In contrast, there was a second subset of patients in whom the triggers and/or drivers of AF were not exclusively located in the PVs. In these patients, full defragmentation can theoretically be of interest. However, based on the positive results observed in the PVI-only group, it seems that patients with non-PV-dependent AF were significantly under-represented in this CHASE-AF (Randomized Catheter Ablation of Persist End Atrial Fibrillation Study) cohort. Accordingly, as the investigators acknowledged in this population, left atrial size was smaller than that in most persistent AF studies, and “short-duration persistent AF” was the rule, with most episodes lasting for less than a year, and time since diagnosis being less than 5 to 6 years. Atrial dilation and AF duration are known to be associated with a higher relapse rate, and thus, are likely to be associated with a more resistant persistent AF phenotype (3) due to structural and electrical atrial remodeling, which is non-PV-dependent.

Therefore, this study illustrates that persistent AF seems to be composed of 2 completely different patient populations: those with PV-dependent and non-PV-dependent AF. Until we are able to clearly identify them, research on the best approach to ablate persistent AF is clearly compromised, and all results will be very difficult to interpret.

The current classification for AF based on symptom and/or episode duration is clearly subjective and insufficient, and this study proves it is poorly associated with the underlying pathophysiological mechanisms. What is required is a more comprehensive AF classification scheme that takes into account multiple cardiovascular risk factors, including hypertension, diabetes, structural heart disease, lipid profile, body mass index, as well as specific electrophysiological (e.g., surface electrocardiographic parameters, endocardial voltage, and electrographic features) and structural phenotypes (e.g., left atrial pressure and/or compliance [4], fibrosis found on magnetic resonance imaging [5]) if validated across multiple centers, a low voltage area in atrial tissue on mapping, mitral valve disease, and left ventricular function) to facilitate stratification of AF phenotypes and identify key factors to determine therapeutic approaches, analogous to the CHA2DS2-Vasc scoring system.

Without such a systematic approach, we will continue to compare “apples with oranges” and fail to assess the true impact of different catheter-based and drug interventions, compromising our efforts to halt the progression of this epidemic. International registries of outcomes that incorporate agreed upon clinical, structural, and electrophysiological data, as well as documented procedural approaches, would be a step in the right direction to develop such a scoring system to predict clinical response to ablation.

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http://dx.doi.org/10.1016/j.jacc.2016.01.090

Please note: Dr. Lambiase has received educational grants from Boston Scientific. Dr. Providencia has reported that he has no relationships relevant to the contents of this paper to disclose.

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Atrial Fibrillation
Beyond the Pulmonary Veins

We read with great interest the results of CHASE-AF (CatHeter Ablation of perSistEnt Atrial Fibrillation) by Vogler et al. (1), who reported that in patients with persistent atrial fibrillation (AF), a strategy aimed at defragmenting the atria via pulmonary vein isolation (PVI), complex fractionated atrial electrograms ablation, and linear ablation resulted in similar arrhythmia-free outcomes compared to a PVI-only strategy. The authors should be commended for rigorously conducting this important study that attempts to address the unanswered question of what to ablate beyond the pulmonary veins in AF patients.

Particularly remarkable are the 25% of study patients (52 of 205) in whom AF terminated acutely with PVI only, which is higher than previously published rates of 8% to 16% (2). The authors provide no additional information about these
patients either in terms of differences in baseline characteristics or outcomes. These patients may represent an interesting population due to the mechanism by which their AF terminated, based on previous reports that coincidental elimination (e.g., via circumferential PVI) of rotors and localized AF-sustaining mechanisms may explain termination (3). Specifically, it would be informative to know whether AF terminated prior to isolation of the pulmonary vein (PV) (suggesting coincidental ablation of a localized source) or at the completion of PV isolation (suggesting PV-dependent AF).

The resounding message of CHASE-AF and similar studies is that more is not better with respect to AF ablation. Despite these elegant studies, electrophysiologists continue to seek guidance over what to target in 2 important AF patient populations: persistent AF and recurrent AF. Because recent published data shows that established ablation strategies including complex fractionated atrial electrograms ablation and linear lesions serve primarily to elevate complication risk without improving outcomes, it is incumbent upon future studies to evaluate in randomized fashion ablation strategies that evaluate alternative lesion sets versus those that target AF-sustaining mechanisms in these challenging patient subgroups.

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http://dx.doi.org/10.1016/j.jacc.2016.01.092

Please note: Dr. Krummen has received grant support from NIH and UCSD Clinical Translation Research Institute; has consulted for Topera (terminated >14 months ago); and has received EF fellowship support from Biotronik, Biosense-Webster, Boston Scientific, Medtronic, and St. Jude. Dr. Hsu has received honoraria from St. Jude Medical, Medtronic, and Biotronik; and has served on the advisory board for Janssen Pharmaceuticals and Bristol-Myers Squibb. Dr. Schricker has reported that he has no relationships relevant to the contents of this paper to disclose.

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**REPLY: Persistent Atrial Fibrillation**
**Time to Stop Comparing Apples With Oranges**

**Atrial Fibrillation**
**Beyond the Pulmonary Veins**

We thank Drs. Providencia and Lambiase and Dr. Schricker and colleagues for their important comments on our paper. We agree with them that choosing the optimal ablation strategy based on the currently existing classification of atrial fibrillation (AF) according to the latest European Heart Rhythm Association/European Society of Cardiology definition based on AF “phenotype” only is critical and of limited value. The cutoff value to distinguish between paroxysmal, persistent, long-standing persistent, and permanent AF is arbitrary and does not reflect the pathophysiology of AF, especially not of persistent AF. Selecting patients with persistent AF according to that definition does not result in a homogenous collective of persistent AF patients. Up to a quarter of patients (potentially even more) in a study by Tilz et al. (1) and approximately 60% in the CHASE-AF (CatHeter Ablation of perSistEnt Atrial Fibrillation) trial turned out to benefit from pulmonary vein (PV) isolation (PVI) (“PV-dependent persAF”) alone after a follow-up of 12 months and even after a follow-up of up to 5 years. These patients remained in sinus rhythm after direct current cardioversion following PVI. It is even more remarkable – as stated by Dr. Schricker – that AF terminated in 25% of the study patients prior to or at the completion of PVI (which occurred in either case). We agree with Dr. Schricker that these patients are an interesting population and deserve focused further research for improvement of patient selection.

We will obviously not be able to demonstrate a benefit of additional ablation strategies like the step-wise approach or newer techniques in persistent AF as long as a significant amount of our so-called persistent AF patients are suffering from a “PV-dependent form of AF” and as long as we do not completely understand the underlying pathophysiology. This might be a reason why we failed to demonstrate a benefit of the stepwise approach, although we tried to overcome that problem by excluding patients with termination of AF during PVI. Patient selection prior to the procedure based on AF duration, the type of persistent AF (primary persistent AF versus secondary persistent AF [2]), left atrial size, function, and fibrosis, risk factors of AF and potentially electrophysiological criteria will be crucial in the future. International registries—as proposed by Dr. Providencia and Dr. Lambiase—as