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

Dr. BobbieJean Sweitzer: Hello. I’m BobbieJean Sweitzer, Professor of Anesthesiology at Northwestern University and 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.

And today we are speaking with the author of a publication that appears in the February 2019 issue of Anesthesiology. With us is Dr. Daniel I. Sessler. Dr. Sessler is the senior author of an article titled “Triple-low Alerts Do Not Reduce Mortality: A Real-time Randomized Trial.” Dr. Sessler is a Professor in the Department of Outcomes Research at the Cleveland Clinic in Cleveland, Ohio. Welcome, Dr. Sessler.

Dr. Daniel I. Sessler: Thank you.

Dr. BobbieJean Sweitzer: So, what was your primary goal or aim in doing this study?

Dr. Daniel I. Sessler: We sought to determine whether intervening for triple-low events would reduce mortality.

Dr. BobbieJean Sweitzer: So, tell us what a triple-low event is or how you define triple-low events.

Dr. Daniel I. Sessler: Triple-low events are the simultaneous combination of mean arterial pressure less than 75 mm of mercury, bispectral index less than 45 and volatile anesthetic MAC fraction less than 0.8.

Dr. BobbieJean Sweitzer: So, right off the top of my head these numbers don’t seem like sort of typical triggers that I think the average anesthesiologist would be terribly concerned about. Is it the combination of all three of these that you think are important?

Dr. Daniel I. Sessler: That’s exactly right. Individually none of these is an important threshold and individually none of them is linked to mortality, but combined they are. So, a combination of any two and especially all three together is a strong predictor for postoperative mortality.

Dr. BobbieJean Sweitzer: So, you touched a little bit on this. Can you give us more details about what we know about these triple-low events and specifically outcomes before you did this study?

Dr. Daniel I. Sessler: There have been several previous studies showing that the combination of all three of these events, which we term a triple-low, predicts a 30-day and 90-day mortality after surgery. A reasonable question is, why that should be? These events appear to be prognostic because they are identifying patients at risk. So, consider a patient who has a high bispectral index who’s not very anesthetized but has a low blood pressure. This is not a normal combination; you’re identifying a patient who is fragile. Similarly, a patient who has a low MAC fraction should have a high bispectral index. But if the patient has a low bispectral index, that would indicate a patient who’s excessively sensitive to volatile anesthetics. So, these combinations identify patients who are fragile, who are susceptible and, therefore, it’s perhaps unsurprising that they have high mortality after surgery.

Dr. BobbieJean Sweitzer: So, I guess I could rephrase it: you’re talking about a patient who doesn’t require much anesthesia but ends up with a low BIS and a low blood pressure.

Dr. Daniel I. Sessler: Exactly. That’s an unusual combination; it is a combination that identifies a patient as being particularly sensitive to anesthesia. Well, patients who are sensitive to anesthesia are fragile; they’re probably not in very good health to start with and, consequently, it’s unsurprising that they don’t tolerate surgery well and end up having high mortality.

So, there’s no question that triple-low events are prognostic. This has been shown now in two different studies: double low, that is any two-low events—or especially the combination of three-low events—predicts mortality. The question we asked is whether intervening prevents this increase in mortality. And that’s not obvious; those are different events.

You could have a situation where triple-low events are prognostic, but they are not themselves causal; that would happen if triple-low events simply detect fragile patients, but the triple-low events themselves are not harmful. But our theory was the triple-low events themselves are harmful and, therefore, that intervening to prevent them would reduce mortality and that was the purpose of the study and that’s what was different about this study versus the previous ones which were observational.

Dr. BobbieJean Sweitzer: And a very important question because I guess it’s one thing to say they’re associated, it’s another thing to say the cause and effect truly.

Dr. Daniel I. Sessler: Exactly. Lots of things are associated that are not causal. Now, associations can still be useful; they’re prognostic, they tell you what’s going to happen, they allow you to predict this patient is more likely to get into trouble and maybe you use that to tell patients or their families that this is a high-risk situation or you try to admit patients to an ICU and try to moderate the expected increase in mortality.

