Association of Race/Ethnicity with Oral Anticoagulant Use in Patients with Atrial Fibrillation

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Background: The updated 2018 CHEST guidelines for antithrombotic therapy for atrial fibrillation (AF) by the American College of Chest Physicians (ACCP) recommend direct-acting oral anticoagulants (DOACs) over warfarin in patients with AF. The cost of DOACs may be a barrier for patients, leading to the use of warfarin. It is unknown if racial and ethnic differences are associated with differences in the use of oral anticoagulants (OACs), including DOACs, after controlling for clinical and socioeconomic factors. Racial differences have been noted in prevalence and outcomes of AF. There’s a lower prevalence of AF in African Americans and Hispanics, yet these populations experience a higher risk of stroke and worse outcomes compared to Caucasians.

Objective: To determine if there are any racial/ethnic differences among patients taking an OAC for the treatment of AF.

Study Design: The US-based Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II), a prospective registry from February 2013 to July 2016 of outpatient patients 21 years and older with AF, was utilized to create this cohort study. Data from ORBIT-AF II was analyzed to include 12,417 patients with AF in this study – 11,100 (89.4%) Caucasians, 646 (5.2%) African Americans, and 671 (5.4%) Hispanics. The participants were followed at 6-month intervals for 1 to 2 years depending on their enrollment date. Use of any OAC, with a focus on DOACs, was the primary outcome of the study. Secondary outcomes were quality of anticoagulation therapy received by the participants and OAC discontinuation rates after one year.

Results: Compared to Caucasian patients, Hispanic and African Americans patients were more likely to have Medicaid insurance (Caucasian 2.9%, Hispanic 15.5%, African American 11.6%, P<0.001) and less likely to have a college degree (Caucasian 29.6%, Hispanic 17.2%, African American 17.2%, P<0.001). After baseline clinical features were adjusted (i.e. demographics, medical history, medications, laboratory data, AF status, and enrolling physician specialty), African Americans were less likely to receive any OAC compared to Caucasians (adjusted odds ratio [aOR], 0.75 [95% CI 0.56-0.99], P=0.04). If on an OAC, African Americans were also less likely to be prescribed a DOAC compared to Caucasians (aOR, 0.63 [95% CI 0.49-0.83], P<0.001). When baseline socioeconomic markers were adjusted (i.e. median household income, level of education, and insurance type), a significant difference in DOAC prescribing remained between African Americans and Caucasians (aOR, 0.73 [95% CI 0.55-0.95], P=0.02).
Objective: The purpose of this study was to determine if there are differences in VTE risk based on type of HRT formulation and dosing.

Study Design: This study utilized a nested case control design, using two primary care research databases in the United Kingdom. A total of 80,396 women aged 40-79 years were registered between 1998 and 2017 and were matched with 391,494 controls. Each participant was matched with up to five controls from the same practice with the same year of birth. Exclusion criteria consisted of previous history of VTE, less than one year of medical records, or more than one type of HRT prescription written in the last 90 days. The various formulations and regimens were compared against each other as well as against no HRT use. Overall exposure to HRT was defined as any exposure to oral or transdermal preparations. The study focused on recent exposure, since distant past exposure has not been associated with increased risk. Exposure was categorized as recent (within 90 days), past (91-365 days), or no exposure. Dose was categorized as low (<0.625 mg oral conjugated equine estrogen, <1 mg oral estradiol, <50 micrograms for transdermal estradiol) or high. Analyses adjusted for confounding factors, such as chronic and acute conditions, lifestyle factors, and social deprivation. Raloxifene use was also included in analysis, as its use for osteoporosis may be common in this patient population.

Results: The study found increased VTE risk for all oral HRT formulations, regardless of presence or absence of progestin (OR 1.58 [95% CI 1.52 - 1.64]), and this finding persisted across all age groups. Conjugated equine estrogens were associated with 17% increased risk when compared to estradiol (OR 1.49 versus OR 1.27). The formulation carrying the highest risk of VTE was conjugated equine estrogen in combination with medroxyprogesterone acetate (OR 2.1 [95% CI 1.92 - 2.31]). Estradiol in combination with dydrogesterone was associated with the lowest risk, but this product is not currently available in the United States. Overall, cyclical and continuous dosing for oral formulations were associated with increased VTE risk compared to no HRT use (OR 1.55 [95% CI 1.44 - 1.66]), but transdermal preparations were not associated with higher risk of VTE when compared to no HRT, regardless of formulation. In regard to patient characteristics, being overweight was associated with higher risk (OR 1.50 [95% CI 1.37 - 1.64]). More than half of the women who experienced VTE were aged 65 or older, and were more likely to have comorbidities (e.g., cancer, cardiovascular disease, chronic renal disease) compared to controls. Raloxifene use was associated with significantly increased VTE risk (OR 1.49 [95% CI 1.24 - 1.79]).
Conclusions: Currently, the majority of women using HRT are prescribed oral formulations. Oral conjugated equine estrogen, combined or estrogen only, are associated with higher VTE risk compared to estradiol based preparations. Higher estrogen doses are likewise associated with higher risk. However, transdermal preparations are not associated with increased risk and should thus be given greater consideration, especially in women already at increased risk due to comorbidities (i.e. age or obesity). This study provides clinicians with more information to present to patients regarding relative VTE risks when discussing therapy options.

