ORIGINAL RESEARCH

Major Cardiovascular Events in Patients with Gout and Associated Cardiovascular Disease or Heart Failure and Chronic Kidney Disease Initiating a Xanthine Oxidase Inhibitor

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BACKGROUND: Several observational studies and meta-analyses have suggested that treating hyperuricemia in patients with gout and moderate or severe chronic kidney disease (CKD) may improve renal and cardiovascular (CV) outcomes.

OBJECTIVE: To evaluate the impact of initiating allopurinol or febuxostat treatment on major CV events in patients with gout, preexisting CV disease (CVD) or heart failure (HF), and stage 3 or 4 CKD in a real-world setting.

METHODS: Patients with gout (aged >18 years) who initiated allopurinol or febuxostat treatment between 2009 and 2013 after a diagnosis of stage 3 or 4 CKD and CVD—including coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease (PVD)—or HF were selected from the MarketScan databases. The major CV events included CAD-specific, cerebrovascular disease–specific, and PVD-specific events. Cox proportional hazards modeling identified the predictors of major CV events in aggregate, and of CAD, cerebrovascular disease, and PVD events, individually.

RESULTS: During follow-up, 2426 patients (370 receiving febuxostat and 2056 receiving allopurinol; 63% male; mean age, 73 years) had 162 major CV events (3.8% in those receiving febuxostat vs 7.2% in those receiving allopurinol; $P = .015$). The rates of major CV events per 1000 person-years were 51.8 (95% confidence interval [CI], 28-87) in patients initiating febuxostat and 99.3 (95% CI, 84-117) among those initiating allopurinol. Overall, 49.4% of patients had a CAD event, 32.5% had a PVD event, and 23.5% had a cerebrovascular disease–specific event. Febuxostat initiation was associated with a significantly lower risk for a major CV event versus patients who initiated allopurinol (hazard ratio, 0.52; $P = .02$), driven in large part by lower PVD-specific events ($P = .026$).

CONCLUSION: Patients with moderate-to-severe CKD and CVD or HF who initiated febuxostat treatment had a significantly lower rate of major CV events than patients who initiated allopurinol.

KEY WORDS: allopurinol, cardiovascular disease, chronic kidney disease, febuxostat, gout, hyperuricemia, major CV events, urate-lowering therapies, xanthine oxidase inhibitors

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Gout is a metabolic disorder that causes flares of arthritis in the joints and occurs with the onset of inflammation as a result of excess serum uric acid in the blood (ie, hyperuricemia) and the deposition of crystals in tissue. Gout affects 3.9% of the US adult population,[1] and its prevalence is rising as a result of the increasing rates of comorbidities that promote hyperuricemia and extensive use of thiazide and loop diuretics for the treatment of cardiovascular (CV) diseases (CVD).[2-4]

Patients with gout have substantial rates of renal disease and CVD.[5] Among patients with gout in the 2007-

KEY POINTS

- Emerging evidence suggests a link between hyperuricemia and CVD, although this continues to be the subject of some debate.
- This retrospective, real-world cohort study compares major cardiovascular events in patients with gout and concurrent CVD and chronic kidney disease who receive febuxostat or allopurinol.
- Major cardiac events were 48% lower among patients initiating febuxostat therapy versus those initiating allopurinol therapy (P = .021), driven largely by lower rates of peripheral vascular disease.
- More real-world clinical trials are needed to address challenges faced by clinicians who manage gout in renally compromised patients with multiple chronic diseases.

2008 National Health and Nutrition Examination Survey study, 71% had stage ≥2 chronic kidney disease (CKD), 14% had a history of myocardial infarction (MI), 11% had a history of heart failure (HF), and 10% had a history of stroke.[5] Conversely, the presence of CKD was associated with a significantly higher incidence and prevalence of gout, with some studies suggesting that the prevalence of gout increases 2- to 3-fold for each 30-mL/min/1.73 m^2 decrease in glomerular filtration rate (GFR).[6,7] Roughley and colleagues recently estimated the pooled prevalence of moderate to severe (stage ≥3) CKD in patients with gout to be 24%.[8] Patients with CKD are at increased risk for CVD, and studies have suggested that they are more likely to die from CVD than to progress to end-stage renal disease (ESRD).[9]

A number of researchers have suggested an independent link between hyperuricemia and an increased risk for metabolic syndrome, diabetes, hypertension, kidney disease, and CVD, including HF,[10-18] with the relationship between hyperuricemia and renal function itself the subject of several recent systematic reviews and meta-analyses.[9,19,20] Kanji and colleagues used trial data to conduct a meta-analysis that evaluated whether treating hyperuricemia in patients with stages 3 to 5 CKD might improve renal and CV outcomes.[9] The investigators observed a small but significant improvement in estimated GFR (eGFR) and serum creatinine; however, they also noted, as did 2 other systematic reviews on this topic, that the analyses were limited by the overall paucity of data, which was insufficient to support an evaluation of CVD and almost exclusively focused on a single urate-lowering agent.[9,19,20]

Urate-lowering therapies, such as allopurinol and febuxostat, are the primary therapies for the management of patients with chronic gout and for the prevention of gout flares.[21] The goal of treatment is to achieve a serum urate level of <6 mg/dL.[2] However, the management of gout in patients with concomitant CVD and CKD is complex, with several factors influencing treatment choice, most notably in patients with advanced disease (ie, stage ≥3).[22] A reduced starting dose of allopurinol is recommended in patients with renal impairment because of the potential for hypersensitivity reactions.[23] These patients may fail to reach target serum urate, leading to an increased risk for gout flares for which nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated, and corticosteroids and colchicine are used with restriction.[24]

Several studies have suggested that febuxostat may be more effective in reducing serum urate levels than allopurinol,[22,25-28] but concerns about the higher drug acquisition cost of febuxostat[29,30] and the potential for serious CV events may also influence treatment choice.[22,31,32] Conversely, some studies suggest that febuxostat may be less costly when evaluating the overall patient expenditure,[33-36] particularly when evaluating CVD-specific cost,[34] although theoretical models have suggested that dose escalation with allopurinol may affect its overall cost-effectiveness.[37]

The goal of this study was to evaluate the impact of initiating allopurinol or febuxostat treatment on major CV events in patients with gout, preexisting CVD or HF, and stage 3 or 4 CKD in a real-world setting.

Methods

This retrospective cohort study used data from the Truven MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases. Eligible patients (aged ≥18 years) had to have gout, stage 3 or 4 CKD, and a history of CVD or HF and received first-line treatment with a xanthine oxidase inhibitor (ie, allopurinol or febuxostat) for ≥31 days of continuous therapy between January 1, 2009, and June 30, 2013. Gout was defined as ≥1 diagnoses of gout (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] 274.xx) and CKD was defined as stage 3 or 4 disease (*ICD-9-CM* 585.3 or 585.4) on a nondiagnostic claim during the 12-month baseline period after the study index date (ie, the date of initiating allopurinol or febuxostat).

A history of CVD was defined as an *ICD-9-CM* diagnosis (see **Appendix Table 1**, at **www.AHDBonline.com**) of coronary artery disease (CAD), cerebrovascular disease, or peripheral vascular disease (PVD) on ≥1 inpatient claims or ≥2 nondiagnostic outpatient claims, or evidence of a previous revascularization procedure or nontraumatic lower-extremity amputation (see **Appendix**

Table 2, at **www.AHDBonline.com**). Patients were included if they were continuously enrolled in the MarketScan databases for ≥12 months before (baseline) and ≥31 days after the index date, with complete data availability.

Patients were excluded if they received pegloticase ≤2 months before the index date, or if they had evidence of organ transplant at baseline, ESRD (ie, dialysis, a diagnosis of stage 5 CKD), a nonskin malignancy, or HIV/AIDS. Patients whose baseline CV or HF status could not be determined were also excluded from the study. Enrolled patients were followed until their disenrollment from the MarketScan databases, discontinuation of the qualifying study agent, use of the alternate study agent, onset of any of the exclusion disease states, or postindex exposure to pegloticase. Treatment discontinuation was defined as no additional evidence of a prescription for the qualifying agent or a gap of >45 days in the available supply of medication.

