Citation: Carella AM, Marinelli T, Melfitano A, Pumpo MD, Modola G, et al. (2017) Hyperuricemia and global Cardiovascular Risk: State of the art and preventive prospects. Arch Prev Med 2(1): 022-027.

**Abstract**

Over the last years, scientific research has focused its interest on a potential role of hyperuricemia as cardiovascular risk factor; main interest has been directed to persistent raised plasma levels of uric acid. Although some studies have not shown a close correlation between hyperuricemia and cardiovascular risk, most scientific evidence agrees that hyperuricemia plays a key role in determining cardiovascular events and in development of other risk factors often associated with only moderately increased serum uric acid levels. Pathophysiological mechanism underlying this association mainly include a hyperuricemia-induced endothelial dysfunction, inflammatory and oxidative stress induced by high serum uric acid levels. Early diagnosis, follow-up and prevention programs and effective treatment of hyperuricemia are recommended in particular in patients with other concomitant cardiovascular risk factors. Urate-lowering therapy should be aimed at reaching at least a serum uric acid level below 6 mg/dL (360 μmol/L) though in high risk patients the lowest possible value of uric acid is better.

**Introduction**

Cardiovascular risk is a cluster of factors including hypertension, diabetes, overweight/obesity, dyslipidemia, metabolic syndrome, tobacco use and others, which predispose and increase the risk of cardiovascular events, mainly cardiac ischemic disease and stroke [1]. Over the last years, scientific research has focused its interest on a potential role of hyperuricemia as cardiovascular risk factor; main interest has been directed to persistent raised plasma levels of uric acid [2].

Uric acid, an heterocyclic organic compound, is the final oxidation product of exogenous and endogenous purine metabolism and is excreted in urine. The endogenous production of uric acid is mainly from liver and intestines and represents the main amount of circulating uric acid, about 600–700 mg daily; diet and animal proteins contribute to exogenous purine pool, for about 100–200 mg daily. In human, the enzyme Xanthine oxido-reductase catalyzes two terminal reactions of purine catabolism, leading to formation of uric acid from xanthine and hypoxanthine, which in turn are produced from other purines, primarily adenine and guanine [3]. In the extracellular compartment, urate is largely present as monosodium urate, with a low solubility limit of about 6.8 mg/dL (404 μmol/L) [4]. Most of circulating uric acid is freely filtered in the kidney and roughly 90% of the filtered load is normally reabsorbed along the proximal tubules of nephrons.

Renal excretion of uric acid represents approximately 60–70% of total uric acid excretion from the body; a smaller proportion of uric acid is secreted in the intestine, and is further metabolized by resident gut bacteria in a process termed intestinal uricolysis [5].

Asymptomatic hyperuricemia is common and usually does not progress to clinical Gout, a chronic inflammatory arthritis caused by a disorder of the purine metabolism leading to hyperuricemia. Possible complications of hyperuricemia are Acute uric acid nephropathy, Uric acid nephrolithiasis and Chronic urate nephropathy [6].

There is evidence that chronic increased uricemia seems to behave in a not dissimilar way to other traditional cardiovascular risk factors that are often associated with hyperuricemia in so close relationship to suggest the existence of a pathogenetic link [7]. Moreover, hyperuricemia is prevalent in subject with poor control of blood pressure values and in those with higher grade of obesity and lower HDL-cholesterol plasma levels [8].

**Scientific evidences**

In 1999, data from the Framingham Heart Study, that examined a possible relation of serum uric acid levels to cardiovascular disease, concluded that uric acid does not have a causal role in the development of coronary heart disease, death from cardiovascular disease, or death from all causes.
Any apparent association with these outcomes were probably due to the association of uric acid levels with other risk factors [9]. However, one year later, results from the NHANES I study showed that increased uric acid levels had a positive relationship to cardiovascular mortality and were independently and significantly associated with the risk of cardiovascular mortality [10]. Afterwards, data from a prospective study and meta-analysis stated that serum uric acid levels is unlikely to enhance usefully the prediction of coronary artery disease and this humoral parameter is unlikely to be a major determinant of the disease in general populations [11]. More recently, two meta-analysis, have reported that hyperuricemia may lead to a modest increment in the risk of stroke incidence and mortality [12] and increases the risk of all-cause mortality and cardiovascular mortality [13].

