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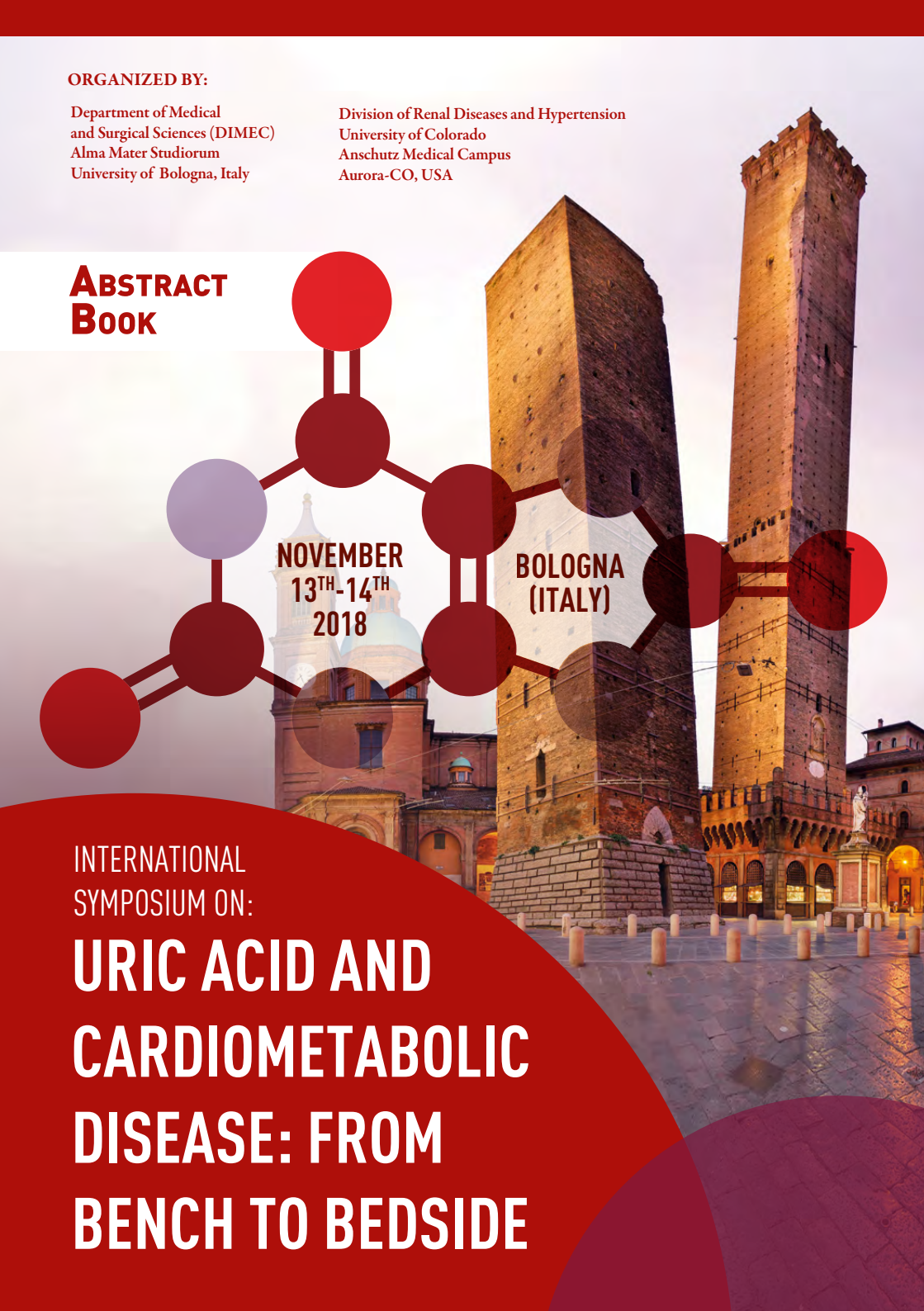
**ABSTRACT
BOOK**

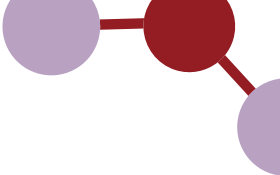
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**BOLOGNA
(ITALY)**

INTERNATIONAL
SYMPOSIUM ON:

**URIC ACID AND
CARDIOMETABOLIC
DISEASE: FROM
BENCH TO BEDSIDE**





After more than a century of active research, uric acid has gained the stage as one of the most reliable candidates for the huge amount of residual cardio-metabolic risk.

The involvement of uric acid in the pathophysiology of hypertension, diabetes and metabolic syndrome, particularly at younger ages, supports the importance of the research in this area.

The interaction between genetics, biochemistry, epidemiology and lifestyle is the engine that has boosted the worldwide interest for uric acid and cardio-metabolic disease.

Now it's time to move from academic to clinical practice since we urgently need a reliable tool to identify which patients deserve something more than theory and hypothesis.

The 4th edition of the Bologna meeting will be focused on the patient with the goal to discuss several burning topics:

- Are all the patients with elevated serum uric acid levels the same?
- What is the threshold level for “cardio-metabolic” hyperuricemia?
- How to identify the patients at risk of cardio-metabolic disease?
- What about in children and adolescents?
- What are the differences with cardiovascular complicated gout?
- What are the preventive/therapeutic strategies?
- What is the role of ULT?
- What advantages/harm of the use of non-ULT drugs affecting uric acid?
- What is the current position of Guidelines?

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ABSTRACT BOOK

INTERNATIONAL SYMPOSIUM ON:

**URIC ACID AND CARDIOMETABOLIC
DISEASE: FROM BENCH TO BEDSIDE**





SESSION I – URIC ACID AND GOUT: TALES FROM THE ANCIENT WORLD

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Uric acid represents a key chemical component in human biology and its fundamental role in pathological processes has been elucidated more and more over the decades following its discovery by the Swedish chemist Carl Wilhelm Scheele (1742–1786) and the clarification of the causal link existing between it and gout, highlighted by Alfred Garrod (1819-1917).

While a substantial body of information exists on these studies occurred in the last two centuries, how much is known about the most ancient presentation of uric-acid related pathology? This talk, by adopting the methodologies used in historico-medical and palaeopathological research, shall analyse the time period going from the very dawn of recorded history till the coinage of the word “gout” by Randolphus of Bocking (1197–1258). Ancient medical treatises, occasional mentions in the rich body of ancient literatures, as well paleopathological reports of gout in ancient times will be presented, with a particular focus on Ancient Egypt, Greece and Rome. Besides clinical and epidemiological remarks and the description of notable cases, changing notions of patho-physiological rationale will be explained and the evolution of the therapeutical approaches in the considered timeframe will be examined. Finally, general considerations on what impact uric-related pathology might have had on past populations will be expressed.

Literature

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SESSION I – THE CARDIOMETABOLIC INVOLVEMENT IN GOUT. THE POSITION OF GUIDELINES

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Hyperuricemia (HU) is a condition predisposing to the formation and deposition of urate crystals in multiple organs or tissues, in particular joints, classically known as gout. An increasing body of studies increasingly demonstrated that gout is associated with many other severe diseases, including hypertension, type 2 diabetes mellitus (T2DM), obesity, chronic kidney disease (CKD) and cardiovascular disease (CVD). Among the CVD, there are also coronary atherosclerotic heart disease, atrial fibrillation, and heart failure. A randomized study showed that SUA lowering drugs were able to reduce blood pressure values in adolescent pre-hypertensive and hypertensive individuals. All these studies demonstrate that hypertension is related with high level of SUA. Hyperuricemia can lead to hypertension by blocking the production of nitric oxide (NO). NO can induce vasodilation to increase blood flow, reduce vascular smooth muscle cell proliferation, and modulate thrombosis, so it plays an important role in protecting the vasculature under physiological concentrations. As regard the complex correlations between hyperuricemia and coronary heart disease (CHD), a study carried by Kim et al. observed the relationship between uric acid and coronary artery calcification by studying 4884 participants without overt coronary artery disease. The CAC score showed a significant positive association with the SUA level, with retention of statistical significance after adjusting for confounding factors. Also atrial fibrillation (AF) seems related to HU, as demonstrated by a study by Kuwabara et al. analyzing 49,292 subjects without competing risk factors (hypertension, type 2 diabetes mellitus, cardiovascular disease, chronic kidney disease, heart failure) and observed that hyperuricemia was an independent competing risk factor for AF in an apparently healthy general

population. The increased incidence of CVD in patients with gout is often attributed to the strong associations between prevalent hyperuricaemia and comorbid conditions such as metabolic syndrome, renal dysfunction and hypertension. However, large epidemiological studies have now demonstrated that gout is an independent risk factor for incident coronary heart disease (CHD), peripheral arterial disease, heart failure, stroke and death due to cardio-vascular causes. For these reasons, most important scientific societies, not only of rheumatological areas, have proposed recommendations or guidelines to prevent the occurrence or progression of CVD.

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SESSION I – HOW CAN WE QUANTIFY THE CARDIOMETABOLIC RISK IN PATIENTS WITH GOUT? AN EPIDEMIOLOGICAL PERSPECTIVE

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Many studies in adults have shown that uric acid is a risk factor for cardiovascular disease both in primary as well as secondary risk settings. Also patients with manifest gout have an increased risk for cardiometabolic diseases. A relationship between uric acid and inflammatory markers and multiple cytokines is also well documented. Serum uric acid also exhibits direct immune-modulating effects, implying a potential role for uric acid in atherosclerosis and other cardiometabolic disorders characterized by low grade inflammation such as obesity, the metabolic syndrome, hypertension, diabetes, other inflammatory processes, and especially, with renal function (1).

However, whether the suggested relationship is of causal nature or not, and, if not, it's therefore only an epiphenomena difficult to assess. In contrast to well-controlled randomized clinical studies which are free of confounding and have therefore a high degree of internal validity, the evidence describing the relationship between serum uric acid levels or gout, respectively, comes mainly from observational studies and these studies are prone to bias and confounding (2). Randomization of gout is not possible and therefore observational studies are the only ethical means to study the long-term effect of gout on risk of cardiometabolic diseases. Many issues such as study design, the way study participants are selected into a study and the response, how information is obtained and measurement issues, and the way the information about exposure and outcomes are statistically analyzed, determine the internal value and the generalizability of observational research - and also the level of evidence an observational study is delivering.

The talk will review the general study designs that are available to evaluate the association between uric acid or gout and cardiometabolic diseases and elude on specific strength and limitations. Consideration of causal association will be discussed. In addition, several examples will be used to demonstrate how specific study techniques such as systematic reviews or meta-analyses can help to evaluate and summarize so far available evidence. Moreover, specific techniques such as Mendelian Randomization studies will be presented to discuss how evidence from observational studies can be used to support an unconfounded risk assessment and support a causal interpretation of specific findings. Nevertheless, research is cumulative and the evidence from several sources has to be considered, the quality assessed and put into an overall picture to strengthen the ability to make causal inferences from available study data.

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SESSION I – THE MANAGEMENT OF CARDIO-METABOLIC RISK IN PATIENTS WITH GOUT

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Gout is an independent cardiovascular risk factor. Patients suffering from gout show a higher incidence of all forms of the atherosclerotic disease, as well as cardiovascular and all-cause mortality. This appears related to both comorbidities and urate crystal-led inflammation. Thus, gout, along with being the most common form of inflammatory arthritis in rich countries, carries with significant morbidity and mortality.

