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Two still unanswered questions about uric acid and cardiovascular prevention: Is a specific uric acid cut-off needed? Is hypouricemic treatment able to reduce cardiovascular risk?☆

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ABSTRACT

Aims: The most frequent consequence of elevated uric acid (UA) levels is the development of gout and urate kidney disease. Besides these effects, several studies have investigated the association between hyperuricemia and cardiovascular (CV) disease. High serum UA has been identified as an important determinant of all-cause and CV mortality and CV events (acute and chronic coronary syndrome, stroke and peripheral artery disease). Despite the high number of publications on this topic, there are two questions that are still unanswered: do we need a specific CV cut-off of serum UA to better refine the CV risk? Is urate lowering treatment (ULT) able to reduce CV risk in asymptomatic patients? In this review, we will focus on these two points.

Data synthesis: Although no doubt exists that the relationship between CV events starts at lower levels than the actually used cut-off, different papers found dissimilar cut-offs. Furthermore, heterogeneity is present depending on the specific CV events evaluated and none of the found cut-off have been tested in external populations (in order to confirm its discriminatory capacity). Furthermore, only few randomized clinical trials on the role of hypouricemic agents in reducing the CV risk have been published giving heterogeneous results. The last published one (ALL-HEART) has strong limitations, that we will deeply discuss.

Conclusions: A definitive answer to the two questions is impossible with the actually published paper but, over identifying current gaps in knowledge we try to individuate how they can be overruled.

1. Introduction

Uric acid (UA) is the final product of the exogenous and endogenous purine metabolism. The exogenous pool varies significantly with diet, whereas the endogenous one is largely derived by from protein metabolism and is mainly excreted by the kidney [1]. Therefore, different conditions can raise UA levels: a diet rich in purine or fructose, a tumor lysis syndrome, or some drugs (chemotherapy and pyrazinamide), a

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decrease in UA renal excretion, various metabolic disturbance often involving a UA overproduction [2,3].

The most frequent consequence of elevated UA levels is the development of articular gout and kidney disease. Besides these effects, several studies have investigated the association between hyperuricemia and cardiovascular (CV) disease [2]. UA has been repeatedly identified as an important determinant of all-cause and CV mortality [4] and CV events related to atherosclerosis development such as acute and chronic coronary syndrome (ACS and CCS respectively) [5], stroke [6] and peripheral artery disease [7]. However, the relationship between UA and CV system is more complex, since it also includes other diseases not directly linked only to atherosclerosis, such as heart failure (HF) [8] and atrial fibrillation [9].

In fact, hyperuricemia has been recognized as an independent CV risk factor, able to reclassify the CV risk of patients, as suggested in the European guidelines on arterial hypertension [10].

From a strictly cardiological point of view, UA has a strong role as risk factor in both ACS, CCS [5] and HF. In patients experiencing an ACS, high levels of UA are a common finding, that correlates with in-hospital and long term all-cause and CV mortality [11,12]. Moreover, some studies identified UA as associated to a more severe coronary artery involvement, a larger infarct size [13] and a great risk of acute plaque complications [14].

In CCS the relationship between UA and severity of the coronary artery disease, is less clear. In fact, some publications showed a significant association [15–17], whereas others did not [18–20]. A positive association was found in patients with recent diagnosis of coronary artery disease or in never treated subjects (recent onset angina, first coronary angiography and revascularization) [15–17], while in patients with previous ACS/revascularization or with several CV risk factors, this correlation cannot be demonstrated [20]. These findings suggest the hypothesis that the relationship is present in the early phase of the atherosclerotic disease, whereas, in more advanced stages, other CV risk factors, i.e. aging, smoking, or previous revascularization, can limit the possibility to find a significant correlation, overshadowing the role of UA.

Regarding HF, studies suggested UA as an independent predictor of all-cause mortality, CV death and risk of hospitalization [21]. Moreover, UA has been related to HF severity. Indeed, higher levels of UA have been found in HF patients with lower ejection fraction, higher ventricular filling pressures and volumes, higher circulating levels of natriuretic peptides, and more limited functional capacity [22,23].

The relationship with HF is complex and bidirectional, since some factors related to HF may increase UA that can be merely an epiphenomenon of the cardiac damage. In HF patients, several factors can be responsible for an increase UA, such as reduction in renal urate clearance [24], the use of high doses of diuretics (incrementing renal tubular UA reabsorption) [25], increase in the levels and activity of Xanthine Oxidase (XO) and increase in purine turnover caused by hypoxia and tissue catabolism [26]. Nevertheless, it is also possible that UA can have an independent causative role in determining the disease [27].

Despite the high number of publications on this topic, there are two questions that are still unanswered: do we need a specific CV cut-off of serum UA to better refine the CV risk of patients? Is urate lowering treatment (ULT) able to reduce CV risk in asymptomatic patients?

In this review, we will focus on these two questions, evaluating published literature and trying to identify actual gaps in knowledge and how they can be overruled.

