Transcript Details
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A Case for 4F-PCC: Mortality & Safety Data vs. Plasma

Announcer Introduction:
Welcome to ReachMD. This medical industry feature, titled “Practice Protocols: The Case for 4F-PCC,” is sponsored by CSL Behring.

Here’s your host, Dr. Jennifer Caudle.

Dr. Caudle:
When it comes to reversing a Vitamin K antagonist like warfarin, the four-factor prothrombin complex concentrate—or 4F-PCC— called KCENTRA was approved by the FDA in 2013 as an alternative to plasma.[1] But with thromboembolic events being a serious concern for patients after warfarin reversal, does KCENTRA pose an increased risk?

This is ReachMD, and I’m your host Dr. Jennifer Caudle. And joining me to discuss the risk factors for thromboembolic events and 4F-PCC as a treatment option for major bleeds is Dr. Michelle Kincaid, who’s a trauma surgeon and Director of Surgical Critical Care at OhioHealth Grant Medical Center in Columbus.

Dr. Kincaid, it’s wonderful having you here.

Dr. Kincaid:
Yeah. Thanks so much for having me.

Dr. Caudle:
Before we begin, let’s review some Important Safety Information about the product we’ll be talking about today.

Announcer:
KCENTRA®, Prothrombin Complex Concentrate (Human), is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA–eg, warfarin) therapy in adult patients with acute major bleeding or the need for urgent surgery or other invasive procedure. KCENTRA is for intravenous use only.

Stay tuned for the complete Important Safety Information for KCENTRA throughout this podcast.

Dr. Caudle:
So, Dr. Kincaid, can you start us off with a little background about the risk of thromboembolic events after acute and urgent vitamin K antagonist reversal?

Dr. Kincaid:
Sure. Well, in cases of major bleeds brought on by Vitamin K antagonists or VKAs, such as warfarin, physicians have a few options to choose from. Traditionally, the standard of care has been to use plasma to reverse major bleeds, and KCENTRA has been approved for reversing major bleeds since 2013,[1] and has changed this standard.

Randomized clinical trials have shown that patients chronically treated with VKA therapy may be at increased short-term risk for thromboembolic events after treatment with either plasma or four-factor PCC, but these trials had low event rates, little diversity within the patient population, and smaller sample sizes.[1]

And because four-factor PCC was the first treatment of its kind, the FDA required its manufacturer to conduct a post-marketing study on the short-term risks of thromboembolic events with both plasma and four-factor PCC.

And so, for me, this is a really novel study, as this is a medication I use really frequently in my practice, and so to have such a large real-

world study on safety is incredibly important for our patients.

Dr. Caudle:
And what are the details of this study?

Dr. Kincaid:
So, to satisfy this FDA requirement, CSL Behring, the maker of KCENTRA, in close partnership with Kaiser Permanente, conducted a large observational, multicenter study to determine KCENTRA's safety.[1] This was the longest study ever conducted for safety in patients receiving these risk – reversal agents.[1]

And thanks to Kaiser Permanente, the study investigators had access to data from 2 integrated healthcare delivery systems servicing more than 9 million members with 36 medical centers.[1]

And so, with this many patients and so much data available, this is also the largest study of four-factor PCC for VKA reversal.

The purpose of this study – this long-term study was to compare the 45-day risk of thromboembolic events in adults with warfarin-associated major bleeding after treatment with KCENTRA or plasma,[1] and because observational studies, you know, always have this potential for bias, investigators used propensity matching to try to eliminate as much bias as possible. They created a cohort of patients receiving four-factor PCC and matched them one-to-one to the historical patients who received plasma, and they were matched based on age, sex, type of bleeding, and a high-dimensional propensity score for their receipt of four-factor PCC, and this final model – this high-dimensional propensity score – included 300 different variables per patient,[1] which in my experience, this is very unusual. You know, this is incredibly complex statistical analysis and really just adds to the strength of these statistics within the study.[1]

