ESC European Society of Cardiology

European Heart Journal (2018) **39**, 1281–1291
doi:10.1093/eurheartj/ehx465

CLINICAL RESEARCH
Valvular heart disease

The MIDA Mortality Risk Score: development and external validation of a prognostic model for early and late death in degenerative mitral regurgitation

Francesco Grigioni[1]*, Marie-Annick Clavel[2], Jean-Louis Vanoverschelde[3], Christophe Tribouilloy[4], Rodolfo Pizarro[5], Marianne Huebner[6], Jean-Francois Avierinos[7], Andrea Barbieri[8], Rakesh Suri[9], Agnés Pasquet[3], Dan Rusinaru[4], Gaetano D. Gargiulo[1], Pablo Oberti[5], Alexis Théron[7], Francesca Bursi[8], Hector Michelena[2], Siham Lazam[3], Catherine Szymanski[4], Vuyisile T. Nkomo[2], Martin Schumacher[10], Letizia Bacchi-Reggiani[1], and Maurice Enriquez-Sarano[2], on behalf of the MIDA Investigators†

[1]Department of Experimental, Diagnostic and Specialty Medicine, S. Orsola-Malpighi Hospital, University of Bologna, Via Massarenti n. 9, Bologna 40100, Italy; [2]Mayo Clinic, Division of Cardiovascular Disease, Mayo Medical School, 200 First St. SW. Rochester, MN 55905, USA; [3]Cardiovascular Department, University Catholic of Louvain, Avenue Hippocrates 10, 1200 Bruxelles, Belgium; [4]University of Amiens, Cardiology, CHU Amiens-Picardie – SITE SUD, 80054 Amiens Cedex 1, France; [5]Department of Cardiology, Hospital Italiano de Buenos Aires, Juan D. Péron 4190, Buenos Aires, Argentina; [6]Michigan State University, Department of Statistics and Probability, 619 Red Cedar Rd C413, East Lansing, MI 48824, USA; [7]University of Marseille, La Timone Hospital, Service de Cardiologie B, Boulevard Jean Moulin, 13005 Marseille, France; [8]Department of Diagnostic Medicine, Clinical and Health Public, University of Modena, Via del Pozzo 71, 41124 Modena, Italy; [9]Cleveland Clinic, Department of Executive Administration, Al Maryah Island, Abu Dhabi, United Arab Emirates; and [10]Institute for Medical Biometry and Statistics, Medical Center-University of Freiburg, Stefan-Meier-Str. 26, 79104 Freiburg, Germany

Received 6 December 2016; revised 8 April 2017; editorial decision 5 July 2017; accepted 24 July 2017; online publish-ahead-of-print 13 August 2017

See page 1292 for the editorial comment on this article (doi: 10.1093/eurheartj/ehx583)

Aims In degenerative mitral regurgitation (DMR), lack of mortality scores predicting death favours misperception of individual patients' risk and inappropriate decision-making.

Methods and results The Mitral Regurgitation International Database (MIDA) registries include 3666 patients (age 66 ± 14 years; 70% males; follow-up 7.8 ± 5.0 years) with pure, isolated, DMR consecutively diagnosed by echocardiography at tertiary (European/North/South-American) centres. The MIDA Score was derived from the MIDA-Flail-Registry (2472 patients with DMR and flail leaflet-Derivation Cohort) by weighting all guideline-provided prognostic markers, and externally validated in the MIDA-BNP-Registry (1194 patients with DMR and flail leaflet/prolapse-Validation Cohort). The MIDA Score ranged from 0 to 12 depending on accumulating risk factors. In predicting total mortality post-diagnosis, the MIDA Score showed excellent concordance both in Derivation Cohort ($c = 0.78$) and Validation Cohort ($c = 0.81$). In the whole MIDA population ($n = 3666$ patients), 1-year mortality with Scores 0, 7–8, and 11–12 was 0.4, 17, and 48% under medical management and 1, 7, and 14% after surgery, respectively ($P < 0.001$). Five-year survival with Scores 0, 7–8, and 11–12 was 98 ± 1, 57 ± 4, and 21 ± 10% under medical management and 99 ± 1, 82 ± 2, and 57 ± 9% after surgery ($P < 0.001$). In models including all guideline-provided prognostic markers and the EuroScoreII, the MIDA Score provided incremental prognostic information ($P \leq 0.002$).

Conclusion The MIDA Score may represent an innovative tool for DMR management, being able to position a given patient within a continuous spectrum of short- and long-term mortality risk, either under medical or surgical management.

† A complete list of the MIDA investigators is reported in the Appendix.

* Corresponding author. Tel: +39 2143702, Fax: +39 051 6363766, Email: francesco.grigioni@unibo.it

This innovative prognostic indicator may provide a specific framework for future clinical trials aiming to compare new technologies for DMR treatment in homogeneous risk categories of patients.

Keywords Mitral regurgitation • Prognosis • Surgery • Mitral repair • Percutaneous mitral repair • Percutaneous mitral replacement

Introduction

Mitral regurgitation is a public health problem, as the most frequent valvular disease[1] leading to frequent referrals, hospitalizations, and cardiac surgery,[2] and its burden is expected to increase with ageing of the population.[1] Degenerative mitral regurgitation (DMR) with mitral valve prolapse is the most frequent organic mitral regurgitation and the most repairable, but it is often undertreated in routine clinical practice.[3] This prevalent under treatment in both Europe and North America has multiple causes,[4] but is favoured by sub-optimal risk assessment.[2] In DMR, individual risk factors have been identified[5–11] and endorsed by clinical guidelines.[12,13] However, while guidelines strongly recommend a combination of those risk factors in an integrated process,[12,13] there has so far been no attempt at deriving and validating a risk score satisfying such unmet need. The lack of an integrated risk score usable at diagnosis contrasts with the availability of surgical risk scores,[14] which are nevertheless instrumental mainly in surgical decisions. Current unavailability of a mortality score in DMR should not be surprising, since very large cohorts of patients with uniform diagnosis and comprehensive clinical data are required, warranting multi-centre collaboration to obtain separate cohorts for the derivation and validation process (the two mandatory steps to obtain a score and to make it applicable to daily practice). The international MIDA registries[15,16] provide the unique opportunity to analyse a comprehensive set of risk markers (prospectively and homogeneously collected) in an integrated manner, allowing derivation and subsequent external validation of a MIDA Score specifically applicable to DMR.

Accordingly, we aimed at developing a risk score easily derivable from routinely collected clinical/echocardiographic parameters endorsed by guidelines and at validating this score externally. We also wanted to verify the hypothesis that a user-friendly MIDA mortality score is independently and incrementally predictive of short- and long-term survival after diagnosis of DMR. In summary, we aimed at providing for the first time a tool able to position a given patient within a continuous spectrum of mortality risk whether assigned to surgical treatment or to continuing medical therapy.

