Hyperuricemia as a Risk Factor for Cardiovascular Diseases

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Abstract
Serum uric acid level above 7 mg/dl is defined as hyperuricemia, which gives rise to the monosodium urate (MSU), causing gout and urolithiasis. Hyperuricemia is an independent risk factor as well as a marker for hypertension, heart failure, atherosclerosis, atrial fibrillation and chronic kidney disease. MSU crystals, soluble uric acid (UA) or oxidative stress derived from xanthine oxidoreductase (XOR) might be plausible explanations for the association of cardio-renovascular diseases with hyperuricemia. In macrophages, MSU activates the Nod-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome and proteolytic processing mediated by caspase-1 with enhanced interleukin (IL)-1β and IL-18 secretion. Soluble UA accumulates intracellularly through UA transporters (UAT) in vascular and atrial myocytes, causing endothelial dysfunction and atrial electrical remodeling. XOR generates reactive oxygen species (ROS) that lead to cardiovascular diseases. Since it remains unclear whether asymptomatic hyperuricemia could be a risk factor for cardiovascular and kidney diseases, European and American guidelines do not recommend pharmacological treatment for asymptomatic patients with cardio-renovascular diseases. The Japanese guideline, on the contrary, recommends pharmacological treatment for hyperuricemia with CKD to protect renal function, and it attaches importance of the cardio-renal interaction for treatment of asymptomatic hyperuricemia patients with hypertension and heart failure. In this review, the authors report the associations of hyperuricemia with cardiovascular diseases, and discuss its underlying mechanisms and the clinical implication of Japanese guideline 3rd edition of management for hyperuricemia and gout.

Keywords: hyperuricemia; cardiovascular disease; uric acid transporter; xanthine oxidase; inflammasome; guideline

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INTRODUCTION
Hyperuricemia occurs in 20 % of men and in 5 % of women in the entire Japanese population.1 Gene mutations may accelerate uric acid production or reduce either renal or extrarenal excretion of uric acid.1 In addition, a diverse range of environmental factors causes hyperuricemia. Hyperuricemia is defined as the serum urate level above 7.0 mg/dl.1 Hyperuricemia increases the uric acid pool to give rise to MSU crystals, which causes gouty arthritis and ureteral calculus and kidney failure.

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While clinical studies suggested that asymptomatic hyperuricemia frequently associates with cardiovascular diseases, it remains unclear whether hyperuricemia could be a risk factor for cardiovascular diseases (CVD), hypertension, stroke, atrial fibrillation (AF), metabolic syndrome (Mets), nonalcoholic fatty liver disease (NAFLD), chronic kidney disease (CKD) and diabetes mellitus (DM) (Table 1). The underlying mechanisms on the associations of hyperuricemia with cardiovascular diseases and the clinical implication of Japanese guideline 3rd edition of management for hyperuricemia and gout have been discussed.

Formation and physical properties of uric acid and the definition of hyperuricemia
1) Formation of uric acid
Since evolutionally loss of uricase activity, uric acid has been the end product of purine metabolism in the human body. Uric acid is synthesized from xanthine by xanthine oxidoreductase as well as from guanosine. The free purine bases, yielded by nucleoside cleavage are adenine, guanine, hypoxanthine and xanthine. Since purine nucleoside phosphorylase acts with relatively higher affinity on inosine and guanosine, the major bases generated are hypoxanthine and guanine. Hypoxanthine is oxidized to xanthine by xanthine oxidoreductase (XOR) and then further oxidized to uric acid by the same enzyme, while guanine is oxidized to xanthine. Uric acid synthesis happens mainly in the liver, where XOR is richly expressed.  

