(Combination Assessment of Ranolazine In Stable Angina) trial,[14] however, the addition of ranolazine—an inhibitor of late sodium influx—to atenolol, diltiazem, or amlodipine, was associated with improved exercise duration (albeit with the far-less strenuous modified Bruce protocol), and a reduction in both angina frequency and short-acting nitrate usage. The benefit of ranolazine seemed to be least in patients who received either atenolol or diltiazem.

The ASSOCIATE study investigators have delivered a well-designed, carefully conducted, multicenter trial, which shows that ivabradine therapy is safe, improves exercise performance, and delays the development of ischemia in patients with chronic stable angina being treated with atenolol. These data are consistent with the findings of the BEAUTIFUL (morbidity–mortality evaluation of the I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) study,[15] in which ivabradine was well tolerated in patients with coronary artery disease and left ventricular dysfunction, many of whom were being treated with a β-blocker. Angina frequency was not significantly reduced, although this could be explained either by the low symptom burden in the recruited study population, or by the fact that patients exercise more in daily life on active treatment simply because they are able to do so. The pharmacologic management of patients affected by angina despite β-blocker therapy remains challenging. The addition of ivabradine should be considered in symptom-limited patients when heart rate is suboptimally controlled.

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1. Fox, K. *et al.* Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur. Heart J.* **27**, 1341–1381 (2006).
2. Kannel, W. B. & Feinleib, M. Natural history of angina pectoris in the Framingham study. Prognosis and survival. *Am. J. Cardiol*. **29**, 154–163 (1972).
3. Gibbons, R. J. *et al.* ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients With Chronic Stable Angina). *J. Am. Coll. Cardiol*. **41**, 159–168 (2003).
4. Tardif, J. C., Ponikowski, P. & Kahan, T. Efficacy of the I_f current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur. Heart J.* **30**, 540–548 (2009).
5. Fox, K. M. Exercise heart rate/ST segment relation. Perfect predictor of coronary disease. *Br. Heart J.* **48**, 309–310 (1982).
6. Gislason, G. H. *et al.* Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur. Heart J.* **27**, 1153–1158 (2006).
7. Fox, K. M., Mulcahy, D., Findlay, I., Ford, I. & Dargie, H. J. The Total Ischaemic Burden European Trial (TIBET). Effects of atenolol, nifedipine SR and their combination on the exercise test and the total ischaemic burden in 608 patients with stable angina. The TIBET Study Group. *Eur. Heart J.* **17**, 96–103 (1996).
8. Klein, W. W., Jackson, G. & Tavazzi, L. Efficacy of monotherapy compared with combined antianginal drugs in the treatment of chronic stable angina pectoris: a meta-analysis. *Coron. Artery Dis.* **13**, 427–436 (2002).
9. Knight, C. J. & Fox, K. M. Amlodipine versus diltiazem as additional antianginal treatment to atenolol. Centralised European Studies in Angina Research (CESAR) Investigators. *Am. J. Cardiol*. **81**, 133–136 (1998).
10. Borer, J. S., Fox, K., Jaillon, P. & Lerebours, G. Antianginal and antiischemic effects of ivabradine, an I_f inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation* **107**, 817–823 (2003).
11. Tardif, J. C., Ford, I., Tendera, M., Bourassa, M. G. & Fox, K. Efficacy of ivabradine, a new selective I_f inhibitor, compared with atenolol in patients with chronic stable angina. *Eur. Heart J.* **26**, 2529–2536 (2005).
12. Boden, W. E. *et al.* Optimal medical therapy with or without PCI for stable coronary disease. *N. Engl. J. Med.* **356**, 1503–1516 (2007).
13. Daly, C. A. *et al.* The initial management of stable angina in Europe, from the Euro Heart Survey: a description of pharmacological management and revascularization strategies initiated within the first month of presentation to a cardiologist in the Euro Heart Survey of Stable Angina. *Eur. Heart J.* **26**, 1011–1022 (2005).
14. Chaitman, B. R. *et al.* Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA* **291**, 309–316 (2004).
15. Fox, K., Ford, I., Steg, P. G., Tendera, M. & Ferrari, R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* **372**, 807–816 (2008).