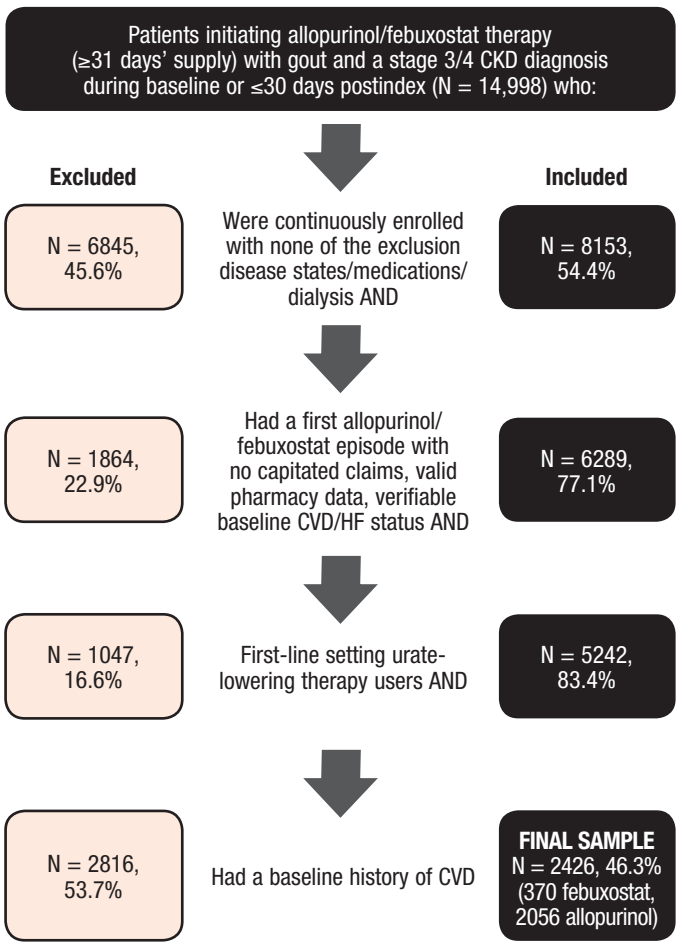
The primary outcome was the occurrence of major CV events during follow-up. The 3 types of major CV events included CAD-specific, cerebrovascular disease–specific, and PVD-specific events. CAD-specific major CV events required evidence of MI or coronary revascularization. Acute MI was captured using a validated definition[38] (sensitivity, 79%; specificity, 99.5%; positive predictive value, 86.1%), which required a discharge diagnosis of MI (*ICD-9-CM* 410.x0 or 410.x1) in the primary or secondary diagnosis position on an inpatient claim. CAD revascularization was defined as coronary artery bypass graft and/or percutaneous revascularization procedures.

Cerebrovascular disease–specific major CV events included ischemic or hemorrhagic stroke, transient ischemic attack, or cerebrovascular disease revascularization. Patients were classified as having an ischemic or hemorrhagic stroke if they had ≥1 inpatient claims with a discharge *ICD-9-CM* diagnosis code (primary or secondary) of 433.x1, 434.xx-436.xx (ischemic), or 430.xx-431.xx (hemorrhagic). CVD-specific revascularization was defined as embolectomy, thrombectomy, thromboendarterectomy, percutaneous revascularization, and/or bypass graft.

PVD-specific major CV events included lower-limb amputation (ie, toe, metatarsal, foot, ankle, thigh, leg, or abdominopelvic) classified as nontraumatic (ie, no evidence of *ICD-9-CM* diagnosis codes 800-999) and lower-limb revascularization, which was defined as resection, atherectomy, endarterectomy, or angioplasty.

The secondary outcome was the incidence of gout flares, identified based on an algorithm that defined an acute gout attack using 1 of 2 main criteria of (1) an office visit for gout (*ICD-9-CM* 274.xx), with the diagnosis of gout in any position on the claim and a new dispensing of colchicine, selective or nonselective NSAIDs, or oral or injectable glucocorticoids within 14 days of the office visit, or (2) an emergency department or inpatient visit coded (diagnosis in any position on the claim) for gout.[39] A clean period or "gap" of 21 days between attacks was required.

Figure 1 Study Eligibility and Attrition

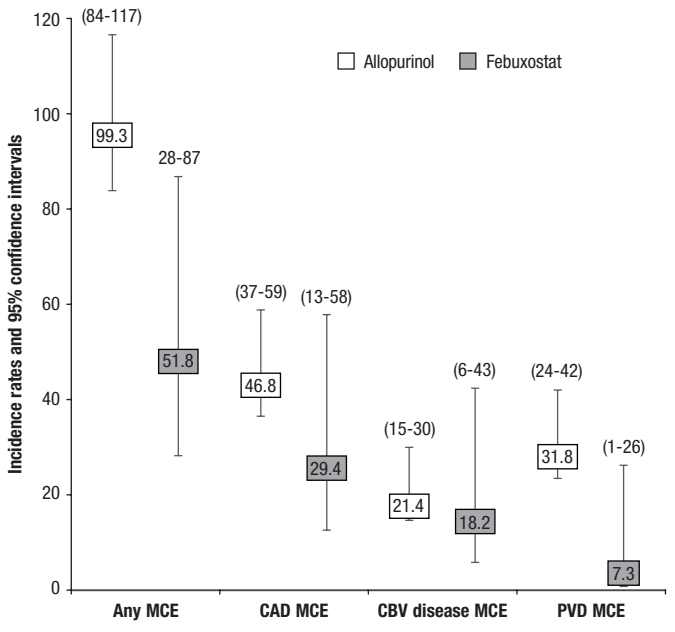


CKD indicates chronic kidney disease; CVD, cardiovascular disease; HF, heart failure.

Cox proportional hazards models assessed the predictors of any major CV event in aggregate, and of CAD, cerebrovascular disease, and PVD events individually. The Cox proportional hazards model was tested to ensure that proportionality assumptions were met. Appropriate fit was assessed using the likelihood ratio, score, and Wald tests. Explanatory variables tested for inclusion in the model included basic demographics, baseline CVD type, baseline history of other comorbid conditions, baseline medication exposure, and CKD stage nearest the index date.

Measures of gout severity in the model included baseline evidence of tophi (*ICD-9-CM* diagnosis 274.03, 274.81, or 274.82), baseline gout flare frequency, and acute gout flare medications. For the secondary outcome

Figure 2 Major CV Event Rates per 1000 Person Years of Observation, Unadjusted, by Urate-Lowering Therapy Cohort



CAD indicates coronary artery disease; CBV, cerebrovascular; CV, cardiovascular; MCE, major CV event; PVD, peripheral vascular disease.

of gout flares, an additional extended Cox model (Anderson-Gill) was developed to assess the relative hazard of the repeated measure of gout flare.

Results

Among the 1.2 million adults with a diagnosis of gout in the MarketScan databases between January 1, 2009, and June 30, 2013, a total of 14,998 patients who initiated treatment with allopurinol or with febuxostat had at least a 31-day supply of the drug and a diagnosis of stage 3 or 4 CKD. **Figure 1** depicts the impact of the population selection criteria.

The final study population included 2426 patients (370 receiving febuxostat and 2056 receiving allopurinol). The mean preperiod enrollment was fixed at 12 months, and the mean duration during follow-up was 9 months (standard deviation [SD], 7.5 months) in the febuxostat cohort and 9.2 months (SD, 8.2 months) in the allopurinol cohort. The primary reason for the end of observation window was the discontinuation of urate-lowering therapies or a gap in receiving urate-lowering therapies. The median daily dose was 150 mg (interquartile range [IQR], 100-250 mg) in the allopurinol cohort and 40 mg (IQR, 40-60 mg) in the febuxostat cohort.

