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RESEARCH ARTICLE

The interaction between atrial fibrillation and mitral regurgitation: Insights from the CABANA randomized clinical trial

Sebastiaan Dhont[1,2], Philippe B. Bertrand[1,2], Jonas Erzeel[1,2], Sébastien Deferm[1,2], Laurent Pison[1,2], Pieter M. Vandervoort[1,2], Wilfried Mullens[1,2], W.H. Wilson Tang[3,4]* 𝕏, and Pieter Martens[1,2]

[1]Department of Cardiology, Ziekenhuis Oost-Limburg A.V, Genk, Belgium; [2]Hasselt University, Diepenbeek, Belgium; [3]Cardiovascular and Metabolic Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA; and [4]Kaufman Center for Heart Failure Treatment and Recovery, Department of Cardiovascular Medicine, Heart Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, OH, USA

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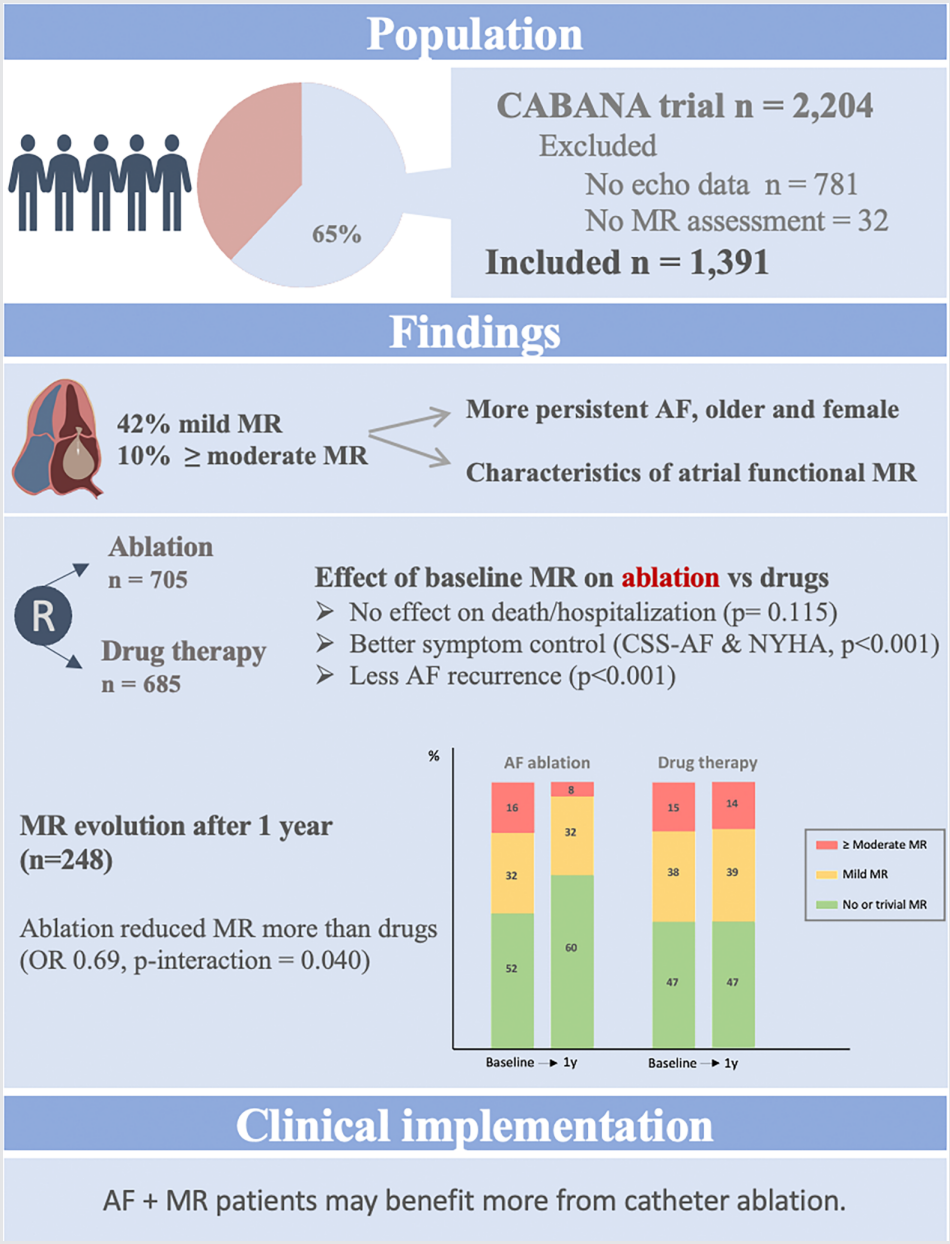
Aims Atrial fibrillation (AF) and mitral regurgitation (MR) frequently coexist. While catheter ablation is a key rhythm-control strategy in AF, its impact on MR severity remains uncertain. This study evaluates the effects of catheter ablation on AF recurrence, functional status, and MR progression in patients with AF and baseline MR.

