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Title of Article: Behind the Valve: Small Device, Giants in Medicine
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Name of interviewee(s): Dr. Martin B. Leon, MD and Craig R. Smith, MD
The title and department affiliation of interviewee(s):

Dr. Martin B. Leon: Professor of Medicine at Columbia University Irving Medical Center, Chief Innovation Officer and the Director of the Cardiovascular Data Science Center for the Division of Cardiology, Founder and Chairman Emeritus of the Cardiovascular Research Foundation

Dr. Craig R. Smith: Chair, Department of Surgery, Surgeon-in-Chief, NewYork-Presbyterian Hospital / Columbia University Medical Center

In Rouen, France, 2002, Dr. Alain Cribier successfully completed a procedure that had long been thought impossible: he replaced a stenotic valve in his patient's heart by guiding a new one in using a thin wire threaded through his patient's body. A revolutionary procedure at the time, this technique known as transcatheter aortic valve replacement, or TAVR, has since became the standard of care for patients with aortic stenosis – a condition characterized by the narrowing and calcification of the three-leafed valve in the aorta. Treatment of aortic stenosis can be truly life changing. Whereas untreated aortic stenosis patients may feel severely short of breath, have chest pain, dizziness and even faint, with treatment all those symptoms may resolve. As a minimally invasive procedure, TAVR offers its recipients several advantages over the historic treatment of open-heart surgery: no chest incision and shorter hospitalization times to name a few. Most importantly though, in certain patient groups TAVR reduces postoperative mortality due to any cause by 20%. The only other therapy that has been able to achieve a similar outcome in terms of mortality reduction in cardiovascular disease is heart transplantation. The technique changed the face of medicine and, like many such developments, took a fair bit of patience and teamwork. But the creation of TAVR was also intimately tied to the stories of two doctors. One, Dr. Martin B. Leon, sought to improve on the shortcomings of cardiac surgery after an unsuccessful operation on a relative. Another, Dr. Craig Smith, had spent his career practicing that very same surgical specialty. Together, the unlikely pair worked together to bring a new device to the forefront of medicine.

Born and raised in Brooklyn, Dr. Leon had interest in medicine from a young age. After attending Yale for medical school and completing his residency and fellowship in cardiology there as well, Dr. Leon went down to Bethesda to do research at the NIH for nine years. It was there that Dr. Leon was exposed to some of the skills he would need in the future when developing TAVR. At the NIH, Dr. Leon got in on the ground floor on research with balloon angioplasty – the technique of using balloons to prop open narrowed blood vessels – which was a precursor therapy to TAVR. Perhaps even more important, as Dr. Leon explained in an interview, he learned how to be "an experimentalist" and how "to amass that survey of skill sets that would allow me to be effective" in taking a device from basic science research all the way to clinical trials. When asked why he chose to do research as opposed to only practicing clinical medicine like many other doctors do, Dr. Leon answered:

> In medical school I had role models, people I really respected…and they were great clinicians, but they also did research. They were looking forward, they were looking at different ways to approach things, which to a large extent is what research is…and clinical medicine follows the research, so the question is do you want to always be the clinical end-user, waiting for someone else to do the work, or do you want to be in the arena doing it yourself?

Dr. Leon also recounted that his interest in non-invasive heart valve treatments specifically came from personal experiences, from a more emotional and less "analytic" place. He explained that when he was younger a close relative of his had passed away after a routine coronary artery bypass surgery, which had left an impression on him: "I gravitated in my mind that if we

could do these things in a lesser [sic] invasive way…what exciting an impact that would have on patients, on families, on the entire healthcare system."

Dr. Leon offered similar observations of a patient he took care of during his rotation in cardiothoracic surgery in his second year of medical school. The patient was a young woman in her twenties with congenital aortic stenosis, who was operated on twice and almost died. Dr. Leon commented: "You know, as an impressionable medical student, you latch onto some of those key patients and I became very involved in her case. I got to know the family, got to know her, and I was really impressed with some of the things that we can and can't do with cardiac disease, and I became interested in aortic stenosis…but we didn't have any ways to treat it other than surgery." Dr. Leon subsequently became involved in the early technology to use balloons to open up aortic valves, but the technique had minimal success in treating the disease. It was during the "stent era" when they "began to dream that we could transplant an aortic bioprosthetic valve without opening the chest. And that was something that was thought to be completely out of this world, that we were crazy, totally crazy."

