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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. McMurray JJ, Packer M, Desai AS, et al. Angiotensin–Neprilysin Inhibition Versus Enalapril in Heart Failure. N Engl J Med. *2014;371:993–1004.*

This study generated some excitement in the lay press, since it was purported to show improved survival for heart failure patients treated with a new drug. This is, more or less, the case, with the caveat that the study drug is actually a combination of 2 drugs, one of which is an ARB (valasartan).

The authors randomized 8442 patients with NYHA class II-IV heart failure to receive either the study drug combination or enalapril alone. The study drug contained both valasartan and the novel agent sacubitril, an inhibitor of neprilysin. Then endogenous peptidase neprilysin degrades several vasoactive peptides including the natriuretic peptides. Inhibition of the breakdown of these substances would improve natriuresis by prolonging their half-life in the body. A majority of patients in each group were male (78%), Caucasian (66%) and had NYHA class II functional status (70%). The mean age was 63.8. The study subjects were followed for a median of 27 months. The trial was stopped early due to the achievement of prespecified endpoints indicating ''overwhelming benefit.''

This benefit amounted to a 20% decrease (HR: 0.80) in the risk of the primary endpoint – a combination of death from cardiovascular causes of hospitalization for heart failure). This was accompanied by a similar 20% decrease in the risk of cardiovascular death alone and heart failure hospitalization alone. A hazard ratio for all-cause mortality was 0.84 (95% CI: 0.76-0.93). The authors note that this degree of risk reduction is similar to that found in the initial trials of ACE-inhibitors for heart failure.

The authors reported a similar or slightly better side effect profile with the study drug compared to enalapril, though symptomatic hypotension was more prevalent. One concern not addressed by the study is the fact that one of the proteins known to be degraded by neprilysin is beta amyloid, which accumulates in the brains of those with Alzheimer's disease. It is therefore plausible that the study drug could hasten, worsen, or even cause dementia if taken over a long period of time.

The impact of this study on the plausibility of insuring the lives of those with heart failure is hard to gauge. Though the article

does include a cumulative mortality plot, the fact that the age distribution is not included and that the study subjects were located all over the world (Asia, Western and Central Europe, North America and Latin America) would make the construction of a reasonable expected mortality table challenging. *Submitted by Steven J. Rigatti, MD*

2. Chiang YP, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH1, Egorova NN. Survival and Long-term Outcomes Following Bioprosthetic vs Mechanical Aortic Valve Replacement in Patients Aged 50 to 69 Years. JAMA. *2014;31213:1323–1329.*

Long term outcomes of the options in aortic valve replacement are a challenge. This study involved 4253 patients with a mean age of 61 who required aortic valve replacement. Those receiving coronary artery bypass grafting or thoracic aorta surgery were excluded. The primary outcome was all-cause mortality; secondary outcomes were stroke, reoperation and major bleeding.

Results

There were no differences in 15-year survival between the patients who received a bioprosthetic valve as compared with a mechanical aortic valve. At 15 years, 60% of each study arm was alive. Each group suffered a mortality rate of 40% over the 15 year period. In evaluating secondary outcomes, bioprosthetic valves experienced 12% reoperation rate as compared to 7% in the mechanical valve population. The mechanical valve group experienced 13% major bleeding events as compared to 6% of the bioprosthetic arm. Both groups experienced about 8% stroke events.

The conclusion of the study was that in the age group of 50-69 year olds that either a bioprosthetic or a mechanical valve experiences the same mortality in a 15 year period. The stroke rate was similar and those on Coumadin had twice the bleeds but half of the need for reoperation.

This study involved the better candidates for aortic valve replacement, yet there was 40% mortality in 15 years. Either choice for therapy has significant mortality and number of strokes, bleeds and the need for reoperation. *Submitted by John Kirkpatrick, MD*

3. Gladstone DJ, Spring M, Dorian P, et al. Atrial Fibrillation in Patients with Cryptogenic Stroke. NEJM. *2014;370:2467–2477.*

Stroke is a significant cause of mortality and morbidity. Atrial fibrillation is a leading preventable cause of recurrent stroke. Early detection and treatment leads to improvement in outcomes. Of the 12 million ischemic strokes annually, 25% have no identifiable cause after evaluation and are considered 'cryptogenic'. Current clinical guidelines for evaluation in a new patient with a stroke include 24-hour ECG monitoring. This study compared the standard 24-hour ECG monitoring with a 30-day ECG monitoring protocol. The control group of the 24-hour monitoring protocol was assigned a second 24-hour recording as well.

