Alma Mater Studiorum-Universita di Bologna

Dottorato in Fisiopatologia dell'Insufficienza Cardiaca

Coordinatore Prof. Angelo Branzi

Nuove acquisizioni in termini di insufficienza mitralica. Complicanze trombo-emboliche dopo chirurgia della valvola mitrale: incidenza, predittori e implicazioni cliniche.

Tesi di Dottorato

Presentata dal Dott.

ANTONIO RUSSO

Relatore Chiar.mo Prof.

ANGELO BRANZI

Esame finale anno 2007

Alma Mater Studiorum-Universita di Bologna

Dottorato in Fisiopatologia dell'Insufficienza Cardiaca

Coordinatore Prof. Angelo Branzi

Nuove acquisizioni in termini di insufficienza mitralica: complicanze tromboemboliche dopo chirurgia della valvola mitrale: incidenza, predittori e implicazioni cliniche

Tesi di Dottorato

Presentata dal Dott.
ANTONIO RUSSO

Relatore Chiar.mo Prof.
ANGELO BRANZI

Esame finale anno 2007

Abstract

Objectives To define in patients undergoing surgery for mitral regurgitation (MR) the risk of thrombo-embolic complications, particularly ischemic stroke (IS) compared to that in the general population.

Background MR is frequent, occurs mostly in the elderly and guidelines recommend surgery in asymptomatic patients but IS risks are unknown.

Methods In 1344 patients (65±12 years) consecutively operated for MR (procedures: 897 valve repair, MRep; 447 valve replacement, 231 mechanical, MVRm; 216 biological, MVRb), thrombo-embolic complications particularly IS (diagnosed by a neurologist) during follow-up were assessed early (<30 days), mid-term (30-180 days) and long-term (≥180 days).

Results IS occurred in 130 patients and IS or transient ischemic attack in 201. IS rates were 1.9±0.4% and 2.7±0.5%, at 30 and 180 days and 8.1±0.8% at 5 years. IS rates were lowest after MRep vs. MVRb and MVRm (6.1±0.9, 8±2.1 and 16.1±2.7% at 5 years, $p<0.001$). Comparison to IS expected rates in the population showed high risk within 30 days of surgery (Risk-ratio 41[26-60], $p<0.001$ but $p>0.10$ between procedures) and moderate risk after 30 days (risk-ratio 1.7 overall, $p<0.001$; 1.3 for MRep, $p=0.07$; 0.98 for MVRb, $p=0.95$; 4.8 for MVRm, $p<0.001$). Beyond 180 days, IS risk declined further and was not different from the general population for MRep (1.2, $p=0.30$) and for MVRb (0.9, $p=0.72$). Risk of IS or transient ischemic attack was higher than the general population in all groups up to 180 days. The risk of bleeding beyond 30 days was lowest in

MRep vs. MVRb and MVRm (7±1, 14±4 and 16±3% at 10 years, p<0.001).
Conclusion Thrombo-embolic complications after MR surgery are both reason for concern and encouragement. IS risk is notable early, irrespective of the procedure performed, but long-term is not higher than in the general population after MRep and MVRb. Preference for MRep should be emphasized and trials aimed at preventing IS should be conducted to reduce the thrombo-embolic and hemorrhagic risk in patients undergoing surgery for MR.

CONTENTS

INTRODUCTION

Thromboembolic events (TE) are serious complications that may occur after every modality of cardiac surgery.[1-3] Most TE are cerebrovascular[4] with the most serious ischemic stroke (IS) resulting in poor quality of life and excess mortality[1, 3, 5, 6]. The incidence of IS early after cardiac surgery was reported mostly after coronary artery by pass grafting (CABG) surgery between 1 to 8%[1, 5, 7], but is less known after valve surgery[8, 9], particularly for mitral regurgitation (MR). The issue of TE following MR surgery is of particular importance because MR is frequent with aging[10] and is the main reason for mitral surgery currently, because valve repair (MRep) is the modality of choice for surgical treatment of MR so that previous data following valve replacement may be changed[11] and because surgery has been proposed for asymptomatic patients[12] in whom any complication represents serious concern. It is thus unclear if TE is related to the type of surgery, if TE risk is low with MRep making anticoagulation unnecessary or if surgery multiplies the spontaneous risk of stroke[13], particularly in elderly patients with MR, a fact that may affect the new indications for surgery in such patients. Resolving this question is particularly difficult because, with the decrease in

rheumatic valve disease[14], older patients with MR [10] referred to surgery incur spontaneously higher risk of TE and stroke during follow-up. Therefore it is essential not only to assess the absolute risk of TE and IS after mitral valve (MV) surgery but also to compare the observed risk with that expected in the general population [15]. It is also crucial to compare over the early and late post-operative period, the TE risk associated with MRep and mitral valve replacement (MVR) to determine if the survival advantage associated with MRep is additive to lower embolic rates throughout follow up.

Thus we examined the TE risk associated with various modalities of surgical correction of MR, particularly comparing IS risk to that expected in the population

METHODS

The present study was based on a review of our experience with MRep and MVR for the surgical correction of MR.

Eligibility Criteria

Inclusion criteria were organic, ischemic and functional MR as defined by echocardiographic and surgical evaluation which underwent repair or replacement between January 1, 1980, and December 31, 1995. Patients with associated CABG surgery were included in the study.

Exclusion criteria were presence of mitral stenosis, congenital defects except small patent foramen ovale and atrial septal defect, constrictive pericarditis, previous mitral valve surgery: plication, valvuloplasty, annuloplasty, valve replacement, repair of mitral valve, previous or simultaneous aortic or tricuspid valve replacement (tricuspid repair was not an exclusion criteria).

Surgical procedure

Surgical repair of the mitral valve involved subvalvular (chordal shortening

or artificial chord insertion), valvular (mostly resection or plication) and annular (mostly ring insertion) intervention. The decision to perform MV repair versus replacement was based on the surgeon's examination of the lesions. The lesions repaired compared with those replaced involved MV prolapse in 648 versus 208, were ischemic in 148 versus 113, were endocarditic in 39 versus 37, were rheumatic in 20 versus 66 and were miscellaneous in 42 versus 23.

The types of prosthesis used in MV replacement were Carpentier-Edwards (159), Starr-Edwards (143), St. Jude (59), Ionescu-Shiley (43), Bjork-Shiley (27), Hancock (11), Medtronic intact (3) and Hall-Medtronic (2).

CABG was performed in 338 patients (38%) with MRep, 77 patients (33%) with mechanical prosthesis and 92 patients (43%) with biological prosthesis.

Clinical definitions

Baseline characteristics, cardiovascular history and comorbidity were noted. Follow-up events were determined by review of medical records or by questionnaires or by telephone calls. Ischemic stroke was defined as the persistence for > 24 hours of a focal neurological deficit caused by altered circulation of the cerebral hemispheres, brain stem or cerebellum with or without computed tomography (CT) or magnetic resonance imaging (MRI)

documentation.[16] Transient ischemic attack (TIA), was defined as focal neurologic event of complete and rapid resolution (<24 hours) related to altered circulation of the brain [16 15 17]. Peripheral embolic event was defined as operative, autopsy, or clinically documented embolus that produces symptoms from complete or partial obstruction of a peripheral (non cerebral) artery[16].

Bleeding event was defined as any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury or necessitates transfusion [16]. Intracranial hemorrhage (ICH) was assigned only after documentation by CT or MRI or autoptic confirmation.

Atrial fibrillation, paroxysmal or permanent, was considered present if recorded on ECG. All the patients of the study were managed with contemporary anticoagulation guidelines.

Statistical analysis

Baseline characteristics are presented as mean ± standard deviation (SD) for continuous variables.

Group comparisons were performed with a standard *t* test or x^2 test when appropriate. Event rate estimations were expressed by actuarial analysis and, to summarize the incidence of multiple events in individual patients, by

yearly linearized rates, expressed in percent per year ± standard error (SE) and calculated as the number of events divided by the total patient-years[16]. Observed IS, combined IS/TIA and combined IS/intracranial hemorrhage (ICH) rates were compared with expected in the Olmsted County population (counted from the Rochester Minnesota Stroke Registry rates) by use of the 1-sample log-rank test. Expected IS, IS/TIA, combined IS/ICH hazard were calculated from incidence rates of IS, combined IS/TIA, combined IS/ICH from the Olmsted County population with age and sex similar to those of the population of the study. Baseline clinical, operative and echocardiographic variables were tested to find possible predictors of IS and bleeding events with Cox proportional-hazards modeling and logistic regression analysis was used to find predictors of IS and bleeding on the first 30 days after surgery and between 30 and 180 days. Variables with $P<0.10$ by univariate analysis were incorporated into multivariate models, and $P<0.05$ was considered significant.

