RESEARCH UPDATES

**LEGEND Study: An Effectiveness and Safety Comparison of Chlorthalidone and Hydrochlorothiazide**

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**Background:** Chlorthalidone and hydrochlorothiazide are classified as thiazide/thiazide-type diuretics. These medications work by inhibiting the reabsorption of sodium in the kidneys and are first-line treatment options for hypertension according to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) hypertension guidelines. While hydrochlorothiazide is the most commonly prescribed thiazide/thiazide-type diuretic, the 2017 ACC/AHA hypertension guidelines include a statement that chlorthalidone is preferred. This statement is based on the fact that chlorthalidone has a longer half-life and has shown a reduction of cardiovascular disease in previous meta-analyses. Prior to this study from Hripcsak et al., there were no large randomized clinical trials available that directly compared chlorthalidone and hydrochlorothiazide.

**Objective:** The objective of this study was to evaluate and compare the effectiveness and safety of chlorthalidone and hydrochlorothiazide for use as first-line treatment options for hypertension in treatment-naïve patients.

**Study Design:** This study is a Large-Scale Evidence Generation and Evaluation in a Network of Databases (LEGEND) retrospective, observational, comparative, controlled cohort study. Data from three Observational Health Data Sciences and Informatics (OHDSI) databases in the United States was collected from January 2001 to December 2018. Individuals starting chlorthalidone or hydrochlorothiazide at any dose for first-line treatment of hypertension were included in the study. Patients were included if they had a diagnosis of hypertension on or before the index time, which was defined as the first exposure to either treatment medication. Patients were excluded if they had previous exposure to any hypertension treatments prior to the index time. A total of 36,918 patients received chlorthalidone and 693,337 patients received hydrochlorothiazide. Baseline covariates between the two treatment groups were adjusted for with propensity score stratification. The primary efficacy outcomes included acute myocardial infarction (MI), hospitalization for heart failure, stroke, and a composite cardiovascular disease outcome that included the first three primary outcomes plus sudden cardiac death. This study evaluated 51 secondary safety outcomes, including electrolyte imbalances and renal abnormalities.

**Results:** There were no statistically significant differences found between chlorthalidone and hydrochlorothiazide at any of the primary endpoints using an on-treatment analysis. The hazard ratios for all endpoints were reported as calibrated hazard ratios. The composite primary endpoint occurred in 149 out of 36,628 patients receiving chlorthalidone and 3,089 out of 687,106 patients receiving hydrochlorothiazide (HR 1.00 [95% CI 0.85-1.17]). The hazard ratios for occurrence of
Atrial Fibrillation: Apixaban versus Rivaroxaban* 3

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Background: Direct oral anticoagulants (DOACs) are commonly used to prevent thromboembolic events in patients with atrial fibrillation, with apixaban and rivaroxaban being the most common medications used in this class. While the 2018 CHEST guidelines on atrial fibrillation recommended DOAC use over warfarin, there is little head to head evidence between the DOACs.

Purpose: To compare the safety and efficacy of apixaban versus rivaroxaban for the prevention of thromboembolic events in patients with nonvalvular atrial fibrillation.

Study Design: This study was a retrospective, active-comparator cohort study that used a nationwide commercial insurance claims database. This study compared patients aged 18 years and older who had a diagnosis of atrial fibrillation or atrial flutter and who had received a new prescription for apixaban 5 mg or rivaroxaban 20 mg between December 28, 2012 and January 1, 2019. Date of entry for inclusion in the analysis was considered to be the date of the first prescription for apixaban or rivaroxaban. Patients were excluded if they had any of the following characteristics within 180 days of starting the medication: stage 5 chronic kidney disease requiring dialysis, cancer, valvular heart disease, venous thromboembolism, hip surgery, or knee surgery. The primary effectiveness outcome was a composite of ischemic stroke or systemic embolism and the primary safety outcome was a composite of gastrointestinal bleeding or intracranial hemorrhage.

