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**LITERATURE REVIEW**

# *JIM* Reading List



Our Literature Review section continues with another installment of summaries from the medical literature. Our authors have found recent articles that have direct relevance to the practice of insurance medicine. The intent of the reading list is to provide the highlights of articles, not an in-depth analysis. Contributions to the reading list are invited. Please forward your citation and summary to Michael L. Moore, MD, Associate Editor, Literature Review at Moorem1@Nationwide.com. We will acknowledge all contributors in each issue's installment.

## CARDIOLOGY

1. *Cipolletta E, Tata Laila J, Nakafero G, et al. Association Between Gout Flare and Subsequent Cardiovascular Events Among Patients With Gout.* JAMA. *2022;328(5):440-450. doi:10.1001/jama.2022.11390.*

In this retrospective observational study from England, electronic health records from January 1, 1997 to December 31, 2020, were examined to see if there was an association between acute gout flares and subsequent cardiovascular events. A total of 1421patients with gout were studied compared to a study control population of 62,574. Gout flares were determined by using hospitalization, primary care records and prescription data. Cardiovascular events were described as either a myocardial infarction or stroke. The mean age of the study group was 76.5 years with nearly 70% being male and 30% female. The time periods that were examined were from 0 to 60 days and from 61 to 120 days.

Data showed that during the time period 0 to 60 days following a gout flare there were 2% of patients who suffered a cardiovascular event vs 1.4% in the control group. In the subsequent 61 to 120 days, there continued to be an increased incidence of cardiovascular disease of 1.6% vs 1.3%. The data showed that after 120 days differences in cardiovascular events were negligible between the 2 groups.

I believe that this study shows that there is a slight increase in the incidence of cardiovascular events in individuals following an acute gouty attack. It is noteworthy that the mean age of the participants was 76.5 years and the overall incidence of cardiovascular events, even than those without gout, could still expected to be significant. While this study shows that there may be an association between the acute inflammation that occurs with gout, it is not clear if this is a single direct cause or is merely reflective of an overall more impaired individual. Nevertheless, it is one more aspect to be taken into consideration when evaluating the overall risk in an applicant who has had a recent gout flare.
*Submitted by Michael L Moore, MD*

2. *Freeman MW, Halvorsen YD, Marshall W, et al. BrigHTN Investigators. Phase 2 Trial of*

*Baxdrostat for Treatment-Resistant Hypertension. N Engl J Med. 2023;388:395-406. doi: 10:1056/NEJMoa2213169*

*Leopold J, Ingelfinger J. Aldosterone and Treatment-Resistant Hypertension. N Engl J Med. 2023;388:464-467. doi: 10.1056/NEJMe2213559*

This *Journal's* literature review normally focuses on issues around mortality of this or that treatment or illness. However, we all appreciate hypertension's causative role in the cardiovascular diseases, including stroke, atrial fibrillation, and chronic kidney disease, and anything that contributes to treatment failure of hypertension is, therefore, relevant to mortality.

**Review of mortality of hypertension**

Hypertension is defined as blood pressure of 130/80 mm Hg or higher; this definition is based on evidence from epidemiologic studies and clinical trials that examined the relationship between higher blood pressure and major adverse cardiovascular events. According to the Centers for Disease Control and Prevention, 116 million adults in the United States, or 47% of adults in the population, have hypertension. The death rate attributable to hypertension has increased by 34.2% over the past decade; in 2020, hypertension was a primary or contributing cause of more than 670,000, or 20% of all deaths in the United States. Although hypertension is a modifiable risk factor, only 24% of adults with hypertension have adequately controlled blood pressure (defined as a blood pressure of less than 130/80 mm Hg who have received lifestyle interventions and medications).

Treatment-resistant hypertension is defined as hypertension in a patient who is taking 3 or more medications, including a diuretic, to lower blood pressure. Many persons with treatment-resistant hypertension have salt-sensitive hypertension, whereby activation of the sympathetic nervous system results in impairment of suppression of the renin-angiotensin-aldosterone system. Consequently, levels of aldosterone increase. Aldosterone increases sodium reabsorption and thus passive water reabsorption across the distal tubule of the nephron, thereby contributing to hypertension. Although a decrease in salt intake may reduce blood pressure, it is usually insufficient to achieve normotension.