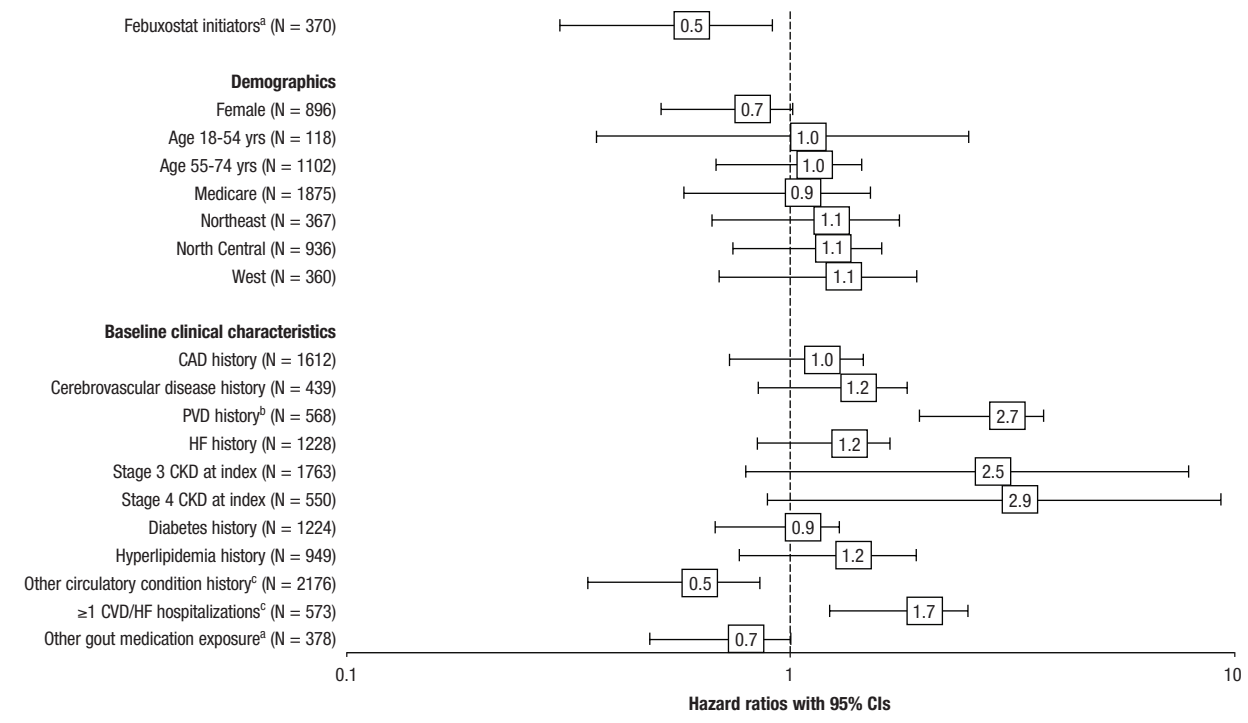
Overall, 63.1% of the study population were male, with a similar mean age in the cohorts (73.4 years with febuxostat vs 73.1 years with allopurinol; $P = .733$). Both cohorts had many comorbidities, with a mean Deyo-adapted Charlson Comorbidity Index[40] of 4.9 (SD, 1.8) for febuxostat and 4.8 (SD, 1.9) for allopurinol. Overall, 50% of the patients had diabetes, 39.1% had dyslipidemia, and 50.6% had evidence of HF. The majority of patients had CAD (63.5% and 67.0% with febuxostat vs allopurinol, respectively; $P = .194$), followed by cerebrovascular disease (17.6% vs 18.2%, respectively; $P = .774$) and PVD (26.5% vs 22.9%, respectively; $P = .129$). In all, 24% of patients had a baseline hospitalization for CVD or HF (21.4% with febuxostat vs 24.0% with allopurinol; $P = .265$); 70.5% and 73.1% ($P = .318$) had moderate (stage 3) CKD, and 24.9% and 22.3% ($P = .274$) had severe (stage 4) CKD. (These percentages do not add up to 100% because CKD status can change over time, and these data reflect the first 30 days after the index date.) There were no significant differences between the cohorts in baseline CKD stage. See **Table 1** (at **www.AHDBonline.com**) for baseline comorbidities.

Although the 2 cohorts were generally well-balanced, several important and significant differences exist in baseline characteristics. The patients who initiated allopurinol were significantly more likely than patients initiating febuxostat to have a baseline diagnosis of HF (51.8% vs 44.3%, respectively; $P = .009$) and chronic obstructive pulmonary disease (21.7% vs 16.2%, respectively; $P = .016$), as well as significantly greater use of an angiotensin-converting enzyme inhibitor at baseline (42.9% vs 37.6%, respectively; $P = .054$). The patients who initiated febuxostat had significantly higher baseline use of calcium channel blockers compared with those who initiated allopurinol (51.9% vs 43.4%, respectively; $P = .003$) and antibiotics (77.3% vs 71.0%, respectively; $P = .013$), as well as marginally higher use of angiotensin II receptor blockers (38.6% vs 33.5%, respectively; $P = .053$) and antidiabetes agents (49.5% vs 44.8%, respectively; $P = .097$).

Patients who initiated febuxostat also had more aggressive gout during baseline than those initiating allopurinol. The patients who initiated febuxostat were significantly more likely than those initiating allopurinol to fill prescriptions for colchicine (49.2% vs 35.6%, respectively; $P < .0001$), glucocorticoids (63.5% vs 57.6%, respectively; $P < .03$), and probenecid (4.3% vs 1.3%, respectively; $P < .0001$). Those who initiated febuxostat were also more likely to have tophi documented at baseline (4.6% vs 2.5%, respectively; $P < .03$), have had at least 1 baseline gout flare (55.9% vs 47.4%, respectively; $P < .003$), and higher mean baseline monthly flares (SD, 0.8 vs 0.6, respectively; $P < .001$).

Overall, 162 (6.7%) patients had at least 1 of the major CV events during follow-up (3.8% with febuxostat vs

Figure 3 Multivariable Adjusted Hazard Ratios for Any Major CV Event



[a]*P* <.05.
[b]*P* <.001.
[c]*P* <.01.
CAD indicates coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure; PVD, peripheral vascular disease.

7.2% with allopurinol; *P* = .015) with an unadjusted incidence rate per 1000 person-years of 51.8 (95% confidence interval [CI], 28-87) in the febuxostat cohort and 99.3 (95% CI, 84-117) in the allopurinol cohort (**Figure 2**).

Cox model results showed a significantly increased likelihood of any major CV event among patients with PVD (hazard ratio [HR], 2.69; 95% CI, 1.95-3.71; *P* <.001) or a baseline CVD or HF hospitalization (HR, 1.75; 95% CI, 1.22-2.50; *P* = .002), and a significantly decreased likelihood of any major CV event among febuxostat initiators (HR, 0.52; 95% CI, 0.30-0.91; *P* = .021), patients with a baseline history of an "other" circulatory disorder (primarily hypertension, dysrhythmia, and conduction disorders; HR, 0.54; 95% CI, 0.35-0.85; *P* = .008), and those receiving baseline antigout medications, such as colchicine, glucocorticoids, or NSAIDs (HR, 0.69; 95% CI, 0.48-1.00; *P* = .049; **Figure 3**).

A total of 80 (3.3%) patients had a CAD-specific major CV event (2.2% with febuxostat vs 3.5% with allopurinol; *P* = .184), with incidence rates per 1000 person-years of 29.4 (95% CI, 13-58) and 46.8 (95% CI, 37-59) in the febuxostat and allopurinol cohorts, respectively. There was a significantly increased likelihood of CAD major CV events among patients with baseline PVD (HR, 2.04; 95% CI, 1.27-3.26; *P* = .003) and those with a baseline CVD or HF hospitalization (HR, 1.83; 95% CI, 1.11-3.02; *P* = .018).

A total of 38 (1.6%) patients had a cerebrovascular disease–specific major CV event (1.4% with febuxostat vs 1.6% with allopurinol; *P* = .718), with an incidence rate per 1000 person-years of 18.2 (95% CI, 6-43) for febuxostat and 21.4 (95% CI, 15-30) for allopurinol. The likelihood of a cerebrovascular-specfiic major CV event was increased among patients with baseline cerebrovascular disease (HR, 2.55; 95% CI, 1.25-5.20; *P* = .010) and those with a baseline CVD or HF hospitalization (HR, 2.20; 95% CI, 1.03-4.71; *P* = .042). In addition, a significantly decreased likelihood of cerebrovascular disease–related major CV events was seen in female patients (HR, 0.41; 95% CI, 0.19-0.91; *P* = .029) and those with a history of a non-CVD circulatory system disorder (HR, 0.32; 95% CI, 0.15-0.71; *P* = .005).

