OVERVIEW

Dr. Brian Mandell and Dr. Naomi Schlesinger discuss recent published evidence related to gout, as well as study results presented at the American College of Rheumatology Convergence 2020 virtual annual meeting. Dr. Schlesinger begins with an introduction on a recent published systematic review indicating that the manifestations of gout extend beyond the joints, affecting other organs and tissues. Dr. Schlesinger also provides an overview of some of the challenges encountered in clinical practice with the use of urate-lowering therapy. Dr. Schlesinger focuses on two abstracts concerning gout-related comorbidities, particularly cardiovascular disease. Dr. Mandell focus on two abstracts related to the safety and use of urate-lowering therapy, specifically allopurinol, febuxostat, and pegloticase. Dr. Mandell also discuss 2 abstracts related to the systemic nature of gout; one abstract focuses on heart failure, while the other focuses on the lumbar spine.

CONTENT AREAS

- Systemic burden of gout
- Gout comorbidities
- Allopurinol
- Febuxostat
- Pegloticase

TARGET AUDIENCE

This activity is intended for rheumatologists and nephrologists.

FACULTY

Brian Mandell, MD, PhD
Professor of Medicine
Chairman of Academic Medicine
Cleveland Clinic
Cleveland, Ohio

Naomi Schlesinger, MD
Professor of Medicine
Chief, Division of Rheumatology
Rutgers-Robert Wood Johnson Medical School
New Brunswick, New Jersey

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Summarize the latest evidence related to combination pharmacologic treatment of patients with gout who do not achieve the target serum urate level with monotherapy
- Summarize the latest evidence related to complications associated with gout
- Incorporate evidence-based research into clinical practice

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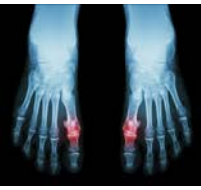

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INTRODUCTION

Systemic Urate Deposition: An Unrecognized Complication of Gout?

Khanna P, et al.
Link: Systemic Urate Deposition: An Unrecognized Complication of Gout?

Dr. Schlesinger: Gout is a very common disease of which hyperuricemia is a key characteristic. Deposition of monosodium urate crystals in the joints, around the joints, can lead to inflammation and, hence, bone erosions, tophi, and lead to severe tophaceous gout. To prevent further damage and reduce the uric acid pool, it's been stated that we should lower the uric acid, urate in the blood, uric acid in the urine, to a level of less than 6.8 mg per dL. To make it easier, it's been 6 mg per dL, and that is the treatment target of urate-lowering therapy.

It's been thought that deposition of monosodium urate crystals in extraarticular sites is uncommon. However, recent evidence has demonstrated that this is not the case and that deposition of monosodium urate crystals is seen in a wide variety of tissues and actually is much more common than was thought before.

A recent systematic review by Dr. Khanna et al, is a very large review. It includes 290 articles, including clinical trials, abstracts, case reports, case series, over many years, from 1920 to 2020. This review finds extensive evidence of monosodium urate crystal deposition in the cardiovascular system, the renal system, the spine, and other organs and tissues. And dual-energy computer tomography (DECT), a new technology has emerged where there are 2 energy beams, as opposed to 1 energy beam with a CAT scan, with special software that can actually see uric acid deposits as well as calcium, that has enhanced our understanding of monosodium urine deposition, as well as the pathology.

We see using dual energy CT, the monosodium urate crystals deposit in coronaries, other major arteries, but also the heart's myocardium, endocardium, heart valves. Hyperuricemia, too, has been shown to be an independent risk factor for cardiovascular disease and even cardiac death. We know that tophaceous gout is a risk factor for cardiac death, as well.

In the kidneys, monosodium urate crystal deposits are observed in the renal medulla, within the collecting ducts, and medullary interstitium. Monosodium urate crystal deposits are usually surrounded by inflammatory cells. As we discussed, monosodium urate crystal deposition leads to inflammation. And this is further surrounded usually by fibrosis.

In addition, involvement of the renal artery, the renal vasculature may be evident.

Extensive evidence demonstrates that monosodium urate crystal deposition in facet joints, intervertebral discs, hence in the spine, ligaments, ligamentum flavum, other tissues within the cervical, thoracic, and most commonly lumbar spine, are not uncommon. And, in fact, in our patients with gout that have back pain, one has to think of whether they have actually monosodium urate crystal deposition or tophi in their spine.

Monosodium urate crystal deposits were reported nearly everywhere, in the eye, manifesting in a wide range of signs and symptoms, including scleritis, episcleritis, uveitis, and ulcers. Gastrointestinal system has been involved, and, as we know, it can affect the liver, pancreas, and the bowel. Other areas, monosodium urate crystal deposits are also in the larynx, the ears, the nose.

This review, systematic review, also suggests that gout is a systemic inflammatory disease that can

affect multiple organ systems causing a wide variety of cardiovascular, renal and other diseases. But this is not just the systematic review. We know that both gout and hyperuricemia can lead to many comorbidities and cause disease outside the joint. So, gout is not just about joints, it's a systemic disease.

It is, therefore, critically important that all people with gout be treated using urate-lowering therapy with this goal of serum urate of 6 mg per dL, or less. This is the American College of Rheumatology's long-standing recommendation, which is included in their updated 2020 practice guidelines.

