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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 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, Deputy Editor, Literature Review at Moorem1@Nationwide.com. We will acknowledge all contributors in each issue's installment.

## CARDIOVASCULAR SAFETY OF TESTOSTERONE REPLACEMENT THERAPY

1. *Lincoff AM et al. CV safety of testosterone-replacement therapy*. N Engl J Med. *2023;389(2):107-117*. doi: 10.1056/NEJMoa2215025; PMID: 37326332

Concerns regarding the cardiovascular safety of testosterone replacement therapy (TRT) have been somewhat inconclusive based on previous trials with conflicting results. Before 2010, studies suggested that TRT maybe protective against cardiovascular (CV) disease, but then from 2010 to 2014, four studies came out suggesting increased risk for CV events, resulting in a decline in prescribing. Labeling of testosterone products in fact specifically have indicated that long term safety cannot be assessed. Limitations of these prior trials included smaller sample sizes and lack of randomization or placebo control. In 2015, the FDA thus required testosterone manufacturers to conduct a large clinical trial to assess CV safety, the (TRAVERSE Trial), resulting in a placebo-controlled study of 5,200 men, age range 45-80 randomized to receive testosterone gel or placebo, the results of which were published in NEJM in July, 2023.

Enrollment criteria required two fasting serum testosterone levels <300 ng/dl and symptoms of hypogonadism (including decreased libido, ED, fatigue and low or depressed mood). A key point of this study is that enrollees had to have known CV disease or multiple CV risk factors (at least 3 out of 8). Participants received transdermal 1.62% topical gel or placebo and target testosterone levels were between 350-750 ng/dl. Mean duration of treatment and follow-up were 22 and 33 months respectively.

The primary endpoint was first occurrence of any component of major adverse cardiovascular events, a composite of death from CV disease, nonfatal MI or nonfatal stroke. These primary end-point events occurred in 182 patients (7%) in the testosterone group and 190 patients (7.3%) in the placebo group. There was a slight increase in pulmonary embolism, 0.5% in placebo group vs 0.9% in TRT group. Prostate cancer occurred in 12 patients in the TRT group (0.5%) and 11 patients of placebo (0.4%).

Overall, the results of this TRAVERSE trial appear to provide reassurance for men under TRT with known CV disease or with

multiple CV risk factors and that TRT was noninferior compared to placebo with the occurrence of major CV events during the mean 22-month follow-up.

Limitations of this study include the relatively short duration and longer-term studies will need to be conducted to assess if this safety data holds. As well it is unclear how well these results would carry over to the 'insured-life' population we assess as medical directors as it is not uncommon to see individuals who are treated more as lifestyle medicine and may not meet the more stringent diagnostic criteria noted above. As well the individuals in this study were closely monitored and managed and it is not unusual to see individuals under treatment with supratherapeutic testosterone levels, polycythemia and/or gaps in appropriate monitoring. *Submitted by Ted W. Gossard, MD*

## HIGH BLOOD PRESSURE IN ADOLESCENCE AND RISK FOR FUTURE CV EVENTS

2. *Rietz et al. Blood pressure level in late adolescence and risk for cardiovascular events. A cohort study*. Ann Intern Med. *2023;176(10):1289–1298*. doi: 10.7326/M23-0112; PMID: 37748180

There has been little long-term data to date regarding adolescent blood pressure levels and cardiovascular outcomes as this has been most extensively studied in the older adult population. This study from Sweden addresses this question and is remarkable in that it includes a very large sample size (1.4 million adolescents) with up to 50 years of follow-up.

Participants of this retrospective cohort study are Swedish males, conscripted to the military from 1969 to 1997, with a mean age of 18 at onset, whose baseline BP was measured at the time of conscription. Median follow-up was 36 years. The primary outcome was a composite of CV death or first hospitalization for myocardial infarction, heart failure, ischemic stroke or intracerebral hemorrhage.