A total of 51 (2.1%) patients had a PVD-specific major CV event (0.5% with febuxostat vs 2.4% with allopurinol; *P* = .023), with incidence rates per 1000 person-years of 7.3 (95% CI, 1-26) and 31.8 (95% CI, 24-42) in the

febuxostat and allopurinol cohorts, respectively. The likelihood of a PVD-related major CV event was significantly increased among patients with a baseline PVD event (HR, 6.02; 95% CI, 3.36-10.79; *P* <.001) and among those aged 55 to 74 years at the time of treatment initiation compared with being aged ≥75 years (HR, 2.05; 95% CI, 1.09-3.87; *P* = .027). Febuxostat initiation was associated with a significant reduction in PVD-related major CV events (HR, 0.20; 95% CI, 0.05-0.82; *P* = .026).

The frequency of acute gout flare (patients with ≥1 flares) was 23% overall, 27.8% for febuxostat initiators, and 22.6% for allopurinol initiators (*P* = .028). Unadjusted, the febuxostat cohort had a significantly higher incidence (488.0; 95% CI, 398-592) of acute gout flare per 1000 person-years than the allopurinol cohort (359.6; 95% CI, 328-394). The adjusted analysis demonstrated a significantly increased likelihood of gout flare among patients with baseline hypertension (HR, 1.29; 95% CI, 1.04-1.60; *P* = .019), colchicine prescription (HR, 1.26; 95% CI, 1.06-1.50; *P* = .010), steroid prescription (HR, 1.56; 95% CI, 1.29-1.88; *P* <.001), and those with ≥1 baseline gout flares (HR, 1.19; 95% CI, 1.07-1.32; *P* = .002). The likelihood of a gout flare was reduced significantly in patients with a diuretic prescription (HR, 0.80; 95% CI, 0.65-1.00; *P* = .046) and in those with stage 3 or 4 CKD (HR, 0.70; 95% CI, 0.50-0.98; *P* = .036).

Discussion

This is one of the first real-world, retrospective cohort studies to compare major CV event outcomes in patients with gout and concurrent CVD and CKD who initiated allopurinol or febuxostat therapy. This study follows a recent study that showed that increased gout-specific cost (*P* <.001) in patients initiating febuxostat treatment was offset by significantly reduced cardiac- and renal-related expenses (*P* <.001).[34] The significantly lower major CV event rate in febuxostat initiators in the current study, which was driven in large part by lower PVD events, may help to elucidate the clinical drivers of the lower cost observed in other studies. A number of studies have assessed the impact of urate-lowering therapies on CVD-specific outcomes in the general population. MacIsaac and colleagues (2016) reported that treatment at different dosing levels of allopurinol significantly improved CVD outcomes in 2032 patients with hypertension who were aged ≥65 years using data from the United Kingdom Clinical Research Practice Datalink.[41] These patients were propensity matched and compared with a control group without exposure. Active treatment with allopurinol reduced the risk for stroke by 50% and for a CV event (MI, acute coronary syndrome) by 39%; the reduction was significantly larger in patients who received higher dosages of allopurinol.

Dubreuil and colleagues also used the UK general practitioners database to assess the impact of allopurinol on mortality in patients aged ≥40 years who had at least 1 episode of hyperuricemia.[42] Dubreuil and colleagues observed modest reductions in the risk for death in patients with hyperuricemia and patients with gout.[42] Similarly, in a retrospective case-matched cohort study in Taiwan, Chen and colleagues assessed the impact of urate-lowering therapies (ie, allopurinol, benzbromarone) on CV mortality.[43] The authors observed significantly lower all-cause mortality in the cohort receiving urate-lowering therapies, but they were constrained by the small number of mortality events in their evaluation of CVD-specific mortality.

Wei and colleagues also conducted a cohort study using a record-linked UK-based database to evaluate the impact of allopurinol on the combined outcome of nonfatal MI, nonfatal stroke, and CVD mortality.[44] The authors found no significant impact of allopurinol on CVD risk; however, fewer than 50% of patients reached their target urate concentration. In addition, compared with low-dose allopurinol use, high-dose allopurinol use was associated with reduced CVD events (adjusted HR, 0.69; 95% CI, 0.50-0.94) and all-cause mortality (adjusted HR, 0.75; 95% CI, 0.59-0.94).

Finally, Kim and colleagues conducted a cohort study among patients with gout using US insurance claims data to compare incidence ratios of a composite CVD outcome (MI, coronary revascularization, stroke, or HF) for initiators of xanthine oxidase inhibitors and nonusers.[45] The investigators concluded that xanthine oxidase inhibitor initiators were not at an increased or decreased risk for a CVD event, although they did note that low adherence to xanthine oxidase inhibitor therapies may explain the lack of association.

Although notable, the 5 studies discussed above did not restrict study entry based on renal function and, differences in outcome definition aside, may not be adequate benchmarks for the existing study results. In addition, all of these studies were retrospective and observational in nature. Data from clinical trials are limited. Kanji and colleagues used data from randomized controlled trials in a meta-analysis designed to evaluate whether treating hyperuricemia in patients with stages 3 to 5 CKD might improve renal and CV outcomes.[9] The researchers observed a small but significant improvement in eGFR and serum creatinine, but they were unable to evaluate CVD-specific outcomes, because of the paucity of data.

The most notable and relevant trial cited, Goicoechea and colleagues conducted a 2-year, single-blind, randomized controlled trial of allopurinol treatment in patients with CKD to assess renal and CVD outcomes (ie, MI, coronary revascularization or angina pectoris, congestive HF, cerebrovascular disease, and PVD).[46] Pa-

tients who received allopurinol in that study had fewer CVD events compared with the control group (HR, 0.43; 95% CI, 0.21-0.88; P = .02).[46] Although the findings from this study are similar to our own, the population was not restricted to patients with CKD, concurrent gout, and preexisting CVD. Moreover, because it was a controlled trial, the population might have been less heterogeneous and more adherent to treatment than patients in the real world. Given the lack of specificity about allopurinol dosing protocols in renally compromised patients, we expect that there was less variability in the dosing levels of allopurinol.

In a subgroup analysis by Sezai and colleagues of 109 patients with CKD from the NU-FLASH trial, patients with hyperuricemia who had undergone cardiac surgery were randomized to febuxostat or to allopurinol therapy.[27] The end points included serum urate levels and a variety of antioxidant and inflammatory markers. Serum creatinine, urinary albumin, cystatin-C, oxidized low-density lipoprotein, eicosapentaenoic acid/arachidonic acid ratio, high-sensitivity C-reactive protein, and serum urate values were significantly lower in the febuxostat group than in the allopurinol group.[27]

The results of our study may have important implications for the management of patients with gout and polychronic disease. Although the mechanisms linking elevated serum urate levels with CVD are likely multifactorial, studies have implicated low-grade systemic inflammation, xanthine oxidase activity, and the harmful effects of hyperuricemia itself on CVD.[15,28] In a recent editorial, Borghi and Desideri have suggested that a decrease in serum urate levels may moderate hypertension in patients with CVD and, hence, reduce all-cause and CVD-specific mortality.[15] Study results have also suggested that the alkaloid colchicine, which is indicated for the treatment of acute gout, may also reduce the risk for CV events, most particularly in patients with cardiac disease.[47]

Limitations

This study has several limitations. The study database was a nonrandom sample of patients, primarily with employer-sponsored coverage, and may therefore not be generalizable to other populations. The sample selection was dependent on claims-based diagnostic data, which are limited in their clinical detail.

In addition, event counts were likely constrained by the short duration of follow-up observed in this study in both cohorts. Cerebrovascular disease and PVD models were most affected by low event counts, with the number of events per predictor model lower than the customary threshold of 10. Although simulation models have suggested that type II errors are of greatest concern under these circumstances,[48] it is possible, given the low prevalence of some of the predictor variables, that bias away from the null might have been exacerbated.

To maximize event counts per predictor, baseline covariates, which were marginally significant, were not included in the Cox models unless they improved the model fit and/or altered the study findings. For example, including baseline exposure to angiotensin II receptor blockers in MV models did not improve model fit or alter the study findings, because the HR (0.52) and P value (= .02) for febuxostat were unchanged.

Furthermore, because of the lack of sufficient laboratory data, it was not possible to account for differences in serum urate levels between the cohorts.

