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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 Moor em1@Nationwide.com. We will acknowledge all contributors in each issue's installment.

CARDIOLOGY

1. The Emerging Risk Factors Collaboration. Association of Cardiometabolic Multimorbidity With Mortality. JAMA. *2015;314(1):42–60.*

When it comes to the assessment of mortality risk in those with multiple impairments, underwriters and medical directors often struggle with the additivity of debits assigned for the specific issues. It is generally considered that debits from 2 largely unrelated disease processes, for example coronary artery disease and celiac disease would be additive, while those for 2 or more related disease factors would be somewhat more or less than additive depending on the circumstances. This is an area of considerable conjecture because there are relatively few studies which have enough data to quantify these risks and their interrelationships.

In this study, the authors used 2 very large cohorts – 689,000 subjects from the Emerging Risk Factors Collaboration (1960–2007) and the more recent UK Biobank (499,808 participants, 2006–2010). Both were followed up to 2013. The ERFC group (average age 52 years) contained over 128,000 deaths, while the UK Biobank (average age 56 years) contained 7995 deaths. Each group was subdivided into 8 mutually exclusive categories: those with a history of stroke, those with a history of MI, those with a history of diabetes, those with 2 of these conditions (3 groups), those with all of them, and those with none (reference group).

Cox models were used to determine hazard ratios between the reference group and those with 1 or more of the conditions of interest. The models were stratified by sex and controlled for age – in a supplementary analysis the authors also controlled for intermediate measures like cholesterol, but the results were little changed. In the ERFC, the hazard ratios (95% CI) were 1.9 (1.8 to 2.0) for diabetes alone, 2.0 (1.9 to 2.2) for MI alone, 2.1 (2.0–2.2) for stroke alone, 3.7(3.3 to 4.1) for MI plus diabetes, 3.8(3.5 to 4.2) for stroke plus diabetes, 3.5(3.1 to 4.0) for stroke plus MI, and 6.9(5.7 to 8.3) for diabetes plus stroke plus MI. Hazards were similar for the UK Biobank group. The authors used some additional statistical analyses to calculate that a history of any 2 of these conditions is associated with a loss of 12 years of life expectancy at age 60, while a history of all 3 is associated with a loss of 15 years.

The results of this study serve to confirm what for many has been a well-grounded *a priori* assumption, that the risks of these related cardiovascular factors is multiplicative (synergistic) rather than additive. That is

stroke, diabetes and MI alone all more or less double the rate of mortality. This would generally be approximately 100 debits (200% mortality) for each. But we see that any 2 of them results in a hazard of approximately 4 times the baseline which is 400%, mortality or the equivalent of 300 debits. [Note: The mention of debits here is only for example and should not be taken as an implication or endorsement of any particular rating for these conditions]. *Submitted by Steven J. Rigatti, MD*

2. van Nimwegan FA, Schaapveld M, Janus CP, et al. Cardiovascular Disease after Hodgkin Lymphoma Treatment. JAMA Intern Med. *2015;175:1007–1017.*

It is well accepted that patients who have received radiation as treatment for their Hodgkin's disease have an increased risk of subsequent secondary malignancies. This retrospective study from the Netherlands looks at whether there is an increased cardiovascular disease risk following treatment for Hodgkin's with radiation and anthracycline chemotherapy.

This study consisted of 2500 Dutch patients who were diagnosed with Hodgkin's disease at age younger than 51 years old (median age 27 years old) who were treated between 1965 and 1995 and survived at least 5 years from the time of their diagnosis. Records were examined to see those patients who developed coronary heart disease, valvular heart disease or cardiomyopathy and congestive heart failure.

Overall, 1713 cardiovascular events were identified in 797 patients. After 35 years or more following treatment, patients had a 4 to 6 fold increase in the incidence of coronary disease or congestive heart failure. This corresponded to 857 excess events per 10,000 person years. Fifty-one percent of patients with cardiovascular disease had multiple events. Highest risks were seen in patients treated before the age of 25. For those patients treated before age 25, the incidence of coronary disease by age 60 was 20%, valvular disease 31%, and congestive heart failure 11%. Mediastinal radiation increased the hazard ratio for coronary disease to 2.7, for valvular heart disease a hazard ratio of 6.6, and CHF a hazard ratio of 2.7. Anthracycline containing chemotherapy had similar though less impressive increase in risk.