2) Solubility of uric acid in plasma
The weak acidity of uric acid is due to ionization of hydrogen atoms at positions 9 (pKa=5.75) and 3 (pKa=10.3). The ionized forms of uric acid easily form monosodium urate (MSU), and at pH7.4, approximately 98% of uric acid takes this form. When the concentration of MSU exceeds the solubility limit of body fluid, the crystals as monosodium urate monohydrate are formed in the synovial fluid or the tophi. Based on the MSU solubility product is 4.9x10⁻³, aqueous solution with the sodium concentration under physiological conditions is saturated with MSU at 6.4 mg/dl at 37℃. MSU solubility in the presence of 140 mM Na⁺ depends on temperature and is saturated with 6.8mg/dl at 37℃. Solubility of uric acid and MSU also depends on pH: with increasing pH uric acid is more soluble, whereas MSU is less. Seegmiller et al reported that when MSU crystal was incubated with serum obtained from gouty or nongouty subjects at 38℃, actual determination MSU in human plasma indicated that saturation occurs at about 7mg/dl. Considerably higher concentrations of MSU in plasma above 7 mg/dl can be achieved in a supersaturated solution, since serum contains factors that enhance urate solubility such as proteins. However, these solutions are unstable and MSU readily precipitates out. Thus, based on the solubility of MSU in plasma, hyperuricemia is defined as the serum urate level above 7mg/dl.

3) Crystalline Forms
Hyperuricemia was previously categorized to three types: the urate over-production type, the urate underexcretion type and the mixed types. Recently, the reduced urate extrarenal excretion type due to impaired uric acid secretion transporter, ABCG2 has been added. SUA level above 7mg/dl increases the frequency of gout arthritis. MSU occurs as monohydrate and forms crystals that are needle- or bar-shaped in a monoclinic or triclinic system. When rapidly crystalized in a pure solution, crystals are very fine and appear amorphous. Tissue deposits are composed of MSU monohydrate, while urinary stones are composed largely of uric acid. Both urate and uric acid crystals show strong negative birefringence when viewed under polarized light. MSU crystals are taken up by macrophages in the joint. In these cells, the assembly of the NLRP3 inflammasome activates caspase-1, leading to production of IL-1β and IL-18.

Evidence for the role of hyperuricemia and gout as a risk factor for cardio-renovascular diseases
1) Uric Acid and Hypertension
Hyperuricemia is a common complication of hypertension. 17 to 25% of hypertensive patients have hyperuricemia and this ratio increases to 65~75% in those with untreated hypertension. Decreased renal blood flow and tubular secretion of uric acid have been reported to cause hyperuricemia in hypertension. Hyperuricemia secondary to insulin resistance has also been reported to contribute to its association with hypertension via enhancing renal reabsorption of uric acid through URAT1. Enhanced myogenic production of uric acid precursor hypoxanthine is associated with elevation of SUA level in untreated hypertension.

Uric acid could be a risk factor for hypertension. Kuwabara et al reported that the occurrence of hypertension in hyperuricemic patients was 1.5 times higher than that in normouricemic patients. A meta-analysis on 18 cohort studies revealed the relative risk for hypertension of 1.41 (Table 1). Uric acid lowering agents might reduce blood pressure in certain hypertensive patients. Administration of allopurinol or probenecid reduced the SUA and this decrease was accompanied by reduction of blood pressure in adolescent male prehypertension subjects. A meta-analysis using interventional studies indicated that allopurinol reduced systolic blood pressure by 3.3 mmHg and diastolic blood pressure by 1.3 mmHg. Taken together, hyperuricemia could not only be a marker but also a risk factor for hypertension.

2) Uric Acid and Heart Failure
Hyperuricemia is often accompanied by heart failure (HF), since 47-56% of patients with heart failure has been reported to associate with hyperuricemia. In patients with HF, the prevalence of hyperuricemia ranges from 30 to 60%. Incidence of heart failure was 6-fold higher in patients with the highest quartile of serum uric acid (>6.3 mg/dL) than in those with the lowest quartile (<3.4 mg/dL). Adjusted hazard ratio for the highest quartile of serum uric acid compared with the lowest was 2.1 (1.04 to 4.22). Ogino et al reported that the prevalence of hyperuricemia increased in line with the NYHA classification and that the level of serum uric acid correlated to insulin resistance and renal function.
Mortality of patients with HF depends on the level of SUA. Hyperuricemia was also an indicator of poor prognosis in HF. A meta-analysis of observational studies showed that hyperuricemia was associated with an increased risk of HF and the risk of all-cause mortality and the composite endpoint, respectively.

