Statins for Primary Prevention of Cardiovascular Events and Mortality in Older Adults

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Background: The efficacy of statins for secondary prevention of cardiovascular events in older patients is well established. However, less is known regarding the benefits of statins in older adults with no history of atherosclerotic cardiovascular disease (ASCVD). This uncertainty also holds true for those with type 2 diabetes, a notable risk factor for ASCVD. Age itself is a risk factor for ASCVD, and it is estimated that ASCVD incidence and mortality rates are almost three times higher in those over age 74 years than in younger adults. As both the population’s longevity and statin prescriptions in older adults are increasing, it is imperative to determine whether statins benefit older adult patients with or without type 2 diabetes.

Objective: To determine whether statin use is linked to incidence of ASCVD and all-cause mortality in older adults (defined as 75 years and older) with or without type 2 diabetes.

Study Design: Authors utilized the Spanish Information System for Development of Research in Primary Care (SIDIAP) database to conduct this retrospective cohort study. Subjects included all registered persons age 75 years and older between July 2006 and December 2007. Notable exclusion criteria included ASCVD history, medications for cardiac diseases, type 1 diabetes, and prior lipid lowering treatment. “Statin non-users” were compared to “statin new users” (defined as having initiated a statin in the previous 18 months), and data was stratified according to the presence of type 2 diabetes. Information collected included age, sex, blood pressure, body mass index, vascular risk factors, comorbidities, lipid panel, cholesterol reduction capacity of statin (if applicable), and other medications. Of note, statin adherence rate was not assessed. Multiple imputations were performed for any missing data. Primary outcomes were all-cause mortality and ASCVD, defined as a composite of coronary heart disease and stroke. A simulated intention-to-treat method was used, which prevented a subject from switching study groups despite any changes in statin treatment. A parallel statistical analysis was performed by stratifying subjects by the following age groups: old (75-84 years) and very old (≥85 year).

Results: The study population included 46,864 persons, including 7,502 (16%) “statin new users.” Among all subjects, 7,880 (17%) had type 2 diabetes.
diabetes. The majority (>70%) of statin new users took statins considered to have “moderate” cholesterol lowering capacity (defined as a 31-40% reduction). Of note, numerical baseline rates of hypertension, hypercholesterolemia, obesity, tobacco use, and concurrent medication use (including aspirin and beta blockers) were greater in the diabetes group; however, this did not translate to any statistically significant baseline differences between groups. Median follow-up was 5.6 years. In the non-diabetes group, there was no significant difference in ASCVD or all-cause mortality between statin non-users and statin new users in either age group. In the diabetes group, there was a 24% reduction in ASCVD (HR 0.76 [95% CI 0.65 - 0.89]) and a 16% reduction in all-cause mortality (HR 0.84 [95% CI 0.75 - 0.94]) in statin new users age 75-84 years. No significant difference in ASCVD risk or all-cause mortality was seen in subjects with diabetes and age ≥85 years.

**Conclusions:** In participants age 75 years and older, statin use did not confer a reduction in ASCVD or all-cause mortality. In those with type 2 diabetes and age 75-84 years, statin use significantly decreased the incidence of ASCVD and mortality; however, this benefit was not seen in patients age 85 years and older. Of note, the trial involved older patients initiated on statins, thus data may not apply to patients continuing statin therapy that was initiated at a younger age. Further, the authors note that LDL cholesterol was low at baseline in patients with diabetes (ranging from 54 to 66 mg/dL among subgroups). Thus, study results bring to question potential for harm in treating to very low LDL levels. In addition, the trial population primarily consisted of those living in Spain, thus potential differences in other ethnic groups should be considered.

**Key Points:** Regarding primary prevention in older patients, initiating a statin may provide ASCVD and mortality benefit for those age 75-84 years with type 2 diabetes. Initiating a statin in patients without diabetes age 75 years and older or in patients with diabetes age 85 years and older is unlikely to provide cardiovascular or mortality benefit. Overall, shared decision making between patient and care team is essential any time statin therapy is considered in an older patient.

**The Role of Vitamin D Levels in Patients with Painful Diabetic Neuropathy**

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**Background:** Low vitamin D levels have been linked to numerous health conditions including diabetic peripheral neuropathy (DPN). Vitamin D’s role in pain may be attributed to its action in the small nerve fibers of the dorsal root ganglia.

**Purpose:** The study by Shillo et al. sought to further differentiate patients with painful and painless neuropathy to investigate if there was a significant difference in 25-hydroxyvitamin D levels in patients with differing severities of DPN.

**Study Design:** The study included 59 white Europeans into four groups – patients without diabetes (n=14), Type 2 diabetes with no neuropathy (n=14), painless DPN (n=14), and painful DPN (n=17). Patients were placed in the different groups using standardized neuropathy assessment tools. Participants completed a sunlight exposure questionnaire, vitamin D assay, and skin biopsy procedure.