Methods and results This sub-analysis included 1423 patients (65% of the overall CABANA cohort) with available baseline echocardiography. Participants were randomized to catheter ablation or pharmacological therapy. The primary endpoint was the composite of all-cause mortality and cardiovascular hospitalization. Secondary endpoints included AF recurrence, changes in MR severity, and functional status. At baseline, 722 patients (52%) had MR, including 582 with mild and 140 with ≥moderate MR, with characteristics suggestive of an atrial functional mechanism. Catheter ablation significantly reduced AF recurrence compared to pharmacological therapy (odds ratio [OR] 0.56, 95% confidence interval [CI] 0.50–0.62, $p < 0.001$). The presence or absence of MR did not interact with randomization in terms of its neutral effect on all-cause mortality and cardiovascular hospitalization (p for interaction = 0.115). Baseline MR increased the risk of AF recurrence (OR 1.46, 95% CI 1.40–1.74, $p < 0.001$). However, the benefit of ablation on functional status was greater in patients with MR compared to those without (p for interaction < 0.001). Follow-up echocardiography ($n = 248$) showed a greater reduction in MR severity in the ablation group versus drug therapy (p for interaction = 0.040).

Conclusion Catheter ablation was superior to pharmacological therapy in rhythm control and may reduce MR severity over time. These findings highlight ablation's potential structural and symptomatic benefits, pending specifically designed clinical trials.

*Corresponding author. Kaufman Center for Heart Failure Treatment and Recovery, Department of Cardiovascular Medicine, Heart Vascular and Thoracic Institute, 9500 Euclid Avenue, Desk J3-4, Cleveland Clinic, Cleveland, OH 44195, USA. Tel: +1 216 444-2121, Fax: +1 216 445-6165, Email: tangw@ccf.org

Graphical Abstract



Effects of baseline mitral regurgitation in the CABANA trial: randomization to catheter ablation versus drug therapy in patients with atrial fibrillation. AF, atrial fibrillation; CCS, Canadian Cardiovascular Society; MR, mitral regurgitation; NYHA, New York Heart Association; OR, odds ratio.

Keywords Atrial fibrillation • CABANA trial • Catheter ablation • Mitral regurgitation

Introduction

The functioning of the mitral valve is an intricate process that depends not only on the structural integrity of its leaflets but also on the coordinated involvement of its supportive apparatus, which includes the chordae tendineae, papillary muscles, left ventricle, and mitral annulus.[1,2] Mitral regurgitation (MR) may result from intrinsic leaflet pathology (primary or organic MR) or secondary to alterations in these supporting structures (secondary or functional MR). The regurgitant volume adds an additional load to the left

atrium and ventricle, which contributes to increased morbidity and mortality, even in cases of mild MR.[3,4]

While the association between functional MR and reduced left ventricular (LV) function is well-established, the emergence of MR as a consequence of left atrial (LA) remodelling has only recently been recognized.[5–7] This subtype, termed atrial functional MR, is frequently observed in patients with heart failure with preserved ejection fraction (HFpEF) or atrial fibrillation (AF)—two intertwined diseases that are both on the rise due to overlapping risk factors.[8] Current therapeutic approaches for atrial functional MR, however, remain insufficiently validated.[9]

Mitral regurgitation is a known precipitant of AF and significantly increases the risk of its recurrence, while AF itself can initiate or worsen atrial functional MR, establishing a bidirectional relationship.[10–12] Although growing evidence supports (early) rhythm control as an effective strategy in AF management, the presence of MR poses unique challenges.[13] Observational data suggest that rhythm control is associated with a lesser degree of MR.[14,15] Postulated mechanisms include the pre-systolic atrial contraction in sinus rhythm improving proper systolic mitral valve closure, and preventing further atrial remodelling over time.[16,17] However, there is a pressing need for randomized controlled trials (which inherently eliminate residual confounding) to investigate the impact of rhythm control for patients with AF and MR, particularly regarding its effects on MR progression and the success of attaining sinus rhythm. This sub-analysis of the CABANA trial therefore aims to assess the efficacy of AF ablation versus drug therapy in patients with versus without MR, while also examining the temporal evolution of MR across both randomization arms.

