Do We Need Another Look at Serum Uric Acid in Cardiovascular Disease? Serum Uric Acid as a Predictor of Outcomes in Acute Myocardial Infarction

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1 Introduction

In humans and other higher primates, uric acid (UA) is the end product of purine metabolism generated by oxidation of xanthine catalyzed by xantine oxidase (XO) (EC 1.17.3.2) (Figure 1). In other mammals, UA is further oxidized by uricase (EC 1.7.3.3) to yield highly soluble allantoin, which is then excreted from the body. From the evolutionary standpoint, the reasons for the mutations resulting in a nonfunctioning *uricase* gene (pseudogene) in higher mammals are still unclear. In contrast to allantoin, uric acid is poorly hydrosoluble (water solubility of its salts, the urates, is slightly higher) and when its serum concentrations exceed the theoretical limit of solubility (around 415 μmol/L, or 7 mg/dL), urate crystals are likely to be formed. Approximately two thirds of the daily UA turnover is eliminated by the kidney (glomerular filtration, tubular re-absorption and secretion) and one third *via* the gastrointestinal system.

Xanthine oxidase is an ubiquitous enzyme, distributed in the liver (particularly), gut (particularly), kidney, heart (capillary endothelium primarily, but has been proven in cardiomyocytes, as well), brain, as well as in plasma. Besides the conversion of hypoxanthine to xanthine and xanthine to UA, it has a number of other functions, including hydroxylation of various purines, pterins, aromatic heterocycles and aliphatic and aromatic aldehydes (for a detailed review on XO see Pacher et al., 2006). Serum levels of UA (serum uric acid, SUA) are governed by the rates of its production and elimination, and are susceptible to a variety of nutritional, genetic, pharmacological and morbidity influences (Table 1). Hyperuricemia, a state of overtly high SUA concentration, is typically defined as SUA >360 μmol/L in women and >420 μmol/L in men, whereas values 310-420 μmol/L in men and 250-360 μmol/L in women are conventionally considered as "high-normal".
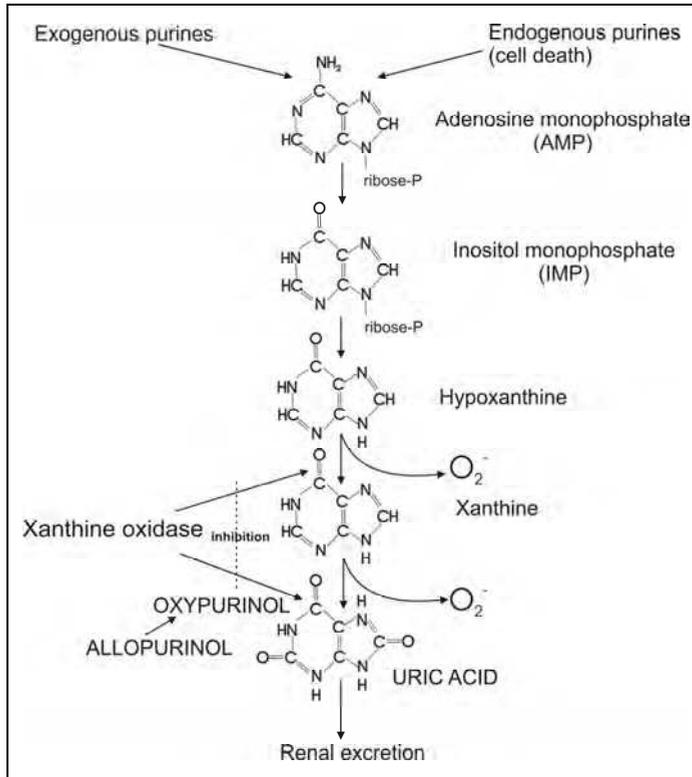
Fig. 1. Metabolism of uric acid.

*Dietary factors: increased purine intake in animal products especially internal organs (liver, kidney, brain, meat extracts), sweetbreads, anchovies, sardines, herring, mackerel, game meats, gravy, high fructose intake, alcohol
*Reduced excretion by diseased kidneys
*Malignancies, polycythemia vera, myelodysplastic syndromes, hemolytic anemias or other conditions with a rapid cell turnover
*Use of diuretics
*Mutations in proteins involved in the urate metabolism, especially xanthine oxidase, urate transporter/channel (UAT), organic anion transporters 1 and 3 (OAT1 and OAT3) and urate transporter 1 (URAT1)

Table 1. The main causes of hyperuricemia (after Lippi et al., 2008)

Ever since the late 19th century, and particularly since the 1950s, the potential role of SUA, specifically, increased SUA in cardiovascular diseases (CVD) has attracted much attention. A plethora of non-clinical, clinical and epidemiological studies have accumulated over the decades that aimed to elucidate molecular and cellular mechanisms of UA and the role of SUA as a diagnostic or a prognostic aid, or as a therapeutic target. Uric acid has a number of molecular effects potentially interesting in respect to CVD. One of the first recognized was

the antioxidant potential of UA – together with ascorbic acid which recycles the UA radicals, it is the most important antioxidant in plasma that effectively scavenges the superoxide anion, hydroxyl radicals and singlet oxygen and may chelate transitional metals. Furthermore, UA blocks the reaction in which peroxynitrite (generated in reactions by which superoxide anion inactivates nitric oxide, NO) attacks and nitrosylates tyrosine residues in various proteins. Moreover, UA inhibits degradation of the extracellular superoxide dismutase (SOD3), which then is able to convert superoxide anion into hydrogen peroxide, and thus prevent NO inactivation (by the superoxide anion). Based on the knowledge about the role of oxidative stress in various aspects of CVD (e.g., endothelial function, myocardial function), it has been suggested that the loss of uricase activity in humans should be viewed as an "evolutionary benefit", protective of the cardiovascular system. Indeed, there is solid evidence that a transient rise in SUA reduces markers of oxidative stress, which then correlates well with improvements in some of the indices of cardiovascular function. For example, it has been rather well elaborated that the cardiovascular benefit of moderate wine drinking (with food) is largely due to an acute and transient wine-induced rise in SUA that counter-acts the food-induced oxidative stress. However, prolonged/excessive increase in SUA is clearly associated with cardiovascular risks or "damage" (see below), rather than with a cardiovascular benefit. Although we are still far from full understanding of molecular/cellular mechanisms of UA, the knowledge is extensive and some effects have been well documented and provide a sound mechanistic rationale. As most of the other antioxidants, under certain conditions (e.g., high concentrations, low pH, like in hypoxic tissues, low levels of other antioxidants) UA may promote oxidative stress. For example, it depletes ascorbic acid (used to re-cycle UA radicals), and thus reduces re-cycling of α-tocopherol and, consequently, β-carotene, other potent antioxidants, which, overall, may results in a reduced antioxidant activity. *In vitro*, UA (but not its precursors xanthine and hypoxanthine) exerts a number of effects on vascular smooth muscle cells: enters the cells *via* organic anionic transporters and activates transcriptional factors, like nuclear factor *kappa* B (NF-κB) and activation protein 1 (AP-1); induces the tissue renin-angiotensin-aldosterone system and angitensin II production; induces cell proliferation (via MAPK and Erk1/2 kinases); induces COX2 activity and thromboxane synthesis; induces synthesis of the monocytic chemoatractant protein 1 (MCP-1, *via* p38 MAPK) which is important in the pathogenesis of atherosclerosis; induces production of c-reactive protein (CRP) (*via* p38 MAPK). Uric acid also stimulates the mononuclear cells to production of interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α). Clearly, UA may recruit a whole armamentarium of molecular/cellular "players" that are known to be involved in the pathophysiology of vascular changes underlying CVD. Indeed, it has been repeatedly shown that infusion of UA in humans induces platelet aggregation and endothelial dysfunction with reduced NO production, an effect also seen within the kidneys. However, when discussing the potential role of UA as a "direct pathogen" in CVD, one should also keep in mind that, inherently, SUA levels are a marker of the activity of XO, an enzyme that *per se* has an important role in the oxidant-antioxidant system. While measuring SUA in humans is simple, accurate and cheap, there is no routine method to directly measure XO activity. Xanthine oxidase has been strongly implicated in CVD. The enzyme is expressed in the endothelium, but it is generally thought that XO released from the liver and the gut into the circulation and then bound to the endothelial cell is the important factor. It is in a complex relationship with NO – XO generates superoxide anion (e.g., during xanthine oxidation) that inactivates NO and tonically suppress NO

synthase (NOs), whereas conversely, NO may suppress XO activity and XO is also capable of reducing nitrates and nitrites back to NO. As already mentioned, superoxide-NO reactions and reactions between the superoxide and various nitrosothiols generate peroxynitrite that can inflict oxidative and nitrosative injury to proteins, enzymes, lipids, DNA. There are observations regarding endothelial dysfunction that "shift" the focus from SUA itself to XO – while infusion of UA may induce it, uriocosuric agents, that reduce SUA, have failed to improve endothelial function; on the other hand, XO inhibitors (like allopurinol) improve the disrupted endothelial function even before changes in SUA occur. Therefore, considerations of "elevated SUA" and its role in CVD inevitably subsume its potential direct effector mechanisms, but also those effects of XO which are UA-independent and for which elevated SUA is (just) a marker.

