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RESEARCH UPDATES

Empagliflozin in Heart Failure with Preserved Ejection Fraction[1]

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Background: Previous studies have shown sodium-glucose cotransporter 2 inhibitors (SGLT2i) reduce development and progression of heart failure in patients with type 2 diabetes and heart failure with reduced ejection fraction (HFrEF). The effects of this class of medications in patients with heart failure with preserved ejection fraction (HFpEF) have not been well studied.

Purpose: The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) aimed to evaluate the effects of empagliflozin on major heart failure outcomes in patients with HFpEF.

Study Design: This was a randomized, double-blind, parallel-group, placebo-controlled, event-driven trial conducted at 622 centers in 23 countries. To be eligible, participants had to be over the age of 18, have New York Heart Association (NYHA) functional class II-IV chronic heart failure with left ventricular ejection fraction (LVEF) of more than 40%, and have an N-terminal pro-B type natriuretic peptide (NT-proBNP) level of greater than 300 pg/dL (participants with atrial fibrillation at baseline required greater than 900 pg/mL). Participants were excluded if they had a condition, independent of heart failure, that could change their clinical course or jeopardize patient safety, including but not limited to: current/prior use of an SGLT2i, history of ketoacidosis, acute/chronic liver disease, or chronic pulmonary disease requiring home oxygen, oral corticosteroid therapy or hospitalization for exacerbation in the last 12 months. Participants were not required to have type 2 diabetes to be included in the study. Randomization was performed with permuted block design and was stratified by geographic region, diabetes status, estimated glomerular filtration rate (eGFR), and LVEF. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure. The secondary outcomes were the occurrence of all hospitalizations due to heart failure, including first and recurrent events, and rate of decline in eGFR during treatment.

Results: Of the 11,583 patients screened for eligibility, 5,988 patients were assigned to empagliflozin 10 mg daily (n=2997) or placebo (n=2991), in addition to usual heart failure therapy including renin-angiotensin inhibitors with or without neprilysin inhibitor, mineralocorticoid receptor antagonists, and beta-blockers. Characteristics between the two treatment groups were similar at baseline, including diabetes status (48.9% in empagliflozin group vs. 49.2% in placebo group) and eGFR. The primary composite outcome event occurred in 415 patients (13.8%) in the empagliflozin group and 541 patients (17.1%) in the placebo group ($p<0.001$). These results were also significant among subgroups, including those with or without diabetes, LVEF between 40-60%, and eGFR less than 60 mL/min/1.73 m2. At the median trial period of 26 months, the NNT with empagliflozin to prevent one primary outcome event was 31. The total

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of hospitalizations for heart failure was lower with the empagliflozin group compared to placebo (n=259 vs. 352; p<0.001). Additionally, rate of decline in eGFR was slower in the empagliflozin group than placebo (-1.25 vs. -2.62 mL/min per 1.73 m2 per year; p<0.001). Adverse events and discontinuation rates were similar between the two groups, with genital and urinary tract infections and hypotension being the most common concerns in patients treated with empagliflozin. Rates of hypoglycemic events were similar between empagliflozin and placebo, both in patients with and without diabetes (2.4% vs. 2.6%).

Conclusion/Key Point: Empagliflozin was shown to reduce the risk of composite cardiovascular death and hospitalization for heart failure in patients with HFpEF. This was seen regardless of diabetes status and in patients with an eGFR less than 60 mL/min/1.73 m2. Additionally, the use of empagliflozin was shown to slow the rate of eGFR decline. The use of empagliflozin may be considered in patients with HFpEF with or without diabetes to reduce the risk of composite cardiovascular death and hospitalization.

What are the effects of combining varenicline with nicotine patches and extending treatment duration on smoking cessation?[2]

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Background: Various strategies and interventions to enhance the effectiveness of lasting smoking cessation have been explored. Previous research on the combination of nicotine replacement therapy (NRT) with varenicline versus varenicline alone has shown differing results. A meta-analysis performed on previous studies showed statistical benefit in favor of combination therapy. After reviewing this meta- analysis, the American Thoracic Society conditionally recommended the combination of varenicline plus NRT versus varenicline alone while most guidelines continue to recommend monotherapy of varenicline, bupropion, NRT, or combination therapy of different NRTs. Due to this, a randomized clinical trial was performed that evaluated the effects of combining varenicline with NRT and extending varenicline treatment duration since limited evidence has been seen thus far.

Purpose: To compare the effectiveness of varenicline plus a nicotine patch versus varenicline alone for 12 weeks or 24 weeks on smoking cessation treatment.

Study Design: The study was a double-blind, 2x2 factorial randomized clinical trial that began initial enrollment on November 11, 2017 and was completed on July 9, 2020. The visits throughout the study occurred in one of two research clinics in Wisconsin. Eligible participants were individuals who smoked at least five cigarettes per day in the last six months, spoke English, were at least 18 years old, had exhaled carbon monoxide (CO) of five parts per million or greater indicating that they smoke cigarettes consistently, had a desire to quit smoking, did not use any other tobacco products in the past 30 days, had phone access, and were willing and able to use both NRT and varenicline. A total of 1,251 people were randomized evenly into four different groups. The four groups were varenicline monotherapy for 12 weeks (n=315), varenicline plus nicotine patch for 12 weeks (n=314), varenicline monotherapy for 24 weeks (n=311), and varenicline plus nicotine patch for 24 weeks (n=311). Varenicline dosing was titrated to 2 mg daily after one week appropriately and participants in the patch groups received 14mg nicotine patches. Additionally, a placebo patch was given to participants that had varenicline monotherapy and placebo varenicline was given to participants who were in the 12 week duration study arms to be used during the remaining 12 weeks. The primary outcome collected was self-reported seven-day point prevalence abstinence at 52 weeks after the target quit day which was biochemically confirmed by CO testing.

Results: For the primary endpoint, 967 of the 1,251 participants provided self-reported data. Of the 967, 477 participants claimed abstinence and 317 of those underwent CO testing which confirmed abstinence in 247 of those participants. These results found no significant interaction between medication type or medication duration (1.03 [95% CI 0.91 - 1.17], P= 0.66). Additionally, for all secondary outcomes assessed, no significant findings were found.

Conclusion: Based on the study results, there was no significant difference in smoking cessation rates from the use of varenicline for 12 weeks when compared to a longer duration or addition of nicotine patches. No subgroup of participants showed significant results in favor of any specific treatment. This trial had several limitations. Some participants were not able to have a CO confirmation test at follow-up due to COVID-19 restrictions. Another limitation was that 23% of the sample population was lost to follow-up throughout the 52-week follow-up period and adherence to the medication(s) declined over time. The average initial adherence rate across the treatment groups were between 75-81% and by week 23 were between 40-55%.

Key Point: The use of varenicline in extended durations or in combination with nicotine replacement therapy did not show benefit in this study. Smoking cessation strategies are often very patient dependent. No treatment group showed to be safer than others, and for the usual population, combination therapy or increased duration did not improve outcomes in this study.

