

Updates in Pharmacotherapy

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Research Updates

A Multicenter Observational Study of Incretin-based Drugs and Heart Failure¹

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Background: Incretin-based medications, including dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) analogues, are commonly used medications to treat diabetes mellitus type II (DMII). However, there has been recent concern with these two medication classes potentially increasing the risk of heart failure. This controversy has arisen from Saxagliptin Assessment of Vascular Outcomes Recorded in Myocardial Infarction 53 (SAVOR-TIMI 53) trial where saxagliptin was found to increase the risk of hospitalization for heart failure by 27% compared to placebo in patients with DMII with established cardiovascular disease or multiple risk factors for vascular disease. However, the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) and Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trials showed no increase in overall hospitalization from heart failure risk among patients on alogliptin or sitagliptin. With conflicting data, this new trial was designed to have enough power to address this safety issue.

Purpose: To determine if incretin-based medications, when compared with other oral antidiabetic medication combinations used in clinical practice, are associated with an increased risk of heart failure hospitalizations in patients with or without a history of heart failure.

Study Design: In this retrospective cohort analysis, population-level healthcare data on physician billing claims, diagnosis and procedures from hospital discharge abstracts, and records on prescription drug dispensing from patients with DMII in Alberta, Manitoba, Ontario, Saskatchewan, United States, and the United Kingdom was obtained. The study population included patients that were prescribed a first-ever prescription for non-insulin antidiabetic medications including biguanides, sulfonylureas, meglitinides, sodium-glucose cotransporter 2 inhibitors, or a combination of these. Exclusion criteria included persons under 18 years of age (except in Ontario where participants less than 66 years were also excluded), and patients who had previously been on antidiabetic drugs, patients with a history of current insulin use when entering the cohort, women with a history of polycystic ovarian syndrome, and women with gestational diabetes. Additional exclusions for the study cohort included participants with a history of human immunodeficiency virus (HIV) infection or patients who had received highly active antiretroviral therapy at any time before entering the cohort.

From the base cohort, a study cohort of participants started on incretin-based medications was formed including those who were newly diagnosed with DMII and those who were previously on oral antidiabetic drugs. The study cohort was further divided into two cohorts of participants with or without a history of heart failure.

The two study cohorts were analyzed using nested case-control analysis. Cases were defined as hospitalization for heart failure, including fatal and nonfatal events.

Results: The study cohorts included 1,499,650 participants with 29,741 participants hospitalized for heart failure during 3,242,291 person-years of follow-up. In participants without a history of heart failure, treatment with incretin-based medication was not associated with increased risk of hospitalization for heart failure compared to other oral antidiabetic drug combinations (HR 0.82 [95% CI 0.67 to 1.00]). Similar results were found when sub-categorizing them into DPP-4 inhibitors (HR 0.84 [95% CI, 0.69 to 1.02]) and GLP-1 analogues (HR 0.95 [95% CI 0.83 to 1.10]). Additionally, there was no evidence of dose-response relationship, effect from presence or absence of history of myocardial infarction, or duration of treated DMII. For those with a history of heart failure, similar results were found with no additional risk for heart failure hospitalization (HR 0.86 [95% CI 0.62 to 1.19]). These results did not differ when subcategorized into each class, duration of use, history of myocardial infarction, or duration of overall DMII treatment.

Conclusions: Incretin-based medications, such as DPP-4 inhibitors and GLP-1 agonists, were not associated with an increased risk of hospitalization for heart failure in patients with or without a history of heart failure when compared to other oral antidiabetic drug combinations.

Key Point: This trial suggests that DPP-4 inhibitors and GLP-1 agonists are safe to use in patients with and without a history of heart failure and will not increase the risk of heart failure hospitalizations when compared to other oral antidiabetic drug combinations (excluding pioglitazone).

Cumulative Use of Strong Anticholinergics and Incident Dementia²

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Background:

The adverse cognitive effects of anticholinergic medications are a regular consideration when treating common conditions such as depression, incontinence, and allergic rhinitis. This consideration is especially important when treating elderly patients, as they have increased sensitivity to these medications leading to potentially more pronounced adverse effects.

Objective: To determine whether an increased cumulative exposure to anticholinergic medications is associated with an increase in dementia incidence.

