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# Mitral mechanical replacement in young rheumatic women: Analysis of long-term survival, valve-related complications, and pregnancy outcomes over a 3707–patient-year follow-up

Luca Salvatore De Santo, MD,[a] Gianpaolo Romano, MD,[b] Alessandro Della Corte, MD,[a] Francesco Tizzano, MD,[a] Andrea Petraio, MD,[a] Cristiano Amarelli, MD,[b] Marisa De Feo, MD,[c] Giovanni Dialetto, MD,[b] Michelangelo Scardone, MD,[b] and Maurizio Cotrufo, MD, FECTS[a]

Figures E1 to E3 are available online.

**Objective:** A follow-up study was performed to assess long-term survival, valve-related complications, and pregnancy outcomes in young rheumatic women undergoing isolated mitral mechanical replacement. The influence of prosthetic type on outcomes was also investigated.

**Methods:** Between 1975 and 2003, 267 isolated mitral mechanical prostheses were implanted. Follow-up reached 3707.8 patient-years.

**Results:** Actuarial survival at 1, 5, 10, 15, 20, and 25 years was 97% ± 0.01%, 90.4% ± 0.017%, 85.3% ± 0.023%, 82.3% ± 0.025%, 71.7% ± 0.036%, and 70.2% ± 0.038%, respectively. At multivariate analysis, atrial fibrillation at follow-up was identified as an independent risk factor for late mortality, whereas left ventricular ejection fraction at 12 postoperative months proved to be a protective factor. Freedom from thromboembolism at 1, 5, 10, 15, 20, and 25 years was 98.1% ± 0.01%, 94.1% ± 0.015%, 89.1% ± 0.021%, 85.9% ± 0.025%, 81.1% ± 0.031%, and 75.3% ± 0.063%, respectively. Atrial fibrillation and Carbomedics device were significantly associated with an increase in thromboembolic events. Freedom from reoperation at 1, 5, 10, 15, 20, and 25 years was 99.2% ± 0.005%, 95% ± 0.014%, 91.6% ± 0.018%, 88.6% ± 0.022%, and 85.7% ± 0.041%. Type of prosthesis (tilting disc) was identified as a predictor of reoperation. At the end of the study, 208 patients were still alive: 94.7% were in New York Heart Association class I or II. When receiving warfarin therapy, no patient undertaking pregnancy (n = 35) experienced adverse cardiac or valve-related events. Fetal events were significantly less frequent with a daily warfarin dose less than 5 mg.

**Conclusions:** Mechanical devices provided excellent performance, safety, and durability. The prognostic role of left ventricular function and atrial fibrillation overwhelmed any differences that might exist between different prosthetic designs. Pregnancies entail virtually no maternal risk and predictable fetal complications.

From the Department of Cardio-Thoracic and Respiratory Sciences, Second University of Naples, V. Monaldi Hospital, Naples, Italy,[a] Department of Cardiovascular Surgery and Transplantation, V. Monaldi Hospital, Naples, Italy,[b] and PhD Program in "Medical-Surgical Physiopathology of the Cardio-Respiratory System and Associated Biotechnologies," Second University of Naples, Naples, Italy.[c]

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Address for reprints: Luca Salvatore De Santo, MD, Department of Cardio-Thoracic and Respiratory Sciences, Second University of Naples, V. Monaldi Hospital, Via L. Bianchi, 80131 Naples, Italy (E-mail: lucas.desanto@unina2.it).

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The optimal surgical strategy for rheumatic mitral valve disease is still highly debated.[1-3] The peculiar management issues relating to the childbearing potential of young women, a highly represented patient subset, add to the intrinsic challenge of dealing with this topic.[4]

The primary purpose of this article was to provide long-term follow-up data of isolated mitral valve replacement with mechanical prostheses over a 27-year period in a young rheumatic population. Maternal and fetal outcomes of pregnancies were also investigated. The secondary aim was to evaluate the influence of the type of replacement device on outcomes.

## Material and Methods

### Patient Population

Between January 1975 and December 2002, 1567 patients were referred to the Department of Cardiothoracic and Respiratory Sciences of the Second University of Naples for mitral rheumatic disease. Reparative procedures were performed in 905 patients (57.7%). The study population included young female patients (defined as 15 to 40 years old) who underwent isolated mitral valve replacement with mechanical prosthesis (n = 267).