While many medications are effective in lowering the serum urate, many patients do not reach their serum urate target of 6 mg per dL, or less. There are many reasons for this. Some are our fault as clinicians. We do not routinely give our patients urate-lowering therapy, and when we give urate-lowering therapy, we do not follow their serum urates. And patient adherence to treatment is poor as well. In fact, only about a third of patients with gout are treated with urate-lowering therapy, and adverse events are not uncommon.

Combination treatment with different urate-lowering therapies has been required in patients that don't respond to oral therapies or maybe had adverse events with some of these urate-lowering therapies. Safety and tolerability concerns, limitation of effectiveness of xanthine oxidase inhibitors such as allopurinol, febuxostat, have led to the search of additional medications.

Lesinurad, which was on the market for a very short time in the United States, was taken off the market in the United States in February 2019.

Pegloticase, which has been on the market for approximately 10 years, is an alternative urate-lowering therapy for patients with chronic gout refractory to conventional therapy, and lowers serum urate effectively to 1 mg per dL. And really lower than the 6 mg per dL, our target.

One currently used strategy to reduce the risk of infusion reaction, which is something that happens when one uses uricase, pegloticase, is giving steroids, antihistamines. But currently in trials and some anecdotal reports is the use of immunosuppressant therapy with small doses of disease-modifying anti-rheumatic drugs, such as methotrexate, mycophenolate mofetil (Cellcept), azathioprine (Imuran). And those are helpful in the trials.

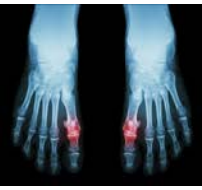
Other medications under investigation for urate-lowering therapy include verinurad and another uricase SEL-212.

MODULE 1

Long Term Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Chronic Gout: The Febuxostat versus Allopurinol Streamlined Trial (on Behalf of the FAST Investigators)
MacDonald T, et al.

Link: Long Term Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Chronic Gout: The Febuxostat versus Allopurinol Streamlined Trial (on Behalf of the FAST Investigators) - ACR Meeting Abstracts (acrabstracts.org)

Dr. Mandell: I want to discuss the Long-Term Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Chronic Gout. This was the Febuxostat vs Allopurinol Streamlined Trial known as the FAST trial, by MacDonald et al. So, the study results were presented at the ACR 2020, and published online in *The Lancet* in November of 2020. And I believe that this really much anticipated paper, at least in the gout world, will likely have the greatest impact on clinical practice over the next year of any



paper at the ACR this year, as it counterbalances a black box warning which had been placed by the FDA on the febuxostat label.

Now in the summary, down and dirty, this was that a treatment with febuxostat over a median of 4 years, was noninferior to allopurinol with respect to significant cardiovascular events in patients with established gout, one-third of whom had known cardiovascular disease. All of them had risk of cardiovascular disease. This was in contrast to the results from the 2018 Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial, which has suggested an increase in cardiovascular and all-cause mortality in patients taking febuxostat vs allopurinol, and this is what led to the FDA warning. So, although this paper addresses, really, a straightforward question, there's really a complex background to this study with several aspects that interface gout, hyperuricemia, the gout therapies, and cardiovascular disease.

Serum urate is clearly associated with hypertension, chronic kidney disease, and cardiovascular disease of all flavors. There's likely a stronger association of gout than hyperuricemia with cardiovascular events, likely impacted by issues of flares with cytokine release with true gout, as well as preserving greater urate deposition in those who have gout and asymptomatic hyperuricemia. But it's really unclear if urate lowering impacts the outcomes of cardiovascular disease. Animal models demonstrate a relation with blood pressure elevation, observational data are very suggestive, but the interventional data, in other words lowering the serum urate is very mixed, negative in chronic kidney disease, and very, very mixed in cardiovascular disease.

It raises the question of, might urate-lowering drugs have effects independent of the serum urate? Allopurinol may reduce total cardiovascular events. There are some papers that suggest this, even with the possibility of a J-curve function. And this may be due to intracellular oxygen stress on myocytes and endothelial cells.

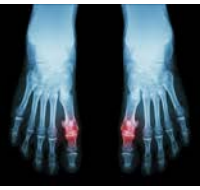
With febuxostat it's even less clear that there's any effect on cardiovascular events. Probenecid, a uricosuric drug blocking urate uptake into cells, interestingly, has been shown in 1 study to reduce cardiovascular events.

Then there are the confounders, the influences of IL-1 levels and other factors. Colchicine, many studies now reduce cardiovascular events. Non-steroidal anti-inflammatory drugs (NSAIDs) seem to increase slightly cardiovascular events. And the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) showing that canakinumab blocks the effects of IL-1 and reduced cardiovascular events.

In the clinical trials leading to the registration of febuxostat, which compared the drug with placebo with allopurinol, there was a non-dose-related numerical, but not a statistical, increase in cardiac events with febuxostat. And this was really only about one-per-thousand patient-years. But both the US and the European regulatory bodies required collection of post-approval safety data, and this led to the CARES trial in the US and the FAST trial in the UK and Denmark.

The CARES trial, which importantly enrolled those with a very significant history of cardiovascular disease, showed an increase in cardiac and an increase in all-cause mortality without any increase in the primary composite cardiovascular endpoint, or other specific components of those predefined parts of the primary composite endpoint. However, in this trial, 57% of participants discontinued drug therapy early, and 45% were lost to follow-up.