Proper management is essential. The purpose of this lecture is to analyze the potential strategies aimed to control the cardiovascular risk in patients with gout. In gout, the monosodium urate crystals deposition is the responsible for all the clinical manifestations. Taken as danger signals by the innate immune system, monosodium urate crystals lead to inflammation by the NLR-P3 inflammasome–interleukin1beta pathway. In clinics, we see the acute inflammatory bouts (gout flares), but a persistent, subclinical inflammation also occurs, as demonstrated when synovial fluids samples between flares are analyzed. In analogy to other conditions such as rheumatoid arthritis or systemic lupus erythematosus, an accelerated process of atherosclerosis derives from the persistent inflammation. To this also contributes the hyperuricemia, which favors a pro-inflammatory and pro-oxidative state. The management of gout achieves to dissolve monosodium urate crystals and normalize serum urate levels, and should help to reduce the cardiovascular risk as well. Ethical considerations impede intervention studies assessing urate-lowering therapy versus no intervention or placebo to this endpoint, and

population-based studies available to date have reported conflicting results. In clinical practice, gout management is often poor and in need of improvement, so any analysis derived from population-based claims databases should be taken with care.

In clinical practice, patients with gout are very often diagnosed of other cardiovascular, metabolic and renal diseases. In published series, numbers largely vary, likely related to selection issues such as geographical areas, ancestry, patients' source or disease duration. Nevertheless, hypertension, dyslipidemia or obesity are present in over two thirds of cases – prevalence rates that are clearly above the general population –, renal disease in half of them, diabetes mellitus in a quarter, and established cardiovascular disease in around 10-15% of cases. These numbers are even higher if a focused screening program is performed at clinics. In the general population, comorbidities contribute to around 50% of the cardiovascular load, reinforcing the value of prevention. To date, no study has focused on the effect of comorbidities management on the cardiovascular risk in patients with gout, though there is no reason to consider a different result here. The 2016 EULAR guidelines strength the need for paying particular attention to cardiovascular comorbidities and their management, especially with strategies and drugs that may also help to control serum urate levels, such as considering diuretics withdrawal or using losartan, amlodipine, atorvastatin or fenofibrate. A nurse-led clinic or the collaboration between the specialists involved in managing patients with gout are also helpful.

The assessment of cardiovascular risk in patients with gout is essential to tailor the management strategies. In the general population, the use of risk assessment tools, such as Framingham Heart Study or SCORE, that allows to predict fatal or nonfatal cardiovascular events through evaluating a set of cardiovascular risk factors is extended. However, the value of the risk scores in gout population appears limited and inferior to imaging techniques for screening subclinical atherosclerosis. The prevalence of carotid atheroma plaques reaches up to 40% of patients

with at rheumatology clinics, that, in combination with the clinical assessment, allows to gauge that two over three patients depict a high cardiovascular risk, equal to have already suffered from a cardiovascular event. This shows with clarity the strong impact of gout in the morbidity and mortality of the patients.

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SESSION I – TREATING GOUT IN PATIENTS WITH CARDIOVASCULAR DISEASE

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It is estimated that more than 8 million Americans suffer from gout (1). Hyperuricemia, resulting from the increased production and/or decreased excretion of uric acid (UA), underlies its development. Additionally, hyperuricemia has been associated with excess risk of cardiovascular disease (CVD) (2). This association is not coincidental as systemic inflammation and oxidative stress underlie both gout and CVD. Vascular-derived xanthine oxidase (XO) is a potential source of oxidant stress in inflammatory conditions (3). During purine metabolism, increased XO activity leads to production of superoxide and uric acid. Allopurinol and febuxostat act by inhibiting XO and decreasing UA production. By contrast, the uricosuric agent probenecid promotes UA excretion by inhibiting UA reabsorption in the proximal tubule. All these agents have anti-inflammatory properties that may explain “off-target” effects on CVD outcomes. Recently, there has been increasing interest by clinical investigators and regulatory agencies in defining the benefit vs. risk of pharmacotherapy in chronic disease states associated with CVD, such as diabetes and gout.

Recently, Kim et al. (4) examined the effect of UA lowering therapy with probenecid or allopurinol on cardiovascular risk in older patients with gout. Using Medicare claims data over a 6-year period, they identified more than 38,000 older adults that were naïve of UA lowering therapy for at least 1 year prior to drug initiation, and estimated incidence rate and hazard ratio for the composite endpoint of hospitalization for myocardial infarction (MI) or stroke. In the primary analysis, the incident rate of

the composite endpoint was 2.36 events per 100 person-years among probenecid initiators compared to 2.83 among allopurinol initiators (hazard ratio 0.80). Incident rates of selected secondary outcomes, including worsening heart failure (HF) and mortality, were also lower in the probenecid group. All these associations were observed on top of background cardioprotective therapy with RAS inhibitors, beta-blockers and statins.

Prior studies in patients with hyperuricemia (with or without gout) show that probenecid and allopurinol are equally effective at lowering serum UA levels in a dose-dependent manner (5). Therefore, any difference in subsequent cardiac risk would be expected to be independent of UA lowering effects. Probenecid may exert additional effects on cellular and molecular mechanisms that could explain CVD benefit. Probenecid is a partial agonist of the transient receptor potential vanilloid (TRPV) type 2 channel (6). Stimulation of TRPV2 under physiological conditions leads to improved cardiac inotropy and lusitropy in vitro and in vivo. Beyond the heart, TRPV2 may function as an important stretch receptor in vascular smooth muscle cells raising the possibility that probenecid exerts vasodilator effects. In addition, the vascular effects of probenecid may be augmented by an inhibitory effect on pannexin-1 channels (7). Whether one or more of these mechanisms explains the protective effect of probenecid on stroke or MI in the study of Kim et al. (4) remains to be determined.

In an earlier study using US insurance claims data, Kim et al. (8) found no difference in the risk of CVD in patients with gout initiated on XO inhibitors (allopurinol or febuxostat) compared to those with untreated hyperuricemia. More recent data showed a lower risk of major cardiovascular events in patients with chronic kidney disease and either CVD or HF who initiated febuxostat compared to allopurinol (HR 0.52), a difference driven largely by lower peripheral arterial events (9). Colchicine, a non-uric acid lowering therapy, may also reduce the risk of cardiovascular events in patients with gout (10) through one of several anti-inflammatory mechanisms. These observational data, however, have been overshadowed by prospective studies. Most recently, data from the

CARES trial (11) led the FDA to release a communication warning against the use of febuxostat. Another large, randomized study comparing the cardiovascular safety of allopurinol and febuxostat in the management of symptomatic hyperuricemia is nearing completion and will help clarify these findings (12).

There remain practical hurdles of uricosuric therapy including renal contraindications, dosing and gastrointestinal side effects. Recent experience with allopurinol in HF highlights the importance of performing prospective clinical trials even when the underlying pathophysiology and mechanisms seem clear. Numerous lines of basic and clinical evidence pointed to an important role of XO in ventricular and vascular remodeling (3). Furthermore, observational studies and a post-hoc subgroup analysis of the oxypurinol HF study suggested that XO inhibition may exert clinical benefits in HF patients with hyperuricemia. In the EXACT-HF study, we randomized 253 patients with symptomatic HF and UA levels ≥ 9.5 mg/dl to receive allopurinol or placebo in a double blind multicenter study (13). Despite significant UA lowering at 24 weeks, XO inhibition failed to improve clinical status, exercise capacity, quality of life or left ventricular function.

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**SESSION I – FROM URIC ACID TO CARDIO-METABOLIC DISEASE:
CAN WE IDENTIFY THE PATIENTS AT RISK?**

Richard J. Johnson

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Epidemics classically refer to the spread of communicable diseases. However, the twentieth century exploded with major epidemics in cardio-metabolic diseases, including in obesity, diabetes, hypertension, stroke, heart failure and coronary heart disease. The commonly held concept was that societies suddenly had inexpensive available sources of sugar and high fat foods, coupled with breakthroughs that led to a reduction in exercise and the development of sedentary behavior. Overnutrition and lack of exercise led to obesity, hypercholesterolemia, hypertension and coronary artery disease. What started out as rare diseases in 1900 rapidly overtook societies in most westernized countries, and then further spread rampantly in developing countries.

In some respects there appear to be two different epidemics. One epidemic was more related to atherosclerosis, leading to coronary artery disease and cerebral vascular disease. This epidemic peaked in the 1960s and 1970s but overall mortality rates have fallen since then, largely because the prevalence of atherosclerosis appears to be decreasing, but also because our treatments have become more effective. Indeed, two of the major breakthroughs were the recognition of the importance of smoking and the significant decrease in tobacco use, and the importance of hypercholesterolemia and the use of statins and other agents to control lipid levels. Other treatments have also had major impact, such as the use of antihypertensive agents, RAS blockers, beta blockers, anti-platelet agents, thrombolytic therapies, angioplasty/stents and coronary artery bypass surgery.

In contrast, a second epidemic has been the rise of small vessel disease (arteriosclerosis) that appears to be strongly associated with hypertension, the metabolic syndrome, obesity, diabetes fatty liver and chronic kidney disease. Here the major problem appears to be sugar intake **(1)**, and to a lesser extent the intake of salt, high glycemic carbs, and umami-rich meats. This epidemic has run unabated for decades, although in the last few years there has been a slowing in the rise of obesity and diabetes. A key question is the identification of the mechanisms driving these diseases so that we can identify the patients at risk. One well known risk factor associated with these conditions is gout and hyperuricemia. For years, however, the presence of gout was thought to be secondary to these conditions. However, experimental and clinical evidence in the last decade has strongly challenged this concept **(2)**.

In this lecture we will review the evidence of how uric acid may contribute to cardiometabolic disease. First, we will review the experimental evidence that shows that uric acid can induce hypertension and microvascular disease, activating the renin angiotensin system and causing oxidative stress and endothelial dysfunction. Second, we will show that uric acid can cause chronic kidney disease, identify both mechanisms by which it may cause both glomerular injury (via glomerular hypertension) and tubular injury. Third, we will show that uric acid acts on mitochondria to induce changes that lead to fatty liver, obesity and diabetes **(3)**.

We will then use this evidence to explore clinical studies that have investigated the role of uric acid in disease. Here we will utilize our experimental data to provide explanations for discrepancies in various studies. A discussion of the different approaches to uric acid lowering might result in different outcomes and how to design further studies will be made. For example studies on the role of uric acid in hypertension suggest that lowering uric acid will have less blood pressure effects in longstanding hypertension or when subjects are receiving renin angiotensin inhibitors. Likewise, the lowering uric acid in chronic kidney disease may be more likely to be protective in trials in which substantial fall in kidney function occurs in the control group over the clinical trial as opposed to shorter trials in which progression is slow or flat.

Finally, we will end by discussing of future directions in uric acid research and clinical application, and how such approaches might provide new insights into how to end these important epidemics that dominate the major diseases of our times. This includes presentation of new data showing that uric acid may work in part by activating other enzyme systems, such as the polyol and fructokinase pathways. These types of observations will also provide insights why xanthine oxidase inhibition provides less protection than expected based on the strong epidemiological evidence linking uric acid with obesity and diabetes. In summary, we will make the case that hyperuricemia remains a very important biomarker for individuals at risk for both arteriolosclerotic and atherosclerotic disease.

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SESSION II – URIC ACID AND BLOOD PRESSURE

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Several epidemiological studies have demonstrated an association between serum uric acid (sUA) and the incidence of elevated blood pressure (BP). A large body of observational studies documented a progressive increase in the relative risk of hypertension with increasing levels of sUA, an effect that appears to be independent of traditional risk factors. A meta-analysis conducted in 18 prospective cohort studies representing data from 55,607 participants who were normotensive at baseline demonstrated that hyperuricemia was associated with an increased risk for incident hypertension. For 1 mg/dl increase in uric acid level, the pooled relative risk for incident hypertension after adjusting for potential confounding was 1.13. these effects were significantly larger in younger study populations and tended to be larger in women.