On the other hand, beyond these conflicting results, it is undeniable that there is a lot of evidence that shows the link between high plasma levels of uric acid and cardiovascular risk. Animal [14–16], and clinical studies [17–20], have shown as hyperuricemia is associated with high blood pressure and with increased future risk of incident hypertension, independent of other risk factors; this risk appears more pronounced in younger individuals and women [21]. Elevated serum uric acid is also independently associated with left ventricular mass index [22]. Although a recent meta-analysis states that hyperuricemia may modestly increase the risk of hypertension incidence, consistent with a dose-response relationship [23], high plasma levels of uric acid were identified as independent predictive factors of hypertension development. A significant epidemiological correlation was also found between hyperuricemia, insulin resistance and other components of metabolic syndrome [19,24], moreover, serum uric acid levels are positively associated with the development of type 2 diabetes regardless of various study characteristics [25]. In patients with insulin-resistance the increase in serum urate has often been considered to be secondary; however, in a long-term prospective study high levels of serum uric acid were found to be a strong and independent predictor of incident metabolic syndrome [26]. Moreover, a recent metaanalysis provided strong evidence that hyperuricemia is a risk factor for developing type 2 diabetes in middle-aged and older people, independent of other established risk factors, especially metabolic syndrome components [27]. Although these evidences suggest that hyperuricemia may play a pathophysiological role in glucose dysmetabolism, further research should attempt to determine whether it is effective to utilize uriciemia plasma levels as a predictor of type 2 diabetes for its primary prevention [28]. It has been also found that serum uric acid concentration is associated with microalbuminuria, glyated hemoglobin and carotid intima-media thickness in type 2 diabetes [29,30]. In two recent Italian longitudinal studies of a cohort of type 2 diabetics, mild hyperuricemia was found strongly associated with the risk of chronic kidney disease [31] and increased serum uric acid is found to be an independent predictor factor of this complication [32]. Randomized trials have also shown that reducing hyperuricemia by anti-hyperuricemic treatment leads to significant improvement in endothelial function [33,34], this effect has been observed in diabetic patients with [35] and without hypertension [36,37]. Moreover, long-term and high-dose therapy with the anti-hyperuricemic drug Allopurinol has allowed to achieve significant improvement in glycated hemoglobin values in type 2 diabetic patients [36]. These data might well hypothesize a role of hyperuricemia even in the determination of vascular complications of diabetes.

In addition, correlations were found between hyperuricemia and microvascular damage in kidney and it has been shown that hyperuricemia is also an independent risk factor for the development of chronic renal dysfunction in general population [38,39], in patients with hypertension [40] and in diabetics [32,41].

**Potential pathogenetic mechanisms**

Pathophysiological mechanisms underlying the association between hyperuricemia and cardiovascular risk mainly include a hyperuricemia-induced endothelial dysfunction. The main determinants of vascular damage are the activation of the renin–angiotensin–aldosterone system and the production of reactive oxygen species resulting in cytokines production and in reduced endothelial bioavailability of nitric oxide. Uric acid has pro-inflammatory activity by stimulating the production of Interleukin-1β, Interleukin-6, Tumor necrosis factor-alfa and other cytokines [42,43]. Another possible pathogenetic mechanisms that can explain the vascular damage uric acid-related is the hyperactivity of the enzyme Xanthine oxidoreductase observed in hyperuricemic patients. Xanthine oxidoreductase catalyzes the last two steps of purine catabolism, the oxidation of hypoxanthine to xanthine and the oxidation of xanthine to uric acid. This enzyme exists in two forms: Xanthine dehydrogenase, which prefers NAD+ as electrons acceptor, and Xanthine oxidase, which generates electrons that are transferred directly to molecular oxygen; as a result of these reactions are produced two reactive oxygen species, superoxide anion and hydrogen peroxide, that contribute to amplify the oxidative stress and endothelial dysfunction [44,45].

In summary, hyperuricemia negatively affect vascular function by exerting pro-oxidant effects and by decreasing nitric oxide bioavailability, thus inducing inflammation and endothelial dysfunction, which may promote hypertension, diabetes, metabolic syndrome, nephropathy and cardiovascular disease.

