Host: Welcome to the Anesthesiology journal podcast, an audio interview of study authors and editorialists.

Dr. BobbieJean Sweitzer: Hello. I'm Dr. BobbieJean Sweitzer, an associate editor for Anesthesiology, and you are listening to an Anesthesiology podcast designed for physicians and scientists interested in the research that appears in our journal. Today we are speaking with two authors of publications that appear in the July 2021 issue of the journal.

With us is Dr. Jashvant Poeran. Dr. Poeran is the first author of an article titled "Safety of Tranexamic Acid in Hip and Knee Arthroplasty in High-Risk Patients." Dr. Poeran is an associate professor in the Leni and Peter W. May Department of Orthopedics and the Department of Population Health Science and Policy at the Icahn School of Medicine at Mount Sinai in New York, New York. He also directs the Center for Clinical and Outcomes Research, a formal collaboration between the two departments. Welcome, Dr. Poeran.

Dr. Jashvant Poeran: Great. Thank you for having me and thank you for your interest in our study.

Dr. BobbieJean Sweitzer: And joining Dr. Poeran is Dr. Calin S. Moucha. Dr. Moucha is the senior author on Dr. Poeran's manuscript. Dr. Moucha is an associate professor in the Leni and Peter W. May Department of Orthopedics at the Icahn School of Medicine at Mount Sinai and chief of adult reconstruction and joint replacement surgery at the Mount Sinai Hospital in New York, New York. Welcome, Dr. Moucha.

Dr. Calin S. Moucha: Great. Thank y'all for having this.

Dr. BobbieJean Sweitzer: And joining Dr. Poeran and Dr. Moucha is Dr. Sachin Kheterpal. Dr. Kheterpal wrote an accompanying editorial: "Tranexamic Acid in High-Risk Arthroplasty Patients: How Will We Adapt to Evolving Evidence?" Dr. Kheterpal is professor of anesthesiology, University of Michigan in Ann Arbor, Michigan. Welcome, Dr. Kheterpal.

Dr. Sachin Kheterpal: Thank you. Great to be speaking with you today.

Dr. BobbieJean Sweitzer: Dr. Poeran, let's start with you. What question or questions were you trying to address with this study?

Dr. Jashvant Poeran: So the questions we are trying to address in this study are related to a follow-up on a previous study our study team did on tranexamic acid where we looked at all total joint arthroplasty. What we did differently in the current study here is we set out to investigate the use of tranexamic acid in specifically high-risk patients undergoing these surgeries. And we wanted to look at the association with not just blood transfusions but also safety outcomes, such as new-onset venous thromboembolism, myocardial infarction, seizures, or ischemic stroke or transient ischemic attack. This was the question that we really kept on coming back, and we realized we had access to a data source to look at this.

Dr. BobbieJean Sweitzer: Yes. (Sounds like: Excellent). I know in my own practice this question has often came up around safety in certain patients. So how did you actually conduct this study?

Dr. Jashvant Poeran: Yes. So this was a retrospective study where we used claims data from 500 hospitals in the U.S., more than 500 hospitals. We looked at billing for tranexamic acid among patients undergoing hip and knee arthroplasty surgery, and we focused on high-risk patients, such as those with a previous venous thromboembolism, myocardial infarction, seizures, or previous ischemic stroke or transient ischemic attack. We also looked at those with a history of renal disease and those with a history of atrial fibrillation.

So looking at these, we identified up to 46,000 high-risk patients in the period 2013 to 2016. We applied regression modeling to look in these high-risk groups at the association between tranexamic acid and outcomes. This included complications. We wanted to figure out if there's an association with increased odds of these complications when tranexamic acid was used in these high-risk patients. And what we additionally did – we also looked at general utilization patterns.

Dr. BobbieJean Sweitzer: Dr. Moucha, I believe this study was a collaboration among clinicians and scientists. Can you tell us more?

Dr. Calin S. Moucha: Absolutely. Our study was a collaboration between orthopedic surgeons and scientists in the population health department here at Icahn School of Medicine at Mount Sinai. This has been a very powerful working model that we have used for research at our institution because really clinicians like myself come up with specific questions, and the scientists—in this case, Dr. Poeran—are able to offer specific methods of answering these questions. In this case, the primary question was really should TXA be used in high-risk patients undergoing joint replacement surgery?