Further data from the PAMELA trial documented that hyperuricemia represents an independent predictor of new-onset hypertension as diagnosed by ambulatory and home BP, and that an increase in sUA of 1 mg/dl also independently predicted cardiovascular and all-cause mortality. These data allow to conclude that sUA independently predicts new-onset out-of office hypertension, and long-term cardiovascular and all-cause mortality.

In addition, in a longitudinal cohort of healthy subjects, a baseline UA level greater than 6.5 mg/dL was associated with a 25% increase in the risk of hypertension. A prospective study including subjects without any baseline cardiovascular disease showed that increased sUA was strongly

associated with intima media thickness leading to the incidence of hypertension. Interestingly, sUA shows a stronger association in younger subjects, an effect likely resulting from the absence of major confounding risk factors in this population. An early causal effect of hyperuricemia in the development of hypertension is also proposed by a study conducted in 125 children with untreated newly diagnosed hypertension and normal renal function. In these patients sUA was directly correlated with SBP and DBP. In line with these data, results from the Bogalusa Heart Study indicate that hyperuricemia in childhood is associated with hypertension in both childhood as well as adult life.

With respect to the pathophysiological mechanisms accounting for the association between hypertension and sUA, animal models of hyperuricemia documented that the subsequent incidence of hypertension was accompanied by an increased renin levels and decreased nitric oxide synthase in the macula densa, as well as tubulointerstitial injury, thus highlighting important pathological findings relating sUA to hypertension and kidney disease. In addition, further experimental studies documented a strong association between sUA and an increased reactive oxygen species and angiotensin II production.

In humans, few clinical trials investigated a possible beneficial effect of sUA reduction on hypertension. In a randomized crossover study conducted in hyperuricemic adolescents with a new diagnosis of essential hypertension, treatment with allopurinol resulted in a significant decrement in the 24-h systolic BP. In another randomized, double-blinded, placebo controlled trial, pre-hypertensive adolescents treated with urate-lowering therapy showed a significant reduction in clinic systolic and diastolic BP. Again, in a prospective trial investigating the role of allopurinol in hyperuricemic patients, it was documented that allopurinol 300 mg/day resulted in a significant decrease in mean BP. In conclusions, a large body of evidence homogeneously indicates a strong association between sUA and incidence of hypertension.

For these reasons, the recent 2018 ESH/ESC Guidelines for the management of arterial hypertension recommend measurement of sUA as part of the screening of hypertensive patients.

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SESSION II – URIC ACID, LEFT VENTRICULAR FUNCTION AND HEART FAILURE

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Heart failure (HF) is a major epidemic and significant public health burden in our ageing society. HF is a major cause of hospitalisation in adults over 60 years and is a major cause of mortality. The association of serum uric acid (SUA) and coronary heart disease (CHD) has long been recognised and has sparked enormous debate about the role of SUA as a risk factor for CHD and the potential benefits of uric lowering drugs in hypertensive patients. In recent years there has been growing interest regarding elevated SUA and HF. It is well established that elevated SUA is commonly seen in patients with HF and is known to be associated with high morbidity and mortality in HF [1]. In more recent years several studies and meta-analysis have reported raised SUA to be associated with increased risk of incident HF in population studies [2] suggesting that elevated SUA could be a risk factor for HF. Whether SUA is merely a marker or whether this association is causal is still a matter of debate. SUA is dependent on xanthine oxidase (XO) activity, a known cause of oxidative stress which is implicated in the pathophysiology of HF as well as hypertension [3]. SUA may be a marker of increased XO activity which is up-regulated in the failing heart and may thus identify patients with increased HF risk. SUA concentration is commonly measured in hypertensive patients who are at high risk of developing HF but the role of serum uric acid (SUA) as a prognostic marker for incident HF in hypertensive subjects has been less studied and in the few that have the findings have been inconsistent. In this presentation I discuss the epidemiological evidence regarding the association between SUA and HF and its value as a prognostic marker. I present recent findings from the British Regional Heart Study on the

prognostic role of SUA and incident HF in older men on antihypertensive treatment as well as in those who are not. The British Regional Heart Study is a large prospective study of cardiovascular disease among men drawn from General practices in 24 British towns. In this study raised SUA ($>410\mu\text{mol/l}$) was associated with significantly increased risk of HF in men on antihypertensive treatment but not in those without. In men on antihypertensive treatment those with raised SUA ($>410\mu\text{mol/l}$) had the most adverse risk profile for HF including underlying ischaemia, subclinical cardiac dysfunction, atrial fibrillation, inflammation and renal dysfunction. Treated hypertensive men with SUA levels $>410\mu\text{mol/l}$ showed an increase in risk of HF of more than twofold compared to those on treatment with levels $<350\mu\text{mol/l}$ even after adjustment for lifestyle characteristics and biological risk factors. The findings that SUA predicts HF in those on antihypertensive treatment only suggests that SUA does not have an intrinsic relationship with HF but may be a marker of other pathways. It is yet not well understood what role SUA plays in the development of HF. Hypertension is a major risk factor for HF and regardless of whether SUA is causally related to HF, the evidence from this and other studies suggests that SUA as a marker of increased XO activity may be a useful biomarker of increased HF risk in hypertension and raises the issue of whether SUA levels should be routinely monitored in older hypertensive patients in primary care. Whether the use of XO inhibitors in hypertensive patients reduces incident HF is yet to be established. Primary intervention trials in older hypertensive people at high risk of HF are needed to confirm whether lowering SUA would reduce risk of HF in this group.

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SESSION II – URIC ACID AND CORONARY ARTERY DISEASE

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Cardiovascular diseases are the major cause of death in the Western world as a consequence of the large prevalence and poor control of several major cardiovascular risk factors (hypertension, dyslipidemia, diabetes, etc.). Elevated levels of serum uric acid (SUA) are directly responsible for the development of gout and significantly contribute to the increase in the relative risk of CV diseases in addition with the more consolidated CV risk factors. The hypothesis linking uric acid with cardiovascular disease is strongly supported by both experimental and clinical data. In particular, the presence of hyperuricemia is associated with an increase in blood pressure and the development of metabolic diseases that can largely contribute to the overall CV risk observed in the population. The pathogenetic role of SUA has been recently extended to the development of cardiovascular disease and in particular coronary artery disease. Data from observational studies have demonstrated a causal relationship between plasma levels of SUA and the incidence of myocardial infarction with a dose-dependent effect that support a threshold level for uric acid between 5 and 6 mg/dL. In addition, elevated SUA have been reported to worsen the clinical prognosis of acute myocardial infarction and the rate of hospital re-admission after acute coronary syndrome. As far as the possible mechanism responsible for the relationship between SUA and CHD, there is a possibility that the levels of SUA must be considered only as the marker of the oxidative stress associated with the activation of xantino-oxidase that is involved in its production. This hypothesis opens an interesting interpretation of the role of SUA in CHD patients where the oxidative stress related to uric

acid could be responsible for the development of endothelial dysfunction leading to coronary atherosclerosis. In addition, the same mechanism could be responsible for the oxidation of LDL-C and a tissue activation of RAS system resulting in a thinning of the fibrous cap and an increase in lipid content leading to plaque instability and increased risk of thrombosis. The association between serum uric acid and CHD might be favorably modified by appropriate treatment strategies involving drugs inhibiting the xanthine-oxidase (Allopurionol, Febuxostat) that could represent a possible solution for the management of CV risk in patients, with CHD. This hypothesis is currently under investigation by randomized clinical trials that should definitely evaluate the cardiovascular preventive effects of urate lowering treatment.

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SESSION II – URIC ACID AND ATRIAL FIBRILLATION

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As the burden of cardiovascular disease constitutes a major health problem with increasing prevalence globally, the concern of health professionals is focused on the metabolic factors that may play a key role as risk factors and thus could be altered. In this setting during the last decades scientific research has often turned its attention to serum uric acid (SUA) levels due to the fact that hyperuricemia, with steadily increasing prevalence of >20% in both genders in western world, has been positively correlated to a large number of established cardiovascular risk factors. In a recent study which assessed the predictive value of SUA for the incidence of coronary artery disease in 2,287 essential hypertensive patients who were followed up for a mean period of 8 years, among established confounders, high SUA (hazard ratio=1.216, $p=0.016$) turned out to be independent predictor of coronary artery disease. On the other hand, atrial fibrillation (AF) is the most common arrhythmia and is associated with increased morbidity (especially stroke and heart failure) and mortality. The prevalence and incidence of AF is increased and will further increase over the next decades. It is estimated that in the US by the year 2050 the number of adults with AF will be more than doubled. However, the pathogenesis of AF remains incompletely understood. The recognition of AF risk factors is essential to prevent it and reduce the risk of death. SUA levels have been associated with some cardiovascular conditions that are considered important risk factors for AF. There are data showing the association of high SUA levels with high blood pressure, insulin resistance, metabolic syndrome, obesity and chronic kidney disease. The question that arises is

whether there is a specific role for uric acid in atrial fibrillation. A meta-analysis of three cohort studies which evaluated 138,306 individuals reports that high SUA is associated with AF. The relative risk of having AF for those with high SUA was 1.67 (95% CI 1.23–2.27) compared with those with normal SUA. This association was consistently seen in both cross-sectional and cohort studies and it was also seen with different types of analyses that included univariate, multivariate and subgroup analyses. It was also seen consistently in multiple and diverse populations. A more recent meta-analysis of six cohort studies confirmed this association showing that hyperuricemia was significantly associated with increased risk of AF (relative risk 1.49, 95% CI 1.24–1.79). Also, in a large population-based cohort study, over a mean 2-year follow up, the incidence rate of AF per 1,000 person-years was 7.19 in patients with gout after adjusting for other risk factors. In the multivariable Cox regression analysis, adjusting for age, sex, comorbidities, medications and healthcare usage, the hazard ratio of AF in gout was 1.13 (95% CI 1.04–1.23). Furthermore, a recent comprehensive umbrella review of meta-analyses of studies examining the associations between SUA level and multiple health outcomes has shown that there is suggestive evidence of an association between uric acid and atrial fibrillation. There are also studies suggesting that hyperuricemia might have a role in the left atrium and left ventricular remodeling and through this in the development of AF. In a study based on a single-center database (n=3,043) the left atrium diameter was significantly correlated with uric acid. The same authors found in a nationwide longitudinal cohort (n=122,524) that the AF occurrence rate was higher in patients with hyperuricemia than in those without it (2.1% vs 1.7%; p value <0.001). In terms of pathophysiology, inflammation, oxidative stress and atrial tissue remodeling seem to be the linking pathophysiological issues between AF and SUA. Inflammatory indices such as CRP, IL-6 and TNF have been related with AF and left atrial enlargement. At the same time, these inflammation mediators are also related to higher uric acid levels. It seems that hyperuricemia and gout exert pro-oxidant effects and decrease nitric oxide bioavailability in the vessel wall, inducing inflammation and endothelial dysfunction. Regarding therapy, the

reduction of oxidative stress through inhibition of xanthine oxidase using allopurinol or other similar drug, or the use of N-acetylcysteine might be beneficial. Moreover, uric acid - lowering strategies may play a role in the prevention and treatment of AF. Based on the results of Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, the ability of losartan to lower SUA levels could explain partly the beneficial effect on atrial remodeling and the significantly lower risk of stroke vs atenolol, in hypertensive patients with left ventricular hypertrophy, despite similar reductions in blood pressure. More studies are needed to obtain a more comprehensive understanding of the pathophysiology of AF and measures to prevent it, including lowering serum uric acid levels.