**Anti-hyperuricemic treatment and serum uratic target**

There is no universally accepted definition of hyperuricemia. A physicochemical definition of hyperuricemia, based upon the solubility limit of urate in body fluids is widely preferred over a statistical definition because of the non-normal distribution of serum urate concentrations in most populations. This physicochemical definition corresponds to urate concentrations exceeding about 6.8–7 mg/dL (404–416 μmol/L), as measured by automated enzymatic (uricase) methods in routine clinical laboratory use; these values are approximately 1 mg/dL (60 μmol/L) lower than those obtained with colorimetric methods [6,46].
Therapeutic approach of hyperuricemia, and its prevention, include lifestyle and dietary recommendations. Since high uric acid levels are often associated with metabolic syndrome, weight reduction with daily exercise should be encouraged to prevent hyperuricemia by reducing insulin resistance. Changes in eating habits and in nutritional style would help reduce uric acid levels; low intake of dietary purine as red meat, animal entrails, crustacean and high–purine vegetables, as asparagus, spinach, peas, cauliflower or mushrooms, is recommended. Heavy drinking, ethanol and high fructose corn syrup–sweetened sodas should be avoided; whereas moderate drinking, sweet fruits, and seafood intake, particularly oily fish, should be tailored to the individual, considering their anticipated health benefits against cardiovascular diseases. Dairy products, vegetables, nuts, legumes, fruits (less sugary ones), and whole grains are healthy choices for the comorbidities of hyperuricemia and may also help prevent it by reducing insulin resistance. Adequate hydration may be useful to maintain a high urine output of at least 2 L daily; supplement of potassium citrate and occasionally sodium bicarbonate may be required to alkalize the urine and to increase the solubility of uric acid. Folate intake, vitamin C supplementation and coffee consumption seem associated with a lower risk of incident gout, while thiazide and loop diuretics can increase blood uric acid levels by interfering with renal clearance. [6,47,48].

Allopurinol, a competitive inhibitor of Xanthine oxido-reductase, is the most widely used anti-hyperuricemic agent, though not all patients are able to achieve a sufficient therapeutic response. Allopurinol can be used in almost any hyperuricemic state and the usual maintenance dose for adults is 200–300 mg once-daily; however a dose adjustment is required in patients with chronic renal failure because a higher incidence of adverse effects is observed if the dose is not adjusted. Allopurinol is well tolerated, but potential severe or fatal hypersensitivity reactions may develop; hepatotoxicity, bone marrow depression, and interstitial nephritis are rare but serious side effects of Allopurinol [49]. As well as being the most widely used anti-hyperuricemic, Allopurinol is also the most studied agent. Several studies have shown that anti-hyperuricemic treatment with Allopurinol has allowed to achieve a reduction in systolic and diastolic blood pressure values [50], regression of left ventricular mass in type 2 diabetic patients [51] and a prolonged exercise capability in patients with chronic stable angina [52]. It has also been shown that Allopurinol slows down the progression of renal failure in patients with chronic kidney disease [53]. At last, as already mentioned, Allopurinol allows to obtain a significant improvement in endothelial function [34–37], by reducing oxidative stress in the vasculature and improving endothelium-dependent dilation [54]. Another novel Xanthine oxido-reductase inhibitor, approved by the US Food and Drug Administration (FDA) in 2009 for long-term treatment of hyperuricemia in patients with gout, is Febuxostat [55]. In the CONFIRMS trial [56], a comparative study between Febuxostat and Allopurinol, Febuxostat 40 mg daily was statistically not inferior to Allopurinol 300 mg daily in lowering uric acid levels in patients with normal renal function, while Febuxostat 80 mg daily proved superior to both in such patients (p < 0.001); moreover, in patients with mild-to-moderate renal failure, Febuxostat at any dose was superior to Allopurinol in lowering uric acid levels and no dose adjustment was required in these patients. Although in the CONFIRMS study cardiovascular event rates were 0.0% for Febuxostat 40 mg and 0.4% for both Febuxostat 80 mg and Allopurinol 300 mg, some previous studies have identified cardiovascular events during Febuxostat treatment so that large ongoing trials are comparing the cardiovascular safety of Febuxostat versus Allopurinol [55]. In the FLORE study, a recent large adult trial carried out in tumor lysis syndrome prevention, Febuxostat at fixed dose of 120 mg daily has also achieved a significant superior serum uric acid control in comparison to Allopurinol, with comparable renal function preservation and safety profile [57].