That's previously published in Steven Porter's paper, I believe, reference number 22 in the Journal of Arthroplasty. We were able to answer this question using a much larger database. So this was really a complementary paper to that one and taken together should allow clinicians to feel more comfortable giving tranexamic acid in these particular cases.

Dr. BobbieJean Sweitzer: So, Dr. Kheterpal, in your editorial, you write about the changes over the last 10 years in tranexamic acid use and patients having more extremity joint replacements. Can you recap some of that for us?

Dr. Sachin Kheterpal: Yes. It's been quite interesting the evolution that we've seen just in my own clinical practice. I do joint arthroplasty anesthesia on my clinical days. And it's interesting how over the last decade tranexamic acid has gone from this interesting drug that used to be limited to high blood loss surgeries but has now become essentially a commonly used medication for most joint replacement surgeries, certainly lower extremity as well. It went from being something that the anesthesiologist and the CRNAs would ask, "What is that thing? How am I supposed to give it?" to every resident, CRNA knows that if we're doing a joint room that day, whether it's a hip, knee, or even our shoulder rooms, they know they got to have the tranexamic acid out ready to go.

There's discussion about dosing for that particular patient and timing. But what we've seen is an evolution from a small minority of patients, less than 10%, receiving a decade ago to the majority of patients now receiving it nationally. And that evolution has not necessarily had the greatest amount of safety evidence evaluating it, which is why the work that we're discussing today is so important.

Dr. BobbieJean Sweitzer: Dr. Poeran, you indicate that the purpose of this study was to determine safety in a potentially high-risk population. Were you only focused on patients with high risk of bleeding and/or thrombosis? Or how did you define high risk, I guess? Based on other risk factors as well?

Dr. Jashvant Poeran: Yes. So, actually, in addition to that, we also looked at patients with renal disease as one high risk group. And we were specifically interested in that group as well for a variety of reasons. One of them was tranexamic acid is renally eliminated with a potential for accumulation and renal disease. So this is a concern that we found particularly in the literature for tranexamic acid in cardiac surgery. On top of that, there's a common exclusion criterion in trials focusing on tranexamic acid in lower extremity joint arthroplasty. So we really didn't have any good data out there on the use and safety in this specific subgroup.

Dr. BobbieJean Sweitzer: Mm. So what conditions were specifically included in your high-risk populations?

Dr. Jashvant Poeran: We looked at three specific definitions of high risk to be as complete as possible. The first one was patients with a history of venous thromboembolism, which include a deep venous thrombosis and pulmonary embolism; myocardial infarction; seizures; or ischemic stroke or transient ischemic attack. The second high-risk group was patients with a history of renal disease, and the third one was patients with a history of atrial fibrillation as it represents a thromboembolic risk factor.

Dr. BobbieJean Sweitzer: So at any time period in their history, or would it have to be within a certain period of time? And was it active atrial fib or even a history of previous atrial fibrillation?

Dr. Jashvant Poeran: At any point in their history.

Dr. BobbieJean Sweitzer: Got it. So can you tell us a bit more about the database that you used, including the, I guess, advantages and disadvantages perhaps of this database?

Dr. Jashvant Poeran: Yes. There are many advantages and disadvantages. So the data set we used is the Premier Healthcare data set, which is a claims-based data set that includes detailed information on everything that is billed for during hospitalization. So think of pharmaceuticals, medical devices, and any services. And I guess that would represent one of the main pros is that we're able to look at variables that you wouldn't necessarily have access to in other data sets. Think of variables such as the use of general or neuraxial anesthesia, a detailed look at multimodal regimens or enhanced recovery protocols—all things we were able to look at in this data set. Another pro, I think, is the large number of hospitals included that allows us to look into practice patterns and how this differs between hospitals, which in turn, I guess, enhances generalizability.

The main cons, as in any database study, is that important clinical information is lacking. So, for example, in our study, we didn't have any information on reasons why tranexamic acid was used or not or what local transfusion protocols looked like. It is very important here to know that we're also dependent on the accuracy of medical billing and that it's always something to take into account. Specifically, asking the question to what extent this potential bias may impact your study results.