RESULTS

Study population

During the study period 1344 patients had MV surgery for MR. The surgical procedure performed was MRep in 897 patients (67%), MVRm in 231 patients (17%) and MVRb in 216 patients (16%). Reoperation was performed in 133 patients during the follow-up, 84 after MRep, 20 after MVRm and 29 after MVRb. 544 patients were in AF preoperatively and 168 patients developed AF during the follow up.

Baseline Characteristics

The preoperative baseline characteristics of the three groups are summarized in Table 1. The results show significant differences between the three groups regarding clinical, echocardiographic and operative characteristics, mostly consistent with a better prognosis in patients with MRep. Instead patients who received MVRb were older and more likely to be symptomatic, hypertensive and diabetic.

Incidence of ischemic stroke after MV surgery

A total of 130 patients experienced an IS: 65 after MRep, 44 after MVRm and 21 in MVRb group. Among them 29 patients suffered a second event, 9 in MRep group, 19 in MVRm, 1 in MVRb and 13 patients had multiple events, 1 in MRep, 11 in MVRm and 1 in MVRb. During the early postoperative period (within 30 postoperative days) overall incidence of IS was 1.92±0.4%, lower in MRep, 1.47±0.4% and in MVRm, 1.33±0.8% compared with MVRb 4.62±1.5%. MRep showed the lowest incidence at 6 months, 2.06±0.5%, compared with 3.19±1.2% in MVRm and 5.2±1.6% in MVRb (no difference between groups were detected during the period 1-6 months, P=NS). MRep showed also the lowest long term incidence of IS, 6.08±0.9% at 5 years and 9.9±1.3% at 10 years (1.15±0.1 per 100 patients-years), smaller compared with MVRm, respectively 16.1±2.7% and 23.3±3.5% (2.74±0.4 per 100 patients-years) (P<0.0001), not different from MVRb, 8.01±2.1% and 12.2±2.9% respectively (1.65±0.4 per 100 patients-years)(P=NS) (Actuarial incidence of IS in Figure 1) (Results summarized in Table 2)

Incidence of ischemic stroke compared with expected

Comparing incidence of IS observed with incidence expected in the Olmsted County population all the patients during the first postoperative month showed a remarkable excess of risk of IS (overall relative risk 40.73): as high as 30.94 ($P<0.001$) after MRep and even more high after MVRm , 43.36 ($P<0.001$), and after MVRb, 72.29 ($P<0.001$). Beyond the first month the relative risk strongly decreased in all the groups, but while in MVRm still persisted noteworthy excess of risk (RR, 4.77; $P<0.001$), it normalized in MVRb group (RR, 0.98) and the residual excess of risk in the MRep was not significant (RR, 1.30 $P=0.07$). Beyond 6 months MVRm still showed increased risk (RR, 4.31, $P<0.0001$), while in the other groups the risk became not different from the risk in the population (RR, 1.17, $P=0.302$ in MRep; RR, 0.90, $P=0.729$ in MVRb)

Predictors of ischemic stroke

Logistic regression analysis was used to predict IS on the first month after surgery and between 1 and 6 months, Cox proportional-hazards modeling was used to predict IS after 6 months.

For those IS during the first postoperative month, at the univariate analysis predictors were age, female sex, intra aortic balloon pump (IABP), presence of coronary artery disease (CAD), hypertension and MVRb; female sex (P=0.047; odds ratio, 2.28; 95%CI 1.01 to 5.38) resulted the only independent predictor. For those IS occurring between 1-6 months, independent predictors were age (P=0.048; odds ratio/5 years, 1.44; 95%CI 1.00 to 2.25), hypertension (P=0.027; odds ratio 4.33; 95%CI 1.16 to 20.33) and MVRm (P=0.018; odds ratio 6.04; 95%CI 1.38 to 25.24).

At the univariate analysis predictors of IS occurring beyond 6 months resulted age, mechanical prosthesis, combined atrial fibrillation at surgery/prior the event and left atrial dimension (LAD) >50 mm; independent predictors were age (P=0.006; risk ratio/5 years, 1.14; 95%CI, 1.03 to 1.26) and MVRm (P<0.001; risk ratio, 3.02; 95%CI, 1.94 to 4.65). MRep was an independent favorable predictor of long term survival free from ischemic stroke (P=0.002; risk ratio, 0.52; 95%CI, 0.34 to 0.79).(Results summarized in Table 4-5)

Combined IS /TIA: absolute incidence and rates compared with expected

Incidence of the combined end point ischemic stroke/TIA was analyzed. While during the first month and during the period 1-6 months there was no difference between groups regarding the incidence of ischemic stroke/ TIA, also for ischemic stroke/TIA MRep presented the lowest long term incidence, 10.9±1.1% at 5 years and 16.6±1.7% at 10 years (2.02±0.2 per 100 patients-years), not different from MVRb, respectively 13.19±2.6% and 19.1±3.4% (2.58±0.46 per 100 patients-years) (P=NS), smaller compared with MVRm, respectively 23.4±3.1% and 32±3.7% (4.09±0.5 per 100 patients-years) (P<0.0001). (Actuarial incidence of ischemic stroke/TIA in Figure 3) (Results summarized in Table 6).

In comparison to incidence of ischemic stroke/TIA expected in the general population, during the first postoperative month all the patients showed an important excess of risk (overall relative risk, 42.67), regardless of the type of MV surgery. In fact the risk ratio was as high as 38.54 (P<0.001) after MRep, 42.61 (P<0.001) after MVRm and 56.92 (P<0.001) after MVRb. Beyond 1 month, the relative risk strongly decreased in all the groups but still persisted in all of them an excess of risk, higher in MVRm (RR, 5.37

P<0.001), not indifferent in MRep (RR, 1.81 P<0.001) and in MVRb (RR, 1.57 P=0.035) the MVRb. Beyond 6 months the relative risk persisted lightly increased in the MRep group (RR 1.55, P<0.001) and in the MVRb (RR 1.36, P=0.18704), severely increased in MVRm (RR 4.92, P<0.001) (Results summarized in table7).

ICH and combined IS/ICH: absolute incidence and rates compared with expected

Only 10 patients experienced an ICH during the follow up: 1in MRep, 5 in the MVRm and 4 in the MVRb and only 1 patient suffered a SAH, in the MVRm group. Compared with expected in the general population, only patients in MVRm group presented long term excess risk of ICH (RR 3.76, P=0.003), while patients with MVRb showed excess risk only in the first 30 days (RR 55.07, P<0.0001) (Results summarized in table 8).

A total of 140 patients experienced the combined end point IS/ICH stroke: 66 were in MRep group, 49 were in MVRm group and 25 were in MVRb group.

In comparison to incidence expected in the general population, also for the combined end point IS/ICH there was in all the groups an excess of risk during the first month, beyond 1 month only the MVRm group showed increased risk (RR, 4.87, P<0.0001) (Results summarized in table 9)

Incidence of total thromboembolic events (ischemic stroke, TIA, peripheral and mesenteric embolism).

Over the entire follow-up a total of 212 patients experienced a TE: most, 201, experienced a CV-TE, 9 had a peripheral event and 2 had a mesenteric event; 114 were in the MRep group, 64 in the MVRm group and 34 were in the MVRb group.