Methods

A fully detailed 'Methods' section is available as Supplementary material online, whereas a more concise version is reported below.

Study design

The Mitral Regurgitation International DAtabase (MIDA) registries were created by systematically merging a series of prospectively assembled electronic institutional echocardiographic databases, each originally generated to optimize echocardiographic reporting (see Appendix). All patients provided prior informed consent for anonymous publication of their clinical data; the study was conducted in accordance with institutional guidelines, national legal requirements, and the revised Helsinki declaration. The present reporting complies with the TRIPOD statement and dedicated tutorials.[17 18]

General inclusion/exclusion criteria of the MIDA registries

All MIDA registries share analogous general eligibility criteria: (i) inclusion of consecutive patients with primary DMR by transthoracic echocardiography; (ii) availability of a comprehensive clinical/instrumental evaluation at index echocardiography; (iii) exclusion of secondary (functional) mitral regurgitation of any aetiology, ischaemic regurgitation, significant concomitant aortic disease, mitral stenosis, active endocarditis, congenital diseases, prior valve surgery.

Derivation Cohort

Patients analysed in the Derivation Cohort were those included in the MIDA-Flail Registry encompassing 1/1/1980 to 12/31/2005.[15] Patients enrolled in the MIDA-Flail Registry fulfilled the general inclusion/exclusion criteria of the MIDA registries, but, as an additional requirement, they all received a diagnosis of DMR *and* flail leaflets.

Validation Cohort

The Validation Cohort consists of consecutive patients enrolled in the MIDA-BNP Registry, encompassing 1/1/2000 to 31/12/2013.[16] The MIDA-BNP Registry fulfils the general inclusion/exclusion criteria of the MIDA registries, but it additionally requires -as a specific inclusion criterion- a blood sample collection. The diagnosis of flail leaflets is not mandatory for the MIDA-BNP Registry, and both DMR and mitral valve prolapse *or* DMR and flail leaflets can be included. By study design, patients could be part of only one of the two cohorts.

Echocardiography

Echocardiographic data were analysed as collected at the time of echocardiography[19] without subsequent modification. The severity of DMR was based on the final diagnosis reported in the original echocardiographic report, which was performed by integrating all recorded echocardiographic parameters.[12,13,20]

Statistical analysis

Prognostic markers analysed to create the MIDA Score were selected on the basis of their known link to outcome in DMR and their guideline-based mention as a potential trigger for surgery (i.e. age ≥65 years, left atrial diameter ≥55 mm, ejection fraction ≤60%, left ventricular end-systolic diameter ≥40 mm, heart failure symptoms, atrial fibrillation, and right ventricular systolic pressure >50 mmHg).[11–13]

Study end points and follow-up

The primary end point was long-term survival. The secondary end point was 1-year survival. Outcome was ascertained by investigators blinded to baseline predictors of outcome. The follow-up was completed up to death, end of the study or at least 5 years in 3322 (91%) patients.

Competing risk models and development of the MIDA Score

Since surgery is a competing risk event when analysing survival under medical management, we took advantage of competing risk analysis. This approach makes it possible to estimate hazard rates separately for each transition, diagnosis to surgery, or diagnosis to death, stratified by centre. A Markov proportional hazards model was used to estimate the hazard ratios (HR) for predictors at transitions from diagnosis to surgery, or diagnosis to death. Proportional hazard assumptions were evaluated with scaled Schoenfeld residuals.

Hazard ratios of univariate competing risk models were estimated in the Derivation Cohort for the components of the Score. Weights for these risk factors were calculated by redoing the univariate, transition-specific HR. In order to capture the risk attached to the consequences of volume overload (rather than the nonspecific risk of death related to aging),[11] the weight for age ≥ 65 years in keeping with the results of competing risk analysis was set at a value of 3 (see Supplementary material online for more explanation). For each patient the MIDA Score was calculated as the sum of these weights (*Table 2*).

The predictive ability of the MIDA Score for survival under medical management was described using a Harrell's C-statistic for the survival models.[21] The C-statistic ranges from 0.5 to 1.0, with values of 0.5 indicating no predictive ability, and a value of 1.0 indicating perfect predictive ability. The C-statistic was estimated by fitting a competing risk model to the derivation data and the validation data separately.

Missing data

Since some variables may not have been detectable (e.g. systolic pulmonary pressure in the absence of tricuspid regurgitation), the main analysis was based on the clinical principle that absent or missing variables are counted as negative. As an additional analysis, multiple imputation was used to generate 10 data sets and then to average the results.

Predictive ability of the MIDA Score for 1-year mortality

Association of the MIDA Score with 1-year mortality was analysed with a logistic regression model in the Derivation Cohort and validated for the Validation Cohort. The C-statistic (Somer's D) was used to examine the predictive power of the score in the Validation Cohort.

Results

Baseline characteristics and MIDA Score in the Derivation Cohort

Baseline characteristics of 2472 patients included in the Derivation Cohort are summarized in *Table 1* (left column). Flail leaflet was idiopathic in 2301 (93%) patients, caused by healed endocarditis in 171 (7%). Involvement was confined to the posterior leaflet in 1956 (79%) patients and to the anterior leaflet in 346 (14%), while both leaflets were involved in 170 (7%) patients.

During follow-up (9.2 ± 5.4 years), 960 deaths occurred (390 under medical management). Overall survival at 10 years was 68 ± 1% (56 ± 2% in patients symptomatic at diagnosis).

At univariate analysis, symptom presence, ejection fraction ≤60%, left-ventricular end-systolic diameter ≥40 mm, atrial fibrillation presence, right ventricular systolic pressure ≥50 mmHg, left atrial diameter ≥55 mm, and age ≥65 years were all associated with survival

Table 1 Baseline characteristics of the study population ($n = 3666$)

	Derivation Cohort ($n = 2472$)	Validation Cohort ($n = 1194$)	Combined Cohort ($n = 3666$)	*P*-value
Age (years)	67 ± 13	64 ± 15	66 ± 14	<0.001
Male gender	1766 (72%)	779 (65%)	2545 (70%)	<0.001
Asymptomatic	1643 (67%)	520 (43%)	2163 (59%)	<0.001
Heart rate (bpm)	76 ± 16	70 ± 14	74 ± 16	<0.0001
Sinus rhythm	1916 (77%)	982 (82%)	2898 (79%)	0.008
History of atrial fibrillation	710 (28%)	212 (18%)	922 (25%)	<0.001
Severe mitral regurgitation	2362 (96%)	918 (77%)	3280 (90%)	<0.001
Left atrial diameter (mm)	50 ± 9	49 ± 8	50 ± 9	<0.001
Left ventricular end-diastolic diameter (mm)	58 ± 7	56 ± 7	57 ± 7	<0.001
Left ventricular end-systolic dimension (mm)	36 ± 7	35 ± 7	36 ± 7	<0.001
Left ventricular ejection fraction (%)	64 ± 10	63 ± 9	64 ± 10	0.07
Right ventricular systolic pressure (mmHg)	44 ± 17	38 ± 16	42 ± 17	<0.001
Vasodilators	1037 (42%)	510 (43%)	1547 (42%)	0.66
Beta blockers	436 (18%)	469 (39%)	905 (25%)	<0.0001
Diuretics	837 (34%)	569 (48%)	1406 (38%)	<0.0001
Digoxin	589 (24%)	101 (9%)	690 (19%)	<0.0001
EuroScore II	1.15 [0.74–1.83]	1.20 [0.79–2.48]	1.17 [0.75–1.98]	0.24
Charlson score	1.36 ± 1.65	1.12 ± 1.81	1.28 ± 1.70	<0.0001

