



Updates in Pharmacotherapy

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RESEARCH UPDATES

Effectiveness of Vitamin D Supplementation on Preventing Acute Respiratory Infections¹

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Background: There have been heterogeneous results when studying the use of vitamin D supplementation to reduce the risk of acute respiratory infections (ARIs). The past findings have shown vitamin D metabolites support immune response to respiratory viruses. Additionally, this hypothesis has been supported by observational studies that have reported an association between low concentrations of the biomarker for vitamin D, 25-hydroxyvitamin D (25[OH]D) and an increased risk of ARI.

Purpose: This systematic review and meta-analysis aimed to evaluate the effects of vitamin D supplementation on ARI risk, considering such factors as baseline 25[OH]D levels, vitamin D dosing regimen, and age.

Study Design: A systematic review and meta-analysis was completed using MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov, with studies from database inception to 2020. The earliest study included was in 2009. Studies included randomized, double-blind, trials of vitamin D supplementation with a placebo control group that reported the incidence of ARI. Studies were only included if ARI was studied prospectively and listed as an efficacy outcome. The primary outcome was the proportion of participants with one or more ARI, which was defined as an upper respiratory infection, lower respiratory infection, or location unclassified. Secondary outcomes focused on a lower or upper respiratory infection, emergency medical attention or hospital admission for an ARI, death associated with an ARI, or antibiotic use for an ARI. Forty six studies were eligible out of 1528 studies assessed in the database search, which included 75,541 randomized participants.

Results: The results of the primary outcome showed a significantly lower proportion of participants taking vitamin D having one or more ARIs compared to placebo (OR 0.92 [95% CI 0.86-0.99]). Further evaluation of this effect explored baseline 25[OH]D concentration, age, and vitamin D dosing. There was no significant effect of vitamin D supplementation on ARIs for patients with a baseline 25[OH]D less than 25 nmol/L (0.81 [0.57-1.15]), 25-49.9 nmol/L (1.04 [0.94-1.15]), 50-74.9 nmol/L (0.88 [0.76-1.02]), or more than 75nmol/L (1.00 [0.85-1.58]). A significant protective effect of vitamin D on ARI was seen for participants 1.00-15.99 years old (0.71 [0.57-0.90]), but not significant in participants less than 1 year old (0.95 [0.82-1.10]), 16 to 64.99 years (0.97 [0.93-1.09]), or over 65 years (0.96 [0.90-1.02]). The protective effect of vitamin D was seen when vitamin D was given daily (0.78 [0.65-0.94]), but not when given weekly (0.97 [0.88-1.06]). Doses of vitamin D also had an effect of the significance of the protective effect, finding doses of 400-1000IU daily (0.70 [0.55-0.89]) was protective against ARI, while

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doses less than 400IU were not (0.65 [0.31-1.37]). Interestingly, doses of 1000-2000IU daily (0.97 [0.93-1.02]) were also insignificant. The results of the secondary outcomes did not find significance.

Conclusions: Despite heterogeneity across trials evaluated, it was concluded that vitamin D supplementation significantly reduced the risk of ARI compared with placebo. Protection was significant with daily doses of 400-1000IU vitamin D daily at ages of 1.00-15.99 years. The magnitude of this effect was small (0.92 [0.86-0.99]) and was less for those with a baseline 25[OH]D concentration less than 25 nmol/L.

Key Point: Vitamin D supplementation can reduce the risk of ARI at doses of 400-1000IU daily for patients 1.00-15.99 years old.

Antihypertensive Drug Targets and the Potential Effects on Psychiatric Disorders²

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Background: There have been observational studies that suggest an association between antihypertensive medications and psychiatric disorders. There have also been reports of hallucinations and reversible psychosis after angiotensin converting enzyme (ACE) inhibitor treatment. Given that many patients with psychiatric disorders have higher risk for cardiovascular morbidity and mortality and require antihypertensive medications, there is value in exploring this association.

Objective: The purpose of this study was to identify an association between antihypertensive treatment and psychiatric disorders.