In our case, we have no reason to believe that billing for tranexamic acid would be dependent on potential undercoding for complications, such as venous thromboembolism. And we assume that this limitation may only minimally affect your results. We did also perform various sensitivity analysis in our study to address some of these shortcomings and found the same results.

Dr. BobbieJean Sweitzer: Dr. Kheterpal, can you tell us a bit more about tranexamic acid? How does it work?

Dr. Sachin Kheterpal: Sure. The drug was first identified in the mid-'60s. It really works by putting in that balance of clot formation, clot breakdown. So as you know, in the human body, we're constantly making clots due to tissue injury or through normal homeostasis. But there's a kind of counterbalancing clot breakdown as well.

Whereas a lot of agents that try to decrease bleeding may actually try to increase clot formation, tranexamic acid is what's known as an anti-fibrinolytic, where it decreases the clot breakdown. So if your body happens to make clot in a particular location, tranexamic acid decreases the likelihood that that clot will be broken down by your body's normal homeostasis. The end result that we've seen is that it can be used to help decrease bleeding overall in a variety of situations.

Dr. BobbieJean Sweitzer: Dr. Poeran, I noticed that in the methods section you specifically wrote, I quote, "A data analysis and statistical plan was written, date-stamped, and recorded in investigators' files before the data were accessed." Why was this important?

Dr. Jashvant Poeran: Thank you for noticing that. This is something that really comes up more and more during the peer-review process of our papers, and we feel that this is a good development. And we've incorporated this in our team's workflow, which mainly is to make sure that there's a detailed analysis plan before data access.

There are multiple reasons for this, but the most important one, I believe, is that it is a way for us to make sure that there is a thorough and systematic thought process on analyses before we access data. And as someone who has worked with these data sets for so long, it is just so easy to just check something before writing it down, and you really do increase your risk of false positive findings do that.

Another reason to create a thorough analysis plan before accessing data is that you improve transparency and subsequent trust in the research process. This is also something that applies to the peer-review process. I've gone through many of those processes where reviewers ask for additional analyses, including this paper, actually, which is all fine, but it all impacts your chances of a false positive finding.

What I try to do in my papers is always clearly delineating what analyses were added after our initial analysis plan. Transparency is really something that's always important in research no matter what type of research, but I feel it's even more important than observational research because it's really just so easy to cheat.

Dr. BobbieJean Sweitzer: So is this what people talk about data mining, and what you're doing here is avoiding that?

Dr. Jashvant Poeran: That is correct.

Dr. BobbieJean Sweitzer: Um-hum [affirmative]. Thank you. So, Dr. Moucha, the other day I was providing anesthesia for a patient having breast surgery. I know you're not a breast surgeon but an orthopedist and – but the surgeon used topical tranexamic acid. I know some orthopedists inject this drug into joints. Did you guys look at only intravenous tranexamic acid or any route of administration? And before you answer that question, I need you to just tell us a little bit about sort of the different routes and the benefits or pros or cons of the different routes, especially in your orthopedic use and why one chooses to give it intravenously or intra-articularly.

Dr. Calin S. Moucha: Sure. So I believe the tranexamic acid can be given either orally or intravenously, actually. As many of you know, this drug is one of the essential drugs on the World Health Organization list. But the majority of TXA usage in our patients that we looked at, 94% was intravenous, which is really the most common manner in which we use it clinically. Occasionally we do use tranexamic acid topically. My current indications are when the anesthesiologist does not feel comfortable giving intravenous TXA.

My main indication for not giving TXA intravenously is in patients who've had a significant thromboembolic event that is 100% confirmed to have been unprovoked. So if we know that somebody had an unprovoked DVT or pulmonary embolus, to me that raises some red flags, and that's someone that I would prefer to give topical TXA. And it's really the same dose. I think the reason we don't use topical on a regular basis is there's always the concern for infection, especially during these arthroplasty cases. So giving an intravenous just seems to be a little bit safer from that standpoint.

Dr. BobbieJean Sweitzer: Mm. So do you mind sharing with us what a typical concern an anesthesiologist would giving it IV, and did this have something to do with prompting your interest in this study?