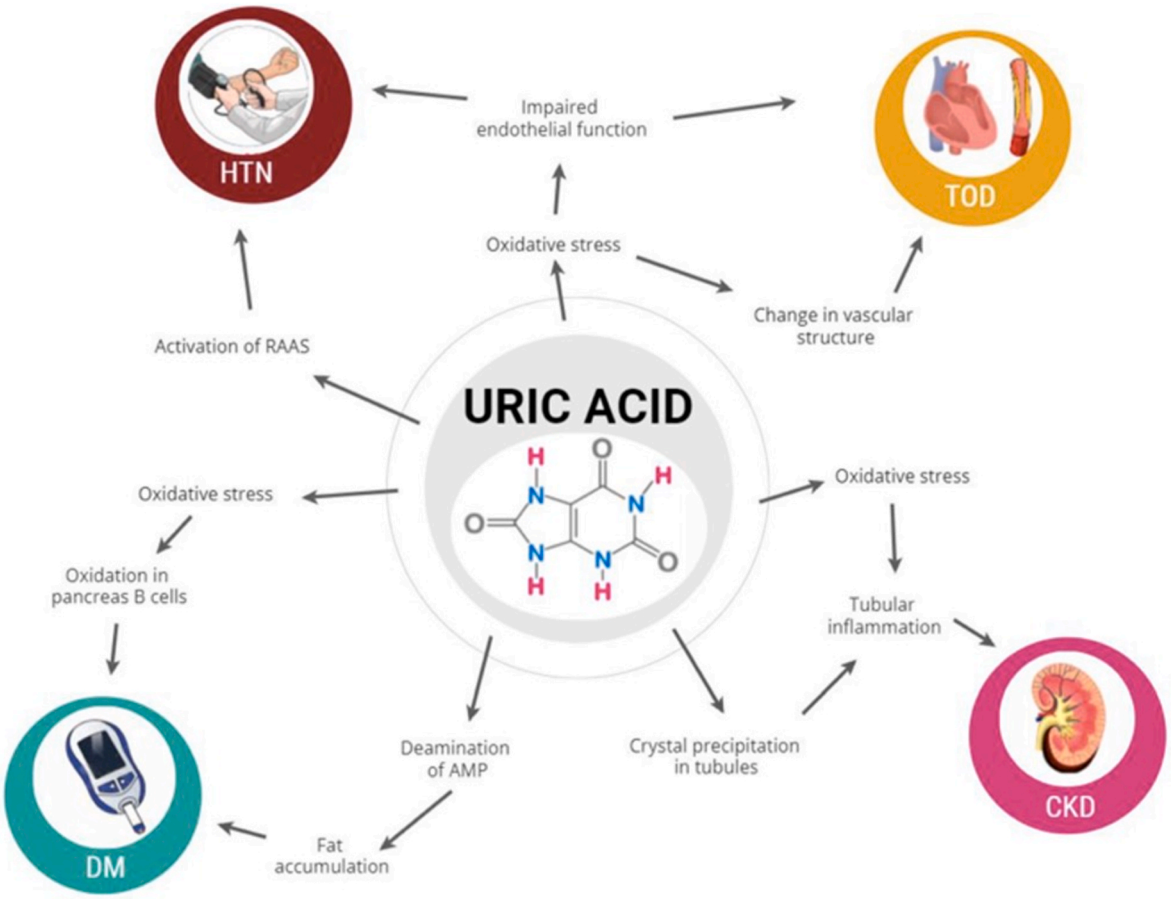

Fig. 1. Mechanisms contributing to the relationship between uric acid and cardiovascular diseases. HTN = Arterial Hypertension; DM = Diabetes Mellitus; CKD = Chronic Kidney Disease; TOD = Target Organ Damage. With permission from Ref. [5].

2. Mechanisms linking uric acid and cardiovascular diseases

The role of UA in determining CV events has not been definitively clarified, but it probably involves multiple mechanisms of action not necessarily including the joint and tissue deposition (Fig. 1).

The solubility of UA in water is low and its average concentration in blood is close to the solubility limit, which is 6.8 mg/dL. Above these levels, it precipitates in crystals of monosodium urate. This is the main pathological process linking UA to articular and kidney deposition, with tissue crystal accumulation [28].

This mechanism cannot explain the link of UA with CV disease that has been described with lower UA values, when crystal formation and deposition is not possible.

XO activity catalyzes the two final steps in the biochemical chain leading to UA production, but also to the formation of oxidative reactive species. The latter can determine vascular endothelial dysfunction, low-density lipoprotein (LDL) oxidation and activation of the inflammasome, that are all well-known mechanisms related to the atherogenic processes [4].

Furthermore, high intracellular UA levels promote the expression of vasoconstrictive substances (Angiotensin II, thromboxane, and endothelin-1), inflammatory molecules (C-reactive protein, nuclear factor κB) and chemokines via activating mitogen-activated protein kinases that are able to regulating inflammatory signal pathways, such as NLRP3-inflammasomes and macrophage M1/M2 polarization. UA can also cause platelet activation, adhesion and aggregation and inhibit nitric oxide production [29]. All these factors are able to promote atherosclerosis. In fact, optical coherence tomography showed a significant increase in plaque rupture in patients with UA > 8.0 mg/dL [30] and UA was found to be an independent predictor of coronary artery calcium score in 9297 healthy subjects evaluated by computer tomography [31].

Furthermore, high UA has been linked to many CV risk factors such as arterial hypertension [32], diabetes mellitus [33] and metabolic syndrome [34].

Several studies have demonstrated an association between UA and hypertension [35]. Possible mechanisms are the already mentioned impairment in endothelial function [36] and the activation of renin-angiotensin-aldosterone system, causing kidney vasoconstriction, ischemia, and oxidative stress [37]. Arterial stiffness and inflammation may also be involved in the risk of development of hypertension. In a large-scale meta-analysis of 55,607 subjects in 18 prospective cohort studies every 1 mg/dl rise in UA increase the incidence of hypertension by 13 % [38].

Hyperuricemia is not only related to the development of diabetes, but also to its chronic complications with an increased prevalence of peripheral neuropathy, retinopathy and nephropathy [39]. Inflammation, oxidative stress, and endothelial dysfunction [33], but also a direct inhibition of insulin signaling and induction of insulin resistance [34], are the mechanism linking UA and diabetes, as well as to metabolic syndrome. UA mediated reactive oxygen species increase production inhibit insulin-induced glucose uptake that could lead to cardiac dysfunction.