It was at this point that Dr. Leon began to collaborate with Dr. Alain Cribier and two other engineers, to form a company called Percutaneous Valve Technologies (PVT), with the declared goal of developing a catheter-based treatment for severe aortic stenosis in patients who are not candidates for surgery. At the onset, it was very difficult to find investors for the company, because "everybody thought [the project] was completely insane. They would list all the reasons why we would fail." So the group decided to personally invest a small amount of money, and they were able to develop a partnership with an engineering group in Israel that developed the prototype devices. They then began testing the newly invented balloon-expandable valves first in animals, and then in human cadavers. It was at this point that Dr. Leon described having an "Aha existential moment", that this could really work. Finally, in 2002 in France, the then-experimental valve was successfully implanted in a human using TAVR. Fifteen minutes after the patient woke up and was in stable condition, Dr. Cribier asked the million-dollar question: "What's next?"

What would follow was just as critical as the painstaking work of developing the new TAVR valves: a series of studies to test whether TAVR really worked for a wider range of patients. Much like any other new medical invention, one amazing success was not enough to prove TAVR's safety and efficacy – rigorous clinical trials were needed. And yet those studies would be difficult without the cooperation of cardiac surgeons, the very specialty that Dr. Leon had once left behind. Few were more prominent in the field than Dr. Craig Smith, the current Chair of the Department of Surgery at Columbia University, who became one of the principal investigators of the so-called PARTNER trials that compared TAVR to the standard of care for patients of increasingly lower surgical risk. Thus the PARTNER trials involved both cardiothoracic surgeons and cardiologists in its design and execution. This is even more interesting considering that TAVR was poised to divert a significant amount of business away from surgeons if it proved to be legitimate. In an interview, Dr. Smith described his motivation for joining the PARTNER studies. He explained that "a poorly set up clinical trial can give misleading results" so he wanted to make sure that an accurate and unbiased comparison was

being made between TAVR and the then gold-standard treatment, surgery, as he had personal experience with improperly run trials in the past. Dr. Smith criticized an unfortunate attitude among surgeons who were resistant to TAVR because it “encroached on their turf” so to speak, explaining that what’s best for the patient should always be a physician’s top priority, and not financial considerations. Dr. Smith advocated instead for a team-based approach, noting how the PARTNER trials, which ultimately showed TAVR to be equal to if not better than surgery in certain cases, also revealed how effective interdisciplinary collaboration can be. While there can often be a wall between departments at big hospital systems, Dr. Smith credited a “friendly rapport” between the departments of surgery and cardiology that he inherited when he became chair of the department at Columbia that allowed for his partnership with Dr. Leon to come about in the first place. When asked how one can create such a collaborative atmosphere at other institutions where it may unfortunately not be present, Dr. Smith answered: “with a carrot or a stick” – the carrot being a demonstration of the benefits of working together, like the creation of TAVR, and the stick being altering hospital or government guidelines so that departments must cooperate. The latter was actually also present in the development of TAVR, since both a surgeon and a cardiologist were needed as part of the “heart team” to sign off that a patient is a good candidate for the TAVR procedure. Dr. Leon also commented on the value of collaboration: “I think the TAVR story is a good story because it shows what a little luck and a lot of work and putting a good team together and committing to some proper clinical values, what can come out of that.”

The story of TAVR is the story of a long scientific journey, but also a story of success and failure, of doubt, of emotion, and of collaboration. Drs. Smith and Leon, the two co-principal investigators of the TAVR PARTNER trials, when asked what advice they would give others based on what they learned from TAVR, touched on a lot of these themes. Dr. Leon emphasized the value of working with others as a way to improve yourself: “You want to surround yourself with really smart people…and not feel threatened” by them as it’s a wonderful opportunity to gain “knowledge and experience.” Dr. Smith echoed this idea saying: “A’s surround themselves with A’s, B’s surround themselves with C’s.” Dr. Smith for his part also urged people to follow their passions in research, because you “can’t predict where the next groundbreaking idea will be.” Dr. Smith and Dr. Leon are two great examples of practicing what they preach. Though seemingly set up to be at odds, their stories and the story of TAVR proves what good can result when two brilliant scientists work together to push the boundaries of medicine forward.

Reference:

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