Examing the Correlation Between Antidepressant Target Dose Optimization and Achievement of Glycemic Control
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Background: Patients with comorbid diabetes and depression are shown to have lower levels of self-care, lower chances of achieving glycemic control, and incur higher medical costs. Consequent to these findings, the American Diabetes Association (ADA) recommends screening and addressing depression for all diabetic patients at least annually. It has been well documented that glycemic control improves when depression is addressed by clinicians in this subset of patients. However, there is little available evidence concerning the achievement of optimal antidepressant dosing and its effect on reducing hemoglobin A1c (HbA1c) in patients with comorbid diabetes and depression.

Objective: To assess the effect of antidepressant target dose optimization on glycemic control in patients with comorbid diabetes and depression.

Study Design: The CommUnityCare Health Centers in Texas conducted an electronic health record-based cohort study of patients with comorbid diabetes and depression who were initiated on first-line antidepressants between January 1, 2015 and September 30, 2015. Patients aged 18-89 years old were included if they had uncontrolled diabetes (defined as HbA1c >7%) within the previous 4 months and kept at least 2 office visits during the study period. Patients were excluded if they had an active prescription for an antipsychotic or lithium. First-line antidepressant therapy included selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and bupropion; which were the most commonly prescribed antidepressants by CommUnityCare primary care providers. Twelve months after therapy initiation, patients were separated into one of two groups: those who met target dose and those who did not. Target doses were defined prior to the study, using the Primary Psychiatry website as a reference. There were 723 patients initiated on a low antidepressant dose during the study period. Only 178 of these patients fit the inclusion criteria;76 patients achieved an optimal dose (target group) and 102 patients did not (control group).

Results: Patients in both the target and control groups had similar baseline HbA1c values (9.29% and 9.24%, respectively). At the end of the study period, only 48 patients in the target group and 23 patients in the control group had all the required follow-up data. Those who met HbA1c goal of <7% in the target and control groups were 22.9% and 4.3% of patients, respectively (P<0.05). The average HbA1c was 8.4% in the target group, compared to 8.96% in the control group, and deemed non-significant by the authors. No relationship between HbA1c and PHQ-9 could be established due to inadequate PHQ-9 reporting.

Conclusions: The results of the study suggest that antidepressant dose optimization in patients with diabetes may lead to an increased likelihood of achieving an HbA1c goal <7%. There was insufficient evidence to draw conclusions regarding reaching HbA1c goal and improvement in depression.

Key Point: When treating patients with comorbid diabetes and depression, it is important to screen for and address depression at least annually. Optimizing antidepressant therapy may aid in the achievement of glycemic control.

Therapeutic Thoughts

SGLT2 Inhibitors: Are We Throwing the Baby Out With the Bathwater
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SUPERVALU

Background: Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are the most controversial novel antidiabetic medications. Their benefits appear to far exceed those expected from their modest antihyperglycemic effects alone. Randomized controlled trials (RCT) continue to suggest several protective cardiovascular and renal effects. However, these same trials and ongoing post-marketing surveillance have identified several risks associated with SGLT2i. Careful consideration must be taken when weighing potential benefits and risks for patients with type 2 diabetes.
Evidence: As recently published in Lancet, Zelniker and colleagues conducted a systematic review and meta-analysis of cardiovascular and renal outcomes trials using SGLT2i. This analysis included the EMPA-REG OUTCOME, CANVAS (CANVAS and CANVAS-R), and DECLARE-TIMI trials (n=34,322). The investigators stratified patients according to baseline presence of atherosclerotic cardiovascular disease (ASCVD) vs. cardiac risk factors, heart failure, and glomerular filtration rate (eGFR). Zeliker et al. concluded that use of SGLT2i reduced major adverse cardiovascular events (MACE) by 11% (HR 0.89 [95% CI 0.83-0.96]) but only in those with established ASCVD (HR 0.86 [95% CI 0.80-0.93]). SGLT2i reduced the risk of cardiovascular death or hospitalization for heart failure by 23% (HR 0.77 [95% CI 0.71-0.84]) in all patients regardless of baseline ASCVD or history of heart failure.

