ACCP Adult Medicine PRN

Spring 2021 Newsletter

Edited by Rachel Flurie, PharmD, BCPS and Leslie Wooten, PharmD, BCPS

Message from the Chair

It's hard to believe it has been just over a year since the pandemic hit. This past year has brought many clinical, social, economic, academic, and political challenges. For many of our PRN members, it has been a year of increased workload and a plethora of virtual meetings. And while technology has allowed us to remain connected, it has left many of us feeling more disconnected than ever. Thankfully, the arrival and administration of COVID-19 vaccines has brought a newfound hope! Hope that we can once again gather in groups, vacation, and visit loved ones.

Carmen B Smith, PharmD, BCPS

The arrival of COVID-19 vaccines is also an exciting time for our profession. We as pharmacists not only play a crucial role in educating on the importance of receiving the vaccine but we are also able to increase access to the vaccines. On a daily basis, pharmacists across the nation are providing thousands of vaccinations to our communities. Whether you practice in a clinic or in the hospital, I hope that you have the opportunity to help with the vaccination efforts and be a part of ending this pandemic.

Despite the many changes this year has brought, I am proud to say that the efforts and commitment of our PRN members remain steadfast. This past fall, we once again had a record number of members sign up for committee involvement. Thanks to this dedication to committee involvement, the PRN continues to provide education to our members through resident journal clubs, student grand round presentations, educational webinars, and biannual PRN newsletters. These educational materials can be accessed at any time via the PRN webpage:

- Journal Clubs, Webinars, Grand Rounds: http://amedprn.accp.com/links.aspx
- PRN Newsletters: http://amedprn.accp.com/business_docs.aspx

The PRN also continues to give back to its members through research and travel funding. Financial support is available for those interested in pursuing ACCP's FIT and MeRIT programs and Seed Grants are provided to support 1-2 qualified research projects yearly (application required). Travel funds to attend the ACCP Annual Meeting are awarded to student, resident, and practitioner members each year. More information on how to apply for a Seed Grant or Travel Award can be found on our PRN webpage:

- Seed Grant and Award Criteria: http://amedprn.accp.com/business_docs.aspx

The above opportunities would not be possible without our members volunteering their time, so thank you! If you have not yet had a chance to be involved in committee work, I encourage you to sign up when the call comes next October. For those interested in taking a more involved role within the PRN, please consider submitting your name for an Adult Medicine PRN Officer position (email Nominations Committee Chair, Ryan Owens, by April 30th).

Lastly, I want to thank all of our AMED members for the hard work you do each day to provide patients the best care possible and for giving back to the profession through scholarship and teaching. We have so many members doing great things that deserve to be recognized! Please consider taking a moment to "name drop" a colleague (http://tinyurl.com/AMEDnamedropper) to be considered for one of our many PRN Awards.

I look forward to seeing everyone in-person at the 2021 Annual ACCP Meeting in Phoenix, AZ!

@ACCPAMEDPRN
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ACCP Adult
Medicine PRN

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Save The Date

May 24-30:
Posters available for asynchronous viewing and comment

May 25 and 26 7-9 PM EST:
interactive sessions

accp
American College of Clinical Pharmacy

2021 ACCP Annual Meeting
October 16-19, 2021
Phoenix Convention Center

ACCP Adult Medicine PRN Announcements

Nominations Committee

Call for Officer Nominations
The Nominations committee is now accepting nominations for Chair-Elect & Treasurer/Secretary. Please consider nominating yourself or a colleague for one of these leadership positions within our PRN! More information regarding officer roles can be found on our Adult Medicine PRN business documents page. Nominations are due by April 30th. To nominate or learn more, please contact the committee chair r.owens@wingate.edu

AMED Name Dropper
Don't want to make a formal nomination of a colleague? You can use the AMED PRN Name Dropper to let us know of any colleagues you think would be great to run for a PRN officer position or an outstanding candidate for an ACCP/PRN award! We can help facilitate the nomination process if you'll just share their name with us!
https://forms.gle/ByT19ZtTfAHy3RnP6

Walk Rounds Committee

Research Poster Highlights
Have you been recognized as having a top poster at Virtual Poster Symposium or Annual Meeting? Do you want to learn more about the research of our top posters? Follow AMED PRN on social media as the Walk Rounds Committee collaborates with External Affairs to highlight the research work of our members!

Virtual Poster Symposium (VPS)
Mark your calendars for the VPS May 25 & 26, 2021. The Walk Rounds Committee will be coordinating poster reviews of all AMED PRN posters and will be soliciting volunteers in May 2021. Please consider volunteering.

Trainee Engagement Committee

Resident-led Journal Club
There are 3 eJournal Club sessions left for the 2020-2021 year and some great topics coming up. Be on the lookout to sign up to be a presenter (PGY2 resident) or mentor for the 2021-2022 residency year.

Medicine Grand Rounds Series
We will be looking for students to participate in our medicine grand rounds series in the upcoming months. Please consider students who might be interested in this opportunity.

Seed Grant Award Winner 2020

Study Title: Impact of Inpatient Pharmacy-Driven Transitions of Care Services on Clinical Outcomes

Study Investigators: Nicole L. Metzger, PharmD, BCPS (*pictured*), Heidi King, PharmD, Megan Bereda, PharmD, Carrie Tilton, PharmD, BCPS, Jessica Nave, MD

Several years ago we implemented a diverse set of transitions of care (TOC) initiatives to improve patient care in our hospital medicine patients. We conducted medication histories, educated patients about select medications, and verified medication access at discharge by checking insurance coverage and completing prior authorizations for high cost, high-risk medications. There are many studies evaluating multi-step approaches to improving TOC in the hospital but few studies include medication access initiatives. Our IRB-approved, single-center, retrospective cohort study evaluates the clinical impact of these interventions on patient care. To date, we have collected data from 155 case patients who will be matched 1:1 with controls based on medication, age $\pm$ 5 years, Charlson Comorbidity Index (CCI) score $\pm$ 1, medical unit at discharge, and insurance status. Our primary outcome is hospital length of stay with secondary outcomes of all-cause readmissions at 7-days, 30-days, and 90-days. For case patients, we collected descriptive data on the medication access interventions. Primary and secondary outcomes will be compare cases to controls using two sample *t*-test and Chi-square. Multivariable analysis using a general linear model will be used to estimate the adjusted difference in hospital length of stay between the two groups after adjusting for other factors.

