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NEAR EAST UNIVERSITY
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Cardiovascular Events of Febuxostat Compared to Allopurinol: A Systematic Review and Meta-Analysis

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Approval

We certify that we have read the thesis submitted by Yazan Awad titled **"Cardiovascular Events of Febuxostat Compared to Allopurinol: A Systematic Review and Meta-Analysis"** and that in our combined opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Educational Sciences.

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DEDICATION

I dedicate this work to my beloved grandparents, cousin, and best friend, who were constant sources of encouragement and inspiration but are no longer with us; they are waiting for us in a better place with Allah's mercy. This thesis is dedicated to them.

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First of all, I want to thank **Dr. Onur Gültekin**, for being an advisor and a friend who provided me with guidance, support, and inspiration throughout my studies. I will always be eternally grateful to him.

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ABSTRACT

Background: Background: Febuxostat is an antihyperuricemic agent that was approved in 2009. Its usage became limited by FDA after reports indicated to increase the cardiac-related death due to the drug.

Objective: The main aim of this meta-analysis is to investigate the cardiovascular safety of febuxostat in comparison to allopurinol.

Method: Randomized controlled trials were synthesized by systematic research using 2 databases (Pubmed and Scoupus). The primary and secondary endpoints composite of the major adverse cardiovascular events (MACE), in addition to subgroup analysis according to dose, are represented as risk ratios (RR) with 95% CIs. A fixed-effect model was used with heterogeneity defined as an I^2>50%. P value, P<0.05 was considered significant.

Results: A total number of 20,321 participants from 12 trials were included in this study. The primary endpoint revealed a lower risk ratio of MACE with the febuxostat group in comparison to allopurinol (RR: 0.90, 95% CI: 0.81, 0.99 p = 0.03). However, the secondary and subgroup analysis did not show a significant difference between allopurinol and febuxostat groups.

Conclusion: Febuxostat has a lower risk ratio in terms of cardiovascular events in comparison to allopurinol independent of the dose.

Keywords: Febuxostat, Allopurinol, Gout, Hyperuricemia, Major adverse cardiovascular events.

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LIST OF ABBREVIATIONS:

ABBREVIATIONS	EXPLANATION
AP	Allopurinol
CV	Cardiovascular
CVD	Cardiovascular death
CKD	Chronic kidney disease
EULRA	European Alliance of Associations for Rheumatology
FBX	Febuxostat
FDA	Food and Drug Administration
HPRT	Hypoxanthine Phosphoribosyltransferase
MACE	Major Adverse Cardiovascular Event
MI	Myocardial Infraction
PRPP	Phosphoribosylpyrophosphate
RCT	Randomized Clinical Trial
SU	Serum Urate
SUA	Serum Uric Acid
UA	Uric Acid
ULT	Urate Lowering Therapy
URAT1	Uric Acid Transporter 1

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1 Introduction

Hyperuricemia and gout are two pathological disorders that are ordinarily related to each other. Hyperuricemia is a condition where there is an excessive production or insufficient excretion of uric acid in the urine. A purine-based catabolic mechanism is just one of the many causes of this. Gout and hyperuricemia are frequently linked to long-term conditions such as high blood pressure, diabetes, metabolic syndrome, renal disease, and cardiovascular disease (Gliozzi et al., 2016). Gout is the most common hyperuricemia complication, affecting approximately 4% of the population in the United States. On the other hand, asymptomatic hyperuricemia is surveyed to impact up to 21% of common people and 25% of hospitalized patients (George & Minter, 2021).

Unlike allopurinol, the most commonly used drug for hyperuricemia management, the chemical structure of febuxostat is non-purine-like. The mechanism of action of febuxostat acts on the inhibition of xanthine oxidase and it is used in the management of hyperuricemia (Bredemeier et al., 2018). The Food and drug administration, on the other hand, issued a febuxostat alert on November 17, 2017, based on preliminary findings from the CARES trial (Center for Drug Evaluation and Research, 2022) which compared febuxostat cardiovascular safety to that of allopurinol in over 6000 patients. Although there was no difference in overall cardiovascular events, the febuxostat group had a higher risk of all-cause and cardiovascular mortality. In 2019, FDA added a black boxed warning to febuxostat (White et al., 2018).

Despite the fact that febuxostat has been linked to an increase in cardiovascular events, febuxostat was found to be more effective than allopurinol at the commonly recommended fixed daily dosage of 300 mg (Becker et al., 2006). This meta-analysis assesses whether there is a cardiovascular risk associated with febuxostat use when compared to other anti-hyperuricemic medications, primarily allopurinol.

The main reason behind conducting this analysis is to evaluate the cardiovascular safety of febuxostat usage, especially after adding the box warning by FDA. Also, the physicians in clinical practice do not prefer to use febuxostat as a new drug for managing hyperuricemia and gout. They always prefer to prescribe allopurinol as a traditional treatment plan ignoring the high efficacy of the drug. However, there is no meta-analysis that focuses mainly on the dose in terms of cardiovascular safety.

1.1 Overview of Systematic Review and Meta-analysis

A systematic review compiles all potential research with a certain topic and design, and then examines and evaluates their findings (Barza et al., 2009). The quality of research is assessed throughout the systematic review process, and the findings of the studies are then the subject of a quantitative meta-analysis based on the quality of the investigations. A valid, impartial, and scientific approach to evaluating and combining several results is a meta-analysis. A meta-analysis is typically focused on randomized controlled trials (RCTs), which have a high degree of evidence, in order to produce more trustworthy results (Ahn & Kang, 2018).

Several studies have given standards for publishing RCT meta-analyses since 1999. A considerable number of systematic literature reviews have been reported as a result of the Quality of Reporting of Meta-analyses (QUORUM) statement (Moher et al., 1999), and the appearance of registers like the Cochrane Library's Methodology Register. The publication of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) declaration in 2009 (Liberati et al., 2009) significantly contributed to the standardization and enhancement of the calibre of systematic reviews and meta-analyses (Willis & Quigley, 2011).

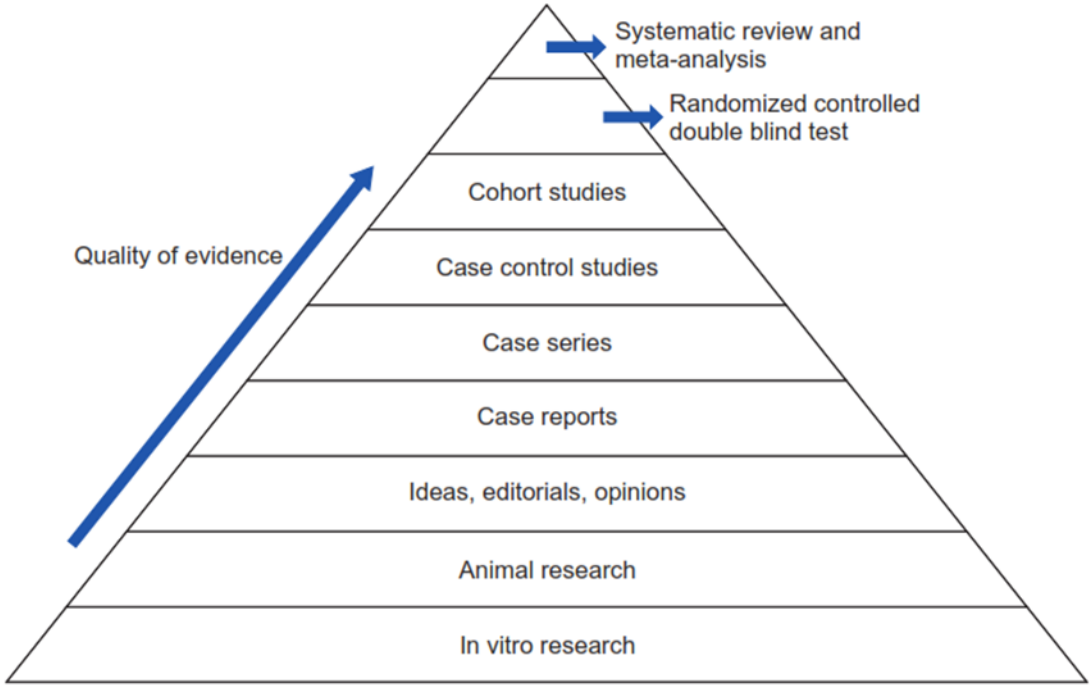


Figure 1 Funnel plot of subgroup analysis

1.2 Hyperuricemia

High uric acid levels are the metabolic anomaly which is responsible for gout occurrence. Hyperuricemia is defined as urate levels exceeding 6.8 mg/dl or 0.408 mmol/l. The most common causes of hyperuricemia are uric acid overproduction or underexcretion, with the latter occurring in 90 % of gout patients (Choi et al., 2005). Hyperuricemia, or having a high level of uric acid in the blood serum, is strongly associated with an increased risk of developing gout (Campion et al., 1987). Depending on age and gender, the serum UA's normal referral value may change. For premenopausal women, the normal serum urate range is typically 2.6 to 5.7 mg/dl, while for men, it often ranges from 3.5 to 6.8 mg/dl (Chen et al., 2016).

Uric acid is produced by the body when purines are broken down. The process of purine metabolism takes place primarily in the liver; nevertheless, it can occur in any organ that contains xanthine oxidase enzymes such as the intestines. The uric acid is eliminated mainly through the kidneys, only one-third is expelled through the intestines. It is filtered and excreted by the kidneys, with 90% being reabsorbed. Due to the activity of uricase, other mammals have lower levels of uric acid. This enzyme converts uric acid into allantoin, which is more soluble in water (Yakupova, 2018).

A high-purine food, endogenous purine production, and high cellular breakdown promote urea production, which is responsible for a small percentage of hyperuricemia. A diet rich in purine includes all types of meat, especially offal (kidneys, liver, “panettone”). , game meat and some shellfish (anchovies, herring, scallops). Beer, which is high in purines, increases uric acid levels by reducing kidney excretion. a defect in the regulatory enzyme hypoxanthine phosphoribosyltransferase (HPRT Some physiological conditions serve as a source of purine which is able to accelerate the cellular breakdown or turnover such as rhabdomyolysis, hemolysis, and tumour lysis, which leads to an increase of uric acid production (Gliozzi et al., 2016).

Urate elimination takes a place predominantly in the kidneys and is liable for hyperuricemia in 90% of the population. The fundamental reason for the inability to excretion the uric acid is due to a combination of decreased glomerular filtration, decreased tubular discharge and expanded tubular reabsorption. A temporary or permanent decrease in glomerular filtration can cause hyperuricemia. "Uric acid transporter 1" or "URAT1" is a protein that regulates uric acid reabsorption in the

proximal tubule. Organic acids (lactate and acetoacetate, as well as beta-hydroxybutyrate) and drugs (niacin, pyrazinamide, ethambutol, cyclosporin, and chemotherapy) can all enhance the above transport, resulting in hyperuricemia (Barkas et al., 2018). Uric acid and gout, on the other hand, are independent risk factors for cardiovascular disease, and the use of xanthine oxidase inhibitors (XOI) may reduce the risk of MACE (Richette et al., 2014; Grimaldi-Bensouda et al., 2015; Okafor et al., 2017).

1.3 Gout

Gout is considered one of the most common diseases whcih is caused by monosodium urate crystal deposition in articular and non-articular structures. Four pathophysiological stages might be thought of as the stages in gout develop (Dalbeth et al., 2021):

1- The emergence of hyperuricemia.
2- Crystals of monosodium urate are deposited.
3- Clinical manifestation of acute inflammatory reactions to accumulated crystals that cause gout flares.
4- Clinical manifestation of an advanced illness tophi-characterized.

Since most patients who suffer from hyperuricemia are asymptomatic with no gout development, it is not enough to induce clinically evident illness (Campion et al., 1987). The deposition of Monosodium urate crystal is another evidence of gout progression which can be identified using specialized imaging instruments (Campion et al., 1987; Howard et al., 2011).