Results

The primary outcome was detection of atrial fibrillation with duration of ≥30 seconds. The control group of 24-hour ECG monitoring found 3.2% meeting the primary outcome. The 30-day event loop monitoring group found 16.1% meeting atrial fibrillation events of more than 30 seconds.

The EMBRACE (30 day Cardiac Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event) study is one of a few recent major studies that are evaluating the stroke risk in atrial fibrillation patients. A prolonged event monitor is a relatively inexpensive, non-invasive test, which can help stratify higher risk cryptogenic stroke patients. *Submitted by John Kirkpatrick, MD*

4. Hyacock P, Heydon EE, Kaptoge S, et al. Leucocyte Telemere Length and Risk of Cardio-

vascular Disease: Systematic Review and Meta-Analysis. BMJ. *2014;349:g4227.*

Telomeres are DNA – protein structures at the end of linear chromosomes and have been noted as possible markers of biological aging. With each cell division they are shortened and thereby reflect the amount of cellular turnover within any one individual. Their length varies considerably between individuals including those of the same chronological age. The rate of attrition of telomere length has been linked to exposure to high oxidative stress and inflammation. In this study, which included nearly 44,000 participants of which 8400 had cardiovascular disease, telomere length was compared. The individuals were divided into three groups: short, average, and long telomere length. In comparison of the shortest vs the longest telomere length group the pooled relative risk for coronary disease was 1.54. (CI 1.30 to 1.83). While this study appears to show a statistical relationship between telomere length and the risk of cardiovascular disease, a causal mechanism has not been established although telomere shortening might contribute to atherosclerosis through various biological aging pathways.

It is noteworthy that it is now possible for the general public to have their telomere length measured via consumer ordered testing. One company, www.lifelength.com, currently offers telomere determination for less than $500. As an industry it would certainly be prudent for us to continue to monitor the development of consumer direct testing which offers a significant insight into mortality related illnesses. *Submitted by Michael L Moore, MD*

ENDOCRINOLOGY and METABOLISM

5. Vigen R, O'Donnell CI, Barón AE, et al. Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels. JAMA. *2013;310:1829.*

It's almost impossible to watch television or read a publication these days without seeing an advertisement for ''low T'', and many men applying for life insurance are now taking supplemental testosterone preparations. Annual prescriptions for testosterone increased more than 5-fold from 2000 to 2011, reaching 5.3 million prescriptions and a market for $1.6 billion in 2011. Testosterone is often promoted to increase muscle mass/strength, bone density, libido, and general well-being. Despite this, long term safety studies regarding the use of testosterone are lacking, and the relationship between testosterone and heart disease remains complex. Researchers in this retrospective study evaluated data from over 8700 male veterans having coronary artery disease or risk factors who underwent coronary angiography and had testosterone levels less than 300 ng/dL. Mean age was 63 years. Over a mean follow up of 27 months, myocardial infarction, stroke or death occurred in 26% of men who received testosterone and in 20% of those who did not. The investigators concluded that the use of testosterone therapy was significantly associated with adverse outcomes despite the lower prevalence of baseline co-morbidities in the testosterone therapy group, an association that was consistent among patients with and without coronary artery disease. They believe this may be the first observational study to suggest that testosterone therapy is associated with adverse cardiovascular outcomes. Several potential mechanisms by which testosterone might increase cardiovascular risk were considered by the authors:

1. Testosterone has been associated with an increase in platelet thromboxane A2 receptor density and platelet aggregation. It is known that platelets play a role in coronary plaque formation, beginning with platelet adhesion and eventual thrombus formation, with plaque rupture resulting in acute coronary syndrome.
2. Dihydrotestosterone, a testosterone metabolite, increases smooth muscle

proliferation and expression of vascular cell adhesion molecule 1, which enhances monocyte activation in the endothelium. Monocytes promote atherosclerosis through their effects on inflammatory cytokines and matrix metalloproteinases and are implicated in the pathogenesis of acute coronary syndromes.

3. Testosterone has been shown to worsen sleep disordered breathing among patients with severe obstructive sleep apnea, which is a risk factor for atherosclerosis.

