IMMREVIEW

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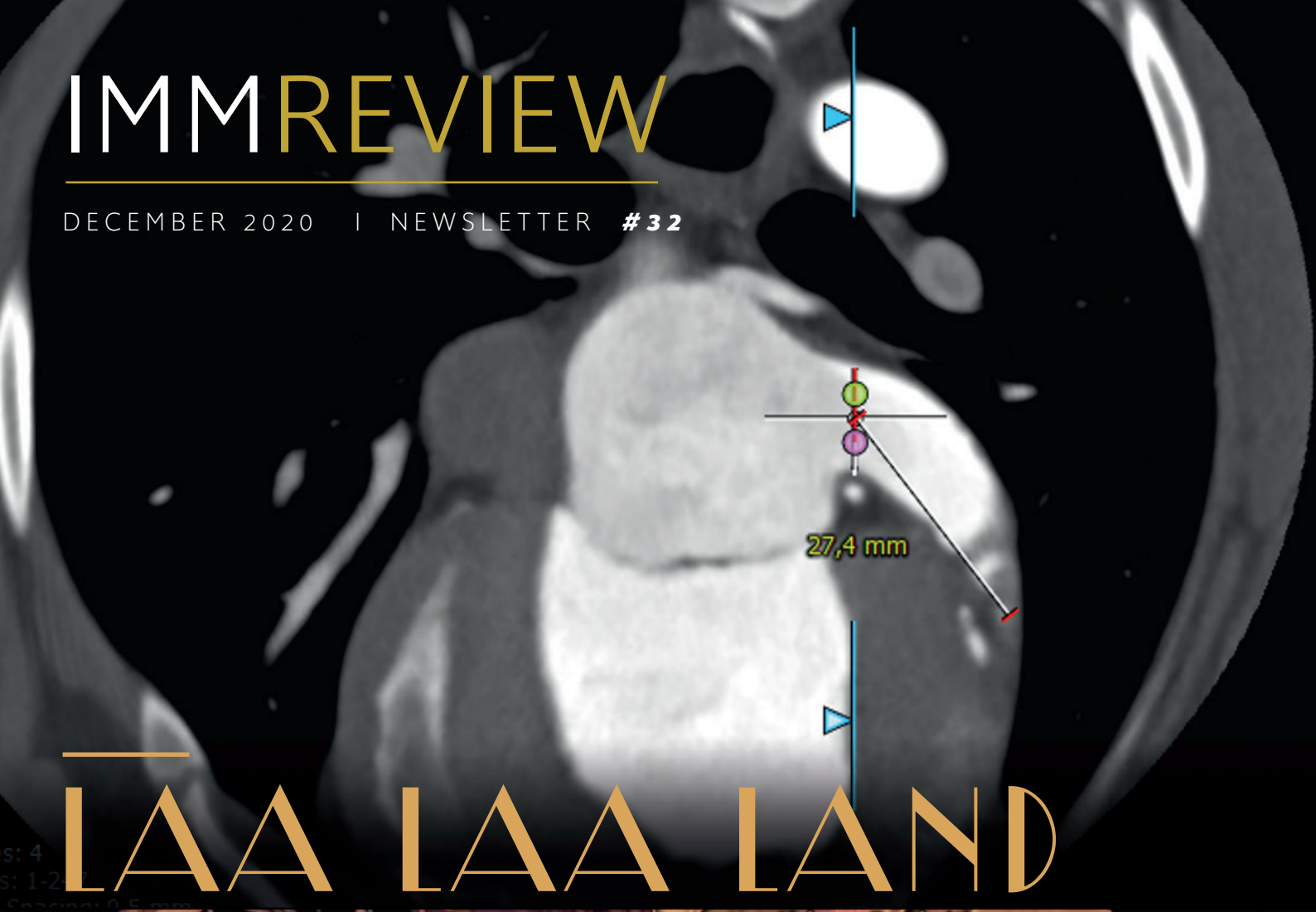


LAA LAA LAND

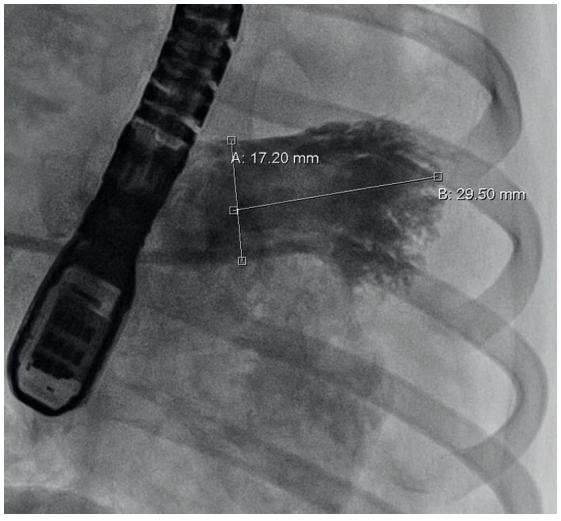
IMMR Accelerating your innovative research

Nicolas Borenstein, DVM, PhD
Scientific Director - Founding Partner - Board Member.