Table 2 Development of the MIDA Score (Derivation Cohort)

	HR Cox	HR competing risk	HR competing risk and imputation	Points
Age ≥ 65 year	5.1 [2.9–10]	3.9 [2.4–6.4]	5.1 [3.6–7.2]	3
Symptoms	1.99 [1.4–2.8]	2.69 [1.9–3.9]	2.55 [1.9–3.3]	3
Atrial fibrillation	1.06 [0.8–1.5]	1.09 [0.8–1.5]	1.29 [1.1–1.6]	1
Left atrial diameter ≥ 55 mm	1.64 [1.2–2.3]	1.70 [1.2–2.4]	1.48 [1.1–1.9]	1
Right ventricular systolic pressure > 50 mmHg	1.99 [1.4–2.7]	1.71 [1.2–2.5]	1.71 [1.3–2.3]	2
Left ventricular end-systolic diameter ≥ 40 mm	1.48 [1.0–2.2]	1.62 [1.1–2.5]	1.29 [1.0–1.8]	1
Left ventricular ejection fraction ≤ 60%	1.0 [0.7–1.4]	0.88 [0.6–1.3]	1.17 [0.9–1.5]	1

The hazard ratio (HR) refers to Cox proportional hazard analysis, competitive risk analysis, and competitive risk analysis and imputation with overall mortality as the end point; the points contributing to the MIDA Score are weighted according to the HR obtained. As an example, a patient presenting all the above seven risk factors would totalize a MIDA Score of 12; a 55-year-old asymptomatic patient in sinus rhythm with normal left ventricular size and function presenting only left atrial diameter ≥ 55 mm and right ventricular systolic pressure > 50 mmHg would totalize a MIDA Score of 3 (see the text for more explanation).

Table 3 MIDA Score distribution of the study population

	Derivation Cohort ($n = 2472$)	Validation Cohort ($n = 1194$)	Combined Cohort ($n = 3666$)	*P*-value
MIDA Score 0	330 (14%)	203 (17%)	533 (14%)	0.013
MIDA Score 1–2	329 (13%)	77 (6%)	406 (11%)	—
MIDA Score 3–4	779 (31%)	390 (33%)	1169 (32%)	—
MIDA Score 5–6	442 (18%)	226 (19%)	668 (18%)	—
MIDA Score 7–8	350 (14%)	204 (17%)	554 (15%)	—
MIDA Score 9–10	195 (8%)	83 (7%)	278 (8%)	—
MIDA Score 11–12	47 (2%)	11 (1%)	58 (2%)	—

after diagnosis (all $P \leq 0.001$). The HR [95% confidence interval (CI)] obtained by including all prognostic factors in the Cox-proportional hazard, competing risk and competing risk with imputation models and their consequent weights contributing to the Score are reported in *Table 2*.

In the Derivation Cohort, the median MIDA Score was 4 (25th–75th percentile: 2–6) (*Table 3*). The MIDA Score adjusted for age was independently associated with an increased risk of death under medical follow-up (adjusted HR [95% CI] per unit 1.20 [1.15–1.25] $P < 0.001$). The independent prognostic significance of the MIDA-Score was also confirmed by competing risk model and multiple imputation (adjusted HR [95% CI] per unit 1.18 [1.13–1.23] $P < 0.001$). The concordance for the model with the MIDA Score adjusted for age in the Derivation Cohort was satisfactory [$c = 0.78$; standard deviation (SD) 0.02].

Mitral valve surgery was eventually performed in 1934 (78%) patients (89% repair). The median time (25th–75th percentile) from the baseline echocardiogram to the operation was 0.2 (0.1–1.9) years. During a post-surgical follow-up of 9.2 ± 4.8 years (median [25–75th percentile], 8.7 [6.3–12.1] years), 570 patients died. The MIDA Score regardless of age was associated with an increased risk of post-surgical death (adjusted HR [95% CI] per unit 1.15 [1.11–1.19] $P < 0.0001$). Data on recurrence of regurgitation after repair were available for 1480/1713 patients; 20 years' freedom from ≥3+ mitral regurgitation was 88% (95% CI, 86–90).

Baseline characteristics and MIDA Score in the Validation Cohort

Baseline characteristics of the Validation Cohort ($n = 1194$) and MIDA Score distribution are depicted in *Tables 1* and *3*, respectively. When compared to the Derivation Cohort, patients included in the Validation Cohort were more often symptomatic, although showing less severe consequences of DMR. These findings can be explained by the limited reproducibility of symptom assessments, the higher prevalence of female patients in the Validation Cohort, and the higher use of beta-blockers rather than digoxin in this group.[22] During a follow-up of 4.8 ± 2.4 years, 191 deaths occurred (131 under medical management). Overall survival at 10 years was 68 ± 5% (59 ± 7% in patients symptomatic at diagnosis). Surgery was eventually performed in 725 patients (93% repair).

Competing risk analysis confirmed the MIDA Score to be regardless of age associated with long-term risk of death under medical management (adjusted HR [95% CI] per unit 1.13 [1.01–1.22]; $P < 0.001$) ($c = 0.81$; SD 0.03). The MIDA Score regardless of age also predicted long term post-surgical outcome (adjusted HR [95% CI] per unit 1.35 [1.19–1.54]; $P < 0.001$). Association of the MIDA Score with 1-year mortality was analysed with a logistic regression model in the Derivation Cohort and validated in the Validation Cohort and found to be satisfactory (Derivation Cohort: $c = 0.7540$; Validation Cohort: $c = 0.7537$) (*Figure 1*).