Several studies asked whether uric acid lowering agents could influence the prognosis of HF. In meta-analysis of 5 case-controlled studies, uric acid lowering agents reduced cardiovascular mortality in patients with heart failure. There were two reports of randomized control trials in patients with chronic HF treated with xanthine oxidase inhibitors. In OPT-CHF study, oxipurinol did not influence the composite primary end points in patients with HF. In EACT-HF study, which examined whether allopurinol suppresses the cardiovascular mortality of patients with HF whose SUA >9.5mg/dl, there was no difference either in cardiovascular mortality or re-hospitalization between allopurinol and placebo group. Taken together, hyperuricemia is a marker of HF, but it remains unelucidated whether hyperuricemia is a risk factor for HF.

### 3) Uric acid and renal disease

Hyperuricemia is recognized as a risk of CKD as shown in meta-analysis (Table 1). A meta-analysis, with 255 patients in the drug intervention group and 239 subjects in the control group, showed a statistically significant difference in the amount of change determined as 4.12 mL/min/1.73 m2. A meta-analysis, with 134 patients in the drug intervention group and 106 subjects in the control group, revealed a risk ratio on the onset of renal events of 0.51, indicating a statistically significant difference between groups. Taken together, hyperuricemia is an independent risk factor for CKD.

### 4) Uric acid and atherosclerosis

Because of oxidative stress induced by SUA, hyperuricemia is associated with endothelial dysfunction and atherosclerosis. Flow-mediated vasodilation (FMD), an index of endothelial function, was impaired in patients with hyperuricemia. Since activation of XOR would increase both SUA and ROS, XOR inhibitors could be beneficial to prevent endothelial dysfunction.

According to a double-blind study, allopurinol improved endothelial function measured by the forearm blood flow response to acetylcholine, in subjects with chronic HF.

Incidence of hyperuricemia in patients with myocardial infarction is 48%. Three meta-analyses indicated that high SUA increased the risk of MI (RR: 1.20) and mortality (RR: 1.22). A meta-analysis enrolling 8776 patients with acute coronary syndrome (ACS) showed that higher SUA level increased the risk of MACE (RR: 1.86), all-cause mortality (RR: 1.86) and cardiovascular mortality (RR: 1.74). As shown in Table 1, the relative risk of morbidity and mortality of ischemic heart disease were reported to be 1.09 and 1.16, respectively, in patients with hyperuricemia. Urate-lowering have been shown to reduce the risk of MI. Taken together, hyperuricemia is a predictor of atherosclerosis and may be a risk factor for ischemic heart disease.

### 5) Uric acid and atrial fibrillation

Prevalence of hyperuricemia in patients with atrial fibrillation (AF) was higher (2.1%) than in those without hyperuricemia (1.7%). Incidence of AF in patients with gout increased with hazard ratio of 1.61 and the estimated prevalence was 7.42%. A follow up for 9 years of SUA in 107,360 Chinese patients revealed that the highest quartile of SUA had 1.91 times higher risk of AF in comparison to the lowest quartile. Incidence of AF with elevated SUA correlates linearly with age (OR: 2.08). A cohort study in Korea enrolling 282,473 patients indicated that the risk of AF in woman was 6.93-fold higher in the highest quartile of SUA than the lowest quartile, although in the men it was higher in the third and the highest quartile with hazard ratio 1.53 and 1.60 respectively. In Japanese patients with hyperuricemia had an increased risk to develop AF (OR: 3.187). Similarly (Table 1), SUA ≥6.5 mg/dl in men and SUA ≥4.9 mg/dl in women induced AF with hazard ratio of 1.60 and 1.64, respectively. Meta-analysis revealed that the relative risk of AF in patients with high SUA was 1.67. Data from another meta-analysis indicated that in hyperuricemia patients the risk of new onset or recurrence of AF was 1.66 and 2.07, respectively. Reduction of SUA with a use of urate-lowering therapy reduced incidence of AF (HR: 0.65). Taken together,
hyperuricemia could be an independent risk factor for AF.