Also for the combined end point total TE MRep presented the lowest long term incidence, 11.6±1.1% at 5 years and 17.2±1.7% at 10 years, (2.1±0.2 per 100 patients-years), smaller compared with MVRm, respectively 23.8±3.1% and 33.1±3.8% (4.3±0.5 per 100 patients-years) (P<0.001), not different from MVRb, respectively 14.9±2.8% and 20.8±3.5%, (2.8±0.5 per 100 patients-years) (P=NS)(Result summarized in Table 10)

Incidence and predictors of Bleeding

A total of 136 patients experienced a Bleed event over the entire follow up (58 in the MRep group, 39 in the MVRm group and 39 in the MVRb group). Incidence was high during the first postoperative month, especially in the MVRb group (a total of 51events, 18 in the MRep, 11 in the MVRm and 22 in the MVRb). MRep presented the lowest long term incidence of Bleed, 1.0±0.1 per 100 patients-years smaller than MVRm, 2.3±0.3 per 100 patients-years (P<0.001) and MVRb, 3.4±0.5 per 100 patients-years (P<0.001), but not different from MVRb when we excluded the perioperative Bleed. (0.7±0.1 per 100 patients-years in MRep and 1.5±0.4 per 100 patients-years in MVRb, P=NS). MVRm showed, compared with MRep also after 1 month (1.7 per 100 patients-year) significant increase of Bleed risk. The only independent predictor for the postoperative Bleed resulted age at surgery (P=0.007; odds ratio/5 years, 1.19; 95%CI, 1.04 to 1.39), while mechanical prosthesis, age and male gender resulted independent predictor of Bleed beyond 6 months. (Incidence and Predictors of Bleed are summarized in table 11-12)

DISCUSSION

The present study, by analyzing a large cohort of patients who underwent surgery for MR, by analyzing the time dependence of TE events after surgery and by comparing IS rates to those in the general population provides a unique view of TE events after surgery for MR. Moreover at our knowledge this is the first study in which incidence of IS and any CV events observed after cardiac surgery was compared with incidence expected in the normal population to demonstrate, removing the confounding factor of natural events, any excess of risk directly related to the surgical procedure and to the different modalities of MV surgery for MR. The observations in the present study are both concerning and encouraging. Indeed, the concerns stem from the fact that surgery is associated with excess risk of IS and of the combined complication IS-TIA. The encouraging results are related to the decline of TE events over time after surgery for MR, so that in patients who receive either MRep or MVRb, IS rates are not different long-term from those in the general population. Thus, MRep which compared to MVR, results in restoration of life expectancy has also the advantage of imposing no excess IS risk beyond the 6^{th} post-operative month and is confirmed as the preferred mode of surgical correction of MR. Conversely, MVRm is

associated, in addition to the excess mortality previously noted, with sustained risk of IS and bleeding and in that is the least desirable mode of correction of MR.

Early Thromboembolic events

Thrombo-embolic events occurring early after cardiac surgery have been the main focus of research, and were addressed mostly in pazients undergoing coronary by pass surgery. [1, 3, 5, 6]. The focus on early events is justified by direct casual link between the operative procedure and the TE event.

The early postoperative (<30 days) incidence of IS or IS/TIA 1.9% and 2.6% are lower than those reported after coronary[1, 3, 5, 6] or mitral [3, 18] surgery . This lower rate pertains in part to strict definition of IS or TIA by a neurologist[15] but nevertheless is high enough to justify careful attention. Although macro embolization is now rare , mechanisms involving thrombotic, fat or gaseous micro-emboli from the extracorporeal circulatory system or aortic atherosclerotic lesions have been suggested. [19, 20 21] However the risk is not only due to the surgical procedure and remains high during the first post-operative month, resulting approximately 40 times the spontaneous risk of stroke in the general population with similar characteristics of age and sex. It is well known that prosthetic materials involved in all valve surgeries

activate platelets leading to increased platelet deposition [22] and clot formation. Thus our results which show that IS rate is high during the first post-operative month independently from the procedure performed strongly recommend prevention of thrombus formation in all patients undergoing MR surgery. The fact that female sex turned out to be an independent risk factor for TE and IS is not well explained, but it is coherent with other observations in the literature.[9, 23] .

Long-term thrombo-embolic and haemorrhagic complications

The risk of TE complications in patients with MVRm is well known. Although a clinical trial suggested that mechanical mitral prostheses were not associated with higher risk of stroke [24], clinical practice studies showed high TE rates [2 25]. Our long-term large study emphasizes the higher TE and IS rates with MVRm than MVRb and MRep. Despite TE and IS risk decline over time, an excess risk associated with MVRm is evident beyond 6 months. However the effective risk is difficult to estimate since patients with MVRm are younger than patients with MVRb. Thus comparison to expected rate of IS or IS/TIA is essential by showing that MVRm multiplies long-term IS risk by 4 to 5. This excess risk is supported by multivariate analysis showing that, adjusting for all the other independent risk factors of

IS, MVRm is associated with 3 times higher risk of IS compared with MVRb. In addition, since all patients with MVRm are on anticoagulation therapy, the rates of bleeding is notable in MVRm, more than 3% per year, and in multivariate analysis is 2.5 times higher than with MVRb.

This combined excess risk in patients with MVRm support the fact to avoid this type of procedure if it is possible.

For both MVRb and MRep we observed, similarly to MVRm, a marked decline of the risk of TE and IS after the first postoperative month. Of all the procedure MRep was associated with the lowest absolute rates of TE, IS and IS/TIA. Such an advantage with MRep has been controversial [26 27] probably because its demonstration requires large samples and long-term analysis. However, since the group with MVRb and MRep are different in age, interpretation of TE rates requires comparison to expected rates. While the combined endpoint of IS/TIA occurs at an excess rate with both procedures beyond the first post-operative month, underscoring the need for exploring further preventive measures, our study provides remarkable results. Indeed, the risk of IS, the most frequent and serious TE complication, in MVRb and MRep beyond 180 days is similar and compared with expected in the general population is not significantly elevated. This very important result support the fact that MRep results in long-term restoration not only of life

expectancy [28] [29] but also of the IS risk. MRep is also remarkable by providing the lowest long-term risk of bleeding so that MRep is unique in combining long-term morbidity to mortality benefit.

Mechanism of early and long-term TE

In the present study most part of the TE were noted during the first month. It is well known that the events leading to TE start during surgery. In fact, although macro embolization is less common during modern cardiac surgery, thrombus, lipid or gaseous microemboli can originate from the extracorporeal circulatory pump system and from atherosclerotic lesion in the ascending aorta manipulated during CABG and heart valve surgery. [30] [19] [20] [31] [32] [21]. Particularly heart valve procedures, as Abu-Omar et al reported [33], compared with CABG and off-pump CABG, showed higher incidence of microemboli detected by transcranial Doppler ultrasound. In clinical studies not always heart valve surgery compared with CABG surgery showed higher rate of postoperative IS and TE [34] [30] [8] [35].

During heart valve surgery the damaged perivalvular tissue and the prosthetic materials activate platelets as soon as blood starts flowing across the valve, leading to immediate platelet deposition[22, 36, 37]. A Dacron or Teflon sewing ring is common to mechanical and biological prostheses and

an annuloplasty ring is almost always used during repair of the MV. Platelet deposition on the prosthetic ring start immediately activiting the clotting system. At the same time start the process of healing of the MV wounds but the exact timing of restoration of the endothelial lining, which represents the only one surface resistant to thrombus formation, is not well known. Tamura et al [38] found in a study on sheep that, compared with myocardial wounds (after MI) and with wounds in other tissues, the healing of MV leaflet is a much slower process. In fact it requires 8-12 weeks for the formation of a dense collagenous scar and complete restoration of the endothelial lining, Possible explanations for this delay in the healing process were the low degree of inflammatory cell infiltration compared with normal healing process present in other tissue and the lack of newly formed blood vessels until 12 weeks. The delay in the MV healing process can at least in part explain the persistency of TE in MRep after the early postoperative phase. Della Barbera et all [39] studied the histological process after placement of a new generation annuloplasty ring in MV position in adult sheep. After 63-110 days from implantation the ring, surrounded by inflammatory cells and neovessels, was fully encapsulate by fibrous tissue and a continuous lining of endothelium coated the fibrous tissue surface. But in the study they tested a “new” generation annuloplasty ring, coated with Carbofilm, that

enhance biocompatibility of the artificial product, then the “old” ring could need even more time for a complete encapsulating and endothelization.

In the present study patients with MVRb showed high rate of early embolization (first month) with complete normalization of the risk of serious emboli after 1 month. Biological valves, principally due to the toxic effect of pre-operative fixation with glutaraldehyde, show a lack of host endothelial cell ingrowth on the valvular surface [40 41 42] that promotes thrombus formation explaining the early postoperative high TE rate; nevertheless partial in-vivo re-endothelialization has been reported[40, 43, 44].

Emboli after cardiac surgery could be also related to the presence of AF. In fact AF, which is associated with embolic event, and stroke in particular, in the general population [45-47], is a common complication in the early postoperative period. Previous studies reported strong correlation between postoperative AF development and incidence of stroke.[48]In this study the presence of AF was a predictor of IS beyond 6 months at the univariate analysis (RR, 1.83; 95%CI, 1.22 to 2.74; P=0.003).

Is well known that left atrial appendage (LAA) plays a fundamental role in the formation of atrial thrombus and probably in causing IS both in patients with AF and sinus rhythm.[49-51].

One suggestive surgical procedure that could be safely[52] performed during MV surgery to reduce incidence of IS is the ligation of the LAA. Garcia-Fernandez et all found that LAA ligation during MV surgery reduce the risk of late embolism[53], but in this study most of the patients had rheumatic valve disease and were in AF. Further randomized trials are needed to determine if LAA ligation effectively reduces incidence of IS in patients underwent MV surgery.