But it’s different to say that an event is actually causal because then you could intervene and prevent the harm.

Dr. BobbieJean Sweitzer: So, can you postulate on what perhaps is the path of physiologic mechanisms that account for this? Are these cardiovascular deaths or do we know why these patients with this association die?

Dr. Daniel I. Sessler: We don’t specifically know why patients with triple-low events die, but we do know that myocardial injury is the leading cause of 30-day mortality after surgery. So, it’s likely that myocardial events contribute.

Dr. BobbieJean Sweitzer: Well, especially with the hemodynamic changes that we’re talking about. So, what kind of a study was this? Was this a randomized prospective trial or some other design?

Dr. Daniel I. Sessler: This was a randomized controlled trial, so patients with triple-low events were identified and then randomized to either an alert or not. So, this is an important distinction from a conventional trial. Conventionally, qualifying patients would be approached, consented and then assigned to one treatment protocol or another.

The difficulty with that approach here is that most patients having surgery don’t have triple-low events. So, we would have to consent an enormous number of patients to identify some who have triple-low events. Furthermore, we needed an enormous number of patients for this study. Our sample size ended up being about 7,500 patients with triple-low events. You need that kind of sample size if your outcome is mortality, which, fortunately, is relatively rare after anesthesia.

So, we used a different approach: we got a waiver of consent from our IRB and then we screened patients electronically. To be enrolled in the study, patients had to have bispectral index monitoring and had to get a volatile anesthetic. That put them into screening for the study.

And then our decision support system evaluated patients at one-minute intervals looking for triple-low events. When a triple-low event was identified, the system on the fly instantly randomized patients to either no alert or some other intervention. The providers were then free to respond or not respond as they considered appropriate.

The alert said, “This patient is having a triple-low event. Consider hypoperfusion.” The providers were then free to respond or not respond as they considered appropriate.

Dr. BobbieJean Sweitzer: Interesting. What kind of an alert did the providers get? This was a—something that popped up on their EMR or a page or...?

Dr. Daniel I. Sessler: It was both, actually. The alert was provided on the electronic medical record screen and both the clinician in the room—typically a resident or a CRNA—and the attending anesthesiologist were both paged.

Dr. BobbieJean Sweitzer: Interesting. And did they have to activate the EMR to say okay to acknowledge the alerts?
Dr. Daniel I. Sessler: They eventually had to acknowledge the alert on the EMR, but they didn’t have to do anything about it.

Dr. BobbieJean Sweitzer: Right. And you guys didn’t guide them on what to do; you didn’t make suggestions or anything. They were left up at their discretion to either treat or not treat.

Dr. Daniel I. Sessler: Well, on an individual basis, no. But we did have department meetings about this. So, the clinicians did know the theory of triple low, they knew that triple-low events were prognostic for death and they were aware of our recommendation that patients be treated.

And the treatments that we considered most helpful would be to give a vasopressor which would quickly increase the blood pressure or to decrease the volatile anesthetic. Decreasing the volatile anesthetic would also increase the blood pressure and increase the bispectral index.

Dr. BobbieJean Sweitzer: Is this alert system a standard part of the EMR or is it a specialized tool that you had to build?

Dr. Daniel I. Sessler: It was a tool that we built specifically for this study.

Dr. BobbieJean Sweitzer: And how could you tell if the providers responded to the alerts? I mean, I guess if they said okay, you knew they acknowledged seeing it. But was there a time period if they changed the anesthetic or delivered that you utilized to say this was in response to this alert?

Dr. Daniel I. Sessler: Yes. And our criteria for response was either a vasopressor given within five minutes or a 20% decrease in the volatile anesthetic administration within 15 minutes. So, we didn’t go by whether they acknowledged the alert because that doesn’t tell us whether they did anything about it. What we wanted to know was whether they did something functional and we used those two criteria for defining what we considered to be a useful response to a triple-low event.