Based on a single BP reading at the onset of the study, 17% of conscripts had normal BP (<120/80), 29% had elevated BP but not hypertension (120-129/<80), 35% had Stage-1 HTN and 19% had Stage-2. During the median follow-up of 36 years, almost 80,000 individuals experienced a primary outcome. The adjusted hazard ratio was 1.1 for elevated BP, 1.15 HR for isolated systolic HTN, 1.32 HR for Stage-1 HTN and 1.71HR for Stage-2 HTN. The cumulative risk for CV events increased gradually across these BP stages from 14.7% for normal BP to 24% for Stage-2 HTN by age 68 years.

There are many self-evident limitations to this study including the narrow representative sample population of Swedish teenage males, the assessment of blood pressure and diagnosis of HTN with just a single initial BP reading and also a lack of information regarding who might have received treatment or follow-up care. But regardless, it is insightful that a single blood pressure measurement at age 18 in this large study population was predictive of future CV events over the next several decades. As high blood pressure is one of the most important modifiable CV risk factors, this study speaks to the importance of the identification of these individuals at a young age and managing appropriately. As well this study has potential relevance with the underwriting assessment of younger individuals with pediatric hypertension increasing and often underrecognized. *Submitted by Ted W. Gossard, MD*

## DELAY IN SURGERY AND PAPILLARY THYROID CANCER SURVIVAL IN THE UNITED STATES: A SEER-MEDICARE ANALYSIS

3. *Natalia Chaves, Jordan M. Broekhuis, Scott C. Fligor, Reagan A. Collins, Anna M. Modest, Sumedh Kaul, and Benjamin C. James*. The

Journal of Clinical Endocrinology & Metabolism, *2023;108:2589–2596*. https://doi.org/10.1210/clinem/dgad163

In breast, lung, and colorectal cancer, decreased survival is associated with a delay in surgical intervention. However data is conflicting for less aggressive malignancies such as PTC.

This study looked at disease specific and overall survival in PTC and time to surgery in three intervals: within 90 day, 91 to 180 days, >180 days.

This observational population based cohort study used SEER Medicare data from 1999-2018. ICD codes were used to select patients. Exclusion criteria: prior PTC, age <65, nonpapillary types, no primary lesion, RAI or chemo prior to surgery.

Among 8170 patients analyzed, mean age was 69.3 (SD+/− 11.4) years, and 69.6% were female. Individuals having 90 days or less between diagnosis and surgery made up 89.8% of the cohort, 7.8% made up the 91 to 180 days group, and 2.4% made up the more than 180 days group. Mean follow-up time for the cohort was 99.3 ± 53.0 months.

For stage, 64% of patients had localized disease, 28% had regional disease, and 8% had distant disease; frequencies were similar across time groups. Nearly 50 percent of patients (49.7%) had a pathologic T stage of 1, 81.8% had N0 disease, and 97.6% had no distant metastases (M0). Eighty-three percent of the cohort underwent a total thyroidectomy. Patients had a mean of 1 positive node (SD+/− 3.4), and 45 percent of patients received radioactive treatment after surgery.