Comparison of New Pharmacologic Agents With Triptans for Treatment of Migraine[3]

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Background: Triptans, or 5-hydroxytryptamine1B/1D (5-HT1B/1D) receptor agonists, are widely regarded as the standard of care for the treatment of acute migraine. However, there are concerns with the efficacy and high discontinuation rate of these agents. Frequent use of triptans may also lead to medication overuse headaches. Additionally, these agents are contraindicated in patients with high cardiovascular risk due to their mechanism of inducing vasoconstriction. Two new classes of migraine drugs have been developed to provide improved outcomes for patients in whom triptans are either ineffective or unsafe. These two classes are the ditans, which are 5-hydroxytryptamine1F (5-HT1F) agonists and the gepants, which are calcitonin gene-related peptide (CGRP) antagonists. Limited information is available regarding the efficacy and safety of these newer agents compared to the standard of care for migraine treatment.

Purpose: To compare the benefits and adverse effects of triptans with newer agents 5-HT1F agonists (lasmiditan) and CGRP antagonists (rimegepant, ubrogepant) for the treatment of acute migraine attacks.

Study Design: This was a systematic review and meta-analysis that included double-blind randomized clinical trials (RCTs) with participants 18 years or older, reviewed currently available acute treatments for migraine at doses widespread in clinical use, had comparisons between specific therapies and/or placebo, and used the International Headache Society criteria for migraine diagnosis. Articles were excluded if they compared the same medication using different routes of administration. The Cochrane Register of Controlled Trials, Embase, and PubMed were searched from the databases' inception to March 5, 2020. A total of 261 articles were considered and 64 trials met inclusion criteria. The primary outcome was freedom from pain two hours after treatment. The secondary outcomes were pain relief two hours after treatment and tolerability determined by the number of adverse effects. For each specified outcome, the odds ratio (OR) was estimated with 95% CI using random-effects models.

Results: A total of 64 RCTs were included with 46,442 patients aged 36-43 years old and included 74-87% females. Triptans had a higher rate of pain freedom at two hours compared with 5-HT1F agonist, lasmiditan (range: OR, 1.72 [95% CI, 1.06-2.80] to OR, 3.40 [95% CI, 2.12-5.44]). Triptans also had a higher rate of pain freedom compared with CGRP antagonists, rimegepant (range: OR, 1.58 [95% CI 1.07-2.33] to OR, 3.13 [95% CI 2.16-4.52]) and ubrogepant (range: OR, 1.54 [95% CI 1.00-2.37] to OR, 3.05 [95% CI 2.02-4.60]). Triptans were associated with significantly better pain relief at two hours compared to lasmiditan, rimegepant, or ubrogepant. Lasmiditan had the highest OR of any adverse events compared to placebo. Triptans such as rizatriptan, sumatriptan, and zolmitriptan were associated with a higher OR of adverse events than the CGRP antagonists. Specifically, triptans had a higher OR of chest symptoms in all adverse events including chest pain, tightness, heaviness, and pressure compared to CGRP antagonists. Most patient reported adverse events were mild to moderate and were considered tolerable.

Conclusion: Newer agents lasmiditan, rimegepant, and ubrogepant were associated with lower ORs for pain freedom and pain relief at 2 hours post dose compared to most triptans. However, there still may be a benefit of these newer agents for patients who have failed triptans or have cardiovascular contraindications. A key limitation of the study is the focus on short-term efficacy and safety after a single dose for a single migraine attack rather than long-term use when used for repeated migraine attacks. This study also did not specify the types of adverse events, and instead compared the overall rates of adverse events from each study included in the meta analysis.

Key Point: Triptans were shown to be more effective for pain freedom and pain relief at 2 hours post dose compared to newer agents lasmiditan, rimegepant, and ubrogepant. The benefits of the newer agents may be found in their use for repeated migraine attacks, and for patients who have failed, had adverse effects, or have contraindications to triptan use.

THERAPEUTIC THOUGHT

Reassessing Race in the CKD-EPI Equation[4-9]

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Background: In comparison to White patients, Black patients experience worse outcomes in regard to timely nephrology referrals, waitlisting for kidney transplantation, and being less likely to receive sodium-glucose cotransporter-2 inhibitor (SGLT2i) therapy. Over the past decade, the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine (CKD-EPIcr) equation has been used to calculate estimated glomerular filtration rate (eGFR). This equation included "race" (Black or non-Black) as a variable after findings from Levey et. al. deemed the equation more accurate than other commonly used equations at that time. However, Black patients have a higher calculated eGFR than non-Black patients compared to their actual measured GFR, which experts concur may delay access to kidney transplantation and kidney care, such as initiating SGLT2i therapy to stabilize kidney decline. One significant case report outlines a self-identified Black female who could have had a transplant two years sooner if the race variable was not used when calculating her eGFR--despite only having 48% African ancestry per an

Ancestry.com genetic test. Therefore, experts from the National Kidney Foundation (NKF) and American Society of Nephrology (ASN) formed a Task Force to reassess the evidence of including race in eGFR. While conducting an evidence-based review, the panel also interviewed a myriad of health professionals, experts, and patients and ultimately recommended immediate implementation of a, re-fitted CKD-EPIcr (2021) equation without a coefficient for race.

Evidence & Discussion: The Task Force explicitly states their evidence-based rationale highlighting that race is a social and not a biological construct, the need to improve the equity of health and social justice and citing the issues that arise when utilizing race for clinical algorithms (potential implicit and explicit bias). Additionally, the Task Force analyzed a plethora of studies with subsequent modified CKD-EPI equations, taking into consideration six "attributes": Equation performance; patient-centeredness; assay availability and standardization; population diversity in equation development; consequences to clinical care, research, and population tracking; and implementation challenges. Ultimately, the authors found that the re-fitted CKD-EPI equation without a race coefficient would pose minimal challenges in implementation, included diversity in its development, and does not disproportionately affect any group compared to keeping the CKD-EPIcr (2009) equation with the race factor or simply removing race from the CKD-EPIcr (2009).

The recommendation to simply remove race from the current eGFR equations did not go without debate. A 2020 cross-sectional review (also authored by Levey) cautioned against the removal of race from the CKD-EPIcr (2009) equation and reporting the same results for everyone. The authors found eliminating the race coefficient was associated with a systematic bias in underestimation of eGFR in Black individuals. Additionally, Casal et. al. was published shortly after the publication of the Task Force recommendation and cautioned against removal of race from CKD-EPIcr (2009) eGFR calculations. This study analyzed the eGFR with and without the race variable of Black patients undergoing phase one chemotherapy trials from 1995-2010. Importantly, both criticising studies utilized the CKD-EPIcr (2009) equation with or without the removal of race in their data analysis. The Task Force utilized a new, validated CKD-EPIcr (2021) equation without the coefficient of race with slightly adjusted multipliers to mitigate these proposed consequences (see below). Ultimately, the inclusion of comprehensive studies, formation of a multidisci-plinary Task Force across multiple organizations, and considera-tion of social implications warrant the recommendation to utilize the re-fitted CKD-EPIcr (2021) equation without a race coefficient.

Clinical Impact: Aside from an earlier diagnosis of Chronic Kidney Disease (CKD) and decreased kidney transplant waitlist time in in Black individuals, the clinical impact of this recommendation centers around pharmacotherapy adjustments and eligibility. With a decreased eGFR, by utilizing the CKD-EPIcr (2021) equation Black patients will have expanded access to SGLT-2i initiation, which can slow the progression of kidney disease. In contrast, Black patients may require dose adjustments of certain medications (such as metformin or sulfonylureas). Overall, this change is patient-centered, evidence-based, and may improve equity of health for Black individuals.