SESSION III – URIC ACID AND NEW ONSET METABOLIC SYNDROME

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Uric acid is the end product of nucleic acid metabolism, which is generated by intracellular xanthine oxidase, transported into circulation, and exists as a form of sodium urate in plasma. In population of industrialized countries on traditional Western diet, serum uric acid concentration is 3–8 mg/dL which is higher compared to the population on non-Western diet (2–4 mg/dL) or most mammals (1–3 mg/dL) possessing the enzyme uricase. Urate is excreted mainly by the kidney, which can be altered by many factors including diet, renal function, medication, and status of insulin resistance.

The association of uric acid with renal and cardiovascular disease has been documented since 19th century, however it has been always controversial whether uric acid per se or its metabolism is an independent risk factor for the development or aggravation of these diseases. In terms of metabolic diseases, hyperuricemia was also known to be associated with prediabetes, diabetes, and metabolic syndrome. Again, these clinical entities are all accompanied with insulin resistance, which lead to a reduction in renal uric acid excretion and an elevation of serum uric acid levels even before the development of renal dysfunction. Therefore, uric acid has been considered neither as a key component of diagnosis nor a therapeutic target of metabolic syndrome.

Epidemiologic studies reported a strong association of obesity and metabolic syndrome in patients with gout or hyperuricemia. Recent

studies showed the relationship of uric acid with the component of metabolic syndrome in various population including even high school students. Insulin resistance can account for the association between an increased uric acid and metabolic syndrome. The mechanisms by which insulin decreases renal uric acid excretion are the stimulation of urate-anion exchanger URAT-1 and/or sodium-dependent anion co-transporter by insulin in brush border of proximal tubular cells in the kidney. In addition to an association between uric acid and metabolic syndrome, in recent years, hyperuricemia has also been found to independently predict the development of diabetes or obesity.

Experimental studies have demonstrated that hyperuricemia mediates insulin resistance, fatty liver, and dyslipidemia in both fructose-dependent and -independent models of metabolic syndrome. Given the consideration an increased fructose intake in modern society and the ability of fructose to uric acid generation via rapid depletion of ATP and purine nucleotide degradation, the experimental studies in fructose-induced hyperuricemic rats are expected to provide the mechanistic insight on potential mechanism of uric acid-induced metabolic syndrome. Fructose feeding in rats resulted in an elevation of blood pressure, serum triglyceride, fatty liver, and insulin resistance. Similar studies in human also documented that fructose caused visceral fat accumulation, dyslipidemia, and a decrease in insulin sensitivity.

The mechanism for uric acid-induced insulin resistance appears to be mediated by the development of mitochondrial oxidative stress and endothelial dysfunction manifested as an impairment of insulin-dependent stimulation of nitric oxide in endothelial cells. Lowering uric acid in fructose-fed rats demonstrated an improvement of the components of metabolic syndrome, including a reduction in blood pressure, serum triglyceride levels, hyperinsulinemia, and weight gain. This finding suggests that uric acid may have a causal role in the pathogenesis of metabolic syndrome, at least in hyperuricemic animal model induced by fructose.

There are limited clinical studies investigating the effect of uric acid lowering on insulin resistance or the components of metabolic syndrome. Several studies showed that uric acid-lowering therapy either by xanthine oxidase inhibitor or uricosuric agents in patients with insulin resistance has been shown to improve blood pressure, fasting glucose concentrations, or serum lipid profiles. Another study demonstrated allopurinol reduced markers of hepatic inflammation with an improved lipid profile in patients with non-alcoholic fatty liver disease, however not all the studies proved the beneficial effects of uric acid-lowering therapy. All of these previous studies were small pilot studies with uncontrolled and non-randomized design.

In summary, despite a long history of the association between hyperuricemia and metabolic syndrome, the causative role of uric acid in new metabolic syndrome remains controversial. Recent understanding on the mechanism of uric acid-induced hypertension, obesity, and insulin resistance provided by experimental studies shed some light on the insight on the role of uric acid in development and/or aggravation of metabolic syndrome. Well-powered, placebo-controlled randomized clinical trials to determine the effect of uric acid-lowering therapy in metabolic syndrome are needed.

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SESSION III – THE INTERACTION BETWEEN URIC ACID AND LIPID PROFILE

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Many studies showed the interaction between uric acid and dyslipidemia (hypertriglyceridemia and hypercholesterolemia) since Hutchinson (1889) presented a case of xanthomatosis and gout.¹ Chauffard and Troisier reported that serum cholesterol levels could be raised in gout in 1921 and Boas and Adlersberg reported hyperuricemia was found in 7 out of 15 hypercholesterolemic patients in 1945.¹ We have well known this interaction, but there are many discussions about the causality.

Some recent studies showed hyperuricemia itself becomes a risk for developing dyslipidemia. We checked 5,899 healthy Japanese adults over 5 years, who did not have overweight/obesity, hypertension, diabetes mellitus, dyslipidemia, history of gout or hyperuricemia on medications, and/or chronic kidney disease (eGFR <60 ml/min/1.73m²) at the baseline. In this cohort, asymptomatic hyperuricemic subjects (>7.0 mg/dL of serum uric acid in men and ≥6.0 mg/dL in women) showed significantly higher cumulative incidence of dyslipidemia over 5 years compared to normouricemia (23.1% vs 15.5%, p<0.001).² Moreover, hyperuricemia and higher serum uric acid levels also remained independent risk factors for dyslipidemia in men after multiple adjustments for age, sex, body mass index, smoking and drinking habits, baseline serum triglyceride, LDL cholesterol and HDL cholesterol.² We also showed that high baseline serum uric acid levels was an independent risk for developing high LDL cholesterol both in men (OR: 1.159 per 1 mg/dl increase, 95% CI:1.009-1.331) and women (OR: 1.215, 95% CI:1.061-1.390), as well as hypertriglyceridemia (OR: 1.370, 95% CI: 1.179-1.591 in men and OR: 1.942, 95% CI: 1.462-2.578 in women).³ Similarly, high triglyceride levels

was a risk factor for developing hyperuricemia (OR: 1.003 per 1 mg/dL increase: 1.003, 95% CI: 1.002-1.003).³ Recently, Jensen T et al. reported that higher baseline serum uric acid levels and increased serum uric acid over 5 years became independent risks for developing fatty liver disease.⁴ From the Brisighella Heart Study, the main predictors of an increase in pulse-wave velocity (PWV) were age, systolic blood pressure, oxidized LDL, apolipoprotein B and serum uric acid ($p < 0.05$) in subjects with normal or mildly reduced renal function.⁵ However, oxidized LDL and serum uric acid were not a predictor of PWV in the patient with established renal disease. The results suggest serum uric acid and oxidized LDL are more important for arterial stiffness in subjects with normal or preserved renal function than in patients with chronic kidney disease.

These studies are observation studies, and it cannot show the causal relationships between serum uric acid and dyslipidemia or fatty liver disease. Intervention studies are needed to clarify whether the treatments for hyperuricemia are useful to prevent the development of dyslipidemia and fatty liver disease. However, we should account for hyperuricemia as a predictor for dyslipidemia and fatty liver disease.

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SESSION III – URIC ACID AND RENAL DYSFUNCTION: WHAT IS THE EGG?

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Over the last several years, evidence has been accumulating that increased serum uric acid (SUA) levels and gout are associated with subclinical organ damage (1, 2) and a greater risk of cardiovascular and renal events. Several pathogenetic mechanisms have been shown to link SUA to the development of vascular damage. In an experimental model of mild hyperuricaemia, rats were shown to develop hypertension possibly through mechanisms related to the inhibition of nitric oxide and activation of the renin angiotensin system. Accordingly, progressive renal damage has also been shown to be due to vasoconstriction and increase in glomerular pressure under chronic hyperuricemia. Finally, uric acid may stimulate the synthesis of monocyte chemoattractant protein-1 by vascular smooth muscle cells, leading to enhanced macrophage infiltration and worsening of the atherosclerotic process. However, it remains to be clarified whether SUA has an independent role in the pathogenesis of renal disease or simply reflects a reduction in glomerular filtration rate. Hyperuricaemia has been independently associated with an increased risk of chronic kidney disease in cross-sectional studies in Europe, Asia, USA, and China both in the general population and in hypertensive patients. However, prospective studies have shown contrasting results on the independent role of uric acid in the development of kidney disease. In the long-term follow-up of the MRFIT trial Ishani et al., found that higher uric acid levels were associated with the development of end stage renal disease in men, although the strength of this relationship is weakened when individuals with baseline CKD were excluded. This finding was taken to suggest that uric acid may be a marker of diminished kidney function rather than a direct cause of incipient kidney

disease. Nevertheless, strong evidence in favour of the hypothesis that elevated SUA itself contributes to the development of kidney disease has recently been published. In a large study on healthy participants, followed-up prospectively for a median of 7 years, slightly elevated SUA levels independently increased the risk of new-onset kidney disease by 26 %, even after adjusting for several potential confounding factors, including baseline GFR. Similarly, in the ARIC and the CHS trials, conducted on over 13,000 participants with normal kidney function, the fully adjusted model showed a 7 % increased risk for incidental kidney disease associated with each 1 mg/dL increase in baseline SUA levels. Interestingly, baseline SUA levels predicted the development of micro- or macroalbuminuria in patients with type 1 diabetes, in healthy Korean men and in a community based Taiwanese cohort. Moreover, elevated SUA levels have also been found to independently predict graft failure in transplant patients. More recently, in a large Italian cohort of type 2 diabetic patients with hypertension and normal renal function at baseline, it has been demonstrated that increased uric acid values predict the development of CKD stage 3 or higher, independent of several clinical variables (3). In conclusion, clinical and experimental evidence supports an independent role for increased uric acid levels in the development and progression of renal damage. Preliminary studies have suggested that pharmacologic reduction of uric acid might be associated to renal and cardiovascular protection, especially in high risk subgroups. Larger, well conducted studies are clearly needed to verify the hypothesis that mild hyperuricemia may be a target for treatment in patients with CKD.

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SESSION III – URIC ACID, PREGNANCY AND CARDIO-RENAL DISEASE

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Pre-eclampsia is a clinical syndrome defined as the new onset of hypertension and proteinuria during the second half of pregnancy. It affects approximately 2-8% of all pregnancies and is associated with several complications. Pre-eclampsia is a leading cause of maternal mortality, especially in developing countries. In developed countries, pre-eclampsia is an important cause of premature delivery because the only known remedy is delivery of the placenta.

The diagnosis of pre-eclampsia is clinical requiring blood pressure \geq 140/90 mmHg on two occasions combined with significant proteinuria ($>$ 300 mg/24h or albumin-to-creatinine ratio in a spot urine sample \geq 30 mg/mmol).

Hyperuricemia, which is more likely to be present in women with pre-eclampsia than in normotensive pregnant women, has been used as a diagnostic aid and to predict adverse outcomes in pre-eclampsia, but its predictive value is generally modest.

In normal pregnancy, serum uric acid concentrations decrease as a result of pregnancy-induced volume expansion, increase in renal blood flow and glomerular filtration rate, and the uricosuric action of estrogen. By mid-pregnancy, serum uric acid concentrations are usually in the 3–4 mg/dl range (180–240 μ mol/l). They then slowly increase reaching 4-5 mg/dl (240–300 μ mol/l) by term.

In patients with pre-eclampsia, serum uric acid concentrations are relatively increased compared with normal pregnancy. The primary mechanism for the increased serum uric acid in pre-eclampsia is a

reduction in renal excretion of urate, which is probably mediated by the system vasoconstriction, reduction in renal blood flow and decrease in glomerular filtration rate that accompany this disease. There is also evidence for increased generation of uric acid from the ischemic placenta.

There are a number of epidemiological features that link uric acid to pre-eclampsia.

