Association of Genetic Variants with Lipoprotein Levels and Cardiovascular Risk¹
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**Background:** Many studies have shown that a reduction in low-density lipoprotein cholesterol (LDL-C) is associated with lower risk of cardiovascular disease. It has been suggested that the reduction of cardiovascular risk is proportional to the reduction in LDL-C. However, cholesteryl ester transfer protein (CETP) inhibitors have not been shown to follow this pattern. These medications increase high-density lipoprotein cholesterol (HDL-C) and lower LDL-C, yet studies show no change in the reduction of risk of cardiovascular events. This raises question that the reduction in cardiovascular risk by lowering LDL-C may be dependent on the mechanism of which LDL-C is lowered.

**Objective:** This study was designed to evaluate the association between lower levels of LDL-C and the risk of cardiovascular events due to genetic variants that code for the target of CETP inhibitors in comparison to the gene code targets of statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

**Study Design:** The study was divided into three separate parts, each with its own objectives that contributed to the final conclusion. The first was a mendelian randomization study of 14 cohort or case-control studies (n=102,837) evaluating the association between CETP variants in genes that encode targets of CETP inhibitors, statins, ezetimibe and PCSK9 inhibitors, changes in LDL-C and apolipoprotein B (apoB) levels, and risk of cardiovascular events.

The second part was another mendelian randomization of the same studies which measured combined exposure to CETP and HMG-coA reductase (HMGR) inhibitors to evaluate changes in lipid and lipoprotein levels, and risk of cardiovascular events. This combination was compared to both HMGR variants and CETP variants alone to determine if CETP effects on lipid changes are modified by HMGR inhibition. The third part of the study included external replication and validation analyses from a total of 48 studies from the coronary artery disease genome meta-analysis plus the coronary artery disease genetics consortium (n=184,305). This study compared variants and changes in LDL-C and apoB levels to assess if risk of cardiovascular events was dependent on the type of cholesterol particle carried.

CETP genetic scores were calculated by the sum of effects on HDL-C for all genetic variants included. Linear regression was utilized to determine the difference between biomarkers, and logistic regression was utilized to determine the associated risk with cardiovascular events.
Safety outcomes were also analyzed, which included analysis was performed separately for each study and then mendelian randomization estimates were obtained to determine the correlation between variants.

Results: The results of the first portion of the study showed participants with higher CETP scores had lower mean CETP activity, resulting in 4.62 mg/dL higher mean HDL-C, 2.15 mg/dL lower mean LDL-C, 1.39 mg/dL lower apoB, and a corresponding lower risk of cardiovascular events (OR 0.964 [95% CI 0.955-0.983] p<0.001).

The results of the second part of the study showed that scores above the median for both CETP and HMGCR variants (analogous to combination therapy with CETP inhibitor and a statin), resulted in a 4.81 mg/dL increase in HDL-C, 2.21 mg/dL decrease in LDL-C, 2.06 mg/dL decrease in apoB, and an overall statistically significant reduction in cardiovascular events (OR 0.946 [95% CI, 0.921-0.972], p<0.001) compared to when both CETP and HMGCR scores below the median. When above median CETP and HMGCR scores were compared to below median CETP and above median HMGCR scores, there was a 4.42 increase in HDL-C, 2.08 decrease in LDL-C, 0.59 decrease in apoB, and no significant difference in cardiovascular events (OR, 0.985 [95% CI, 0.959-1.012]; p=0.26).

In the external validation analyses in the third part of the study, 21 genetic variants were identified that had a discordant reduction in LDL-C and apoB levels, compared to 36 variants that have shown to lower LDL-C and apoB proportionally. The genetic score consisting of the 21 variants was associated with a smaller risk reduction of coronary heart disease (CHD) per 10 mg/dL decrease in LDL-C compared to the risk reduced when including all 36 variants with the same lowering of LDL-C (OR, 0.916 [95% CI, 0.890-0.943] vs 0.831 [95% CI, 0.816-0.847]; P = 2.9 × 10−8 fordifference). The effect of a 10 mg/dL decrease in apoB on CHD in the 21 variants versus the 36 variants was not significantly different (OR, 0.772 [95% CI, 0.701-0.844] vs 0.788 [95% CI, 0.769-0.807]; P = 0.79 for difference).

Conclusions: The study determined genetic variants targeting CETP inhibitors were associated with higher HDL-C levels and concordant reductions in LDL-C and apoB levels, corresponding to a lower risk of cardiovascular events. The analysis suggests that the clinical benefit of lowering LDL-C is dependent on the mechanism in which LDL-C is lowered. The benefit of lowering LDL-C corresponds to the absolute reduction in concentration of apoB containing particles. Therapies such as statins, ezetimibe, and PCSK9 inhibitors that lower LDL-C by reducing the circulating LDL particles, should reduce the risk of cardiovascular events proportional to the absolute reduction in LDL-C, or apoB levels. In contrast, therapies that lower LDL-C without reducing apoB levels will have a decrease in cardiovascular risk proportional to the change in apoB level, not LDL-C.