Dr. Calin S. Moucha: Well, it's really all the factors that we looked at here, you know, these patients with a history of VTE, history of ischemic strokes, patients with a history of atrial fibrillation. So many of the anesthesiologists that I work with to this day—and, hopefully, this study will help change their minds a little bit—they still will not give intravenous TXA in patients with – that were described earlier as high risk. So in those patients, if we agree upon before the case, I will give it topically.

Dr. BobbieJean Sweitzer: Well, I either hope those anesthesiologists are listening, or I suggest that maybe the next time you're in (sounds like: the napping room), that once this podcast is available you just play it continuously (sounds like: on loop).

Dr. Calin S. Moucha: {Laughs} I already have given them the article.

Dr. BobbieJean Sweitzer: {Laughs} Dr. Poeran, did the design of your study likely capture all of the adverse events of interest?

Dr. Jashvant Poeran: No. It is very likely that this was an undercount as we were really dependent on coding for this adverse event. As I had mentioned before, this is really something that is inevitable in observational research. And what you have to do is you have to keep on asking yourself the question how does this potential bias impact my study, and is this a fatal flaw? Here in our study, we assume that undercoding for adverse events is independent of tranexamic acid use, and therefore, it minimizes the impact of this limitation.

Dr. BobbieJean Sweitzer: Dr. Kheterpal, what do we already know about the safety of tranexamic acid? Maybe not necessarily just for joint replacement surgery but also more broadly.

Dr. Sachin Kheterpal: Yes. Tranexamic acid is one of those unique medications that we are using more and more often. And the more and more we study it, the safer and safer it appears. This can tend to occur with most practice (sounds like: schemes). We eventually get to a point where the bounds of our enthusiasm for helping our patients eventually identify an area where maybe we extended too far.

There's been, you know, some high-quality randomized controlled trial evidence in a couple different patient populations. Those were the CRASH trials and the WOMAN trial. The CRASH trials were looking at major trauma and use of tranexamic acid to help prevent hemorrhage and hemorrhage-associated mortality. That CRASH trial was followed up by, I believe, CRASH-2 or 3, which looked at traumatic brain injury and the safety signal there.

And then, finally, the WOMAN trial looked at maternal hemorrhage, post-partum maternal hemorrhage, and the use of tranexamic acid in that population. Those were three large, very well-conducted multi-center studies, and they all provided overwhelming safety benefit – risk-benefit evidence there.

There's also been a couple important meta-analyses looking at randomized controlled trials in a range of surgical procedures. And each of those have shown that overall in the patients that were included in those randomized controlled trials, that overall there's a clear transfusion benefit without a noticeable change in thromboembolic events.

The caveat there and the reason why this paper was necessary is that most of those randomized controlled trials that were done outside the trauma literature didn't typically include patients with a history of DVT, PE, stroke, and things like that. So we don't historically have great evidence on the safety profile of this medication in those patient populations, and hence you see the reticence on the part of many providers to be using it in those settings.

That being said, patients with atrial fibrillation, myocardial infarction history, renal failure, many of the conditions that were defined as high risk, those have probably more theoretical risk concerns. And this literature that we now see today in this paper really helps settle those concerns. But, overall, this is – in the studied population been an overall very safe drug that we really have found cases series identifying complications. And when we do see those complications associated with administration, it's typically limited to – seizures is a known complication. In cardiac surgery population, we've seen some seizures related to that. Typically, that's high dose use of tranexamic acid with high blood concentrations. And then there's theoretical risk related to DVT and PE but no clear signals on those areas.

Dr. BobbieJean Sweitzer: Thank you, gentleman, for all of that background, but now, Dr. Poeran, we want you to tell us what you found.

Dr. Jashvant Poeran: Yes. So what we found is we had 28,000 to 46,000 high-risk patients we were able to identify based on the definitions used that underwent elective lower extremity joint replacement surgery. In this group, we found an increase in tranexamic acid use over time, and tranexamic acid use was not used any differently in terms of utilization rate and dosing schemes in high risk compared to non-high-risk patients.

When we looked at the impact of its use, we found that tranexamic acid use was consistently associated with decreased odds of blood transfusions. And most importantly, it was not associated with increased odds of a variety of complications in these high-risk patients.