Damage-associated crystalline monosodium urate initiates the stimulation of innate immune pathways. The beginning of a gout flare is significantly influenced by the monosodium urate crystals' activation of the (NLRP3) inflammasome in macrophages and monocytes (Martinon et al., 2006). The NLRP3 inflammasome relies on a two-signal initiation system to prevent uncontrolled activation that could harm the host. The first signal activates NF-B via TLR4 and TLR2, as well as the production of pro-IL-1 and inflammasome components (Liu-Bryan et al., 2005; Bauernfeind et al., 2009). The second activation signal causes the inflammasome to assemble and caspase-1 to activate, converting pro-IL-1 to mature IL-1 (Martinon et al., 2002). IL-1

then binds with the IL-1 receptor, triggering a downstream signaling cascade involving proinflammatory cytokines and chemokines, resulting in neutrophil and other cell migration to the crystal deposition site. Due to the two steps initiation process of NLRP3 inflammasome, monosodium urate crystals solely might not has an inflammatory outcome, and that is what explains how the presence of monosodium urate crystals in the joint does not necessarily cause a clinically apparent inflammation (Pascual et al., 1999; De Miguel et al., 2012).

Tophi are characteristic of the advanced stage of gout. Tophi are commonly found at damaged sites in gout (McQueen, 2009), with so many osteoclasts at the tophus-bone interface (Dalbeth et al., 2008). Furthermore, monosodium urate crystals decrease osteoblast viability and function in a direct and indirect way, favouring bone resorption and inflammation (Chhana et al., 2011; Chhana et al 2018).

1.4 Comorbid Disorders

According to the National Health and Nutrition Examination Survey conducted in 2007–2008, which is a part of the National Center for Health Statistics (NCHS) that belongs to the Centers for Disease Control and Prevention (CDC), gout is a disease that is commonly associated with comorbidities, including hypertension, chronic kidney disease, obesity, diabetes, and cardiovascular diseases (Zhu et al., 2012). (Table 1) summarizes some comorbidities and their percentage of prevalence. Moreover, extensive prospective studies have revealed that gout is linked to a higher mortality risk, particularly heart-related diseases (Choi & Curhan, 2017). Despite the fact that mendelian randomization studies have demonstrated a causality relationship between serum uric acid concentration levels and gout, these analyses have not consistently revealed a link between elevated serum urate concentrations and coronary heart disease, impaired renal function, high blood pressure, or diabetes type 2 Hughes et al., 2014; Sluijs et al., 2015; White et al., 2016; Keenan et al., 2016; Choi & Curhan, 2017). Even though, there has been some evidence to suggest that hyperuricaemia may be causally linked to worse endpoints in renal and heart disorders (Testa et al., 2014; Kleber et al., 2015; Mallamaci et al., 2015).

Table 1 The prevalence of comorbidities in hyperuricemia and gout

Comorbidity	Percentage
Hypertension	74%
Chronic kidney diseases	71%
Obesity	53%
Diabetes	26%
Myocardial infraction	14%
Stroke	10%

Cerebro-vascular and cardio-vascular disorders seem to be primary causes of mortality in hyperuricemic individuals who are treated with antihyperuricemic drugs, but hyperuricemia does not constitute a solo factor that increases the risk for atherosclerosis, cerebrovascular disease, or coronary artery disease occurrence (Reunanen et al., 1982; Beard, 1983; Petersson & Trell, 1983; Brand et al., 1985).

Although hyperuricemia is still debated as just an independent factor that increases the risk of atherosclerosis, overweight, hypercholesterolemia, and high blood pressure, which are common elements of the clinical manifestations of gout, are recognized risk factors for atherosclerosis and its related disorders (Tsutsumi et al., 1996). Thus, it is sensible to monitor gouty patients for dyslipidemia and to vigorously treat obesity and high blood pressure to avoid cardiovascular diseases, along with any worsening in kidney dysfunction.

1.5 Drug-induced gout and hyperuricemia

In clinical practice, drug-induced hyperuricemia and gout are emerging and growing concerns. However, the precise frequency and incidence of drug-induced hyperuricaemia remain unknown (Paulus et al., 1970). (Table 2) shows the common drugs causing hyperuricemia.

Table 2 Common drugs causing hyperuricemia

Drug	Suggested mechanism
Anti-tubercular drugs	Increased uric acid reabsorption (pyrazinamide) Decreased uric acid secretion (pyrazinamide) Reduction in the fractional excretion of uric acid (ethambutol)
Aspirin (low dose)	Increased uric acid reabsorption Decreased uric acid secretion
Cytotoxic chemotherapy	Massive disruption of tumour cells
Diuretics	Increased uric acid reabsorption in the proximal tubules Increased uric acid secretion Volume contraction
Immunosuppressant agents	Increased uric acid reabsorption in the proximal tubules (ciclosporin) Decreased glomerular filtration rate secondary to afferent arteriolar vasoconstriction (ciclosporin) Reduced urate excretion (tacrolimus)
Testosterone	Increased uric acid reabsorption
Xylitol	Increased purine degradation Increased production of lactate

1.5.1 Diuretics

Diuretics are among the most primary triggers of secondary hyperuricemia. Loop diuretics, thiazide diuretics, and thiazide-like diuretics have all been linked to an elevated risk of gout incidence (Choi et al., 2012; Bruderer et al., 2014). The symptoms of diuretic-induced gout are similar to those seen in other types of gout. The elevation in blood UA levels caused by diuretics may be observed within a couple days of therapy commencement. It appears to be dose dependent and to persist after prolonged dosing (Handler, 2010; Palmer, 2015). The increase in serum UA

produced by diuretics ranges from 6 to 21% above similar baseline levels (Reyes, 2003). After discontinuing diuretics, the uric acid level normally returns to normal within a couple of months.

Diuretics differ in how they affect the way the kidneys process uric acid and, consequently, how often gout develops. Loop diuretics and gout appear to have a stronger relationship than thiazides (Waller & Ramsay, 1989; Hunter et al., 2006). Comparing differences between diuretic subclasses or between specific diuretic drugs has only been the subject of a few research. Recent research assessed the risk of gout between two thiazides, chlorthalidone and hydrochlorothiazide (Wilson et al., 2014). According to this study, those who take chlorthalidone for hypertension are just as likely to get new-onset gout as people who take hydrochlorothiazide at an equivalent dose.

Data are inconclusive for amiloride and triamterene. While no effect was seen in some investigations, prolonged usage of triamterene was demonstrated to cause elevated levels of serum UA without the presence of clinical signs of gout (Kelley, 1975). It has been established that amiloride does not affect uric acid levels.

Spironolactone investigations on blood UA levels revealed contradictory findings, similar to triamterene research. According to earlier research, spironolactone generally reduces the levels serum uric acid levels alone (Falch & Schreiner,1983). Although, a new study found that individuals with chronic renal disease who take low doses of spironolactone have higher serum UA levels (Cabrera et al., 2014). In a smaller trial, the impact of spironolactone on the renal elimination of UA was examined. They discovered that, like many other diuretics, spironolactone results in a reduction in renal excretion of UA, which is likely mediated by the induction of volume depletion and an increase in plasma renin activity. However, the serum UA levels are unaffected by this reduction in elimination because endogenous UA production is likely inhibited to roughly the same extent (Roos et al., 1982).

1.5.2 Antitubercular Drugs

Anti-mycobacterial medication pyrazinamide not only causes hyperuricemia but also has the potential to cause severe gout episodes. It is a potent urate retention agent, reducing kidney uric acid elimination by more than 80% at a therapeutic daily dose of 300 mg (Pham et al., 2014).

Another antitubercular medicine called ethambutol also causes a considerable rise in serum UA concentration. During the second, third, and fourth weeks of ethambutol medication, this impact was primarily noted (Narang et al., 1983). Furthermore, as early as 24 hours following the administration of only one dose of ethambutol, an elevation in the serum urate content was seen. Ethambutol treatment can trigger gouty arthritis and elevate serum UA levels (Khanna, 1980). Ethambutol discontinuation caused serum UA concentration to return to baseline. Hyperuricaemia returned once the medication was administered again (Postlethwaite et al., 1972; Khanna et al., 1984). Although the actual mechanism of ethambutol-induced hyperuricaemia is unknown, patients receiving this medication saw a significant decrease in their fractional elimination of UA (Postlethwaite et al., 1972).

1.5.3 Immunosuppressant Agents

With incidence rate between 5 to 84% for hyperuricaemia and 1.7 to 28% for gout, hyperuricaemia and gout are frequent side effects after organ transplants (White et al., 2016). Ciclosporin, a calcineurin inhibitor, is regarded as the main risk factor for the onset of gout in transplant recipients (Stamp et al., 2005). Hyperuricaemia was discovered in 25% of kidney transplant recipients before to the broad usage of ciclosporin, but this number grows to nearly 80% after that time (Mazzali, 2005).

Ciclosporin medication may result in an expedited type of gout, even though tophi appear in uncommon areas such as soft tissues, intraspinal sites, and sacroiliac joints (Baethge et al., 1993; Cohen & Cohen, 1995). Gouty arthritis occurs in 410% of all individuals on ciclosporin (Burack et al., 1992). The average duration between transplant and the first incidence of gout was a couple months. In comparison to individuals with hyperuricemia absent gout, others with gout attacks caused by ciclosporin were often men, took diuretics, and had more progressive kidney failure (Lin et al., 1989). Ciclosporin might enhance proximal uric acid reuptake, especially when there is of volume reduction from diuretic usage, as well as a reduction in glomerular filtration rates due to afferent arteriolar vasoconstriction (Marcén et al., 1995; Hansen et al., 1998).

Tacrolimus, another calcineurin inhibitor, may similarly produce hyperuricemia in recipients of kidney transplantation (Kanbay et al., 2005). The rate of hyperuricemia in tacrolimus individuals was much less than in ciclosporin individuals (Uslu

Gokceoglu., et al 2013). However, there are studies that suggest that there is no significant difference in the prevalence of hyperuricaemia between the two medications (Balal et al., 2004).

Mizoribine, a powerful immunosuppressant extensively used in Asia, was similarly associated with hyperuricaemia (Guo, 2010). It usually happened within a couple of weeks and was merely temporary. It could be because of the drug effect, which suppresses the synthesis of guanine nucleotides (Yoshioka et al., 2000).

1.5.4 Aspirin

Aspirin may cause hyperuricaemia and decrease UA elimination when used in modest doses (60–300 mg once daily), whereas greater doses are uricosuric (Caspi et al., 2000). The two ways that aspirin interacts with the urate monocarboxylate exchanger (URAT1) to produce that paradoxical effect are by serving as an exchange substrate to promote UA reabsorption with low doses and as an inhibitor of urate reabsorption at high doses (Ohtsu et al., 2010). The impact of aspirine on kidney UA retention was exacerbated by hypoalbuminemia and concurrent use of diuretics.

1.6 Management of Hyperuricemia and Gout

Hyperuricemia, or an increase in the concentration of uric acid in the blood, is a prevalent condition in clinical practice. While there are established recommendations for treating symptomatic hyperuricemia in acute situations such as gout, urolithiasis, and acute urate nephropathy, there is even less information about secondary prevention. Moreover, in spite of the ceaseless debate with respect to the role of UA within the etiology of CKD, high blood pressure and heart diseases, the treatment of asymptomatic hyperuricemia in patient populations with these chronic illnesses is still largely left to clinicians' discretion. When recommending urate-lowering treatment, individual concerns should always be taken into account (Dalbeth et al., 2009).

1.6.1 Pharmacological Treatment Options for Hyperuricemia and Gout

The pharmacological treatment of gout and hyperuricemia consists of two strategies. Initially, decreasing the inflammation and pain attack is achieved by NSAID, colchicine, corticosteroid and intralukines-1 antagonist. On the other hand, the decline

of the levels of serum uric acid by using xanthine oxidase inhibitors, uricosuric agents, selective inhibitors of URAT1 transporter, uricosuric agent and uricase agents are used for this purpose (Engel et al., 2017). A summary of the drug options used for the management of hyperuricemia and gout are listed in (Table 3 and Table 4).