Dr. BobbieJean Sweitzer: So, I guess you defined the change in the volatile agent by a percentage, but was it considered an appropriate response if the provider just actually gave any amount of vasopressor or did they have to prove or did you look for correction of the blood pressure to some degree?

Dr. Daniel I. Sessler: We used any vasopressor administration as one of the criteria for an effective response. But, yes, we also looked at how long the triple-low events last which is basically how long it took before something improved the bispectral index increased, MAC fraction increased or the blood pressure increased.

Dr. BobbieJean Sweitzer: So, I know you defined the triple low at the beginning, but I guess for our listeners now that we talked about all of this kind of process and methods, can you tell us again what these levels were: what were the levels of volatile agents, blood pressure, that you were defining as triple low?

Dr. Daniel I. Sessler: Triple-low events are defined by mean arterial pressure less than 75 mm of mercury, bispectral index less than 45 and MAC fraction less than 0.8.

Dr. BobbieJean Sweitzer: Got it. So now, tell us a bit about the population of these patients. Do you take all types of surgery; ambulatory, would that be major surgeries? What on average were ASA physical status scores of your patients and the overall predicted risk? Are we talking about a higher-risk population of these 7,500 patients or whole spectrum?

Dr. Daniel I. Sessler: This was essentially the whole spectrum because the enrollment criteria or bispectral index monitoring and a volatile anesthetic and it had to be adults and noncardiac surgery; and that was about it for enrollment criteria. So, this was a pretty good cross section of the Cleveland Clinic noncardiac surgical population.

Now, of course, we’re a tertiary center, our patients are relatively sick. So, a very good fraction are ASA III and IV; most of them, in fact.

Dr. BobbieJean Sweitzer: So, I think earlier you mentioned about how these events are associated with mortality. Is that all you measured was mortality or were there other outcomes that you measured? And what was the time, was it 30-day mortality or a different timeline?

Dr. Daniel I. Sessler: The primary outcome was 90-day mortality but we also evaluated 30-day mortality and one-year mortality.

Dr. BobbieJean Sweitzer: But not MINS or acute kidney injury, just mortality?

Dr. Daniel I. Sessler: We did not evaluate myocardial injury or kidney injury in this study.

Dr. BobbieJean Sweitzer: Pretty definitive outcome, right? If the patient is dead you can’t quibble much about that.

Dr. Daniel I. Sessler: Well, it has the advantage of being a hard outcome not subject to bias or…

Dr. Daniel I. Sessler: …measurements or – you’re pretty sure about it. On the other hand, it’s not very sensitive and I think that’s what you’re getting to…

Dr. BobbieJean Sweitzer: Right.

Dr. Daniel I. Sessler: …is had we looked at more sensitive outcomes, we might have seen benefit that we missed in this study.

Dr. BobbieJean Sweitzer: Your bar was pretty high. You were looking at pretty significant (sounds like: PURA) outcome. So, how common were the triple-low events in this study? Of these 7,500 patients I guess you can either give us a number or a percentage.

Dr. Daniel I. Sessler: Yes. We screened more than 36,000 patients to identify more than 7,500…

Dr. BobbieJean Sweitzer: Oh, I’m sorry. I misunderstood that; 7,500 were the ones who had the triple low?

Dr. Daniel I. Sessler: Yes. To get 7,500 triple-low patients, we screened 36,000 patients. You can see that this would be absolutely impossible to do as a conventional trial. We could not possibly individually get consent from 36,000 patients.

So, this study was only possible because of this electronic real-time randomization which, by the way, is a novel study design. This is something that’s not been done previously.

Dr. BobbieJean Sweitzer: Yes, thanks for pointing that out because I think we kind of glossed over it or I did at first with some of the other interesting questions that your discussion was raising. But that is very – the fact that also the IRB allowed you to waive consent. Do you want to talk about that a little bit more?