While it is customary to add a small rating for insurance applicants who have been successfully treated for Hodgkin's lymphoma due to secondary malignancy concern, this study suggests that additional risk may be present for the development of significant cardiovascular disease. While this is a relative small study based solely on one demographic group, the results are significant enough to warrant further investigation. *Submitted by Michael L Moore, MD*

3. Leong DP, Teo KK, Rangarajan S, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. Lancet. *2015;386:266–273.*

Could something as simple as grip strength be an accurate predictor of longevity of cardiovascular disease? The results from the Prospective Urban Rural Epidemiology (PURE) study would suggest that perhaps it is possible. Over four years 140,000 adults in 17 countries had their handgrip strength measured annually. After 4 years, 2% of the participants had died. Perhaps more impressively, for every 5 kg decrease in grip strength there was a:

- 16% increase in death rate overall
- 17% increase in cardiovascular mortality
- 17% increase in non-cardiovascular mortality
- 7% increase in risk for myocardial infarction
- 9% increase in risk for stroke
- no increase in risk for diabetes, pneumonia or COPD or injury from a fall or fracture

While currently no insurer is using this grip strength parameter in risk selection, this study would suggest that the use of such an easy, inexpensive and non-invasive test is

worthy of further study. *Submitted by Michael L. Moore, MD*

DERMATOLOGY

4. Li WQ, Qureshi AA, Robinson KC, Han J. Sildenafil use and increased risk of incident melanoma in US men: A prospective cohort study. JAMA Intern Med. *2014;174:964–970.*

Sildenafil (Viagra) is a phosphodiesterase 5A (PDE5A) inhibitor now widely advertised and prescribed for treatment of erectile dysfunction. Prior studies have indicated that this class of drugs can promote melanin synthesis, which may in turn promote melanoma development. Published research has also linked sildenafil and other PDE5A inhibitors to promotion of melanoma cell invasion, especially in those carrying a mutation in the BRAF gene. BRAF activation down-regulates PDE5A levels, and low PDE5A expression by BRAF activation or sildenafil can theoretically increase the invasiveness of melanoma cells.

To explore this potential risk of sildenafil use, these Boston investigators conducted a prospective cohort study of almost 26,000 men participating in the long-term Health Professionals' Follow-up Study (HPFS) between 2000 and 2010. They did not include other PDE5A inhibitors like tadalafil (Cilalis) and vardenafil (Levitra) simply because they had not been approved for use when the cohort study began. About 6% of HPFS participants reported past or recent use of sildenafil at baseline. Men who reported prior cancers of any type were excluded. The incidence of skin cancers was obtained in self-reported questionnaires biennially.

Over 10 years of observation, 142 incident cases of melanoma were noted, as were 580 cases of squamous cell carcinoma (SCC) and 3030 cases of basal cell carcinoma (BCC). Controlling for multiple risk factors (age, smoking, BMI, family history, etc), analysis of the data showed that those who had ever used sildenafil were significantly more likely than non-users to be diagnosed with invasive melanoma. The hazard ratio was about 1.8–1.9 and the age-standardized absolute risk was 81 cases per 100,000 person-years. No association was found between sildenafil use and risk for SCC or BCC.

Although the researchers did not include other PDE5A inhibitors in their study, they speculated that the observed association between sildenafil use and melanoma might be partly attributed to the later use of the longer-acting tadalafil and vardenafil among recent sildenafil users, because the longer clearance time of other PDE5A inhibitors could possibly have augmented the observed hazard ratio for sildenafil. The possibility that sildenafil and similar drugs might almost double the risk for melanoma is certainly worrisome, and should prompt further studies, but does not yet warrant any change in current clinical recommendations for use of medications in this drug class.

I'm reminded of my pharmacology professor in medical school, who used to begin every lecture with the words "All drugs are poisons." I suspect as our understanding of molecular genetics improves more such associations will be discovered. *Submitted by David S. Williams, MD*

NEUROLOGY

5. Levine DA, Galecki AT, Langa KM, et al. Trajectory of Cognitive Decline after Incident Stroke. JAMA. *2015;314:41–51.*

There is a debate among stroke researchers about the course of cognitive decline before and after stroke. As a result a few studies published between 2006 and 2014, the prevailing thought has been that stroke does not alter the rate of cognitive decline unless another stroke occurs. This is biologically plausible since the neuronal loss during stroke would be expected to result in just a particular deficit without necessarily promoting further neuronal loss beyond further stroke events. On the other hand, if one has cerebrovascular disease sufficient to bring

about stroke, concomitant microvascular changes may be severe enough to cause subclinical events and further cognitive degradations.

This article serves as a counter to the current prevailing wisdom, as it demonstrates an acceleration of cognitive decline after incident stroke. It relied on a population of 23,572 American adults aged 45 or older with no history of cognitive impairment. They were followed for a mean of 6.1 years, which resulted in 515 incident strokes that were independently adjudicated by medical record review. All participants in the study are evaluated annually for cognitive function using a battery of telephone-administered tests. The six-item screen (SIS) tests cognitive function using immediate and delayed word recall as well as orientation. The Word List Learning Test evaluates new learning. Ten-word delayed recall was used to test verbal memory, and the animal fluency test was used to evaluate executive function. Those with incident stroke were evaluated with this battery at least once after the stroke.

The authors found that stroke was associated with acute decline in new learning, global cognition and verbal memory. In the post-stroke period, global cognition and executive function declined faster than during the pre-stroke period. Though all of the above finding reached statistical significance, in some cases the differences were small (the decline in global cognition after stroke was 0.1 points on a 6-item battery), or of questionable clinical significance. Also, the statistical methodology was very complex and difficult to understand. Though this likely represents cognitive deficits in the reviewer, the necessity to use such arcane methods argues for the use of caution when drawing conclusions from the study.