Over the decades, at the clinical and epidemiological level, the "issue" of (S)UA and CVD has been encompassed by a controversy – should the relationship be perceived as a *causative* one, or as a mere *association*? In part, it has been fuelled by the mechanistic knowledge about the direct (possible) deleterious effects of UA and the fact that, at the same time, it might be just a marker of other events (e.g., XO activity). Additional contribution to the controversy comes from the inconsistency of observations (both "negative" and "positive" observations in many settings) and the nature of (some of) the clinical/epidemiological observations. First, SUA has been related not only to CVD or its "endpoint-events", like development of coronary artery disease (CAD) and related mortality, chronic heart failure, acute myocardial infarction or stroke, but also to a number of conditions that *per se* are CVD risk factors, e.g., hypertension, glucose intolerance, insulin resistance, dyslipidemia, obesity, metabolic syndrome, renal failure. Second, some of the studies were conducted in a way that allowed only for detection of associations, which were frequently difficult to interpret. For example, in some cases it was not possible to "isolate" an independent relationship (*association*) (independent of other risk factors) between SUA and the end point, either a direct one (of the type SUA $\Rightarrow$ endpoint) or a mediated one (of the type SUA $\Rightarrow$ other risk factor $\Rightarrow$ endpoint). Furthermore, the interpretation of associations in terms of "causes and consequences" is frequently complexed by the fact that both is possible, e.g., while there is evidence that hyperuricemia may promote renal failure, renal failure inevitably results in hyperuricemia. Generally, in biomedicine, the dilemma about causation vs. association has important practical implications – if a causative relationship is established between variables, then the "cause" clearly is a potential target for an intervention (preventive, therapeutic). It is the opinion of the authors of this text that in the specific case of SUA and CVD, this dilemma might not be as relevant. First, if there is a "marker" that can be determined easily, reproducibly and accurately and at low cost (SUA), that independently, consistently and accurately predicts future events (a reliable predictor), than, irrespective of the nature of its relationship with these "future events", it *per se* is valuable (assessment of risk). One could easily agree that despite all the existing knowledge, there is still space for improvements in risk assessment in CVD. Next, considering the nature of a potential intervention (inhibition of XO, e.g., allopurinol), it seems irrelevant whether UA itself is a cause (acting directly on the endpoint variable, or through "intervening" or "mediation" variables [other risk factors], of both) or just a marker of increased XO activity, which in fact, is the cause (or – both!) – the intervention is likely to yield a benefit. It is far beyond the scope of this text to discuss in detail all the aspects of the complex relationship between SUA and CVD. For this purpose, reader is referred to comprehensive reviews on the topic, some

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of which are listed at the end of this chapter (Johnson at al., 2003, Baker et al., 2005, Duan&Ling 2008, Naquibullah et al., 2007, Lippi et al., 2008, Feig et al., 2008, Doehner et al., 2008, Gagliardi et al., 2009, Bergamini et al., 2009, Kim et al., 2009 and 2010, Wechter et al., 2010). The main points could be summarized as follows:

Hypertension, metabolic syndrome, renal failure and other risk factor for CVD. There is now sufficient evidence to strongly support a claim that increased SUA is an important etiological factor in at least one form of hypertension – early-onset primary hypertension. The sequence of events includes chronic hyperuricemia in mothers that may be transferred to the fetus and result in intrauterine growth retardation and a reduced number of nephrons. The reduced number of nephrons (and renal function), together with environmental and genetic factors, contributes to permanent hyperuricemia that reduces intra-renal NO release, activates the renin-angiotensin system, promotes vascular inflammation and inhibits endothelial cell proliferation, thus leading to a vasoreactive hypertension in the first step, and eventually to a salt-sensitive hypertension (Figure 2).
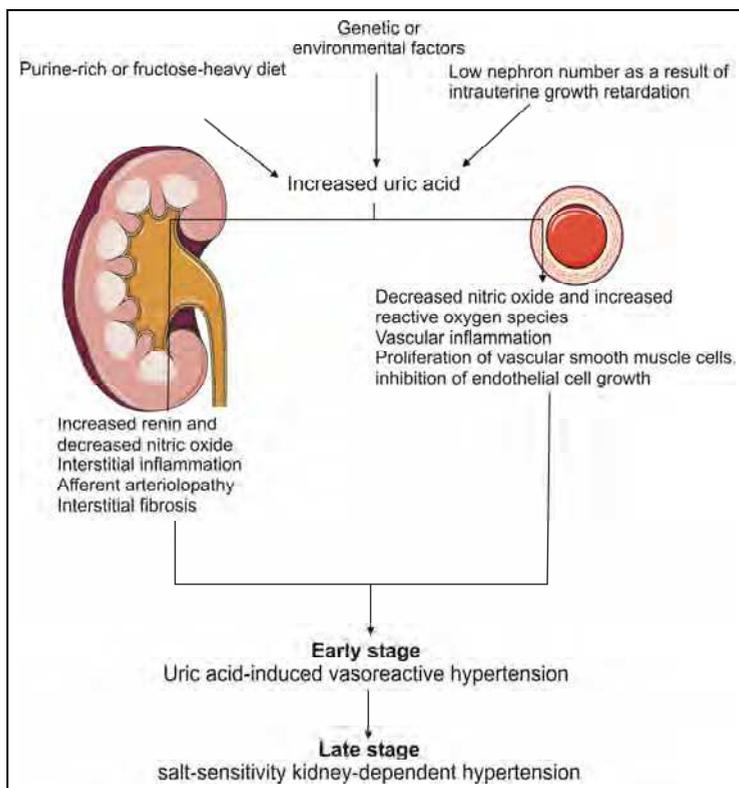

Fig. 2. Development of uric acid-induced hypertension (re-drawn and modified after Feig et al., 2008).

Otherwise, increased SUA has been repeatedly shown associated with hypertension and prehypertension. Moreover, in a number of prospective epidemiological studies in

normotensive subjects, increased SUA has repeatedly consistently predicted development of hypertension independently of other risk factors. The adjusted relative risk depended on the observational period, as well as on qualification of "increased SUA". As reviewed by Feig et al. (Feig et al., 2008), in 6 studies with a total of 17 629 adult subjects, adjusted relative risks of development of hypertension (over 6-21 years) varied between 1.25 and 2.10 for "high vs. low" quartile or quintile of SUA, or for SUA levels >416 or >387 μmol/L in men (vs. lower) and >357 μmol/L in women (vs. lower) (all these cut-off points are lower than the conventional limits of hyperuricemia, see above). In the other 8 studies with a total of 25 500 adult subjects, adjusted relative risks of hypertension (over 4 to 12 years) varied between 1.10 and 1.65 for increase in SUA by one standard deviation or by 60 μmol/L. Increased SUA has been repeatedly found in patients with metabolic syndrome, obese subjects, patients with dyslipidemia or glucose intolerance. In animal models, UA may induce a correlate of human metabolic syndrome. In a sample of a general population in Japan, irrespectively of gender, SUA levels >416 μmol/L in men and >357 μmol/L in women were found to cluster with hypertension, obesity, hypercholesterolemia, hypo-HDL hypercholesterolemia and hypertriglyceridemia (Nagahama et al., 2004).

Stroke. A recent analysis of 16 prospective cohort studies that embraced 238 500 subjects and assessed predictivity of hyperuricemia (different definitions, but generally >380-416 μmol/L irrespective of gender; or >416 μmol/L in men and >360 μmol/L in women) for development of stroke, indicated that in 10/10 studies which reported on stroke incidence, adjusted relative risks (RR) were >1.0. At the same time, adjusted relative risks of stroke-related mortality were >1.0 in 10/11 studies that reported this outcome. The meta-analysis of adjusted RRs (random-effects with practically no heterogeniety) indicated RR of stroke: 1.91 (95% CI 1.06-2.75) in a mixed population; 1.42 (0.94-1.90) in men, 1.42 (1.03-1.80) in women and 1.47 (1.19-1.76) overall (Kim et al., 2009). Relative risks of stroke-related death were: 1.61 (95% CI 1.13-2.09) in a mixed population; 1.20 (1.05-1.35) in men, 1.35 (1.04-1.66) in women and 1.26 (1.12-1.39) overall (Kim et al., 2009).

Chronic heart failure (CHF). Chronic heart failure (CHF) is a typical setting in which the dilemma about UA as a "cause" or a (mere) "marker" is particularly actual (Duan & Ling, 2008, Doehner et al., 2008, Bergamini et al., 2009). Numerous animal models have clearly confirmed the role of reactive oxygen species (ROS) in pathophysiology of the heart failure – there is a clear correlation between increased markers of oxidative stress within the heart and systemically, poorer survival and a number of functional measures of cardiac functions and hemodynamic consequences. The mechanisms of direct deleterious effects of ROS within the heart include alterations of calcium metabolism and propagation of endothelial dysfunction, inflammation and cellular responses resulting in remodeling, and they sum-up with their effects on the kidneys and systemic vasculature. The sources of cardiac ROS are multiple, but there is clear evidence, including humans, of increased cardiac XO activity. It inevitably results in enhanced production of UA, besides the generation of reactive oxygen and nitrogen species. Hence, it seems practically impossible to "separate" the effects of UA *per se* from those of activated XO. Be it as it may, increased SUA in CHF patients is associated with worse functional tests and, clearly, with a worse long-term survival. An analysis in CHF patients showed doubling and tripling of the adjusted relative risk of death (over time) (i.e., "independent effect of SUA") for each 200 μmol/L increase of SUA above the cut-off point of 400 μmol/L. Moreover, the death risk was particularly increased when

SUA >565 µmol/L was combined with a score of 2 or 3 based on the heart failure survival scoring system (Anker et al., 2003). Similarly, a study in acute HF patients demonstrated an increased risk of death in patients with SUA >458 µmol/L as compared to those with SUA <416 µmol/L (adjusted RR=1.45, 95% CI 1.03-2.05) and increase in RR by around 8% (CI 1-15%) for each 60 µmol/L increase in SUA (Alimonda et al., 2009). As reviewed by Pacher et al. (2006) and Bergamini et al. (2009), several randomized trials indicated improvements in cardiac and hemodynamic parameters in CHF patients treated with allopurinol (an XO inhibitor), even with indications of improved survival, but not all trials have been "positive" and uricosuric agents seemingly were not effective.