Study Design: This was a prospective cohort study which analyzed population health plan data of patients aged 65 and above with no history of dementia over a ten year period. The study enrolled 3,434 patients who were mostly white (91.4%), female (59.6%), with some college education (66.4%). The average age of patients at initiation was 74.4 years. Participants were screened for dementia at baseline and at each biennial study visit. In order to assess anticholinergic medication use, researchers used prescription fill data from the health plan. Anticholinergic medications were defined as those with a strong anticholinergic effect categorized by an expert panel and included tricyclic antidepressants, antihistamines, GI antispasmodics, antiemetics, bladder antimuscarinics, among other medications with known anticholinergic properties based on mechanism of action or adverse effect profile. Exposure to these medications was calculated using drug dose and duration to give a total standardized daily dose (TSDD). Exposure was then quantified on a range from 1 to >1095 (number of days in 3 years). An example of the >1095 category would be if a person were to take any of the following medications for more than 3 years: oxybutynin chloride 5 mg, olanzapine 2.5 mg, meclizine hydrochloride 25 mg, or doxepin hydrochloride 10mg.

Results: After a mean follow-up time of 7.3 years, 797 participants (23.2%) developed dementia. Patients in the >1095 TSDD exposure category had a statistically significant increase in their risk for dementia (adjusted HR 1.54 [95% CI 1.21 to 1.96]). Patients with TSDD scores below 1095 showed some or no increased risk of dementia but none were statistically significant.

Conclusions: Increased exposure to anticholinergic medications in patients 65 years and older was associated with a greater risk of developing dementia.

Key Point: Health care professionals, including pharmacists, should recognize the potential long-term effects of medications with anticholinergic properties and seek to decrease their use among elderly patients. If these medications are therapeutically appropriate or patients have failed other therapies, health care professionals should seek to use the lowest effective dose for the shortest amount of time possible to decrease overall cumulative exposure.

Pioglitazone and Prevention of Secondary Cardiovascular Events in Patients Without Diabetes³⁻⁷

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Background: A history of ischemic stroke or transient ischemic attack (TIA) is known to increase the risk for secondary cardiovascular events.¹ Insulin resistance is a risk factor for vascular disease and is associated with hypertension, hyperglycemia, dyslipidemia, and hypercoagulability.² In addition to exercise, diet, and weight reduction, thiazolidinediones (TZDs) are a class of medications that improve insulin sensitivity.³ Since over 50% of patients with a history of stroke or TIA have insulin resistance, it is important to explore the utility of TZDs in patients without diabetes.⁴

Objective: The Insulin Resistance Intervention after Stroke (IRIS) trial assessed the use of pioglitazone to prevent secondary cardiovascular events in patients without diabetes.⁵

Study Design: Kernan *et al.* conducted this double-blind, placebo-controlled clinical trial using data collected between 2005 and 2013 from 179 international hospitals and clinics. The primary outcome measured was stroke or myocardial infarction (MI). Prespecified secondary outcomes were stroke, acute coronary syndrome, diabetes, death by any cause, cognitive decline and combination of stroke, MI, or heart failure leading to hospitalization or death. The cohort included 3876 patients who were at least 40 years old with a history of ischemic stroke and/or TIA within six months prior to randomization, and with confirmed insulin resistance. Exclusion criteria included a diagnosis of diabetes confirmed by fasting plasma glucose or the use of diabetes medications, HbA1C \geq 7.0%, history of heart failure, and bladder cancer. The characteristics of both study groups were similar, including a mean age of 63.5 years and a mean HbA1C of 5.8%. Patients were

randomized in a 1:1 ratio, initially receiving either 15 mg of pioglitazone or placebo and being titrated to 45 mg over the course of 12 weeks if tolerated. Patients were followed for up to five years and contacted every four months, with adherence being accounted for throughout the study period.

Results: The primary outcome occurred in 9.0% of the treatment group (HR 0.76 [95% CI 0.62 to 0.93]) versus 11.8% of the placebo group. The rate of progression to diabetes was lower in the group receiving pioglitazone, 3.8% vs 7.7% (HR 0.48 [95% CI 0.33 to 0.69]). This remained true even when using the HbA1C cutoff of 6.5%. No significant differences were seen in effect on cognition or all-cause mortality. Patients receiving pioglitazone exhibited a greater frequency of side effects including weight gain of more than 4.5 kilograms, edema, and bone fracture requiring surgery or hospitalization.

