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Review

Uric acid: from a biological advantage to a potential danger. A focus on cardiovascular effects

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ABSTRACT

Non-communicable diseases represent nowadays the most common cause of death worldwide, having largely overcome infectious diseases. Among them, cardiovascular diseases constitute the majority.

Given these premise, great efforts have been made by scientific societies to emphasize the fundamental role of cardiovascular prevention and risk factors control. In addition to classical cardiovascular risk factors such as smoking, arterial hypertension, hypercholesterolemia and male gender, new risk factors are emerging from international literature. Among them, uric acid is the protagonist. Several evidences show a direct role of hyperuricemia in the determinism of metabolic and vascular disorders. From the other hand, some researchers have demonstrated that uric acid is only a marker of cardiovascular damage and not a risk factor for its development.

Aim of this review is to evaluate the scientific evidences on the role of uric acid in cardiovascular diseases in order to shed light on this confusing topic.

1. Introduction

In 2015, cardiovascular (CV) diseases represented the first causes of deaths worldwide [1].

In Europe they have been responsible for over 3.9 million deaths a year (45% of all deaths) 1.8 million deaths in men (40% of all deaths), and 2.1 million deaths in women (49% of all deaths), according to recent estimates [2].

In addition to traditional ones, new risk factors seem to play an important role in the development of these pathological conditions [3]. Several epidemiologic studies demonstrated that serum uric acid (SUA) concentration is an independent predictor of CV events, especially in patients with arterial hypertension, heart failure and diabetes [4,5]. Hyperuricemia represent a predictor of mortality for coronary artery disease (CAD), heart failure and stroke [4,5]; moreover, the close association between high SUA concentration and insulin resistance, type 2 diabetes, metabolic syndrome, and obesity is also well-known [3,6].

On the other hand, the western lifestyle, characterized by high caloric intake and sedentariness, has favoured the increase in the prevalence of hyperuricemia and its direct consequences [gout arthropathy, both acute arthritis or chronic tophaceus gout, uric acid (UA) urolithiasis and gouty nephropathy], making the link between SUA and CV disease a very debated topic [7].

At this purpose, some researchers speculated that high UA is not a risk factor but only a marker of augmented CV risk [4,5]. In fact, hyperuricemia is frequently associated with other CV risk factors and often co-exists with manifest CV disease. Therefore, is difficult to understand its specific role in the pathogenesis of atherosclerosis [4,5].

The aim of this manuscript is to review the available scientific evidences analyzing the relationship between SUA and CV disorders, as well as focusing on the possible pathogenetic explanations i.e. the inflammation-mediated damage caused by UA.

Abbreviations: AF, atrial fibrillation; AMP, adenosine monophosphate; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; c-IMT, carotid intima-media thickness; CRP, C-reactive protein; CV, cardiovascular; FMD, flow mediated dilation; HF, heart failure; HR, hazard ratio; NO, nitric oxide; OR, odd ratio; RAGE, receptor for advanced glycation end products; RR, relative risk; SUA, serum uric acid; UA, uric acid; VSMC, vascular smooth muscle cells

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An extensive review has been conducted on scientific literature published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and Google Scholar from January to May 2017.

Additional relevant studies published after the initial review were also considered during the period of March 2018–May 2019, in which the writing process of this manuscript has been conducted.

Preclinical data: an extensive analysis was conducted with the aim of defining the molecular characteristic of UA, to evaluate the different factors that may modify its concentration, the consequences of high circulating levels and the available tools for treating them. An in-depth evaluation was also conducted on the biological role of UA, on mechanisms at the basis of its oxidant and antioxidant power that could explain its importance in CV diseases.

1.1. Uric acid metabolism

UA (molecular formula: $C_5H_4N_4O_3$, molecular mass 168 Da) is a 7,9-dihydro-3H-purine-2,6,8-trione, the final product of purines metabolism (adenine and guanine) which occurs in the liver, kidney, intestine and vascular endothelium [8,9]. The main endogenous source of purines are nucleic acids deriving from living and dying cells while the exogenous pool derived from animal proteins and fructose catabolism [8]. Through deamination, hydrolysis and phosphorylation processes the single nucleotides, adenosine monophosphate (AMP), guanosine monophosphate and inosine monophosphate are converted into hypoxanthine, xanthine and guanine. Hypoxanthine is converted to xanthine via xanthine oxidase, while guanine via deamination. Xanthine is then oxidized to the final product, UA, by the xanthine oxidase enzyme (Fig. 1). UA is finally excreted by the kidneys (65–75%) and intestines (25–35%). It is a weak acid with a pKa of 5.8. Therefore, at physiologic pH it exists mainly as urate, its correspondent salt. The solubility of the compound is relatively low, as human average blood levels of UA are close to the solubility limit (6.8 mg/dl). Over this limit, crystals of monosodium urate form. In most mammals, hepatic enzyme uricase (urate oxidase) converts UA into allantoine. In humans and other primates this enzyme is not functional [10], thus leading to higher and more variable SUA levels in humans than other species [9] (Fig. 1).

Foods, like fatty meat, organ meat, seafood, rich in purines, cause an increase in UA production [11] as well as fruits rich in fructose do, see later [12].

Also, alcohol abuse is associated to increased circulating SUA, secondary to renal retention, the so-called alcoholic hyperuricemia [13].

Moreover, some drugs like salicylate, thiazide, loop diuretics, niacin, and calcineurin inhibitors interfere with renal excretion and/or stimulate the production of UA causing hyperuricemia [14].

1.2. The fructose pathway

Several biological processes link UA metabolism with fructose. First, fructose introduced with food undergoes a phosphorylation process catalysed by fructokinase enzyme with concomitant conversion of adenosine triphosphate into adenosine diphosphate and then into AMP (Fig. 1). This process mainly occurs in the liver, without any negative feedback and determines the depletion of intracellular phosphate and adenosine triphosphate storage [15].

This negative change of intracellular phosphates stimulates AMP deaminase, which convert AMP to inosine monophosphate that is finally transformed into UA [12].

Moreover, UA plays a significant role in the lipogenesis associated with fructose intake, favouring fat accumulation in the liver and metabolic syndrome [6].

Finally, the renal carrier of fructose and glucose, SLC2A9, has been recently identified as UA transporter, is able to significantly modify plasma concentration of UA in response to dietetic uptake of fructose [16].