CKD-EPIcr (2009) Equation: $eGFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{age} \times 1.018$ [if female] x 1.159 [if black]
**where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1*

CKD-EPIcr (2021) Equation: $eGFR = 142 \times \min(Scr/k,1)^{\alpha} \times \max(Scr/k,1)^{-1.200} \times 0.9938^{age} \times 1.012$ [if female]
**where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1*

ACE Inhibitors vs. ARBs[10-12]

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Background: Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are widely used in the United States for the treatment of hypertension and are among first-line therapy options, along with calcium channel blockers and thiazide or thiazide-like diuretics. Both work on the renin-angiotensin system (RAS) in the kidneys, however, they have different sites of action. ACE inhibitors inhibit the conversion of angiotensin I to angiotensin II, while ARBs block receptor binding of angiotensin II. Generally, both classes are interchangeable and yield similar efficacies. Over the years, ACE inhibitors have been more widely used than ARBs due to previously lower cost, as well as additional benefits seen with improving mortality in heart failure and post-myocardial infarction (MI) along with renal protection in patients with diabetes. Generally well-tolerated, patients taking ACE inhibitors or ARBs occasionally complain of a chronic, dry, non-productive cough. Hyperkalemia and an increase in serum creatinine may be seen while using these agents. This can be serious since hyperkalemia can cause cardiac issues, including arrhythmias, which can be life-threatening. Lab monitoring, especially upon initiation of one of these agents, is imperative for patient safety. Generally, there is no difference between selecting an ACE inhibitor or ARB for first-line use in hypertension, although a new analysis of a large trial suggests otherwise.

Evidence: A recent large analysis of a major trial, LEGEND-HTN, originally published in American Heart Association Hypertension, now claims that ARBs are preferred over ACE-inhibitors for first-line treatment of hypertension. LEGEND-HTN is the largest head-to-head comparison trial with almost 3 million patients with hypertension who were started on a first-line antihypertensive including: ACE inhibitors, ARBs, dihydropyridine or non-dihydropyridine calcium channel blockers, and thiazide or thiazide-like diuretics. Researchers aimed to identify differences between the drug classes including incidence of acute MI hospitalization for heart failure, stroke, or a composite of these cardiovascular outcomes plus sudden cardiac death. Secondary efficacy and safety outcomes also were examined. Prior to LEGEND-HTN, Cochrane published a large review between ACE inhibitors and ARBs for primary hypertension. Findings from this analysis suggest that while ARBs are slightly better tolerated than ACE inhibitors, there is a higher quality of data supporting the use of ACE inhibitors to prevent strokes, heart disease, and death, which makes ACE

inhibitors, as a class, preferable over ARBs. Findings from the new analysis show that ARBs may move up and surpass ACE inhibitors for first-line hypertension treatment due to similar efficacy with better tolerability. Furthermore, there was no statistical difference in the primary cardiac outcomes between the two groups. However, patients receiving ARBs had lower incidence of angioedema, cough, acute pancreatitis, and gastrointestinal bleeding compared to those receiving ACE inhibitors. Lisinopril made up over 80% of the ACE inhibitor group, which may have carried disproportionate weight in the drug-class comparison. This study was designed around patients who were receiving antihypertensive medications for the first time. The results do not factor in patients who already take one of the drugs and are considering switching or adding another medication to their regimen.

Clinical Impact and Discussion: Both ACE inhibitors and ARBs are effective blood-pressure lowering medications that have been on the market for years. If clinically indicated, either agent would likely be effective in patients with hypertension. Cost differences between the two drug classes are minimal since both have generic products that are readily available. New data suggests that ARBs are just as efficacious as ACE inhibitors with fewer adverse effects associated with their use, including reduction in angioedema, cough, and potentially a decreased risk of pancreatitis and gastrointestinal bleeding, although more research is needed to validate these claims. When faced with a clinical decision to start a patient on an ACE or ARB, opting for an ARB may be a slam dunk by providing good blood pressure lowering, improving cardiovascular outcomes, and fewer adverse events compared with commonly prescribed ACE inhibitors.

Here we go again! The Ever-Changing Use of Aspirin for Primary Prevention of Atherosclerotic Cardiovascular Disease[13-16]

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Background: The use of low-dose aspirin has found its place in secondary prevention of atherosclerotic cardiovascular disease (ASCVD), however its role in primary prevention of ASCVD is ever-changing and controversial. The mechanism behind aspirin's potential benefit in the prevention of ASCVD is its irreversible inhibition of cyclooxygenase-1 activity and thromboxane A2 synthesis, which leads to suppression of platelet activation and aggregation. The optimal dosing in support of this mechanism is less than 100mg (81mg in the U.S.). A patient's 10-year risk of experiencing ASCVD can be calculated using the Pooled Cohort Equations developed by the American College of Cardiology (ACC) /American Heart Association (AHA). While the true benefits of aspirin therapy in primary prevention have been debated, the increased risk of major bleeding with aspirin therapy has been clearly documented. This risk increases in patients who are greater than 70 years old, have a history of gastrointestinal bleeding, chronic kidney disease, coagulopathy, or are on concomitant medications that enhance bleed risk such as non-steroidal anti-inflammatory drugs or anticoagulants.

Recommendations surrounding the use of aspirin in primary prevention have been published by the American College of Chest Physicians in 2012, U.S. Preventive Services Task Force (USPSTF) in 2016, and the ACC/AHA in 2019. With each iteration of guidelines being released, the benefits of aspirin therapy in certain age groups and patient populations have narrowed.

Evidence & Discussion: The 2021 USPSTF Statement on Aspirin Use to Prevent Cardiovascular Disease is the newest recommendation, after the 2019 ACC/AHA Guidelines for Primary Prevention of Cardiovascular Disease. The 2019 ACC/AHA guideline recommends aspirin for primary prevention of ASCVD among adults 40-70 years old who have an ASCVD risk > 10% but are not at increased risk for bleeding. Additionally, aspirin is not recommended on a routine basis for patients > 70 years old or in any patients at increased risk of bleeding.

In a microsimulation model conducted by USPSTF to estimate the magnitude of the net benefit of aspirin for preventing ASCVD, the data suggests that a modest net benefit in quality-adjusted life and life-years gained is seen in patients 40-59 years old with a > 10% 10-year ASCVD risk. The benefits of initiating aspirin use are greater for individuals at higher risk for future ASCVD which was identified to be those with > 15% or > 20% 10-year ASCVD risk. Conversely, a range of slightly positive and negative impacts on the quality-adjusted life-years gained was seen in patients 60-69 years old, and an overall loss of both quality-adjusted life-years and life-years was seen in patients 70-79 years old.

The 2021 USPSTF Statement concluded that the decision to initiate aspirin in patients 40-59 years old for primary prevention should be an individual decision based on clinician and patient discussion of risks and benefits. Furthermore, they recommend that aspirin should not be initiated in patients > 60 years old and consideration for stopping treatment should occur around 75 years old.

Clinical Impact: Healthcare providers should recognize the ever-changing guidance surrounding aspirin use for primary prevention and consider patient specific characteristics (age, risk of ASCVD, and risk of bleed) when deciding to initiate therapy. The release of the 2021 USPSTF recommendations may decrease the initiation of aspirin in patients greater than 60 years old and lead to the discontinuation of aspirin at 75 years old or sooner depending on when risk of aspirin therapy outweighs potential benefits.