- 1.** Individuals at risk for developing pre-eclampsia often have high serum uric acid before pregnancy (e.g., obesity, black race, insulin resistance, and essential hypertension are predisposing factors for the development of pre-eclampsia).
- 2.** In patients destined to develop pre-eclampsia, one of the earliest biochemical changes is a decrease in renal urate excretion, which can be detected as early as the first trimester (13 weeks). Serum uric acid subsequently increases; by 20–28 weeks, there is a tendency for greater uric acid concentrations in individuals who will develop pre-eclampsia than those who will not. However, because of overlapping values, uric acid concentrations were found to be minimally predictive of the development of pre-eclampsia in one study, and not predictive in others.
- 3.** Serum uric acid is increased in the individual once pre-eclampsia has developed. The degree of the increase has been correlated with the severity of the maternal syndrome including the renal biopsy findings. Uric acid concentrations are the highest in those with eclampsia followed by pre-eclampsia, pre-eclampsia complicating pre-existing hypertension, gestational hypertension, and normal pregnancy. However, because of the significant overlap in uric acid values among the hypertensive groups, uric acid was not clinically useful in distinguishing pre-eclampsia from gestational hypertension.
- 4.** A number of studies have also reported that serum uric acid can predict fetal outcome in individuals with pre-eclampsia. Several groups have reported that the ability of uric acid to predict fetal outcome is best when it is measured before 35 weeks, although most studies still show a significant inverse relationship between uric acid and birth weight in pre-eclamptic individuals at the time of delivery.

5. Serum uric acid is intricately linked to the pre-eclamptic syndrome. Although serum uric acid may be clinically useful as a predictor for the development of pre-eclampsia, it is generally increased in these women once they manifest the disease, and the degree of increase thus correlates with maternal and fetal risk, particularly when measured early in the course of severe disease. These studies thereby raise the possibility that increased uric acid concentrations might contribute to the pathogenesis of the clinical syndrome.

There has been only one study in which allopurinol was randomly administered to individuals with pre-eclampsia. Allopurinol (200 mg) with vitamins E and C or placebo were given to patients with established pre-eclampsia beginning 25 weeks of pregnancy. The allopurinol group had a longer period before delivery but there were no differences in maternal complications and fetal outcome. However, in this study, uric acid concentrations during allopurinol treatment were still greater than 5 mg/dl. The study does not adequately address the issue whether decreasing uric acid concentrations to values associated with normal pregnancy can prevent or treat the pre-eclamptic condition.

A study from Magee-Womens Research Institute in Pittsburgh, USA, found uric acid as important as proteinuria in identifying fetal risk in women with gestational hypertension. Similar results were obtained by a retrospective cohort study by Hawkins et al. showing that hyperuricemia in hypertensive pregnancy identifies women at increased risk of adverse maternal, and particularly fetal outcome; the latter even in women with gestational hypertension and without any feature of pre-eclampsia.

Healthy pregnant women have marked glomerular hyperfiltration (by 40–60%) in the second half of pregnancy. Contrarily, women with pre-eclampsia have significantly lower GFR. This decrease in GFR coincides with typical histopathological changes in the kidney called glomerular endotheliosis, characterized by fibrin deposition, endothelial swelling and loss of capillary space. While these lesions resolve variably after delivery, characteristic renal changes may persist.

Proteinuria in patients with pre-eclampsia may not only be mediated by classically described endothelial alterations but, also, by podocyte biology

disturbances, including enhanced apoptosis and downregulation of nephrin and other key proteins of the slit diaphragm.

In conclusion, serum uric acid is increased in women with clinically evident pre-eclampsia. However, there is no consensus as to the sensitivity and specificity of hyperuricemia as a prognostic indicator of future pre-eclampsia. On the other hand, there is growing evidence that hyperuricemia in hypertensive pregnancies identifies women at increased risk of adverse maternal and fetal outcome. A worsening of serum uric acid in women with pre-eclampsia and/or HELLP (hemolysis, elevated liver enzymes, and low platelets) is a useful indicator when considering elective delivery.

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SESSION IV – IS DRUG INDUCED HYPERURICEMIA A CARDIOMETABOLIC RISK FACTOR?

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A number of experimental and clinical studies reported that an elevated level of circulating uric acid can favour the development of hypertension, diabetes and the metabolic syndrome as well is combined to an increased incidence of cardiovascular events and/or renal disease (1-4). The underlying mechanism is unknown, but the paradoxical pro-oxidant effects exerted by an elevated concentration of uric acid and/or the ability of hyperuricemia to decrease nitric oxide bioavailability have been suggested to be responsible for the onset of insulin resistance and the metabolic syndrome and, as a consequence, cardiovascular and renal disease (1).

In keeping to this, several epidemiological studies are at least compatible with the underlying hypothesis that hyperuricemia may be an independent risk factor for cardiovascular and renal disease, as well as for an increased cardiovascular mortality (1-5). Although such evidence is supported by those studies, continuing doubt remains as to whether hyperuricemia can actually be considered a causal major cardiovascular risk factor.

In addition to the above, available data suggest that treatment may be beneficial, even in the absence of overt gout, when hyperuricemia accompanies other clinical conditions, such as urate deposition, advanced chronic kidney disease, or cardiovascular risk factors (6). However, conflicting results do not support the generalized treatment of asymptomatic hyperuricemia to reduce cardiovascular risk and/

or to prevent the progression of renal disease. There would seem to be sufficient evidence to warrant clinical trials to determine whether lowering uric acid levels would be of clinical benefit in the prevention or treatment of cardiovascular and renal diseases.

Although a causal linkage between uric acid and cardiovascular disease has not been fully identified, uric acid has the potential to negatively influence metabolic and vascular functions by either its pro-oxidant effects or by decreasing nitric oxide bioavailability, or both. This may explain the complex interrelation among hyperuricemia, endothelial dysfunction, metabolic disturbances, hypertension and cardiorenal disease, also by a common mechanistic point of view (1-2).

In this context, some data indicate that uric acid levels start to favour the onset of the metabolic syndrome since the range of normality, with a cut-off value of 5.0 mg/dL. Under a practical profile, it becomes progressively more important to investigate the possibility of reducing serum uric acid levels in the general population below the level of 5.0 mg/dL. Regardless to the threshold for treatment, hyperuricemia is a very common clinical condition. In the general population, drug-induced hyperuricemia presents an emergent and increasingly prevalent problem. Diuretics are one of the most important causes of secondary hyperuricemia. However, also other drugs – commonly used in cardiovascular prevention – can raise serum uric acid level by an increase of uric acid reabsorption and/or decrease in uric acid secretion. Several drugs may also increase uric acid production. Obviously, also drug-induced hyperuricemia must be considered as a potential favouring agent in the fields of gout, metabolic syndrome and/or cardiorenal disease (7). Thus, it is necessary to improve the awareness of drugs that can induce hyperuricemia. Monitoring and prevention are key elements for reducing the morbidity related to drug-induced hyperuricaemia.

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SESSION IV – IS THE GENETIC APPROACH THE RIGHT SOLUTION?

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Inherited genetic variants explain a significant proportion of the population variance in serum urate levels, and therefore the risk of gout. Thus, in order to understand the molecular processes leading to hyperuricemia and the progression from hyperuricemia to gout identifying and characterising genetic risk variants is a powerful approach and a correct solution. I will describe how genome-wide association signals are being translated into understanding the molecular pathogenesis of hyperuricemia, an essential prerequisite to evaluating the possibility of intervention. The translation includes identifying uncommon and/or population-specific and more penetrant protein-coding variants. I will finish by presenting gene x environment interactions in gout - these interactions also yield important insights into pathophysiology.

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SESSION IV – IS THE GENETIC PROFILE USEFUL FOR CLINICAL PRACTICE?

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In recent years numerous studies have explored the genetic basis of hyperuricaemia, whether genetic risk of hyperuricaemia is associated with cardiovascular risk and whether genetic factors predispose to risk of side effects from urate lowering drugs. This talk will review whether these developments are ready for incorporation into routine clinical practice and highlight areas where further research is needed.

First the genetic factors associated with hyperuricaemia will be discussed, along with studies relating these factors to risk of cardiovascular diseases including hypertension, stroke, and ischaemic heart disease. Next, the risk of allopurinol related side effects will be discussed along with genetic risk factors for allopurinol hypersensitivity.

In recent years several new genetic loci for uric acid levels have been discovered. These fall broadly into 4 main categories; uric acid transporters, genes related to glucose metabolism, genes for transcription factors, and other genes (1). These genes each account for only a small proportion of the variance in serum uric acid levels. The results of clinical studies exploring instrumental genetic variables for uric acid and cardiovascular risk have not always supported a causal association and require thorough consideration. However, some studies do support a causal association for cardiovascular disease where the risk of CV death was increased in people with high genetic risk for hyperuricaemia (2). Finally, if uric acid is a risk factor for cardiovascular disease, then

reduction in levels may improve outcomes. This will involve use of urate lowering drugs such as allopurinol. Allopurinol hypersensitivity is the most feared complication but is thankfully rare. A number of studies in recent years have helped us better understand who is at risk and we may be able to refine the risk benefit ratio through pharmacogenomic approaches (3).

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SESSION IV – IS IT REASONABLE TO CONSIDER A FUNCTIONAL INDEX?

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Patients with gout have an increased risk of cardiovascular disease, which is often attributed to the hyperuricemia.¹ With a prevalence of 20% asymptomatic hyperuricemia is far more prevalent than gout,² and has indeed been associated with an increased risk for hypertension and cardiovascular diseases.³⁻⁵ However, there has been much debate on the causal nature of these associations. Some argue that elevated serum urate is just an innocent bystander in the pathogenesis of hypertension and cardiovascular diseases. From 2001 onwards, experimental studies have however established plausible mechanisms linking urate with the development of hypertension by using rat models.^{6,7} One insight derived from these studies assigns an important role to the generation of free radicals during the production of urate.

In the two terminal steps of urate production, XOR is the sole enzyme responsible for the oxidation of hypoxanthine to xanthine, and the latter to urate. XOR exists in two forms, xanthine dehydrogenase (XDH) and xanthine oxidase (XO), which both occur *in vivo*. Initially, the XOR enzyme exists in XDH form, but when released into the circulation it is converted into XO and circulates to remote sites where it binds to the surface of endothelial cells.⁸⁻¹⁴ Although XDH preferentially reduces nicotinamide adenine dinucleotide (NAD⁺), both forms of the enzyme can also reduce molecular oxygen to form the reactive oxygen species (ROS) superoxide and hydrogen peroxide. Thus, during the production of urate, ROS are formed which may cause oxidative stress. Furthermore, the generated superoxide increases the formation of peroxynitrite, leading to an increase in endothelial NO synthase (eNOS)

uncoupling resulting in even more ROS formation. Next to this, angiotensin II substantially increases endothelial XO activation in cultured endothelial cells, subsequent to NAD(P)H oxidase activation, leading to even more ROS formation and inactivation of the vasodilator NO.¹⁵

So far, epidemiological studies have focused on the association between blood pressure and concentrations of urate in serum or plasma and have ignored the distinction between urate *concentration* and its *production*.⁵ Since the production of urate may contribute, independent of urate concentration, to the pathogenesis of hypertension, the production should be investigated as well. Facing the problem that it is not possible to directly measure urate production in a large population of individuals and the concentration of urate in serum is not an adequate marker for production, proxies for urate production need to be investigated. Three different proxies for urate production were investigated: (i) variants of the XOR gene, (ii) different ratios of the purine metabolites, and (iii) 24-h urinary urate excretion.