Finally, because the study design was observational, there is potential unmeasured confounding as a result of channeling bias, specifically regarding socioeconomic factors that cannot be measured in this data source, especially given the label warnings for the 2 agents considered in this study. For example, it is conceivable that clinicians are cautious in using febuxostat in patients with CVD, given the label warning about potential CV thromboembolic events; they may therefore self-select patients with comparatively stable CVD. The CARES trial is a phase 3B, multicenter, randomized, double-blind study comparing the CV safety of febuxostat and allopurinol in patients with gout and a history of major CVD or cerebrovascular disease. Initiated in 2010, the study planned to enroll and follow approximately 7500 patients until 624 major CV events occurred (approximately 9 years).[49,50] It is also conceivable that clinicians are cautious in using allopurinol in patients with renal disease, given the label warning of the risk for hypersensitivity reaction. Accordingly, they may self-select patients with comparatively stable renal function.

Conclusion

The study results suggest that patients with gout and moderate-to-severe CKD and CVD or HF who initiate febuxostat treatment may have lower rates of major CV events than patients who initiate allopurinol therapy. It is unclear if this is because of channeling, allopurinol underdosing in renally impaired patients, or greater clinical effectiveness of febuxostat, either directly through lower serum urate levels or indirectly by reduced oxidative stress or other pleiotropic effects on the endothelium. This finding adds to a growing body of observational studies suggesting that lower uric acid levels are associated with fewer CV events in renally compromised patients. Clinical trials that mitigate the selection bias associated with observational studies are needed to reflect real-world challenges facing clinicians in treating renally compromised patients with gout and polychronic disease. ■

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Author Disclosure Statement

Dr Foody is an employee of Janssen Pharmaceuticals; Dr Turpin and Dr Lawrence are employees of Takeda Pharmaceuticals USA; Ms Tidwell and Ms Schulman are consultants to Takeda Pharmaceuticals USA.

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STAKEHOLDER PERSPECTIVE

The Growing Role of Real-World Evidence in Clinical Decision-Making

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DRUG MANUFACTURERS/REGULATORS: Recently, much has been written about the importance of using real-world evidence in clinical decision-making and payer management of medical and pharmacy treatment options. The US Food and Drug Administration (FDA) recently noted that "Real world data and real world evidence are playing an increasing role in health care decisions."[1] In particular, they note that real-world evidence is currently used (1) by the FDA to monitor postmarketing drug safety and side effects and to make regulatory decisions, (2) by the healthcare community to aid coverage decisions and to create guidelines and decision support tools for use in clinical practice, and (3) by pharmaceutical manufacturers to support clinical trial designs (eg, large, simple trials or pragmatic clinical trials) and observational studies to generate innovative new treatments.[1]

According to the FDA, real-world evidence is defined as "the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD [real-world data]."[1] With the transition to electronic records and the development of large claims and registry databases in recent years, the ability to store and analyze these data has increased dramatically.

However, a recent study by Hurwitz and colleagues attempted "to evaluate evidence sources cited in P&T [Pharmacy & Therapeutics] committee monographs and therapeutic class reviews and assess the design features and quality of cited real-world evidence studies."[2] The researchers concluded that real-world evidence is rarely used in therapeutic class reviews and is never used in single-drug P&T monographs. Specifically, published real-world evidence comprised only 4.8% of 439 therapeutic class review references and none of the 126 monograph references.[2]

PAYERS/PROVIDERS: In their article in this issue of the journal, Foody and colleagues used extensive real-world data sets to analyze a particularly complex and difficult-to-treat group of patients with hyperuricemia and a diagnosis of stage 3 or 4 chronic kidney disease (CKD) and cardiovascular disease (CVD), including coronary artery disease, cerebrovascular disease, and peripheral vascular disease, or heart failure (HF).[3] Foody and colleagues note that previous studies had concluded that the treatment of hyperuricemia in these patients could lower the risk for a major cardiac event. Their ultimate conclusion is that "Patients with moderate-to-severe CKD and CVD or HF who initiated febuxostat treatment had a significantly lower rate of major cardiac events than patients who initiated allopurinol."[3]

Although the ultimate cause for this difference could not be concluded from this study, the authors note that further investigation should be undertaken to determine if their findings result from fundamental differences in the drugs, more aggressive lowering of urate with febuxostat in the setting of CKD, underdosing of allopurinol in this setting, or another, yet unknown, factor. Thus, this sets the stage for the potential development of future trials, which the FDA has noted as an important use for real-world evidence.

The information in this article should give payers food for thought about reassessing the current low-level use of real-world evidence in their P&T decisions. By incorporating such evidence in their therapeutic class assessments, decisions may become more complex, but payers will benefit from the additional insight provided by such studies. In some cases, assumed therapeutic equivalency may not be present in the real-world setting. We should encourage more studies of this type, and, ultimately, real-world evidence should become an essential element of clinical and economic decision-making. ■

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Table 1 Baseline Clinical Characteristics[a]

Baseline comorbid conditions, N (%)	Allopurinol (N = 2056)	Febuxostat (N = 370)	*P* value
Asthma	91 (4.4)	10 (2.7)	.127
Cerebrovascular disease (any)	374 (18.2)	65 (17.6)	.774
Hemorrhagic stroke	12 (0.6)	1 (0.3)	.447
Ischemic stroke	144 (7.0)	25 (6.8)	.864
Transient ischemic attack	77 (3.7)	17 (4.6)	.436
Occlusion/stenosis precerebral arteries	180 (8.8)	29 (7.8)	.563
Other/unspecified hemorrhage	6 (0.3)	1 (0.3)	.943
Other cerebrovascular disease	107 (5.2)	18 (4.9)	.786
Cerebral/carotid revascularization	17 (0.8)	5 (1.4)	.327
CAD/CHD (any)	1377 (67.0)	235 (63.5)	.194
Myocardial infarction	201 (9.8)	29 (7.8)	.241
Unstable angina	98 (4.8)	20 (5.4)	.599
Other CHD	1317 (64.1)	226 (61.1)	.274
Unknown CAD/CHD	23 (1.1)	4 (1.1)	.949
Coronary revascularization	333 (16.2)	53 (14.3)	.365
PVD (any)	470 (22.9)	98 (26.5)	.129
Lower-extremity PAD	411 (20.0)	85 (23.0)	.190
Abdominal aortic aneurysm	62 (3.0)	12 (3.2)	.815
Amputation	8 (0.4)	3 (0.8)	.266
Unknown PVD	4 (0.2)	2 (0.5)	.217
PVD revascularization	48 (2.3)	11 (3.0)	.463
Other circulatory system disorders	1845 (89.7)	331 (89.5)	.871
Aneurysms (not abdominal aortic)	19 (0.9)	7 (1.9)	.096
Cardiomyopathy	282 (13.7)	41 (11.1)	.170
Dysrhythmias and conduction disorders	851 (41.4)	160 (43.2)	.506
Embolism and thrombosis	88 (4.3)	13 (3.5)	.497
Hypertension	1588 (77.2)	288 (77.8)	.800
Infectious/inflammatory conditions	19 (0.9)	3 (0.8)	.832
Valvular disorders	49 (2.4)	8 (2.2)	.796
Heart failure	1064 (51.8)	164 (44.3)	.009
Chronic liver disease	16 (0.8)	5 (1.4)	.273
Chronic obstructive pulmonary disease	447 (21.7)	60 (16.2)	.016
Diabetes mellitus	1027 (50.0)	197 (53.2)	.244
Dyslipidemia	813 (39.5)	136 (36.8)	.312
Osteoarthritis	378 (18.4)	72 (19.5)	.625
Psoriasis	8 (0.4)	3 (0.8)	.266
Rheumatoid arthritis	38 (1.8)	9 (2.4)	.453

