti-inflammatory effects by reducing the expression of IL-6, IL-18 and cyclin-dependent kinase inhibitor 2a. Furthermore, PDE5is were shown to inhibit chamber and cardiomyocyte hypertrophy and to improve heart function [111].

In a small randomized, placebo-controlled crossover study, enrolling 23 men with congestive HF, single dose of sildenafil (50 mg) improved the exercise capacity, reducing the V_E/V_{CO2} slope and increasing the peak $*O_2$ and the exercise time [112].

In a meta-analysis published in 2014 including 9 RCTs and 612 HF patients, sildenafil improved hemodynamic parameters particularly in HF patients with reduced ejection fraction (HFrEF), but not in those with preserved ejection fraction (HFpEF). In HFrEF patients, sildenafil was associated with a marked improvement in hemodynamic parameter peak V_{O2} (MD 3.25, 95% CI: 2.07-4.42; p<0.00001) and in LV ejection fraction (MD 5.89, 95% CI: 4.01-7.78; p<0.00001) compared to placebo [113]. The effectiveness of PDE5is in HFrEF but not in HFpEF patients was confirmed by a more recent meta-analysis of 13 RCTs (including 9 studies of the previous meta-analysis) enrolling 898 HF patients. In HFrEF patients, PDE5is improved peak V_{O2} (MD 3.76 mL/min/kg, 95% CI: 3.27-4.25; p<0.00001), V_E/V_{CO2} slope (MD -6.04, 95% CI: -7.45 to -4.64; p<0.00001), LVEF (MD 4.30%, 95% CI: 2.18-6.42; p<0.0001), and pulmonary vascular resistance (MD -80.74 dyn·sec/cm^5, 95% CI: -110.69 to -50.79; p<0.00001) [114]. Furthermore, in a randomized placebo-controlled study published in 2017 enrolling 52 patients with HFpEF and pulmonary hypertension, 12 weeks of sildenafil treatment (60 mg three times daily) failed to improve parameters of left and right systolic function, left diastolic function, and cardiac dimensions and diameters [115]. In seeking the potential reasons for such a failure, it should be considered that HFpEF patients usually develop more severe endothelial dysfunction and lower natriuretic peptide levels than HFrEF patients. Thus, reduced PKG activity and lower myocardial cGMP concentration attributed to decreased NO signaling, a lack of PDE5A up-regulation, and inadequate dose or duration of PDE5is should be considered [113,116]. PDE5is were also shown to play

a role in myocardial protection against IR injury in several animal models [111], but their effectiveness is currently unexplored in humans, except for one study. In fact, a recent retrospective cohort study of men with T2DM (n=5,956) showed that PDE5is were associated with a reduced risk of all-cause mortality (HR 0.69, 95% CI: 0.64-0.79; p<0.001). Interestingly, PDE5is was associated with lower risk of mortality (HR 0.61, 95% CI: 0.45-0.81; p=0.001) in those with a history of acute MI (n=1,031), and with a reduced incidence of an acute MI in men with no prior CVD history (n=432) (IRR 0.62, 95% CI: 0.49-0.80; p<0.0001) [117]. Similar cardioprotective effect was reported in a Swedish nationwide cohort study published in 2017 enrolling men with a first MI (n=43,145), in which PDE5is treatment improved the incidence rate for death (adjusted HR^{adj} 0.62, 95% CI: 0.50-0.77) compared with those without PDE5is or alprostadil [118].

Overall, strong evidence support the use of PDE5is in patients with HFrEF, but not with HFpEF. Furthermore, recent data suggest that PDE5is might elicit cardioprotective effects in patients with CVD and/or T2DM.

Currently, on-going studies are evaluating the effects of sildenafil on pulmonary vascular resistance (PVR) and occurrence of right heart failure in patients with left ventricular assist devices (LVAD) implantation (http://www.ClinicalTrials.gov NCT03356353), and changes in six minute walk test and New York Heart Association (NYHA) function class in patients with chronic heart failure (NYHA class II and III) with evidence of systolic dysfunction (EF ≤40%) and secondary pulmonary hypertension (http://www.ClinicalTrials.gov NCT03460470 and NCT01616381). The effect of tadalafil on change of left ventricular torsion, cardiac strain and assessment of inflammatory indices, cardiac remodeling indices, endothelial function markers and

oxidative stress markers will be studied in patients with endocrine cardiomyopathy (http://www.ClinicalTrials.gov NCT02611336 and NCT02611258).