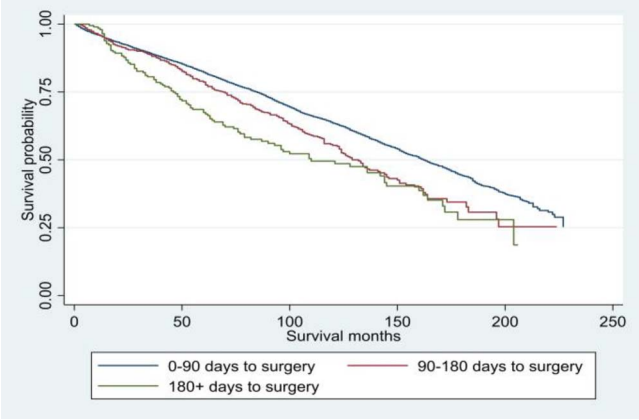


**Figure 1.** *Kaplan-Meier estimated overall survival by time to surgery (log-rank test P < .001)*

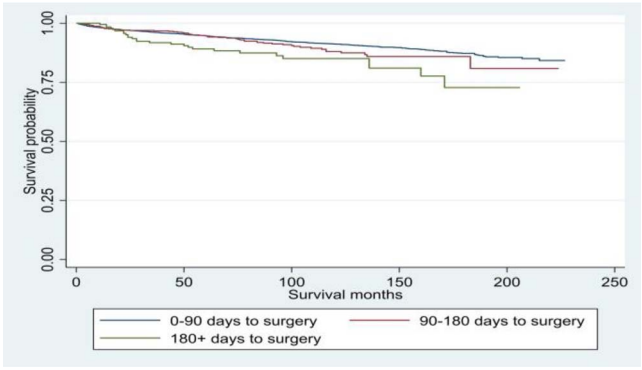


**Figure 2.** *Kaplan-Meier estimated disease-specific survival by time to surgery (log-rank test P < .001).*

**Results.** Overall survival: After adjusting for demographic and clinical covariables, increased time to surgery was associated with decreased overall survival in the > 180 day group only. When broken down by disease type, localized disease had progressive higher mortality in the 91-180 d and >180 d groups. No difference for regional or metastatic disease.

**Table 3.** Cox Proportional Hazards Model for Overall and Disease-Specific Survival in Papillary Thyroid Cancer

| | HR (95% CI) | Adjusted HR (95% CI) |
|---|---|---|
| Overall survival | | |
| Time to surgery | | |
| ≤90 days | Reference | Reference |
| 91–180 days | 1.3 (1.1–1.4) | 1.05 (0.93–1.19) |
| >180 days | 1.6 (1.3–2.0) | 1.24 (1.01–1.53) |
| Disease-specific survival | | |
| Time to surgery | | |
| ≤90 days | Reference | Reference |
| 91–180 days | 1.2 (0.89–1.5) | 0.76 (0.58–1.01) |
| >180 days | 1.9 (1.3–2.8) | 1.07 (0.70–1.62) |

Abbreviations: HR, hazard razio.

Data presented as HR and 95% CI.

Adjusted for age, race, ethnicity, sex, Charlson score, summary stage, radiation timing, type of primary surgery, positive nodes, and diagnosis year.

Disease specific survival: no difference with overall time to surgery. However those with localized disease in the >180 d group had more than three times the rate of mortality. No association in the 91-180 d group. Regional disease- no association. Distant disease- decreased risk in both 91-180 d and >180 d group.

They found that the extent to which time to surgery impacts DSS and OS in PTC is limited but may be important in localized disease, 24% increased mortality risk in OS and more than 3 times the estimated disease-specific mortality with delays greater than 180 days.

The authors postulate that "there is a window of opportunity during which earlier intervention may impact survival for localized PTC. By the time the tumor has progressed in size or presents with nodal metastasis, it is possible that a small difference in time to surgery may not result in significant differences in survival."

Limitations:

- Observational Study
- Age of participants (PTC tends to affect younger patients than this group)
- Low mortality in general

**In Summary.** In a SEER Medicare population, patients with localized PTC would benefit from early surgical resection to avoid nodal metastasis. Stage at surgery may be more critical to survival than time of surgery in relation to diagnosis. *Submitted by Rachna Relwani, MD, Clinical Endocrinologist*

## MISSING AMERICANS: EARLY DEATH IN THE UNITED STATES— 1933–2021

4. *Jacob Bor, Andrew C Stokes, Julia Raifman, Atheendar Venkataramani, Mary T Bassett, David Himmelstein, Steffie Woolhandler, Missing Americans: Early death in the United States—1933–2021*, PNAS Nexus, *Volume 2, Issue 6, June 2023, pgad173*, https://doi.org/10.1093/pnasnexus/pgad173; PMID: 37303714

In this fascinating study, authors make extensive use of the Human Mortality Database and explore the difference between mortality rates in the United States and those in other wealthy nations (specifically Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Japan, Luxembourg, The Netherlands, new Zealand, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom). Some small adjustments were needed due to the lack of availability of the data for some countries in some years. For each country and year age-standardized mortality rates (ASMRs) were collected. This technique accounts for differences between countries in the distributions of ages.