Dr. BobbieJean Sweitzer: So you found no difference in adverse events based on dose of tranexamic acid that's administered.

Dr. Jashvant Poeran: Yes. To be (sounds like: perfectly clear also), there was no increased odds. There were some decreased odds, actually, but no increased odds.

Dr. BobbieJean Sweitzer: Hm. Interesting. So, Dr. Kheterpal, do you believe the design of Drs. Poeran and Moucha's study adequately was able to be considered definitive at this point? Was it as good or better than a randomized controlled trial?

Dr. Sachin Kheterpal: That's a great question with a complex answer depending upon which patient population we're looking at. So I think all studies have their strengths and limitations. When we try to compare studies of different methodologies, it becomes really difficult. So, you know, ideally there would be a randomized controlled trial of "high-risk patients," placebo controlled, rigorous follow-up using a clinical registry with administrative data only where necessary.

The reality is that trial might never occur in our current world now because the benefits of tranexamic acid from a transfusion avoidance perspective are so clear in many patient populations. One might question whether it would be ethical to randomize a patient to be receiving tranexamic acid. So I think from the concept of definitive evidence, it is quite definitive in the patient populations that had a adequate sample size and adequate generalizability, which includes the high-risk populations of atrial fibrillation, myocardial infarction, and renal disease.

I think the authors would agree that there are some patient populations that we often define as high risk that are still pretty small in this data set. You know, we still had less than, I think, 200 patients with a history of DVT, less than 100 patients with a history of PE. With sample sizes like that, it's pretty hard to take a look at a rare event like venous thromboembolism or seizure and decide whether or not it was occurring more often.

So I think we can say these data are definitive in the context of baseline randomized controlled trials that have established a therapeutic benefit. The data here show a clear transfusion benefit in these populations. But there's certainly some more work to be done, and I'm sure these great authors will be doing it in these kind of more – I wouldn't call them rare because we see them in our ORs all the time. We see people with a history of unprovoked DVT.

And then as Dr. Moucha was saying, it's still unclear what the right answer is for that patient with a history of DVT. You know, a randomized controlled trial in that population is probably feasible because there is still clinical equipoise. The question is how long will it take, and how many centers would it take to actually do that randomized controlled trial and to get that definitive safety evidence, knowing that it takes thousands of patients in each arm to start identifying the non-inferiority of one option versus the other?

So I think these data certainly are very reassuring regarding our current practice patterns. They certainly are definitive regarding my practice pattern in my ORs and my colleagues' ORs. Like all research, it does leave some questions unanswered just like randomized controlled trials do. So great RCTs answer two or three questions and then bring up a few more. So no trial and no observational analysis ends the questioning. It just advances it.

Dr. BobbieJean Sweitzer: So, Dr. Moucha, you mentioned that you had given this paper to some of your anesthesiology colleagues who you work with. Have you seen a change in their practice patterns or their comfort level thus far?

Dr. Calin S. Moucha: Interestingly, the more senior anesthesiologists have changed their practice pattern. The younger ones have not.

Dr. BobbieJean Sweitzer: Hmm.

Dr. Calin S. Moucha: So it's kind of anecdotal response, but I guess that's how the question is. But they also – I don't think they've reviewed it at their journal club yet. Hopefully, they will. Hopefully, once that happens, things will change a little bit.

Dr. BobbieJean Sweitzer: Dr. Poeran, if I am reading table one correctly, it appears that only 53% of patients having lower extremity joint replacement surgery in your data set received tranexamic acid. This seems really low to me. Your thoughts about that?

Dr. Jashvant Poeran: Yes, no, you are correct. That is low, and it's probably because the most recent year we included in this study was 2016. Given that it's increasingly considered a standard of care, it's probably much higher in more recent years, so we would see a different pattern if we would look in more recent years.

Dr. BobbieJean Sweitzer: Um-hum [affirmative]. So you also found, I think, that tranexamic acid was used less commonly in patients having general anesthesia compared to other types of anesthesia.