Methods

Trial design and patient population

The design and results of the CABANA randomized trial (NCT00911508) have been published previously, involving 126 centres in 10 different countries.[18] Briefly, patients aged 65 years or older, or those under 65 with at least one stroke risk factor (hypertension, heart failure, history of stroke, diabetes, or other cardiovascular conditions), were eligible for inclusion if they had experienced two or more episodes of paroxysmal AF or a single episode of persistent AF in the previous 6 months. Exclusion criteria included prior AF ablation or failure of two or more antiarrhythmic medications. Ethical approval for the trial was obtained from the institutional review board or ethics committee at each participating site, and all participants provided written informed consent. Access to the CABANA trial data was granted through the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). This trial was funded by grants awarded by the National Institutes of Health and adheres to the Declaration of Helsinki and complies with the STROBE guidelines for randomized controlled trials.

Intervention

Participants in the CABANA trial were randomly assigned in a 1:1 ratio (permuted block with stratification by clinical site) to undergo either AF ablation or drug therapy. Randomization was accomplished using a centralized, interactive voice response and web-based randomization system (IXRS; Almac). The block size (concealed from investigators) was randomly selected with equal probability between 2 and 4. The primary objective in the AF ablation arm was to eliminate AF. In the drug therapy arm, patients initially underwent rate control, aiming to achieve a resting heart rate of <80 bpm and an exercise heart rate (measured during a 6-min walk test or Holter monitoring) of <110 bpm. If these rate control targets were not met, or if patients experienced symptoms despite achieving the target rates, rhythm control could be pursued using antiarrhythmic drugs (the choice of which was based on the patient's specific profile). Cardioversion to sinus rhythm was performed if deemed necessary. In the AF ablation arm, patients underwent pulmonary vein isolation. The choice of the guiding system, as well as any additional ablation strategies beyond pulmonary vein isolation, was left to the discretion of the treating physician.

Assessment of mitral regurgitation

Although not required by protocol, baseline standard two-dimensional transthoracic echocardiography was highly recommended prior to enrolment. Data were collected electronically following a standardized clinical assessment. Measurements of chamber size and function were obtained where possible. Valvular disease was recorded in a binary manner (presence or absence), and if present, the severity was further assessed (categorized as mild, moderate, moderate to severe, or severe) using a multiparametric approach. LA size was measured both in the anterior–posterior direction in the parasternal long-axis view and in biplane views in the 4-chamber and 2-chamber views where possible. The latter measurements were normalized to body surface area to calculate indexed LA volume. No central echocardiography core lab analysis was performed in the CABANA trial; all echocardiographic data used in this analysis were site-reported. Echocardiographers were not blinded to treatment allocation, consistent with the open-label design of the trial. After randomization, sites were encouraged to provide follow-up echocardiographic data at 3-month intervals, enabling regular assessment of echocardiographic parameters.

Endpoints

To assess the impact of AF ablation in patients with and without MR, relevant cardiovascular endpoints were selected in alignment with the original design of the CABANA trial. The endpoints for this sub-analysis were the composite risk of cardiovascular hospitalization and all-cause mortality, the risk of AF recurrence during follow-up, the patient-reported functional status (New York Heart Association [NYHA] class and Canadian Cardiovascular Society [CCS] severity of AF) and the evolution of MR during follow-up based on the randomization group where applicable. All events were reviewed and adjudicated in a blinded fashion by an independent clinical events committee using prospectively determined event definitions.

Statistical analysis

Baseline characteristics were presented as means with standard deviations, medians with interquartile ranges (25th–75th percentile), or as counts and percentages. These variables were analysed using the independent samples *t*-test, Mann–Whitney U test, or χ^2 test, depending on the data type. The combined endpoint of all-cause mortality and cardiovascular hospitalization was assessed through a time-to-first-event analysis using a Cox proportional hazards model,

incorporating treatment group and its interaction with baseline MR to estimate hazard ratios (HR) with 95% confidence intervals (CI) and to report the interaction p-value. AF recurrence during follow-up, a binary outcome, was analysed using a generalized linear mixed model, which accounts for repeated measures. This model included a fixed treatment effect and random intercept to estimate odds ratios (OR) with 95% CI. Baseline MR was entered as a fixed interaction term in the model to evaluate the interaction with treatment assignment. The progression of MR over time and the patient-reported functional status was similarly analysed using a linear mixed effect model for repeated measurements, including a fixed treatment effect and the interaction with baseline MR and a random intercept. Secondary analyses were exploratory in nature, as no multiplicity adjustments were applied. Hypothesis testing was two-sided with a significance level of $\alpha = 0.05$. All analyses adhered to the intention-to-treat principle and were performed using SPSS version 25.

