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

Dr. BobbieJean Sweitzer: Hello. I am 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.

Today we are speaking with the author of a publication that appears in the February 2020 issue of the journal. With us is Dr. Dan Longrois. Dr. Longrois is the lead author of an article titled “Timing of Beta-Blocker Reintroduction and the Occurrence of Postoperative Atrial Fibrillation after Cardiac Surgery.”

Dr. Longrois is Professor of Anesthesia and Intensive Care, Bichat-Claude Bernard Hospital, APHP, Paris, France. Welcome, Dr. Longrois.

Dr. Dan Longrois: Thank you very much.

Dr. BobbieJean Sweitzer: Let’s start with examining, I think, where your study fits in with others. I think there have been other studies examining the issue of perioperative beta blockers, even specifically for atrial fibrillation. So, tell us why your study is unique.

Dr. Dan Longrois: You’re right. There have been several studies, not necessarily prospective randomized; mostly of them observational that looked at the benefits of reintroduction of beta blockers in patients who were under chronic treatment versus nonreintroduction.

And the conclusion was that nonreintroduction of beta blockers following cardiac surgery was associated with a statistically significant increase in the risk of having postoperative atrial fibrillation. In those studies, the way one looked at the reintroduction of beta blockers was yes or no and there were no details neither on the timing of beta-blocker reintroduction nor on the time sequence of beta-blocker reintroduction versus the occurrence of postoperative atrial fibrillation.

And the unicity of our study is that we looked specifically at the timing, both of the beta-blocker reintroduction and also at the occurrence of atrial fibrillation because if beta-blocker reintroduction is to be effective in preventing atrial fibrillation, it has to precede the occurrence of atrial fibrillation.

So, the absence of timing, you only look at events that can be either related or totally independent and I think this is the unique: that we looked at the very fine granularity at this issue of beta-blocker reintroduction after cardiac surgery.

Dr. BobbieJean Sweitzer: I understand. So, can you tell us why this topic is so important? Is this a common problem?

Dr. Dan Longrois: So, atrial fibrillation actually concerns 40% to 50% of patients who undergo adult cardiac surgery. So, in the publication that we present here in ANESTHESIOLOGY, we got 40% of the patients who had atrial fibrillation within the first seven days after cardiac surgery.

So, the topic is important because the risk factors for occurrence of atrial fibrillation are, in general, not modifiable; that means age, the length of aortic clamping and cardiopulmonary bypass or the history of paroxysmal atrial fibrillation.

And when you look at the modifiable factors, there are very few of them and one of them is actually the way beta blockers are reintroduced. And this is, I think, it’s focusing on modifiable risk factors, factually get the shift from (sounds like: epidemiology) to clinical interventions.

Dr. BobbieJean Sweitzer: Wow, that’s a lot of patients: 40% of cardiac surgical patients. We’re talking a few million a year, correct, worldwide?

Dr. Dan Longrois: Yes, correct. And while publications after publications years after years, the percentage of patients having transient postoperative atrial fibrillation did not decrease. So, it’s consistent with other studies; while, of course, it varies by a few percentages, at least one of our every three patients that have atrial fibrillation after cardiac surgery.

Dr. BobbieJean Sweitzer: So, I know you briefly talked about what you were looking at, but can you be more specific now about what your primary endpoint or endpoints of this study were?

Dr. Dan Longrois: So, the primary endpoint was the delay in hours between the last prescription of beta blockers before surgery—it’s usually on the morning of surgery—and the first prescription of beta blockers after surgery. And this is because when you look at and you read the guidelines, the guidelines tell physicians to reintroduce beta blockers in those patients who have chronic beta-blocker therapy as soon as possible without any specific details on the timing, of course if there are no contraindications.

And it’s something particular in the study because we calculated the number of patients that we needed to study by looking at a secondary endpoint which was the occurrence of atrial fibrillation and the risk factors. And this is why we came up with about 700 patients that needed to be studied prospectively to have the statistical power to detect the relationship between beta-blocker reintroduction and the occurrence of atrial fibrillation.

Dr. BobbieJean Sweitzer: Then you were actually looking at the timing of that association of when the beta blockers.