Table 3 Pharmacological options used for the management of gout (Engel et al., 2017)

Substance/group	Proposed therapy	Adverse drug effects	Major Contraindications	Comments
Nonsteroidal anti-inflammatory drugs (NSAIDs) PO	Maximum dose; 5 to 10 days or until symptoms resolve	Renal dysfunction	Renal failure	Early start of treatment more important than choice of NSAID
Corticosteroids PO	30 to 35 mg predni - solone PO for 5 days	Overproduction of stomach acid, Cushing's syndrome, metabolism disorder, hypertension/hypotension	– Infection in particular – Poorly managed diabetes mellitus or arterial hypertension – Ulcerating wound(s)	
Colchicine PO	Low-dose therapy: 2 × 0.5 mg initially, then single administration 0.5 mg after 1 hour	Gastrointestinal effects in particular	Reduced creatinine clearance or liver failure; concomitant administration of CYP3A4 inhibitors, e.g. statins	If gout flare was no longer than 24 hours ago
Cortisone IA or IM		Overproduction of stomach acid, Cushing's syndrome, metabolism disorder, hypertension/hypotension		IM or IA corticosteroid injection possible in exceptional cases
Interleukin-1 antagonists Canakinumab SC	Single administration (150 mg SC), repeat administration after no less than 12 weeks	Infections (e.g. urinary tract infections, airway infections); local skin reactions at site of injection	If active infections present	If all 3 standard treatment options contrain - dicated/not tolerated

Table 4 Pharmacological options used for the management of hyperuricemia (Engel et al., 2017)

Substance/group	Proposed therapy	Adverse drug effects	Major contraindications	Comments
Xanthine oxidase inhibitor: allopurinol	Initially 50 to 100 mg/ day; increase to max. 800 mg/day	Diarrhea, nausea, vomiting, increased liver enzymes, skin reactions (2%), hypersensitivity syndrome (0.1%)	Known hypersensitivity to allopurinol	Adjust dose in cases of known renal failure Monitor liver and kidney enzyme levels
Xanthine oxidase inhibitor: febuxostat	Initially 80 mg/day, increase to 120 mg/day if necessary	Liver dysfunction, diarrhea, nausea, headache, skin rash	Ischemic heart disease <12 months or decompensated heart failure	If allopurinol not tolerated, in cases of renal failure, or if target uric acid level not achieved despite increased allopurinol dose
Uricosuric agent: probenecid	Probenecid can be combined with allopurinol if allopurinol alone is insufficiently effective	Irritation of gastrointestinal tract, skin reactions, anorexia	Urolithiasis, advanced renal failure (creatinine clearance <50 mL/min), or increased uric acid production (e.g. during chemotherapy)	Take with sufficient fluids to prevent kidney stone formation
Selective inhibitor of URAT1 transporter: lesinurad	Authorized in combination with xanthine oxidase inhibitor for treatment-refractory cases since February 2016	Headache, influenza-like symptoms increased creatinine levels, gastroesophageal reflux	Severe renal failure, tumor lysis syndrome, Lesch–Nyhan syndrome	Further studies required on cardiovascular safety according to the European Medicines Agency (EMA). Therefore not currently recommended for patients with cardiovascular events <12 months
Uricosuric agent: benzbromarone	Not recommended by these authors due to liver toxicity			
Uricase: pegloticase	Taken off the market in July 2016	Uric acid levels reduced due to breakdown of uric acid into allantoin, which is eliminated in the urine. Adverse drug effects: infusion issues, anaphylaxis, antibody formation.		

1.6.2 Comparison of the Guidelines for Gout and Hyperuricemia Management: 3E, ACR and EULAR

The American College of Rheumatology (ACR) approved guidelines for the management of hyperuricemia in gout patients in 2012 (Khanna et al., 2012), which were updated in 2020 (FitzGerald et al 2020), the "3E" Initiative “Evidence, Expertise, Exchange Initiative” guidelines issued in 2014 (Sivera et 2014), and the The European Alliance of Associations for Rheumatology (EULAR) recommendations released in 2016 (Richette et al., 2017). (Table 5) shows the similarities and differences between them and Figure 2 show the steps of management of hyperuricemia and gout.

In patients who have previously been diagnosed with gout, abruptly increasing purine intake through diet nearly fivefold increases the risk of recurrence (Zhang et al., 2012). Reduced consumption of red meat, alcohol (particularly beer), and sugary beverages, along with increased coffee consumption, are potentially beneficial diet and lifestyle changes in secondary gout prevention (Choi, 2010). The usage of vitamin C supplements is not recommended due to the lack of data related to its efficacy in order to prevent gout (FitzGerald et al 2020). However, in overweight or obese patients, weight loss is encouraged, but it needs to be done gradually to prevent an acute gout crisis caused by ketonemia. Dietary treatments, when used in conjunction with ULT, assist attain target UA levels even though they appear to be less effective than ULT at lowering UA levels (Skoczyńska et al., 2020; FitzGerald et al 2020).

First-line pharmacotherapy includes xanthine oxidase inhibitors such as allopurinol and febuxostat. These medications prevent uric acid precursors from being converted to uric acid. The most commonly used drug is allopurinol with a typical dose of 100 mg for the first day (Skoczyńska et al., 2020).

Testing for the HLA-B*5801 allele prior to allopurinol treatment should be considered in certain populations, such as Southeast Asian or African American descent, because of the increased likelihood hypersensitivity induced by allopurinol, in addition to a fatal drug reaction with eosinophilia and systemic syndrome "DRESS" (Khanna et al., 2012; FitzGerald et al 2020).

Rashes, pruritus, cytopenia, diarrhea, toxic epidermolysis, and Stevens-Johnson syndrome are some of the other adverse effects of allopurinol. In patients with

preexisting renal insufficiency, standard doses of allopurinol may cause renal failure progression. The renal clearance of oxypurinol, the main metabolite of allopurinol, is inversely correlated with renal creatinine clearance. Therefore, the dose of alopurinol must be adjusted (e.g., a starting dose of 50 mg/day) in patients with renal insufficiency to avoid life-threatening toxicity (Hande et al., 1984). If allopurinol is ineffective or tolerable, febuxostat, a non-purine selective inhibitor of xanthine oxidase, may be prescribed. Using both xanthine oxidase inhibitors at the same time is not advised. The recommended starting dose for febuxostat is 40-80 mg/day (Skoczyńska et al., 2020). If the target level of uric acid is not reached after two weeks, as demonstrated by the UA crystallization threshold, the febuxostat dose could be raised by 40 mg/day. Febuxostat is processed in the liver, and a slight increase in transaminases is the most common side effect (Gunawardhana et al., 2018).A uricosuric substance may be combined to a xanthine oxidase inhibitor or used alone to reach the therapy aim of complete remission of remaining symptoms including tophi and UA below target levels. By inhibiting URAT1 in renal tubules, uricosurics increase UA renal excretion (Skoczyńska et al., 2020). Because of its severe hepatotoxicity, benzbromarone has been banned in the United States and most European countries, but it is still used with caution in Asia. Both FDA and EMA authorized the innovative uricosuric drug lesinurad as second-line therapy between 2015 and 2016 (Skoczyńska et al., 2020). Statins, fibrates, and losartan, among other medicines used to treat hyperlipidemia and hypertension, enhance UA excretion and may amplify the uricosuric impact (Zhang et al., 2015; Aminiahidashti et al., 2017). Loop diuretics and thiazides, on the other hand, raise the uric acid levels in gout patients (Aminiahidashti et al., 2017). The above diuretics function by trying to compete with uric acid for cell membrane transporters in the proximal tubules. Hydrochlorothiazide should be avoided in gout patients if at all possible, according to the most recent ACR guidelines (FitzGerald et al 2020).

Figure 2 Steps of gout and hyperuricemia management

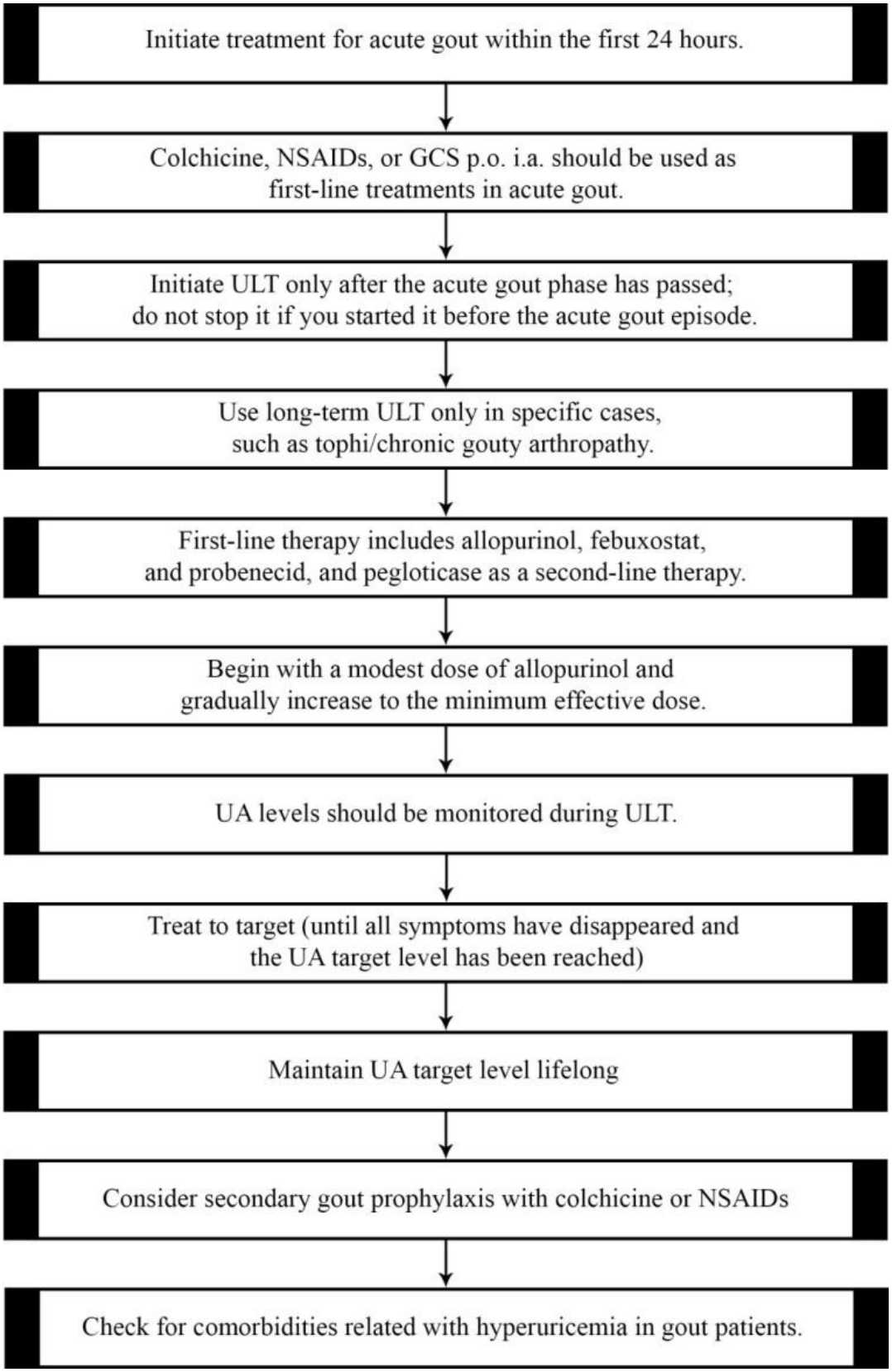


Figure 3 Similarities and differences between ACR, 3E Initiative and EULAR guidelines

Parameters	ACR	3E Initiative	EULAR
Maximum dose of colchicine during the first 24 hours of a severe gout attack	1.8 mg	2.0 mg	1.5 mg
Indications for ULT	≥ 1 tophi; radiographic damage due to gout; ≥ 2 episodes/year; conditionally in coexisting chronic renal disease stage III–V or nephrolithiasis or UA > 9 mg/dl or infrequent recurrence (< 2 episodes/year)	Tophi; chronic gouty arthropathy	Tophi; chronic gouty arthropathy; > 2 episodes/year; diagnosis at the age of < 40; UA > 8 mg/dl; nephrolithiasis or other comorbidities
Initial allopurinol dose and mode of escalation	Initially 50–100 mg; adding 100 mg every 2–5 weeks	Initially 50–100 mg; adding 100 mg every 2–4 weeks	Initially 100 mg; adding 100 mg every 2–4 weeks
UA target level	< 6 mg/dl	< 6 mg/dl; < 5 mg/dl in the presence of tophi or chronic gouty arthropathy	< 6 mg/dl; < 5 mg/dl in the presence of tophi or chronic gouty arthropathy or > 2 episodes/year
Duration of secondary gout prophylaxis with small-dose colchicine or NSAIDs	At least 3–6 months	Depending on physician's judgement	6 months

1.6.3 Acute Gout Attack Management

NSAIDs and oral colchicine are the first-line treatments for gouty arthritis attacks. Colchicine has been demonstrated to be less toxic and more efficient at smaller doses than were previously typical. A comparison between giving patients 1.0 mg preceded by 0.5 mg an hour later and giving them 1.0 mg preceded by 0.5 mg every 2 hours until Gastro intestinal toxic effects was published. At 48 hours, the anti-inflammatory efficacy of the 2 treatments was equivalent, with the low-dose group showing less toxic effects. (Table 5) shows summary of the contraindications and relative contraindications of colchicine use (Newcombe & Robinson, 2013).