Results

Patient population

The CABANA trial included a total of 2204 participants between November 2009 and April 2016, of whom 1423 (65%) had documented baseline echocardiography assessment and were included in this sub-analysis. This rate is consistent with the CABANA protocol, which recommended—but did not require—echocardiography as part of routine pre-enrolment evaluations. An additional 32 patients were excluded due to missing data on MR assessment. Of the remaining 1391 patients, 706 (51%) were randomized to AF ablation and 685 (49%) to drug therapy. At baseline, 722 patients (52%) had more than trivial MR. Of these, 582 had mild MR, while 140 had ≥ moderate MR (124 moderate, 10 moderate-to-severe, and 6 severe MR). Furthermore, 580 patients (42%) had paroxysmal AF while the other patients had long-standing or persistent AF. The prevalence of paroxysmal AF decreased with increasing MR severity, occurring in 47% of patients with no or trivial MR, 39% of patients with mild MR, and 26% of patients with moderate or greater MR ($p < 0.001$) (*Figure 1*).

Characteristics according to mitral regurgitation severity

The baseline clinical characteristics, stratified by MR severity, are presented in *Table 1*. Patients with increasing MR severity were generally older and more frequently female. Other differences were minimal, with comparable rates of obesity, H_2FPEF scores, and comorbidities between groups. Additionally, no differences in baseline symptoms were observed, as measured by NYHA class. Echocardiographic findings revealed that patients with more severe MR had in general a slightly lower LV ejection fraction, larger left and right atria, without significant differences in LV hypertrophy or diastolic dysfunction. Notably, patients with ≥ moderate MR showed a trend toward increased all-cause mortality, regardless of the treatment randomization (HR 1.9, 95% CI 0.95–3.64, $p = 0.072$).

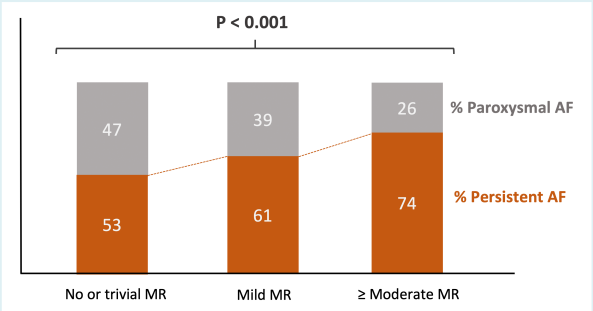


Figure 1 Percentage of persistent or long-standing versus paroxysmal atrial fibrillation (AF) by mitral regurgitation (MR) severity.

Predictors of mitral regurgitation

Results of the univariate and multivariate analyses assessing the variables associated with the presence of MR are shown in *Table 2*. In the univariate analysis, factors significantly associated with the presence of MR included increasing age (OR 1.02, 95% CI 1.00–1.03, $p = 0.021$), indexed LA volume (OR 1.05, 95% CI 1.03–1.07, $p < 0.001$), female sex (OR 1.34, 95% CI 1.08–1.67, $p = 0.008$), increasing RA size (OR 1.48, 95% CI 1.31–1.67, $p < 0.001$), and persistent AF (OR 1.48, 95% CI 1.26–1.75, $p < 0.001$). There was a marginal protective association with BMI (OR 0.98, 95% CI 0.96–1.00, $p = 0.042$). In multivariate analysis, only increasing age (OR 1.05, 95% CI 1.02–1.09, $p = 0.003$), indexed LA volume (OR 1.05 95% CI 1.03–1.07, $p < 0.001$) and persistent AF (OR 1.52, 95% CI 1.01–2.30, $p = 0.047$) remained independently associated with MR as well-known risk factors for atrial functional MR.