VALVE DISEASE

Asymptomatic mitral regurgitation: does surgery save lives?

David H. Adams and Anelechi C. Anyanwu

Management of asymptomatic patients with severe mitral valve regurgitation is controversial—conservative surveillance and early mitral valve repair have both been advocated as reasonable approaches on the basis of divergent data. A new study by Kang *et al.* fuels this debate. However, careful assessment of the existing literature can provide insight into the optimal care of this population of patients.

There is disagreement among experts about the necessity for, and timing of, surgical intervention in patients with asymptomatic severe mitral valve regurgitation. This disparity is reflected in current management guidelines; in US guidelines,[1] early surgery is recommended, while European guidelines[2] indicate that conventional treatment ('watchful waiting') is sufficient. Kang and colleagues have now reported that 7 year cardiac-event-free survival was 99% among patients with asymptomatic severe mitral regurgitation who had early surgery, compared with 85% in those who underwent watchful waiting.[3] This finding led the authors to recommend early surgery as the treatment of choice for these patients.

The investigators used data from a prospective echocardiography registry to retrospectively compare the long-term outcomes of 161 patients who had early surgery with 286 patients who received conventional treatment between 1996 and 2005.[3] Exclusion criteria were factors that indicated a need for surgery, as defined by the 1998 US guidelines for management of valvular

heart disease.[4] The choice of treatment after diagnosis of severe mitral regurgitation was based primarily on physician judgment and preference. Most patients underwent transesophageal echocardiography to assess the feasibility of valve repair, which suggests that valve morphology had a role in determining treatment strategy. The authors did not provide data on freedom from all-cause mortality, and they excluded deaths from other causes (including stroke and infection) from the primary end point. Far from ending the transatlantic controversy on intervention for asymptomatic mitral regurgitation, this study only intensifies the debate, and the data warrant close scrutiny.

The basis upon which patients were selected for early surgery or medical management is not clear, but it seems implicit from the data that there was a tendency to assign patients with less complex valve pathology to early surgery. Prolapse without a flail leaflet (implying chordal elongation), which is more prevalent in Barlow's disease and requires a high level of skill and expertise to repair,[5] was notably more prevalent in the conventional-treatment group than in the surgery group (68% versus 49%, $P<0.001$). The lower rate of valve repair for patients in the conventional-treatment group who subsequently underwent surgery (85% versus 94% in the early surgery group) further suggests that patients in the conventional-treatment group had more complex valve pathology, which the authors found more difficult to repair. The probable influence of surgical expertise and valve complexity on therapeutic choices is emphasized by the observation that 12% of asymptomatic patients with bileaflet prolapse had valve replacement, even though a contemporary series indicates that these valves are repairable,[6] and US guidelines[1] recommend that surgery should only be undertaken in asymptomatic patients when repair can predictably be achieved. An anticipated suboptimal repair rate for complex valve pathology—possibly suggested by the investigators' previous experience or reports in the literature—could have swayed the choice of management towards watchful waiting in such patients. The data also hint at a reluctance to operate on patients once a watchful-waiting approach had been initiated, indicating that the factors preventing early surgery (for example, surgical complexity or physician bias) might continue to preclude subsequent surgery.

