Adult Medicine PRN Spring Newsletter

Edited by Carmen B. Smith PharmD, BCPS and Sarah E. Petite PharmD, BCPS

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Message from the Chair

Andrew Miesner, PharmD, BCPS

"Just keep swimming, swimming, swimming. What do we do? We swim." I looked up from my iPad as my children were watching Finding Nemo for perhaps the twentieth time. While they listened to Dory the blue tang fish sing to cheer up her pessimistic friend Marlin, I was reading one of the most disheartening articles of my career in pharmacy: Trends in the Pharmacist Workforce and Pharmacy Education (Am J Pharm Educ. 2019;83(1)Article 7051). A 10-year pharmacist workforce growth 25% below the national rate. A reduction in the median salary. One in five pharmacists unable to find full time employment. An expansion in pharmacy schools with a concomitant decrease in overall enrollment. An economic and professional forecast that evokes nothing less than storm clouds. Then I heard it again. "Just keep swimming,swimming,swimming." This endearing message of fortitude from an animated fish juxtaposed with my reading made me think of my colleagues at my own college of pharmacy and practice site. It made me think about the innovative practices and unique research that so many of you members of the Adult Medicine PRN take on to advance patient care. "Just keep swimming" doesn't mean we accept the status quo. It means we keep doing what ACCP first set out to do 40 years ago. We improve human health by continuing to extend frontiers. When faced with such adversity in the profession, we innovate. We swim.

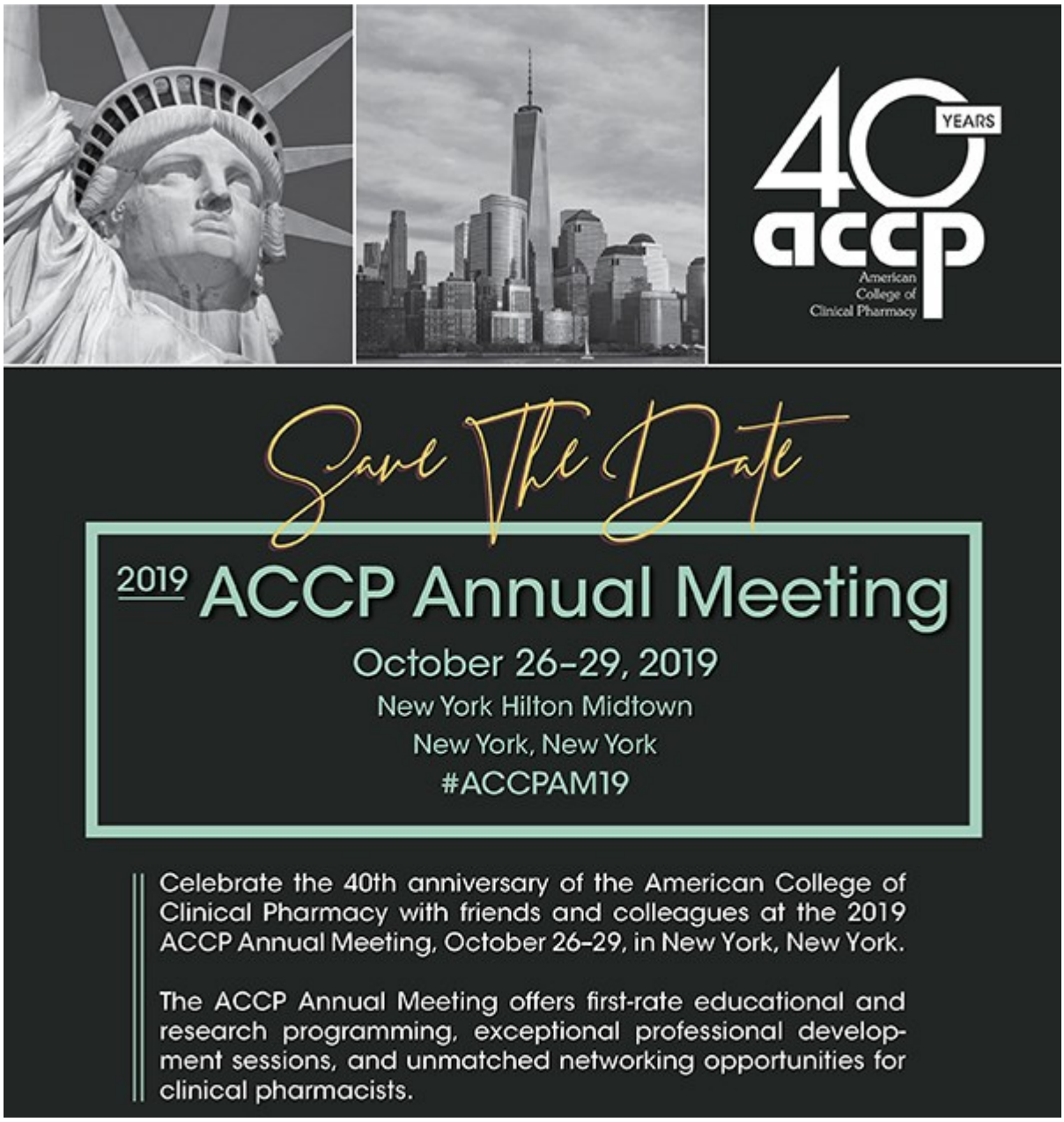
For this year, the AMED PRN officers have developed a set of committee charges that encourage practice and research innovation while investing in the future of the PRN. Given the generosity of the PRN members in their willingness to serve in a leadership role, standing committees now have both a chair and a vice-chair with a planned succession where possible. This will ensure consistent operational transition of committees from year to year. The External Affairs Committee (Chair: **Jennifer Austin Szwak**, Vice-Chair: **Jamie Sebaaly**) and Training and Travel Awards Committee (Chair: **Yulia Murray**, Vice-Chair: **Asha Tata**) both have tasks which will engage student and resident members of ACCP to help bring new pharmacists and student pharmacists into the PRN. The Nominations Committee (Chair: **Leigh Anne Hylton-Gravatt**, Vice-Chair: **Erin Hennessey**) has recently made its first call for the next set of PRN leaders. Nominations and self-nominations of officers are due by April 29th. The Research Committee (Chair: **Rima Mohammad**, Vice-Chair: **Joel Marrs**) has an all new set of charges and tasks which include selection and awarding of Seed Grants to PRN members with funding needs for a research project in its early stages. Look for the full announcement later in the newsletter. The Programming Committee (Chair: **Ryan Owens**, Vice-Chair: **Andy Crannage**) and the Walk Rounds Committee (Chair: **Jon Wietholter**, Vice-Chair: **Ryan D'Angelo**) are already hard at work preparing for the PRN's activities at the Annual Meeting in New York this October. The Internal Affairs Committee (Chair: **Carmen Smith**, Vice-Chair: **Sarah Petite**) will have the unique opportunity to develop a revamped PRN history prior to the celebration of the College's 40th anniversary. This will also mark the 20th anniversary of the PRN, so this will also serve as an opportunity to reflect on the leadership of those who helped establish the PRN and provided a strong footing for years to come.

