LEGACY PI Throws Down the Gauntlet to US Physicians
John M. Mandrola, MD, Prashanthan Sanders, MBBS, PhD  |  April 16, 2015

John M. Mandrola, MD: Hi everyone. This is John Mandrola with theheart.org on Medscape. I am at the American College of Cardiology meeting in San Diego, California. I am very excited to speak with Dr Prash Sanders from the University of Adelaide, in Australia, about the exciting, late-breaking results of the LEGACY trial.[1] Dr Sanders, can you tell us about the top-line results?

Prashanthan Sanders, MBBS, PhD: The LEGACY study looked at the impact of weight loss on atrial fibrillation (AF). We found three important effects. First, weight reduction results in a dose-related impact on AF burden. Second, weight fluctuations seem to dampen that effect. Third, a clinic dedicated to managing weight and risk factors effectively achieves and maintains these results in the long-term. I believe that is the crux of the message from the LEGACY study.

Dr Mandrola: What were your primary findings?

Dr Sanders: As patients lose weight, we can see the AF symptoms and AF burden recede. Over the 5-year period of follow-up, 46% of people who had lost more than 10% of baseline body weight were able to sustain a normal rhythm without the use of antiarrhythmic drugs or ablation.

Dr Mandrola: That is almost 50%.

Dr Sanders: Yes, almost 50%—a striking result. The likelihood of achieving a normal rhythm was lower for those who lost between 3% and 9% of baseline body weight, and for those who did not lose any weight, the results were worse. Now, weight loss was also of benefit for people who used antiarrhythmic drugs or had ablation, with a similar gradation in terms of the amount of weight loss, suggesting that this is a dose-related impact on the incidence of AF.

Dr Mandrola: This did not affect AF burden alone. Other factors improved as well.

Dr Sanders: Many factors improved. We observed that most of the cardiometabolic risk factors improved with weight loss. This makes sense; these conditions coexist in most patients. We saw blood pressure improving to a greater degree if you lose more weight, and this was achieved with less use of antihypertensive drugs. Lipid profiles, glucose levels, and sleep apnea improved. Thus, we found that treating weight is treating all of these problems together.

Dr Mandrola: I believe it bears repeating. Did you say that blood pressures improved with less medicine?

Dr Sanders: Absolutely. The patients who lost more weight used less antihypertensive medication but had better blood pressure control. This suggests that it is not that we had a pool of patients who are simply more compliant who achieved this, but that we are seeing a biological change. We also saw loss of left ventricular hypertrophy and a dramatic reduction in the atrial size. This alters the impact for AF as well.

Dr Mandrola: So the heart actually changed?

Dr Sanders: The heart changes as a result of weight reduction.

Dr Mandrola: Your study also looked at weight fluctuation. What did you find?

Dr Sanders: One of our clinical observations was seeing a dramatic improvement in patients' symptoms when they lose weight, but then, when they gain a couple of kilos, fibrillation returns. The weight gain acts as a bit of a warning for the patient.

Having seen that, we decided to quantify this. We looked at the group who from year to year had a gain and a loss,
or a loss and a gain. This group did not have as good a success as those who sustained weight loss from year to year.

Unfortunately, most patients who lose weight do fluctuate in their weight. Thus, we need to ensure that patients sustain their weight loss and continue to lose when we design a weight management program, and we need to explain the importance of maintaining the weight loss. Patients who have symptomatic AF and have been able to lose this weight are a motivated group; we can easily incorporate this sort of information into their program.

Dr Mandrola: One special feature of your program is the weight loss clinic, and it is kind of special. Can you speak to that?

Dr Sanders: As electrophysiologists who see patients with symptomatic AF, we are dealing with a lot of material in terms of AF-specific treatment. To incorporate the entirety of weight and risk factor management into this discussion without losing the patient's focus is nearly impossible. I present a unified message to the patient, emphasizing the importance of these risk factors and weight. They then see my colleague, who runs a dedicated weight management and risk factor clinic; that is all they talk about in that clinic.

Initially, patients attend these clinics every 3 months. Patients can make more frequent appointments as required. As risk factors and symptoms begin to improve, they can attend more or less frequently, depending on when they need that help.

We work closely with the patient; it is one physician with one patient, and no specific props or aids are used. The program involves really getting to know your patients; motivating your patients in terms of understanding their diets and their exercise programs; and giving them goals that they can achieve. Working with the patients to set the goals is what enables them to achieve this.

Dr Mandrola: Yes. Providing goals is important.

Dr Sanders: It is very important. It involves motivational teaching, really. If you set a goal of losing 20 kilograms, this is unachievable. But if the goal is to lose a couple of kilograms by the next time you meet me, this is an achievable goal. If they have not achieved that goal, you can reassess their exercise and food diary to see where you can make differences. Together, you make these differences to facilitate achieving those goals.