One of the joys of my work is to see how engineers and physicians from diverse backgrounds come up with different strategies to solve an unmet medical need. As regards transcatheter mitral valve replacement (TMVR) for instance, there are all sorts of ways to anchor or to deliver a stent on the complex mitral apparatus. It stands to reason that for an endeavor seemingly as straightforward as "plugging a hole," to fill or otherwise exclude the left atrial appendage (LAA), there would not be that many strategies. The fact is, there are. Many. All sorts of devices and techniques, with or without ablation, absorbable or not, from the inside of the heart or from the outside, etc.
We have been extremely busy with groups of different nationalities. It is an extremely dynamic and exciting landscape.

LAA LAA Land

Zachi Berger is a successful serial entrepreneur with whom we have worked for the past several months. He is currently the Founder and CEO of Append Medical operating at the MEDX Xelerator in Or Yehuda, Israel near Tel Aviv. We thought it would be great to hear his insights into the field of LAA exclusion. Since our collaboration began during the COVID pandemic, we also thought it would be interesting to ask him whether it was worth the effort to come to Paris under the circumstances.



Angiography of the canine left atrial appendage

Welcome Zachi. Would you please begin by describing what the left atrial appendage (LAA) is, and what clinical problem LAA exclusion is intended to address?

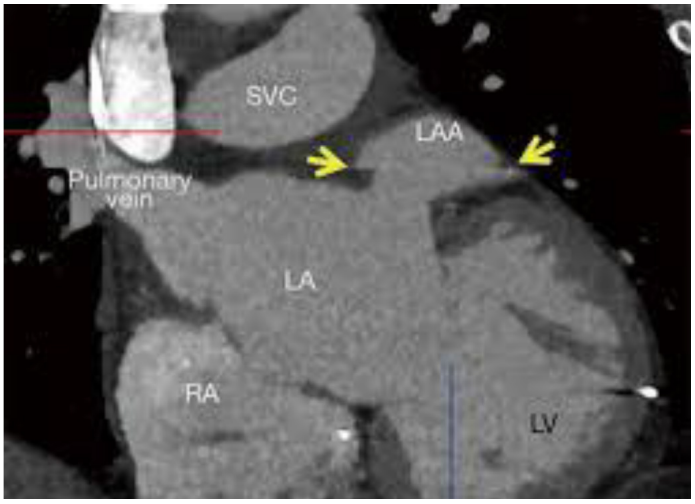
The LAA is a small sac-like structure off the left atrium of the heart. Research has shown that it can be a source of blood clots and thromboembolic stroke in patients with atrial fibrillation (AF). Exclusion of the LAA through percutaneous or surgical means has developed as a non-pharmacological strategy for preventing thromboembolic stroke in AF patients.

The market for LAA exclusion devices is young, with the Watchman device being approved just over 5 years ago. How has it grown, and what are the projections for future growth?

We believe that worldwide, the overall market is worth approximately US $25B, and that the addressable market opportunity may reach at least $10B. In 2019, the US market exceeded $500M, and market research suggests that from 2020 through 2027 it will grow at a compound annual growth rate (CAGR) of nearly 22%. LAA exclusion may be the second fastest growing segment of the cardiovascular medical device market after heart valve replacement and repair. The market is looking for something newer and simpler that will benefit both physicians and patients. There is currently a second generation of products, for example the Boston Scientific FLX and the new Abbott Amulet; J&J has WaveCrest in the pipeline, Gore is developing a device, as well as others. The number of companies working on solutions demonstrates that there is a need, and the market is huge.

As shown by Professor Horst Sievert and colleagues at TCT 2019, there are a plethora of companies developing endocardial, epicardial and surgical approaches to LAA exclusion. Are there still important limitations of existing technologies that need to be addressed?

My understanding from speaking with Professor Sievert and others is that procedures that use current devices remain complicated and time consuming, requiring multiple measurements and alignments, sometimes rivaling TAVR and other valve procedures in their complexity. In addition, there remains a small but significant ~2% residual stroke risk resulting from several factors, including device leakage (~3%) or device-related thromboembolism (DRT, ~2-3%). This is especially true of metallic devices on which thrombi can form. Additionally, in rare cases, the device itself can embolize.



MRI regular LAA LA view, ©Append Medical

OUR PROCEDURE DOES NOT REQUIRE MEASUREMENTS AND ALIGNMENTS AND CAN OFTEN BE PERFORMED WITHIN 30 MINUTES.