UA has a bidirectional relationship with chronic kidney disease (CKD). High UA levels predict the development of albuminuria and both the occurrence and progression of renal disease. On the other hand, a decrease in kidney function increase UA due to a reduced excretion, enhanced reabsorption and insufficient secretion by renal tubules [40]. Renal injury can be mediated by many mechanisms involving renal vasoconstriction mediated by endothelial dysfunction, inflammation and macrophage infiltration into the vascular wall and activation of the renin–angiotensin system and [41,42]. All these factors have been associated with rapid loss of kidney function in patients with CKD [43,44].

Finally, UA has been related to target organ damage (TOD) at the cardiac and vessels level.

The relationship between UA and pulse wave velocity (PWV), which is the most widely used measurement of arterial stiffness, has been extensively evaluated. UA contributes to the arterial stiffness with different mechanisms: oxidative stress, pro-inflammatory effects and due to the activation of renin-angiotensin system [45].

Several studies about cardiac TOD, largely carried out in hypertensive patients [46–48], have found a correlation between UA and echocardiographic left ventricular mass index and hypertrophy. The combination of hyperuricemia with left ventricular hypertrophy is an independent predictor for CV death [49].

3. Overproduction or underexcretion: a critical issue

In physiological conditions, UA is produced and excreted in equal amounts. Thus, hyperuricemia may result from overproduction or underexcretion or a combination of these two mechanisms.

Many factors seem to be involved in increased UA production. Firstly, endogenous production accounts for almost two-thirds of the total, so that just a minor part depends on external factors and the role of dietary habits is still debated [50]. A European population study involving more than 400,000 subjects showed a role for BMI and genetics in determining UA levels, while diet had only a minor impact [51]. Similar evidence emerged from a recent meta-analysis of 5 cohort studies including 16,760 subjects, in which only a weak association between diet and variance in UA levels was observed. On the other hand, genetic variants were found to have a predominant role; these include a complete or partial deficiency of hypoxanthine guanine phosphoribosyltransferase (as in Lesch-Nyhan syndrome and Kelley-Seegmiller syndrome respectively) or an increase in 5-phospho-alpha-d-ribosyl pyrophosphate activity [52].

Regarding obesity, several studies showed that higher BMIs was associated to higher UA levels [53,54] and a decrease was showed after significant weight loss determined by bariatric surgery [55]. Finally, UA overproduction could also occur during the tumor lysis syndrome during chemotherapy [56].

However, renal underexcretion is the most frequent cause of hyperuricemia. Urate handling by the kidneys involves filtration at the glomerulus, reabsorption, secretion and post secretory reabsorption. Consequently, altered UA excretion can result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption [57]. Proximal tubular reabsorption is controlled by uric acid transporter 1, that can be stimulated by different agents, such as organic acid and some medications, resulting in hyperuricemia [58]. In fact, decreased tubular secretion of UA occurs in patients with acidosis (i.e. diabetic ketoacidosis, ethanol or salicylate intoxication, starvation ketosis). Moreover, enhanced reabsorption of UA distal to the site of secretion is the mechanism thought to be responsible for the hyperuricemia caused by diuretic therapy (see specific paragraph below).

Finally, there are also some genetic conditions related to underexcretion of uric acid, such as

familial juvenile hyperuricemic nephropathy which is a rare autosomal-dominant disease characterized by hyperuricemia of underexcretion type, gout, and progressive CKD [59].

4. The hyperuricemia cardiovascular cut-off

The definition of the cut-off value of UA that is significantly associated with CV events and mortality, is still an open issue and different values have been proposed so far.

In medicine the standard definition of a reference range for a particular measurement is defined as the interval between which 95 % of values of a reference population fall into, so that 2.5 % values will be under the lower limit and 2.5 % will be over the upper one of the intervals.

According to this definition, serum UA levels between 3.5 mg/dL and 7.2 mg/dL in adult males and post-menopausal women and between 2.6

mg/dL and 6.0 mg/dL in pre-menopausal women are considered normal in many countries [60,61]. The typical cut-off of hyperuricemia is 6 mg/dL in women and 7 mg/dL in males and is based on population distribution of UA values and on the already mentioned saturation point of 6.8 mg/dL.

Nonetheless, a remarkable amount of data has suggested that UA may have dangerous effects on the CV system already at lower levels. It has been definitively proven that these effects are evident also for levels below the saturation limit, thus independently of precipitation of urate monosodium crystals [60].

Papers reporting on hyperuricemia cut-off for all-cause and CV mortality and CV events were systematically assessed. Relevant studies were identified by PubMed and Embase sources up to April 2024. The following search term was used: "Hyperuricemia" AND "cut-off" AND ("all-cause mortality" OR "cardiovascular mortality" OR "myocardial infarction" OR "acute coronary syndrome" OR "chronic coronary syndrome" OR "stroke" OR "heart failure"). After excluding duplicates, title and abstract have been screened and only English writes papers based on adults' populations were considered. 15 significant papers were found and have been discussed below and summarized in Table 1.