The authors found that, between 1933 and about 1960, the US enjoyed a lower ASMR than the average of peer countries. Between 1960 and 1980, the US ASMR was similar to other countries. Beginning around 1980, the US began to accumulate significant excess deaths beyond those of peer nations. To describe this trend, authors created a measure called "missing Americans" - which is the number of American deaths that would have been avoided if the US had ASMRs similar to the average of the other nations. By 2015, the number of missing Americans had reached 500,000 and stayed there until a massive spike occurred in 2020 and 2021 due to the COVID-19 pandemic. Of course, all nations experienced a surge in deaths in these years, but the surge in American deaths was disproportionate to the others, such that the number of missing Americans reached over 1 million in 2020, and was nearly 1.1 million in 2021.

These excess deaths occurred disproportionately black and Native Americans. The mortality ratio between the US and other nations was highest in the 20-40 age group (about 3 in 2019, and 3.7 in 2020 and 2021). In black Americans this ratio was nearly 5, and among Native Americans it was over 8. In life insurance underwriting terms, being a young (age 15-44) American carried a rating of 190 debits vs. similarly aged groups in peer nations.

Before the pandemic, in 2019, this rating was 140 debits. These ratios for the 45-64 age group were 1.6 (60 debits) in 2019, 1.8 (80 debits) in 2020, and 2.0 (100 debits) in 2021.

The authors go into a very detailed explanation of possible culprits in terms of the causes of this pre- and peri-pandemic excess mortality. High rates of obesity, diabetes, drug overdose, HIV and homicide account for much of the difference in the 1990s and early 2000s. After that, the large increases in mortality in the under-65 group were due to "drug overdoses, alcohol-related mortality, suicides, and cardiometabolic diseases. During the pandemic, the authors point out, the US had a disorganized response, which, when combined with the lack of universal access to healthcare, mistrust of the medical establishment, and many other factors, lead to the overall poor performance in controlling pandemic mortality compared to other nations.

Some have pointed out that excess deaths during the late phases of the COVID pandemic and afterward were partially or mostly made up of non-COVID deaths. While this is true, when measuring "excess" deaths in this context, the comparator is the US pre-pandemic death rate. This article helps us to understand that that pre-pandemic level is, itself, abnormally high - and we should likely be paying more attention to the excess deaths vs. other peer nations than the month-to-month variability in COVID or non-COVID deaths. *Submitted by Steven J. Rigatti, MD, Founder, Rigatti Risk Analytics, LLC*

## USE OF CHAT GPT-4 TO MAKE MEDICAL DIAGNOSES

5. *Research Letter: Kanjee Z, Crowe B, and Rodman A. Accuracy of Generative Artificial Intelligence Model in a complex Diagnostic Challenge*. JAMA *2023;330(1): 78–80*. doi: 10.1001/jama.2023.8288

In a recent issue of the Journal of the American Medical Association (*JAMA*, July 3, 2023. Vol: 330, Issue: 1) researchers at the Beth Israel Deaconess Medical Center use a large language model AI (Chat GPT-4) to analyze a series of difficult cases. The cases were gathered from the *New England Journal of Medicine* - specifically the "Clinicopathologic Case Conference" series. These articles, published in most issues of the *NEJM* since the 1950s, discuss the initial presentation, lab tests, radiological tests and pathological findings of challenging cases from the Mass General Hospital. These findings are then discussed among the eminent clinicians, radiologists, and finally pathologists, to identify the underlying diagnosis.

As an aside, I can remember seeing the *NEJM* for the first time as a first-year medical student. Because "case conference" was the only phrase I understood in the Table of Contents I attempted to read it. Within the first few sentences I was lost in an avalanche of medical terminology I did not yet understand. Two years later, as a third-year student, I read it again and was astounded by the fact that I understood it. I still had absolutely no idea how the diagnosis was made, but at least I could comprehend the words. It was, and has remained, my favorite feature of the *NEJM* or indeed any medical journal.

In any case, researchers found that the AI obtained either the correct diagnosis or a list of diagnoses that contained the correct one about 64% of the time. This is fairly impressive given that the diagnoses included such enigmas as *Erysipelothrix rhusiopathiae* infection and encephalopathy due to Behcet disease.

