It is clear that the global burden of atrial fibrillation (AF) and its associated economic footprint in terms of healthcare utilization is rising exponentially.\textsuperscript{3} Cumulative evidence suggests that catheter ablation is superior to antiarrhythmic drugs in the management of paroxysmal and persistent AF in terms of improved quality of life, AF-free survival, and AF burden.\textsuperscript{2} It is hoped that catheter ablation may ultimately provide a long-lasting cure, at least in patients with paroxysmal AF (PAF). Despite this desire, the published literature on long-term outcomes, 3 to 6 years after pulmonary vein isolation (PVI) have reported only a modest single procedural efficacy of \(\approx 50\%\) in the absence of antiarrhythmic drugs.\textsuperscript{3,4}

In this context, the report by Gokoglan et al\textsuperscript{5} provides a timely opportunity for a discussion on the progress of catheter ablation of PAF. Uniquely, this is the first study of its kind that reports more than a decade of follow-up of 513 patients with drug-refractory PAF who underwent catheter ablation between 2000 and 2002 (time period chosen to allow 12-year follow-up). The authors report a single-procedure success rate of 58.7\% at 12 years and a multiprocedure success rate of 86.9\% after a mean of 1.4±0.6 procedures per patient. Of the patients with AF recurrence, approximately three quarters (156 patients) had a repeat procedure. The majority (118 patients or 76\% of the reablation cohort) underwent 2 ablation procedures (including the index ablation), 32 (20.1\%) patients underwent 3 procedures, and 6 (3.8\%) patients required 4 ablation procedures.

During the second procedure, the mechanism of AF recurrence was attributed to PV reconnection in 31\% and non-PV triggers in the remaining 69\% of patients. In patients in whom non-PV triggers were successfully identified, the majority were identified in the coronary sinus (59\% of all non-PV triggers), crista terminalis (22\%), interatrial septum (17\%), superior vena cava (13\%), and the left atrial appendage (10\%). Notably, no patient had PV conduction recovery beyond the second procedure. Indeed, the mechanism of AF recurrence was surmised to be new non-PV triggers in 92\% of patients in the third procedure (8\% because of previously identified non-PV triggers) and new non-PV triggers in all 6 patients in the fourth procedure. New sites for non-PV triggers were identified from left atrial appendage (73\%), coronary sinus (58\%), and interatrial septum (13\%). Some insightful data on the timing of AF recurrence were also reported. In patients who were AF free after 2 years and went on to experience a recurrence, just over one half experienced recurrence between 6 and 12 years, one third between 6 and 8 years and the remainder in 4 and 5 years after the index ablation. Importantly, age \(\geq 64\) years, left atrial (LA) diameter, female sex, and obesity (body mass index \(\geq 30\)) were independently associated with AF recurrence.

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It is critical that the representative patient population, time period of the study, ablation methodology, intraprocedural end points, and follow-up protocol be appropriately highlighted in the context of the efficacy of catheter ablation for PAF. It is well acknowledged that PVI is the sine qua non of contemporary ablation techniques with the greatest efficacy as a standalone procedure in patients with PAF.\textsuperscript{4} The past decade has seen profound evolution in techniques and technologies used to facilitate PVI from the initial reports of focal elimination of PV triggers,\textsuperscript{6} to empirical ostial PVI to wide area circumferential isolation\textsuperscript{7} facilitated by 3-dimensional mapping systems, intracardiac echocardiography, multipolar mapping catheters, electrophysiological and pharmacological provocation maneuvers to confirm PV isolation and to uncover dormant PV reconnection, elimination of non-PV foci and more recently, the use of contact force sensing catheters. The present study provides a timeline of the evolution of procedural practices among the operators in the study. By their own report, all patients had their index ablation (between 2000 and 2002) with an 8-mm nonirrigated or a 4-mm cooled-tip catheter, with open irrigation only incorporated after 2006, meaning that it was only available for patients during redo procedures. Because of this, there was considerable variability in power and tip temperature settings (8-mm catheter: tip temperature 55°C, power \(\leq 70\) W titrated to microbubble formation; 4-mm cooled tip: 35±7 W to maintain a target temperature of 35–40°C titrated to microbubble formation). This reduces the generalizability and applicability of the results to the contemporary era when most institutions around the world use open-irrigated catheters.

