The HUNT Study: Proton Pump Inhibitors and Fracture Risk

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Background: Proton pump inhibitors (PPIs) are broadly prescribed for gastrointestinal conditions. These medications have been correlated with an increased risk of fractures in multiple previous studies, however a definite causative link is not well understood. The FDA requires PPI packaging information to include a warning about increased hip, wrist, or spine fracture risk with long term and high dose PPI use. Many mechanisms for this risk have been proposed including reduced calcium and magnesium absorption, though these have not been adequately demonstrated in humans.

Purpose: The Nord-Trøndelag Health Study (HUNT) study aimed to examine a possible association between the use of PPIs and risk of fracture in a large group of Norwegian individuals.

Study Design: A total of 15,017 women and 13,241 men aged 50 to 85, with a mean age of 65 years old were analyzed. Data was retrospectively reviewed from a large Norwegian Health Study (HUNT3), the Norwegian Fracture Registry, and the Norwegian Prescription Database. The fracture registry collects information on hip and forearm fractures. History of exposure to PPIs, anti-osteoporotic drugs (AODs), and oral glucocorticoids (GCs) were pulled from the prescription database. Individuals were followed from their date of participation in the health study in 2006-2008 until the date of their first fracture, death, or study completion in 2012. PPI exposure was defined as a minimum of 90 days and on a daily dose equivalent to or greater than omeprazole 20 mg, lansoprazole 30 mg, esomeprazole 30 mg, or pantoprazole 40 mg. Four different COX proportional hazard models were used for analysis and included variations of time dependent exposure to PPIs as well as age, FRAX score, milk intake, and exposure to AODs and GCs.

Results: In total, 17.9% of women and 15.5% of men had PPI exposure, with 11.7% of women and 10% of men exposed for greater than one year. The mean duration of PPI therapy was 3.8 years, with a range from 6 months to 7 years. Over a median of 5.2 years, 266 women and 134 men had a hip fracture; 662 women and 127 men had a forearm fracture. Overall, after adjusting for age, they found no increased risk of fracture with PPI exposure (Hazard Ratio - Women: 0.82 [95% CI 0.67-1.01], Men: 1.05 [95% CI 0.72-1.52]). After adjusting for use of AODs and FRAX score, there was an overall decline in hazard ratio but still no increased risk identified (Women: 0.80 [95% CI 0.65-0.98], Men: 1.00 [95% CI 0.69-1.45]). The lack of association between PPIs and fractures was true across all of the hazard model groups. There was also no difference found between high and low dose PPI users, which looked at doses above and below the defined dose equivalencies of the different PPIs. It was noted that PPI users were older, had a higher BMI, higher FRAX score, more previous fractures, and were on more GCs and AODs. For women, use of additional medication use was higher in the PPI group than the no PPI group (AOD 14.5% vs. 8.5%, GC 27.2% vs. 10.6%).
Conclusions: The use of PPIs over an average of 3.8 years of exposure was not associated with increased risk of fractures in a large retrospective, population based study of individuals aged 50-85 years old in Norway. Interestingly, PPI users seemed to be higher risk but were also more protected from fracture due to more prevalent AOD treatment. In the adjusted model, the hazard ratio was actually significant for reduced fracture risk in women, though the authors did not identify reduced risk as a finding since they were looking to prove increased risk. It should be noted that the fracture registry only had the ability to collect information on hip and forearm fractures. Additionally, many previous studies linked rabeprazole to fracture risk, however rabeprazole was not included in this study as it is not approved in Norway. The findings of this study interestingly contradict many previous studies about fracture risk, however the retrospective design and lack of vertebral fracture inclusion limit its application to practice.

Key Point: The link between PPIs and increased fracture risk may be less correlated than previously thought. However, pharmacists should continue assessing the need for PPIs and de-escalating therapy as appropriate.

A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke

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Background: Limited evidence is available to support a specific low-density lipoprotein (LDL) cholesterol target level following ischemic stroke or transient ischemic attack (TIA). According to the 2018 American College of Cardiology and American Heart Association (ACC/AHA) guidelines, high-intensity or maximal intensity statins are recommended in patients with clinical atherosclerotic cardiovascular disease (ASCVD), and the addition of ezetimibe in very high-risk ASCVD patients is reasonable if LDL levels are >70 mg/dL. According to the American Heart Association and the American Stroke Association (AHA-ASA), intense statin therapy is recommended after an ischemic stroke of atherosclerotic origin however no specific LDL target levels are listed.