Higher baseline renal function was associated with a larger response to SGLT2i for prevention of hospitalization for heart failure.1 This risk was reduced by 40% in patients with a baseline eGFR less than 60 mL/min (HR 0.5 [95% CI 0.47-0.77], 31% in patients between 60-90 mL/min (HR 0.69 [95% CI 0.57-0.83], and non-significantly in patients above 90 mL/min. SGLT2i use reduced risk for worsening renal function, end-stage renal disease, or renal death (HR 0.55 [95% CI 0.48-0.64]) with a magnitude of reduction directly proportional to baseline renal function. Patients with eGFR of less than 60 mL/min at baseline experienced a 33% risk reduction (HR 0.67 [95% CI 0.51-0.89]), those 60-90 ml/min a 44% risk reduction (HR 0.56, [95% CI 0.46-0.70]), and those 90 ml/min or greater a 56% risk reduction (HR 0.44, [95% CI 0.32-0.59]). This was independent of ASCVD at baseline. Evidence of renoprotective effects is corroborated by other emerging data. In July of 2018, Janssen Pharmaceuticals announced the early termination of the CREDENCE trial based on achievement of pre-specified efficacy endpoints. CREDENCE was a Phase 3 trial evaluating the composite endpoint of time to dialysis or kidney transplant, doubling in serum creatinine, and renal or cardiovascular death in patients taking canagliflozin or placebo with baseline chronic kidney disease (CKD).

In May of 2015 the FDA warned of SGLT2i use and risk for diabetic ketoacidosis (DKA). Between March 2013 and May 2015, 73 cases of DKA were reported to the FDA Adverse Drug Event Reporting System (FAERS) database. Notably, at least 15 of these were in patients with type 1, for which SGLT2i use is off-label and without the recommendation of the American Diabetes Association (ADA). Zelnicker et al. found an increased relative risk of 2.2 [95% CI 1.25-3.87] but a low absolute incidence; less than 1 per 1000 patient years. In a review of SGLT2i-associated DKA events, Goldenberg et al. identified several risk factors including insulin non-adherence, discontinuation, or dose reduction; severe acute illness with dehydration, low-carbohydrate diets, intense exercise, surgery, or alcohol binges.

SGLT2i use may increase risk for Fournier’s gangrene. In August 2018 FDA issued a drug safety communication warning of this association based on 12 cases between March 2013 and May 2018. Fournier’s gangrene is extremely rare, but more common in males than females. However, 5 of the 12 cases identified by FDA occurred in women. FDA simultaneously reviewed FAERS for other antihyperglycemic agents over a period of more than 30 years and identified only 6 cases, all male. Urinary tract (UTI) and genital mycotic infections are a well-recognized adverse effect of SGLT2i. CANVAS reported an incidence of male genital infection, mycotic female genital infection, and UTI of 34.9, 68.8, and 40.0, respectively, per 1000 patient years in the canagliflozin group. It is notable that these were adjudicated and reported separately. Interestingly, there was no significant difference in incidence of UTI in DECLARE-TIMI 58, though this trial did report a 0.9% risk of genital infection vs. 0.1% with placebo. Similarly, in EMPA-REG OUTCOME, empagliflozin did not appear to increase risk for UTI or complicated UTI but did increase risk for genital infection (6.4% vs. 1.8%) with a similar effect in males and females (although females had a higher absolute risk).

CANVAS raised alarm over risk for lower limb amputation (6.3 vs. 3.4 per 1000 patient years). EMPA-REG OUTCOME did not directly adjudicate this event, but there was no significant difference in amputation rates for patients in DECLARE-TIMI 58. Buse and colleagues analyzed data from four large U.S. claims databases, including 142,000 patients taking canagliflozin, 110,000 taking empagliflozin dapagliflozin, and 460,000 using other antidiabetic medications. This analysis of more than 700,000 patients using SGLT2i for a median duration of 6 months found no increased risk for below knee amputation.

Finally, SGLT2i have been associated with increased risk of bone fracture. CANVAS reported an incidence of 15.4 fractures per 1000 patient years with canagliflozin vs. 11.9 for placebo (P=0.02). However, both EMPAREG-OUTCOME and DECLARE-TIMI 58 found no significant difference in fractures with SGLT2i compared to placebo. In September 2015, FDA revised label requirements of canagliflozin to include warnings of increased risk of fractures. FDA pooled data from 9 clinical trials and determined that over a mean exposure of 85 weeks, incidence of bone fracture for placebo, 100 mg daily, and 300 mg daily canagliflozin was 1.1, 1.4, and 1.5 per 100 patient years respectively. Interestingly, this review determined these fractures were more likely
to be associated with ‘low-trauma’ falls while CANVAS reported a non-significant difference in ‘low-trauma’ fractures. This may be due to small SGLT2i-induced increases in serum phosphate (between 2.9 and 5.2% with canagliflozin) which may trigger an increase in parathyroid hormone activity and subsequent calcium release from bone stores.

Discussion: SGLT2i appear to confer a modest benefit to risk for adverse cardiovascular effects, but only in patients with established ASCVD. They offer a far greater benefit with respect to reduction in cardiovascular death or hospitalization for heart failure and progression of renal disease that is independent of baseline ASCVD or heart failure. Initiation of an SGLT2i earlier (that is, in patients with more preserved eGFR) results in a greater renoprotective effect. Concern for adverse effects may discourage use of SGLT2i. The most well-established of these is risk for genital mycotic infections (especially in females), and to a far lesser extent UTI/urosepsis. SGLT2i have a similar magnitude of increased risk for genital infections in men and women, but women have a higher absolute risk. Fournier’s gangrene, while extremely rare, is increased in both sexes but by a greater magnitude in women. SGLT2i are associated with an approximate doubling in risk for DKA, but mostly in conjunction with other precipitating factors. Absolute risk for DKA in any patient with type 2 remains very low regardless of SGLT2i use. Further, this can be mitigated by avoidance of precipitating circumstances, holding the drug during severe acute illness, and maintaining proper hydration.