Coronary heart disease (CAD). The link between SUA and CAD is two-fold. First, regardless of the actual mechanism (etiological factor vs. marker), increased SUA is clearly related to a number of CAD risk factors (hypertension, renal function, obesity, dyslipidemia, metabolic syndrome) and seemingly does independently predict CAD (regardless of whether a "direct" effect or "mediated" through other risk factors). A recent review and meta-analysis embraced 26 prospective cohort studies with 403 000 participants that reported on predictivity of SUA for occurrence of CAD and/or CAD-related mortality (Kim et al., 2010). The effect of SUA was expressed through a contrast of "hyperuricemia" vs "no hyperuricemia" (very different definitions in different studies; cut-offs for men ranged from 321 µmol/L to 458 µmol/L; for women they ranged from 280 µmol/L to 393 µmol/L; and for mixed population from 387 µmol/L to 416 µmol/L) or as the effect of increase in SUA by 60 µmol/L. Based on 9 studies that reported adjusted risks of CAD incidence (adjusted for known CAD risk factors), pooled RRs for CAD incidence for "hyperucemia" vs. "no hyperuricemia" were: 1.04 (95% CI 0.90-1.17) in men; 1.07 (0.82-1.32) in women; 1.32 (0.57-2.07) in mixed populations and 1.09 (1.03-1.16) overall (all random-effects estimates with very low-to-mild heterogeneity). Based on 9 studies that reported adjusted risks of CAD-related mortality (adjusted for known risk factors), pooled RRs for CAD-related mortality for "hyperucemia" vs. "no hyperuricemia" were: 1.09 (95% CI 0.98-1.19) in men; 1.67 (1.30-2.04) in women; and 1.16 (1.01-1.30) overall (all random-effects estimates with very low-to-mild heterogeneity). Based on 4 studies that reported adjusted risks of CAD-related mortality based on increase in SUA by 60 µmol/L, pooled RRs were: 1.10 (95% CI 0.96-1.24) in men; 1.17 (0.97-1.38) in women; 1.10 (1.06-1.14) in mixed population and 1.12 (1.05-1.19) overall (random-effects, low heterogeniety). Second, in animal models as well as in humans, cardiac ischemia-reperfusion injury involves increased ROS generation. The sources of ROS are, likely, multiple (as in the failing heart), but it is hypothesized that activation of XO contributes. The proposed mechanism is summarized in Figure 3: ischemia favors both intracellular accumulation of hypoxanthine and free calcium; the latter activates proteases that convert xanthine dehydrogenase to xanthine oxidase with a consequent generation of superoxide anion and UA. Several randomized trials, but not all, have shown that in patients undergoing elective coronary by-pass surgery allopurinol may reduce arrhythmias, improve cardiac index and cardiac output and reduce mortality (Wechter et al., 2010).

In contrast to the broad attention that it has received in relation to the mentioned cardiovascular disease, until the recent years SUA has practically not been investigated in the setting of the outcomes of the acute myocardial infarction (AMI) or acute coronary syndromes in general. Several studies addressing this issue have been published since 2005 and they are the main objective of this chapter. As in other SUA-CVD settings, the topic deserves some attention: an easily and reproducibly available marker with a consistent
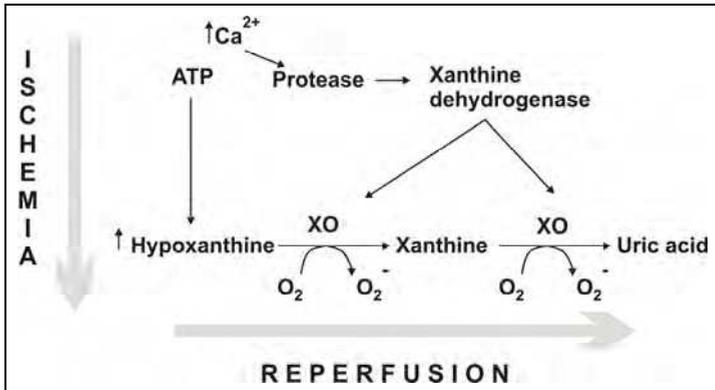
Fig. 3. Proposed effects of ischemia-reperfusion for intracardiac activation of xanthine oxidase (XO) and generation of superoxide anion (O2-) and uric acid (re-drawn and modified after Pacher et al. 2006).

predictive value may well improve risk stratification in AMI patients (and reflect on clinical decisions); considering the mechanisms relating SUA to ischemia-reperfusion (Figure 3) and other relevant intra- and extra-cardiac factors, it seems that, should a SUA-AMI outcome relationship be established, there would be a sound rationale for implementation of an intervention based on XO inhibition, regardless of whether SUA is primarily an effector or a "mere marker".

2. Do serum uric acid levels predict outcomes in acute myocardial infarction patients?

2.1 Chronology and a general description of the relevant studies

Study essentials are summarized in Table 2.

In 2005, Kojima and colleagues (Kojima et al., 2005) published the results of the Japanese Acute Coronary Syndrome Study (JACSS) – a retrospective analysis of a database on acute coronary syndrome patients generated as a result of collaboration of 35 institutions in Japan during 2002 (January – December). Patients (N=1124) were defined as consecutive AMI patients admitted to a hospital within 48 hours since the symptom onset (with SUA determined on admission). No distribution of patients by AMI type was given – whether with (STEMI) or without (NSTEMI) ST elevation. However, 943 (84%) patients underwent immediate reperfusion [predominantly by a percutaneous coronary intervention (PCI) and only sporadically by pharmacological thrombolysis] (Table 2) and could be considered as STEMI patients, whereas the remaining 181 could be considered as NSTEMI patients. Men prevailed (70%) and the mean age was 68 years. Higher on-admission SUA values were independently associated with the male sex, higher body mass index (BMI), higher serum creatinine, higher Killip's class and a history of hypertension and a previous AMI. Patients were classified based on the on-admission SUA quartiles and the analysis focused on a comparison of the outcomes between patients within the 4th quartile [(n= 276, SUA >399 μmol/L, which is higher than the cut-off value for hyperuricemia in women, and is just below the cut-off value of hyperuricemia in men (420 μmol/L)] and those within the 1st

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quartile [n=273, SUA <274 μmol/L, which is within the range of "low-normal SUA" in men, and just above the cut-off value of "low-normal SUA" in women (250 μmol/L)]. The primary outcome of interest was all-cause mortality (survival) during the observational period, which averaged 450 days and the maximum length was 700 days. The death-rate was higher among the 4th quartile patients (12% vs. 3%) and 4th quartile SUA values were found independently predictive of all-cause mortality: in a Cox proportional hazard regression model with adjustment for the Killip's class, age and peak creatine phosphokinase (CPK) value (selected through a stepwise procedure among a number of others, p<0.05), HR was 3.72 (95% CI 1.42-9.74). The analysis that considered SUA as a continuous variable indicated an adjusted death risk increase of around 22% by each increase in SUA by 50 μmol/L (HR= 1.22, 95% CI 1.11-1.35). No increase in the risk of death was found in patients within the 2nd (n=299, SUA 274-333 μmol/L) or the 3rd (n= 276, SUA 333-399 μmol/L) quartile.

In 2007, Valente and colleagues (Valente et al., 2007) reported the results of a prospective study conducted at a single PCI-performing center in Italy. The report focused on STEMI patients presenting with a cardiogenic shock and undergoing acute PCI, i.e., within 6 hours since the symptom onset (between January 2004 and June 2005) (N=45). Patients were classified as those who died during the in-hospital stay ("cases", n=20, 13 men, mean age 78 years) and those who survived (n=25, 19 men, mean age 66 years). Serum uric values taken on admission to intensive coronary care unit (ICCU) were higher in "cases" than in "survivors": (mean±SD) 434±137 μmol/L vs. 351±137 μmol/L (p=0.040). In a univariate test, on-admission SUA >387 μmol/L (vs. below) (which qualifies as hyperuricemia in women, but not entirely in men) was associated with higher odds of in-hospital death: OR= 6.7 (95% CI 1.4-31.8), but this association did not hold in a multivariate model (adjusted OR not reported).

The same group (Lazzeri et al., 2010) extended their study report by including all consecutive STEMI patients who underwent acute PCI (within 12 hours since the symptom onset), regardless of the clinical presentation (N=466). Patients were classified as those with on-admission (to ICCU) SUA >387 μmol/L ("high", n=100, 78.5% men, average age 72 years) and those with SUA ≤387 μmol/L ("normal", n=366, 78.6% men, average age 64 years). In-hospital mortality, the primary outcome, was higher in "high" SUA patients (9.0% vs. 2.5%). "High" on-admission SUA was found independently predictive of higher in-hospital mortality: in a logistic regression model with adjustment for age, left ventricular ejection fraction (LVEF), fibrinogen and peak troponin I levels (selected through a backward procedure among a number of others, p<0.05), OR was 1.82 (95% CI 1.15-2.86). With further adjustments for sex, Killip's class and diuretic use, OR=2.02 (95% CI 1.47-2.78).