Objective: The objective of this study was to determine if an LDL cholesterol target of <70 mg/dL resulted in fewer overall cardiovascular events compared to those with an LDL cholesterol target range of 90–110 mg/dL in patients with evidence of atherosclerosis who recently had an ischemic stroke or TIA.

Study Design: The Treat Stroke to Target trial was a randomized, parallel-group, event-driven trial conducted in France and South Korea. Adult patients with atherosclerotic disease were eligible for the trial if they had an ischemic stroke within the past 3 months or a TIA within the past 215 days. The primary endpoint was a composite of major cardiovascular events (adjudicated nonfatal cerebral infarction or stroke of undetermined origin, nonfatal myocardial infarction, hospitalization for unstable angina, TIA treated with urgent carotid revascularization, or cardiovascular death). Primary efficacy analysis of the intention to treat population was assessed using a Cox proportional-hazards regression model. An enrollment of 3,786 patients followed for three years was estimated to result in 385 primary end-point events, which would achieve a power of 80% to detect a 25% lower relative risk of major cardiovascular events in the lower-target group (<70 mg/dL) than in the higher-target group (90-110 mg/dL). Alpha was set to 0.05. Patients were randomized in a 1:1 ratio to either the lower-target or higher-target group. Investigators were allowed to prescribe any statin and additional lipid-lowering agents such as ezetimibe in order to reach the assigned LDL cholesterol target.

Results: The primary composite endpoint occurred in 121 of 1430 patients in the lower-target group and in 156 of 1430 patients in the higher-target group (adjusted HR 0.78 [95% CI 0.61 – 0.98] P=0.04). Intracranial hemorrhage occurred in more patients in the lower-target group (28) compared to the higher-target group (13) (HR 1.38 [95% CI 0.68 – 2.82]). The percentage of time that patients were in assigned therapeutic range of LDL cholesterol in the lower-target group and higher-target group were 52.8% and 32.2%, respectively. The addition of ezetimibe to statin therapy occurred in 33.8% of patients in the lower-target group and 5.8% of patients in the higher-target group. Of note, recruitment was extended to include more patients as a result of slow enrollment, and the trial was stopped early due to lack of funding. Although the study was stopped early with fewer patients and fewer primary end-points than estimated, the follow up duration was extended from three years to the duration of the trial allowing sufficient power to detect a 25% lower relative risk in the lower-target group.

Conclusion: In patients with recent ischemic stroke or TIA and evidence of atherosclerosis, a lower-target LDL level of <70 mg/dL resulted in fewer composite cardiovascular events compared to a higher-target LDL range of 90-110 mg/dL, with no significant difference in intracranial hemorrhages. Study limitations include early discontinuation of the trial due to lack of funding and low external validity with the patient population consisting of French and Korean patients.

Key Points: Treatment with a statin +/- ezetimibe towards an LDL target of <70 mg/dL reduced the risk of cardiovascular events compared to an LDL target of 90-110 mg/dL in patients with evidence of atherosclerosis who recently had an ischemic stroke or TIA. This study supports the ACC/AHA recommendation to consider the addition of ezetimibe to maximally tolerated statin therapy in patients with very high-risk ASCVD and LDL ≥70 mg/dL.
Migraine Pharmacotherapy and Novel Agents3-8
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Background: The landscape of migraine pharmacotherapy has been shifting in recent years due to development of agents targeted specifically at the condition’s underlying pathophysiology. In light of these emerging therapies, the American Headache Society (AHS) published a consensus statement in December 2018 to provide guidance on preventive and acute treatment of migraine. The goal of this article is to summarize current recommendations and highlight recently approved agents since the publication of these guidelines.