They recommended future studies including randomized controlled clinical trials to properly characterize the potential risks of testosterone therapy in men with co-morbidities. This is a very relevant issue to many of us, simply because so many male applicants are now taking testosterone, a large number of whom qualify for best risk class. *Submitted by David S. Williams, MD*

6. Srikanthan P, Karlamangla AS. Muscle Mass Index as a Predictor of Longevity in Older Adults. Am J Med. *2014;127:547–553.*

While the association between obesity and increased mortality has been well established in younger and middle-aged individuals this association has been inconsistent in older adults. The authors contend that obesity is not associated with increased mortality in older adults if one adjusts for the weight loss associated with severely ill individuals near the end of life. The focus of this study, however, is to see whether increased muscle mass is associated with a decrease in mortality in the elderly. Using NHANES III data, a total of 3659 individuals met the criteria of age 55 or older for men, 65 years or older for women; BMI greater than 18.5; waist size greater than 50 cm and survived at least 2 years since the start of the study. Data was collected between 1988 and 1994. During the follow-up period of 13 years, 2012 participants died.

In looking at the data the unadjusted all cause mortality risk was significantly higher in the lowest muscle mass index quartile compared with the highest muscle mass index quartile. Specifically 58% compared with 41%, a relative reduction of 30%. Those individuals in the two middle quartiles did not show as much significant reduction.

The authors postulate that there are three possible reasons for this reduction in mortality. First is that the metabolism conducted by muscle vs fat is very different. Even correcting for traditional cardiovascular risk factors such as elevated lipids, hypertension, diabetes and inflammation did not explain the difference in mortality. The authors suggest that relative muscle mass may be an independent prognostic marker for survival in older adults. The second alternative theory that is proposed is simply that people who have more muscle mass have a better lifestyle which increases cardiovascular fitness. The third and less likely potential cause for this reduction in mortality is the role that muscle plays as a reliable protein reserve.

The bottom line is, as one might suspect, is that elderly people who have increased muscle mass tend to do better health wise than those who have less muscle mass. Accordingly just looking at BMI measurements is inadequate in order to differentiate between those who have increased muscle mass vs those who have increased fat stores. The authors propose that determination of muscle mass in the elderly should be considered as a routine measurement. Until this occurs, I have found that using waist size, which is usually available on male applicants, to be a useful marker for obesity vs muscle mass when the BMI is elevated. *Submitted by Michael L Moore MD*

7. Schottker B, Jorde R, Peasey A, et al. Vitamin D and Mortality: Meta-Analysis of Individual Participant Data from a Large Consortium of Cohort Studies from Europe and the United States. BMJ. *2014;348:g3656.*

This study adds to the literature on the effects of vitamin D by analyzing data from NHANES III and 6 similar European cohort

studies. Researchers were primarily interested in vitamin D as a predictor of all-cause, cardiovascular and cancer mortality. Because vitamin D is known to vary by season of testing (higher in summer and fall), age (lower with increasing age), sex (higher in men), and geography (lower levels at higher latitudes), the authors spent considerable effort categorizing vitamin D levels in a way that was reproducible across the various cohort studies which made up the meta-analysis. In the end, the vitamin D levels were categorized by within-cohort quintiles. The highest quintile was used as the reference values and the primary results were reported in terms of the hazard ratios between the lowest and highest quintiles. The age range of the study was 50-79 years, and average follow-up ranged from 4.2 to 15.9 years. Mortality ascertainment had over 98.5% coverage with cause of death available in over 97% of cases.

Three Cox models were used to ascertain hazard ratios. Model 1 contained covariates for age, sex, and season of blood draw. Model 2, the main results model, contained additional covariates for education, BMI, smoking and physical activity. Model 3 added in history of diabetes, hypertension and cancer.

In terms of the pooled Model 2 hazards, the researchers found that the lowest quintile of vitamin D levels was associated with a hazard ratio of 1.57(95%CI: 1.38 to 1.81). When analyzed by cause of death, the risk ratio was stronger for cardiovascular disease – 1.41(95%CI: 1.18 to 1.68) for those with no prior history of CVD and 1.65(95%CI: 1.22 to 2.22) – and weaker for cancer – 1.70(95%CI 1.00 to 2.88) for those with a history of cancer and 1.03(95%CI 0.89 to 1.20) for those with no history of cancer. This is essentially saying that vitamin D levels were most useful as a predictor of cardiovascular death, and only useful to predict cancer death in those who had a history of cancer. Authors speculate that some of this may be to reverse causation. Individuals ill with cancer may not go outside much and therefore may have lower vitamin D levels.