In 2009, Car and Trkulja (Car&Trkulja, 2009) reported a retrospective analysis of consecutive AMI patients [N=621, 481 STEMI (77.5%), 140 NSTEMI; 64.7% men, average age 65 years) treated exclusively conservatively (between 1996 and 2001), with a low rate of fibrinolytic reperfusion (10% of STEMI patients), at a single center in Croatia, all admitted within 48 hours since the symptom onset. Outcomes of primary interest were in-hospital mortality, 30-day mortality and, for those who survived the first 30 days post-index event (considering that mortality after AMI is higher within the first 30 days than in any other subsequent 30-day period), long-term all-cause mortality (n=544; follow-up extended to up to 13 years).

In-hospital mortality was 10% and 30-day mortality was 12.4%. Higher on-admission SUA was independently predictive for both outcomes: in modified Poisson regression models (to yield relative risk, rather than odds ratio), with adjustment for age; sex; history of stroke, hypertension, AMI and HF; peak creatine phosphokinase (CPK), right bundle branch block (RBBB), serum creatinine (selected through a backward procedure, p<0.1) and AMI type (forced), RR for each increase in SUA by 50 μmol/L was 1.08 (95% CI 1.01-1.16) for in-hospital mortality, and it was 1.08 (95% CI 1.02-1.15) for 30-day mortality. Among those who survived the first 30-day post-index event, mortality during the subsequent period (up to 13 years) was 32.2%. Higher on-admission SUA was independently predictive of poorer long-term survival: in a Cox proportional hazard regression model, with adjustment for age, serum creatinine, heart failure at discharge, use of digitalis and SUA*age interaction (selected through a stepwise procedure among a number of others, p<0.1), HR for each increase in SUA by 50 μmol/L was 1.65 (95% CI 1.10-2.44).

In 2010, Rentoukas and colleagues (Rentoukas et al., 2010) reported on a small, single-center randomized controlled trial in Greece in which consecutive acute STEMI patients (June 2005 – June 2006) undergoing PCI within 3-12 hours post-symptom onset were randomized to receive allopurinol (n=21, 15 men, mean age 65 years) or placebo (n=19, 14 men, mean age 64 years) for 30 days. A loading dose of allopurinol (400 mg) was administered as soon as AMI was diagnosed, and treatment continued with 100 mg/day. During the observed 30 days, allopurinol-treated patients had lower peak CPK, peak CK-MB and lower peak troponin I levels, and a higher proportion of patients experienced a complete ST-elevation resolution (all p<0.05).

In 2010, Kowalczyk and colleagues (Kowalczyk et al., 2010) published a retrospective analysis of consecutive STEMI patients undergoing PCI at a single center in Poland (between 2000 and 2007). Timing of PCI relative to the symptom onset was not specified. Patients were selected as those having "impaired renal function": either having a "baseline kidney dysfunction" (BKD) defined as estimated glomerular filtration rate (eGFR) <60 mL/min71.73m² based on serum creatinine taken on admission or within 12 hours since admission, or having a "contrast-induced nephropathy" (CIN) defined as an increase in serum creatinine >44.2 μmol/L or >25% from the baseline value, within 48 hours since PCI. A total of 1015 such patients were included. They were classified as those with hyperuricemia (SUA >420 μmol/L determined at the same time as serum creatinine; which is in line with the definition of hyperuricemia in men, and is above the cut-off value of hyperuricemia in women) (n= 352, men 64.2%, mean age 67 years) and those without it (n= 663, men 59.6%, mean age 64 years). The observational period extended to up to 7 years post-PCI (average 3 years). Besides being older and with a higher prevalence of men, hyperuricemic patients were more frequently diabetic, had previous PCI, hypertension, eGFR <60 mL/min/1.73 m² and had lower LVEF at discharge. In-hospital, 30-day, 1-year and entire-period all-cause mortalities were higher in hyperuricemic vs. non-hyperuricemic patients (Table 2). The main analysis was that of all-cause mortality over the entire observed period (case-fatality rate 32.7% for hyperuricemia vs. 18.6% for no hyperuricemia). Hyperuricemia independently predicted mortality: in a Cox proportional hazard regression model with adjustment for age, cardiogenic shock on admission, diabetes, eGFR <60 mL/min/1.73 m², LVEF at discharge, incomplete revascularization and lack of TIMI flow grade 3 after PCI of the infarct-related artery (selected among a number of other covariates

in a stepwise procedure, p<0.05), adjusted HR=1.17 (95% CI 1.05-1.29). In the same model but considering SUA as a continuous variable, HR (by 50 μmol/L increase in SUA)= 1.04 (95% CI 1.02-1.06).

The patients were further analyzed separately as BKD (n=503; with hyperuricemia n=225, without it n=278) and as CIN patients (n= 693, with hyperuricemia n=243, without it n=450) (these two subgroups partly overlapped – some patients with BKD later-on developed CIN). Crude mortality rates for BKD and CIN patients are summarized in Table 2. High SUA independently predicted mortality in both subgroups. BKD: adjusted HR for hyperuricemia = 1.38 (95% CI 1.23-1.53), adjusted HR by 50 μmol/L SUA increase = 1.05 (95% CI 1.03-1.07); CIN: adjusted HR for hyperuricemia = 1.21 (95% CI 1.05-1.37), adjusted HR by 50 μmol/L SUA increase = 1.06 (95% CI 1.04-1.09).

In 2011, Basar and colleagues (Basar et al., 2011) reported on their prospective observational study in 185 consecutive STEMI patients undergoing PCI within 12 hours since the symptom onset (N=185) (time-period not reported, most author affiliations in Turkey). Patients were classified as those having on-admission SUA >387 μmol/L ("high"; above the cut-off of hyperuricemia in women, but below it in men) (n= 45, 80% men, mean age 60 years) and those with on admission SUA below this level ("normal", n= 140, 80% men, mean age 58 years). Patients with "high" SUA more frequently had a history of hypertension, prior AMI, multivessel disease and had higher Killip's class at presentation. They were followed-up for 1 year. In-hospital mortality was higher in patients with "high" SUA (6.6% vs. 2.8%). The main outcomes of interest were all-cause mortality within 1-year period and proportion of patients with abnormal myocardial perfusion at 1 year post-PCI based on TIMI myocardial perfusion grade. "High" SUA independently predicted both outcomes. In a logistic regression model with adjustment for TIMI risk score, abnormal TIMI perfusion grade at discharge, LVEF at discharge, multivessel disease (selected among a number of covariates in a stepwise procedure, p<0.1), time to reperfusion and serum creatinine (forced covariates), OR for death was 1.29 (95% 1.14-2.08). When SUA was considered as a continuous variable (with the same adjustments), OR by 50 μmol/L increase in SUA was 1.10 (95% CI 1.02-1.14). Considering the proportion of patients with abnormal myocardial perfusion, adjusted OR (Killip class, multivessel disase, corrected TIMI time-frame count, selected based on p<0.05) was 2.14 (95% CI 1.17-4.19).

In 2011, Bae and colleagues (Bae et al., 2011) published a retrospective analysis of a multicenter AMI registry in South Korea. Embraced were 850 consecutive AMI patients (during 2006 and 2007), 391 (46%) of whom were depicted as STEMI patients. The remaining patients were likely NSTEMI, since typical clinical AMI presentation with an increase in cardiac enzymes was prerequisite for inclusion. Overall, 623 (73.3%) patients underwent PCI. Other reperfusion procedures were not specified. Also, time elapsed between the symptom onset and admission and timing of SUA measurement were not specified. SUA values were collected retrospectively since they had not been originally entered into the registry. Patients were classified as those who, during a 6-month period, experienced a composite outcome of death or non-fatal reinfarction or revascularization (MACE) (n=109) and those who did not (n=741). They were also classified as those with on-admission SUA >420 μmol/L (cut-off for hyperuricemia in men, and higher than that in women) (n= 172, 74.4% men, mean age 66.5 years) and those with lower SUA levels (n= 678, 67.2% men, mean age 67 years). Besides the fact that they were more frequently men and somewhat older, hyperuricemic patients more