Study Design: This study utilized a 2-sample mendelian randomization (MR) analysis using publicly available expression quantitative trait loci data and summary data from the most recent genome-wide association study (GWAS) of psychiatric disorders. The study authors defined an MR analysis as a "statistical genetics approach that uses genetic variants that are robustly associated with an exposure as potentially unconfounded instruments to infer whether observed association between the exposure and outcome is causal or not." The authors identified genes whose protein products were targeted by an active ingredient in different classes of antihypertensive medications. Genes that did not reflect a decrease in systolic blood pressure were excluded. Using GWAS summary data for schizophrenia, bipolar disorder, and major depressive disorder, summary-based MR analysis was run to determine the association of a one standard-deviation (SD) change in drug target blood gene expression level with outcomes of disease. A default heterogeneity independent instrument (HEIDI) $P < 0.01$ was used to exclude pleiotropic single nucleotide variants.

Results: In total there were 110 genes that were identified whose encoded protein activity had been shown to be modified by one or more antihypertensive medications. Only 61 of these genes were able to be queried due to one gene not being expressed in blood and lack of data for the other 48 genes. A one SD decrease in ACE expression in blood was associated with a decrease in systolic blood pressure of 4.0 [95% CI 2.7-5.3] mmHg and a higher risk of schizophrenia 1.75 [95% CI 1.28-2.38; $P = 3.95 \times 10^{-4}$]. Similar association was seen in the prefrontal cortex 1.33 [95% CI 1.13-1.56, cerebral spinal fluid 1.12 [95% CI 1.05-1.19], and plasma 1.04 [95% CI 1.01-1.07]. Other gene targets that were associated with schizophrenia and bipolar disorder were ruled out due to the significant HEIDI P values suggesting these associations were likely due to linkage.

Conclusions: Based on the findings in this study, there may be an association between lower ACE messenger RNA and protein levels and an increased risk of schizophrenia. If lower ACE levels have an effect on schizophrenia risk, then it could be hypothesized that inhibiting ACE may also have a similar effect, thus worsening schizophrenia symptoms. In light of these statistical findings, further research into the role of ACE in schizophrenia may be warranted.

Key Point: This study brings to light the potential for lower ACE levels, and potentially ACE inhibitors, contributing to worsening symptoms in schizophrenia.

Comparing Efficacy and Safety of Different Doses of Dulaglutide in Metformin-Treated Patients with Type 2 Diabetes³

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Background: Type 2 diabetes is a chronic disease that often requires more than one medication to reach control. Current American Diabetes Association guidelines recommend the addition of a glucagon-like peptide-1 receptor agonist (GLP-1RA) to metformin therapy because of their efficacious glucose-lowering properties, low hypoglycemia risk, weight loss benefit, and proven cardiovascular benefit.

Objective: The purpose of this study was to evaluate the safety and efficacy of dulaglutide at doses of 3 mg and 4.5 mg versus 1.5 mg in patients with type 2 diabetes who were uncontrolled with metformin monotherapy. The study looked at whether or not doses above 1.5 mg of dulaglutide showed superiority in reducing A1C levels after 36 weeks.

Study Design: This study was a double-blind, randomized, parallel armed trial conducted in 203 sites across 15 countries. To be eligible for this study, the participant must have been over the age

of 18, had type 2 diabetes for more than six months, an A1C between 7.5-11% at screening, naive to both GLP-1RA and insulin, and a metformin dose of 1500 mg or greater for at least three months. A minimum body mass index threshold was also used in an attempt to avoid limitations of gastrointestinal tolerability during dose titrations. Individuals were excluded if they were taking antidiabetic medications besides metformin within three months of randomization, had calcitonin levels at or above 20 ng/L, had pancreatitis/ketoacidosis/hyperosmolar state or a recent cardiovascular event, or had active cancer. The primary outcome assessed was the change in A1C from baseline over 36 weeks. The secondary outcomes assessed were the proportion of patients achieving an A1C less than 7%, change in fasting baseline serum glucose levels, and change from baseline in body weight. The 1842 patients enrolled in the study were split into three treatment groups as follows: dulaglutide 1.5mg, dulaglutide 3mg, and dulaglutide 4.5mg.