The paradoxical risk for amputation observed in earlier (that is, in patients with more preserved eGFR) results in a greater renoprotective effect. Concern for adverse effects may discourage use of SGLT2i. The magnitude of this effect appears small.

Clinical Impact: There is no ‘ideal’ candidate for an SGLT2i. However, this does not preclude their use in patients who are adequately monitored, on safe concomitant medication regimens, and with established comorbidities such as ASCVD, CHF, or CKD. SGLT2i undeniably increase risk for genital infections, but data for other adverse effects is far less robust and conclusive. Conversely, SGLT2i confer profound and irrefutable benefits such as preservation of renal function, avoidance of hospitalization in heart failure, and secondary prevention of ASCVD. The adverse events associated with SGLT2i are much rarer and far more easily-managed than occurrence of MACE, hospitalization for heart failure, or progression of renal disease. These outcomes are far more likely to occur in patients with type 2 diabetes and can result in irreparable damage with lasting repercussions in terms of quality of life and total cost of care.

Pharmacist Impact on Deprescribing in Older Adults

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Background: Caring for geriatric patients requires different approaches to manage common chronic disease states. Physiological changes occur as the body ages, thereby changing the pharmacokinetics of many drugs. This may mean alterations in the metabolism and excretion of medications, resulting in increased sensitivity to medications in older adults. This may also lead to an increase in drug-drug interactions, cognitive impairment, adverse events, and a prescribing cascade. As a patient’s preferences, side effects, and goals of therapy change with age, a focus on deprescribing becomes important.

Many patients over the age of 65 are prescribed potentially inappropriate medications. A study by Patel et al. published in 2018 estimated that 29% of Medicare beneficiaries aged 65 years and older in the United States filled a prescription in 2015 for at least one medication listed on the 2015 American Geriatrics Society Beers Criteria list of drugs. Another study by Perez et al. in 2018 found that prevalence of Beers listed medications ranged from 45.3% in 2012 to 51% in 2015. This can be serious, as these high risk medications in the older adult can be associated with emergent hospital admissions, as demonstrated by Budnitz et al. in 2011. Extra measures to aid in deprescribing these medications in the older adult may prove to be necessary in order to help prevent adverse drug events and hospitalizations. Pharmacist-led interventions may prove to be useful in deprescribing potentially inappropriate prescriptions in older adults.

Evidence: In a recent longitudinal retrospective study of 44 different primary care practices from Perez et al. (2018), hospital admission was associated with a higher rate of potentially inappropriate prescribing in the older adult. Potentially inappropriate prescribing was defined using 45 criteria from the Screening Tool for Older Persons’ Prescription (version 2). Following hospital admission, patients were 72% more likely to have a potentially inappropriate medication prescribed to them than before. This was independent of other patient-related factors. Hospital admission, advancing age, polypharmacy, and multiple comorbidities were all associated with a higher rate of potentially inappropriate prescribing. A recent randomized clinical trial from Martin et al. (2018) compared pharmacist-led educational intervention versus usual care for deprescribing inappropriate medications among community dwelling older adults. There were 248 patients in the intervention group where pharmacists sent patients educational deprescribing brochures and sent their physicians an
COPD is a preventable and manageable disease currently ranked as the 4th leading cause of death worldwide according to the 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Risk factors for developing COPD include smoking tobacco, biomass fuel exposure, and air pollution. Each year, GOLD releases an updated summary highlighting diagnostic criteria and treatment guidelines for the management of COPD. Three main areas were updated in the 2019 guidelines: 1) simplification of treatment options, 2) use of the ABCD assessment, and 3) incorporation of management cycles.

Evidence: The updated guidelines continue to recommend the utilization of the ABCD assessment tool for the initial treatment of COPD, but no longer recommend its use to adjust treatment thereafter. This tool is used to direct pharmacological treatment based on a patient’s modified Medical Research Council (mMRC) dyspnea scale or COPD Assessment Test (CAT) score and the number of exacerbations leading to hospitalizations. When comparing the 2018 and 2019 GOLD guidelines, the initial treatments for Groups A, B, C, and D are similar with the exception that the 2019 guidelines do not include the preferred treatment algorithm. The initial treatment is now streamlined: Group A) bronchodilator; Group B) LABA or LAMA (there is evidence monotherapy is sufficient at symptom control and combination therapy is not twice as effective); Group C) LAMA; Group D) LAMA, LABA + LAMA (in addition to symptoms and CAT >20), or ICS + LABA (depending on specific lab values).