Achieving durable PVI is a key challenge and the mechanism of AF recurrence in the short run is overwhelmingly associated with electric reconnection of the PVs (>90\% of instances),\textsuperscript{6–10} with non-PV triggers incited as a major contributor in the presence of durably isolated PVs beyond \(\geq 2\) procedures.\textsuperscript{11} Commendably, only one third of patients undergoing repeat ablation had PV reconnection. Based on data in the present study, one would expect a long-term, single-procedure success rate of \(\approx 70\%\), at best, if all PVs remained isolated.
after the index procedure. The high rate of non-PV triggers seems to align with those of more recent studies, suggesting that non-PV foci may contribute to AF initiation identifiable at the index ablation.\textsuperscript{12,13} It is plausible that trigger ablation at the index procedure may have improved outcomes even further, as suggested recently.\textsuperscript{12,13}

Although the patient population recruited appears young with a typical incidence of hypertension (35%), obesity (30.6%), and little or no left atrial dilatation that is expected of PAF patients, atrial scar was present in one quarter of patients and mean left ventricular ejection fraction was 54.4±7.6%, suggesting at least some patients had structural remodeling, potentially contributing to AF triggers beyond the PVs in this population.\textsuperscript{14} The nonrandomized study design also leaves open the possibility that more extensive initial ablation may have contributed to a proarrhythmic substrate. The lesion set in all patients included antral PVI, left atrial posterior wall, and superior vena cava isolation facilitated by intracardiac echo and a circular mapping catheter with confirmation of entrance and exit blocks. In this hypothesis, triggers may have been created either within the border zones of atrial scar regions after ablation or by a secondary global effect induced by atrial remodeling from ablation-induced scar. Notably, single-procedure efficacy of 58.7% at 12 years is not dissimilar to that reported at 4 to 6 years in published literature,\textsuperscript{4} despite the wide lesion set deployed during the index ablation. It is unclear what impact trigger ablation would have at the index procedure because the majority emerged beyond 3 years after the index procedure, and it is thus theoretically possible that even further de novo triggers may evolve beyond the follow up of this study. Identification of factors that lead to a progressive atrial myopathy may thus be of greater importance in preventing AF progression. Indeed, the finding that obesity and left atrial diameter are independent predictors of AF recurrence highlights the crucial role of modifiable AF risk factors and their impact on AF outcomes.\textsuperscript{15}

Whether there was progression of such risk factors over the study time period and the potential influence of their management on long-term AF recurrence remain unknown.

It also seems that the techniques of predicting durable PVI at the index procedure have substantially evolved since the time period reported in the study. The authors used entrance and exit blocks for PVI. Indeed, entrance and exit blocks are frequently found before complete anatomic encircling, suggesting that they should not be sufficient end points alone for predicting durable PVI.\textsuperscript{16} Whether other intraprocedural markers for exposing ablation line gaps such as waiting time, adenosine, loss of pace, and exit blocks. In this hypothesis, triggers may have been created either within the border zones of atrial scar regions after ablation or by a secondary global effect induced by atrial remodeling from ablation-induced scar. Notably, single-procedure efficacy of 58.7% at 12 years is not dissimilar to that reported at 4 to 6 years in published literature,\textsuperscript{4} despite the wide lesion set deployed during the index ablation. It is unclear what impact trigger ablation would have at the index procedure because the majority emerged beyond 3 years after the index procedure, and it is thus theoretically possible that even further de novo triggers may evolve beyond the follow up of this study. Identification of factors that lead to a progressive atrial myopathy may thus be of greater importance in preventing AF progression. Indeed, the finding that obesity and left atrial diameter are independent predictors of AF recurrence highlights the crucial role of modifiable AF risk factors and their impact on AF outcomes.\textsuperscript{15}

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Follow-up intensity declined beyond the first year, where annual clinical examination and patient self-taught AF detection were predominantly used to detect recurrences. Intermittent rhythm monitoring is notably inferior to continuous monitoring and may not identify AF recurrence in a great proportion of patients\textsuperscript{18} or allow appropriate classification of the temporal persistence of AF.\textsuperscript{19} Hence results from the present study may have misclassified some of the patients as having paroxysmal AF (episodes lasting <7 days) before the index ablation and under-represented the true incidence of AF recurrences.

In conclusion, the study by Gokoglan et al\textsuperscript{5} is the largest of its kind reporting 12-year follow-up in >500 patients treated in the hands of experienced operators and provides an important insight into the evolution of the PVI procedure and the potential contribution of non-PV triggers for remote arrhythmia recurrences. It provides impetus that much further work is needed if we are to get beyond a 50% chance of success from a single procedure. For PVI, which is in its infancy compared with other established medical procedures, attempting decremental follow-up is invariably challenging and will incorporate heterogeneities that are both necessary and critical to the future refinement of the procedure. As the procedure evolves even further, so will our understanding of mechanism, end points and outcomes and only randomized comparisons will allow us to weigh important elements that might improve procedural efficacy.

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References


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