Effect of atrial fibrillation ablation on outcome according to mitral regurgitation status

Over a median follow-up of 4 (2.5–5.2) years, there were 365 primary outcome events (52%) in the group randomized to AF ablation (337 hospitalizations and 28 mortality events), compared to 404 events (59%) in the group randomized to drug therapy (362 hospitalizations and 42 mortality events). Randomization to AF ablation showed a non-significant protective effect on the composite endpoint (time to first event analysis: HR 0.88, 95% CI 0.76–1.01, $p = 0.073$). The presence or absence of MR at randomization did not affect this treatment effect (interaction $p = 0.115$). In terms of functional status, AF ablation compared to drug therapy led to a significantly lower CCS-AF severity class, with a notable interaction for baseline MR (interaction $p < 0.001$). For AF patients with baseline MR, there was an average reduction of 0.26 points (95% CI 0.33–0.20, $p < 0.001$) compared to 0.21 points (95% CI 0.27–0.15, $p < 0.001$) in those without MR, indicating a numerical higher improvement in functional status with AF ablation if MR versus no or trivial MR. Similarly, an interaction was observed between change in NYHA class, randomization towards

Table 1 Clinical characteristics of the patient population according to mitral regurgitation severity

Parameter	No or trivial MR ($n = 669$)	Mild MR ($n = 582$)	≥Moderate MR ($n = 140$)	*p*-value
Clinical characteristics				
Age (years)	66 [60–71]	66 [61–71]	68 [63–73]	**0.002**
Female sex, *n* (%)	236 (35)	234 (40)	68 (49)	**0.008**
BMI (kg/m^2)	30.0 [26.6–34.6]	29.8 [26.4–33.7]	29.7 [25.5–34.1]	0.172
Systolic BP (mmHg)	130 [120–140]	128 [120–139]	126 [116–140]	0.444
Diastolic BP (mmHg)	80 [70–84]	80 [70–84]	80 [70–87]	0.931
MRA use, *n* (%)	28 (4)	24 (4)	10 (7)	0.267
NYHA class, *n* (%)				0.133
≤I	432 (65)	332 (57)	80 (57)	
II	171 (26)	192 (33)	44 (31)	
III	63 (9)	54 (9)	14 (10)	
Family history of AF, *n* (%)	78 (12)	67 (12)	19 (14)	0.771
Comorbidities				
H_2FPEF score	6 [5–7]	6 [5–7]	6 [5–7]	0.923
Hypertension, *n* (%)	523 (78)	492 (85)	109 (78)	**0.011**
Diabetes, *n* (%)	188 (28)	114 (20)	21 (15)	**<0.001**
Sleep apnoea (%)	158 (24)	110 (19)	30 (21)	0.128
Coronary artery disease, *n* (%)	103 (15)	109 (19)	31 (22)	0.093
Prior stroke, *n* (%)	35 (5)	34 (6)	12 (8)	0.308
Thromboembolic events, *n* (%)	26 (4)	17 (3)	7 (5)	0.422
Echocardiographic characteristics				
LV ejection fraction (%)	60 [55–65]	59 [54–63]	55 [50–60]	**<0.001**
LA size (cm)	4.3 [3.9–4.7]	4.4 [4.1–5.2]	4.5 [4.1–4.9]	**<0.001**
LA volume index (ml)	35.3 [29.0–42.0]	42.0 [34.6–51.0]	44.8 [35.4–56.2]	**<0.001**
RA size, *n* (%)				**<0.001**
Normal	389 (58)	233 (40)	50 (36)	
Mild	139 (21)	183 (31)	37 (26)	
Moderate	45 (7)	90 (16)	31 (22)	
Severe	13 (2)	16 (3)	6 (4)	
LV hypertrophy, *n* (%)	247 (37)	293 (50)	52 (37)	0.062
LV septum, mm	13 [12–14]	13 [12–14]	13 [12–14]	0.166
Diastolic dysfunction, *n* (%)	79 (12)	84 (14)	25 (18)	0.233

Values are presented as *n* (%), or median [interquartile range].
AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; DD, diastolic dysfunction; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RA, right atrial.