**Results:** Compared to healthy volunteers and the no-DPN and DPN groups had a higher mean BMI (P=0.02, DPN M=32.8 mg/kg², no-DPN M=30.1 mg/kg², healthy M=26.1 mg/kg²), were older (P=0.009, DPN M=61.8 years, no-DPN=55.4 years, healthy M=52.1 years), and had longer median duration of diabetes (DPN m=15 years, no-DPN m=6.5 years); but there were no significant differences in HgbA1c or estimates of sunlight exposure between groups (P=0.63). After adjusting for age, BMI, activity score and sunlight exposure, vitamin D levels were significantly lower in the 17 participants with painful DPN (P=0.03). Skin biopsy data revealed a significant positive correlation between sub-epidermal nerve density and vitamin D levels (P=0.01, r=0.42) indicating those with the lowest nerve fiber density had the lowest vitamin D levels. Researchers additionally found a significant negative correlation between vitamin D levels and pain scores; meaning people with the highest pain scores had the lowest serum vitamin D levels (P=0.02, r=-0.3).

**Conclusion:** The results demonstrated that patients with lower nerve fiber density had lower vitamin D levels. Clinically, those with painful DPN had the lowest vitamin D levels. Results may suggest a role for vitamin D supplementation in painful DPN compared with painless DPN as indicated by lower serum vitamin D levels.

**Key Point:** Additional research is needed to determine if supplementation with vitamin D helps improve the severity of painful DPN.

**Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients**

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**Background:** Obesity is associated with several other medical conditions including hypertension, coronary artery disease, heart failure, type 2 diabetes, and dyslipidemia. Lorcaserin, a selective agonist of the 5-hydroxy-tryptamine 2C serotonin receptor (5-HT2C), in conjunction with a reduced calorie diet and increased physical activity has shown efficacy for weight loss. Yet, the cardiovascular safety of lorcaserin in overweight or obese patients is not known.

**Objective:** The cardiovascular and metabolic effects of lorcaserin in overweight and obese patients-thrombolysis in myocardial infarction 61 trial (CAMELLIA-TIMI 61) was designed to measure the cardiovascular and metabolic safety and efficacy of lorcaserin in overweight or obese patients with high cardiovascular risk.

**Study Design:** CAMELLIA-TIMI 61 was a multisite trial enrolling participants in eight countries. Study participants had a body mass index (BMI) ≥27, were willing to comply with reduced caloric diet and increased physical activity regimen, and had established cardiovascular risk. Cardiovascular risk was defined as either 1) age ≥40 years with established cardiovascular disease (history of myocardial infarction, ischemic stroke, revascularization, peripheral artery disease, or significant unrevascularized coronary artery stenosis), or 2) women age ≥55 years or men age ≥50 years with type 2 diabetes, without established cardiovascular disease, but at least one additional cardiovascular risk factor (hypertension, dyslipidemia, impaired glomerular filtration rate (GFR), high sensitivity C-reactive protein (hsCRP) >3 mg/L, or urinary albumin-to-creatinine ratio (ACR) ≥30 µg/mg). Randomization to either lorcaserin 10 mg twice daily or matched placebo was double-blind and stratified by cardiovascular disease status. All participants were strongly encouraged to participate in a weight management program (behavioral therapy with dietary and exercise guidance).

The primary safety composite outcome of major cardiovascular events was defined as either cardiovascular death, myocardial infarction, or stroke. The primary cardiovascular efficacy outcome was also composite, including cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or any coronary revascularization. Statistical analysis was performed using the intention-to-treat method. The non-inferiority margin was set at 1.4 for lorcaserin v. placebo.

**Results:** A total of 12,000 participants were randomized, with 64.2% being male and an overall high burden of coexisting conditions such as hypertension, hyperlipidemia, diabetes and chronic kidney disease. The median age was 64 years and median BMI was 35. The median follow-up period was 3.3 years. At the time of trial completion, the primary safety outcome of major cardiovascular events had occurred in 364 patients in the lorcaserin group (6.1%) and 369 patients in the placebo group (6.2%), HR 0.99 [95% CI 0.85 - 1.14] for non-inferiority. The primary efficacy outcome result for lorcaserin v. placebo was HR 0.97 [95% CI 0.87 - 1.07]. Considering weight changes, the difference in weight loss between study arms was -1.9 kg at 40 months, remaining significant. Participants in the lorcaserin arm had -4.0 kg weight change and participants in the placebo arm had -2.1 kg weight change. Majority of the participants who discontinued prematurely, 12% per year in the lorcaserin and 12.7% per year in the placebo group, stopped because of patient choice unrelated to an adverse event. However, dizziness, fatigue, headache, diarrhea, and nausea were the most commonly reported side effects that resulted in trial discontinuation.