As promising as this sounds, it is important to note that the input into the AI was the full text of the clinicopathologic case conference (without the answers, of course). Seldom will you find a more organized, logical, concise format than the Socratic-method-on-paper presented in these articles. Hence they are **nothing** like the current state of raw medical records, where the pertinent information is buried under tons of useless, repetitive and irrelevant text. Also, there are many "misses" by the AI. So it would seem what Dr. Eric

Topol has said remains true: "AI will not replace doctors, but doctors who use AI will replace doctors who don't". *Submitted by Dr. Steve Rigatti, Rigatti Risk Analytics*

## EXCESS MORTALITY IN SEVERE MENTAL HEALTH DISORDERS: A REVIEW

6. *Ali S, Santomauro D, Ferrari AJ, and Charlson F. Excess Mortality in Severe Mental Disorders: A Systemic Review and Meta-Regression.* Journal of Psychiatric Research. *2022;149:97–105.*

The authors systematically reviewed available literature from 1980 to 2020 on mortality in people with psychotic disorders and bipolar disorder (based on DSM III and IV or ICD 9 or 10 criteria) compared to the general population to produce estimates of all-cause and cause-specific mortality. The review included 76 studies from 23 countries which were primarily in Western Europe. The sample sizes were from 22 to 664,094 and follow up period from 1 to 45 years (median 10 years). The observation period was from 1965 to 2016 with the majority (68%) published from 2010 or after. The specific cause mortality categories examined were as follows: accidents, cancer, circulatory system, respiratory, suicide, natural, and unnatural.

Twenty-three studies were included in the meta-regression analyses for all-cause mortality in schizophrenia, and mortality risk was increased across all age and sex groups. The relative risk (RR) for both sexes was 2.89 (95% CI 2.50-3.34) at the mean age of 53, and there were no overall sex-differences. The RR decreased with age with males having a slightly larger decrease than females. The RR was also different based on treatment setting with inpatients having a higher RR than studies including inpatients and outpatients or community/outpatient populations.

For studies including both schizophrenia and schizoaffective disorder, there were 15 studies included. The RR was 3.43 (95% CI 3.05-3.85) for both sexes; however, there was a between sex difference with a higher RR for females versus males. The RR again decreased with age, but the decrease was slightly more for females in this case. For "psychosis", there were 21 studies included, and the RR was 3.42 (95% CI 2.90-4.04) for both sexes with a higher RR for males. In contrast to the other studies, these data showed increasing mortality over time.

There were 20 studies included in the analysis for bipolar disorder which indicated an elevated mortality for each cause of death. The RR was 2.51 (95% CI2.10-3.00) which decreased with age. The between sex differences were similar to the studies including schizophrenia and schizoaffective disorder with a higher RR for females with a larger decrease in mortality over time for females than males.

In all diagnostic groups, unnatural causes were associated with the highest RRs compared to the general population. It is important to remember, however, that the majority of people with severe mental disorders (SMD) die of natural rather than unnatural causes. The mortality risk for natural causes is also elevated in those with SMD compared to the general population. For those with schizophrenia, the RR for natural causes of death was 2.80 (2.49-3.15) with the highest RR for a respiratory cause (4.26; 3.89-4.66), and the RR for unnatural causes was 8.83 (6.88-11.33). Of note, the RR for circulatory system mortality was not elevated for females with schizophrenia compared to the general population. The RR for natural causes of death for those with bipolar disorder was 2.04 (1.79-2.31) with the highest rate also for respiratory cause 2.99 (2.33-3.84), and the RR for unnatural causes was 9.58 (8.14-11.27). Specific cause mortality was not reported for the "other psychosis" group.

The authors opine that their results may be more robust than prior studies due to adjusting for covariates in their analyses. They also