Conclusions: Treatment with pioglitazone in insulin resistant patients without diabetes and a recent history of ischemic stroke or TIA lowered the risk of secondary stroke or MI and diabetes diagnosis. This prevented an event in three out of 100 patients after five years of treatment. However, treatment was associated with a greater risk of weight gain, edema and fracture compared to placebo. The exclusion of patients with diabetes and heart failure prevent us from drawing conclusions about the utility of this treatment for cardiovascular prevention in these higher risk populations. The five year follow-up provides valuable insight into the long-term benefits and risks of treatment, but a risk-benefit analysis beyond the five-year study period will require further research.

Key Point: Further investigation is warranted for using insulin-sensitizing medications, including thiazolidinediones, to prevent cardiovascular events in patients with insulin resistance regardless of a diagnosis of diabetes.

Therapeutic Thoughts

2016 USPSTF Update: Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer⁸⁻¹⁰

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Background: In 2011, more than half of all deaths in the United States were caused by heart disease, cancer, and stroke. More specifically, cardiovascular disease

(CVD), which included myocardial infarction (MI) and stroke, was responsible for 30% of all deaths.³ Aspirin, a nonsteroidal anti-inflammatory drug (NSAID), was first found to be effective in the prevention of CVD in the 1980s, and has since become a mainstay in the primary and secondary prevention of MI, stroke, and colorectal cancer (CRC).¹ Studies have shown that nearly 40% of adults over the age of 50 years use aspirin for primary or

secondary prevention of CVD, although the role of aspirin for primary prevention of CVD, optimal dosing, and administration are still unclear.^{1,2,3} Many clinical guidelines provide recommendations for the use of aspirin in specific patient populations; the United States Preventative Services Task Force (USPSTF) recently updated their recommendation in a statement for the use of aspirin for primary prevention of CVD and CRC.³

Evidence: The USPSTF updated recommendations considered 11 randomized control trials (RCTs). Eight of these trials showed that the use of low-dose aspirin (75-100 mg per day) reduced nonfatal MI and coronary events by 17%. When all doses of aspirin (81-325 mg daily) were considered in a total of ten pooled trials, a 22% risk reduction was shown. Pooled trial results showed a statistically significant reduction in all-cause mortality with all aspirin doses. In addition, three trials showed a 40% reduction in CRC incidence with aspirin use. This benefit was only observed for patients who used aspirin for at least five to ten years.³ Four recent RCTs published between 2008 and 2014 have not been able to show this benefit of aspirin use for reducing cardiovascular events, which may be due to increased use of statin therapy and better blood pressure control compared to earlier trials. There are currently four trials underway that may provide clarity for the use of aspirin in specific populations. These studies will include patient populations with moderate CVD risk (men ≥ 55 year of age with two to four CVD risk factors or women ≥ 60 years of age with three or more CVD risk factors), patients over 70 years of age, patients with type I or type II diabetes, and will analyze the benefit of aspirin use in combination with a statin versus aspirin alone.²

Discussion: Based on the current body of literature, the USPSTF suggests that a reasonable approach may be to assess CVD and bleeding risk factors starting at age 50 years, and periodically thereafter. In addition, they recommend reassessing aspirin use when CVD and bleeding risk factors are detected or changed. The USPSTF recommends using the American College of Cardiology and American Heart Association pooled cohort equation to estimate 10-year CVD risk score. This calculator predicts the 10-year risk of a first hard atherosclerotic CVD event, defined as nonfatal MI, coronary heart disease (CHD) death, and fatal or nonfatal stroke. Risk factors that are accounted for include: age, gender, race/ethnicity, lipid levels, blood pressure, diabetes, and smoking status.³

The 2016 USPSTF update now recommends low-dose aspirin for primary prevention of CVD and CRC in

patients age 50-59 years who have a 10% or greater 10-year CVD risk that are not at increased risk of bleeding, have a life expectancy of at least 10 years and are willing to take aspirin for at least 10 years. The recommendations state that the decision to initiate low-dose aspirin use for the primary prevention of CVD or CRC in adults age 60-69 years who have a 10% or greater 10-year risk of CVD should be individualized. Risk factors for gastrointestinal (GI) bleeding include: high dose and long duration aspirin use, history of GI ulcers or upper GI pain, bleeding disorders, renal failure, severe liver disease, thrombocytopenia, concurrent use of anticoagulation or NSAIDs, uncontrolled hypertension, male sex, and older age. There is no evidence that enteric-coated or buffered formulations reduce the risk of GI bleeding.³