Additionally, the 2019 update focuses on using the ABCD assessment to determine initial treatment only and then utilizing the management cycle to follow-up and make changes to treatment. The management cycle involves a three step process: review, assess, and adjust, designed to treat COPD based on symptoms and exacerbations. Recommendations at follow-up are no longer dependent on the patient’s GOLD group (A, B, C, D) at diagnosis.

Another update includes new evidence to incorporate the use of peripheral blood eosinophil counts (EOS) to estimate the efficacy of inhaled corticosteroids (ICS) for exacerbation prevention. The use of ICS is no longer recommended in Group C for initial therapy and the use of an ICS for initial therapy is based on if a patient falls into Group D and has an EOS count ≥ 300 cells/µL. The use of ICS at follow-up is determined based on symptoms of dyspnea and exacerbations. Therapies can be escalated or de-escalated based on specific medication-related factors or symptom control.

The guideline recommended three steps be conducted at each visit to ensure appropriate management of COPD. At each visit, a provider should review symptoms, assess inhaler technique, adherence and non-pharmacological approaches (such as smoking.
cessation, pulmonary rehabilitation, exercise training, etc.), and adjust medications if needed. If a patient’s current treatment achieves treatment goals, no changes in treatment are recommended during assessment. If the treatment is not optimized, consider therapy changes based on separate dyspnea and exacerbation algorithms. If a patient presents with both dyspnea and an exacerbation, the exacerbation algorithm should be used.

**Discussion and Clinical Impact:** The majority of the recommendations involving diagnosis remained the same as previous updates. An ICS is no longer recommended in GOLD Group C for initial therapy. ICS are only recommended for initial treatment in patients that fall into Group D with elevated EOS. Additionally, the guideline highlighted a follow-up management guide to better manage patients with COPD. Guidelines no longer recommend using mMRC or CAT scores directly to manage treatment options after initiating therapy, but symptom assessment at each visit is important to determine if therapy changes are necessary. Clinically, it is important to treat each patient as an individual, follow the new highlighted treatment algorithms, and utilize the management cycle during follow-up.

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**Polypharmacy Effects in Patients with Nonvalvular Atrial Fibrillation on Rivaroxaban or Warfarin**

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**Background:** Patients with nonvalvular atrial fibrillation (NVAF) often have concomitant conditions requiring additional chronic medications. Polypharmacy and the associated drug-drug interactions may increase the risk of thrombotic events or bleeding events. In the Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) trial, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism (SSE) and no significant difference for the risk of major bleeding was found. Baseline data for concomitant cardiovascular medications were reported, but this trial did not specifically measure or analyze polypharmacy. The question remains whether polypharmacy has an effect on the safety and efficacy of anticoagulants in patients with NVAF.

**Objective:** The Influence of Polypharmacy on the Effectiveness and Safety of Rivaroxaban Versus Warfarin in Patients with Nonvalvular Atrial Fibrillation study sought to evaluate the safety and efficacy of rivaroxaban versus warfarin in patients with NVAF who are experiencing polypharmacy in a real-world setting.

**Study Design:** This study was a retrospective analysis of claims data. Truven MarketScan, a database combining data from commercial and Medicare supplement products, was utilized. Patients included in the analysis needed to meet the following inclusion criteria: two or more international classification of diseases (ICD) codes for atrial fibrillation, have polypharmacy (taking five or more concomitant chronic medications), have insurance coverage, and be oral anticoagulant (OAC) naive for 12 months prior to the dispense date of either rivaroxaban or warfarin. Patients who had a history of venous thromboembolism (VTE) were excluded. A second analysis reviewed patients with substantial polypharmacy, defined as concomitant medications being ten or more. Each eligible patient taking rivaroxaban was matched 1:1 with a patient taking warfarin using propensity score matching. The primary efficacy outcome was the combination of SSE. The primary safety outcome was major bleeding. Patients were followed until SSE combined or major bleeding event, OAC discontinuation or switch, termination of insurance, or end-of-study follow-up. Results were reported as hazard ratios with p-value <0.05 as statistically significant.

**Results:** A total of 13,981 patients taking rivaroxaban (15 or 20 mg) were matched to 13,981 patients taking warfarin. Overall, the baseline characteristics between groups were well balanced. The median age was 71 years with a median follow-up of 1.7 years. Median CHADS2VASC and modified HAS-BLED scores were three and two respectively. The primary efficacy outcomes of SSE for rivaroxaban versus warfarin resulted in a HR of 0.66 [95% CI 0.50 - 0.88] favoring rivaroxaban. There was no major difference for the safety outcome of major bleeding with HR 1.08 [95% CI 0.92 - 1.28]. In the subanalysis of patients with 10 or more concomitant medications, a total of 3530 patients were analyzed. There was no statistically significant difference between rivaroxaban and warfarin for either outcome. Polypharmacy drug interactions were seen most commonly with warfarin inhibitors and inducers, particularly diltiazem and amiodarone.

