SPRING 2023

ADULT MEDICINE PRN NEWSLETTER

The biannual newsletter of the ACCP Adult Medicine PRN

Message from the Chair

By: Rachel Khan, PharmD, BCPS

Having two kids under 2 years of age, I'm watching a lot of Sesame Street these days. Besides feeling really good about my spelling and counting skills, I've learned a new problem solving strategy. When there's a problem to solve on Sesame Street, they say "I wonder. What if? Let's try!". I've been an officer in this PRN since the pandemic, and I've seen many new problems emerge and old problems seem worse. While there's not enough time to detail how this mantra could solve all of life's problems, I wanted to highlight a few instances of outstanding application of this strategy by our members.

Our External Affairs Committee wondered how they could draw in new members and engage current members. They created google forms to make it easier for people to share ideas, advertise, and speak out about what's important to them. They developed a sustainable mentor-mentee program. This year, led by Nikki Patel and Health D'Amico, they'll push beyond our own PRN and participate in a collaborative PRN Instagram.

Our Internal Affairs Committee wondered how they could prioritize learners and focus on what members wanted to read most. They created a repository of adult medicine-based clinical references easily accessible to members on our PRN page. They embraced creative software for the bi-annual newsletter and engaged learners in medical writing. This year, led by Kristina Evans and Alex Ebied, they'll reimagine the clinical articles published in the newsletter.

WHAT'S INSIDE THIS ISSUE?

Message from the Chair Continued...

Our Research Committee wondered how they could foster continuous collaborative projects worthy of publication. They published the first internal medicine residency survey of its kind in JACCP and are on track to produce a steady stream of scholarship. This year, led by Lisa Hong and Jenn Austin Szwak, they'll promote collaboration and mentorship in scholarship and work with other PRNs to develop online training. In each instance, they've focused on what matters to members and how we can show our profession's worth.

Our Trainee Engagement Committee wondered how they can maintain regular online programming for trainees. They created guides for multiple educational programming for trainees to maximize attendance. This year, led by Matt Laws and Tressa McMorris, they'll operationalize a feedback form and scoring tool to give meaningful feedback to participants.

Our Walk-Rounds Committee wondered how they could fully support our members presenting research. They created a poster review service for trainees and advertised member posters to encourage support among colleagues. This year, led by Lindsay Brust-Sisti and Abby Krauter, they'll formalize their poster feedback to benefit our members.

In every instance, it was a collective voice. Not "I wonder.", but "We wonder!" Our PRN is proof that collaboration and creativity get the job done. As sure as you can know that Oscar will always be grouchy, our PRN continues to be a force in clinical pharmacy. It almost has me feeling like it's a sunny day, sweepin' the clouds away…

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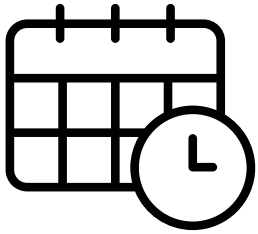
UPCOMING DATES



ACCP Virtual Poster Symposium Research in Progress abstracts due	**May 23-24** April 15
ACCP Elections Vote for: • President-elect • Secretary • Regent • ACCP Foundation Trustee	**Vote by April 21**
AMED PRN Officers Nominations Due	**May 12**

Watch for registration to open in June for the ACCP Annual Meeting in Dallas, TX November 11-14, 2023

AMED PRN Committee Updates

Walk Rounds Committee

VOLUNTEER TO BE A POSTER REVIEWER

The ACCP AMED PRN Walk Rounds Committee will coordinate reviews for posters with AMED members listed as authors at the 2023 Virtual Poster Symposium. The sessions will take place on May 23rd and May 24th from 7:00-9:00 PM EST. Last year, 27 posters were presented and reviewed by the AMED PRN!

If you can serve as a reviewer, please note your availability through the survey using this QR code:

Assigned posters, instructions, and evaluation rubrics will be provided by the Walk Rounds Committee prior to the Symposium. If you have any questions, please contact Lindsay Brust-Sisti [lbrust@pharmacy.rutgers.edu], Walk Rounds Chair. Thank you for your service!

Nominations Committee

Interested in serving as an **AMED PRN Officer**? The Nominations Committee is looking for candidates for Chair-Elect and Secretary-Treasurer. Check your email this spring for more details. Nominations will be due in May 12th to Jon Wietholter [jwietholter@hsc.wvu.edu].

Do you know any outstanding AMED PRN members? Consider nominating a colleague for the **2023 AMED PRN Awards**. Check your email this summer for details on how to submit a nomination. Final nominations will be due in early August.

Research Committee

Are you interested in collaborating with other members on a research project or opinion paper? The Research Committee invites you to submit your ideas! You can submit them via the link found on the AMED PRN website under Announcements. The Research Committee will review submissions at least quarterly, assist with connecting collaborators, and provide guidance for next steps.

AMED PRN Committee Updates
Continued

Training and Travel Committee

The Training and Travel Awards Committee offers three awards every year to support attendance and travel to the annual ACCP meeting. The awards include:

- Student Research Award
- Resident/Fellow Research Award
- Adult Practitioner Registration Award

Specific details regarding the award criteria and timeline will be released in the coming months. Please consider applying and sharing with other interested parties as this is a great way to be involved with ACCP and the AMED PRN. For specific questions regarding these awards, please reach out to Abigail Hoff [ab.hoff12@gmail.com] and Megan Roberts [mrober19@samford.edu].

External Affairs Committee

Don't forget to follow the AMED PRN on the following platforms:

ACCP Adult Medicine PRN
facebook.com/accpamedprn

ACCP Adult Med PRN
twitter.com/accpamedprn

Internal Affairs Committee

Thank you!

Thank you to the committee for their hard work in putting this newsletter together.

If you have feedback or any ideas for future newsletters, please use the QR code below to link to the survey.

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Image from https://www.accp.com/meetings/gc22/index.aspx

The AMED PRN was represented well in San Francisco at the Global Conference!

AMED PRN and GI/Liver/ Nutrition PRN Focus Session

Are you a beLIeVER in Albumin and Proton Pump Inhibitors for Cirrhosis?