Author/ year	Design/type	Patients	Outcomes	Univariate effects	Multivariate effects
Kojima et al. 2005	Retrospective, observational, prognostic	Consecutive AMI, type not specified; admission ≤48 hrs since onset; N= 1124 Reperfusion= 943 (84%): stent 743, balloon 146, thrombolysis 54. No reperfusion: 181 (16%)	*30-day* MACE, cardiac mortality, all-cause mortality *Long-term* All-cause mortality, follow-up maximum 700 days	**4th vs. 1st quartile SUA** *30-day MACE*. 14% vs. 5%; OR=2.83, p=0.001 *30-day cardiac death*. 11% vs. 2%; OR=6.54, p<0.001 *30-day all death*. 11% vs. 2%, OR= 5.63, p<0.001 *All-cause mortality long-term.* 12% vs. 3%, HR= 3.75, p<0.001 **SUA by 50 µmol/L** *All-cause mortality long-term.* HR= 1.28, p<0.001	**4th vs. 1st quartile SUA** *All-cause mortality long-term.* HR=3.72 (95% CI 1.42-9.74) **SUA by 50 µmol/L** *All-cause mortality long-term.* HR= 1.22 (95%CI 1.11-1.33) Ajdust: Killip's class, peak CPK and age (p<0.05)
Valente et al. 2007	Prospective, observational, prognostic	Consecutive STEMI with CS, undergoing PCI within 6 hrs since onset, N=45	In-hospital mortality	SUA >387 µmol/L (vs. below) – OR= 6.7, p=0.016	Not significant
Lazzeri et al. 2010	Extension of the above, same protocol	Consecutive STEMI under-going PCI within 12 hrs since onset, N=466	In-hospital mortality	SUA >387 µmol/L (vs. below) – 9.0% vs. 2.5%, OR=3.9, p=0.006	SUA >387 µmol/L (vs. below) OR= 1.82 (95%CI 1.15-2.86)/Adjust: age, LVEF, fibrinogen, peak Tn I (p<0.05) OR=2.02 (95%CI 1.47-2.78) / further: sex, COPD, Killip's class, use of diuretics
Car&Tr kulja 2009	Retrospective, observational, prognostic	Consecutive AMI; admi-ssion ≤48 hrs since onset; N= 621, STEMI n=481 (77.5%), NSTEMI n=140 Reperfusion: 10% of STEMI (thrombolysis)	*Short-term* In-hospital and 30-day all-casue mortality *Long-term* All-cause mortality, follow-up up to 13 years; n=544 who survived first 30 days	*In-hospital mortality* SUA 50 µmol/L: RR=1.20, p<0.05 *30-day mortality* SUA 50 µmol/L: RR=1.19, p<0.05 *All-cause mortality long-term* SUA 50 µmol/L: HR=1.14, p<0.05	*In-hospital mortality* SUA 50 µmol/L: RR=1.08 (95%CI 1.01-1.16) *30-day mortality* SUA 50 µmol/L: RR=1.08 (95%CI 1.02-1.15) Ajdust: age; sex; AMI type; prior CVI, hypertension, AMI, HF; peak CPK, RBBB, serum creatinine, (p<0.1). *All-cause mortality long-term* SUA 50 µmol/L: HR=1.65 (95%CI 1.13-2.18) Adjust: creatinine, age, HF, use of digitalis, age*SUA interaction (p<0.1)
Rentouk as et al. 2010	Therepeutic, RCT, allopuri-nol vs. placebo	Consecutive STEMI under-going PCI 3-12 hrs since onset. Allop. n=21, Plac. n=19	30-day treatment and assessment: peak CPK, peak CK-MB, peak Tn I, resolution of ST elevation	Allopurinol: lower peak CPK, MB-CPK and Tn I, greater proportion of "full ST recovery" within 30 days (all p<0.05).	Not reported

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Author/ year	Design/type	Patients	Outcomes	Univariate effects	Multivariate effects
Kowalc zyk et al. 2010	Retrospective, observational, prognostic	Consecutive STEMI under-going PCI (time since onset not specified) with reduced renal function (N=1015), further subdivided (partly overlapping): eGFR on admission <60 mL/min/1.73m² (BKD) (n=503) and patients with PCI-induced nephropathy (CIN) (n=693)	*Short-term* In-hospital mortality 30-day all-cause mortality *1 year* All-cause mortality *>1 year* All-cause mortality	**SUA >420 μmol/L (vs. below)** *In-hospital mortality* All: 14.5% vs. 7.1%, p<0.001 BKD: 18.2 vs. 12.2%, p=0.060 CIN: 19.0% vs. 6.4%, p<0.001 *30-day mortality* All: 16.9% vs. 7.7%, p<0.001 BKD: 19.6% vs. 12.9%, p=0.04 CIN: 19.8% vs. 6.9%, p<0.001 *1-year mortality* All: 25.0% vs. 13.7%, p<0.001 BKD: 31.5% vs. 18.3%, p<0.001 CIN: 28.0% vs. 13.1%, p<0.001 *>1 year mortality* All: 32.7% vs. 18.6%, p<0.001 BKD: 41.3% vs. 25.9%, p<0.001 CIN: 35.4% vs. 16.7%, p<0.001	**SUA >420 μmol/L (vs. below)** *Overall observed period* All: HR= 1.17 (95% CI 1.05-1.29) BKD: HR= 1.38 (95% CI 1.23-1.53) CIN: HR= 1.21 (95% CI 1.05-1.37) **SUA by 50 μmol/L** *Overall observed period* All: HR= 1.04 (95% CI 1.02-1.06) BKD: HR= 1.05 (95% CI 1.03-1.07) CIN: HR= 1.06 (95% CI 1.04-1.09) Adjust: All - age, CS on admission, DM, LVEF at discharge, incomplete revascu-larization, lack of TIMI flow grade 3 after PCI of the infarct-related artery, BKD BKD – age, CS on admission. LVEF at discharge, incomplete revascularization, lack of TIMI flow grade 3 after PCI of the infarct-related artery CIN: age, CS on admission, LVEF at discharge, incomplete revascularization, BKD/ (all adjustments p<0.05)
Basar et al. 2011	Prospective, observational, prognostic	Consecutive STEMI under-going PCI within 12 hrs since onset (N=185).	In-hospital mortality 1-year impaired myocar-dial perfusion 1-year all-cause mortality	**SUA >387 μmol/L (vs. below)** *In-hospital mortality* 6.6% vs. 2.8%, p<0.01 *1-year all-cause mortality* 11.1% vs. 5.7%, OR=1.19, p<0.01 **SUA continuous** *1-year impaired perfusion* correlation *r*=0.46, p<0.001	**SUA >387 μmol/L (vs. below)** *1-year all-cause mortality* OR= 1.29 (95%CI 1.14-2.08)/Adjust: TIMI risk score, abnormal TIMI perfusion grade at discharge, LVEF at discharge, multi-vessel disease (p<0.1) + time to reperfu-sion, serum creatinine *1-year impaired perfusion* OR= 2.14 (95% CI 1.17-4.19)/Adjust: Killip multives. disease, TIMI time-frame count **SUA by 50 μmol/L** *1-year all-cause mortality* OR=1.10 (95% CI 1.02-1.14) /Adjust: same

Author/ year	Design/type	Patients	Outcomes	Univariate effects	Multivariate effects
Bae et al. 2011	Retrospective, observational, prognostic	Consecutive AMI, N=850, 391 (46%) STEMI, other not specified (likely NSTEMI – positive enzymes); 623 (73.3%) underwent PCI, other reperfusion not specified; timing admission vs. onset not specified	6-month occurrence of MACE: death or non-fatal AMI or revascularization	**SUA >420 μmol/L (vs. below)** MACE 24.4% vs. 9.9%, p<0.001 **SUA continuous** Patients with MACE (n=109) had higher SUA than those without MACE (n= 741), p<0.001	**SUA 50 μmol/L** HR: 1.24 (95% CI 1.06-1.46) /Adjust: age, BMI, systolic blood pressure, heart rate, diabetes, hyperlipidemia, previous AMI, Killip class, PCI, WBC, hemoglobin, sodium, potassium, eGFR, NT-ProBNP, hs-CRP (all univariate p<0.05).
Park et al. 2011	Retrospective, observational, prognostic	Consecutive patients undergoing PCI (N=1247), however, only 310 (24.9%) acute PCI due to STEMI (other procedures elective)	Development of acute kidney injury within 7 days post-PCI (creatinin incrase >44μmol/L or >50% vs. baseline)	**SUA >416 (M) or >387 (F) μmol/L** OR= 5.48 (95% CI 3.06-9.84)	**SUA >416 (M) or >387 (F) μmol/L** OR= 4.74 (95% CI 1.96-11.4) /Adjust: contrast amount, diabetes, hemoglobin, PCI post-AMI, eGFR <60 mL/min/1.73m²

SUA – serum uric acid; OR – odds ratio; RR – relative risk; HR – hazard ratio (relative risk); M – male, F – female, BKD – baseline kindey dysfunction; CIN – contrast-induced nephropathy; COPD – chronic obstructive pulmonary disease; CPK – creatine phosphokinase; CPK-MB – creatine phospnokinase myocardial band; CS – cardogenic shock; CVI – cerebrovascular insult; DM – diabetes mellitus; eGFR – estimated glomerular filtration rate; HF – heart failure; hs-CRP – highly specific c-reactive protein; LVEF – left ventricular ejection fraction; MACE – major adverse cardiac events, NSTEMI – non-ST-elevation myocardial infarction; NT-ProBNP – N-termina-pro-B type natriuretic peptide; PCI – percutaneous coronary intervention; RBBB – right bundle branch block; RCT – randomized controlled trial; STEMI – ST-elevation myocardial infarction

Table 2. Summary of the studies of prognostic value of serum uric acid levels (SUA) in patients with acute myocardial infarction (AMI). Data are listed as presented in orginal publications. However, odds ratios and relative risks associated with SUA as a continuous variables were all re-calculated to 50 μmol/L increase to enable comparability of results.

frequently presented with a higher Killip class, more frequently had a history of hypertension and coronary artery disease, less frequently underwent PCI, had lower hemoglobin and serum sodium, lower eGFR, lower LVEF, and had higher potassium, high-sensitivity CRP and higher levels of pro-B-type natriuretic peptide (NT-ProBNP). Patients experiencing MACE had higher SUA levels and patients with hyperuricemia more frequently experienced MACE (24.4% vs. 9.9%, p<0.001). Higher on-admission SUA independently predicted 6-month occurrence of MACE: in a proportional hazard regression model with adjustment for age, BMI, systolic blood pressure, heart rate, diabetes, hyperlipidemia, previous AMI, Killip class, PCI, WBC, hemoglobin, sodium, potassium, eGFR, NT-ProBNP, hs-CRP (all showing univariate associations with the outcome, but not all were independently associated with the outcome), HR for MACE by 50 μmol/L increase

in SUA was 1.24 (95% CI 1.06-1.46). They also noticed that SUA and NT-ProBNP additively improved the predictivity of the entire model (as judged on global chi-square increase): adding SUA or NT-ProBNP to conventional risk factors comparably increased the global chi-square, whereas adding both, yielded a model with the highest chi-square.