Key Point: The clinical benefit of lowering LDL-C levels is likely dependent on the reduction in apoB containing lipoprotein particles.

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation
(RE-DUAL PCI)
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Background: Among patients with atrial fibrillation who have CHA2DS2-VASc score of 2 or greater, the 2014 AHA guideline recommends long-term use of an oral anticoagulant to prevent thromboembolic events. In patients with coronary artery disease (CAD) following coronary revascularization including percutaneous coronary intervention (PCI) with stent, dual-antiplatelet therapy (DAPT), which includes aspirin and a P2Y12 inhibitor, is recommended to prevent stent thrombosis. Therefore, in patients with atrial fibrillation who underwent coronary stenting, guidelines recommended triple therapy consisting of DAPT and an oral anticoagulant. Studies have shown, however, that triple therapy can increase major and minor bleeding risk and should be avoided. In order to avoid this bleeding risk, the safety and efficacy of an alternative combination of an anticoagulant and one antiplatelet was studied.

Objective: Compare the use of two regimens of dabigatran and a P2Y12 inhibitor with triple therapy (warfarin-based regimen) among atrial fibrillation patients who underwent PCI.

Study Design: An open-label noninferiority design was conducted at 414 sites in 41 countries. Despite having unblinded participants, primary and secondary endpoints were analyzed by an independent committee who were not aware of treatment groups. Adult patients with nonvalvular atrial fibrillation who underwent successful PCI were included in this study. Patients with renal insufficiency (CrCl <30) or a heart valve complication were excluded. A total of 2725 participants were eligible for this study and randomized to either dabigatran 110 mg twice daily plus a P2Y12 inhibitor, dabigatran 150 mg twice daily plus a P2Y12 inhibitor or triple therapy (warfarin, aspirin and a P2Y12 inhibitor). The primary endpoint was the first major or clinically relevant nonmajor bleeding event. The secondary end-point was a composite efficacy of thromboembolic events, including myocardial infarction,
stroke, systemic embolism, death or unplanned revascularization. The endpoints were analyzed by cox-proportional hazard model with noninferiority margin of 1.38 for upper boundary.

**Results:** A total of 2,725 eligible participants were assigned to one of the treatment groups: 981 participants in dual therapy with dabigatran 110 mg and a P2Y₁₂ inhibitor, 761 participants in dual therapy with dabigatran 150 mg and P2Y₁₂ inhibitor, and 981 participants in triple therapy. The mean duration was 12.3 months. The mean age was 70.8 years. In triple therapy, the mean percentage of in-range INR was 64%.

- **Primary endpoint:** With statistical significance, the incidence of major or clinically nonmajor bleeding events were lower in both groups of dual therapies when compared to the triple therapy group (HR 0.52 [95% CI 0.42-0.63] p<0.001) in dabigatran 110 mg and (HR 0.72 [95% CI 0.58-0.88] p<0.001) in dabigatran 150 mg).

- **Secondary endpoint:** The incidence of composite thromboembolic events was 13.7% in combined dual therapy groups compared with 13.4% in the triple therapy group (HR 1.04 [95% CI 0.84-1.29] p=0.005). In subgroup analysis there was no statistical significance in composite thromboembolic events in either dabigatran 110 mg (HR 1.13 [95% CI 0.90-1.43] p=0.30) or dabigatran 150 mg (HR 0.89 [95% CI 0.67-1.19] p=0.44) when compared with triple therapy.

- **Serious adverse effects:** Serious adverse events were reported in 42.7% of dual therapy patients taking dabigatran 110 mg, 39.6% in dual therapy with dabigatran 150 mg and 41.8% in the triple therapy group.

**Conclusions:** Dual therapy with dabigatran (either 110 mg twice daily or 150 mg twice daily) and a P2Y₁₂ inhibitor showed a significantly lower rate of major and clinically relevant nonmajor bleeding events when compared to triple therapy with warfarin. In addition, the results showed that the incidence of composite thromboembolic events of dual therapies were noninferior to triple therapy with warfarin.

**Limitations:** There were multiple limitations of this study:
1. The noninferiority margin used in this trial was set by FDA for registration trial on non-vitamin K anticoagulation to evaluate its efficacy on stroke and embolism prevention. However, the authors used this margin to calculate sample size and evaluate for safety of the treatments.
2. The original protocol was amended. The composite efficacy endpoint was used as the primary endpoint in the original protocol; however, to adjust sample size number, the protocol was amended and the composite efficacy endpoint was changed to a secondary endpoint. Furthermore, efficacy was inconclusive due to underpower.
3. P2Y₁₂ inhibitors were limited to clopidogrel and ticagrelor in this trial. Additionally, some elderly patients outside the United States were not eligible for dabigatran 150 mg according to their countries’ label.
4. This study included both patients with bare-metal stents and drug-eluting stents in PCI, in which patients with bare-metal stents had a shorter time period on triple therapy than those with drug-eluting stents. Subgroup analysis should be performed.