Evidence and Discussion: The AHS Consensus Statement summarizes first-line oral therapies for the prevention of migraines as antiepileptic drugs (valproic acid, topiramate), select beta-blockers (metoprolol, propranolol, timolol), and frovatriptan (specifically for menstrual migraine). General recommendations for these oral agents are to start at low dose, titrate slowly, and allow an adequate trial of at least eight weeks at an effective dose. First-line agents for the acute treatment of migraines include NSAIDs, nonopioid analgesics, acetaminophen, or caffeinated analgesic combinations for mild-to-moderate attacks. Triptans or dihydroergotamines are recommended for moderate-to-severe attacks or mild-to-moderate attacks that do not respond to other first-line therapies. It is generally recommended that patients limit treatment to an average of two headache days per week to avoid medication overuse.

Medications targeting calcitonin gene-related peptide (CGRP) are an exciting development as the first class of medications specifically designed for the preventive treatment of migraines. This class of medications targets the vasoactive peptide CGRP which is involved in a signaling cascade that perpetuates cranial vasodilation, neurogenic inflammation, and release of toxic substances from mast cells. Designed as monoclonal antibodies, these agents either act by antagonizing the CGRP receptor or binding the CGRP ligand to prevent action at its receptor. Currently approved for both episodic and chronic migraine prevention, erenumab (Aimovig®) and galcanezumab (Emgality®) are administered subcutaneously once monthly while fremanezumab (Ajovy®) is administered either once monthly or quarterly. Eptinezumab is another CGRP-targeted agent pending FDA approval, which is given by intravenous infusion. According to the AHS guidelines, the lack of need for dose titration and rapid onset of efficacy for these injectable therapies are notable differences when compared to oral agents. To assess therapeutic benefit, AHS recommends a three-month trial for the monthly injections and six-month trial if administered quarterly. Due to limited drug interactions, the CGRP-targeted agents may be used alone or in combination with other preventive treatments.

The most common adverse event with these agents is injection site reactions. Due to the high cost associated with these agents, the AHS has developed indications for initiation which involve criteria of previous treatment failures and severity of disease.

In October and December 2019, the FDA approved two novel oral agents for the acute treatment of migraine with or without aura in adults, lasmiditan (Reyvow®) and ubrogepant (Ubrelvy®), respectively. Lasmiditan is a first-in-class selective serotonin (5-HT1F) receptor agonist, while ubrogepant is the first oral CGRP receptor antagonist approved by the FDA. According to publications by Dodick et al. on ubrogepant and Wietecha et al. on lasmiditan, both agents were found in phase III clinical trials to have improved pain freedom and absence of most bothersome symptoms at two hours as compared to placebo. These results were statistically significant across all studied doses of the two agents. The most common adverse events of lasmiditan included dizziness, fatigue, somnolence, nausea, vomiting, and paresthesia. The most common adverse events of ubrogepant included nausea, somnolence, and dry mouth. Given their lack of vasoconstrictive properties, these agents may be beneficial in those with cardiovascular contraindications to triptans. Rimegepant (Nurtec ODT®) is another oral CGRP-targeted agent for acute treatment of migraine which recently received approval from the FDA on February 27th, 2020.

In addition to pharmacotherapy, the AHS emphasizes the benefit of other treatment modalities for treatment or prevention such as neuromodulation, cognitive behavioral therapy (CBT), and optimized biobehavioral therapies focused on avoidance of triggers and adequate nutrition, exercise, and hydration.  

Clinical Impact: Emerging treatments with novel mechanisms for both the preventive and acute treatment of migraine provide promising new strategies. Knowledge of novel therapies and comprehensive review of individualized medication histories, disease severity, and non-pharmacological strategies will be crucial to optimize drug selection and achieve cost-effectiveness.

Antihypertensive Treatment Update9-12
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Background: For years, there has been very little guidance from the hypertension guidelines about the optimal first-line agent to treat high blood pressure (BP), as well as timing of medication dosing. The 2017 ACC/AHA High Blood Pressure Clinical Practice Guidelines suggest that patients with BP 130-139/80-89 mmHg with an ASCVD risk >10%, or >140/90 mmHg irrespective of ASCVD risk should receive BP-lowering medication. First-line agents include thiazide or thiazide-type diuretics, ACE inhibitors, ARBs, CCB-dihydropyridines, and CCB-nondihydropyridines.
For patients without comorbidities, these are recommended with equal weight. In patients with comorbidities, chlorthalidone is preferred in cardiovascular disease (CVD), ACE inhibitors and ARBs are preferred in chronic kidney disease (CKD), CCB-nondihydropyridines should be avoided in heart failure (HF) and CCB-dihydropyridines should be used cautiously in HF.