Table 5 Contraindication and relative contraindications of cholchicine (Newcombe & Robinson, 2013).

Colchicine contraindications	Relative contraindications
Inflammatory bowel disease	Neutropenia
Pregnancy	Renal failure
Nursing mothers	Hepatocellular disease
Hepatic dysfunction	Gastrointestinal disease (mucosal lesions)
Decreased renal function	Agranulocytosis
	Aplastic anemia
	Infertility (azoospermia)
	Myopathy
	Elderly patients with cardiovascular, renal, or gastrointestinal diseases

Acute gout can be treated with the NSAIDs as well. Multiple NSAIDs have similar effect, according to research. Such drugs raise serious concerns about upper gastrointestinal toxic effects and hemorrhage. If proton pump inhibitors or Cox-2 selective inhibitors are used concurrently, this probability might well be minimized. NSAIDs can cause cardiovascular events, but compared to other NSAIDs, naproxen seems to pose a lower risk (Newcombe & Robinson, 2013).

In patients who have significant kidney impairment and other multimorbidity, corticosteroids are the treatment of choice because they are effective for treating acute gout. Prednisone or its equivalent in doses ranging from 40 to 60 mg per day, tapering off over the course of around 10 days, could be orally administered. For the management of acute gout, intra-articular glucocorticoids are efficient and secure,

particularly when monoarticular. Synovial fluid samples can be taken concurrently for crystal culture and analysis (Newcombe & Robinson, 2013).

1.6.4 Chronic Gout Management

Patients who suffer from frequent acute gout attacks, tophi on medical assessment, or radiological gout modifications should receive uric acid-lowering therapy. ULT aims to disintegrate monosodium urate that is already existent in body tissue and stop additional crystallization by reducing serum UA to levels under the monosodium urate saturation point. A serum UA level of less than 6.0 mg/dl is the target for the treatment in real terms (Newcombe & Robinson, 2013).

The ULT must be administered in sufficient doses to accomplish this aim; otherwise, the medical intervention will be inefficient. ULT is typically advised against beginning during an acute attack. If a patient is already receiving ULT at the time of an attack, the medication might be preceded throughout the attack (Newcombe & Robinson, 2013).

Allopurinol is the urate-lowering medication that is most frequently perscribed. In individuals with regular kidney efficacy, it should be initiated at a dose of 100 mg/day and risen every 2-4 weeks till the goal level of serum UA is achieved. The required dose varies depending on the patient. The FDA has authorised daily doses as high as 800 mg. Since up to 5% of patient populations might have an allergy to allopurinol while a much smaller percentage could experience the possibly deadly allopurinol hypersensitivity syndrome, in addition it is crucial to educate users of potential adverse reactions (Newcombe & Robinson, 2013).

Febuxostat is a helpful ULT. For individuals who have allergy to allopurinol, this medication is enormously beneficial, and since it is widely accessible, desensitization to allopurinol is rarely required. Furthermore, because it is metabolized by the liver, it can be used in patients who have mild nephrotic syndrome. If necessary, the dosage can be raised to 120 mg/day from the recommended starting dose of 40 mg/day (Newcombe & Robinson, 2013).

The uricosuric agents are an alternative ULT. Probenecid is the drug that is administered the most frequently, and sulfinpyrazone is used less frequently. However, these medications should not be administered if the patient has previously experienced UA kidney stones as regular or only mildly abnormal kidney function is

needed. The doses of uricosuric medications should be sufficient to decrease the serumUA to the desired values, similar to other ULT (Newcombe & Robinson, 2013). Despite of the medication prescribing, prophylaxis against acute attacks must be taken for at least the first few months of ULT. Colchicine, at a dose of 0.5 or 0.6 mg once or twice daily as tolerated, is the most widely popular medication. Even though there is little research supporting the efficacy of NSAID prophylaxis, NSAIDs may be used if colchicine is not permitted. Prophylaxis is often advised for a duration of six months, but it could be necessary for much extended durations because it could need longer periods to dissolve all of the tissue urate, particularly in individuals with tophaceous gout (Newcombe & Robinson, 2013).

1.6.5 Asymptomatic Hyperuricemia Management

There are few medical conditions of absence-drug-related asymptomatic hyperuricemia are summarized in (Table 6) which is treated by XOIs.

Table 6 Allopurinol indications (Newcombe & Robinson, 2013).

Heritable enzyme deficiencies
Hypoxanthine-guanine phosphoribosyltransferase
PRPP synthesase over-activity
Glycogen storage disease
Renal Calculus
Calcium oxalate
Uric acid
Increased risk of renal calculus or tophaceous deposits
Urinary uric acid excretion of more than 1,000 g/day
Serum uric acid greater than 8-10 mg/dl
Single function kidney
Prophylaxis for cytotoxic chemotherapy or radiotherapy
Secondary hyperuricemia
Urinary uric acid greater than 1,000 mg/day
Serum uric acid of 8 mg/dl or more
Renal disease

Patients with any of the inherited genetic enzyme deficiencies linked to irregularities in purine metabolism and excessive UA production should unquestionably receive allopurinol treatment as they are more likely to experience renal calculi and/or tophaceous gout (Newcombe & Robinson, 2013).

The need for therapies to lower increased uric acid serum levels in patients who suffer from CKD is still up for debate. Although serum UA levels are typically less than 10 mg/dl and the renal illness typically advances very gradually, CKD is frequently linked to hyperuricemia. There is insufficient proof that allopurinol therapy significantly slowed the progression of renal damage in those individuals (Rosenfeld, 1974). However, ULT may be necessary in indiviruals who have single functioning renal and noticeable modifications in the metabolism of UA. There are few exceptional cases to these suggestions, as one might expect, as well as no specific standards for most of these therapeutic interventions. Additionally, the SA serum levels chosen as indicators of the necessity for therapy have been chosen arbitrarily and may change from doctor to another. They are not chosen using information obtained through experiments (Newcombe & Robinson, 2013).

If CKD and a corresponding decreased elimination of waste products containing nitrogen are excluded, drug-induced hyperuricemia is likely an often common trigger of increased serum UA levels seen among patient populations. With a few significant exceptions that are debated below, drug-therapy is rarely necessary for asymptomatic hyperuricemia brought on by medications, particularly diuretics. Different diuretics can induce hyperuricemia in different ways. Raised serum UA levels may result from capacity contraction secondary to diuresis that stimulates proximal renal tubular reabsorption of urate (Steele, 1969; Steele & Oppenheimer, 1969). Both diazoxide and furosemide cause hyperlacticacidemia that also decreases UA elimination through the renal tubules and raises serum levels of UA (Schultz et al., 1966; Gershon & Fox, 1974). The plasma proteins bind furosemide and its congeners, that aren't significantly altered at the glomerulus. They are transported by an organic transport system from the proximal tubules into the renal tubular fluid, and probenecid, a uricosuric agent, inhibits the action of furosemide by trying to prevent its entrance into the tubular fluid (Newcombe & Robinson, 2013).

Gout sufferers are much more likely than others to develop high blood pressure, and these two conditions commonly coexist (Kuzell et al., 1955; Barlow & Beilin, 1968). Diuretic medications for high blood pressure might worsen gouty occurrences in

individuals who already have the condition, as well as individuals with high blood pressure may develop a new case of severe gout attacks as a result of taking diuretics. This is because diuretics are frequently pescribed to treat high blood pressure. Behavior for the onset of gout in high blood pressure patients have been identified in new research to include males, increased alcohol intake, overweight, and the use of loop diuretics (Waller & Ramsay, 1989). It's interesting to note that while loop diuretics are more tightly correlated to gout in patients with hypertension than thiazide diuretics are. Furthermore, since the overall prevalence of gout has been noted in patients with both no kidney dysfunction and those with lowered kidney function, the correlation between gout and the use of loop diuretics has been found to be linked to diminished kidney function. Hydrochlorothiazide is a less effective hypotensive agent than chlorthalodine, which also raises UA levels (Newcombe & Robinson, 2013).

Therefore, it is still unclear if the treatment for diuretic-induced hyperuricemia in the presence of nonurate nephrotic syndrome must vary from that given for diuretic-induced hyperuricemia in the lack of kidney impairment. Controlled research is necessary to ascertain the possible impact on the nephrons' ability to eliminate urate of the added burden of diuretic-induced hyperuricemia. In the lack of such information, the argument for therapies is based on the hypothesis that intervention will prevent the sudden decline of surviving kidney function which results from the hyperuricemic condition. Those who are against therapy contend that the main hazards of hypouricemic medications vastly outweigh their advantages. Long-term follow-up research findings of diuretic-induced hyperuricemia which demonstrate slight proof of significant renal impairment (Lant, 1985; Langford et al., 1998) are proof that these arguments are reasonable. However, whenever the serum UA levels in individuals without hemoconcentration are between 8 and 10 mg/dl, a few more physicians recommend treating hyperuricemia. Individuals with urate nephropathy and drug-induced hyperuricemia should follow the same treatment protocol. A serum UA level of 10–13 mg/dl or higher may warrant the use of hypouricemic medications.

The mechanism causing hyperuricemia seems to be more complicated in individuals who have asymptomatic hyperuricemia that are being managed with nondiuretic-hyperuricemic medications. Salicylates induce urate accumulation in the nephrons in small doses (1.2 g/day), but they are uricosuric at larger doses (2-4 g/day) (Crone & Lassen, 1955; Yu & Gutman, 1955). Low-dose salicylates very seldom increase

serum UA concentrations by more than 1 mg/dl, but when combined with uricosuric agents, they neutralize their effects (Gutman & Yu, 1951; Steel & Boner, 1973).

Despite the fact that uricosuric medications are ineffective in treating pyrazinamide-induced hyperuricemia, large doses of salicylates (2-4 g/day) can overturn the condition (Dalbeth et al., 2015; Martinon et al., 2006). Ingesting 3-6 g/day of nicotinic acid results in hyperuricemia and reduces the uricosuric effects of sulfinpyrazone (Anturane) and iopanoic acid (Gershon & Fox, 1974). Because of this cause, allopurinol is typically used as treatment for nicotinic acid-induced hyperuricemia. Therapy is infrequently necessary for this type of situation. Increased serum UA levels respond to either uricosuric agents or xanthine oxidase inhibitors, and ethambutol (12–19 mg/kg body weight/day) is expected to raise serum UA levels (Postlethwaite & Kelly, 1972).

1.6.6 Symptomatic Drug-Induced Hyperuricemia

The most straightforward way to treat drug-induced hyperuricemia is to switch to a medication which does not produce it. In some circumstances, the problematic medication is totally pointless and may be completely stopped. For instance, several individuals are using aspirin, aspirin-containing medications, or over-the-counter NSAIDs on a constant schedule for non-specific maladies, and the doctors can tend to break this routine (Newcombe & Robinson, 2013). Pharmacologic agents that lessen the acute intra-articular inflammatory reaction are used to treat acute gouty arthritis, a side effect of drug-induced hyperuricemia. Despite their being uncommon, tophi as a side effect of drug-induced hyperuricemia are an absolute prescribed for antihyperuricemic therapy. Guidelines for the use of antihypertensive medications to avoid renal insufficiency continue to stay empirical in the apparent lack of a straightforward, non-invasive approach to the detection of UA nephropathy and clinical data that unequivocally demonstrate the impacts of hyperuricemia on kidney function. The therapies for any underlying illness that increases the risk of kidney damage must receive the majority of awareness. So, rather than using antihyperuricemic medications and aggressive control of high blood pressure; being overweight, hypercholesterolemia, and diabetes mellitus should be prioritized. Allopurinol is nevertheless occasionally prescribed in order to stop the decline in renal function when serum uric acid levels exceed 8–10 mg/dl, despite the fact that, as

was already mentioned, there is little proof to back up such a claim. When serum creatinine levels are consistently high, the dosage of allopurinol must be initially reduced. This prevents the retention of both allopurinol and its oxidation product, oxypurinol (Elion et al., 1966; Elion et al., 1968). To avoid sodium urate crystal accumulation, the dose of allopurinol must be increased sufficiently to lower serum UA levels to 6 mg/dl. Both allopurinol and oxypurinol can accumulate in the renal parenchyma and are comparatively insoluble (Newcombe & Robinson, 2013).