**Conclusions:** Lorcaserin demonstrated non-inferiority for cardiovascular safety when compared to placebo in the CAMELLIA-TIMI 61 trial. Therefore, lorcaserin may be an optimal therapy choice for weight management overweight or obese patients with established cardiovascular disease or multiple risk factors for cardiovascular disease.

**Key Point:** Lorcaserin is an effective pharmacotherapy option for weight management in high cardiovascular risk patients with BMI ≥27 who are also committed to non-pharmacotherapy improvements, with no significant difference in cardiovascular safety outcomes when compared with placebo.

**Cost-Effectiveness of a Pharmacogenetic Test to Guide Treatment for Major Depressive Disorder**

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**Background:** Major depressive disorder (MDD) is a complex, yet commonly diagnosed medical condition. Signs and symptoms can range from decreased energy to difficulty concentrating and persistent feelings of hopelessness that directly impacts patients’ daily living activities. Suicide rates are higher for patients with treatment-resistant depression (0.16%) than patients who responded to therapy (0.09%). There are numerous pharmacotherapeutic options available to treat MDD which are selected based on specific patient factors, costs, and provider comfortability. More recently, pharmacogenomics have been utilized to further individualize MDD therapy by identifying possible genetic
profile-drug interactions, thus increasing the response rate.

Objective: The authors investigated the use of IDgenetix (IDGx) pharmacogenetic testing prior to initiating pharmacotherapy and compared this approach to medication management, the current standard of care (SOC), to determine which process was more cost-effective and had higher rates of successful treatments. Study Design: Authors collected data from a large prospective, multicenter, randomized control trial of patients with inadequately controlled MDD who received either IDGx or SOC. The study evaluated the effects of poorly treated and untreated disease burden on quality-adjusted life-years (QALYs), total costs (direct and non-direct), and suicide rates over a three-year period. Researchers utilized the 17-item Hamilton Rating Scale for Depression to determine the severity of depression. Utility scores were also obtained from a previous study through a standardized tool used to measure generic health outcomes and examine cost-effectiveness with new treatments among responders and non-responders. Univariate, one-way sensitivity analyses were performed based on 95% confidence intervals for response rates, suicide rates, and utility scores.

Results: Results were favorable for patients with moderate to severe MDD who had received IDGx prior to clinician initiating pharmacotherapy in terms of QALYs, costs to patients, and response rates. After a period of three years, the model estimated a score of 2.07 QALYs for IDGx group compared to that of 1.97 QALYs for SOC group. The probability of death from suicide was also lower with the IDGx group [0.328%] than the SOC group [0.351%]. Overall cost in the three-year period ($44,697) was lower for IDGx group than SOC group even factoring in the initial cost of $2,000 for the pharmacogenetic testing to be performed. Conclusions: Based on QALYs and death from suicide rates, it is estimated that 4,300 patients would need to be tested to prevent one death from suicide. This is significant as 6.7% of the United States population is affected by MDD. It is estimated that IDGx application can prevent 5,000 deaths from suicide which would approximately be a 12% reduction. The initial cost of $2,000 for IDGx may deter some patients and clinicians from initiating the tests. However, these costs can be recovered within two years. The use of pharmacogenetic testing can further help clinicians successfully select the appropriate antidepressant therapy to minimize side effects while maximizing response rates and reducing costs.

Key Point: When treating patients with moderate to severe major depressive disorder, pharmacogenetic testing can help improve the quality of life and minimize healthcare costs. Pharmacists should be aware of the implications with this expanding tool and expect its use to be more widespread in the coming year.

Updated Guidelines for Management of Hyperglycemia in Type 2 Diabetes

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Background: The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have issued a consensus report outlining the management of hyperglycemia in type 2 diabetes mellitus (T2DM). Although the ADA 2018 Standards of Medical Care in Diabetes guidelines recommended empagliflozin and liraglutide in patients with T2DM and established cardiovascular disease (CVD), the ADA/EASD consensus report goes further by providing a new approach to diabetes care in the context of comprehensive cardiovascular risk management.

Evidence: The ADA/EASD consensus report was issued after a systematic evaluation of literature published from January 1, 2014 to February 28, 2018. A comprehensive search was conducted on PubMed for randomized clinical trials, systematic reviews, and meta-analyses that examined the effectiveness or safety of pharmacological or nonpharmacological interventions in adults with T2DM.

Discussion: This report outlines an approach to glucose lowering in T2DM that takes into consideration patient specific factors and new evidence for the benefit of specific medications to reduce mortality, heart failure (HF), and progression of renal disease in the setting of established CVD. Patient centered care, diabetes self-management and education support, and metformin as first-line therapy are recommended for all patients with T2DM.