First, among 2769 participants of the Flemish Study on Environment, Genes, and Health Outcomes (FLEMENGHO) and European Project on Genes in Hypertension (EPOGH) we genotyped 25 tagging XOR SNPs and measured blood pressure at baseline and last available measurement at follow-up (median 8.8 years). The relation between variants of the XOR gene with changes in pulse pressure and mean arterial pressure over time; and incidence of hypertension, were analysed. Three of 25 tagging XOR single nucleotide polymorphisms (SNPs) were associated with the increase in pulse pressure (rs11904439), mean arterial pressure (rs2043013), or the risk of hypertension (rs148756340 and rs11904439). In normotensive participants (n=2050) the risk of hypertension was 30-70% higher in minor allele carriers of rs148756340 and rs11904439, respectively. With a false discovery rate set at 0.25, the aforementioned associations retained significance. It is of note, serum levels of urate at baseline (n=1949) were not associated with variation in XOR (P-value ≥ 0.05).

Second, among 246 school-age children from the KOALA Birth Cohort Study ratios of the different purine metabolites (precursors of urate), as proxies for XOR activity, were used to examine the cross-sectional

association between urate production and blood pressure. Higher ratios of urate/xanthine and xanthine/hypoxanthine, indicating higher XOR activity, were associated with higher diastolic blood pressure. Furthermore, higher plasma urate concentration was associated with higher diastolic blood pressure. However, no association with systolic blood pressure was found. Third, among 2555 participants of The Maastricht Study the cross-sectional association between 24-h urate excretion in urine, as a proxy for urate production, with the steady and pulsatile blood pressure components and the prevalence of hypertension was investigated. In addition, we investigated whether serum urate was associated with one of these outcomes. After adjustment for traditional hypertension risk factors, serum urate and 24-h urinary urate excretion were both associated with mean arterial pressure and hypertension. The association of both serum and urinary urate with mean arterial pressure remained significant after further adjustment for urinary or serum urate, respectively.

Taken together, these findings suggest that urate production might be associated with elevated blood pressure, in particular with the steady component of blood pressure and hypertension. Regardless of the difference in studied proxies and study populations, our results point towards the same direction. Further research on the validation of the proxies and confirmation of the hypothesis is required before the clinical relevance can be considered.

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SESSION V – AGE-DEPENDENT PREVENTION OF HYPERURICEMIA: THE EARLIER IS THE BETTER?

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Over the last several years, observational studies have indicated that high levels of serum uric acid are associated with the risk of cardiovascular disease. However, the specific role of uric acid levels in cardiovascular risk is not well understood and controversy remains as to whether uric acid is an independent casual factor, a mediator or merely a marker for the development of hypertension and metabolic abnormalities. In the pediatric age the association of uric acid with cardiometabolic risk factors is less known since the data are scarce and they have been analyzed in heterogeneous populations. However, during the pediatric age the role of uric acid in the development of cardiovascular risk factors deserves special attention considering that cardiovascular disease has its roots in the early years of life. This is even more relevant when other conditions such as overweight or obesity are present.

Overweight and obesity in children and adolescents has drastically increased overtime, and they have become a significant public health issue. Obesity is strongly related with cardiometabolic abnormalities, such as insulin resistance, dyslipidemia and high blood pressure, with the subsequent increment of risk for cardiovascular disease. In the presence of these abnormalities elevated uric acid may further add to the burden of risk. Understanding the early stages of this relationship will help in the early identification of subjects at risk.

Among the relevant issues to consider are those factors associated with

the increment of uric acid in early age and the relationship of the uric acid levels with cardiometabolic risk factors even in the first years of life. First, research of our group identified that birth weight, used as a proxy for intrauterine life, was inversely associated with an increment in uric acid levels at five years of age. Uric acid was higher in small for gestational age children than it was in appropriate or large ones. Second, uric acid levels were positively associated with fasting insulin, HOMA index, triglycerides and office blood pressure. An association is shown not only with office systolic blood pressure but also with ambulatory systolic blood pressure during daytime and nighttime. Along with these associations, systolic office, daytime, and nighttime blood pressure, are independent determinants of uric acid in a regression model, even when using specific body mass index z-scores rather than raw height and weight values.

The fact that increased uric acid levels are strongly associated with the degree of clustering of adverse levels of individual cardiometabolic risk factors is interesting data. Therefore, the recognition of serum uric acid must be taken into consideration at the time of assessing risk of overweight and obese children. The clustering of clinical abnormalities characterized by increased waist circumference (or obese by increased body mass index z-score in pediatrics), elevated blood pressure, hypertriglyceridemia, hyperglycemia, and low HDL cholesterol, has been used to define metabolic syndrome, traditionally based on abnormalities in at least three of those factors. Further studies need to assess the mechanistic link between uric acid and the cardiometabolic risk factors.

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SESSION V – THE ROLE OF FRUCTOSE CONSUMPTION AND DIETARY APPROACHES

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There is increasing evidence that dietary fructose results in increased risk for hypertension, cardiovascular disease and progression of chronic kidney disease. Observations from several longitudinal studies demonstrate an association between sugar-sweetened beverage consumption, a common surrogate for fructose intake, and weight gain, type 2 diabetes risk, hypertension, cardiovascular morbidity. Other studies show a decline in glomerular filtration rate in populations with and without chronic kidney disease. The later association is particularly strong in patients with diabetes. As is true of most observational trials, there are many potential confounders and causality cannot be determined. Small scale clinical trials in high fructose feeding demonstrate that in as little as 2 weeks, subjects on very high fructose diet (200gm/d) will have significant increases in serum uric acid and serum triglycerides as well as an increase in systolic and diastolic blood pressure and development of insulin resistance (1). Small fructose intake reduction studies, mean reduction of 60g/d to 12g/d, has shown some reduction in serum uric acid, triglycerides and blood pressure over a 6 week time frame. These beneficial effects persisted for a time after a “normal diet,” around 60g/d was resumed (2). There are 3 main hypotheses for the effects of fructose. The first is in regard to the metabolic differences between glucose and fructose metabolism. Hexokinase, which provides the initial phosphorylation step of glucose metabolism, is subject to product inhibition by both Glucose-6-phosphate and ADP. In contrast, fructokinase is not subject to product inhibition. In conditions of high fructose, hepatocytes, lipocytes or myocytes have unchecked production of fructose-6-phosphate which results in the non-oxidative metabolism of fructose-6 phosphate and

produces triglycerides, as well as resulting in excess ADP which enters the purine disposal pathway and uric acid production. Uric acid in turn has been implicated in increased BP in adolescents and progression of chronic kidney disease (CKD) (3). The second hypothesis is that high fructose intake reduces leptin expression resulting in markedly delayed satiety, weight gain and increases in numerous cardiovascular risk factors (4). Finally, the third proposed mechanism is fructose uptake induces glycogen storage, increased metabolic energy efficiency and a hibernation phenotype. One possible explanation for population tolerance of fructose mediated effects is the high degree of population variability in gastrointestinal absorption (5). As much of 30% of the population has impaired GI fructose uptake resulting in loose stools, rather than metabolic effects, in response to high fructose intake (6). These mechanisms are not mutually exclusive. There are numerous dietary and medicinal compounds, including carotenoids and flavonoids that have been proposed as agents to mitigate the metabolic effects of fructose. There are; however, few human data and no definitive trials of these agents so primary prevention of the deleterious impact of dietary fructose on health remains in the dietary realm. There are several public health barriers to population-wide efforts to reduce fructose, consumption. First is the ubiquity of high fructose corn syrup (HFCS) as an inexpensive sweetener and preservative in prepared foods and beverages. Second is over the last 4 decades sweetener rich foods have become much less expensive compared to fresh fruits, vegetables and meats making fructose reduction expensive and compounding socioeconomic factors in cardiovascular and renal disease risk. Finally, there is considerable public misunderstanding regarding the actual fructose content of many foods making dietary change a protracted and multi-tiered educational endeavor.

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SESSION V – THE MANAGEMENT OF ADDITIONAL RISK FACTORS IN PATIENTS WITH HYPERURICEMIA

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Serum uric acid (SUA) has been shown to be associated with a number of metabolic abnormalities as well as with the development and progression of hypertension and related target organ damage. The metabolic alterations include, for example, diabetes mellitus for which development SUA may have a positive predictive value. This has been recently shown by two meta-analyses which documented that elevated levels of SUA are associated with a significant increased risk of type 2 diabetes mellitus, independently of other risk factors. Other major metabolic abnormalities include overweight, obesity and metabolic syndrome as well. As far as metabolic syndrome is concerned our group has recently examined the association between SUA and metabolic factors in the prospective database of the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. The results have provided evidence that even after adjusting for confounders, a one standard deviation increase of baseline SUA was not associated with an increased risk of new-onset metabolic syndrome, but with new-onset impaired fasting glucose. It was associated with a 29% increased risk of new-onset diabetes mellitus, that was more than twice in the highest as compared with the lowest quartile of baseline SUA. Focusing the analysis on the individuals with age above the median value, SUA increase was significantly associated with an increased risk of new-onset metabolic syndrome, IFG and diabetes mellitus.

These presentation will review the available data on the importance of SUA in determining associated clinical conditions, including metabolic disarray

and hypertension. It will also examine the therapeutic interventions needed to correct the above mentioned alteration when SUA levels are above the normal range.

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SESSION V – IS THE DETERMINATION OF SERUM URIC ACID ENOUGH?

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During the last few decades several epidemiological studies have reported a relation between serum uric acid levels and traditional cardiovascular risk factors, including hypertension, metabolic syndrome and diabetes mellitus, suggesting a possible pathophysiologic link between these conditions (1,2). In humans, hyperuricaemia is associated with an increased risk of incident hypertension and other components of the metabolic syndrome as well (1,3,4). In addition, epidemiological data support a strong association between gout, hyperuricemia and cardiovascular diseases (1-4). The relationship between serum uric acid levels and cardiovascular events is also evident for moderately increased levels of uric acid or for values corresponding to the upper limit of the actual normal range (1,2). These evidence support the hypothesis that uric acid might play a pathophysiological role in many cardio-nephro-metabolic disorders. This involvement seems to be independent on the deposition of monosodium urate crystals, since it is evident also for serum uric acid concentrations below the saturation point for monosodium urate (1,2,3). According to these findings it has been proposed to carefully reconsider the concept of “asymptomaticity” for chronic hyperuricemia and to consequently revise the normal range of serum uric acid levels. A threshold value for serum uric acid < 6.0 mg/dL (< 360 μ mol/L) should reasonably be considered for all subjects (1). This threshold value seems to better identify subjects at increased risk for developing the entire spectrum of clinical condition related to uric acid metabolism, including subclinical deposition of monosodium urate and cardio-nephro-metabolic disorders.