Many papers suggest lower cut-off levels of UA for all-cause and CV mortality, with a small variability across the evaluated population. In the PAMELA study, a strong relationship between UA and CV events has been demonstrated: an increase of 1 mg/dL was associated with a greater risk of CV death of 22 % and of all-cause death of 12 % [32]. In this paper, a hyperuricemia cut-off that better relates to CV and all-cause death was identified as 5.4 and 4.9 mg/dL, respectively [29]. Another prospective study, involving healthy middle-aged men, found the most significant increase for CV death at a serum level higher than 5.21 mg/dL [62]. The issue was investigated also in hospitalized (for any reasons) patients were a cut-off of 6.7 mg/dL in men and 5.4 mg/dL in women was effectively associated with all-cause in-hospital mortality

Table 1
Summary of studies results on the topic of uric acid cardiovascular cut-off. PAMELA = Pressioni Arteriose Monitorate E Loro Associazioni; URRAH = Uric acid Right for heaRt Health.

Study	Type of study	Number of patients (N)	Mean age (standard deviation)	Males (%)	Type of population	Event	Serum uric acid cut-off, mg/dL
PAMELA Bombelli M 2014 [29]	Population-based study	2045	50.9 (13.7)	51	General	CV death All cause death	5.4 4.9
Niskanen LK 2004 [62]	Population-based prospective cohort study	1423	52.3 (5.3)	100	Middle-aged men	CV death	5.21
Kang MW 2019 [63]	Retrospective cohort study	18,444	59.0 (16.6)	52	Hospitalized patients	All-cause mortality and in-hospital mortality	6.7 (men) 5.4 (women)
Kerola T 2019 [64]	Population-based study	4696	44 (9)	58	General (participants of Coronary Artery Disease of the Finnish Mobile Clinic)	All-cause mortality and MACEs (CHD death, hospitalization due to CHD, congestive heart failure)	4.7 (women)
Perticone M 2023 [65]	Population prospective study	1650	52.2 (11.3)	53	Never-treated hypertensive	Cerebrovascular Events MACE Coronary events All-cause mortality	4.8 (women) 5.6 (men) 5.2 (women) 5.3 (men) 5.2 (women) 5.3 (men) 4.9 (women) 5.3 (men)
Letho S 1998 [66]	Population-based study	1017	57.2 (0.3)	54	Non-insulin-dependent diabetic patients	Stroke	4.96
Talpur AS 2023 [67]	Population-based study	2747	46.5 (8.5)	50	General	Non-fatal Myocardial Infarction	7
URRAH study Maloberti A 2023 [68]	Retrospective observational cohort study	23,475	57 (15)	51	General (mainly hypertensive patients)	Fatal miocardial infarction Cardiovascular mortality Non fatal heart failure Fatal heart failure Stroke Total mortality	5.7 5.6 5.34 4.89 4.79 4.7
Braga F 2016 [73]	Meta-analysis	457,915	NA	53	General	Coronary event	7
Akgul O 2014 [74]	Prospective observational study	464	55.4 (12.4)	73	Patients with STEMI undergoing pPCI	6-months all-cause mortality	5.7
Akpek M 2011 [75]	Prospective observational study	289	63 (11)	76	Patients with STEMI undergoing pPCI	Poor coronary blood flow (following pPCI) In-hospital MACE (in stent thrombosis, non-fatal myocardial infarction, in-hospital mortality)	5.4
Browne LD 2021 [76]	Retrospective cohort study	26,525	53.8 (15.5)	52	General	All cause death	Women: 4.62 Men: >5.13 but also <3.43
Tseng WC 2018 [77]	Prospective cohort study	127,771	72.6 (6.3)	52	General	CV death and all-cause mortality	>8 but also <4
Cho SK 2018 [78]	Retrospective cohort study	375,163	40 (9.8)	55	General	All-cause mortality, cardiovascular disease, cancer mortality	>9.5 (men); >8.5 (women) but also <3.2 (men); <2.5 (women)
Gao B 2023 [79]	Cross sectional study	23,413	47 (0.2)	48	General	Stroke	>6.8 but also <6

Abbreviations: PAMELA = Pressioni Arteriose Monitorate E Loro Associaioni; URRAH = Uric acid Right for heaTt Health.

[63].

Some other studies have focused also on CV events and not only on mortality. A SUA level >4.7 mg/dL in women was found to be independently associated with a higher risk of mortality and a combined end-point of Major Adverse Cardiovascular Events (MACE), in a population-based study including 4696 patients [64].

Some interesting studies try to found if the cut-off could change for different specific CV outcomes. In a population-based study of 1650 never-treated hypertensive patients a UA level higher that 5.2 mg/dL was found to be significantly related to a composite outcome of MACE and to coronary events in female patients while the cut-off for cerebrovascular events was 4.8 and for all-cause mortality was equal to 4.9 mg/dL. For male patients, a UA level higher 5.3 mg/dL was associated with a significantly higher risk of coronary events, MACE and all-cause mortality, while a value of 5.6 was found for cerebrovascular events [65]. In another study a specific cut-off of 4.96 mg/dL was found in 1017 type 2 diabetes mellitus patients [66], while a value of 7 mg/dL was identified as a reliable cut off for non-fatal ACS in a general population cohort of 2747 patients [67].

Similar results derive from the URRAH (Uric acid Right for heArt Health) study, a multicenter retrospective, observational cohort study involving over 22,000 subjects with a follow-up period of at least 20 years. Many different analyses have been carried out, identifying specific cut-off levels for all cause and CV mortality as well as for the different CV events. An association with all-cause and CV mortality has been shown with a cut-off of 4.7 and 5.6 mg/dL respectively [68]. The latter has been confirmed also in diabetic and metabolic syndrome subjects [69,70]. Furthermore, a threshold of 5.34 and 4.89 were identified as the values better predicting HF and fatal HF respectively [27], while specific cut-offs of 4.79 and 5.7 were identified for stroke and ACS respectively [71,72].