The Prevention and Treatment of Hypertension with Algorithm-based Therapy-2 (PATHWAY-2) trial showed that spironolactone addresses this pathway. Spironolactone competes with aldosterone to bind to the mineralocorticoid receptor (also known as the aldosterone receptor), which is expressed in the distal convoluted tubule cells of the kidney. The binding of spironolactone to the receptor inhibits aldosterone-dependent sodium-potassium exchange, leading to excretion of sodium and water and retention of potassium. Unfortunately, spironolactone is a weak diuretic and usually requires administration with another drug that targets the proximal tubules to increase diuresis. Spironolactone is nonselective – it binds androgen and progesterone receptors, leading to off-target effects such as gynecomastia.

Baxdrostat is a small-molecule drug (a chemical compound with a low molecular weight [typically 0.1 to 0.6 kD] that can penetrate cell membranes and bind intracellular targets – generally more stable than biologic drugs and can be administered orally) that decreases levels of aldosterone by inhibiting its synthesis. It does so by inhibiting the CYP11B2 enzyme (also know as aldosterone synthase) that catalyzes the final steps of aldosterone synthesis from cholesterol.

In this multicenter, placebo-controlled trial, 248 patients with treatment-resistant hypertension were randomly assigned to receive either a placebo or 1 of 3 doses of baxdrostate (0.5 mg, 1 mg, or 2 mg) once daily for 12 weeks. The −12 mm Hg decrease in BP with the 0.5 mg dose was not significantly changed from placebo (−9.4 mm Hg decrease), but the systolic pressures were

−20.3 mm Hg with the 2 mg dose compared to placebo and −17.5 mm Hg with the 1 mg dose compared to placebo. The difference in the change in systolic blood pressure between the 2-mg group and the placebo group was −11 mm Hg (95% CI, −16.4 to −5.5; P < 0.001), and the difference in this change between the 1-mg group and the placebo group was −8.2 mm Hg (95% CI, −13.5 to −2.8; P = 0.003).

There were no serious adverse events attributed by the investigators to baxdrostat, and there were no instances of adrenocortical insufficiency. Baxdrostat-related increases in the potassium level to 6.0 mmol per liter or greater occurred in 2 patients, but these increases did not recur after withdrawal and reinitiation of the drug.

**Assessment**

A careful review of blood pressures in patients on 3 or more antihypertensive drugs should be done to rule out treatment-resistant hypertension defined as multiple readings greater than 130/80. If aldosterone is one of the medicines being used, baxdrostat is a much better choice to address the effects of this renin-angiotensin pathway. If policy amounts allow, deferment rather than declination might be considered, with the agent or applicant made aware of this new pharmacology for treatment-resistant hypertension. *Submitted by Rodney C Richie, MD*

## ENDOCRINOLOGY

3. *Cao Zhi, Li Wenyuan, Wen Chi Pang, et al. Risk of Death Associated With Reversion From Prediabetes to Normoglycemia and the Role of Modifiable Risk Factors.* JAMA *Network Open. 2023;6:e234989. doi:10.1001/jamanetworkopen.2023.4989*

Prediabetes, defined by mild insulin resistance and beta cell dysfunction leading to dysglycemia, is considered a high-risk state for Type 2 Diabetes Mellitus, and it is associated with higher risks for CV disease, CKD, cancer, dementia and death.

Progression from prediabetes to diabetes has been associated with a higher risk of death, and 25% prediabetes progress to full blown DM within 3-5 years. This study questioned whether reversion to normoglycemia affects that death risk. Primary outcomes: all-cause mortality, CVD related mortality, and cancer related mortality.

This population based prospective cohort study considered 45,782 subjects with prediabetes from the Taiwan MD Cohort Study. Of those, 63% male, avg age 45, median follow-up was 8 (5-12) years. In that group, 3.9% developed diabetes, 37% reverted to normoglycemia. Fasting plasma blood glucose samples were used to classify patients by American Diabetes Association Criteria (<110, 110-125, 126 and above). Patients were recruited from 1996-2007, death data thru 2011. In the group, there were 1528 deaths, 671 from cancer and 308 CVD.

In the adjusted model, compared with participants with persistent diabetes, those who experienced progression to diabetes within a 3-year period had a 50% (HR 1.50; 95% CI 1.25-1.79), higher risk of all cause death and a 61% (HR 1.61; 95% CI 1.12-2.33) higher risk of CV related death. However, reversion to normoglycemia was **not** associated with the risk of all-cause death (HR 0.99; 95% CI 0.88-1.10) or CV-related death (HR 0.97; 95% CI 0.75-1.25). In addition, no association was found between reversion to normoglycemia (HR 0.91; 95% CI 0.77-1.08) or progression to diabetes (HR 1.12; 95% CI 0.83-1.52) and the risk of cancer related death. (See Table 2 from original article)

Modifiable Risk Factors also played a role. The HR of all cause death among individuals who reverted to normoglycemia were 0.72 (95% CI 0.59-0.87) for those who were active (≥7.5 MET hours/week), though similar results were not seen at lower levels of activity.