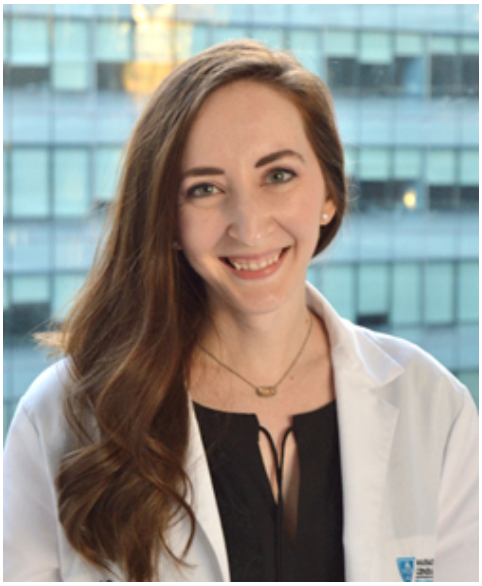
We have preliminary data for 155 case patients at this time. The case patients were 50.3% male with a mean age of 54 $\pm$ 20 years and 47.7% Caucasian. The mean CCI score was 3.3 $\pm$ 2.9 and 87.7% of patients had insurance. The most common classes of drugs that we intervened on were anticoagulants, antibiotics, and antidiabetic agents. The mean length of stay for case patients was 9.1 $\pm$ 9.7 days and 5.8% of patients were readmitted in 7-days, 16.1% were readmitted within 30-days, and 26.5% were readmitted within 90-days. Of the case

patients who received medication access interventions, 20.6% required prior authorizations and 100% of those were approved. Twenty-nine percent received coupons to reduce their cost and 12.3% were enrolled in patient assistance programs. The majority of access interventions took between half an hour to one hour to complete.

In early 2020, we completed a prospective survey of 26 hospitalists (72% response rate) and all respondents strongly agreed that TOC was important, that they valued pharmacy assistance with medication reconciliation and medication access, that pharmacy involvement in TOC services should be expanded, and that having pharmacy assist in TOC contributed to their work satisfaction. Only nine (34.6%) strongly agreed or agreed that they had time to work on TOC issues.

Our study analysis is still underway. We hope to demonstrate that pharmacists and their trainees can help hospitalists reduce length of stay and readmissions by proactively intervening to ensure medication access at discharge for high-cost, high-risk medications.

New Practitioner Award 2020



Hello AMED PRN! My name is Alexandra Tatara, and I am thrilled to have been the recipient of the AMED PRN New Practitioner Award this year. I am currently practicing as an Advanced Clinical Pharmacist at Massachusetts General Hospital in Boston, Massachusetts. Prior to moving to Boston, I was a Clinical Pharmacy Specialist at Houston Methodist Hospital in Houston, Texas, where I also completed my residency training (PGY1 and PGY2 Internal Medicine). One of my goals as a new practitioner has been to become involved in ACCP, specifically the AMED PRN, to give back to the profession that has given so much to me. I started my involvement by joining the AMED PRN Research Committee, and at the annual meeting, I served as a poster reviewer for the Walk Rounds Committee and decided to join them in the new year. The AMED PRN has given me the opportunity to network with and learn from fellow AMED pharmacists around the country, and I look forward to where my involvement will take me next. This award represents a first step which I hope to use to build upon my contributions to the AMED PRN as my career progresses.

Resident Research Award

"Acute Kidney Injury (AKI) associated with area under the curve (AUC_{24}) versus trough monitoring of vancomycin in obese patients."

Heather Rucker, PharmD, PGY2 Internal Medicine University of Kentucky HealthCare

Student Research Award

"The Clinical Impact of Rifamycins on the Efficacy and Dosing of Opioid Agents: a Systematic Review."

Sandhya Vijapurapu, PharmD Candidate Duquesne University

"Safety and efficacy of intravenous hydralazine and labetalol for the treatment of asymptomatic hypertension in hospitalized patients: a systematic review."

Katie DeBaisio, PharmD Candidate Duquesne University

Member Accomplishments

Promotions

Alexandra Whiddon Tartara: Advanced Clinical Pharmacist at Massachusetts General Hospital

Leslie Wooten: Internal Medicine Clinical Pharmacy Manager

Awards

Sarah L. Anderson: ACCP AMED PRN Mentoring Award.

Paul P. Dobesh: Distinguished Teaching Award – University of Nebraska College of Pharmacy.

Paul P. Dobesh: South Dakota State University College of Pharmacy and Allied Health Professions Distinguished Alumnus Award.

Donald Moore: 40 Under 40 in Cancer 2020 – National Community Oncology Dispensing Association.

Mate Soric: Editor's Choice Award, Journal of the American College of Clinical Pharmacy.

Asha Tata: Society of Hospital Medicine Maryland Chapter, Non-Physician Clinician of the Year Award 2020.

Grants

Metzger NL, Tilton CS, King H, Nave J. Awarded a $5000 Adult Medicine PRN Seed Grant from ACCP for the project entitled, Impact of Inpatient Pharmacy-Driven Transitions of Care Services on Clinical Outcomes.

Publications

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2020 ACCP Fellows

Jon P. Wietholter

Other Notable Achievements

Ashley Otto: American Academy of HIV Medicine – HIV Pharmacist (AAHIVP) Certification.

Jennifer Austin Szwak: Chair of the Vizient Pharmacy Network Research Committee.

PRN Officers

2020-2021 ACCP Adult Medicine PRN Officers
Chair: Carmen B Smith, PharmD, BCPS
Chair-Elect: Jon P Wietholter, PharmD, BCPS, FCCP
Secretary-Treasurer: Rachel Flurie, PharmD, BCPS
Immediate Past Chair: Ryan Owens, PharmD, BCPS

Venous Thromboembolism Prophylaxis in Hospitalized Patients with COVID-19

Kerri McGrady, PharmD, PGY-2 Internal Medicine Resident, Virginia Commonwealth University Health System

Sarah Petite, PharmD, BCPS, Assistant Professor of Pharmacy Practice, University of Toledo

Introduction

In December 2019, cases of acute respiratory illness caused by severe acquired respiratory syndrome coronavirus-2 (SARS-CoV-2) occurred in Wuhan, China.[1] This virus spread quickly to other countries and ultimately, throughout the globe, developing into a global health crisis. To date, over 117 million people have been affected by coronavirus disease 2019 (COVID-19) worldwide, leading to over 2 million deaths. Although COVID-19 primarily affects the respiratory system, other organ systems may be affected especially under conditions of increasing disease severity. Thrombotic complications are of particular interest and varying rates of thromboembolic events have been reported with COVID-19, leading to questions regarding pathophysiology, appropriate prevention, and treatment of these events.

In hospitalized patients, the rate of venous thromboembolism (VTE) ranges from 5-15%, and the use of prophylactic anticoagulation reduces the risk to 2.8-5%.[2] This risk increases to 10-30% in critically ill patients, but is reduced to 5.1-7.7%, again, with the use of pharmacologic prophylaxis.[2-4] A recent meta-analysis, including 66 studies and 28,173 patients, revealed that the overall prevalence of VTE in hospitalized patients with COVID-19 was about 14.1%.[5] This prevalence was higher in critically ill patients (22.7% versus 7.9%). To date, no placebo-controlled randomized trials have been conducted, which makes defining the true risk of VTE in patients with COVID-19 difficult to determine.