In follow-up of the study, post-hoc ascertainment of those lost patients actually showed more deaths in the allopurinol-treated patients than in febuxostat, and the statistical significance that was shown in the initial evaluation, showing more deaths with



febuxostat, disappeared. Also, a majority of the events actually occurred after participants had stopped taking the trial drugs. And there was an imbalance in aspirin and NSAID use, and the effect of not taking aspirin with febuxostat vs allopurinol.

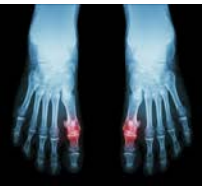
All of those things, together, led to a little bit of a jaundiced eye in looking at those trial results. Nonetheless, the prescribing information for febuxostat since 2019 has included a boxed warning indicating that in patients with gout and established cardiovascular disease, treatment with febuxostat results in a higher rate of cardiovascular death compared to allopurinol. And in the 2019 ACR gout guideline, allopurinol is listed as the first-choice xanthine oxidase inhibitor and suggests consideration to actually change from febuxostat to an alternative medication.
This was a very long introduction to the FAST trial, which is the abstract that was presented. But I think it was important to do that to really set the stage to understand the significance in the gout community, and the internal medicine community, for this trial.

The FAST trial done in the UK and Denmark was prospective, randomized, open-label blinded, and multicenter, including eligible patients who had known gout and who were already receiving allopurinol for an average of 6 years. So, everybody in this trial was already receiving allopurinol. They were over the age of 60 years and they had all at least 1 cardiovascular risk factor, and severe congestive heart failure was excluded. Very different than in the earlier CARES trial.

The dose of allopurinol was increased prior to randomization to achieve a serum urate level of less than 6 mg per dL (mg/dL), the accepted target pretty much internationally for treatment of patients with gout. 36% of patients, at starting this trial, had actually a urate level greater than 6 mg/dL. So, after the patients achieved a level less than 6 mg/dL, they were then randomized to receive either allopurinol at the preselected dose that was effective, or febuxostat 80 mg, which could be increased to 120 mg to get the serum urate level less than 6 mg/dL. Realize this is in Europe, and the dosing of febuxostat is higher in Europe than it is in the United States. When you looked at the patients once they were entered, there were higher doses of both allopurinol and higher doses of febuxostat than in the CARES trial. And like CARES, there was no control group, there was no group of gout patients who were just watched.

6,000 plus patients were randomized. One-third had established cardiovascular disease, all, as I said, had risk. The median follow-up was 4 years. 16% of the allopurinol group and 32% of the febuxostat group withdrew from treatment. However, unlike in the CARES trial, only about 5% to 6% of patients were actually lost to follow-up, despite withdrawing from treatment. The primary outcome was the composite of hospitalization for nonfatal myocardial infarction, biomarker positive acute coronary syndrome, nonfatal stroke, or cardiovascular death. In the intention-to-treat analysis, there were 2 events per 100 patient-years in the febuxostat group, and 2.3 events per 100 patient-years in the allopurinol group. In the on-treatment analysis, there were 1.7 events per 100 patient-years in the febuxostat group, and 2 events per 100 patient years in the allopurinol group. 7.2% of patients receiving febuxostat died, compared with 8.6% in the allopurinol group. Slightly more febuxostat patients were actually on colchicine, which actually was offered to both groups for the first 6 months.

What's my takeaway from this? I really had not been previously too concerned regarding the cardiovascular signal from the CARES trial to begin with. It had always been a second-line agent for me due to cost and the difficulty to titrate the dose, the pills are not scored. The box warning, however, matters to many, both insurance companies and providers and patients, and for a disease that is already undertreated with few therapy options, this was problematic. So, I think the FAST trial provides for a higher comfort level with using febuxostat, but it



must be noted that the FAST patients did not have the significant baseline cardiovascular disease as in CARES. Also, their genetic background was different, far fewer African Americans, and the previous use of allopurinol for an average of 6 years prior to randomization in the FAST trial, not done in the CARES trial, weeded out patients with allopurinol intolerance.

I'd like to see the black box disappear. I'm not sure that's going to happen. And unanswered is the question of whether any approach to urate lowering will reduce the risk of cardiovascular events, since there was no control group. A major sidebar take-home message from this study is that, when you look at the protocol-mandated dose adjustment, almost 100% of participants hit that target level of 6 mg/dL, which means that allopurinol is actually very effective as a urate-lowering drug if it's prescribed and monitored appropriately. And unfortunately, this is a very far cry from routine practice outcomes.

Management of Gout with Pegloticase; Real-World Utilization and Outcomes from Trio Health and the American Rheumatology Network (ARN)

Soloman N, et al.

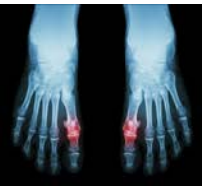
Link: Management of Gout with Pegloticase; Real-World Utilization and Outcomes from Trio Health and the American Rheumatology Network (ARN) - ACR Meeting Abstracts (acrabstracts.org)

Dr. Mandell: I want to discuss Management of Gout with Pegloticase; Real-World Utilization and Outcomes from Trio Health and the American Rheumatology Network. And this was presented at the ACR by Dr. Soloman and colleagues. It was actually presented in 2 abstracts, numbers 1628 and 1629.