Clinical Impact: The USPSTF 2016 update has simplified recommendations for initiating aspirin for primary prevention of CVD and CRC. This new recommendation statement is more consistent with other clinical guidelines as outlined in Table 1. Evidence suggests that aspirin doses of 75 mg daily seems as effective as higher doses, but with a lower risk of bleeding. The 2016 USPSTF update suggests that the benefits of aspirin use in adults age 50-59 years with a 10-year CVD risk score of 10% or greater include the prevention of MI and ischemic stroke as well as reduced incidence of CRC with long-term use. They suggest that the decision to initiate aspirin in adults age 60-69 years with a 10-year CVD risk of 10% or greater be individualized because the net benefit is not as great for older individuals due to increased risk of GI bleeding. Once initiated, aspirin therapy should be continued unless contraindicated by an adverse bleeding event.³

Table 1. Comparison of clinical guidelines for the use of low-dose aspirin.

Clinical Guideline	Aspirin Recommendations for Primary Prevention of CVD
United States Preventative Services Task Force	Low-dose aspirin for adults age 50-59 years who have a 10% or greater 10-year CVD risk The decision to initiate low-dose aspirin in adults age 60-69 years who have a 10% or greater 10-year risk of CVD should be individualized
American Heart Association* American Stroke Association	Low-dose aspirin for adults with a 10-year CVD risk of 6-10%
American Diabetes Association	Low-dose aspirin for adults >50 years who have a 10-year CVD risk of 10% or greater
American College of Chest Physicians	Low-dose aspirin for adults >50 years of age without symptomatic CVD

*The most recent lifestyle and cholesterol guidelines from the American College of Cardiology and American Heart Association did not address the use of aspirin for primary prevention of CVD.²

The HOPE-3 Trial: Expanding Use of Statin Therapy for Patients with Intermediate Cardiovascular Risk¹¹⁻¹⁶

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Background: Elevated blood pressure and cholesterol are the leading causes of cardiovascular disease (CVD). Many CVD events are reported in people with intermediate risk and no previous CVD. The role of antihypertensive agents for intermediate risk patients who have no history of CVD and systolic blood pressure less than 160 mmHg is not clear. Additionally, the benefit of statins in intermediate risk and ethnically-diverse patient populations is not clear. The Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial studied patients with intermediate CV risk and was structured as a double-blind, randomized, multi-center, placebo-controlled trial using a two-by-two factorial design for a median follow up of 5.6 years. The HOPE-3 trial is three related studies which evaluate the incidence of cardiovascular events in intermediate risk patients treated with a statin (rosuvastatin 10 mg) versus placebo, angiotensin-receptor blocker plus a thiazide (candesartan 16 mg daily and hydrochlorothiazide 12.5 mg daily) versus placebo, and the combination of both interventions versus dual placebo. The inclusion criteria were men 55 years of age and older and women 65 and older without CVD and at least one additional risk factor for CVD. Women over 60 years of age were included if two risk factors were present. The first coprimary outcome was the composite of death from CV causes, non-fatal myocardial infarction, or non-fatal stroke. The second coprimary outcome was revascularization, heart failure, and resuscitated cardiac arrest. The authors hypothesized that CVD events would be reduced with addition of blood pressure lowering agents and cholesterol lowering agents.

Evidence: The HOPE-3 trial found significant differences with a moderate potency statin alone or with antihypertensive agents for intermediate risk patients with no CVD. The first coprimary outcome occurred in 235 participants in the rosuvastatin group and 304 in placebo group (HR 0.76 [95% CI 0.64 to 0.91]; p=0.002). Additionally, the average LDL was lowered by 26.5% in the rosuvastatin group compared to placebo. The average LDL decreased on average greater by 33.7 mg/dL in the combined therapy group versus dual placebo (p<0.001).

Systolic blood pressure decreased by 6.2 mmHg more from baseline in the combined treatment group compared to the placebo group. Interestingly, there were no benefits seen with antihypertensive agents alone for

either co-primary endpoint unless systolic blood pressure was above 140 mmHg. The baseline mean blood pressure for the entire trial population was 138.1/81.9 mmHg. The systolic blood pressure decreased by an average of 6.0 points and the diastolic by an average of 3.0 points more in the candesartan plus hydrochlorothiazide group compared to placebo. The first coprimary outcome occurred in 260 participants in the candesartan plus hydrochlorothiazide group compared to 279 in the placebo group (HR 0.93 [95% CI 0.79 to 1.10]; p=0.40).