Results: Compared with the 1.5 mg dose, the 3 mg and the 4.5 mg doses of dulaglutide resulted in significantly greater A1C

reductions after 36 weeks ($P < 0.001$). Significantly more patients achieved an A1C of less than 7% in the treatment groups with the 3 mg and 4.5 mg dulaglutide. In addition, those who were taking the 4.5 mg dose of dulaglutide were two times more likely to reach their A1C target compared to those on the 1.5 mg dose ($P < 0.001$). Only the 4.5 mg dose was superior in terms of lowering the fasting blood sugar levels. Dulaglutide 4.5 mg was superior to 1.5 mg in lowering body weight ($P < 0.001$). The proportion of patients reporting at least one treatment-emergent adverse event was similar across all groups. The most common adverse effect reported was stomach upset, which tended to appear early in the trial and abate thereafter. Gastrointestinal upset increased as the dose increased overall.

Conclusions/Key Point: Patients with type 2 diabetes previously taking metformin with inadequate glycemic control could benefit from initiating and titrating dulaglutide from 1.5 mg to 3 mg or 4.5 mg over time to improve glycemic control and reduce body weight. Stomach upset might occur with dose increases but would likely abate with time and be mild in severity.

THERAPEUTIC THOUGHT

To Crush or Not to Crush: Novel Drug Formulations⁴⁻⁸

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Background: Ambulatory care providers often adjust dosage forms and administration of oral medications for patients who may have trouble swallowing or have malabsorptive issues to overcome. Tablets can be cut or crushed, while capsules can be opened and sprinkled on food or into a liquid for the ease of administration to patients. Along with the medication package insert, the Institute for Safe Medication Practices (ISMP) "Do Not Crush" list is often used by healthcare providers to determine if a medication can be safely split or crushed. However, this list was last updated in 2016, and there is no set schedule in place for regular revisions. In recent years, two notable novel drug formulations have been developed to improve oral bioavailability: nanocrystals and amorphous solid dispersions. There are now over 30 FDA-approved oral medications that utilize one of these two innovative technologies. The availability of these new formulations has led to a lack of clarity over which products may be altered prior to administration. A recent review by Uttaro, *et al.* aims to summarize evidence to guide healthcare practitioners in the proper administration of these drug formulations.

Evidence & Discussion: Both nanocrystal and amorphous solid dispersion formulations were developed to increase the oral bioavailability of tablets and capsules by increasing drug dissolution rate in the gastrointestinal (GI) tract. Nanocrystal

technology involves reducing active drug into tiny crystalline particles and packaging these particles into a unit dose. The smaller particle size increases the total surface area of drug and thus enhances dissolution rate and rate of absorption. However, publications by Jermain, *et al.* and Zhang, *et al.* highlight the unique stability of drug nanocrystals positioned within the polymers of a tablet. Cutting or crushing the nanocrystal formulation disrupts the stabilizing polymer structure and allows moisture to initiate crystal growth. As the nanocrystals begin to clump together and form larger crystals outside of the integrity of the original tablet, surface area decreases and drug dissolution actually slows compared to the intended effect of this technology. Examples of drugs that are supplied in a nanocrystal formulation include: Emend™ (aprepitant), TriCor™ (fenofibrate), and Triglide™ (fenofibrate).