Dr. Jashvant Poeran: Yes, that is correct. It was very interesting to see, and it is something we come across actually quite often, differences in practice patterns. We can only speculate with this data, but it could be something like in those hospitals with higher use of general, even though regional being the standard of care, there could be a slower adoption of changes in standards of care in these hospitals.

Dr. BobbieJean Sweitzer: Interesting, yes. So also referring to table one, I'm a bit confused by the reporting of the type of anesthesia used for patients in the study population. It appears on – that on average, 75% of the patients in both groups received general anesthetics, and the others were either unknown. Am I reading this correctly?

Dr. Jashvant Poeran: So when looking at table one, we see that – and we provide column percentages. We see that among patients receiving tranexamic acid, 53.6% received general anesthesia only, and this percentage is 62.5% among patients not receiving tranexamic acid. And around 15% to 20% received either only neuraxial or neuraxial combined with general anesthesia. This seems like a low percentage with neuraxial increasingly seen as the standard. A part may be as it is some older data, so it's five-year-old data.

We did look at this separately in another study we published in another anesthesia journal, and we found a very slow increase in adoption of regional anesthesia in these surgeries. We really don't know exactly what is behind this, and it probably deserves its own study looking at specifically what are the limiting factors that prohibit a wider adoption of these practices.

Dr. BobbieJean Sweitzer: Dr. Kheterpal, as the anesthesiologist in this crowd, I thought there were advantages of using anesthetic techniques other than general for lower extremity joint replacements. Can you give us some perspective on this? And then do you think this impacted Dr. Poeran's study at all?

Dr. Sachin Kheterpal: Yes. You know, I think the evolution is occurring not just in tranexamic acid utilization but also in anesthesia technique, whether it's neuraxial, whether it's adjunct, peripheral nerve blocks. We're seeing that uptake with variant speed in different places. I think the concept of the relatively low use of general anesthesia, as Jashvant was saying, is, you know, really emblematic of the data set itself. The most recent patients were from 2016, if I remember correctly. Practice has changed quite a bit in those five years, continues to change rapidly.

I think just as important as the evolution in anesthesia (inaudible) – that's something that we as anesthesiologists notice in this table, but just as important are the baseline transfusion rates. So let's keep in mind that one of the key values of tranexamic acid is a reduction in transfusion. Well, you know, as Jashvant was mentioning earlier, there's protocols related to transfusion at each facility. And if you have a baseline transfusion rate of only 5% or 10%, the theoretical benefit of tranexamic acid might be more limited than what we see in this paper. Whereas if you're at a hospital that's got a transfusion rate of 25%, you might be avoiding lots of transfusions.

So I think the general anesthesia rate in this paper is an example of a lot of other practice changes that are occurring when it comes to joint replacement. And we should think of this as, hey, we need to be doing another version of this study in the near future to look at the modern practice with modern transfusion practices with modern same-day discharge for some joint replacements, as we're seeing in many facilities that might not even be in this data set, such as ambulatory surgery centers.

So I think the general anesthesia piece is something that we would focus on as anesthesiologists, but there's many practice changes going on when it comes to lower extremity joint replacement that would clearly, I think, have an impact on the benefit profile of tranexamic acid. And that's why we need to probably do a version of this project again soon when those more recent data are available.

Dr. BobbieJean Sweitzer: Dr. Poeran, were you able to determine if this high-risk population of patients derived the same benefits as the more average risk or lower-risk patients did from the use of tranexamic acid?

Dr. Jashvant Poeran: Yes, we did look at that, specifically odds of blood transfusions. And what we found is there were universally lower odds of blood transfusions in high-risk and non-high-risk patients, both similar beneficial effects. In fact, some of the effect estimates we found for complications also showed some protection with the use of tranexamic acid. And this brings up the discussion on something Dr. Kheterpal touched upon briefly on what is more important when you look at the cumulative effect of tranexamic acid in high-risk patients.

On one side, you have the potential beneficial effects of avoidance of blood loss in transfusion. And on the other side, you have potential direct negative effect of tranexamic acid. And from our study, it seems that the balance is more towards the potential beneficial effects of avoidance of blood loss.

Dr. BobbieJean Sweitzer: Hmm. Interesting. I recall that you note in your manuscript that the use of tranexamic acid is considered off label for use in total hip and knee arthroplasties. Should our listeners be concerned about this?