For patients with T2DM and established CVD, sodium-glucose cotransporter-2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonists (GLP-1 RA) with proven CVD benefit are recommended. If HF or chronic kidney disease (CKD) predominates then an SGLT2i with evidence of reducing HF and/or CKD progression is preferred over a GLP-1 RA with CVD benefit. Evidence of CVD benefit is liraglutide > semaglutide > exenatide.
extended release for GLP-1 RA, and empagliflozin > canagliflozin for SGLT2i. Liraglutide and empagliflozin are FDA approved for the reduction of cardiovascular events in patients with diabetes and CVD. Both empagliflozin and canagliflozin have shown reductions in HF and CKD progression.

For patients with T2DM and without established CVD or CKD, treatment decisions are guided by other patient specific factors. For those concerned with weight loss, a GLP-1 RA or SGLT2i is recommended. Evidence for weight loss among GLP-1 RA is semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide. For those concerned with minimizing hypoglycemia, medication options include GLP-1 RA, SGLT-2i, dipeptidyl peptidase 4 inhibitors (DPP-4i), or thiazolidinediones (TZD). For those concerned with cost, a sulfonylurea or TZD is recommended.

Clinical trials within each drug class have been heterogeneous and it is not clear whether benefits in CVD, HF, CKD, and weight loss are drug-class effects. Clinical trials may have different findings for individual medications due to differences in trial design and conduct, or there may be real differences between medications within a drug class due to properties of the individual compounds.

In patients who need an injectable medication, GLP-1 RA are the preferred choice to insulin. GLP-1 RA have a lower risk of hypoglycemia, are associated with weight loss, and some are available as once weekly injections. Insulin requires at least daily injections, is associated with weight gain, and has a greater risk of hypoglycemia. Trials comparing GLP-1 RA and insulin (basal, premixed, or basal-bolus) show similar or even better efficacy in HbA1c reduction. However, Insulin is still recommended for patients with extreme and symptomatic hyperglycemia.

Clinical Impact: CVD is the leading cause of death in patients with T2DM. Diabetes confers substantial independent CVD risk, and most patients with T2DM have additional risk factors such as hypertension, dyslipidemia, obesity, physical inactivity, CKD, and smoking. The T2DM treatment algorithm outlined in this guideline incorporates new evidence that specific SGLT2i and GLP-1 RA improve CVD, HF, and CKD outcomes in patients with established CVD or CKD.

Aspirin for Primary Prevention7-13

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Background: Aspirin is commonly used to reduce the risk of cardiovascular events. Use in secondary prevention is well established, while primary prevention has been controversial. Currently, guidelines are recommending aspirin therapy for primary prevention if patients have diabetes and/or an additional risk for cardiovascular disease (CVD) such as ≥10% 10-year risk of CVD, family history of CVD, hypertension, dyslipidemia, and smoking. However, Zhang et al. concluded patients with diabetes on aspirin therapy did not reduce the risk of CVD without increasing the risk of major bleeding. After reviewing five additional studies on primary prevention of CVD and colorectal cancer (CRC), the U.S. Preventive Services Task Force (USPSTF) updated their recommendations to recommend aspirin for primary prevention with increased risk of CVD. New studies have been published looking at aspirin therapy for primary prevention: ASCEND, ASPREE, and ARRIVE trials.

Evidence: A 2009 meta-analysis by Zhang et al. reviewed seven prospective randomized controlled trials comparing aspirin therapy to placebo in patients with diabetes for primary prevention. Aspirin therapy non-significantly reduced major cardiovascular (CV) events (RR 0.92 [95% CI 0.83-1.02]; P=0.11), all-cause mortality (0.95 [95% CI 0.85-1.06]; P=0.33), CV mortality (0.95 [95% CI 0.71-1.27]; P=0.71), stroke (0.83 [95% CI 0.63-1.10]; P=0.20), and myocardial infarction (MI) (0.85 [95% CI 0.65-1.11]; P=0.24). Aspirin also non-significantly increased the risk of major bleeding (2.46 [95% CI 0.70-8.61]; P=0.16).

The ASPREE trial was a randomized controlled trial that compared enteric-coated aspirin 100 mg once daily to placebo in 19,114 participants who were ≥70 years (≥65 years in African American or Hispanic populations) with no history of CVD, dementia, or disability. After five years, aspirin therapy was found to have no significant difference on the primary composite outcome (death, dementia, or persistent physical disability) (1.01 [95% CI 0.92 - 1.11]; P=0.79) or reducing CV events (0.95 [95% CI 0.83 - 1.08]). Subgroup analysis also resulted in non-significant differences. Aspirin did significantly increase the risk of major bleeding (1.38 [95% CI 1.18 - 1.62]; P<0.001) and risk of death from any cause (1.14 [95% CI 1.01 - 1.29]).