Thank you to the record 115 PRN members who volunteered and currently serve on a committee. AMED PRN would not be successful without your faithful efforts. But most of all, thank you to all the Adult Medicine PRN members who continue to serve their patients in innovative ways and just keep swimming!

May 28-29th: Virtual Poster Symposium

Annual Meeting Research Abstract Due Dates:

- **June 17th:** Original Research
- **July 15th:** (Research-In-Progress)



ADULT MEDICINE PRN ANNOUCEMENTS

NOMINATIONS COMMITTEE

April 29th: PRN Officer Nominations Due

- Chair-Elect
- Treasurer/Secretary

RESEARCH COMMITTEE

The ACCP Adult Medicine PRN is proud to provide SEED GRANT(s) to support 1-2 high quality research projects to the PRN members (up to $5,000 funding available). If funding is provided by the applicant's institution, it will need to be disclosed and considered. The award may serve as the total support for a project or supplement an existing research effort as long as a specific portion of the research is identified as being made possible by this award, and provided that the investigator states specifically how the balance will be funded and provides evidence of its guaranteed availability. The award must not duplicate funding for a research project.

WHO IS ELIGIBLE TO APPLY?

All members of the Adult Medicine PRN except those members of the Research Committee. Students, residents, and fellows are not eligible to apply as principal investigator (project mentor could apply for student, resident, fellow projects).

HOW DO I APPLY FOR THE GRANT?

Applications should be sent to the chairman of the Adult Medicine PRN FIT/MeRIT and SEED Grant Subcommittee (ejchristenberry@utep.edu) by **August 15, 2019.** Only one application per person will be accepted. Additional information including the updated application will be sent out via the Adult Medicine PRN listserv in early June.

UPCOMING PRN JOURNAL CLUBS:

MAY 15TH

JUNE 19TH

FOLLOW US ON SOCIAL MEDIA:

@ACCPAMEDPRN

#AMEDPRN

FACEBOOK.COM/AMEDPRN

***Nominate a member, resident, or student chapter to be featured in the AMED Facebook Spotlights!*

Aspirin for Primary Prophylaxis

By: Kathleen Adams, PharmD, BCPS

"Clinicians should implement a patient-centered approach when prescribing aspirin for primary prophylaxis"

Background

The utility of aspirin for primary prophylaxis remains unclear despite multiple studies verifying risk and benefit. A 2009 meta-analysis evaluating six studies, illustrated that aspirin use was associated with 50% relative increase in bleeding, while only providing a 12% relative reduction in serious vascular events.[1] As a result, the United States Preventive Services Task Force (USPSTF) guidelines assigned the use of aspirin for primary prophylaxis a grade B recommendation to a small subset of patients (age 50 – 59 with an estimated 10-year ASCVD risk >10% who were not at an increased risk for bleeding, had a life expectancy of at least 10 years, and were willing to take aspirin for at least 10 years). The utility in patients age 60 – 69 with the same criteria was assigned a grade C recommendation. Evidence is currently insufficient to make a recommendation for patients <50 years and >70 years of age and thus there are no current recommendations.[2]

ASCEND 2018[3]

The 2009 meta-analysis responsible for the USPSTF's recommendations included only 4% diabetic patients. Investigators of the ASCEND trial posed the question: In patients with diabetes without cardiovascular disease, does enteric-coated aspirin 100mg reduced cardiovascular events compared to placebo?

The ASCEND trial included men and women of at least 40 years of age with a diagnosis of diabetes mellitus without known cardiovascular disease. Patients were excluded if they had a contraindication or clear benefit of receiving aspirin. Patients were also excluded if they had a "clinically significant condition" that may impede adherence during the 5-year trial. Potential participants were required to participate in a run-in period of up to 10 weeks. Participants became ineligible if they did not remain adherent during this initial run-in period.

Patients were randomized 1:1 to 100mg aspirin (N = 7740) or placebo (N=7740) from June 2005 – July 2011. Participants were also assigned n-3 fatty acid or matching placebo as part of an alternative randomized controlled trial that will not be discussed here. Patients participated in questionnaires every 6 months addressing adherence, adverse events, and concomitant medications.

The primary efficacy outcome was first serious vascular event including myocardial infarction, stroke, or death from any vascular cause. The primary safety outcome was the first major bleeding event, including intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding. Secondary outcomes included gastrointestinal tract cancer.

The primary efficacy outcome occurred at a statistically significantly lower rate in the aspirin group as opposed to the placebo group (8.5% vs. 9.6%; CI 0.79 – 0.97; P=0.01). There was a significant increase in the rate of major bleeding in the aspirin group compared to placebo. (4.1% vs. 3.2%; CI 1.09 – 1.52; P=0.003), with the most common site of bleeding being gastrointestinal. The incidence of fatal bleeding and hemorrhagic stroke was similar among both groups. There was no difference in the two groups with regards to gastrointestinal tract cancer.

In patients who had diabetes without cardiovascular disease, taking aspirin at 100mg daily for 7.4 years resulted in a risk of serious vascular events that was 12% lower than with placebo, however this was counteracted by a risk of major bleeding that was 29% higher, leading to a number needed to treat (91) was similar to the number needed to harm (112) over a 7.4-year period. In summary, the ASCEND trial suggests that aspirin may have a slight benefit in reducing vascular events in patients with well-controlled diabetes, however this is counterbalanced by an almost identical risk of major bleeding. Bayer, the developer of aspirin, provided funding for the trial, commented on the design, and helped draft the manuscript.

ARRIVE 2018[4]

The benefit of low dose aspirin (81mg) for secondary prevention in patients with acute coronary syndromes, previous myocardial infarction, stroke or transient ischemic attacks is supported by over 200 studies that include more than 200,000 patients. In contrast, the role of aspirin for primary prevention is less clear despite the extensive amount of literature available.

The Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial was a randomized, double-blind, placebo-controlled, multicenter primary prevention study, that included patients from seven countries across Europe and the United States. The goal of ARRIVE was to investigate the efficacy and tolerability of 100 mg enteric-coated aspirin daily versus placebo in reducing the incidence of myocardial infarction, stroke, and related cardiovascular conditions in moderate risk patients -defined as 10 – 20% 10 -year coronary heart disease

Patient eligibility differed by sex. Male patients at least 55 years old with 2-4 risk factors or female patients at least 60 years old with 3+ risk factors. High risk factors included high cholesterol (total >200mg/dL or LDL >130mg/dL for men; total cholesterol >240mg/dL or LDL >160mg/dL for women), smoking within the past twelve months, low HDL cholesterol (<40mg/dL), high blood pressure (systolic blood pressure > 140 mm Hg), receiving medication to treat high blood pressure, and a positive family history of cardiovascular disease.

Patients were excluded if they had a clear indication for aspirin or if they were at high risk for bleeding. Patients were not excluded for history of gastric or duodenal ulcers, history of gastrointestinal bleeding, and those requiring concomitant anticoagulants or frequent nonsteroidal anti-inflammatory medications. Patients were randomly assigned 1:1 to receive aspirin or placebo once daily. Patients were followed by their primary care physician with established data collection every six months.

The primary efficacy endpoint was a composite outcome that included time to first occurrence of:

- Myocardial infarction
- Stroke
- Cardiovascular death
- Unstable angina
- Transient ischemic attack

Secondary endpoints:

- Composite time to first cardiovascular death/myocardial infarction/stroke
- Time to individual components of this composite secondary outcome
- Time to first occurrence of unstable angina
- Time to first occurrence of transient ischemic attack
- Time to and incidence of all-cause mortality

The study had the ability to examine effects of aspirin on incidence of all cancers, however the results were not reported in the ARRIVE manuscript.

Between 2007 and 2016, over 12,000 participants were enrolled and assigned to receive aspirin (n = 6,270) or placebo (n = 6,276). The average course of follow up was 60 months, with 29% of patients in both the placebo and aspirin group terminating enrollment. Background population included 70% male; 98% white; 28% cigarette smoker; average 82kg; with a mean Framingham 10-year ASCVD risk score of 14% and a mean estimate ACC/AHA 10-year ASCVD risk score at baseline of 17%.

In an intention to treat analysis, the primary endpoint occurred in 4.29% of the patients in the aspirin group, and 4.48% of the patients in the placebo group. In a per protocol analysis, the primary endpoint occurred in 3.4% of the patients in the aspirin group and 4.19% of the placebo group (p = NS). There were no significant differences in the two groups based on secondary efficacy

endpoints. There were similar rates of death between the two study groups, with statistically significant increases in rates of gastrointestinal bleeding ($p < 0.05$). Overall, aspirin did not lower the risk of major cardiovascular events in the enrolled patients with a clinically significant increase in drug-induced adverse events.

ASPREE 2018[5]

The goal of the Aspirin in Reducing Events in Elderly (ASPREE) trial was to determine whether 100mg enteric-coated aspirin once daily would prolong life expectancy of elderly patients.

The trial involved patients from both Australia and the United States. Inclusion by age differed based on country of origin. Patients were included if they were ≥ 70 years of age or ≥ 65 years of age among black and Hispanics in the United States. 19,114 patients were assigned to either 100 mg enteric-coated aspirin daily or placebo from March 2010 through December 2014. Blacks and Hispanics made up more than 50% of the 2,411 patients from the United States. Baseline characteristics included a median age of 74 years old, 56% female, and a total cholesterol of 202 mg/dL.[6]

1,052 (5.5%) of patients died during the duration of the trial. The risk of death from any cause was 12.7 events per 1,000 person-years in the aspirin group versus 11.1 events per 1,000 person-years in the placebo group (hazard ratio, 1.14; 95% confidence interval [CI], 1.01 to 1.29). Analysis showed an increase risk in cancer-related death, specifically colorectal cancer, in patients receiving aspirin versus placebo.

According to this trial, the use of 100mg daily aspirin did not prolong disability-free survival among patients 70 years of age or older and was associated with increased mortality. The increased rates of mortality were largely attributed to cancer-related mortality, which contradicts previous randomized trials which suggest a protective effect of aspirin against cancer-related death. That being said, previous primary prophylaxis trials evaluated younger patients.

Conclusion

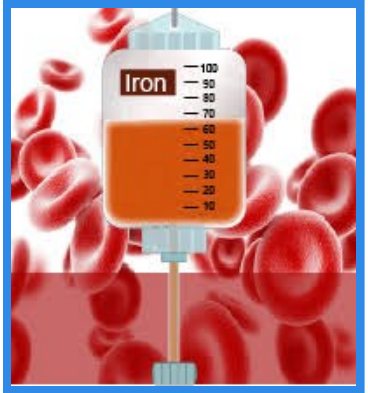
The three major trials that evaluated aspirin for primary prophylaxis in 2018 do not provide robust data to support the utility of aspirin in all patients. They have also illustrated an increase in known risks, such as gastrointestinal bleeding and increased rates of cancer. Moving forward, clinicians should evaluate not only the USPSTF guidelines, but additionally these newer randomized controlled trials to implement a patient-centered approach when evaluating whether to prescribe aspirin for primary prophylaxis.

USPSTF			
• Aspirin is recommended in patients age 50 – 59 with an estimated 10-year ASCVD risk >10% who were not at an increased risk for bleeding, had a life expectancy of at least 10 years, and were willing to take aspirin for at least 10 years (Grade B) • The utility in patients age 60 – 69 with the same criteria was assigned a grade C recommendation. • Evidence is currently insufficient to make a recommendation for patients <50 years and >70 years of age and thus there are no current recommendations			
	ASCEND	**ARRIVE**	**ASPREE**
Clinical Question	Is there a benefit of administering enteric-coated aspirin 100mg vs. placebo in patients with diabetes without cardiovascular disease?	Is there a benefit of 100 mg enteric-coated aspirin daily versus placebo in the reduction of incidence myocardial infarction, stroke, and related cardiovascular conditions in non-diabetic patients at moderate cardiovascular risk?	Is there a benefit of 100mg enteric-coated aspirin daily in healthy patients ≥ 70 years old?
Conclusion	NNT 91 vs NNH 112 over 7.4-year period.	Aspirin use was not associated with a reduction in cardiovascular events, with higher rates of GI and minor bleeding.	Aspirin was associated with increased rates of mortality, specifically cancer-related mortality.