Pathophysiology

The pathophysiology of thrombosis in COVID-19 is currently incompletely elucidated. However, there is likely a complex interplay between inflammatory and hemostatic systems through coagulopathy, immuno-thrombosis, complement activation and hypoxia.[6,7]

Markers of coagulopathy are present in COVID-19. Patients often have elevated levels of fibrinogen and D-dimer, a mild thrombocytopenia and prolongation of the prothrombin time (PT). Activated prothrombin time (aPTT) may also be present.[8-11] Elevations in D-dimer have been associated with disease severity, and may allow for predicting those at the highest risk of developing VTE.[8,11] The club-shaped spike (S) protein of SARS-CoV-2 has a high affinity for the angiotensin-converting enzyme 2 (ACE2), which is predominately found on cell membranes in the lungs, cardiac myocytes, and vascular endothelium.[12,13] The binding of ACE2 to the S protein leads to an increase in production of angiotensin II (ATII) which leads to a downstream increase in thrombotic potential.[14,15] Activation of the coagulation cascade occurs

from both the intrinsic and extrinsic pathways via damage to endothelial cells and neutrophil release in COVID-19, thereby increasing the risk of thrombosis.[14;] Immuno-thrombosis, defined as the connection between the immune response, inflammation, and thrombosis, is also present in COVID-19. Viral proteins inhibit interferon production which allows for rapid viral replication and neutrophil recruitment in the lung parenchyma.[12] Subsequently, the high levels of proinflammatory cytokines such as interleukin (IL) 1β, IL-6 and tumor necrosis factor-α along with the hyperinflammatory response which damages tissues, initiate thrombotic processes.[13] SARS-CoV-2 may also trigger complement activation through its recognition by the host as a foreign pathogen. It does this by acting as a cofactor to enhance lectin pathway activation, and by direct host-cell injury.[16] Finally, patients with COVID-19 are often hypoxic, especially those with severe disease.[17] Hypoxemia triggers expression of hypoxemia-inducible factors which activate coagulation proteins and platelets, increase tissue factor expression and PAI-1, and inhibit anticoagulant protein S, further promoting a pro-coagulable state.

Clinical Presentation

COVID-19 related thromboembolic presentations vary widely. Macrovascular thrombotic events including pulmonary embolism (PE) and deep vein thrombosis (DVT) are well described in this population. As evidenced by a recent meta-analysis, prevalence of VTE was higher in critically ill patients and in studies where ultrasound screening was employed.[5] The authors endorsed a high level of heterogeneity of included studies and the possibility of higher rates of VTE in critically ill patients, therefore, confounding the overall prevalence in the population. Reports of PE in autopsies of patients with COVID-19 indicate rates as high as 60%.[18] Other systemic thromboses have also been reported including cerebral venous thrombosis, femoral artery thrombosis, and acute superior mesenteric artery thrombosis.[19-21] Additionally, microvascular thrombotic events have also been reported. Lung autopsies of patients who died from COVID-19 revealed micro-thrombosis in up to 80% of patients.[22] These micro-thrombi are not, however, restricted only to the lungs; they have been found in various other organ systems including the heart and kidneys.[23]

Diagnosis

At hospital admission, it is reasonable to obtain a D-dimer, although guidelines do not provide a recommendation for or against this practice.[24-27] It is not recommended to routinely obtain diagnostic imaging testing for all hospitalized COVID-19 patients to screen for PE or DVT.[25] Presence of an elevated D-dimer should be used in combination with clinical signs and symptoms to determine the need for further diagnostic testing. If diagnostic testing is pursued for PE, a computed tomography angiogram (CTA) should be used first line, if possible, due to potential difficulties with obtaining a ventilation/perfusion (VQ) scan based on the severity of respiratory symptoms.

Elevated D-dimer levels are associated with worse clinical outcomes and patients with higher initial D-dimer levels are at greater risk of developing a VTE.[5,28,29] Various D-dimer cut-offs have been evaluated for predicting VTE, including greater than 2,590 ng/mL and 1,500 ng/mL, in the absence of anticoagulation..[28,29] There is insufficient evidence to recommend obtaining repeat D-dimer values but

such actions may be reasonable in patients who are not improving despite other appropriate COVID-19 therapies. Therefore, if a patient has unexplained clinical deterioration during hospitalization, it is reasonable to obtain repeat D-dimer and evaluate for thromboembolic disease.

Inpatient Anticoagulant Prophylaxis

There are several organizations with guidance on VTE treatment and prophylaxis for patients with COVID-19.[24-27,30,31] A summary of recommendations for inpatient VTE prophylaxis in the non-intensive care unit (ICU) setting is provided in Table 1. All hospitalized patients with COVID-19 in the non-ICU setting should receive prophylactic dose anticoagulation. Several societies recommend low molecular weight heparin (LMWH), or fondaparinux, instead of unfractionated heparin (UFH), due to the reduced risk of infection spread for caregivers with once daily anticoagulant administration.[24,26,30] Use of oral anticoagulants is not recommended due to the prolonged half-life compared to LMWH or UFH.[27] Limited guidance is available for management of an inpatient already receiving an oral anticoagulant prior to hospital admission but it may be reasonable to use a parenteral agent if there is a concern for a thrombotic event. Initiation of VTE prophylaxis within 24 hours of hospital admission is associated with lower risk of 30-day mortality compared to no anticoagulation.[32] Additionally, initiation of VTE prophylaxis was associated with a lower risk of 28-day mortality in patients with a D-dimer ≥ 6 times the upper limit of normal (32.8% vs 52.4%; P=0.017) in one retrospective study.[29]

Intermediate dose or full-dose (therapeutic) anticoagulation have also been explored in many studies primarily in the ICU setting.[30,33] Intermediate dose anticoagulation is enoxaparin 0.5 mg/kg subcutaneous every 12 hours or subcutaneous heparin 7500 mg every 8 hours. A meta-analysis included 35 observational studies in a total of 4,685 patients comparing no anticoagulation, prophylactic dose, intermediate-dose and therapeutic dose anticoagulation. VTE occurred at a lower rate in patients receiving pharmacologic therapy (41.9% vs 19.8% vs. 11.9% vs. 10.5%) and was numerically lower in patients receiving intermediate dose or therapeutic dose anticoagulation. No statistically significant difference was observed between prophylactic dose and intermediate dose (p=0.32) or prophylactic dose and therapeutic dose anticoagulation (p=0.18). Rates of bleeding were numerically higher in patients receiving full dose (6.3%) compared to prophylactic dose anticoagulation (1.7%). These results are similar to an American Society of Hematology meta-analysis.[30] No difference in VTE rate was observed between prophylactic dose and intermediate or therapeutic dose anticoagulation (OR 0.87 [95% CI 0.45-1.67]). Development of a PE was lower with intermediate dose or therapeutic anticoagulation, compared to prophylactic dose anticoagulation (OR 0.09 [95% CI 0.02-0.57]. However, higher rates of major bleeding were found with intermediate or therapeutic anticoagulation (OR 3.84 [95% CI 1.44-10.21]). Since the findings from these two meta-analyses, a large cohort study in the ICU setting in the United States found no difference in mortality between therapeutic anticoagulation and non-therapeutic dose anticoagulation.[34]

Optimal VTE prophylaxis dosing for COVID-19 patients continues to be investigated. Most recently, three different studies combined clinical-outcome information with pre-print, non-peer reviewed data presented in January 2021.[35] These studies are: 1. Antithrombotic therapy to ameliorate complications of COVID-19 (ATTACC); 2. Randomized embedded multi-factorial, adaptive platform trial (REMAP-CAP); 3.