Comparing Newborn Outcomes After Prenatal Exposure to Individual Antidepressants: A Retrospective Cohort Study[17-18]

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Background: A Centers of Disease Control and Prevention (CDC) study found that 1 in 10 women in the United States reported experiencing major depression symptoms in 2018 and 1 in 8 women experience symptoms of postpartum depression (PPD). PPD can cause lower rates of breastfeeding initiation, poorer maternal-infant bonding, and infant developmental delays. Untreated depression in pregnancy can cause preterm delivery, preeclampsia, behavioral disturbances in babies at birth, and maternal suicidal ideations or attempts. In addition to cognitive behavioral therapy, antidepressants may also reduce the complications associated with major depression during pregnancy and PPD; however, because pregnant women are often excluded from studies, there is a lack of evidence supporting the safety of antidepressants in this population. Current depression guidelines support the safety of selective serotonin reuptake inhibitors (SSRIs) and selective-norepinephrine reuptake inhibitors (SNRIs) over other antidepressant drug classes for the general population. This study explored the safety of using SSRI and/or SNRI agents during pregnancy to help guide clinical decisions in this population.

Purpose: To compare safety outcomes in newborns of different antidepressant agents during pregnancy and help guide recommendations in the ambulatory care practice.

Study Design: Investigators pulled retrospective data from January 2010 to December 2019 from electronic medical records of several large health systems in Indiana to find patients that were prescribed an SSRI and/or SNRI starting from 100 days before the last menstrual period through the date of delivery. The study controlled for maternal age (average age was 29 + 5.8 years), race, insurance, estimated gestational age at delivery, and newborn weight, length, and head circumference between drug groups. SSRIs included citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. SNRIs included bupropion, desvenlafaxine, duloxetine, and venlafaxine. Primary outcomes included neonatal intensive care unit (NICU) admission and any signs of adaptation syndrome (such as respiratory distress, feeding difficulty, jitteriness, or irritability). For this study, adaptation syndrome included diagnosis of neonatal abstinence syndrome (NAS) and pediatric adaptation syndrome (PAS). Women were categorized as either early exposure (within three months before pregnancy began or in the first trimester) or third trimester exposure (after 28 weeks of gestation).

Results: The study included 3694 women who were prescribed sertraline, escitalopram, fluoxetine, bupropion, citalopram, duloxetine, venlafaxine, paroxetine, and/or desvenlafaxine (n = 1653, 581, 579, 406, 385, 139, 132, 55, and 16, respectively). Bupropion had the lowest rate of adverse events of all agents, and was therefore used as the reference to compare the other agents (22.4% NICU admission and 4.7% any adaptation syndrome). Meanwhile, sertraline had the second lowest rate in adverse events after bupropion (23.3% NICU admission and 4.5% adaptation syndrome). In contrast, duloxetine had the highest rates of NICU admission (39.6%) and any adaptation syndrome (15.1%). Paroxetine also had higher rates of adaptation syndrome (12.7%) while venlafaxine had the highest rate of transient tachypnea of the newborn (TTN; 18.2%).

Women with early pregnancy exposure to duloxetine and/or escitalopram had increased odds of any adaptation syndrome, adjusted odds ratio (aOR) 2.31 [95% CI 1.11 - 4.8] and aOR 1.72 [95% CI 1.09 - 2.71], respectively, compared to women that did not have exposure to any antidepressants during early pregnancy. Alternatively, in third trimester exposure versus no exposure to any antidepressant, citalopram, duloxetine, escitalopram, fluoxetine, sertraline, and venlafaxine had greater odds of adaptation syndrome and bupropion, citalopram, duloxetine, escitalopram and fluoxetine had higher odds for NICU admissions.

Conclusions: The safety of medications in pregnancy is challenging due to the ethical and logistical barriers to investigating therapies in this population. This retrospective study evaluated the rate of adaptation syndrome, NICU admission, and TTN to unveil the safety of SSRI and/or SNRI exposure during pregnancy. Results found that duloxetine and escitalopram had the greatest risk for any adaptation syndrome and NICU admission, while bupropion and sertraline tended to have the lowest risk for these outcomes and were the most used antidepressants during this study. These outcomes may be related to the agent's affinity for SERT (serotonin transporter) but further investigation should be done to draw this conclusion. The study was not able to account for under- or over-capturing outcomes due to inconsistencies with use of ICD9/10 codes, variability in dosing, and influence of other onboard therapies like opioids. Also, adherence was assumed but cannot be guaranteed as a retrospective study.

Key Points: The findings from this study can help guide recommendations in ambulatory care practice when selecting safer antidepressant agents for individuals that are pregnant or planning on becoming pregnant.

A Tool for Pharmacists to Predict 30-day Hospital Readmission in Patients with Heart Failure (ToPP-HF)[19]

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Background: Despite a nationwide effort to improve readmission rates in patients with heart failure (HF), over 20% of these patients

still experience 30-day rehospitalizations. Pharmacists are equipped to provide transitions of care (TOC) services to patients with HF which can reduce the burden on other healthcare providers while ensuring safer and higher-quality care for patients. These pharmacist-led TOC services can include medication review, drug monitoring, adherence reinforcement, and patient education. However, interventions for these patients exceed the capacity of some TOC pharmacists due to time constraints and limited resources. Identifying and prioritizing HF patients at highest risk for readmission could help pharmacists to target patients most likely to benefit from their services.

Purpose: This study aimed to develop and validate a user-friendly prediction tool to assist pharmacists in efficiently identifying high-risk patients with HF admitted for any reason for 30-day all-cause unplanned hospital readmission to aid in prioritizing TOC services. This tool was specifically designed to be used by inpatient pharmacists to guide TOC interventions prior to hospital discharge.

Study Design: The Tool for Pharmacists to Predict 30-day hospital readmission in patients with Heart Failure (ToPP-HF) was based on a retrospective cohort study which analyzed data of HF patients admitted to a health system over a three year period. The study included adults (> 18 years old) with HF admitted to two hospitals within a health system and randomly divided the population into two subcohorts of development (n=2,114) and validation (n=1,089). One hundred potential predictor variables were collected, and nine variable selection models were used to determine the final model. The final set of variables were inputted into a logistic regression model. Scores were then assigned by a pharmacist to each level of each variable, allowing both positive and negative values (ranging from -30 to 49), and rounding to the nearest integer.

Final Score Distribution	ToPP-HF Score Ranges	Risk of Readmission
> 90th percentile	17 to 49	High-risk
81st - 90th percentile	12 to 16	Moderate- to High-risk
51st - 80th percentile	0 to 11	Moderate-risk
< 50th percentile	-30 to -1	Low-risk

The data was assessed using the C statistic and calibration using the Hosmer-Lemeshow goodness-of-fit test and was then analyzed using SAS and Stata software.

Results: To make the tool user-friendly, the final ToPP-HF scoring was comprised of only 13 variables which included number of hospital admissions in previous six months; admission diagnosis of HF; number of scheduled medications; chronic obstructive pulmonary disease diagnosis; number of comorbidities; estimated glomerular filtration rate; hospital length of stay; left ventricular ejection fraction (LVEF); critical care requirement; renin-angiotensin-aldosterone system inhibitor use; antiarrhythmic use; hypokalemia; and serum sodium. The 30-day readmission outcome occurred in 16.7% of the overall study population (15.7% in the development subcohort and 18.8% in the validation subcohort). The risk prediction models showed good discrimination performance (C statistic of 0.69 [95% CI 0.65 – 0.73]) and calibration (Hosmer-Lemeshow P=0.28).

