Original research

Early percutaneous mitral commissurotomy or conventional management for asymptomatic mitral stenosis: a randomised clinical trial

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ABSTRACT

Objective The decision to perform percutaneous mitral commissurotomy (PMC) on asymptomatic patients requires careful weighing of the potential benefits against the risks of PMC, and we conducted a multicentre, randomised trial to compare long-term outcomes of early PMC and conventional treatment in asymptomatic, severe mitral stenosis (MS).

Methods We randomly assigned asymptomatic patients with severe MS (defined as mitral valve area between 1.0 and 1.5 cm^2) to early PMC (84 patients) or to conventional treatment (83 patients). The primary endpoint was a composite of major cardiovascular events, including PMC-related complications, cardiovascular mortality, cerebral infarction and systemic thromboembolic events. The secondary endpoints were death from any cause and mitral valve (MV) replacement during follow-up.

Results In the early PMC group, there were no PMC-related complications. During the median follow-up of 6.4 years, the composite primary endpoint occurred in seven patients in the early PMC group (8.3%) and in nine patients in the conventional treatment group (10.8%) (HR 0.77; 95% CI 0.29 to 2.07; p=0.61). Death from any cause occurred in four patients in the early PMC group (4.8%) and three patients in the conventional treatment group (3.6%) (HR 1.30; 95% CI 0.29 to 5.77). Ten patients (11.9%) in the early PMC group and 17 patients (20.5%) in the conventional treatment group underwent MV replacement (HR 0.59; 95% CI 0.27 to 1.29).

Conclusions Compared with conventional treatment, early PMC did not significantly reduce the incidence of cardiovascular events among asymptomatic patients with severe MS during the median follow-up of 6 years.

Trial registration number NCT01406353.

INTRODUCTION

Although percutaneous mitral commissurotomy (PMC) has become the standard treatment for symptomatic patients with rheumatic mitral stenosis (MS),[1 2] most asymptomatic patients are not candidates for PMC due to the small but inherent procedure-related risks. The decision to perform PMC on asymptomatic patients requires careful weighing of the potential benefits against the risks of early PMC. Current guidelines have discouraged intervention in patients with mild MS, but recommended PMC for asymptomatic patients with significant pulmonary hypertension, high thromboembolic risk or very severe MS.[1 2] However, the evidence base for these recommendations is insufficient and controversies about indications for PMC exist in most asymptomatic patients with severe MS. Asymptomatic patients with MS show good survival rates up to 10 years,[3] but sudden deterioration is provoked by atrial fibrillation (AF) or systemic embolism.[4 5] In a recent observational study,[6] early PMC was associated with a reduction of embolic events, suggesting that the risk–benefit ratio might be shifted towards the benefit for early PMC in experienced centres.

Because the success rates of PMC in experienced centres were improved to more than 95% in ideal patients[6 7] and later performance of PMC in the presence of advanced structural deformity might result in worse outcomes,[8] we designed the MITIGATE (Mitral Intervention vs Conventional Management in Asymptomatic Mitral Stenosis) trial to compare clinical outcomes between early PMC and conventional management in asymptomatic patients with severe MS (1.0 cm^2 ≤mitral valve area (MVA)≤1.5 cm^2). The major hypothesis of this trial was that early PMC would decrease the rate of cardiovascular mortality and systemic thromboembolic events, as compared with conventional treatment.

METHODS

Study design

We conducted this prospective, multicentre, randomised, parallel-group, open-label trial involving asymptomatic patients with severe MS who were candidates for either early PMC or conventional treatment at three medical centres in Korea. The study protocol was approved by the institutional review board at each participating centre. The principal investigator designed the protocol (online supplemental file 2) and conducted the trial in accordance with the principles of the Declaration of Helsinki. Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our study. An independent clinical events committee adjudicated all serious adverse events, and a data and safety monitoring board oversaw the safety of the trial.