In summary, this is an observational description of the real-world use of pegloticase. Selected data was extracted from chart review from a registry of greater than 200 rheumatologists across the United States. Two hundred thirteen patients from this group had received pegloticase, 110 received their final infusion between 2015 and 2019, and had greater than 180 days follow-up from the initiation of therapy. Also, all the patients included in the analysis had at least 2 serum urate measurements that could be evaluated. Successful treatment course was achieved in a significant minority of patients, less, in fact, than in the initial randomized clinical trials. And it was more likely to be achieved in patients receiving methotrexate co-therapy in this real-world experience.

A little background on this. All practice reviews to date have highlighted the suboptimal management of patients with gout. And while, honestly, much of the blame can be on us for undertreatment, underprescription, there are additional issues of noncompliance in patients, likely which could be remediated with significant education provided by us. But there are some patients who truly are resistant to current traditional therapies when urate-lowering therapy at a maximally tolerated dose can't lower the serum urate to the desired target level. In some, this target may be below 6 mg/dL, a standard target, but in others, where the tophaceous load is so extensive, or the location of the deposit so severely limits normal activities, that a far, far lower serum urate is desirable as the target for patient and treating physician. And the lower the serum urate, we realized the faster those tophaceous deposits are going to dissolve, and the faster improvement in function will ensue.

Humans lack the functional enzyme, uricase, urate oxidase, that converts urate to allantoin. By utilizing enzyme replacement therapy, providing uricase treatment, the serum urate can be dropped



significantly to levels really approaching unmeasurable or zero. Purified uricase, however, is extremely immunogenic and thus, various pegylated preparations have been prepared, and 1 is currently approved for clinical use. Unfortunately, and ironically, the dense pegylation of the molecule, of the uricase, has itself turned out to be immunogenic, and in the randomized clinical trials used for registration, only about 50% of patients were able to continue with effective, every 2-week IV infusions. This was due to the development of high-titer, anti-PEG-directed antibody, which led to increased clearance of the drug and loss of efficacy.

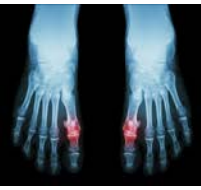
In practice, that loss of activity can be functionally detected by demonstrating the rise in the serum urate prior to the planned next every 2-week infusion. So, when the serum urate rises to greater than 6 mg/dL pre-infusion, it's recognized there are high levels of antibodies, the drug is cleared, and the drug is not going to be as effective. And for many patients, it has to be realized that this represents the last, or due to severity of their gout, clearly the best, therapeutic option.

When that serum urate rises to above 6 mg/dL prior to infusion, generally the infusions are going to be stopped because it's those patients who have a rising level of serum urate, rising level of anti-drug-antibodies, those are the patients who get infusion reactions. So, stopping the infusions will obviously prevent future infusion reactions.

The use of pegloticase remains fairly low in most clinical practices and concern over possible infusion reactions, the lack of continued responsiveness seen in the randomized trials, pose significant barriers to care for the subset of patients with this extremely severe gout.

It's very useful to look at how physicians, rheumatologists in particular, have utilized this therapy in the real world. This included patients from the American Rheumatology Network, ARN, registry, a network of independent practices with, as I said, greater than 200 rheumatologists across the US. Patient data included the electronic medical record, medical claims, as well as specialty pharmacy data. The patients who were evaluated were those with diagnosed gout who initiated their last course of pegloticase between 2015 and 2019. They had to have more than 180 days of follow-up from the time pegloticase was initiated. And a course of treatment was defined as a pegloticase infusion occurring less than 90 days apart, so they had to have several doses of pegloticase given within that timeframe. Patients had to have serum urate levels measured at least twice during the treatment, and again I emphasize, normal practice is to check this prior to every infusion.

What did they find? They found, of the 213 patients with gout treated with pegloticase, 110 met the study criteria and were evaluated. Ninety-five of these 110 had actually finished a therapeutic course, but this was either completed in the planned course, or was discontinued early. These patients were males, as in most gout series, were over the age of 60 years, and the mean follow-up was about 500 days. Interestingly, in this real-world study, 25% received concurrent immunosuppressive therapy; 25 of the 28 of those patients received methotrexate. I don't have a lot of information as to why, but I'm assuming that in the overwhelming majority of people receiving methotrexate, the methotrexate was given for prevention of the development of the anti-drug-antibodies. Of the 95 patients, only 19% finished treatment because the treatment goals weren't met. 39% discontinued treatment due to a lack or loss of efficacy, 16% due to adverse events, and the others discontinued for various reasons. The median times to discontinuation were about 22 weeks for nonplanned discontinuation, longer than when failure is usually seen, in fact, which means that for some reasons the infusions were continued in many of these patients. After the completion of the pegloticase course, only 70% were on urate-lowering therapy within 90 days after the time pegloticase treatment was continued. So, patients with less than



2 serum uric acid levels greater than 6 mg/dL were classified as being controlled.