3.7 Donezepil and others cholinesterase inhibitors

Donepezil is a cholinesterase inhibitor (AChI) approved for the treatment of mild-to-moderate Alzheimer's disease (AD). AChIs are usually associated with peripheral adverse reactions, including cardiovascular effects such as syncope, bradycardia, QT prolongation and *torsades de pointes* ventricular tachycardia [119]. However, AChIs could also exert beneficial effects on the cardiovascular system. Experimental studies showed that donezepil inhibits atherogenesis, and improves hemodynamics, long-term survival and cardiac remodeling in models of chronic heart failure [119].

In a retrospective cohort study of 156 patients with AD and vascular dementia, donepezil-treated patients had lower total mortality risk (HR^{adj} 0.68, 95% CI: 0.46–0.99; p=0.045) and also lower cardiovascular mortality risk (HR^{adj} 0.54, 95% CI: 0.30–0.98; p=0.042) [120]. Furthermore, in a prospective study of 49 dementia patients free of any cardiovascular events, donezepil decreased the BNP levels (116.39 ± 76.58 pg/mL at baseline to 82.24 ± 46.64 pg/mL at first evaluation; p=0.011) with a further tendency to reduction in the 6-months follow-up period in patients with high level of BNP (>60 pg/mL) [121]. These promising results are supported by those obtained in a recent retrospective cohort study of 7,073 AD patients, showing that treatment with AChIs was associated with a lower risk of MI (HR 0.62, 95% CI: 0.40-0.95). This effect was more evident in patients taking the highest recommended AChIs doses (HR 0.35, 95% CI: 0.19-0.64) [122]. Finally, in a clinical study on a sample of 23 patients affected by mild-to-moderate dementia of

Alzheimer, AchIs treatment was associated with improvement of diastolic performance [123].

Currently, the data are far to demonstrate the possible clinical use of donezepil in cardiovascular diseases, but support the rationale for future studies in animals and then in humans.

3.8 Allopurinol and other xanthine oxidase inhibitors

Allopurinol is currently approved by FDA for primary and secondary gout, management of patients with leukemia, lymphoma and malignancies who are receiving anti-cancer therapy, which induces hyperuricemia, tumor lysis syndrome, and calcium oxalate calculi. It inhibits xanthine oxidase, an enzyme that regulates uric acid production.

Emerging evidence from recent large-scale epidemiological studies have showed that elevated serum uric acid levels are an independent risk factor for cardiovascular disease, including heart failure and coronary artery disease [124]. Furthermore, in experimental models of vascular diseases, uric acid was able to turn on “inflammatory”, cytotoxic, and dysfunctional responses, such as up-regulation of the renin-angiotensin system in endothelial cell cultures, arterial smooth muscle cell proliferation and migration, and scavenging of NO in endothelial cells [125]. Xanthine oxidase also promotes oxidative stress in endothelial cells, and impairs endothelial function independent of uric acid generation [125]. Finally, cardiomyocyte hypertrophy, myocardial oxidative stress, interstitial fibrosis, and impaired diastolic relaxation were associated with serum uric acid levels in mice fed Western diet [126] and with increased xanthine oxidase in MI mice [125]. Allopurinol treatment

significantly attenuated LV dilatation, hypertrophy, fibrosis and dysfunction, through inhibition of S6 kinase-1 (S6K1), TGF-b1 and MMP-9 [125,126].

Thus, allopurinol was suggested as a potential therapeutic option in the management of cardiovascular disease.

In chronic heart failure, several RCTs evaluated the effectiveness of xanthine oxidase inhibitors with conflicting results. Indeed, two small RCTs suggested that xanthine oxidase inhibitors could improve myocardial efficiency in HF patients. In the first RCT (n=50 patients), allopurinol (300 mg/day for 3 months) reduced BNP levels (11.9 pmol/l *vs* 14.4 pmol/l; p=0.035) although failed to improve exercise capacity [127]. In the second one (n=60 chronic HF patients) oxypurinol (600 mg/day for 4 weeks) improved LVEF of 6.8% ± 2.8% from baseline compared to placebo (p<0.02) in patients with LVEF ≤ 40% [128]. These results were not confirmed by more recent studies.