This study does hold some relevance to insurance medicine. Specifically, it helps add some data to the question of how much cognitive dysfunction can be blamed on a history of stroke in a hypothetical applicant who demonstrates a mild degree of cognitive impairment on required testing. Also, it allows some degree of anticipation of a modestly faster rate of cognitive decline post-stroke, which has particular implications for the underwriting of living benefit products. *Submitted by Steven J. Rigatti, MD*

6. Billioti de Gage S, Moride Y, Ducruet T, et al. Benzodiazepine use and risk of Alzheimer's disease: Case-control study. BMJ. *2014;349:g5205.*

While the deleterious effects of benzodiazepines on memory and cognition are well documented, the possibility of an increased risk of dementia remains debatable. The frequency of symptoms highly correlated with prescription of benzodiazepines (anxiety, insomnia, depression, etc) increases in the years before a diagnosis of dementia; hence, these drugs might not cause the disease but rather be prescribed to treat its prodromes.

In this case-control study using an administrative claims database, these investigators examined the association between exposure to benzodiazepines and the risk for developing Alzheimer's disease (AD). Cases were almost 1800 randomly selected older community dwellers in Quebec who had received first diagnoses of AD and been followed for 6 years prior to their AD diagnosis. Controls were about 7200 similar residents who were matched by age, sex and duration of follow up. To minimize reverse causality, only benzodiazepine exposures that occurred over 5 years before the diagnosis of AD were considered. After adjusting for multiple variables, any benzodiazepine use was associated with excess risk for AD. Cumulative exposure to 1 to 90 prescribed daily doses was not associated with excess risk, but higher exposures were, in a dose-dependent fashion. The association was stronger for longer-acting than for shorter-acting benzodiazepines. Put another way, they demonstrated a dose-effect relation between benzodiazepine use and increased risk of AD in older people treated previously for more than 3 months, with the risk being higher for longer acting formulations.

Whether causal or not, the nature of the link cannot be definitively established: benzodiazepine use might also be an early marker of a condition associated with an increased risk of dementia. The authors of the study further noted that chronic benzodiazepine use induces a down regulation of their binding receptors, and that a reduction in the number of these receptors has been correlated with cognitive decline. They suggested the most plausible hypothesis would be the limitation in cognitive reserve capacity induced by the long term use of benzodiazepines, which might reduce a person's ability to cope with early phase brain lesions by soliciting accessory neural networks. *Submitted by David S. Williams, MD*

RESPIROLOGY

7. Gifford AH, Sabadosa KA, Quinton HB, Knapp EA, Goss CH, Marshall BC. Longevity of patients with cystic fibrosis in 2000 to 2010 and beyond: Survival analysis of the Cystic Fibrosis Foundation Patient Registry. Ann Intern Med. *2014;161:233–241.*

Despite improvements in medical care, cystic fibrosis (CF) remains a life-shortening disease, and one that is generally not insurable. To evaluate trends in survival among those having CF, these investigators analyzed data on more than 34,000 patients in the Cystic Fibrosis Foundation Patient Registry from 2000 to 2010. This registry has documented the natural history of the disease since 1966, at which time life expectancy was often limited to early childhood, and deaths were more often a result of malnutrition than compromised lung function. They found:

1. The median age of CF patients enrolled in the database increased from 14.3 years in 2000 to 16.7 years in 2010. Males had a 19% lower adjusted risk of death than females, resulting perhaps from differences in sex hormones and their effect on chloride secretion.
2. If mortality were to remain constant at 2010 levels, median survival of children born and diagnosed with CF in 2010 would be 37 years for females and 40 years for males.
3. If survival were to continue to improve at the rate observed between 2000 and 2010, increasing about 1.8% annually, median survival of children born with CF in 2010 would be 54 years for females and 58 years for males.
4. Female sex, ethnicities other than nonwhite, and F508del mutations are associated with increased CF-related mortality risk.

The researchers found that nationalized newborn screening has reduced the median age at diagnosis from 6 months to 1 month, and the proportion of individuals homozygous for the delta F508 deletion has decreased as more mutations causing this disease have been identified and detected. They also detected vulnerability in adolescence. Until age 10 years, annual mortality is less than 0.5%. It then spikes before leveling-off at age 25 years, at 3%–4% per year in women and 2%–3% per year in men. This might be a result of poor nutrition and compliance with therapies, as well as acquisition of pathogens such as pseudomonas aeruginosa and methicillin-resistant staphylococcus aureus.

The investigators noted that as CF patients live longer, the respiratory component of the disease has presented as a new therapeutic target, and preventing or controlling pulmonary exacerbations has contributed to survival. They expressed the belief that as promising new treatments continue to emerge, particularly at the molecular level, a huge jump in predicted survival might occur, perhaps approaching that of the general population. *Submitted by David S. Williams, MD*