However, evidence from mendelian randomization studies demonstrated that the simple determination of serum uric levels could be not enough to discriminate the cardio-nephro-metabolic risk associated with serum uric acid levels (5). Indeed, serum urate levels increase due to the genetic score is not associated with type 2 diabetes mellitus, coronary heart disease, ischemic stroke or heart failure. These results are in contrast with previous prospective studies that did observe increased risks of these cardiometabolic diseases for an equivalent increase in circulating urate levels (1-4). However, increase in serum urate levels due to the genetic score is associated with increased risk of gout, which is directionally consistent with previous observations. From a pathophysiological point of view these data suggest that while increased circulating levels of uric acid, leading to monosodium urate crystals formation, represent the main determinant of gout, the pathogenetic link between uric acid metabolism and cardio-nephro-metabolic disorders is likely more complex. In this regard, it should be considered that uric acid is excreted by the kidney and therefore is a marker of renal function which is also strongly associated with cardiovascular outcome. In this regard, while some interesting evidence demonstrated that uric acid increases blood in adolescents and that this effect can be mitigated by urate-lowering therapy, independently on the use of a xanthine oxidase inhibitor or a uricosuric agent (6), other evidence demonstrate that the reduction of uric acid levels is associated with an improvement of endothelial function in patients treated with a xanthine oxidase inhibitor but not in those receiving a uricosuric treatment (7). Taken together this finding suggest that also the degree of activity of xanthine oxidase should be considered to better clarify the relationship between serum uric levels and cardiovascular risk (8). In this regard, variation in uric acid production, as captured by genetic variation in xanthine oxidase, might be a predictor of changes in blood pressure and in the risk of hypertension (9). Several small and medium sized studies have examined the effect of pharmacological xanthine oxidase inhibition on cardiovascular function in a variety of patient populations. However, there are theoretical reasons why xanthine oxidase inhibition could improve, worsen, or have no effect on cardiovascular outcomes according to the degree of xanthine oxidase

activity. Indeed, it has been recently demonstrated that xanthine oxidase activity is closely associated with poor clinical outcomes in patients with congestive heart failure after adjusting for confounding risk factors (10). Interestingly, the prevalence rates of high and low xanthine oxidase activity activities increased with advancing NYHA functional class and there is a U-shape relationship between xanthine oxidase activity and the cardiac event rate in patients with heart failure. As a consequence, the indication for a xanthine oxidase inhibitor could be different in different patients for the same NYHA functional class according to the degree of xanthine oxidase activity. These findings suggest that measuring xanthine oxidase activity could help identify high-risk patients and xanthine oxidase inhibitors may be a useful therapeutic target for cardiovascular prevention for most but not for all hyperuricemic subjects.

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SESSION VI – SGLT-2 INHIBITORS AND CONTROL OF URIC ACID: MECHANISM AND POTENTIAL ADVANTAGES

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The sodium/glucose cotransporter (SGLT) 2 inhibitors represent a new drug class for the treatment of type 2 diabetes with a great potential. Studies like EMPA-REG Outcome for empagliflozin and CANVAS for canagliflozin have documented clinical benefits with these drugs versus placebo in patients with type 2 diabetes and a previous coronary event. This was especially noticed for the reduction of cardiovascular mortality and congestive heart failure. In the near future, another similar study (DECLARE) will report on the efficacy of dapagliflozin versus placebo in high risk patients with type 2 diabetes. This will substantially contribute to the evidence-base for these drugs that are in general well tolerated. Side effects include genito-urinary infections and in rare cases also normoglycaemic ketoacidosis.

The clinical effects on glycaemic control and the vascular system of SGLT-2 inhibitors are mediated by increased glucosuria, but also a diuretic effect with blood pressure lowering properties contributes to the reduced cardiovascular risk. Regarding the regulation and renal excretion of serum uric acid (SUA), it has been shown that this excretion is increased by use of SGLT2-inhibiting drugs [1]. For example, in a study of 26 weeks, canagliflozin treatment decreased serum uric acid in patients with type 2 diabetes, including those with baseline hyperuricaemia [2]. In a recent meta-analysis of randomized studies, the effects on uric acid was investigated. From the meta-analysis it was revealed that in subgroup analyses, greater reductions could be observed during the course of early diabetes but the SUA-lowering effect was abolished in patients with chronic kidney disease (eGFR <60 mL/min per 1.73 m²). The effect of SGLT-

2 inhibitors on SUA reduction suggests that this class of drugs might be beneficial for diabetic patients with hyperuricaemia [3]. These effects on SUA could play a role within the overall metabolic effect profile of SGLT-2 inhibitors, now documented not only for cardiovascular protection but also renal protection. This could imply that the increased excretion of SUA could be linked to improved renal function, probably also related to beneficial hemodynamic changes in renal glomeruli. Still more studies are needed to better understand if both the secretion and excretion of SUA are affected by SGLT-2 inhibitor treatment to a similar degree, and whether this plays a more causal role for protection or is just a marker of other processes. Background factors such as insulin resistance, chronic inflammation and oxidative stress should also be taken into account when studying the interplay between SGLT-2 inhibition, SUA dynamics and clinical outcomes.

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SESSION VI – URATE LOWERING DRUGS AND PREVENTION OF CARDIOMETABOLIC DISEASE: THE EVIDENCE

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There has been a historical link between urate levels and the development of cardiometabolic disease. However the evidence for benefit using urate lowering agents in pre-existing conditions such as heart failure is controversial with similar numbers of studies both showing benefits, no effect or detriment. In the specific area of prevention of cardiometabolic disease, data has largely been observational and there is a significant need for large clinical trials to address the issue of the role of urate lowering in primary prevention. Key considerations that remain unresolved include the exact phenotype of cohorts that would benefit from urate lowering, the level of urate that should trigger the institution of therapy and indeed the exact mechanism by which urate lowering exerts its beneficial effect seen in smaller mechanistic clinical trials.

There have been a number of primary prevention cohorts studied and not all have demonstrated benefit. The cohorts that have thus far demonstrated benefit are those with hyperuricemia, established cardiovascular diseases and therefore inflammation and oxidative stress. Urate is a known physiological antioxidant and is indeed the most abundant aqueous antioxidant present in humans. It switches from an antioxidant to pro-oxidant entity under the influence of certain well described milieu such as ischemia and inflammation. Xanthine oxidase is also, unlike NADPH oxidase, expressed constitutively at a low level and up-regulated significantly during periods of ischemia and inflammation.

The talk will focus on the evidence in prevention of cardiometabolic disease for the most common urate lowering agents in clinical practice today: uricosuric drugs such as benzobromarone and probenecid and xanthine oxidase inhibitors such as allopurinol and febuxostat. Other agents such as rasburicase and pegloticase are mainly used in specialist situations such as chemotherapy induced purine breakdown and severe acute resistant hyperuricemia and therefore will not be discussed here.



SESSION VI – RECENT EVIDENCE IN CARDIORENAL PROTECTION WITH URATE LOWERING TREATMENT

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Hyperuricaemia, an abnormally high serum uric acid (SUA) level, is the cause of gout and is associated with arthritis and tophus. Previous studies revealed that hyperuricaemia might contribute to the development and progression of cardiovascular and renal diseases and/or mortality. While these studies have suggested that SUA is a powerful risk marker for cardiovascular disease (CVD) and chronic kidney disease (CKD), whether it might also acquire the role of a risk factor for the same diseases in patients with and without gout or previous CVD remains uncertain. Clinical randomised trials using SUA lowering drugs could answer to this important question.

Febuxostat is a nonpurine xanthine oxidoreductase inhibitor (XOI) that has a more potent serum uric acid–lowering action compared with allopurinol. However, the superiority of the XOI for better cardiovascular outcomes is controversial as the clinical trials testing its efficacy compared to placebo and allopurinol in patients with gout showed a tendency to a greater rate of major cardiovascular events in the febuxostat than the allopurinol group. Recently, three major randomised clinical trials reported on the cardiovascular and renal safety of febuxostat: the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial, the Febuxostat for cerebral and cardiorenovascular events prevention study (FREED) and the Febuxostat Versus Placebo Randomized Controlled Trial Regarding Reduced Renal Function in Patients With Hyperuricemia Complicated by Chronic Kidney Disease Stage 3 (FEATHER). Interestingly, while the primary outcome of the first two trials was composite and mainly focused on the risk of cardiovascular events, they reported somewhat conflicting findings.

Similarly, some differences can be observed between the results reported in the FEATHER and the FREED trial.

The CARES trial was conducted between 2010 and 2017 under the pressure of the US Food and Drug Administration to determine whether febuxostat was noninferior to allopurinol on major cardiovascular events in patients with gout and cardiovascular disease. It was a very large, multicenter, double-blind, non-inferiority RCT of people with gout and established CV disease, comparing febuxostat to allopurinol. The primary endpoint was a composite of major adverse CV events (MACE), consisting of a composite of nonfatal myocardial infarction, nonfatal stroke, urgent revascularisation for unstable angina, and death because of cardiovascular causes. A non-inferiority upper margin of 1.3 was used by the investigators to determine the trial sample size. While febuxostat resulted in a greater reduction of SUA than allopurinol, the overall rates of MACE with febuxostat were comparable to those of allopurinol, but cardiovascular death and deaths from any cause were higher on febuxostat.

In turn, the FREED trial showed that lowering SUA levels with febuxostat might result in cardiovascular benefits. This was a multicenter, prospective, randomised open-label, blinded endpoint study, where a total of 1070 elderly patients with hyperuricaemia at risk for cerebral, cardiovascular or renal disease (defined by the presence of hypertension, type 2 diabetes, renal disease or history of cerebral or cardiovascular disease) were randomised to febuxostat and non-febuxostat groups and were observed for 36 months. Death due to cerebral or cardiorenal vascular disease, new or recurring cerebrovascular disease, new or recurring non-fatal coronary artery disease, cardiac failure requiring hospitalisation, arteriosclerotic disease requiring treatment, renal impairment, new atrial fibrillation were defined as the primary composite endpoint. Its results have been recently reported at the European Society of Cardiology Congress 2018. Again, febuxostat resulted in a greater reduction of SUA levels than in the non-febuxostat group but, in this trial, the composite event rate was significantly lower in the febuxostat group than in non-febuxostat treatment, mainly due to a reduction in the risk of renal impairment, recorded in the febuxostat group than in non-febuxostat treatment.

While the FREED trial suggests a potential positive effect of SUA lowering treatment on renal function, the results of the FEATHER trial seems not to confirm this evidence. The FEATHER trial was a randomised, double-blind, placebo-controlled trial that enrolled 443 patients with stage 3 CKD and asymptomatic hyperuricemia, assigned to febuxostat and placebo. In contrast with the FREED trial, the use of urate-lowering agents was not permitted in the placebo group of the FEATHER trial. Patients were monitored for 108 weeks after study onset and the primary end point was the slope (in mL/min/1.73 m² per year) of estimated glomerular filtration rate (eGFR). Secondary end points included changes in eGFRs and SUA levels at 24, 48, 72, and 108 weeks of follow-up and the event of doubling of serum creatinine level or initiation of dialysis therapy. Compared to placebo, febuxostat did not mitigate the decline in kidney function among patients with stage 3 CKD and asymptomatic hyperuricemia. In subgroup analyses, the lack of differences between groups was mainly due to the subjects with more severe impairment of renal function at baseline, expressed as both a lower eGFR or the presence of proteinuria. While the trial was not planned to address other research questions, it is important to notice that subjects in the febuxostat group did not have an increase of cardiovascular or cerebrovascular-related adverse events or serious adverse events. Results of the CARES, FREED and FEATHER trials were anxiously expected. Disappointingly, they confirmed that febuxostat has a more powerful hypouricemic effect but did not contribute to clarify the nature of the association of SUA with cardiovascular and renal disease. A careful assessment of the results, taking into account differences in the study design, the population targeted, and the potential limitations of each trial might provide, however, important information that could be used in the future to address more effectively these unresolved questions.



SESSION VI – IS THERE ANY “J-SHAPED” CURVE FOR SERUM URIC ACID?

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An accumulating body of evidence has linked elevations in serum uric acid with increased total and cardiovascular mortality (1-5). These associations have lent credence to the argument that elevations in uric acid beyond specific thresholds are detrimental to health and underscore evidence from experimental models of hyperuricaemia which demonstrate biological mechanisms of injury (6).

However, the relationship between serum uric acid and survival does not always follow a linear association and conversely some studies have clearly revealed that low levels of uric acid also correlate with higher mortality (7-8). The presence of a U-shaped or J-shaped association of serum uric acid with mortality has cast doubts on the nature of uric acid and its consideration as a true risk factor for mortality. Debate has re-ignited on how to classify uric acid, optimal threshold values for intervention (beyond treatment of gout), and whether low levels of uric acid are indeed detrimental to health and should be avoided. The contribution of confounding from malnutrition, unmeasured comorbidity, and disease severity may partly explain the elevated mortality risk among those with low serum uric acid levels (8).