In comparison, the 2014 JNC8 Guidelines recommend treating to a goal of <150/90 mmHg for patients >60 years of age, and <140/90 mmHg for patients <60 years of age. The JNC8 supports initiating any of the following drug treatments with equal weight in the nonblack hypertensive population: ACE inhibitors, ARBs, any CCB, or thiazide and thiazide-type diuretics, which is similar to the 2017 ACC/AHA guideline. In the black hypertensive population, including those with diabetes (DM), any CCB, or thiazide and thiazide-type diuretics are recommended as initial therapy. They also recommend initiating therapy with an ACE inhibitor or ARB in persons with CKD to improve kidney outcomes.

**Evidence:** In a new comprehensive analysis, outcomes in a new-drug user cohort across 4.9 million patients were explored. Researchers used data from a global network of six administrative claims and three electronic health record databases to estimate the relative risks of three primary endpoints (acute myocardial infarction (MI), hospitalization for HF, and stroke), six secondary effectiveness endpoints, and 46 safety outcomes when comparing all first-line classes of drug therapy. Most estimates revealed no difference in effectiveness between classes, however thiazide and thiazide-type diuretics showed better outcomes for primary endpoints than ACE inhibitors: acute MI (0.84 [95% CI 0.75–0.95]), hospitalization for HF (0.83 [95% CI 0.74–0.95]), and stroke (0.83 [95% CI 0.74–0.95]). In 16 different statistically significant safety outcomes including mortality, gastro-intestinal side effects, and renal disorders, thiazide and thiazide-type diuretics were favored over ACE inhibitors. The CCB-nondihydropyridines were significantly inferior to the other classes.

Additionally, the Hygia Chronotherapy Trial provides some evidence that taking at least one BP medication at bedtime can improve BP lowering and CVD outcomes. Over 19,000 patients who took antihypertensive medications at bedtime had significantly lower hazard ratios for asleep systolic blood pressure (SBP) mean, sleep-time relative SBP decline, and primary CVD outcome (0.55 [95% CI 0.50-0.61], P < 0.001). This statistically significant outcome was observed across all cases (CVD death (0.44 [95% CI 0.34-0.56]), MI (0.66 [95% CI 0.52-0.84]), coronary revascularization (0.60 [95% CI 0.47-0.75]), HF (0.58 [95% CI 0.49-0.70]), and stroke (0.51 [95% CI 0.41-0.63]), even when adjusted for influential characteristics (age, sex, type 2 diabetes, CKD, smoking, HDL cholesterol, etc.).

**Who Should Receive PCV13?**

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**Background:** Since 2014, the Advisory Committee on Immunization Practices (ACIP) has recommended routine immunization with Prevnar13® (PCV13) followed by Pneumovax®23 (PPSV23) in one year for all patients ≥65 years old. At the time that this recommendation was established, ACIP recognized that routine use of PCV13 among adults ≥65 years old may not be recommended long term and opted to re-evaluate in four years. Standard pediatric immunization with PrevnarTM(PCV7) and PCV13 has decreased the prevalence of these pneumococcal strains and, as a consequence, there has been a notable decline in pneumococcal disease in children and adults over the past twenty years.

**Evidence:** From 2014-2018, there was a substantial increase in the administration of PCV13 among patients ≥65 years old (2018 coverage estimated at 47%). However, this increase in PCV13 use did not translate into decreased rates of invasive pneumococcal disease (IPD). Incidence of PCV13-type IPD remained stable from 2014 to 2017 both among adults ≥65 years old and among adults ages 19-64 who experience indirect protection from increased administration of PCV13. One cohort study found a reduction in all-cause pneumonia caused by PCV13-types when comparing 2014 to 2015-16 (10% in 2014 to 4% in 2015-16), suggesting that PCV13-types are not as often the cause of pneumonia cases.