Dr. Dan Longrois: Yes, correct.

Dr. BobbieJean Sweitzer: So you mentioned about recommendations of guidelines. Can you maybe go into a little bit more detail about what these guidelines are, where they are derived from, do they differ from— I know the US has guidelines, the European societies have guidelines, regarding the use of perioperative beta blockers for the prevention of atrial fibrillation specifically, maybe the types of drugs or the types of doses or...?

Dr. Dan Longrois: So, the only specific recommendation is to avoid nonreintroduction because nonreintroduction has been statistically associated with an increased risk of postoperative atrial fibrillation. And then following this recommendation, it is as fast as possible without any recommendation on the dose of reintroduction. It is usually half of the preoperative dose or, at most, the full dose. And then there are not specific details about in the absence of contraindications.

So, the guidelines look like a slogan, both in the United States and in European, coming from the observational studies. And, therefore, there are very, very few prospective randomized studies and most of them concern short-acting intravenous beta blockers. But this is not yet a common clinical practice.

So, the routine clinical practice is to reintroduce oral beta blockers and the lack of details about the reintroduction, timing, effectiveness actually were incentive for us to perform our study.

Dr. BobbieJean Sweitzer: MAKes sense. So, can we talk a little bit about the importance of beta blockers, per se? Or, I mean, are— do beta blockers have advantages over, say, other agents as amiodarone or other ways to prevent atrial fibrillation?

Dr. Dan Longrois: Well, there’s very strong evidence that there’s a common pathway—not the only one—but a common pathway that pathophysiologically explains the occurrence of atrial fibrillation after cardiac surgery. There’s an overactivity of the sympathetic nervous system and this overactivity can probably best be dealt with beta blockers. In addition to blocking this overactive sympathetic system, the beta blockers actually allow a reduction in the rate.

And if you look at amiodarone, amiodarone is a good drug to prevent occurrence of a subsequent episode of an atrial fibrillation, but amiodarone is a poor weight reducer. But physicians still like amiodarone very much because the hemodynamic tolerance of amiodarone is probably much better than other beta blockers because if there’s a heart failure or intracardiac conduction block, beta blockers, of course, can unmask them. And in addition, beta blockers can unmask also hypervolemia.
So therefore, the perception of the clinicians is that the therapeutic index of amiodarone is probably better than the therapeutic index of beta blockers when one has to either prevent or treat atrial fibrillation.

So, the guidelines recommend the use of beta blockers for prevention and there’s strong evidence that they are effective. Amiodarone also could prevent, but for treatment of atrial fibrillation, the number one drug is beta blockers.

And if they are contraindicated, then it would be non-dihydropyridine calcium channel blockers and amiodarone would more likely either prevent the occurrence of subsequent episode of paroxysmal atrial fibrillation or actually facilitate the effectiveness of an external electrical shock.

Dr. Bobbie Jean Sweitzer: Maybe we should back up just a little bit and maybe you can tell us a bit more about postoperative atrial fibrillation. Is it harmful? What do we know about the patients who develop atrial fibrillation after cardiac surgery?

Dr. Dan Longrois: So, there’s very strong evidence that atrial fibrillation is an independent risk factor for increased postoperative mortality after cardiac surgery. This is not as strong in noncardiac surgery. But for cardiac surgery, the occurrence of atrial fibrillation is strongly and statistically related to increased mortality and it is also related to an increase in morbidity.

And interestingly, atrial fibrillation is responsible for about 15% to 20% of postoperative stroke, which is a devastating event in patients. And therefore, in addition to this morbidity, it also increases the duration of stay and, therefore, costs. And I think even more interestingly, if you have had an episode of transient atrial fibrillation after cardiac surgery, so it’s 40% of the patients, when you look at patients leaving the hospital, only two of them leave with persistent atrial fibrillation.

But the occurrence of a paroxysmal and transient atrial fibrillation episode is associated with mortality at one year after cardiac surgery. So, the evidence that attempts to modify either the incidence or the duration of atrial fibrillation with interventions that are not harmful, again, it’s quite a strong incentive to do something about atrial fibrillation. So, I think there’s no doubt about it.