The ASCEND trial was a randomized controlled trial that compared enteric-coated aspirin 100 mg once daily to placebo in 15,480 participants who were ≥40 years with diabetes and no history of CVD. After a mean follow-up of 7.4 years, aspirin significantly reduced the risk of serious vascular events (0.88 [95% CI 0.79 - 0.97]; P=0.01). However, the risk of major bleed was also significantly greater in aspirin group (1.29 [95% CI 1.09 - 1.52]; P=0.003).

The ARRIVE trial was a randomized controlled trial that compared enteric-coated aspirin 100 mg daily to placebo
in 12,546 participants who were men ≥55 years with two to four CV risk factors and women ≥60 years with three or more CV risk factors. After a five year follow-up, there was a non-significant difference in composite CV event rate (0.96 [95% CI 0.81 to 1.13]; P=0.6038). The risk of gastrointestinal (GI) bleed significantly increased (2.11 [95% CI 1.36 to 3.28]; P=0.0007). There was a non-significant difference in the GI bleed event rate compared to the expected event rate.

**Discussion:** The USPSTF has a grade B recommendation to start low dose aspirin for primary prevention of CVD and CRC in adults 50 to 59 years old with ≥10% 10-year CV risk who also have a low bleed risk, life expectancy of at least ten years, and the desire to take aspirin. The USPSTF has a grade C recommendation to consider the risk and benefits individually in 60 to 69 years old with ≥10% 10-year CV risk. The meta-analysis by Zhang et al. concluded non-significant differences in all outcomes between aspirin and placebo therapy. However, meta-regression to appraise the impact of gender suggested a potential risk reduction of stroke in women with diabetes and MI in men with diabetes. For this reason, more research is needed to understand how gender may impact MI and stroke risk with aspirin therapy. The ASPREE trial found aspirin to significantly increase the risk of major bleeding and risk of death. The researchers suggested cancer to confound the high mortality rate in the aspirin group. The ASCEND trial found a significant reduction in vascular events and increased risk of bleeding events. A limitation to the ARRIVE study was the underestimation of CV risk. The study aimed for patients with a moderate 10-year CV risk score. Instead, the study population had a low CV risk. There was no reduction in CV events with aspirin therapy, and yet there was a two-fold risk of GI bleeding.

**Clinical Impact:** From the new primary prevention studies, there is insufficient evidence to support the use of aspirin in primary prevention for patients ≥70 years or patients without diabetes and an estimated 10-year CV risk score <20% and a high bleed risk. There may be a shift in aspirin therapy in primary prevention of CVD guideline recommendations in the future.

**A Closer Look at the Updated 2018 Chest Guidelines Expert Panel on Atrial Fibrillation**

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**Background:** In 2012, authors of the CHEST guidelines recommended vitamin K antagonists (VKAs) as the mainstay treatment for atrial fibrillation (AF). In 2018, the CHEST guidelines were updated to include direct oral anticoagulants (DOACs) as the preferred treatment option in patients with AF in valvular heart disease (VHD), excluding those with mechanical heart valves and those with significant mitral stenosis. Now, there is more evidence showing DOACs are better at preventing hemorrhagic stroke and embolic events compared to VKAs. In addition, patients should be stratified for risk of stroke by calculating their CHA2DS2-VASc. When considering VKAs, a validity tool known as the SAME-TT2R2 should be calculated.

**Evidence:** A subanalysis of the ROCKET-AF study examined outcomes for patients based on valve disease location, specifically comparing aortic stenosis to mitral regurgitation or aortic regurgitation. Although stroke or side effects occurred twice as often in the aortic stenosis group (4.21 events/100 patient-years) compared to the mitral regurgitation group, the aortic regurgitation group, and the non-VHD group (2.01 events/100 patient-years; P<0.05 and 2.09 events/100 patient-years; P=0.05 respectively), the efficacy of rivaroxaban was consistent among those with or without VHD.

The ARISTOTLE trial excluded patients with moderate or severe mitral stenosis and those with mechanical prosthetic heart valves. For subanalysis comparison, 4,808 (26%) patients had a history of moderate or severe VHD, the majority being mitral regurgitation. Patients with VHD were older (71 vs 69 years; P < 0.0001), more likely to have heart failure (48.6% vs 30.7%; P<0.0001), and less likely to have hypertension (85.3% vs 88.2%; P < 0.0001) and diabetes (22.6% vs 25.8%; P < 0.0001) when compared to the warfarin group. Apixaban efficacy was similar in prevention of stroke or side effects in those with VHD (1.46% apixaban vs 2.08% warfarin; HR 0.70 [95% CI 0.51-0.97]) compared with those without VHD (apixaban 1.20% vs 1.43% warfarin; HR 0.79 [95% CI 0.67-1.04]).