To evaluate an economic perspective, two independent models were generated which predicted 76-175 cases of PCV13-type IPD and 4,000-11,000 cases of PCV13-type pneumonia over the lifetime of 2.7 million adults aged 65 years. Based on this data, the estimated cost effectiveness ratios were $200,000 to $560,000 per quality adjusted life year. When compared to the corresponding cost effectiveness ratio of $65,000 per quality adjusted life year in 2014, evidence suggests that the continued routine use of PCV13 in patients ≥65 years old may not be economically responsible.

**Discussion:** Based on the aforementioned data outlining the decline in pneumonia cases caused by PCV13-types and the significant predicted economic burden, ACIP now recommends against the routine use of PCV13 in adults ≥65 years old. Instead, a shared clinical decision making process should be used for adults ≥65 years old without cochlear implant, an immunocompromising condition, or a CSF leak who have not previously received PCV13.

**Clinical Impact:** Pharmacists and other healthcare professionals will now have to use a higher level of clinical evaluation when considering the administration of PCV13 in adults. Patients who may be at an increased risk of pneumonia due to PCV13-types include those residing in long-term care facilities or those living in
THERAPEUTIC THOUGHT (cont.)

locations with low pediatric utilization of PCV13. Unfortunately, ACIP does not define a threshold for “low pediatric utilization,” however, according to the Minnesota Department of Health, the Minnesota PCV childhood immunization rate is 81.8%. Those also at increased risk of PCV13-type IPD include patients with chronic heart, lung, or liver disease, diabetes, alcoholism, and those who smoke cigarettes with more than one chronic medical condition. It may be noted, however, that the 2020 American Diabetes Association Standards of Medical Care in Diabetes Guidelines did not mention a recommendation for routine vaccination with PCV13 in adults ≥65 years old with diabetes.

Overall, the decision to administer PCV13 in adults ≥65 years old will now be multifactorial and require consideration of patient social history, place of residence, medical history, and individual vaccination preferences. It is also currently unknown if PCV13 will continue to be covered by payers following the updated ACIP recommendation. Risks to the patient associated with administration of the immunization remain low, however pharmacists should also consider the potential negative economic impact when recommending frequent use of PCV13 in this population. The ACIP recommendation for administration of PPSV23 in all adults ≥65 years old remains in place and, if administration of PCV13 is indicated based on shared clinical decision making, PCV13 should continue to be administered at least one year prior to PPSV23. As ACIP continues to assess trends in pneumococcal disease, PCV13 and PPSV23 vaccination recommendations may continue to evolve.

FROM THE PHARMACY PRESS

Direct Oral Anticoagulant Therapy in Cancer
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MOBE

Background: Patients diagnosed with different types of cancer are at an increased risk of thrombosis as well as an increased risk of bleeding. Currently, low-molecular-weight heparin (LMWH) is the standard treatment to prevent venous thromboembolisms (VTE) in patients with cancer, which was determined in the early 2000’s by the CLOT trial (LMWH compared to vitamin k antagonist). Since then, direct oral anticoagulants (DOAC) have been introduced and have many advantages including fewer food and drug interactions and more predictable pharmacodynamics and pharmacokinetics. This study aimed to compare the safety and efficacy of DOACs and LMWH in cancer-associated VTE.

Evidence: This study was a retrospective analysis in an academic teaching hospital. Patients included were aged 18 to 89 years old with active cancer being treated with a DOAC or LMWH for VTE. Patients were excluded if there was a documented history of atrial fibrillation, vascular disease, weight >120 kg or body mass index >40 kg/m², hypercoagulable disorder, pregnancy, severe renal impairment, hepatic impairment, or concomitant use of a strong CYP-450 3A4 or P-glycoprotein inhibitor/inducer. The primary outcome of this study was the frequency of VTE reoccurrence in each patient. There were multiple secondary outcomes including major and minor bleeding events and occurrence of other thrombosis.

Of the 456 patients identified for the study, 156 patients were included in the study population. All patients were prescribed the manufacturer recommended dose of a DOAC or LMWH. Both the DOAC and LMWH groups contained an equal number of patients both the DOAC and LMWH groups contained an equal number of patients (n=78). In the DOAC group, 76% of the patients were on rivaroxaban, 18% on apixaban, and 6% on dabigatran. All patients in the LMWH group were on enoxaparin. The primary outcome of VTE occurred in 5 patients in the DOAC group and in 8 patients in the LMWH group, 6.4% and 10.3% respectively, (0.6 [95% CI 0.19 - 1.92]). The secondary outcome of major bleeding (0.49 [95% CI 0.9 - 2.74]) and minor bleeding (1.32 [95% CI 0.47 - 3.75]) were similar when comparing the DOAC group to the LMWH group.