Baseline comorbid conditions, N (%)	Allopurinol (N = 2056)	Febuxostat (N = 370)	*P* value
Index CKD stage[b], N (%)			
Stage 1	18 (0.9)	4 (1.1)	.701
Stage 2	78 (3.8)	13 (3.5)	.794
Stage 3	1502 (73.1)	261 (70.5)	.318
Stage 4	458 (22.3)	92 (24.9)	.274
Polychronic diseases, mean (SD)	7.3 (2.4)	7.2 (2.3)	.379
CCI, mean (SD)	4.8 (1.9)	4.9 (1.8)	.484
CVD/HF-specific hospitalizations,[c] N (%)	494 (24.0)	79 (21.4)	.265
Baseline cost per month,[d] $, mean (SD)	2394 (2900)	2565 (2940)	.297
Baseline medications, N (%)			
Antibiotics[e]	1460 (71.0)	286 (77.3)	.013
Antidiabetes agents	921 (44.8)	183 (49.5)	.097
Antigout agents			
Colchicine	732 (35.6)	182 (49.2)	<.001
Glucocorticoids	1184 (57.6)	235 (63.5)	.033
Prescription NSAIDs	643 (31.3)	115 (31.1)	.941
Probenecid	26 (1.3)	16 (4.3)	<.001
Opiate analgesics and agonists	1299 (63.2)	233 (63.0)	.939
Antihyperlipidemics	1572 (76.5)	284 (76.8)	.901
Cardiac agents			
ACE inhibitors	883 (42.9)	139 (37.6)	.054
Angiotensin II receptor blockers	688 (33.5)	143 (38.6)	.053
Antiarrhythmic agents	237 (11.5)	45 (12.2)	.726
Anticoagulants	674 (32.8)	129 (34.9)	.433
Antiplatelets	659 (32.1)	125 (33.8)	.512
Beta blockers	1565 (76.1)	290 (78.4)	.346
Calcium channel blockers	893 (43.4)	192 (51.9)	.003
Digitalis preparations	229 (11.1)	34 (9.2)	.267
Diuretics	1647 (80.1)	298 (80.5)	.847
Hemorrheologic agents	20 (1.0)	4 (1.1)	.846
Vasodilators	943 (45.9)	162 (43.8)	.456
Medication classes, mean (SD)	7.9 (2.4)	8.3 (2.2)	.001
Baseline gout severity measures, N (%)			
Presence of tophi	52 (2.5)	17 (4.6)	.028
Patients with ≥1 gout attacks	975 (47.4)	207 (55.9)	.003
Mean (SD) number of attacks	0.6 (0.7)	0.8 (0.8)	<.001

[a]As measured during baseline (ie, 12 months before the index date), unless otherwise noted.

[b]CKD stage based on baseline data plus the first 30 days postindex. Each patient is represented once, by the CKD stage reported closest to index. If multiple stages were reported on the same date, we report the highest stage.

[c]Hospitalization with a primary discharge diagnosis of CAD/CHD, cerebrovascular disease, or PVD.

[d]Baseline monthly cost included the actual health plan paid amounts, coordination of benefits, and patient copayment, deductible, and coinsurance amount, standardized to 2013 US dollars using the medical component of the Consumer Price Index.

[e]Antibiotic classes captured include beta-lactams, glycopeptides, aminoglycosides, quinolones, sulfonamides, and macrolides.

ACE indicates angiotensin-converting enzyme; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure; NSAID, nonsteroidal anti-inflammatory drug; PAD, peripheral arterial disease; PVD, peripheral vascular disease; SD, standard deviation.

Appendix

Major Cardiovascular Events in Patients with Gout and Associated Cardiovascular Disease or Heart Failure and Chronic Kidney Disease Initiating a Xanthine Oxidase Inhibitor

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This Appendix has not been edited and is provided as supplemental materials for this article, which was published in *American Health & Drug Benefits* in November 2017.

Appendix Table 1: ICD 9 CM Diagnosis Codes Used To Define CVD

CVD Group	CVD Subtype	Dx Code	ICD 9 CM Dx Description
Coronary Artery Disease/ Coronary Heart Disease	Other CHD	411.81	Acute coronary occlusion without myocardial infarction
	Other CHD	411.89	Other acute and subacute forms of ischemic heart disease, other
	MI	410.xx	Acute myocardial infarction
		412.xx	Old myocardial infarction
	Other CHD	411.0x	Post myocardial infarction syndrome
	Unstable Angina	411.1x	Intermediate coronary syndrome
		413.xx	Angina pectoris
	Other CHD	414.xx	Coronary atherosclerosis
		440.0x	Atherosclerosis of aorta
		440.1x	Atherosclerosis of renal artery
		440.8x	Atherosclerosis of other specified arteries
		440.9x	Generalized and unspecified atherosclerosis
	Unspecified CHD	V45.81	Aortocoronary bypass status
	Unspecified CHD	V45.82	Percutaneous transluminal coronary angioplasty status
Heart Failure		402.01	Malignant hypertensive heart disease with HF
		402.11	Benign hypertensive heart disease with HF
		402.91	Unspecified hypertensive heart disease with HF
		404.01	Hypertensive heart and chronic kidney disease, malignant, with HF and with CKD I through stage IV, or unspecified
		404.03	Hypertensive heart and chronic kidney disease, malignant, with HF and with CKD stage V or

			ESRD
		404.11	Hypertensive heart and chronic kidney disease, benign, with HF and with CKD stage I through stage IV, or unspecified
		404.13	Hypertensive heart and chronic kidney disease, benign, with HF and CKD stage V or ESRD
		404.91	Hypertensive heart and chronic kidney disease, unspecified, with HF and with CKD stage I through stage IV, or unspecified
		404.93	Hypertensive heart and chronic kidney disease, unspecified, with HF and CKD stage V or ESRD
		428.xx	Heart failure
Cerebrovascular Disease	Occlusion / stenosis precerebral arteries	433	Occlusion and stenosis of basilar artery w/o cerebral infarction
		433.1	Occlusion and stenosis of carotid artery w/o cerebral infarction
		433.2	Occlusion and stenosis of vertebral artery w/o cerebral infarction
		433.3	Occlusion/stenosis of multiple/bilateral precerebral art w/o mention of cerebral infarction
		433.8	Occlusion/stenosis of other specified precerebral artery w/o mention of cerebral infarction
		433.9	Occlusion/stenosis of unspecified precerebral artery w/o mention of cerebral infarction
	Hemorrhagic Stroke	430.xx	Subarachnoid hemorrhage
		431.xx	Intracerebral hemorrhage
	Other & Unspfd Hemorrhage	432.xx	Extradural, subdural or unspecified intracranial hemorrhage
	Ischemic Stroke	433.x1	Occlusion & stenosis of precerebral arteries with mention of infarct
		434.xx	Occlusion of cerebral arteries
	TIA	435.xx	Transient cerebral ischemia
	Ischemic Stroke	436.xx	Acute, but ill-defined, cerebrovascular dz
	Other Cerebrovascular Disease	437.xx	Other & ill-defined cerebrovascular dz
		438.xx	Late effects of cerebrovascular dz
Peripheral Vascular Disease	Lower Extremity PAD	250.7	Diabetes w/ peripheral circulatory disorders, type II or unspd type, not stated as uncontrolled
		250.72	Diabetes with peripheral circulatory disorders, type II or unspecified type, uncontrolled
		443.81	Peripheral angiopathy in diseases classified elsewhere
		444.22	Arterial embolism and thrombosis of lower extremity

		444.81	Embolism and thrombosis of iliac artery
		440.2x	Atherosclerosis of native arteries of the extremities
		440.3x	Atherosclerosis of bypass graft of the extremities
		440.4x	Chronic total occlusion of artery of the extremities
		443.8x	Other specified peripheral vascular disease
		443.9x	Peripheral vascular disease, unspecified
		447.1x	Stricture of artery
	Abdominal Aortic Aneurysm	441.3x	Abdominal aneurysm, ruptured
		441.4x	Abdominal aneurysm without mention of rupture
		441.5x	Aortic aneurysm of unspecified site, ruptured

Appendix Table 2: CVD ICD 9 and CPT Revascularization Procedure Codes

Revascularization Type	ICD 9 Code	ICD 9 Procedure Description
Coronary Artery/Heart Disease	0.66	PTCA or coronary atherectomy
	36.03	Open Chest Coronary Artery Angioplasty
	36.04	Intracoronary Artery Thrombolytic Infusion
	36.06	Insertion Of Non-Drug-Eluting Coronary Artery Stent(s)
	36.07	Insertion Of Drug-Eluting Coronary Artery Stent(s)
	36.09	Other Removal Of Coronary Artery Obstruction
	36.1	Aortocoronary Bypass For Heart Revascularization, NOS
	36.11	Aortocoronary Bypass Of One Coronary Artery
	36.12	Aortocoronary Bypass Of Two Coronary Arteries
	36.13	Aortocoronary Bypass Of Three Coronary Arteries
	36.14	Aortocoronary Bypass Of Four Or More Coronary Arteries
	36.15	Single Internal Mammary-Coronary Artery Bypass
	36.16	Double Internal Mammary-Coronary Artery Bypass
	36.17	Abdominal-Coronary Artery Bypass
	36.19	Other Bypass Anastomosis For Heart Revascularization
	36.2x	Heart Revascularization By Arterial Implant
	36.31	Open Chest Transmyocardial Revascularization
	36.32	Other Transmyocardial Revascularization
	36.33	Endoscopic Transmyocardial Revascularization
	36.34	Percutaneous Transmyocardial Revascularization
	36.39	Other Heart Revascularization
Cerebrovascular Disease	0.61	Percutaneous Angioplasty Of Extracranial Vessel(s)
	0.62	Percutaneous Angioplasty Of Intracranial Vessel(s)
	0.63	Percutaneous Insertion Of Carotid Artery Stent(s)
	0.64	Percutaneous Insertion Of Other Extracranial Artery Stent(s)