Discussion: The HOPE-3 trial supports a risk-based approach to statin use instead of LDL cholesterol level, which is similar to current recommendations. Side effects including muscle weakness and dizziness were reported more often in the combined therapy group compared to placebo; these side effects were reversed when therapy was discontinued. In cholesterol lowering alone, the HOPE-3 trial found that statin use is associated with reduced CV events in an ethnically-diverse patient population with intermediate risk. The HOPE-3 trial used a moderate-intensity dose statin, which lowers risk for safety concerns. In addition, HOPE-3 results were similar to findings in the JUPITER trial, which studied CV benefits while on moderate-intensity rosuvastatin. HOPE-3's blood pressure lowering group included systolic blood pressures at baseline that were normal to high range; this is similar to ACCORD and SPRINT trials, however the trial findings were not the same due to difference in study design. For example, the treat-to-target approach found in ACCORD and SPRINT was more complex, resulting in lower blood pressures obtained compared to HOPE-3. Determining blood pressure goals that maximize CVD benefit (or reduce CVD events) continues to be challenging. No benefits were shown with baseline systolic blood pressure of 143.5 mmHg or less.

Clinical Impact: Statins alone or combined with antihypertensive agents should be considered in a diverse patient population with intermediate risk and no CVD history to prevent CVD events. No clear CVD benefit was shown when comparing use of antihypertensive therapy alone versus placebo in intermediate risk patients.

Exploring Potential Adverse Effects of Proton Pump Inhibitors¹⁷⁻²¹

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Background: Proton pump inhibitors (PPIs) are one of the most widely prescribed classes of medications across the world. Their use has continued to increase,

especially in the elderly population. The two most common indications for PPIs are gastroesophageal reflux disease (GERD) and peptic ulcers. Observational studies have found that about 40-60% of PPI prescriptions are inappropriate. Recently, various studies have brought the potential long-term adverse effects of PPIs to the forefront. These questionable long-term risks associated with PPI use include the development of dementia, chronic kidney disease (CKD), major cardiovascular events, osteoporosis, and community acquired pneumonia (CAP).

Evidence: A study by Gomm et al. assessed for the diagnosis of incident dementia; patients receiving routine PPI therapy had a statistically significant increased risk of incident dementia compared to patients not receiving routine PPI therapy (HR 1.44 [95% CI, 1.36 to 1.52]; $P < 0.001$).

Lazarus et al. conducted a study to quantify the association between PPI use and incident CKD. Their results showed that PPI use was associated with incident CKD in an unadjusted analysis; an analysis adjusted for demographic, socioeconomic, and clinical variables; an analysis with PPI ever use modeled as a time-varying variable; and when directly compared with H2 receptor antagonist (H2RAs) users. Twice daily dosing of PPIs (adjusted HR 1.46 [95% CI 1.28 to 1.67]) was associated with an even higher risk of CKD compared to once daily dosing (adjusted HR 1.15 [95% CI 1.09 to 1.21]).

To assess the risk of adverse cardiovascular effects associated with PPI use, Shah et al. completed a data mining analysis to explore the risk in the general population. They found that patients exposed to PPIs had a 1.16 fold increased association with myocardial infarction. Survival analysis of a prospective cohort found a twofold increase in association with cardiovascular mortality. Lastly, they compared these findings to patients using H2RAs and demonstrated that H2RAs were not associated with an increase in cardiovascular risk.

Gray et al. used data from the Women's Health Initiative to assess the risk of fractures associated with PPI use. They found that PPI use was associated with an increased risk of clinical spine fractures (HR 1.47 [95% CI 1.18 to 1.82]), forearm and wrist fractures (HR 1.26 [95% CI 1.05-1.51]), and total fractures (HR 1.25 [95% CI 1.15 to 1.36]) but not associated with an increased risk of hip fractures (HR 1.0 [95% CI 0.71 to 1.40]). In comparison, they did not find any association between H2RAs and hip, clinical spine, or forearm and wrist

fractures, but they did see a slight increase in total fractures (HR 1.08 [95% CI 1.02 to 1.14]).

Lastly, Lambert et al. conducted a systematic review and meta-analysis to determine the association of outpatient PPI therapy and the risk of CAP. They found a pooled risk of CAP with outpatient PPI therapy of 1.49 [95% CI 1.16 to 1.92]. PPI therapy was also found to increase the risk of hospitalization for CAP (OR 1.61 [95% CI 1.12 to 2.31]).

