JOURNAL OF INSURANCE MEDICINE

J Insur Med 2015;45:121–126

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.

ENDOCRINOLOGY and METABOLISM

1. Dormuth CR, Filion KB, Paterson JM, et al. Higher potency statins and the risk of new diabetes: Multicentre, observational study of administrative databases. BMJ. *2014;348:g3244.*

Since early 2012, statin drugs have carried a FDA warning regarding a possible increased risk for development of diabetes mellitus, as well as for worsening glycemic control in those already known to be diabetic. To further investigate the reported association of statin medications with the risk for developing diabetes mellitus, these Canadian investigators analyzed data from eight population-based studies carried out in the US, UK, and Canada. This involved about 137,000 patients age 40 and above who were hospitalized for adverse cardiovascular events and prescribed high-potency or low-potency statins for secondary prevention. All patients had established cardiovascular disease, and about two thirds of those given a statin were prescribed a high-potency statin. Diabetes incidence in new users of high-potency statins was compared with incidence in new users of low-potency statins. Within the first 2 years of statin use, new onset diabetes was significantly more common with high-potency statins than with low-potency statins. Risk was highest during the first 4 months of use. While the relative risk was increased by 15%, the absolute risk remained small. The investigators estimated that 342 secondary-prevention patients would have to be treated with a high-potency-statin instead of a low-potency statin for 2 years to cause one additional case of diabetes. The mechanism of action of this association was not clear and no speculation was made as to possible causes, other than to note that it was most likely statin-specific. This class of drugs can reduce insulin sensitivity and increase insulin resistance in a dose-dependent fashion through a number of possible mechanisms. Their direct effect on levels of adiponectin, glucose transporters, and insulin signaling, may well play a role. Likewise they might attenuate beta-cell function, and also reduce synthesis of ubinquinones, which may result in diminished insulin release. In any event, this is a finding that may offset a small amount of the considerable risk-reduction provided by statin drugs. *Submitted by David S. Williams, MD*

2. Sjöström L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA. *2014; 311:2297–2304*.

Bariatric surgery has become safer, more effective, and much more common with the growing obesity epidemic in this country. It has been demonstrated to produce higher short-term remission rates for type 2 diabetes mellitus than medical management, but longer term data in this regard has been lacking. These Swedish researchers compared long-term outcomes among 343 diabetic patients who underwent bariatric surgery with outcomes of 260 diabetic patients who received counseling for appropriate lifestyle modification. Both groups received individualized medical management for diabetes as indicated. In this observational study lasting almost two decades, the groups had a similar mean age of about 50 years and initial BMI of about 40-42. Mean weight loss in the bariatric surgery group was 58 pounds at 2 years and 50 pounds at 10 years. Mean weight loss in the control group was 7 pounds at 2 years and 10 pounds at 10 years. The proportion of bariatric surgery patients who remained in diabetes remission at 2 and 15 years was 72% and 30%, respectively, compared with 16% and 6% in the control group. Over mean follow-up of about 18 years, microvascular and macrovascular complications were 50% and 33% less in bariatric surgery patients, compared to the control group. These results applied regardless of the type of bariatric surgery. In sum, bariatric surgery was associated with more frequent remission and fewer complications, after many years, than usual care in patients having type 2 diabetes. Validation of these results might require a randomized study, but they certainly provide some additional insight for our risk assessment, given the increasing number of obese diabetic applicants we see who have undergone bariatric surgery. *Submitted by David S. Williams, MD*

INFECTIOUS DISEASES

3. Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: A self-controlled case-series study. Clin Infect Dis. *2014;58:1497–1503.*

Herpes zoster infection is common in aging populations, affecting 1 million Americans every year. These British researchers analyzed a clinical data base of over 5 million patients spanning 25 years to investigate the association between herpes zoster virus and stroke, given multiple case reports suggestive of a possible link. Within-person comparisons were undertaken using the self-controlled case-series method, and about 6600 individuals fulfilled study inclusion criteria. They found that among adults having a new diagnosis of herpes zoster, the overall risk for both ischemic and hemorrhagic stroke rose significantly in the first month after diagnosis, slowly decreased during the following 6 months, and disappeared at 1 year. Among patients receiving anti-viral medication, the risk for stroke in the first month was not significantly different from baseline and was about 50% that of untreated patients. In these treated patients, stroke risk exceeded baseline only in the second and third months following diagnosis. Herpes zoster involvement of the trigeminal nerve branches raised stroke risk almost three times higher than herpes zoster in other dermatomes. This risk peaked in the second and third months after diagnosis, and while it was lessened somewhat by anti-viral treatment, it remained significantly above baseline risk. Some studies have suggested there might be additional risk for transient ischemic attack and myocardial infarction associated with acute herpes zoster infection. The common denominator might be some type of generalized endothelial dysfunction associated with acute infection, and/or some zoster-specific damage to vascular walls, against a background of pre-existing arteriopathy. This study is interesting because it made note of a risk of which I was not aware, one that might be ameliorated somewhat with anti-viral treatment and/or possibly prior vaccination. It may be relevant to us when considering an older insurance