1.6.7 Hyperuricemia Associated with the Treatment of Neoplastic Disease

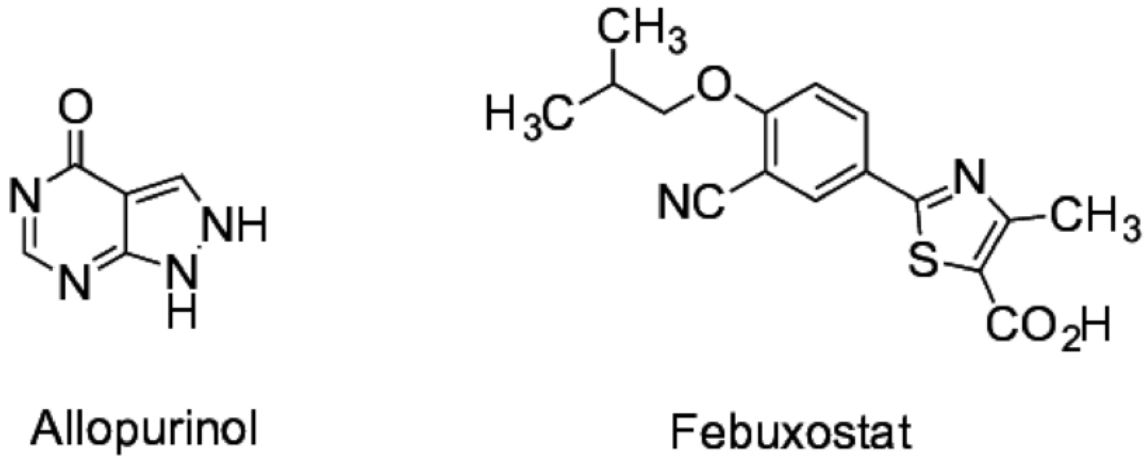
A common issue for patients being treated for neoplastic diseases is drug-induced hyperuricemia, which is accompanied by a higher output of UA. Severe uric acid nephropathy, a severe side effect of antineoplastic therapy, is brought on by apoptosis, purine metabolic processes, and the renal excessive UA excretion as a consequence. Initiating allopurinol treatment in patient populations who might be planned to receive chemotherapy or radiation therapy for tumors is therefore standard practice. To guarantee sufficient solubility of UA and the pyrazolopyrimidines, allopurinol treatment must always be administered alongside fluid hydration, preferably prior to the administration of antineoplastic treatment. Allopurinol must be given at a daily dose of 300 mg/m day in the first 48 hours, followed by a dose of 300 mg daily, in order to quickly inhibit xanthine oxidase. The common procedure to divide the overall dose is to administer it twice daily; a workable protocol for the majority of antineoplastic symptom management is to first administer allopurinol 300 mg twice daily, followed by 150 mg twice daily. Hydration can be achieved either orally or intravenously. A reasonable therapeutic primary objective is to consume between three and five liters more fluids per day than usual (Newcombe & Robinson, 2013).
However, alkalinization is typically not required in the context of antineoplastic therapy unless severe UA nephropathy develops. Urinary alkalinization with sodium bicarbonate or acetazolamide also improves the solubility of UA and allopurinol and its metabolites. Because sodium bicarbonate is preferred for urinary alkalinization when using acetazolamide because it is linked to a rebound acidosis; finding out if the individual is anuric is the primary step in treating severe UA nephropathy (Maisey & Brown, 1981). Hemodialysis offers the most efficient type of therapy for anuric patients (Rundles, 1985). Only when the ureters are blocked are ureteral lavage with

alkali solution and urate sludge surgical excision suggested. In patient populations who can consistently stabilize a sufficient urinary output, conservative control ought to be used. This includes taking steps to improve flow of urine, solubilize urates, and lessen UA output. Once underlying chronic lung disorder, kidney diseases, or diabetes mellitus exist, this conservative treatment plan necessitates constant maintenance of the amount of urine renal excretion, urinary pH, plasma electrolytes, arterial pH, and ketone bodies. Once arterial pH levels are lower than 7.2 or lactic acid is a factor in the acidosis, inhibiting carbonic anhydrase with acetazolamide to increase bicarbonate excretion by the kidney is considered unsafe. Allopurinol raises the toxic effects of 6-mercaptopurine, azathioprine, and other purine analog antimetabolites while blocking their own diminishment, so their dose must be decreased by at least a 1/3 to prevent allopurinol's toxic activity of such antimetabolite impacts (Rundles, 1985). Because of the higher toxicity of these antimetabolites, close observation of the patient on such a dual regimen is also required to detect bone marrow suppression and secondary infections (Rundles, 1985).

2 Febuxostat and Black-Box Warning

Febuxostat composites of a non-purine chemical structure and it act selectively on the inhibition of the purine catabolism enzyme xanthine oxidase (Khosravan et al., 2006). The xanthine oxidase enzyme catalyzes two processes in which hypoxanthine is converted to uric acid. The xanthine oxidase inhibitor febuxostat inhibits the enzyme's activity by forming a stable complex with both the reduced and oxidized versions of the enzyme. In both animals and people, febuxostat treatment lowers serum uric acid levels. The capacity of febuxostat to lower blood uric acid levels in individuals with hyperuricemia, defined as uric acid serum concentrations exceeding the solubility of uric acid (about 7 mg/dL), is the basis of its therapeutic impact (Becker et al., 2009; Richette et al., 2017). Febuxostat does not appear to be able to block other enzymes in the nucleotide catabolic pathways, and its molecular structure is unrelated to that of purines or pyrimidines (Mayer et al., 2005).

Figure 4 Chemical structure of allopurinol and febuxostat (Jordan & Gresser (2018)



Febuxostat is taken orally, with a starting dose of 40 mg per day (Gray & Walters-Smith, 2011). It can be taken without regard for food or antacids. After two weeks of treatment with 40 mg, if the patient's serum uric acid level has not decreased to less than 6 mg/dL, the physician may raise the dose to 80 mg daily, provided the individual does not have severe kidney damage (defined as a clearance of 15 to 29 mL/min). When taken orally, it is thought that more than 49% of the dose of febuxostat, which comes in tablet forms of 40 mg and 80 mg, is absorbed (Gray &

Walters-Smith, 2011). Gout flares may occur after starting febuxostat treatment (Bruce, 2006). As a result, flare prevention with an NSAID or colchicine is indicated concurrently with febuxostat treatment and can last up to six months (Schumacher et al., 2008; Jackson et al., 2012). Febuxostat is taken orally, with a starting dose of 40 mg per day (Gray & Walters-Smith, 2011). It can be taken without regard for food or antacids. After two weeks of therapy with 40 mg, if the patient's serum uric acid level has not decreased below 6 mg/dL, the physician may elevate the dose to 80 mg daily, provided the patient does not have severe renal impairment. It is estimated that when taken orally, more than 49% of the dose of febuxostat, which comes in tablet form of 40 mg and 80 mg, is absorbed (Gray & Walters-Smith, 2011). Gout flares may occur after starting febuxostat treatment (Bruce, 2006). As a result, flare prevention with an NSAID or colchicine is indicated concurrently with febuxostat treatment and can last up to six months (Schumacher et al., 2008; Jackson et al., 2012).

The most common adverse effects of febuxostat are abnormal liver function, dizziness, arthralgia, nausea, and rash (Schumacher et al., 2008). Nevertheless, based on the results of the CARES trial, the FDA added a Boxed Warning for febuxostat on November 15, 2017. (Center for Drug Evaluation and Research, 2022). In comparison to allopurinol, the data demonstrated that febuxustat did not enhance the risk of these combination occurrences. When the outcomes were examined independently, febuxustat was found to increase the probability of heart-related fatalities as well as death from any cause. For every 1,000 patients treated with febuxustat over a year, there were 15 heart-related deaths, as opposed to 11 heart-related deaths for every 1,000 patients treated with allopurinol over the same period. Furthermore, compared to allopurinol, febuxustat caused 26 deaths from any cause per 1,000 patients over the course of a year as opposed to 22 deaths per 1,000 patients (Center for Drug Evaluation and Research, 2022). Although febuxostat is an effective urate-lowering therapy, in 2019, FDA had set limits on the approved use of febuxostat to certain individuals who cannot be treated effectively or experienced serious adverse effects with allopurinol

This meta-analysis used 12 studies including CARES trial in order to investigate the cardiovascular safety of febuxostat. The research includes 20,321 participants. The main aim behind this meta-analysis is to investigate if a cardiovascular risk is associated with febuxostat use compared to allopurinol.

3 Methodology

3.1 Protocol and Registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations were followed for the systematic review. The study protocol is registered at Near East University, department of clinical pharmacy.

3.2 Search Strategy

The systematic review search is conducted using PubMed and Scopus databases. The following filters and keywords are used:

- For PubMed febuxostat AND cardiovascular events Filters: Randomized Controlled Trial
- For Scopus (febuxostat AND randomized controlled trial AND cardiovascular events) AND (EXCLUDE (DOCTYPE , "re") OR EXCLUDE (DOCTYPE , "sh") OR EXCLUDE (DOCTYPE , "cp") OR EXCLUDE (DOCTYPE , "ed"))

Also, a manual search was conducted on Google scholar in order to synthesis RCT which has the same criteria of this meta-analysis.

3.3 Population

Gouty or hyperuracemic patients who are aged over 18 years old from both genders are included in this meta-analysis

3.4 Inclusion Criteria

All the studies are selected according to the following inclusion criteria:

I. Head-to-head randomized clinical trials (RCT), which compared febuxostat to allopurinol.
II. Reported adverse events including cardiovascular events.
III. Long-term RCTs which are not less than 6 months.

3.5 Exclusion Criteria

I. Documents in languages other than English.
II. Studies without data on cardiovascular-related adverse events.
III. Short-term RCTs less than 6 months.
IV. Any literature reviews, systematic reviews and meta-analysis, non-randomized clinical trials survey, conference paper, editorial cohort, cross-sectional studies, or case reports are excluded.

3.6 Study Selection and Eligible Criteria

The titles and abstracts of the synthesized literature were screened initially then the non-related studies were excluded. The studies were fully reviewed by the author, and the study selection was determined according to the inclusion and exclusion criteria. Each step was revised twice by the author.

3.7 Intervention and Comparator

This meta-analysis is designed of the main intervention febuxostat compared to allopurinol in order to evaluate the risk ratio of cardiovascular events in the intervention group.

3.8 Data Extraction

All data which are related to cardiovascular adverse events are extracted. Data are collected according to the following information:

I. Authors, dates of study
II. Number of participants
III. Interventions
IV. Follow-up time
V. Outcomes.

3.9 Primary and Secondary Endpoints

Major adverse cardiovascular events (MACE) are the primary endpoint. Nonfatal myocardial infarction (MI), angina pectoris, heart failure, ischemic coronary artery diseases, and cardiovascular-related fatalities are all considered MACE. Secondary endpoints defined as nonfatal myocardial infraction, nonfatal stroke, and urgent

revascularization for unstable angina are used to assess the influence of febuxostat on individual endpoints.

3.10 Subgroup Analysis

The subgroup analysis is performed according to the dose of febuxostat in order to investigate if there is an association between the febuxostat dose and increased major adverse cardiovascular events (MACE). The low-dose group includes patients receiving febuxostat doses less than 80mg. on the other hand, the high dose of febuxostat is determined 80 mg or above. Both groups are compared with control groups which is allopurinol.