So, each study arm included 1,119 patients – one arm receiving plasma and the other four-factor PCC – for a total of 2,238 participants, all with no history of thromboembolic events,[1] and these patients presented with complicated medical histories with bleeding types including intracranial hemorrhage – about 68% – and 31% GI bleeds.[1]

The primary endpoint of the study was the incidence of acute thromboembolic event, and so that includes a venous thromboembolism, pulmonary embolism, and arterial thromboembolism,[1] and the secondary endpoint identified all-cause mortality risk within 45 days post treatment, again, in these patients without a history of thromboembolic events.[1]

Now, an additional secondary analysis was conducted that did include patients with a history of thromboembolic events,[1] but we'll talk about that a little bit later.

Dr. Caudle:
Thanks, Dr. Kincaid, and before we get into the results, let's pause for some important safety information.

Announcer:
WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS

Patients being treated with Vitamin K antagonists therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the risk of thromboembolic events, especially in patients with history of such events. Resumption of anticoagulation therapy should be carefully considered once the risk of thromboembolic events outweighs the risk of acute bleeding. Both fatal and nonfatal arterial and venous thromboembolic complications have been reported in clinical trials and postmarketing surveillance. Monitor patients receiving KCENTRA and inform them of signs and symptoms of thromboembolic events. KCENTRA was not studied in subjects who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. KCENTRA might not be suitable for patients with thromboembolic events in the prior 3 months.

Dr. Caudle:
So, going back to our study, Dr. Kincaid, what results were observed between plasma and KCENTRA?

Dr. Kincaid:
Investigators found no significant adjusted difference in the 45-day risk of thromboembolic events after receiving KCENTRA versus plasma.[1] This was the primary endpoint, and it proved that we're not increasing the risk of thromboembolic events using KCENTRA instead of plasma, which has been the standard of care for so many years.

Now, as for the secondary endpoint, the study found adjusted all-cause mortality was significantly lower in patients receiving KCENTRA. KCENTRA mortality was 13% versus plasma mortality was 18%. That's a 41% risk reduction compared to plasma.[1]

And, you know, what's interesting about this secondary endpoint was that despite excellent matching between the groups, those receiving four-factor PCC actually had a higher residual prevalence of thromboembolic risk factors compared to the matched plasma treated patients, which would really kind of bias towards a worse rather than a better outcome for those receiving four-factor PCC.[1] So, this means that the investigators actually expected patients to not do as well on KCENTRA, and in terms of adjusted all-cause mortality within 45 days post treatment.

However, you know, per the results of the study, KCENTRA patients had less all-cause mortality than patients treated with plasma. And I think, finally, when you look at the eligibility criteria in this study, while this particular study didn't include those acute surgical patients, KCENTRA pivotal trials do include data on those patients requiring urgent surgery.

Dr. Caudle:
Thanks, Dr. Kincaid, and now earlier you mentioned a secondary analysis. So, what can you tell us about that?

Dr. Kincaid:
Yeah. So, in the secondary analysis that was conducted, the investigators wanted to take a closer look at those high-risk patients, meaning those with a history of thromboembolic events. So, 101 KCENTRA patients and 101 historical plasma patients that were diagnosed within a thromboembolic event within 90 days before study entry were also grouped in a one-to-one individually matched cohorts based on propensity scores.

And so during the 45-day follow-up period after the VKA reversal, there was no statistically significant difference in the adjusted risk of thromboembolic events between the KCENTRA treated patients and the plasma treated patients.

And so even though, you know, many of us are reluctant to change these study results should be truly considered practice changing, in my opinion, especially since the guidelines have recommended KCENTRA for urgent warfarin reversal over plasma since 2013 and still continue to do so.[2-8]

Dr. Caudle:
You're listening to ReachMD, and I'm your host, Dr. Jennifer Caudle. Joining me today to talk about KCENTRA, an alternative to plasma for VKA reversal, is Dr. Michelle Kincaid.

Now that we've reviewed the study details and its meaningful results, let's talk about how we can bring this data into real-world practice. Based on your experience, Dr. Kincaid, what patients are appropriate for KCENTRA versus plasma?