Dr. Bobbie Jean Sweitzer: So, if the patients, though, are not in atrial fibrillation, is it possible that this increase in mortality or adverse outcomes long term just indicates that maybe atrial fibrillation is just a marker of some kind of underlying cardiac risk these patients have and it’s not from the atrial fibrillation, per se?

Dr. Dan Longrois: It may well be and we don’t have those studies in which an intervention would allow a decrease in the incidence of atrial fibrillation after cardiac surgery and then look at the long-term mortality. I think we don’t have those data yet.

So, you’re fully right, it may well be that it’s a marker of underlying cardiac disease or sympathetic versus parasympathetic nervous system instability or other unknown pathophysiological events. So, the causality of linking transient postoperative atrial fibrillation with long-term mortality is still to be demonstrated.

Dr. Bobbie Jean Sweitzer: In your study were you just looking at occurrence or not? Not necessarily adverse events related to atrial fibrillation?

Dr. Dan Longrois: No, we didn’t look at that. We would not have had the statistical power because the mortality rate was quite low. So, it — we didn’t even try to analyze those events, neither morbidity nor mortality.

Dr. Bobbie Jean Sweitzer: So, can you tell us a little bit about this population of patients? I mean, I know they were having cardiac surgery, but what types of surgeries were included in your study? And are — do you think these patients and the types of surgeries were representative of typical cardiac surgery patients?

Dr. Dan Longrois: So, the inclusion criteria was very large. The patient needed to be on chronic—that is more than 30 days—beta-blocker therapy and then needed to be older than 18 years of age without a pacemaker and without permanent atrial fibrillation.

And except for those contraindications, there were none others, and we had about 50% of patients who had coronary artery bypass graft surgery and the others had valve or other complex or combined surgeries.

So, this is representative of what we see in Europe and what we see also in the United States and worldwide with slight difference from center-to-center according to the recruitment of the patients by different surgical teams. But I think this is very representative of what we see in present-day, modern cardiac surgery. Dr. Bobbie Jean Sweitzer: Did the patients have to take their beta blocker on the day of surgery or within 24 hours? Or did you look at the timing of the preoperative…?

{Crosstalk}

Dr. Dan Longrois: We recommend that the patients should take their last beta-blocker regimen on the morning of surgery except for unusual situations such as severe bradycardia. But in all the patients that we included, the beta blocker was given on the morning of surgery.

Dr. Bobbie Jean Sweitzer: And so, you didn’t look at any patients who previously were not on beta blockers?

Dr. Dan Longrois: No, because we specifically looked at this issue of reintroduction. So, in order to reintroduce, the patient needed to be on chronic—that is more than 30 days—beta-blocker therapy.

Dr. Bobbie Jean Sweitzer: So, there’s no recommendations that one just administers beta blockers prophylactically to people who aren’t on them postoperatively to prevent postoperative atrial fibrillation?

Dr. Dan Longrois: The reintroduction is not prophylaxis. So, the term of prophylactic beta blockade in patients who are naïve of beta blockers has been in randomized studies. So, if you separate two groups of patients in one, you would introduce—not reintroduce—introduce beta blockers preoperatively as has been done with sotalol and the other is placebo.

The fact of giving prophylactically beta blockers results into a 30% decrease in the incidence of postoperative atrial fibrillation. But this issue of prophylactic beta blockers is fairly controversial because there have been other studies in noncardiac surgery where a prophylactic beta blocker is given preoperatively did decrease cardiac events but increased the risk of hypertension and increased the incidence of stroke; and, therefore, the resultant effect of the combined beneficial effect on cardiac events and the deleterious effects on the brain was an increase in mortality.

So, the prophylactic beta blocker is a different topic. We’re here to talk about reintroduction which is not prophylactic reintroduction. It is still an only reintroduction.

Dr. Bobbie Jean Sweitzer: Maybe you should tell us what you found. Did providers promptly reintroduce beta blockers or not?