In the OPT-CHF study enrolling 405 patients with HF and LVEF ≤ 40%, oxypurinol (100 mg/day for 1 week and 600 mg/day for 24 weeks) did not improve clinical outcomes, but showed a trend towards an increased risk of CV death or hospitalization for HF (HR 1.8, 95% CI: 1.0-3.1; p=0.055). A sub-group analysis found that oxypurinol therapy was associated with favourable clinical response in patients with elevated baseline serum uric acid levels (p=0.02) and in those who exhibited the greatest reductions in serum uric acid (p=0.0006) [129]. Similar results were obtained in 2 RCTs evaluating allopurinol. In the EXACT-HF study, a RCT published in 2015 involving 253 hyperuricemic HF patients, allopurinol (600 mg/day for 24 weeks) had no effect on clinical status (p=0.68), quality of life (p=0.16), 6-min walk test (p=0.64), LVEF or the rate of serious adverse event rates (20% *vs* 15%, p=0.36) [130]. In the second RCT (n=52 patients), allopurinol (300 mg/day for 36

weeks) did not produce significant clinical and functional improvement, but suggested that allopurinol is useful in patients with elevated serum uric acid in a manner according to degree of serum uric acid reduction [131]. This hypothesis is strengthened by the results obtained by a large cohort study, which demonstrated favourable effects for allopurinol in HF patients with a history of gout (a surrogate marker for elevated serum uric acid levels), resulting in reduced HF readmission or death (RR^{adj} 0.69, 95% CI: 0.60–0.79; p<0.001) and all-cause mortality (RR^{adj} 0.74, 95% CI: 0.61–0.90; p<0.001) [132]. In patients undergoing primary angioplasty, xanthine oxidase inhibitor therapy showed promising results. Indeed, in a prospective open-label study enrolling 38 AMI patients undergoing primary PTCA, allopurinol induced a higher cardiac index (2.6±0.2 *vs* 2.2±0.1 l/min/m^2; p=0.043) and improved LVEF (57 *vs* 49%; p=0.04) [133]. Similarly, in a RCT enrolling 40 STEMI patients undergoing primary PCI, allopurinol (loading dose 400 mg followed by 100 mg for 1 month) resulted in a more effective ST-E recovery (p<0.05 for all comparisons), lower peak values of troponin I (p=0.04), CPK (p=0.01) and CK-MB (p=0.03) and 13% lower incidence of major adverse cardiac events (p=0.002), but it failed to improve EF [134]. In patients undergoing elective CABG, the effectiveness of allopurinol is controversial. In a RCT enrolling 169 patients, pre-treatment of allopurinol (400 to 800 mg/day for 2 days) reduced in-hospital mortality (4 *vs* 18%; p=0.014) and the need for post- operative inotropic or mechanical support (12 *vs* 26%; p=0.021) [135]. Peri-operative allopurinol treatment (300 – 600 mg/day for 5 days) also reduced the risk of cardiac complications, including arrhythmias (p<0.01), MI (p<0.01) and requirement for intra-aortic balloon pump support (p=0.05) [136]. On the contrary, other studies failed to show benefit with allopurinol treatment. In a RCT involving 52 patients, allopurinol (800 mg for 1 day) did not improve left ventricular function,

arrhythmias or post-operative inotropic support requirement [137]. In another RCT (n=20 patients), peri-operative allopurinol (600 mg/day for 2 day) had no demonstrable effect on cardiac troponin, CK-MB, myoglobulin release or ECG changes [138]. A recent RCT published in 2018 showed that allopurinol treatment (10 mg/kg/dose for 2 days for a total of 5 doses; n=25 patients) was also effective in patients undergoing intracardiac repair of tetralogy of Fallot, reducing inotropic scores (10 *vs* 15; p=0.02), duration of mechanical ventilation (6.5 *vs* 8 hours; p=0.01), intensive care unit stay (31.5 *vs* 48 hours; p=0.001), hospital stay (5 *vs* 6 days; p=0.01) and favourable biochemical markers of inflammation [such as SOD, malondialdehyde (MDA), IL-6, IL-1β and cardiac Tropinin I] compared to placebo (n=25 patients) [139]. The effectiveness of allopurinol was also evaluated in patients with STEMI who did not undergo to primary PCI, but were treated with streptokinase. In a RCT enrolling 140 patients, allopurinol (100 mg/daily for 28 days) resulted in higher ST resolution rate ≥50% (68.8% *vs* 50%; p=0.04) and lower levels of peak CK (p=0.003), CK-MB (p=0.005), and cardiac troponin I (p<0.001). Allopurinol also decreased the rate of in-hospital major adverse cardiovascular events (MACE) (p=0.03), but failed to improve in-hospital mortality and cardiac events [140]. In patients with acute coronary syndrome (ACS) (n=50), including STEMI, NSTEMI and unstable angina pectoris, allopurinol (600 mg/day during ACS period and then 200 mg/day until 4 weeks) significantly reduced MDA and ox-LDL (oxidative stress indicators), CRP and TNF-α (inflammatory reaction indicators), the total effective rate of angina pectoris (93.2% *vs* 76%) and of ECG (96% *vs* 82%), and the incidence of cardiovascular events (10 *vs* 30) compared to placebo (n=50) [141].