**Figure 1.** Activation of NLRP3-inflammasome by MSU crystal
After priming through activation of toll-like receptor (TRL), which produces pro-IL-1β and pro-IL-18, MSU crystal absorbed in macrophage activates NLRP3-inflammasome via either K⁺ efflux, ROS or lysosomal damage, leading to process caspase1, which cleavages pro-IL-1β and pro-IL-18 to produce IL-1β and IL-18

**Mechanisms Underlying Cardiovascular Risk Due to MSU Crystals, Soluble Uric Acid and Xanthine Oxidase**

1) **Monosodium Urate and Cardiovascular Diseases**

Inflammation underlies various diseases such as rheumatic, gout and cardiovascular diseases. Hyperuricemia causes nucleation of monosodium urate (MSU) crystals, causing gout. The inflammatory response due to MSU crystals is affected by their size, electrostatic charge, state of aggregation and the presence and nature of coating proteins.³ MSU crystals are taken up by macrophages. In these cells, assembly of the NLRP3 inflammasome activates caspase-1 (Figure 1). Caspase-1 cleaves pro-IL-1β leading to secretion of active IL-1β.³³³³ NLRP3 inflammasome may play a pivotal role in the onset of not only gout but also various diseases such as chronic kidney disease, cardiovascular disease, atrial fibrillation, metabolic syndrome and diabetic complications.³⁴

2) **Soluble uric acid and cardiovascular diseases.**

In humans, 90% of uric acid filtered at the glomeruli is reabsorbed in the renal tubules. Uric acid is reabsorbed...
by the urate transporter 1 (URAT1) localized on the apical side of proximal tubular cells, whereas it exits the cells via voltage-driven urate transporter 1 (URAT1) located at the basolateral side. Recent experimental studies have shown that uric acid transporters are expressed not only in renal tubular cells but also in other types of cells, and that four uric acid transporters URAT1, MCT9, ABCG2 and MRP4 are commonly expressed in various organs. URAT1 and MCT9 belong to the influx transporter that reabsorbs uric acid, whereas ABCG2 and MRP4 belong to the efflux transporter that secretes uric acid.

Mishima et al. demonstrated that in HUVECs, uric acid reduced NO production through eNOS dephosphorylation and that NO production were restored by urate transporter inhibitors, suggesting that uric acid absorbed into endothelial cells causes inflammation, oxidative stress and dephosphorylation of eNOS [Figure 2].

Mouse atrial myocytes express at least four UATs: URAT1/GLUT9, ABCG2, MRP4 and MCT9. Uric acid could stabilize Kv1.5 channel proteins in mouse atrial myocytes (HL-1 cells) (Figure 3), resulting in an increase of ultra-rapid delayed-rectifier current (I\textsubscript{Kur}) and shortening of the atrial action potential through UATs. Inhibition of uric acid-influx UATs by benzbrromarone attenuated UA-induced enhancement of Kv1.5 protein expression. Inhibition of uric acid-efflux transporter ABCG2 accelerated UA-induced enhancement of Kv1.5 protein expression. Intracellular uric acid damaged the cells via an increase of oxidative stress and activation of the ERK1/2/Akt pathway together with phosphorylation of HSF-1 and HSP70. This effect was oxidative stress-dependent, since the enhancement of Kv1.5 protein expression by uric acid was reversed by the antioxidant N-acetylcysteine and the NADPH-oxidase inhibitor apocynin. This process involved the ERK1/2 pathway as part of the downstream signaling of urate-derived ROS, which was in consistent with the findings of other studies. An antioxidant may be a novel therapeutic approach against AF in hyperuricemic patients.

**Figure 3. Intracellular uric acid causes the electrical remodeling of atrial myocytes**

Accumulation of intracellular uric acid through UAT (URAT1/MCT9) induces nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase-dependent reactive oxygen species (ROS) production to increase Kv1.5 through Akt/ERK/HSF-1/HSP70 pathway. Akt, protein kinase B; HSF-1-S326, Ser 326 at heat shock factor 1; Hsp70, heat shock protein 70; URAT1/MCT9, influx uric acid transporters. ABCG2/MPR4, efflux uric acid transporters

3) Xanthine oxidase and cardiovascular diseases

XOR is a central player in the formation of uric acid. XOR is composed of XDH and XO. XO is generated from XDH by its protein modification and catalyses the last few steps of the reactions that convert hypoxanthine to xanthine, and xanthine to uric acid. These reactions yield hydrogen peroxide and reactive oxygen species (ROS). A high activity of XO creates pro-oxidative condition by generating O\textsubscript{2}\textsuperscript{-} which results in a decrease in nitric oxide expression, and endothelial dysfunction. Although XOR is highly active in the liver and small intestine, it also exists both in the cytoplasm and on the surface of endothelial cells. Recently, XOR was found to exist in human plasma. This circulating XOR is believed to be released from XO-rich organs such as liver. It binds glycosaminoglycans on the surface of endothelial cells and may be subsequently endocytosed [Figure 3].