Park and colleagues (Part et al. 2011) recently reported a retrospective analysis of 1147 consecutive patients from a single center in South Korea (between mid 2006 and end of 2009) who underwent PCI. However, only 310 (24.9%) were STEMI patients undergoing acute PCI, whereas the rest underwent elective procedures. The report is interesting because it showed that SUA >416 μmol/L in men and >387 μmol/L (in line with "conventional" definition of hyperuricemia) independently predicted development of acute kidney injury (AKI) (increase in serum creatinine > 44 μmol/L or >50% over baseline) within 7 days from PCI. Hyperuricemia was particularly predictive of AKI when combined with eGFR before PCI <60 mL/min/1.73 m². Also, in univariate tests, AKI strongly predicted in-hospital mortality (19.6% vs. 0.8%, OR= 28.9 (95% CI 11.4-73.3), as did hyperuricemia – OR= 3.01 (95% CI 1.19-7.87).

From the viewpoint of predictive value of SUA for AMI outcomes, 7 out 9 of the described studies are of primary interest. The small RCT of allopurinol in STEMI patients undergoing PCI is interesting in that indicates the potential of an intervention affecting the XO-SUA system in this setting (Rentoukas et al., 2010). The study from South Korea (Park et al., 2011) reporting on consecutive PCI patients (predominantly elective, but 25% also acute) is of interest as it indicates a possible element of mechanism(s) by which increased SUA, or a condition characterized by increased SUA (specifically, hyperuricemia), might influence AMI outcomes in subjects undergoing acute PCI (potential effects on the renal function).

Most of the seven studies of primary interest were retrospective (Table 2), which, *per se*, could be viewed as a methodological drawback. However, considering the particulars of AMI and AMI treatment (an acute condition, typically handled after a standardized procedure with a detailed prospective monitoring and data recording), a retrospective data analysis is less likely to be biased in this setting than in some other situations. Clearly, however, susceptibility to some sources of bias remains (e.g., patient selection, physician's skill, accuracy in data recording, pattern of missing data etc.). The fact that data come from different parts of the world (Japan, Korea, various European and Middle-East countries) and different settings (STEMI, NSTEMI, mixed, PCI, thrombolysis or no reperfusion) should be viewed as a possibility to evaluate whether predictivity of SUA in this setting is robust and holds across genetic and cultural (e.g., nutrition, alcohol consumption, smoking habits) differences that might influence SUA levels and across different AMI types and treatment modalities.

2.2 Prediction of short-term outcomes

When considering predictivity of "on-admission" SUA levels (that is, taken at hospital admission, before any major intervention, as a part of a diagnostic work-up), one question is inevitable: what do the "on-admission" SUA levels reflect? A pre-existing condition? An acutely developed condition induced by AMI? Or, both?. Indeed, AMI *per se* causes a reduction in renal function (thus potentially reflecting on SUA levels due to a reduced excretion – studies on kinetics of creatinine elimination suggest that changes due to a sudden decline in renal function are to be expected within 5-6 hours (Hallynck et al., 1981, Hillege et al., 2003). Furthermore, as depicted in Figure 3, cardiac ischemia is likely to result

in activation of XO. However, a reduction in glomerular filtration seen after AMI has been estimated at 1-3 mL/min for the period between AMI onset and day 3 post-AMI (Hillege et al., 2003), and by analogy to a failing heart (Doehner et al., 2008), increased cardiac XO activity apparently also needs certain time to occur. Therefore, it is likely that "on-admission" SUA values, when taken, for example, within first 48 hours since AMI onset are likely to largely represent the pre-existing condition. From the viewpoint of predictive power of UA, these observations are not crucial, because the question is simple: does this marker, taken at this very moment (regardless of what it represents), predict future events? They are, however, of interest when considering the possible "mechanistic" contribution of SUA to events that are to occur in a short subsequent period of time (e.g., in-hospital mortality or 30-day mortality) – clearly, the molecular/cellular mechanisms of SUA (or XO, for that matter) elaborated earlier also need to act for a certain period of time for their detrimental effects to become obvious.

In the subsequent text, word "effect" will be used to describe the relationship between SUA (as a potential predictor) and the outcomes. It does not imply causal relationship between the two, but is used simply because it is inherent to regression analysis on which all of the studies were based. Furthermore, the focus will be on adjusted estimates (ORs, RRs), i.e., those obtained in individual studies by accounting for relevant confounders. Where applicable, pooled estimates based on adjusted individual results were generated by conventional meta-analytical methodology for summary results. Since most of the studies reported on event rates >10% and used odds ratios, whereas some reported relative risks, adjusted odds ratios were corrected and transferred into relative risks as described by Zhang and Yu (Zhang&Yu, 1998) in order to allow for pooling of data.

2.2.1 Overall effect of "high" SUA (hyperuriceima)

As depicted in Table 2, in all studies that reported on short-term outcomes, i.e., in-hospital mortality and 30-day mortality, higher on-admission SUA, depicted as values above some cut-off (and regardless of this value) or treated as a continuous variable – consistently was associated with higher mortality: in STEMI patients treated with PCI, in STEMI PCI-treated patients with impaired renal function (as a pre-existing condition or contrast-induced), in a mixed population of NSTEMI and STEMI patients with poor reperfusion treatment). Hence, it appears safe to say that, regarding short-term outcomes, increased SUA (regardless of how defined) is a "robust" predictor that does not appear conditional on type of AMI and/or treatment modality. Table 3 summarizes the pooled estimate of unadjusted relative risk of in-hospital mortality for "high" SUA (based on studies in Table 2). Practically without inconsistency, the pooled estimate indicates around 2.57 times higher (unadjusted) risk of in-hospital mortality associated with "high" SUA.

Only 2 studies reported adjusted estimates of risk associated with "high SUA" in respect to in-hospital mortality, Lazzeri et al., 2010 as odds ratio, and Trkulja&Car 2009, using SUA as a continuous variables. Data from Lazzeri et al., 2010 were converted to adjusted relative risk – 1.97 (95% CI 1.45-2.66); and data from Car&Trkulja 2009 were used to calculate adjusted relative risk for "high" SUA – 1.82 (95%CI 1.13-2.93). The pooled estimate of these two adjusted RRs is 1.93 (95% CI 1.49-2.49). Hence, "high" SUA (defined here more or less consistently as SUA within the range of "hyperuricemia") apparently independently predicts in-hospital mortality.

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Author	Patients	"High" SUA (µmol/L)	"High SUA" n/N	"Normal SUA" n/N	RR (95% CI)
Lazzeri 2010	STEMI, PCI	>387	9/100	9/366	3.66 (1.53-8.69)
Car&Trkulja 2009	STEMI (77.5%) poor reperfusion, NSTEMI	>420 M, >360 F	42/171	35/450	3.16 (2.09-4.75)
Kowalczyk 2010	STEMI, PCI	>420	51/352	47/663	2.04 (1.41-2.96)
Basar 2011	STEMI, PCI	>387	3/145	4/140	2.33 (0.60-8.92)
Total			105/633	95/1619	
Pooled (random) (I²=0.5%, heterogenitey p=0.389)					2.57 (1.97-3.34)

Table 3. Meta-analysis of unadjusted relative risk of in-hospital mortality associated with "high" SUA. Valente et al., 2007 was not considered separately, because reported patients were included also in Lazzeri et al., 2010. Data for Car&Trkulja 2009 were recalculated from original data (since not reported in the original publication).

Table 4 summarizes the pooled estimate of unadjusted relative risk of "30-day mortality" for "high" SUA (based on studies in Table 2). With rather high inconsistency, the pooled estimate indicates around 2.82 times higher (unadjusted) risk of 30-day mortality associated with "high" SUA.

Author	Patients	"High" SUA (µmol/L)	"High SUA" n/N	"Normal SUA" n/N	RR (95% CI)
Kojima 2005	STEMI (84%), PCI; NSTEMI	>399	30/276	20/848	4.61 (2.68-7.92)
Car&Trkulja 2009	STEMI (77.5%) poor reperfusion, NSTEMI	>420 M, >360 F	42/171	41/450	2.70 (1.82-3.97)
Kowalczyk 2010	STEMI, PCI	>420	51/352	47/663	2.07 (1.45-2.98
Total			123/799	108/1961	
Pooled (random) (I²=65.3%, heterogenitey p=0.056)					2.82 (1.86-4.29)

Table 4. Meta-analysis of unadjusted relative risk of 30-day all-cause mortality associated with "high" SUA. Data for Car&Trkulja 2009 were recalculated from original data (since not reported in the original publication).

No study reported an adjusted risk of 30-day mortality for "high" SUA. Car&Trkulja 2009 (Table 2) reported an adjusted RR considering SUA as a continuous variable. Original data were used to calculate RR for "high" SUA (>420 or >360 µmol/L in men and women, respectively) with the same adjustments as depicted in Table 2 – RR= 1.50 (95% CI 1.05-2.40). Hence, it appears that "high" SUA (defined more or less consistently as "hyperuricemia") independently predicts 30-day mortality after AMI.