Patient selection

We screened consecutive patients who were 20–70 years of age and presented with severe MS, which was assessed by transthoracic echocardiography. According to the 2014 American College of Cardiology/American Heart Association guidelines,[1] we defined severe MS as an MVA between 1.0 and 1.5 cm^2. In accordance with the current guidelines on indications of intervention for severe MS,[1 2] patients were excluded if they had exertional dyspnoea, left ventricular ejection fraction <50%, moderate or severe mitral regurgitation, significant aortic valve disease, total echocardiographic score >10, left atrial (LA) thrombi or Doppler-estimated pulmonary artery systolic pressure >50 mm Hg. Exercise testing was performed to confirm the absence of symptoms in patients with non-specific symptoms. We also excluded those who were not candidates for early PMC due to old age or poor medical condition such as malignancy. All the participants provided written informed consent.

Study procedures

Eligibility was determined after each patient undergoes a thorough evaluation of symptomatic status and medical records, and results of echocardiographic study and exercise testing were reviewed. Details of echocardiographic study and exercise testing are provided in the online supplemental appendix. Patients were randomly assigned in a 1:1 ratio to early PMC or conventional treatment using a web-based interactive response system (https://mitigate.e-crf.co.kr). The assignment to each treatment group was computer-generated and stratified according to the participating centre, cardiac rhythm and previous history of PMC using a permuted-block sequence with variable block size. The protocol specified that patients assigned to the early PMC group should undergo PMC within 3 months of randomisation. Transoesophageal echocardiography was performed to detect LA thrombi before PMC. PMC was performed by experienced interventional cardiologists using the Inoue balloon technique as described previously.[9] A successful immediate result was defined as a MVA >1.5 cm^2 without the development of moderate to severe mitral regurgitation.[10] Patients assigned to the conventional treatment group were managed according to current guidelines[1 2] and they were referred for intervention if they became symptomatic during follow-up, or if MVA decreased to smaller than 1.0 cm^2 on follow-up echocardiography.

All patients were followed up at 4 weeks, 3 months, 6 months, 9 months and 1 year; and at 3–6 month intervals thereafter until close-out of the study, and the study coordinators called them if they missed their scheduled appointment for follow-up. Anticoagulation was effectively maintained during the entire follow-up period in patients with AF or prior embolic events.

Study endpoints

The primary endpoint was a composite of PMC-related complications (including procedural mortality and urgent MV surgery), cardiovascular mortality, cerebral infarction and systemic thromboembolic events that occurred during entire follow-up (continuing for >3 years after the last subject was enrolled). Cardiovascular mortality was defined as sudden cardiac death and death from myocardial infarction, systemic thromboembolic events, congestive heart failure, complications of cardiac surgery or intervention, cerebrovascular disease or other cardiovascular disease. Prespecified secondary endpoints included death from any cause and MV replacement during follow-up. All endpoints were adjudicated according to the prespecified definition by an independent clinical events committee whose members did not know treatment-group assignments. Specific definitions of endpoints are shown in the online supplemental appendix.

Statistical analysis

Based on our previous observational study,[6] we estimated that a sample size of 166 patients would provide the trial with 80% power, at a two-sided significance level of 0.05, to detect a significant difference in terms of the primary endpoint, assuming that the incidence of the primary endpoint would be 13% in the conventional treatment group and 2% in the early PMC group during a follow-up period that continued until 3 years after the last subject was enrolled. In calculating the sample size by means of a log-rank survival power analysis, we also assumed that an accrual period of 2 years would be required to complete enrolment, and that the rate of loss to follow-up would be 5%.