applicant having a current or recent untreated herpes zoster infection, particularly in those cases with trigeminal nerve involvement. *Submitted by David S. Williams, MD*

ONCOLOGY

4. Pathak N, Dodds J, Zamora J, Khan K. Accuracy of urinary human papillomavirus testing for presence of cervical HPV: systematic review and meta analysis. BMJ. *2014;349:g5264.*

Cervical cancer is the most common malignancy in women under the age of 35. There is no doubt of the association between human papillomavirus and the development of cervical cancer. HPV is one of the most common sexually transmitted diseases. It is been estimated that up to 80% of sexually active women are infected at some point in their life and that 10%-20% develop persistent infection. Traditionally, screening for cervical malignancy has been conducted by use of cervical cytology collected as part of a pelvic exam and submitted for Papanicolaou staining. Lately, the process has been increasingly automated with computer aided diagnosis, but overall this process has remained unchanged for decades. In addition to the labor intensiveness of this process, the cost and the invasiveness of the collection has limited participation by many women.

In this meta analysis of 14 studies, a total of 1443 women underwent urinary HPV testing to compare the accuracy versus traditional cervical cytology. Using commercial polymerase chain reaction methods on first voided urine samples produced the following results: urine detection of any HPV had a sensitivity of 87% and a specificity of 94%. Urine detection of high risk HPV had a sensitivity of 77% and a specificity of 88%. Urine detection of HPV 16 and 18 had a sensitivity of 73% and a specificity of 98%.

The findings suggest that urinary HPV detection on a first void sample has outstanding specificity. The sensitivity is still good for all HPV but declines slightly when looking for pathogenic strains. Nevertheless, the potential for this technology to read as traditional PAP smear testing is exciting. Not only should cost and convenience issues be nearly eliminated for the insurance medicine population the ability to perform such a useful test in a convenient fashion greatly enhances our ability to screen for potentially serious illness. As this technology becomes more refined it will be interesting to see if the insurance laboratories are able to provide these tests and if our results in our applicants will be similar to these prior studies. *Submitted by Michael L Moore, MD*

5. Rebbeck TR, Mitra N, Wan F, et al. Association of Type and Location of BRCA1 and BRCA2 Mutations With Risk of Breast and Ovarian Cancer. JAMA**.** *2015;313(13):1347–1361.*

It is well recognized that deleterious mutations in the genes called BRCA1 and BRCA2 lead to elevated risks of breast and ovarian cancer in women who carry them. It has also been reported that the relative risk of breast vs ovarian cancer may be related to the specific location and type of mutation. Specifically, in 2002 it was reported that mutations in exon 11 of BRCA1 were associated with higher risk of ovarian cancer and lower risk of breast cancer than mutations in other locations. A similar "ovarian cancer cluster region" (OCCR) was identified for exon 11 of BRCA2. This study sought to clarify the existence of such risk variations by evaluating data from a large, international consortium, spanning 33 countries on 6 continents. The data consisted of genetic analyses and outcomes on women who were evaluated between 1937 and 2011 (median 1999), and found to have disease-associated mutations in BRCA1 (n=19,581), or BRCA2 (n=11,900). The 84 women who carried mutations in both genes were eliminated from analysis.

For each gene a number of "bins" were created (30 for BRCA1, 19 for BRCA2). Each bin corresponded to a contiguous segment of

DNA in the gene where a mutation may be located. These were determined such that approximately equal numbers of individuals were represented in each bin. Cox models were then constructed using the bin number, with either breast or ovarian cancer as the outcome variable. In this way, hazard ratios were determined for breast and ovarian cancer bin by bin. The authors then computed a statistic they called the ratio of hazard ratios (RHR). When larger than 1, this ratio implies a higher risk of breast cancer relative to ovarian cancer, and when smaller than one a higher risk of ovarian relative to breast cancer. When the RHR was significantly different from 1, an ovarian or breast cancer-associated bin had been identified. When multiple such bins were adjacent, a breast or ovarian cancer cluster region had been identified. This computation revealed that indeed there did seem to be 3 breast cancer cluster regions, and 1 ovarian cancer cluster region in BRCA1 – the OCCR corresponding to exon 11. For BRCA2, multiple BCCRs and 3 OCCRs were identified.