**Key Point:** Dual therapy with dabigatran could minimize risk of major and clinically relevant nonmajor bleeds in patients with atrial fibrillation who underwent PCI. However, the conclusion from this study should be carefully interpreted based on the study’s limitations.

**Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease³**
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**Background:** Aspirin therapy lowers risk of cardiovascular (CV) events and death and is widely used as a secondary prevention therapy. Yet each year, 5-10% of patients with CV disease have a recurrent event. Treatment with anticoagulants such as warfarin increases risk of bleeding and is not recommended in this setting. Rivaroxaban, a selective direct factor Xa inhibitor used for stroke prevention in atrial fibrillation and treatment or prevention of venous thromboembolism, is another potential therapy for secondary CV prevention.

**Purpose:** The purpose of this study was to determine whether rivaroxaban alone or rivaroxaban plus aspirin would be more effective than aspirin alone for secondary prevention of cardiovascular events.

**Study Design:** This was one of two randomized comparisons in the COMPASS trial, which was double-
is to limit treatment to headaches, so a common conservative recommendation between high doses of abortive agents and worsening We do not have definitive studies showing causality medication needed to cause MOH. consensus pharmacotherapy used; however, there is little criteria for various MOH types based on pharmacotherapy used; however, there is little consensus on the duration of use, amount, and type of medication needed to cause MOH.

We do not have definitive studies showing causality between high doses of abortive agents and worsening headaches, so a common conservative recommendation is to limit treatment to no more than 10 to 15 days per month to prevent headache frequency progression. In addition, medication withdrawal is often recommended as a first step in the treatment of frequent headaches. A recent article in Neurology questioned existing data regarding overuse of medications for headaches with the uncertainty that withdrawing these medications from people with frequent headaches solely to prevent or treat medication overuse headaches may be inappropriate.

Evidence: The argument presented by the recent Neurology article included evidence from studies focused on MOH. One longitudinal population-based study followed individuals with episodic migraines for a year and compared the types of medication used, frequency of medication used, and the frequency of headaches. After controlling for sex, headache frequency and severity, and preventive medication use, researchers found that people with episodic migraines...
who used medication containing opioids or barbiturates were more likely to progress to chronic migraine than the reference group of acetaminophen users. Frequency of medication use by itself was not associated with chronic migraine incidence after controlling for headache frequency, although there was a dose-response relationship for frequency of use of barbiturates. In addition, four studies considered whether MOH occurs when pain medications are used for other conditions. Two of these studies concluded that there was no association between regular or frequent use of medication for nonheadache pain and the development of chronic headache. The other two studies concluded that frequent analgesic use for nonheadache pain was associated with the development of chronic migraine only in those with a preexisting history of migraine. On the other hand, others argue that evidence shows that the majority of patients with MOH improve after discontinuation of the overused medication, as does their responsiveness to preventative treatment. In addition, there have been studies looking at the importance of support for patients during medication withdrawal: one study showed that patients who received support from a headache nurse showed an increased chance of successful withdrawal from medications compared to those without support.

Discussion: The existence of MOH as a diagnostic category and as a potentially modifiable risk factor for headache chronification is well recognized by most headache specialists. However, the concept of MOH and its treatment has been uncomfortable for clinicians as the advice to patients to minimize or discontinue their most needed and likely safest medication is counterintuitive and seems to contradict the goal of minimizing pain. It is difficult to truly study the effects of medication overuse. This type of study would require randomly assigning individuals to overuse or not overuse medication and compare rates of headache progression in the two groups. However, this would be unethical. Observational studies that show an association between frequency or type of medication used and worsening headache can provide useful prognostic information, but cannot answer the question of whether the association is bidirectional. Increased attention to this clinical gray area topic, more research, and available resources to patients and practitioners would be helpful.

Clinical Impact: The topic of MOH has provoked passionate debate among clinicians for years. There is conflicting evidence on appropriate management strategies. In order to best assess and treat patients with MOH, we should consider that characterization of frequently recurring headaches generally requires a headache diary to record information on pain and associated symptoms on a daily basis for at least a month. Sample diaries are available at [http://www.i-h-s.org](http://www.i-h-s.org). Shared decision-making models and a team-based approach are necessary in treating patients with MOH.

Smoking Cessation and Secondary Stroke Prevention

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Background: Many studies have shown that smoking increases risk of stroke, while quitting smoking quickly reduces this risk. However, few studies have shown the effect of quitting smoking after a stroke or transient ischemic attack (TIA) as secondary prevention. The American Heart Association and American Stroke Association guidelines for secondary stroke prevention list smoking cessation as a Class 1 recommendation, however it is only supported by a level of evidence C because of the limited data regarding an association between smoking and recurrent stroke. As research is continuously conducted, more evidence is emerging suggesting that quitting smoking can reduce risk for secondary stroke or TIA.