Acknowledgements: Article peer-reviewed and edited by Jordan Kelley, PharmD and Casey Washington, PharmD, BCPS

Pumping Iron: Proactive IV Iron Regimen in Chronic Hemodialysis Patients

By: Stanley A. Luc, PharmD, BCPS and Mary R. Shreffler, PharmD, BCPS



"There is utility of proactive administration of high -dose IV iron therapy in eligible chronic HD patients"

In addition to intravenous (IV) iron's recent rise as a promising therapy in heart failure patients, it has already proven itself as one of the cornerstones for anemia management in chronic kidney disease (CKD), especially for those on hemodialysis (HD).[1,2] Randomized clinical trials have demonstrated IV iron administration results in improved hemoglobin counts, reduced total usage of erythropoietin-stimulating agents (ESA), and fewer blood transfusions when compared to placebo or oral iron.[2,3]

Despite the well-documented benefits, there are numerous safety concerns with IV therapy.[4] Earlier IV iron formulations were associated with rare serious allergic reactions, but several dosage forms have been developed and approved in the last few decades, leading to a decreased risk in severe infusion reactions.[5] A list of relevant IV iron products is displayed in Table 1.[6] As iron is essential for bacterial growth, multiple studies have also associated IV therapy with an increased risk of infection.[3] In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Anemia in CKD suggested against the administration of IV iron during active infection, however this was an ungraded recommendation due to the lack of clear clinical evidence at the time.[7] Subsequently, the REVOKE trial (n=136), which evaluated the effect of IV vs. oral iron on glomerular filtration rate in patients with CKD stages 3 / 4 and iron deficiency anemia (IDA) in the United States (US), found an increased risk of infections resulting in hospitalizations for IV iron sucrose treated patients when compared to those on oral therapy [adjusted incidence rate ratio (AIRR) 2.12, 95% CI 1.24 - 3.64, p<0.006].[8] In addition, serious cardiovascular events occurred more frequently in the IV iron group (AIRR 2.51, 95% CI 1.56 – 4.04, p<0.001). Correspondingly, iron is thought to influence oxidative stress, which can theoretically promote atherosclerosis, but there are primarily mixed results in the literature concerning IV iron and its link to cardiovascular events.[4] Lastly, iron overload is a concern as inflammation and relatively high levels of hepcidin in HD patients impair ferroportin function, decreasing iron release from reticulo-endothelial and hepatocyte stores.[4] Studies with non-invasive detection of hepatic iron content in HD patients indicate signs of iron overload.[9,10] For HD patients, serum ferritin levels are positively correlated with mortality but high ferritin levels are linked with inflammatory states and other comorbidities as well.[11] Therefore, it is difficult to determine if mortality risk is more dependent on increased iron storage or merely the inflammation as a result of comorbidity(s).

Current guidelines outline slightly different serum ferritin goals and thresholds for appropriate IV iron use for management of anemia in CKD. In 2012, the KDIGO Anemia Work Group suggested administering IV iron in adult CKD patients if transferrin saturation (TSAT) ≤ 30% and ferritin ≤ 500 ng/mL.7 Interestingly, findings from the DRIVE trial (n=134) supported IV ferric gluconate for anemia management in HD patients on ESA therapy with ferritin 500 to 1200 ng/mL and TSAT ≤ 25% as there was a statistically significant increase in hemoglobin with serious adverse events rates similar to that of placebo, but trial outcomes were measured for only six weeks.[12] Over a longer treatment period of 12 months, the FIND-CKD trial (n=626) assessed the effects of IV ferric carboxymaltose in predominantly European non-dialysis-dependent CKD patients who had IDA and were not on ESA.[13] The authors found IV therapy targeting a "high" serum ferritin of 400 to 600 ng/mL versus that with a "low" ferritin target of 100 to 200 ng/mL and oral therapy led to improvement in hemoglobin and similar rates of serious adverse events.

Furthermore, the National Institute for Health and Care Excellence (NICE), which is based in the United Kingdom (UK), included more ferritin values in its 2015 guideline and suggested using iron for maintaining TSAT > 20% and ferritin > 100 ng/mL while avoiding rises above 800 ng/mL and reviewing iron dosing when ferritin reaches 500 ng/mL.[14] NICE utilized a ferritin upper limit of 800 ng/mL to match the European Best Practice Guidelines from 1999, whose statement was based on pre-ESA studies linking ferritin > 1000 ng/mL to iron deposition in tissues.[14,15] In 2017, the Renal Association stated "serum ferritin consistently > 800 ng/mL with no evidence of inflammation (normal C-reactive protein) may be suggestive of iron overload"

for CKD patients on iron therapy.[16] With known and theoretical risks of IV iron, minor discrepancies in guideline suggestions, and lack of strong clinical evidence to support a safe upper limit for ferritin, IV iron administration in HD patients with proverbially "high" ferritin levels is controversial, especially since this group typically has increased mortality risk.[11]

Table 1: IV Iron Formulations and Dosing for IDA in CKD [6]

Product (brand name, FDA approval year)	Non-dialysis-dependent CKD dosing	Dialysis-dependent CKD dosing
Iron dextran (INFeD®, 1992)	25 mg test dose prior to initiation, and total dose (mL) = 0.0442 (desired Hgb - observed Hgb) x LBW + (0.26 x LBW) where each mL contains 50 mg of iron (max daily dose 100 mg or 2 mL per manufacturer)	
Ferric gluconate (Ferrlecit®, 1999)	125 mg to 250 mg per dose until hematologic goal met*	125 mg per dialysis session (repletion may need 8 doses)
Iron sucrose (Venofer®, 2000)	200 mg x 5 different occasions within 14 days	HD: 100 mg during consecutive HD sessions x 10 PD: 300 mg x 2 doses 14 days apart, followed by 400 mg 14 days later
Ferumoxytol (Feraheme®, 2009)	510 mg x 2 doses 3 to 8 days apart	
Ferric carboxymaltose (Injectafer®, 2013)	< 50 kg: 15 mg/kg x 2 doses at least 7 days apart ≥ 50 kg: 750 mg x 2 doses at least 7 days apart	

Note: *off-label dosing. Abbreviations: IV (intravenous), IDA (iron deficiency anemia), CKD (chronic kidney disease), FDA (Food and Drug Administration), Hgb (hemoglobin), LBW (lean body weight), HD (hemodialysis), PD (peritoneal dialysis)

The Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial compared a proactive, high-dose iron dosing strategy to one with reactive, low-dose iron in adults recently initiated on HD within the previous year.[17] The study was a randomized controlled trial conducted across 50 separate sites in the UK from November 2013 to June 2018. Patients were included in the trial if they had been on dialysis for less than 12 months, baseline ferritin < 400 ng/mL, and TSAT < 30% while receiving ESA therapy. Exclusion criteria were not directly stated.