Table 2 Predictors of baseline mitral regurgitation in patients with atrial fibrillation

Variable	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
Age	1.02 (1.00–1.03)	**0.021**	1.05 (1.02–1.09)	**0.003**
LA volume index	1.05 (1.03–1.07)	**<0.001**	1.05 (1.03–1.07)	**<0.001**
Female sex	1.34 (1.08–1.67)	**0.008**	1.25 (0.76–2.07)	0.375
Hypertension	1.18 (0.96–1.46)	0.122		
BMI	0.98 (0.96–1.00)	**0.042**	1.00 (0.96–1.04)	0.892
LV ejection fraction	0.99 (0.97–1.00)	**0.011**	0.97 (0.94–1.05)	0.056
RA size	1.48 (1.31–1.67)	**<0.001**	1.02 (0.78–1.32)	0.912
H_2FPEF score	1.00 (0.91–1.09)	0.960		
MRA use	1.11 (0.66–1.84)	0.703		
Persistent AF	1.48 (1.26–1.75)	**<0.001**	1.52 (1.01–2.30)	**0.047**

AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; LA, left atrial; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; RA, right atrial.

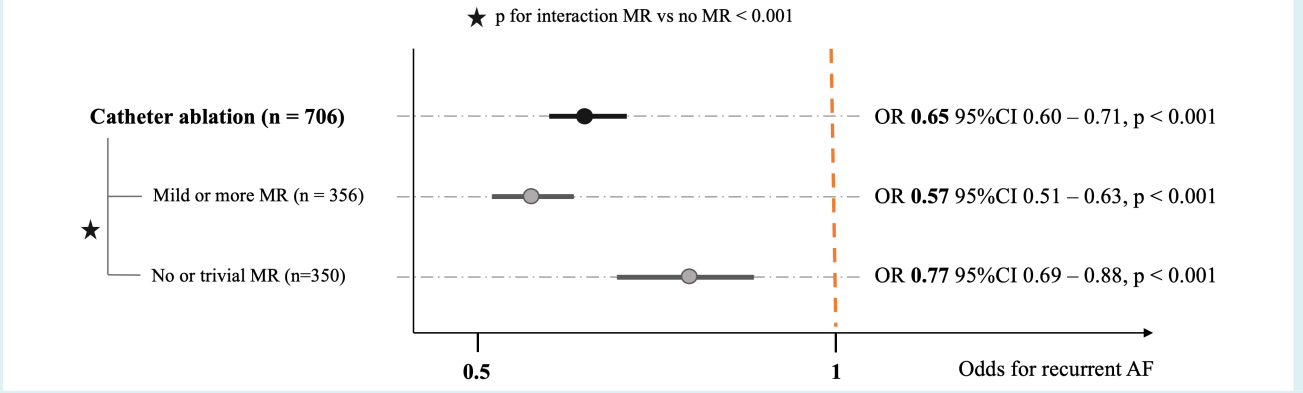


Figure 2 Effect modification of atrial fibrillation (AF) ablation treatment on AF recurrence by mitral regurgitation (MR) status. CI, confidence interval; OR, odds ratio.

AF ablation, and baseline MR (interaction $p < 0.001$), with a more favourable effect on symptom scores in AF patients with baseline MR (average reduction of 0.08 points, 95% CI 0.15–0.02, $p = 0.008$) compared to those without MR (average reduction of 0.03 points, 95% CI 0.03–0.08, $p = 0.338$).

Effect of atrial fibrillation ablation on atrial fibrillation recurrence according to mitral regurgitation status

The recurrence of AF following randomization over the entire study duration (post 3-month blanking period) was 55% in the catheter ablation group, compared to 69% in the drug therapy group (OR 0.56, 95% CI 0.50–0.62, $p < 0.001$). Regardless of randomization, the presence of MR at baseline was associated with an increased risk of AF recurrence, with recurrence rates of 58% in the non-MR group and 66% in the MR group (OR 1.46, 95% CI 1.40–1.74, $p < 0.001$). Randomization to AF ablation (*Figure 2*) resulted however in a lower risk for AF recurrence in both patients without MR (OR 0.66, 95% CI 0.56–0.79, $p < 0.001$) and those with MR (OR 0.49, 95% CI 0.42–0.56, $p < 0.001$). Notably, the magnitude of the treatment effect was larger in patients with baseline MR, as demonstrated by a significant interaction effect (interaction $p < 0.001$), indicating that most AF recurrences are likely to occur in patients with MR who were randomized to drug therapy.

Evolution of mitral regurgitation according to randomization

In a small subset of the overall study population ($n = 248$, representing 18% of the total cohort), follow-up echocardiography was performed 1 year after randomization, to assess and quantify MR. The progression of MR severity over this period is depicted in *Figure 3*. Patients who were randomized to undergo catheter ablation showed a significantly greater reduction in MR severity compared to those receiving drug therapy only (OR 0.69 95% CI 0.47–0.98, interaction $p = 0.040$).