Evidence: A recent article published in October 2017 by the American Academy of Neurology assessed whether smoking cessation after an ischemic stroke or TIA improves outcomes compared to continued smoking. The study looked at the effect of smoking cessation among participants enrolled in the Insulin Resistance Intervention After Stroke (IRIS) trial. IRIS was a study conducted from 2005 to 2013 involving 3,876 participants from 179 hospitals and clinics in 7 countries. It was a randomized, double-blind, placebo-controlled study. The participants were insulin-resistant, nondiabetic patients with a recent ischemic stroke or TIA. IRIS was designed to test whether pioglitazone, an insulin-sensitizing drug of the thiazolidinedione class, would reduce the incidence of myocardial infarction (MI) and stroke. Patients in the study were followed up for up to 5 years from randomization or to the last scheduled follow-up contact before August 1, 2015, whichever came first. Additionally, IRIS participants were classified according to smoking status at the time of randomization: never smokers, former smokers (stopped smoking before the stroke or TIA event), quitters (quit after the event and not smoking at the time of randomization), or continuing smokers.

The secondary analysis that was completed after the conclusion for the IRIS study was not part of the initial protocol or analysis plan, but was designed after the fact because observational research showed that smoking cessation in patients with established coronary heart disease reduced subsequent all-cause mortality or recurrent cardiovascular events. The primary goal of this secondary analysis was to compare the risk of stroke,
MI, or death in patients who quit smoking versus patients who continued to smoke after their index event. Average follow up occurred at 4.8 years. After this time, stroke, MI, or death had occurred in 60 patients in the quitter group and in 121 in the continuing smoking group, HR 0.66 [95% CI 0.48–0.90]. Death occurred in 23 quitters and 66 continuing smokers, HR 0.49 [95% CI 0.30 – 0.79]. A large difference in death caused by cancer was seen between the quitters group and the continuing smokers. Seven deaths from cancer was seen among the quitters group, compared to 21 among the continuing smokers. This is likely due to the beneficial effects of smoking cessation on reducing cancer risk because at baseline, quitters and continuing smokers had similar cancer and exposure to tobacco histories. Although this study is very compelling, limitations are present. The analysis of the effects of smoking on TIA/stroke was not included in the initial study design and was not the intent of the IRIS trial. This was a secondary analysis of data from a clinical trial which enrolled insulin-resistant, nondiabetic patients; therefore, the results presented in this analysis may not be applicable to all people who have had a stroke and also smoke.

Discussion: The results of these studies suggest that quitting smoking after an ischemic stroke or TIA would decrease the likelihood of a secondary MI, stroke or death in the following 4.8 years. This study supports the guideline recommendations to quit smoking after stroke or TIA to prevent secondary ischemic events. Although the IRIS trial was not designed to study the impacts of smoking on secondary stroke prevention, the outcomes of the analysis show strong correlation between quitting smoking and reducing outcomes of MI, stroke, and death. More studies designed to study these specific outcomes may be beneficial to further confirm the correlation.

Clinical Impact: When counseling patients on ways to reduce risk of a secondary stroke after a primary stroke, smoking cessation should always be a part of that conversation. Utilizing motivational interviewing while discussing various nonpharmacological methods and pharmacological options to tobacco cessation with patients may increase the likelihood of quitting. Education about the risks and benefits of quitting may also improve motivation for quitting tobacco use.

Is Biotin Baffling Your Lab Results?11-13
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Background: Biotin (Vitamin B7) is an over the counter supplement that is commonly used for stronger hair, skin, and nails. The recommended daily intake for biotin is 30 µg for adults, but over the counter supplements often provide as much as 5,000-10,000 µg per dose. Emerging evidence from the Endocrine Society and other professional organizations suggests that this simple water-soluble vitamin may actually be causing interference in common lab results. Biotin is a major component in a number of immunoassays commonly used on hormone markers such as TSH, T4, T3, prolactin, and parathyroid hormone. This is particularly troublesome in thyroid tests where biotin can lead to the false diagnosis of Graves’ disease. Large doses of biotin can cause TSH results to be falsely low and T3, T4, and TSH antibody results can be falsely elevated, which mimics the lab results that are diagnostic for Graves’ disease. Recent reports have described several patient’s being erroneously diagnosed with Graves’ disease despite having no clinical symptoms of the disease based solely on their lab results.

Evidence: A recent study by Lani et al. investigated four different clinical laboratories with different diagnosis systems to see if short-term use of biotin 10 mg (10,000 µg) per day in healthy adults could alter the levels of 11 hormone and non-hormone analytes in six healthy adults. Patients gave blood samples before starting biotin, after a week of taking biotin 10 mg/day, and a week after discontinuation of biotin. Tests included TSH, T4, free-T4, T3, free-T3, parathyroid hormone, prolactin N-terminal pro-brain natriuretic peptide (NT-proBNP) and 25-hydroxyvitamin D (25-OHD). In male patients, they also tested ferritin and prostate specific antigen. Several of the tests found a statistically significant difference in the laboratory results from baseline and after biotin administration. Biotin ingestion was associated with statistically significant false increases in 4 assays: Roche cobas e602 with total T3, free T3, and free T4; and the Siemens Vista Dimension 1500 free T3. Further, it falsely increased the Roche cobas 25-OHD results by a mean of 9.25 ng/mL [95% CI 5.72–12.8 ng/mL; P<0.001] higher than the baseline. Biotin also resulted in a statistically significant decrease with the Ortho Clinical Diagnostics Vitros parathyroid hormone concentrations by about 61% from baseline and pro-BNP levels by an average of more than 13.9 pg/mL. When comparing the serum biotin levels from baseline and a week after biotin discontinuation there was no statistical difference between these two time periods.