Patients were randomized in a 1:1 ratio then further stratified based on vascular access, concomitant diagnosis of diabetes, and length of hemodialysis (≥ or < 5 months). Patients in each group had monthly ferritin and TSAT measured to determine the iron dose to be given the following week during dialysis. The dosing strategy is summarized in Table 2. The primary end point consisted of a composite of non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for heart failure, or death from any cause evaluated as time to event. Secondary efficacy end points consisted of individual components of the primary end point as well as dose of ESA, blood transfusion need, and quality of life measures. Safety end points included infections, thromboses at vascular accesses, and any hospitalizations. The authors calculated a sample size of 2080 to provide 80% power to determine non-inferiority with assumptions of a three-year event rate of 40% in the low-dose group and 10% loss to follow-up. The non-inferiority limit for the hazard ratio was 1.25.

Of 2589 patients screened, 2141 met criteria for randomization. Majority of the patients were white males in their sixties with renal failure primarily caused by diabetic nephropathy. The baseline characteristics were similar between the groups with notable exceptions of having more current smokers and a higher hemoglobin level at baseline in the proactive, high-dose iron treatment group. The median ferritin levels of the high and low-dose groups at baseline were 214 ng/mL (IQR 132 – 305) and 217 ng/mL (IQR 137 – 301), respectively, and the median TSAT for both groups was 20% (IQR 16 – 24%). The reactive, low-dose iron treatment group had more patients taking an angiotensin-converting enzyme inhibitor / angiotensin receptor blocker and phosphate binder.

For the primary composite end point, the study found a proactive, high-dose IV iron regimen to be non-inferior to a reactive, low-dose iron regimen, 29.3% vs. 32.3% (hazard ratio 0.85, 95% CI: 0.73 - 1.00; p<0.001). This allowed the study to be analyzed for superiority where the p-value was 0.04. The absolute risk reduction was 3% for the primary composite end point, allowing for a number needed to treat (NNT) of 34 patients. The primary and secondary end points are outlined in Table 3. With a median follow-up of 2.1 years, the high-dose group was also found to have

fewer recurrent events such as death from any cause, MI, stroke, or hospitalization due to heart failure (19.4% vs. 24.6%, rate ratio 0.77, 95% CI: 0.66 – 0.92). The trend favoring the high-dose IV iron treatment group was consistent in the individual components of the primary end point assessed as secondary efficacy end points.

Fewer patients in the high-dose IV iron treatment group required blood transfusions (18.1% vs. 21.6%). Throughout the duration of the study, the high-dose IV iron treatment group expectedly maintained higher median serum ferritin concentrations and TSAT while requiring a lower dose of ESA therapy. In terms of the analyzed safety end points, there were no statistically significant differences in vascular access thrombosis and hospitalizations (secondary to any cause or infection).

Table 2: Iron Dose based on Ferritin and/or TSAT Results

Proactive, High-Dose Iron Therapy	
Initial Month of therapy	200 mg iron sucrose x 3 consecutive dialysis sessions
Months 2+	Ferritin ≤ 700 ng/mL: 200 mg iron x 2 consecutive dialysis sessions Ferritin > 700 ng/mL and/or TSAT ≥ 40%: iron therapy held
Reactive, Low-Dose Iron Therapy	
Treatment Duration	Ferritin < 100 ng/mL and TSAT < 40%: 200 mg iron x 2 consecutive dialysis sessions Ferritin 100 – 200 ng/mL and TSAT < 40%: 200 mg iron x 1 dialysis session Ferritin 201 – 700 ng/mL and TSAT ≤ 20%: 100 mg iron x 1 dialysis session Ferritin > 200 ng/mL and TSAT > 20 %: iron therapy held Ferritin > 700 ng/mL and/or TSAT ≥ 40%: iron therapy held

Abbreviation: TSAT (transferrin saturation)

Overall, Macdougall and colleagues concluded HD patients treated with proactive, high-dose IV iron therapy had a lower risk of death or major cardiovascular events when compared to those on reactive, low-dose IV iron therapy. The proactive, high-dose IV iron group was less likely to be hospitalized due to heart failure while requiring a smaller monthly dose of ESA, which is consistent with findings in prior randomized clinical trials.[1,2] The authors noted strengths of the trial were the large sample size and a longer follow-up period than previous studies in this area.

In spite of the large sample size, the trial included only HD patients in the UK, so there is uncertainty if these results can be extrapolated to HD patients in other countries. In the US HD population, the median ferritin level is 718 ng/mL (IQR 439 -1026) and that of Europe is 405 ng/mL (IQR 224 - 640).[11] If the study's dosing protocol was followed, the relatively high serum ferritin in the US HD population would lead to potentially fewer opportunities to administer high-dose, proactive IV iron, which may limit its supposed benefit in reducing major cardiovascular events. Another notable difference is the prevalence of concomitant diabetes: 61% of the US HD population vs. 45% of the UK-based trial population. With a higher proportion of diabetics in US HD patients, their inherent risks for cardiovascular events and infections may be greater than that of UK HD patients.

As the study was set in an ambulatory setting that followed chronic HD patients, the results may not translate into the inpatient setting which typically features an acute illness where inflammatory markers may be elevated. The additional elevation of ferritin as an acute phase reactant may also limit the number of IV iron doses a patient would receive if the study protocol was followed inpatient. However, the reduction of major cardiovascular events seemingly demonstrated with high-dose iron in the study shows support for initiating IV iron early in the dialysis course for patients. This may be an important treatment option for reducing mortality in patients who may be on dialysis for an extended period of time. Nonetheless, the effects of proactive, high-dose IV iron are difficult to determine beyond the roughly 4.5 years allowed in the study. Future research would need to be conducted before extending the benefits of proactive, high-dose IV therapy beyond this time frame. It is also important to note the initiation of proactive, high-dose IV iron was in the early stages of chronic dialysis, and results may not be as robust if the dosing regimen is started in patients who have been on dialysis for longer than a year.

Table 3: Select PIVOTAL Trial End Points

End Point	Proactive, high-dose IV iron (n=1093)	Reactive, low-dose IV iron (n=1048)	Estimated Treatment Effect
Primary End Point	320 (29.3)	338 (32.3)	0.85 (0.73 to 1.00)
Secondary End Points			
Death from any cause	246 (22.5)	269 (25.7)	0.84 (0.71 to 1.00)
Fatal or nonfatal MI	78 (7.1)	102 (9.7)	0.69 (0.52 to 0.93)
Fatal or nonfatal stroke	34 (3.1)	35 (3.3)	0.90 (0.56 to 1.44)
Heart failure hospitalization	51 (4.7)	70 (6.7)	0.66 (0.46 to 0.94)
Thrombosis (vascular access)	262 (24.0)	218 (20.8)	1.15 (0.96 to 1.38)
Any cause hospitalization	651 (59.6)	616 (58.8)	1.01 (0.90 to 1.12)
Infection causing hospitalization	323 (29.6)	307 (29.3)	0.99 (0.82 to 1.16)
Any blood transfusion	198 (18.1)	226 (21.6)	0.79 (0.65 to 0.95)
Median monthly dose of ESA in IU (IQR)	29,757 (18,673 to 48,833)	38,805 (24,377 to 60,620)	-7,539 (-9485 to -5582)