Other novel anti-hyperuricemic agents are Rasburicase, Pegloticase and Lesinurad; Rasburicase [58], is a recombinant urate oxidase that facilitates the conversion of urate to a more soluble product, allantoin. It is approved, at a dose of 0.2 mg/kg daily as a 30-min infusion, in preventing complications of hyperuricemia for patients at high risk of tumor lysis syndrome [59]. Pegloticase is a recombinant, pegylated, uric acid–specific enzyme, administered by intravenous infusion that catalyzes the oxidation of uric acid to allantoin. It is approved for use in adults with chronic gout that is refractory to conventional therapy. During Phase-3 trials with Pegloticase were reported three cases of heart failure exacerbation and a case of nonfatal myocardial infarction; high cost and safety profile might limit its use in clinical practice [60]. Lesinurad is an oral selective uric acid reabsorption inhibitor approved by the FDA for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a Xanthine oxido-reductase inhibitor alone. It reduces hyperuricemia by inhibiting the urate transporter protein URAT1 that is responsible for the majority of the renal reabsorption of uric acid; moreover, Lesinurad also inhibits organic anion transporter OAT4, a uric acid transporter involved in diuretic-induced hyperuricemia. Administration of Lesinurad may be associated with an increased serum creatinine levels therefore renal function should be assessed before initiating therapy and periodically thereafter; more frequent monitoring is required for an estimated creatinine clearance below 60 mL/min and therapy should not be started if creatinine clearance is below 45 mL/min. Lesinurad is not approved for asymptomatic hyperuricemia and it is contraindicated for increased uric acid levels resulting from tumor lysis syndrome [61]. Other uricosuric agents that act on the proximal tubules in the kidneys, where they interfere with the reabsorption of uric acid through blocking URAT1, are Probencid, Sulfipyrazzone and Benzbromarone. Although these uricosuric agents provide the most time–honoured approach to the control of hyperuricemia, their place in the armamentarium has been eclipsed by that of Xanthine oxidase inhibitors [62].

At last, it is worth noting that some drugs with other primary uses, as Losartan [63], Atorvastatin, Simvastatin [64] and Fenofibrate [65], can have known uricosuric properties; these findings should be considered in hyperuricemic patients with comorbidity as hypertension and dyslipidemia.

Citation: Carella AM, Marinelli T, Melfitano A, Pumpo MD, Modola G, et al. (2017) Hyperuricemia and global Cardiovascular Risk: State of the art and preventive prospects. Arch Prev Med 2(1): 022-027.
However, regardless of the treatment used, urate-lowering therapy should be aimed at reaching at least a serum uric acid level below 6 mg/dL (360 μmol/L) and this value is considered the minimum serum urate target [6,46]. Actually we have found that the relationship between uric acid and cardiovascular events is evident not only in the presence of overt hyperuricemia but also for moderately increased levels of uric acid or for values corresponding to the upper limit of the actual normal range [66–68]. Moreover, a significant independent association between serum urate concentrations and subsequent hazard of incident hypertension was reported even at concentrations below the conventional hyperuricemia threshold of 6.8 mg/dL [20]. At last, the presence of only moderately increased serum uric acid levels (> 5.3 mg/dL in women and > 7.0 mg/dL in men) was also associated with a significantly increased risk of developing type 2 diabetes mellitus [69]. We retain that, according to the control of serum urate, particularly in patients with other cardiovascular risk factors, the lowest possible value of uric acid is better.

Conclusion

Although some studies have not shown a close correlation between hyperuricemia and cardiovascular risk, most scientific evidence agrees that hyperuricemia plays a key role in determining cardiovascular events and in development of other risk factors often associated also with moderate increases of serum uric acid levels. Early diagnosis, follow-up and prevention programs and effective treatment of hyperuricemia are recommended in particular in patients with other concomitant cardiovascular risk factors. Urate-lowering therapy should be aimed at reaching at least a serum uric acid level below 6 mg/dL (360 μmol/L); however, because relationship between hyperuricemia and cardiovascular events is evident also for moderately increased levels of uric acid or for values corresponding to the upper limit of the actual normal range, in high risk patients the lowest possible value of uric acid is better.