Another possible source of TE is the presence of AF. In several studies, in fact, the Cox-Maze procedure resulted effective to eliminate AF and restore sinus rhythm during MV surgery[54, 55] reducing incidence of stroke[55-58]. Therefore Cox-Maze procedure should be carefully evaluated in patients in AF who undergo MV surgery.

Atherosclerosis of the ascending aorta is known to be an important risk factors for IS and embolization after cardiac surgery[32, 59]. Since for evaluation of ascending aorta epiaortic ultrasonography is superior to transesophageal echocardiography and palpation[60]it should be performed during cardiac surgery for the detection and the quantification of

atherosclerosis at this level. Surgical techniques, like changes in the position of aortic cannula[61, single clamp technique{Grega, 2003 #2051], aortic resection and graft replacement[62]and applying intra-aortic filtration before aortic cross-clamping[63], showed to reduce systemic and cerebral embolization due to ascending aorta atherosclerosis.

Predictors of ischemic stroke

The identification of female sex as an independent risk factor for those IS which occur early after surgery is not new[8]; in another previous study female sex was associated to delayed strokes after cardiac surgery[23]. Age, CAD and IABP, which were predictors of early IS in the univariate analysis, appeared to be risk factors also in previous studies [1, 5, 23, 59, 64-69]. Age, hypertension and MVRm, independent predictors of delayed IS, were already found to be predictors of IS in other studies[23, 64].

CONCLUSION

This large study of MR surgery provides observations both concerning and encouraging. It is concerning that MR surgery is followed by excess risk of TE compared to the general population. Indeed all the modalities of MR surgery have a high risk of TE during the first postoperative month. It is also concerning that throughout follow-up patients with MVRm incur high risk of TE or bleeding. From the other side it is encouraging that the risk of TE declines after the high-risk early post-operative phase and that patient who receive MRep or MVRb incur long-term TE rates similar to those in the general population.

CLINICAL IMPLICATION

In the present study MRep provides, in addition to its low mortality, the lowest morbidity and is confirmed to be the preferred mode of surgical correction of MR. Conversely, MVRm is associated, in addition to the excess mortality previously noted, with sustained risk of TE and bleeding and thereby is the least desirable modality of correction of MR. Regarding TE and bleeding MVRb showed to be in the present study a good alternative to MRep and should be seriously considered whenever MRep is not performable.

To support the guideline recommendation of early MR surgery in asymptomatic patients, MRep is an essential condition and clinical trial should be designed to minimize the risk of stroke in the first months following MR surgery.

REFERENCES

1. Roach GW, Kanchuger M, Mangano CM, et al. Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. N Engl J Med 1996;335(25):1857-63.

2. Fuster V, Pumphrey CW, McGoon MD, Chesebro JH, Pluth JR, McGoon DC. Systemic thromboembolism in mitral and aortic Starr-Edwards prostheses: a 10-19 year follow-up. Circulation 1982;66(2 Pt 2):I157-61.

3. Taylor NE, O'Brien S, Edwards FH, Peterson ED, Bridges CR. Relationship between race and mortality and morbidity after valve replacement surgery. Circulation 2005;111(10):1305-12.

4. Fuster V, Danielson M, Robb R, Broadbent J, Brown AJ, Elveback L. Quantitation of left ventricular myocardial fiber hypertrophy and interstitial tissue in human hearts with chronically increased volume and pressure overload. Circulation 1977;55:504-8.

5. Tuman KJ, McCarthy RJ, Najafi H, Ivankovich AD. Differential effects of advanced age on neurologic and cardiac risks of coronary artery operations. J Thorac Cardiovasc Surg 1992;104(6):1510-7.

6. Stamou SC, Hill PC, Dangas G, et al. Stroke after coronary artery bypass: incidence, predictors, and clinical outcome. Stroke 2001;32(7):1508-13.

7. Reed GL, 3rd, Singer DE, Picard EH, DeSanctis RW. Stroke following coronary-artery bypass surgery. A case-control estimate of the risk from carotid bruits. N Engl J Med 1988;319(19):1246-50.

8. Hogue CW, Jr., Murphy SF, Schechtman KB, Davila-Roman VG. Risk factors for early or delayed stroke after cardiac surgery. Circulation 1999;100(6):642-7.

9. Ruel M, Masters RG, Rubens FD, et al. Late incidence and determinants of stroke after aortic and mitral valve replacement. Ann Thorac Surg 2004;78(1):77-83; discussion -4.

10. 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(9540):1005-11.

11. Orszulak TA, Schaff HV, Pluth JR, et al. The risk of stroke in the early postoperative period following mitral valve replacement. Eur J Cardiothorac Surg 1995;9(11):615-9 discuss 20.

12. Bonow RO, Carabello BA, Kanu C, 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 2006;114(5):e84-231.

13. Avierinos JF, Brown RD, Foley DA, et al. Cerebral ischemic events after diagnosis of mitral valve prolapse: a community-based study of incidence and predictive factors. Stroke 2003;34(6):1339-44.

14. Boudoulas H, Vavuranakis M, Wooley CF. Valvular heart disease: the influence of changing etiology on nosology. J Heart Valve Dis 1994;3(5):516-26.

15. Brown R, Whisnant J, Sicks J, O'Fallon W, Wiebers D. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. Stroke 1996;27:373-80.

16. Edmunds LJ, Clark R, Cohn L, Miller D, Weisel R. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ann Thorac Surg 1988;46:257-9.

17. Brown RD, Jr., Petty GW, O'Fallon WM, Wiebers DO, Whisnant JP. Incidence of transient ischemic attack in Rochester, Minnesota, 1985-1989. Stroke 1998;29(10):2109-13.

18. Bucerius J, Gummert JF, Borger MA, et al. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. Ann Thorac Surg 2003;75(2):472-8.

19. Davila-Roman VG, Murphy SF, Nickerson NJ, Kouchoukos NT, Schechtman KB, Barzilai B. Atherosclerosis of the ascending aorta is an independent predictor of long-term neurologic events and mortality. J Am Coll Cardiol 1999;33(5):1308-16.

20. Mackensen GB, Ti LK, Phillips-Bute BG, Mathew JP, Newman MF, Grocott HP. Cerebral embolization during cardiac surgery: impact of aortic atheroma burden. Br J Anaesth 2003;91(5):656-61.

21. Mullges W, Franke D, Reents W, Babin-Ebell J. Brain microembolic counts during extracorporeal circulation depend on aortic cannula position. Ultrasound Med Biol 2001;27(7):933-6.

22. Chesebro J, Adams P, Fuster V. Antithrombotic therapy in patients with valvular heart disease and prosthetic heart valves. J Am Coll Cardiol 1986;8:41-56b.

23. Doenst T, Ivanov J, Borger MA, David TE, Brister SJ. Sex-specific long-term outcomes after combined valve and coronary artery surgery. Ann Thorac Surg 2006;81(5):1632-6.

24. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol 2000;36(4):1152-8.

25. Saour JN, Sieck JO, Mamo LA, Gallus AS. Trial of different intensities of anticoagulation in patients with prosthetic heart valves. N Engl J Med 1990;322(7):428-32.

26. Akins G, Hilgenberg A, Buckley M, et al. Mitral valve reconstruction versus replacement for degenerative or ischemic mitral regurgitation. Ann thorac Surg 1994;58:668-76.

27. Perier P, Deloche A, Chauvaud S, et al. Comparative evaluation of mitral valve repair and replacement with Starr, Bjork, and porcine valve prostheses. Circulation 1984;70:I187-92.

28. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. N Engl J Med 2005;352(9):875-83.

29. Tribouilloy C, Enriquez-Sarano M, Schaff H, et al. Impact Of Preoperative Symptoms On Survival After Surgical Correction Of Organic

Mitral Regurgitation: Rationale For Optimizing Surgical Indications. Circulation 1999;99:400-5.

30. McKhann GM, Grega MA, Borowicz LM, Jr., Baumgartner WA, Selnes OA. Stroke and encephalopathy after cardiac surgery: an update. Stroke 2006;37(2):562-71.

31. Hangler HB, Nagele G, Danzmayr M, et al. Modification of surgical technique for ascending aortic atherosclerosis: impact on stroke reduction in coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003;126(2):391-400.

32. Djaiani G, Fedorko L, Borger M, et al. Mild to moderate atheromatous disease of the thoracic aorta and new ischemic brain lesions after conventional coronary artery bypass graft surgery. Stroke 2004;35(9):e356-8.