Two RTCs suggested that allopurinol could also reduce blood pressure (BP) in hyperuricemic adolescents. In a cross-over study (n=30 patients), allopurinol (200 mg

twice daily for 4 weeks) induced a higher decrease of the mean systolic (-6.9 mmHg *vs* -2.0 mmHg; p=0.009) and diastolic BP (-5.1 mmHg *vs* -2.4 mmHg; p=0.05) compared to placebo [142]. In the second RCT, adolescents treated with a xanthine oxidase inhibitor showed a significant change in systolic (-10.2 mmHg *vs* +1.7 mmHg) and diastolic BP (-9.0 mmHg *vs* +1.6 mmHg) compared to placebo [143].

Notably, in a cohort of 2,032 adult hypertensive patients, allopurinol treatment significantly reduced the risk of a cardiac event (HR^{adj} 0.61, 95% CI: 0.43-0.87) compared to placebo. When compared to placebo, this effect was still present in high-dose treatment (HR^{adj} 0.38, 95% CI: 0.22-0.67), but not in low-dose treatment (HR^{adj} 0.87, 95% CI: 0.56-1.35). High-dose (≥300 mg/day) treatment was associated with a reduction in risk of a cardiac event (HR^{adj} 0.65, 95% CI: 0.46-0.93) when compared with low-dose treatment [144]. By contrast, in a RCT published in 2019 enrolling normouricemic hypertensive patients (n=72), 12 months of high-dose allopurinol (600 mg/day) induced a significant increase of thiobarbituric acid reactive substances (TBARS) level (0.26±0.85 *vs* -0.34±0.83 μmol/l; p=0.007) and reduced LV mass regression (-0.37±6.08 *vs* -3.75±3.89 g; p=0.012) [145].

Finally, there are a number of clinical trials that have evaluated the allopurinol effect on endothelial function with promising results in different patient populations. A review and meta-analysis published in 2018 including 12 RCTs summarized these results and found that allopurinol significantly improved endothelial function in patients with mild-moderate CHF (SMD 0.776, 95% CI: 0.429-1.122; p<0.001) and CKD (SMD 0.350, 95% CI: 0.009-0.690; p=0.04) but not in T2DM (SMD 1.331, 95% CI: -0.781 to +3.444; p=0.217) [146].

The potential cardiovascular protective effect of allopurinol was pointed out by two recent studies. In a retrospective cohort study of patients with gout and diabetes,

involving 5,621.3 person years of current allopurinol use and 4,576.5 person years of prior allopurinol use, current allopurinol users had significantly lower risk of incident of stroke or MI (HR 0.67, 95% CI: 0.53-0.84; p=0.0006) [147]. Similarly, a systematic review and meta-analysis published in 2018 including 91 RCTs, which tested xanthine oxidase inhibitors (XOI) compared with placebo or no treatment, showed that the use of XOI was not significantly associated with the risk of major adverse cardiovascular events (MACE) [Peto odds ratio (OR_p) 0.71, 95% CI: 0.46-1.09] or death (OR_p 0.89, 95% CI: 0.59-1.33), but reduced risk of total CV events (OR_p 0.60, 95% CI: 0.44–0.82; p<0.001), and hypertension (OR_p 0.54, 95% CI: 0.37-0.80; p=0.002). There was protection for MACE in patients with previous ischemic events (OR_p 0.42, 95% CI: 0.23-0.76; p=0.004). Purine-like XOI (allopurinol or oxypurinol) protected from MI (OR_p 0.38, 95% CI: 0.17-0.83; p=0.0015), hypertension (OR_p 0.32, 95% CI: 0.18-0.58; p<0.001), total CV events (OR_p 0.57, 95% CI: 0.46-0.72; p<0.001) and serious CV events (OR_p 0.59, 95% CI: 0.46-0.76; p<0.001) [148]. In conclusion, there are several data, often obtained by small studies, suggesting beneficial effects of xanthine oxidase inhibitors in coronary angioplasty and bypass surgery. Additionally, a number of evidence indicate a potential favourable effect of xanthine oxidase inhibitors on endothelial dysfunction and LV function in heart failure patients, particularly in those with raised serum uric acid levels. Thus, to clearly define their possible clinical use, large-scale prospective studies are needed.

Currently, two on-going studies are now expected to further investigate the role of xanthine oxidase inhibitors in the following setting: allopurinol in the treatment of patients with diabetes mellitus and multivessel coronary artery disease treated by either PCI or CABG (http://www.ClinicalTrials.gov NCT03700645); allopurinol on the stability of coronary plaques in patients with acute coronary syndrome

(NCT03745729).