Results: Patients were divided into groups via 1:1 propensity score matching. In total, the study analyzed 78,702 patients with 39,351 patients in each arm of the study. Mean follow-up for apixaban was 288 days and 291 days for rivaroxaban. The patient in the apixaban group were slightly older, had more diagnoses of kidney or cardiovascular disease, and were receiving slightly more medications at baseline. Fewer patients in the rivaroxaban group had a history of smoking or hyperlipidemia and more had received warfarin in the preceding 30 days. After propensity score matching, 206 patients in the apixaban group had the primary outcome or 6.6 events per 1000 person-years compared to 251 patients in the rivaroxaban group or 8.0 events per 1000 person-years, 0.82 [95% CI, 0.68 - 0.98]. A subgroup analysis for patients older than 70 years old was conducted and in this subgroup 132 patients had the primary outcome in the apixaban group (8.3 events per 1000 person years) and 165 patients had the primary outcome in the rivaroxaban group (10.5 events per 1000 person years) 0.79 [95% CI, 0.63 - 0.99]. In regards to the primary safety outcome, after propensity score matching, the rate of major bleeding was 401 events or 12.9 per 1000 person years for apixaban and 685 events or 21.9 per 1000 person years for rivaroxaban, 0.58 [95% CI 0.52 - 0.66].

Conclusions: This retrospective cohort study suggests that apixaban is more likely to prevent a stroke or systemic embolism and is less likely to cause a major bleed than rivaroxaban for patients with nonvalvular atrial fibrillation. Interestingly, the subgroup of patients greater than 70 years old (a population that would be at greater risk for an embolic event and major bleed) also showed significance for apixaban over rivaroxaban. Until head to head randomized controlled trials are conducted on these medications, the results presented in this study support apixaban use over rivaroxaban when available.

Key Point: In patients with atrial fibrillation, apixaban may be safer and more effective than rivaroxaban due to results from a retrospective analysis.

Making Prevention of Diabetic Kidney Disease a PRIORITY* McKenzie Moore, Pharm.D.
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**Background:** Diabetic kidney disease, a leading cause of renal failure, is also associated with increased risk of cardiovascular disease. With the rate of diabetes increasing, the number of people being treated for end-stage kidney disease has more than doubled. Considering this, there is a need for improved treatment of diabetic kidney disease, potentially through prediction and prevention. Currently, diabetic kidney disease is diagnosed by albuminuria, a decrease in estimated glomerular filtration rate (eGFR), or both. Microalbuminuria (urine albumin-to-creatinine ratio [UACR] >30mg/g in at least two of three consecutive urine samples) and macroalbuminuria (UACR>300mg/g) is commonly treated with renin-angiotensin-aldosterone system (RAAS) blockers, however prognosis remains poor. There is consideration for more complete inhibition of RAAS with mineralocorticoid receptor antagonists (MRAs), such as spironolactone, for further renal effects. In studies using RAAS blockade for the prevention of microalbuminuria, results have been conflicting. If biomarkers could be utilized to identify those who would respond to preventive therapy, this intervention may prove more successful. A high-dimension urinary biomarker pattern of 273 peptides associated with overt kidney disease, CKD273, has been described and found to be robust across many causes of kidney disease, including diabetic kidney disease. In retrospective analyses, CKD273 identified those at risk of diabetic kidney disease and progression in albuminuria sooner than current clinical practice indices like eGFR and albuminuria.

**Purpose:** The goals of the PRIORITY study were to show association between CKD273 and progression to microalbuminuria in a prospective study setting and determine if increased RAAS inhibition (with addition of spironolactone) reduces the risk of microalbuminuria in those with high-risk CKD273 pattern.

**Study Design:** PRIORITY was a prospective, double-blind, randomized, placebo-controlled, international, multi-center clinical and observational study. Patients with type 2 diabetes, normoalbuminuria (UACR<30mg/g), and eGFR>45 ml/min aged 18-75 were recruited. Exclusion criteria included dual use of RAAS blockade or MRA, or heart failure. Proteomic analysis of urine samples were completed with CKD273 score used to stratify patients into high- or low-risk groups. Those in the high-risk group were randomized to receive spironolactone 25mg daily or matching placebo in addition to current therapies. Follow-up took place every 13 weeks to receive the study drug and complete UACR monitoring. Low-risk participants continued current treatments and were followed without further intervention beyond yearly UACR monitoring. The primary endpoint was development of microalbuminuria with >30% increase in UACR from the initial sample or more than 40mg/g over the study period. The secondary endpoint was comparing progression to microalbuminuria in high-risk patients prescribed spironolactone versus placebo.