33. Abu-Omar Y, Balacumaraswami L, Pigott DW, Matthews PM, Taggart DP. Solid and gaseous cerebral microembolization during off-pump, on-pump, and open cardiac surgery procedures. J Thorac Cardiovasc Surg 2004;127(6):1759-65.

34. Salazar JD, Wityk RJ, Grega MA, et al. Stroke after cardiac surgery: short- and long-term outcomes. Ann Thorac Surg 2001;72(4):1195-201; discussion 201-2.

35. Kuroda Y, Uchimoto R, Kaieda R, et al. Central nervous system complications after cardiac surgery: a comparison between coronary artery bypass grafting and valve surgery. Anesth Analg 1993;76(2):222-7.

36. Dewanjee MK, Trastek VF, Tago M, Kaye MP. Radioisotopic techniques for noninvasive detection of platelet deposition in bovine-tissue

mitral-valve prostheses and in vitro quantification of visceral microembolism in dogs. Invest Radiol 1984;19(6):535-42.

37. Dewanjee MK, Fuster V, Rao SA, Forshaw PL, Kaye MP. Noninvasive radioisotopic technique for detection of platelet deposition in mitral valve prostheses and quantitation of visceral microembolism in dogs. Mayo Clin Proc 1983;58(5):307-14.

38. Tamura K, Jones M, Yamada I, Ferrans VJ. Wound healing in the mitral valve. J Heart Valve Dis 2000;9(1):53-63.

39. Della Barbera M, Laborde F, Thiene G, et al. Sovering annuloplasty rings: experimental pathology in the sheep model. Cardiovasc Pathol 2005;14(2):96-103.

40. Ishihara T, Ferrans VJ, Jones M, Boyce SW, Roberts WC. Occurrence and significance of endothelial cells in implanted porcine bioprosthetic valves. Am J Cardiol 1981;48(3):443-54.

41. Gendler E, Gendler S, Nimni ME. Toxic reactions evoked by glutaraldehyde-fixed pericardium and cardiac valve tissue bioprosthesis. J Biomed Mater Res 1984;18(7):727-36.

42. Speer DP, Chvapil M, Eskelson CD, Ulreich J. Biological effects of residual glutaraldehyde in glutaraldehyde-tanned collagen biomaterials. J Biomed Mater Res 1980;14(6):753-64.

43. Zavazava N, Simon A, Sievers HH, Bernhard A, Muller-Ruchholtz W. Porcine valves are reendothelialized by human recipient endothelium in vivo. J Thorac Cardiovasc Surg 1995;109(4):702-6.

44. Simon A, Wilhelmi M, Steinhoff G, Harringer W, Brucke P, Haverich A. Cardiac valve endothelial cells: relevance in the long-term function of biologic valve prostheses. J Thorac Cardiovasc Surg 1998;116(4):609-16.

45. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet 1989;1(8631):175-9.

46. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22(8):983-8.

47. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arch Intern Med 1987;147(9):1561-4.

48. Lahtinen J, Biancari F, Salmela E, et al. Postoperative atrial fibrillation is a major cause of stroke after on-pump coronary artery bypass surgery. Ann Thorac Surg 2004;77(4):1241-4.

49. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. Heart 1999;82(5):547-54.

50. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61(2):755-9.

51. Agmon Y, Khandheria BK, Gentile F, Seward JB. Clinical and echocardiographic characteristics of patients with left atrial thrombus and sinus rhythm: experience in 20 643 consecutive transesophageal echocardiographic examinations. Circulation 2002;105(1):27-31.

52. Healey JS, Crystal E, Lamy A, et al. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. Am Heart J 2005;150(2):288-93.

53. Garcia-Fernandez MA, Perez-David E, Quiles J, et al. Role of left atrial appendage obliteration in stroke reduction in patients with mitral valve prosthesis: a transesophageal echocardiographic study. J Am Coll Cardiol 2003;42(7):1253-8.

54. Handa N, Schaff HV, Morris JJ, Anderson BJ, Kopecky SL, Enriquez-Sarano M. Outcome of valve repair and the cox maze procedure for mitral regurgitation and associated atrial fibrillation. J Thorac Cardiovasc Surg 1999;118(4):628-35.

55. Kobayashi J, Sasako Y, Bando K, et al. Eight-year experience of combined valve repair for mitral regurgitation and maze procedure. J Heart Valve Dis 2002;11(2):165-71; discussion 71-2.

56. Cox JL, Ad N, Palazzo T. Impact of the maze procedure on the stroke rate in patients with atrial fibrillation. J Thorac Cardiovasc Surg 1999;118(5):833-40.

57. Bando K, Kobayashi J, Kosakai Y, et al. Impact of Cox maze procedure on outcome in patients with atrial fibrillation and mitral valve disease. J Thorac Cardiovasc Surg 2002;124(3):575-83.

58. Ad N, Cox JL. Combined mitral valve surgery and the Maze III procedure. Semin Thorac Cardiovasc Surg 2002;14(3):206-9.

59. Gardner TJ, Horneffer PJ, Manolio TA, et al. Stroke following coronary artery bypass grafting: a ten-year study. Ann Thorac Surg 1985;40(6):574-81.

60. Bolotin G, Domany Y, de Perini L, et al. Use of intraoperative epiaortic ultrasonography to delineate aortic atheroma. Chest 2005;127(1):60-5.

61. Borger MA, Taylor RL, Weisel RD, et al. Decreased cerebral emboli during distal aortic arch cannulation: a randomized clinical trial. J Thorac Cardiovasc Surg 1999;118(4):740-5.

62. Rokkas CK, Kouchoukos NT. Surgical management of the severely atherosclerotic ascending aorta during cardiac operations. Semin Thorac Cardiovasc Surg 1998;10(4):240-6.

63. Christenson JT, Vala DL, Licker M, Sierra J, Kalangos A. Intra-aortic filtration: capturing particulate emboli during aortic cross-clamping. Tex Heart Inst J 2005;32(4):515-21.

64. Frye RL, Kronmal R, Schaff HV, Myers WO, Gersh BJ. Stroke in coronary artery bypass graft surgery: an analysis of the CASS experience. The participants in the Coronary Artery Surgery Study. Int J Cardiol 1992;36(2):213-21.

65. Newman MF, Wolman R, Kanchuger M, et al. Multicenter preoperative stroke risk index for patients undergoing coronary artery bypass graft surgery. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Circulation 1996;94(9 Suppl):II74-80.

66. Ozatik MA, Gol MK, Fansa I, et al. Risk factors for stroke following coronary artery bypass operations. J Card Surg 2005;20(1):52-7.

67. Almassi GH, Sommers T, Moritz TE, et al. Stroke in cardiac surgical patients: determinants and outcome. Ann Thorac Surg 1999;68(2):391-7; discussion 7-8.

68. McKhann GM, Grega MA, Borowicz LM, Jr., et al. Encephalopathy and stroke after coronary artery bypass grafting: incidence, consequences, and prediction. Arch Neurol 2002;59(9):1422-8.

69. Ricotta JJ, Faggioli GL, Castilone A, Hassett JM. Risk factors for stroke after cardiac surgery: Buffalo Cardiac-Cerebral Study Group. J Vasc Surg 1995;21(2):359-63; discussion 64.

Baseline, operative and post-operative characteristics

Population	Overall	MRep	MVRm	MVRb	P
Variables					
No of patients	**1344**	**897**	**231**		
Clinical characteristics					
Age	65±12	65±12	60±11	70±11	<0.0001
Male sex, %	61	64	62	48	<0.0001
Hypertension, %	36	37	29	39	0.03
Diabetes, %	10	8	11	13	0.07
Creatinine, mg/dl	1.4±0.6	1.4±0.7	1.3±0.6	1.3±0.4	0.92
Atrial Fibrillation, %	41	37	51	44	0.0006
NYHA class III-IV, %	57	48	69	78	<0.0001
Organic MR (%)	81	83	80	69	<0.0001
Echocardiography characteristics					
EF (%)	58±13	59±12	56±14	56±14	0.02
LVD (mm)	61±9	61±9	61±9	61±9	0.91
LVS (mm)	39±12	39±13	39±10	39±10	0.97
LA (mm)	54±10	54±9	54±10	54±11	0.85
Operative and Post-operative characteristics					
Bypass time	98±48	90±47	110±49	118±50	<0.0001
CABG (%)	38	38	33	43	0.13
Coumadin therapy (%)	51	41	95	44	<0.0001

Table 1: Baseline, operative and post-operative characteristics
NYHA, New York Heart Association; EF, Ejection Fraction; LVD, Left Ventricle Diastolic diameter; LVS, Left Ventricle systolic diameter; LA, Left Atrial; CABG, Coronary Artery Bypass Grafting;