Dr. Daniel I. Sessler: I would love to. The basic problem is that the highest level of clinical evidence in medicine is randomized trials. But randomized trials are expensive and they take a long time to do. There will never remotely be enough clinical trials to answer all the questions we have. Especially, there won’t be really large randomized trials.

The number of randomized trials with thousands of patients per group is just tiny. We get a couple of these each year, but we have thousands of important questions. So, it’s actually really important to develop novel trial methods that allow us to do studies that are quicker, easier and much less expensive than a conventional trial.

This is one that we’ve developed and I think it’s a powerful tool. It depends critically on getting waived consent from the IRB, but it turns out that there are national rules; there’s actually federal law that describes when waived consent is allowed.

All research needs to be approved by the IRB, but the IRB has the authority to waive consent when it’s appropriate and the rules include that this cannot be for FDA registration. You would never do this for a novel drug, for example. You’re supposed to get waived consent only if conventional consent is impractical.

Now, what impractical is is defined differently by different IRBs, but I think most would agree that getting consent from 36,500 patients doesn’t qualify as practical. This study never would have happened had we been
required to get consent from more than 36,000 patients; it just would not be possible. So, it certainly met that criteria.

And then it has to be minimal risk and that’s why we have this fairly unusual study design because ideally you would have defined protocol. So, had it been up to me to design this in a world without constraints, I probably would have said, “You have a triple-low event, you have to give a vasopressor. That’s the protocol.”

Then it becomes less than minimal risk because some of the patients getting a vasopressor might not be appropriate for this. So, we gave that authority back to the clinicians. All we did was provide an alert that said, “Your patient is having a triple-low event.” Clinicians could respond or not, as they felt appropriate.

And because clinicians were involved and because clinicians presumably only did things they thought were good for their patients, the IRB, I think, very appropriately, concluded that risk was minimal.

Dr. BobbieJean Sweitzer: Yes, because I guess it came down to the usual care, right? Those anesthesiologists were allowed to do usual care.

Dr. Daniel I. Sessler: Exactly. So, an alert is not going to hurt patients. An alert could hurt patients if people read the alert and did something stupid, but we presume our clinicians are excellent here. They get the alert, they will process the alert, they will have more information than they did before. Now, technically they can look at the monitors and figure out themselves whether a patient is having a triple-low event, but it takes a tremendous amount of mental energy to do this every minute through the whole case, so most people probably don’t.

So, the alerts gave them new information and they could act on it as they believed appropriate.

Dr. BobbieJean Sweitzer: I mean, it’s not dissimilar to an alarm, right? The alarm goes off and…

Dr. Daniel I. Sessler: Oh, it is an alarm.

Dr. BobbieJean Sweitzer: Right. Thank you for sharing that. That is a very interesting component of this study.

Dr. Daniel I. Sessler: It is, indeed, an interesting part of the study and it’s almost as interesting as the study itself because this is a methodology that we in the anesthesia community should start using more often. We have the luxury of now having ubiquitous electronic records. There is some effort involved, but electronic records can be set up to look for various events, generate alarms and perhaps improve care.

A corollary of that is that many electronic records have various alarms inserted into them just because people think it sounds logical. My theory is that alarms should be treated like drugs and devices and should be tested formally because many of them will not turn out to be helpful and the ones that aren’t helpful actually could be harmful in that they distract clinicians.

So, I think all alarms and alerts should go through a formal testing process and this is exactly how you would do it: you would randomize patients to either generate an alert or not and then see if you improve at least a mediator if not an outcome.

Dr. BobbieJean Sweitzer: Yes. I like to say that the electronic medical record, I believe, is the most important piece of a medical equipment that we use that is not FDA regulated. I think there should be perhaps more oversight into these electronic records.

You must be familiar and many of our listeners who use the electronic records, of these things called BPAs, best practice alerts; something pops up and tells you or warns you or advises you to perhaps do something or that there’s some issue. And I think that that’s another analogy to describe what these alerts were kind of like.