In addition, subjects who reverted to normoglycemia had a life expectancy of 2.5 years longer if they remained physically active (95% CI 1.0-3.9 years) compared with those who had persistent prediabetes and were physi-

**Table 2.** Multivariable-Adjusted Hazard Ratios for Associations Between Changes in Prediabetes Status and All-Cause and Cause-Specific Death

| Outcome by change in prediabetes status | Cases No./total No. | Mortality rate per 1000 person-years (95% CI) | Risk of death HR (95% CI) |
|---|---|---|---|
| **All Cause Death** | | | |
| Reversion to normoglycemia | 477/17 021 | 3.26 (2.98-3.56) | 0.99 (0.88-1.10) |
| Persistent prediabetes | 910/26 975 | 4.29 (4.02-4.58) | 1 |
| Progression to diabetes | 141/1786 | 9.65 (8.18-11.38) | 1.50 (1.25-1.79) |
| **Cancer-related death** | | | |
| Reversion to normoglycemia | 207/17021 | 1.41 (1.23-1.62) | 0.91 (0.77-1.08) |
| Persistent prediabetes | 417/26 975 | 1.97 (1.79-2.17) | 1 |
| Progression to diabetes | 47/1786 | 3.22 (2.42-4.28) | 1.12 (0.83-1.52) |
| **CVD-related death** | | | |
| Reversion to normoglycemia | 89/17 021 | 0.61 (0.49-0.75) | 0.97 (0.75-1.25) |
| Persistent prediabetes | 185/26975 | prediabetes 0.87 (0.75-1.01) | 1 |
| Progression to diabetes | 34/1786 | 2.33 (1.66-3.26) | 1.61 (1.12-2.33) |

cally inactive. As expected, shorter life expectancies were seen in those who smoked regardless of glycemic status. Obesity was also a factor in shorter life expectancy regardless of glycemic status.

Strengths of this study include the large number of subjects, and that the mortality data was obtained from the death registry (no issues with follow-up).

Limitations include: Using FPG- Single fasting plasma glucose alone may not be the best indicator of glycemic status. Population - The study was with Asian patients exclusively.

SES- The population in the study was of an above average socioeconomic status, which may also impact the results, especially in relation to modifiable risk factors.

In summary, prediabetes is associated with increased risk of mortality, and bringing that value down to normal glucose levels does not automatically reduce mortality unless individuals are physically active and not obese. *Submitted by Rachna Relwani, MD*

## INFECTIOUS DISEASES

4. *Global Burden of Disease Long COVID Collaborators; Hanson, Sarah Wulf, Abbafati Cristiana, Aerts Joachim G, et al. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021.* JAMA. *2022;328:1604-1615. doi:10.1001/jama.2022.18931*

Our understanding of Long-COVID continues to evolve, in particular the data about the prevalence of Long-COVD globally, the duration of symptoms and who is affected. This observational analysis reviewed 54 studies and two medical record databases worldwide across 22 countries to collect data on 1.2 million individuals who experienced symptomatic SARS-CoV-2 infection in 2020-2021. Using the 2021 World Health Organization definition of Long-COVID (defined as symptoms that are present 3 months after infection with a minimum duration of 2 months and cannot be explained by an alternative diagnosis), the authors sought to determine the prevalence of symptoms at 3 months after symptomatic infection across 3 accepted clusters of symptoms, which include: 1) persistent fatigue with bodily pain or mood swings, 2) respiratory symptoms, and 3) cognitive changes.

After adjusting for pre-COVID health status, an estimated 6% of individuals

experienced at least 1 of the 3 symptom clusters at least 3 months out (95% uncertainty interval 2.4-13.3). This includes 3.2% with persistent fatigue with bodily pain or mood swings, 3.7% with ongoing respiratory symptoms and 2.2% with cognitive problems. Among hospitalized patients, the prevalence is much greater. For those admitted to the ICU, 43% experienced persisting symptoms of Long-COVID (95% UI 23-65) and for those admitted to general hospital wards 27.5% (95% UI 12-49) compared to 5.7% for those not hospitalized. In more than a third of all Long-COVID cases (38%), 2 or all 3 of the symptom clusters overlapped.