This presentation will summarise mechanistic pathways through which uric acid may mediate adverse outcomes and mortality, interrogate findings from observational studies that have shown divergent results on uric acid-mortality relationships, and provide new insights from recent clinical trials (9-10). In doing so, we should be able to determine the roadmap for further

studies that will help clarify the nature of the relationship between uric acid and mortality and better define optimal values for health.

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SESSION VI – HYPERURICEMIA AND CARDIOMETABOLIC DISEASE: THE ROLE OF RENAL IMPAIRMENT

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The primary role of cardio-metabolic diseases among the causes of death in the industrialized world is well defined by several epidemiological studies showing a close interaction between metabolic risk factors and cardiovascular diseases. Elevated levels of serum uric acid (SUA) are largely represented in the general population where they can be directly responsible for the development of gout and cardio-metabolic diseases. The hypothesis linking uric acid with cardio-metabolic disease is strongly supported by both experimental and clinical data. In particular, the presence of elevated levels of serum uric acid are associated with an increase in blood pressure and metabolic syndrome that can be demonstrated also in the adolescent population where they contribute to the increased rate of hypertension and diabetes later in life. The relationship between hyperuricemia, hypertension and metabolic abnormalities has been confirmed by several observational studies and after adjustment for almost all of the confounding risk factors. In particular, the results of NHANES, MRFIT, Brisighella Heart Study, PAMELA studies clearly support a pathogenetic role of elevated SUA in patients with initially normal blood pressure or normal glucose levels through a negative impact of elevated SUA on insulin resistance that has been confirmed more recently in humans. The mechanism involved in the cardio-metabolic abnormalities could be an increased level of oxidative stress that can be observed at the circulatory/tissue and intracellular levels and involving an activation of the redox systems (NADPH, XOR) leading to an impaired insulin sensitivity. Conversely, most of the negative effects of SUA on blood pressure and metabolic profile can be prevented by the use of xantine-oxidase inhibitors leading to a decrease in serum uric acid and a prevention of oxidative stress.

The role of renal function in the development of cardiometabolic diseases associated with hyperuricemia, can be twofold. Basically, a decline in renal function can increase the plasma levels of uric acid and contribute to the negative effects of hyperuricemia and to the development of gout and related cardiovascular disease. On the other hand, the oxidative stress associated with uric acid production can promote a negative intrarenal vascular response leading to hypertension and salt sensitivity. However, the role of renal function could be also an indirect marker of the underlying mechanisms responsible for elevated uric acid levels. The presence of hyperuricemia with preserved (or more preserved) renal function is probably a measure of the overproduction of SUA by xantino-oxidase and could be associated with a higher risk of cardiometabolic diseases. An inverse relationship between elevated levels of SUA and CV disease has been described in some typical insulin resistant conditions as heart failure and renal failure and confirmed in hypertensive population where the presence of LDL-oxidation and arterial stiffness is inversely related to renal disease. A recent study published in patients with renal disease has reported a better blood pressure control by febuxostat in patients with better preserved renal function. This suggests the possibility that the concomitant presence of elevated levels of uric acid and normal renal function might be considered a potential index for the identification of patient prone to cardiometabolic disease that should be managed more aggressively in terms of cardiovascular prevention and urate lowering treatment.

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SESSION VI – THE TREATMENT OF ASYMPTOMATIC HYPERURICAEMIA: WHO, WHEN AND WHY?

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The evidence is fairly consistent that uric acid is associated with increased risk. This evidence is apparent in many different populations of patients, including patients who have had cardiovascular events such as myocardial infarction. Uric acid is also associated with increased risk of death as well as the development of atrial fibrillation (AF), the progression of diabetic nephropathy and the metabolic syndrome

The key question is whether uric acid is causal in these risks or is an innocent bystander. This is a constant question in much of clinical research and can be very difficult to answer, except by large, randomised and expensive clinical trials where one group takes a drug which lowers uric acid levels. Short of such expensive clinical trials, a new way to gain insight as to whether uric acid is causal or not is to investigate observational data by doing a Mendelian randomisation study whereby genetic variants which alter uric acid are studied to see if they are linked to increased or decreased risk (or no risk). Although Mendelian randomisation studies are much better than purely observational data on its own, they are not nearly as definitive as a large randomised controlled trial would be (nor are they as expensive!)

Therefore, are there any clinical diseases where randomised clinical trials of reducing uric acid have shown benefit? One situation is Angina Pectoris or Myocardial Ischaemia where allopurinol has been shown to reduce the symptom of chest pain (as well as signs of ischaemia on the ECG)

during exercise (Noman et al 2010). Indeed the latest European Society of Cardiology guidelines suggest allopurinol as another option to reduce symptoms in Angina Pectoris, after more conventional antianginal drugs have been tried. However the therapy of angina is complex in that the treatments which reduce symptoms (nitrates, calcium antagonists) are almost completely different from those treatments which prolong survival (statins, aspirin): beta blockers are the only treatment which improve both symptoms and survival in angina pectoris. In fact there is an ongoing study (the ALLHEART study) to see if allopurinol reduces cardiovascular events and prolongs survival in patients with myocardial ischaemia (MacKenzie et al 2016). However we do not need to wait for the ALLHEART study results for allopurinol to be used to treat SYMPTOMS in angina pectoris, since there is this major disconnect between drugs which improve symptoms as opposed to those which improve survival in angina pectoris.

What about other clinical situations? Can we yet recommend urate lowering therapy to reduce high uric acid levels in asymptomatic patients? Certainly there is not yet enough data from randomised clinical trials for any guidelines to recommend such an approach. However a lower threshold of evidence is often applied in practice in treating family members (or even oneself). This may also be true in practice in difficult patients where standard treatment is not solving the clinical problem. Certainly if I had had a myocardial infarction and hyperuricaemia or diabetic microalbuminuria and hyperuricaemia, I may well use urate lowering therapy (ULT) even if I could not point to a definitive RCT that shows that such an approach would be beneficial.

In summary, these questions will be partially answered in the future by Mendelian randomisation studies but what we need to convince guidelines are randomised controlled trials of ULT therapy in high risk individuals in order to provide definitive answers.

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SESSION VI – THE NON-PHARMACOLOGICAL APPROACH TO HYPERURICEMIA. SOLUTIONS BEYOND DIET

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Hyperuricemia is highly prevalent and especially prevalent in subjects with metabolic, cardiovascular and renal diseases. In addition, there are also special populations in which hyperuricemia might have a causal role for the developing of hypertension; such is the case of children, adolescents, and pregnant women. Uricemia is generally regulated by uric acid (UA) excretion which is accomplished by kidney handling (2 thirds of the excretion) and intestinal microbiome uricolysis (one-third of the excretion). However, in chronic kidney disease, excretion mainly relies on gut uricolysis. Current therapy for lowering serum UA includes lifestyle changes usually with low adherence and withdrawal, and drugs that may produce undesired secondary effects. Therefore, there is a need for better and safer therapies for lowering serum UA concentrations.

Probiotics supplementation has proven to provide therapeutic benefit in several pathological conditions. Individual strains of probiotics may have multiple mechanisms of action, one of them is the production of specific enzymes that help with the clearance of potentially toxic substances. Therefore, we designed a preclinical study to evaluate the potential of two probiotic supplements to reduce systemic uric acid concentrations. We used the rodent model of uricase inhibition with oxonic acid to produce hyperuricemia in rats. Probiotics formulas contained *L. acidophilus* KB27, *L. rhamnosus* KB79, strains selected for its strong uricolytic activity. Both strains of probiotics are generally recognized as safe (GRAS certified). In addition, the prebiotics xylooligosaccharide (Formula 1) and

xylooligosaccharide plus curcumin (Formula 2) were selected for enhancing probiotics effects. Secondary objectives were to assess whether the hypouricemic effect related to a therapeutic benefit on the hyperuricemia-induced renal damage and hypertension.

Oxonic acid-induced hyperuricemia produced hypertension and renal functional and structural changes, along with modest changes in the overall composition of fecal microbiota. Both probiotic-containing diets prevented HU, elevated UA urinary excretion and intrarenal UA accumulation induced by oxonic acid. The hypouricemic effect conferred by probiotic supplementation also prevented the renal changes and hypertension caused by hyperuricemia. However, probiotic treatment did not restore the fecal microbiota. In conclusion, we demonstrated for the first time the ability of probiotics containing uricolytic bacteria to lower serum uric acid in hyperuricemic animals with beneficial consequences on blood pressure and renal disease. As probiotics supplements are innocuous for human health, we recommend clinical studies to test if probiotic supplements could benefit hyperuricemic individuals.

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SESSION VI – HOW TO INVESTIGATE THE CARDIOVASCULAR AND RENAL EFFECTS OF URATE-LOWERING DRUGS?

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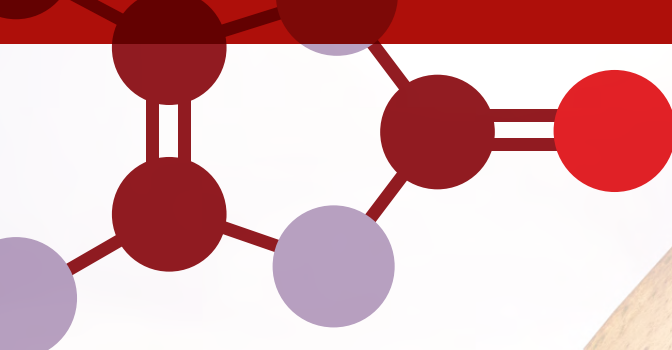
Serum urate has been shown to be an independent predictor of chronic kidney disease (CKD) and renal function decline in patients with overt CKD [1]. Although the underlying mechanism for this has been has not been fully elucidated preclinical models of CKD showed that hyperuricemia per se had a detrimental effect on the progression of existing renal disease [2]. Small prospective clinical trials have shown that lowering blood urate levels by a xanthine-oxidase inhibitor slows down progression of CKD using allopurinol [3] as well as febuxostat [4]. Although these findings could be confirmed in a meta-analysis [5] the so far largest prospective randomized trial in CKD 3 patients showed that compared to placebo, febuxostat did not mitigate the decline in kidney function and asymptomatic hyperuricemia [6], although non-proteinuric patients seemed to benefit on subgroup analysis. Further support for the potential nephroprotective role of the xanthine oxidase inhibitor febuxostat comes from the FREED trial I which ta composite renal endpoint was reduced over a three year period [7]. Despite the fact that there is a rationale to lower urate levels in CKD, the number of patients receiving urate lowering therapy (ULT) in CKD is low. In a large cohort of patients it was shown that both, gout and hyperuricemia are undertreated [8]. One reason for this might be the fact that the classical xanthine-oxidase inhibitor allopurinol exhibits an accumulation of its main metabolite, i.e. oxipurinol, in the setting of reduced eGFR [9]. Therefore, a dose reduction that parallels the decline in glomerular filtration rate is recommended by the manufacturer as well as the current guidelines [10]. In a large US population it has however been shown that physicians fail to

adapt the dose of allopurinol to the different stages of CKD [11]. But also other drugs used to lower urate might interfere with and depend on renal function, especially uricosuric drugs. Further, co-medication such as with thiazide diuretics and loop diuretics, both frequently used in the treatment of cardiovascular disease, can induce hyperuricemia. As even low doses (40 mg/d) of febuxostat had been shown to successfully lower urate levels well below 6 mg/dl this approach seems to be appealing in the treatment of both, renal and cardiovascular diseases.

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