Accelerating COVID-19 therapeutic interventions and vaccines (ACTIV-4a). Hospitalized adults in the non-ICU and ICU setting are randomized to either therapeutic anticoagulation or prophylactic anticoagulation (LMWH or UFH) with both interventions dosed according to the institution's policy . The primary outcome is 21-day "organ support-free" days, defined as an ordinal scale of in-hospital mortality, requiring critical care support, mechanical ventilation, vasopressors, ECMO, or high flow oxygen. Interim results in 2,895 patients indicate a mortality benefit, regardless of baseline D-dimer, with therapeutic anticoagulation compared to prophylactic dose anticoagulation for patients in the non-ICU setting (5.7% vs 7.7%; OR 1.57 [95% CI 1.14-2.19]), but no benefit in the critical care setting (35.3% vs 32.6% OR 0.76 [95% CI 0.6-0.97]).

Discharge Anticoagulant Therapy

A meta-analysis assessing in-hospital prophylaxis to extended-duration prophylaxis in acutely-ill hospitalized patients found that prophylaxis can reduce the risk of VTE but increases the risk of hemorrhage.[36] However, there is currently no data from randomized controlled trials to assess the risk of post-discharge VTE in patients with COVID-19. Recent retrospective data suggests that the incidence of 30-day post-discharge VTE is low (0.6%), with a similar incidence of major hemorrhage (0.7%).[37] Recommendations for post-discharge VTE prophylaxis are summarized in Table 1. However, it is notable that not all published guidelines make recommendations on this subject. Overall, it is recommended to consider both risk factors for VTE, bleeding risk and feasibility when discussing extended VTE prophylaxis. If the decision is made to pursue post-discharge prophylaxis, it is recommended to use an agent which has previously been studied or approved for this purpose (i.e. . Betrixaban, rivaroxaban, or enoxaparin).[31]

Conclusion

Based on the available evidence, prophylactic dose anticoagulation started at hospital admission is the most appropriate therapy for most hospitalized, non-ICU patients with COVID-19. The eventual peer-reviewed, published results of the ATTACC, REMAP-CAP and ACTIV-4a studies may change recommendations for initial anticoagulation strategies. In the setting of increasing D-dimer or unexplained acute decompensation, escalation in dosing of anticoagulation may be reasonable, due to the likelihood of VTE development. Specific D-dimer recommendations may be based on previous evidence, such as greater than 1500 ng/mL or 2590 ng/mL, since these levels are predictive of subsequent VTE.

References available here

Table 1. Summary of Venous Thromboembolism Prophylaxis Recommendations for Hospitalized, non-Intensive Care Unit Patients[24-27,30,31]

Guideline	Release Date	Recommendations
NIH	2/2021	• All hospitalized patients should receive prophylactic dose anticoagulation • Insufficient evidence to support higher doses of anticoagulation • Post-discharge prophylaxis is not recommended
ASH	10/2020 1/2021	• Prophylactic dose anticoagulation suggested over intermediate or therapeutic anticoagulation • Plans to update guidelines with results of REMAP-CAP, ACTIV-4 and ATTACC studies
CHEST	9/2020	• All hospitalized patients should receive prophylactic dose anticoagulation. LMWH or fondaparinux preferred to UFH • Antiplatelet therapy should not be utilized for VTE prophylaxis • Insufficient evidence to support higher doses of anticoagulation • Extended prophylaxis should be considered in patients with low bleeding risk
ISTH	8/2020	• Prophylactic dose anticoagulation with LMWH or UFH should be used. LMWH preferred • May consider intermediate dose LMWH • Post-discharge prophylaxis should be considered for all patients that meet high risk VTE criteria, and be continued for 14-30 days
Anticoagulation Forum	5/2020	• Prophylactic dose anticoagulation recommended for all patients • No evidence to suggest D-dimer to guide anticoagulation intensity • Post-discharge prophylaxis is not recommended for all patients; decision based on risk factors and feasibility
ACC	4/2020	• All hospitalized patients should receive prophylactic dose anticoagulation. LMWH preferred to UFH. • Higher intensity anticoagulation can be considered, but should be reserved for clinical trials due to lack of evidence

Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors in Patients Without Type 2 Diabetes Mellitus

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Introduction

Poorly controlled diabetes is often associated with macrovascular and microvascular complications, including cardiovascular disease, cerebrovascular disease, and nephropathy.[1] In 2008, in response to previous safety concerns related to type 2 diabetes mellitus (T2DM) therapies, the U.S. Food and Drug Administration published guidance requiring new T2DM medications to include large cardiovascular outcomes trials (CVOTs) to evaluate the risks and benefits of new treatment options. Required cardiovascular events include cardiovascular mortality, myocardial infarction, and stroke. Additional endpoints, such as heart failure (HF) hospitalization or renal risk (e.g. reduced estimated glomerular filtration rate [eGFR], albuminuria, or progression to end-stage kidney disease), may also be included.[2] Published CVOTs assessing sodium-glucose cotransporter 2 (SGLT2) inhibitors, including empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin, for T2DM reveal additional beneficial effects on heart failure and renal outcomes to varying degrees through subgroup analyses (Table 1). Although these subgroup analyses have been indicative of SGLT2 inhibitors' potential in managing HF and chronic kidney disease (CKD), additional studies have been needed to confirm their safety and efficacy in patients without diabetes mellitus (DM).[3-6]

SGLT2 inhibitors' impact heart failure outcomes through various mechanisms, including the class' impact on diuresis, myocardial metabolism, and vascular function. This drug class offers osmotic and diuresis effects through the inhibition of sodium reabsorption in the proximal tubules of the kidney, resulting in up to 60% increase in urinary sodium excretion.[7-8] Through this effect, SGLT2 inhibitors only modestly lower blood pressure, which ultimately lowers cardiac afterload to improve cardiac efficiency. Porcine models of heart failure suggest that empagliflozin decreases cardiac remodeling by enhancing myocardial energy production.[9] Additional mechanisms are likely involved to fully explain the benefit of SGLT2 inhibitors on both cardiovascular and renal function.[8]

The mechanism in which SGLT2 inhibitors improve renal outcomes is still somewhat unknown but is thought to be due to their ability to reduce intraglomerular pressure induced by vasoconstriction through tubuloglomerular feedback as opposed to their antihyperglycemic effects.[10-11] There is an initial decrease in eGFR given this mechanism followed by restoration of sodium delivery to the macula densa which promotes increased afferent arteriolar tone and adenosine production. The reduced intraglomerular pressure and reduction in hyperfiltration has been hypothesized to suppress downstream glomerular

fibrosis and inflammation, as well, which could explain SGLT2 inhibitors' benefits in diabetic kidney disease.[12]

Evidence

Table 1 highlights key inclusion criteria, baseline characteristics, HF and renal outcomes, and adverse effects from SGLT2 inhibitor CVOT, HF-focused, and CKD-focused clinical trials.