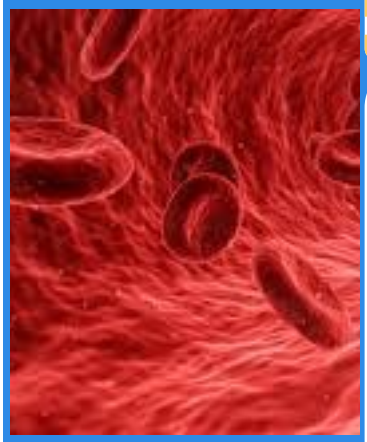
Note: End points and treatment effect presented as n (%) and hazard ratio (95% CI), respectively, unless otherwise noted. Confidence intervals for secondary end points were not adjusted for multiple comparisons. Abbreviations: IV (intravenous), MI (myocardial infarction), ESA (erythropoietin-stimulating agents), IU (international units), IQR (interquartile range)

The results of this study support the utility of proactive administration of “high-dose” IV iron therapy in eligible chronic HD patients, and the findings also provide some evidence against previously discussed theoretical risks of IV iron such as infection and atherosclerosis. Despite this, the value of this dosing protocol within the US HD population and acute care setting is unclear due to relatively high serum ferritin and concomitant acute illness, respectively. In these situations, it is prudent to weigh all benefits and risks of IV iron therapy while assessing the patient’s prognosis and clinical status, which includes iron and other hematologic parameters. There is currently no definitive clinical evidence that IV iron administration worsens active infections or increases the mortality of HD patients with serum ferritin > 800 ng/mL. Unless the HD patient is significantly iron deficient, it is likely advisable to delay high-dose IV iron therapy in the acute care setting in the presence of active infection or very high ferritin until his or her clinical condition improves and/or stabilizes.

Acknowledgements: Article peer-reviewed and edited by Heather Kehr, PharmD, BCPS and Lauren McCluggage, PharmD, BCPS

Role of Direct Oral Anticoagulants in Cancer-Associated Venous Thromboembolism

By: Taylor Steuber, PharmD, BCPS and Erika Brechtelsbauer, PharmD, BCPS



"Select DOACs are acceptable initial treatment for select patients with cancer-associated VTE"

Introduction

The risk of thrombosis, recurrent thrombosis, and major bleeding are higher among patients with cancer as compared to patients without cancer. [1,2] Based on the results of the CLOT trial and several confirmatory trials, low-molecular weight heparin (LMWH) has been the preferred agent over warfarin for treatment of venous thromboembolism (VTE) in patients with active cancer for almost 20 years. [3-7] In patients without cancer, the recommended treatment for VTE has shifted away from warfarin to the direct oral anticoagulants (DOACs) in the last decade. [8] The landmark trials for the four DOACs with VTE indications (dabigatran, rivaroxaban, apixaban and edoxaban) included small numbers of patients with active cancer. Subgroup analyses of this population within each study found that there were no differences in the rate of VTE recurrence or major bleeding as compared to warfarin. [9-12] Subsequent meta-analyses further demonstrated that DOACs seem to be as safe and effective as warfarin for preventing recurrent VTE in patients with cancer. [13] Given the low patient representation, exclusion of patients with advanced cancer, and lack of LMWH comparison, the most recent CHEST VTE update in 2016 recommended LMWH over warfarin and DOACs for cancer-associated VTE .[8]

In clinical practice, DOACs are commonly used in patients with cancer-associated VTE due to the inconvenience of injections, issues with adherence, and cost of LMWH. Several observational and retrospective studies have been published comparing the safety and efficacy of DOACs to LMWH in this population. A systematic review of observational studies found that almost all of the studies reported lower rates of recurrent VTE in patients treated with a DOAC compared to those treated with LMWH. Not all studies reported major or clinically relevant non-major bleeding (CRNMB), but DOACs tended to have higher rates of both types of bleeds. The most common comparators were rivaroxaban and enoxaparin. [14] Until recently, there was a lack of prospective, randomized trials comparing the DOACs and LMWH in patients with active cancer. The results of two trials, Hokusai VTE Cancer and SELECT-D, have spurred changes to practice guidance documents within the oncology community, providing evidence to support the use of DOACs in cancer-associated VTE.

Randomized Controlled Trials

Hokusai VTE Cancer Trial[15]

The Hokusai VTE Cancer trial was a multicenter, open-label, randomized, non-inferiority trial that evaluated the use of edoxaban versus LMWH (dalteparin) for the treatment of cancer-associated VTE . The primary outcome was the composite of recurrent VTE (symptomatic or incidental) and major bleeding (using International Society on Thrombosis and Haemostasis [ISTH] criteria) during 12 months after randomization. Patients were adults with confirmed

symptomatic or incidentally detected VTE (including DVT or PE) and cancer (except basal- or squamous-cell skin cancer) that was being actively treated or diagnosed within the previous 2 years. Patients were randomized in a 1:1 fashion to receive treatment with LMWH for at least 5 days, then to receive edoxaban or dalteparin. Edoxaban was dosed at 60 mg by mouth once daily. Patients received a reduced dose of 30 mg by mouth once daily if their creatinine clearance (CrCl) was 30 to 50 mL/min, body weight was less than or equal 60 kg, or they were treated with a concomitant potent p-glycoprotein inhibitor. Dalteparin was dosed at 200 IU per kilogram of body weight subcutaneously once daily for 30 days (max 18,000 IU/day), then 150 IU per kilogram once daily thereafter.

A total of 1,046 patients were included in the modified intention-to-treat analysis (edoxaban: 522 vs dalteparin: 524). Baseline characteristics were similar between groups in terms of demographics, qualifying diagnosis, and risk factors for bleeding. Of note, death occurred in almost 40% of the population during the study period (39.5% edoxaban vs 36.6% dalteparin). The primary outcome occurred in 67 of 522 patients (12.8%) in the edoxaban group and 71 of 524 patients (13.5%) in the dalteparin group (HR 0.97, 95% CI 0.70–1.36; p=0.006 for non-inferiority; p=0.87 for superiority). Concerning individual components of the primary outcomes, recurrent VTE occurred in 41 patients (7.9%) in the edoxaban group and 59 patients (11.3%) in the dalteparin group (HR 0.71, 95% CI 0.48–1.06; p=0.09). However, significantly more major bleeding occurred in patients taking edoxaban (n=36, 6.9%) compared to dalteparin (n=21, 4.0%) with a number needed to harm of 35 patients (HR 1.77, 95% CI 1.03–3.04; p=0.04). Of note, the majority (24 patients, 66.7%) of major bleeding events in the edoxaban group were a category 2 bleed (not a clinical emergency). In contrast, the majority of major bleeding events (13 patients, 61.9%) in the dalteparin group were category 3 or higher (clinically emergent bleeding, such as bleeding with hemodynamic instability or intracranial bleeding with neurologic symptoms or bleeding that led to death). There was no difference in the rate of CRNMB between edoxaban and dalteparin (14.6% vs 11.1%, respectively; HR 1.38, 95% CI 0.98–1.94).