Discussion: The above data suggests that the risk of adverse effects from PPIs is not well documented. Furthermore, the mechanisms by which PPIs cause these adverse effects are not well understood. Further investigation into these adverse effects is warranted in order to determine the risks and benefits of therapy. However, this information provides a compelling argument to reduce the use of PPIs by using the lowest effective dose for the least amount of time. Patients should be tapered off of these medications over the course of weeks, or even months, to prevent rebound GERD. Given the extensive use of PPIs, these long-term adverse effects and complications could translate into a considerable burden on the healthcare system.

Clinical Impact: In the clinical setting, the continued indication for PPI therapy should be reassessed on a regular basis. Patients should be educated about the possible long-term risks that may be associated with PPI use. With so much unknown, patients deserve to be educated about the potential risks that come with the benefits of therapy. If alternate therapies are available, such as H2RAs, these may be a more ideal choice of therapy to use if not already attempted.

From the Pharmacy Press

The Evaluation of Home-Based Medication Therapy Management (MTM) Service Integration²²

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Background: Home-based care programs were developed in response to the needs and preferences of families to care for family members at home and due to the limitations and costs associated with institutional care. Home-based Medication Therapy Management (MTM) has been an established service that primarily caters to specific conditions and medications, in addition to patients recently discharged from the hospital. However, few studies exist that assess the benefits of home-based MTM within an ambulatory care setting.

Study Design: This prospective observational study detailed the integration of home-based MTM services and its outcomes within the Hennepin County Medical Center (HCMC) of Minnesota, from September 2012 to December 2013. The HCMC health system setting provides approximately 10,000 MTM encounters annually.

The structure of the home-based MTM encounters mirrored that of a clinic based encounter involving a 60 minute pharmacist review of both over-the-counter and prescription medications and their indications, effectiveness, safety, convenience, medication adherence, and medication box organization.

Patients were recruited for home-based MTM services based on clinic provider referrals ordered through the HCMC electronic health record (EHR). Referrals were then processed and patients were contacted to schedule appointments. Prior to the home-based MTM visit, pharmacists would review patient charts.

Documentation within the EHR of the home-based MTM visit included assessments on medical conditions, number of medication related problems (MRPs), current medication list, patient education, recommended medication changes, time spent with patient, and summaries documenting patient symptoms/concerns and living environment. Upon home-based MTM visit completion, patients received written instructions of important points discussed during the session. Billing and reimbursement rates for home-based MTM services are equal to that of MTM services provided in any other setting, however, billing differed in that facility fees were

not billed and pharmacists were reimbursed the cost of travel to patient homes.

Data collection was obtained through the EHR and evaluated based on the number of referrals, the reason for referral, type of provider referring, and the number and type of MRPs.

Results: A total of 74 home-based MTM encounters were provided to 53 patients. Approximately 87% of patients were 51 years of age and older, 55% were African American, and 57% female. Median values of 12 medications and 3 MRPs per patient were observed, with compliance (40%) being the most common MRP. Approximately 50% of referrals were received by physicians (51%), citing referrals mostly due to non-adherence (17%), transportation barriers (17%), and needed medication reconciliation with public health nurse (17%). Follow up post home-based MTM with a primary care provider occurred in 54% of patients within 30 days and in 92% of patients within 120 days.

Discussion: Home-based MTM demonstrated advantages of allowing pharmacists to see living environments of their patients to assess medication organization more fully and resolve medication related inconsistencies with patient caregivers, thus bridging the gap between home and clinic care. There were several limitations found in providing home-based MTM, including the additional training required by pharmacists to provide the service. Additionally, the current cost of providing the home-based MTM service is more than usual clinic MTM reimbursements received from insurance plans. The study did not compare home-based MTM to clinic-based MTM, so it is difficult to ascertain the benefits of one setting over the other in catering to certain patient populations. Further research is needed to better understand the place of home-based MTM services within the healthcare system.

Key Point: The integration of home-based MTM within a health system is a care model that gives both patients and pharmacists the advantage of seeing a patient's living environment, allowing pharmacists to cater better to patients' medication needs, competencies, and streamline care between caregivers. However, a statistical assessment, cost analysis, and comparison with other usual MTM services must be performed before a conclusion can be made.