The endothelial dysfunction has further consequences including reduced vascular elasticity, platelet aggregation, increased proliferation of smooth muscle cells, and fibrotic remodelling.

A study using mice fed with Western diet showed the high SUA level was followed by an increase in XO activity. The mice developed cardiac hypertrophy, oxidative stress in myocardium, interstitial fibrosis and impaired diastolic relaxation, which were improved after allopurinol therapy. An in-vivo study in dogs assessed the effect of allopurinol on the progression of atrial vulnerability. Allopurinol was able to suppress AF by inhibiting both electrical and structural remodelling of the atrium, suggesting the role of XO in enhancement of atrial vulnerability.

Uric Acid-Induced Modification of Neurohumoral Factors in The Cardiovascular System

1) Uric Acid and Insulin Resistance

Insulin resistance is the core of pathophysiology in metabolic syndrome and is linked to several diseases including diabetes mellitus, stroke, and coronary artery disease. The increase of SUA is accompanied by increased prevalence of the metabolic syndrome. Choi et al reported that elevation of fasting plasma insulin level correlates with elevation of SUA. Hyperinsulinemia due to insulin resistance enhanced both renal reabsorption of uric acid via activation of URAT1 and hepatic production of uric acid.

Hyperuricemia may in turn, cause insulin resistance. Insulin stimulates release of NO from endothelial cells, which causes vasodilation and aids delivery of glucose to the skeletal muscle. Uric acid reduces endothelial NO via several mechanisms, including inhibition of L-arginine uptake, stimulation of L-arginine degradation and chelating NO, leading to suppression of vasodilation and glucose delivery.

Uric acid may also induce insulin resistance via its effects on adipocytes. Uric acid enters adipocytes via URAT-1 and increases oxidative stress in these cells via...
activation of NADPH oxidase, generating oxidized lipids and inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1). These events lead to inflammation, insulin resistance, and a decrease in adiponectin synthesis. In the hyperuricemic mouse, allopurinol attenuates the inflammatory response in the visceral fat, reduces the expression of inflammatory cytokines, and enhances circulating levels of adiponectin. Likewise, administration of allopurinol or benz bromarone in the fructose-fed rat resulted in less insulin resistance and decreases the leptin level in the visceral fat.

2) Uric Acid and the Renin-Angiotensin System (RAS)

Hyperuricemia has been reported to activate the systemic RAS in the kidney. Uric acid increases renin expression, and studies in adult patients with essential hypertension and hyperuricemic children have also found an association of the plasma renin activity (PRA) and SUA. SUA level also correlated with urinary excretion of aldosterone in healthy men. Renal biopsy from rats demonstrated a correlation between SUA and the number of renin positive juxtaglomerular cells. Hyperuricemic rats exhibited increased juxtaglomerular renin and decreased macular densa neuronal NOS.

Uric acid stimulates formation of angiotensin II in vascular endothelial cells via activation of the inflammatory pathway. Cellular uptake of uric acid into cells via URAT1, induces oxidative stress, activation of mitogen activated protein kinases, and the nuclear factor kappa B and APO-1. These processes lead to release of vasoconstrictors, including thromboxane, endothelin-1 and angiotensin II. Uric acid is an antioxidant in the extracellular environment, but it has direct prooxidative effects once it gains entry into cells such as endothelial cells, adipocytes and vascular smooth muscle cells. This is followed by activation of the local RAS, angiotensin II type 1 and type 2 receptor expression, and the induction of senescence and apoptosis of endothelial cells.