**Table 3.** Adjusted relative risks for eath disorder and cause of death

| Disorder/cause of death | *n* studies(estimates) | HR (95% CI) | | |
|---|---|---|---|---|
| | | Both sexes | Female | Male |
| Schizophrenia | | | | |
| All-cause[a] | 23 (70) | 2.89 (2.50–3.34) | 2.87 (2.48–3.33) | 2.90 (2.51–3.36) |
| Accidents[b] | 6 (13) | 6.07 (4.52–8.13) | – | – |
| Cancer[b] | 7 (16) | 1.76 (1.24–2.51) | – | – |
| Circulatory system[c] | 5 (10) | 2.13 (1.01–4.49) | 1.89 (0.90–3.98) | 2.41 (1.15–5.08) |
| Respiratory system[d] | 4 (7) | 4.26 (3.89–4.66) | 3.90 (3.52–4.33) | 4.65 (4.18–5.16) |
| Suicide[e] | 10 (20) | 20.38 (13.94–29.81) | 25.70 (17.50–37.74) | 16.16 (11.04–23.67) |
| Natural[d] | 7 (24) | 2.80 (2.49–3.15) | 2.74 (2.43–3.08) | 2.86 (2.54–3.23) |
| Unnatural[e] | 7 (24) | 8.83 (6.88–11.33) | 11.20 (8.69–14.42) | 6.96 (5.42–8.94) |
| BIpolar disorder | | | | |
| All–cause[a] | 29 (70) | 2.51 (2.10–3.00) | 2.59 (2.16–3.09) | 2.43 (2.03–2.91) |
| Accidents[b] | 4 (7) | 3.53 (3.22–3.87) | – | – |
| Cancer[b] | 9 (18) | 1.15 (1.02–1.29) | – | – |
| Circulatory system[c] | 10 (24) | 2.00 (1.67–2.38) | 2.04 (1.70–2.45) | 1.95 (1.62–2.35) |
| Respiratory system[d] | 5 (9) | 2.99 (2.33–3.84) | 2.73 (2.11–3.52) | 3.27 (2.54–4.23) |
| Suicide[e] | 10 (18) | 18.91 (14.62–24.48) | 24.21 (18.63–31.46) | 14.77 (11.39–19.77) |
| Natural[d] | 10 (39) | 2.04 (1.79–2.31) | 2.09 (1.84–2.37) | 1.99 (1.75–2.26) |
| Unnatural[e] | 11 (41) | 9.58 (8.14–11.27) | 11.34 (9.61–13.39) | 8.09 (6.86–9.54) |
| Schizophrenia and schizoaffective disorder[g] | 15 (94) | 3.43 (3.05–3.85) | 3.69 (3.29–4.15) | 3.18 (2.83–3.57) |
| Psychosis[h] | 21 (55) | 3.42 (2.90–4.04) | 3.12 (2.64–370) | 3.74 (3.17–4.43) |

RR, relative risk; CL confidence interval. The RR corresponds to the exponentiated intercept of each multivariate meta-regession model. Covariates included in each model; [a]age, sex, age-sex interaction, inpatient and mid-year; [b]no covariates in final modal; [c]age, sex and age-sex interaction; [d]age and sex; [e]sex; [f]age, sex, age-sex interaction community/outparient and mid-year; [g]age, sex, age-sex interaction and follow-up time; [h]age,sex. age-sex interaction, mid-year and follow up time.

point out that people with SMD are at increased risk for multi-morbidity so the causes of death coded should be interpreted with caution. Other limitations included high risk of bias in over half of the studies according to the Newcastle-Ottawa scale, most of the heterogeneity between studies could not be accounted for by the covariates included suggesting there are additional factors that influence mortality in those with SMD in varying cohorts, and most of the studies were from high income countries limiting the generalizability of the findings. Although not discussed by the authors, it is important to note that smoking rates are typically higher for those with SMD compared to the general population, and smoking status is not included in the data analysis. *Submitted by Stephanie Hrisko, MD*

## DIABETES TRENDS REVIEW AND MORTALITY

7. *Ali MK, Pearson-Stuttard J, Selvin E, and Gregg EW. Interpreting global trends in type 2 diabetes complications and mortality*. Diabetologia. *2022;65:3–13*. https://doi.org/10.1007/s00125-021-05585-2

This literature review on trends in rates of complications and mortality associated with diabetes was conducted to provide an update on a similar review completed from studies published up to 2015. As such, the studies

reviewed were published from 2015-2021; however, the data from the included studies spanned from 2001-2019 for complications and from 1979-2018 for mortality.

