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In this issue

Clinical Pearl: Reversal of Oral Anticoagulants

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Anticoagulation therapy represents the cornerstone of treatment of acute venous thromboembolism (VTE), prevention of recurrent VTE, and prevention of stroke and systemic embolism in patients with atrial fibrillation. An estimated six million patients receive oral anticoagulant (OAC) therapy in the United States. Anticoagulant-associated bleeding remains a major concern.[1]

The most current expert consensus on the management of OAC-associated bleeding was published by the American College of Cardiology (ACC) in 2017—prior to the approval of andexanet alfa (Andexxa®).[2] In July 2018, the ACC published a fact sheet summary of its expert consensus, with the addition of andexanet alfa as the first line agent to reverse rivaroxaban (Xarelto®) and apixaban (Eliquis®). Alternative agents in order of place in therapy, include four-factor prothrombin complex concentrate (4F-PCC; KCentra®) 50 units/kg IV, activated prothrombin complex concentrate (aPCC) 50 units/kg IV, or activated charcoal 50 g within 2 hours of ingestion.[2,3]

Andexanet alfa is expected to become a universal reversal agent for all direct and indirect factor Xa inhibitors because of its ability to bind and sequester both rivaroxaban and apixaban, as well as generate thrombin by blocking the tissue factor pathway inhibitor.[4, 5] Andexanet alfa received accelerated approval based on ANNEXA-A and ANNEXA-R studies, which showed a decrease in anti-factor Xa activity in healthy volunteers of >90%. Improvement in hemostasis has not been established. Continued approval, as well as the incorporation of andexanet alfa into clinical practice guidelines and institutional protocols, depend on future results of ANNEXA-4.[4-6]

The Blunt Truth: Medical Marijuana in New York State

By Hongkai (Jack) Bao, PharmD and Jorie Frasiolas, PharmD, BCPS

In the world of illicit substances, there is perhaps none more controversial than marijuana. Classified as a schedule I substance by the Controlled Substances Act, U.S. federal law determines marijuana, or cannabis, to have high abuse potential and no accepted medicinal use.[1] This classification as a schedule I substance prevents the Food and Drug Administration from conducting large-scale clinical trials to assess any medicinal benefit of marijuana. Despite this, marijuana currently stands as the most used illicit substance in the U.S.[2] In fact, throughout the decades, numerous states and jurisdictions have attempted to challenge its illegal status, crediting its medicinal properties and low potential for abuse. Beginning with California's Proposition 215 in 1996, which allowed California to become the first state to legalize marijuana for medical use, 29 states have legalized medical marijuana (MM) since then.[3]

This drastic legalization of marijuana has only been possible with the support of legislation, namely, the Rohrabacher-Farr Amendment and the Cole Memorandum. The Rohrabacher-Farr Amendment was first introduced in 2001 and was implemented more than a decade later in 2014.[4] The amendment, which failed seven times before being passed, prohibits the Department of Justice from using funds to prevent states from implementing their own laws on medical marijuana use, distribution, possession, and cultivation.[4] With a similar focus, the Cole Memorandum was drafted into effect by former U.S. Attorney General James Cole in 2013.[5] It prioritized federal enforcement and allocation of funds towards more significant threats regarding marijuana, including distribution to minors, illegal drug trade, drugged driving, and illegal growth.[5] In short, as long as states had strict laws regarding medical marijuana, the federal government would adopt a laissez-faire approach rather than enforce legal action in these states. In recent news, this memorandum was rescinded by current U.S. Attorney General Jeff Sessions on January 4, 2018, complicating the issue of medical marijuana further.[6] He stated that Congress has long determined marijuana to be a dangerous drug and therefore, "[the Cole Memorandum] is unnecessary and is rescinded, effective immediately."[6]

At the time, these pieces of legislation were what eventually led New York State (NYS) to pass the Compassionate Care Act (CCA) on July 7, 2014.[7] The CCA was signed into effect by Governor Andrew Cuomo, making NYS the 23rd state to legalize MM.