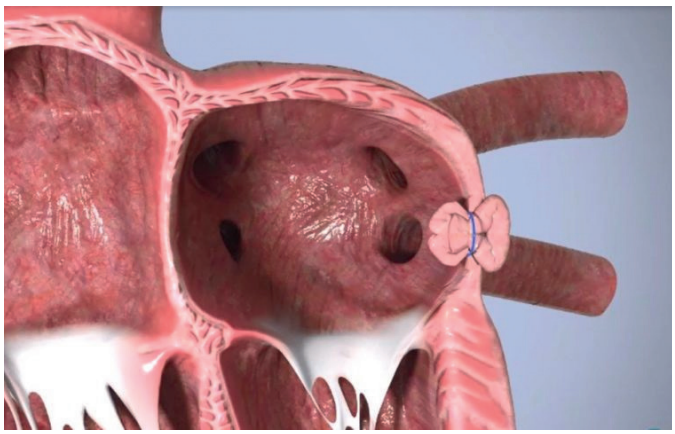
With these limitations in mind, what are some of the unique features of Append's Appligator system?

Our approach is straightforward and perhaps represents a new, third generation concept. During a transcatheter procedure, we invaginate the LAA into the left atrium and secure it with a suture. The LAA tissue is then promptly resorbed into the wall of the left atrium. Our procedure does not require measurements and alignments and can often be performed within 30 minutes. Our system can also avoid DRT because we do not leave any device in the heart, only the suture. As our solution was not the first in this market, we have the benefit of seeing the experience of others and what the market needs moving forward. We think our product is completely different from all other products in the LAA closure market, including those under development.

Is the Appligator an innovation of yours, and how did you go about setting up the company to develop it?

Append is based on an invention by Professor Leonid Sternik, the head of the cardiac surgery department at Sheba Medical Center. Professor Sternik and I co-founded Append Medical based on his invention, and for the past two and a half years have further developed the device as a portfolio company of MEDX Xelerator, a medical device and medtech incubator formed by Boston Scientific, The Sheba Medical Center, Intellectual Ventures and MEDX Ventures. >>>

Zachi Berger, Founder and CEO of Append Medical (Or Yehuda, Israel), which is developing an implant-free Left Atrial Appendage exclusion device. He shared with us his thoughts on the current landscape of LAA exclusion devices.



The Append Medical Appligator™ device, ©Append Medical

As originally described, the LAA invagination technique, originated by Professor Sternik, is performed during an open cardiac surgical procedure. We achieved proof of concept for the approach involving LAA exclusion through tissue manipulation. Two patients were treated successfully in Sheba Medical Center, and MRI scans demonstrated that the LAA was fully absorbed into the left atrium walls following the procedure.

We licensed the patent for this approach from the Sheba Medical Center with an eye towards developing it into a percutaneous, transvenous and transseptal system, and are preparing several additional patents of our own. The first patent was issued in the United States, Europe, and Israel; a second patent is in the National phase; a third one is in the PCT stage, and now we are filing a fourth patent for our newest concepts.

We have two outstanding engineering leaders, the R&D Manager Shay Raviv and Oded Meiri as a consultant, who are largely responsible for our substantial progress. We have a great team.

What are the considerations regarding animal model selection for preclinical evaluation of LAA exclusion technologies, and what has been your preclinical experience thus far?

The current recommendation from the FDA for GLP studies intends that regulatory approval should advance to human clinical evaluation using the canine model. This is because the LAA of a dog is the one that most resembles that of humans with respect to its size and shape. By contrast, pigs, sheep and other species have very different LAAs and left atria. For this reason, all of the LAA companies are developing devices by working with canines. Thus far we have performed a four-animal canine study at IMMR. This initially included two acute procedures and now we have two additional cases in chronic follow up currently up to 90 days post-procedure. The results thus far are very promising as the invaginated LAAs look as expected and we're monitoring their reabsorption.

ENTERING FRANCE DURING THE CORONAVIRUS PANDEMIC IS DIFFICULT, BUT THE IMMR TEAM HELPED GUIDE US THROUGH THE REGULATIONS. IMMR DEMONSTRATED EXCEPTIONAL KNOWLEDGE AND STRONG COLLABORATION THAT HELPED US MOVE FORWARD VERY QUICKLY. IN SHORT, YES, IT WAS WORTH THE TRIP.

What was it like to travel to Paris during the pandemic for these studies, and was it worth the effort to make the trip?

We flew to France twice during the coronavirus pandemic, once in March and the second time in September. On both occasions it was difficult to enter France due to travel restrictions, but the IMMR team helped guide us through the regulations. When we returned to Israel, we had to be in quarantine for two weeks, but it was worthwhile. IMMR demonstrated exceptional knowledge and strong collaboration that helped us move forward very quickly. Based on our collaboration, we derived some new concepts that refine the system to the point that it is potentially a whole new device, which we intend to develop further. In short, yes, it was worth the trip.

What's next for Append Medical?

We are moving forward towards a human clinical trial planned for 2022. We are also working towards regulatory submissions.

Zachi, it's been a pleasure speaking with you, and good luck for continued success!

Thank you very much.

Editor: Nicolas Borenstein
Photos: © Nicolas Borenstein

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