**Conclusions:** In patients with NVAF taking five or more chronic medications, rivaroxaban may be more effective in preventing SSE events than warfarin. However, this study is limited by the retrospective design and further prospective randomized trials are recommended to confirm results. Additionally, the median duration was only 1.7 years, meaning results do not consider long-term outcomes.
term efficacy. It should also be noted that INR results for patients on warfarin and adherence to either medication were not tracked or analyzed.

**Key Point:** When polypharmacy and drug-drug interactions are concerning in NVAF patients requiring anticoagulation therapy, rivaroxaban may be more effective in preventing SSE events than warfarin.

**Initiation of Triple Therapy in Chronic Obstructive Pulmonary Disease**

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**Background:** The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 guidelines provide recommendations for the pharmacological management of COPD based on an individualized assessment of symptoms and exacerbation risk. Long-acting muscarinic antagonists (LAMAs) and long-acting beta2-agonists (LABAs), alone or in combination, are preferred therapeutic options for patients with COPD. Triple therapy with a LAMA, LABA, and inhaled corticosteroid (ICS) has previously been reserved for patients with severe COPD and a high risk of exacerbations. The updated 2019 GOLD guidelines outline new recommendations for initiating add-on ICS therapy in patients with COPD exacerbations based on blood eosinophil count. Although these evidence-based recommendations exist for the treatment of COPD, studies suggest that real-world treatment patterns do not always follow clinical practice guidelines.

**Objective:** The purpose of this study was to (1) measure the time from COPD diagnosis to the initiation of monotherapy with a LAMA or dual therapy with LAMA/LABA or LABA/ICS, (2) estimate the time to initiation of triple therapy, and (3) identify factors contributing to the progression to triple therapy.

**Study Design:** This study was a retrospective analysis of patients with COPD who initiated LAMA monotherapy or dual therapy with LAMA/LABA or LABA/ICS between July 1, 2010 and March 31, 2013. The Humana research database was utilized to obtain healthcare claims data for these fully insured patients with commercial or Medicare Advantage Prescription Drug (MAPD) insurance plans. Patients were required to have a diagnosis of COPD, which was identified using ICD-9 codes for chronic bronchitis, emphysema, and chronic airway obstruction. Patients aged 40 years or older with COPD as a diagnosis for at least one hospitalization claim, one emergency department claim, or one medical claim for an office visit in the year prior to study initiation were included. Patients were excluded if claim records indicated prior use of LAMA, LAMA/LABA or LABA/ICS, those with comorbid respiratory-related conditions, those who switched plan type from commercial to MAPD, or those who were contractually excluded from research. The study was sponsored by GlaxoSmithKline, who also played a role in the study design, data analysis, data interpretation, and writing of the manuscript.

**Results:** There were 13,541 patients with a confirmed diagnosis of COPD. Of these patients, 4000 initiated LAMA monotherapy, 8207 initiated LABA/ICS dual therapy, and 77 initiated LAMA/LABA dual therapy at the beginning of the study. The mean time from COPD diagnosis to initiation of therapy was 178 (± 134) days for LAMA monotherapy, 185 (± 130) days for LABA/ICS dual therapy, and 252 (± 124) days for LAMA/LABA dual therapy. Of these patients, 28% receiving LAMA monotherapy and 20% receiving dual therapy (LAMA/LABA or LABA/ICS) progressed to triple therapy. Triple therapy was initiated after a mean of 367 (± 362) days for those receiving LAMA monotherapy, 393 (± 366) days for those receiving LABA/ICS, and 617 (± 454) days for those receiving LAMA/LABA.

Exacerbations occurred within the 60 days prior to initiating triple therapy in approximately 22% of patients receiving monotherapy or dual therapy. When considering the 12 months before initiating triple therapy, exacerbations occurred in about 50% of patients. Factors that were significant predictors of progression to triple therapy included race/ethnicity, geographic region, discontinuation of therapy, smoking history, use of LAMA monotherapy, and concomitant use of ICS, xanthenes or short-acting beta2-agonists.

**Conclusions:** In this study, 23% of patients with COPD progressed to triple therapy within 12 months of starting treatment with monotherapy or dual therapy. Only 50% of these patients had exacerbations in the year prior to progressing to triple therapy. Several factors were identified that predicted progression to triple therapy. The authors suggested that these factors may help identify patients that could benefit from earlier intervention with triple therapy. The study indicated that those who discontinued therapy, had a smoking history, received LAMA monotherapy, or used concomitant xanthenes or short-acting beta2-agonists were more likely to progress to triple therapy. However, additional studies are necessary to determine whether time to initiation of triple therapy is associated with patient outcomes.

Although there were various limitations to the study design, the treatment patterns identified do not appear to align with current practice guidelines. The majority of
patients in this analysis were initiated on ICS/LABA dual therapy after COPD diagnosis. Furthermore, the 2019 GOLD guidelines take into account that several recent studies have demonstrated that blood eosinophil counts predict the magnitude of the effect of ICS add-on therapy in preventing future exacerbations. Therefore, these guidelines emphasize the importance of evaluating blood eosinophil count along with exacerbation risk when considering triple therapy with ICS.