Moderator: Kelsey M. Rife, PharmD, BCACP
Speakers: Payal Kakadiya, PharmD, BCPS
Kiya K. Bennett, PharmD, BCPS
Brian L. Erstad, PharmD, MCCM, FCCP, FASHP, BCPS

The joint focus session included a Pro:Con debate for the use of albumin in ascites/decompensated cirrhosis and a discussion on the safe use of proton pump inhibitors in patients with cirrhosis.

We are fortunate that the presenters of the Pro:Con debate have created a review of their presentation for this newsletter (see on the following page).

Also be on the lookout for Dr. Erstad's review article in progress on the safe use of proton pump inhibitors in cirrhosis.

AMED PRN Awards

Two outstanding members of the Adult Medicine PRN were recognized during the 2022 ACCP Global Conference in San Francisco, CA with a plaque and $200 honorarium. Congratulations!

Emerging Member Award
Melanie M. Manis, PharmD, BCPS

Intent: To recognize excellence in adult medicine pharmacy clinical practice, research, and service to the PRN by an active member of the ACCP Adult Medicine PRN in the early stages of their pharmacy career.

Clinical Practice Award
Jennifer Austin Szwak, PharmD, BCPS, DPLA

Intent: To recognize excellence in adult medicine pharmacy clinical practice by an active member of the ACCP Adult Medicine PRN

Award winners with Nominations Commitee Chair Carmen Smith, photos by Kristina Evans

Albumin for patients with ascites/decompensated cirrhosis and for hyponatremia in patients with cirrhosis

a recap from the PRN Focus Session

The Pro Debate

By: Payal Kakadiya, PharmD, BCPS

Due to impaired hepatocellular function in cirrhosis, there is a decrease in both quantity and quality of albumin.(1) It is a necessity in cirrhosis as it helps to vasoconstrict splanchnic vessels, maintain oncotic pressure, and downregulate aldosterone activation to decrease risk of ascites, hyponatremia, and renal hypoperfusion.(2) Aside from the three established uses of albumin in cirrhosis, there have been studies looking into its use short- and long-term benefits on ascites, infections, and survival.(3,4)

The use of albumin in hospitalized patients with cirrhosis started back in 1999. Gentilini et al developed a protocol to provide hospitalized patients with refractory ascites diuretics alone or diuretics plus albumin (12.5g/day).(5) Patients saw resolution of ascites with addition of albumin to diuretics (90.5% vs 74.7%, p<0.05). Fernandez et al developed the INFECIR-2 trial in 2019 to assess efficacy of short-term albumin in prevention of acute-on-chronic liver failure (ACLF) and hospital mortality in patients with bacterial infections unrelated to spontaneous bacterial peritonitis.(6) They found that using albumin 1.5g/kg on day 1 followed by albumin 1g/kg on day 2 plus antibiotics significantly decreased cytokine production compared to antibiotics alone.

Long-term use of albumin in cirrhosis was evaluated by four different groups. Interestingly, Gentilini et al also studied the effects of diuretics plus albumin 25g/week for one year and every other week for two more years.(5) They concluded a reduction in ascites (19% vs 30%, p<0.02) at year one as well as years two and three with no difference in mortality. Romanelli et al repeated the study in 2006 to investigate the effects on survival, recurrence of ascites, and onset of other complications. (8) They found a greater cumulative survival rate in those who received albumin weekly (108 months vs 36 months) with a reduction in recurrent of ascites. They also observed no adverse effects from albumin administration. In 2019, Di Pascoli et al increased the amount of albumin to 20g twice per week to see effects on 24-month mortality.(9) They concluded a reduction in mortality (41.6% vs 65.6%, p=0.032) with decreased number of emergent hospitalizations due to

The Con Debate

By: Kiya Bennett, PharmD, BCPS

Currently, the FDA approved indications for the use of albumin in cirrhosis of the liver include large volume paracentesis, spontaneous bacterial peritonitis and hepatorenal syndrome.(1) However, there is growing interest to extend the use of albumin to treat and/or prevent other complications of cirrhosis.(2) Though much of the evidence demonstrates a potential role for off-label uses of albumin, there are many limitations in the data.

Expanding the role of albumin in hospitalized patients with cirrhosis has been addressed in various studies. Notably, the use of albumin in hospitalized patients with decompensated cirrhosis has been studied in the ATTIRE trial.(3) This retrospective study assessed patients who received 20% albumin to target a serum albumin of > 3.5 g/dL (n=380) vs. standard of care (n=397) and found no difference for the primary composite outcome of infection from any cause, kidney dysfunction or death (p=0.98; CI 0.71-1.33). Unfortunately, there was a trend toward a greater incidence of pulmonary edema in the albumin group which raises concern for harm (3.8% vs 1%). The impact of albumin on hyponatremia in hospitalized patients was assessed in a retrospective study by Bajaj et al and included patients who received albumin for any reason (n=777) vs. those who did not (n=349).(4) There was a significantly greater percentage of patients who experienced resolution of hyponatremia in the albumin group, defined as sodium > 135 meq/L, vs. the control group (69% vs. 61%; p=0.0085). The multivariate analysis showed a 30-day survival benefit with hyponatremia resolution; however, it did not directly show a 30-day survival benefit with albumin. This study is limited by the indirect evaluation of the intervention as albumin was given for reasons outside of hyponatremia. Additionally, the populations were not well balanced at baseline and there was no standard dose of albumin.

The largest body of evidence involves long-term albumin infusions in patients with cirrhosis and ascites. The ANSWER trial sought to evaluate differences in 18-month mortality in patients receiving 20% albumin 40 g twice weekly for 2 weeks, then weekly thereafter (n=213)

The Pro Debate Cont.

complications. Fernandez et al also published the results of the Pilot-PRECIOSA study in which they concluded high dose albumin (1.5g/kg/week) normalized serum albumin level ($p<0.001$) and reduced systemic inflammation and cardiocirculatory dysfunction.(6) Finally, the ANSWER trial showed a reduction in mortality (NNT=10) by providing patients with albumin 40g twice weekly for two weeks followed by weekly for up to 18 months.(10) This method also prevented recurrence of ascites, HRS, HE, infections, and hospital readmissions.