SGLT2 Inhibitors and Heart Failure (HF)

As the prevalence of HF continues to rapidly increase, with an estimated 6 million American adults diagnosed with HF from 2015 to 2018, its associated healthcare costs, morbidity, and mortality have prompted a great need for continued pharmacotherapy optimization.[13] Guideline-directed medical therapy (GDMT) includes pharmacotherapy proven to reduce mortality in patients with HF with reduced ejection fraction (HFrEF), including angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB)/angiotensin receptor-neprilysin inhibitor (ARNI), beta blockers, and mineralocorticoid receptor antagonists.[14] However, recent data reveals 5-year mortality for patient with remains high (75%), and this disease state is associated with frequent hospital readmission, highlighting the need for maintaining GDMT and additional disease-modifying pharmacotherapy.[14-15] The American Diabetes Association recognizes the utility of SGLT2 inhibitors in reducing rates of HF hospitalizations in patients with T2DM based on data based on results from the EMPA-REG OUTCOME (empagliflozin), DECLARE-TIMI 58 (dapagliflozin), and CANVAS (canagliflozin) trials; however, only approximately 10% of patients had history of HF at baseline in these trials.[3-6,16] Until recently, limited data has been available to assess the safety and efficacy of this drug class in managing HF without concurrent T2DM.

Dapagliflozin

The DEFINE-HF trial randomized 263 patients with New York Heart Association (NYHA) class II-III HF and left ventricular ejection fraction (LVEF) ≤ 40%, eGFR > 30 ml/min/1.73m^2, and elevated natriuretic peptides (NT-proBNP) to receive dapagliflozin 10 mg daily or placebo for 12 weeks. Dual primary outcomes were evaluated: 1) mean NT-proBNP and 2) proportion of patients with at least 5-point increase in HF disease-specific health status on the Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS) score, or a ≥ 20% decrease in NT-proBNP. At baseline, GDMT was largely optimized with 97% of patients on beta blockers, 61% on mineralocorticoid antagonists, 59% on ACEi/ARBs, and 33% on ARNI. While this trial did not identify a statistically significant difference in average 6- and 12-week adjusted NT-proBNP, 61.5% of dapagliflozin patients met the second dual-primary outcome as compared to 50.4% of patients treated with placebo (adjusted OR 1.8, 95% CI 1.03-3.06, p=0.039). The change in patient-reported KCCQ-OS score, which reflects symptoms and physical limitations, was achieved in the setting of highly optimized GDMT for HFrEF. Despite the study's short duration, large outcome trials subsequently further expanded on these results through clinical outcomes, such as HF hospitalization and cardiovascular death.[17]

The DAPA-HF trial randomized 4744 patients with NYHA class II-IV HF and LVEF ≤ 40% into two cohorts that received dapagliflozin 10 mg daily (n=2373) or placebo (n=2371) to evaluate the composite primary outcome of worsening HF (hospitalization or urgent visit resulting in intravenous therapy for HF) or

cardiovascular death. Enrolled patients were required to receive GMDT, consisting of ACEi/ARB (82.8%) or ARNI (10.9%) and beta blocker (96.2%) unless use was contraindicated or not tolerated. Doses of these medications could be further titrated as clinically appropriate. The study revealed that patients who received dapagliflozin experienced a significant reduction in the composite endpoint compared to placebo (16.3% vs. 21.2%; HR 0.74; 95% CI, 0.65-0.85) over the median follow-up duration of 18.2 months. Each component of the composite endpoint also favored dapagliflozin. Notably, only 41.8% of enrolled patients had history of T2DM, and the primary outcome result was consistent among those with T2DM and most other subgroups. In regard to safety outcomes, 1.2% of patients in the dapagliflozin group developed serious adverse events related to volume depletion as compared to 1.7% in the placebo group. The DAPA-HF trial found a modest reduction in blood pressure with the use of dapagliflozin. Ultimately, dapagliflozin was found to decrease the risk of worsening HF and cardiovascular death regardless of concurrent T2DM with limited serious adverse events.[18]

Based on the results of DAPA-HF alongside the data available from the DECLARE-TIMI 58 trial, the FDA has approved the use of dapagliflozin to reduce the risk of cardiovascular death and hospitalization for HF in patients with HFrEF regardless of the presence of concurrent DM.[19]

Empagliflozin

The EMPEROR-Reduced trial randomized 3730 patients with NYHA class II-IV HF and LVEF $\leq$40% to receive either empagliflozin 10 mg daily or placebo to evaluate the primary composite outcome of cardiovascular death or worsening HF resulting in hospitalization. This trial cohort consisted of patients with primarily NYHA II or III HF, and 50% of the population had a history of T2DM. Enrolled patients received GMDT, including ACEi/ARB (68.9%), beta-blocker (94.7%), mineralocorticoid antagonist (72.6%), or ARNI (20.7%). Among patients with and without T2DM, 19.4% of patients in the empagliflozin versus 24.7% of patients in the placebo group experienced the primary outcome (HR 0.75; 95% CI, 0.65-0.86, p<0.001) during the median follow-up period of 16 months. These results were overall consistent with the results of the DAPA-HF trial. Notably, the use of empagliflozin was associated with an increased risk of genital infection; however, these were generally mild in severity.[20]

The EMPATROPISM trial evaluated the impact of empagliflozin use in HF patients on left ventricular (LV) volume, mass, and function as compared to placebo. This trial enrolled 84 patients with NYHA class II-III HF, LVEF < 50%, and stable symptoms and pharmacotherapy regimen for HF over the previous three months. Over the course of six months, empagliflozin was found to be associated with a significant change in both LV end-systolic volume from baseline (-26.6 mL v. -0.5 mL, p<0.001) and LV end-diastolic volume from baseline (-25.1 mL v. -1.5 mL, p<0.001). Empagliflozin was also associated with a statistically significant change in LVEF, LV mass, peak max oxygen consumption (VO_2), and 6-minute walk test over the course of three months.[21] This study supports the impactful clinical outcomes identified with the EMPEROR-Reduced trial with additional insight to potential mechanisms of this drug class' beneficial effects.[20-21]

Boehringer Ingelheim and Eli Lilly have submitted a new drug application for use of empagliflozin in HF. Empagliflozin is also being investigated for use in chronic HF with preserved ejection fraction (HFpEF) in the EMPEROR-Preserved trial; however, results are currently unavailable.[22]

SGLT2 Inhibitors and Renal Outcomes

The renal benefits of the SGLT2 inhibitors canagliflozin, empagliflozin, and dapagliflozin have been widely published in the large-scale CVOT trials in thousands of patients with T2DM, including decreased rates of progression to macroalbuminuria [defined as a urine albumin-to-creatine ratio (UACR) >300 mg/g], end-stage kidney disease, and need for renal replacement therapy as well as decreased numbers of renal deaths and slower declines in eGFR.[4,5,23] Ertugliflozin, the newest FDA-approved SGLT2 inhibitor in the United States, did not show a statistically significant difference in renal outcomes when compared to placebo in the recent VERTIS CV trial but did trend towards benefit with ertugliflozin.[6]