Key Point: The results from this study highlight the discrepancy between clinical practice guidelines and real-world treatment patterns in the pharmacological management of COPD. Pharmacists have the opportunity to intervene and promote the utilization of evidence-based treatment recommendations. With the expansion of available LAMA, LAMA/LABA, LAMA/LABA/ICS inhalers, it is also important to educate providers on these new medications.

Patients’ interpretation of responsibility with warfarin therapy27
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Background: Even for patients who take their medications as directed, Internal Normalized Ratio (INR) values for those receiving warfarin can vary for numerous reasons. Most patients are not aware of the misconceptions involved in the cause of INR variation, and this may lead to misplaced blame for an INR outside the target range.

Purpose: The study by Gillespie et al. sought to characterize the experience of warfarin treated patients regarding medication administration, communicating with clinical pharmacists, and INR monitoring.

Study Design: The study included 40 telephone interviews among eight Veterans Health Administration outpatient anticoagulation clinics in the New England region. Of the 40 patients included, there were 34 males and six females. The mean age of the participants was 73.4 years old. The duration of warfarin therapy varied among patients, but each person had experienced an INR value that was out-of-range at some point in the past.

Results: Interview results indicated that many patients view variation in INR values as their fault due to dietary and lifestyle behaviors. Patients often felt as though the pharmacist was blaming them for their INR variation, based on the questions that were asked to identify the cause of INR variation. This perception may indirectly lead to adverse consequences such as withholding information from anticoagulation care providers or skipping appointments. Quantitative data regarding the study results was not included in the article.

Conclusions: Qualitative interviews with patients receiving warfarin resulted in misinterpretation of questioning about INR variation, indicating that patients are responsible for failing to meet INR goals. When patients feel they are to blame for INR variation, they are sometimes reluctant to be honest with a pharmacist about their behaviors, potentially leading to suboptimal clinical outcomes.

Key Point: An INR value outside the goal range poses a teachable moment for patient education. Although it is necessary to ask the right questions to evaluate INR variation, pharmacists may consider emphasizing that not all out-of-range INR values are due to specific action by the patient and sometimes variation occurs due to factors that are beyond one’s control.

FDA takes steps to make naloxone OTC28
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According to FDA Commissioner Scott Gottlieb, MD, overdose deaths involving prescription and illicit opioids is a growing problem in the U.S. with nearly 48,000 deaths in 2017. Naloxone is currently being used to combat this epidemic as it rapidly reverses opioid overdose effects after administration. Availability of this life-saving medication is a potential barrier for people who aren’t under the care of a physician, or for those who may be afraid or embarrassed of admitting to issues with substance abuse, due to its prescription status.

The FDA is working to overcome this barrier by encouraging drug companies to develop OTC naloxone products. All OTC products would require a consumer-friendly Drug Facts Label (DFL) that ensures consumers can understand how to use the product without the supervision of a healthcare professional. For the first time, the FDA has proactively developed and tested consumer comprehension of two naloxone DFLs, one for a nasal spray and one for an auto-injector, that drug companies can use to obtain approval for an OTC formulation. Consumer comprehension of these DFLs were successfully tested by over 700 participants including people who use heroin, people who use
prescription opioids, family and friends of people who use opioids, adolescents, and the general public.

Manufacturers now have the option to simply add product specific information to the model DFL for final comprehension testing and do not have to generate an entire DFL independently. The FDA is hopeful these model DFLs will jumpstart the development of OTC naloxone products and increase access to this life-saving medicine.

**FDA approves the return of OTC Primatene® Mist**

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Primatene® Mist (epinephrine) is an OTC inhaler removed from the market in 2011 due to the harmful environmental effects of chlorofluorocarbon (CFC) propellants. With a new hydrofluoroalkane (HFA) propellant, Primatene® Mist is again available OTC after its recent approval by the FDA for the temporary relief of mild symptoms of intermittent asthma in patients aged 12 years and older. This 160-spray metered-dose-inhaler administers 125 mcg epinephrine per spray and is currently available for $29.99 at Walgreens and CVS. For many patients, including low-income, elderly, or uninsured individuals who might have limited healthcare access, Primatene® Mist may provide much needed relief if used appropriately. The inhaler does need to be shaken and then sprayed into the air one time before each use, and should be cleaned every day after use to prevent medication buildup.

Although potential benefits exist, several respiratory medicine associations including the American College of Chest Physicians have raised concerns regarding the approval of this inhaler, pointing out that epinephrine is only symptomatic, not therapeutic, treatment for asthma and it is not a recommended treatment option under the National Institute of Health’s asthma guidelines. Frequent use of rescue inhalers has been associated with increased morbidity and mortality, and there is concern that patients attempting to self-manage their asthma symptoms with Primatene® Mist may delay in seeking necessary medical care, resulting in worse asthma outcomes. The FDA remains confident in the safety and efficacy of this OTC inhaler when used as directed for appropriate patients.