Dr. Jashvant Poeran: That was something that we added to provide more context to the current use in the USA but not necessarily to warn and caution. With the current overwhelming evidence of the benefits of tranexamic acid in the total joint arthroplasty population, in our study and others as well that focus on specifically high-risk patients, evidence is really mounting that it is safe to use.

Is this all definitive? By no means, but there are really no big studies showing that it is not safe to use. So the reverse has not been shown yet in a large study.

Dr. Calin S. Moucha: I just want to add that in hindsight we probably should not have used the word off label and probably have used the more modern term, which is physician directed.

Dr. BobbieJean Sweitzer: Yes. I think there's so many drugs that we use. I think we can probably all agree that on average the majority of uses of most medications would be considered off label because the studies weren't designed to meet the FDA requirements that are needed to put it on the label, right? Aspirin use, fentanyl use in very young children. Lots of commonly used drugs would be considered "off label."

So, Dr. Kheterpal, at this point is tranexamic acid use considered standard of care for lower extremity joint replacement surgeries or, in fact, for any surgery with a high bleeding risk? And this is really, you know, directed so that this answer to those clinicians out there who perhaps are not using it or still having some reservations about using it.

Dr. Sachin Kheterpal: That's a great question that has a nuanced answer, unfortunately. I think standard of care means something very specific in legal terms, which is if you don't do it, are you providing reasonable care or not? I almost like to translate this question into would I want a family member to get? {Laughs} And that's probably the most important standard of care one can imagine, which is if your loved one was on the table having a joint replaced and they were one of these either high-risk patients—atrial fibrillation, myocardial infarction history, or renal failure, renal disease—or a standard risk patient that didn't have any of those three things, as has been stated by a bunch of different societies –

I think the Society of Regional Anesthesia and Pain Medicine, the American Association of Hip and Knee Surgeons, the American Academy of Orthopedic Surgeons, they've got a consensus statement recommending the use of tranexamic acid in these populations. And so I think, to that end, we really need to be looking in the mirror if we've got some reticence about using it in a patient, even with some of these "higher risk features." And certainly that's what I had to do a couple years ago.

As I mentioned in my editorial, I remember getting into a somewhat heated argument the first time one of my orthopedic surgery colleagues

asked me to give this drug that I hadn't used before. I'd use it in my liver transplant patients. It was considered a cardiac surgery or liver transplant drug when I started first using it, and I was completely wrong. And I think we need to recognize that evidence evolves and that oftentimes our colleague across the drape might know more about the evidence than we do. And in this case, that surgeon definitely had thought more about this and had looked at the literature.

And at this point in 2021, the current usage pattern of tranexamic acid, which includes, as the data show, high-risk patients are getting TXA just as often as low-risk patients. So the current practice patterns certainly suggest a benefit. I don't think it's standard of care for those unique high-risk patients—history of seizures, history of DVT or PE—where we just don't have that overwhelming data yet. I think it's still a judgment call there, and I look forward to seeing some great papers to help answer that.

Dr. BobbieJean Sweitzer: Dr. Poeran, to follow up on that, as Dr. Kheterpal has noted and earlier in this conversation that there were some groups that had very small numbers of patients included in those defined high-risk categories. I believe it was VTE and PE. Is it possible that your findings were influenced by the chance that providers self-selected patients who weren't – they felt were not candidates for tranexamic acid and simply did not administer it to the "high-risk patients"?

Dr. Jashvant Poeran: Yes, that's definitely possible. I think there's two answers to that question. One of them is that the potential for undercoding of these comorbidities, which I explained before. I don't necessarily think it impacted our results that much.

And the other piece is potential selection bias, right? And I think that's definitely possible. You find this especially in contexts where you study an intervention that is not universally used or not yet universally used. And we addressed this – or we tried to address this in several different ways.

First, we did a multivariable model where we adjust for confounders. But secondly, I think more importantly is we also included the sensitivity analysis in our original data analysis plan, where we looked at only hospitals with a high use of tranexamic acid under the assumption that when tranexamic acid use is the norm in a hospital, you're less likely to have selective use. And what we found in that sensitivity analysis using that alternative cohort, it really did not change our main findings.