**Results:** Median follow-up was 2.5 years. The primary endpoint of microalbuminuria was increased in the high-risk group compared to low-risk (HR 3.92 [95% CI 2.90-5.30]). In those with baseline eGFR >60 ml/min, development of stage 3 chronic kidney disease was more frequent in the high-risk group compared to low-risk group (HR 3.50 [95% CI 2.50-4.90]). Percentage decrease in eGFR from baseline by 30% and 40% was more frequent in the high-risk group (HR 16.70 [95% CI 4.31-64.67] and 5.15 [95% CI 3.41-7.76] respectively). Progression to albuminuria and decrease in eGFR was faster in those in the high-risk group. The secondary study endpoint evaluating use of spironolactone in the high-risk group resulted in no significant difference (HR 0.81 [95% CI 0.49-1.34]). However, the medication was generally well-tolerated with low rates of discontinuation due to gynecomastia (3%) and hypotension (3%), and few mild episodes of hyperkalemia (13%).

**Conclusions:** Higher CKD273 classifier scores were associated with increased risk of progression to microalbuminuria and a decrease in renal function. Spironolactone did not delay the development of microalbuminuria or declining eGFR. This lack of difference could have been related to not meeting study power, the short duration of the study, or true absence of effect in this population. Although progression can be linked to CKD273 classifier scores, there is no evidence to suggest progression of microalbuminuria can be delayed with treatment, leaving use of CKD273 without a cost-effective place in clinical practice. It could however be used to enhance high-risk population identification in clinical trials for the time being.

**Key point:** Microalbuminuria is the earliest clinical marker for renal damage, but at the time of detection, histological changes may already be advanced. The urinary proteomic biomarker CKD273 could be used to predict which individuals are at high-risk for progression to microalbuminuria and worsening renal function.

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**THERAPEUTIC THOUGHT**

**Updates in the Pharmacological Management of COPD**

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**Background:** Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the United States with more than 140,000 deaths each year. Although there is currently no cure for COPD, both pharmacological and non-pharmacological treatments can control symptoms, reduce frequency of exacerbations and improve quality of life (QOL). Their recommendations resulted from a comprehensive literature review of studies between 1990 and July 2019. The ATS guidelines...
convey similar guidance as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 report, however there are some key features that differentiate between guidelines.

Evidence: The purpose of the ATS guideline update was to address six specific questions related to pharmacological management of COPD. In question number one, ATS analyzed whether long-acting beta agonists (LABA) in combination with long-acting muscarinic antagonists (LAMA) was more effective than and as safe as either agent alone in patients with COPD who complain of dyspnea or exercise intolerance. The ATS strongly recommends the use of a LABA/LAMA in combination and concluded that dual therapy significantly reduces exacerbations and hospital admissions while also improving dyspnea and QOL. Additionally, ATS did not reveal any evidence of harm from dual therapy compared to monotherapy. The GOLD report also strongly recommends combination treatment with LABA/LAMA including evidence of increasing forced expiratory volume in one second (FEV1).

For question number two, ATS investigated if triple therapy with inhaled corticosteroids (ICS)/LABA/LAMA was more effective than and as safe as dual therapy with LABA/LAMA in patients who complain of dyspnea or exercise intolerance despite the use of dual therapy. In patients who have a history of >1 exacerbations in the past year requiring antibiotics, oral steroids or hospitalization, ATS suggests the use of triple therapy with ICS/LABA/LAMA over dual therapy with LABA/LAMA. The ATS noted although triple therapy increases the risk of pneumonia, the benefits of exacerbation reduction outweighs this risk. The GOLD guidelines also endorse triple therapy with ICS/LABA/LAMA and report evidence of improved lung function, increased health status and reduction of exacerbations compared to ICS/LABA, LABA/LAMA or LAMA alone. GOLD also mentions these effects are more prominent in patients “who are severely symptomatic, have moderate to very severe airflow obstruction, and a history of frequent and/or severe exacerbations.”

In question number three, ATS examined whether the ICS should be withdrawn in patients with COPD who are on triple therapy with ICS/LABA/LAMA. The ATS recommends ICS can be withdrawn in patients with no exacerbations in the past year, conveying there was no statistically significant difference in risk of pneumonia, all-cause mortality, or risk of exacerbation. On the other hand, the GOLD guidelines caution against de-escalating ICS in patients who were severely symptomatic, with moderate to severe airflow obstruction, and had a history of frequent and/or severe exacerbations before disease state stability. The studies in the GOLD guidelines report decreased FEV1 and increased exacerbations among patients with eosinophils >300 cells/μL.