1.3. Genetic polymorphism of uric acid metabolism

In addition to diet and lifestyle, genetic components play a fundamental role in determining the serum concentration of SUA, with an estimated contribution of around 40% of the total [17].

Some monogenic disorders are associated with high levels of circulating UA and with the pathological consequences of its accumulation: i.e. mutations of the phosphoribosyl pyrophosphate synthetase gene, the hypoxanthine guanine phosphoribosyl transferase gene (Lesch-Nyhan syndrome) and the uromodulin gene [18].

On the other hand, genome-wide association studies identified about thirty genes involved in the regulation of SUA concentration. These genes encode urate transporters, proteins involved in glucose metabolism and insulin response, proteins that interact with urate transporters, transcription factors or growth factors or protein of unknown or poorly described function with an unclear relationship with uric acid regulation. Table 1 shows genes with known role in UA metabolism [18].

2. Uricase mutation: a biological advantage?

The mutation of the uricase enzyme has developed in the evolutionary line of man in the middle Miocene, about 15 million years ago. For this reason, while in mammals with functional uricase, SUA concentration is in the 1–2 mg / dl range (0.06 to 0.12 mM), in man and in the Great and Lesser Apes, the concentration is higher [19].

Several theories have been developed to explain this change.

Proctor [20] and later Ames et al. [21] hypothesized that uricase gene mutation occurred to reinforce the antioxidant power of the plasma after the loss of ascorbate synthesis.

According to Orowan [22] the increase of SUA was fundamental to favor the mental performance of man.

Others hypothesis focused on the ability of monosodium urate crystals to activate the immune response against infection and cancer [23].

Finally, it has been supposed that the loss of uricase function gave a survival advantage as higher levels of SUA helped to maintain high blood pressure (BP), stimulate salt-sensitivity, and induce insulin resistance and mild obesity, favouring survival during a period of famine or stress, like the mid Miocene, the period in which the uricase mutation occurred [19,24].

This latter theory explains the negative consequences of SUA on metabolic and CV system as determined by the imbalance of its antioxidant and oxidant effects, see later, in favor of the seconds, due to the high circulating levels of SUA in contemporary humans (range 4–10 mg/dl) compared to primates that lack uricase (where SUA levels are typically in the 3–4 mg/dl range) [19].

3. Uric acid and its pathological consequences

Hyperuricemia, defined as a serum urate level greater than either 6.5 or 7.0 mg/dl [25] is the main determinant of gout, a metabolic disorder which classically manifests itself with recurrent and characteristic attacks of arthritis, characterized by the presence of monosodium urate crystals in the synovial fluid leucocytes [14].

In the long-lasting forms, urate deposits (tophi) in soft tissue around joints of extremities can be observed.

The deposition of monosodium urate crystals can also affect the kidney determining urolithiasis and more rarely chronic interstitial nephropathy [14].

Epidemiological data show that gout and hyperuricemia represent nowadays increasingly common medical problems, reflecting the spread of Western habits characterized by poor physical activity and a diet high in meats and fructose. According to the National Health and Nutrition Examination Survey, the prevalence of gout among United States adults in 2007–2008 was 3.9%, 5.9% in men and 2.0% in

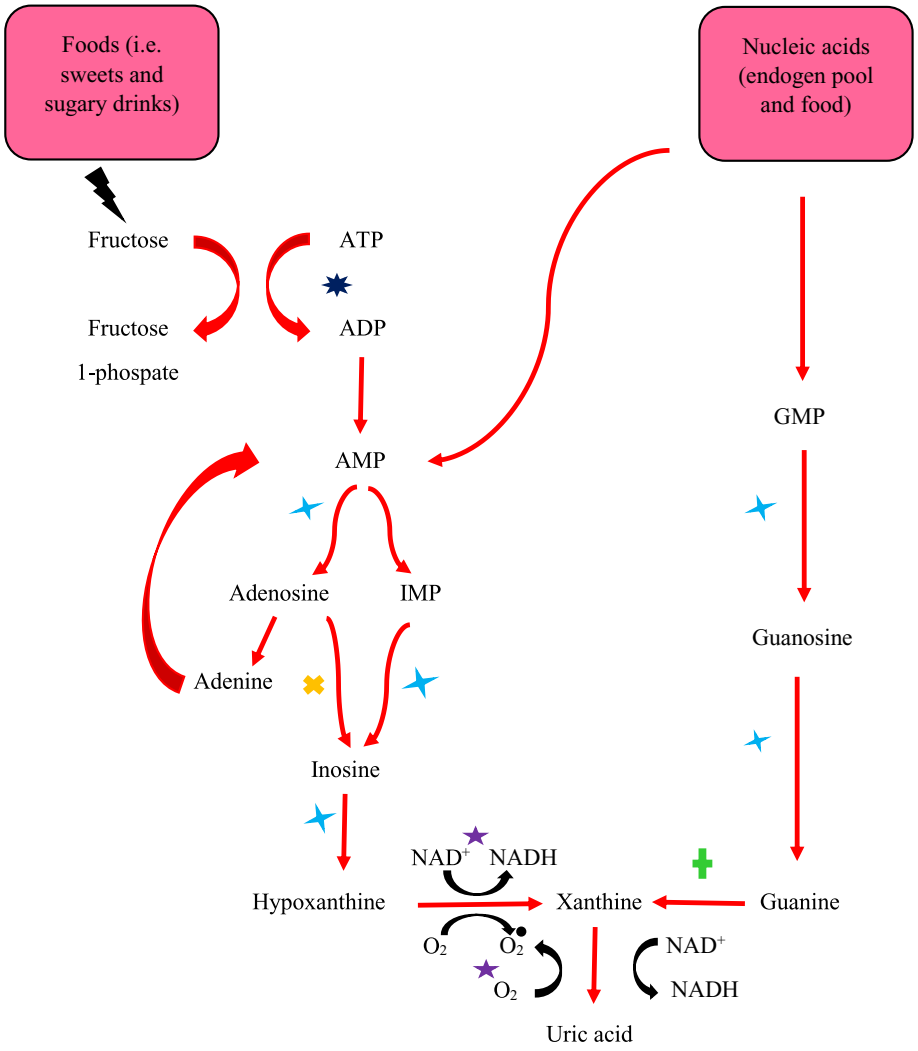

Fig. 1. Figure shows the main metabolic pathways leading to uric acid formation. Nucleic acids (adenosine monophosphate, guanosine monophosphate and inosine monophosphate) deriving from living and dying cells and from animal proteins and fructose catabolism undergo deamination, hydrolysis and phosphorylation processes with the formation of hypoxanthine, xanthine and guanine. Hypoxanthine is converted to xanthine via xanthine oxidase, while guanine via deamination. Xanthine is then oxidized to the final product, uric acid, by the xanthine oxidase enzyme, see text.