Dr. Dan Longrois: So, this was not the case. It was early. There’s no definition of early reintroduction, but because the peak of occurrence of atrial fibrillation in the literature is between 48 and 60 hours following the end of surgery, we considered the early reintroduction of beta blockers would be in the first 48 hours. And in our study only 40% of the patients had beta blockers reintroduced in the first 48 hours.

And, of course, the study was also designed to look at the reasons of nonreintroduction. So, therefore, at the other end of the spectrum when you look in the first seven days, 80% of the patients had beta blockers reintroduced. So, 40% had early—less than 48 hours after surgery—reintroduction and in the 60% others, their reintroduction was late. So, it is this issue of early versus later reintroduction which actually allowed us to focus on timing.

And the main reason for nonreintroduction was the concomitant prescription of catecholamines and then it was a perceived risk of unmasking
heart failure and the perceived risk of respiratory complications in patients who had preoperative COPD.

And in about 30% to 40% of the situations, there were no reasons for nonreintroduction. So, this is an important topic because we do not concomitantly use—or there are very few exceptions, catecholamines and the beta blockers—but the possibility exists that if a patient is on levosamadan, then beta blockers can be prescribed.

So, this is an issue which requires further studies and I think it provides some of the explanation of the absence of early reintroduction of beta blockers.

**Dr. BobbieJean Sweitzer:** Interesting. So, I can kind of get the concept of the heart failure and the catecholamine contraindications, but the COPD is kind of puzzling because these are patients who had been taking beta blockers, right, the preoperatively? So, why would one be so concerned then that they wouldn’t tolerate them postoperatively?

**Dr. Dan Longrois:** Well, for many reasons because even you have been stabilized with COPD and beta blockers, well, there’s an increased risk of bronchial edema, there’s an increased risk of cardiac surgery; and, therefore, there’s a kind of probably perception or misperception that one could increase the risk of bronchial constriction with beta blockers.

I’m not saying that this is a rational approach, but this is the observation that we did.

**Dr. BobbieJean Sweitzer:** Sure, yes. I mean, obviously there’s risk of postoperative pulmonary complications, but usually for different reasons, not from the bronchial spastic kind of etiologies.

**Dr. Dan Longrois:** Right.

**Dr. BobbieJean Sweitzer:** So, you mentioned that I think overall you saw about a 40% incidence of atrial fibrillation. Did you see a difference in the timing of the occurrence of atrial fibrillation in those patients who either got the early or the late beta blocker?

**Dr. Dan Longrois:** So, the interesting observation is that when you compare patient with beta blockers reintroduced versus not reintroduced, reintroduction effectively decreases the risk of atrial fibrillation occurrence only 72 hours after the reintroduction.

And we interpret this as a fact related too lack of effectiveness. And the lack of effectiveness was demonstrated by the fact that when you compare patients with early versus later or nonreintroduction, the heart rate values in patients with beta blockers reintroduced versus not reintroduced were not different until 72 hours after reintroduction. That means that the way we reintroduce beta blockers orally is not effective.

So, this opens a second window of opportunity, not early reintroduction versus nonreintroduction but effective reintroduction versus not effective reintroduction. And heart rate is probably a good way of reading the effectiveness of reintroduction.

And we confirmed this hypothesis by also looking at reintroduction of statins. So, statins, the reintroduction is also statistically associated with a decreased occurrence of atrial fibrillation but only at a later timepoint, as if there were a window of opportunity between the moment that the clinician decides the beta blockers might be reintroduced orally and a way of improving the effectiveness—and this is something we are working on now—is to do a randomized study in which patients who have beta blockers reintroduced are randomized into an intravenous bridge versus placebo.

And the working hypothesis is that once you reintroduce orally, you would need to enhance the effectiveness of beta blockers with a short-acting intravenous beta blocker. And this is probably the most interesting result of our study is that the early versus later introduction are probably not very effective. And, therefore, if you do not want to take a bet on oral beta blockers, you need to bridge the oral beta blocker with a short-acting intravenous beta blocker.

And if you go wrong, that is if you unmask hypervolemia or heart failure, you just stop the short-acting intravenous beta blocker.