Analyses were done on an intention-to-treat basis. Differences between the treatment groups were evaluated using Student's t-test for continuous variables and Fisher's exact test for categorical variables. Because randomisation was stratified according to the participating centre, we analysed the endpoints with the use of stratified Cox proportional hazards regression with Firth correction. Estimates of cumulative incidences were calculated by the Kaplan-Meier method and were compared by means of the log-rank test. For the Kaplan-Meier analysis, we analysed all clinical events according to the time to the first event. HRs with 95% CIs were derived using the stratified Cox proportional hazards model with Firth correction. The proportional hazards assumption was checked by testing of partial (Schoenfeld) residuals, and no relevant violation was found. Subgroup analyses were performed to determine whether the result of the primary endpoint was consistent in two prespecified subgroups of cardiac rhythm (sinus rhythm vs AF) and previous PMC (presence vs absence). A per-protocol analysis of the endpoint was also performed. This analysis excluded all patients who had a protocol deviation and those in the early PMC group in whom PMC was not performed within 3 months of randomisation. All reported p values were two sided, and a value of $p<0.05$ was considered to indicate statistical significance. SAS software, V.9.4 (SAS Institute), was used for statistical analyses.

RESULTS

Patients

From July 2011 to November 2015, a total of 374 asymptomatic patients with severe MS were assessed for eligibility, and 167 were enrolled. We randomly assigned these patients to conventional treatment (83 patients) or early PMC (84 patients) (figure 1). After randomisation, 5 patients assigned to conventional treatment crossed over to early PMC, and 13 patients assigned to early PMC crossed over to conventional treatment; PMC in these 13 patients was later performed after development of symptoms in 3 and was not attempted in 10.

The treatment groups were generally well balanced with regard to baseline clinical characteristics (table 1). The mean (±SD) age of the patients was 54.7±9.0 years and 83% were women. The mean MVA was 1.23±0.19 cm^2, and the mean transmitral pressure gradient was 8.2±3.8 mm Hg, and the total echo score averaged 8.1±1.1. Medication at baseline was also similar in the two groups.

PMC procedures

In the early-PMC group, PMC was successfully completed in all 74 patients in whom PMC was attempted, and there was no procedure-related mortality or thromboembolic event. All the

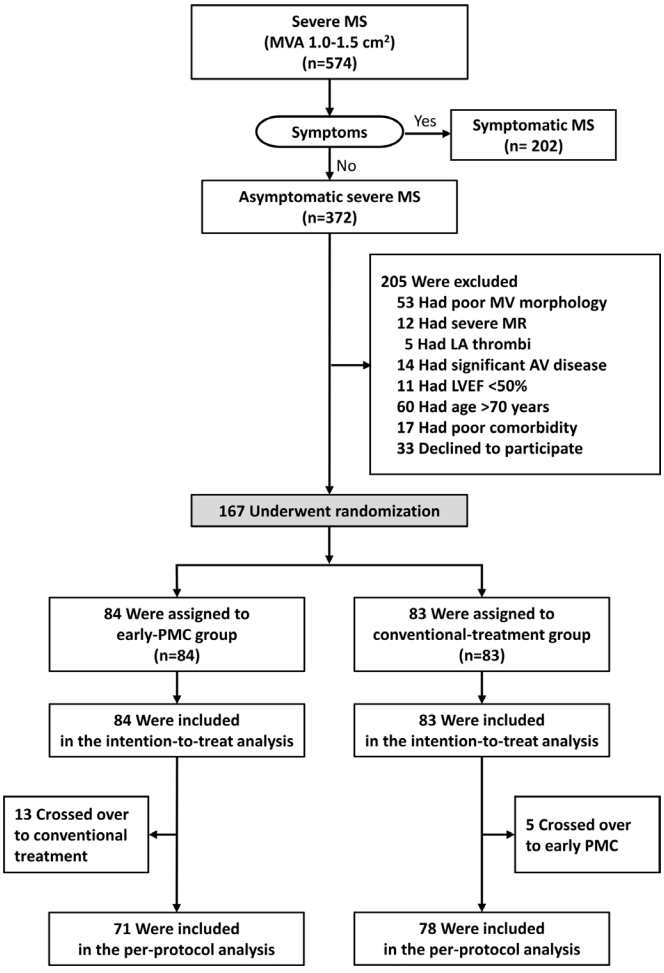

Figure 1 Enrolment, randomisation and follow-up. Of the 574 patients with severe mitral stenosis (defined as mitral valve area between 1.0 and 1.5 cm^2), 202 patients with symptoms were excluded; 372 asymptomatic patients were assessed for eligibility, 205 of whom were excluded. Of the 167 patients who underwent randomisation, 84 were assigned to the early PMC group and 83 to the conventional treatment group; all these patients were included in the intention-to-treat analysis. In the per-protocol analysis, 13 patients in the early PMC group and 5 in the conventional treatment were excluded because of cross-over. AV, aortic valve; LA, left atrial; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVA, mitral valve area; PMC, percutaneous mitral commissurotomy.