Conclusion: This study concluded that the ToPP-HF is a well-designed and easy-to-use tool for pharmacists to predict 30-day all-cause, unplanned, hospital readmission and can help pharmacists to identify high-risk patients with HF who may benefit from pharmacist-led TOC services. One limitation of this study was that the data collected was from only one health system's electronic medical records (EMR) which could have missed external readmission records or most recent LVEF if a patient received care outside of the two hospitals within the system. In addition, it may be difficult and time-consuming for pharmacists to calculate the ToPP-HF score by hand as it includes 13 variables, so technology resources to automatically calculate the score would be helpful if EMR integration is possible. However, given that one focus of this study was to make the ToPP-HF tool user-friendly, it may be at the expense of accuracy as it was limited to 13 easy to evaluate variables which were not the most clinically significant predictors for readmission and could result in a less accurate prediction of readmission. Future studies may be warranted to assess generalizability of ToPP-HF to other institutions.

Key Point: Pharmacists are well positioned to transition HF patients from the hospital to an outpatient setting by optimizing guideline-directed pharmacotherapy treatments, encouraging medication adherence, and providing patient education. The ToPP-HF can help to identify HF patients most likely to benefit from pharmacist-led interventions through TOC services to prevent hospital readmission, likely leading to improved patient outcomes and decreased costs for the health system. However, further research should be conducted to evaluate whether pharmacist TOC interventions reduce readmissions for those selected by the ToPP-HF as highest risk.

Calculating Creatinine-Based Kidney Function With and Without Sex Assigned at Birth Among Transgender Adults)[20]

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Background: Hormone therapy typically causes marked physiologic and body composition changes within months of initiation among transgender adults. The alterations in lean muscle mass due to hormone therapy is expected to have a corresponding impact on serum creatinine, as this is a known breakdown product of muscle. What is less understood is whether hormone therapy influences kidney function directly and how

clinicians should utilize gender as it relates to estimated creatinine clearance (eCrCl) and glomerular filtration rate (eGFR) equations to provide the most accurate results. As a way to account for the average body composition differences between sexes, clinicians have recommended using equations based on gender identity, rather than one's sex assigned at birth in transgender adults utilizing hormone therapy.

Objectives: The primary endpoint was the percent difference in median eCrCl three to six months and six to twelve months post initiation of hormone therapy compared with baseline using the Cockcroft-Gault (C-G) renal function estimation equation. The secondary objective was to re-analyze Cockcroft-Gault, modification of diet in renal disease (MDRD), and chronic kidney disease epidemiology study (CKD-EPI) estimates three to six months and six to twelve months post-index date using equations associated with gender identity (male-based equations in the testosterone group; female-based equations in the estrogen group) and compared these with baseline estimates using sex assigned at birth.

Study Design: This study was a single-system, multicenter, retrospective cohort study of healthy transgender adults. Patients were identified over a ten year period as having completed at least one transgender health-related clinical visit based on validated diagnosis codes. Eligible patients were prescribed hormone therapy, either testosterone or estrogen, for at least 90 days, with the index date set as the first hormone order date, and at least one creatinine measurement within six months pre-index date at baseline.

Results: In total, 989 patients completed at least one clinical visit for transgender related care. Of those 989 patients, 70 were analyzed, 29 of whom were prescribed testosterone and 41 were prescribed estrogen. At baseline and follow-up visits, laboratory values, body composition, eCrCL and eGFR using estimating equations based on sex assigned at birth, and gender identiy were assessed and recorded. In the testosterone group, using female-based equations, Cockcroft-Gault estimates significantly decreased from baseline only at the six to twelve-month follow-up assessment. Also, in the testosterone group, median MDRD and CKD-EPI estimates had a significant decrease at both the three to six month and six-to-twelve-month follow-up when compared to baseline (see Table 1 below). In the estrogen group, using male-based equations, there were no statistically significant changes at either the three to six month or six-to-twelve-month follow-up assessments. When applying gender identity, using male based equations in the testosterone group at follow-up, median MDRD and CKD-EPI estimates were significantly higher at both the three to six month and six-to-twelve-month visits, compared to baseline (see Table 2 below). The authors note that these findings suggest on average, neither testosterone or estrogen treatment are likely associated with significant changes in estimated kidney function, and feel that these findings align with previous studies recommending clinicians use male-based equations after at least six months of testosterone therapy.

Table 1. Abbreviated Testosterone Group Results at Baseline and Follow-up (n = 29).

Percent Change	Baseline (range)	3-6 Months (range)	6-12 Month (range)
eCrCL C-G (ml/min)	120 (97-143)	94 (93 - 114) -3%: female-based P = 0.3125 +21%: male-based P > 0.025	93 (83 - 119) -14%: female-based P = 0.0181 +5%: male-based P > 0.025
eGFR MDRD (ml/min/1.73m^2)	99 (83 - 120)	89 (81 - 96) -7%: female-based P = 0.0013 +26%: male-based P = 0.0005	80 (71 - 100) -18%: female-based P = 0.0006 +11%: male-based P = 0.0003
eGFR CKD-EPI (ml/min/1.73m^2)	116 (97 - 124)	105 (94 - 112) -7%: female-based P = 0.0046 +13%: male-based P = 0.0007	94 (83 - 113) -9%: female-based P = 0.0009 +4%: male-based P = 0.0094

Table 2. Abbreviated Estrogen Group Results at Baseline and Follow-up (n = 41).

Percent Change	Baseline (range)	3-6 Months (range)	6-12 Months (range)
eCrCL C-G (ml/min)	129 (112 - 153)	125 (116 - 144) +5%: male-based P = 0.2842 -12%: female-based P < 0.0001	145 (105 - 163) 0%: male-based P = 0.6567 -17%: female-based P < 0.0001
eGFR MDRD (ml/min/1.73m^2)	111 (94 - 125)	105 (101 - 120) +4%: male-based P = 0.2451 -23%: female-based P < 0.0001	117 (90 - 133) 0%: male-based P = 0.6476 -26%: female-based P < 0.0001
eGFR CKD-EPI (ml/min/1.73m^2)	117 (104 - 126)	116 (109 - 126) +1%: male-based P = 0.2348 -19%: female-based P < 0.0001	122 (101 - 130) 0%: male-based P = 0.9705 -15%: female-based P < 0.0001

Conclusions: It still remains unclear whether sex-based or gender-identity-based kidney function estimation equations are accurate for transgender adults using hormone therapy. Female-based equations may underestimate eCrCl or eGFR amoung transgender adults undergoing either testosterone or estrogen therapy within the first year of therapy. Clinicians should recognize the potential for underestimation of kidney function when utilizing female based estimation equations and dosing medications in transgender individuals when using kidney-based dose adjustments. Authors also note that larger prospective studies with measured GFRs are needed to determine the impact of hormone therapy on kidney function in transgender adults during both short and long-term therapy.