The Certification Process

Currently, as of March 6, 2018, there are 46,971 certified MM users in NYS, a statistic that grows each day.[7] Due to the prohibited nature of marijuana, there is an extensive process to become a certified MM patient. Patients must first possess an indicated disease state as well as an associated or complicating symptom (Table 1).[8] Next, patients must visit registered MM practitioners who will determine if they are appropriate candidates. Patients can then visit the

The recommended dosing regimen for andexanet alfa (standard or high dose) depends on the last dose and timing of rivaroxaban or apixaban. The standard dose is an initial IV bolus of 400 mg at a target rate of 30 mg/min, followed by a continuous IV infusion of 4 mg/min for up to two hours. The high dose is double the standard dose with an initial IV bolus of 800 mg at a target rate of 30 mg/min, followed by a continuous IV infusion of 8 mg/min for up to two hours.[3, 5]

Boxed warnings for andexanet alfa include arterial and venous thromboembolic events; ischemic events; cardiac arrest; and sudden death. These events occurred in approximately 18% (33/185) of patients in the ongoing prospective study, ANNEXA-4. Incomplete reversal or re-elevation of anti-Xa activity was also observed post-infusion in ANNEXA-4 patients. Common adverse reactions—which occurred in ≥5% of patients—include urinary tract infections, pneumonia, and infusion site reactions.[5]

Idarucizumab (Praxbind®) is the first line agent for the reversal of dabigatran (Pradaxa®), a direct thrombin inhibitor. Idarucizumab is a humanized monoclonal antibody, which binds to dabigatran with an affinity 350 times greater than dabigatran binds to thrombin, thereby neutralizing the anticoagulant effect.[7] It is administered as a 5 g IV infusion in two separate infusions of 2.5 g over five to 10 minutes—no more than 15 minutes apart. Warnings include thromboembolic risk, re-elevation of coagulation parameters, hypersensitivity reactions, and adverse reactions in patients with fructose intolerance due to sorbitol excipient. In the case of re-elevation of coagulation parameters, an additional 5 g dose may be administered. Common adverse reactions observed in ≥5% of patients include headache, constipation, and nausea.[8] In the REVERSE-AD study, idarucizumab's median time to achieving hemostasis is approximately 2.5 hours, as demonstrated in patients with uncontrolled bleeding in the REVERSE-AD study.[7] 4F-PCC, aPCC, and activated charcoal may be used as alternative agents for the reversal of dabigatran.[2]

Although 4F-PCC may be administered for bleeding associated with non-vitamin K antagonists, it is FDA approved exclusively for the reversal of vitamin K antagonists, such as warfarin (Coumadin®).[2] Efficacy of 4F-PCC is attributed to its ability to increase levels of Vitamin K-dependent coagulation factors and protein C and S. 4F-PCC is dosed based on the patient's INR and weight in conjunction with vitamin K at a rate of 0.12 mL/kg/min to 8.4 mL/min.[9] The ACC also recommends a fixed dose of 1000 units for any major bleed or 1500 units for intracranial hemorrhage, which

Department of Health online portal and register as a certified patient, at which point, they can designate up to two caregivers. These caregivers are unique in the sense that they are able to acquire, possess, deliver, transport, or administer MM to their patients.[8] At the conclusion of this process, patients and their caregivers will receive their MM registry cards in the mail and can go about purchasing MM products from registered dispensaries. Approved products in NYS include metered liquid or oil preparations; solid and semisolid preparations (e.g. capsules, chewable and effervescent tablets, lozenges); metered ground plant preparations; and topical forms and transdermal patches.[9] Smoking is not an approved method of administration.[9]

Self-administration in Hospitals

The regulations and privileges established by the CCA gave much needed support to MM patients, but mainly on the outpatient side. Support for inpatients was still somewhat unclear. This discrepancy was largely due to the fact that Centers for Medicare & Medicaid Services (CMS) require hospitals to comply with all federal, state, and local laws.[10] Although the CCA legalized MM in NYS, federal law still prohibits the use of marijuana. This meant that for many MM patients admitted to hospitals, they were barred from using marijuana to self-treat.

On May 17, 2017, NYS Codes, Rules, and Regulations were amended.[11] This amendment established clear guidelines that allow MM patients to self-administer their therapy in hospital settings (Table 2).[11] Though this amendment offered guidance to institutions, it also left many questions unanswered. For example, an institution that allowed MM patients to self-administer was also intimately involved in handling MM products, a privilege only given to patients or their caregivers. More importantly, MM is still considered an illegal substance by federal law and this amendment did not protect hospitals against federal prosecution.