Patients with concurrent use of immunomodulatory therapy experienced a significantly longer duration of pegloticase treatment, and in these patients, the median time to unplanned pegloticase discontinuation was 34 weeks, compared with 12 weeks in patients who had not received immunomodulatory therapy. Again, in the randomized trials of an earlier use of this drug, immunomodulatory immunosuppressive therapy such as methotrexate was not part of routine care. But in this group, none of the 12 patients who discontinued pegloticase due to infusion or allergic reactions had been receiving immunosuppressive therapy. And after completion of pegloticase therapy, only 50% of the patients who went back on urate-lowering therapy were able to maintain a serum urate level less than 6 mg/dL. Meaning that, again, this is a very difficult population of patients to treat. So it really was critical, if you're going to give pegloticase, to do everything you can to try to get the patients to be able to tolerate the drug and have it be effective.

What is my take on all of this? This is a relatively small set of patients who, by the time they see a rheumatologist, have truly severe gout, and either are resistant or intolerant to standard urate-lowering therapy in adequate doses, or need more rapid resolution of deposits than traditional therapy will give. And the only real option for these patients in 2020 remains pegloticase. So, I believe this therapy is underutilized, but problematic is the high frequency of drug failure due to the development of, or even the presence of, these anti-PEG antibodies, even before treatment is given, that neutralize the drug and are associated with infusion reactions. So, this happened in approximately 50% of patients in the randomized control trials, and Soloman et al report here that only 19% of patients in their group, in this real-world study, were able to stay on therapy for the planned duration of treatment.

Interestingly, despite the fact that there's an apparent resistance of rheumatologists to use this drug at all, 25 patients were on concurrent immunosuppressive therapy. It is not clear why they were on these medications, and 25-28 were on methotrexate, but as I said, I believe they were given by rheumatologists with the hope of preventing anti-drug-antibodies, which seems to be actually an effective approach. And notably, these patients had more durable treatment courses, suggesting the baseline treatment blunted the development of anti-PEG antibodies, permitting longer treatment. This is consistent with several other preliminary observational studies, and the randomized trial using mycophenolate, presented at European League Against Rheumatism (EULAR) and also at the American College of Rheumatology (ACR) meetings, indicating that this is a potentially useful treatment strategy. Unfortunately, most of the observational studies are exactly that, and did not have a control arm, and the real-world use of pegloticase has changed in other ways that may also influence the development of neutralizing antibodies in ways that we don't understand.

My own experience with pegloticase, without using immunosuppressive co-therapy, has also been far superior to the 50% success rate reported in the initial randomized trials. I don't know the explanation for that. As to the low percentage of patients maintaining an appropriate target serum urate after completing, or after discontinuing early, their pegloticase course of therapy, this is likely, I suspect, in large part, really a representation of the challenges in treating this subset of patients who have very severe gout and have only very few therapeutic options.

MODULE 2

Analysis of Common Gout Comorbidities in the UK Biobank Cohort Reveals Sex-Specific Effects and Genetic Differentiation

Sumpter N, et al.

Link: Analysis of Common Gout Comorbidities in the UK Biobank Cohort Reveals Sex-Specific Effects and Genetic Differentiation - ACR Meeting Abstracts (acrabstracts.org)

Dr. Schlesinger: To summarize this abstract, the study aimed to estimate the extent to which gout-associated genetic variants are associated with the presence or absence of common comorbidities in gout patients in this UK Biobank cohort.

Why is this important? Key points of this abstract are that this study confirmed findings from previous studies showing that women with gout tend to be more likely than men with gout to suffer from a variety of comorbidities. The study also demonstrated the significant contribution of gout genetic risk variants to the presence or absence of any comorbidity in gout patients, raising the concept of primary vs secondary gout.

How was the study done? What are the methods of the study? The study involved persons included in the UK database. Comorbidities were identified using self-reported data, ICD-10 codes denoting the different comorbidities, gout medications, and measured biomarkers and metrics. Each comorbidity was tested for association with gout using generalized linear models adjusted for age and sex. Variant genotypes from 12 genome-wide significant gout loci from the UK Biobank were used to calculate an effect size-weighted gout genetic risk score. The gout genetic risk score was then tested for association using a generalized linear model with the presence of any comorbidity within the gout cohort adjusting for age and sex.

This is very important because women tend to get gout when they're postmenopausal, and some would say, well, they're older so, hence, they'll have more comorbidities, but this is adjusted to their age.

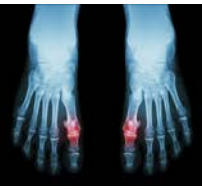
What were the key findings of this abstract? That UK Biobank included over 332,000 people of whom a little over 7000, or 2.2%, had gout. The mean age of the entire cohort was 57 years, and approximately half were male. All comorbidities were approximately 2-3 times more common in people with gout vs people without gout.

For example, heart failure was observed in 1.8% of people in the entire UK Biobank cohort, and in 6.5% of people with gout. Findings for other comorbidities where 9.5% in the entire cohort of coronary heart disease and in 21.7% or 22% of people with gout. This is a major increase, a significant increase.

How about hypertension, another known comorbidity to be associated with gout? 35.2% of this UK Biobank cohort suffered from hypertension and almost 70% of people with gout. So, gout leads to very common hypertension in this biobank.

Similar associations were observed for other comorbidities that we know are commonly associated with gout. Sleep apnea, cerebrovascular disease, obesity, chronic kidney disease, type 2 diabetes mellitus, and dyslipidemia.