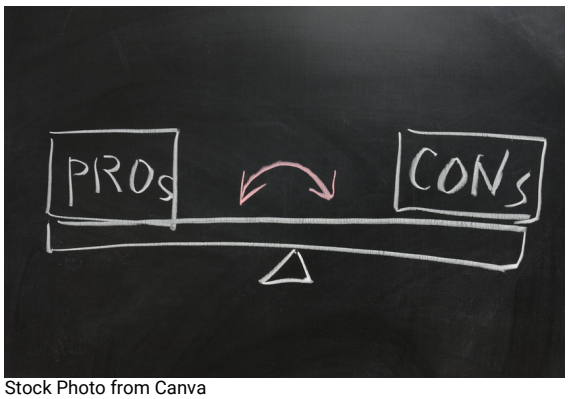
Hyponatremia in cirrhosis is a poor prognostic marker in cirrhosis with an increased mortality rate. The ANSWER trial showed promising results in that providing albumin long-term decreased patients risk of hyponatremia ($Na<130mmol/L$).(10) Bajaj et al reviewed the rate of hyponatremia resolution and 30-day survival in a retrospective study in hospitalized patients who received albumin.(11) Albumin administration was associated with greater resolution of hyponatremia, which was associated with a better 30-day survival rate in their multivariate analysis.

In conclusion, albumin in cirrhosis has potential benefits both short-term and long-term. It helps to decrease systemic inflammation, improve circulatory function, and improve diuresis in the short-term. Patients that may benefit from short-term albumin use include those with refractory ascites with diuretic therapy alone. For long-term, albumin has shown a decrease in 18- and 24-month mortality, faster resolution of hyponatremia, prevention of recurrent ascites, renal dysfunction improvement, incidence of infections, and hospital admissions. Patients who may benefit from weekly to twice weekly albumin include those at higher risk of hospitalizations due to recurrent complications such as ascites, spontaneous bacterial peritonitis, and hyponatremia.

Scan the QR code to access the references

Thank you

for representing the AMED PRN!



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The Con Debate Cont.

vs. standard of care (n=218).(5) The albumin arm had a higher survival rate compared with placebo (77% vs 55%; $p=0.0285$); however, this study was limited by the exclusion of patients with ongoing alcohol abuse and refractory ascites. Additionally, those who experienced refractory ascites during the study were censored, which poses a concern for bias in the estimated survival rates. In the MACHT trial, the treatment group (n=87) received 20% albumin 40 g every 15 days with midodrine and the placebo group (n=86) received 0.9% saline in place of albumin.(2) There was no difference found between groups for the composite primary outcome of renal failure, hyponatremia, bacterial infections, hepatic encephalopathy, and gastrointestinal bleeding ($p=0.402$). Additionally, there was no significant change in mean arterial pressure or inflammatory markers (IL-1 and TNF-alpha). This trial is unique in that it is the first study of this nature to offer a true placebo. It has been heavily critiqued for its short follow up period of 60 days due to a high transplant rate during the study period. Furthermore, the dosing strategy used was much lower than that of the ANSWER trial which could have contributed to the lack of difference shown.(2)

Though some positive outcomes have been observed, these studies are not sufficient to recommend the routine use of albumin outside of the current FDA approved indications. The data is significantly limited by methodological flaws, variability in patient characteristics, poor representation of patients with severe disease (i.e. Child-Pugh C, MELD >20), inconsistent reporting of dosing strategies, and lack of in-depth evaluation of cost-benefit in the United States population.(6) This has led to conflicting results between the various studies, leaving concerns for how to apply the evidence and whether benefits truly outweigh risks. There remains a need for large, placebo-controlled randomized controlled trials performed in the United States to elucidate these outcomes and identify patients who may benefit the most from this intervention.(6)

Resident eJournal Club Summaries

Trainee Engagement Committee

On the third Wednesday of the month, the Trainee Engagement committee hosts an eJournal club. The journal club pairs a pharmacy resident (PGY2 Internal Medicine or PGY1/2 Pharmacotherapy resident) with a volunteer mentor. Starting with this issue, we will begin to include select eJournal club summaries.

Acetazolamide in Acute Decompensated Heart Failure

Resident: Chelsea Barvian, PharmD
PGY2 Internal Medicine, Buffalo General Medical Center
Mentor: Kendra Nielsen, PharmD, BCPS

Citation: Mullens W, Dauw J, Martens P, et al. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. New Engl J Med. 2022; 387:1185-95. doi: 10.1056/NEJMoa2203094

Introduction: The 2022 ACC/AHA Heart Failure guidelines recognize loop diuretics as the cornerstone treatment for congestive acute decompensated heart failure (ADHF). Acetazolamide, a carbonic anhydrase inhibitor, may have synergistic effects on diuresis when added to loop diuretics. The ADVOR trial assessed if addition of acetazolamide to loop diuretics would improve decongestion.

Methods: This was a multicenter, randomized, parallel-group, double-blinded, controlled trial of adult patients admitted for ADHF who were receiving a maintenance loop diuretic prior to admission (PTA). Intravenous acetazolamide (500 mg once daily) was compared to placebo, both given in addition to a standardized loop diuretic regimen. The primary outcome was successful decongestion within 3 days without an indication for escalation of decongestive therapy.

Results: Out of 519 randomized patients, those receiving acetazolamide were 46% more likely to achieve successful decongestion within 3 days compared to placebo (42.2% vs 30.5%, RR 1.46, 95% CI 1.17-1.82), with benefits persisting at discharge. Higher PTA loop diuretic requirements (defined as >60 mg/day furosemide equivalents) were associated with less benefit with acetazolamide compared to lower requirements (RR 1.08, 95% CI 0.76-1.55).

Impact to Patient Care: Acetazolamide in addition to loop diuretics may serve as a diuretic sparing approach in patients with decompensated heart failure who have not yet developed diuretic resistance. Acetazolamide lacks strong indications for use in de novo heart failure or patients requiring higher maintenance loop diuretic doses.