4. Conclusion

Several experimental and epidemiological evidence have strongly highlighted the central role of inflammation in the onset and progression of atherosclerosis and its clinical manifestations, such as coronary artery disease (CAD) that can lead to acute coronary syndrome (ACS). However, lack in anti-inflammatory drugs without adverse cardiovascular safety profile had limited the possibility to examine the potential role of anti-inflammatory treatment in cardiovascular field.

Thus, drug repurposing has emerged as an interesting strategy to identify safe and effective drugs in cardiovascular diseases. The possibility to use monoclonal antibody-based immunotherapy targeting cytokines has provided an exiting challenge to address this issue in human trials. Although the results of large RCTs don't support the repurposing of TNF-α blockers in patients with chronic heart failure, small RCTs suggest beneficial effects in subclinical atherosclerosis, artery stiffness and Kawasaki disease. Furthermore, IL-1β antagonist was effective in reducing cardiovascular event rates in patients with high cardiovascular risk, whereas, IL-6 antagonist reduced myocardial injury in NSTEMI patients undergoing PCI. Overall, the data are promising, but the ratio cost-effectiveness and the occurrence of adverse-effects, such as impaired host defences and tumor surveillance, need to be evaluated in future studies. Other anti-inflammatory agents, as colchicine, methotrexate and allopurinol, used primarily to treat inflammatory diseases, have been repurposed for treatment of cardiovascular diseases. The beneficial effects exerted by colchicine and allopurinol in patients with ACS and STEMI underwent PCI are still needed to be confirmed by already on-going or future large RCTs.

Also, anti-diabetic drugs, metformin and incretin mimetics, were demonstrated to control inflammatory process. Strong evidence indicates that these drugs exert cardioprotective effects in patients with T2DM, but future RCTs are needed to provide evidence for their use also in patients with CAD without T2DM.

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Figure legends

Figure 1. The anti-cytokine therapy blocks several cytokine-mediated pathological mechanisms, which involved inflammatory and vascular cells during atherothrombotic process. Monocytes migrate into the sub-endothelial space interacting with adhesion molecules, differentiate into macrophages, and change to foam cells after oxLDL up-taking. Macrophage-derived cytokines activate vascular smooth muscle cells (VSMCs) and endothelial cells to produce an array of pro-inflammatory mediators (i.e. adhesion molecules, TXA_2, PGI_2 and several cytokines). Furthermore, macrophages and dendritic cells stimulate T cells differentiation into effector T cells (Th1, Th2, and Th17). These T cells release cytokines and chemokines, which increase the migration of VSMCs and other inflammatory reactions. Finally, besides release of inflammatory mediators, neutrophils markedly contribute to recruitment of monocytes, while neutrophil extracellular traps (NETs) may promote lesional macrophage accumulation and activation.

Figure 2. The Colchicine mechanisms of action. Colchicine influences cytoskeleton rearrangement and NALP3 inflammasome formation. These effects could reduce some cellular functions mainly in leucocytes, but also in endothelial cells and VSMCs, leading a decrease of synthetized or activated inflammatory factors.

Figure 3. The methotrexate mechanisms of action. Methotrexate inhibits dihydrofolate reductase (DHFR), which leads to a reduced synthesis or methylation

of DNA and RNA, and aminoimidazole carboxamidoribonucleotide (AICAR) transformylase with subsequent activation of the adenosine A_{2A} receptor. These effects could reduce the expression of some pro-inflammatory mediators (i.e. cytokines, chemokines and MMPs) in neutrophils, macrophages, T-cells and endothelial cells. This leads to less inflammation and endothelial dysfunction, and to improved plaque stability.

Figure 4. The potential underlying molecular mechanisms of action of metformin. The activation of AMPK/SIRT1 pathway by metformin regulates several cellular mechanisms, such as autophagic processes, oxidative stress and mitochondrial biogenesis, through activation of p53/p21, FOXO transcription factors and PGC1-α, respectively. Furthermore, in AMPK-dependent manner, metformin reduces the activity of NADPH oxidase, NF-kB and CHOP, improving oxidative stress, inflammation and mitochondrial protection. AMPK activation also increases the phosphorylation of eNOS, which in turn increased eNOS activity and NO bioavailability. Finally, metformin inhibits PI3K/AKT/mTOR and RAS/MEK/ERK pathways in AMPK -dependent and -independent manner, regulating cell hypertrophy, cell proliferation and autophagic processes.