Best Bang for Your Buck: DOACs vs Warfarin for Atrial Fibrillation[21]

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Background: Since direct oral anticoagulants (DOACs) have gained popularity as guideline-supported therapy, cost has been a major factor in their utility, especially compared to warfarin which is thought to be inexpensive. Now that DOACs have gained popularity, a new question has started to arise. What would be more cost efficient; DOACs or warfarin with lab monitoring? Which of these two options provide a longer survival for patients? Can the current studies done on this topic be applied to the Veteran Affairs population? With the acceptance and increased use of DOACs in atrial fibrillation (AF), several studies have been completed on the affordability compared to warfarin. However, few studies have been applicable to the Veteran Affairs (VA)-Medicare dual enrolled population.

Purpose: This study's purpose was to assess the total medical expenses for nonvalvular atrial fibrillation (AF) patients who were either on a DOAC or warfarin and enrolled in the VA Healthcare System and fee-for-service Medicare.

Study Design: This nationwide retrospective cohort study looked at data collected between 2012 and 2015 primarily from the VA's Corporate Data Warehouse which contained care tracking from all VA facilities. The study analyzed 48,297 VA-Medicare dual enrolled patients: 31,276 receiving warfarin and 17,021 patients receiving a DOAC. Total expenditures were presented in table format. Each year was analyzed using a Kaplan-Meier estimator.

Inclusion criteria consisted of those with at least one prescription fill for warfarin or a DOAC within the time period. Exclusion criteria were those without a diagnosis of non-valvular AF or those with missing facility level identifiers. This was done to ensure complete data was being used for VA patients with fee-for-service Medicare. Lastly, those who had switched or discontinued anticoagulants within one year of the index date were excluded. The primary outcome was total medical expenditure over three years following treatment initiation.

Results: Overall, warfarin patients had a higher total healthcare cost than those who were on a DOAC. The cost of medical services was calculated from public payer perspective (VA and Medicare) using health service utilization and prescription drug fills. This held true for both the unadjusted average and three year adjusted expenditures. The study found that those on warfarin had an additional adjusted expenditure of $25,688 ($P<0.001$). Not only was this discovered, but the study also found that the survival rate was lower among warfarin patients by 0.52 years (95% CI=−0.695 to −0.349). The study noted that the increased cost and lower survival rate was potentially due to higher stroke rate and bleeding events with warfarin use than those on DOACs, which was also demonstrated in previous studies. Two of the prominent limitations with this study were having such a specific population as well as grouping patients based on DOAC class use, not a specific medication. With the population of the study only containing VA patients, it may not be generalizable to other populations. The limitation with just grouping patients based on DOAC medication class use and not a specific type of DOAC may not accurately capture the expenditure difference from DOAC to DOAC.

Conclusion: VA patients with nonvalvular AF who are being started on warfarin will incur a higher cost overall than those started on a DOAC. These patients also had a lower survival rate than those on DOACs.

Key Points: Important outcomes identified included patients on warfarin not only had a higher total overall healthcare cost but they also had a lower survival rate than those on DOACs. When the study assessed expenditures it was done yearly over a three year time span. Lastly, both in adjusted and raw scenarios, DOACs were most cost effective in the long run.

MISCELLANEOUS NEWS

Easing Patient Fears - Recalls due to Impurities[22-25]

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In recent years, there have been several high-profile recalls of drugs due to nitrosamine impurities. Nitrosamines are often formed as unintentional by-products during food processing. They are commonly found in processed meats, alcoholic beverages, and tobacco smoke. Trace amounts have also been identified in drinking water and some cosmetics. Several studies have concluded that prolonged exposure to high levels of some nitrosamine compounds can cause cancer in rats. Due to this, nitrosamines have been classified as probable or possible carcinogens in humans.

Recalls of ranitidine and metformin due to nitrosamine impurities in 2019 and 2020 caused much confusion for the public and prompted reckless headlines such as "Does Metformin Give You Cancer?". A similar response occurred after the latest recall of varenicline (Chantix®). It is imperative that pharmacists are prepared to discuss these recalls with patients and provide insight about the reason behind the uptick in recalls. First and foremost, it

is important to help patients understand that these recalls are related to impurities, rather than the medication itself. The Food and Drug Administration has found that the source of nitrosamines can be related to the drug's manufacturing process, its chemical structure, or storage conditions. The increased prevalence of nitrosamines in pharmaceuticals is thought to be largely due to advancements in the technology used to detect such compounds. Additionally, pharmacists can help provide context around the relative risk of these impurities. After Pfizer announced the voluntary recall of varenicline due to the presence of N-nitroso-varenicline, the FDA released a statement saying that there were no urgent risks to the patients taking the medication and that there had been no reports of adverse events related to the recall. Patients may have concerns about continuing a medication that was impacted by a recall, even if they received a lot number that was not affected. With the current Chantix® recall, pointing out the nitrosamine content of cigarettes (up to 1,760 ng/cigarette vs. 4 to 460 ng/tablet of varenicline) could be a useful point to bring up when discussing risks and benefits of continuing therapy.

Easing Patient Fears - Recalls due to Impurities[26-28]

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In August and September 2021, two new mobile health apps were launched; Docket and Freestyle Libre 2®. The Docket® app allows individuals to securely view and share their immunization records found on the Minnesota Immunization Information Connection (MIIC). Individuals can view all immunizations administered in Minnesota, New Jersey, or Utah, in one record, even if they were given by different healthcare providers, health systems, or pharmacies. This app launch comes as a direct response to the growing number of individuals requesting access to their vaccine information. Requests to access MIIC information has nearly doubled in 2021 as individuals need access to covid-19 vaccination records to attend certain events or activities. The Docket app creates an easy and convenient avenue for individuals to find, view, and share personal immunization records without needing to submit a formal request and wait to receive their records. This app is free and available to download for both Apple and Android devices.

The Freestyle Libre 2® app was cleared for use by the Food and Drug Administration (FDA) in conjunction with the Freestyle Libre 2® continuous glucose monitoring (CGM) system in early August. Clearance of this app now allows users of the Freestyle Libre 2® CGM system to scan their sensor, view blood glucose readings, and set real-time glucose alarms for hypoglycemia from their mobile device. The new Freestyle Libre 2® CGM differs from the original Freestyle Libre 14 day® CGM as it has added Bluetooth connectivity and the ability to set alarms for hyper and hypoglycemia. The Freestyle Libre 2® app can be connected to LibreView, a secure cloud-based data management platform that allows individuals to share their real-time glucose readings with healthcare providers and caregivers. The release of this app now makes the Freestyle Libre 2® CGM system comparable to other CGM systems currently on the market which also have their own apps. This app is free to download and available to individuals who have an Apple or Android device. To use on Apple products, an Apple brand mobile device (iPhone 7 or newer) or a device that runs on an iOS platform (14.0 or newer) is required. To use on Android products, a current mobile device (Google Pixel, LG Nexus 5X, Samsung Galaxy S7 edge, Sony Xperia 1 or newer) that runs on an Android platform (8.0 or newer) is required.

The demand for easily accessible health records and information is evident as more individuals opt for mobile apps to help manage chronic conditions and access their personal health records. The Docket and Freestyle Libre 2® apps are the newest to join the growing number of health-related apps available and will be beneficial in connecting patients to their health information quickly and conveniently.