Table 1
Genes with known role in UA metabolism.

Gene	Gene product	Role in UA metabolism
ABCG2	ATP Binding Cassette B member 2	Urate transporter
HNF4G	Hepatocyte nuclear factor 4	Growth factor
PDZK1	PDZ domain containing 1 protein	Interaction with urate transporters
SLC17A1	NPT1 (renal sodium phosphate transporter protein 1)	Urate transporter
SLC17A3	NPT4 (renal sodium phosphate transporter protein 1)	Urate transporter
SLC22A11	Solute carrier family 11 r (related to URAT1)	Urate transporter
SLC22A12	URAT1	Urate transporter
SLC2A9	GLUT 9 (glucose transporter)	Urate transporter

UA: uric acid. For more detail see text.

women, while the hyperuricemia prevalence is of 21.2% and 21.6%, respectively. These estimates are higher compared to those in National Health and Nutrition Examination Survey -III [26], with an increase of 1.2% in the prevalence of gout and 3.2% in the prevalence of hyperuricemia.

Similarly, in Europe the prevalence and incidence of gout and hyperuricemia are progressively growing: data from United Kingdom showed an increase of gout prevalence from 4.3/1000 in 2001 to 4.7/1000 in 2007 [27], while the prevalence of gout and of hyperuricemia increased from 0.67% in 2005 to 0.9% in 2009 and from 8.5% in 2005 to 11.9% in 2009, respectively in an Italian nationwide population-based study [28].

The American College of Rheumatology recommend to lower serum urate level sufficiently to improve signs and symptoms of gout, with the target < 6 mg/dl at a minimum, and even < 5 mg/dl [14].

4. Prophylaxis and management of hyperuricemia and gout

A proper diet and lifestyle modification with a hypocaloric regime in the presence of overweight and obesity, a reduced consumption of meat, fish, saturated fats, and simple carbohydrates are the first line treatment in hyperuricemia management [14]. Urate-elevating medications should be eliminated or substituted if non-essentials. About aspirin, although it has been demonstrated that low-dose (< 325 mg daily) determines the elevation of serum urate, there are no evidence to recommend the discontinuation of the drug when used for CV disease prophylaxis in gout patients [14].

Current guidelines recommend xanthine oxidase inhibitor therapy with allopurinol or febuxostat as the first-line pharmacological approach in gout [14].

If the xanthine oxidase inhibitor is ineffective or contraindicated, an uricosuric agent (e.g., probenecid, lesinurad, fenofibrate, or losartan) can be used [14,29].

Finally, pegloticase is the third line treatment in patients with severe gout disease, refractory to conventional treatment or where conventional therapy is not tolerated [14].

5. Uric acid: molecular mechanisms associated with it

UA represents a potent antioxidant, contributing to about two/third of the antioxidant plasma power in Humans [30].

It can react with several reactive molecules, i.e. hydrogen peroxide, hydroxyl radical, peroxynitrite, and nitric oxide (NO), forming stable compounds [31].

Moreover, evidences suggest that it can directly stimulate superoxide dismutase activity, favouring its scavenger activity on radical oxygen species [32].

On the other hand, several evidences demonstrated the oxidant effects of UA, both in soluble form and in the form of crystals, at the base of its negative metabolic and CV effects.

About the soluble form, studies on rodent models showed that hyperuricemia favours the development of hypertension and renal damage by negatively affecting NO generation in macula densa of the kidneys and then leading to the stimulation of renin angiotensin system [33].

Other mechanisms by which UA can cause endothelial dysfunction are the inhibition of neuronal NO synthase in kidneys [34], the stimulus of the conversion of NO into other molecules such as glutathione [33] or the inhibition of its production [35].

It has been postulated that xanthine oxidase-derived radical oxygen species (superoxide anion radical and/or hydrogen peroxide) can rapidly react with NO to form cytotoxic oxidant peroxynitrite; with a consequent depletion of NO, thus determining endothelial dysfunction, in addition to a direct contribution of the peroxynitrite itself [36].

Hence the importance of xanthine oxidase activity in the physiopathology of CV disease: the hyperactivation of this metabolic pathway leads to the production of free radicals and UA, both associated to endothelial dysfunction and consequent vascular damage, see later for details [37].

It has also been demonstrated that, in endothelial cells, UA favours the production and release of high mobility group box chromosomal protein 1. This is a nuclear DNA binding protein, that, in specific circumstances can be translocated from the nucleus to the cytosol and then released extracellularly by activated monocytes [38]. In this setting high mobility group box chromosomal protein 1 acts as an inflammatory cytokine [39], able to induce an oxidative status and consequently endothelial dysfunction, through the activation of the receptor for advanced glycation end products (RAGE) [40]. The key role of this molecular messenger in the pathogenesis of CV disease [41], has been demonstrated by the inhibition of the progression of atherosclerotic changes obtained by the blockage of the RAGE -dependent signalling determined by soluble RAGE particles in diabetic mice, effects attributed to the suppression of nuclear factor k-B pathway [42].

In addition, UA can cause endothelial dysfunction increasing intracellular expression and activity of aldose. Aldose reductase is the polyol pathway rate-limiting enzyme, one of the main actors in the pathogenesis of diabetic complications and atherosclerosis [43]. Its expression is highlighted in endothelial cells in presence of high SUA concentrations [44]. The increase activity of aldose reductase is associated with an increment of radical oxygen species production with the related consequences i.e. cell injury, apoptosis, altered ion regulation, and mitochondrial dysfunction [45].