The CREDENCE trial was the first study evaluating an SGLT2 inhibitor (canagliflozin) vs. placebo in patients with T2DM and albuminuric CKD based on the renal outcomes noted in EMPA-REG, CANVAS, and DECLARE-TIMI 58. Patients in CREDENCE were defined as having CKD with an eGFR 30-90 mL/min/1.73m^2 and UACR of 300-5000 mg/g. Patients were required to be on a stable dose of an ACEi or ARB for at least four weeks prior to enrollment as tolerated. The CREDENCE trial was stopped early given benefit noted with canagliflozin with the primary composite outcome of end-stage kidney disease (maintenance dialysis $\geq$30 days, eGFR <15 mL/min/1.73m^2, or kidney transplant), doubling of serum creatinine (SCr) levels from baseline, or death from renal or cardiovascular causes being significantly decreased with canagliflozin (43.2 per 1000 patient-years) vs. placebo (61.2 per 1000 patient-years) (HR 0.70, 95% CI, 0.59-0.82, p=00001). The authors concluded that over the median 2.62-year treatment duration, canagliflozin decreased the risk of renal worsening in patients with T2DM and albuminuric CKD.[24] Ultimately, the results of the CREDENCE trial led to a Class Ia recommendation in the KDIGO 2020 Clinical Practice Guidelines for Diabetes Management in Chronic Kidney Disease to initiate SGLT2 inhibitors in patients with T2DM and CKD with eGFR $\geq$30 mL/min/1.73m^2.[24,25]

Although CREDENCE only included patients with T2DM, recent trials evaluating SGLT2 inhibitors in patients with HF were the first studies to assess renal outcomes in patients on SGLT2 inhibitors with and without T2DM. In the DAPA-HF trial, a non-statistically significant decrease in the composite renal outcome of sustained decline in eGFR $\geq$50%, end-stage kidney disease, or renal death was noted with dapagliflozin (n=28, 1.2%, 0.8 events per 100 patient-years) vs. placebo (n=39, 1.6%, 1.2 events per 100 patient-years) (HR 0.71, 95% CI, 0.44-1.16).[18] However, a statistically significantly decreased rate of decline in eGFR with empagliflozin (-0.55 mL/min/1.73m^2) in comparison to placebo (-2.28 mL/min/1.73m^2) was seen in the EMPEROR-Reduced trial (between group difference 1.73, 95% CI, 1.10-2.37, p<0.001). The composite of chronic dialysis or renal transplant or a sustained reduction in eGFR was also found to be lower with empagliflozin (HR 0.50, 95% CI, 0.32-0.77) in EMPEROR-Reduced.[20]

DAPA-CKD, published in late 2020, was the first randomized controlled trial examining the long-term safety and renal efficacy of an SGLT2 inhibitor (dapagliflozin) in patients with CKD regardless of the presence of T2DM. Key inclusion criteria were the presence of CKD (defined as an eGFR 25-75

mL/min/1.73m^2), presence of albuminuria (defined as a UACR 200-5000 mg/g), and treatment with a stable dose of an ACEi or ARB at least four weeks prior to the trial start as tolerated. The DAPA-CKD trial concluded early given efficacy noted with dapagliflozin for the primary composite outcome of the first occurrence of a decline in eGFR of ≥50%, onset of end-stage kidney disease (defined as eGFR <15 mL/min/1.73m^2, maintenance dialysis, or kidney transplantation), or death from renal or cardiovascular causes occurring significantly less with dapagliflozin (n=197, 9.2%) vs. placebo (n=312, 14.5%) (HR 0.61, 95% CI, 0.51-0.72, p<0.001). Notably, 67.5% of patients in DAPA-CKD had previous diagnoses of T2DM upon enrollment, and the results for the primary outcome remained consistent in those with T2DM (HR 0.64, 95% CI, 0.52-0.79) and those without T2DM (HR 0.50, 0.35-0.72). The incidence of the secondary composite renal outcome also significantly decreased with dapagliflozin (HR 0.56, 95% CI, 0.45-0.68, p<0.001). Overall adverse event rates were similar in the dapagliflozin and placebo groups for events of interest, including amputations and fractures, and no patients receiving dapagliflozin experienced DKA nor Fournier's gangrene. In conclusion, the DAPA-CKD trial found that patients with CKD had a significantly lower risk of renal worsening with dapagliflozin vs. placebo over the 2.4-year follow-up duration, regardless of the presence or absence of T2DM.[26]

Empagliflozin is currently being evaluated in patients with CKD with and without T2DM in the EMPA-KIDNEY trial. EMPA-KIDNEY is enrolling patients with CKD, regardless of presence of T2DM, and will be randomized to receive empagliflozin or a matching placebo. Study participants are being stratified between eGFR ≥20-44 mL/min/1.73m^2 and eGFR 45-90 mL/min/1.73m^2 and UACR >200 mg/g. The primary outcome of EMPA-KIDNEY is a composite of a sustained decline in eGFR to <10 mL/min/1.73m^2, end-stage kidney disease, renal death, or cardiovascular death. The trial is projected to conclude in 2022.[27,28]

Table 1. Compilation of SGLT2 Inhibitor Landmark Clinical Trials with Heart Failure and Renal Outcomes Data

Trial	Study Population	LVEF	eGFR*	Intervention	Heart Failure/Renal Outcomes (SGLT2 inhibitor vs. placebo)	Select Safety Outcomes (SGLT2 inhibitor vs. placebo)	Notes
Wanner et al. 2016 EMPA-REG OUTCOME n=7,020	T2DM with ASCVD 80.7% on ACEi or ARB; 65% on BB	N/A	Included ≥ 30 Mean eGFR for ≥60: 83.	Empagliflozin 10 mg daily vs. 25 mg daily vs. placebo	Hospitalization for HF: 2.7% v. 4.1%; HR 0.65 (95% CI 0.50-0.85; p=0.002) Composite renal outcome: 12.7% vs. 18.8%; HR 0.61 (95% CI, 0.53-0.70, p<0.001)	Genital infection: 6.4% v. 1.8% (p<0.001) Volume depletion: 5.1% v. 4.9% (NS)	10.5% of enrolled patients had history of HF at baseline 25.5% had eGFR <60 Mean eGFR <60: 48.5