A new challenger enters the field: FDA approves the first interchangeable biosimilars[29-37]

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Within 2021, the US Food and Drug Administration (FDA) has given the green light for two biosimilars to obtain interchangeable status. The FDA granted the first of these on 28 July 2021 to Semglee® (insulin glargine-yfgn) and the second on 18 October 2021 to Cyltezo® (adalimumab-adbm). With this interchangeable designation, pharmacists will be able to substitute each of these products for their reference biologics - Lantus® (insulin glargine) and Humira® (adalimumab), respectively.

Insulin glargine is a long-acting insulin that is crucial to the regimen of many insulin-dependent patients with diabetes. However, a study published by Herkert et al showed that high costs and copays for this medication resulted in an estimated 25 percent of patients underusing their insulin and obtaining poor glycemic control. It is hoped that the approval of an interchangeable for Lantus® will result in more affordable insulin, but complicated drug prices make it difficult to determine the extent to which patients can benefit. To add to the complication, Biocon, maker of Semglee®, announced the release of both a branded and an unbranded version of insulin glargine-yfgn on 16 November 2021. As of November 2021, RED BOOK Online reports the average wholesale price (AWP) of a 5-pack of the new Semglee® (insulin glargine-yfgn) pens to be $484.85, 95 percent of the AWP of a 5-pack of Lantus® pens at $510.37. In comparison, a 5-pack of insulin glargine (insulin glargine-yfgn) pens has an AWP of $177.58, 35 percent of Lantus® pens, per RED BOOK Online. These two insulin

glargine-yfgn will both be interchangeable by pharmacies, though coverage by insurance will be determined on a plan-by-plan basis.

Less is known about the expected price and financial impact of Cyltezo®, the interchangeable for Humira®. Humira® is the number one drug in terms of revenue generation in the US, topping the market at $19.8 million in total sales in 2020, according to an article by Buntz. The AWP of a 2-pack (approximately one month supply) of Humira® 40 mg/0.8 mL is $7,161.82, according to RED BOOK Online. While the expected financial impact of an interchangeable for Humira® is exciting, there are a couple limitations. First, the FDA only approved Cyltezo® in the 40 mg/0.8 mL and 20 mg/0.4 mL formulations. Humira® is available in a higher concentrated 80 mg/0.8 mL pen, which could leave Humira® as the preferred product when higher doses of adalimumab are indicated. Secondly, Boehringer Ingelheim announced in 2019 that Cyltezo® will not be introduced to the US market until 1 July 2023 due to litigation agreements with AbbVie, the maker of Humira®. The FDA's second interchangeable approval has many implications for patients, pharmacists, and the US market, but it will be another year until these implications are realized.

New Drug Review

Qulipta™ (Atogepant), AbbVie Inc[38-41]

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Indication: Prevention of episodic migraines in adults.

Mechanism of Action: Atogepant is a calcitonin gene-related peptide (CGRP) receptor antagonist. When CGRP is released in excess, it causes intense pain and inflammation in the meninges. Atogepant works by blocking the release of CGRP, thus, preventing the underlying mechanism of migraine attacks.

Dosage and Administration: Atogepant is given as a 10mg, 30mg, or 60mg once daily oral tablet with or without food. For patients with severe renal impairment or concomitant strong CYP3A4 inhibitor use, the dose is 10mg orally once daily. Its use should be avoided in patients with severe hepatic impairment. For patients with concomitant OATP inhibitor use, the dose is 10 or 30mg orally once daily. The dose is 30 or 60mg orally once daily for patients on moderate to strong CYP3A4 inducers.

Effectiveness: In the first efficacy trial done to evaluate atogepant, 910 patients were randomized to receive atogepant 10mg, 30mg, 60mg, or placebo once daily for 12 weeks. The primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD). The mean change from baseline MMD across 12 weeks was -3.7 days for atogepant 10mg, -3.9 for atogepant 30mg, -4.2 for atogepant 60mg, and -2.5 for placebo ($p<0.001$ for all three atogepant arms).

Safety: In the 12-week clinical trials for atogepant, the most common adverse effects reported were nausea, constipation, and fatigue. The events had an incidence rate that was at least 4% greater than placebo. Decreased appetite was another reported adverse event, however, the difference in incidence between placebo and the atogepant arms was not significant.

Cost: The average wholesale price (AWP) for 30 tablets of any strength (10mg, 30mg, or 60mg) is $1,189 according to RED BOOK online.

Place in Therapy: Atogepant is a once daily oral tablet approved as first-line therapy to prevent chronic migraines in adults.This is currently the only available oral option for CGRP receptor antagonists. In addition to easier administration, this medication has shown efficacy and tolerability in clinical trials. However, it may only be available to certain patient groups due to its steep cost.

REFERENCES

1. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385(16):1451-1461. doi:10.1056/NEJMoa2107038.
2. Baker TB, Piper ME, Smith SS, Bolt DM, Stein JH, Fiore MC. Effects of combined varenicline with nicotine patch and of extended treatment duration on smoking cessation: a randomized clinical trial. *JAMA*. 2021;326(15):1485-1493. doi:10.1001/jama.2021.15333.

(continued)

3. Yang CP, Liang CS, Chang CM, et al. Comparison of new pharmacologic agents with triptans for treatment of migraine: a systematic review and meta-analysis. JAMA Network Open. 2021;4(10):e2128544-e2128544. doi:10.1001/JAMANETWORKOPEN.2021.28544
4. Delgado C, Baweja M, Crews DC, et al. A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease [published online ahead of print, 2021 Sep 22]. *Am J Kidney Dis.* 2021;S0272-6386(21)00828-3. doi:10.1053/j.ajkd.2021.08.003.
5. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461-470. doi:10.7326/0003-4819-130-6-199903160-00002.
6. Delgado C, Baweja M, Burrows NR, et al. Reassessing the Inclusion of Race in Diagnosing Kidney Diseases: An Interim Report from the NKF-ASN Task Force. *J Am Soc Nephrol.* 2021;32(6):1305-1317. doi:10.1681/ASN.2021010039.
7. Levey AS, Tighiouart H, Titan SM, Inker LA. Estimation of Glomerular Filtration Rate With vs Without Including Patient Race. *JAMA Intern Med*. 2020;180(5):793-795. doi:10.1001/jamainternmed.2020.0045
8. Casal MA, Ivy SP, Beumer JH, Nolin TD. Effect of removing race from glomerular filtration rate-estimating equations on anticancer drug dosing and eligibility: a retrospective analysis of National Cancer Institute phase 1 clinical trial participants. *Lancet Oncol.* 2021;22(9):1333-1340. doi:10.1016/S1470-2045(21)00377-6.
9. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385(19):1737-1749. doi:10.1056/NEJMoa2102953.
10. Abbasi J. Choose ARBs over ACE inhibitors for first-line hypertension treatment, large new analysis suggests. *JAMA*. 2021;326(13):1244–1245. doi:10.1001/jama.2021.14017.
11. Chen R, Suchard MA, Krumholz HM, et al. Comparative First-Line Effectiveness and Safety of ACE (Angiotensin-Converting Enzyme) Inhibitors and Angiotensin Receptor Blockers: A Multinational Cohort Study. *Hypertension AHA*. 2021;78:591-603. doi:10.1161/hypertensionaha.1201667.
12. Li ECK, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. *Cochrane Database of Syst Rev*. 2014;(8): CD009096. doi: 10.1002/14651858.CD009096.pub2. Accessed 10 November 2021.
13. Vandvik P, Lincoff A, Gore J, et al. Primary and secondary prevention of cardiovascular disease: antithrombotic therapy and prevention of thrombosis. *Chest*. 2012; 141(2 Suppl): e637S–e668S. doi: 10.1378/chest.11-2306
14. US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;316(19):1997-2007.
15. Arnett D, Blumenthal R, Albert M, et al. 2019 ACC/AHA guidelines on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice. *Circulation*. 2019;140:e596-e646
16. Aspirin use to prevent cardiovascular disease: preventative medication. US Preventive Services Task Force. October 12, 2021. Accessed November 13, 2021. https://www.uspreventiveservicestaskforce.org/uspstf/draft-recommendation/aspirin-use-to-prevent-cardiovascular-disease-preventive-medication#bootstrap-panel--5
17. Marks C, Silvola R, Teal E, Quinney SK, Haas DM. Comparing newborn outcomes after prenatal exposure to individual antidepressants: a retrospective cohort study. *Pharmacotherapy: official journal of the American College of Clinical Pharmacy*. 2021;(0). doi:10.1002/phar.2628
18. Bauman BL, Ko JY, Cox S, et al. Vital Signs: Postpartum depressive symptoms and provider discussions about perinatal depression - United States, 2018. MMWR Morbidity and mortality weekly report. 2020;69(19):575-581. doi:10.15585/MMWR.MM6919A2
19. Riester MR, McAuliffe L, Collins C, Zullo AR. Development and validation of the Tool for Pharmacists to Predict 30-day hospital readmission in patients with Heart Failure (ToPP-HF). *Am J Health Syst Pharm*. 2021;78(18):1691-1700. doi:10.1093/ajhp/zxab223
20. Fadich SK, Kalayjian A, Greene DN, Cirrincione LR. A Retrospective Analysis of Creatinine-Based Kidney Function With and Without Sex Assigned at Birth Among Transgender Adults. *Annals of Pharmacotherapy*. October 2021. doi:10.1177/10600280211050l
21. Wong, E., Done, N., Zhao, M., Woolley, A., Prentice, J. and Mull, H., 2021. Comparing total medical expenditure between patients receiving direct oral anticoagulants vs warfarin for the treatment of atrial fibrillation: evidence from VA-Medicare dual enrollees. *Journal of Managed Care & Specialty Pharmacy*, 27(8), pp.1056-1066.