For question number four, ATS evaluated whether treatment in patients with COPD and blood eosinophilia (>150 cells/μL) should include an ICS in addition to a long-acting bronchodilator. The ATS recommends ICS as additive therapy to a long-acting bronchodilator in patients with blood eosinophilia and a history of >1 exacerbation per year requiring antibiotics, oral steroids or hospitalization. On the contrary, the GOLD report suggests use of ICS may be considered in patients with one moderate COPD exacerbation per year or blood eosinophils 100-300 cells/μL. The GOLD guidelines more strongly supports the addition of an ICS with one or two long-acting bronchodilators in patients with a history of hospitalizations for COPD exacerbations, >2 moderate exacerbations of COPD per year, blood eosinophils >300 cells/μL, or history of, or concomitant, asthma.

In question number five and six, ATS explored if maintenance oral steroid therapy or opioid-based therapy is more effective than and as safe as no additional therapy in patients with COPD who have a history of severe and frequent exacerbations regardless of optimal therapy. ATS and GOLD both recommend against the use of maintenance oral corticosteroids, suggesting lack of benefit and increased harm such as side effects and steroid myopathy. In regards to opioid therapy, ATS suggests evidence of dyspnea improvement with opioid treatment and recommends treatment to be considered through shared-decision making. The GOLD report specifically mentions opiates, such as immediate-release morphine rather than synthetic opioids, along with neuromuscular electrical stimulation, oxygen and fans blowing air on to the face for palliative treatment of dyspnea.

Discussion and Clinical Impact: While the majority of the ATS recommendations for pharmacologic management of COPD were similar to the previously published GOLD 2020 report, the main difference was the blood eosinophil cut-offs for addition of an ICS. Both guidelines recommend the option to withdraw an ICS from treatment however the GOLD recommendations are more reserved. Although pharmacological therapy for COPD can control symptoms, reduce frequency of exacerbations and improve QOL, treatments have not been proven to prevent progression of disease or reduce mortality. When determining treatment for COPD, patient involvement through shared-decision making may be as important as safety, efficacy, and convenience.

U Direct Oral Anticoagulant for Treatment of Venous Thromboembolism in Obese Patients8–11

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Background: Direct oral anticoagulants (DOACs) have demonstrated similar safety and efficacy to vitamin K antagonists for the prevention of stroke in atrial fibrillation (AF) and management of venous thromboembolism (VTE). With the advantages of fewer interactions, fixed dosing, and lack of routine monitoring compared to vitamin K antagonists, DOACs have
become increasingly popular in the outpatient setting. Due to pharmacodynamic (PD) and pharmacokinetic (PK) differences and limited safety and efficacy data, use has been cautioned in obese patients. Specifically, the 2016 International Society on Thrombosis and Haemostasis (ISTH) discourages the use of DOACs in patients with a body mass index (BMI) >40 kg/m2 or weight >120 kg and recommends peak and trough laboratory monitoring if utilized.

**Evidence:** A recent review article examined 19 studies including PK studies and clinical trials conducted on DOACs. PK studies in both healthy and VTE patients suggest the effects on the PK and PD properties are variable and may be dependent on which DOAC is used in obesity. Throughout the reviewed clinical trials, there does not appear to be increased risk in the use of DOACs in obese patients, although most data is based on patients with AF. Studies examining safety and efficacy in VTE is lacking; however, three studies following the 2016 ISTH guideline release suggest DOACs may have similar safety and efficacy for VTE in obese patients.

Spyropoulos et al. is a 1:1 propensity matched retrospective cohort study (n = 2890) comparing the use of rivaroxaban and warfarin after a VTE in patients with a diagnosis of “morbid obesity.” The study found no difference in risk of recurrent VTE (0.99 [95% CI 0.85 - 1.14]) or major bleeding (0.75 [95% CI 0.47 - 1.19]). They did observe decreased health care utilization and medical costs in the rivaroxaban group for hospitalizations (0.86 [95% CI 0.77 - 0.96]), outpatient visits (0.23 [95% CI 0.10 - 0.56]), and per patient per year cost ($34,824 vs $37,653).

Perales et al. examined the use of rivaroxaban (n = 84) compared to warfarin (n=92) retrospectively for initial treatment of either AF or VTE in patients with a BMI >40 kg/m2 or body weight >120 kg. Rivaroxaban treated patients had lower rates of combined VTE recurrence, stroke, or mortality within 12 months of initiation compared to warfarin treated patients although without statistical significance (5% vs 13%, P=0.06). Further, rivaroxaban patients had shorter lengths of stay (two days vs four days, P<0.001) with a non-statistically significant increase in bleeding complications (8% vs 2%, P=0.06).