The increase in major bleeding observed with edoxaban compared to dalteparin is likely multifactorial. Patients with a history of gastrointestinal (GI) cancer were more likely to bleed with edoxaban than dalteparin during treatment (p=0.02 for interaction in the safety population), and the edoxaban group had more patients with GI cancer (6.3% vs 4.0%). Additionally, more bleeds experienced in the edoxaban group than the dalteparin group were attributed to GI bleeds (3.8% vs 1.1%), specifically upper GI bleeds (n=17 patients in edoxaban). Finally, patients were observed on study drug significantly more time in the edoxaban group compared to dalteparin, potentially widening the differences between the results (211 days vs 184 days, respectively; p=0.014). However, sensitivity analysis for 6 vs 12 months of follow-up showed consistency in the trends. The authors therefore concluded oral edoxaban was noninferior to subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding with a higher rate of major bleeding.

SELECT-D Trial[16]

The SELECT-D trial was a multicenter, open-label, randomized, controlled trial that evaluated the use of rivaroxaban versus LMWH (dalteparin) for the treatment of cancer-associated VTE . The primary outcome measured was VTE recurrence at 6 months. Safety outcomes measured included major bleeding (ISTH criteria) and CRNMB. Adult patients were included who had active cancer (diagnosed or treated in last 6 months or not in remission) and symptomatic PE, incidental PE, or symptomatic lower extremity DVT. Patients were randomized in a 1:1 fashion to receive treatment rivaroxaban or dalteparin. Rivaroxaban was dosed at 15 mg by mouth twice daily for 3 weeks followed by 20 mg by mouth once daily for a total of 6 months. Dalteparin was dosed at 200 IU per kilogram of body weight subcutaneously once daily for 30 days (max 18,000 IU/day), then 150 IU per kilogram once daily thereafter for a total of 6 months.

A total of 406 patients were included in the intention-to-treat analysis (rivaroxaban: 203 vs dalteparin: 203). Baseline characteristics were relatively similar between groups in terms of demographics, qualifying event, and primary cancer type. The most notable difference was patient sex (male: 57% rivaroxaban vs 48% dalteparin). Death occurred in 28 patients (13.8%) in the rivaroxaban group and 33 patients (16.3%) in the dalteparin group. The primary outcome of VTE recurrence at 6 months occurred in fewer patients taking rivaroxaban (n=8, 3.9%) than dalteparin (n=18, 8.9%) which was statistically significant

(HR 0.43, 95% CI 0.19–0.99). Predictors of VTE recurrence included site of primary tumor (stomach or pancreas vs other; HR 5.55, 95% CI 1.97–15.66; lung, lymphoma, gynecologic, or bladder vs other; HR 2.69, 95% CI 1.11–6.53) and VTE type (symptomatic VTE vs incidental PE; HR 2.78, 95% CI 1.20–6.41). Major bleeding was similar between rivaroxaban and dalteparin (5.4% vs 3.0%, respectively; HR 1.83, 95% CI, 0.68 to 4.96) with the majority attributed to GI bleeding. However, CRNMB was significantly higher with rivaroxaban than dalteparin (12.3% vs 3.4%, respectively; HR 3.76, 95% CI 1.63–8.69) with the majority attributed to GI bleeding followed by urologic bleeding. It is likely the increased observance of bleeding with rivaroxaban can be attributed to the higher rates of GI bleeding. The authors concluded that rivaroxaban was associated with lower rates of VTE recurrence but higher CRNMB compared with dalteparin.

Gastrointestinal Bleeding

These two studies demonstrated lower rates of recurrent VTE and higher rates of bleeding, in particular GI bleeding, with either DOAC compared to LMWH. In both studies, upper GI bleeds were reported more frequently with either DOAC.[15,16] When GI bleeding was reported in the landmark DOAC trials in patients with non-valvular atrial fibrillation, it occurred at higher rates with all of the DOACs as compared to warfarin, with the exception of apixaban and low-dose edoxaban.[17-20] Further analysis of GI bleeding events found that patients experienced more lower GI bleeds on dabigatran and more upper GI bleeds on rivaroxaban .[21,22] Upper and lower GI bleeds were reported with edoxaban at similar rates, however there was a trend towards more upper GI bleeds. [23] In observational studies of patients with non-valvular atrial fibrillation, GI bleeding occurred at lower rates in patients prescribed apixaban than other anticoagulants.[24,25] For the landmark trials evaluating VTE, this finding was often not reported or too few in number to detect a difference .[26-29]

In cancer-associated VTE, higher rates of GI bleeding may be associated with the malignancies themselves, the known systemic anticoagulation effects, or due to the absorption profile of the DOACs. In the latter case, the DOACs are incompletely absorbed in the GI tract with varying bioavailability, thus inducing a topical injury.[30] Dabigatran has low bioavailability and the prodrug, dabigatran etexilate, is converted to the active form during transit in the small bowel through intraluminal activation. Additionally, the excipient, tartaric acid, induces gastric irritation which can increase the risk of bleeding and impair healing. The mechanism of lower GI bleeding is thought to be through the incomplete absorption in the upper GI tract which leads to increased dabigatran exposure to the lower GI tract to induce a mucosal injury.[30,31] The mechanism of GI bleed via mucosal injury with the factor Xa inhibitors is not as well understood. The factor Xa inhibitors have higher bioavailability and are transported via p-glycoprotein efflux pumps which may affect GI concentrations. It has been theorized that the once daily dosing of rivaroxaban and edoxaban results in higher peak concentrations thus increasing exposure and risk of GI bleeding compared to twice-daily dosing of apixaban .[30,32] Regardless of mechanism, GI bleeding remains an important consideration in patients with cancer-associated VTE.

