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


Medical underwriting is an exercise in risk prediction, and the modern paradigm of risk prediction based on risk factor analysis largely had its start with the Framingham study, and its findings that serum lipid levels were associated with the risk of cardiovascular disease. Since then medical science has been searching for improvements and refinements to the traditional variables (age, sex, blood pressure, total cholesterol, HDL cholesterol, smoking and diabetes). One area that has generated much interest is non-traditional lipid measurements. These include such factors as apoliporotein B and A-1, lipoprotein(a), and lipoprotein-associated phospholipase A2.

The authors of this study used meta-analysis techniques to attempt to determine if these non-traditional lipid measures are better or worse at predicting incident cardiovascular events (heart attacks and strokes) than the traditional risk factors. Additionally, they analyzed various mathematical transformations of the traditional factors (cholesterol:HDL-C ratio, non-HDL cholesterol, and others) to see if risk prediction could be improved. The study incorporated records from over 165,000 pooled participants with an average follow up of over 10 years, who experience over 15,000 incident events.

The study found that when non-traditional measures were used to replace conventional risk factors, risk prediction was significantly worse, as measured by the C-statistic and the net reclassification index. When non-traditional measures were used in addition to conventional risk factors, prediction was improved only slightly, with lipoprotein(a) and lipoprotein-associated phospholipase A2 performing best.

As is usually the case with meta-analyses, there are multiple possible sources for bias in this study. From a medical underwriting point of view, the most troubling aspect is that the analysis focused on subjects who were at intermediate risk for CVD – those with a predicted 10-year risk of 10–20%. This was done because it is these patients who face a somewhat difficult decision on whether or not to begin statins, aspirin or other preventive treatments. For life insurance medical directors, though, the groups in the low and high-risk categories are also important.

In conclusion, this study would seem to cast some serious doubts on the marginal
utility of non-traditional lipid measurements in the prediction of cardiovascular disease. Submitted by Steven J. Rigatti, MD


This study, completed in Iceland, is compelling because it not only examines the sensitivity of new (cardiac MRI) and old (EKG) tests for the detection of unrecognized myocardial infarction (UMI), but it also reports and compares mortality rates for those with UMI stratified by the method of detection. A total of 936 older (ages 67 to 93) individuals were recruited and classified as either having recognized myocardial infarction (RMI) based on their medical history, or UMI based on ECG or cMRI.

Many more MIs were detected by cMRI (157) than by EKG (46) or clinical history (91). The overall agreement between ECG and cMRI was fairly poor; 27 individuals had MI by EKG but not by cMRI, and 138 had MI by cMRI but not by ECG. This leaves only 19 individuals who had UMI, for whom the two tests were in agreement. Unless we arbitrarily assign one of these tests a “gold standard” designation, it is not possible to determine which test better represents the truth. However, in following these patients prospectively for a median of 6.4 years, it was discovered that those with UMI by cMRI had a cumulative mortality rate of 28%, which was similar to the cumulative mortality of those with RMI (33%), and significantly higher than those with no MI (17%). After adjustment for age, sex, diabetes and RMI, UMI by cMRI remained significantly associated with mortality (HR: 1.45, 95% CI: 1.02–2.06), while UMI by EKG did not (HR: 0.88, 95% CI: 0.45 to 1.73). The authors also noted that those with a history of RMI were much more likely to be taking medications to control risk factors (statins, aspirin and beta blockers) than were those with UMI.

The implications of this study are rather far reaching. First, UMI by cMRI in this population was much more prevalent than RMI, which implies that there is a large burden of occult cardiac disease in the older population, especially those with diabetes, in whom the rate of UMI was higher. Second, the UMIs detected by cMRI are just as lethal, in the long term, as recognized MI. Third, the MIs detected by ECG seem to carry a much lower risk of mortality than those detect by cMRI. The authors do point out that the mortality of RMI may be lower due to survivor bias, and that the mortality of UMI by ECG is lower than found in prior studies. Submitted by Steven J. Rigatti, MD


Kidney donors apply for life insurance like everyone else, and we review their medical records on a regular basis. Currently about 6000 people per year donate a kidney to someone in this country. Although reduced renal function has been associated with excess risk for cardiovascular (CV) disease, it’s unclear whether living kidney donors actually have any increased CV risk. Canadian researchers sought to answer the question with this large, retrospective, population-based, matched cohort study.