Perhaps the most relevant part of this study to life insurance is figure 3, which is a plot of risk ratios vs vitamin D quintiles. The all-cause mortality sub-plot demonstrates that the risk is quite flat from the second through the 5th quintiles, and is only elevated significantly for the lowest quintile. Therefore, if one were considering underwriting action for those with low levels of vitamin D, it would be logical to restrict that action to the lowest quintile. However, this study in no way addresses how valuable vitamin D may be in a fully underwritten population. The question remains as to how much of this excess risk would be identified by traditional markers such as cholesterol, EKGs, or newer markers such as natriuretic peptides. The study authors also recommend that vitamin D levels be considered in the context of region, sex and season. *Submitted by Steven J. Rigatti, MD*

ONCOLOGY

8. Zlotta AR, Egawa S, Pushkar D, et al. Prevalence of Prostate Cancer on Autopsy: Cross-Sectional Study on Unscreened Caucasian and Asian Men. J Natl Cancer Inst. *2013;105:1050–1058.*

Prostate cancer remains the most common malignancy other than superficial skin cancer, and is the second leading cause of cancer-related death in American men. This was an interesting autopsy study in which researchers examined the prostate glands of 220 Russian and 100 Japanese men who had no histories of prostate cancer and died of other causes. Prostate glands were prospectively examined during autopsies performed in Moscow and Tokyo from 2008-2011. These countries were chosen because neither has widespread prostate cancer screening in place. Mean age of the Russian men was 63 years, and mean age of the Japanese men was 69 years. The overall prevalence of prostate cancer was 37% in Russian men and 35% in Japanese men. In the Russian

cohort, the prevalence of prostate cancer was about 45% for men in their 60s and 70s. None in this group were older than 80 years. In the Japanese cohort, the prevalence of prostate cancer was 31%, 44%, and 59% for men in their 60s, 70s, and 80s, respectively. Among those with prostate cancer, the prevalence of tumors having a Gleason score of 7 or greater was 23% in the Russian cohort and 51% in the Japanese cohort. Extra-prostatic disease was noted in 11% of cancers in each cohort. By studying these two distinct populations, these researchers showed that despite differences in incidence and mortality rates, as well as in genetic and lifestyle factors, the prevalence of prostate cancer was similar and relatively high in both Caucasian and Asian men. Although some of these cancers may have eventually become symptomatic had the men lived long enough, earlier detection of cancer would probably have been of little benefit in men destined to die of something else. This reminds us of a problem often posed by widespread screening: any benefits for a few may come at the expense of over diagnosis and over treatment for a far greater number of patients. The investigators believe this is another study that underscores the need for better screening methods that don't just determine if a man has prostate cancer, but confirm whether it is an aggressive and life-threatening form of the disease. They note that the definition of clinically insignificant prostate cancer might be worth re-examining. *Submitted by David S. Williams, MD*

RESPIROLOGY

9. Gami AS, Olson EJ, Shen WK, et al. Obstructive Sleep Apnea and the Risk of Sudden Cardiac Death: A Longitudinal Study of 10,701 Adults. J Am Coll Cardiol. *2013;627:610–616.*

Untreated obstructive sleep apnea (OSA) has been associated with many adverse health conditions, including hypertension, heart failure, and dysrhythmia. Researchers in this study examined the relationship between OSA and sudden cardiac death, expanding from their prior 2005 study that found people with OSA more frequently died suddenly from cardiac causes during the hours of 10 pm to 6 am, which is the least likely time for sudden cardiac death to occur in the general population. To determine if OSA might also be associated with sudden cardiac death, they analyzed data from more than 10,000 adults referred to the Mayo Clinic sleep lab between 1987 and 2003. Mortality and cause of death were determined from death records. During an average follow up of 5.3 years, 142 patients experienced resuscitated or fatal sudden cardiac death, corresponding to an annual rate of 0.27%. An apnea-hypopnea index greater than 19 was associated with a significantly increased risk for sudden cardiac death (hazard ratio=1.6), as was mean nocturnal oxygen saturation less than 94% (hazard ratio=2.9), lowest oxygen saturation of less than 79% (hazard ratio=2.6), and age greater than 60 years (hazard ratio=5.5). Lowest nocturnal oxygen saturation was an independent predictor of sudden cardiac death, even after adjusting for hypertension, coronary artery disease, cardiomyopathy, and ventricular dysrhythmia. This observational study confirmed that an OSA patient's risk of sudden cardiac death does not simply shift from day-time hours to night-time hours, but that their overall risk of sudden cardiac death is higher than that for people not having OSA. While the precise link between OSA and sudden cardiac death remains unknown, several possible physiological mechanisms were considered, including OSA's effect on: cardiac autonomic dysfunction, heart rate variability, QTc interval dispersion, chronic sympathetic overdrive, neurohumoral activation, and myocardial remodeling. In any event, these findings implicate OSA, an increasingly prevalent disorder in this country, as a novel risk factor for sudden cardiac death. *Submitted by David S. Williams, MD*