Discussion: The investigators described this study as one of the first to compare DOACs to LMWH in patients with cancer in a real-life setting. There are some limitations including a single-center chart review, lack of patient adherence tracking, potential bleeding or VTE recorded at a different institution, difference in the length of follow-up between and within groups, and difference of metastatic disease between groups. With the few limitations and size of the study, additional studies evaluating the safety and efficacy of using DOACs for VTE prevention in patients with cancer are warranted.

Clinical Impact: This study showed a similar occurrence of VTE when using DOACs and LMWH in patients with cancer. With a similar VTE and bleeding frequency, this potentiates the use of DOACs as an alternative for VTE prevention in cancer patients. The use of DOACs will allow patients an oral agent option, with less follow-up required, and fewer drug and food interactions.

Examining the Medicare Part D Medication Therapy Management Program in the Context of Mental Health
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Background: Mental health conditions can often lead to increased medical complexity due to increasing comorbid conditions, higher medication burden, increased utilization of the healthcare system, and fragmented care. Given the medical complexity, those with mental health conditions may benefit from use of medication therapy management (MTM) services. Mental health is one of the nine core chronic conditions outlined by the Center for Medicare and Medicaid Services (CMS) for eligibility for MTM services, however a study determining the utilization of these services with respect to those with mental health diagnoses has not been evaluated. Mental health conditions disproportionately affect Medicare beneficiaries compared with the general population; approximately 26% of Medicare beneficiaries carry mental health diagnoses.

Objective: To describe and compare the delivery of MTM services to Medicare beneficiaries with and without mental health conditions.

Study design: This cross-sectional study examined randomly sampled 2014 Medicare parts A, B, and D claims data, comparing this data to 2014 MTM data. Medicare data included participants that were continuously enrolled in Medicare part A, B, and D; data was evaluated for 825,003 beneficiaries that were MTM-enrolled. Patients with end-stage renal disease were excluded based on their complexity and potentially increased medication burden.

Results: Beneficiaries were categorized into mental health cohorts (3,016,620 individuals, or 43%) and non-mental health cohorts (3,997,105 individuals, or 57%). The study found that there was a significantly higher MTM enrollment in the mental health cohort (17.4% vs. 7.5%, P<0.001). Once enrolled, a greater proportion of the non-mental health cohort received comprehensive medication review (19.3% vs. 17.7%, P<0.001). Those in the mental health cohort were more likely to have an emergency department visit or be hospitalized, and overall, used more medications than the non-mental health cohort (16 medications vs. 12 medications, P<0.001). Additionally, those in the mental health cohort were more likely to have a medication therapy problem (MTP) identified and resolved, when compared to the non-mental health cohort.

Of note, use of MTM was further reduced among beneficiaries in the mental health cohort that may have had lower socioeconomic status, were a part of racial and ethnic minority communities, were more medically complex, or classified as having schizophrenia and other psychotic disorders.

Conclusions: Despite beneficiaries from the mental health cohort being more likely to be enrolled in MTM, they were less likely to receive MTM services than the non-mental health counterpart. As the study identified more MTPs and a higher medication burden within this population, it is important to recognize a gap in care that could be better addressed by MTM delivery in the mental health population. Specifically, pharmacists could impact this disparity by considering outreach to patients who may benefit from this service, whether this be through unique care delivery models such as home visits or other considerations to close this gap.

Key point: A clear disparity exists between those with mental health diagnoses covered for MTM services through Medicare and those who receive the services. Pharmacists can help recognize this gap and work to better serve this patient population and resolve unmet medication-related needs.