patients except those who crossed over underwent PMC within 3 months after randomisation; the median time between randomisation and PMC was 22 days (IQR 8–37). Immediately after PMC, MVA significantly increased from 1.21±0.12 to 1.83±0.24 cm^2 (p<0.001), and mean mitral gradient significantly decreased from 8.6±3.6 to 6.1±2.4 mm Hg (p<0.001). MVA >1.5 cm^2 was achieved in 72 (97%) patients; moderate to severe MR occurred in 2 (3%) patients and no patient required urgent surgery. Thus, successful immediate results were achieved in 70 (95%) patients.

Of the 83 patients assigned to the conventional treatment, 22 (27%) patients underwent PMC due to development of symptoms (11 patients) or progression to very severe MS alone (6 patients) during follow-up, or crossover to early PMC (5 patients). One patient required emergent MV replacement due to cardiac perforation. The PMC resulted in a significant increase in MVA from 1.18±0.11 to 1.74±0.23 cm^2 (p<0.001) and a significant decrease in mitral gradient from 8.1±3.5 to 5.5±2.8 mm Hg (p<0.001). A successful immediate result was achieved in 19 (86%) patients, and there was also no procedure-related mortality or thromboembolic event among patients who underwent later PMC during watchful observation; the median time from randomisation to PMC was 561 days (IQR 110–1053). Detailed PMC procedures and results are provided in online supplemental table S1.

Table 1 Clinical and echocardiographic characteristics of the patients at baseline, according to treatment group*

Characteristics	Conventional treatment (n=83)	Early PMC (n=84)
Age, years	55.5±9.4	54.0±8.7
Female sex, n (%)	70 (84.3)	69 (82.1)
Body surface area	1.64±0.17	1.69±0.17
Body mass index	24.0±2.6	24.7±3.4
Diabetes, n (%)	6 (7.2)	4 (4.8)
Hypertension, n (%)	41 (49.4)	33 (39.3)
Smoking, n (%)	11 (13.3)	17 (20.2)
Coronary artery disease, n (%)	1 (1.2)	0 (0)
Previous myocardial infarction, n (%)	0 (0)	0 (0)
Previous stroke, n (%)	7 (8.4)	9 (10.7)
Previous PMC, n (%)	22 (26.5)	17 (20.2)
Peripheral vascular disease, n (%)	0 (0)	0 (0)
Chronic pulmonary disease	0 (0)	0 (0)
Limited mobility	0 (0)	2 (2.4)
Serum creatinine, mg/dL	0.81±0.14	0.80±0.17
Age-adjusted Charlson Comorbidity Index, median (25th–75th percentile)	1 (1–2)	1 (0–2)
Previous embolism, n (%)	2 (2.4)	5 (6.0)
Atrial fibrillation, n (%)	40 (48.2)	45 (53.6)
Paroxysmal	1	7
Persistent/permanent	39	38
Medication, n (%)		
Aspirin	16 (19.3)	22 (26.2)
Other antiplatelet drug	3 (3.6)	2 (2.4)
Warfarin	45 (54.2)	48 (57.1)
Angiotensin-converting enzyme inhibitor	4 (4.8)	4 (4.8)
Angiotensin-receptor blocker	14 (16.9)	14 (16.7)
Calcium antagonist	11 (13.3)	8 (9.5)
Beta-blocker	23 (27.7)	27 (32.1)
Diuretic	45 (54.2)	36 (42.9)
Statin	21 (25.6)	21 (25.0)
Echocardiographic findings		
Mitral valve area, cm^2		
Planimetry	1.24±0.15	1.23±0.13
Pressure half-time method	1.26±0.17	1.28±0.19
Mean mitral gradient, mm Hg	8.1±4.0	8.2±3.6
Total echo score	8.2±1.1	8.0±1.0
Peak velocity of TR, m/s	2.6±0.3	2.7±0.3
Moderate or severe TR, n (%)	6 (7.2)	7 (8.3)
Left atrial dimension, mm	49.8±6.7	50.6±6.2
Left ventricular ejection fraction, %	61.8±6.5	61.8±6.2