Discussion: This study identified that there are some potentially clinically important assay interferences that can occur with biotinylated assays when patients ingest
Implementation of this program involved health system medications. Morbidity and mortality attributed to these high-risk substances, improve patient outcomes, reduce misuse and abuse, and decrease patient morbidity and mortality attributed to these high-risk medications. Implementation of this program involved health system leadership revising policies and procedures in regards to controlled substances throughout the organization. These policies require all patients who have been prescribed controlled substances to provide informed consent, acknowledging the high risks associated with these medications. Patients were also required to sign an annual contract, agreeing to random urine screening for drugs, and a random pill count to verify adherence to prescribed directions. The organization also decided to not prescribe controlled substances to patients using marijuana due to lack of safety support. Apart from these new policies and procedures, a controlled substances initiative (CSI) committee was formed with the intent of improving safe medication usage and reducing opioid-related premature deaths, defined as patients who died before the age of 60 years old. This multidisciplinary committee consisted of physicians, nurse practitioners, a pain specialist, a psychiatrist, a care management social worker, pharmacists and pharmacy residents. The electronic medical record was used to generate a report of patients on high dose opioids for the treatment of chronic pain (100 MME or more per day). Pharmacy residents would review patient cases on a weekly basis and record pertinent information including appropriateness of therapy, previous treatment methods, concurrent mental health conditions, and other comorbid medical conditions in a standardized form. Evidence-based recommendations were made to primary care providers via email for intervention. These recommendations included opioid or benzodiazepine tapers, cognitive behavioral therapy, non-opioid pharmacologic treatment, and osteopathic manipulation. Pharmacy residents would then follow up at 1 and 3 month intervals to assess the implementation of these recommendations.

Results: Since the establishment of this program, 1,300 patient reviews have been completed. The number of

**Pharmacist Involvement in Opioid Stewardship and its Impact in a Small Community Health System**

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CashWise Pharmacy

**Background**: Penobscot Community Health Care (PCHC) is a system of Federally Qualified Health Centers (FQHC) stretching across much of rural central Maine. In 2013, Maine as a state was in the midst of the opioid crisis. From 2011 to 2014, Maine observed a 34% increase in the number of all drug related overdose deaths, and in 2014, 89% of drug overdose deaths involved pharmaceutical drugs. During the same time, at PCHC, the average patient receiving an opioid prescription exceeded a dose equivalent to 290 morphine milligram equivalents (MMEs) per day. The health systems responded with a pharmacist led opioid stewardship program with a focus on population health management to impact the entire community.

**Objective**: The purpose of this study was to share the experiences of patient centered medical home that improved population health management through opioid stewardship, utilizing and leveraging internal resources and external partnerships to create a community-based approach to manage the opioid epidemic.

**Methods**: PCHC responded to the opioid epidemic by developing a comprehensive approach to controlled substance stewardship. Internally, this term was defined as a coordinated effort to promote the appropriate use of controlled substances, improve patient outcomes, reduce misuse and abuse, and decrease patient morbidity and mortality attributed to these high-risk medications. Implementation of this program involved health system leadership revising policies and procedures in regards to controlled substances throughout the organization. These policies require all patients who have been prescribed controlled substances to provide informed consent, acknowledging the high risks associated with these medications. Patients were also required to sign an annual contract, agreeing to random urine screening for drugs, and a random pill count to verify adherence to prescribed directions. The organization also decided to not prescribe controlled substances to patients using marijuana due to lack of safety support. Apart from these new policies and procedures, a controlled substances initiative (CSI) committee was formed with the intent of improving safe medication usage and reducing opioid-related premature deaths, defined as patients who died before the age of 60 years old. This multidisciplinary committee consisted of physicians, nurse practitioners, a pain specialist, a psychiatrist, a care management social worker, pharmacists and pharmacy residents. The electronic medical record was used to generate a report of patients on high dose opioids for the treatment of chronic pain (100 MME or more per day). Pharmacy residents would review patient cases on a weekly basis and record pertinent information including appropriateness of therapy, previous treatment methods, concurrent mental health conditions, and other comorbid medical conditions in a standardized form. Evidence-based recommendations were made to primary care providers via email for intervention. These recommendations included opioid or benzodiazepine tapers, cognitive behavioral therapy, non-opioid pharmacologic treatment, and osteopathic manipulation. Pharmacy residents would then follow up at 1 and 3 month intervals to assess the implementation of these recommendations.