Moreover, soluble UA, through the activation of the mitogen-activated protein kinase pathway, can induce vascular smooth muscle cells (VSMC) proliferation [46]. In kidneys it can contribute to renal microvascular disease and afferent arteriolopathy, leading to hypertension [47]. UA also induces generation of the following inflammatory molecules: monocyte chemoattractant protein-1, the transcription nuclear factor k-B cascade, interleukin 1, interleukin 6 and tumor necrosis factor-alpha [48]. On the other hand, these inflammatory messengers increase UA production enhancing xanthine-oxidase activity [49]. UA works as an inflammation-mediator itself. In facts, after cell damage or death, nucleotide degradation to UA acts as an endogenous danger signal that starts maturation and immune-stimulatory activity of dendritic cells for the removal of cellular debris [23].

Furthermore, it was demonstrated in animal models that UA can upregulate production of C-reactive protein (CRP) in VSMC and endothelial cells, thus favouring the development of atherosclerosis [50]. Three mechanism explain the correlation between CRP and CV diseases: first high level of serum CRP has been associated with the occurrence of CV diseases, second CRP have shown to exert direct proatherogenic effects on cultured mammalian cells, third CRP mechanically interact both with modified forms of low-density lipoproteins and both with native low-density lipoproteins favouring atherogenesis [50].

UA induces inflammation also in form of crystals. Deposits of monosodium urate crystals are localized in connective tissues of the joints, tendons, kidney, and rarely in heart valves and pericardium [51].

The resident macrophages and mast cells of the above-mentioned tissues phagocytise the UA crystals with subsequent activation and release of hydrolytic enzymes, radical oxygen species and proinflammatory proteins interleukin -1b and interleukin −18 [52].

Moreover, crystals of monosodium urate, with a spine structure, are harmful for the surface membrane of surrounding cells and are recognized by the receptors of the toll-like receptor family, toll-like receptor −2 or toll-like receptor −4, as danger signals, with generation of pro- interleukin -1b and tumor necrosis factor alpha [53].

In addition to the well-known functions as inflammatory mediator (as endogenous pyrogen, chemokine, pro-apoptosis molecule), interleukin -1b plays an important role in determining CV events, as recently demonstrated by the CANTOS trial, in which the administration of the anti- interleukin-1β monoclonal antibody canakinumab at the dosage of 150 mg every 3 months, in patients with previous myocardial infarction and a high-sensitivity CRP level ≥ 2 mg per liter, led to a significantly lower rate of recurrent CV events than placebo, independent of lipid-level lowering, at the 48 months-follow up [54].

Table 2 summarize the mechanisms underlining the pathological consequences of high SUA.

Clinical data: we selected only peer-reviewed publications that reported clinical trials, systematic reviews, metanalysis, cohort observational studies or cross-sectional studies analyzing the association between hyperuricemia/gout and CV diseases. Due to the high number of existing literature data, we limited the analysis to a maximum of ten references for each topic, preferring randomized clinical trials, systematic reviews, metanalysis and the observational studies with the largest number of subjects.

Table 2
Mechanisms underlining the pathological consequences of high uric acid.

Organ systems	Pathological effects	Mechanism
Vascular system	-Arterial hypertension	• Endothelial dysfunction: -Increased oxidative stress -pro-inflammatory state (NF-??B; CRP; IL-1; IL-6; IL-18; MHGB1/RAGE pathway)
	-Atherosclerosis	• Increased arterial stiffness • Renal vascular damage; • Salt-sensitivity • Reduced nephron number; • XOR genetic polymorphism
Heart	-Coronary artery disease -Microvascular angina -Heart failure -Atrial fibrillation	-Arterial hypertension; -ox-LDL -Metabolic syndrome and type 2 diabtes -Coronary endothelial dysfunction; - Increased oxidative stress -pro-inflammatory state (NF-??B; CRP; IL-1; IL-6; IL-18; MHGB1/RAGE pathway).

Abbreviations:
CRP: C-reactive protein; eNOS: endothelial nitric oxide synthase; IL: interleukin; MCP-1: monocyte chemoattractant protein-1; MHGB1/RAGE: high mobility group box chromosomal protein 1/ receptor for advanced glycation end products; NF-??B: transcription nuclear factor k-B; NO: nitric oxide; ox-LDL: oxidized low-density lipoprotein; XOR: xanthine oxidoreductase.

6. Arterial hypertension

Several clinical observational and prospective studies show an independent association between hyperuricemia and arterial hypertension, especially in female and younger [55,56].

In the National Health and Nutrition Examination Survey (NHANES) cohort of 6036 adolescents (aged 12–17 years), the OR of elevated BP was 1.38 for each 0.1 mg/dl increase in SUA level (95% CI, 1.16 to 1.65). A SUA level ≥ 5.5 mg/dl was associated to a 2.03 times higher risk of having elevated BP (95% CI, 1.38 to 3.00) [57]. Moreover, in young untreated hypertensive patients, allopurinol can reduce BP and plasma renin activity [58].

Jiang M et al. metanalysis found a strict relationship between elevated SUA levels and risk of prehypertension [59].

A positive association between incident hypertension and SUA levels was also shown in two meta-analysis [60,61].

A 10-years longitudinal study (118,920 healthy adults, aged 40–70 years), demonstrated a gradual increase of the risk of developing arterial hypertension, starting from a value of 3–4 mg/dl [62].

Moreover, a Japanese cross-sectional analysis on 85,286 subjects showed a significant association between hyperuricemia and SUA with arterial hypertension in males and females [63].

Recently a review performed by the Cochrane Hypertension Information Specialist demonstrated that hypouricemic drugs were effective in reducing BP values in hyperuricemic adolescents with prehypertension or mild primary hypertension, but not in hyperuricemic adults [64].

7. Cardiovascular disease

The existence of a cause-effect correlation between SUA and established CV disease is currently under debate.

A clear relation is difficult to establish for the existence of several confounding factors: cardiological patients often suffer conditions that determine the increase in circulating uricemia such as arterial hypertension, metabolic syndrome and diabetes, alcohol consumption and treatment with diuretics [65].

On the other hand, several evidences demonstrated a correlation between SUA level and subclinical atherosclerosis [66–68].

7.1. Asymptomatic atherosclerotic organ damage

7.1.1. Carotid intima-media thickness

The ultrasound evaluation of carotid intima-media thickness (c-IMT) at the level of common carotid artery is a noninvasive, sensitive, and reproducible technique for identifying the presence of arterial injury, a marker of subclinical atherosclerosis but not only.