In the ENGAGE AF-TIMI 48 trial, a limited number of patients with other types of VHD were included. Of the 21,105 patients enrolled, 2824 (13%) of patients had a history of moderate or severe VHD, the most common being mitral regurgitation. Patients with VHD who received edoxaban 60 mg had similar rates of stroke or systemic embolism compared to those without VHD; HR 0.69 [95% CI 0.44-1.07] vs HR 0.91 [95% CI 0.53-1.02].

With ongoing use of VKAs, a validated tool called SAME-TT2R2 allows providers the ability to predict the likelihood of patients to succeed with this therapy. The formulation of SAME-TT2R2 is based on many clinical factors that impact a patient’s time within therapeutic range. A score of less than 2 correlates to a high likelihood of remaining within therapeutic range while on VKA treatment.

**Discussion:** Overall, each subanalysis of the DOAC trials indicated that efficacy did not differ between
patients with or without VHD. In terms of safety, bleeding risk was about the same in dabigatran and apixaban, but rivaroxaban was associated with a higher risk of bleeding. Although the results are promising, the findings should be interpreted with caution as these were not prespecified subgroup analyses.

**Clinical Thought:** DOACs should be considered first line treatment in place of warfarin for patients with a history of atrial fibrillation and valvular heart disease (in the absence of significant mitral stenosis or mechanical heart valve) as these patients were just as effectively managed compared to those with valvular heart disease. Calculations such as CHA2DS2-VASc and SAME-TT2R2 can help identify which patients are at higher risk for stroke and those who are appropriate candidates for VKAs.

**From the Pharmacy Press**

**A Review of Suicide Prevention Programs and Training Policies for Pharmacists**

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**Background:** Suicide is the 10th leading cause of death in the United States according to the American Foundation for Suicide Prevention. It is unknown how often a pharmacist encounters a patient at risk of suicide in the United States; however, the likelihood will most likely increase with the unfortunate rise in suicide rates each year. Pharmacists are accessible health care providers, especially where pharmacy locations and hours are often convenient and open late in the evening. No studies have been conducted in the United States regarding pharmacists’ barriers to counseling patients at risk of suicide, and it is unknown what training programs or resources are available for those in the pharmacy field. The objectives of this study were to determine if 1) any states required suicide prevention training for pharmacists and 2) to describe any training materials or educational resources available for pharmacists encountering patients at risk of suicide.

**Methods:** In order to determine state requirements in suicide prevention for pharmacists, a continuing education (CE) website was utilized to distinguish the number and types of CE required in each state by pharmacists. Then, each state board of pharmacy was contacted between July and November 2017 via phone or e-mail to verify the CE information found on the website. A literature review was conducted to evaluate whether training materials or educational resources were available for pharmacists. Articles were included if they described an educational or training program for pharmacists or pharmacy students, were not focused solely on a depression screening program or pharmacists’ attitudes on suicide/assisted suicide, and provided sufficient detail about the training program or resource. Two independent coders extracted the following data from the resources that met inclusion criteria: “1) name of training program; 2) format of training program (e.g., in person, online); 3) length of training; 4) target of training (e.g., student pharmacists, pharmacists); 5) learning methods (e.g., didactic presentation, role-play, case studies); 6) topics covered; 7) program outcomes assessed (e.g., satisfaction, knowledge); and 8) cost.”

**Results:** Only the state of Washington requires a licensed or active pharmacist complete a one-time 3-hour CE course on suicide awareness and prevention training as of August 2017. The literature and Google review resulted in 16 pharmacist or student pharmacist targeted suicide training materials or educational resources: eight in-person courses, six online courses, and two written resources. Five of the resources were designed specifically for pharmacists, whereas the others were intended for both pharmacists and other pharmacy staff/students or healthcare professionals. The majority of the programs included suicide statistics, identifying individuals at risk of suicide, how to communicate with patients who are suicidal, and how to refer patients to resources if they were experiencing suicidal thoughts. Nine of the resources (56%) discussed medications that may be linked with risk of suicidal ideation.

**Conclusion:** There are many comprehensive training materials and educational resources pharmacists can utilize to better educate themselves when interacting with patients at risk of suicide. Although suicide prevention training is not mandated in 49 states, pharmacists have the opportunity to expand their own knowledge, improve communication skills and confidence in a difficult situation, and become better prepared to potentially impact patients’ lives.

**Association Between Use of Benzodiazepines and Development of Dementia**

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**Background:** Benzodiazepines are widely prescribed in adults and older adults, but may also be considered concerning as they can cause cognitive deficits. Several studies indicate that benzodiazepine use can increase the risk of developing dementia; however, others have
shown they may potentially offer a protective benefit against developing the disease. Other studies have also identified that there may be no association between benzodiazepine use and dementia development. Interestingly, results from these studies can be confounding; prodromal symptoms of dementia such as anxiety or decreased sleep quality can appear almost a decade before dementia is clinically diagnosed. Benzodiazepines are often prescribed to treat these symptoms; as such, studies are often plagued with protopathic bias (when a drug is prescribed to treat symptoms of a yet-to-be diagnosed disease).