A recent meta-analysis of 15 articles evaluating more than 450,000 primary prevention subjects found that the coronary events risk was significantly higher when serum uric acid is > 7 mg/dL, though levels <6 mg/dL may be considered advisable [73].

When we move from primary prevention to population with specific cardiological diseases the number of papers significantly decrease with two regarding ACS subjects and no paper focused on HF and CCS patients. Regarding patients hospitalized for ACS a cut-off of 5.7 mg/dL predict short-term (6-months) subsequent mortality [74] and a similar cut-off (5.4 mg/dL) was related to in-hospital MACE in another ACS population [75].

Interestingly, the dangerous effects of UA have been observed also when its values are too low. A recent retrospective cohort study showed a U-shape relationship between UA levels and mortality in men, with a significantly increased risk for values higher than 5.13 mg/dL, but also lower than 3.43 mg/dL. In women, instead, a J-shaped relationship has not been found, meaning that hyperuricemia (>4.62 mg/dL) was associated to an increased mortality [76].

A Taiwanese cohort study including 127,771 adults aged more than 65 years old observed a significant increase of all-cause and CV mortality in patients with UA higher than 8 mg/dL, but also lower than 4 mg/dL, confirming the U-shaped relationship [77]. Another validation of this finding comes from a cohort study conducted in South Korea enrolling more than 375,000 subjects where both high and low UA levels were related to higher all-cause and CV death [78]. Finally, a population of 23,413 subjects confirmed the relevance of high and low UA levels on the risk of stroke [79].

However, conflicting results have emerged from other studies [80–82], confirming that the complex relationship between UA and CV events is not yet completely understood.

In conclusion, the threshold values currently used for the definition of hyperuricemia may not be appropriate for the estimate of CV risk and, taking into account the various results described, a value < 5.5 mg/dL should be reasonably considered for the future. In specific patients subset (ACS, CCS, HF) it is possible that this cut-off could change but more studies are needed in order to solve this issue.

5. Cardiovascular therapies that are able to modify uric acid levels

Before looking at hypouricemic agents we need to evaluate two drugs that could increase UA levels: aspirin and diuretics. The role of aspirin on UA metabolism is debated: the traditional model presents a bimodal effect with uricosuric properties at high dosage while with lower one (such as the dose used in CV secondary prevention) it is able to determine a 15 % decrease in the rate of UA excretion and so an increase in its levels [83].

However, some papers don't find any significant association between low dose aspirin and hyperuricemia [84,85]. Similarly, recently published data coming from the NHANES study showed that low dose aspirin does not increase the hyperuricemia risk in people over 50 years. However, in some subgroup there were a significant relationship between aspirin and UA levels increase, in particular those aged between 40 and 50 years, Hispanic American, and those with CKD [86].

In any case low dose aspirin remains a cornerstone of CV secondary prevention, and its prescription should not be influenced by considerations regarding UA levels.

Regarding diuretics, both loop one and thiazides, are well-known cause of significant increase in UA. This is determined by volume depletion but mainly by the reduction of UA tubular secretion determined by direct competition with UA for renal tubular secretion mediated by organic anion uptake transporters [87,88].

The relative elevation in SUA secondary to diuretics administration varies from 6 to 21 % from baseline levels [89] and diuretic-related secondary hyperuricemia carries a similar risk of CV events and all-cause mortality when compared with non-diuretic related hyperuricemia [90].

However, as also regarding aspirin, is it important to point out that the prescription of these drugs (commonly used in arterial hypertension and HF) should take into account the impact on the patient's overall prognosis without focusing only on UA alterations.

6. HOW to treat hyperuricemia in symptomatic patients

Current recommendations for hyperuricemia treatment are limited to symptomatic patients, i.e. the one with gout and renal involvement. In these patients, diet and lifestyle measures, such as limiting alcohol, purine and high-fructose corn syrup intake, and weight loss may be useful in the initial approach to hyperuricemia [91]. Selected healthy eating patterns, such as the Mediterranean diet, with or without caloric restriction and weight loss, can lower UA levels, although the size of the effects of these interventions is obviously smaller than that produced by urate-lowering drugs [92].

From a pharmacological point of view, lowering UA can be achieved mainly by reducing its production (through XO inhibition) or by increasing its renal excretion.

Two XO inhibitors are currently used for the treatment of hyperuricemia: allopurinol and febuxostat, being the first a purinic and the latter a non-purinic inhibitor.

Allopurinol is strongly recommended as first line agent in all patients with gout, including in those with CKD stage >3 [91]. It is rapidly and extensively absorbed with its active metabolite, oxypurinol, detected in the circulation within 15 min of oral administration. Up to 80 % of allopurinol is found in the urine within 24 h, mainly in the form of oxypurinol [93]. Low dose, like 100 mg/day (and lower in CKD), with subsequent dose titration should be preferred over starting at higher dose [91]. Despite is extensively prescribed, and generally well tolerated, allopurinol can be responsible for severe life-threatening cutaneous adverse drug reactions such as Dress or Stevens-Johnson syndrome [94]. Those reaction are strongly associated with HLA-B*5801 and therefore, before prescribing allopurinol, genetic

testing is recommended in patients at elevated risk, such as patients of Asian and African American descent [91,95].