Increase in c-IMT is also the result of nonatherosclerotic processes, secondary to an adaptive response to changes in flow and wall tension, leading to medial hypertrophy and arterial remodeling for smooth muscle cell hyperplasia and fibro-cellular hypertrophy [69].

UA, inducing the proliferation of VSMC and favouring the inflammatory process, my determine the intima-media thickening, but available data analyzing the relation between high UA and the c-IMT increase are conflicting.

Several data referred a positive link between SUA concentrations and increased c-IMT in healthy subjects [66], in hypertensive patients [67], in postmenopausal women independently from other CV risk factors [68] and in the elderly (> 65 years) population without metabolic syndrome [70].

Treatment of hyperuricemia with allopurinol for 3 years was able to reduce c-IMT in diabetic subjects [71].

A multicenter, prospective, randomized, open-label and blinded-endpoint evaluation (PRIZE) is underway to evaluate the effects of febuxostat on c-IMT in hyperuricemic patients. [72].

On the other hand, other literature sources showed no association between SUA and subclinical atherosclerosis at least when assessed by c-IMT [73–75].

A cross-sectional study on 2388 hospitalized patients with type 2 diabetes, demonstrated an association between SUA, on one hand, and metabolic syndrome and arterial hypertension on the other hand, but no association between SUA and carotid and lower limb atherosclerosis assessed using eco color Doppler ultrasound [73].

Similarly, no significant association was found between c-IMT and SUA level in apparently healthy subjects [74,75].

7.1.2. Arterial stiffness

Arterial stiffness is a measure of vascular distensibility and compliance. It represents the first step of several pathological conditions that could led to CV disease and can predict CV risk in subjects whit hypertension, diabetes and cerebrovascular diseases [76–78].

Pulse-wave velocity (PWV) represents the gold standard method for the assessment [79].

UA may promote stiffening of the arterial wall by inducing an inflammatory status and proliferation of VSMC [47] but also in this case, results from studies examining the potential relationship between SUA levels and arterial stiffness are conflicting.

The analysis on 4140 participants from the Generation 3 Framingham cohort, showed a significant relation between SUA and carotid-femoral pulse-wave velocity, also after the adjustment for the

confounding factors [80].

Moreover, SUA represents an independent determinant of PWV in subjects with essential hypertension [81,82], and in male patients with newly diagnosed type 2 diabetes mellitus [83].

In a longitudinal Chinese study on 1447 subjects, carotid-femoral pulse-wave velocity was strongly correlated with baseline and follow-up (4.8 years) SUA. A higher baseline SUA level resulted an independent predictor of follow-up arterial stiffness [84].

SUA levels were positively correlated with PWV in males (b = 0.0006, $p < .0001$) and in females (b = 0.0001, $p = ¼ 0.04$), without an association with c-IMT in either gender in the Korean Multi-Rural Communities Cohort [85].

Moreover, SUA levels were independently correlated with the cardio-ankle vascular index in a large Japanese prospective analysis of healthy subjects [86] and were positively associated with increased brachial-ankle PWV in apparently healthy women [87].

However, no significant associations were found between SUA and arterial stiffness (assessed by carotid femoral PWV and carotid radial PWV) in a recent Chinese study on 979 subjects from real world population [88], while the association between mild hyperuricemia and aortic stiffness was weaken in a study on 222 untreated and uncomplicated hypertensive subjects [89].

7.1.3. Endothelial function

The endothelium is a single vessel layer covering the inner wall of the vessels in direct contact with the blood. It is one of the largest organs in the body comprising of up to trillion cells, weighing over 1 kg, and covering nearly 3 m^2 in a 70 kg male [89].

It performs several essential tasks for life, regulating the haemostatic balance between thrombosis and anticoagulation, vascular tone, angiogenesis, wound healing, smooth muscle cell proliferation, fibrosis, and inflammation [89].

In conditions of rest, the endothelium maintain the vessel in a neutral state favouring dilatation over constriction, mainly through the release of NO which induces the intracellular production of cyclic Guanosine monophosphate, determining the relaxation of vascular smooth cells [90]. Endothelial dysfunction is a state of activation of the endothelium, characterized by an imbalance in NO production and consumption resulting in a reduced bioavailability [91]. This pathological condition favours platelet and leukocyte activation and adhesion, the release of inflammatory cytokines, the increase of vessel permeability to oxidized lipoproteins, finally resulting in structural damage of the arterial wall with smooth muscle cell proliferation and atherosclerotic plaque formation [91].

Flow mediated dilation (FMD) of brachial artery represents the most commonly accepted non-invasive method to measure vascular endothelial function, representing a functional bioassay for endothelium-derived NO bioavailability in humans [92].

It measures the vasodilation of brachial artery which occurred following an acute increase in blood flow, typically induced via circulatory arrest in the arm (supra-systolic cuff occlusion) for a period of time [93].

As already shown, several molecular mechanisms have been described to explain the effects of hyperuricemia on endothelial function.

Accordingly, several works in literature showed an association between SUA and endothelial dysfunction.

Kato et al. demonstrated that elevated SUA is associated with impaired endothelial function in hyperuricemic patients without any overt CV disease [94]. Zhang et al. [95], demonstrated lower FMD values in first-degree relatives (of subjects with type 2 diabetes) with or without hyperuricaemia (both $p < .001$) compared with controls, and, among first-degree relatives, FMD was lower in subjects with hyperuricemia. Stepwise multiple regressions demonstrated that SUA was a significant determinant of FMD independently of other variables in these subjects.

Zoccali et al. demonstrated an inverse relation between SUA and acetylcholine-stimulated vasodilation in 217 patients with uncomplicated, untreated essential hypertension, independent of traditional CV risk factors [96].

Recently, a meta-analysis of randomized placebo-controlled trials showed an improvement of FMD after allopurinol treatment. Nitroglycerine-mediated dilation was not altered by allopurinol treatment (weighted mean difference 0.88%, 95% CI - 1.15-2.91, $p = .395$; I 2: 80.88%) [97].