**Clinical Impact**: The Endocrine Society suggests asking patients about any supplements they may be taking, including biotin, when discussing and reviewing laboratory results. They further recommend thorough screening for symptoms of Grave’s Disease and other hormone syndromes to be used in comparison to laboratory results when making a diagnosis for patient. It is also not well established how long a patient should discontinue their biotin supplement before performing the laboratory test. As it is water-soluble, it is thought to wash out of the body quickly. The Endocrine Society was unable to recommend a specific time-frame for discontinuation. However, they acknowledge that even a day off of the supplement can improve the testing results if another diagnostic test cannot be performed.

**From the Pharmacy Press**

**Pharmacist Involvement in Opioid Stewardship and its Impact in a Small Community Health System**

Barbara Truskolawski, PharmD
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patients receiving chronic opioids has decreased by 67.2% from October of 2013 to March of 2017. There was also a 65.6% decrease in the number of patients receiving benzodiazepines during a similar time period. Premature deaths were reviewed to identify associations with opioids prescribed at the time of death. This revealed a decline of 50% (55 cases to 28 cases) between 2013 and 2015.

**Discussion:** This controlled substance stewardship program is a prime example of how health systems of all sizes can implement strong, evidence-based medicine in a protocol to improve patient outcomes and reduce opioid usage. Organizational involvement and investment into this program has led to significant achievements in the quadruple aim of improving health care delivery through enhanced patient experience, improved quality of care, reduced costs, and better provider satisfaction. The authors admit that this initiative was initially met with resistance from both patients and prescribers. Providers that had difficulty bringing up controlled substance use now had tools to rely on; this eased implementation to provide evidence based medicine supported by organization wide policies.

**Weighing in on Amazon’s Entry into the Pharmacy Industry**

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**Background:** Healthcare in the United States has been a hot-button issue following last year’s heated presidential election. Proposed legislation to restructure designated federal funding outlined by the Affordable Care Act (ACA) has been the primary focus of the ongoing debate on Capitol Hill; as these policy changes would have a significant impact on those currently enrolled in ACA plans and the types of healthcare services covered by individuals’ insurance. While the best course of action to improve the health of our nation may be ambiguous, the need for change in the healthcare system is evident. The Commonwealth Fund, a private foundation whose purpose is to promote a high performing healthcare system, recently published a report comparing healthcare across 11 high-income countries. Data shows that the U.S. has spent more on healthcare than any other country in the world since 1980. This amount continues to increase at a disproportionate rate when compared to other developed nations, yet the U.S. consistently ranks low, if not the lowest, in performance rankings such as healthcare access (in terms of affordability), equity (in regards to disparities between low and high income adults), outcomes (i.e. infant mortality, life expectancy) and administrative efficiency (i.e. coverage restrictions).

As the “baby boomers” age, the number of individuals living with chronic disease will continue to increase along with the demand for primary care services. Poor access to primary care contributes to inadequate prevention and management of chronic disease, delayed diagnoses, non-adherence to medication regimens, wasteful use of drugs and technologies, as well as safety concerns and poor coordination of care. There does not appear to be any resolution to the current political stalemate in the near future, but recent events in the private sector may cause enough disruption of the current climate to provide us opportunities to perform at a higher level.

**Recent Events:** Media coverage on Amazon’s entry into the pharmaceutical arena has been picking up steam even though the company has yet to make any official comment. The online retail giant purchased Whole Foods® earlier in June, offering the company its first physical presence. Amazon continues to attract attention from news outlets as evidence continues to be uncovered and suggest the rumors are true, further fueling speculation on the impact they could have on drug distribution. Journalists have also started to discuss Amazon’s potential to shake things up in managed care, and other developments indicate some pharmacy benefit manager (PBMs) are already feeling the pressure from the potential competitor. While shares of drug store chains have dropped sharply in recent weeks, CVS Caremark began merger talks with Aetna and made an announcement in November of 2017 that its pharmacies will offer next-day delivery of prescriptions (and even same-day services in some big cities) as early as December 2017.

**Discussion:** Health leaders are faced with a difficult task when it comes to developing a strong strategic plan given the uncertainty of the current and future climate of healthcare. Predicting the many possible landscapes that could result from a disruption can only help to prepare those in the industry to effectively utilize the new environment to innovate the way healthcare is provided. Leading change efforts that drive innovation in the delivery of care should focus on improving upon identified weaknesses as well as preparing for anticipated needs of the system. Meeting the demands of healthcare’s current needs will provide a favorable environment to assist patients with meeting their health goals.

The debate continues whether or not Amazon will actually enter the prescription marketplace due to the logistical barriers imposed by the numerous and
complex regulatory requirements, which can vary from state to state. However, many healthcare experts offer opinions on Amazon's potential to create waves throughout the industry. Amazon strives to stay true to its mission of supplying consumers with a desired product at the lowest possible price and the utmost convenience. The new physical space, potential buying power, and distribution system provide the business an opportunity for optimizing the distribution and dispensing of prescription medications if able to overcome the expected barriers. Of the current 300,000 pharmacist workforce, there is an abundance working in practice settings overburdened by dispensing tasks and administrative duties. These demanding responsibilities often prevent pharmacists from utilizing their expertise and clinical knowledge based in the pharmacology and pharmacotherapy of drug therapies. If the medication dispensing process is able to be optimized and reduce pharmacist workload, it will provide the profession appropriate opportunities to fulfill the current need for primary care services.