About 2000 living kidney donors were matched with over 20,000 healthy non-donors. The median age at kidney donation was 43 years, and a little over half of the donors were female. After a median follow-up of 6 1/2 years, the risk for death or first major CV event was 1/3 lower in kidney donors than in non-donors. The risk for major CV events and death did not differ significantly between these two groups. Likewise, time since kidney donation and age at donation did not impact the results.
In sum, these investigators demonstrated that the risks for death and major CV events are not higher for living kidney donors as opposed to healthy non-donors. This is consistent with several other studies which have shown no long-term excess mortality following kidney donation. Those who donate kidneys lose half their renal mass but not half their renal function, due to compensatory hypertrophy of the remaining kidney. Some studies have, in fact, shown that mean glomerular filtration rate is reduced by only one quarter in kidney donors after many years of follow-up. There’s probably also some favorable selection bias given kidney donors are rigorously screened to ensure they are healthy enough to donate in the first place. These results provide further reassurance and support for positive consideration of these applicants. Submitted by David S. Williams, MD


About 20% of embolic strokes have no obvious cause and are thus termed cryptogenic. Patients having cryptogenic strokes tend to be younger (less than 55 years) and have a much higher prevalence of patent foramen ovale (PFO), which makes possible paradoxical embolization via right-to-left shunting. While up to 40% of those having experienced a cryptogenic stroke may have a PFO, this common finding has a prevalence of about 25% in the general population, making it somewhat speculative to determine cause and effect. A variety of cardiac devices available for repairing atrial septal defects have been used to close PFOs following a cryptogenic stroke, yet there is no solid medical evidence to support this common practice. This study specifically addressed this issue.

These investigators identified over 900 study participants having had a recent stroke or transient ischemic attack (TIA), with a PFO demonstrating right-to-left shunting on echocardiography, and no other identifiable etiology for their stroke. They then randomized the subjects, ranging in age from 18–60 years old, to undergo PFO closure using the same device, or receive medical therapy alone in the form of aspirin and/or warfarin. PFO closure was successful in about 87% of patients undergoing placement of a device to correct the shunt. Over a period of about 2 years, recurrent embolic stroke or TIA occurred in 5.5% of the closure group and 6.8% of the medical therapy group, a non-significant difference. Furthermore, in both groups most recurrent strokes or TIAs had an identifiable cause other than right-to-left shunting facilitated by a PFO.

Although this study may not have had a sufficient number of patients to gain the statistical power to rule out a small benefit from PFO closure, its results do indicate that stroke or TIA recurrence in this population is uncommon. For this reason, procedural complications have to be exceptionally low to improve on the natural history of uncorrected but medically-treated PFO in these patients. Although PFO closure might be of value for some yet-to-be identified higher risk groups with paradoxical embolism, its routine use is not supported for most patients. This impairment surfaces periodically in underwriting. The results of this study would suggest that insurance applicants having had a cryogenic stroke or TIA with PFO can be assessed similarly whether they have had PFO closure or medical treatment alone. It also provides reassurance that the risk for recurrent embolic events may not be as high as once thought. Submitted by David S. Williams, MD

ENDOCRINOLOGY


This retrospective study followed 11,271 patients who underwent annual health examination screening in Japan. They were
followed for 7 years. The group did not have type 2 diabetes mellitus (T2DM) at entry and were free from chronic diseases that may affect the HgA1C level such as anemia or cirrhosis. The aim of the study was to determine the HgA1C cut off for defining a high risk group of developing T2DM. The HgA1C levels were compared to fasting plasma glucose (FPG).

Subjects were considered as incident cases of T2DM if they met accepted diagnostic criteria (consistent with the ADA criteria) or were under treatment for T2DM for the first time within the follow up period.

There were 860 incident cases.

Results

For both FPG and HgA1C levels, the risk of T2DM increased as the FPG and HgA1C increased. There was no clear cut off point above which the risk of diabetes increases markedly. Rather, there was a progressive, linear association. The increase in the incidence rate of diabetes vs FPG and HgA1C were similar curves. The conclusion of the authors was that “therefore, a certain degree of arbitrariness in the cut off point for the high risk group is unavoidable.” Their data, collected in a Japanese population was consistent with the American Diabetes Association conclusions. The hazard ration of developing diabetes in the group of a HgA1C 5.6% to 5.9% was approximately 5–20. The hazard ratio of the group with a HgA1C 6.1%–6.4% was 50. The American Diabetes Association lumps the two groups together under the label of pre-diabetes. The Japanese Diabetes Association splits the group in to ‘increased risk for diabetes’ and ‘suspected diabetes cannot be excluded’. As the level of HgA1C increases, so does the risk of developing T2DM, and there is no clear cutoff point to the increased risk.

Submitted by John E. Kirkpatrick, MD

ONCOLOGY


Current clinical guidelines do not recommend routine serum alpha-fetoprotein (AFP) testing as surveillance screening for hepatocellular carcinoma (HCC) in patients having chronic hepatitis C. But we still see this done quite often as we review medical records, and abnormal AFP results usually prompt immediate referrals to the medical director. This study revisited this issue.

Researchers measured serum levels of AFP and 2 other biomarkers, AFP-L3 and des-gamma-carboxyprothrombin (DCP), every 3 months for 4 years in about 900 patients with advanced chronic hepatitis C. All study participants underwent yearly ultrasound imaging of the liver, and over the 4 year period 46 subjects (5% of the original group) developed HCC.