Still the causal relation between SUA levels and endothelial dysfunction remains somewhat controversial. A recent randomized double-blind placebo-controlled trial of non-hypertensive, overweight, or obese individuals with higher SUA (body mass index ≥ 25 kg/m^2 and SUA ≥ 5.0 mg/dl) did not demonstrate any significant change in endothelium-dependent vasodilation measured by brachial artery ultrasound after the lowering of SUA levels through probenecid (47 subjects) and allopurinol (49 subjects) compared to placebo (53 subjects) [98].

Also, endothelial function assessed by FMD, by intra-arterial infusion of acetylcholine (endothelium-dependent vasodilation) and sodium nitroprusside (endothelium-independent vasodilation) did not show any significant correlation with SUA, independently of confounders, including body mass index and trunk fat mass in a cohort of elderly community-dwellers, suggesting that SUA is only a metabolic marker without a role in endothelial function [99].

7.1.4. Coronary microvascular disorders

Coronary microvascular disorders refer to the presence of chest pain and evidence of myocardial ischemia with a non-invasive stress test and normal epicardial coronary arteries [100] commonly known as microvascular angina and cardiac syndrome X and recently classified in a new clinical category, myocardial infarction with non-obstructive coronary arteries [101].

Functional abnormalities of coronary arteries linked to endothelial dysfunction are at the base of this clinical entity [102], which is more common in the female gender during the postmenopausal period [103].

Several evidences show an association among hyperuricemia, endothelial dysfunction, and CAD. An observational-analysis showed that, in women, a high SUA level was an independent predictor of major CV adverse events after an acute coronary syndrome [104]. Prasad et al. examined the relationship of SUA, inflammation, and coronary endothelial dysfunction in postmenopausal women [105]. Among 229 postmenopausal women without epicardial stenosis, those with coronary endothelial dysfunction (< 50% increase of coronary blood flow with acetylcholine at coronary angiography) had significantly higher SUA compared with those with normal response to intracoronary acetylcholine (4.9 ± 1.3 versus 4.4 ± 1.3 mg/dl; $p = .02$).

On the other hand, allopurinol, significantly reduced SUA compared with placebo (−48 ± 24% vs 1.9 ± 11%, $p < .001$) without any effects on coronary flow reserve (assessed with the ultrasound method after adenosine infusion) and FMD of the brachial artery in a recently randomized, double-blind, placebo-control trial (6-week treatment and 4-week washout) on nineteen patients (mean age 59 ± 10 years, 11 women and 8 men) with cardiac syndrome X [106].

7.1.5. Coronary calcification

The degree of coronary calcification, as measured by multidetector computed tomography is a widely accepted tool for detecting coronary atherosclerosis, strongly associated with the risk of CV events in asymptomatic subjects. [107].

Santos et al. showed a strong and independent association between high SUA values, the presence (OR.47, 95% CI 1.26 to 9.53, $p = .01$) and the amount (OR.74, 95% CI 1.15 to 6.50, $p = .02$) of coronary artery calcium in subjects with metabolic syndrome [108].

Moreover, Kim H. et al. demonstrated an independent link between asymptomatic hyperuricemia and coronary artery calcification in the absent of overt CV diseases [109].

7.2. Overt atherosclerotic organ damage

7.2.1. Carotid artery plaques

Ischaemic stroke has become one of the leading causes of death and adult disability and the vulnerable atherosclerotic plaque represents the most common cause [1].

Hyperuricemia appears to be independently associated to the presence of carotid plaques [110]. The multicentre study Family Heart Study tried to assess genetic and non-genetic determinants of heart disease. In the sub-analysis regarding SUA levels and CV disease, a total of 4886 participants from community-based cohorts at four sites were included. Higher SUA was related to a greater prevalence of carotid plaques in males, but surprisingly not in females, after adjusting for potential confounders. The relationship showed a dose-response trend both in presence and in the absence of CV risk factors [OR 1.0, 1.29, 1.61, 1.75, for SUA categories < 5, 5 to < 6, 6 to < 6.8, ≥ 6.8 mg/dl, respectively; $p = .002$] [110].

The Asymptomatic Polyvascular Abnormalities Community (APAC) study confirmed this finding [111]. Results of this cross-sectional study conducted on adults aged 40–59 years, showed an independent association between SUA values, even within a normal range (i.e., 4.1–5.0 mg/dl) and the presence of atherosclerotic vulnerable carotid plaques, with a dose–response relationship [111].

However, data that deny any associations between SUA and atherosclerotic lesions are also available. The cross-sectional study conducted by Li et al. [112], including 2388 hospitalized patients with diabetes, showed a strong association of SUA levels with arterial hypertension and metabolic syndrome, but not with carotid and lower limb atherosclerotic lesions [113].

These findings indicate that higher SUA levels could be not associated with the presence of carotid atherosclerotic plaque, but with vulnerability of the plaque itself.

7.2.2. Coronary artery disease

Many clinical evidences show a relation between hyperuricemia and the incidence of CAD and prove the prognostic importance of SUA levels in such clinical context.

First, the Rotterdam study demonstrated in a population of 4385 participants free from stroke and coronary heart disease, after an 8.4 years follow-up, that high SUA levels at baseline were associated with risk of myocardial infarction and stroke [113].

A retrospective study conducted by Dunkelgrun reported that elevated SUA levels were associated with higher global mortality, higher CV mortality and non-fatal cardiac events in 936 patients with CAD [114]. Hyperuricemia showed to be an independent predictor for intrahospital mortality in a retrospective analysis of 466 patients with acute myocardial infarction [115]. A meta-analysis of prospective studies showed that baseline SUA level was an independent predictor for future CV mortality. [116].

In another meta-analysis of prospective studies, each increase of 1 mg/dl in SUA concentration led to a 12% augmented risk of mortality in CAD patients, independently of traditional CAD risk factors [117].

Moreover, CAD seemed more frequent in women with hyperuricemia [118,119]. By the way, up until now, SUA is only correlated with prognostic parameters in CAD patients but not with the extent of coronary disease. In a single centre cohort study fasting SUA levels were evaluated in 1173 diabetic patients undergoing coronary angiography [120]. After correction for baseline differences, SUA showed no association with the extent and severity of CAD. Moreover, also platelet reactivity had no significant correlation with SUA levels [121].