**Complications.** *Lower Extremity Amputations (LEA)*. Study locations investigating LEAs included USA, South Korea, Hong Kong, and Taiwan. The USA study was data from the Veterans Affairs database and included incidence of LEA in all Veterans. In the South Korean study, the sample group was narrowed to those with diabetic foot and also assessed revascularization. For the study in Hong Kong, the study group was those with diabetes and narrowed the outcome to hospitalizations related to LEA. The Taiwan study population was those specifically with type 2 diabetes mellitus and the outcome assessed was diabetic foot complications. The USA and South Korean studies both showed an increase in overall LEAs; although, there was a decrease in incidence for women in the USA study, and the South Korean study indicated stable to decreased *major* amputations and an increase in revascularization interventions. Of note, the USA study also indicated that 62% of the increase was toe amputations. The Hong Kong and Taiwan studies showed a decrease in hospitalizations for LEAs and for overall LEAs, respectively.

*Hospitalizations for Reasons Other than LEA*. The study locations included Spain (2 studies), Portugal, South Korea (2 studies), and Brazil. In Spain, among those with diabetes (DM), admissions for UTIs increased (however, there was also a noted increase in those without DM) and admissions for hypoglycemia decreased. Using population data, the study in Brazil showed an increase in DM related hospitalizations over time which were higher in females, and one of the studies in South Korea indicated an initial increase (2004-2006) followed by a decrease (2007-2013) in hospitalizations related to hyperglycemia. Preventable hospitalizations decreased from 2016-2017 for those with DM in Portugal, and overall hospitalizations for cardiovascular disease (CVD) events declined in South Korea. However, hospitalizations for congestive heart failure and peripheral artery disease increased.

*Incidence of Multiple Complications*. One US study examined the incidence of 13 different diabetic complications in the same incident DM type 2 population. Neuropathy, chronic kidney disease (CKD), and CVD were the most common complications; however, the 5 year incidence rates of complications overall declined over time from 2003-2014.

**Mortality.** Country-specific studies which included data prior to the late 1990s to early 2000s overall indicated an increase in mortality. Whereas, those which examined data in the early 2000s to 2018 indicated a decrease in mortality. Exceptions included a study from South Africa that examined deaths in 2010 which indicated an increase in cause-specific mortality and a study from Ghana which showed an increase in in-hospital mortality in people with DM from 1983-2014. One study from USA and another from Hong Kong, while following the overall trend of declining mortality rates over time for all cause and DM-specific mortality in those with DM pointed out that there was no decline in those less than 45, and a study from Taiwan reported a shorter life expectancy with earlier onset of DM. In contrast, the study from Argentina indicated higher mortality in those older than 50. Global data for people with DM from the WHO mortality database, however, indicated an increase in mortality rates due to renal, ophthalmic, neurological and peripheral circulatory complications from 2000-2016 (exceptions noted were Asia and South America which had declining mortality rates). In particular, there were increases for those with DM type 2 and decreases for those with DM type 1. There were also increases globally in total and hypoglycemia related mortality from 2000-2014; however, the lowest mortality and declining rates were noted in Europe, USA, Canada, Japan, New Zealand, and Australia. Country-specific studies that included cause-specific mortality indicated

declines in all areas except dementia and liver disease (UK), more marked declines for vascular than cancer deaths (USA), and stable pneumonia related mortality (Australia).

**Considerations for Data Interpretation.** *Population characteristics and analyses*. There were fewer low and middle income countries represented by the data. The studies often did not differentiate between type 1 and type 2 or other types of diabetes (although it is estimated that type 2 DM accounts for approximately 90-95% of all DM). There was little investigation of trends in rates by socioeconomic status or racial/ethnic groups which could differentially impact DM risk and associated complications/mortality. The studies examining complications did not explore differences between age groups. The sources of data (e.g., population registry, administrative datasets, EMR, death certificates, etc.) may also impact the accuracy of the results. Additionally, trends in excess mortality attributable to DM may be a more useful end point rather than mortality rates alone because mortality rates in the general population without diabetes have also decreased over time.