Facilities as Caregivers

To address some of the challenges of the self-administration amendment, NYS Codes, Rules, and Regulations were emergently amended on October 5, 2017.[12] Previously, only natural persons could become designated caregivers. This new amendment allows facilities, including hospitals, to possess, acquire, deliver, transfer, transport, and administer MM to certified inpatients.[12] However, several limitations exist, one being that each designated caregiver may only serve as a caregiver for up to five patients.[13] Although not an issue in smaller facilities, large academic medical centers may oversee more than five MM patients at one time. To address this issue, the amendment states that each division, department, component, floor, or other unit within a facility is considered its own facility.[14] Another limitation is that an institution is not permitted to serve as a blanket caregiver for all admitted MM patients. Instead, institutions must register as individual caregivers for each newly admitted MM patient. This inherently becomes an issue for hospitalized patients as the turnaround time for hospitals to become caregivers may be longer than actual inpatient stays.

Current Considerations

The two aforementioned amendments made tremendous strides in providing guidance for administration of MM in hospitals. However, hospitals and other facilities must be cognizant and address the unanswered questions that surround the use of a schedule I substance. Hospitals must decide if they will allow the use of an illegal substance like MM at all. For those who permit its use, polices must address the ordering, storage, visual inspection, verification, permitted products, and disposal, among other considerations:

- Which parties are responsible for visual inspection and verification of the products?

(continued on p 3)

Table 1. Qualifying conditions and associated or complicating symptoms for medical marijuana[8]

Qualifying condition	Associated or complicating symptom
Amyotrophic lateral sclerosis	Cachexia/wasting
Cancer	Severe/chronic pain
Chronic pain	Severe nausea
Epilepsy	Severe or persistent muscle spasms
HIV/AIDS	Seizures
Huntington's disease	
Inflammatory bowel disease	
Multiple sclerosis	
Neuropathies	
Parkinson's disease	
Spinal cord injury	
Post-traumatic stress disorder	

various hospitals administer prior to the availability of INR results.[2] Boxed warnings for 4F-PCC include arterial and venous thromboembolic complications. General warnings include hypersensitivity reactions and the risk of transmitting infectious agents—as 4F-PCC is a human blood product. 4-PCC is contraindicated in patients with disseminated intravascular coagulation, heparin-induced thrombocytopenia, or severe systemic reactions to components of 4F-PCC. Common adverse reactions observed in ≥2.8% of patients include headache, nausea, vomiting, hypotension, and arthralgia.[9]

If 4F-PCC is not available, plasma 10-15 mL/kg may be administered, but would require more volume and greater infusion time than 4F-PCC due to its 25 times lower concentration.[2,10] In two head-to-head trials, 4F-PCC demonstrated superiority to plasma in three of four efficacy endpoints.[10,11]

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Marijuana (continued)

- Which dosage forms are permitted in hospitals?
- How will the hospital store and handle the product?
- Will self-administration be witnessed and documented?
- How will hospitals handle out-of-state products?
- Will hospital staff be willing to comply with MM policy?
- Will practitioners be allowed to newly start MM in patients or simply continue existing MM therapy?
- How will MM be disposed of after patient death?

There are a slew of difficult questions to be answered before dealing with MM or implementing a policy, especially at a large institution in NYS. MM has come a long way since its legalization in NYS in 2014, and one can only hope that patients continue to benefit from its expanded use in the future.

Table 2. Six requirements before patients can self-administer medical marijuana in hospitals

Order from registered practitioner	Capacity of the patient or caregiver to self-administer assessed
Product inspected for integrity	Security of product addressed
Administration documented in patient record	Disposal of product after patient death addressed

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Volunteers at the 2018 New York City Marathon

PCSK9 inhibitors: Translating LDL-C Reduction into Clinical Benefit

By Michelle Ubowski, PharmD Candidate, St. John Fischer College, and Andrea Traina, PharmD

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a class of monoclonal antibodies that exert their action by blocking PCSK9—a protein responsible for tagging the low-density lipoprotein receptor (LDL-R) for destruction.[1] Inhibiting the action of PCSK9 extends the duration of action of the LDL-R by allowing it to recycle back to the plasma membrane to bind to serum low-density lipoprotein. This results in increased low-density lipoprotein cholesterol (LDL-C) clearance from the plasma.[1]