Most recently, a retrospective propensity matched study, Coons et al., examined patients with an acute deep vein thrombosis (DVT) and body weight of 100-300 kg treated with either apixaban, dabigatran, or rivaroxaban (n=632) or warfarin (n=1208). Between the two groups there was no difference in VTE recurrence (6.5% vs 6.5%, P=0.93) or pulmonary embolism (PE) and DVT occurrence (3.7% vs 3.8%, P=0.94 and 3% vs 3.5%, P=0.56, respectively). Likewise, there was no difference in bleeding between the two groups (1.7% vs 1.2%, P=0.31).

**Discussion and Clinical Impact:** All three studies are retrospective cohort studies. Randomized control trials with similar outcomes would provide stronger evidence that these medications could be used safely in obese patients. Since differences in PK and PD properties have been observed in obese patients taking DOACs, studies demonstrating safe and efficacious drug levels would further support use of these medications. The studies discussed demonstrate that DOACs, specifically rivaroxaban, may have similar outcomes data compared to vitamin K antagonists. Taking into account the trial design and need for further evidence, these studies alone do not provide evidence for the safe use of DOACs in obese patients; however, should be considered as the use of DOACs will continue to change the landscape of anticoagulation.

**Deprescribing Proton Pump Inhibitors**

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**Background:** Proton pump inhibitors (PPIs) are a widely used medication class for the treatment of many GI disorders. An article from Lee and McDonald stated that the United States spent roughly $79 billion on PPIs from 2007 to 2011. Although PPIs are effective inhibitors of gastric acid secretion, they may also cause adverse effects and health risks. Some of the most common adverse effects associated with PPIs include headache, nausea, diarrhea, and rash. However, they are also associated with more serious health implications including higher risk of fractures, *C. difficile* infection, community-acquired pneumonia, vitamin B-12 deficiency, and hypomagnesemia. A recent systematic review and meta-analysis published by Willems et al. explored the association between the use of acid suppressants and the risk of colonization with multidrug-resistant microorganisms (MDROs). This study reviewed 17 observational studies and found that patients treated with PPIs had increased odds of MDRO colonization by approximately 8x (1.81 [95% CI 1.52-2.16]). Studies cited in Canadian clinical practice guidelines for deprescribing PPIs consistently estimate that inappropriate use of PPIs occurs in 40% to 65% of patients to whom they are prescribed. This demonstrates the importance of routine reassessment of indication for PPI use and consideration of deprescribing, which Thompson and Farrell define as “the process of tapering, stopping, discontinuing, or withdrawing drugs, with the goal of managing polypharmacy and improving outcomes.”

**Evidence and Discussion:** To date, there are few guidelines for deprescribing PPIs; however, a publication in the Canadian Family Physician systematically reviewed the evidence for deprescribing PPIs and developed a decision-support algorithm to help guide clinicians in the deprescribing process. The algorithm is targeted toward adults over the age of 18 who have been taking a PPI for at least four weeks with symptom resolution for treatment of upper GI symptoms including esophagitis, gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), and stress ulcer prophylaxis. The algorithm should not be used for those with...
with Barrett’s esophagus, severe esophagitis grade C or D, or history of bleeding GI ulcers as a gastroenterologist should be consulted if deprescribing PPIs is considered in these patients. The algorithm provides equally strong recommendations to either lower the current PPI dose or switch from continuous to on-demand use of PPIs, which is defined as discontinuing the medication after symptom resolution and waiting until symptoms recur, at which point the medication is taken daily again until symptoms resolve. The current evidence suggests a minimal risk of returning symptoms with the above deprescribing practices. Patients should be monitored at four weeks post-deprescribing to assess symptom control and again at 12 weeks to assess symptom control and need for on-demand treatment or return to continuous treatment. The algorithm places a weak recommendation on step-down to H2-receptor antagonists due to higher risk of symptom return. In addition, they discuss that the use of nonpharmacologic interventions and OTC antacids can be beneficial to manage occasional breakthrough symptoms. This algorithm and other deprescribing resources are readily available at deprescribing.org.

**Clinical Impact:** Although there is insufficient evidence from randomized clinical trials that one tapering approach is better than another, the above guidance can be used by clinicians as a tool along with consideration of what is most convenient and acceptable to the patient when deprescribing PPIs. Patients and caregivers may be more likely to trial deprescribing of PPIs if they understand the rationale for doing so, including risks of continued or long-term PPI use. Inclusion of pharmacists as a part of the patient care team may be beneficial to help facilitate patient education, dose changes, and monitoring for symptom recurrence.