The comorbidities were significantly more prevalent in women with gout vs men with gout. For example, the odds ratio for hypertension in women with gout was 7.18 vs 2.98 in men with gout. So, it's not just that the gout patients had higher prevalence of these diseases, the association was even more remarkable in the women compared to men with gout.



The gout genetic risk score was confirmed to associate with gout in the entire cohort and the gout genetic risk score was found to be associated with the reduced likelihood of having the comorbidity among people with gout. This was primarily due to variants at the following loci, *ABCG2* locus and *ADH1B* locus.

The Association Between Gout and Cardiovascular Disease Outcomes: Assessment and Recalibration of Individual-level Primary Prevention Risk Prediction Equations in Approximately 450,000 New Zealanders

Cai K, et al.

Link: The Association Between Gout and Cardiovascular Disease Outcomes: Assessment and Recalibration of Individual-level Primary Prevention Risk Prediction Equations in Approximately 450,000 New Zealanders - ACR Meeting Abstracts (acrabstracts.org)

Dr. Schlesinger: In summary, epidemiological studies have demonstrated a relationship between gout and cardiovascular disease. Individual level cardiovascular risk prediction equations have been developed and validated in New Zealand for the New Zealand population using a comprehensive primary care database called PREDICT or PREDICT-1. This software has been developed and validated to assess individual level cardiovascular risk in a primary care population in patients with no history of cardiovascular disease, renal disease, or congestive heart failure. The current cardiovascular risk prediction equations underestimate the risk of cardiovascular disease in people with gout. Despite the adjustment for known cardiovascular risk factors, gout independently increased the hazard ratio for cardiovascular events.

What is the importance? Increasing evidence indicates that gout is an independent risk factor for cardiovascular disease.

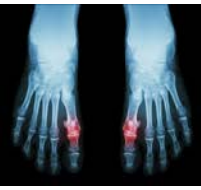
How was this done? What are the methods for this study? Baseline estimates of 5-year cardiovascular risk, and these include cardiovascular death, nonfatal myocardial infarction, stroke, and other vascular events, were calculated using this set specific PREDICT-1 that was used previously in primary care. Risk scores and initially assessed via the slope between estimated and observed risk on the calibration plot, which is the slope, and gout was added as a binary predictor that recalibrated risk models.

The PREDICT study population consisted of patients in New Zealand whose primary care clinicians use the PREDICT software to assess their patients' risk profile for cardiovascular disease. The primary care dataset, as I said, was PREDICT-1. And the software was prospectively linked to the national ICD coded hospitalization and mortality databases.

This is basically a nationwide database. The study population included men and women ages 30 to 74 years who had no history of cardiovascular disease, renal disease, or congestive heart failure. And it used again a validated national health data definition of gout in adults with diagnosed gout in New Zealand where gout is very common. Approximately 15% of the Maoris have gout. So, this is a major problem in New Zealand.

What were the key findings in this study? From 2007 through 2018 over 441,000 adults were seen in primary care and were in this PREDICT-1 database, and underwent the risk assessment.

A little more than 50% were men, and of this cohort, a little over 23,000 met the definition of gout. They were mostly men, which is what we expect, and 3325 females and almost 20,000 men. 69% of women and 77% of men received urate-lowering therapy. This is



remarkable because as I said in the previous abstract, approximately a third of patients usually are on urate-lowering therapy worldwide. And here in New Zealand, you find in this cohort, over 70% receiving urate-lowering therapy.

In the entire cohort, 3.3% had the first cardiovascular events within 5 years of risk assessment. And of these, 6.5% had gout and 3.2% did not have gout.

The risk scores underestimated the risk for cardiovascular events in adults, those with gout vs those without gout. Then you see the slope of 0.88. The underestimated risk of cardiovascular event was more pronounced in women. Women with gout vs women without gout were 3 times more likely to experience a fatal cardiovascular event within the first 5 years in this cohort. And men with gout vs men without gout were twice as likely to have a fatal cardiovascular event.

Thus, this is very common in gout patients. Adding gout to the recalibrated risk estimates demonstrated that gout was independently associated with increased risk of cardiovascular events, with hazard ratio, you can see are higher for women, 1.24, and 1.21 for men.

Summary

What have we learned from both of these abstracts? One. We know that gout is the most common inflammatory arthritis globally. It's prevalence is increasing. Obesity, a major problem, and a vital contributor to the marked increase in gout prevalence. But there are other causes. We've discussed genetics. Genetics are important and you can see in New Zealand that they're working on the genetics.

The burden of gout is intensified by comorbidities commonly associated with gout. The comorbidities include sleep apnea, cerebrovascular disease, and this includes heart failure, coronary artery disease, as we discussed fatal myocardial infarction, congestive heart failure, and so on. Obesity, chronic kidney disease, type 2 diabetes mellitus, dyslipidemia.

The comorbidities are common and they're associated with increased morbidity and mortality risk in our patients with gout. And that is important. Our patients are more prone to cardiovascular death and other reasons for death. The gout genetic risk score may lead to better understanding of who is at risk for comorbidities and which, as well as a better understanding of why women with gout tend to have more comorbidities independent of age. Remember, postmenopausal women are those who get gout. It's interesting why they would have, regardless of age, more comorbidities than men.

Gout is associated with an increased estimated risk of cardiovascular events calculated from a population level, of cardiovascular risk equations. And cardiovascular risk prediction equations underestimate the cardiovascular risk in gout. And despite adjustment for known cardiovascular risk factors, gout independently increases the hazard ratio for cardiovascular disease, more so in women.