Discussion

The bidirectional relationship between MR and AF remains insufficiently investigated, as most available evidence is derived from observational studies. This sub-analysis leverages the strength of the randomized design of the CABANA trial, where AF risk is modulated through AF ablation, and provides a unique opportunity to track changes in MR severity over time (*Graphical Abstract*). Available echocardiographic data were analysed to gain deeper insights into this important interplay between AF and MR: (i) MR is frequently encountered in patients with AF; (ii) interestingly, AF ablation is even more effective in maintaining sinus rhythm and controlling symptoms in AF patients with baseline MR compared to those without MR; and (iii) rhythm control has a beneficial impact on MR severity over time.

This sub-analysis revealed a high prevalence of MR among patients with AF, with 52% of included patients showing more than trivial MR. Among these, 80% had mild MR, while the remaining 20% presented with ≥ moderate MR. The presence of MR, especially at higher severity levels, was associated with an adverse effect on all-cause mortality. Modulating risk factors associated with baseline MR included older age, persistent AF, and female sex. These characteristics are indicative of atrial functional MR, with AF as a primary underlying cause.[5,6] Additionally, HFpEF commonly coexists with AF, as also reflected in this CABANA sub-cohort by a median H_2FPEF score of 6. This suggests that at least 50% of patients had either a sub-clinical diagnosis or a high probability of HFpEF.[19] Importantly, the presence of baseline MR did not impact the treatment effects on the combined primary outcome of all-cause death and cardiovascular hospitalization when comparing AF ablation with drug therapy.

Consistent with the main CABANA study findings,[18] AF ablation proved significantly more effective than drug therapy in maintaining sinus rhythm (OR 0.56, 95% CI 0.50–0.62, $p < 0.001$). Our study further demonstrated that AF patients with baseline MR had a higher risk of AF recurrence during follow-up compared to those without MR (OR 1.46, 95% CI 1.40–1.74, $p < 0.001$). Notably, AF ablation compared to drug therapy was significantly more effective

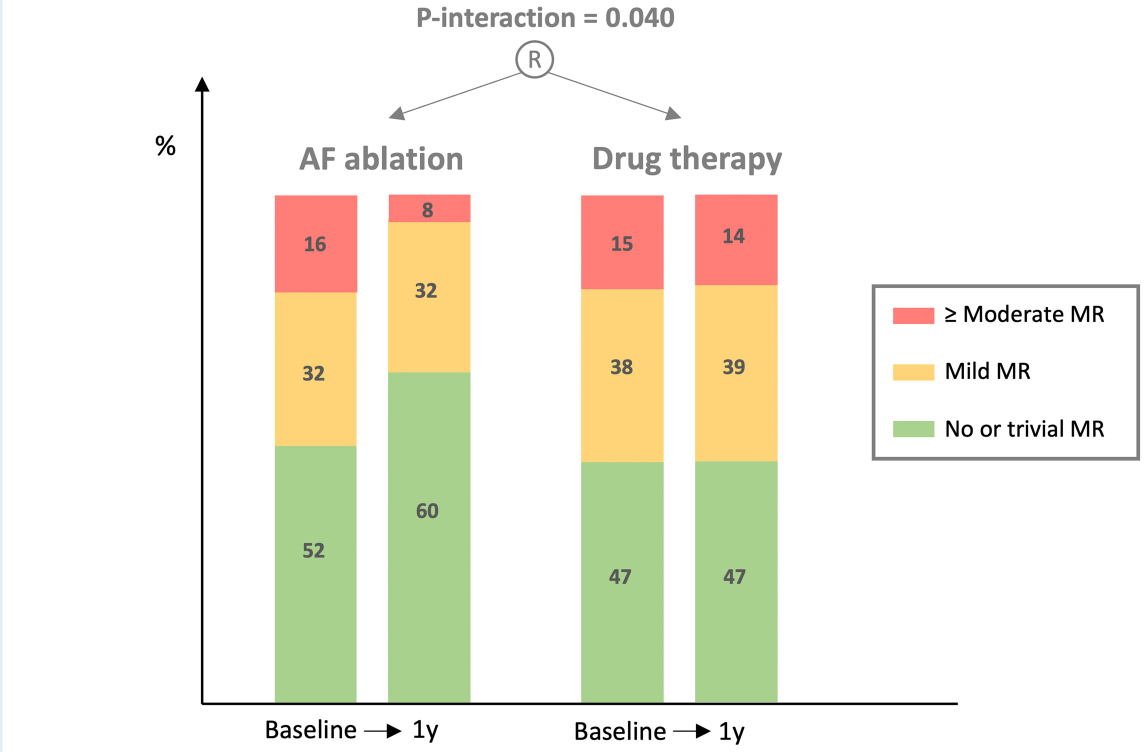


Figure 3 Distribution of mitral regurgitation (MR) severity at baseline and 1 year in ablation versus drug therapy. AF, atrial fibrillation.

