in-Silico TRials guide optimal stratification of ATrIal FIbrillation patients to Catheter Ablation vs pharmacological medicaTION: The i-STRATIFICATION Study

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Persistent atrial fibrillation (AF) patients show a 50% recurrence after pulmonary vein isolation (PVI), and no consensus is established for following treatment. The aim of our i-STRATICICATION study is to provide evidence for optimal stratification of recurrent AF patients to pharmacological versus ablation therapy, through in-silico trials in 800 virtual atria. The cohort presents variability in anatomy, electrophysiology, and tissue structure (low voltage areas, LVA), and is developed and validated against experimental and clinical data from ionic currents to ECG. AF maintenance is evaluated prior- and post-PVI, and atria with sustained arrhythmia after PVI are independently subjected to seven state-of-the-art treatments for AF (**Figure**).



Figure 1. Design of the i-STRATI-FICATION

study: Atria with sustained arrhythmia after PVI are independently subjected to two antiarrhythmic drugs and five catheter ablation strategies.

The results of the i-STRATICICATION study show that the right and left atrial volume dictate the success of ablation therapy in structurally-healthy atria (LVA<1%). On the other hand, LVA ablation, both in the right and left atrium, is required for atria presenting LVA remodeling and short refractoriness. This atrial refractoriness, mainly modulated by L-type Ca²⁺ current, I_{CaL}, and fast Na⁺ current, I_{Na}, determines the success of pharmacological therapy. Therefore, our study suggests the assessment of optimal treatment selection using the above-mentioned patient characteristics. This provides digital evidence to directly integrate human in-silico trials into clinical practice.