Safety Comparison of High-Intensity Atorvastatin vs. High-Intensity Rosuvastatin
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Background: The 2019 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on the Prevention of Cardiovascular Disease recommend high-intensity statin therapy for most patients with clinical ASCVD. Atorvastatin doses of 40 or 80 mg and rosuvastatin doses of 20 or 40mg are defined as high intensity statin therapies (decrease LDL cholesterol by 50% or more). Many randomized controlled trials support the efficacy of high-intensity statin therapy in reducing major cardiovascular events; however, guidelines do not identify differences in safety profiles between different statin agents and previous studies had not been powered to detect a difference in adverse reaction rates between high-intensity rosuvastatin and high-intensity atorvastatin. In 2011, the Veterans Health Administration switched formulary statin agents from rosuvastatin to atorvastatin because of significant cost savings, as rosuvastatin was still under patent at that time.

Purpose: Determine if high-intensity atorvastatin is associated with an increased incidence of adverse drug reactions (ADRs) compared with high-intensity rosuvastatin in the Veteran population.

Study Design: Retrospective electronic database review was conducted at the James A. Haley Veterans’ Hospital (JAHVH) in the Greater Tampa Area. Patients with an active outpatient order for a high-intensity statin at JAHVH within the prespecified time frame time period were included: rosuvastatin 20-40 mg from January 2009 to November 2011 or atorvastatin 40-80 mg from May 2012 to June 2016. Patients were excluded if they had a documented ADR or allergy prior to the formulary switch or if they did not receive 1 refill of high intensity statin therapy at any time within the study time frame. The primary endpoint was any documented ADR to statin therapy. Secondary endpoints included...
FROM THE PHARMACY PRESS (cont.)

rates of abnormal liver function tests (LFTs), elevated creatine kinase (CK) levels, and statin-associated muscle symptoms (SAMSs) in patients on high intensity atorvastatin compared to high intensity rosuvastatin. ADRs were identified from documented ADRs within the allergy/ADR package in VistA, the electronic health record used by the VA. Adverse muscle reactions including SAMSs, muscle pain, and rhabdomyolysis were identified using ICD-9 or ICD-10 for myalgia or rhabdomyolysis. LFT and CK elevations were identified using laboratory values during the study period.

Results: A total of 10,017 patients were identified to be on high-intensity statin therapy in the prespecified time frame with 5,852 patients in the atorvastatin group, 4,165 in the rosuvastatin group, and 1,920 patients in both groups due to the formulary change. A statistically significant difference was found in the primary objective of overall ADRs between the atorvastatin and rosuvastatin groups (4.59% vs 2.91%, P<0.05). A higher rate of SAMSs was documented for atorvastatin vs rosuvastatin (1.14% vs. 0.50%, P<0.05). A total of 3.99% of patients in the atorvastatin group had LFTs greater than 3X upper limit of normal compared to 1.39% in the rosuvastatin group (P<0.005). No significant difference was noted between groups for CK elevations. Patients were on therapy for an average of 274 days in the atorvastatin group and 669 days in the rosuvastatin group prior to having a documented ADR. In a subgroup analysis, ADRs were noted to be higher in the atorvastatin 80 mg group (7.22%) than the 40 mg group (4.09%) (P<0.05). ADRs were found to be higher in the rosuvastatin 20 mg group compared to the 40 mg group (3.35 vs. 1.09%, P<0.05). No differences in ADRs were found between the atorvastatin 40 mg group and the rosuvastatin 20 mg group, however there was a significant difference between the atorvastatin 80 mg group and rosuvastatin 40 mg group (7.22% vs. 1.09%, P<0.05).

Conclusions: This observational study suggests that high intensity atorvastatin is linked to an increased incidence of overall ADRs, specifically statin-associated muscle symptoms and LFT elevations, compared with high intensity rosuvastatin in the Veteran population (4.59% vs. 2.91%). These differences were found to be more prominent in a subgroup analysis comparing atorvastatin 80 mg vs. rosuvastatin 40 mg. Additionally, patients were on rosuvastatin 2.5 times longer than patients on atorvastatin prior to the development of an ADR.

Key Point: In this study, high-intensity atorvastatin was linked to an increased incidence of overall ADRs when compared with high-intensity rosuvastatin in the Veteran population. The results of this study may be used to promote awareness of the suggested safety differences between high-intensity statin therapies.