A causal relationship between UA and macrovascular disease, through a genetic risk score (evaluating the strength of the effects of seventeen single nucleotide polymorphisms related to UA on SUA levels) has been demonstrated in a Chinese population of diabetes females [122].

Furthermore, results of a longitudinal study enrolling 493 subjects under dual antiplatelet therapy with clopidogrel or ticagrelor after acute coronary syndrome or percutaneous coronary intervention, showed no influence of SUA levels on platelet activity, assessed by whole blood impedance aggregometry [123].

8. Heart failure

The pro-oxidant effect of UA in determining endothelial dysfunction could be at the basis of the link between hyperuricemia and heart failure (HF) [124] as confirmed by the improvement of vasodilator capacity and endothelial dysfunction after allopurinol treatment allopurinol in subjects with HF [125,126].

Elevated UA levels were associated with the presence of chronic kidney disease and with a poor prognosis in subjects with acute HF [127], and in subjects with all grades of chronic HF [128]. This latter finding has also been shown in a meta-analysis [129].

High SUA values were associated with the development of HF in men under antihypertensive treatment, compared to those not on treatment ($p = .003$ for interaction), in a 15-years longitudinal study on 3440 men aged 60–79 [130].

SUA levels > 410 μmol/L were associated to a doubled risk of developing HF, compared to SUA levels < 350 μmol/L, in hypertensive subjects [adjusted HR 2.26 (1.23,4.15)] [130].

9. Atrial fibrillation

The proinflammatory effect of UA explains the pathogenic link between UA and atrial fibrillation (AF), as inflammation is one of the pathophysiological mechanisms of AF [131].

First, as described before, UA is associated with arterial hypertension and metabolic syndrome [3,6,67], two of the most important risk factors for AF.

Moreover, there are many evidences demonstrating the close link between these two actors.

A strong association was found between SUA and the prevalence of AF in both sex ($p < .001$), which becomes independent from the other CV risk factors for AF if we consider only women (OR, 1.888; 95%CI: 1.278–2.790), in a cohort of 7155 patients [132].

An independent association was also found in 285,882 Japanese subjects of both sexes, aged 58 ± 15 years [133]. A significant association between hyperuricemia and the increased risk of AF has also been demonstrated by several meta-analysis [134–136].

On the other hand, an US cohort study evaluating the risk of incident AF in patients with gout (70,015 subjects) versus osteoarthritis (210, 045 subjects) underwent a two-year follow-up, shown only a modest increased risk in gout subjects after adjusting for other risk factors (HR 1.21, 95% CI 1.11 to 1.33) [137].

In a retrospective analysis of 1359 patients with AF underwent transesophageal echocardiography before catheter ablation, SUA values showed to be an independent risk factor of LA thrombus (odds ratio, 1.004; 95% CI, 1.000–1.008; $p = .028$). [138].

Finally, contrarily to the findings of Xu X et al. metanalysis [135], a recent study aiming to examine any potential association between SUA and AF recurrence after catheter ablation, did not find any associations. However, the limited number of studies and the heterogeneity of AF type, of the follow-up duration, and of ablation technique limit the reliability of the data [139].

Table 3 shows metanalysis that analysed the effects of SUA on CV endpoints.

10. The effects of the pharmacological reduction of SUA on the main CV outcomes

Several trials have analysed the effect of the pharmacological reduction of SUA on major CV outcomes, with conflicting results. The Efficacy and Safety Study of Oxypurinol Added to Standard Therapy in

Table 3
Summary of metanalysis that have analysed the effects of UA on cardiovascular endpoints.

Topic	First author, year of publication (ref)	Number of studies analysed (number of patients)	Outcome	Follow-up (years)	Adjusted risk ratio
Arterial pre-hypertension (SBP: 120–139 mmHg or DBP: 80–89 mmHg)	Jiang M. 2016 (59)	8 prospective studies (21,832 participants)	Incidence of arterial pre-hypertension	Not defined	OR 1.84 (95% CI, 1.42–2.38)
Arterial hypertension	Grayson P, 2011 (60)	18 prospective studies (55,607 participants)	Incidence arterial hypertension	3–21.5	RR 1.13 (95% CI, 1.06–1.20).
Arterial hypertension	Wang J, 2014 (61)	25 prospective studies (97,824 participants)	Incidence arterial hypertension	2–20	RR 1.16, (95% CI, 1.10–1.22)
Endothelial function	Cicero A. F. G. (97)	10 randomized controlled trials (670 subjects)	Improved FMD after allopurinol treatment	0.5–1	Significant increase in FMD (weighted mean difference1.79%, 95%, CI 1.01–2.56, $p < .001$; I^2: 86.77%).
CAD	Zhao G (117)	11 prospective studies (172,123 participants)	CAD incidence and mortality	4–20	RR 1.24; 95% CI, 1.09–1.42 for all-cause mortality; RR 1.37; 95% CI 1.19–1.57, for cardiovascular mortality
CAD	Kim S.Y. (118)	26 prospective studies (402,997 participants)	CAD incidence and mortality	5–23	RR 1.09 (95% CI, 1.03–1.16) for CAD incidence; RR: 1.12 (95% CI: 1.05–1.19). for CAD mortality.
HF	Huang H. (129)	5 prospective studies (427,917 participants) on the incidence of HF, and 28 prospective studies on the HF outcome (427,917 participants)	HF incidence and outcomes	2–29 1–5	HR for HF incidence 1.65, 95% CI, 1.41–1.94); for each 1 mg/dl increase in serum UA, the risk of composite endpoint (combined death or cardiac events) increase of 28%
AF	Zhang CH (134)	6 prospective studies (426,159 participants)	Incidence of AF	2–16.8	RR: 1.49, 95% CI, 1.24–1.79
AF	Xu X (135)	7 prospective studies (146,792 participants)	Recurrence of AF	1.6–16.8	RR for new-onset AF: 1.85, (95% CI, 1.34–2.56), RR for AF recurrence: 2.07, (95%, CI 1.61–2.67)
AF	Tamariz L (136)	9 studies – 6 cross- sectional (1603 with AF vs 6327 without AF) 3 prospective studies (138,306 participants)	The mean difference of UA in those with AF and those without AF Incidence of AF.	10–20 for prospective studies	Mean difference of UA was 0.42 (95% CI 0.27–0.58) RR of incidence AF was 1.67 (95% CI 1.23–2.27)
AF	Zhao J (139)	4 prospective studies (2 retrospective with 556 subjects and 2 prospective with 742 subject)	Recurrence of AF following catheter ablation	1.6–2.5 for prospective studies	OR:1.37, (95%, CI: 0.98–1.93)

Abbreviations: RR: relative risk; CI: confidence interval; UA: uric acid; OR: odd ratio; FMD: flow mediated dilation; CAD: coronary artery disease; HF: heart failure; AF: atrial fibrillation.