### FROM THE PHARMACY PRESS

**Weight Loss with Empagliflozin versus Liraglutide**

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**Background:** Newer agents for Type 2 Diabetes Mellitus (T2DM), glucagon-like peptide-1 agonists (GLP-1 RAs) and sodium glucose cotransporter 2 (SGLT2) inhibitors, are being prescribed with increasing frequency thanks to their beneficial cardiovascular outcomes, ability to cause weight loss, and support for their use in the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) guidelines. Weight loss is known to improve glycemic control and reduce cardiovascular risk and is often in line with the patient’s personal health goals. Both the SGLT2 inhibitor empagliflozin and the GLP-1 RA liraglutide were shown to cause weight loss in clinical trials, but there are no head-to-head trials comparing weight loss outcomes for these agents.

**Objective:** To assess the differences in weight loss outcomes of empagliflozin and liraglutide in overweight or obese veterans with T2DM.

**Study Design:** This study was a multi-site, observational, cohort study including veterans with T2DM who had a hemoglobin A1c ≥7%, a body mass index (BMI) ≥27 kg/m², and who were not prescribed insulin at baseline. This cohort was prescribed either liraglutide or empagliflozin and followed for one year; the primary outcome assessed was change in weight using multiple regression. The secondary outcomes assessed were the change in A1c and the proportion of study subjects reaching ≥5% weight loss.

**Results:** The final cohort consisted of 298 patients treated with liraglutide and 247 patients treated with empagliflozin. The average weight loss in both groups was two to three kilograms over one year. Weight loss was not significantly different between liraglutide (−2.17 kg [95% CI −2.91 to −1.42]) and empagliflozin (−2.81 kg [95% CI −3.43 to −2.20]) groups. These results were adjusted for covariates, such as BMI, age, insulin exposure, and medication adherence, and the difference between the agents remained insignificant. For secondary outcomes, there was no difference found in A1c change from baseline, with liraglutide lowering A1c by 0.83% [95% CI −1.05% to −0.62%] and empagliflozin lowering A1c by 0.71% [95% CI −0.89% to −0.53%; P>0.05]. Finally, the proportion of patients with ≥5% weight loss was not statistically significant between liraglutide (6.4%) and empagliflozin (4.5%) groups (P>0.05).

**Limitations:** The study population was primarily older white males with average renal function, making these findings less applicable to the general population. A second limitation is that some study subjects required treatment with insulin during the study period, which is known to cause weight gain. Other limitations include considerable differences in baseline characteristics between study arms, a relatively small sample size, and the participation of some study subjects in weight management programs.

**Conclusions:** This study did not show a significant difference in weight loss outcomes between empagliflozin and liraglutide at one year. There was no significant difference in A1c lowering or proportion of subjects with ≥5% weight loss. Both medications caused modest weight loss and improvement in the A1c. When selecting between these agents, the decision should be based on patient preference, route of administration, cost, and comorbidities.

**Key Point:** Despite popular belief that GLP-1 RAs lead to more weight loss than SGLT2 inhibitors, empagliflozin and liraglutide had no significant difference in weight outcomes at one year.
Medication Dosing in Transgender Patients
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Background: The term transgender describes people whose gender identity differs from their sex assigned at birth. They are a unique population and are often the targets of discrimination and harassment. This may lead to higher instances of comorbid conditions including depression, substance abuse, and suicide compared to their cisgender counterparts. Unsurprisingly, access to quality healthcare may be limited in this population because of the lack of confidence transgender patients and providers have in each other to provide adequate care. Guidelines for transgender care do exist; however, they do not include guidance on how to calculate creatinine clearance (CrCl) or ideal body weight (IBW) necessary to dose many medications. The consequences of overdosing or underdosing medications in transgender patients include drug toxicity or therapeutic failure especially if they receive doses inconsistent with their current physiology.

Evidence: A literature review from Webb et al. looked at the current evidence on the effect of gender-affirming hormone therapy on serum creatinine concentration and lean body mass to inform a recommendation for drug dosing. Four studies were found on the effect of hormone therapy on biometric laboratory values. One study reported a range of values that more closely resembled those associated with sex at birth while still overlapping with values associated with gender identity. However, Webb et al. concluded that the results from this study were difficult to interpret since normal ranges for cisgender men and women already overlap.