### Operative Technique, Type of Prosthesis, and Anticoagulation Management

Prosthesis implantation was performed by using the same principles of technique throughout the study period. All the prostheses were implanted at the supra-annular level by using Tevdek 2-0 (Genzyme Surgical Products, Tucker, Ga) mattress sutures. Given the severe involvement of the subvalvular apparatus, chordal preservation in this subgroup was feasible in only 12 cases (4.45%). Biological prostheses were not favored in this patient subset by policy. The choice of prosthetic model was made on the basis of availability, surgeon preference, or both. Seventy-three patients received a caged ball, 133 a tilting disc, and 61 a bileaflet prosthesis. Anticoagulation with warfarin was begun on the second postoperative day in all patients. The targeted international normalized ratio (INR) ranged from 3.0 to 4.0 for patients with caged ball or tilting disc prostheses and from 2.5 to 3.5 for those with bileaflet valves. Prophylaxis included aspirin 100 mg/d in 79.4% of the patients receiving a caged ball prosthesis. The adequacy of the anticoagulation level was followed up in our Anticoagulation Outpatient Clinic, and doses of warfarin were adjusted according to INR assessments performed at least monthly.

### Management of Pregnant Women

Our anticoagulation protocol was based on sodium warfarin administration. Only 2 patients, after general practitioner counseling, preferred heparin treatment (unfractionated subcutaneous heparin). As previously described,[4,5] cesarean delivery was scheduled before the end of the 37th gestational week. Warfarin therapy was discontinued only 2 days before delivery and was restarted 1 day after delivery: during that period, heparin was not administered, and INR was checked daily. Throughout pregnancy, INR was estimated weekly at our outpatient clinic and recorded along with prescribed warfarin doses. Echocardiographic follow-up was performed monthly, and ultrasound evaluations of the fetus were performed at the third, fifth, and eighth months. Neonates underwent clinical examination soon after birth and then at 4 and 12 months to ascertain or exclude the diagnosis of warfarin embryopathy.

### Follow-up and Statistical Analysis

Data on patients undergoing valve replacement at the Department of Cardio-Thoracic and Respiratory Sciences were entered into a data chart archive. Data regarding hospitalization were obtained from hospital records. Patients were followed up at our outpatient clinic 15 days, 1 month, 12 months, and then yearly after surgery. On each visit, patients underwent physical examination, laboratory tests, and electrocardiogram. The first follow-up echocardiographic evaluation was performed at our institution 6 months after surgery. Questionnaires were sent to the general practitioners of all patients not seen at the outpatient clinic. Follow-up was completed with phone interviews to either the patients or relatives if data were missing. All the available follow-up data were entered into a computerized database. The guidelines of The American Association for Thoracic Surgery and The Society of Thoracic Surgeons were used for reporting mortality, morbidity, and valve-related complications.[6] As to pregnancy outcomes, main end points were maternal cardiac events (cardiac decompensation, valve thrombosis, and thromboembolism) and the occurrence of spontaneous abortion, stillbirth, or embryopathy.

SPSS software (version 10.1; SPSS Inc, Chicago, Ill) was used for statistical analysis. Data were expressed as mean ± SD or counts and percentages when appropriate. Differences in categorical variables were compared by means of the $\chi^2$ Pearson test or Fisher exact test. Continuous variables were analyzed with 2-tailed Student $t$ tests. Nonparametric tests were used when necessary. With regard to survival, we considered the patient as a statistical unit, whereas in the analysis of valve-related events we followed the fate of the implanted mechanical prostheses: in case of reoperation with valve prosthesis replacement, the follow-up was truncated at the time of reoperation. Incidences of postoperative events are presented as absolute frequencies and linearized rates (percentage per patient-year) and were compared by using the likelihood ratio test. Actuarial survival, freedom from reoperation, and thromboembolism were calculated with the time–life table method. Comparisons between groups were performed with the nonparametric Wilcoxon-Gehan pairwise test. The Cox proportional hazards model (multivariate forward stepwise regression) was used to determine the relative risk of late death and valve-related complications (thromboembolism and reoperation) associated with perioperative variables. All variables tested at univariate analysis were also included in this analysis (Appendix 1). Predictive factors for poor pregnancy outcome were assessed in univariate and multivariate analyses of the following variables: patient age, prosthetic model, average INR, and average warfarin daily dose. Units of analysis were pregnancies rather than women because the focus was on the effect on the fetus of drug assumption. However, because pregnancies occurring in the same woman share some common risk factors, we analyzed differences between first and subsequent pregnancies, and eventually we adjusted for it in multivariate analysis. These analyses were performed by S-Plus software (S-PLUS 2000; MathSoft, Inc, Cambridge, Mass). The effect of drug assumption on pregnancy outcome after adjustment by order of pregnancy (first or subsequent) was evaluated by the exact logistic regression model with LogXact software to account for the small sample size (LogXact-Turbo; CYTEL Software Corporation, Cambridge, Mass).

## Results

Baseline characteristics and operative variables are summarized in Table 1.

### Hospital (30-Day) Mortality

Overall 30-day mortality was 1.12% (3 patients). Causes of death were cardiogenic shock in 2 cases and cardiac rupture in 1.