*Plus-minus values are means±SD. There were no significant differences between the two groups.
PMC, percutaneous mitral commissurotomy; TR, tricuspid regurgitation.

Follow-up and endpoints

Data collection was completed in May 2020, when the last enrolled patient had finished 4 years of follow-up. The median

Table 2 Primary and secondary endpoints

Outcome	Conventional treatment (n=83)	Early PMC (n=84)	HR* (95% CI)	P value
Composite primary endpoint, n (%)	9 (10.8)	7 (8.3)	0.77 (0.29 to 2.07)	0.61
PMC-related complications	1 (1.2)	0 (0)		
Procedural mortality	0	0		
Urgent mitral valve surgery	1	0		
Cardiovascular mortality	0 (0)	3 (3.6)		
Non-fatal cerebral infarction	6 (7.2)	3 (3.6)		
Systemic thromboembolic event	2 (2.4)	1 (1.2)		
Secondary endpoints, n (%)				
Death from any cause	3 (3.6)	4 (4.8)	1.30 (0.29 to 5.77)	0.73
Mitral valve replacement	17 (20.5)	10 (11.9)	0.59 (0.27 to 1.29)	0.19

*HRs were calculated with the use of stratified Cox proportional hazards models with Firth correction.
PMC, percutaneous mitral commissurotomy.

follow-up was 6.3 years (IQR 5.1–7.3) in the early PMC group and 6.4 years (IQR 5.2–7.3) in the conventional treatment group. No patients were lost to follow-up. In an intention-to-treat analysis including all the study patients, the composite primary endpoint occurred in 7 of 84 patients assigned to early PMC (8.3%) and 9 of 83 patients assigned to conventional treatment (10.8%) (HR 0.77; 95% CI 0.29 to 2.07; p=0.61) (table 2). The cumulative incidence of the primary endpoint, as calculated by means of a Kaplan-Meier analysis, was not significantly different between the early PMC group (6.0% at 4 years and 9.8% at 8 years) and the conventional treatment group (6.0% at 4 years and 12.7% at 8 years) (p=0.59 by log-rank test) (figure 2A). During follow-up, new onset of AF occurred in 10 patients (11.9%) in the early PMC group and 8 patients (9.6%) in the conventional treatment group. In the early PMC group, one fatal and three non-fatal cerebral infarctions and one systemic embolic event occurred, and six non-fatal cerebral infarctions and two systemic embolic events occurred in the conventional treatment group. The cumulative incidence of thromboembolic events at 8 years was 7.4% in the early PMC group and 11.5% in the conventional treatment group (p=0.39 by log-rank test) (online supplemental figure S1).

A total of four deaths from any cause (4.8%) occurred in the early PMC group and three deaths from any cause (3.6%) occurred in the conventional treatment group (HR 1.30; 95% CI 0.29 to 5.77; p=0.73). The cumulative incidence of all-cause death was similar between the two treatment groups (6.3% at 8 years in the early PMC group and 5.0% at 8 years in the conventional treatment group; p=0.70 by log-rank test) (figure 2B). Details regarding patients who died or had non-fatal thromboembolic events are summarised in online supplemental table S2 and S3. During follow-up, 10 patients (11.9%) in the early PMC group and 17 patients (20.5%) in the conventional treatment group underwent MV replacement (HR 0.59; 95% CI 0.27 to 1.29; p=0.19).