Febuxostat, a thiazolecarboxylic acid derivative, is a non-purinic selective XO inhibitor. It was approved in 2008 by European Medicines Agency and in 2009 by the United States Food and drug Administration for the management of hyperuricemia in adults with urate deposition. The usual starting dose is 40 mg once a day that can be increased to 80 mg after two weeks of treatment if serum UA target is not achieved. It is rapidly and extensively absorbed, after oral administration with a volume of distribution at steady state of 0.7 L/kg. Febuxostat is highly bound to circulating plasma proteins, primarily albumin, undergoes hepatic metabolism in the cytochrome P450 (CYP) enzyme system into acylglucuronide and is eliminated by the kidney, with a mean half-life of 9.1 h [96]. Febuxostat demonstrated a superior efficacy in lowering UA levels compared to allopurinol in all three registration studies: APEX [97], FACT [98] and CONFIRMS [99], all conducted in gout affected patients.

Finally, there is also the possibility to reduce serum UA by increasing urate renal excretion through uricosuric agents (benzbromarone and probenecid). Their use in clinical practice remains uncommon and should be avoided in patients with urolithiasis or severe renal impairment. Furthermore, benzbromarone was withdrawn from many countries after the reports of serious hepatotoxicity [100]. Probenecid [101] is a benzoic acid derivative, firstly used as a penicillin sparing agent during the second world war and only later introduced as a UA lowering drug. Its mechanism of action consists in the inhibition of UA tubular re-uptake [102]. Despite its proven efficacy in clinical, often in combination with allopurinol [103], the drug is not currently available in Europe. Lesinurad another uricosuric agent with a weak effect in combination with a XO inhibitor, was withdrawn from the market due to the low number of prescription and its kidney toxicity.

Losartan and fenofibrate have been associated with mild uricosuric effects in patients with gout [104], and the use of losartan was associated with a significantly reduced risk of incident gout (RR = 0.81, 95 % CI 0.70, 0.94). However, their use is not recommended by guidelines for gout therapy unless it is needed for comorbidities like arterial hypertension and hypertriglyceridemia.

Finally, also sodium glucose cotransporter 2 inhibitors (sGLT2-i) have a favorable effect on UA. This drug class had an indirect uricosuric effects that is determined by a reduction in uric acid proximal tubule reabsorption mediated by the inhibitions of glucose transporter 9 but also to an inhibition of urate transporter determined by the glycosuria itself. In fact, the UA reduction is directly related to the glycosuric effects [105]. They are able to increase uric acid excretion from 3 to 5 % [106] that determine a reduction in serum UA from 0.8 to 1.6 mg/dL. This determines important clinical implication with a reduction of 57 % in ULT initiation (HR, 0.43; 95 % CI, 0.34–0.53) [107] and of 45 % in gout flares (HR 0.55, 95 % CI 0.45–0.67) [108] in patients on sGLT2-i compared to placebo. However, despite this very significant results, sGLT2-I are not approved nor suggested by guidelines for asymptomatic hyperuricemia and gout treatments.

Pegloticase is an intravenous mammalian recombinant uricase (uricolytic drug class) which allow enzymatic degradation of UA to allantoin, which is subsequently excreted without difficulty [109]. However, it is immunogenic and determine an increase in oxygen reactive species formation. Moreover, being an infusion drugs it is often used as the last line of therapy for patients with uncontrolled gout [110].

7. Does asymptomatic patients need urate-lowering treatments?

Current guidelines do not support the need for treatment in asymptomatic patients with elevated serum UA. However, because of UA significantly correlates with CV death at level higher than 5.5 mg/dL [68], one could speculate that its reduction in all the patients above this value, could contribute to the decline of the CV global burden irrespective of the presence of gout. Some specific trials have been designed to try to answer this question including some CV safety trial with allopurinol and febuxostat in patients with gout and high CV risk profile.

The CARES trial is a multicenter, randomized, double blind non-inferiority study requested by US Food and Drug Administration. The trial enrolled patients with gout with a major CV condition showing that febuxostat was non-inferior to allopurinol with respect to the composite primary endpoint of the study (death from CV causes, myocardial infarction, stroke, or unstable angina with urgent revascularization) that occurred at similar rates in the two groups: 10.8 % in febuxostat and 10.4 % in allopurinol patients). Unexpectedly, all-cause and CV mortality were higher with febuxostat than with allopurinol [111]. These results led US Food and drug Administration to limit the approved use of Febuxostat to patients' poor responders or experiencing severe side effects with allopurinol.

Those unexpected results have generated an active discussion around three fundamental topics [112]. First of all, the lack of a placebo group with the consequent impossibility to attribute the presumed excess mortality to a negative effect of febuxostat rather than a more protective action of allopurinol. Second point, the extremely high (i.e. 56.6 %) premature drug discontinuation during the follow up, in many cases within 24 months from randomization, without differences between febuxostat and allopurinol. Furthermore, 45 % of the patients did not complete all the trial visits with more than 8 % of the patients completely lost to follow-up. Finally, the lack of data regarding concomitant CV therapies, such as lipid lowering or anti-hypertensive therapies.

These discussed negative findings were not confirmed in another subsequent randomized double blind post-licensing trial recommended by European Medicines Agency: the FAST trial. In this study febuxostat was found to be non-inferior to allopurinol therapy with respect to the primary CV endpoint (a composite of hospitalization for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; non-fatal stroke; or cardiovascular death). Long-term use of febuxostat was not associated with an increased risk of death or serious adverse events compared with allopurinol [113]. The discontinuation rate was 16.5 % in the allopurinol group and 32.4 % in the febuxostat group.

Many prospective and retrospective not randomized studies have been published on urate-lowering therapies and their possibility to reduce the risk of CV events with conflicting results [114–116]. However, the risk of confounding and potential biases in observational and small studies is an important limitation, leading to the need for prospective randomized trials in this area on which we will focus.