Table 1 | Major studies of watchful waiting in severe asymptomatic mitral regurgitation

Parameters	Results		
	Asan Medical Center, Seoul, Korea (Kang *et al.*)[3]	Medical University of Vienna, Austria (Rosenhek *et al.*)[7]	Mayo Clinic, Rochester, MN, USA (Enriquez-Sarano *et al.*)[8]
Number of patients	286	132	198
Study period	1996–2005	1995–2002	1991–2000
Mean patient age (years)	51	55	61
Patients who underwent mitral surgery during follow-up (%)	19	26	82
Patients symptomatic at time of surgery (%)	94	69	41
Repair rate at surgery (%)	92	83	91
Surgical mortality (%)	0	0	1
Midterm patient survival	Not given	91% at 8 years[a]	58% at 5 years[b]
Cardiac-event-free survival	85% at 7 years	55% at 8 years	38% at 5 years

[a]Expected survival: 90%. [b]Expected survival: 78%

Among patients who underwent conventional treatment and subsequently had surgery, 94% did so because they began to experience symptoms. This finding is in stark contrast to epidemiological studies of the natural history of asymptomatic mitral regurgitation, in which a much lower percentage of patients who underwent surgery were symptomatic.[7,8] Over a third of patients in the series studied by Kang *et al.*[3] were admitted to hospital with heart failure before surgery was considered, raising the possibility that waiting might not have been so 'watchful', and that appropriate surgical therapy might have been delayed in these patients. Furthermore, five patients in the conventional-treatment group who developed heart failure did not undergo surgery because of their high surgical risk. These individuals subsequently died, which again indicates possible reluctance to operate on patients who were on the conventional-treatment pathway. Selection bias, and a lack of defined follow-up routines and prompt surgical intervention in the watchful-waiting group could have contributed to the exceptional benefit of early surgery over conventional treatment reported by Kang and colleagues.

> The risk associated with mitral valve repair in asymptomatic patients seems to be quite low

How does this new study fit with the two major published series on outcomes of watchful waiting in patients with asymptomatic mitral regurgitation—Rosenhek *et al.* (Medical University of Vienna, Austria),[7] who recommend watchful waiting, and Enriquez-Sarano *et al.* (Mayo Clinic, Rochester, MN, USA),[8] who recommend early surgery? The key features of these three studies are compared in Table 1. Ironically, although Kang *et al.*[3] conclude that their findings support early surgery for patients with asymptomatic mitral regurgitation, their data can also be used to validate a watchful-waiting strategy. The patients in their study who did not undergo surgery had a remarkably benign course, with 85% freedom from cardiac events at 7 years. Such a low event rate raises the question of whether prophylactic surgery is necessary. The implication that severe mitral regurgitation is benign, however, seems biologically implausible. Indeed, the Mayo Clinic data indicate that even mild and moderate mitral regurgitation are risk factors for late morbidity and mortality.[8] Notably, 80% of asymptomatic patients in the Mayo Clinic cohort developed a guideline indication for surgery within 1.2 years.[8] By contrast, only 19% of conservatively managed patients in the series by Kang *et al.*,[3] and 26% in the Vienna study,[7] underwent surgery during the study period (mean follow-up 5 years). Therefore, either patients' characteristics, the surveillance approach, or the threshold for surgical

Box 1 | Summary of conclusions

- Management of asymptomatic severe mitral regurgitation is controversial
- Severe mitral regurgitation is associated with increased risk of midterm cardiac mortality and morbidity
- If a watchful-waiting strategy is used, very careful surveillance to detect symptoms or ventricular dilatation or dysfunction is crucial
- Early surgery for asymptomatic severe mitral regurgitation before onset of ventricular dilatation or dysfunction is increasingly recommended
- A repair probability approaching 100% and operative mortality risk ≤1% is fundamental to the use of an early surgery approach, particularly in patients with normal ventricular function

intervention differed across the three studies. Echocardiographic indications for surgery, such as left ventricular dilatation, should be detectable before the onset of symptoms. The effectiveness of surveillance is, therefore, a key factor that influences the outcomes associated with a watchful-waiting strategy; close surveillance should ensure that patients are referred for surgery before the onset of major symptoms. Symptoms were the trigger for surgery in 94% of patients in the investigation by Kang *et al.*,[3] compared with 69% in the Vienna study[7] and 41% in the Mayo Clinic series.[8] Conversely, surgery was reported as being necessitated by progressive cardiac dilatation or left ventricular dysfunction in 26% of patients in the Vienna series[7] and 39% of the Mayo Clinic patients,[8] compared with none of the patients in the study by Kang *et al.*[3] A high incidence of surgery in conservatively managed patients who develop symptoms raises questions about the adequacy of surveillance. There is a possibility that a more rigorous echocardiographic surveillance schedule in the Mayo Clinic study resulted in earlier recognition of guideline indications for surgery, which emphasizes the importance of strict echocardiographic surveillance in any watchful-waiting strategy.