Clinical Application

Based on the evidence in Hokusai Cancer VTE and SELECT-D, the ISTH and the National Comprehensive Cancer Network (NCCN) have published guidance documents that now recommend select DOACs as acceptable initial treatment for select patients with cancer-associated VTE. Both guidance documents emphasize the importance of individualized treatment with shared decision making between providers and patients. The ISTH recommends rivaroxaban or edoxaban in patients with low risk of bleeding and no drug interactions with chemotherapy, with LMWH as an alternative. For patients at high risk of bleeding, certain gastrointestinal cancers, gastrointestinal mucosal abnormalities or cancers with risk of bleeding from genitourinary tract, LMWH is preferred, with rivaroxaban or edoxaban as alternatives.[33] As for apixaban and dabigatran, the ISTH guidance document states that the difference in mechanism of action and metabolic clearance profile precludes an assumed class effect of all DOACs in treating cancer-associated VTE at this time. The NCCN recommends rivaroxaban, edoxaban, or LMWH as preferred agents for cancer-associated VTE. Unlike the ISTH guidance document, the NCCN guidelines state that apixaban or dabigatran can be considered in patients who refuse or have a compelling reason to avoid LMWH.[34] It also states that DOACs should be used with caution in patients with genitourinary or gastrointestinal tract lesions, pathology or instrumentation .

While there is now high-quality evidence to support edoxaban, rivaroxaban, and LMWH as safe and efficacious treatment options for cancer-associated VTE, several patient-specific considerations must be made when selecting an agent. A recent meta-analysis of studies evaluating the "real-world" use of rivaroxaban in cancer-associated VTE found similar rates of VTE recurrence and major bleeding as the two aforementioned trials. However, patients in the meta-analysis had lower rates of all-cause mortality. This finding indicates that in practice, providers may be selecting rivaroxaban for patients with less severe disease.[35] Rivaroxaban or edoxaban may not be appropriate in patients with severe disease, gastrointestinal or genitourinary cancers, high risk of bleeding, or history of GI bleeding. Additionally, renal and hepatic function must be taken into consideration for all of the preferred agents but drug interactions mediated through CYP3A4 and p-glycoprotein transporters are specific to the DOACs.[36-38] In regards to patient tolerability, daily injections are a major perceived limitation for long-term use of LMWH. However, treatment with edoxaban requires at least 5 days of parenteral anticoagulation prior to initiation, so the need for injections is not completely eliminated .[37] The emetogenic potential of many chemotherapy agents needs to be considered as it may interfere with a patient's ability to consistently take a DOAC. This is especially important with rivaroxaban as it should be taken with the largest meal of the day to increase absorption. Patients who require enteral feeding can crush either DOAC for administration, but rivaroxaban cannot be administered distal to the stomach .[36]

In addition to selecting an agent, it is important to incorporate strategies to mitigate the inherit risk of bleeding. The use of aspirin and other antiplatelet agents should be avoided unless the patient has a compelling indication or used concomitantly for the shortest duration. Patients should be counseled to avoid nonsteroidal anti-inflammatory medications and herbal supplements without consulting a provider or pharmacist. It may be appropriate to recommend a proton pump inhibitor (PPI) in patients taking medications that increase the risk of bleeding or with a history of GI bleeding. Based on a retrospective cohort of Medicare beneficiaries, patients who were prescribed oral anticoagulants (apixaban, dabigatran, rivaroxaban and warfarin) and PPIs had overall lower rates of hospitalization for upper GI bleeds than those patients who were not prescribed a PPI across all the anticoagulants. Of note, patients not taking a PPI but taking rivaroxaban had the highest incidence of hospitalization for upper GI bleed while patients taking apixaban had the lowest incidence.[39]

The consistent evidence that apixaban is associated with lower rates of GI bleeding makes it a more appealing agent for all indications. The results of the ongoing CARAVAGGIO trial are highly anticipated, as it will be the largest prospective trial that compares apixaban and LMWH for cancer-associated VTE.[40] In the interim, the abstract for the ADAM-VTE trial was recently presented that evaluated these comparators in the same population with major bleeding as the primary endpoint. The rates of major bleeding were similar in both groups as was the secondary endpoint of major bleeding plus CRNMB. Recurrent VTE occurred less frequently in the apixaban group, and apixaban was favored by patients based on a quality of life survey.[41] The final results of these trials are highly anticipated as they have the potential to elevate apixaban to the DOAC of choice in cancer-related VTE.

Given the complex, high-risk nature of cancer-associated VTE and its treatment, the availability of multiple options benefits patient adherence and satisfaction. However, the introduction of more options also brings new risks that require thoughtful consideration of patient-specific factors to ensure the safest and most effective treatment course.

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PRN Member Accomplishments

Promotions:

- **Mate M. Soric:** Acting Chair, Department of Pharmacy Practice, Northeast Ohio Medical University College of Pharmacy
- **Leigh Anne Hylton Gravatt:** Vice-Chair of Education for the Department of Pharmacotherapy and Outcomes Sciences, VCU School of Pharmacy
- **Branden Nemecek:** Associate Professor of Pharmacy Practice with Tenure - Duquesne University, Pittsburgh PA
- **Jennifer Twilla:** Clinical Pharmacy Manager, Methodist University Hospital

Awards:

- **Caitlin M Gibson:** UNT Class of 2019 Professor of the Year Award (University of North Texas System College of Pharmacy)
- **Tiffany Pon:** Pharmacotherapy Outstanding Reviewer, University of California, San Francisco
- **Jennifer Twilla:** 2018 ASHP Foundation Award for Excellence in Residency Training, Methodist University Hospital PGY1 Pharmacy Program, RPD: Jennifer Twilla
- **Nathan Lian:** 2018 Nevada State Pharmacist of the YearCaitlin M Gibson, PharmD, BCPS, BCCP

Grants:

- **Caitlin M Gibson:** ACCP Education & Training PRN Grant ($750)
- **Nicole L. Metzger** (Senior Investigator) and Carrie Tilton, PharmD (PGY2 Internal Medicine Resident Investigator)**:** ASHP Foundation Pharmacy Resident Practice-Based Research Grant for the project, "Advancing the Pharmacist's Role in Preventing Healthcare Facility-Onset C. difficile: Expansion of a Risk Prediction Model." $4968
- **Jennie B. Jarrett:** ACCP Adult Medicine PRN Seed Grant Award. Combating Implicit Bias in the Healthcare Team: A Pharmacist's Role. $5000
- **Jennie B. Jarrett:** University of Illinois Hans W. Vahlteich Research Scholar Award. Entrustable Professional Activities Assessment within Experiential Curricula: A Primer for Evaluation. $50,000 ACCP Education & Training PRN Grant ($750)

Publications:

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Other Notable Achievements:

- **Caitlin M Gibson**: Board certified in cardiology (BCCP)
- **Alex Ebied**: Internal Medicine Interview with CNN regarding rising drug overdoses: https://www.cnn.com/2018/08/16/health/us-overdose-death-report-cdc/index.html

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