2.2.2 Effect of high SUA in respect to gender and AMI type

All studies reporting the effects of SUA on short-term outcomes of AMI (Table 2) included patients of both sexes, but men prevailed in all studies. Two of these studies (Kojima et al., 2005, Car&Trkulja 2009) included both STEMI and NSTEMI patients, while remaining included exclusively acute PCI-treated STEMI patients (Table 2). Considering the overall effects of SUA (Table 3, Table 4), it seem reasonable to assume that the effects of SUA are consistent in both genders and both in STEMI and NSTEMI. For the purpose of this text, original data reported by Car&Trkulja 2009, apart from 8 patients who presented with cardiogenic shock (which troubles the interpretation of on-admission SUA) were analyzed for the effects of SUA on 30-day mortality by sex and type of AMI. SUA levels were considered as a continuous variable or a 3-level categorical variable: low-normal SUA values were defined as <310 µmol/l in men and <250 µmol/l in women; hyperuricemia was defined as SUA >420 µmol/l in men and >360 µmol/l in women; whereas high-normal SUA was defined as values between these limits. Figure 4 summarizes univariate effects of SUA on 30-day mortality. Mortality consistently increased across the range of SUA values, but the most prominent increase in mortality was observed at the cut-off of hyperuricemia, particularly in NSTEMI patients.

Figure 5 summarizes univariate effects of SUA on 30-day mortality in sex-by-AMI-type subgroups. Mortality consistently increased across the range of SUA values, but the most prominent increase in mortality was seen at the cut-off of hyperuricemia. The particularly prominent increase in mortality of NSTEMI is apparent in both men and women.

In multivariate analysis, a number of potential covariates were considered: pre-index event medical history, on-admission laboratory data (creatinine and eGFR [<60 mL/min/1.73 m^2], triglycerides, total and HDL and LDL cholesterol, peak CPK-MB, serum fibrinogen, white blood cells, hemoglobin, CRP), electrocardiographic particulars, pre-index event treatment and treatments delivered between the index event and 30-day post symptom onset. Multivariate model-building details are given in caption to Figure 6 which summarizes univariate and multivariate effects of SUA, as a continuous variable or as a contrast of "hyperuricemia" vs. "normal SUA", on 30-day mortality across gender, AMI type and gender-by-AMI-type subgroups. Data strongly suggest that high SUA (and specifically hyperuricemia) independently predicts 30-day mortality across all subgroups. The pronounced increase in mortality in hyperuricemic NSTEMI patients is maintained in multivariate analysis, as well. In practical terms, it may suggest that hyperuricemic NSTEMI patients might require a particularly closer monitoring. Of notion, however, the analyzed cohort was treated exclusively conservatively with very scarce use of thrombolytic reperfusion in STEMI patients.

Considering limited subgroup size/number of deaths, models in gender-by-AMI type subgroups included only selected adjustments (stepwise, p<0.1 to enter, p<0.05 to stay). Adjustments in men-STEMI: prior AMI and post-index event treatments – antiplatelets, ACE inhibitors, class I/III antiarrhythmics. Adjustments in women-STEMI: right bundle branch block and post-index event treatments – antiplatelets, ACE inhibitors, diuretics and beta blockers. Adjustments in men-NSTEMI: age. Adjustments in women-NSTEMI: prior symptomatic chronic heart failure, post-index event antiplatelet use.
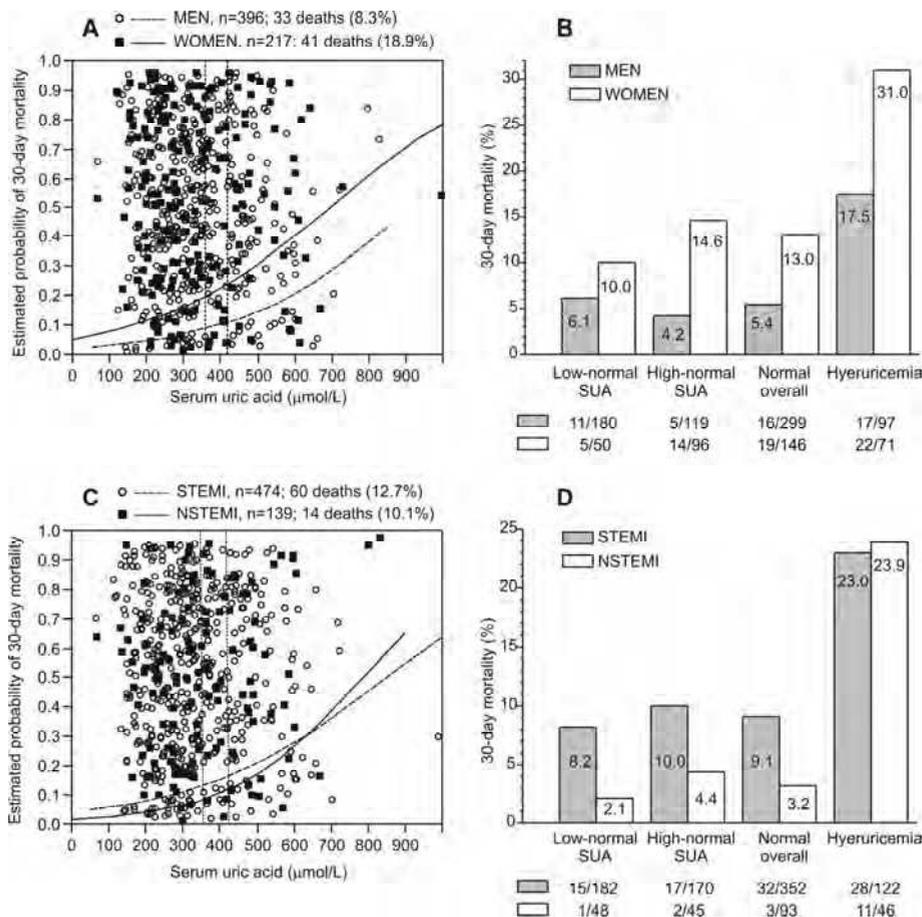
Fig. 4. Univariate effects of SUA on 30-day mortality by sex and AMI type. Estimate probability of dying across the range of SUA values (A, B) and proportion dying among low-normal, high-normal SUA and hyperuricemic patients (B, D) (based on the cohort described in Car&Trkulja 2009). Vertical lines in A and B denote the limits of hyperuricemia in men and women.

2.2.3 Effect of high SUA in respect to renal function

All studies reporting effects of SUA on short-term outcomes (Table 2) included a variable proportion of patients with reduced renal function (e.g., eGFR <60 mL/min/1.73 m²). The study by Kowalczyk and colleagues (Kowalczyk et al., 2010) specifically included only patients with an impaired renal function (eGFR <60 mL/min/1.73 m² at baseline or contrast-induced renal injury). The consistency of the effects of SUA across trials suggests that, likely, effects of SUA hold in both patients with a reduced and those with a preserved renal function. No study reported specifically on patients with different levels of eGFR. For the purpose of this text, the cohort by Car&Trkulja (Car&Trkulja 2009) is re-analyzed
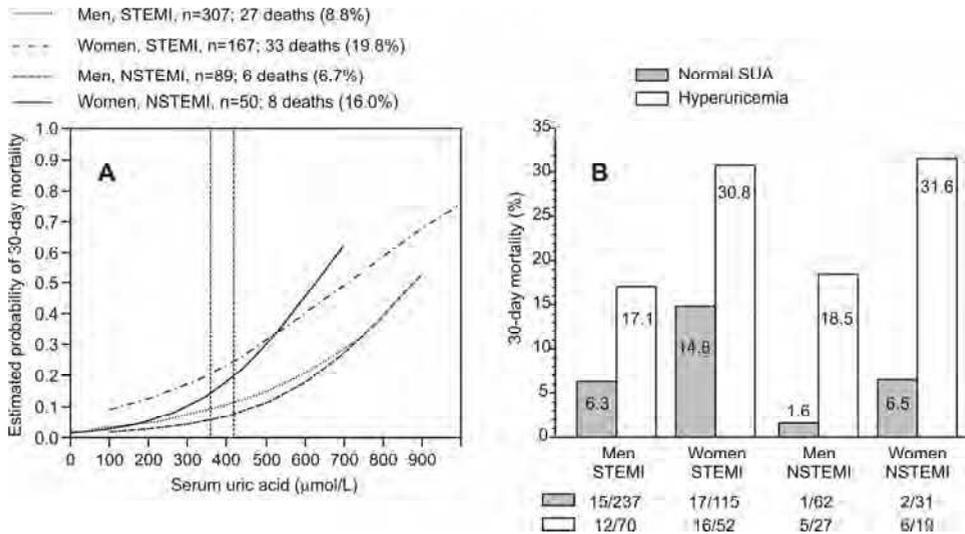
Fig. 5. Univariate effects of SUA on 30-day mortality in sex-by-AMI-type subgroups (based on the cohort described in Car&Trkulja 2009). Estimated probability of dying across the range of SUA values (A) and proportion dying among low-normal, high-normal SUA and hyperuricemic patients. Vertical lines in A denote limits of hyperuricemia in men and women.