We set a goal of about 3% reduction in weight over the first 3 months. If the patient does not achieve that, then we look at tightening that up in terms of diet; about 10% had to use meal replacements. But in general, patients do this with their own diet.

Dr Mandrola: Some colleagues think they need a clinic with waterfalls, massage therapists, and multiple teams of specialists, but your clinic is not like that is it.

Dr Sanders: No. Our clinic involves one physician seeing one patient. We use one-on-one goal setting, and getting to know your patient and the patient getting to know you. The question is whether this can now be replicated in multiple clinics. Perhaps we will need to involve allied professionals to be able to undertake this on a mass level. This needs to be evaluated on its own, and we are undertaking that currently.

Dr Mandrola: One of the biggest problems with weight loss is durability; your study spoke to that.

Dr Sanders: That was an important feature of the study. Most weight loss clinics find that people manage to lose weight, but they then put it back on. That has been a big negative. We found that patients who attend our dedicated weight reduction and risk factor management clinic are much more likely to keep that weight off over the 5-year period. In fact, 66% of people kept the weight off if they lost it in their first year, and 85% of them attended this clinic. The people who gained weight tended to be the ones who did not attend the clinic. I believe it is a question of continual reinforcement in this group that maintains that weight reduction.

Dr Mandrola: Explain the biological, mechanistic link as to why this weight reduction and risk factor reduction would reduce AF so significantly.
**Dr Sanders:** For a number of years, we have been documenting that many of these conditions—obesity, sleep apnea, hypertension—result in changes in the atria. It may be dilatation or fibrosis of the atria, resulting in some electrical changes especially concerning conduction, which allows fibrillation to form.

We had not realized that we may be able to reverse this change. We have been excited about the results of some of our studies. We have done preclinical studies in sheep\(^2, 3\) that show those changes in the atria when they put on weight; then, when the sheep lose weight, we were able to show the size of the atria decreasing, the pericardial fat volume disappearing, and scarring that had occurred in the atria disappearing. That was a tremendous finding that allowed us to speculate that perhaps by treating the primary cause, we could reverse the stress that had been put on the atria and reverse the scarring.

I believe that is what we are observing in the clinic. We have been able to transform people who have persistent AF into people who have only paroxysmal or no AF. This outcome may not only change how much we need to do for the patient, but also change entirely our approach to managing these patients as we go forward. The scarring disappearing is a dramatic finding for us.

**Dr Mandrola:** The old teaching is that scar never changes and once it is scarred it is too far gone, but your findings may change that view.

**Dr Sanders:** Absolutely. In part, this changes our understanding of what we have termed "scar." We are used to scarring in myocardial infarction, where the tissue is completely damaged. But this is different. I believe these risk factors cause a state of interstitial fibrosis rather than cellular death fibrosis. I believe the interstitium is an organ that can lay fibrous tissue and absorb it. That is what we are seeing. As the stress is taken away, the interstitial fibrosis disappears; it is absorbed.

**Dr Mandrola:** What do you say to the North American physician who responds that this cannot be done in North America?

**Dr Sanders:** This is crucial. Several years ago, data from the Mayo Clinic\(^4\) showed that by 2050, America will have 15 or 16 million people with AF. They suggest that it may go even higher than that. We may not have the resources at the moment to create these clinics, but we cannot afford not to create these clinics if we want to avoid the healthcare burden that will come from this.

**Dr Mandrola:** How has this changed your approach to the patient with AF, and how should it change my approach to the patient with AF?

**Dr Sanders:** It has certainly changed our approach. The important message to our patients is that this is a team sport. This is not something where patients will take a pill or have a procedure and get better. This is something that we have to work together to achieve. One of the motivating factors is for them to know that almost one half of the patients no longer needed to take medication or have a procedure. They can manage this on their own and make it go away. It is the remaining half that we may have to do something for, and even in that group, the results show that they are far better off if you treat both obesity and AF than targeting the AF with a pill.

**Dr Mandrola:** In your previous work, you have found that even in patients who have AF and undergo procedures, this weight management strategy improves AF ablation success.

**Dr Sanders:** Exactly. The ARREST-AF study\(^5\) was published at the end of 2014 and showed that single-procedure success and multiple-procedure success were diametrically improved if risk factors were modified at the same time. The ablation procedure is almost not worth doing if patients are not willing to attend to their risk factors. Those factors are the primary reason the patient developed AF in the first place. That is an important message for patients to understand in terms of taking ownership of managing this with us.

**Dr Mandrola:** Thank you for being with us.

I hope you enjoyed our interview with Dr Sanders and this remarkable study. I know that I have. I hope you too will take this new information into your practice.
References


© 2015 WebMD, LLC

Cite this article: LEGACY PI Throws Down the Gauntlet to US Physicians. Medscape. Apr 16, 2015.