Patients With New York Heart Association Class III-IV Congestive Heart Failure (OPT-CHF study) was a multicenter, randomized, double-blind, placebo-controlled, parallel group study, aiming to evaluate the benefit of the XO inhibitor, oxypurinol, in patients with New York Heart Association functional class III to IV HF due to systolic dysfunction on top of medical treatment [145]. Four hundred and five patients were randomized to receive oxypurinol (600 mg/day) or placebo for 24 weeks. A composite end-point of HF morbidity, mortality, and quality of life was assessed at the end of follow-up. Results showed no difference in clinical improvements between the two groups, however a post-hoc analysis suggests a benefit of oxypurinol treatment in term of clinical improvement in patients with elevated SUA ($>$ 9.5 mg/dl, $n = 108$), proportional to the degree of SUA reduction [140].

The Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) trial, was a multicenter, 1:1 randomized, double-blind, placebo-controlled, 24-week trial of allopurinol in 253 patients with symptomatic HF with left ventricular systolic dysfunction (LVEF $\leq$40%) and elevated SUA levels ($\geq$9.5 mg/dl) with at least 1 additional high-risk marker among an acute HF event (hospitalization or emergency department visit) within 12 months, severe LV dysfunction ($\leq$25%), or an elevated natriuretic peptide level (B-type natriuretic peptide $>$ 250 pg/ml or N-terminal pro-B-type natriuretic peptide $>$ 1500 pg/ml).[141].

At the end of follow-up, SUA levels were significantly reduced with allopurinol in comparison with placebo ($p < .0001$) with no significant difference in clinical status between the allopurinol- and placebo-treated patients ($p = .68$) [141].

The Nihon University working group study of Febuxostat and usuaL Allopurinol therapy for patientS with Hyperuricemia (NU-FLASH study) was a randomized, single-blind study aiming to compare febuxostat and allopurinol in cardiac surgery patients with hyperuricemia (141 patients, age range $\geq$ 20 years to $<$ 90 years, SUA $\geq$ 8 mg/dl). Results at 1–3- and 6-months follow-up showed the reduction of UA level, serum creatinine, urinary albumin, cystatin-C, oxidized low-density lipoproteins, systolic BP, PWV and left ventricular mass index in the febuxostat group compared to the allopurinol one ($p < .05$) [142].

The post-hoc analysis of the NU-FLASH Trial on subjects with chronic kidney disease (eGFR $\leq$60 ml/min/1.73 m2 and stage 3CKD), the Comparison of febuxostat and allopurinol for hyperuricemia in cardiac surgery patients with chronic kidney disease (NU-FLASH trial for CKD) [143], showed significant lower UA levels in the febuxostat group compared to the allopurinol one from 1 month of treatment onward ($p < .05$). On the other hand, the serum creatinine, urinary albumin, cystatin-C, oxidized low-density lipoproteins, eicosapentaenoic acid/arachidonic acid ratio, and high-sensitivity CRP were also significantly lower in subjects under febuxostat treatment ($p < .05$).

Recently, the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial, a multicenter, randomized, double-blind noninferiority trial comparing febuxostat or allopurinol in 6198 patients with gout and CV disease, followed for a median of 32 months, showed all-cause and CV mortality rates (hazard ratio for death from any cause, 1.22 [95% CI, 1.01 to 1.47]; hazard ratio for CV death, 1.34 [95% CI, 1.03 to 1.73]) higher in the febuxostat group than in the allopurinol group at the end of follow-up [144].

The Febuxostat Versus Placebo Randomized Controlled Trial Regarding Reduced Renal Function in Patients With Hyperuricemia Complicated by Chronic Kidney Disease Stage 3 (FEATHER) trial that randomly assigned in a 1:1 ratio 467 patients with stage 3 CKD and asymptomatic hyperuricemia to receive febuxostat or placebo for 108 weeks, did not showed any significant improvement of kidney function in subjects treated with febuxostat compared to placebo (P = ns) [145].

Finally, in the Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy (FREED), 1070 elderly patients with hyperuricaemia (serum uric acid $>$ 7.0 to $<$ 9.0 mg/dl) at risk for cerebral, cardiovascular, or renal disease, were randomized to febuxostat and non-febuxostat treatment and observed for 36 months. Results showed lower UA level in the febuxostat group ($n = 537$) compared to the non-febuxostat one ($n = 533$), UA levels: 4.50 ± 1.52 mg/dl and 6.76 ± 1.45 mg/dl, respectively ($p < .001$). Cerebral, cardiovascular, renal events and all deaths (the primary end-point) rate was significantly lower in the febuxostat group than in non-febuxostat one [hazard ratio (HR) 0.750, 95% confidence interval (CI) 0.592–0.950; $p = .017$] and the most frequent event was renal impairment (febuxostat group: 16.2%, non-febuxostat group: 20.5%; HR 0.745, 95% CI 0.562–0.987; $p = .041$) [146].

11. Conclusion

UA is the final product of purine metabolism and shows a strong correlation with CV diseases. Its concentration is directly correlated with the presence of arterial hypertension, asymptomatic and overt atherosclerotic CV diseases, HF and AF. Multiple pathogenic mechanisms are involved, such as direct endothelial damage, vascular dysfunction mediated by oxidative stress and reduced NO production. Both soluble UA and urate crystals are able to elicit a local and systemic inflammatory response that underlies all these negative mechanisms.

The balance of available evidences is in favor of the existence of a positive correlation between SUA levels and CV diseases.

In this regard, the last European guidelines on arterial hypertension have introduced UA among the factors able to influence CV risk in patients with arterial hypertension, although the burden of evidence in favor of a causal link between UA and CV disease is still considerably low in comparison to the “traditional” CV risk factors [147].

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