**Purpose:** As the data surrounding this topic is controversial, a group of researchers from Brazil investigated if an association exists between benzodiazepine use and dementia.

**Study Design:** The study was a systematic review and meta-analysis evaluating 12 studies published between 2011 and 2017: one retrospective and four prospective cohort studies and seven case-control studies. Overall, data from over 980,000 patients was evaluated. Included patients were adults or older adults of any gender; there were no restrictions on previous health conditions. Studies were excluded if patients had diagnoses of dementia at the start of the study. Additionally, studies were excluded if treatment or outcomes were not reported with accuracy. Methodological quality of included studies was assessed by the Newcastle-Ottawa scale and found that the majority of included studies were rated as high quality.

**Results:** Of the 11 studies included in the meta-analysis (one study evaluated overlapping participants and was not included in the analysis), eight studies determined benzodiazepine use as a risk factor for developing dementia, two studies showed no association, and one study found benzodiazepines offered protection from developing dementia. Evaluating these results, the meta-analysis of these studies concluded that users of benzodiazepines are 1.38 times more likely to develop dementia when compared with never users [95% CI 1.07-1.77]. Additionally, benzodiazepine users experience a 28% higher risk of developing dementia than never users [95% CI 1.06-1.55].

When subgroup analyses of included studies were considered, there was no association between benzodiazepine use and development of dementia. When users of short- and long-acting benzodiazepines were directly compared, there was no significant difference in the development of dementia.

**Conclusions:** Grading of Recommendations Assessment, Development, and Evaluation (GRADE) rating scoring was used to assess the quality of included evidence; the results of this meta-analysis regarding the association between benzodiazepine use and development of dementia is considered very low quality. Despite including carefully selected evidence and using quality methodology, the heterogeneity of the data had a considerable effect on the low confidence of the results. Although many included studies used a lag time to help minimize protopathic bias (i.e. a latency period before follow-up where benzodiazepines could not be used or dementia could not be diagnosed), there were studies that did not. These studies were more likely to show a lack of association between benzodiazepines and dementia, as perhaps some patients who developed dementia within the timeframe of the study already had dementia before study initiation or use of benzodiazepines, but had not yet been diagnosed. However, it should be noted that when a subgroup analysis was done on only studies that controlled for protopathic bias, authors still found no significant association.

Some key considerations were determined by subgroup analysis. Use of long-acting benzodiazepines was associated with the development of dementia, but use of short-acting benzodiazepines was not. It should be noted that this association was not supported as a statistically significant result of the meta-analysis.

**Key Point:** The authors of the study recommend a cautious interpretation of the low confidence results suggesting an association between the use of benzodiazepines and development of dementia. Additional long-term, prospective studies are needed that are powered to assess for this outcome. An ambulatory care pharmacist could consider that short-acting benzodiazepines were associated with a lower risk of developing dementia; however, the results were not statistically significant.
A Look into the Safety of Probiotic Supplements

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Probiotic supplements have become a common addition to patients’ medication regimens. Their use is generally associated with preventing C. difficile infections and antibiotic-associated diarrhea. Although probiotics are thought to promote digestive health, they may not be safe for everyone – in particular for those who are immunocompromised because these supplements are live microorganisms. Case reports have described serious adverse events, including fungemia and bacteremia, in such patients. The lack of effective ways to detect post marketing harm from supplements also likely contributes to underreporting of these adverse effects.

The poor quality of regulation surrounding over-the-counter products in the United States is also concerning. Even though the U.S. Food and Drug Administration has established good manufacturing processes for all dietary supplements, not all manufacturers follow them. With low manufacturing compliance, probiotic supplements may contain contaminants and incorrect species of bacteria – something that may be harmful if consumed by an immunocompromised patient.

Another unique risk of probiotic supplements that health professionals need to be aware of is their potential to promote antibiotic resistance. In vitro and rodent models have shown that probiotics signal the presence of a mobile gene that is capable of transferring antibiotic resistance to pathogenic bacteria. Though more research needs to be done with human data, the remote possibility of conferring antibiotic resistance needs to be seriously considered when approaching patients who are on or looking to start probiotic supplements. With the lack of laws and regulations surrounding the manufacturing practices of live microorganisms, it should not be assumed that labeling is accurate. Combining the lack of manufacturing regulation with the possibility of promoting antibiotic resistance, probiotic supplements may not be safe for every patient and need to be carefully considered moving forward.