The authors then evaluated mutations by type (missense, nonsense, in-frame deletion, etc.). To evaluate the differential influence that type had on breast vs ovarian cancer risk, all mutations were compared to exon 11 nonsense mutations because they are common across ethnicities. Recall that nonsense mutations create a premature stop codon in DNA resulting in a foreshortened mRNA strand. This strand may undergo nonsense-mediated decay (NMD) such that the mutant protein is not produced or only produced in small amounts. The authors found that mutations conferring NMD were associated with earlier age onset for breast cancer for both BRCA1 and BRCA2.

For the life insurance medical director, this study is a stepping stone. It is showing that not all BRCA mutations are alike, and that different mutations may affect breast and ovarian cancer risks differently. In the future, such analyses might be used to tailor prevention strategies for women faced with the difficult task of deciding whether or not to pursue risk reduction surgery. For now, the differential risks are not so large as to warrant an underwriting strategy which takes the specific mutation into account – unless perhaps that mutation is known to not cause disease. *Submitted by Steven J. Rigatti, MD*

6. Iqbal J, Ginsburg O, Rochon PA, et al. Differences in Breast Cancer Stage at Diagnosis and Cancer-Specific Survival by Race and Ethnicity in the United States. JAMA. *2015;313(2):165–173. doi:10.1001/jama.2014.17322*

It is well recognized in the field of breast cancer that American black women have lower survival rates compared to other ethnicities. This mortality gap may be due to a host of socioeconomic reasons having to do with equitable access to quality healthcare. It is also plausible that there are biological differences between races and ethnicities, which impact the mortality risk. The authors of this study sought to clarify the contribution of biological issues to this difference in survival experience.

To do this, the authors did a retrospective study using SEER data from all 18 SEER sites. They restricted their analysis to women diagnosed between 2004 and 2011 (N=452,215). Mean follow-up time was 40.6 months. Race/ethnicity was determined using the relevant SEER variables, which are, in turn based on reports made to state cancer registries. There are a total of 30 race/ethnicity groups available, which the researchers combined into 8 broader groups (non-Hispanic white, Hispanic white, black, Chinese, Japanese, South Asian, other Asian, and other ethnicities). Exclusions were made for stage 0 or unknown stage, unknown or borderline receptor status, and prior history of cancer, leaving 373,563 women in the final analysis. In addition to looking at the overall survival using Cox models to determine hazard ratios, the researchers evaluated the likelihood of a stage I diagnosis using logistic regression to establish odds ratios.

The results demonstrated a lower likelihood of being diagnosed at stage I for black vs white women (37% vs 51%), and a higher risk of death when the initial tumor was <2.0cm for black vs. white women (6.2% vs 3.0% 7-year actuarial mortality). This difference persisted after controlling for income (as determined by Zip code), estrogen receptor status, and after exclusion of triple-negative cases. However, the hazard ratio for race was mitigated by the inclusion of estrogen receptor status in the model. Asian women had lower risks than white women overall. Specifically, Japanese women had a 56% rate of stage I diagnosis, and a 1.4% 7-year actuarial mortality. Further analysis demonstrated that black women with small breast tumors were more likely than other races/ethnicities to have stage IV disease (1.5%), positive nodes (24.1%), negative estrogen receptors (26.4%) and triple negative disease (17.2%). This last factor was especially relevant, as no other racial/ethnic group had a rate of triple negative disease higher than 10%.

The authors pointed to this as evidence for inherent biological differences in breast cancer among the various racial/ethnic groups evaluated. In an accompanying editorial, Drs. Daly and Olopade of the University of Chicago point to a large number of studies demonstrating differences in cancer care and in access to care among American women by ethnicity and conclude that both biological and socioeconomic factors play an important role in the mortality gap in breast cancer. *Submitted by Steven J. Rigatti, MD*

NEUROLOGY

7. Berkhemer OA, Fransen PS, Beumer D, et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. N Engl J Med. *2015;372:11–20.*

Acute ischemic stroke is a devastating event which causes significant morbidity and mortality burden. This study (MR CLEAN) enrolled patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation. Patients were assigned to standard treatment with IV alteplase alone versus IV alteplase plus intraarterial intervention. The intervention protocol included intraarterial thrombolysis, mechanical treatment or both. The primary endpoint measured was using a modified Rankin score at 90 days. Secondary outcomes used were vessel patency at 24 hours, infarct measured size, occurrence of major intracranial bleeding and use of the National Institute of Health stroke scale. By design the study was open label but blinded assessment.