In the conventional treatment group, out of the 61 patients who did not undergo PMC until the end of follow-up, 42 (69%) remained asymptomatic and did not develop any endpoint, while 68 (81%) patients remained free of any endpoint and asymptomatic in the early PMC group. Among the 133 surviving patients without MV replacement, the last echocardiographic follow-up examination was performed at a median interval of 5.1 years (IQR 4.0–6.9) in the early PMC group and 4.7 years (IQR 3.8–6.5) in the conventional treatment group (table 3). Although the patients in the early PMC group had a larger final MVA than those in the conventional treatment group, the change in the LA volume index did not differ significantly between the treatment groups (p=0.17).

The results of per-protocol analysis were consistent with those of the primary intention-to-treat analysis (online supplemental table S4 and figure S2). Subgroup analyses with interaction testing were performed to assess the consistency of the results regarding the primary endpoint and death from any cause in two prespecified subgroups (online supplemental table S5). There

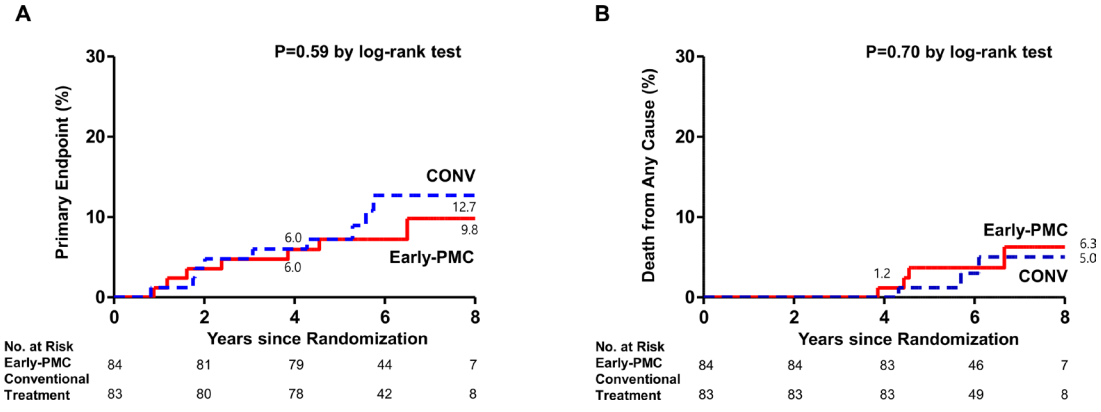

Figure 2 Time-to-event curves for the primary composite endpoint and death from any cause. Shown are Kaplan-Meier estimates of the cumulative incidence of the primary composite endpoint of percutaneous mitral commissurotomy (PMC)-related complications, death from cardiovascular causes, cerebral infarction and systemic thromboembolic events during the follow-up period (panel A) and of the major secondary endpoint of death from any cause during follow-up (panel B) among patients who were randomly assigned to undergo either early PMC or conventional treatment.

Table 3 Follow-up changes according to treatment group

	Baseline		Follow-up		Change		
	Conventional treatment	Early PMC	Conventional treatment	Early PMC	Conventional treatment	Early PMC	P value
Echocardiographic variables	n=63	n=70	n=63	n=70	n=63	n=70	
Mitral valve area, cm^2	1.25±0.15	1.22±0.13	1.21±0.26	1.57±0.33	−0.045±0.300	0.349±0.344	<0.001
Mean mitral gradient, mm Hg	8.4±4.1	8.1±3.5	8.2±4.3	6.2±3.1	−0.14±3.51	−1.77±3.48	0.008
Peak velocity of TR, m/s	2.6±0.3	2.7±0.3	2.6±0.5	2.6±0.5	−0.02±0.53	−0.08±0.52	0.53
LA volume index, mL/m^2	77.6±31.9	73.2±21.2	84.3±34.2	76.3±27.5	6.7±20.0	3.1±19.2	0.17

LA, left atrial; PMC, percutaneous mitral commissurotomy; TR, tricuspid regurgitation.

were no significant interactions between the treatment groups and these events according to cardiac rhythm or previous performance of PMC.