This newest class of lipid-lowering medications consists of two approved agents: evolocumab (Repatha®) and alirocumab (Praluent®), both of which are fully human monoclonal antibodies. Alirocumab is indicated as an adjunct to diet and maximally tolerated statin therapy in adults with either heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease (ASCVD).[2] Unlike alirocumab, evolocumab is currently indicated to reduce the risk of myocardial infarction, stroke and coronary revascularization in patients with a history of cardiovascular disease.[3] Evolocumab can be used as an adjunct to diet, alone or in combination with other lipid-lowering agents for primary hyperlipidemia and/or as an adjunct to diet and other LDL-lowering therapies for patients with homozygous familial hypercholesterolemia.[3]

Efficacy Related to Surrogate Markers of Cardiovascular Risk

Both evolocumab and alirocumab's efficacy are well established. The MENDEL-2 study evaluated monotherapy lipid-lowering regimens consisting of evolocumab 140 mg once every two weeks, evolocumab 420 mg once monthly, ezetimibe 10 mg daily or placebo in patients with LDL-C levels ≥ 100 mg/dL but ≤ 190 mg/dL and Framingham risk scores ≤ 10%.[4] All doses of evolocumab demonstrated superiority in terms of LDL-C reduction compared to both placebo and ezetimibe at the end of 12 weeks (57% reduction for biweekly and 56.1% for monthly dosing, $p < 0.001$).[4] In addition, the DESCARTES trial established that evolocumab retained efficacy across a range of background lipid-lowering therapies. LDL-C reductions ranged from 48.5% to 61.6% over at least 52 weeks in patients with baseline LDL-C ≥ 75 mg/dL.[5] A third trial—GAUSS-3—randomized patients with confirmed statin intolerance and uncontrolled LDL-C levels (mean LDL-C ~219 mg/dL) to receive either ezetimibe 10 mg daily or evolocumab 420 mg once monthly for 24 weeks.[6] Evolocumab was superior with a decrease in baseline LDL-C of 54.5% compared with 16.7% for those who received ezetimibe. Finally, the double-blind, placebo-controlled GLAGOV trial found the addition of evolocumab 420 mg monthly to statin therapy in patients with demonstrated angiographic coronary disease reduced percent atheroma volume significantly more than the addition of placebo.[7]

The ODYSSEY MONO trial evaluated alirocumab 75 to 150 mg biweekly and ezetimibe 10 mg daily as monotherapy in patients with moderate cardiovascular risk and LDL-C levels between 100 mg/dL and 190 mg/dL.[8] Alirocumab showed a significantly greater reduction in LDL-C when compared with ezetimibe (47.2% vs. 15.6%, respectively). The ODYSSEY COMBO II trial found greater LDL-C reductions in patients randomized to alirocumab 75 mg every two weeks compared to ezetimibe 10 mg daily when added to background statin therapy (50.6% vs. 20.7%, respectively).[9] Finally, the ODYSSEY ALTERNATIVE study demonstrated the clinical utility, effectiveness and superiority of alirocumab 75 to 150 mg every two weeks over ezetimibe 10 mg daily in patients with statin intolerance.[10]

In terms of safety, a meta-analysis of 35 randomized controlled trials utilizing PCSK9 inhibitors found no safety endpoints that differed from placebo.[11] Although there has been speculation regarding an association with PCSK9 inhibitors, low LDL-C levels, and cognitive impairment, the results of the randomized EBBINGAHUS trial did not support this relationship.[12]

Atherosclerotic Cardiovascular Disease Benefit

The 2017 American Association of Clinical Endocrinologist's Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease recommend a goal LDL-C (and non-high-density lipoprotein cholesterol [non-HDL-C]) level based on risk stratification, with targets as low as < 55 mg/dL for patients at extreme risk of developing ASCVD, as

evidenced by the results of the IMPROVE-IT study with ezetimibe.[14,15] Despite guideline recommendations, a review of the medical records of 10,040 patients with established coronary artery disease found that although 79% of identified patients in clinical practice were able to achieve a LDL-C goal of <100 mg/dL, only 35% of patients were able to achieve a LDL-C goal of <70 mg/dL, indicating the need for more aggressive lipid management.[16]