Three studies reported that the values of transgender patients more closely resembled the standard values of their gender identity versus sex at birth after hormone therapy. The first study, an observational cross-sectional study, found that median lean body mass (LBM) was lower in transgender women than in cisgender men (51.2 kg versus 61.8 kg, P<0.001). Median serum creatinine (SCr) was also lower in transgender women than in cisgender men (0.78 mg/dL versus 0.94 mg/dL, P<0.001). A retrospective cohort study comparing laboratory values between baseline, three to six months, and six to 18 months revealed that both transgender women and transgender men experienced changes in biomarkers used to calculate CrCl and IBW as soon as three months after hormone therapy initiation. Transgender women did not experience a significant change in body mass index (BMI), but their SCr decreased from a baseline mean of 0.97 mg/dL to 0.89 mg/dL (P<0.001), whereas LBM remained mostly unchanged from 56.9 kg to 56.6 kg (P=0.56). In transgender men, mean LBM increased from 44.4 kg to 48.1 kg (P<0.001). Both groups experienced an increase in mean total BMI, from 21 to 21.9 (P=0.005) in transgender women and from 21.9 to 23.2 (P<0.001) in transgender men.

Discussion: The literature indicates that after hormone therapy, transgender patients’ physiology more closely reflects their gender identity than their sex at birth. Furthermore, considerations to start using biometric laboratory values based on gender identity was suggested after six months of hormone therapy due to amenorrhea commonly occurring at that time in transgender men. Despite the lack of literature and the small number of participants in these studies, the findings are useful because they offer guidance to pharmacists regarding medication dosing in transgender patients. Dosing medications based on CrCl and IBW calculations consistent with gender identity after a patient has been on hormone therapy for six months or longer supports safe and effective treatment for transgender patients.

Workload Evaluation of Clinical Pharmacists in the Ambulatory Care Setting
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Purpose: The main purpose of this workload evaluation study was to articulate and measure the time spent on prespecified daily activities by clinical pharmacists in an ambulatory care setting. This study also assessed for differences in the distribution of workload between pharmacists and aimed to identify current inefficiencies in workflow and areas of opportunity for optimizing pharmacist-delivered patient care in the ambulatory care setting.

Study Design: This study was a prospective, ethnographic, observational pilot study conducted at six pharmacist-integrated, multidisciplinary, ambulatory care clinics. The clinical pharmacists needed to have been employed in their current position for six months or more to be included in the study. Participants completed a survey describing their demographics, clinical site characteristics, and self-reported engagement in direct patient care activities. Additionally, participants were observed for up to three non-consecutive clinic workdays where clinical and administrative workload activities were evaluated through direct observation. Observation data was used to calculate the proportion of time spent on pre-visit, visit, post-visit, administrative, or other activities. Additionally, time spent on these activities was documented by the observer and categorized according to each step of the pharmacists’ patient care process (collect, assess, plan, implement, follow up, and collaborate/communicate/document). The primary outcome was
to measure the time spent on daily activities performed and was analyzed using descriptive statistics.

**Results:** Ten clinical pharmacists were observed for a total of 26 clinic workdays and completed 164 patient encounters; 103 (63%) encounters were targeted (one disease state), 31 (19%) encounters were dual focused (two disease states), and 30 (18%) encounters were comprehensive (three or more disease states). Of the prespecified workload activities, participants spent the greatest amount of time documenting patient care activities after the visit, regardless of the visit type. Time for documentation was a mean (SD) of 6.6 (6.7) minutes for targeted visits, 8.0 (8.2) minutes for dual focused visits, and 7.6 (7.7) minutes for comprehensive visits. Additionally, participants spent a significant amount of time in the collection phase of the patient care process, spending an average of approximately three minutes on each prespecified activity in this category. The plan and implement steps had less prespecified activities, and participants spent less time in these steps. A positive correlation was identified between years in clinical practice and time spent on collect and plan activities ($r=0.653$ [P=0.0407] and $r=0.680$ [P=0.0304], respectively), and a negative correlation with time spent on follow up activities ($r=-0.641$ [P=0.0460]).

**Conclusions:** This study articulated the daily workload activities that are performed by a select group of ambulatory care clinical pharmacists. There was variation in clinical and administrative activities seen among participants. However, years of practice experience, postgraduate training, board certification, duration of practice at the site, and site characteristics did not affect the distribution of time spent on activities comprising the patient care process, with all participants spending the greatest amount of their time documenting patient care activities.