References

1. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, et al. (2007) European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil 2: S1-113. Link: https://goo.gl/5KesSc
2. Puddu P, Puddu GM, Cravero E, Vizioli L, Muscari A (2012) Relationships among hyperuricemia, endothelial dysfunction and cardiovascular disease: molecular mechanisms and clinical implications. J Cardiol 59: 235-242. Link: https://goo.gl/AfPdPS
3. Masseoud D, Rott K, Liu-Bryan R, Agudelo C (2005) Overview of hyperuricaemia and gout. Curr Pharm Des 11: 4117-4124. Link: https://goo.gl/rgxfML
4. Ricchette P, Bardin T (2010) Gout. Lancet 375: 318-328. Link: https://goo.gl/WN3sDd
5. Marangella M (2005) Uric acid elimination in the urine. Pathophysiological implications. Contrib Nephrol 147: 132-148. Link: https://goo.gl/vGyBCD
6. Khanna D, Fitzgerald JD, Khanna PP, Baes S, Singh MK, et al. (2012) 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 64: 1431-1446. Link: https://goo.gl/UYbiAb
7. Shah A, Keenan RT (2010) Gout, hyperuricemia, and the risk of cardiovascular disease: cause and effect? Curr Rheumatol Rep 12: 118-124. Link: https://goo.gl/AqV4Da
8. Juraschek SP, Kovell LC, Miller ER, Gelber AC (2013) Dose-response association of uncontrolled blood pressure and cardiovascular disease risk factors with hyperuricemia and gout. PLoS One 8: e56546. Link: https://goo.gl/K6Gqqs
9. Culleton BF, Larson MG, Kannel WB, Levy D (1999) Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med 131: 7-13. Link: https://goo.gl/f4kTnd
10. Fang J, Alderman MH (2000) Serum Uric Acid and Cardiovascular Mortality: The NHANES I Epidemiologic Follow-up Study, 1971-1992. JAMA 283: 2404-2410. Link: https://goo.gl/mWV7g
11. Wheeler JC, Juzwinski KD, Eiriksdottir G, Gudnason V, Danesh J (2005) Serum uric acid and coronary heart disease in 9,458 incident cases and 155,084 controls: prospective study and meta-analysis. PLoS Med 2: e76. Link: https://goo.gl/9MN7g
12. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, et al. (2009) Hyperuricemia and risk of stroke: a systematic review and meta-analysis. Arthritis Rheum 61: 885-892. Link: https://goo.gl/8q2zSv
13. Zhao G, Huang L, Song M, Song Y (2013) Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: a meta-analysis of prospective studies. Atherosclerosis 231: 61-68. Link: https://goo.gl/QvE9S2
14. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, et al. (2001) Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 38: 1101-1105. Link: https://goo.gl/oP2eYZ
15. Sánchez-Lozada LG, Tapia E, Soto V, Avila-Casado C, Franco M, et al. (2008) Treatment with the xanthine oxidase inhibitor febuxostat lowers uric acid and alleviates systemic and glomerular hypertension in experimental hyperuricemia. Nephrol Dial Transplant 23: 1179-1185. Link: https://goo.gl/8W6HMo
16. Xu W, Huang Y, Li L, Sun Z, Shen Y, et al. (2016) Hyperuricemia induces hypertension through activation of renal epithelial sodium channel (EnaC). Metabolism 65: 73-83. Link: https://goo.gl/v0JWfr
17. Jossa F, Farinano E, Panico S, Krogh V, Celentano E, et al. (1994) Serum uric acid and hypertension: the Olivetti heart study. J Hum Hypertens 8: 677-681. Link: https://goo.gl/SSZEJ1
18. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fuji S, et al. (2001) Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men: The Osaka Health Survey. J Hypertens 19: 1209-1215. Link: https://goo.gl/XKnGqZ
19. Nakanishi N, Okamoto M, Yoshida H, Matsu Y, Suzuki K, et al. (2003) Serum uric acid and risk for development of hypertension and impaired fasting glucose or Type II diabetes in Japanese male office workers. Eur J Epidemiol 18: 523-530. Link: https://goo.gl/wLaHDM
20. Gaffo AL, Jacobs DR Jr, Sirisena F, Lewis CE, Mikuls TR, et al. (2013) Serum urate association with hypertension in young adults: analysis from the Coronary Artery Risk Development in Young Adults cohort. Ann Rheum Dis 72: 1321-1327. Link: https://goo.gl/OxWUr8
21. Grayson PC, Kim SY, LaValley M, Choi HK (2011) Hyperuricemia and incident hypertension: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 63: 102-110. Link: https://goo.gl/n8Gmno