Continuous Blood Glucose Monitoring in a Flash21-23
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Background: On September 27, 2017, the U.S. Food & Drug Administration announced the approval of the FreeStyle Libre Flash Glucose Monitoring System (FSL-CGM), the first continuous glucose monitoring system which does not require a blood sample for calibration, thereby reducing the need for fingerstick testing in patients with diabetes. Most CGM systems on the market currently require at least two fingersticks per day. Prior to approval, the FDA evaluated data from a clinical study to review the device’s performance compared to laboratory analysis of blood glucose values. The device has been approved for use in other countries since 2014.

How to Use: The FSL-CGM comes factory calibrated. Some patients may still use the results of fingerstick tests to assist in calibration of their meter and confirm their FSL-CGM blood glucose readings; however, it is not necessary. Fingersticks are required for treatment decisions when the “Check Blood Glucose” symbol appears on the device, when symptoms do not match the system's readings, when readings are suspected to be inaccurate, or when experiencing symptoms due to high or low blood glucose. The fingerstick reading does not have to be on a FreeStyle product. The FSL-CGM comes with a blood glucose monitor and small, round quarter-sized sensor worn on the upper arm. The sensor has a small wire that is inserted into the skin in order to allow for continuous blood glucose measurements. A handheld mobile reader is moved over the sensor to obtain real-time glucose reading. The mobile reader illustrates trends with a directional arrow and allows review of data for the past 8 hours.

Previously, this data was only retrievable by healthcare professionals, but now FSL-CGM users can view the data themselves. The FSL-CGM is specifically intended for use in patients 18 years of age and older. The sensor can be worn for 10 days prior to need for replacement (approved to be worn up to 14 days in other countries). The waterproof sensor is fully disposable and can be worn while showering and swimming. The sensor is water-resistant in up to three feet of water for a maximum of 30 minutes.

Cost: FSL-CGM will require a prescription in the U.S and will be available in major retail pharmacies across the U.S. by the end of 2017 according to the manufacturer, Abbott Diabetes Care Inc. The expected cost will be around $120 per month for three sensors, the handheld reader will be a one-time purchase of around $60. Patients and providers can sign up on the manufacturer's website to determine when the FSL-CGM will be available at their nearest retail pharmacy.

Welcome to the Quadruple Aim24-31
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Quadruple Aim
The Triple Aim of improving patient experience, population health, and reducing cost have been the guiding principles of healthcare professionals and institutions for decades. More recently however, the need for a fourth, additional aim has become increasingly apparent. The Quadruple Aim retains the original three ideals, but adds caregiver health and wellness. It's a well-known fact that caregiver burnout can decrease patient satisfaction, decrease quality of care, and increase cost, jeopardizing all three original aims. Professional burnout is characterized as feelings of cynicism, low sense of accomplishment, and loss of enthusiasm for work. These feelings are associated with early retirement, depression, and substance abuse. Unfortunately burnout does not discriminate against health care location or specialty of practice.
Approximately 46% of physicians report at least one symptom of burnout. Even more upsetting is that in a 2014 survey, 68% of family physicians and 73% of general internists would not choose the same specialty if they could start their careers anew.

Costs of Burnout
Provider burnout is a major contributor to turnover and is one of the largest factors when deciding to leave a position. All this turnover results in both direct and indirect costs including lost revenue while recruiting and onboarding, and lag time before the provider is efficient in their role. It is estimated that the cost of replacing a physician is about 2-3 times their annual salary. Additionally, the lost billing revenue from an unfilled provider role can be upwards of $990,000. While institutions are aware of these potential losses of revenue, they often overlook them, relying on a new pool of residents and fellows that will command a junior level faculty salary. The largest financial impact is the impact that burnout has on provider productivity. In a study of 2,500 physicians at Mayo Clinic, increases in provider burnout resulted in a 30-50% decrease in work effort over the following 2 years.

Addressing Burnout Return on Investment (ROI)
Efforts to reduce burnout can positively impact the financial bottom line. If an organization employs 450 physicians with an annual turnover of 7.5%, where typical replacement costs are $500,000 per provider, this results in $16.9 million annually on replacing physicians. Not all turnover is related to burnout, but burned-out providers are 50% more likely to quit and have a burnout prevalence of 50%. Therefore, burnout is likely contributing 2.5% to the total 7.5% turnover rate. Potentially, if burnout was addressed, this institution would experience an overall 5% annual turnover. The organization could dedicate one million dollars towards an intervention to reduce burnout from 50% to 40% (20% RRR) of providers, which would be expected to reduce turnover by 0.5% (20% RRR). The result is an ROI of $1.125 million or 12.5% on the initial expenditure. Even more promising is that this ROI does not account for revenue loss from reduced productivity among burned out physicians that don’t leave their role. With a growing body of evidence regarding the cost of provider burnout it may become difficult for even the most business-minded to deny that there is real money in reducing burnout, and improving provider satisfaction. As we begin to better understand the ROI from addressing provider burnout, the more the Quadruple Aim is poised to become the new standard.