3.11 Data Synthesis and Statistical Analysis

The primary endpoints composite of the major adverse cardiovascular events (MACE) are presented as risk ratios (RR) with 95% CIs. All the statistical analyses were performed on Review Manager (RevMan) version 5.4. In order to investigate the cardiovascular effects of febuxostat, a fixed-effect model was used with heterogeneity defined as an I^2>50%. P value, P<0.05 was considered significant. The secondary endpoints and the subgroup analysis are statistically represented as it has been previously.

All the included data were statistically analyzed in order to be compared with CARES study.

3.12 Limitation of Meta-Analysis

Meta-analysis can be a powerful tool for drawing meaningful data-based conclusions and can assist avoid interpreting data incorrectly if done properly. A meta-analysis, however, may not always be helpful. In certain cases, it may even be detrimental (Higgins et al., 2020).

Meta-analyses are frequently criticized for "combining apples with oranges," as the phrase goes. A meta-analysis could be useless and conceal real variations in effects if studies are clinically varied. The comparisons that the key studies are making are one form of variety that is very significant. A single meta-analysis of all involved trials is

frequently senseless because there could be a mix of comparisons of various treatments with diverse comparators, each of which may require its own analysis. Furthermore, it is crucial to avoid combining too many different results. Determinations on what should and shouldn't be combined are always arbitrary, not accessible to statistical explanations, and instead call for dialogue and clinical judgment. Sometimes it may be challenging to come to a consensus. (Higgins et al., 2020).

Meta-analyses of potentially biased studies could be extremely misleading. If bias exists in some of the published research, meta-analysis will merely compound the flaws, producing a false result which could be viewed as more credible. Eventually, meta-analyses with significant publication and/or reporting biases are likely to yield an incorrect summary.

3.13 Publication Bias Assessment

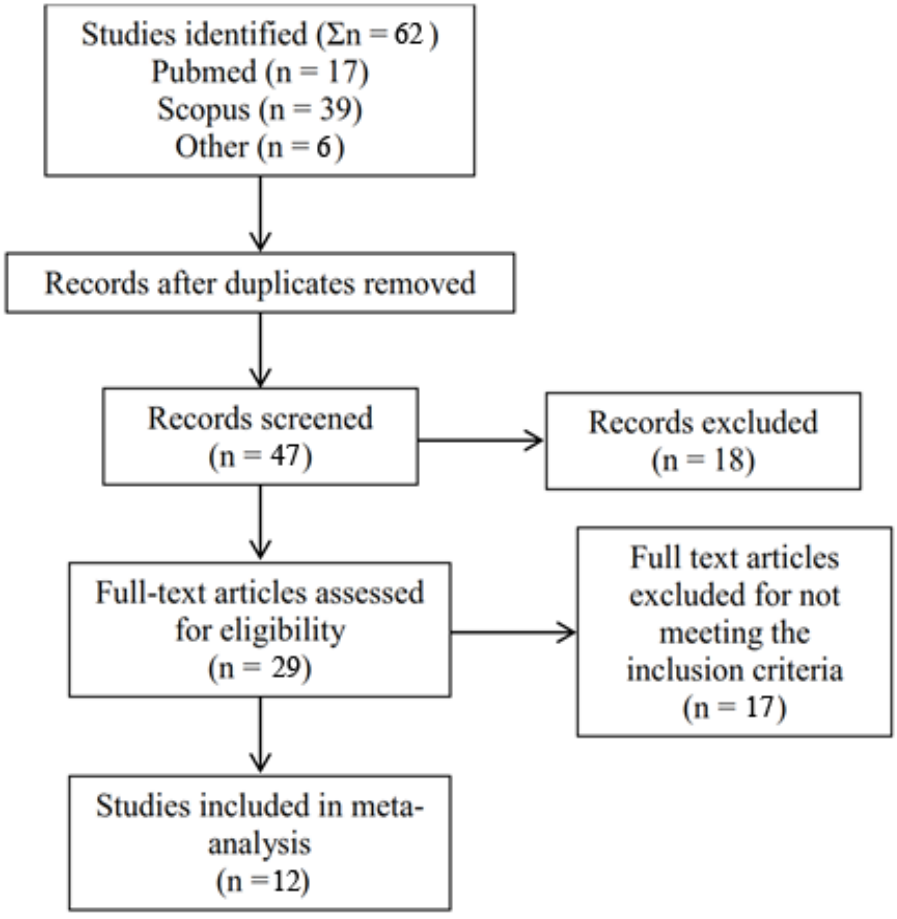
The funnel plot is one of the essential tools which used is to measure publication bias visually. In this meta-analysis, the funnel plot is used to determine the risk of publication bias.

4 Result

4.1 Result of Literature search

The search yielded 62 citations, 17 from Pubmed, 39 Scopus, and 6 articles were added from other sources. After the duplication check, 15 duplicate abstracts were removed. After screening the studies' abstracts, 18 studies were excluded and 23 were selected for full-text review; of these 17 studies were excluded according to the exclusion criteria. Therefore, 12 studies were finally included (Becker et al., 2005; Becker et al., 2009; Becker et al., 2010; Chohan et al., 2012; Jackson et al., 2012; Kojima et al., 2019; Mackenzie et al., 2020; Nakagomi et al., 2015; Schumacher et al., 2008; Spina et al., 2015; White et al., 2018; Xu et al., 2015). Figure 5 shows the flowchart of included and excluded studies. The total number of participants is 20,321. However, the characteristics of the studies are summarized in the following flow diagram (Table 7).

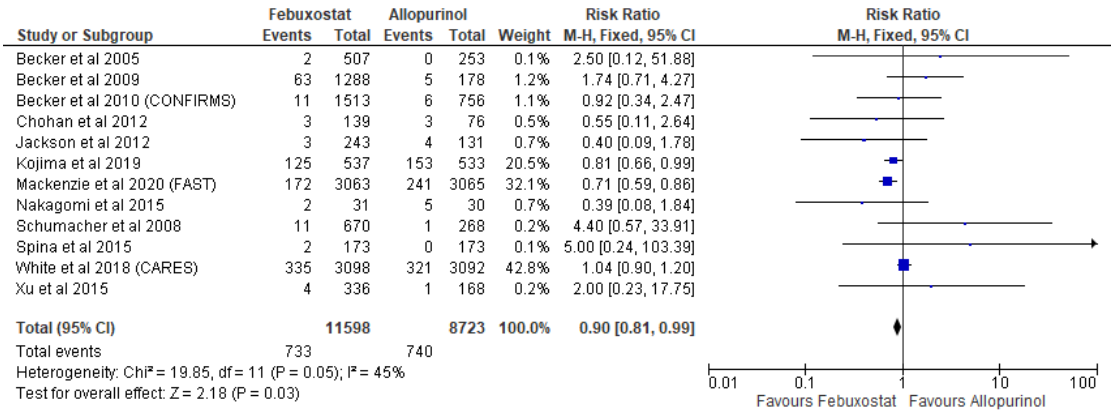
Figure 5 Flow diagram of study section procedure



4.2 Primary Endpoints

Primary endpoint: “composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina”. 12 studies, including CARES, were used in this meta-analysis (Becker et al., 2005; Becker et al., 2009; Becker et al., 2010; Chohan et al., 2012; Jackson et al., 2012; Kojima et al., 2019; Mackenzie et al., 2020; Nakagomi et al., 2015; Schumacher et al., 2008; Spina et al., 2015; White et al., 2018; Xu et al., 2015). Febuxostat shows a lower risk ratio (RR: 0.90, 95% CI: 0.81, 0.99 p = 0.03) for MACE, figure 6. CARES study has the highest weight among the 12 studies with 42.8% while Spina et al., 2015) has the lowest weight 0.1%.

Figure 6 Forest plot of the association between MACE and Febuxostat

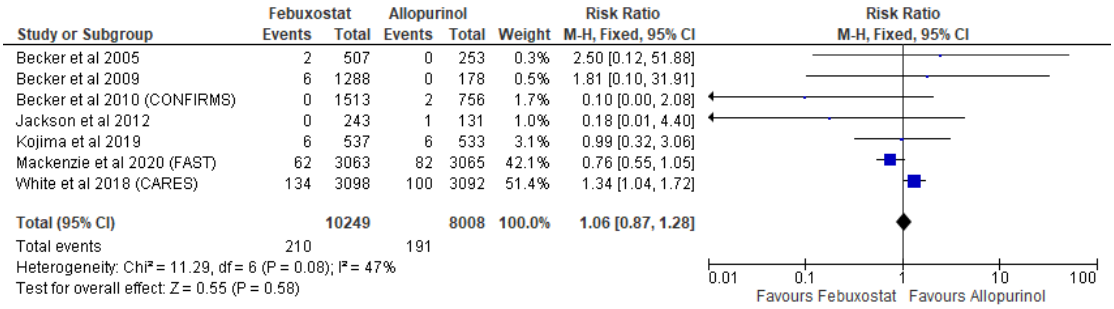


4.3 Secondary Endpoints

The secondary endpoint includes individual events such as “cardiovascular death, nonfatal myocardial infraction, nonfatal stroke and urgent revascularization”.

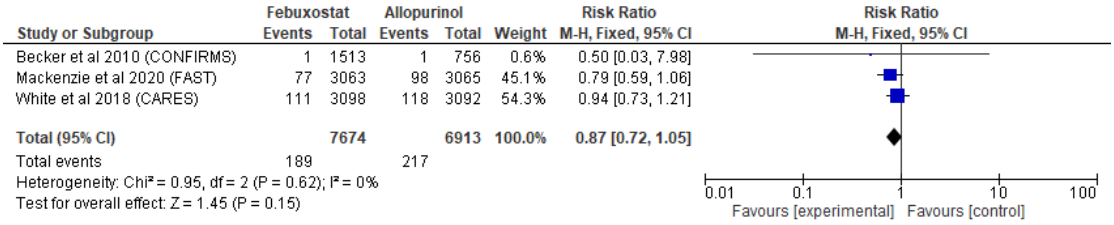
Six studies have been used in order to evaluate the cardiovascular death (Becker et al., 2005; Becker et al., 2009; Becker et al., 2010 ; Kojima et al., 2019; Jackson et al., 2012; Mackenzie et al., 2020; White et al., 2018). The association of cardiovascular death between the febuxostat and allopurinol groups was not statistically different (RR: 1.60, 95% CI: 0.87, 1.28 p = 0.58), figure 7.

Figure 7 Forest plot of the association between cardiovascular death and febuxostat



For nonfatal myocardial infraction, 3 studies have been used (Becker et al., 2010; Kojima et al., 2019; Mackenzie et al., 2020; White et al., 2018). Figure 8 shows that there is no significant difference associated with febuxostat and allopurinol groups (RR: 0.87, 95% CI: 0.72, 1.05 p = 0.15).

Figure 8 Forest plot of the association between nonfatal myocardial infraction and febuxostat



Three studies were used in order to analyze nonfatal stroke and urgent revascularization for unstable angina (Becker et al., 2010; Mackenzie et al., 2020; White et al., 2018). . Figure 9 shows nonfatal stroke (RR: 0.87, 95% CI: 0.69, 1.09 p = 0.23) while figure 10 represents urgent revascularization for unstable angina (RR: 0.85, 95% CI: 0.66, 1.09 p = 0.19).

Figure 9 Forest plot of the association between nonfatal stroke and febuxostat

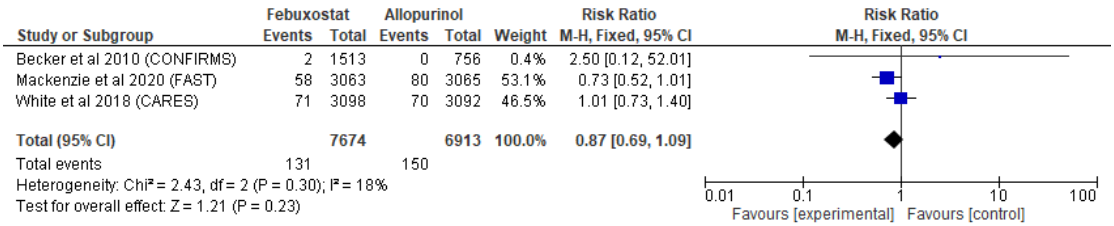
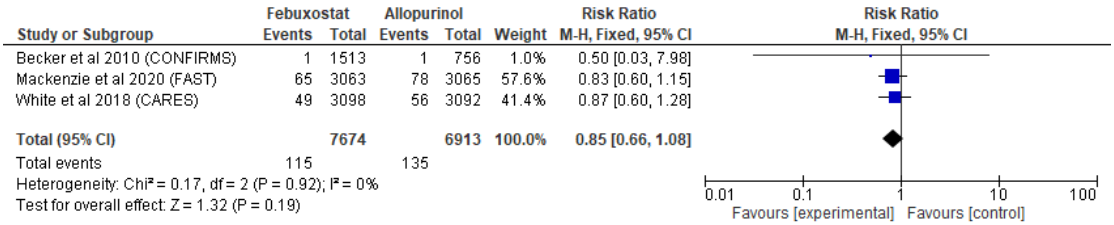


Figure 10 Forest plot of the association between urgent revascularization for unstable angina and febuxostat



4.4 Subgroup Analysis

Subgroup analysis was performed according to the dose of febuxostat. There are 2 groups; the first group includes the studies which used febuxostat 80 mg or less. On the other hand, dose higher than 80 mg were analyzed as well.