Pharmacists in Accountable Care Organizations²³⁻²⁴

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In an attempt to curb healthcare costs, improve quality of care, and improve upon population health, care delivery models have been transitioning toward the accountable care organization (ACO) model. As a result, ACOs have been growing extensively with a recent report from Leavitt Partners indicating that there are more than 780 public and private ACOs operating throughout the nation since 2011. As this trend shifts financial responsibility onto the providers, identifying and optimizing the utility of various health care professionals within the model is crucial. Specifically, ACOs provide the opportunity for pharmacists to ensure optimization of patient's medication therapy in helping to achieve quality outcome measures.

According to a new report from the Pharmacy Benefit Management Institute (PBMI), only 57% of the surveyed ACO respondents employ or contract with a pharmacist, indicating underutilization of pharmacists within ACOs. The vice president of research and education at PBMI, Sharon Frazee, PhD, MPH, MBA, said that despite these statistics, ACOs do recognize the importance of pharmacists within their models, but are still determining how to actually utilize them. Frazee estimates that as more ACOs develop fully, they will likely consider adding pharmacists to the care team.

An article recently published in *Pharmacy Today* by Loren Bonner, MA, highlights this underutilization of pharmacists within ACOs, and outlines various examples in which pharmacists are currently being incorporated within ACOs to help improve care and reduce costs. One example is the pharmacist's ability to provide adequate patient education regarding medications. Specifically, the article outlines the example of providing medication education post-discharge in an attempt to reduce readmissions, as this is an area where hospitals are now

penalized. Fairview Health Services in Minnesota, which employs 24 pharmacists providing direct patient care services including Medication Therapy Management, has internal data indicating that pharmacists collaborating in transitions of care has been shown to reduce readmission rates.

An additional example includes Integrated Care Partners, an ACO in Connecticut covering 190,000 patients. There, one pharmacist is employed for the purpose of providing direct patient care to the highest-risk patients. This ACO is working to establish a pharmacist workflow to identify which patients are at higher risk of readmission and most in need of pharmacist's services. Additionally, they are working to establish a way to track and trend these efforts.

The American Pharmacist Association (APhA) has a collection of eight briefs outlining pertinent information for pharmacists regarding ACOs. Other uses for pharmacists outlined within these briefs include driving medication adherence, tracking and analyzing refill history, identifying gaps in therapy, identifying cost-saving opportunities, managing use of high-risk medications, and measuring generic compliance rates. These can largely be accomplished through the implementation of medication therapy management services within ACOs.

Kristina Lunner, senior director of Leavitt Partners, provides proactive approaches for pharmacists to become involved in ACO organizations. She suggests identifying ACOs or large payers looking into a value-based payment model, gain an understanding of their needs, and demonstrate to the organization that pharmacists can in fact meet these needs. Continuing to measure the effects of pharmacist-provided care already in place at current ACOs can help identify the usefulness of pharmacists' services more fully and pave the way for further implementation into this model.

Miscellaneous News

**Antithrombotic Therapy for VTE Disease Guideline:
New and Improved!²⁵**

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The American College of Chest Physicians has updated the ninth edition of the Antithrombotic Therapy for VTE Disease guideline from 2012, modifying twelve previous recommendations and addressing three topics not previously covered.¹ Updates relevant to ambulatory care include increased use of novel oral anticoagulants (NOACs).

For patients without cancer in need of long-term anticoagulation for deep vein thrombosis (DVT) of the leg or pulmonary embolism (PE), the guideline now recommends use of a NOAC over a vitamin K antagonist (VKA); however, a VKA is still preferred over low molecular weight heparin (LMWH). For patients with cancer-associated thromboses, LMWH is preferred above all oral agents. In patients discontinuing antithrombotic therapy for unprovoked proximal DVT or PE, aspirin is recommended over no aspirin therapy, provided aspirin is not contraindicated. Compression stockings are not recommended for the prevention of post-thrombotic syndrome; however, they do recommend a trial of compression stockings for treatment of symptoms.

For patients who have experienced recurrent VTE while taking an oral agent (VKA or NOAC) who are believed to be adherent to their medication regimen, a minimum of a one-month trial of LMWH is recommended. Patients with recurrent VTE on LMWH should have their dosage increased by one-quarter to one-third. All of these recommendations are weak recommendations with weak to moderate evidence.

**Guideline update: CDC Guideline for Prescribing
Opioids for Chronic Pain²⁶**

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During the 19th century, pain was considered the fifth vital sign, which led to increased pressure on providers to address pain as a priority. Now, fast-forward to the turn of the 21st century: the number of prescriptions and sales of opioids have quadrupled since 1999, and in 2010, there were as many as 2.4 million opioid abusers in the United States. Today, providers and health systems are challenged with assessing and treating

chronic pain (which is defined as pain lasting >3 months or past the time of normal tissue healing) and the balance between potential clinical, psychological and social consequences of pain and opioid use.