When assessing by age, in those under age 20, both sexes were affected equally by Long-COVID (2.8% affected of those with prior symptomatic infection). Among those older than age 20, women were affected at almost double the prevalence at 10.6% (vs 5.4% for men). Estimated symptom duration was 9 months for those hospitalized and 4 months for those who weren't. Notably at 1 year out, 15% of those with symptoms at 3 months were still experiencing Long-COVID symptoms.

This study provides further evidence and insight into the world-wide burden of those experiencing at least 1 of the 3 Long-COVID clusters. While it appears that the majority of cases will recover within 1 year, there are still those who will experience ongoing symptoms of indeterminate duration. Further research will be required to assess outcomes for those beyond the 1-year point. *Submitted by Ted Gossard, MD*

## ONCOLOGY

5. *Effect of Radio therapy Alone vs Radiotherapy with Concurrent Chemoradiotherapy on Survival Without Disease Relapse in Patients with Low-risk Nasopharyngeal Carcinoma: A Randomized Clinical Trial.* JAMA. *2022;328:728-736. doi: 10.2002/jama.2022.13997*

Low-risk nasopharyngeal carcinoma, defined as stage II and T3N0M0, has been heretofore treated with concurrent chemoradiotherapy. This study answers the question of whether intensity-modulated radiation therapy (IMRT) alone is noninferior to standard concurrent chemoradiotherapy for low-risk nasopharyngeal carcinoma. Spoiler-alert: it is.

This multicenter, open-label, randomized, phase 3, noninferiority clinical trial was conducted at 5 Chinese hospitals. All 341 adult patients had low-risk NPC, defined as stage II/T3N0M0 without adverse features (all nodes <3 cm, no level IV/Vb nodes, no extranodal extension, Epstein-Barr virus DNA <4000 copies/mL). Patients were randomly assigned to receive IMRT alone (N = 172) or concurrent chemotherapy (IMRT with cisplatin, 100 mg/m$^2$ every 3 weeks for 3 cycles [n = 169]). The primary end point was 3-year failure-free survival (time from randomization to any disease relapse or death).

Three-year failure-free survival was 90.5% for the IMRT-alone group vs 91.9% for the concurrent chemoradiotherapy group (difference, −1.4%; 1-sided 95% CI, −7.4% to ∞; P value for noninferiority, <0.001). The IMRT-alone group experienced a significantly lower incidence of grade 3 to 4 adverse events (17% vs 46%; difference, −29% [95% CI, −39% to −20%]) and had better QOL scores.

### Conclusion

Among patients with low-risk NPC, treatment with IMRT alone resulted in 3-year failure-free survival that was not inferior to concurrent chemoradiotherapy, with a significant reduction in adverse events. *Submitted by Rodney C Richie, MD*

## PUBLIC HEALTH

6. *Dohnalová L, Lundgren P, Carty JRE, et al. A microbiome-dependent gut–brain pathway regulates motivation for exercise.* Nature. *2022; 612:739-747. https://doi.org/10.1038/s41586-022-05525-z*

I believe that we all subscribe to the concept that exercise is good for physical, cardiovascular, and mental health. However, achieving proper motivation to carry this out is often problematic in this busy world with so many distractions and obligations. Could the desire to exercise be more physiological than behavioral? This University of Pennsylvania study has suggested that might be the case. The study found that "active mice" will run nearly 20 miles on an exercise wheel in 48 hours compared to the "lazy mice" who barely used the wheel at all. While the investigators found no genetic difference between the 2 cohorts of mice, it appeared that the differences in their behavior was caused by a difference in the gut microbiome. The active mice had an abundance of gut bacteria, which produced types of fatty acids that created a series of signals that led to increased dopamine in the brain's reward center so that when the mice exercised they created what has been termed a "runners high." Further evidence was found when the active mice were given antibiotics to kill the microbiome, they turned into lazy mice. Similarly, when lazy mice were given the gut bacteria from the active mice, they began to greatly increase their exercise patterns.

This appears to be 1 more study that shows the importance of the gut microbiome on overall functioning. It bears watching to see if further studies can confirm similar results and if so can products be produced which will increase motivation for individuals to exercise. The whole new definition of a "gym rat" may undergo remarkable alteration. *Submitted by Michael L Moore, MD*