TIMING

Resident: Brooke Hendrix, PharmD
PGY2 Internal Medicine, University of Tennessee Medical Center
Mentor: Leslie Wooten, PharmD, BCPS

Citation: Oldgren J, Asberg S, Hijazi Z, et al. Early Versus Delayed Non-Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation (TIMING): A Registry-Based Randomized Controlled Noninferiority Study. Circulation. 2022; 146:1056-1066. doi: 10.1161/CIRCULATIONAHA.122.060666

Introduction: Oral anticoagulation is the cornerstone of primary and secondary ischemic stroke prevention in patients with atrial fibrillation. Primary literature providing efficacy data for non-vitamin K antagonist oral anticoagulants (NOACs) fails to provide an optimal anticoagulation start time after acute ischemic stroke.

Methods: This study was a prospective, registry-based, multicenter, open-label, noninferiority, randomized controlled study that included adult patients with atrial fibrillation presenting with acute ischemic stroke in Sweden. Patients were randomized to the early-start (≤4 days) versus delayed-start (5 to 10 days) groups within 72 hours of stroke onset. The primary outcome was the composite of recurrent ischemic stroke, symptomatic intracranial hemorrhage (ICH), and all-cause mortality at 90 days.

Results: 888 patients were enrolled, with a median NIH stroke scale score of 4. The primary outcome occurred in 6.89% of patients in the early-start group versus 8.68% in the delayed group (absolute risk difference −1.79% [95% CI, -5.31% to 1.74%]; P=0.004). There were no reports of symptomatic ICH. Superiority of early-start therapy was not achieved.

Impact to Patient Care: Early (≤4 days) initiation of NOAC therapy after acute ischemic stroke in patients with atrial fibrillation is safe and is noninferior to delayed (5-10 days) initiation.

Note: The acronym NOAC was used by the authors of the article

Beta-Lactam plus doxycycline in hospitalized community acquired pneumonia

Resident: Arielle Norton, PharmD

PGY2 Pharmacotherapy, Cooper University Health Care and Philadelphia College of Pharmacy

Mentor: Stephanie Seyse, PharmD, BCPS, FASHP, CACP

Citation: Uddin M, Mohammed T, Metersky M, et al. Effectiveness of beta-lactam plus doxycycline for patients hospitalized with community-acquired pneumonia. Clin Infect Dis. 2022;75:118-25. doi: 10.1093/cid/ciab863

Introduction: The 2019 IDSA guidelines for the treatment of community acquired pneumonia (CAP) in the inpatient, non-ICU setting recommend the use of doxycycline and beta-lactam combination therapy in patients who cannot receive a fluoroquinolone or a macrolide. This study compares the effectiveness of doxycycline-containing therapies with non-doxycycline-containing therapies.

Methods: This was a nationwide, Veterans Affairs, retrospective cohort study that included adults over the age of 65 years who were hospitalized with CAP and received antibiotic therapy in concordance with the 2019 IDSA guidelines. Doxycycline-containing therapies were compared with non-doxycycline containing therapies (i.e. fluoroquinolone or macrolide plus beta-lactam) and the primary outcome was all-cause mortality within 30 and 90 days of admission.

Results: After propensity score matching, 5278 patients were included in each cohort. Doxycycline-containing therapies were found to reduce 30-day mortality (OR 0.72; 95% CI 0.63-0.84) and 90-day mortality (OR 0.83; 95% CI 0.74-0.92) with no significant impact on hospital length of stay. However, given that mortality rates were low throughout the study period, little difference was seen on the adjusted Kaplan-Meier plot for the primary outcome.

Impact to Patient Care: Doxycycline is an effective first-line treatment option for CAP and should be considered even in patients without contraindications to fluoroquinolone or macrolide therapy. Further large studies should be conducted to assess its effects on outcomes such as clinical cure rate, escalation to ICU-level of care, infection recurrence, and emergence of drug-resistant organisms.

Rivaroxaban in Rheumatic Heart Disease- Associated Atrial Fibrillation

Resident: Audra Hannun, PharmD

PGY2 Internal Medicine, New York-Presbyterian

Mentor: Cavan O'Kane, PharmD, BCPS, CTTS

Citation: Connolly SJ, Karthikeyan G, Ntsekhe M, et al. Rivaroxaban in Rheumatic Heart Disease-Associated Atrial Fibrillation. N Engl J Med. 2022;387(11):978-988. doi:10.1056/NEJMoa2209051

Introduction: Vitamin K antagonists (VKAs) are the treatment of choice in rheumatic heart disease (RHD)-associated atrial fibrillation (AF), as testing for direct oral anticoagulants (DOACs) has been limited. The INVICTUS trial seeks to determine whether rivaroxaban is as effective as VKA in the prevention of cardiovascular (CV) events in patients with RHD-associated AF.

Methods: This was a non-inferiority, international, open-label trial that included adult patients with echocardiographically documented RHD-associated AF and any of the following: CHA2DS2VASc score ≥ 2, a mitral-valve area ≤ 2 cm2, left atrial spontaneous echo contrast, or left atrial thrombus. They were randomized to either rivaroxaban or VKAs adjusted to an INR of 2-3. The primary efficacy endpoint was a composite of total stroke and systemic embolism, myocardial infarction, and death from vascular or unknown causes.The primary safety endpoint was major bleeding.

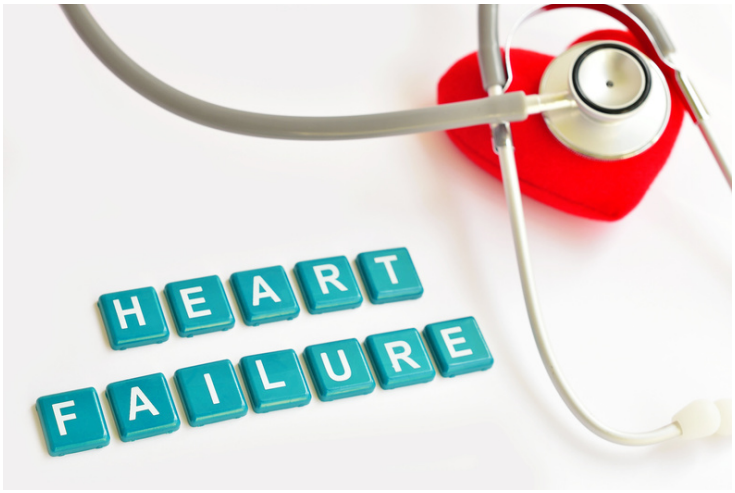
Results: A total of 4531 patients were evaluated. VKAs were superior in reducing the primary composite outcome (HR 1.25, 95% CI 1.10-1.41) with a restricted mean survival time of 1675 days vs 1599 days with rivaroxaban (difference -76 days, $p<0.001$ for superiority). VKAs reduced death from vascular causes with lower rates of both sudden cardiac death and mechanical pump failure. The difference was evident beyond 12-18 months and substantial at 3 years, indicating a possible delayed effect. There was no significant difference in major bleeding between both groups.