Amorphous solid dispersions are created by converting the crystalline form of a drug into an amorphous form, usually by the processes of spray drying or continuous hot melt extrusion. Amorphous drug particles are packaged into a unit dose without any particular order, which differs from the typical order of drug particles in a crystal lattice. Polymers stabilize the amorphous solid drug into position so that a tablet can be manufactured, but the non-ordered formulation allows for the amorphous particles to easily dissociate when exposed to moisture in the GI tract. This allows for stability of the dosage form until administration, when the drug dissolution rate occurs more quickly than it would in a crystal lattice preparation. However, the types of polymer must be

carefully chosen to stabilize amorphous solid dispersions without allowing the drug to convert back into its crystalline form. It is hypothesized that cutting or crushing an amorphous solid dispersion tablet disrupts the precise polymer stabilization and leads to conversion of the drug back to crystalline form, destroying the intended properties of quick dissolution and enhanced bioavailability. In a study by Pas, *et al.*, oral amorphous solid dispersions of Sporanox™ (itraconazole), Intelence™ (etravirine), Noxafil DR™ (posaconazole), and Norvir™ (ritonavir) were assessed *in vitro* for their dissolution rates when fully intact versus after crushing each with a mortar and pestle. Interestingly, crushed ritonavir, itraconazole, and posaconazole showed a more rapid dissolution rate compared to the intact amorphous solid dispersions, which the authors suggest may be due to destruction of tablet film coatings. Crushed etravirine showed a significantly slower dissolution rate compared to intact etravirine tablets. The authors recognize that the study was limited in generalizing its findings to true drug-release kinetics and bioavailability in the human body.

Clinical Impact: Healthcare providers should recognize which oral medications utilize nanocrystal or amorphous solid dispersion technology in order to advocate for appropriate administration of these products. Cutting, crushing, or dissolving nanocrystal or amorphous solid dispersions may inadvertently lead to disruption of the intended drug release properties and could lead to reduced therapeutic efficacy or amplified adverse effects. It is challenging to predict the change in drug dissolution, bioavailability, and effect after cutting or crushing these novel formulations. Until additional *in vivo* research can characterize the impact of manipulating nanocrystal and amorphous solid dispersion formulations, these medications should be administered intact per manufacturer guidance. Pharmacists may recommend an alternative dosage form for patients who are unable to swallow whole tablets or capsules. Furthermore, an update to the ISMP “Do Not Crush” list is warranted to include novel drug formulations that may contribute to undesirable clinical outcomes if cut or crushed.

Safety and Efficacy of Direct Oral Anticoagulants (DOACs) versus Warfarin for Valvular Atrial Fibrillation⁹⁻¹⁰

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Background: The 2018 CHEST Guidelines for Antithrombotic Therapy for Atrial Fibrillation set forth a framework for anti-coagulant therapy for stroke prevention in patients with atrial fibrillation. The majority of the evidence and guidance contained in this document centers around atrial fibrillation secondary to nonvalvular causes. These guidelines do, however, address the ambiguity in the definition and recommendations for pharmacologic therapy in patients with valvular atrial fibrillation. There has previously been large variability in the definitions of valvular

atrial fibrillation and in the exclusion criteria within primary evidence. The CHEST guidelines define the necessity of a vitamin K antagonist for patients with moderate-to-severe mitral stenosis of rheumatic origin and mechanical prosthetic heart valve replacement. They define therapy with either a vitamin K antagonist or a direct oral anticoagulant (DOAC), also considering CHADS₂VASC risk factors, for patients with mitral regurgitation, mitral valve repair, aortic stenosis, aortic regurgitation, tricuspid regurgitation, tricuspid stenosis, pulmonary regurgitation, pulmonic stenosis, bioprosthetic valve replacement and trans-aortic valve intervention. Evidence for the safety and efficacy of DOACs for atrial fibrillation with valvular heart disease has also been ambiguous. Recent evidence has emerged to further suggest safety and efficacy of DOACs for patients with valvular atrial fibrillation.

Evidence: Evidence for the safety and efficacy of DOACs over warfarin in patients with valvular atrial fibrillation, contained in the publication by Dawwas *et al.*, was recently published. This was a new-user, retrospective, propensity score-matched, cohort study that evaluated commercial healthcare claims data for patients newly started on warfarin versus a DOAC (apixaban, dabigatran, edoxaban, rivaroxaban) between January 1, 2010 through June 30, 2019. Their primary outcome related to effectiveness was to evaluate the composite of ischemic stroke or systemic embolism through evaluation of ICD-9 and ICD-10 codes. Their primary outcome related to safety was to evaluate a composite of intracranial or gastrointestinal bleeding through evaluation of ICD-9 and ICD-10 codes.