Dr. Daniel I. Sessler: Yes.

Dr. BobbieJean Sweitzer: So, do you want to tell us what you’ve found specifically around the mortality? Did you find there was a mortality difference in those who got the alerts or did not get the alerts?

Dr. Daniel I. Sessler: There was no difference in mortality.

Dr. BobbieJean Sweitzer: So, even though there was no difference in mortality between those two populations, were you able to show that the providers who received the alerts were more likely to alter their anesthetics or administer vasopressors than the ones who did not get the alerts?

Dr. Daniel I. Sessler: Providers who got the alerts were significantly more likely to give a vasopressor, significantly more likely to decrease the anesthetic concentration but not by a clinically important amount. The difference in providers who made what we consider a useful response was only about 5%.

So, the clinicians largely ignored the alerts or, more generously, they considered the alerts and decided that their patients did not warrant intervention.

Dr. BobbieJean Sweitzer: So, I guess you would say that they did not adequately or appropriately respond.

Dr. Daniel I. Sessler: Well, I don’t want to quite say didn’t respond appropriately. Presumably clinicians were doing what they thought was best for their patients and our clinicians are highly skilled, so I don’t want to second guess them. But for whatever reasons the alerts did not make any important change in behavior which means that the study poorly tested our hypothesis.

Dr. BobbieJean Sweitzer: It struck me a bit that that map of 75, I know there’s a lot of debate and you’ve published so much information on this—what is an appropriate blood pressure or what blood pressure levels are associated with adverse events—and we used to talk about percentage of baseline, but then you published, I believe, data that suggested that one could just use a map of 65. Anything below that and the longer they were below that the higher the risk of adverse outcomes.

And I’ve, over time, come to think that for my healthy patients I’m usually okay with 65 and for my advanced-aged or patients with vascular risk factors or risk factors for kidney injury or underlying vascular disease or kidney disease, I usually aim for a map of 70. I don’t usually think of 75 as being too low. Do you think that has something to do with this?

Dr. Daniel I. Sessler: Absolutely, because many of the blood pressure studies were done in our department at the same time but we’re quite aware of the 65 mm mean arterial pressure threshold.

And as we said in the beginning, 75 is high by itself it’s not concerning. It’s only concerning when you have a mean arterial pressure of 75 combined with other factors. That’s when you begin to get alarmed, but I can understand clinicians looking at a mean arterial pressure of 75 and saying that’s okay because by itself it is okay.

Dr. BobbieJean Sweitzer: But I wonder if it didn’t somehow also allow them to think differently about those other values as well. I don’t know because it is interesting that they – as you said, very experienced good clinicians who work with sick patients would choose to have a certain response to something that was warning them needed adjustments.

Dr. Daniel I. Sessler: Yes. The study would have been easier to interpret if people had responded more aggressively to the alerts. Nonetheless, about half of the patients had what we would term effective responses and about half didn’t.

It was about the same in the alert and the no-alert groups, but nonetheless we got to the study, we had 7,500 patients who had triple-low events; about half had either a vasopressor within five minutes or a 20% decrease in volatile anesthetic concentration within 15 minutes. So, these are effective responses to triple-low events.

There was no improvement in outcome in the ones who had effective responses. Even though it didn’t distribute by group as we had hoped, in fact, half the patients had effective responses, half did not and the outcomes were exactly the same.

So, we conclude from this that triple-low events are not causally related to mortality even though they are prognostically related to mortality.

Dr. BobbieJean Sweitzer: So, as most good studies, it raised questions, more questions.

Dr. Daniel I. Sessler: Indeed.
Dr. BobbieJean Sweitzer: So, was there a decrement in response as time progressed? Did these providers get alarm fatigue?

Dr. Daniel I. Sessler: We did not assess that, so I can’t answer that question. We have these data, but I don’t know.

Dr. BobbieJean Sweitzer: Did you think the providers know they were being studied?