Studies reporting on UA lowering agents and evaluation of CV events were systematically assessed. Relevant studies were identified by PubMed and Embase sources up to April 2024. The following search term was used: ("allopurinol" OR "febuxostat") AND "cardiovascular outcomes". After excluding duplicates, title and abstract have been screened and only randomized clinical trials, English writes papers and adults' populations were considered. 9 significant papers were found and have been discussed below.

Apart the recently published ALL-HEART trial, not formally addressing the treatment of hyperuricemia (50 % of the patients have normal serum UA), only the FREED [117] trial has been specifically designed to assess the possibility of CV events reduction determined by Febuxostat in asymptomatic patients. This is a randomized, open label study conducted in 1070 Japanese subjects with asymptomatic hyperuricemia (UA between 7 and 9 mg/dL) and at least one risks factor for cerebral, CV or renal disease. Febuxostat was compared to usual care (lifestyle modification and allopurinol) only if UA further increase during the study period (prescribed in 27.2 % of patients randomized to non-Febuxostat). Febuxostat significantly reduce the primary composite cardiorenal endpoint (HR 0.750; 95 % CI 0.592–0.950; p = 0.017), which was entirely driven by the reduced progression of renal dysfunction rather than by an effect on the CV events.

However, three other studies focused on progression of kidney disease did not confirm the same significant results. In the CKD-FIX trial

adults with CKD stage 3 or 4 at high progression risk (elevated urinary albumin/creatinine ratio or a relevant estimated glomerular filtration rate – eGFR - decrease in the preceding year) and no history of gout were randomized to receive allopurinol (100–300 mg daily) or placebo. The trial was underpowered and no significant differences were found between the two groups in terms of decline in eGFR with a slight but non-significant improvement in patients treated with allopurinol [118]. Similarly, the FEATHER (Febuxostat versus Placebo) [119] and PERL (Allopurinol vs placebo) [120] failed to demonstrate the possibility of curbing eGFR decline in patient at risk through UA lowering therapy, corroborating the idea that UA is more a marker than a causative agent of CKD. However, the PEARL study was carried out in patients with Type-1 DM a condition where the progression of renal dysfunction is dependent on many different risk factors apart from uric acid (i.e. blood pressure, protein excretion, glucose control, etc.). In the FEATHER study a slower decline in eGFR was observed in the subgroup of patients without proteinuria and higher levels of eGFR [114].

Other small trials focused soft endpoints as the main outcomes have been carried out in patients with HF, CCS and ACS. The OPT-CHF study evaluated the potential role of oxypurinol vs placebo in symptomatic HF with reduced ejection fraction. On 405 patients, no differences were seen in the primary outcome: the improvement of symptoms at week 24). The secondary outcome, a composite of CV death or hospitalization for worsening HF, showed a trend towards harm in the oxypurinol group [121]. However, the oxypurinol treatment resulted in a better clinical outcome in patients with elevated serum UA at baseline suggesting the importance of patient's stratification before identifying those that should be effectively treated with XO-inhibitors. The subsequent EXACT-HF trial randomized 253 patients with reduced left ventricular ejection fraction (LVEF) and UA above 9.5 mg/dL to Allopurinol versus placebo. The primary composite endpoint at 24 weeks was based on survival, worsening HF, and patient global assessment. Secondary endpoints included change in quality of life, submaximal exercise capacity, and ejection fraction. None of the outcomes showed a significant difference between the two groups [122]. However, the rate of hospitalization for HF was largely reduced by allopurinol treatment with a remarkable difference in the Kaplan-Meier curves that did not achieve statistical significance because of the small sample size of the study that was, again, largely underpowered.

In the setting of CCS, a study randomly assigned patients with angiographically documented coronary artery disease, a positive exercise tolerance test and stable chronic angina pectoris to receive allopurinol 600 mg daily versus placebo. Allopurinol increased exercise time and reduced chest pain, suggesting that XO activity contributes somehow to exercise-induced myocardial ischemia [123]. This effect might be related to a reduction in vascular oxidative stress, an improvement of endothelial function and an increase the supply of molecular oxygen in ischemic tissue [124]. Additionally, oxidative stress could directly cause an anti-ischemic effect: substrates for ATP are broken down ultimately by XO, as the inhibition of this enzyme augments high-energy phosphates, which should supply essential energy to tissues that are depleted of energy by ischemic conditions [125].

Finally, in a small non-blinded study, 100 ACS subjects were randomized to allopurinol versus placebo. Allopurinol group showed a better control of angina pectoris recurrence (effective rate 96 % vs 76 %, $p < 0.05$). Furthermore, the incidence of subsequent CV events, a composite endpoint of angina, ACS, HF, stent thrombosis, revascularization and CV death, during a two year follow-up was 30 % in the control group and 10 % in the allopurinol group [126].

So, in the context of ACS, CCS and HF, only studies with a low number of patients were done. Thus, no convincing evidence exists and no definitive conclusions can be drawn.

8. The last trial on uric acid therapies and cardiovascular outcomes: the all-heart study

The last trial published on the treatment of asymptomatic hyperuricemic patients need a specific chapter due to its important clinical and research implications. The ALL-HEART study [127] is a multicenter, prospective, randomized, open-label, blinded-endpoint trial that investigated whether allopurinol improves major CV outcomes in patients with ischemic heart disease (IHD), defined as a history of ACS at any time or angina or other evidence of ischemic heart disease according to investigator opinion. Therefore, it was focused on secondary CV prevention. History of gout, estimated glomerular filtration rate of <60 mL/min, HF with NYHA III-IV, significant hepatic disease, previous severe adverse skin reaction to any drug, or significant malignancy within the past 5 years were exclusion criteria.