	0.65	Percutaneous Insertion Of Intracranial Vascular Stent(s)
	38.11	Endarterectomy, Intracranial Vessels
	38.12	Endarterectomy, Other Vessels Of Head And Neck
	39.22	Aorta-Subclavian-Carotid Bypass
	39.28	Extracranial-Intracranial (Ec-Ic) Vascular Bypass
Peripheral Vascular Disease	0.55	Insertion of drug-eluting stent(s) of other peripheral vessel(s)
	0.6	Insertion of drug-eluting stent(s) of superficial femoral artery
	17.56	Atherectomy of other non-coronary vessel(s)
	38.14	Endarterectomy, aorta
	38.16	Endarterectomy, abdominal arteries
	38.18	Endarterectomy, lower limb arteries
	38.34	Resection of vessel with anastomosis, aorta
	38.44	Resection of vessel with replacement, aorta, abdominal
	39.25	Aorta-iliac-femoral bypass
	39.29	Other (peripheral) vascular shunt or bypass
	39.5	Angioplasty of other non-coronary vessel(s)
	39.52	Other repair of aneurysm
	39.71	Endovascular implantation of other graft in abdominal aorta
	39.9	Insertion of non-drug-eluting peripheral (non-coronary) vessel stent(s)
	84.11	Amputation of toe
	84.12	Amputation through foot
	84.15	Other amputation below knee
	84.17	Amputation above knee
Revascularization Type	**CPT Code**	**CPT Code Description**
Coronary Artery/Heart Disease	33510	Coronary artery bypass, vein only; single coronary venous graft
	33511	Coronary artery bypass, vein only; two coronary venous grafts
	33512	Coronary artery bypass, vein only; three coronary venous grafts
	33513	Coronary artery bypass, vein only; four coronary venous grafts
	33514	Coronary artery bypass, vein only; five coronary venous grafts
	33516	Coronary artery bypass, vein only; six or more coronary venous grafts
	33517	Coronary artery bypass, using venous graft(s) and arterial graft(s); single vein graft
	33518	Coronary artery bypass, using venous graft(s) and arterial graft(s); 2 venous grafts
	33519	Coronary artery bypass, using venous graft(s) and arterial graft(s); 3 venous grafts

	33521	Coronary artery bypass, using venous graft(s) and arterial graft(s); 4 venous grafts
	33522	Coronary artery bypass, using venous graft(s) and arterial graft(s); 5 venous grafts
	33523	Coronary artery bypass, using venous and arterial graft(s); 6 or more venous grafts
	33530	Reoperation, coronary artery bypass or valve procedure, > 1 month after original operation
	33533	Coronary artery bypass, using arterial graft(s); single arterial graft
	33534	Coronary artery bypass, using arterial graft(s); two coronary arterial grafts
	33535	Coronary artery bypass, using arterial graft(s); three coronary arterial grafts
	33536	Coronary artery bypass, using arterial graft(s); four or more coronary arterial grafts
	92928	Percutaneous transcatheter placement of intracoronary stent(s), with coronary angioplasty when performed; single major coronary artery or branch
	92929	Percutaneous transcatheter placement of intracoronary stent(s), with coronary angioplasty when performed; each additional branch of a major coronary artery
	92933	Percutaneous transluminal coronary atherectomy, with intracoronary stent, with coronary angioplasty when performed; single major coronary artery or branch
	92934	Percutaneous transluminal coronary atherectomy, with intracoronary stent, with coronary angioplasty when performed; each additional branch of a major coronary artery
	92937	Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of intracoronary stent, atherectomy and angioplasty, including distal protection when performed; single vessel)
	92938	Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of intracoronary stent, atherectomy and angioplasty, including distal protection when performed; each additional branch subtended by the bypass graft
	92941	Percutaneous transluminal revascularization of acute total/subtotal occlusion during acute myocardial infarction, coronary artery or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty, including aspiration thrombectomy when performed, single vessel

	92943	Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty; single vessel
	92944	Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty; each additional coronary artery, coronary artery branch, or bypass graft
	92980	Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; single vessel
	92981	Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; each additional vessel
	92982	Percutaneous transluminal coronary balloon angioplasty; single vessel
	92984	Percutaneous transluminal coronary balloon angioplasty; each additional vessel
	92995	Percutaneous transluminal coronary atherectomy, by mechanical or other method, with or without balloon angioplasty; single vessel
	92996	Percutaneous transluminal coronary atherectomy, by mechanical or other method, with or without balloon angioplasty; each additional vessel
	C9600	Percutaneous transcatheter placement of drug eluting intracoronary stent(s), with coronary angioplasty when performed; single major coronary artery or branch
	C9601	Percutaneous transcatheter placement of drug-eluting intracoronary stent(s), with coronary angioplasty when performed; each additional branch of a major coronary artery
	C9602	Percutaneous transluminal coronary atherectomy, with drug eluting intracoronary stent, with coronary angioplasty when performed; single major coronary artery or branch
	C9603	Percutaneous transluminal coronary atherectomy, with drug-eluting intracoronary stent, with coronary angioplasty when performed; each additional branch of a major coronary artery
	C9604	Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of drug-eluting intracoronary stent, atherectomy and angioplasty, including distal protection when performed; single vessel
	C9605	Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of drug-eluting intracoronary stent, atherectomy and

		angioplasty, including distal protection when performed; each additional branch subtended by the bypass graft
	C9606	Percutaneous transluminal revascularization of acute total/subtotal occlusion during acute myocardial infarction, coronary artery or coronary artery bypass graft, any combination of drug-eluting intracoronary stent, atherectomy and angioplasty, including aspiration thrombectomy when performed, single vessel
	C9607	Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of drug-eluting intracoronary stent, atherectomy and angioplasty; single vessel
	C9608	Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of drug-eluting intracoronary stent, atherectomy and angioplasty; each additional coronary artery, coronary artery branch, or bypass graft
	G0290	Transcatheter placement of a drug eluting intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; single vessel
	G0291	Transcatheter placement of a drug eluting intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; each additional vessel
	S2205	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using arterial graft(s), single coronary arterial graft
	S2206	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using arterial graft(s), two coronary arterial grafts
	S2207	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using venous graft only, single coronary venous graft
	S2208	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using single arterial and venous graft(s), single venous graft
	S2209	Using two arterial grafts and single venous graft minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision
Cerebrovascular Disease	33891	Bypass graft, with other than vein, transcervical retropharyngeal carotid-carotid, performed in conjunction with endovascular repair of descending thoracic aorta, by neck incision
	34001	Embolectomy or thrombectomy, with or without catheter; carotid, subclavian or innominate artery, by neck incision
	35301	Thromboendarterectomy, including patch graft, if performed; carotid, vertebral, subclavian, by neck incision