**Dr. BobbieJean Sweitzer:** Sounds like a win-win.

**Dr. Dan Longrois:** It’s a working hypothesis, yes.

**Dr. BobbieJean Sweitzer:** You’ve talked about the presumed etiology of the hyper sort of sympathetic activity and the effectiveness of beta blockers to block that. What is the statin benefit? What is the presumed etiology there?

**Dr. Dan Longrois:** So, everything basically after surgery, as aggressive as cardiac surgery, will contribute to activated sympathetic nervous system. It would be the inflammation, it would be the changes in temperature, it would be the exogenous catecholamines, it would be the endogenous catecholamines, it will also by hypoxemia which is quite common after cardiac surgery. Pain as well.

So, basically everything that occurs after surgery would contribute to activating the sympathetic nervous system and there’s quite an interesting observation is that among the cardiac surgery procedures, the one that has the lowest incidence of atrial fibrillation is heart transplantation. And this is probably related to the fact that the transplantation by itself actually blocks the sympathetic outflow to the graft.

And this is quite interesting and I think this is the very good – because inflammation would be the same, complications would be the same in heart transplantation as compared to other types of cardiac surgery and the only difference between them would be that the graft would be denervated.

Now, this is, in my opinion, the best demonstration of the fact that the sympathetic nervous system overflow to the myocardium is the main culprit of the increased incidence of atrial fibrillation after cardiac surgery.

**Dr. BobbieJean Sweitzer:** That is quite interesting. So, following along that same theme, was there an association of atrial fibrillation with the use of postoperative catecholamines? Are they the active substances?

**Dr. Dan Longrois:** When you do a multi-varied analysis—and this is what we did—we had about 50% of the patients who had catecholamines after cardiac surgery. So, in (sounds like: univert) analysis, the prescription of catecholamines is associated with an increased risk of postoperative atrial fibrillation.

In multi-varied analysis, when you introduce into the model the presence of (sounds like: altered) left ventricular ejection fraction—which would be one of the main reasons for prescription of catecholamines after cardiac surgery—then the prescription of catecholamines is not an independent risk factor for atrial fibrillation after cardiac surgery.

So, it is the main reason for nonreintroduction of beta blockers early after a cardiac surgery by itself in our study and also in a few other studies catecholamines are not an independent risk factor of atrial fibrillation occurrence after cardiac surgery.

**Dr. BobbieJean Sweitzer:** So, I think you had mentioned in the beginning a few predictors such as age and now you just now sort of said the catecholamine was not associated. What were some of the other predictors, if any, of which patients developed atrial fibrillation?

**Dr. Dan Longrois:** So, a history of paroxysmal atrial fibrillation was also a strong predictor of the occurrence of atrial fibrillation and this is why your previous remark saying that the occurrence of atrial fibrillation after cardiac surgery and its relationship with the long-term mortality may be a marker of structural alterations of the myocardium and the conduction system.

And the protective factors were, in our study, the introduction of beta blockers at latent timepoints and also the fact that statins were associated with decreased risk of atrial fibrillation after cardiac surgery.
And this is fairly consistent with previous literature showing that there are very few modifiable risk factors and which is – which are the introduction of beta blockers in our studies to prevent atrial fibrillation.

Dr. Bobbie Jean Sweitzer: Do you think the guidelines should maybe reworded that one doesn’t stop them unless there’s strong indications? I think that’s kind of a different approach, right, than saying you stop them and reintroduce them when it’s safe, but say, well, continue them and only withdrawn those that are not safe?

Dr. Dan Longrois: I think it will be difficult to go beyond the present-day recommendations because in noncardiac surgery, the POISE study and the meta-analysis actually are incentives to be very, very cautious when prescribing beta blockers because clinicians intuitively are kind of afraid of beta blockers. So, I think they should be afraid. But once they’re not afraid anymore, so being afraid would mean that you would respect contraindications but once contraindications are nonexistent, then the effort should be to optimize the reintroduction and this is the essence of our study.

So, we do not advocate a more intensive or more frequent use of beta blockers which would bring us back to this issue of prophylactic beta blockers in noncardiac surgery and the POISE study and many other studies. I think the message would be that once you decide on normal contraindications, optimize reintroduction. And the optimization would be increasing the effectiveness of beta blockade.