separately for patients with eGFR <60 mL/min/1.73 m² and those with eGFR ≥60 mL/min/1.73 m². Levels of SUA values were defined as in the previous section. As shown in Figure 7, probability of 30-day mortality increased across the range of SUA values, and particularly at the level of hyperuricemia, in patients with eGFR <60 mL/min/1.73 m², but not in those with eGFR ≥60 mL/min/1.73 m². Multivariate analysis (potential adjustments as described in the previous section) demonstrated an independent association between higher SUA and particularly hyperuricemia and 30-day mortality in patients with reduced, but not in those with a preserved renal function. Univarite and multivariate SUA effects are summarized in Table 5. Reduced renal function is a well-established predictor of poor outcomes in AMI patients (specifically, eGFR <60 mL/min/1.73 m² has been repeatedly shown as a "break-point" of a marked increase in mortality). The present data suggest that increased SUA, i.e., hyperuricemia adds a considerable additional risk in patients with a reduced renal function. However, the current data should be viewed with a caution, since they refer exclusively to patients not treated with PCI. From a mechanistic standpoint, on the other hand, it seem plausible that detrimental effects of increased SUA are particularly obvious in patients with a reduced renal function (and not, or less so, in patients with a preserved renal function) – the potentially contributing molecular and cellular effects of SUA are more likely to manifest under the conditions of increased oxidative stress/reduce antioxidant capacity as it is seen in renal failure.
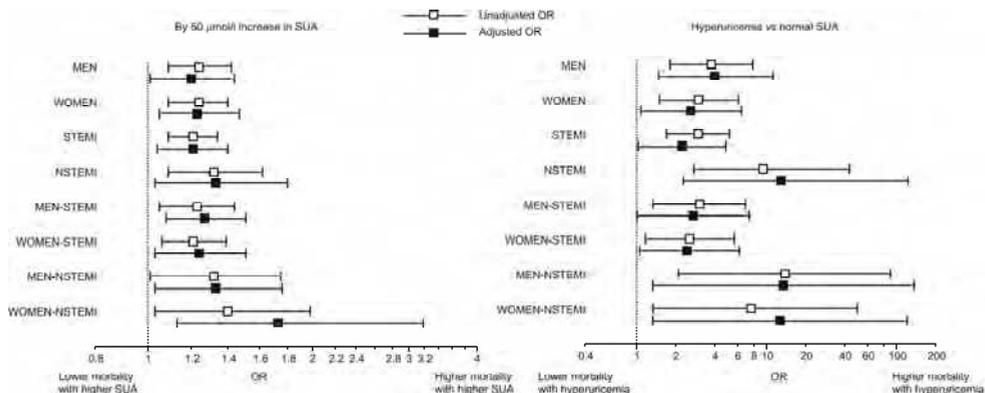
Fig. 6. Univariate and multivariate effects of SUA (as a continuous variable, by 50 µmol/L increase, left; and as a contrast of hyperuricemia vs. normouricemia, right) on 30-day mortality in subgroups by gender and type of AMI (based on the cohort described in Car&Trkulja 2009). Effects are presented as unadjusted and adjusted odds ratios (OR) (horizontal lines are 95% confidence intervals) by 50 µmol/l increase in SUA or for the contrast hyperuricemia *vs* normal SUA. Multivariate models in men, women, STEMI and NSTEMI included lag-time between symptom onset and admission and on-admission estimated glomerular filtration rate (<60 or ≥60 ml/min/1.73 m²) as default adjustments. Other adjustments were selected in a stepwise procedure (p<0.1 to enter and p<0.05 to stay). Selected adjustments in men: prior AMI, right bundle branch block, and post-index event treatments – antiplatelets, beta blockers, diuretics, class I/III antiarrhythmics. Selected adjustments in women: age and post-index event treatments – antiplatelets, class I/III antiarrhythmics and ACE inhibitors. Selected adjustments in STEMI: sex, prior AMI, on-admission triglycerides and post-index event treatments – antiplatelets, ACE inhibitors, beta blockers, diuretics, class I/III antiarrhythmics. Selected adjustments in NSTEMI: age, on-admission total cholesterol and post-index event antiplatelet use.

	eGFR <60 (N=309)		eGFR ≥60 (N=304)	
	OR (95% CI)	P	OR (95% CI)	P
Unadjusted SUA effects				
SUA by 50 µmol/l	1.18 (1.07-1.32)	0.001	0.97 (0.74-1.27)	0.833
Hyperuricemia vs. normal SUA	2.75 (1.55-4.96)	<0.001	1.14 (0.17-4.40)	0.868
Adjusted SUA effects				
SUA by 50 µmol/l	1.24 (1.08-1.44)*	0.003	1.02 (0.74-1.36)**	0.890
Hyperuricemia vs. normal SUA	3.18 (1.49-7.03)*	0.003	1.46 (0.20-6.69**	0.659

*Adjustments, default: sex, on-admission creatinine, lag-time symptoms-admission, prior symptomatic chronic heart failure (p<0.05); selected (all p<0.05): age, post-index event treatments (till day 30 or death, whichever first) – antiplatelets, ACE inhibitors, antiarrhythmics, diuretics.
**Adjustments, default: sex, on-admission creatinine, lag-time symptoms-admission, prior symptomatic chronic heart failure; selected (all p<0.05): prior acute myocardial infarction, post-index event treatments (till day 30 or death, whichever first) – antiplatelets, beta-blockers.

Table 5. Univariate and multivariate effects of SUA on 30-day mortality in AMI patients with eGFR <60 mL/min/1.73 m² or ≥60 mL/min/1.73 m² (based on the cohort described in Car&Trkulja 2009).
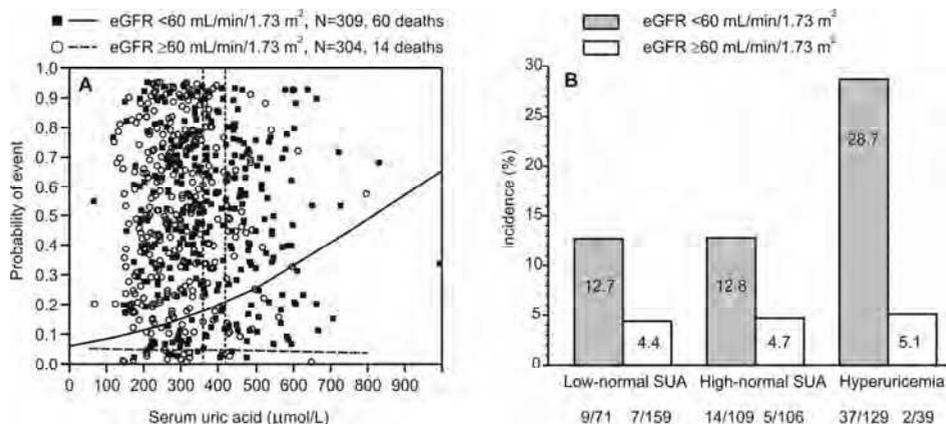
Fig. 7. Effect of SUA on 30-day mortality in AMI patients with on-admission eGFR <60 mL/min/1.73 m² or ≥60 mL/min/1.73 m² (based on the cohort described in Car&Trkulja 2009). Estimated probability of dying (A) and proportions of patients who died in the two subgroups in respect to SUA level (B). Vertical lines in A depict cut-off values of hyperuricemia in men and women.

2.3 Prediction of long-term outcomes

Prediction of medium- and long-term outcomes after AMI based on a single-point value of SUA may not be as straightforward as prediction of short-term outcomes. Namely, SUA levels may oscillate and change over time due to nutritional changes, habits (e.g., alcohol consumption, smoking) and effects of drugs, not only uricosuric or XO- inhibiting drugs, but also drugs commonly used in post-AMI patients, like thiazide diuretics or angiotensin receptor blockers. None of the studies has considered SUA as a time-varying variable. With this limitation acknowledged, all studies that reported on medium- or long-term outcomes after AMI (Table 2) consistently indicated independent unfavorable effects of SUA, either as a continuous variable or as "hyperuricemia", on mortality or other markers of poor outcomes after AMI. Kojima (Kojima et al., 2005) additionally noticed that a combination of high SUA and high(er) Killip class was particularly unfavorable in long-term. Similarly, Bae (Bae et al. 2011) showed the additive increase in risk between hyperuricemia and higher levels of NT-ProBNP. Both results actually depict the combination of a failing heart and hyperuricemia as ominous. Indirectly, these observations are in line with those suggesting that the effects of high SUA might be particularly expressed in patients with a reduced renal function – eventually, hemodynamic consequences of a failing heart would lead to a reduced renal function.

## 3 Conclusions and considerations for the future research

There is a sound mechanistic rationale to support a view that a condition characterized by increased SUA, regardless of whether SUA is viewed as a direct "pathogen" or a (mere) marker of some other underlying processes, might be detrimental for acute AMI patients. Clinical observations accumulated over the past 5-6 years strongly support a view that SUA should be taken into account in the process of risk stratification in AMI patients. Moreover, there are sound indications of a possibility that it could also be a useful therapeutic target. However, larger-scale prospective studies are needed to precisely isolate and quantify the

"SUA" effect, overall, and in different settings – AMI types, reperfusion procedures, renal function. Since SUA is closely associated with various other risk factors in AMI patients, the usual approach of prognostic studies based on regression analysis might not be able to meet this goal. Therefore, data mining techniques might be a valuable tool to identify clusters and/or direct and mediated relationships between different risk factor and AMI outcomes that would improve our risk-stratification methodology.

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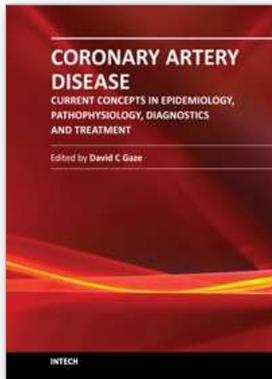
Cardiovascular disease is ranked as the leading cause of death world wide, responsible for 17.1 million deaths globally each year. Such numbers are often difficult to comprehend. Heart disease kills one person every 34 seconds in the USA alone. Although the leading killer, the incidence of cardiovascular disease has declined in recent years due to a better understanding of the pathology, implementation of lipid lowering therapy new drug regimens including low molecular weight heparin and antiplatelet drugs such as glycoprotein IIb/IIIa receptor inhibitors and acute surgical intervention. The disease burden has a great financial impact on global healthcare systems and major economic consequences for world economies. This text aims to deliver the current understanding of coronary artery disease and is split into three main sections: 1. Epidemiology and pathophysiology of coronary artery disease 2. Coronary artery disease diagnostics and 3. Treatment regimens for coronary artery disease

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