The results showed that patients with acute ischemic stroke caused by proximal arterial occlusion showed functional outcome benefit from intraarterial treatment. There was an absolute difference of 13.5 percentage points in the rate of functional independence in favor of the intraarterial group. They noted no increase in symptomatic intracerebral hemorrhage or death.

There is significant controversy with the findings of the MR CLEAN study. First, the three previous studies (IMS-3, SYNTHESIS and MR RESCUE) failed to find an advantage with intraarterial interventions. For example, the IMS-3 study showed the same rates of recanalization in their study arms, same bleeding rates, and the same secondary infarction rates, yet there was no measurable improvement in outcomes. Measurement of soft outcomes, such as a nurse measured modified Rankin score may not be adequate for outcome determination. The MR CLEAN study had a marked decrease in time to intervention, measured in minutes rather than hours. Some feel that this alone may explain the outcome difference. The future seems to hold more arterial interventions for stroke patients. *Submitted by John Kirkpatrick, MD*

8. Zaidat OO, Fitzsimmons BF, Woodward BK, et al. Effect of a Balloon-Expandable Intracranial Stent vs. Medical therapy on Risk of Stroke in Patients with Symptomatic Intracranial Stenosis

(The VISSIT Randomized Clinical Trial). JAMA. *2015;313(12):1240–1248.*

This study was designed to compare balloon expandable stents plus medical therapy to medical therapy alone in symptomatic intracranial arterial stenosis. The study was designed to enroll 250 patients that had either a stroke or TIA. Due to the fact that the NIH sponsored SAMMPRIS trial (also studying stent vs. medical management) was halted early due to a high rate of adverse events in the stenting arm, the VISSIT trial stopped enrollment early at 112 patients.

The VISSIT trial used a different stent however results were similarly dismal. The primary outcomes of stroke or TIA in the same territory as the presenting event were increased in the stenting arm. Safety outcomes also included all-cause mortality and intracranial hemorrhage within 30 days of the procedure. These measurements were also increased in the intervention arm.

The conclusion clear, balloon stenting is not appropriate in the treatment of stroke or TIA caused by intracranial arterial stenosis. *Submitted by John Kirkpatrick, MD*

RESPIROLOGY

9. Carter B, Freedman ND, Jacobs EJ. Smoking and Mortality–Beyond Established Causes. N Engl J Med. *2015;372:631–640.*

With all of the time, effort and research dollars that have been devoted to determining the deleterious effects of tobacco smoking could it possibly be true that the health effects are even worse than what we now know? This retrospective study of nearly 1,000,000 Americans, both men and women age 55 and older would seem to suggest that.

A total of 21 diseases have been formally established as caused by smoking. These include 12 types of cancer, 6 categories of cardiovascular disease, diabetes, chronic obstructive pulmonary disease and pneumonia including influenza.

In this retrospective study sponsored by the American Cancer Society 421,378 men and 532,651 women aged 55 and older were followed from the years 2000 through 2011. Over that period of time there were 181,377 deaths including 16,475 among current smokers.

Diseases that had been established as caused by smoking accounted for 83% of the total excess mortality observed among current smokers. The remaining 17% of excessive mortality among smokers were attributed to: renal failure (relative risk 2.0), intestinal ischemia (relative risk 6.0), hypertensive heart disease (relative risk 2.4), infections (relative risk 2.3), various respiratory diseases (relative risk 2.0), breast cancer (relative risk 1.3) and prostate cancer (relative risk 1.4). Among former smokers, the relative risk for each of these outcomes declined as the number of years since quitting increased.

Overall, the Surgeon General estimates smoking-attributable mortality to be 437,000 deaths per year; however, based on this additional study this may be a significant underestimate. If we account for this additional 17% that would give a annual estimate of smoking related deaths of 556,000 in Americans. For the insurance medical director assuring that tobacco risk pricing meets overall risk is an ever changing environment and should be periodically assessed. *Submitted by Michael L Moore, MD*