In response to this epidemic, the Centers for Disease Control and Prevention (CDC) released an updated guideline in March 2016 to help guide providers in prescribing opioids for non-malignant chronic pain. The guideline consists of 12 recommendations with the goal to improve communication with patients in regards to risks and benefits, improve safety and efficacy outcomes of pain treatment and decrease the risk associated with opioid treatment.

The guideline encourages non-pharmacological and pharmacologic therapy, other than opioids, be used first. Opioids should be considered only when expected benefits outweigh the risks and other treatment options have failed. Benefits, risks and realistic goals of therapy should be discussed prior to the initiation of opioids. When starting opioids, clinicians should prescribe the lowest effective dose of immediate-release options rather than extended/long-acting opioids. When treating acute pain, it is recommended to only prescribe 3-5 days' worth of opioid medication.

With chronic use, the benefits and risks of opioid therapy should be readdressed within 1-4 weeks after initiation and during dose increases. The guidelines also recommend that reevaluation occur every three months. During initiation and reevaluation, clinicians should check the prescription drug monitoring programs to ensure no other opioids are prescribed elsewhere and to lower patient's risk of overdose. When opioid doses are ≥ 50 mg of morphine equivalents per day, clinicians should consider prescribing buprenorphine (Naloxone). It is also recommended that clinicians offer and/or arrange evidence-based treatment in addition to buprenorphine, such as methadone in combination with behavioral therapy (especially for those with opioid use disorder).

The CDC has taken these initial steps to address the opioid epidemic by providing recommendations and clinical guidance to prescribers in hopes of improving prescribing practices and patient health outcomes. In addition to the guideline, the CDC offers resources such as a prescribing checklist, factsheets, and mobile application to help providers through this process. Resources and additional information can be found on

the CDC website at:

<http://www.cdc.gov/drugoverdose/prescribing/resources.html>.

Pharmacist-prescribed Birth Control²⁷⁻³²

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As of January 1, 2016, pharmacists in Oregon can legally prescribe hormonal contraception to women without requiring a prescription from another prescribing clinician.¹ The law only applies to oral hormonal contraception and does not include long acting reversible forms, such as intrauterine devices (IUDs) or contraceptive implants. The law restricts pharmacist prescriptions to women over 18 and requires them to complete a questionnaire screening for potential contraindications prior to receiving a prescription. An example questionnaire used in Oregon can be found here:

<https://www.oregon.gov/pharmacy/Imports/ContraceptivePrescribing/ORSelf-ScreeningRiskAssessmentQuestionnaire.pdf>.

Pharmacists must complete a training program approved by the State Board of Pharmacy prior to prescribing and are also required to refer patients to their primary care provider upon dispensing. The law outlines that the patient must be seen by a primary care or women's health provider within three years of the initial dispensing prior to receiving additional prescriptions.²

California also recently passed similar legislation. The law was initially passed in 2013; however, regulatory

discussions delayed implementation until April 8, 2016. The California law does not have a patient age requirement, but other aspects of the law are similar to Oregon's legislation, including requiring completion of a questionnaire prior to dispensing.⁴ Washington state and Washington D.C. have long allowed pharmacists to prescribe hormonal contraceptives. Legislators in New Mexico, Missouri, Tennessee, South Carolina, and Hawaii have proposed legislation to allow pharmacists to prescribe birth control.⁴

This legislation reduces barriers and increases access to birth control in these states. It is anticipated that increased access could result in a reduction of the number of unintended births and abortions per year.¹ The American College of Obstetricians and Gynecologists (ACOG) supports decreasing barriers to hormonal contraception. In a published committee opinion in 2012, ACOG states that oral contraceptives are generally safe to use, and do not require physician oversight to be prescribed.⁵ Overall healthcare costs may also decrease with this legislation by eliminating potential unnecessary physician visits and preventing costs associated with unintended pregnancy.¹ Planned Parenthood and the ACOG have expressed concerns regarding this legislation, saying that it does not do enough to decrease barriers to hormonal contraception. Both organizations as well as Oral Contraceptives Over the Counter (OCs OTC) Working Group are encouraging the FDA to approve certain birth control methods for over the counter use, which would not require pharmacist screening prior to use.^{1,6}

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