Dr. Daniel I. Sessler: Oh, yes. Yes, we had multiple department meetings about this, substantial effort on my part to encourage people to make what I consider to be useful responses. So, yes, they were perfectly aware of this and, of course, they were getting pager alerts in half of the cases.

Dr. BobbieJean Sweitzer: And you didn’t have to get IRB approval or consent for them? They didn’t have to give consent to be part of the study?

Dr. Daniel I. Sessler: No, we did not have to get consent from the providers.

Dr. BobbieJean Sweitzer: So, if I may summarize, I think your study showed that real-time alerts to these triple-low events did not reduce 90-day mortality and there was no difference between the responses of the providers who were getting these alerts and those who did not get the alerts.

And providers largely either ignored the alerts or perhaps didn’t respond the way you would perhaps would have anticipated they would. So, in this study I guess it didn’t matter whether they did or didn’t; as you said, the outcomes were no different. But if we did want to change behavior of providers, this wouldn’t have done that.

Do you have any insight from this study as to how we do change behaviors of providers?

Dr. Daniel I. Sessler: One thing I’ve learned from this is that we need to have better buy-in from clinicians for this sort of study. Members of the department need to feel that this is their study, that they’re engaged, that they think the hypothesis is important, that the intervention is likely to be helpful and, therefore, will intervene when alerted to particular conditions.

Dr. BobbieJean Sweitzer: Do you have any advice for the average anesthesia provider today? Do they do anything differently based on what you have found from this study?

Dr. Daniel I. Sessler: Our results were negative, so triple-low events while prognostic are not causal and, therefore, I would not recommend any particular intervention for triple-low events. So, based on this study, no, I don’t think clinicians need to change their behavior. There is one thing that clinicians should be aware of and that’s hypotension. It’s not coming out of this study, but you mentioned our work about hypotension and myocardial injury, acute kidney injury and death. There are very strong associations between hypotension and serious outcomes.

A good threshold to keep in mind is a mean arterial pressure of 65 mm of mercury. That doesn’t mean that if you go a few millimeters below that for a couple of minutes that a patient is going to have a heart attack, not at all. But if you go much below that and you stay there for a long time, your patient’s risk of injury goes up. I’m very worried about blood pressure.

Dr. BobbieJean Sweitzer: Yes, I think when many of us have – and especially in the past we were sort of upset at cardiologists when they would make recommendations to avoid hypoxia and hypotension; we would feel like they were telling us something that we already knew: But I don’t know that they weren’t right about warning us to avoid hypotension. I think we still need to do that.

Dr. Daniel I. Sessler: The cardiologists were right both on hypoxia and hypotension are bad. Let me reframe that, though. A question is, why after 150 years of anesthesia we’re just now figuring out what blood pressure is harmful? And it’s not just because we didn’t think of it.

There actually is a reason and the reason is that you need very large accurate datasets that we just didn’t have with paper records. It wasn’t until the advent of electronic records—especially records like ours which have unmodifiable blood pressures on them—where we could collect the tens of thousands of patients necessary to accurately evaluate rare but very serious outcomes.

Now that we have that, it’s becoming clear what pressures are harmful and just how harmful hypotension really is. It’s really frightening because all of us, I think, grew up doing deliberate hypotension but to levels that almost surely were harmful in some patients.

Dr. BobbieJean Sweitzer: And sometimes perhaps not deliberate hypotension, but I think that’s the other thing I’ve been a little bit shocked at is the amount of hypotension these electronic records have sort of elucidated: how frequent, how often and for how long sometimes patients are hypotensive.

Dr. Daniel I. Sessler: Exactly. Intraoperative hypotension is common, profound and prolonged.

Dr. BobbieJean Sweitzer: So, I hope today’s discussion will interest many of our listeners and lead you to read this important article to learn more. Thank you so much, Dr. Sessler, for discussing your work with us today and I wish you well as you continue your herculean efforts to enhance the practice of anesthesiology and strive to improve the care of our patients.

Dr. Daniel I. Sessler: Thank you much.