Citation: Carella AM, Marinelli T, MelfiTano A, Pummo MD, Modola G, et al. (2017) Hyperuricemia and global Cardiovascular Risk: State of the art and preventive prospects. Arch Prev Med 2(1): 022-027.
22. Hiwashima Y, Horio T, Kamide K, Rakugi H, Oghara T, et al. (2006) Uric acid, left ventricular mass index, and risk of cardiovascular disease in essential hypertension. Hypertension 47: 195-202. Link: https://goo.gl/gPRqAFj

23. Wang J, Qin T, Chen J, Li Y, Wang L, et al. (2014) Hyperuricemia and risk of incident hypertension: a systematic review and meta-analysis of observational studies. PLoS One 9: e114259. Link: https://goo.gl/bmnOCvR

24. Bonakdaran S, Kharaqani B (2014) Association of serum uric acid and metabolic syndrome in type 2 diabetes. Curr Diabetes Rev 10: 113-117. Link: https://goo.gl/2LSaSU

25. Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC (2008) High serum uric acid as a novel risk factor for type 2 diabetes. Diabetes Care 31: 361-362. Link: https://goo.gl/dT7v2Y

26. Sui X, Church TS, Meriwether RA, Lobelo F, Blair SN (2008) Uric acid and the development of metabolic syndrome in women and men. Metabolism 57: 845-852. Link: https://goo.gl/UAoqj

27. Lv Q, Meng XF, He FF, Chen S, Su H, et al. (2008) Uric acid and risk of type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. PLoS One 8: e56264. Link: https://goo.gl/c1fN6S

28. Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, et al. (2009) Association between serum uric acid and development of type 2 diabetes. Diabetes Care 32: 1737-1742. Link: https://goo.gl/ED2F6o

29. Neupane S, Dubey RK, Gautam N, Agrawal KK, Jayan A, et al. (2016) Association between serum uric acid, urinary albumin excretion, and glycated hemoglobin in Type 2 diabetic patient. Niger Med J 57: 119-123. Link: https://goo.gl/gLtCLN

30. Fukui M, Tanaka M, Shiraishi E, Harusato I, Hosoda H, et al. (2008) Serum uric acid is associated with microalbuminuria and subclinical atherosclerosis in men with type 2 diabetes mellitus. Metabolism. 7: 625-629. Link: https://goo.gl/cn5yul

31. De Cosmo S, Viazzi F, Pacilli A, Giorda C, Ceriello A, et al. (2015) Serum Uric Acid and Risk of CKD in Type 2 Diabetes. Clin J Am Soc Nephrol 10: 1921-1929. Link: https://goo.gl/1oHUPw

32. Viazzi F, Fiscitelli P, Giorda C, Ceriello A, Genovese S, et al. (2017) Metabolic syndrome, serum uric acid and renal risk in patients with T2D. PLoS One 12: e0176058. Link: https://goo.gl/2UBkA

33. Tsuruta Y, Kikuchi K, Tsuruta Y, Sasaki Y, Moriyama T, et al. (2015) Febuxostat improves endothelial function in hemodialysis patients with hyperuricemia: A randomized controlled study. Hemodial Res 24: 691-697. Link: https://goo.gl/gPqAFj

34. Meléndez-Ramírez G, Pérez-Méndez O, López-Osorio C, Kuri-Alfaro J, Espinola-Zavala N (2012) Effect of the treatment with allopurinol on the endothelial function in patients with hyperuricemia. Endocr Res 37:1-6. Link: https://goo.gl/K7HBWW

35. Butler R, Morris AD, Belch JJ, Hill A, Struthers AD (2000) Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild hypertension. Hypertension 35: 746-751. Link: https://goo.gl/ghnZaG

36. Dogan A, Yarlioglues M, Kaya MG, Karadayag Z, Dogan S, et al. (2011) Effect of long-term and high-dose allopurinol therapy on endothelial function in normotensive diabetic patients. Blood Press 20: 182-187. Link: https://goo.gl/Woq0H