**Key Point:** This study helps provide a more complete understanding of the ambulatory care pharmacist’s daily workload and potentially assists in identifying areas for improvement in efficiency. It demonstrated that pharmacists spend the greatest amount of their time documenting patient encounters.

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**MISCELLANEOUS NEWS**

**Over Half of Americans Starting Opioids May Be Receiving Inappropriate Treatment**

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Researchers from the Mayo Clinic studying use of opioids in the United States not only found opioid overprescribing, but found that overprescription of high-potency opioids has likely influenced the opioid epidemic.

While it is important to note that certain extended-release or stronger opioids may be clinically necessary at times, they carry with them potential serious risks or side effects. The Mayo Clinic researchers were interested to see if tolerance played a factor in these prescriptions. Researchers examined de-identified claims data and linked electronic health records to determine appropriateness of use. Hospitalized patients, those with an opioid poisoning diagnosis within the previous six months, or those without six months of continuous insurance claims at the time of the prescription were excluded from the study.

Of the nearly 300,000 high-potency prescriptions evaluated in a 10-year period, less than half of patients showed evidence of prior opioid tolerance. The researchers found this concerning, because without previous opioid exposure, these patients are at arguably higher risk for side effects. Researchers speculated that some clinicians may have made these decisions out of necessity, such as using fentanyl patches for patients that could not swallow pills; however, a supporting rationale was not found in the chart upon further review.

**A New Insulin Affordability Bill in MN**

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In mid-April, the Governor of Minnesota, Tim Walz, approved and signed a bill promoting insulin affordability for Minnesota residents to combat the continually rising costs of insulin. Effective July 2020, this bill establishes two safety net programs, both short-term and long-term, for patients urgently requiring insulin and struggling to afford medications. This bill does not provide a state-funded insulin access program, but instead requires insulin manufacturers to develop patient assistance programs to ensure affordable insulin for all patients or face regulatory fines for noncompliance.

The bill establishes minimum requirements manufacturers’ programs must follow. Basic eligibility criteria includes that the patient is a Minnesota resident, not be enrolled in medical assistance or MinnesotaCare, and not have prescription drug coverage with existing limits for cost sharing in regards to insulin products of $75 or less per month. Key provisions of the urgent need program include providing patients with a 30 day supply of an insulin product based on the patient’s prescribed dose at a maximum out of pocket cost of $35 to the patient. Patients are eligible to use the urgent fill program once every 12 months. Some patients may be eligible for the continued safety net program, in which patients may receive a 90 day supply of an insulin product for a maximum of $50 in out-of-pocket costs.
A recent article published in the Journal of American Medicine (JAMA) calls into question the use of delayed antibiotic prescribing as an antimicrobial stewardship initiative. Delayed antibiotic prescribing refers to the practice of providing antibiotic prescriptions to patients in the ambulatory care setting with the expectation the patient would not fill the prescription unless improvement of symptoms was not seen within a few days.

Delayed antibiotic prescribing is currently recommended by the U.S. Centers for Disease Control and Prevention program Core Elements of Outpatient Antibiotic Stewardship as a potential action to promote appropriate antibiotic prescribing practice. Prescribers may utilize this practice to reduce overall use of antibiotics and avoid medicalization of self-limiting illnesses.

Additionally, a 2017 Cochrane review suggests delayed antibiotic prescribing practices can significantly reduce antibiotic use; however, it also suggests delayed antibiotic prescribing practices do not improve patient outcomes in non-antibiotic-appropriate conditions such as cough, sore throat, and the common cold in comparison to immediate antibiotic prescribing. Delayed-antibiotic prescribing may also increase antibiotic-seeking behaviors in patients.

The JAMA article suggests reductions in antibiotic prescriptions observed through delayed antibiotic prescribing are driven largely by inappropriate initial use of antibiotics. Delayed antibiotic prescribing also presents notable logistical barriers to its implementation. First, the exact period of how long patients should wait before filling the prescription is poorly defined. Additionally, clinicians must decide how the prescription should be provided to the patient. Several strategies exist, such as the patient being provided a prescription immediately and instructed to wait before filling it, or providing the patient a post-dated prescription.

Overall, delayed antibiotic prescribing may not be the most optimal antimicrobial stewardship practice; however, it may provide some benefit in reducing overall antibiotic use. Using this practice in conjunction with other strategies such as education and training regarding antibiotic use, developing clinical decision making support systems, and utilizing promotional material within practice sites to raise patient awareness about appropriate antibiotic prescribing may improve stewardship efforts overall.

REFERENCES