Dr. BobbieJean Sweitzer: Dr. Moucha, I know that orthopedic surgeons, or at least the ones I've generally worked with, are very concerned about the hypercoagulable effects of joint replacement surgery and that risk that patients face. And many patients, you know, are anticoagulated afterwards. Do you think there's any concern on the part of the orthopedic community about using this drug in maybe higher-risk patients?

Dr. Calin S. Moucha: Not really. I really don't think there is. I think there's enough data now that shows that the transfusion risk is lower. The blood loss is lower. We know that allogenic blood transfusion is an independent risk factor for infections. Infections are very serious consequences, complications of these procedures. So if we could diminish the risk of a blood transfusion, that ultimately diminishes the risk of an infection. Then it's definitely worthwhile.

As far as things like hypercoagulable state, I mean, you know, we're mobilizing patients so much quicker these days, especially these patients that are having spinal anesthetics, multimodal, regional pain control. These patients just get up out of bed very quickly. When they're in bed, they have sequential compression devices, Really the hypercoagulable state is not that much of an issue postoperatively in these patients. And, in fact, the majority of us are now using aspirin as the only chemical DVT prophylaxis.

Dr. BobbieJean Sweitzer: Yes, I have noticed that. And it's interesting how, you know, I guess, the evolution of various practices start to change that, this balance of, you know, which complication or adverse effect is more likely to occur and then how we need to change our practices regarding that.

So, Dr. Kheterpal, I think you discussed the use of prospective registries and administrative data being used to advance safety of perioperative medicine. Can you tell us a little bit about that?

Dr. Sachin Kheterpal: Yes. You know, I think the advancing science requires a unbiased approach to the tool set itself. Some questions are answerable and must be answered using randomized controlled trials only. And we really have to recognize that until those randomized controlled trials come out, it's not a choice of whether or not we used to look at administrative data or whether we choose to look at registry data. It's a choice of, you know, do we go with our own clinician biases and anecdotal experience, or do we look at some data with good methods with good data quality to help make some more informed choices? And that's the context in which I think different science needs to be looked at.

You know, administrative data, such as what we see in the Premier database here, has been fundamental in advancing care in many different ways. (Sounds like: Jocelyn Pena's) team have been key in doing that, and we thank them for it. If it wasn't for their initial work on tranexamic acid, we wouldn't even be at the point of using it in low-risk patients probably at this stage.

I think the value of registries – and you see more and more registries. I know there's the American Joint Replacement Registry, a national one. In the state of Michigan, we participate in the Michigan Arthroplasty Collaborative Quality Initiative. The nice thing about these registries is they have a dual purpose of quality improvement and research. And it's this virtuous circle where everyday clinicians see problems in their ORs, see difficult choices that they're making, and they can say, "You know what? We should start seeing what's going on with this." And they can actually modify the registry with a little bit of time delay, but they can actually change what data elements are being collected. And that informs at least an assessment of practice variation and maybe some outcome variation.

Whereas administrative data sets, oftentimes whatever data you have there is what you have. I've worked with many of them, and you wish you had certain things. But you just – if it's not there, you can't go get it. Whereas with a registry, oftentimes you can say, "Yes, we don't have it historically, but, you know, we're going to make that change in our case report form. And for the next six months, we'll collect it, and that will advance our knowledge."

So I think the role of registries and administrative data is part of the tool set. Randomized controlled trials will always be, you know, in a specific position on the evidence pyramid. We have to make sure that pragmatic trials that reflect real-world practice are part of that decision-making process because the lack of generalizability in some settings can be a real challenge. But we have to recognize that the administrative and registry analyses have their own limitations when it comes to causal inference. But in many situations, we know that well-conducted, well-validated data sets are certainly better than my opinion or Jashvant's opinion about something and that that data if analyzed well, is far better than biases.

Dr. BobbieJean Sweitzer: I hope today's discussion will interest many of our listeners and lead you to read these important articles to learn more. Thank you, Drs. Poeran, Moucha, and Kheterpal for discussing your work with us today. I wish you all well as you continue your efforts to enhance the practice of anesthesiology and strive to improve the care of our patients.

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