(continued)

REFERENCES (cont.)

22. Chan C. Why are numerous drugs being recalled due to cancer-causing contaminants? *Pharmacy Today.* 2021; 27(10): 19. https://www.pharmacytoday.org/article/S1042-0991(21)00723-4/fulltext. Published October 1, 2021. Accessed November 10, 2021.
23. FDA updates and press announcements on nitrosamine in varenicline. U.S. Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamine-varenicline-chantix. Published September 17, 2021. Accessed November 10, 2021.
24. Edwards SH, Rossiter LM, Taylor KM, et al. Tobacco-specific nitrosamines in the tobacco and mainstream smoke of U.S. commercial cigarettes. *Chem Res Toxicol*. 2017;30(2):540-551. doi:10.1021/acs.chemrestox.6b00268. Published December 21, 2016. Accessed November 10, 2021.
25. Laboratory analysis of varenicline products. U.S. Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-varenicline-products. Published August 23, 2021. Accessed November 10, 2021.
26. Minnesota Department of Health. New mobile app gives Minnesotans access to their immunization record faster. https://www.health.state.mn.us/news/pressrel/2021/docket091521.html. Published September 15, 2021. Accessed November 5, 2021.
27. Abbott. Abbott's Freestyle Libre 2 iOS app cleared in U.S., providing a seamless digital experience to simplify diabetes management. https://abbott.mediaroom.com/2021-08-02-Abbotts-FreeStyle-R-Libre-2-iOS-App-Cleared-in-U-S-,-Providing-a-Seamless-Digital-Experience-to-Simplify-Diabetes-Management-. Published August 2, 2021. Accessed November 5, 2021.
28. Abbott. Smartphone compatibility guide. Smartphone compatibility guide - Page | FreeStyle Glucose Meters. https://freestyleserver.com/Payloads/IFU/2021/q4/ART41556-202_rev-B-Web.pdf. Accessed December 5, 2021.
29. Active Ingredient: Adalimumab. RED BOOK Online. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health; 2021. Accessed November 7.2021. https://www.micromedexsolutions.com
30. Active Ingredient: Insulin glargine. RED BOOK Online. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health; 2021. Accessed November 26, 2021. https://www.micromedexsolutions.com.
31. Active Ingredient: Insulin glargine-yfgn, recombinant. RED BOOK Online. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health; 2021. Accessed November 26, 2021. https://www.micromedexsolutions.com.
32. Biocon. Biocon Biologics and Viatris Announce Launch of Interchangeable SEMGLEE® (insulin glargine-yfgn) Injection and Insulin Glargine (insulin glargine-yfgn) Injection. https://www.biocon.com/biocon-biologics-and-viatris-announce-launch-of-interchangeable-semglee-insulin-glargine-yfgn-injection-and-insulin-glargine-insulin-glargine-yfgn-injection/. Published November 16, 2021. Accessed November 26, 2021.
33. Boehringer Ingelheim. Boehringer Ingelheim announces resolution of Cyltezo patent litigation | boehringer-ingelheim.us. https://www.boehringer-ingelheim.us/press-release/boehringer-ingelheim-announces-resolution-cyltezo-patent-litigation. Published May 14, 2019. Accessed November 7, 2021.
34. Buntz B. 50 of 2020's best-selling pharmaceuticals. Drug Discovery and Development. https://www.drugdiscoverytrends.com/50-of-2020s-best-selling-pharmaceuticals/. Published May 14, 2021. Accessed November 7, 2021.
35. Herkert D, Vijayakumar P, Luo J, et al. Cost-Related Insulin Underuse Among Patients With Diabetes. *JAMA Intern Med*. 2019;179(1):112-114. doi:10.1001/JAMAINTERNMED.2018.5008
36. U.S. Food and Drug Administration. FDA Approves Cyltezo, the First Interchangeable Biosimilar to Humira. https://www.fda.gov/news-events/press-announcements/fda-approves-cyltezo-first-interchangeable-biosimilar-humira. Published October 18, 2021. Accessed November 7, 2021.
37. U.S. Food and Drug Administration. FDA Approves First Interchangeable Biosimilar Insulin Product for Treatment of Diabetes. https://www.fda.gov/news-events/press-announcements/fda-approves-first-interchangeable-biosimilar-insulin-product-treatment-diabetes. Published July 28, 2021. Accessed November 7, 2021
38. QULIPTA™ (atogepant) | Episodic Migraine Preventive Treatment. Qulipta.com. https://www.qulipta.com. Published 2021. Accessed November 8, 2021.
39. Rxabbvie.com. https://www.rxabbvie.com/pdf/qulipta_pi.pdf?_ga=2.218844761.1763905657.1638145562-1003065997.1635180855. Published 2021. Accessed November 8, 2021.
40. Episodic Migraine Preventive Treatment | QULIPTA™ (atogepant) HCP. Quliptahcp.com. https://www.quliptahcp.com. Published 2021. Accessed November 10, 2021.
41. Active Ingredient: Atogepant. RED BOOK Online. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health; 2021. Accessed November 19, 2021. https://www.micromedexsolutions.com.