So, in summary, gout is very common. Gout is not just a disease of the joints. You can see from the first review, and this is based on many studies, that gout is a systemic disease. It's not just gout, it's not just arthritis. Inflammation leads to problems elsewhere, cardiovascular disease being a major cause of morbidity and mortality.

MODULE 3

Uric Acid Level Is Associated with Severity of Heart Failure with Preserved Ejection Fraction
Arevalo AB, et al.

Link: Uric Acid Level Is Associated with Severity of Heart Failure with Preserved Ejection Fraction - ACR Meeting Abstracts (acrabstracts.org)

Dr. Mandell: I want to discuss a study looking at the uric acid level being associated with the severity of heart failure with preserved ejection fraction by Dr. Arevalo and colleagues. These results were presented at the 2020 American College of Rheumatology Convergence virtual annual meeting.

This cross-sectional study showed a direct correlation between the serum urate level and the severity of diastolic dysfunction in patients with concomitant gout and heart failure with preserved ejection fraction.

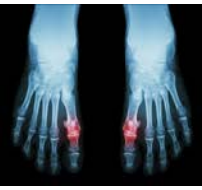
In background to this, the association of hyperuricemia with cardiovascular disease has been demonstrated in many observational studies, and from animal studies a causational role has been suggested. Unlike with gouty arthritis, where the pathogenic role of urate is well established, and is due to extracellular deposition of crystals, in cardiovascular disease, and probably heart failure in specific, the causational role of urate is less certain, and it is proposed that urate may function in soluble form intracellularly, to increase the oxidative stress and contribute to cardiac remodeling, as well as endothelial function and decreased nitric oxide synthesis. As discussed earlier in this program, data from the UK Biobank study showed that heart failure was observed in 1.8% of patients in the entire UK Biobank cohort, but in 6.5% of patients who had gout.

Looking at this abstract, patients with a diagnosis of hyperuricemia were screened by chart review between January 2016 and December 2018. Hyperuricemia was defined as a mean serum urate level greater than 7 mg per dL (mg/dL). And inclusion criteria were hyperuricemia identified greater than 1 year before an echocardiogram was performed, diastolic dysfunction with severity classified according to echocardiographic parameters. The Fisher's exact test was used for qualitative variables, and the chi-square for quantitative variables.

They entered 56 patients who met the inclusion criteria. Of these, approximately 80% had a mean serum urate level greater than 7 mg/dL. Patients with normal left ventricular function and grade I, the earliest diastolic dysfunction, had a mean age of about 66 years. 48% were on urate-lowering therapy, 43% on a diuretic, and 85% had a pre-existing diagnosis of gout.

Patients with grade II or III, more severe diastolic dysfunction, had a mean age of 60 years, 63% were on urate lowering therapy, 69% higher than the other group with lower degree of failure on a diuretic, 94% had a pre-existing diagnosis of gout. The mean serum urate levels were 7.5 mg/dL in patients with normal diastolic function, 8.7 mg/dL in patients with grade I or grade II diastolic dysfunction, and 12.5 mg/dL in patients with grade III, severest diastolic dysfunction. So, the risk of severe diastolic dysfunction increased by 0.05 for every unit of increase in the mean serum urate level, which was quite statistically significant in terms of association.

What do I do when I look at this? Well, I think that this study contributes to the growing and already established literature, which associates hyperuricemia with the presence and severity of cardiovascular and renal disease. A recent study by Kobayashi et al in the *American Journal of Cardiology* in 2020 showed that the serum urate can predict mortality even, in patients with heart failure with



preserved ejection fraction on admission to the hospital with a heart failure diagnosis.

However, the demonstration of causation as opposed to association remains elusive, and this is, in part, due to the large number of confounders, including shared comorbidities, as well as medication effects. And you can see that just from the numbers that I cited to you from the studies. Mendelian randomization studies have yet to help decipher this problem as causation vs association between hyperuricemia and severity and cause of heart failure. And more to the point for clinicians, interventional studies lowering the serum urate level have not been shown to improve clinical outcomes clearly in heart failure. Most recently, Pavlusova published a paper demonstrating lack of true outcome effect of lowering urate in *Clinical Cardiology*, which is similar to the recent situation in patients with chronic kidney disease, where 2 very large studies published in *The New England Journal of Medicine* in June of 2020 failed to show a benefit with urate-lowering therapy slowing the progression of renal disease. What does make clinical sense, however, is to aggressively reduce the number of gout flares in patients with severe heart failure, as the treatment of gout flares with traditional agents poses management challenges, worsening heart failure, and perhaps worsening cardiovascular disease outcomes.

Gout and Serum Urate Levels Are Associated with Lumbar Spine Monosodium Urate Deposition and Chronic Low Back Pain: A Dual-Energy CT Study

Toprover M, et al.

Link: Gout and Serum Urate Levels Are Associated with Lumbar Spine Monosodium Urate Deposition and Chronic Low Back Pain: A Dual-Energy CT Study - ACR Meeting Abstracts (acrabstracts.org)

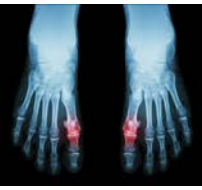
Dr. Mandell: I want to discuss a paper that was presented at the ACR 2020 virtual annual meeting, Gout and Serum Urate Levels Are Associated with Lumbar Spine Monosodium Urate Deposition and Chronic Lower Back Pain: A Dual-Energy CT Study, by Dr. Toprover and colleagues.