DISCUSSION

The MITIGATE trial, the first randomised trial comparing early PMC with conventional treatment in asymptomatic patients with severe MS, showed that early PMC did not significantly reduce the composite endpoint of PMC-related complications, cardiovascular mortality and systemic thromboembolic events (figure 3). The incidence of all-cause death was also similar between the two treatment strategies.

In asymptomatic patients with severe MS, pre-emptive PMC can be justified only when there is clear evidence that early PMC improves long-term outcomes compared with conventional treatment, because it appears relatively safe to delay PMC until symptoms develop following a watchful waiting strategy.[1 2] There is a recent trend towards performing PMC at an earlier stage of disease in selected centres with high rates of successful PMC,[11 12] but there were no significant differences in occurrences of endpoints between the treatment groups.

There may be several explanations for the lack of benefit of early PMC on clinical outcomes. First, the annual incidence rate of thromboembolism in the conventional treatment group (1.4%) was lower than those reported in previous studies (3.6%,[5] 2.1%[6] and 4.2%[13]). It should be noted that symptomatic patients with higher risk features were excluded from this trial, and effective anticoagulation therapy with a target INR in the range of 2–3 was maintained during the entire trial period in all patients with an indication to anticoagulation. Second, early PMC failed to significantly reduce occurrences of systemic thromboembolism. AF occurs commonly, affecting approximately 40% of patients with MS, and predisposes to thromboembolic complications that most frequently involve the brain, and is more related to age than to the severity of stenosis.[14–16] Because relief of haemodynamic obstruction by PMC did not lead to reverse remodelling of the dilated left atrium or rhythm control of AF, we did not observe significant

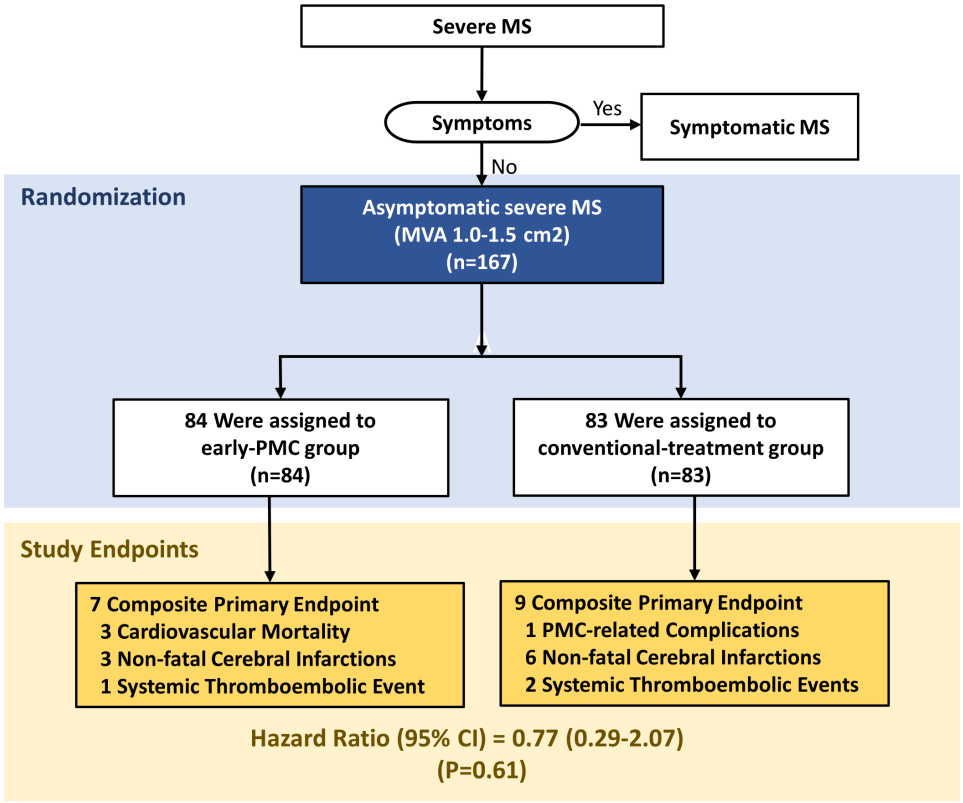

Figure 3 Summary of the MITIGATE (Mitral Intervention vs Conventional Management in Asymptomatic Mitral Stenosis) trial