Impact of the Shingrix Shortage

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Shortage of the newest shingles vaccine, Shingrix®, has been a recent highlight in the news and continues to impact patients, clinics, and pharmacies nationwide. A representative of the manufacturer of the vaccine, GlaxoSmithKline, reported the shortage was not due to any problems in the manufacturing process, but in the high demand for the vaccine. The Centers for Disease Control and Prevention (CDC) recommends that patients ages 50 and older should receive the new vaccine, regardless of prior Zostavax® vaccination status. The vaccine is recommended as a two-dose series with the second dose scheduled two to six months following the first injection. However, when a shortage prevents this, many questions and concerns arise from patients and providers on how to navigate this situation.

Vaccine shortages impact pharmacy practice in various ways. The shortage of the Shingrix® vaccine has created concern related to efficacy in patients who do not receive the second dose within the recommended six month window. According to the CDC, if 6 months pass after receiving the first dose of the Shingrix® vaccine, the series doesn’t need to be restarted. However, the second dose should still be administered as soon as possible because both doses are required for the greater than 90% immunity. In our role as pharmacists, we can provide patients with education related to the vaccine, and encourage patients to contact their pharmacy or clinic to inquire about vaccine prior to arrival for vaccine administration. Additionally, we can manage and discuss processes that facilities may have in place to combat the shortage, such as creating patient call lists or prioritizing patients in need of their second dose. Pharmacists are well positioned to answer questions from both patients and providers during vaccine shortages.

Antibiotic Overprescribing in the Outpatient Setting

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Antibiotics are important medications used to treat many bacterial infections commonly seen in the outpatient setting, including strep throat and ear infections. When indicated, antibiotics are an integral part of preventing the spread of illness and reducing the risk of potential complications of disease. On the other hand, antibiotic treatment will not reduce infection transmission or lead to cure when prescribed for viral illness.

Research shows antibiotics are frequently prescribed for symptoms including sore throat and cough when they are not indicated. Viruses cause many common illnesses seen in the outpatient setting and patients do not benefit from antibiotic therapy due to the viral origin. According to an IDWeek 2018 study, almost half of the outpatient
antibiotics prescribed were given without an infection-related diagnosis. The study included more than 500,000 outpatient antibiotic prescriptions given to patients from November 2015 to October 2017. It was determined that 46% of the total antibiotic prescriptions were prescribed without an infection-related diagnosis. This included 29% of antibiotics associated with a diagnosis that was non-infectious in nature, including high blood pressure or annual visit. Data also showed that 17% of prescriptions were written without a diagnosis at all, which may indicate antibiotic prescribing for unclear or inappropriate reasons.

It is important that all healthcare professionals work together to ensure proper use of antibiotics. We can accomplish this by promoting appropriate utilization, selection, dose, and duration of antibiotics. Antibiotic stewardship is essential to preserve antibiotic effectiveness, prevent harmful side effects that may be caused by the inappropriate use of antibiotics, and protect the public from antibiotic-resistant infections.

**XofluzaTM for the Treatment of Influenza**

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Now that the flu season is in full swing, it is not only important to wash your hands, but it is also important to know what treatment options are available to fight influenza. XofluzaTM (baloxavir marboxil) was recently approved for the treatment of acute, uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. After successful clinical trials in Japan during the 2016-2017 flu season, the FDA approved baloxavir marboxil for use in the United States on October 24, 2018.

These clinical trials resulted in similar times to alleviation of influenza symptoms compared to the current mainstay of therapy, TamifluTM (oseltamivir phosphate). However, some differences are important to note. Baloxavir marboxil was associated with greater reductions in viral load one day after initiation compared to both placebo and oseltamivir phosphate. Baloxavir marboxil also had few incidences of adverse reactions compared to oseltamivir phosphate (20.7% vs. 24.8%, respectively). Overall, these medications resulted in comparable outcomes in regard to treatment of influenza.

Baloxavir marboxil, an endonuclease inhibitor, works differently than oseltamivir phosphate, a neuraminidase inhibitor. This is beneficial as more resistant strains of influenza are emerging. It is also advantageous to have alternatives to therapy for patient-specific reasons including allergies, availability, treatment failure, and cost. With another treatment option available, healthcare professionals have an increased selection of medications to choose from to best treat patients.

An additional benefit of baloxavir marboxil is the short treatment course consisting of one tablet. This may be helpful in patients struggling with adherence compared to oseltamivir phosphate and its twice daily regimen for a total of five days. Unlike oseltamivir phosphate, baloxavir marboxil does not need to be adjusted based on renal function. On the other hand, oseltamivir phosphate is FDA approved for patients two weeks of age and older, can be used prophylactically for influenza, and comes in both a capsule and suspension formulation.

While there are many things to consider when choosing the most appropriate medication regimen to treat influenza, it is helpful to have options. The addition of another antiviral agent to treat influenza is valuable to the healthcare system and may result in better treatment outcomes.


21. Cohen PA. Probiotic safety – no guarantees [published online September 17, 2018]. JAMA


