Reviewer 1

To the authors, the manuscript is well written and highlights a popular topic with AF recurrence after pulmonary vein isolation.

We appreciate the comments of the reviewer.

Reviewer 2

1. The authors state that "Although many studies have assessed predictors of AF recurrence after ablation, predictors of need for repeat ablation have been less well studied". I do not really agree with this statement since the predictors of AF recurrence are also predictors for repeat procedures.

We appreciate the reviewer's comment and agree that the sentence could be misleading. We have modified the sentence in the manuscript as follows (lines 106-107): "Although many studies have assessed predictors of AF recurrence after ablation, it is unclear whether there are additional relevant predictors of need for repeat ablation."

2. **Please add a brief description of AF ablation procedure in Methods. How many patients underwent substrate modification? Which is your approach in these cases (CFAEs, lines)?**

We appreciate the reviewer's comment, and have added the following to the manuscript (lines 175-178): "In addition to PV isolation, 101 (31%) patients underwent additional substrate modification during the initial procedure, including 79 patients who underwent linear lesions (either mitral annulus or LA roof) and 55 patients who had LA complex fractionated atrial electrograms (CFAEs) ablated." We have also clarified in the Methods section (lines 135-136) that pulmonary vein isolation was the goal of all procedures with additional substrate modification performed at operator discretion.

3. How do you explain the high incidence of organized atrial tachycardias (39%) in repeat procedures?

It has been well established that more extensive LA ablation, including substrate based lesions, increase the risk of ATs. Although studies have demonstrated a wide range of AT incidence after AF ablation, index procedures which include linear lesions and CFAE ablation have demonstrated an AT incidence of as high as 40% (Saghy L et al. *Curr Cardiol Rev*. 2015 May;11(2):149-156). Therefore, the incidence of AT likely reflects the frequency of substrate based lesions during the initial procedure.

4. How many patients in repeat procedures displayed all veins isolated? Please provide data in this group of patients. The percentage of an extra-PV focus should be reported.

We have added the following to lines 210-215 of the manuscript:

"Of the 142 patients in the repeat ablation group, 96 (68%) required PV touch-up lesions during the second ablation. Patients who required touchup lesions were more likely to have larger left inferior pulmonary vein diameter on MRI before initial ablation (19.1 +/- 5.7 vs. 17.5 +/- 3.0 mm, p=0.045). Sizes of the other PVs were not significantly different between those who did and did not require PV touch-up at the second procedure".

5. The authors do not report data regarding ATs (mitral flutter, roof flutter, peri-PV ATs, reentries or focal sources). This is important since non-PV ATs are irrelevant to the anatomy of the PVs. On the contrary, non-PV ATs are possibly related to substrate modification.

Of the patients in the repeat ablation group, 61% of the repeat ablations were performed primarily for recurrent atrial fibrillation. The remaining patients underwent repeat ablation primary for organized atrial tachycardias, as we note in lines 165-167 of the manuscript.

Interestingly, there was not a significant correlation between presentation with organized atrial tachycardia at repeat ablation and need for PV touchup at repeat ablation: 32/54 (59%) patients with AT needed PV touchup vs. 64/88 (72%) of patients without AT at repeat ablation needed PV touchup (p=0.10). We routinely perform re-isolation of the PVs at the time of repeat procedures even among those presenting primarily with organized ATs. As detailed in the response to point #3 above, the use of substrate modification at the time of initial ablation likely contributed to the incidence of ATs noted at the

time of repeat procedures. However, although non-PV ATs are a frequent result of substrate modification, it is also well recognized that gaps in PVI lesions may contribute to ATs and therefore, we felt it reasonable to assess correlations in PV anatomy regardless of whether redo procedures were performed primarily for AT or AF.

6. Study design is problematic. Mixed population with paroxysmal and persistent AF underwent different ablation strategies (PVI with or without substrate modification, RF vs Cryo). Many of these patients displayed recurrence of AT and not AF. As stated above AT recurrence is mainly related to substrate modification. It would be more proper to include paroxysmal AF patients with PVI and not substrate modification for the purpose of this study.

Among patients with persistent AF (n=73), there was no statistically significant difference in any of the PV diameters between patients with single ablation (n=38) and those with redo ablation (n=35). If these patients are excluded (*i.e.* only the paroxysmal AF patients are included), the PV size difference is larger between single and redo ablation patients compared to the full population (RSPV: 18.9 +/- 3.9 vs. 21.5 +/- 4.5 $p<0.01$; RIPV: 17.9 +/- 3.6 vs.19.7 +/- 6.5 $p=0.02$; LSPV: 17.3 +/- 3.4 vs. 18.8 +/- 2.8 $p<0.01$; LIPV: 16.6 +/- 2.8 vs. 18.5 +/- 5.7 $p<0.01$).