The FOURIER trial was a prospective, multicenter, international, double-blind, placebo controlled trial designed to evaluate evolocumab's cardiovascular impact in a secondary prevention patient population.[17] Patients with a LDL-C level ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL on at least moderate intensity statin therapy were randomized to receive evolocumab (140 mg once every 2 weeks or 420 mg once monthly) or placebo as add-on therapy. Both the primary (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, or coronary revascularization) and the secondary (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) composite endpoints were found to be significantly reduced in the evolocumab group—15% lower event rate for the primary composite endpoint and 20% lower event rate for the secondary composite endpoint as compared to placebo. This substantial difference was driven primarily by decreases in myocardial infarction, stroke, and coronary revascularization. A sub-analysis of patients stratified by baseline LDL-C found that patients with the lowest baseline LDL-C levels (73 mg/dL) experienced a 22% reduction in the risk of the secondary composite endpoint, suggesting that additional cardiovascular benefit can be achieved above and beyond current LDL-C guideline recommendations. This data further support results from previous outcome trials that demonstrated the addition of a non-statin lipid-lowering therapy to further reduce LDL-C is associated with a reduction in residual cardiovascular risk.[15, 17]

Alirocumab's cardiovascular outcomes were assessed in the phase III ODYSSEY OUTCOMES trial, where it was investigated as add-on to statin therapy (high-intensity or maximally tolerated) at a dose of 75 to 150 mg biweekly in patients with a previous acute coronary syndrome.[18] Although a manuscript is forthcoming, available data demonstrate a 15% relative risk reduction in the primary composite endpoint of coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, and unstable angina requiring hospitalization for patients randomized to alirocumab compared to placebo.[19]

Although both FOURIER and ODYSSEY OUTCOMES were planned to assess cardiac benefit with a PCSK9 inhibitor, there are key differences in their respective trial designs.[17,18] ODYSSEY OUTCOMES enrolled patients specifically who had experienced a recent acute coronary syndrome within the previous 72 hours; FOURIER enrolled patients with established ASCVD. Unlike the set dosing in FOURIER, ODYSSEY OUTCOMES specified a blinded titration schedule based on a patient's lipid levels, allowing for an increase in dose with LDL-C levels ≥ 50 mg/dL, but also decreases in alirocumab dose if a patient's LDL-C levels remain below certain thresholds.

Place in Therapy

AACE guidelines recommend PCSK9 inhibitors in combination with statin therapy for patients with familial hypercholesterolemia or in patients with established cardiovascular disease that are unable to achieve their LDL-C goals despite maximally tolerated statin therapy.[14] These guidelines advocate against monotherapy unless a patient is intolerant to statins. The American College of Cardiology provides guidance for dual therapy for patients not achieving the anticipated percent reduction while on statin therapy, or target LDL-C or non-HDL-C goals.[20] Patients with ASCVD without other comorbidities are recommended ezetimibe as add-on to statin therapy before attempting a PCSK9 inhibitor; however, clinicians can consider a PCSK9 inhibitor (or ezetimibe) as the initial add-on in patients with clinical ASCVD and other cardiovascular factors. A PCSK9 inhibitor would be the preferred add-on if greater than a 25% reduction in LDL-C is required. Like the preceding cohort, clinicians may consider either a PCSK9 inhibitor or ezetimibe for patients with a baseline LDL-C ≥ 190 mg/dL (e.g., familial hypercholesterolemia). If a patient has a baseline LDL-C < 190 mg/dL without evidence of ASCVD, the guidelines do not specifically comment on the use of a PCSK9 inhibitor.

Current evidence suggests that PCSK9 inhibitors are effective in achieving additional LDL-C reductions (50% to 60% reduction) in patients treated with other lipid-lowering therapy (primarily statins), but also in statin intolerant patients. Evolocumab and alirocumab have both demonstrated cardiovascular benefit in a secondary prevention patient population, suggesting a class-wide affect. It remains to be seen if PCSK9 inhibitors will become the standard second line treatment option for patients in the future. In conclusion, recent evidence has demonstrated that the addition of a non-statin lipid-lowering therapy to background statin therapy is associated with additional cardiovascular benefit and that a lower target LDL-C may be considered for many secondary prevention patients. [15, 17, 19]

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Safety of Spironolactone in Patients with Concomitant Heart Failure with Reduced Ejection Fraction and Chronic Kidney Disease

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Spironolactone is an aldosterone antagonist that is commonly used in patients with heart failure with reduced ejection fraction (HFrEF). Due to its primarily renal excretion and side effect of hyperkalemia, it is contraindicated in HF patients with a serum potassium (K+) >5 mEq/L as well as men with serum creatinine (SCr) ≥2.5 mg/dL and women with ≥2 mg/dL.[1, 2]