Rationality of Pharmacological Treatment of Asymptomatic Hyperuricemia

Is asymptomatic hyperuricemia should be treated in patients with cardio-removascular disease? There are different recommendations for pharmacological treatment of asymptomatic hyperuricemic patients between Western countries and Asian country Japan. The European and American guidelines do not recommend use of uric acid lowering agents (ULAs) for asymptomatic hyperuricemia to prevent gout, renal dysfunction and cardiovascular events. In contrast, Japanese guideline recommend use of ULAs for asymptomatic hyperuricemia. Medicare system in Japan cover the medical expense in treatment with ULAs of asymptomatic hyperuricemia. Therefore, it is easy to conduct the clinical trials to examine whether pharmacological treatment of hyperuricemia could be reasonable have been conducted. FEATHER study reported that the treatment with xanthine oxidase inhibitor febuxostat significantly reduce the newly onset of gout in asymptomatic hyperuricemia with CKD compared to placebo, demonstrating the rationality of their pharmacological treatment of asymptomatic hyperuricemia in order to prevent gout.

Japanese guideline states that ULAs may be considered when patients have renal dysfunction, lifestyle related diseases or cardiovascular diseases and their SUA is > 8 mg/dl. The Japanese Guideline for the Treatment of Hyperuricemia and Gout 3rd edition was developed to clarify the rationality of pharmacological treatment in asymptomatic hyperuricemia in order to protect kidney disease or CVD according to GRADE approach. In order to make a recommendation to clinical questions (CQs) in this guideline, after setting the key clinical issues on hyperuricemia and gout, CQs together with advantage and disadvantage outcomes have been selected. Using systematic reviews on reports related to outcome of each CQs, the bias risk of each evidence has been estimated.

Taken together with the certainty in body of evidence, patients’ opinions and medical economics, the recommendation for each clinical question has been determined. As shown in Table 2, the recommendations have 3 elements: direction of recommendation, strength of the recommendation and strength (certainty) of evidence, and recommendations were expressed using combinations of these. The direction of recommendation refers to whether the recommendation will be implemented. Strength of recommendation refers to whether the recommendation is strong or weak, while the strength of evidence corresponds to one of A (strong), B (moderate), C (weak/low), or D (very weak/low) according to the GRADE approach. As referred to CQ (A) in Table 2, ULAs improved the renal function and suppressed the end-stage renal failure in CKD patients, although there was not any significant difference in adverse effects between ULAs treatment and placebo groups, indicating that the benefit of treatment with ULAs is much greater than the harm. Thus, in order to prevent renal failure, ULAs are partially recommended for use in hyperuricemic patients with CKD. There is not enough evidence that ULAs improve the total mortality or cardiovascular mortality in patients with both hypertension (CQ (B)) and chronic heart failure (CQ (C)), although there was no difference in adverse effects between ULAs treatment and placebo groups. Thus, in order to prevent CVD or improve prognosis, ULAs are not partially recommended for use in either hyperuricemic patients with hypertension or hyperuricemic patients with heart failure. Recently, FREED study reported that febuxostat significantly improved the primary composite endpoint of cardio-renovascular events in hypertension, diabetes and cerebro-cardiovascular disease in patients with hyperuricemia. This improvement was attributable to improvement of renal function indicating that improvement in renal function restores cardiac function (cardio-renal continuum). Thus, in order to reduce mortality in cardio-renovascular disease patients, ULAs could be used, when patients agree.

Japanese Medicare system covers the medical expense for treatment with ULAs in patients with asymptomatic hyperuricemia with being different from western countries. Taken together with the evidences reported in CQ (A), (B) and (C), treatment with ULAs...
could not only reduce the onset of gout and CKD, but also decrease the onset of CVDs through improvement of cardio-renal continuum, thus, it is strongly recommended that like Japan, Asian and western country may consider the rationality of pharmacological treatment of asymptomatic hyperuricemia to reduce both gout and reno-cardiovascular diseases.

CONCLUSION
Hyperuricemia together with XO can induce inflammation, endothelial dysfunction and remodeling of the cardiovascular systems through UATs, free radical or crystal induced NLRP3 inflammasome, which play a pivotal role in development of CVDs as a risk. Several lines of evidence report in the Japanese guideline attaches importance of the cardio-renal interaction for treatment of asymptomatic hyperuricemia patients. Thus, this review demonstrates the rationality of pharmacological treatment of asymptomatic hyperuricemia in order to reduce mortality in these patients.

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