Eligible participants included those that were over the age of 18 years with a diagnosis of atrial fibrillation and valvular heart disease (aortic, mitral, tricuspid, or pulmonary valve) that was documented in at least one inpatient or two outpatient visits. Those excluded had end-stage renal disease, were status post hip or knee replacement, had a history of ischemic stroke or systemic embolism, or had a bioprosthetic or mechanical valve replacement. Participants were followed until the end of the study period or until they were censored (treatment discontinuation, gap in care, switch in therapy, outcome occurrence or disenrollment). Death of a participant was considered disenrollment.

Participants were matched in a 1:1 ratio based on propensity score to account for confounding variables. The study included 28,168 newly started DOAC patients and 28,168 newly started warfarin patients. The mean age among study participants was 81 years with nearly 50% being male. 55% of participants had a diagnosis of mitral valve disease, 41% had aortic valve disease and 18.5% had tricuspid valve disease. Comorbid conditions were most commonly hypertension, hyperlipidemia and heart failure.

The authors found that DOACs decreased the risk of ischemic stroke or systemic embolism in comparison to warfarin (HR 0.64

[95% CI 0.59 – 0.70]). The absolute reduction in the probability of stroke or systemic embolism with DOACs versus warfarin was 0.015 within 6 months and 0.026 within one year. These results were consistent across individual DOACs. Additionally, they found a decrease in the risk of major bleeding with DOACs in comparison to warfarin (HR 0.67 [95% CI 0.63 – 0.72]). The absolute reduction in probability of a major bleed with DOACs versus warfarin was 0.019 within six months and 0.035 within one year. This was also found to be consistent among individual DOACs.

Discussion and Clinical Impact: This study adds to a limited body of evidence for the safe and effective use of DOACs for patients with valvular heart disease. It provides a large amount of longitudinal data that examines patient outcomes over a relatively long time period. The study also included patients with different types of valvular heart disease, stroke and bleed risk. Per the authors, they did not have access to lifestyle variables, over-the-

counter medication-use or severity of valvular disease. Additionally, the 2018 CHEST guidelines state that patients with bioprosthetic valve replacements may receive either a DOAC or warfarin while patients with mechanical prosthetic heart valves and moderate-to-severe mitral stenosis of a rheumatic origin must receive warfarin. Patients with bioprosthetic or mechanical heart valves were excluded from this study and we do not know the severity of valvular disease for participants included. Therefore, this may not provide strong new evidence for specific valvular heart diseases. There are certainly cases in which this data would not be applicable, however, this data does contribute to our overall knowledge of the safety and efficacy of DOACs for atrial fibrillation patients with valvular heart disease. This data should most certainly be considered when thinking of patient-specific factors (such as convenience) as well as the risk versus benefit of starting specific anticoagulants in patients with valvular heart disease. This is an area that requires further study.

FROM THE PHARMACY PRESS

The Effect of Ambulatory Care Pharmacists on Clinic Attendance and Patient Engagement¹¹

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Background: Patient engagement is critical for improving patient outcomes, but this can be difficult to measure. A surrogate marker often used for patient engagement is primary care provider (PCP) initial visit attendance. It has been shown that older patients with commercial insurance are more likely to have engagement with their PCP and Medicaid patients are least likely to report to PCP visits. It poses the question as to how the care team with an ambulatory care pharmacist can help to improve patient engagement.

Objective: The goal of this study was to assess if patient engagement improved when associated with different patient characteristics, provided services, or provider participation post-discharge clinic appointments. Patient engagement was defined as attendance to an initial PCP visit to establish care.