The Promise of SGLT-2 Inhibition in Heart Failure
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Recent studies have demonstrated that antidiabetic agents can significantly reduce cardiovascular risk, but only sodium-glucose cotransporter 2 (SGLT2) inhibitors can reduce the risk of the development or progression of heart failure. Two large studies examining empagliflozin (EMPA-REG Outcomes) and canagliflozin (CANVAS) support this finding. In the EMPA-REG trial, statistically significant decreases in hospitalization for heart failure, incidence of heart failure, and use of newly-prescribed loop diuretics were observed. The CANVAS trial found a decrease in the hospitalization for heart failure, however this was not considered statistically significant. While these studies and other existing data support the ability of SGLT-2 inhibitors to prevent heart failure, there is no data on their ability to treat patients with established heart failure.

SGLT-2 inhibitors do not appear to exhibit their cardioprotective effects through glucose reabsorption. The most common proposed mechanism is diuresis. Certain diuretics reduce the incidence of heart failure in patients at increased cardiovascular risk through their short-term increase in urine volume, followed by a sustained decrease in systolic blood pressure. In addition to these effects, SGLT-2 inhibitors have sustained reduction of body weight and plasma volume, without electrolyte disturbances. These important differences imply that SGLT-2 inhibitors do not simply act as conventional diuretics.

The cardioprotective effects of SGLT-2 inhibitors are better explained through natriuresis caused by inhibition of sodium-hydrogen exchangers (NHE3) in the kidneys and heart. The activity of NHE3 is increased in heart failure and believed to be responsible for resistance to diuretics and endogenous natriuretic peptides. In the kidneys, SGLT-2 inhibitors primarily act on the proximal tubule to reduce cardiac wall stress through natriuresis, hemococoncentration, and decreased body weight and blood pressure. SGLT-2 is not expressed in the human heart, but inhibition of SGLT-2 has been found to slow the development and progression of cardiac hypertrophy and cardiomyopathy in animal models.

While studies support the benefit of SGLT-2 inhibition in preventing heart failure, further studies are needed to determine if they have a role as adjunctive treatment in patients with established heart failure.
**Shingrix® (zoster vaccine recombinant, adjuvanted), developed by GlaxoSmithKline**

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**Indication:** On October 20, 2017, the Federal Drug Administration (FDA) approved the zoster recombinant adjuvanted vaccine for prevention of herpes zoster (shingles) in adults aged 50 years and older.

**Mechanism of Action:** The recombinant zoster vaccine contains varicella zoster virus glycoprotein E antigen and an adjuvant to induce an active immune response to the varicella-zoster virus.

**Dosage and Administration:** The vaccine powder product will require reconstitution with a supplied adjuvant suspension prior to administration. Each injection is 0.5 ml, given intramuscularly. This vaccine is a two dose regimen with the two doses given two to six months apart, different than the previous one dose live attenuated zoster vaccine (Zostavax®).

**Effectiveness:** The recombinant zoster vaccine has proven to be effective in patients 50 to 70 years of age and in patients greater than 70 years of age by reducing the incidence of herpes zoster by approximately 97% and 91%, respectively. When compared to the live attenuated vaccine, the recombinant zoster has better efficacy data. The live attenuated vaccine reduced the incidence of herpes zoster by approximately 70%, 64%, 41% and 18% in patient ages 50 to 59, 60-69, 70-79 and 80 or older, respectively. Additionally, patients 70 years of age or older who previously had herpes zoster (shingles) and then received the recombinant zoster vaccine had an approximate 89% reduction in post-herpetic neuralgia. The duration of efficacy remained at approximately 85-93% after 4 years. This vaccine is not intended as treatment for herpes zoster active infection, nor is it indicated for varicella infections.

**Safety:** As with any intramuscular injection, pain, erythema or swelling at the injection site is possible. Patients should be monitored for anaphylaxis and syncope for 15 minutes following administration. The FDA has acknowledged the commitment of GlaxoSmithKline to conduct future studies assessing long term efficacy, immunogenicity and safety of the zoster recombinant adjuvanted vaccine.

**Place in Therapy:** The Advisory Committee on Immunization Practices (ACIP) voted to recommend the recombinant adjuvanted zoster vaccine for 1) the prevention of herpes zoster and related complications for healthy adults age 50 years and older, 2) for adults who previously received the live attenuated shingles vaccine, and 3) as the preferred vaccine for shingles prevention. This third recommendation of preference for the recombinant adjuvanted zoster vaccine over the previous live attenuated zoster vaccine narrowly passed by one vote whereas the other recommendations were very clearly determined. These recommendations will become official policy once approved by the CDC director and published in the Morbidity and Mortality Weekly Report. The recommendations will be included in the 2018 adult immunization schedule. Product availability is anticipated in quarter four of 2017 and the AWP is $168.00 for one vial.

**References**

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