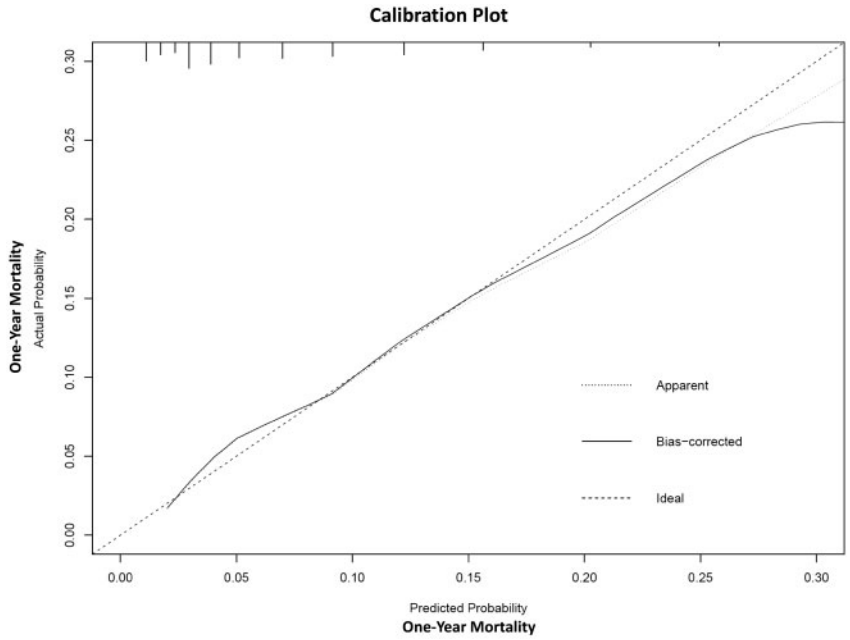


Figure 1 Validation plot (the distribution of the MIDA Score is indicated with spikes at the top of the graph).

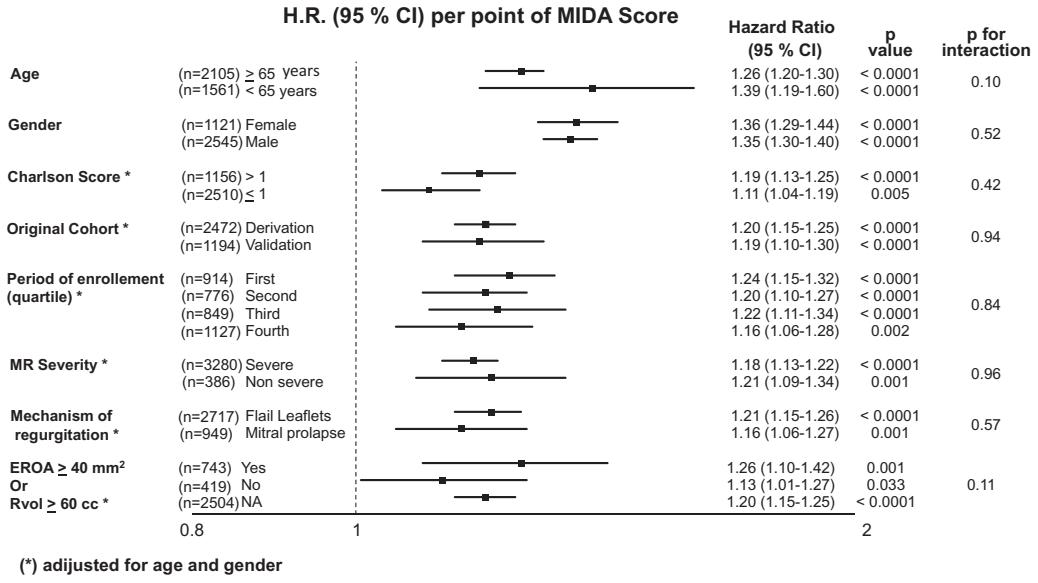


Figure 2 Independent association of the MIDA Score with long-term mortality in selected sub-groups (see text). Regurgitant volume and/or effective regurgitant orifice area were available in 1162 patients.

Specific outcomes in the Combined Cohort

Since remarkably similar 5- and 10-year survival rates were recorded and an analogous prognostic ability of the MIDA Score had been confirmed, we combined Derivation and Validation Cohorts to further increase the sample size in order to facilitate long-term follow-up and sub-group analyses. Baseline characteristics of the Combined Cohort are reported in *Tables 1* and *3*, respectively. During a follow-up of 7.8 ± 5.0 years, 1151 patients died. Overall survival at 5 and 10 years was 84 ± 1 and 69 ± 1% years, respectively.