37. Dawson J, Quinn T, Harrow C, Lees KR, Weir CJ, et al. (2009) Allopurinol and nitric oxide activity in the cerebral circulation of those with diabetes: a randomized trial. Diabetes Care 32: 135-137. Link: https://goo.gl/fAYtYq

38. Iseki K, Oshiro S, Tozawa M, Iseki C, Ikemiy Y, et al. (2001) Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. Hypertens Res 24: 691-697. Link: https://goo.gl/jdBVvo

39. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, et al. (2008) Uric acid and incident kidney disease in the community. J Am Soc Nephrol 19: 1204-1211. Link: https://goo.gl/1U6wa2S

40. Segura J, Campo C, Ruilope L (2002) How relevant and frequent is the presence of mild renal insufficiency in essential hypertension? J Clin Hypertens (Greenwich) 4: 332-336. Link: https://goo.gl/uVvJ3W

41. Tseng CH (2005) Correlation of uric acid and urinary albumin excretion rate in patients with type 2 diabetes mellitus in Taiwan. Kidney Int 68: 796-801. Link: https://goo.gl/lBk7ps

42. Grassi D, Desideri G, Ferri C (2014) New Insight into Urate-Related Mechanism of Cardiovascular Damage. Curr Pharm Des 20(39): 6099-6095. Link: https://goo.gl/K5e7pc

43. Perez-Ruiz F, Becker MA (2015) Inflammation: a possible mechanism for a causative role of hyperuricemia/gout in cardiovascular disease. Curr Med Res Opin 2: 9-14. Link: https://goo.gl/CrK7sB

44. Nishino T, Okamoto K, Eger BT, Pai EF, Nishino T (2008) Mammalian xanthine oxidoreductase - mechanism of transition from xanthine dehydrogenase to xanthine oxidase. FEBS J 275: 3278-3289. Link: https://goo.gl/psYyJ8

45. Chen C, Lu JM, Yao Q (2016) Hyperuricemia-Related Diseases and Xanthine Oxidoreductase (XOR) Inhibitors: An Overview. Med Sci Monit 22: 2501-2512. Link: https://goo.gl/6Y2wKk

46. Richette P, Doherty M, Pascual E, Barskova V, Becce F, et al. (2017) 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 76: 29-42. Link: https://goo.gl/shPrZ4

47. Choi HK (2010) A prescription for lifestyle change in patients with hyperuricemia and gout. Curr Opin Rheumatol 22: 165-172. Link: https://goo.gl/do7oFH

48. Singh JA, Reddy SG, Kundukulam J (2011) Risk factors for gout and prevention: a systematic review of the literature. Curr Opin Rheumatol 23: 192-202. Link: https://goo.gl/okkmn8

49. Day RJ, Kannangara DR, Stocker SL, Carlwand JE, Williams KM, et al. (2017) Allopurinol: insights from studies of dose-response relationships. Expert Opin Drug Metab Toxicol 13: 449-462. Link: https://goo.gl/ueEdYI

50. Feig DI, Soletsky B, Johnson RJ (2008) Effect of allopurinol on the blood pressure of adolescents with newly diagnosed essential hypertension. JAMA 300: 922-930. Link: https://goo.gl/1kTMVL

51. Szewkojkov BR, Gandy SJ Rekhraj S, Houston JG, Lang CC, et al. (2010) Allopurinol reduces left ventricular mass in patients with type 2 diabetes and left ventricular hypertrophy. J Am Coll Cardiol 62: 2284-2293. Link: https://goo.gl/XDkWZd

52. Noman A, Ang D, Ogston S, Lang CC, Struthers AD (2010) Effect of high-dose allopurinol on exercise in patient with chronic stable angina: a randomized, placebo controlled crossover trial. Lancet 375: 2161-2167. Link: https://goo.gl/CkXNrK

53. Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, et al. (2013) Allopurinol reduces left ventricular mass in patients with type 2 diabetes and left ventricular hypertrophy. J Am Coll Cardiol 62: 2284-2293. Link: https://goo.gl/XDkWZd

54. Noman A, Ang D, Ogston S, Lang CC, Struthers AD (2010) Effect of high-dose allopurinol on exercise in patient with chronic stable angina: a randomized, placebo controlled crossover trial. Lancet 375: 2161-2167. Link: https://goo.gl/CkXNrK