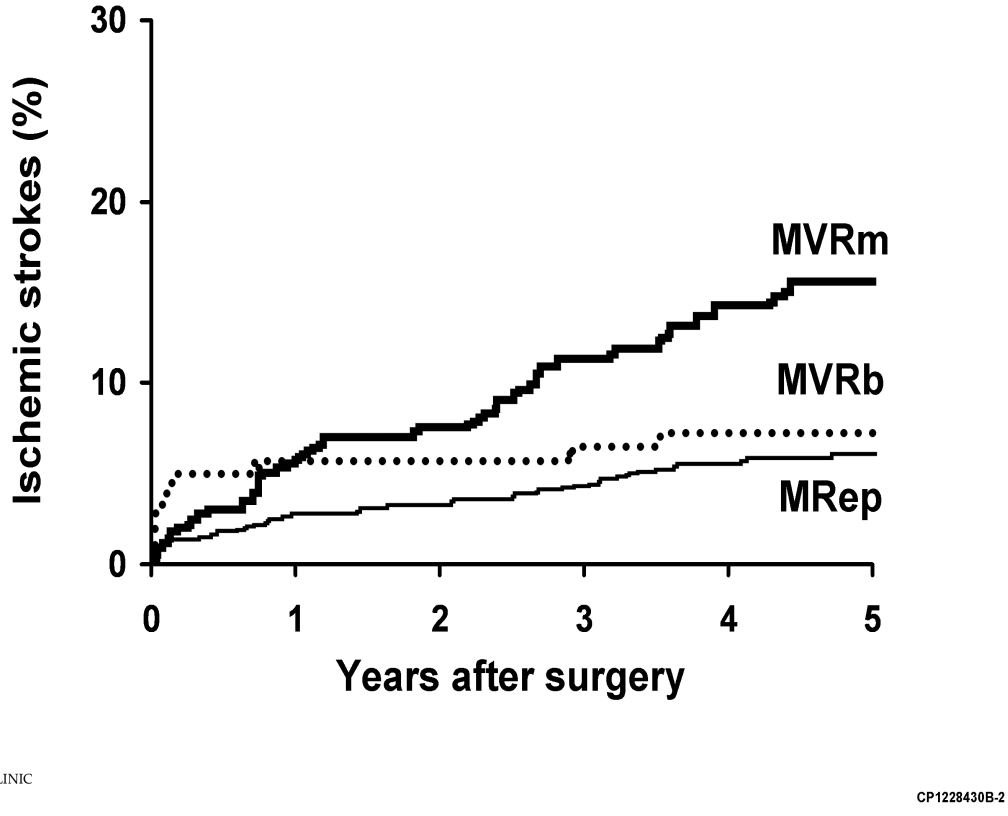

Figure 1. Plot of incidence of IS in the three groups. Note that MRep and MVRb, compared with MVRm present significant lower long term incidence of IS
IS: ischemic stroke

Incidence of IS after MV surgery

Follow up	**Over entire follow up**	**≤30 days postop**	**30-180 days postop**	**Follow up >180 days postop**
Overall	Events: 130 5 years incidence=8.09±0.8% 10 years incidence=12.9±1.2% 1.52±0.1% patients-years	Events: 25 30 days incidence=1.92±0.4% 23.9±4.8% patients-years	Events: 10 180 days incidence=2.73±0.4% Yearly L.R.=2.02±0.6% patients-years	Events: 95 1.19±0.1% patients-years
MRep group	Events: 65 5 years incidence=6.08±0.9% 10 years incidence=9.9±1.3% 1.15±0.1% patients-years	Events: 13 30 days incidence=1.47±0.4% 18.25±5% patients-years	Events: 5 180 days incidence=2.06±0.5% 1.46±0.6% patients-years	Events: 47 0.89±0.1% patients-years
MVRm group	Events: 44 5 years incidence=16.1±2.7% 10 years incidence=23.3±3.5 2.74±0.4% patients-years	Events: 3 30 days incidence=1.33±0.8% 16.6±9.6% patients-years	Events: 4 180 days incidence=3.19±1.2% 4.72±2.3% patients-years	Events: 37 2.46±0.4% patients-years
MVRb group	Events: 21 5 years incidence=8.01±2.1% 10 years incidence=12.2±2.9% 1.65±0.4% patients-years	Events: 9 30 days incidence=4.62±1.5% 59.9±19.9% patients-years	Events: 1 180 days incidence=5.2±1.6% 1.49±1.49% patients-years	Events: 11 0.92±0.3% patients-years

TABLE 2 Incidence of IS during earlythe follow up : actuarial survival and yearly linearized rate.

IS: ischemic stroke

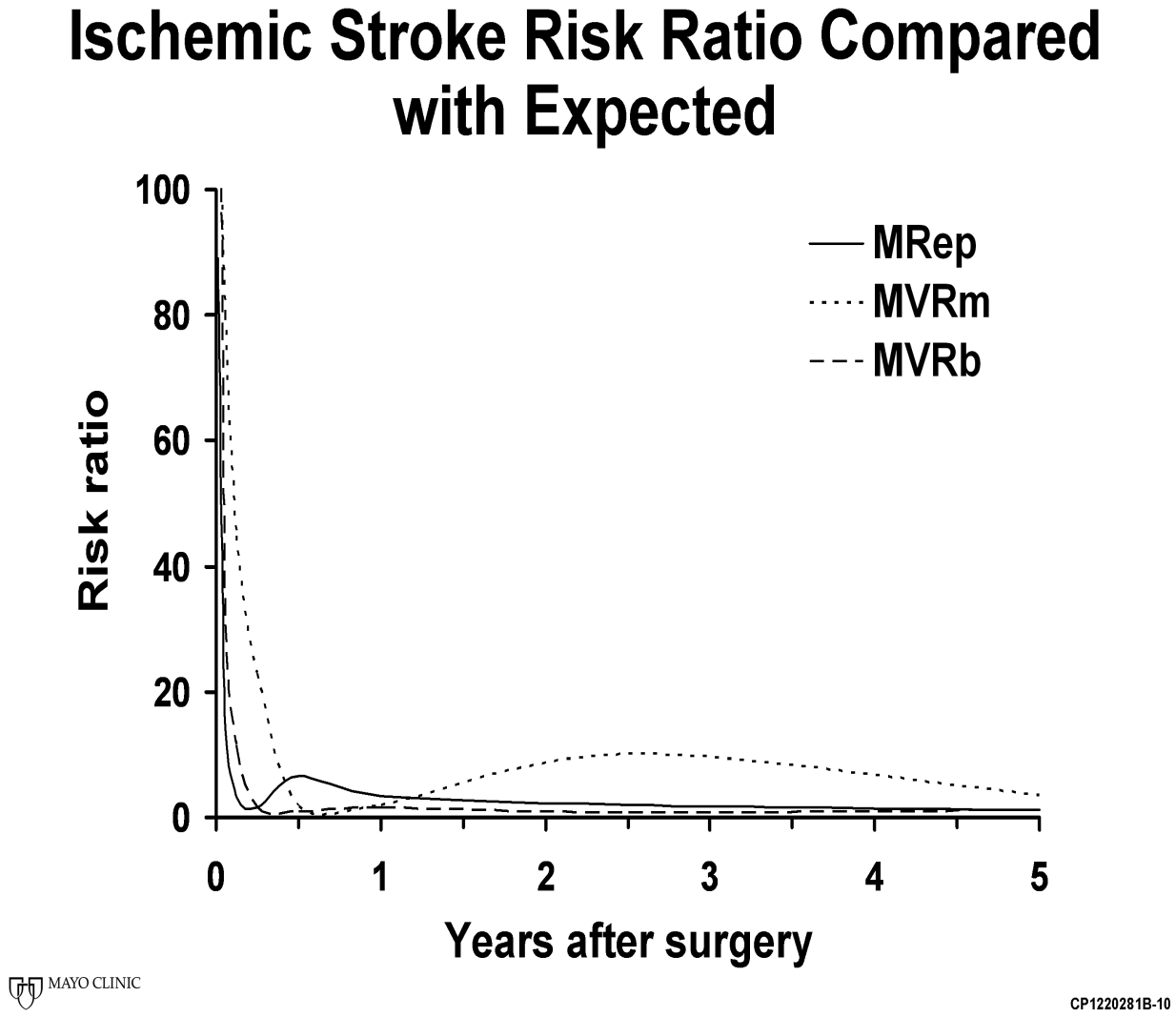

Figure 2. Risk Ratio (RR) of IS observed compared with expected in the general population with characteristics similar to the population of the study.