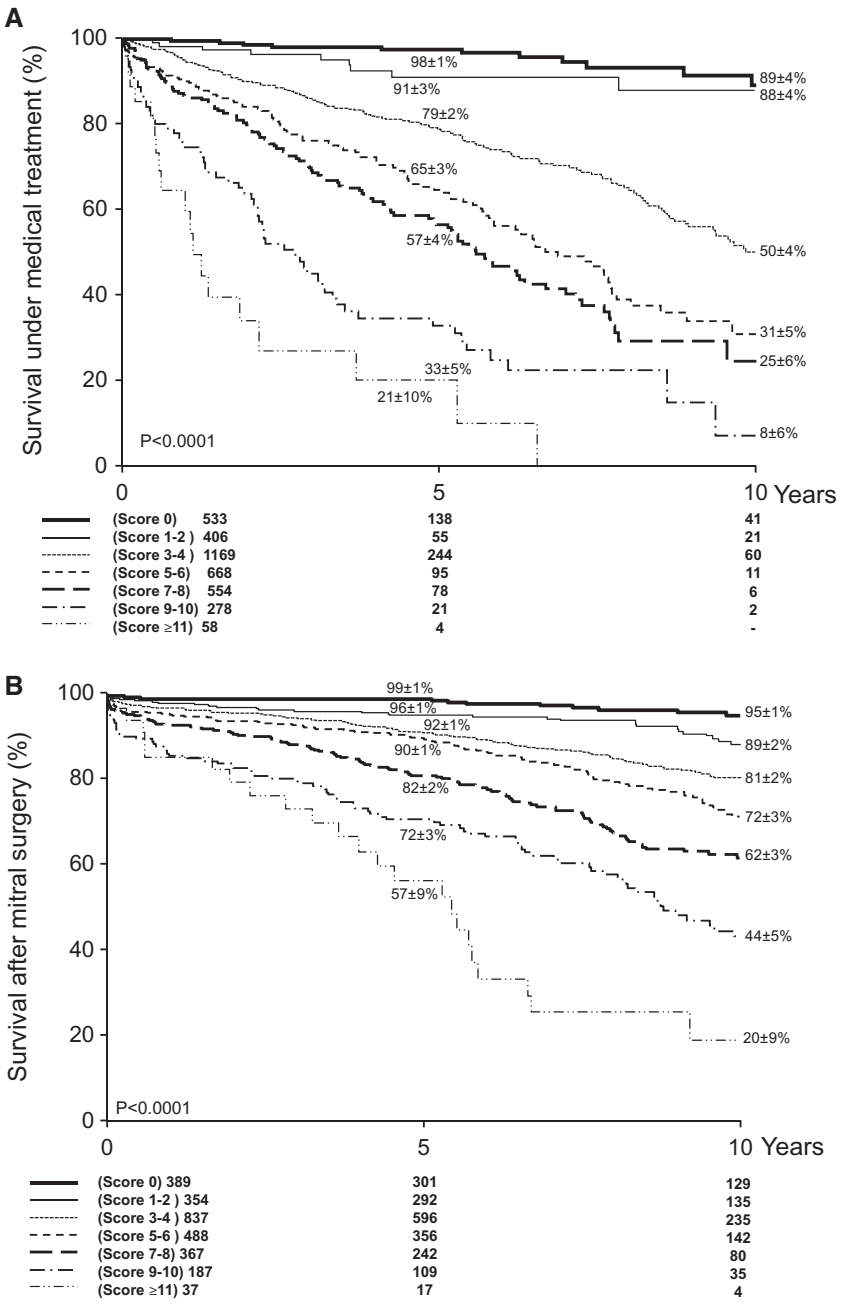


Figure 3 (*A*) Long-term overall survival of 3666 patients affected by degenerative mitral regurgitation *under medical management* according to MIDA Score (Kaplan–Meier analysis). The follow-up was censored at the time of surgery when performed. (*B*) Long-term *post-surgical* overall survival of 2659 patients affected by degenerative mitral regurgitation according to MIDA Score (Kaplan–Meier analysis).

During a medical follow-up of 2.1 ± 3.5 years, 521 patients died. *Figure 2* reports the independent association of the MIDA Score with mortality under medical management in selected sub-groups. Long-term survival according to the categories of MIDA Score is depicted in *Figure 3A* and (using multiple imputation) in *Figure 4A* (see Supplementary material online).

Surgery was eventually performed in 2659 patients (90% repair). During a post-surgical follow-up of 7.8 ± 4.8 years, 630 patients died. Perioperative mortality occurred in 40 patients (1.5%). The mean EuroSCORE II was: 1.72% (median [25–75th percentile] 1.17 [0.75–1.98]) in the entire population; 3.04% in patients who died during the perioperative period (vs. 1.71% in those who survived, $P = 0.004$); 1.99% in those who were treated exclusively medically (vs. 1.62% in those who were operated on, $P < 0.001$).

When the post-surgical outcome was analysed, the MIDA Score retained its independent prognostic significance from age and