Dr. Kincaid:
You know, I really rely on individual patient characteristics, such as the reason why the patient is on warfarin, the bleeding type, baseline INR, and medical history, to determine who should receive KCENTRA versus plasma.

And I really focus my practice on the two indications for KCENTRA, which are episodes of acute major bleeding and patients who need an urgent surgery or procedure, and these include traumatic brain injury patients on warfarin with elevated INR, patients with hip fractures that need surgery within 24 hours after that injury, acute GI bleeding on anticoagulation, and especially those patients who are at risk for fluid overload, such as the elderly, congestive heart failure patients, and patients with chronic kidney disease, and I feel like I see these patients every single day in the hospital.

Dr. Caudle:
And keeping with real-world practice, what can physicians do differently to bring KCENTRA to the forefront of patient care?

Dr. Kincaid:
Yeah, I suggest physicians take a look at their protocols and their treatment algorithms.

You know, experts have already decided in multiple guidelines for the reversal of anticoagulation to support the use of four-factor PCC products like KCENTRA.[2-8]

So, really, we should trust the experts within our field to digest the data, look at all of the literature, and give us the best recommendations as per these guidelines, and in my line of work in trauma and acute care surgery, our – we certainly add these recommendations to our guidelines and protocols within our hospital and also our healthcare system. KCENTRA has been on our protocol for traumatic brain injury and reversal of anticoagulation almost from the beginning in 2013.

Dr. Caudle:
Now, unfortunately, we're almost out of time, but before we close, what key takeaways would you like to leave with our audience?

Dr. Kincaid:

You know, there have been studies and national guidelines supporting the use of KCENTRA,[2-8] and I think the results from this study we just talked about confirm the safety profile that we've already seen in clinical practice, and really this study gives us confidence in KCENTRA's safety in terms of those thromboembolic events and the all-cause mortality in a large patient population.[1]

So, I hope that, you know, we've helped the audience realize the benefits of four-factor PCC over plasma really in a way that translates into a change in behavior and changing protocols. You know, after all, KCENTRA has significantly lower all-cause mortality and has been proven safe and effective since 2013 in pivotal trials, observational studies, and also every day in my practice as a trauma surgeon.[1]

Dr. Caudle:
Thank you so much. Those are great practical takeaways to consider as we end today's program. I'd like to thank my guest, Dr. Michelle Kincaid, for helping us better understand why KCENTRA should be a go-to VKA reversal therapy. Dr. Kincaid, it was great speaking with you today.

Dr. Kincaid:
Yeah. Thank you so much for having me.

Dr. Caudle:
And before we go, let's review some additional Important Safety Information.

Announcer:
KCENTRA is contraindicated in patients with known anaphylactic or severe systemic reactions to KCENTRA or any of its components (including heparin, Factors II, VII, IX, X, Proteins C and S, Antithrombin III and human albumin). KCENTRA is also contraindicated in patients with disseminated intravascular coagulation. Because KCENTRA contains heparin, it is contraindicated in patients with heparin-induced thrombocytopenia (HIT).

Hypersensitivity reactions to KCENTRA may occur. If patient experiences severe allergic or anaphylactic type reactions, discontinue administration and institute appropriate treatment.

In clinical trials, the most frequent (≥2.8%) adverse reactions observed in subjects receiving KCENTRA were headache, nausea/vomiting, hypotension, and anemia. The most serious adverse reactions were thromboembolic events, including stroke, pulmonary embolism and deep vein thrombosis.

KCENTRA is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent and its variant (vCJD), cannot be completely eliminated.

Indications
KCENTRA®, Prothrombin Complex Concentrate (Human), is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA—eg, warfarin) therapy in adult patients with acute major bleeding or the need for urgent surgery or other invasive procedure. KCENTRA is for intravenous use only.

Please see full prescribing information for KCENTRA.

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Announcer:
This program was sponsored by CSL Behring. If you missed any part of this discussion, visit ReachMD.com/Industry-Feature. This is ReachMD. Be part of the knowledge.

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