in maintaining sinus rhythm in the MR group than in the non-MR group (interaction $p < 0.001$), indicating that AF recurrences were predominantly observed in patients receiving drug therapy. The relative benefit of AF ablation thus appears to be greater in AF patients with baseline MR.

To further investigate this paradox, a cohort of patients from this sub-analysis who had follow-up echocardiography 1 year post-randomization was evaluated. Notably, patients randomized to AF ablation demonstrated a significantly higher likelihood of MR severity reduction over time, suggesting that rhythm control using catheter ablation in atrial functional MR may confer structural benefits. This finding aligns with previous research by Gertz *et al.*,[14] who first demonstrated a reduction in atrial functional MR following AF ablation. While other retrospective cohorts have reinforced this observation, our CABANA sub-study provides the first prospective, randomized evidence supporting this hypothesis that rhythm control using ablation may alleviate atrial functional MR severity over time, albeit in a small sub-cohort and should therefore be interpreted with caution.[15]

Furthermore, this reduction in MR was associated with greater symptom relief in patients with baseline MR compared to those without MR following AF ablation, despite equivalent baseline functional status (as measured by NYHA class and CCS-AF severity). This suggests that effective rhythm control addresses two primary sources of symptoms: MR and AF. By reducing MR severity, AF ablation may eliminate a trigger within the underlying AF substrate, potentially explaining the observed lower AF recurrence rates. This highlights the importance of pursuing rhythm control using catheter ablation, as medical therapy alone may be insufficient to manage the structural abnormalities associated with MR.

Limitations

This sub-analysis should be interpreted in the context of certain limitations. First, the analysis was not specifically powered to study MR and is therefore exploratory in nature. Approximately 65% of the CABANA population had baseline echocardiographic data available, with a substantially smaller proportion undergoing follow-up echocardiography potentially introducing a selection bias. The absence of a centralized echocardiographic core laboratory and the lack of blinding of echocardiographers to treatment allocation may have introduced assessment bias in grading MR severity. Furthermore, detailed information regarding the clinical conditions during echo acquisition (e.g. rhythm, heart rate, and fluid status) was not systematically recorded. This limitation reflects the pragmatic and site-directed nature of imaging protocols within the CABANA trial. Despite this, the study represents the most comprehensive and robust evidence to date for rhythm control in atrial functional MR, pending specifically designed clinical trials. Additionally, raw echocardiographic images were not available, preventing a detailed mechanistic analysis; the clinical echocardiographic protocol limited the range of measurements (e.g. strain analysis, annular dimensions, quantitative and qualitative MR assessment). Furthermore, the drug arm allowed for rate control, leaving

it uncertain how AF ablation would perform under a strict rhythm control strategy with drugs. However, it is known that catheter ablation generally performs better in maintaining sinus rhythm.[20–22] Lastly, newer therapies such as glucagon-like peptide 1 analogues, sodium–glucose cotransporter 2 inhibitors or (non-steroidal) mineralocorticoid receptor antagonists may mitigate the haemodynamic impact of MR and reduce AF recurrence, particularly within the HFpEF subgroup. This raises uncertainty as to whether AF ablation would show similar efficacy when these therapies are part of the treatment background.

Conclusion

Atrial fibrillation and atrial functional MR frequently coexist, with each condition exacerbating the progression of the other. Emerging evidence supports a shift toward rhythm control over rate control in managing AF, with catheter ablation playing a key role. Our analysis shows that patients with both AF and MR form a unique subgroup that may significantly benefit from sustained sinus rhythm, in terms of symptom relief and a reduction in MR severity over time. While this sub-analysis provides novel insights into the interplay between MR and AF and underscores the importance of tailored therapeutic strategies to optimize AF management, the findings remain hypothesis-generating and warrant confirmation in future prospective studies.

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