As we note in the response to point #5, nearly 60% of patients who presented with AT at repeat ablation, also had at least one PV reconnection, so if the patients with AT recurrence were excluded, we would also exclude a large number of patients who required PV touchup lesions at repeat ablation.

As detailed above given that ATs may also result in gaps in PVI lesions and that many patients presenting with ATs may require PV touch up, we chose to include a broad spectrum of paroxysmal and persistent patients with and without substrate modification in this analysis.

Reviewer 3

Many thanks for asking me to review this observational study that investigated patient and MRI Predictors of the need for repeat atrial fibrillation ablation. The authors found that increased pulmonary vein size was predictive for the need for repeat AF ablation. However this prediction was only statistically significant for the right upper pulmonary vein. However, there was huge heterogeneity in PV diameters such that a cut-off that could be used to be clinically useful to predict increased AF redo ablation could not be identified. They noted that a 1mm millimeter increase in PV diameter was associated with an approximately 5-10% increased risk of requiring repeat procedures Overall the manuscript was well written and was very easy to follow. However, I have a number of additional comments that I would like to make.

1. I feel the title could be far more precise than it is at present. A much better title would be something like 'MRI and Clinical predictors of the need for repeat atrial fibrillation ablation'.

We appreciate the author's suggestion, and have changed the title to "Clinical and anatomic predictors of need for repeat atrial fibrillation ablation."

2. The authors cited the previous study by Hauser TH, Essebag V, Baldessin F et al where Larger PV size on MRI was found to be independently associated with an increased risk of late AF recurrent after PV isolation However the authors do not cite of the data from CT cross sectional imaging studies such as the two references below for example: Hof I1, Chilukuri K, Arbab-Zadeh A, Scherr D, Dalal D, Nazarian S, Henrikson C, Spragg D, Berger R, Marine J, Calkins H.Does left atrial volume and pulmonary venous anatomy predict the outcome of catheter ablation of atrial fibrillation? J Cardiovasc Electrophysiol. 2009 Sep;20(9):1005-10. For example Stabile G1, Anselmino M2, Soldati E3, De Ruvo E4, Solimene F5, Iuliano A6, Sciarra L4, Bongiorni MG3, Calò L4, Gaita F2. Effect of left atrial volume and pulmonary vein anatomy on outcome of nMARQ? catheter ablation of paroxysmal atrial fibrillation. J Interv Card Electrophysiol. 2016 Oct 6. The data obtained from CT studies looking into PV diameter should be quoted especially as CT provides better image acquisition of the PVs especially as some of these studies were negative failed to show a link between PV anatomy and AF recurrence.

As suggested by the reviewer, we have added reference to these CT based imaging studies and have also highlighted the fact that these prior studies assessed primarily PV anatomic variants rather than specific features of PV size. We have added the following to the Discussion section:

Previous studies have assessed anatomic predictors of AF recurrence after ablation. Two studies which used pre-ablation CT to characterize PV and LA anatomy found that anomalous PV anatomy (e.g. presence of left common PV trunk or presence of middle accessory PVs) was not correlated with procedure outcome (Hof 2009, Stabile 2016). To our knowledge, only one other study investigated the effect of PV size (Hauser 2015). Our findings corroborate the results of Hauser et al. who reported that patients with at least one PV ostial area larger than 461 mm2 were more likely to have early recurrence of AF and those with at least one PV area larger than 371 mm2 were more likely to have late recurrence.

3. It is a huge shame that the authors provide the data on redo ablation as the end point which is highly subjective and not data on the actual AF recurrence rate. Whilst I appreciate that they have cited this as a limitation and the reasons explained however I feel that basic information on the early AF rate for the population should identified and the link between PV diameter and AF recurrence should be provided to strengthen the hypothesis. This additional data should be provided if available.

We appreciate the author's point, and admit that this is a major limitation of our paper. As we point out in the manuscript, we did not report AF recurrence as and endpoint because our ability to monitor for AF improved for patients who had ablations more recently. However, when we use the recurrence data that we do have along with need for DC cardioversion after initial ablation as a combined endpoint (n=116

patients, 35% of total cohort), RIPV was numerically larger in the group who either had AF recurrence or required DC cardioversion (19.5 +/- 6.4 vs. 18.2 +/- 3.4; p=0.07), although this approached but did not reach statistical significance. Other PV diameters were not significantly different across groups.