So, if a patient is given a beta blocker, it is not necessarily better blocked and this is what I was trying to demonstrate. Patients receive the beta blockers but they’re not better blocked less than 72 hours after the prescription of beta-blocker reintroduction. I think this is a strong message of our study: optimizing of reintroduction, not more frequent or more liberal reintroduction.

Dr. Bobbie Jean Sweitzer: Which is actually a nice point to make, that just to be fair, I mean, I think the POISE trial perhaps overlaid the beta blocker; like, large doses, very aggressive dosing and kind of a blanket with everybody getting beta blockers. So maybe the balance is somewhere in between what POISE did and being too conservative or too slow.

Dr. Dan Longrois: Well, POISE was, let’s say, slogan-like. So, give beta blockers prophylactically to everyone…

{Crosstalk}

Dr. Bobbie Jean Sweitzer: In large amounts.

Dr. Dan Longrois: In large amounts of a specific (inaudible) and not titrated and the same dose to all the patients.

But POISE also pointed to the fact that you may have side effects probably related to arterial hypertension and I think that the common sense now is that beta blockers should be used in a personalized way and I do not think we still have the tools to personalize beta blocker use perioperatively both in cardiac surgery and in noncardiac surgery.

Dr. Bobbie Jean Sweitzer: So, were you surprised by any of your findings?

Dr. Dan Longrois: Honestly no, because there was data in the literature suggesting that the way we reintroduce beta blockers now is not the effective way to do it and this is related probably to the fact that the bioavailability of beta blockers – so, a patient who would be on 200 milligrams of (inaudible) preoperatively and who would be given half a dose or even a full dose on Day 2—48 hours—data clearly shows that the bioavailability would decrease by about 50%.

So, I was not surprised, but it needed to be demonstrated and I think that this issue of timing now it becomes a real issue and that gets us from slogans in the guidelines, that are fully respected and respectful, to a more personalized way of doing postoperative medicine.

Dr. Bobbie Jean Sweitzer: So, maybe we can close with that. Can you maybe give some practical suggestions here on perhaps how clinicians can improve this process of reintroducing beta blockers like: What are the absolute contraindications? At what time should you try to do it? What heart rate are you targeting? What drugs should you use?

Dr. Dan Longrois: Looking at your last part of the question, what type of beta blockers should be given? If you look at all beta blockers, carvedilol would probably have some advantages over other types of beta blockers, but this is not rocket science.

So, there have been very few face-to-face comparisons on the effectiveness of different beta blockers after cardiac surgery. So, I would not go into this direction.

My message would be that in our routine clinical practice, once we have decided that the routine contraindications—severe heart failure, intracardiac conduction blocks and severe bradycardia—once those contraindications are lifted and we decide to reintroduce beta blockers, my message would be attempt to look at the effectiveness of beta blockers.

So, when we look at heart rate, because you mentioned them, in our study, the preoperative heart rate was on median about 60. So, that means that the patients were blocked due to beta blockers because the resting heart rate was about 60.

The immediate postoperative heart-rate values in the first three to four days were about 100. That means that the beta blockers were not effective anymore and when you look at the beta-blocker reintroduce group versus beta blockers not reintroduced in the first 48 hours and you look at their heart rate values, they were not statistically different. That means that even in the patients who had beta blockers reintroduced early, the beta blocker’s reintroduction was not effective.

So, I would encourage the clinicians – I don’t have a recipe that would be applied to all types of patients after cardiac surgery. My only message is to look at the effectiveness of beta blockers and if the patients on that are not better blocked with the oral reintroduction, a bridge with a short intravenous drug would probably be useful.

And there’s some convincing data with a drug that comes from Japan, landiolol, that suggestions at least in the Asian population that reintroduction or the use of landiolol after cardiac surgery slightly decreases the incidence of atrial fibrillation.

So, my message is in just one sentence: once you have reintroduced beta blockers, also look at the effectiveness of the reintroduction through the heart rate.

Dr. Bobbie Jean Sweitzer: Excellent practical advice. 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, Dr. Longrois, for discussing your work with us today. I wish you 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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