Impact to Patient Care: VKAs remain the standard of care in patients with RHD-associated AF due to mortality benefit primarily unrelated to stroke reduction.

Clinical Review

An Overview of SGLT2i in HFpEF and HFrEF

By: Emma Studlack, PharmD, BCPS; Marissa Polino, PharmD candidate; Kayleigh Ross, PharmD candidate



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Heart failure (HF) is a common disease state in which symptoms result from structural or functional cardiac disorders that impair the ability of the ventricles to fill with or eject blood appropriately.(1) Heart failure can be classified in a variety of ways, but most commonly include heart failure with reduced ejection fraction (HFrEF) which includes a left ventricular ejection fraction (LVEF) less than 40%, and heart failure with preserved ejection fraction (HFpEF) which includes an ejection fraction of more than 50%. Worldwide, HF is the leading cause of cardiovascular morbidity and mortality due to metabolic abnormalities and heart structure disorders. Guideline directed therapy (GDMT) aims to reduce morbidity and mortality related to HF and has led to a decrease in hospitalization mortality rates.(2,3)

An Introduction to SGLT2 Inhibitors: Mechanism of action

More than 99% of glucose entering the renal system and reaching the glomeruli is filtered through the nephrons. In healthy individuals, the proximal tubules reabsorb glucose from the filtered urine before reaching the loop of Henle. In patients with diabetes mellitus (DM), glucosuria can occur when a surge in plasma glucose leads to an increase in the amount of glucose reaching the kidneys, overwhelming the proximal tubules' reabsorption process. It is now understood reabsorption of glucose in the proximal tubules is managed by the adenosine triphosphate-dependent protein family or sodium glucose co-transporter 2 (SGLT2). Low-affinity and high-capacity SGLT2 is responsible for most of the glucose reabsorption within the tubules. Therefore, SGLT2 inhibitors (SGLT2i) decrease the amount of glucose being reabsorbed, lower the renal threshold for glucose, and subsequently increase urinary glucose excretion.(4)

Central to the pathophysiology of heart failure is dysregulation of sodium and fluid homeostasis. While loop diuretics are a mainstay of therapy, SGLT2i also have a mild diuretic effect. Several studies in euvolemic individuals with DM have demonstrated a reduction in measured blood volume with these agents and evidence of hemoconcentration has been reproducibly observed in large SGLT2i trials.(4) The decrease in volume occurs despite being a weaker natriuretic than loop diuretics. There is evidence that fluid losses with loop diuretics may not correlate to intravascular volume losses due to neurohormonal activation. The proximal tubular location action of SGLT2i leads to increased rather than decreased sodium chloride delivery to the macula densa, which might explain the decreased neurohormonal response and improved outcomes.(5)

Continued... An Overview of SGLT2i in HFpEF and HFrEF

Introduction into the trials that led to approval:
Heart failure with reduced ejection fraction (HFrEF)

In May of 2020, the US Food and Drug Administration (FDA) announced the approval of dapagliflozin to reduce the risk of cardiovascular death and HF-related hospitalization in patients with HFrEF regardless of DM status. This became the first SGLT2i to receive approval for the treatment of adults with New York Heart Association (NYHA) functional class II-IV HFrEF.(6)

The DAPA-HF Trial is a Phase 3, randomized, placebo-controlled clinical trial studying patients with HFrEF and a left ventricular ejection fraction (LVEF) of < 40% and NYHA class II, III, or IV. DAPA-HF included 4,744 patients who were randomly assigned to receive placebo or dapagliflozin 10 mg once a day along with usual HF therapies. Patients were not included in the trial if they had recent treatment with an SGLT2i, unacceptable side effects associated with SGLT2i, a history of T1DM, or hypotension with an SBP less than 95 mmHg. The primary outcome was a composite of worsening of HF status or cardiovascular death. The trial lasted a median of 18.2 months and 386 of the 2,373 dapagliflozin patients experienced the primary outcome (16.3%) compared to 502 of the 2,371 in the placebo group (21.2%; HR: 0.74, 95% CI: 0.65 to 0.85, P<0.001). The authors concluded patients with HFrEF who received dapagliflozin experienced a significant decrease in the primary composite outcome of worsening of HF and cardiovascular death compared with placebo, regardless of diabetic status. In a breakdown of the individual composite outcomes, worsening HF, death from cardiovascular causes, and death from all causes was also significantly lower in the dapagliflozin group compared to placebo.(6)

The US FDA announced the approval of empagliflozin on February 24, 2022, based on the results of the landmark EMPEROR-Reduced Trial showing a reducing risk of cardiovascular death in type 2 DM and reducing the risk of death and hospitalization in HFrEF.(7)
The EMPEROR-Reduced trial is a randomized, placebo-controlled clinical trial evaluating patients with HF and NYHA functional class II, III, or IV, and a LVEF of < 40%. The 3,730 included patients were randomized to receive either 10 mg once daily of empagliflozin or placebo in addition to recommended therapy. The primary outcome measured was a composite of cardiovascular death or hospitalization for worsening heart failure. The trial lasted a median of 16 months and 19.4% of patients receiving empagliflozin experienced the primary composite outcome of cardiovascular death of hospitalization for worsening heart failure compared to 24.7% in the placebo group (HR: 0.75; 95% CI: 0.65-0.86; P<0.001). The effect of empagliflozin on the primary outcome measured was consistent in patients regardless of DM status. The authors concluded that patients with HFrEF who received empagliflozin experienced a significant decrease in the primary composite outcome of cardiovascular death or hospitalization for worsening heart failure compared with placebo.(7)

Heart failure with preserved ejection fraction (HFpEF)