One final issue is that Kang and colleagues' excellent surgical results—99% freedom from cardiac events at 7 years[3]—do not fit with other surgical series, in which thromboembolism, recurrent mitral regurgitation, or heart failure occurred in 5–10% of patients within that time frame.[9,10] An extremely low incidence of cardiovascular events in any surgical cohort raises suspicion of selection bias, incomplete follow-up, or an atypical cohort. Although the surgical results from Kang *et al.*[3] might seem overly optimistic, it is, nevertheless, likely that surgery for echocardiographic indications in asymptomatic patients is independently associated with reduced late mortality, as demonstrated in the Mayo Clinic series (risk ratio 0.31).[8]

The conclusions that can be drawn from these studies[3,7,8] are summarized in Box 1. The risk associated with mitral valve repair in asymptomatic patients seems to be quite low. In all three series, watchful waiting was associated with subsequent development of criteria for surgery in a substantial proportion of patients. Further studies are required to identify patients who are most likely to suffer from the lack of prompt surgical intervention. From a population perspective, however, we believe that early surgery is the best available strategy to prevent cardiac events secondary to severe mitral regurgitation, provided that a durable repair can be achieved with near 100% certainty and low operative risk.

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1. Bonow, R. O. *et al.* ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* **114**, e84–e231 (2006).
2. Vahanian, A. *et al.* Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur. Heart J.* **28**, 230–268 (2007).
3. Kang, D. H. *et al.* Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. *Circulation* **119**, 797–804 (2009).
4. Bonow, R. O. *et al.* ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease. Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). *J. Heart Valve Dis.* **7**, 672–707 (1998).
5. Adams, D. H. & Anyanwu, A. C. The cardiologist's role in increasing the rate of mitral valve repair in degenerative disease. *Curr. Opin. Cardiol.* **23**, 105–110 (2008).
6. Adams, D. H. *et al.* Large annuloplasty rings facilitate mitral valve repair in Barlow's disease. *Ann. Thorac. Surg.* **82**, 2096–2100 (2006).
7. Rosenhek, R. *et al.* Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation* **113**, 2238–2244 (2006).
8. Enriquez-Sarano, M. *et al.* Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N. Engl. J. Med.* **352**, 875–883 (2005).
9. Flameng, W., Meuris, B., Herijgers, P. & Herregods, M. C. Durability of mitral valve repair in Barlow disease versus fibroelastic deficiency. *J. Thorac. Cardiovasc. Surg.* **135**, 274–282 (2008).
10. Russo, A. *et al.* Thromboembolic complications after surgical correction of mitral regurgitation incidence, predictors, and clinical implications. *J. Am. Coll. Cardiol.* **51**, 1203–1211 (2008).

ATRIAL FIBRILLATION

A4 study: proof of concept?

A. John Camm and Irina Savelieva

The A4 and other similar (small) studies strongly support the launch of major trials of left atrial catheter ablation for the maintenance of sinus rhythm, reduction of cardiovascular hospitalizations and improved survival in patients with symptomatic recurrent atrial fibrillation. Will pharmacological therapies continue to have an important place in the management of atrial fibrillation?

Of the two fundamental treatment strategies for management of patients with atrial fibrillation (AF), rhythm control is generally preferred over rate control by the majority of physicians and for the majority of patients. As experience has been gained with improved catheter techniques and imaging tools, ablation has become an