There are no significant differences between the low dose and high dose group which means that the associated risk ratio of MACE with febuxostat is not dose-dependent. (Figure 11).

Figure 11 Subgroup analysis according to dose of Febuxostat

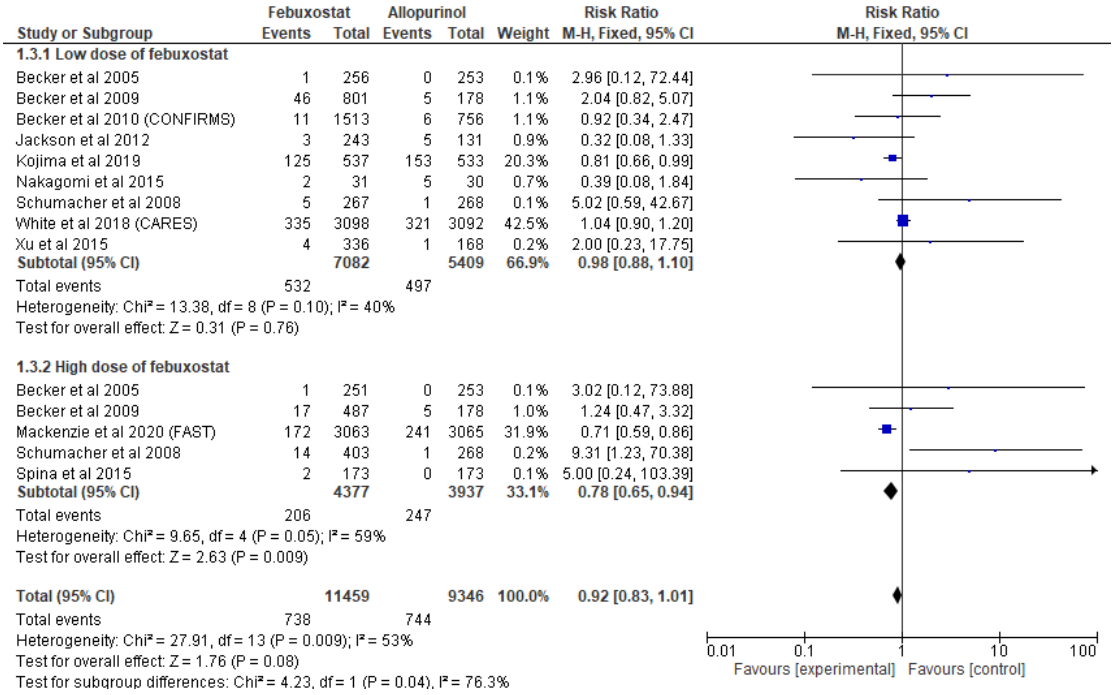


Table 7 Characteristics of the included studies

MACE	Allopurinol	0	5	6	3	4	153	241
	FBX	2	63	11	3	3	125	172
Sample size	Allopurinol	253	178	756	76	131	533	3065
	FBX	507	1288	1513	139	243	537	3063
Follow-up (months)		17	17	6	13	6	36	32
Control		Allopurinol	Allopurinol	Allopurinol	Allopurinol	Allopurinol	Allopurinol	Allopurinol
Intervention		Febuxostat 80 - 120 mg	Febuxostat 80 - 120 mg	Febuxostat 40 – 80 mg	Febuxostat 40 – 80 mg	Febuxostat 40 – 80 mg	Febuxostat 40 mg	Febuxostat 80 – 120 mg
Year		2005	2009	2010	2012	2012	2019	2020
Study		Becker et al	Becker et al	Becker et al 2010 (CONFIRMS)	Chohan et al	Jackson et al	Kojima et al	Mackenzie et al (FAST)

Nakagomi et al	2015	Febuxostat 40 mg	Allopurinol	14	31	30	2	5
Schumacher et al	2008	Febuxostat 80 – 240 mg	Allopurinol	7	670	268	11	1
Spina et al	2015	Febuxostat 120 mg	Allopurinol	24	173	173	2	0
White et al (CARES)	2018	Febuxostat 80 mg	Allopurinol	32	3098	3092	335	321
Xu et al	2015	Febuxostat 40 – 80 mg	Allopurinol	24	336	168	4	1

4.5 Publication Bias Assessment

The assessment of publication bias is evaluated by the funnel plot. The primary endpoint, which is represented with MACE, does not show a perfect symmetry which has a considerable risk of bias. However, the secondary endpoints which composite cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and urgent revascularization, have a considerable asymmetry due to the small number of included studies.

The funnel plot of subgroup analysis is asymmetry which means that it has a high risk of bias.

Figure 12 Funnel plot of the association between MACE and Febuxostat

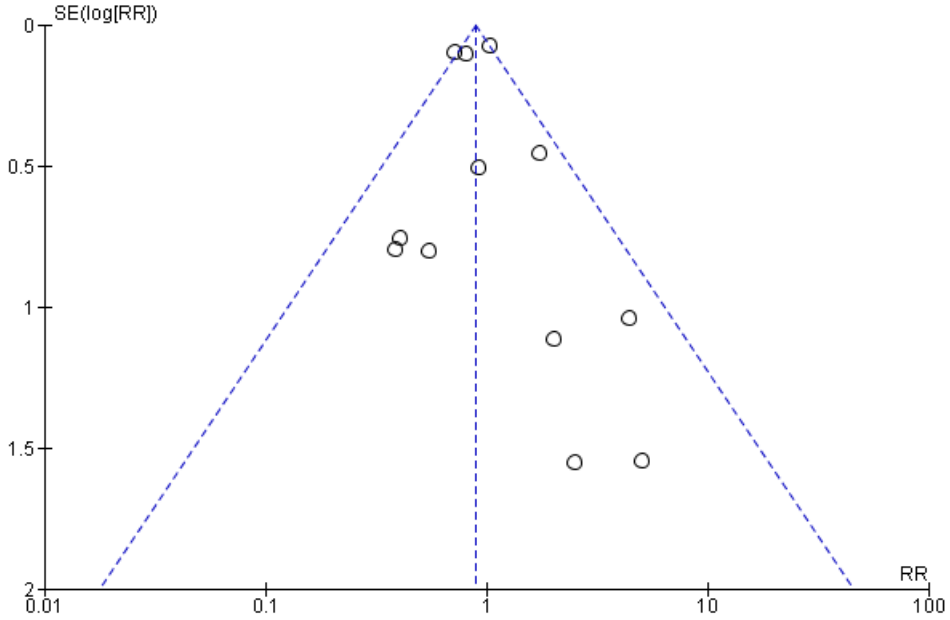


Figure 13 Funnel plot of the association between cardiovascular death and febuxostat

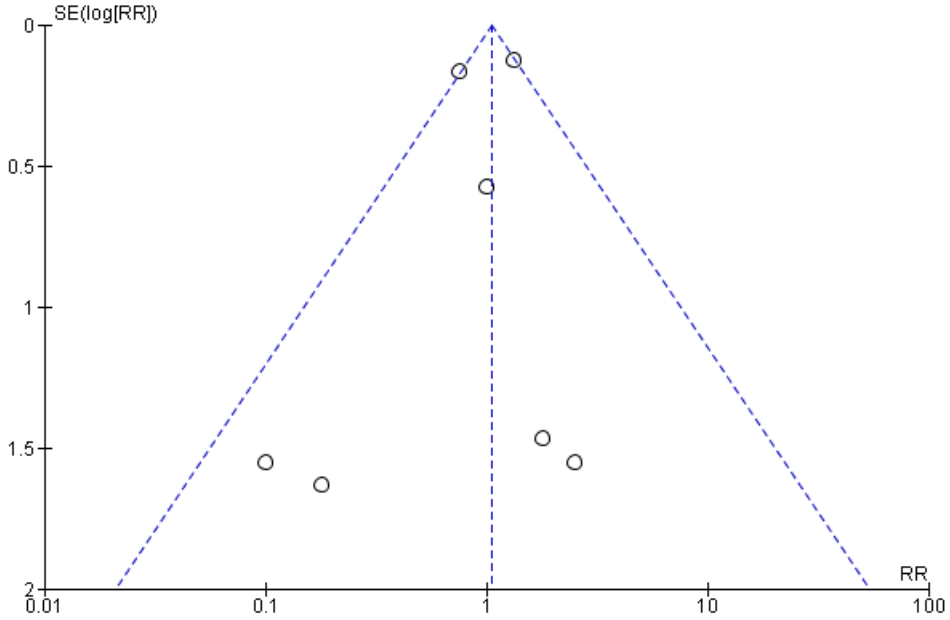


Figure 14 Funnel plot of the association between nonfatal myocardial infraction and febuxostat

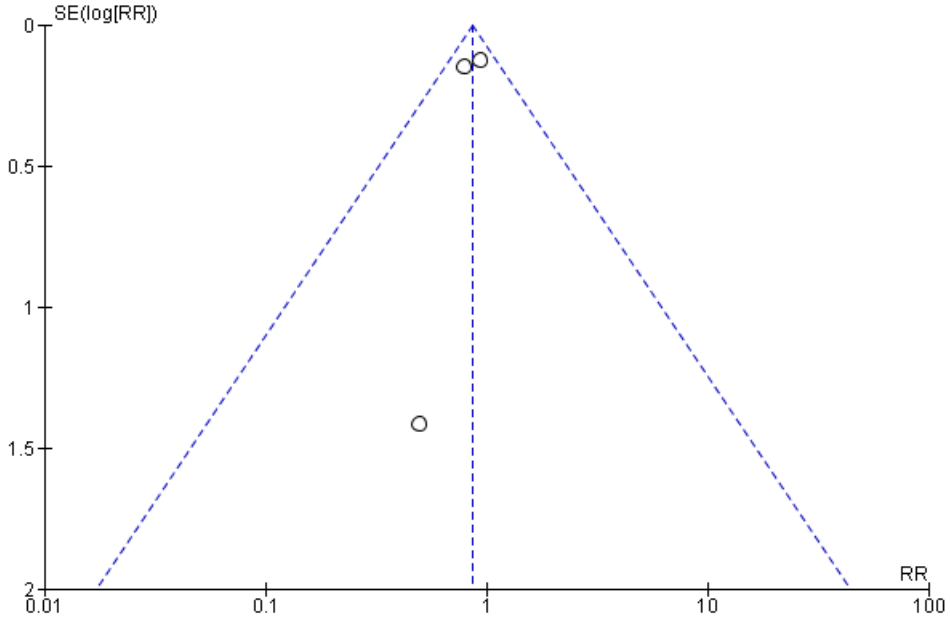


Figure 15 Funnel plot of the association between nonfatal stroke and febuxostat

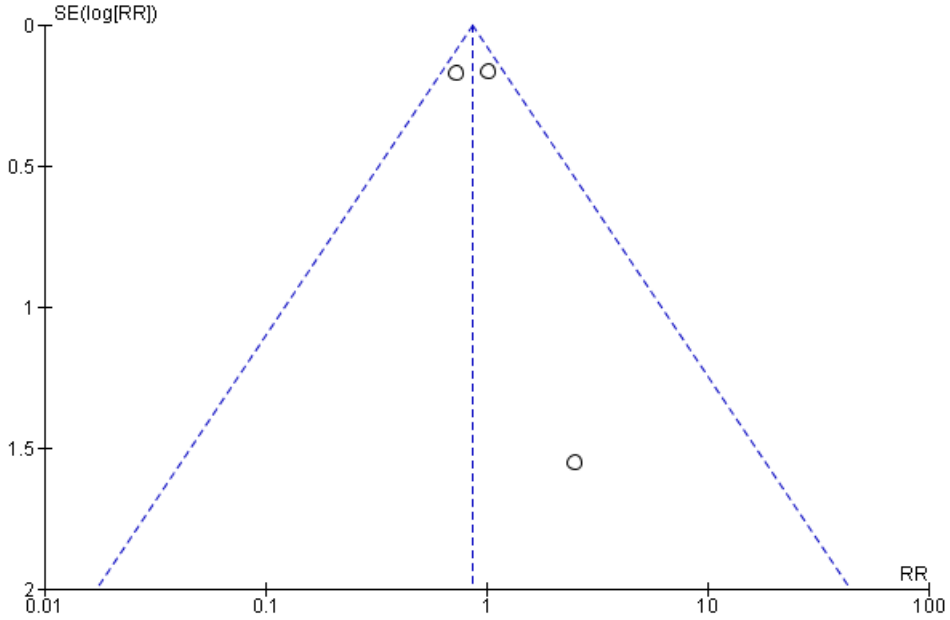


Figure 16 Funnel plot of the association between urgent revascularization for unstable angina and febuxostat