What this summary suggests is the preliminary results from this ongoing study show that patients with gout have deposition of monosodium urate crystals in the spine, increased back pain, compared with controls not having a known gout diagnosis.

The background of this is that gout involving the spine is often considered to be rare, presenting as acute back pain, sometimes with explained fever, and occasionally with symptoms of spinal compression. From my own experience, this has often been in transplant patients, and the elderly with infection, usually the initial diagnosis, even in patients who have known gout. And the diagnosis usually winds up as being based on identification of a mass that was seen on imaging, followed by tissue confirmation, usually with a needle biopsy of monosodium urate crystal deposition because the standard CT and MR imaging does not provide enough evidence to distinguish gout from infection. So that's the clinical scenario that most of us have faced.

Now we have little understanding as to why the distribution of uric acid depositions differs so widely between patients. There's been the assumption that the degree of hyperuricemia and the duration of exposure dictates the degree of deposition in general, but we also do not fully understand why some patients will have flares and others don't.

Now, conceptually, all gout is tophaceous gout, but not all tophaceous deposits are palpable, and those are the ones that are generally termed tophaceous, olecranon, forearm, ears, overlying small joints of the fingers, and are visible on imaging. But newer imaging techniques, including dual-energy CT, permits fairly sensitive detection of uric acid deposits independent



of the classic symptoms, and has really permitted the evaluation of other parts of the body where we have not traditionally thought of as sites for urate deposition. And that includes the spine, and recently, interestingly, includes major vascular structures such as the aorta.

In this study there was a planned recruitment of 75 subjects between the age of 50 and 80 years. Plan is for 25 controls, 25 patients with non-tophaceous gout, tophaceous by the clinical definition, and 25 patients with tophaceous gout by the clinical definition. All patients with gout will meet the ACR criteria, and either have an entry serum urate of greater than 6.8 mg/dL, or greater than 6 mg/dL if they're on urate-lowering therapy for less than 6 months. Patients who have known calcium pyrophosphate crystal deposition, rheumatoid arthritis, spinal arthropathy, or spinal malignancy, will not be included.

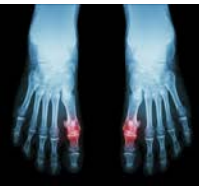
This is an interim report of 61 subjects with an average age of about 62 years, 25 controls, 24 what they term non-tophaceous gout, and 12 what are termed tophaceous gout. Then there are significant differences in the baseline characteristics in the controls vs the patients with gout. The mean body mass, 28.3 kg/m^2 in controls vs 32 kg/m^2 in patients with gout. The mean serum creatinine 1 mg/dL in control vs 1.5 mg/dL in patients with gout. The mean serum urate 5.3 mg/dL in controls, vs 8.7 mg/dL in patients with gout. And the mean sedimentation rate, interestingly, 14 mm/h in controls vs 25 mm/h in patients who have gout. So, clearly there are some clinical separations between the gouty patients and the controls.

Many subjects in each group had no evidence of excessive monosodium urate crystal deposition, despite having demonstrated hyperuricemia. And the apparent deposition of monosodium urate by dual-energy CT was found to be similar in controls vs patients with gout. But to limit possible artifact, a reanalysis of the standard reading of a dual-energy CT using narrower threshold settings by the radiologist was done, and the reanalysis confirmed increased monosodium urate deposition among patients with gout vs controls, which one would biologically anticipate. Data to date showed that monosodium urate crystal deposition is not different between patients with non-tophaceous vs tophaceous gout, and there were no subjects that were enrolled, or studied here, that demonstrated a frank spinal mass, which would've been termed a tophus. So, they were seeing dual-energy CT deposition without true mass. Interestingly, back pain scores were lower in controls, compared with patients with gout.

What are my take home messages from this preliminary study, which I think as it comes to fruition and completion will be very interesting? I think mainly what I took away is the need to discuss carefully with my radiologist, the interpretation of the dual-energy CT prior to using this imaging to make the diagnosis of gout. Which I sometimes will do in patients where aspiration is not easy, or something that patients are willing to do at the time that we want to make a diagnosis. This is, thus far, a very small sample size, but it's interesting that the presence or absence of peripheral tophaceous deposits, what we can feel on exam, do not correlate with the presence of spinal uric acid deposits.

Although this really shouldn't be surprising, I think many of us have not suspected spinal gout, or spinal deposition of urate, in the absence of evidence for significant deposition, which often translates to the presence of palpable peripheral tophi. So, I look forward to the completion of the study to see if the apparent low level of uric acid deposition in the lumbosacral spine, seen with dual-energy CT in both gout patients and control, indeed really does represent artifact. So, it'll be fascinating to see a longer-term follow-up of the patients who get enrolled in the final study.

I do believe that the sample size at present is still too small, with insufficient clinical information provided



to sort out whether the increased back pain experienced by patients with gout compared to controls can really be attributed to the gout or the uric deposition in their spine. But that possibility is clearly intriguing and will influence the way that I conceptually approach a symptom of back pain in my patients who have known gout.