	35390	Reoperation, carotid, thromboendarterectomy, more than 1 month after original operation (list separately in addition to code for primary procedure)
	35501	Bypass graft, with vein; common carotid-ipsilateral internal carotid
	35506	Bypass graft, with vein; carotid-subclavian or subclavian-carotid
	35508	Bypass graft, with vein; carotid-vertebral
	35509	Bypass graft, with vein; carotid-contralateral carotid
	35510	Bypass graft, with vein; carotid-brachial
	35526	Bypass graft, with vein; aortosubclavian, aortoinnominate, or aortocarotid
	35601	Bypass graft, with other than vein; common carotid-ipsilateral internal carotid
	35606	Bypass graft, with other than vein; carotid-subclavian
	35626	Bypass graft, with other than vein; aortosubclavian, aortoinnominate, or aortocarotid
	35642	Bypass graft, with other than vein; carotid-vertebral
	37215	Transcatheter placement of intravascular stent(s), cervical carotid artery, percutaneous; with distal embolic protection
	37216	Transcatheter placement of intravascular stent(s), cervical carotid artery, percutaneous; without distal embolic protection
	61623	Endovascular temporary balloon arterial occlusion, head or neck (extracranial/ intracranial) including selected catheterization of vessel to be occluded, positioning and inflation of occlusion balloon, concomitant neurological monitoring, and radiologic supervision and interpretation of all angiography required for balloon occlusion and to exclude vascular injury post occlusion
	0075t	Transcatheter placement of extracranial vertebral or intrathoracic carotid artery stent(s), including radiologic supervision and interpretation, percutaneous; initial vessel
	0076t	Transcatheter placement of extracranial vertebral or intrathoracic carotid artery stent(s), including radiologic supervision and interpretation, percutaneous; each additional vessel (list separately in addition to code for primary procedure)
Peripheral Vascular Disease	27590	Amputation, thigh, through femur, any level;
	27880	Amputation, leg, through tibia and fibula;
	2788	Amputation, leg, through tibia and fibula; open, circular (guillotine)

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	27884	Amputation, leg, through tibia and fibula; secondary closure or scar revision
	28805	Amputation, foot; transmetatarsal
	28810	Amputation, metatarsal, with toe, single
	28820	Amputation, toe; metatarsophalangeal joint
	28825	Amputation, toe; interphalangeal joint
	34201	Embolectomy/thrombectomy, w/ or w/o catheter; femoropopliteal, aortoiliac artery, by leg incision
	34203	Embolectomy/thrombectomy, w/ or w/o catheter; popliteal-tibio-peroneal artery, by leg incision
	34800	Endovascular repair of infrarenal abdominal aortic aneurysm/dissection; using aorto-aortic tube prosthesis
	34802	Endovascular repair of infrarenal abdominal aortic aneurysm/dissection; using modular bifurcated prosthesis (1 docking limb)
	34803	Endovascular repair of infrarenal abdominal aortic aneurysm/dissection; using modular bifurcated prosthesis (2 docking limbs)
	34804	Endovascular repair of infrarenal abdominal aortic aneurysm/dissection; using unibody bifurcated prosthesis
	34805	Endovascular repair of infrarenal abdominal aortic aneurysm/dissection; using aorto-uniiliac or aorto-unifemoral prosthesis
	34830	Open repair of infrarenal aortic aneurysm/dissection, plus repair of associated arterial trauma, following unsuccessful endovascular repair; tube prosthesis
	34831	Open repair of infrarenal aortic aneurysm/dissection, plus repair of associated arterial trauma, following unsuccessful endovascular repair; aorto-bi-iliac prosthesis
	34832	Open repair of infrarenal aortic aneurysm/dissection, plus repair of associated arterial trauma, following unsuccessful endovascular repair; aorto-bifemoral prosthesis
	35081	Direct repair of aneurysm, pseudoaneurysm, or excision (partial or total) and graft insertion, w/ or w/o patch graft; for aneurysm, pseudoaneurysm, and associated occlusive disease, abdominal aorta
	35082	Direct repair of aneurysm, pseudoaneurysm, or excision (partial or total) and graft insertion, w/ or w/o patch graft; for ruptured aneurysm, abdominal aorta

	35091	Direct repair of aneurysm, pseudoaneurysm, or excision (partial or total) and graft insertion, w/ or w/o patch graft; for aneurysm, pseudoaneurysm, and associated occlusive disease, abdominal aorta involving visceral vessels (mesenteric, celiac, renal)
	35102	Direct repair of aneurysm, pseudoaneurysm, or excision (partial or total) and graft insertion, w/ or w/o patch graft; for aneurysm, pseudoaneurysm, and associated occlusive disease, abdominal aorta involving iliac vessels (common, hypogastric, external)
	35103	Direct repair of aneurysm, pseudoaneurysm, or excision (partial or total) and graft insertion, w/ or w/o patch graft; for ruptured aneurysm, abdominal aorta involving iliac vessels (common, hypogastric, external)
	35302	Thromboendarterectomy, including patch graft, if performed; superficial femoral artery
	35303	Thromboendarterectomy, including patch graft, if performed; popliteal artery
	35305	Thromboendarterectomy, including patch graft, if performed; tibial or peroneal artery, initial vessel
	35351	Thromboendarterectomy, including patch graft, if performed; iliac
	35355	Thromboendarterectomy, including patch graft, if performed; iliofemoral
	35371	Thromboendarterectomy, including patch graft, if performed; common femoral
	35470	Transluminal balloon angioplasty, percutaneous; tibioperoneal trunk or branches, each vessel
	35471	Transluminal balloon angioplasty, percutaneous; renal or visceral artery
	35472	Transluminal balloon angioplasty, percutaneous; aortic
	35473	Transluminal balloon angioplasty, percutaneous; iliac
	35474	Transluminal balloon angioplasty, percutaneous; femoral-popliteal
	35491	Transluminal peripheral atherectomy, percutaneous; aortic
	35492	Transluminal peripheral atherectomy, percutaneous; iliac
	35493	Transluminal peripheral atherectomy, percutaneous; femoral-popliteal
	35494	Transluminal peripheral atherectomy, percutaneous; brachiocephalic trunk or branches, each vessel
	35495	Transluminal peripheral atherectomy, percutaneous; tibioperoneal trunk and branches
	3555	Bypass graft, with vein; femoral-popliteal

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	35571	Bypass graft, with vein; popliteal-tibial, -peroneal artery or other distal vessels
	35583	In-situ vein bypass; femoral-popliteal
	35585	In-situ vein bypass; femoral-anterior tibial, posterior tibial, or peroneal artery
	35587	In-situ vein bypass; popliteal-tibial, peroneal
	35621	Bypass graft, with other than vein; axillary-femoral
	35646	Bypass graft, with other than vein; aortobifemoral
	35651	Bypass graft, with other than vein; aortofemoral-popliteal
	35654	Bypass graft, with other than vein; axillary-femoral-femoral
	35656	Bypass graft, with other than vein; femoral-popliteal
	35661	Bypass graft, with other than vein; femoral-femoral
	35665	Bypass graft, with other than vein; iliofemoral
	35666	Bypass graft, with other than vein; femoral-anterior tibial, posterior tibial, or peroneal artery
	35681	Bypass graft; composite, prosthetic and vein (list separately in addition to code for primary procedure)
	37205	Transcatheter placement of an intravascular stent(s) (except coronary, carotid, vertebral, iliac, and lower extremity arteries), percutaneous; initial vessel
	37220	Revascularization, endovascular, open or percutaneous, iliac artery, unilateral, initial vessel; with transluminal angioplasty
	37221	Revascularization, endovascular, open or percutaneous, iliac artery, unilateral, initial vessel; with transluminal stent placement(s), includes angioplasty within the same vessel, when performed
	37224	Revascularization, endovascular, open or percutaneous, femoral, popliteal artery(s), unilateral; with transluminal angioplasty
	37225	Revascularization, endovascular, open or percutaneous, femoral, popliteal artery(s), unilateral; with atherectomy, includes angioplasty within the same vessel, when performed
	37226	Revascularization, endovascular, open or percutaneous, femoral, popliteal artery(s), unilateral; with transluminal stent placement(s), includes angioplasty within the same vessel, when performed

	37227	Revascularization, endovascular, open or percutaneous, femoral, popliteal artery(s), unilateral; with transluminal stent placement(s) and atherectomy, includes angioplasty within the same vessel, when performed
	37228	Revascularization, endovascular, open or percutaneous, tibial, peroneal artery, unilateral, initial vessel; with transluminal angioplasty
	37229	Revascularization, endovascular, open or percutaneous, tibial, peroneal artery, unilateral, initial vessel; with atherectomy, includes angioplasty within the same vessel, when performed
	37230	Revascularization, endovascular, open or percutaneous, tibial, peroneal artery, unilateral, initial vessel; with transluminal stent placement(s), includes angioplasty within the same vessel, when performed
	37231	Revascularization, endovascular, open or percutaneous, tibial, peroneal artery, unilateral, initial vessel; with transluminal stent placement(s) and atherectomy, includes angioplasty within the same vessel, when performed