In February of 2022, a landmark approval was made for HFpEF regarding the use of empagliflozin following the Phase III EMPEROR-Preserved trial. The EMPEROR-Preserved trial was a double-blind, randomized, placebo-controlled trial. In this trial, 5,988 patients with class II-IV HF and an EF > 40% were randomly assigned to receive empagliflozin 10 mg once daily or

placebo, in addition to standard therapy. The primary outcome was a composite of cardiovascular death or hospitalization for HF. Over 26.2 months, a primary outcome event occurred in 415 of 2,997 patients (13.8%) in the empagliflozin group and in 511 of 2,991 patients (17.1%) in the placebo group (HR, 0.79; 95% CI, 0.69-0.90; P<0.001). The outcomes mainly related to a lower risk of HF hospitalization within the empagliflozin group and were consistent in patients with or without DM. The total number of hospitalizations for HF was lower in the SGLT2i group compared to that of the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio 0.73; 95% CI, 0.61 - 0.88; P<0.001). The authors conclude that empagliflozin reduced the combination risk of cardiovascular death or hospitalization for heart failure in patients with HFpEF.(7)

The DELIVER trial was an international, multicenter, randomized, double-blind, placebo-controlled trial evaluating the effect of dapagliflozin in reducing the composite of CV death and heart failure events in patients with HFpEF. The primary outcome was a composite of cardiovascular death, hospitalization for HF, or urgent HF visit. A total of 6,263 patients with HF and a LVEF >40% were randomized to receive dapagliflozin or placebo. Over 2.3 years the primary outcome occurred in 512 of 3,131 patients in the dapagliflozin group and in 610 of 3,132 patients in the placebo group (16.4% vs 19.5%, HR 0.82; 95% CI,0.73 to 0.92; P<0.0001). The authors concluded that dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction. This effect was similar among patients with an EF > 60%.(8,9)

Safety Concerns/Monitoring:

The most common adverse reactions associated with SGLT2i include polyuria and genitourinary infections. As discussed in detail previously, elevated glucose concentrations throughout the urinary tract leads to osmotic diuresis causing polyuria and volume depletion. Secondary symptomatic hypotension can occur due to volume depletion especially in patients with reduced renal function, older adult patients, concurrent diuretic use or RAAS interfering medications. Volume status should be assessed prior to SGLT2i initiation. Volume depletion may also lead to acute kidney injury (AKI) leading to the need for hospitalization and/or initiation of renal replacement therapy in some cases. In addition, concomitant use of medications that interfere with potassium excretion or the RAAS can place patients at an increased risk of hyperkalemia, especially those with pre-existing renal impairment. Patients with hypovolemia, chronic renal impairment or insufficiency should not be initiated on SGLT2i therapy. More specifically, dapagliflozin should not be initiated in patients with an estimated glomerular filtration rate (eGFR) <25 ml/min/1.732 and empagliflozin with an eGFR of <20 ml/min/1.73^2.(11)

Urinary tract infections with SGLT2i can be severe leading to sepsis or pyelonephritis and may require hospitalization. Consequently, the FDA required the addition of a warning in the products' labeling about the risk of serious UTIs associated with use. Patients at increased risk include female patients or uncircumcised males. Patients should be counseled on the signs and symptoms of UTIs and genital infections and should be instructed to report those symptoms immediately. Any UTIs or genital infections should be treated appropriately.(11) Reports of ketoacidosis have occurred and unlike typical diabetic ketoacidosis, SGLT2i associated ketoacidosis presents with euglycemia or modestly elevated blood glucose

Continued... An Overview of SGLT2i in HFpEF and HFrEF

concentrations (<250 mg/dL) causing delays in detection and treatment. Discontinuation of use is warranted when ketoacidosis is suspected. Temporary discontinuation may be recommended in clinical situations such as prolonged illness or surgery due to increased risk of ketoacidosis.(11)

Leg and foot amputations secondary to gangrene have been reported but predominantly occur with canagliflozin use over other SGLT2i. Nevertheless, patients should notify a healthcare professional if new pain, tenderness, sores, or infections arise on the legs or feet at any point during therapy. Patients with a previous history of prior amputation, peripheral vascular disease, neuropathy, and DM foot ulcers may not be appropriate candidates for SGLT2i therapy.(11)

Table 1. Landmark Trials of SGLT2i in HFpEF and HFrEF

	SGLT2i Trial name	Primary Outcome	Results vs placebo p-value	95% Confidence Interval Hazard Ratio (HR)	Guideline Recommendation
HFpEF	**Empagliflozin, EMPEROR-Preserved(10)**	CV death or hospitalization for HF	13.8% vs 17.1% p<0.001	0.69-0.90 HR: 0.79	2a
HFpEF	**Dapagliflozin, DELIVER(9)**	CV death, hospitalization for HF, or urgent HF visit	16.4% vs 19.5% p<0.001	0.73 to 0.92 HR: 0.82	2a
HFrEF	**Empagliflozin EMPEROR-Reduced(7)**	CV death or hospitalization for HF	19.4% vs 24.7% p<0.001	0.65-0.86 HR 0.75	1a
HFrEF	**Dapagliflozin DAPA-HF(6)**	CV death or hospitalization for HF	16.3% vs 21.2% p<0.001	0.65 to 0.85 HR 0.74	1a

SGLT2i: sodium glucose co-transporter- 2 inhibitor; CV: cardiovascular; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction

Scan the QR code to access the references

AMED PRN Member Accomplishments

August 2022 - February 2023

Promotions

- **Josh Gaborcik**, Director of Ohio State Pharmacy Residency Programs, The Ohio State University Wexner Medical Center & College of Pharmacy
- **Kelly Covert**, Associate Professor of Pharmacy Practice, East Tennessee State University Bill Gatton College of Pharmacy

Awards

- **Jon P. Wietholter**, Member of the Fulbright Specialist Roster (2022-2025) for International Clinical Pharmacy and Education Development, U.S. Department of State's Bureau of Educational and Cultural Affairs
- **Paul Boylan**
  - 2022 Teaching and Mentoring Award, ACCP Education and Training PRN
  - 2022 Outstanding Educator, OUHSC College of Pharmacy - PCAS Department
  - 2022 ACCP Virtual Poster Symposium Top Poster, ACCP Education and Training PRN
  - 2022 ACCP Virtual Poster Symposium Top Poster, ACCP Adult Medicine PRN
- **Ashley Otto**, New Investigator Award, Mayo Midwest Pharmacy Research Committee, Mayo Clinic
- **Corey Guidry**
  - AMED PRN Practitioner Training and Travel Award, ACCP AMED PRN
  - Outstanding Adult Medicine Preceptor, OU College of Pharmacy