Incidence of IS after MV surgery: risk ratio compared with expected

Period of time after MV surgery	Over entire follow-up	≤30 days	>30 days	30-180 days	>180 days
Overall					
RR	2.14	40.73	1.73	2.90	1.56
95% CI	1.78-2.54	26.35-60.12	1.41-2.09	1.39-5.34	1.27-1.91
P	<0.001	<0.001	<0.001	<0.001	<0.001
MRep group					
RR	1.62	30.94	1.30	2.08	1.17
95% CI	1.25-2.07	16.42-52.96	0.97-1.70	0.68-4.84	0.86-1.56
P	<0.001	<0.001	0.070	0.094	0.302
MVRm group					
RR	5.11	43.36	4.77	10.36	4.31
95% CI	3.71-6.86	8.96-126.5	3.42-6.47	2.82-26.55	3.04-5.94
P	<0.001	<0.001	<0.001	<0.001	<0.001
MVRb group					
RR	1.72	72.29	0.98	1.53	0.90
95% CI	1.07-2.63	33.05-137.4	0.51-1.72	0.04-8.50	0.45-1.62
P	0.012	<0.001	0.946	0.642	0.729

MAYO CLINIC

CP1220281B-1

TABLE 3. Risk of IS compared with expected during all the phases of follow

Predictors of IS: univariate analysis

	≤30 days			30-180 days			>180 days		
Risk factors	Odds Ratio	95%CI	P	Odds Ratio	95%CI	P	Risk Ratio	95%CI	P
Age/5 years	1.21	(1.00, 1.50)	0.039	1.30	(0.96, 1.86)	0.088	1.09	(1.00, 1.20)	0.041
Female sex	2.43	(1.09,5.63)	0.028						
CAD	2.56	(1.14, 6.10)	0.021						
IABP	2.98	(0.97, 7.53)	0.054						
MVRb	3.02	(1.26, 6.79)	0.014						
Hypertension	1.95	(0.88, 4.38)	0.098	4.39	(1.21, 20.46)	0.023			
MVRm				3.23	(0.82, 11.4)	0.089	2.77	(1.81, 4.18)	<0.001
LAD>50mm							1.44	(0.96, 2.16)	0.073
AF baseline/before IS							1.83	(1.22, 2.74)	0.003
MRep							0.50	(0.33, 0.76)	0.001

Table 4. Predictors of IS during different phases of follow up: univariate analysis.

CAD:coronary artery disease. IABP: intra aortic balloon pump. LAD; left atrial diameter. IS: ischemic stroke

Independent predictors of IS

	<30 days			30-180 days			>180 days		
Risk factors	Odds Ratio	95%CI	P	Odds Ratio	95%CI	P	Risk Ratio	95%CI	P
Female sex	2.28	(1.01, 5.38)	0.047						
Hypertension				4.33	(1.16, 20.33)	0.027			
MVRm				6.04	(1.38, 25.24)	0.018	3.02	(1.94, 4.65)	<0.001
Age/5 years				1.44	(1.00, 2.25)	0.048	1.14	(1.03, 1.26)	0.006
MRep							0.52	(0.34, 0.79)	0.002

Table 5. Predictors of IS during different phases of follow up: multivariate analysis.

IS: ischemic stroke

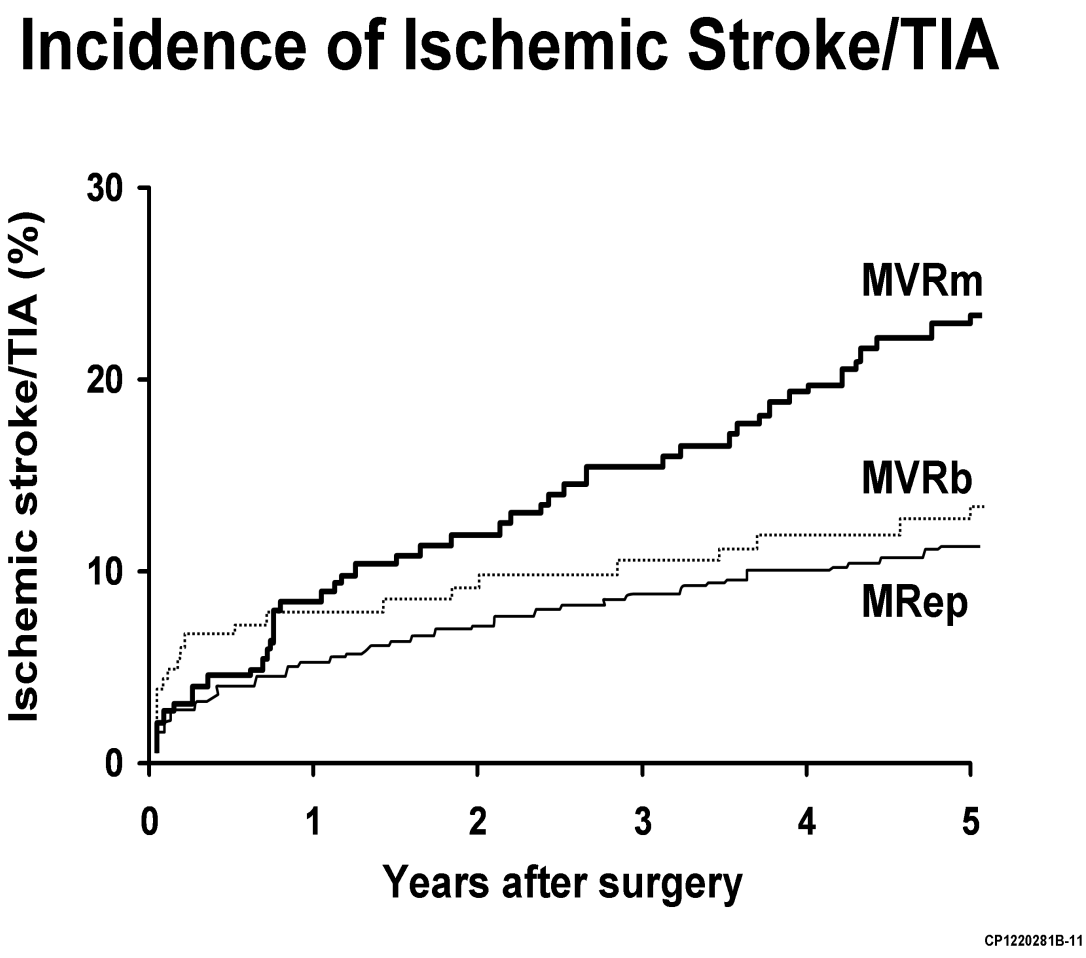

Figure 3. Plot of long term incidence of IS/TIA in the three groups. Note that MRep presents the lowest long term incidence of combined end-point IS/TIA, smaller than MVRm (P<0.0001), not different from MVRb (P=NS).
IS: ischemic stroke; TIA: transient ischemic attack

Incidence of IS/TIA during the follow up

	Over entire follow up	≤30 days postop	30-180 days postop	Follow up >180 days postop
Overall	Events: 201 5 years incidence=13.4±1% 10 years incidence=19.8±1.4% 2.49±0.1% patients-years	Events: 34 30 days incidence=2.62±0.4% 32.7±5.6% patients years	Events: 21 180 days incidence=4.32±0.6% 4.3±0.9% patients years	Events: 146 1.95±0.1% patients-years
MRep group	Events: 109 5 year incidence=10.9±1.1% 10 years incidence=16.6±1.7% 2.02±0.2% patients-years	Events: 21 30 days incidence=2.39±0.5% 29.6±6.4% patients-years	Events: 13 180 days incidence=3.92±0.6% 3.85±1.06% patients-years	Events: 75 1.46±0.16% patients-years
MVRm group	Events: 61 5 year incidence=23.4±3.1 10 years incidence=32±3.7% 4.09±0.5% patients-years	Events: 4 30 days incidence=1.78±0.9% 22.2±11.1% patients-years	Events: 5 180 days incidence=4.1±1.3% 5.95±2.6% patients-years	Events: 52 3.74±0.5% patients-years
MVRb group	Events: 31 5 year incidence=13.19±2.6% 10 years incidence=19.1±3.4% 2.58±0.4% patients-years	Events: 9 30 days incidence=4.62±1.5% 59.9±19.9% patients-years	Events: 3 180 days incidence=6.3±1.7% 4.52±2.6% patients-years	Events: 19 1.69±0.38% patients-years

Table 6. Incidence of IS/TIA during the follow up : actuarial survival and yearly linearized rate.