MISCELLANEOUS NEWS

OTC Tamiflu: Coming Soon to an Aisle Near You?29-31
Meg Tapp, PharmD
Essentia Health

An article by Pharmacy Times published in December 2019 recently announced plans for the common prescription-only medication oseltamivir (Tamiflu®) to switch to over-the-counter (OTC) status. Manufacturer Sanofi signed a deal with current producer Roche Pharmaceuticals in July 2019 which grants exclusive OTC rights for Tamiflu®. Per the Pharmacy Times correspondence, Sanofi commented that OTC status for this medication will “support our global cough and cold strategy by expanding into flu” and increase affordability and availability of the product.

Tamiflu® is an antiviral neuraminidase inhibitor used for treating and preventing influenza post-exposure. It is FDA-approved for patients age 14 days and older, although prophylaxis is typically reserved for those age 3 months and older. Initiation of Tamiflu® must occur within 48 hours of influenza onset for maximum benefit; this is particularly important for patients who are hospitalized, have severe or complicated illness, or who are at higher risk of complications. Overall efficacy remains controversial although one study cites Tamiflu® reduces time to symptom alleviation by 16.8 hours on average (Heneghan et al. 2016). The medication is typically well-tolerated, with most common side effects being nausea, vomiting, and headache.

A Tamiflu® switch to OTC status will undoubtedly expand the scope of pharmacist involvement in initiation of the product. With Tamiflu® on OTC shelves, pharmacists will often be the first line of contact for patients seeking self-treatment. Pharmacists will be relied upon to educate patients on the symptoms of flu versus common cold, as well as proper use, common side effects, and length of treatment duration for Tamiflu®. The pending switch will allow patients to access treatment faster, a proposed benefit given increased efficacy within 48 hours of influenza onset. Still, there will undoubtedly be controversy surrounding appropriate use of Tamiflu® as an OTC product. Per Pharmacy Times, Sanofi will lead FDA negotiations and garner expert support before Tamiflu® hits pharmacy shelves.

While Sanofi has not defined an exact date for the release of OTC Tamiflu® as of this publication, pharmacists and other healthcare providers should be aware of this impending change and what it may mean for their future patients and practices.
FDA Issues Warning of Respiratory Depression with Gabapentinoids

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In December 2019, the Food and Drug Administration (FDA) issued a new warning regarding gabapentinoids, which includes gabapentin, gabapentin enacarbil, and pregabalin. Gabapentinoids now include the warning of increased risk of respiratory depression which may lead to death, especially when used in combination with opioids or other central nervous system (CNS) depressants, elderly patients or those with respiratory conditions.

Use of gabapentinoids have increased over the years, while concerns of misuse and abuse have also risen. Data from various sources have been compiled by the FDA to support this new label change. Case studies, animal studies, clinical trials and observational studies have indicated concerns of breathing difficulties with gabapentinoids in patients with risk factors (ex. respiratory conditions). Manufacturers of gabapentinoids are now required to conduct additional trials regarding abuse potential, especially when co-prescribed with opioids.

The FDA advises providers to use the lowest, most effective dose of gabapentinoids in patients, especially those who are already taking opioid or CNS depressant medications, have respiratory conditions or are elderly. Health care professionals should monitor and educate patients on the risk of respiratory depression. It is important to note, although there is concern and considerations when prescribing these gabapentinoid medications, opioids remain the riskier option for pain treatment at this time.

New Manufacturer: State of California?

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With rising medication costs, California’s governor, Gavin Newsom, has proposed a creative solution - their own generic brand of medications. The proposal suggests that California would contract with one or two drug manufacturers to make the product, which would then be sold under their own generic brand label. The hope is that these products will be more affordable, leading to increased competition in the generic drug market and lower drug prices.

The government has used many methods to directly affect the rising medical costs, but never considered manufacturing of medications. Other companies have tried to address medication costs by manufacturing their own medications. One example is Civica Rx, a non-profit generic injectable drug manufacturer that was created in 2018 to help combat drug shortages and increasing drug costs. Over 1,000 hospitals in the country obtain medications from this company at lower prices compared to other drug manufacturers.

There has been debate and interest regarding this plan in the general public, politicians, health care professionals and drug manufacturers. Although the plan would not likely save California much in healthcare costs, many are applauding the idea of change in the light of inflating medical costs.

REFERENCES