Practice Description: This study occurred at John Hopkins After Care Clinic (JHACC) in Baltimore, MD, an interdisciplinary post-discharge clinic, whose goal is to decrease hospital readmission and establish primary care follow-up. The main goal of this clinic is to make sure these patients are established with a PCP. The patient population seen here is an urban, underserved population with poor social determinants of health. This clinic utilizes an interdisciplinary approach to address the needs of the patients.

Practice Innovation: JHACC works to reduce barriers to follow-up care by assisting patients in the transition to primary care, focusing

on managing all disease states. An interdisciplinary team comprised of physicians/providers, pharmacists, nurses, medical assistants, and community health workers collaborate for each patient encounter. The role of the pharmacist includes medication reconciliation, chronic drug therapy management, patient education, and drug information. This model at JHACC was found to be financially sustainable, generated revenue, and saved over \$1 million for the affiliated hospital (i.e., avoidable hospital admissions and ED visits).

Methods: Patients who were referred to a PCP between January 2016 and January 2018 from within the system were assessed. Patient engagement was defined as patients who saw a PCP within 8 months after the initial JHACC visit. This time frame was used since it included 95% of the data for new patient appointments. Description statistics were determined using means and proportions for patients who attended PCP visits and those who did not. Chi square tests were also utilized to compare the groups.

Results: The study included 717 patients with 423 (59%) attending their initial PCP visit and 294 (41%) not attending. Age was found to be significantly different with an average age of 42.1 years in patients who attended initial PCP visits compared to 38.1 years in those who did not ($P < 0.001$). There was no difference found in attendance between sex, race, or ethnicity. When pharmacists or nurses were involved in the patient visits there was a significant increase in initial PCP visit attendance. Pharmacist involvement resulted in 69.5% attendance versus 30.5% when the pharmacist was not involved ($P = 0.02$). Additionally, disease counseling ($P = 0.001$) and medication education ($P = 0.01$) significantly improved initial PCP visit attendance.

Limitations: Patient attendance to initial PCP visits were used as a surrogate for patient engagement, but there may be other measures that may show engagement or more accurately represent patient engagement. Also, ambulatory care pharmacist roles can vary greatly, and this site was specifically focused on post-discharge visits in conjunction with a medical provider in an urban, underserved population. The outcomes may be different with varying populations and settings. This study did not clearly define what the role of the pharmacist was, making it difficult to replicate and difficult to determine what that the pharmacist was doing that was effective. Pharmacists were also only present in 14.7% of visits (105 visits), so this was a limited sample size. This study was also limited by the design being retrospective, observational.

Conclusion: Ambulatory care pharmacist involvement in post-discharge visits resulted in improved attendance to initial PCP visits. Future studies should be conducted to determine specific pharmacist activities that increase patient engagement, such as adherence interventions, prescription financial assistance, comprehensive medication reviews, etc. This study suggests that medication education and disease counseling have a positive effect on PCP visit attendance, without a clear definition of what this includes.

Pharmacist-led Diabetes Care Associated with Improved Outcomes¹²

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Diabetes is a prevalent and complex chronic disease that requires ongoing management for optimal care. While previous literature has clearly shown that pharmacists play a critical role in improving outcomes and decreasing cost of care, this study adds a new perspective by analyzing baseline patient characteristics and various pharmacist interventions to determine predictors of response to pharmacist-led diabetes care.

This retrospective cohort study was conducted at three primary care clinics in Texas, with two pharmacists practicing under a collaborative practice agreement that allowed for comprehensive medication management. Over a period of four years, adult patients with type 2 diabetes were referred by their primary care provider for diabetes management and participated in at least one visit with the pharmacist. Patients with gestational diabetes, type 1 diabetes, a visit with an endocrinologist, or missing A1c values were excluded. Common comorbid conditions included hyperlipidemia and hypertension. The majority of patients were English-speaking, obese, Hispanic females.