The Randomized Aldactone Evaluation Study (RALES) found that spironolactone reduced the mortality risk by 30% and hospitalization frequency by 35% compared to placebo among 1663 New York Heart Association (NYHA) class III and IV HFrEF patients. The study, however, excluded patients with a baseline SCr >2.5 mg/dL or serum K+ >5 mEq/L.[1-3]

Limited data exist on the use of spironolactone in patients with concomitant chronic kidney disease (CKD) with or without hemodialysis (HD). Studies in non-HD patients with CKD identified age, degree of renal dysfunction, spironolactone dose, and use of concomitant medications that may increase potassium as risk factors for hyperkalemia with spironolactone use.[4] In one study of 19 HFrEF patients on spironolactone who presented to the hospital with a median serum K+ of 8 mEq/L, 15 patients had a SCr >2 mg/dL upon admission and 14 patients were on a spironolactone dose ≥100 mg.[5] In another study, 25 HFrEF patients on a concomitant angiotensin-converting enzyme inhibitor (ACEI) and a mean spironolactone dose of 57 +/- 32 mg per day developed hyperkalemia with a serum K+ of >6 mEq/L. The mean SCr upon hospital admission was 3.8 mg/dL, compared to a mean of 1.9 mg/dL on outpatient records from 13 +/-5 weeks prior. The study authors concluded that the maximum daily spironolactone dose should be 25 mg in patients predisposed to hyperkalemia, with frequent monitoring of SCr and serum K+.[6] Another study analyzed 18 HFrEF patients without obvious renal impairment who developed a serum K+ ≥6 mEq/L on a combination of spironolactone and ACEI. These patients were aged 63 to 85 with a normal mean baseline SCr of 0.9 to 1.2 mg/dL, yet had significantly reduced glomerular filtration rates (GFR) of 43 +/- 10 mL/min. The authors concluded that clinicians should carefully monitor elderly patients' GFR and electrolytes, particularly those on concomitant ACEI therapy. Although patients may meet the SCr cut-off for spironolactone use, they are still at an increased risk for hyperkalemia.[7]

Small studies indicate that spironolactone may not cause a clinically significant increase in serum K+ for HFrEF patients with concomitant CKD on HD. In one crossover study, eight HFrEF patients on HD with a baseline serum K+ <6 mEq/L and concomitant ACEI or angiotensin II receptor blocker (ARB) were administered spironolactone 50 mg or placebo orally twice daily for two weeks. The resulting mean pre-HD serum K+ was not statistically different between the groups. There was, however, a statistically significant reduction of pre-dialysis systolic blood pressure by 11 mm Hg in spironolactone users.[8] Another study of 18 continuous ambulatory peritoneal dialysis patients with HFrEF receiving either spironolactone 25 mg every other day or placebo did not find a statistically significant difference in serum K+ between the groups. One patient in the spironolactone group did develop a serum K+ of 5.7 mEq/L. This study demonstrated a statistically significant improvement in ejection fraction in the spironolactone group.[9] In a cohort study 15 HFrEF patients on intermittent HD with baseline serum K+ of 4.6 +/- 0.6 mEq/L who received spironolactone 25 mg daily for 28 days, the mean serum K+ at study completion was not statistically significantly different at 4.9 +/- 0.9 mEq/L. Four patients developed a serum K+ of 5.5 to 6.0 mEq/L during the study, and one patient became hyperkalemic at 7.6 mEq/L.[10] Likewise, in a prospective study

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of 35 chronic HD patients, the spironolactone group (14 HFrEF patients) was administered a dosage of 12.5 mg three times a week for two weeks, then 25 mg three times a week for the following two weeks, and did not demonstrate a statistically significant difference in serum K+ (4.9 +/- 0.7 mEq/L versus 4.9 +/- 0.3 mEq/L in the control group).[11] Finally, a larger cohort study of 50 oligoanuric HD patients with HFrEF administered spironolactone 25 mg daily showed a statistically significant increase in serum K+ from 4.96 +/- 0.72 to 5.18 +/- 0.72 mEq/L, which the authors viewed as only marginal and not clinically stignificant.[12]

The treatment of HFrEF in HD and non-HD patients with CKD remains unclear. Based on available data, it appears that patients with concomitant HFrEF and CKD may be safely treated with spironolactone in an inpatient setting—where serum creatinine and electrolytes can be closely monitored. In an outpatient setting in which daily monitoring may not be feasible, however, clinicians should consider hyperkalemia risk factors, use lower doses of spironolactone, and frequently monitor renal function and potassium.

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