Neal et al. 2017 CANVAS n=10,142 CANVAS-R n=5,812	T2DM with ASCVD or CV risk factors 80% on ACEi or ARB; 53.5% on BB	N/A	Included > 30 Mean: 76.5	Canagliflozin 100 mg daily (max 300 mg) vs. placebo	Hospitalization for HF: 5.5 events per 1000 patient-years v. 8.7 events per 1000 patient-years; HR 0.67 (95% CI 0.52-0.87) Composite renal outcome: 5.5 per 1000 patient-years vs. 9 per 1000 patient-years; HR 0.60 (95% CI, 0.47-0.77)	Amputation: 6.3% v. 3.4% (p<0.001) Fracture: 15.4% v. 11.9% (p=0.02) Infection of male genitalia: 34.9% v. 10.8% (p<0.001)	14.4% of enrolled patients had history of HF at baseline CANVAS-R progression of albuminuria decreased compared to CANVAS, p=0.02 for homogeneity
Wiviott et al. 2018 DECLARE-TIMI 58 n=17,160	T2DM with ASCVD or CV risk factors 81.3% on ACEi or ARB; 52.4% on BB	N/A	Included CrCl > 60** Mean eGFR: 85.2	Dapagliflozin 10 mg daily vs. placebo	Hospitalization for HF: 2.5% v. 3.3%; HR 0.73 (95% CI 0.61-0.88) Composite renal outcome: 4.3% vs. 5.6%; HR 0.76, 0.67-0.87	Genital infection: 0.9% v. 0.1% (p<0.001) AKI: 1.5% v. 2% (p=0.002)	History of HF: Dapagliflozin: 9.9% Placebo: 10.2% 4% of patients had eGFR <60 due to inclusion criteria of CrCl >60
Perkovic et al. 2019 CREDENCE n=4,401	T2DM with CKD and UACR 300-5000 mg/g *on ACEi or ARB (99.9%); 40.2% on BB*	N/A	Included 30-90 Mean: 56.2	Canagliflozin 100 mg daily vs. placebo	Hospitalization for HF: 15.7 events per 1000 patient-years v. 25.3 events per 1000 patient-years; HR 0.61 (95% CI 0.47-0.80; p<0.001) Primary composite outcome of ESKD, doubling of SCr, or death from renal or CV causes: 43.2 per 1000 patient-years vs. 61.2 per 1000 patient-years; HR 0.70 (95% CI, 0.59-0.82, p=0.00001)	Lower-limb amputation: 12.3 v. 11.2 per 1000 patient-years (HR: 1.11; 95% CI, 0.79-1.56) Fracture: 11.8 v. 12.1 per 1000 patient-years (HR: 0.98; 95% CI 0.70-1.37)	History of HF: Canagliflozin: 14.9% Placebo: 14.7% Did not measure off-treatment eGFR values in patients after trial completion

Cannon et al. 2020 VERTIS CV n=8,246	T2DM with ASCVD 81% on ACEi or ARB; 68.9% on BB	N/A	Included ≥ 30 Mean: ~76	Ertugliflozin 5 mg daily vs. 15 mg daily vs. placebo	Hospitalization for HF: 2.5% v. 3.6%; HR 0.70 (95% CI 0.54-0.90) Composite renal outcome: Trended towards decrease with ertugliflozin vs. placebo; HR 0.81 (95.8% CI, 0.63-1.04)	Amputations: 2% (5mg) v. 2.1% 15mg) v. 1.6% (placebo) Genital mycotic infection (women): 6% (5mg) v. 7.8% (15mg) v. 2.4% (placebo) (p<0.001 for both doses of ertugliflozin v. placebo) Genital mycotic infection (men): 4.4% (5mg) v. 5.1% (15mg) v. 1.2% (placebo) (p<0.001 for both doses of ertugliflozin v. placebo)	History of HF: Ertugliflozin: 23.4% Placebo: 24.5% CV outcomes noninferior for ertugliflozin vs. placebo
McMurray et al. 2019 DAPA-HF n=4,744	HF Class II, II, IV with LVEF ≤40% *on ACEi, ARB, or neprilysin inhibitor (94.3%),on BB (96.1%)* ***+/- T2DM (41.8%)***	Mean: **31.2 ± 6.7%**	Included ≥ 30 Mean: ~66	Dapagliflozin 10 mg daily vs. placebo	Primary composite outcome [hospitalization/ urgent visit for HF, CV death]: 16.3% v. 21.2%; HR 0.74 (95% CI 0.65-0.85, p<0.001) Composite renal outcome: 1.2% vs. 1.6%; HR 0.71 (95% CI, 0.44-1.16)	Amputation: 0.5% v. 0.5% (p=1) Fracture: 2.1% v. 2.1% (p=1)	History of HF hospitalization within 12 months: Dapagliflozin: 47.4% Placebo: 47.5% Serious renal adverse events occurred less with dapagliflozin (1.6%) vs. placebo (2.7%), p=0.009

Packer et al. 2020 EMPEROR-Reduced n=3,730	HF Class II, III, IV with LVEF ≤40% *on ACEi, ARB, or neprilysin inhibitor (89.2%), on BB (94%)* ***+/- T2DM (49.8%)***	Mean: **27%**	Included ≥ 20 Mean: 61	Empagliflozin 10 mg daily vs. placebo	Primary composite outcome [hospitalization for HF, CV death]: 19.4% v. 24.7% ; HR: 0.75 (95% CI 0.75-1.12) Rates of decline in eGFR: Decreased with empagliflozin vs. placebo; Between group difference 1.73 (95% CI, 1.10-2.37, p<0.001)	Genital infections: 1.7% v. 0.6% Urinary tract infections: 4.9% v. 4.5%	23-45 days after trial end: eGFR declined less with empagliflozin vs. placebo
Heerspink et al. 2020 DAPA-CKD n=4,304	CKD and UACR 200-5000 mg/g *on ACEi or ARB (98.1%)* ***+/- T2DM (67.5%)***	N/A	Included 25-75 **Mean: 43.1**	Dapagliflozin 10 mg daily vs. placebo	Composite of death from CV causes or hospitalization for HF: 4.6% v. 6.4%; HR 0.71 (95% CI 0.55-0.92; p=0.009) Primary composite outcome of first occurrence of decline ≥50% in eGFR, ESKD, or death from renal or CV causes: 9.2% (n=197) vs. 14.5% (n=312; HR 0.61 (95% CI, 0.51-0.72, p<0.001)	Amputation: 1.6% v. 1.8% Fracture: 4.0% v. 3.2%	Heart failure at baseline: 11% Results of primary outcome similar in patients with and without T2DM

eGFR: estimated glomerular filtration rate; T2DM: type 2 diabetes mellitus; ASCVD: atherosclerotic cardiovascular disease; SCr: serum creatinine; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta blocker; CV: cardiovascular; CV: cardiovascular; CrCl: creatinine clearance; CKD: chronic kidney disease; UACR: urine albumin-to-creatinine ratio; ESKD: end-stage kidney disease; HF: heart failure; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; AKI: acute kidney injury; *eGFR reported in mL/min/1.73m2 **CrCl reported in mL/min ***Reported outcome rates/incidence reflect selected SGTL2 inhibitor versus placebo respectively