Of the 180 patients who were included, 119 were deemed to be “responders” and 61 to be “non-responders” to pharmacist-led

diabetes management. The term responder indicates that a patient had an A1c reduction of at least 1 percent or otherwise met their documented A1c goal within six months, while a non-responder did not meet either criterion. Baseline demographic characteristics and lab values were similar between the responder and non-responder groups, except that the responder group had a significantly higher baseline A1c (10.1% vs. 9.0%, $P = 0.003$).

The median change in A1c from baseline was -2.2% (-3.7 to -1.3) for responders and 0.4% (-0.4 to 1.05) for non-responders ($P < 0.001$). Common interventions by the pharmacist included starting a new medication (73%), adjusting a medication dose (57%), discontinuing a medication (48%), and providing a log for self-monitored blood glucose (37%). The authors conducted a multivariable logistic regression model of 25 variables to determine predictors of response. Statistically significant predictors of positive response were baseline A1c (OR 1.41; 95% CI 1.08-1.85), completed visits with the pharmacist (OR 1.65; 95% CI 1.03-2.64), and having an intervention to reduce medication dosing frequency (OR 0.69; 95% CI 0.49-0.96).

A1c reduction of greater than one percent is clinically meaningful, as demonstrated by the UKPDS 35 study, which found that each 1 percent reduction in A1c can reduce the risk of microvascular complications by 37 percent and the risk of mortality by 21 percent. This is especially impressive in the short follow-up time frame of 6 months. Other strengths of this study include its diverse patient population, range of antidiabetic medications available as therapeutic options, and multi-site design. One intervention that was challenging to assess was the value of general education provided during the visits, which may impact a patient’s self-efficacy in chronic disease management. An additional limitation of this study is the bias that could be associated with the referral process and the retrospective design that is prone to missing or inaccurate data during chart review.

Overall, higher baseline A1c, more visits with the pharmacist, and reduction in medication dosing frequency were all predictors of clinical response. This study adds to the growing body of literature that demonstrates that clinical pharmacists should continue to be involved in team-based primary care for improved patient outcomes.

Effects of Pharmacist Interventions on Heart Failure Outcomes¹³

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Background: Heart failure is a complex condition associated with many adverse outcomes. Both non-pharmacological and pharmacological therapies, otherwise known as guideline-directed medical therapy (GDMT), have improved heart failure

management. As patients' medications regimens grow in complexity, there is great potential for medication harm among patients with heart failure.

Purpose: A previously published review identified benefits from pharmacist involvement in heart failure care, including reductions in all-cause and heart-failure-related hospitalizations. More recently, additional studies have been published. This study aimed to evaluate recent trials with a focus on improving heart failure outcomes through pharmacist interventions.

Study Design: This study was a systematic review and meta-analysis. After searching terms such as heart failure and pharmacist intervention, randomized controlled trials were included if studies assessed impacts of pharmacist interventions compared to usual or standard care and reported data on mortality, hospitalizations, and quality of life.

Pharmacist interventions included: optimization of GDMT, improvements to patient adherence, provision of patient counseling, medication reconciliation, and identification and mitigation of adverse drug reactions. Pharmacist interventions were also assessed based on service setting and included a variety of practice settings, such as ambulatory settings, acute care settings, telephonic follow-up visits, and community based-settings, including community pharmacy or home-based care.

The primary outcome was all-cause mortality and secondary outcomes included all-cause hospitalization, health-related quality of life (using the Minnesota Living with Heart Failure Questionnaire and 36-item Short Form Survey), and prescribing rates of GDMT.

Results: Of the 15,107 articles screened, 29 randomized controlled

trials were included for analysis. These studies included a total of 6965 patients, with predominantly heart failure with reduced ejection fraction and an average age of 72 years. Most patients were New York Heart Association Functional class II to III with median left ventricular ejection fraction of 38.5%, and the average number of medications per patient was 8 (IQR 6.8-8.9).