difference in the incidence of thromboembolic events between the treatment groups. Third, 69% of patients in the conventional treatment group remained asymptomatic and free of endpoints without undergoing PMC. It is well recognised that the progression of rheumatic MS is generally slow but extremely variable, with more than a third of patients showing no decline in valve area over several years.[8 17–19] Although most patients with very severe MS are symptomatic or will manifest a true reduction in functional capacity,[1 20] clinical courses of asymptomatic patients with severe MS are highly variable. Early pre-emptive PMC in asymptomatic severe MS should be balanced against the indolent and variable natural history, predictive value of symptoms for intervention and the small possibility of complications.[7] Lastly, overall survival was excellent in the conventional treatment group as well as the early PMC group. Following watchful observation strategy, all patients in the conventional treatment group underwent PMC or MV replacement once they developed symptoms, and there was no case of sudden cardiac death or death from heart failure, suggesting that a clinically significant risk of sudden cardiac death or left ventricular dysfunction is not associated with asymptomatic severe MS.[7]

Limitations

Our study has several limitations. First, the study population did not represent all asymptomatic patients with severe MS, since those with very severe MS, pulmonary hypertension, age >70 years, poor medical condition or unfavourable MV morphology for PMC were not included in order to allow for both conventional treatment and early PMC. Second, crossover occurred in 15% of the patients in the early PMC group and in 6% of the patients in the conventional treatment group. Nevertheless, the results of the per-protocol analysis were similar to the results of the primary intention-to-treat analysis. Third, because this trial was not blinded, the non-fatal outcomes could have been influenced by knowing whether the patient underwent PMC or not. Fourth, the median follow-up was 6.4 years and occurrences of AF in the PMC group might be reduced at longer term follow-up. Finally, as in our previous trial for asymptomatic aortic stenosis,[21] the small number of study patients and primary endpoint events is also an important limitation of this trial.

CONCLUSIONS

In this randomised clinical trial, clinical outcomes better than expected were observed in the conventional treatment group, and early PMC did not significantly reduce the incidence of the composite of cardiovascular events among asymptomatic patients with severe MS, and these findings support adherence to current practice guidelines emphasising careful clinical and echocardiographic surveillance in asymptomatic patients with severe MS.

Contributors D-H Kang, G-RH and Sung-Ji Park had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: D-H Kang. Analysis and interpretation of data: D-H Kang, Sung-Ji Park, S-AL, SL, S-CY and G-RH. Drafting of the manuscript: D-H Kang and Sung-Ji Park. Critical revision of the manuscript for important intellectual content: D-H Kang, D-WP, D-H Kim, J-MS, M-KH, SWP and Seung-Jung Park. Final approval of manuscript: D-H Kang, Sung-Ji Park and G-RH.

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Competing interests None declared.

Patient consent for publication Not required.

Key messages

What is already known on this subject?

- Percutaneous mitral commissurotomy (PMC) is indicated for symptomatic, severe mitral stenosis (MS), but controversies about indications for PMC exist in most asymptomatic patients with severe MS.

What might this study add?

- This randomised trial comparing early PMC with conventional treatment in asymptomatic patients with severe MS showed that early PMC did not significantly reduce the composite endpoint of PMC-related complications, cardiovascular mortality and systemic thromboembolic events during the median follow-up of 6 years.

How might this impact on clinical practice?

- Our results support adherence to current practice guidelines emphasising careful clinical and echocardiographic surveillance in asymptomatic patients with severe MS.

Ethics approval Our study obtained ethics approval from Asan Medical Center IRB (approval number 2011-0432).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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