Normal AFP levels vary by lab, but are generally less than 6 ng/ml in healthy adults. At a threshold of 20 ng/ml, an elevated AFP during the last year of surveillance screening had a sensitivity of 60% for the development of HCC during the following 2 years. That said, only 10% of elevated AFP levels were true positives, since true positives were so greatly outnumbered by false positive AFP elevations in the much larger group that never developed HCC. Raising the threshold level to 200 ng/ml improved the positive predictive value of AFP to 31%, but the sensitivity in turn dropped to 20%. Similar large trade-offs between sensitivity and specificity occurred with the other 2 serum biomarkers.

The investigators concluded that AFP and related biomarkers do not have the sensitivity, specificity, and predictive value required for satisfactory HCC surveillance. The problem is that while HCC is a principal tumor secreting AFP, almost any liver condition causing inflammation, fibrosis, and/or regeneration of cells will significantly raise AFP levels. This study supports current clinical guidelines that discourage routine use of AFP for cancer screening in patients.
with hepatitis C. Hopefully it will lead to less unnecessary testing in time, and of course, fewer referrals to the medical director. Submitted by David S. Williams, MD


Hypnotic drugs, more commonly known as “sleeping pills”, have been associated with increased risks for cancer and death in several published studies. The reason they might be is debatable. It could be a direct adverse effect of the drugs, or possibly an indirect effect caused by sedation and impaired judgment leading to increased accidents and suicides. Or perhaps insomnia and disordered sleep might themselves be the primary cause of increased mortality. These investigators from Scripps Clinic sought to better clarify these risks by comparing the medical records of over 10,000 patients receiving prescriptions for hypnotic drugs with those of over 23,000 matched controls not receiving such prescriptions. Median age in both groups was about 54 years. Mortality data was accumulated using the Social Security Death Index.

After a mean follow-up of 2.5 years, 6.1% of patients receiving hypnotic drug prescriptions had died, compared to 1.2% of those not receiving such prescriptions. Stratifying by multiple co-morbidities and adjusting for multiple variables, the hazard ratios for all-cause death were 3.6 for subjects prescribed 1–18 doses annually, 4.4 for subjects prescribed 18–132 doses annually, and 5.3 for subjects prescribed over 132 doses annually, compared with non-users. These results were similar when the analysis was limited to the two most commonly prescribed hypnotic drugs, temazepam (Restoril) and zolpidem (Ambien). In both cases, a definite dose-response relationship was established. Subjects prescribed over 132 doses annually of any hypnotic drug were also found to be at significantly increased risk for cancer, with a hazard ratio of 1.4 compared to non-users. In sum, receiving a prescription for a hypnotic drug, even less than 18 doses annually, was associated with increased all-cause mortality risk, and receiving a prescription for a much larger number of doses (over 132 annually) was associated with increased cancer risk. This study was not designed in such a way as to prove that the use of these medications cause death and cancer, and the inability to control for confounding variables like mental health impairments may have limited their conclusions. The study does however indicate that there may be some genuine safety concerns regarding the use of these commonly prescribed medications. From our perspective, the use of these drugs usually becomes more of an issue when consideration is given for risk assessments better than standard. The study results and conclusions might suggest that additional caution is warranted in these, and perhaps other, circumstances. Submitted by David S. Williams, MD

PSYCHIATRY


While it is readily accepted that physical ailments especially those which significantly affect morbidity and mortality can lead to depression, can the reverse be true in that psychological distress can cause physical illness? This British study would suggest that to be the case. A total of 68,222 British adults over age 35 were followed for over 8 years. They were free of cardiovascular disease and cancer at the start of the study. The General Health Questionnaire (GHQ) was used to assess their level of distress. The GHQ is a 12-question survey that asks responders to gauge their level of agreement with statements such as: Have you been able to
concentrate on what you’re doing?; Have you lost much sleep over worry?; Have you been able to face up to your problems? Answers that were “not at all” or “no more than usual” were assigned no points. Answers that were “more than usual” or “much more than usual” were given 1 point. The total of the 12 responses were divided into 4 groups: asymptomatic (no points), subclinically symptomatic (1–3 points), symptomatic (4–6 points) and highly symptomatic (7–12 points). Based on these 3 symptomatic groups the adjusted hazard ratios for all cause mortality (as compared to the no points group) were: 1.2 (group 1–3), 1.4 (group 4–6) and 1.9 (group 7 and over). Similar dose-response associations were observed between psychological distress and cardiovascular death and death due to external causes (e.g., injury, poisoning). Only high levels of distress (over 7) were associated with cancer mortality.

While we have certainly accepted that there is a mind-body connection to health, I do not believe anyone expected to find such a high level of physical illness based on stratified psychological distress. This does raise the question of did the distress actually cause the illness or was the distress merely a reaction to a pathological process which had not made a clinical appearance yet? More research would seem to be warranted into this fascinating realm. Submitted by Michael L. Moore, MD