Discussion

SGLT2 Inhibitors and HF Outcomes

The DAPA-HF and EMPEROR-Reduced trials sought to further examine SGLT2 inhibitors' efficacy and safety in patients with HFrEF with or without T2DM based on previous findings from landmark CVOTs. The trials ultimately targeted patients with advanced HFrEF with the respective SGLT2 inhibitor, dapagliflozin or empagliflozin, serving as an adjunct therapy to GDMT. While use of GDMT was high in both studies, notably, ARNI therapy use was relatively low in these trials. This may be due to the timing of ARNI approval, integration into HF guidelines, and ultimate insurance coverage. However, individual analyses of the patients in the DAPA-HF and EMPEROR-Reduced trials based on use of ARNI revealed that dapagliflozin and empagliflozin were similarly effective in reducing the rate of the primary composite outcome regardless of baseline ARNI use. In both trials, baseline characteristics revealed that enrolled

patients were primarily Caucasian with less than 5% of patients being African American, limiting the generalizability to this population who are greatly affected by HF. Despite differences in trials, the results revealed similarly proportional reductions in the composite outcome of cardiovascular death or HF hospitalizations. There was a numerical difference in cardiovascular death risk reduction in DAPA-HF (HR 0.82, 95% CI 0.69-0.98) vs. in EMPEROR-Reduced (HR 0.92, 95% CI 0.75-1.12) when assessing the individual components of the respective composite endpoint; however, it is likely that differences in ARNI utilization as well as frequency of recent HF hospitalizations contributed to the difference in this finding.[18,20]

Based on the findings of the DAPA-HF and EMPEROR-Reduced trials, the 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment incorporates recommendations surrounding empagliflozin use. ARNI/ACEi/ARB (ARNI preferred) and beta-blocker therapy remains the recommended first-line therapy for stage C HFrEF. For patients with adequate eGFR and NYHA Class II-IV HF, addition of SGLT2 inhibitor is now recommended. Unlike this medication class' use in T2DM, further titration of dapagliflozin or empagliflozin is not warranted based on available evidence. Specific contraindications and cautions are outlined in Table 2 based on landmark study designs and adverse effect findings.[14]

Table 2. 2021 ACC Heart Failure Guideline Recommendations[14]

Indications for SGLT2 Inhibitor Use	**SGLT2 Inhibitor Contraindications/Cautions**
HFrEF (EF ≤ 40%) with or without diabetes NYHA class II-IV Continuation of HF GDMT	Contraindications: ● Type 1 diabetes mellitus (increased risk of diabetic ketoacidosis) ● Dialysis ● Lactation (no data)
	Cautions: ● Dapagliflozin: eGFR < 30 ml/min/1.73m^2 ● Empagliflozin: eGFR < 20 ml/min/1.73m^2 ● Increased risk of mycotic genital infections ● Volume depletion – consider adjusting diuretic dose ● Ketoacidosis: discontinue SGLT2 inhibitor before scheduled surgery; monitor for signs/symptoms of metabolic acidosis ● Acute kidney injury: discontinue in period of reduced oral intake or fluid loss ● Urosepsis and pyelonephritis ● Necrotizing fasciitis of the perineum

Adapted from 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment

The question of *when* to integrate SGLT2 inhibitors into patients' HF pharmacotherapy regimens remains. Both the DAPA-HF and EMPEROR-Reduced trials utilized the respective SGLT2 inhibitor as an add-on to GDMT.[18,20] Although not yet available in the U.S., sotagliflozin, an SGLT1 and SGLT2 inhibitor approved

for type 1 diabetes mellitus in Europe, was recently studied in the SOLOIST-WHF trial to determine this agent's effect on reducing cardiovascular events among patients with T2DM and recent HF admission. While SGLT2 is found in the kidneys, SGLT1 is located in the intestines; SGLT1 inhibition results in reduced early phase glucose absorption as well as increased serum concentrations of glucagon-like peptide-1 (GLP-1) which may provide cardiovascular benefits in HF.[29] In the SOLOIST-WHF trial, sotagliflozin was either initiated prior to discharge or within three days after discharge. While funding was lost early due to COVID-19, the trial found that initiation of sotagliflozin was associated with a reduction in total cardiovascular death, HF hospitalization, or urgent visit for HF by 28 days of follow-up.[30] This trial may offer future insight to when SGLT2 inhibitor initiation is of greatest benefit.

SGLT2 Inhibitors and Renal Outcomes

The CREDENCE and DAPA-CKD trials are the two publications to date that specifically evaluate SGLT2 inhibitors in patients with CKD and, therefore, were conducted in patients with lower mean eGFRs compared to previous CVOT trials. Additionally, SGLT2 inhibitors were continued until patients required dialysis in both CREDENCE and DAPA-CKD, providing the first bodies of evidence for continued use of SGLT2 inhibitors at eGFR values <30 mL/min/1.73m^2. Both trials also required patients with CKD to have albuminuria, regardless of the presence of T2DM, and excluded patients with non-albuminuric CKD.[24,26] The SCORED trial recently reported renal outcomes with sotagliflozin in patients with T2DM and CKD without significant albuminuria (median UACR of 76). SCORED was stopped early due to loss of funding during COVID-19, but a non-statistically significant decrease in the secondary renal composite outcome in patients with CKD was noted within the study period. However, patients in the SCORED trial had substantially lower UACR values than studied in CREDENCE and DAPA-CKD.[24,26,31] Thus, it is unclear whether SGLT2 inhibitors are beneficial in non-albuminuric CKD.

ACEi and ARB are some of the only known medications that provide renal benefits due to their renin angiotensin-aldosterone system (RAAS) blocking properties and are recommended in various degrees of albuminuric CKD and in T2DM with albuminuria.[31] However, RAAS inhibitor use was required in HF- and renal outcome-focused SGLT2 inhibitor trials, and additional cardiorenal benefits were still observed in patients receiving both an ACEi or ARB and SGLT2 inhibitors.[18,20,24,26] These findings highlight the possibility of SGLT2 inhibitors' dilating of the renal afferent arterioles providing additive benefits to ACEi and ARBs' renal protective dilation of the efferent arterioles. The question that still remains is whether SGLT2 inhibitor monotherapy provides similar renal benefits to what has been observed when given in combination with RAAS inhibitors.

Conclusion

Although not greatly understood, SGLT2 inhibitors' numerous mechanisms outside of their antihyperglycemic effects are notable and are continuing to be studied in patients without T2DM given recent results of HF- and CKD-focused studies. The adverse effects of SGLT2 inhibitors noted in CVOT, HF, and CKD trials should be considered while contemplating initiation. However, the increased rates of amputation and fracture noted in the CANVAS Program trials that have not been maintained in proceeding trials is promising.

Of the currently available SGLT2 inhibitors in the U.S., dapagliflozin has received an FDA-approved indication for use in patients with HFrEF without T2DM given the results of the DAPA-HF, and empagliflozin's supplemental new drug application for its use in HF was accepted by the FDA in January 2021.[15,19] SGLT2 inhibitors' use in albuminuric CKD without T2DM may become mainstay following the results from DAPA-CKD and pending EMPA-KIDNEY's findings, as well. Pharmacists can play a major role in recommending SGLT2 inhibitors in patients with and without T2DM in lieu of the new cardiorenal benefit trials' results to aid in providing optimal patient-centered care.

References available here