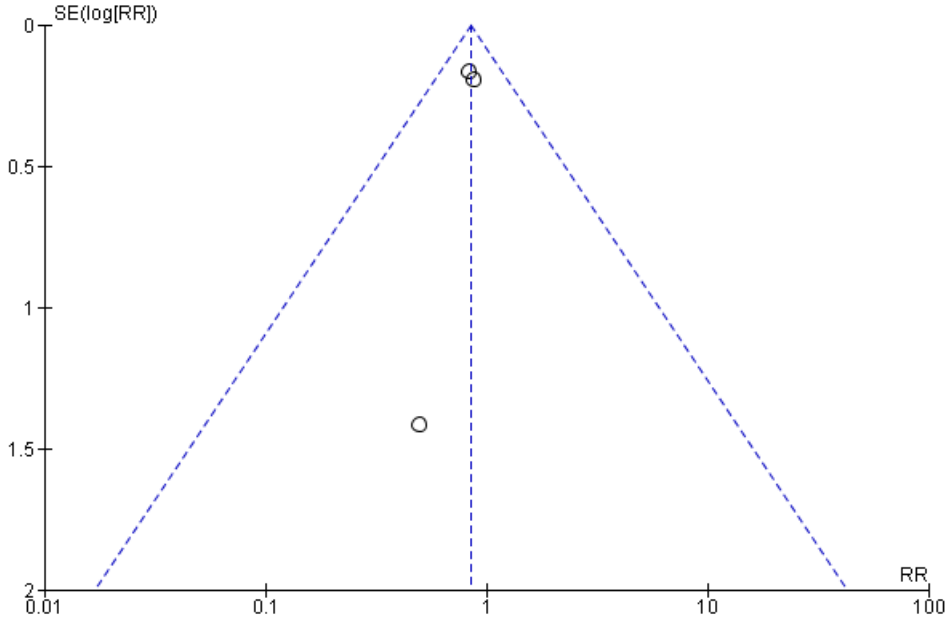
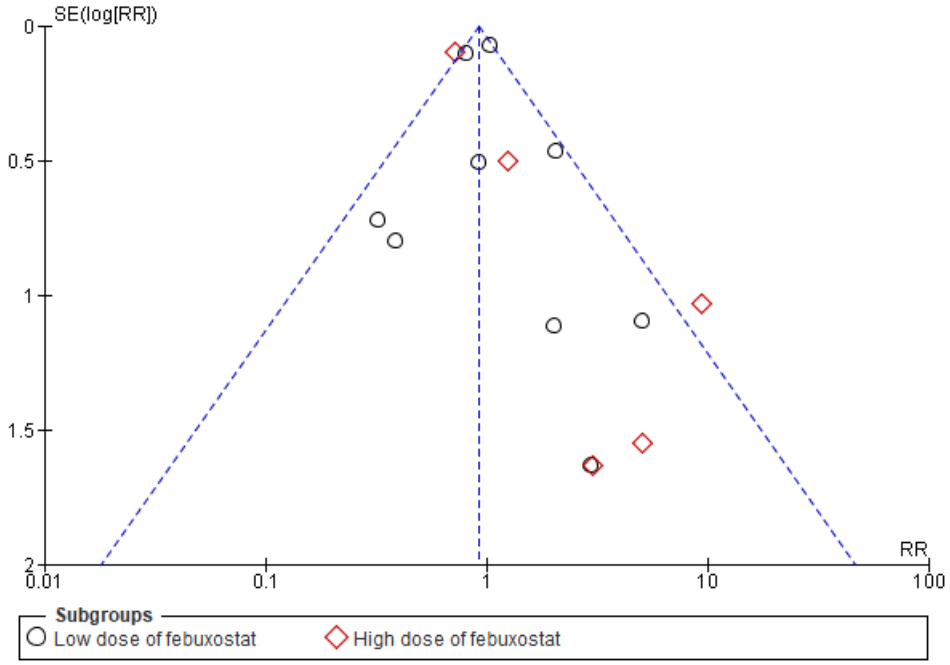


Figure 17 Funnel plot of subgroup analysis



5 Discussion

The primary goal of this analysis is to assess the cardiovascular safety of febuxostat use, particularly in terms of the FDA's addition of the box warning. Additionally, doctors in clinical practice do not favor using febuxostat as a new medication to treat hyperuricemia and gout. Despite the drug's high efficacy, they consistently choose to prescribe allopurinol as part of a traditional treatment strategy.

What makes this meta-analysis unique from others is the subgroup analysis which was performed in terms of the dose. It illustrates that low doses of febuxostat (< 80 mg/day) have decreased the primary major adverse cardiovascular events significantly compared to the control and allopurinol groups. Besides all what had been mentioned before, the design of this meta-analysis was head-to-head whereas the intervention group which is febuxostat was compared with the control group which is allopurinol. There is a lack of head-to-head meta-analysis studies where performed without other interventions such as placebo effect or another urate-lowering therapy.

The study has a number of limitations. Initially, every study has a various therapeutic duration and follow-up time frame, which could lead to bias. Concerning cardiovascular safety, an extended follow-up time frame should be taken into account. Secondly, there is very little data about febuxostat tolerance in females because the clinical trials primarily involved males. Female patients ought to be given serious analysis when observing febuxostat's long-term impacts and cardiovascular safety. Thirdly, because RCT in languages other than English was not included, the Asian subgroup was not noted in the studies that were included. Due to the high prevalence of HLAB5801 among Asian population, it is very important to document the data for the subgroup of asia in order to evaluate the impact of febuxostat on therapeutic and safety aspects. However, One study illustrates that in Han Chinese population who were HLAB*5801-negative, febuxostat shows higher efficacy in controlling uric acid levels in serum without causing any severe dermal hypersensitivity (Yu et al., 2016). The therapeutically use of allopurinol was restricted due to severe skin hypersensitivity, and the leukocyte antigen B*5801 mutation (Hung et al., 2005). According to a study, febuxostat-related skin reaction reactions were significantly less common comparing to allopurinol (Chen et al., 2019).

According to the findings of this meta-analysis, it has been found that the risk of the primary endpoint of the febuxostat group has a significantly lower risk ratio of major adverse cardiovascular events compared to allopurinol and according to the subgroup analysis; this difference was not dose-dependent. However, the secondary endpoints are not increased among individuals who used febuxostat. The use of febuxostat did not raise the risk of nonfatal myocardial infarction, cardiovascular death, urgent revascularization and nonfatal stroke; or overall mortality in comparison to allopurinol.

Three meta-analyses concluded that febuxostat has no effect on the risk of severely adverse cardiovascular endpoint in individuals with gout and hyperuricemia (Cuenca et al., 2019; Al-Abdouh et al., 2020; Zhang et al., 2021). One meta-analysis and one cohort study, on the other hand, suggest that febuxostat may be linked to an increased cardiovascular risk, whereas allopurinol treatments may reduce cardiovascular risk (Ying et al., 2021; Su et al., 2019).

The Food and drug administration obligated Takeda Pharmaceuticals to initiate a clinical trial to examine cardiovascular safety prior to its approval in 2009, and Takeda Pharmaceuticals obliged (Center for Drug Evaluation and Research, 2022), based on clinical trial outcome data revealing a probable increase in cardiovascular events (Becker et al., 2009). The FDA issued a safety alert in November 2017 based on CARES trial which is conducted in order to evaluate the CV safety of febuxostat. This trial did not find any increase in primary MACE, Nevertheless, primary intent to treat and per-protocol analyses did find a higher than expected risk of the secondary endpoints of cardiovascular death. CARES accounts for about 30.2 percent of pooled analysis due to its unique design and status as the only RCT focusing on febuxostat cardiovascular safety at that time.

Several theories could account for these results as well as those of the CARES experiment. First, NSAIDs use has been linked to an elevated risk of cardiovascular events (Patrono & Baigent, 2014), and it is probable that the prophylaxis use of NSAID use for gout management distorted the results (Krishnan, 2010). In CARES, however, individuals taking febuxostat and those taking allopurinol had similar NSAID use and gout outcomes. Colchicine is prescribed as prophylaxis and acute therapy for sever gout attacks, and has been shown to reduce rather than increase

cardiovascular risk, but the data from the experiments did not allow for a thorough analysis of whether colchicine use affected our findings. Third, nitric oxide synthase activity may be compromised by the inhibition of xanthine oxidase (Krishnan, 2010), which would reduce the blood flow in coronary artery, and impair excitation contraction coupling myocardia (Tamariz & Hare, 2015; Zimmet & Hare, 2006). In a paradoxical finding, urate has been shown to reduce the release of nitric oxide from endothelial cells (Gersch et al, 2008; Choi et al., 2014). Because of the limitations of this meta-analysis, it was not possible to determine the impact of SU reduction and NO inhibition on coronary blood flow.

Major cardiovascular events are more common in the elderly, numerous different illnesses are more likely to coexist in them, they experience more maladies, they take more prescribed medication, and their bodies naturally degenerate. Numerous elderly patients are presently afflicted by gout. In the liver, glucuronide oxidation and forming dominate the metabolic activity of febuxostat, with little impact on some other enzymes responsible in purine and pyrimidine biotransformation. Based on the currently offered trial data, f has been demonstrated to be secure and could be used to help individuals who have an allergy to allopurinol as well as renal dysfunction (Goa et al., 235). However, few research have found an increased MACE in febuxostat group among elderly patients (Becker et al., 2005; Schumacher et al., 2008; Schumacher et al., 2009). On the other hand, a study did not find a correlation between febuxostat and increase the risk of MACE. On the other hand, a study illustrates that there is no significant difference between febuxostat and allopurinol in terms of increasing the incidence of MACE (Zhang et al., 2018). A meta-analysis finding has found that the incidence of stroke has decreased significantly with febuxostat in elderly subgroup (Gao et al., 2021).

More research are required to determine whether febuxostat is safe or not. Firstly, by distinguishing the molecular mechanism and intracellular pathway of febuxostat cardiovascular toxicity if there is any. The second solution is performing a wide cohort study that includes a high number of patients taking into consideration multiple factors including the dose, gender, ethnicity, age, pre-existence of CVD, pregnancy and lactation. Moreover, the study must focus on the NSAIDs that are used commonly among gout patients which might be the reason behind increasing the risk ratio of MACE.

6 Conclusion

In conclusion, the primary endpoints findings show that febuxostat has a significantly lower risk ratio of major adverse cardiovascular events compared to allopurinol and according to the subgroup analysis; this difference was not dose-dependent. However, for the secondary endpoints, there are no significant differences between allopurinol and febuxostat. Although febuxostat has a higher efficacy compared to allopurinol according to many studies yet individuals who have a history of cardiovascular events and gout, febuxostat might raise their likelihood of death from cardiovascular causes. With the widespread occurrence and ongoing nature of hyperuricemia and gout; febuxostat must be used with caution in patients with a history of cardiovascular events or diseases according to the risk-benefit ratio. More randomized clinical trials with MACE evaluation as a primary outcome are required to properly assess the risk of cardiovascular death with febuxostat.

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