*Definitions.* In 1997, the ADA lowered the threshold for diagnosis of diabetes from 140 mg/dl to 126 mg/dl. This change may have resulted in the inclusion of persons with different sociodemographic and clinical characteristics after the change compared to prior cohorts. Hemoglobin A1c was recommended by the ADA in 2010 as a diagnostic test for DM which could also change when and for whom diabetes is detected because HbA1c is more specific, capturing a smaller segment of the population than fasting glucose cut offs. Another factor difficult to capture in the presented studies in the rates of undiagnosed DM which may also vary by geographic region or other factors. Clinical characteristics such as comorbidities, average BMI, changes in smoking rates, early versus late detection and pharmacologic interventions may also play a role in changes in mortality rates and disparate rates between geographic regions.

**Overall Conclusion by the Authors.** *Morbidity and Mortality Implications.* "Annual rates of type 2 diabetes-related vascular complications and mortality have been declining in HICs, with persistently high burdens experienced by certain underrepresented and indigenous race/ethnic population groups." Given improvements in vascular complications for those with DM, non-vascular complications for which DM is a risk factor may become more important over time.

*Research Implications.* The paucity of data available for LMICs is a "critical knowledge gap that must be addressed." There need to be improvements in data infrastructure, definitions for diabetes/diabetic complications and standardized methods for collection of data, analysis of data, and reporting. *Submitted by Stephanie Hrisko, MD*

## CARDIOLOGY: AORTIC STENOSIS IN RHEUMATOID ARTHRITIS

7. *Johnson TM, Mahabir CA, Yang T, et al. Aortic Stenosis Risk in Rheumatoid Arthritis. JAMA Intern Med. 2023;183:973–981.* Doi: 10.1001/jama internmed.2023.3087 PMID: 37523173

Rheumatoid arthritis (RA) is associated with increased risk of ischemic cardiovascular events and higher rates of cardiovascular and all-cause mortality rates compared to the general population. While the shift to earlier intensive treatment and disease-modifying medications have contributed to reduced RA mortality rates, circulatory and overall mortality risk remain elevated. This study reports the association between RA and increased risk of incident aortic stenosis (AS), consequent aortic valve intervention and AS-related death.

This retrospective matched cohort study linked national Veterans Health Administration (VHA) and Centers for Medicare & Medicaid Services (CMS) data (2000 to 2019) to identify the risk for the primary outcome, incident AS, defined by AS diagnoses, aortic

valve intervention or AS-related death. The cohort included 73,070 RA patients (64,008 [87.6%] males; mean age, 63.0 years), matched by age and sex with 639,268 controls without RA (554,182 [86.7%] males; mean age, 61.9 years), and 16,109 composite AS outcomes over 6,223,150 person-years.

Incident AS rate for RA patients (n = 2,303/73,070, 3.2%) was 3.97 per 1,000 person-years, and for the control group (n = 13,806/639,268, 2.2%) 2.45 per 1,000 person-years (absolute difference, 1.52 per 1,000 person-years). Risks in the RA group were higher for AS (adjusted hazard ratio [AHR], 1.48; 95% confidence interval [CI], 1.41-1.55), aortic valve intervention (AHR, 1.34; 95% CI, 1.22-1.48) and AS-related death (AHR, 1.26; 95% CI, 1.04-1.54) in the RA group compared to control.

Of the baseline RA-related factors (seropositivity; rheumatoid factor [RF], anti-cyclic citrullinated protein [anti-CCP]; erythrocyte sedimentation rates (ESR), C-reactive protein (CRP) levels), elevated ESR or CRP levels were associated with a higher risk (AHR 1.11; 95% CI, 1.01-1.22, not statistically significant) of developing AS while seropositivity was not associated with AS development (AHR 0.94; 95% CI, 0.86-1.04). Baseline use of biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) (AHR, 1.22; 95% CI, 1.07-1.39) or glucocorticoids (AHR, 1.19; 95% CI, 1.08-1.32) were both associated with higher risk of AS development. Age, body mass index over 30 (BMI, kilograms/meters squared), male sex and hypertension were independently associated with AS development, whereas coronary artery disease, diabetes and lung disease were not.

The authors report that RA was associated with a higher risk of developing AS, with subsequent risks of undergoing aortic valve intervention and with AS-related death. They conclude that the data support the perspective that valvular heart disease, specifically AS, may be a cardiovascular disease complication in RA. *Submitted by Marianne E Cumming, MD*