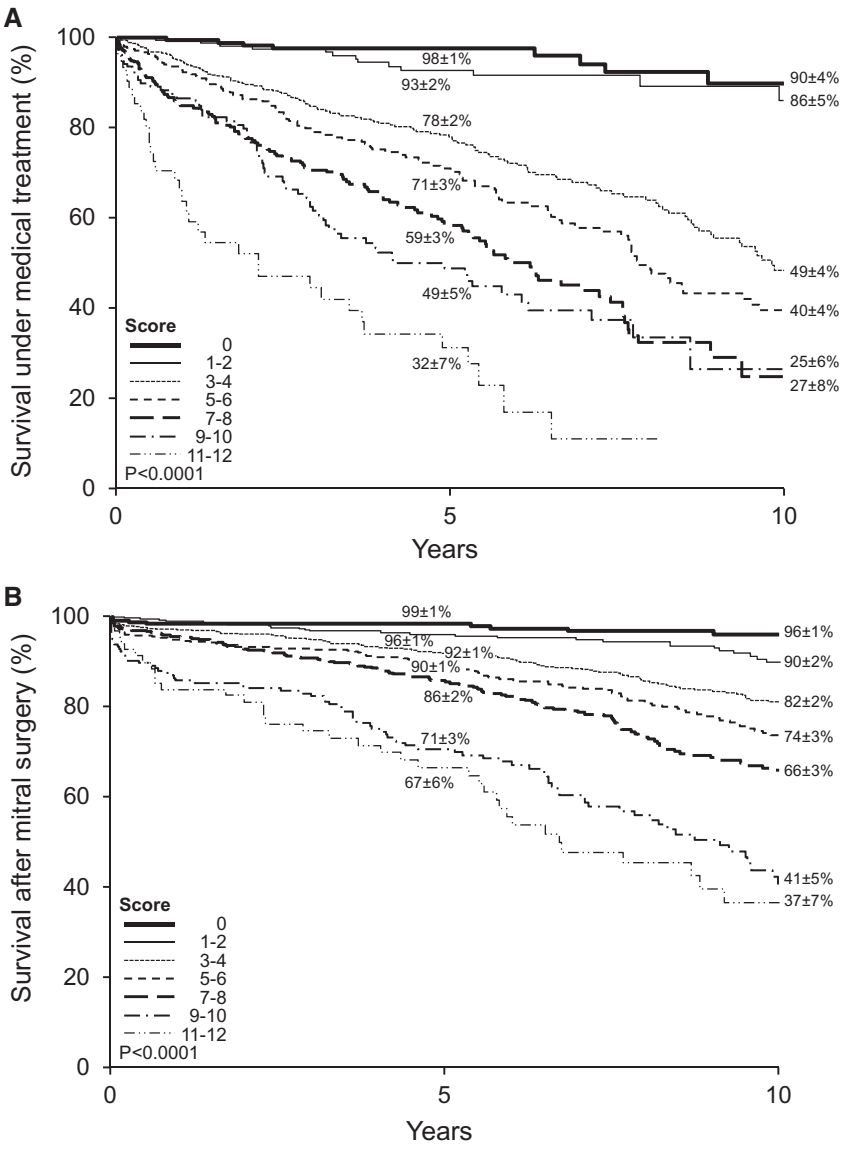


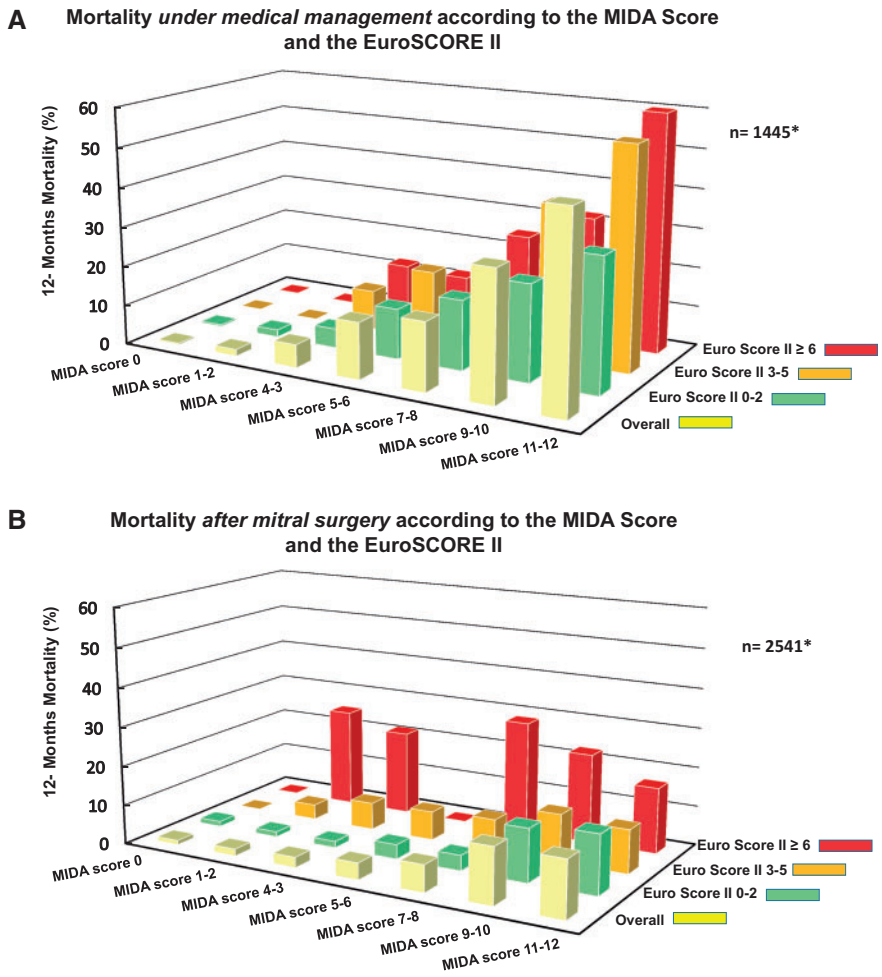
Figure 4 (*A*) Long-term overall survival of 3666 patients affected by degenerative mitral regurgitation *under medical management* according to MIDA Score (Kaplan–Meier analysis and multiple imputation) (see Supplementary material online). The follow-up was censored at the time of surgery when performed. (*B*) Long-term estimated *post-surgical* overall survival of 2659 patients affected by degenerative mitral regurgitation according to MIDA Score (Kaplan–Meier analysis and multiple imputation) (see Supplementary material online).

symptoms with death as the end point (adjusted HR [95% CI] per unit: 1.23 [1.16–1.29]; $P < 0.001$). Long-term post-surgical survival according to the category of MIDA Score is depicted in *Figure 3B* and using multiple imputation in *Figure 4B* (see Supplementary material online).

Take home figure reports 12-month mortality according to the MIDA Score under medical management (*Take home figure A*) and after surgery (*Take home figure B*) overall and by EuroSCORE II.

When the MIDA Score was factored into a model including all seven components of the score itself and surgery (adjusted HR [95% CI] for surgery 0.27 [0.24–0.30]; $P < 0.0001$), the MIDA Score provided incremental information [change in the model X^2 21; $P = 0.002$; net reclassification improvement (NRI) for 5-years mortality 0.12, $P = 0.009$]. When factored into a model including age, surgery and EuroScore II, the MIDA Score provided incremental prognostic significance (change in the model X^2 233, $P < 0.0001$) (NRI for 1-, 3-, and 5-years mortality 0.40, 0.37, and 0.41, respectively; all *P*-values < 0.0001). Adjusted survival curves by MIDA Score category in patients with lower/higher EuroScore II are illustrated in *Figure 5A* and *B* (see Supplementary material online).

The prognostic ability of the MIDA Score was retained when confining the analysis to patients who had mitral repair (adjusted HR [95% CI] per unit: 1.30 [1.11–1.54]; $P = 0.001$), or replacement (adjusted HR [95% CI] per unit: 1.18 [1.15–1.21]; $P < 0.0001$).



Take home figure One-year mortality according to the MIDA Score under medical management (*A*) and after surgery (*B*) overall and by EuroSCORE II. *Only patients observed for at least 1 year under medical follow-up (*A*) or after surgery (*B*) are included in the analysis (or who died within 1 year).

Discussion

The management of DMR—and particularly the indications for surgery—mainly relies on symptoms and/or echocardiographic measurements providing specific cut-offs reflecting the magnitude of volume overload consequences. Physicians are invited by guidelines to search for the presence of any of those during decision-making, but the highly relevant therapeutic consequences deriving from ascertaining the presence of even one risk factor (which may lead '*per* se' to a surgical decision) likely favour DMR under treatment. At the same time, while the operative risk in a given patient is predictable through specific mortality scores, the mortality risk of continuing medical treatment for the same patient is not yet definable.

We analysed the outcome of two cohorts totalling an unmatched sample of 3666 patients, all affected by DMR, to build a risk score integrating the presence of risk factors endorsed by scientific guidelines and their clinical weight. The MIDA Score we derived and validated was able to position a given patient within a continuous spectrum of mortality risk, before or after surgery, at short- and long-term. Because we found a considerable difference in mortality between the MIDA Score levels, our data indicate that the MIDA-Score could generate highly relevant clinical information, of independent prognostic value and incremental to known indicators of current guidelines for the management of DMR.

The EuroSCORE II was significantly higher in patients who were treated exclusively medically as compared to those who received a mitral operation. Taken together, our findings suggest that physicians may underestimate the spontaneous high risk of patients left under medical management, due to the lack of tools defining the risk incurred under such circumstances. By accurately defining not just long-term outcome but also the short-term and 1-year survival under medical management, the MIDA Score could contribute in preventing delays in treating higher risk patients.[13] We found that the MIDA Score retains its prognostic value within each subset of patients categorized by EuroSCORE II (*Take home figure* and *Figure 5*), indicating that in the context of a known risk marker, the MIDA Score maintains an incremental prognostic predictive value.

Percutaneous treatment of DMR represents an increasingly used therapeutic option.[23] Whether a percutaneous treatment of DMR could represent a better strategy as compared to traditional surgery