Pharmacist interventions were associated with a significant reduction in all-cause mortality (RR 0.72 [95% CI 0.58-0.89]; P = 0.003) and all-cause hospitalizations (RR 0.87 [95% CI 0.77-0.99]; P = 0.041) compared to those receiving usual or standard care. Subgroup analysis by service setting noted a significant reduction in all-cause mortality with pharmacist intervention in all settings, except community-based settings. A significant increase in the 36-item Short form Health survey on physical and mental health and significant improvement in Minnesota Living with Heart Failure Questionnaire score were observed among those receiving pharmacist intervention. Pharmacist interventions also led to increases in the prescribing of ACE inhibitors/ARBs and beta blockers.

Conclusion: Pharmacist interventions for heart failure patients significantly decreased rates of all-cause mortality and all-cause hospitalizations as well as increased quality of life. Differences observed based on practice setting suggest positive outcomes of pharmacist interventions are best achieved in an integrated care team. Integration of a pharmacist into an interprofessional heart failure care team should be considered to further optimize patient care.

Key Point: Pharmacist involvement in heart failure care improves patient outcomes and may be best implemented when the pharmacist is part of a multidisciplinary team.

MISCELLANEOUS NEWS

Bringing Awareness of Performance Enhancing Drug Use to the Family Medicine Practitioner¹⁴⁻¹⁵

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Performance enhancing drugs (PEDs) are drugs commonly found in prescription medications or dietary supplements used to enhance mental or physical performance. According to the World Anti-Doping Agency, sports organizations test for PEDs in elite athletes to preserve the integrity of sport by creating a level playing field, to inspire true sport by celebrating and encouraging hard work and dedication, and to protect the rights of athletes. A recent editorial published by Smith and Colleagues in American Family Physician brings awareness to PED use outside of the elite athletic population and inside the family medicine practice setting.

As sports organizations broaden their anti-doping initiatives to detect the use of PEDs in recreational and masters level (>30 years old) athletes, there have been a growing number of positive doping tests. Of the many PEDs used, selective androgen receptor modulators (SARMs), growth hormone and metabolic modulators, and designer stimulants should be on any practitioner's radar as these are easily accessible on the internet and found in dietary supplements. Examples of these include ostarine, meldonium and higenamine, respectively. Knowing if a patient is using these products is particularly important to determine drug interactions or the likelihood of exacerbating underlying conditions. Additionally, the short- and long-term consequences of using these novel drugs are unknown. Because PED use is prohibited in sport, patients who use them and compete as recreational or masters level athletes can experience negative consequences on

their athletic careers. Smith and Colleagues emphasize the importance of family medicine practitioners being alert to the signs of PED use, integrating screening into their workflow, and having open dialogue about the safety and efficacy of using such products. They stress the importance for practitioners to be aware of the competition status of patients and the need for therapeutic use exemptions, which allows patients to use these drugs for legitimate medical conditions. Additionally, pharmacists can play an important role in evaluating the indication, efficacy, and safety of medications and dietary supplements consumed by individual athletes. Resources to check if a medication is permitted in a certain sport can be found at Global Drug Reference Online (<https://www.GlobalDRO.com>).

Old Drug, New Indication? An expanded approval for the use of Entresto™¹⁶⁻¹⁸

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While previously indicated for use solely in those with heart failure with reduced ejection fraction, sacubitril/valsartan (Entresto™) is now approved for use in a larger population. The expanded approval came following the results of the PARAGON-HF study, which compared valsartan to sacubitril/valsartan in patients with an ejection fraction of at least 45%. The primary outcome was a composite of heart failure hospitalizations and cardiovascular death, and while it was not found to be statistically significant, benefit was seen in patients that had an ejection fraction in the lower proportion (45-57%) of those included. Based on these findings, sacubitril/valsartan is now approved for use in patients with an ejection fraction below normal. This expanded approval did not specify an ejection fraction cutoff, therefore requiring the use of clinical judgment when determining which patients are appropriate for use as ejection fraction can vary between patients. As the first approved therapy for both those with heart failure with reduced and preserved ejection fraction, sacubitril/valsartan now has the potential to benefit most patients with heart failure.

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