**Associations Between Initial Opioid Exposure and the Likelihood for Long-term Use**

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According to the Centers for Disease Control and Prevention, more than 700,000 people have died from a drug overdose between 1999 and 2017. Nearly 68% of the 70,200 drug overdose deaths in 2017 involved an opioid. That same year, the opioid epidemic was declared a public health emergency by the U.S. Department of Health and Human Services. Since then, there have been many initiatives to reduce prescribing of opioids and to treat those affected by addiction. Another important area of study is identifying factors that may influence or lead to chronic opioid use. A study in JAPhA examined the association between initial opioid exposure and the likelihood for long-term opioid use.

The study compared two cohorts within the Veteran’s Affairs Health System; 317,367 patients from 2016 compared with 376,140 patients in 2011. The study compared multiple independent variables to identify which, if any, factors of initial opioid exposure are associated with long-term opioid use. These factors included number of opioid prescriptions filled within 30 days, the total morphine milligram equivalents (MME) dispensed, the day supply, and mean daily dose of MME. The number of opioid prescriptions filled within 30 days, the total MME dispensed, and the day supply were all independent risk factors with a positive linear relationship that demonstrated an association with the likelihood of long-term opioid use. The mean daily MME was also associated with an increased likelihood of long-term opioid use, but only when greater than 45 MME per day. Among initial opioid exposure metrics, the findings clarify that cumulative days of exposure, whether delivered in a single prescription or as multiple short-term prescriptions, is the strongest determinant of subsequent long-term use.

This information supports the recent restriction put on new opioid prescriptions by Minnesota Medicaid health insurance as of October 2018. The new restriction limits the day supply of opioid-naive patients to seven days. This limitation should help reduce the risk for future long-term opioid use as a days supply of less than or equal to seven days had the lowest associated risk of long-term opioid use within the study. This information could also be used to proactively identify patients that are at risk for long-term opioid use. Identification of high-risk patient while they are still in the acute or subacute treatment window and subsequent referral to pain specialists may prevent long-term opioid use before it happens.
Revefenacin (Yupelri™) - Theravance Biopharma and Mylan

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**Indication:** Revefenacin inhalation solution is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

**Mechanism of Action:** Revefenacin is a long-acting muscarinic antagonist (LAMA), with similar affinity for both the M1 and M5 subtypes of muscarinic receptors. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor in smooth muscle leading to bronchodilation.

**Dosage and Administration:** Revefenacin is a 175 mcg per 3 mL inhalation solution delivered via nebulizer once daily. No dosage adjustment is required for geriatric patients or patients with renal impairment.

**Effectiveness:** During two 12-week randomized, double-blind, placebo-controlled trials, forced expiratory volume (FEV1) was assessed in patients with moderate to very severe COPD. Pooled data showed that, compared with placebo, patients treated with once daily revefenacin had greater improvements in the 24 hour change from baseline in trough FEV1 on day 85 and the overall treatment effect in trough FEV1 over 12 weeks. In another randomized, double-blind study, 207 patients with moderate to very severe COPD and suboptimal peak inspiratory flow rates (PIFR < 60 L/min) were randomized to receive revefenacin 175 mcg once daily via nebulizer or tiotropium once daily via HandiHaler® for 28 days. On day 29, revefenacin and tiotropium effectively improved trough FEV1 and forced vital capacity (FVC) from baseline. In a prespecified subgroup analysis, revefenacin significantly improved trough FEV1 and FVC (Δ trough FEV1: 47.3 mL, P=0.0302; Δ trough FVC: 99.9 mL, P=0.0407) from baseline compared with tiotropium in patients with severe to very severe COPD.

**Safety:**

**Adverse reactions:** Cough, headache, back pain, nasopharyngitis, and upper respiratory infections

**Serious adverse reactions:** Paradoxical bronchospasm

**Avoid use:** Patients with acutely deteriorating or potentially life-threatening episodes of COPD. Use with caution in patients with narrow-angle glaucoma or urinary retention.

**Contraindications:** Patients with hypersensitivity to revefenacin or any component of this product.

**Place in Therapy:** Revefenacin inhalation solution via nebulizer is similar in efficacy to tiotropium (Spiriva™) via Handihaler® in patients with moderate to very severe COPD. Therefore, it is reasonable to use in patients that have difficulty operating the Handihaler® device or with proper inhalation technique. Revefenacin was shown to be superior to tiotropium in severe and very severe COPD patients, demonstrated by the significant improvement in FEV1 and FVC, however specific patient-oriented outcomes were not studied. Revefenacin maybe preferred over tiotropium in severe to very severe COPD patients. The cost of acquisition via McKesson online warehouse was found to be $995 for a box of 30 vials (90 mL), which is a one month supply. A 30 day supply of Spiriva™ (either the Handihaler® or Respimat®) are both $414.87.

**References**

5. Zelniker TA, Wiviott SD, Kyungah Im IR, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and