Given the limitations of ascertainment for AF recurrence that we outline in the Limitations section, we do not believe the data on AF recurrence is reliable and have chosen not to include it in the manuscript. However, the trend toward larger RIPV size in those with AF recurrence is supportive of our primary findings.

4. Pulmonary vein diameters is not something typically provided on an MRI. Hence was there any blinding of the MRI results to the outcomes?

We have an institutional practice which routinely reports PV ostial diameter as part of the clinical MRI report. This was initially put in place to monitor for PV stenosis after ablation. Therefore, all PV sizes were reported as part of clinical care.

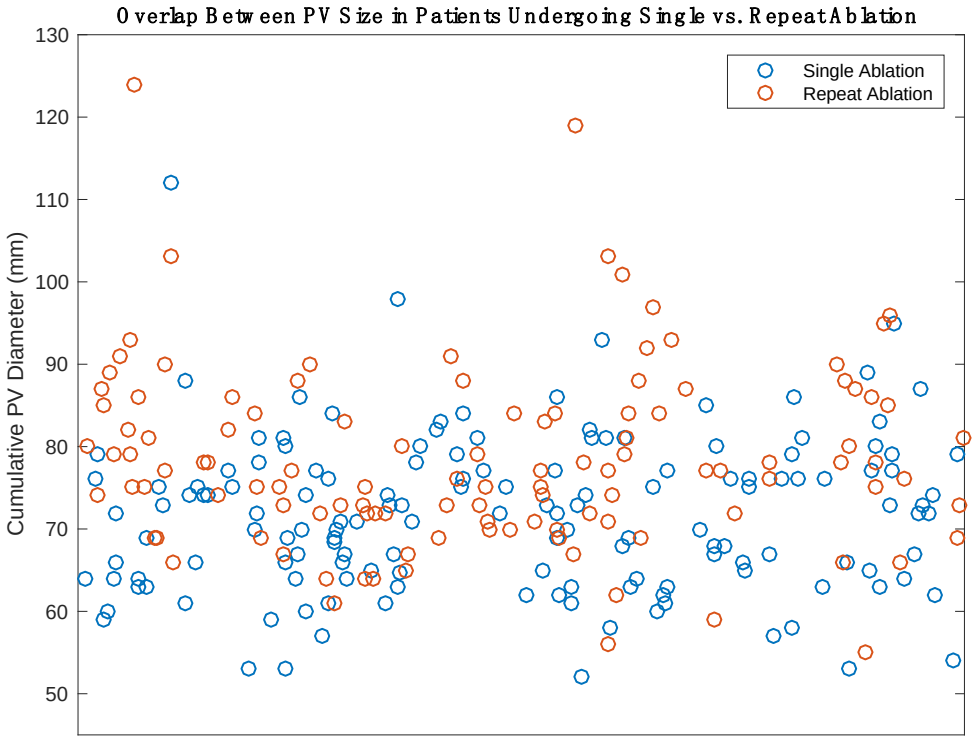
5. I appreciate the PV diameter was numerically higher for all 4 of the PVs among the recurrence group but was only significant for the right upper on multivariate analysis. The authors should additionally document the cumulative diameter for the 4 PVs in the recurrence vs non recurrence group as this would provide a stronger proof of concept as this way they may even be able to derive a more reliable cut off.

We thank the reviewer for this suggestion, and have added this information to the manuscript in lines 207-209. Cumulative PV diameter was significantly larger in patients who required repeat ablation: 78.5 +/- 11.2 mm vs. 71.6 +/- 9.5 mm ($p<0.01$), although, unfortunately, there was still significant overlap in size compared with those with single ablation, making it difficult to derive a better cutoff (see figure below).

6. The correlations between the LA size and PV diameter were really very weak and whilst statistically significant at an R2 of between 0.02 and 0.7 are really very low.

We agree with the author that the correlations are very, very weak. This could suggest that larger PV ostial size in the repeat ablation group was not simply a reflection of larger LA size, and could instead reflect increased AF substrate in the veins. As we discuss in the Discussion section (lines 322-326), the relationship between LA size and PV diameter has been inconsistent in prior studies and a clear direct relationship has not been consistently demonstrated.

Figure:


Overlap Between PV Size in Patients Undergoing Single vs. Repeat Ablation
Single Ablation
Repeat Ablation
Cumulative PV Diameter (mm)
130
120
110
100
90
80
70
60
50