The study included 6134 patients aged 60 years or older, randomized to receive allopurinol, up titrated to a maximum dose of 600 mg/day, plus usual care or usual care alone. Usual was represented by statins, antiplatelet agents, ACE-inhibitors, beta-blockers, anti-anginal medications, diuretics, anticoagulants and diabetes medications as needed, and these drugs does not differ between the two studied groups. Allopurinol was given irrespective of UA levels, in fact patients at the enrollment presented UA values of 5.7 mg/dL.

The primary outcome was a composite of non-fatal myocardial infarction, non-fatal stroke or CV death. In the secondary outcomes also all-cause mortality, hospitalization for ACS, coronary revascularization, hospitalization for HF, all CV hospitalizations and quality of life and cost-effectiveness were also considered. After a follow-up of 4.8 years, there was no evidence of different rates of the primary and of any of the secondary outcomes. Specifically, 314 (11.0 %) participants in the allopurinol group (2.47 events per 100 patient-years) and 325 (11.3 %) in the usual care group (2.37 events per 100 patient-years) had a primary endpoint (HR 1.04; 95 % CI 0.89–1.21; $p = 0.65$). Non-significant difference in all-cause death was reported (HR 1.02; 95 % CI 0.87–1.0; $p = 0.77$); specifically, 288 (10.1 %) participants in the allopurinol group and 303 (10.6 %) in the usual care group died. Even if these results appear convincing in erasing the possibility of treating with urate-lowering therapies patients in secondary prevention, they should be interpreted in the light of some strong limitations of the study.

Firstly, as also found in the CARES [112] and (even less) FAST [113] trial, also in this study more than 50 % of the patients discontinued the study drugs. More specifically, 57.4 % of participants in the allopurinol arm withdrew from randomized treatment during the study. This difference might have been partly driven by the extra visit for patients in the allopurinol group at 6 weeks. Moreover, the absence of a placebo might have led to more unbalanced withdrawal from the study, as well as to more bias in reporting of more subjective adverse events. Furthermore, most of the participants had a long-term history of IHD (median duration 10.2 years), even if patients with recent ACS were not formally excluded. Nevertheless, the findings of the study probably could be not applicable in a population with a shorter history of IHD or recent ACS.

In addition, as already mentioned, many papers found a U-shaped curves for the relationship between UA and CV events. It is possible that an excessive reduction of UA has been obtained in this trial [117] affecting the possibility of gain a reduction of CV events. In fact, the studied population might lack an increased activity of XO at the baseline, as advised by a mean UA level within the normal range (5.7 mg/dL), that goes through 3.0 mg/dL at the end of the study. This level is similar to the one found by many studies and that has been related to an increase in CV events. A sub-analysis should be done in patients with the higher values at the beginning of this study, as well as of other studies focused only on patients with high UA, to evaluate this hypothesis. Finally, it would be interesting to understand whether Febuxostat might have obtain a different result if it had been used instead of allopurinol. Thus, it would be interesting to plan future

studies comparing febuxostat, allopurinol and placebo in a population well-balanced about IHD, specifically enrolling equally patients with a more and less recent history of IHD (i.e. ACS <12 vs > 12 months).

9. Conclusions and future perspectives

The high number of articles published on the topic of UA and CV disease lead us to conclude undoubtedly that this relationship exists and that UA should be considered in patients CV risk re-classification.

However, important questions are still unanswered. The first one is at which UA level this relationship becomes clinically important? Although the relation is linear (or more probably a U-shaped curve) a cut-off point could made easier for clinician to define a diagnosis and a threshold over which treatment is needed. Different papers found dissimilar cut-offs that commonly haven't' been tested in external populations (in order to evaluate its effective discriminatory capacity). While we are waiting for such studies and definitive cut-off, taking together all the actually published paper, we could propose a value of 5.5 mg/dL as the cut-off point over which CV risk significantly increase.

After defining hyperuricemia, it is necessary to decide if patients need to be treated also whether asymptomatic (non-gouty). The results of clinical trials published so far on the role of hypouricemic agents in reducing the risk of CV events have been heterogeneous. This could be explained by the presence of different phenotypes across hyperuricemic patients, identifiable according to different pathophysiological mechanisms and leading to possible different responses to the urate lowering treatment [128,129].

A first phenotype of patients includes those with increased CV risk related to overt or subclinical monosodium urate deposition within the vessels. In this group of patients, urate lowering treatment according to the guidelines can promote the dissolution of urate deposits and prevent the formation of new ones, indirectly determining a reduction in vascular and systemic inflammation.

However, crystal's deposition can't entirely explain the connection between UA and CV risk, and further phenotypes exists. A second group is composed of patients in which the increased CV risk is related to the pro-oxidative properties of UA, independently to the crystal depositions while a third phenotype regards to patients with XO overactivity (determined by genetic, acquired and dietary factors). This has been associated with the production of both reactive oxygen species and UA with a pro-inflammatory and pro-thrombotic effect and a high prevalence of CV risk factors. In these two groups, we still don't have a clear indication for a urate lowering treatments as discussed in our review.

Patients with low XO activity represent the latest phenotype of hypeuricemic subjects. As already seen, a U-shaped relationship have been observed between UA and CV events and the same also applies to XO activity. In fact, a higher XO activity is associated with an increased risk of CV events as well as also low plasma XO activity [129]. This dual effect could represent a critical point regarding the possible use of pharmacological treatment with XO-inhibitors in CV prevention. In fact, patients with a high XO activity should be the ideal target for these therapies while it could be unsuccessful, or potentially harmful, in patients with a low XO activity.

In conclusion, research effort should focus in phenotyping hyperuricemic patients in order to found a personalized approach to therapeutic options.

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