55. McMenamin JR, Verdalles U, Ruiz-Caro C, Ampuero J, et al. (2010) Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 5: 1388-1393. Link: https://goo.gl/vqzZFd

56. Mercuro G, Vitale C, Cerquetani E, Zoncu S, Deidda M, et al. (2004) Effect of hyperuricaemia upon endothelial function in patients with increased cardiovascular risk. Am J Cardiol 94; 932-935. Link: https://goo.gl/dFYUX6

57. Frampton JE (2015) Febuxostat: a review of its use in the treatment of hyperuricaemia in patients with gout. Drugs 75: 427-438. Link: https://goo.gl/iCUIZ8

58. Becker MA, Schumacher HR, Espinoza LR, Wells AF, MacDonald P, et al. (2010) The urate-lowering efficacy and safety of febuxostat in the treatment
of the hyperuricemia of gout: the CONFIRMS trial. Arthritis Res Ther 12: R63. Link: https://goo.gl/SmKkXw

57. Spina M, Nagy Z, Ribera JM, Federico M, Aurer I, et al. (2015) FLORENCE: a randomized, double-blind, phase III pivotal study of febuxostat versus allopurinol for the prevention of tumor lysis syndrome (TLS) in patients with hematologic malignancies at intermediate to high TLS risk. Ann Oncol 26: 2155-2161. Link: https://goo.gl/dwT1tw

58. Cammalleri L, Malagunera M (2007) Rasburicase represents a new tool for hyperuricemia in tumor lysis syndrome and in gout. Int J Med Sci 4: 83-93. Link: https://goo.gl/LS8TnA

59. Dinnel J, Moore BL, Skiver BM, Bose P (2015) Rasburicase in the management of tumor lysis: an evidence-based review of its place in therapy. Core Evid 10: 23-38. Link: https://goo.gl/SF1CXp

60. Shannon JA, Cole SW (2012) Pegloticase: a novel agent for treatment-refractory gout. Ann Pharmacother 46: 368-376. Link: https://goo.gl/4VdwXo

61. Hoy SM (2016) Lesinurad: First Global Approval. Drugs 76: 509-516. Link: https://goo.gl/g6iPN1

62. Bach MH, Simkin PA (2014) Uricosuric drugs: the once and future therapy for hyperuricemia? Curr Opin Rheumatol 26: 169-175. Link: https://goo.gl/W155uM

63. Wolff ML, Cruz JL, Vanderman AJ, Brown JW (2015) The effect of angiotensin II receptor blockers on hyperuricemia. Ther Adv Chronic Dis 6(6): 339-346. Link: https://goo.gl/CHf39x

64. Derosa G, Maffioli P, Reiner Z, Simental-Mendia LE, Sahebkar A (2016) Impact of Statin Therapy on Plasma Uric Acid Concentrations: A Systematic Review and Meta-Analysis. Drugs 76: 947-956. Link: https://goo.gl/zvnVqU

65. Derosa G, Maffioli P, Sahebkar A (2015) Plasma uric acid concentrations are reduced by fenofibrate: A systematic review and meta-analysis of randomized placebo-controlled trials. Pharmacol Res 102: 63-70. Link: https://goo.gl/mo7cgE

66. Feig DI, Kang DH, Johnson RJ (2008) Uric acid and cardiovascular risk. N Engl J Med 359: 1811-1821. Link: https://goo.gl/YTB3AW

67. Niskanen LK, Laaksonen DE, Nyysönen K, Alfthang G, Lakka HM, et al. (2004) Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. Arch Intern Med 164: 1546-1551. Link: https://goo.gl/NPeuB4

68. Verdecchia P, Schillaci G, Reboli G, Santeusario F, Porcellati C, et al. (2000) Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA study. Hypertension 36: 1072-1078. Link: https://goo.gl/KvxyxA

69. Viazzi F, Leoncini G, Vercelli M, Deferrari G, Pontremoli R (2011) Serum uric acid levels predict new-onset type 2 diabetes in hospitalized patients with primary hypertension: the MAGIC study. Diabetes Care 34: 126-128. Link: https://goo.gl/EF5vh2

Copyright: © 2017 Carella AM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Citation: Carella AM, Marinelli T, Melfitano A, Pumpo MD, Modola G, et al. (2017) Hyperuricemia and global Cardiovascular Risk: State of the art and preventive prospects. Arch Prev Med 2(1): 022-027.