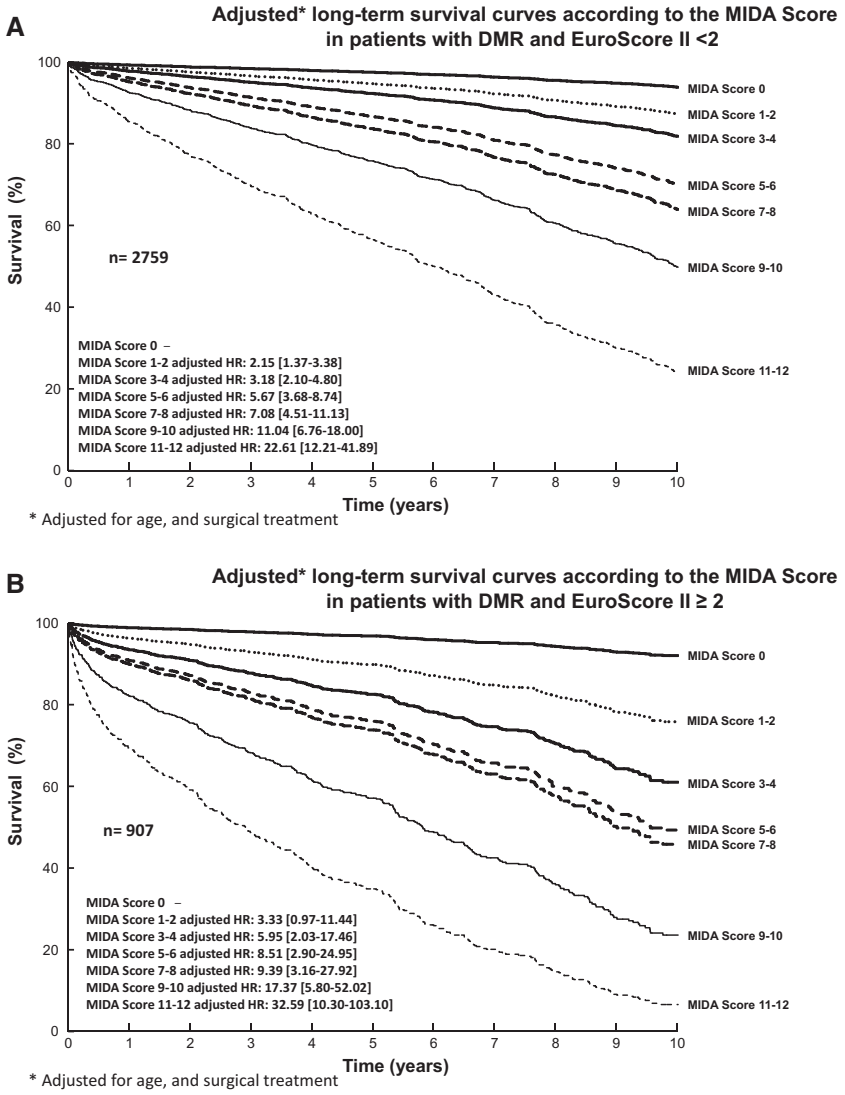


Figure 5 Adjusted survival curves according to the MIDA Score in patients with EuroScore II < 2 (*A*) and ≥ 2 (*B*).

in selected groups of patients with the highest MIDA Score and EuroSCORE II remains unanswered by the present retrospective analysis, but we provide a tool allowing for this hypothesis to be tested in randomized control studies. It is expected that the explosion of new technologies, robotic surgery, percutaneous repair, or replacement may be highly attractive to patients due to their perceived limited invasiveness.[24] However, these new technologies are costly and the goal of their rational dispersion,[25] based on appropriate use definition, cannot be achieved if the risks incurred by patients are not precisely defined. The MIDA Score we developed may represent a useful tool to test the new technologies in patients with homogenous risk of death.

Model discrimination expresses the extent to which the model itself is capable of differentiating patients who have experienced events and it is commonly assessed using the *C-statistic*.[26] We found a C-statistic of the MIDA Score with death as the end point of 0.78 in the derivation MIDA cohort and of 0.81 in the Validation Cohort. These values of C-statistic, although they can be improved, are comparable to those obtained by commonly used clinical scores (including the Heart Failure Survival Score,[26] the Seattle Heart Failure Model,[26] the Logistic EuroSCore, and EuroSCORE II.[27,28] With respect to calibration of the MIDA Score, (i.e. investigating how close the values predicted by the MIDA Score are to the observed values) this was overall quite satisfactory[26] (*Figure 1*). Whether the addition of parameters deriving from cardiopulmonary exercise tests or the use of peptides (currently not yet considered mandatory by guidelines) may enhance the overall performance of the MIDA Score needs to be tested.[29]

Concerning the strength and limitations of the present study, the MIDA Score was derived from the MIDA registries, which although representing the largest international multi centre registries specifically designed to study DMR, are not necessarily

immune from the risk of selection bias. It is reassuring that all prognostic indicators endorsed by American and European scientific guidelines were confirmed as being valid in the present analysis. Concerning the validity of the study findings, we decide to use external validation, which is particularly demanding but at the same time the method with the greatest clinical relevance.[30] The MIDA-Score provides good discrimination, but no therapeutic decision making should exclusively rely on a single number, and should rather be based on an integrated clinical approach.[13] Since the vast majority of the study patients had severe DMR, the role of the MIDA Score in non-severe DMR—although confirmed at subgroup analysis—needs further investigations.

In conclusion, DMR management requires extensive prognostic assessment.[12,13] The MIDA Score, developed using the largest cohorts of DMR medically and surgically treated ever analysed, can for the first time position a given patient within a continuous spectrum of short- and long-term mortality risk, overall, under medical management and after surgery, providing incremental and independent prognostic information. Our findings—generated by analysis of data collected at multiple centres from different continents—may contribute to improve DMR management, by not only facilitating guidelines application but also providing a useful tool to test new therapeutic options for patients with DMR in homogeneous categories of risk.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

The present work was funded by an unrestricted grant donated by the 'Fondazione del Monte di Bologna e Ravenna' and 'Fondazione Luisa Fanti Melloni'.

Conflicts of interest: R.S. received grant funding from Edwards Life Sciences, Sorin Group and St Jude Medical and support for travel and accommodation from Sorin Group. F.G. received payments as a board member from Sorin Group and grant funding from 4Tech. M.E.-S. served as a board member for Valtech and received grant funding from Abbott Vascular.

Appendix

MIDA Investigators

C. Tribouilloy, F. Trojette, C. Szymanski, D. Rusinaru, G. Touati, J. P. Remadi (University of Amiens, France). F. Grigioni, A. Russo, E. Biagini, F. Pasquale, M. Ferlito, C. Rapezzi, C. Savini, G. Marinelli, D. Pacini, G.D. Gargiulo, R. Di Bartolomeo, I. Corazza (University of Bologna, Italy). P. Oberti, R. Pizarro (Hospital Italiano de Buenos Aires, Argentina). J. Boulif, C. de Meester, G. El Khoury, B. Gerber, S. Lazam, A. Pasquet, P. Noirhomme, D. Vancraeynest, J.-L. Vanoverschelde (Université Catholique de Louvain, Belgium). J. F. Avierinos, F. Collard, A. Théron, G. Habib (University of Marseille, France). A. Barbieri, F. Bursi, F. Mantovani, R. Lugli, M. G. Modena, G. Boriani (University of Modena, Italy). M.A. Clavel, J. Maalouf, H. Michelena, Vuyisile T. Nkomo, M. Enriquez-Sarano (Mayo Clinic, Mayo Medical School, Rochester MN, USA). R. Suri (Cleveland Clinic, Abu Dhabi).

Statisticians: L. Bacchi-Reggiani (University of Bologna, Italy), M. Schumacher (University of Freiburg, Germany), M. Huebner (Michigan State University).

