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Cardiovascular Risks of Probenecid Versus Allopurinol in Older Patients With Gout

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ABSTRACT

BACKGROUND Patients with gout are at an increased risk of cardiovascular (CV) disease including myocardial infarction (MI), stroke, and heart failure (HF).

OBJECTIVES The authors conducted a cohort study to examine comparative CV safety of the 2 gout treatments—probenecid and allopurinol—in patients with gout.

METHODS Among gout patients ≥65 years of age and enrolled in Medicare (2008 to 2013), those who initiated probenecid or allopurinol were identified. The primary outcome was a composite CV endpoint of hospitalization for MI or stroke. MI, stroke, coronary revascularization, HF, and mortality were assessed separately as secondary outcomes. The authors estimated the incidence rate and hazard ratio of the primary and secondary outcomes in the 1:3 propensity score–matched cohort of probenecid and allopurinol initiators.

RESULTS A total of 9,722 probenecid initiators propensity score–matched to 29,166 allopurinol initiators with mean age of 76 ± 7 years, and 54% males were included. The incidence rate of the primary composite endpoint of MI or stroke per 100 person-years was 2.36 in probenecid and 2.83 in allopurinol initiators with a hazard ratio of 0.80 (95% confidence interval: 0.69 to 0.93). In the secondary analyses, probenecid was associated with a decreased risk of MI, stroke, HF exacerbation, and mortality versus allopurinol. These results were consistent in the subgroup analyses of patients without baseline CV disease or those without baseline chronic kidney disease.

CONCLUSIONS In this large cohort of 38,888 elderly gout patients, treatment with probenecid appears to be associated with a modestly decreased risk of CV events including MI, stroke, and HF exacerbation compared with allopurinol. (J Am Coll Cardiol 2018;71:994–1004) © 2018 by the American College of Cardiology Foundation.

Gout is the most common inflammatory arthritis with an increasing prevalence in many countries including the United States (1). It is caused by hyperuricemia leading to crystallization of uric acid within the joints and periarticular tissues (2). Urate crystals then activate the NLRP3 inflammasome (i.e., cryopyrin) resulting in the production of interleukin (IL)-1β (3). Overproduction of urate or underexcretion of urate through the kidneys leads to hyperuricemia. Allopurinol, a xanthine oxidase inhibitor, is the mainstay of treatment for gout and can be used in patients who overproduce or

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underexcrete urate. Probenecid is another treatment option, which has been available for gout for many decades. Probenecid inhibits organic acid reabsorption in the renal proximal tubule, causing the excretion of uric acid through the kidneys; it is not recommended in patients with overproduction of uric acid (2,4,5).

It is well known that patients with gout are at an increased risk of cardiovascular (CV) disease (CVD) including myocardial infarction (MI), stroke, and heart failure (HF) (6–8). Although controversies still exist whether uric acid plays a causal role in the development of CVD, beneficial effects of allopurinol on lowering blood pressure and improving endothelial function and metabolic profile have been reported (9–11). A randomized controlled trial in high-risk HF patients, the EXACT-HF (Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients) study, allopurinol did not, however, improve the composite clinical endpoint related to HF (12). Observational cohort studies have shown conflicting results with regard to effect of xanthine oxidase inhibitors, mainly allopurinol, on reducing the risk of future CVD (13–15). However, no data exist with regard to the effect of probenecid on CVD among gout patients. Probenecid is not only a competitive inhibitor of the organic anion transporter (5,16), but also an inhibitor of pannexin 1 channels—an ATP release channel—involved in the activation of the inflammasome which releases IL-1β (17). Therefore, probenecid may exhibit beneficial effects in gout by lowering serum uric acid levels and reducing systemic inflammation through the inhibition of pannexin 1 channels and reduced production of IL-1β (17). IL-1β is also known to play a pivotal role in the pathogenesis of atherosclerosis (18). Furthermore, probenecid may have an effect on CV risk as a potent and selective agonist of transient receptor potential vanilloid 2 (TRPV2) channels (19,20). TRPV2 is expressed in cardiomyocytes, and several experimental studies found an inotropic effect of probenecid (19,21–23). Therefore, it is plausible to hypothesize that probenecid may have cardioprotective effects in gout patients.

SEE PAGE 1005

The primary objective of this study was, therefore, to compare the risk of CV events including MI or stroke in patients with gout initiating probenecid versus allopurinol in a population representative cohort. We also assessed the risk of other CV endpoints including coronary revascularization and HF, and all-cause mortality in patients with gout initiating probenecid versus allopurinol.

METHODS

DATA SOURCE. We used claims data from Medicare Parts A, B, and D for the period from 2008 through 2013. Medicare is a federally funded program and provides health care coverage for nearly all legal residents of the United States ≥65 years of age and selected disabled populations <65 years of age. Medicare Part A generally covers inpatient care, Part B is for outpatient medical services including some drugs given in a physician's office or clinic, and Part D provides outpatient prescription drug coverage (24). Because the Medicare database does not contain laboratory results, we used Medicare data linked with the Brigham and Women's Hospital's electronic medical record (EMR) database (2007 to 2013) to select a subgroup of gout patients enrolled in Medicare who had laboratory test results such as serum uric acid and creatinine levels. The study protocol was approved by the Institutional Review Board of the Brigham and Women's Hospital, which granted a waiver of informed consent.

STUDY POPULATION. We identified adults age 65 years or older who had ≥1 International Classification of Diseases-9th Revision (ICD-9) code for gout (274.x). Use of probenecid or allopurinol was identified through national drug codes. Patients who were continuously enrolled in the Medicare Parts A, B, and D for ≥1 year before the first dispensing date (i.e., index date) of probenecid or allopurinol were selected as probenecid or allopurinol initiators (**Figure 1**). Probenecid initiators were required to be naive to probenecid for the 1-year baseline period before the index date. Similarly, allopurinol initiators were required to be naive to allopurinol for the same baseline period. Patients who started both drugs at the same date were excluded. To assess patients' baseline characteristics adequately, we excluded patients with no active claim in 1 year before the index date. We further excluded patients who used pegloticase or rasburicase, 2 drugs used in severe refractory gout, or had a diagnosis of end-stage renal disease or dialysis at baseline to minimize confounding by the severity of gout and renal function at baseline. For the subgroup in the linked Medicare-EMR database, we applied the same inclusion and exclusion criteria as in the preceding text, and additionally required them to have ≥1 measurement for serum uric acid and serum creatinine level before the index date.

For the primary as-treated analysis, study subjects were followed up from the day after the index date until the earliest event of the following: 1) death;

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
CKD = chronic kidney disease
CV = cardiovascular
CVD = cardiovascular disease
EMR = electronic medical record
HF = heart failure
HR = hazard ratio
IL = interleukin
IQR = interquartile range
IR = incidence rate
ITT = intention-to-treat
MI = myocardial infarction
NSAID = nonsteroidal anti-inflammatory drug
PS = propensity score
TRPV2 = transient receptor potential vanilloid 2