Publications

- **Kathleen Adams**
  - **Adams KK**, Shah S. Large healthcare system evaluation of postoperative moxifloxacin ophthalmic solution cross-reactivity. J Cataract Refract Surg. 2022;48(11):1347-1348.
  - **Adams KK**, et al. Factors that distinguish opioid withdrawal during induction with buprenorphine microdosing: a configurational analysis. Addict Sci Clin Pract. 2022;17(55)
- **Kelly Covert:** Cluck D, **Covert K**, Wagner J, Chastain D. In it for the long-haul: Opportunities for clinical pharmacists in the management of "Post-COVID-19 Conditions". JACCP. 2022;5(7):716-724
- **Taylor Epperson: Epperson T**, Bennett K, Kupiec K, Speigel K, Neely S, Resman-Targoff B, Kinney K, White B. Impact of a pharmacist-managed outpatient parenteral antimicrobial therapy (OPAT) service on cost savings and clinical outcomes at an academic medical center. Antimicrobial Stewardship & Healthcare Epidemiology. 2023;3(e15):1-7.
- **Rachel Flurie Khan**
  - Gibson CM, **Flurie RW**. Nonsteroidal MRAs: Will finerenone take the throne? Cardiology Today. Published Nov 2022.
  - **Flurie RW**, Hylton Gravatt LA, Radwan RM, Salgado TM, Donohoe KL. Residents' assessment of mentoring received on lecture performance in a teaching and learning curriculum program. Curr Pharm Teach Learn. 2022 Nov; S1877-1297(22)00294-5.
  - **Flurie RW**. Disorders of Potassium and Magnesium Homeostasis. In: DiPiro JT et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 12th ed. New York: McGraw-Hill, 2022.
- **Rachel Flurie Khan, Jennifer Szwak, & Branden Nemeck**
  - **Flurie RW**, **Szwak J**, Beck T, Herink MC, Wdowiarz K, Hong L, Hellwig T, **Nemecek B**, Tran E, Mohammad RA. Internal medicine pharmacy residency programs: residents' pursuit of post-residency positions and job market perceptions. J Am Coll Clin Pharm 2023; 6(2): 103-110.

AMED PRN Member Accomplishments

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Publications Continued

- **Megan Kunka Fritz: Fritz MK**, Mangino AA, Hunt TV, Pitcock CT, Dugan AJ, Karri K, Yarra P. Clinical outcomes of oral zinc therapy in hepatic encephalopathy treatment. Ann Pharmacother. 2022 Nov 11: 1-8. [Epub ahead of print]
- **Cait Gibson**
  - Stone KH, Reynolds K, Davis S, Van Tassell B, **Gibson CM**. Comparison of new-onset post-operative atrial fibrillation between patients receiving carvedilol vs. metoprolol after coronary artery bypass graft surgery. Internat J Cardiol. 2022. [Epub ahead of print]
  - **Gibson CM**, Gordon S, White A, Borja-Hart N, Santee J. An assessment of patient experiences as teachers of cultural sensitivity in an interprofessional setting. Curr Phar Teach Learn. 2022;14(8):1032-1039.
  - **Gibson CM**, Larson S, Behnen EM, Dugan SE, Moody AE, Wagner JL. Feeding the soul: The impact of community circles on the AACP Women Faculty SIG. Am J Pharm Educ. 2022; 86(4):Article 8927.
  - Drame I, **Gibson CM**, Nonyel NP, Addo-Atuah J, Butler L, Rile A, Kebodauex C, Borja-Hart N. Toward a programmatic approach for health disparities and cultural competency training: Curriculum and co-curriculum. Am J Pharm Edu. 2022; 86(3):Article 8631.
- **Corey Guidry: Guidry CM**, Jackson BT, Hawkins WA. Layered learning: eight precepting strategies for the new attending pharmacist. Am J Health-Syst Pharm. 2022 (Epub ahead of print).
- **Brandon Nemecek:** Chun, H, Covvey JC, Zimmerman DE, **Nemecek BD**. Initiation of oral antihypertnesives in hosptialized patients with hypertnesive urgency: a descriptive study. Am J Health Syst Pharm. 2022 Dec 2. [Epub ahead of print]
- **Ashley Otto**
  - Zeuli JD, Rivera CG, Smith BL, **Otto A**, Temesgen Z. Cabotegravir: a novel HIV integrase inhibitor combined with rilpivirine as the first long-acting injectable program for the treatment of HIV infection. Drugs Today (Barc) 2022;58(12):555-576.
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- **Mate Soric**
  - **Soric MM.** Overview of the Hematologic System. In: Stuhan MA, ed. Understanding Pharmacology for Pharmacy Technicians. 2nd ed. Bethesda: American Society of Health-System Pharmacists, 2023: 537-546.
  - **Soric MM.** Overview of the Cardiovascular and Renal Systems. In: Stuhan MA, ed. Understanding Pharmacology for Pharmacy Technicians. 2nd ed. Bethesda: American Society of Health-System Pharmacists, 2023: 281-296.
  - **Soric MM.** Hypertension. In: Stuhan MA, ed. Understanding Pharmacology for Pharmacy Technicians. 2nd ed. Bethesda: American Society of Health-System Pharmacists, 2023: 297-316.
  - **Soric MM.** Heart Disease. In: Stuhan MA, ed. Understanding Pharmacology for Pharmacy Technicians. 2nd ed. Bethesda: American Society of Health-System Pharmacists, 2023: 317-352.
  - **Soric MM.** Hyperlipidemia. In: Stuhan MA, ed. Understanding Pharmacology for Pharmacy Technicians. 2nd ed. Bethesda: American Society of Health-System Pharmacists, 2023: 353-365.