References

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;**368**:1005–1011.
2. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003;**24**:1231–1243.
3. Mirabel M, Iung B, Baron G, Messika-Zeitoun D, Detaint D, Vanoverschelde JL, Butchart EG, Ravaud P, Vahanian A. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *Eur Heart J* 2007;**28**:1358–1365.
4. Bach DS, Awais M, Gurm HS, Kohnstamm S. Failure of guideline adherence for intervention in patients with severe mitral regurgitation. *J Am Coll Cardiol* 2009;**54**:860–865.
5. Tribouilloy CM, Enriquez-Sarano M, Schaff HV, Orszulak TA, Bailey KR, Tajik AJ, Frye RL. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. *Circulation* 1999;**99**:400–405.
6. Ling LH, Enriquez-Sarano M, Seward JB, Tajik AJ, Schaff HV, Bailey KR, Frye RL. Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med* 1996;**335**:1417–1423.
7. Grigioni F, Avierinos JF, Ling LH, Scott CG, Bailey KR, Tajik AJ, Frye RL, Enriquez-Sarano M. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. *J Am Coll Cardiol* 2002;**40**:84–92.
8. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, Detaint D, Capps M, Nkomo V, Scott C, Schaff HV, Tajik AJ. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med* 2005;**352**:875–883.
9. Tribouilloy C, Grigioni F, Avierinos JF, Barbieri A, Rusinaru D, Szymanski C, Ferlito M, Tafanelli L, Bursi F, Trojette F, Branzi A, Habib G, Modena MG, Enriquez-Sarano M. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets a long-term follow-up multicenter study. *J Am Coll Cardiol* 2009;**54**:1961–1968.
10. Rusinaru D, Tribouilloy C, Grigioni F, Avierinos JF, Suri RM, Barbieri A, Szymanski C, Ferlito M, Michelena H, Tafanelli L, Bursi F, Mezghani S, Branzi A, Habib G, Modena MG, Enriquez-Sarano M. Left atrial size is a potent predictor of mortality in mitral regurgitation due to flail leaflets: results from a large international multicenter study. *Circ Cardiovasc Imaging* 2011;**4**:473–481.
11. Avierinos JF, Tribouilloy C, Grigioni F, Suri R, Barbieri A, Michelena HI, Ionico T, Rusinaru D, Ansaldi S, Habib G, Szymanski C, Giorgi R, Mahoney DW, Enriquez-Sarano M. Impact of ageing on presentation and outcome of mitral regurgitation due to flail leaflet: a multicentre international study. *Eur Heart J* 2013;**34**:2600–2609.
12. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD. 2014 AHA/ACC guideline 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. *J Am Coll Cardiol* 2014;**63**:e57–185.
13. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Lung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* 2012;**42**: S1–44.
14. Nashef SA, Sharples LD. Editorial comment: pride without prejudice: EuroSCORE II, the STS score and the high-risk patient subset. *Eur J Cardiothorac Surg* 2013;**44**:1012.
15. Suri RM, Vanoverschelde JL, Grigioni F, Schaff HV, Tribouilloy C, Avierinos JF, Barbieri A, Pasquet A, Huebner M, Rusinaru D, Russo A, Michelena HI, Enriquez-Sarano M. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. *JAMA* 2013;**310**:609–616.

16. Clavel MA, Tribouilloy C, Vanoverschelde JL, Pizarro R, Suri RM, Szymanski C, Lazam S, Oberti P, Michelena HI, Jaffe A, Enriquez-Sarano M. Association of B-type natriuretic peptide with survival in patients with degenerative mitral regurgitation. *J Am Coll Cardiol* 2016;**68**:1297–1307.
17. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, Vickers AJ, Ransohoff DF, Collins GS. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015;**162**:W1–73.
18. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J* 2014;**35**:1925–1931.
19. Tajik A, Seward J, Hagler D, Mair D, Lie J. Two-dimensional real-time ultrasonic imaging of the heart and great vessels, technique, image orientation, structure identification, and validation. *Mayo Clin Proc* 1978;**53**:271–303.
20. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;**16**:777–802.
21. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;**15**:361–387.
22. Devereux RB, Kramer-Fox R, Brown WT, Shear MK, Hartman N, Kligfield P, Lutas EM, Spitzer MC, Litwin SD. Relation between clinical features of the mitral prolapse syndrome and echocardiographically documented mitral valve prolapse. *J Am Coll Cardiol* 1986;**8**:763–772.
23. Nickenig G, Estevez-Loureiro R, Franzen O, Tamburino C, Vanderheyden M, Luscher TF, Moat N, Price S, Dall'Ara G, Winter R, Corti R, Grasso C, Snow TM, Jeger R, Blankenberg S, Settergren M, Tiroch K, Balzer J, Petronio AS, Buttner HJ, Ettori F, Sievert H, Fiorino MG, Claeys M, Ussia GP, Baumgartner H, Scandura S, Alamgir F, Keshavarzi F, Colombo A, Maisano F, Ebelt H, Aruta P, Lubos E, Plicht B, Schueler R, Pighi M, Di Mario C. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. *J Am Coll Cardiol* 2014;**64**:875–884.
24. Nishimura RA, Vahanian A, Eleid MF, Mack MJ. Mitral valve disease—current management and future challenges. *Lancet* 2016;**387**:1324–1334.
25. Mack MJ, Holmes DR Jr. Rational dispersion for the introduction of transcatheter valve therapy. *JAMA* 2011;**306**:2149–2150.
26. Alba AC, Agoritsas T, Jankowski M, Courvoisier D, Walter SD, Guyatt GH, Ross HJ. Risk prediction models for mortality in ambulatory patients with heart failure: a systematic review. *Circ Heart Fail* 2013;**6**:881–889.
27. Wang L, Han QQ, Qiao F, Wang C, Zhang XW, Han L, Xu ZY. Performance of EuroSCORE II in patients who have undergone heart valve surgery: a multicentre study in a Chinese population. *Eur J Cardiothorac Surg* 2014;**45**:359–364.
28. Guida P, Mastro F, Scrascia G, Whitlock R, Paparella D. Performance of the European System for Cardiac Operative Risk Evaluation II: a meta-analysis of 22 studies involving 145,592 cardiac surgery procedures. *J Thorac Cardiovasc Surg* 2014;**148**:3049–3057.e1.
29. Pizarro R, Bazzino OO, Oberti PF, Falconi M, Achilli F, Arias A, Krauss JG, Cagide AM. Prospective validation of the prognostic usefulness of brain natriuretic peptide in asymptomatic patients with chronic severe mitral regurgitation. *J Am Coll Cardiol* 2009;**54**:1099–1106.
30. Collins GS, Altman DG. Design flaws in EuroSCORE II. *Eur J Cardiothorac Surg* 2013;**43**:871.