AMED PRN Member Accomplishments

August 2022 - February 2023

Publications Continued

- **Mate Soric**
  - **Soric MM.** Study designs: design and application. In: Bernhardt MB, Blackmer A, Cho HJ, et al., eds. Updates in Therapeutics: Pediatric Pharmacy Preparatory Review and Recertification Course. 2022 ed. Lenexa, KS: American College of Clinical Pharmacy, 2022: 827-856.
- **Jennifer Szwak**: Okoroike H, Patel S, Simone P, Lavelle R, **Szwak J**. Impact of inpatient initiation of sodium-gluocse cotransporter-2 inhibitors on prescription rates in patients with heart failure with reduced ejection fraction. Am J Cardiol 2023; 186:150-155.
- **Alexandra Tatara**: Molleti RR, Bidell MR, **Tatara AW**. Fidaxomicin-Associated Hypersensitivity Reactions: Report of a Morbilliform Drug Eruption. J Pharm Pract. 2022 Sep 16. [Epub ahead of print]
- **Bao Anh Tran:** Ho TT, Noble M, **Tran BA**, Sunjic K, Gupta SV, Turgeon J, Crutchley RD. Clinical Impact of the CYP2C19 Gene on Diazepam for the Management of Alcohol Withdrawal Syndrome. Journal of Personalized Medicine. 2023; 13(2):285.
- **Jon Wietholter: Wietholter JP**. Chapter 66: Primary Open-Angle Glaucoma. In: Pharmacotherapy Principles & Practice Study Guide: A Case-Based Care Plan Approach, 6th ed. New York: McGraw-Hill Medical, 2023.

Presentations

- **Sarah Anderson**
  - Cardiovascular Disease Risk Management for People Living with Mental Illness. Presented at: CPS Winter Meeting; Jan 2023; Beaver Creek, CO.
  - Getting to the Heart of the Matter: Race-based Medicine in Cardiovascular Disease. Presented at: ACCP Global Conference; Oct 2022; San Francisco, CA.
  - Illuminating the Patient Perspective: What Healthcare Professionals Should Know About Living With Nontuberculous Mycobacterial Lung Disease. Presented at: CHEST 2022 Meeting; Oct 2022; Nashville, TN.
- **Peter Boylan**
  - Updates in allergic rhinitis and conjunctivitis: when to recommend the new Rx-to-OTC switches. Presented at: The Walter P Scheffe Continuing Pharmaceutical Education Series; Oct 2022; Oklahoma City, OK.
  - Building a better tomorrow with your colleges of pharmacy. Presented at: National Association of Boards of Pharmacy Districts 6, 7, 8 Meeting; Aug 2022; Oklahoma City, OK.
- **Cait Gibson**: Updates in Cardiology: Last-Chance Pharmacotherapy Review Webinar. Presented at: American College of Clinical Pharmacy; Sept 2022; virtual.
- **Corey Guidry**: Old DOACs, New Tricks. Presented at: Oklahoma Society of Health-System Pharmacists 2022 Fall Meeting; Sept 2022; Broken Arrow, OK.
- **Thaddeus McGiness**: IV Iron Replacement Therapy to Mitigate the Burden of IDA: Updates for Health System Pharmacists. Presented at: ASHP Midyear Clinical Meeting; Dec 2022; Las Vegas, NV.
- **Jennifer Szwak**: Current State of High-Value Pharmacy Enterprise Implementation. Presented at: Vizient Connections Summit, Sept 2022, Las Vegas, NV.

AMED PRN Member Accomplishments

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Presentations Continued

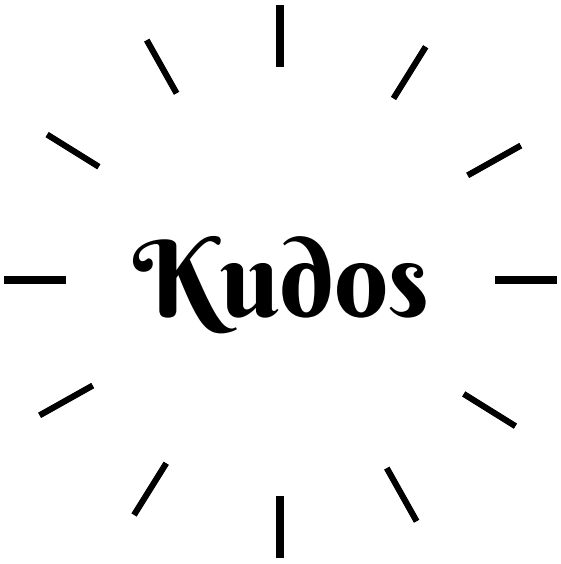
- **Jon P. Wietholter**: ACCP Career Path Roundtable Session: Adult Medicine Acute Care Practice Facilitator. Presented at: ACCP Global Conference on Clinical Pharmacy, Oct 2022, San Francisco, CA.

New ACCP Fellows

- **Gregory Castelli, PharmD, BCPS, BC-ADM**
- **Jenna K. Lovely, PharmD, BCPS**
- **Donald C. Moore III, PharmD, BCPS, BCOP**
- **Gina Prescott, PharmD, BCPS**
- **Jennifer Szwak, PharmD, BCPS, DPLA**

Other Notable Achievements

- **Sarah Anderson:** Use of a Crowdsourced Needs Assessment to Create An Innovative Microlearning Program to Address Healthcare Professionals' Misunderstandings in Applying Hepatitis B Virus Treatment Guidelines. Poster named 1 of 5 finalists for Best Poster Award at the Alliance Annual Conference; Feb 7 2023; Washington, DC.
- **Nicole Metzger:** Evaluation of prior authorization approval and patient assistance program acceptance between pharmacy trainees and clinical pharmacy specialists. Poster awarded 3rd place poster by the ACCP Adult Medicine PRN Walk Rounds Committee at the ACCP Global Conference; October 22; San Francisco, CA.



<u>Thanks to the Internal Affairs Committee for editing the following sections of the newsletter!</u>
Editors: Kristina Evans (chair), Alex Ebied (co-chair)
Committee Highlights: Heidi Berman, Nicole Metzger
PRN Officer Awards: Karissa Chow
Pro/Con Debate: Jen Adema
Resident eJournal Clubs: Ben Pullinger (Trainee Engagement Committee), Susan Smith
Clinical Review: Jen Adema, Amber Hutchinson