IS: ischemic stroke; TIA: transient ischemic attack

Risk of IS/TIA compared with expected in the general population

Period of time after MV surgery	Over entire follow-up	≤30 days	>30 days	30-180 days	>180 days
Overall					
RR	2.74	42.67	2.28	4.73	2.00
95% CI	2.38-3.15	29.54-59.62	1.95-2.65	2.92-7.22	1.69-2.35
P	<0.001	<0.001	<0.001	<0.001	<0.001
MRep group					
RR	2.24	38.54	1.81	4.19	1.55
95% CI	1.84-2.71	23.85-58.91	1.45-2.23	2.23-7.18	1.22-1.94
P	<0.001	<0.001	<0.001	<0.001	<0.001
MVRm group					
RR	5.75	42.61	5.37	9.57	4.92
95% CI	4.40-7.39	11.61-109.2	4.07-6.96	3.11-22.29	3.67-6.54
P	<0.001	<0.001	<0.001	<0.001	<0.001
MVRb group					
RR	2.21	56.92	1.57	3.65	1.36
95% CI	1.50-3.13	26.03-108.2	0.98-2.37	0.75-10.65	0.82-2.12
P	<0.001	<0.001	0.035	0.014	0.187

MAYO CLINIC

CP1220281B-12

Table 7. Risk of IS/TIA compared with expected during the follow up

IS: ischemic stroke; TIA: transient ischemic attack

Risk of ICH compared with expected in the general population

Period of time after MV surgery	**Over entire follow up**	**≤30 days**	**Follow up >30 days**	**30-180 days**	**Follow up >180 days**
Overall	RR=1.13, (0.54, 2.08) P<0.001	RR=11.79, (0.30, 65.45) P=0.001	RR=1.02, (0.46, 1.93) P=0.914	RR=0.00, (0.00, 7.67) P=0.478	RR=1.02, (0.47, 1.93) P=0.917
MRep group	RR= 0.17, (0.00, 0.97) P=0.040	RR=0.00, (0.00, 64.16) P=0.807	RR=0.17, (0.00, 0.97) P=0.040	RR=0.00, (0.00, 11.12) P=0.556	RR=0.17, (0.00, 0.97) P=0.040
MVRm group	RR=3.76, (1.22, 8.76) P=0.003	RR=0.00, (0.00, 404.2) P=0.921	RR=3.76, (1.22, 8.76) P=0.003	RR=0.00, (0.00, 71.37) P=0.812	RR=3.77, (1.22, 8.77) P=0.002
MVRb group	RR=2.23, (0.61, 5.70) P=0.117	RR=55.07, (1.39, 305.7) P<0.001	RR=1.67, (0.35, 4.87) P=0.404	RR=0.00, (0.00, 37.87) P=0.752	RR=1.67, (0.35, 4.87) P=0.402

Table 8. Risk of ICH compared with expected during the follow up

ICH: intracranial haemorrhage

Risk of IS/ICH compared with expected in the general population

Period of time after MV surgery	**Over entire follow up**	**≤30 days**	**Follow up >30 days**	**30-180 days**	**Follow up >180 days**
Overall	RR=2.08, (1.75, 2.46) P=0.00000	RR=38.27, (24.99, 56.07) P=0.00000	RR=1.70, (1.40, 2.04) P=0.00000	RR=2.62, (1.26, 4.83) P=0.00159	RR=1.55, (1.27, 1.88) P=0.00002
MRep group	RR= 1.49, (1.15, 1.89) P= 0.00183	RR=27.95, (14.83, 47.84) P=0.00000	RR=1.20, (0.90, 1.56) P=0.23733	RR=1.88, (0.61, 4.38) P=0.15556	RR=1.08, (0.80, 1.44) P=0.65452
MVRm group	RR=5.19, (3.84, 6.86) P=0.00000	RR=39.38, (8.14, 114.9) P=0.00000	RR=4.87, (3.56, 6.50) P=0.00000	RR=9.41, (2.57, 24.12) P=0.00000	RR=4.46, (3.21, 6.02) P=0.00000
MVRb group	RR=1.86, (1.21, 2.75) P=0.00182	RR=72.40, (34.72, 133.2) P=0.00000	RR=1.12, (0.63, 1.85) P=0.68735	RR=1.38, (0.03, 7.66) P=0.72704	RR=1.05, (0.57, 1.76) P=0.89006

Table 9. Risk of ischemic/hemorrhagic strokes compared with expected during the follow up

IS: ischemic stroke; ICH: intracranial haemorrhage

	Overall 1344 pts	MRep 897 pts	MVRm 231 pts	MVRb 216 pts
IS	130 (10%)	65 (7%)	44 (19%)	21 (10%)
TIA	71 (5%)	44 (5%)	17 (7%)	10 (5%)
Peripheral/ Mesenteric TE	11 (8%)	5 (0.6%)	3 (1%)	3 (1%)
Total TE	212 (16%)	114 (13)	64 (28%)	34 (16)

Table 10. Distribution of any TE in the different groups (Overall, MRep, MVRm and MVRb)

IS: ischemic stroke; TIA: transient ischemic attack

Incidence of total TE during the follow up

	Over entire follow up	≤30 days postop	30-180 days postop	Follow up >180 days postop
Overall	5 years incidence=14.2±1% 10 years incidence=20.7±1.4% Yearly L.R.=2.6±0.2%/y	30 days incidence=2.85±0.5% Yearly L.R.=38.6±5.8%/y	180 days incidence=4.7±0.6% Yearly L.R.=4.72±1%/y	Yearly L.R.=2±0.1% per year
MRep group	5 year incidence=11.6±1.1% 10 year incidence=17.2±1.7 L.R.=2.1±0.2% per year	30 days incidence=2.5±0.5% L.R.=31.05±6.6% per year	180 days incidence=4.15±0.7% L.R.=4.15±1.1% per year	L.R.=1.57±0.17% per year
MVRm group	5 year incidence=23.8±3.1 10 year incidence=33.1±3.8 L.R.=4.3±0.5% per year	30 days incidence=1.78±0.9% L.R.=22.17±11.1% per year	180 days incidence=4.56±1.4% L.R.=7.14±2.9% per year	L.R.=3.91±0.5% per year
MVRb group	5 year incidence=14.9±2.8% 10 year incidence=20.8±3.5% L.R.=2.8±0.5% per year	30 days incidence=5.67±1.6% L.R.=73.49±22.15% per year	180 days incidence=7.39±1.9% L.R.=4.54±2.6% per year	L.R.=1.78±0.4% per year

TABLE 11 Incidence of total thromboembolic events the follow-up: actuarial survival and yearly linearized rate.

Incidence of Bleeding events during the follow up

	Over entire follow up	≤30 days postop	30-180 days postop	Follow up >180 days postop
Overall	5 years incidence=8.6±0.8% 10 years incidence=13.7±1.3% Yearly L.R.=1.6±0.1% per year	30 days incidence=3.9±0.5% Yearly L.R.=49.5±6.9% per year	180 days incidence=4.6±0.6% Yearly L.R.=1.84±0.6% per year	Yearly L.R.=0.96±0.1% per year
MRep group	5 year incidence=6.2±0.9% 10 year incidence=8.6±1.2% L.R.=1.0±0.1% per year	30 days incidence=2±0.5% L.R.=25.3±6% per year	180 days incidence=2.6±0.5% L.R.=1.5±0.6% per year	L.R.=0.7±0.1% per year
MVRm group	5 year incidence=12.3±2.3 10 year incidence=20.5±3.3 L.R.=2.3±0.3% per year	30 days incidence=4.9±1.4% L.R.=62.5±19% per year	180 days incidence=5.8±1.6% L.R.=2.4±1.7% per year	L.R.=1.7±0.3% per year
MVRb group	5 year incidence=15.2±2.6% 10 year incidence=25.2±4.1% L.R.=3.4±0.5% per year	30 days incidence=10.8±2.2% L.R.=154±33% per year	180 days incidence=12±2.3% L.R.=3.1±2.2% per year	L.R.=1.4±0.4% per year

TABLE 12 Incidence of total thromboembolic events during the follow-up: actuarial survival and yearly linearized rate.

Indipendent predictors of Bleeding events

	<30 days			30-180 days			>180 days		
Risk factors	Odds Ratio	95%CI	P	Odds Ratio	95%CI	P	Risk Ratio	95%CI	P
Age/5 years	1.03	(1.04, 1.39)	0.007	1.35	(1.01, 1.92)	0.039	1.14	(1.02, 1.27)	0.010
Male sex							1.65	(1.04, 2.71)	0.031
MVRm							2.46	(1.52, 3.91)	< 0.001
MRep							0.39	(0.25, 0.61)	< 0.001

Table 13. Predictors of Bleeding events during the follow up: multivariate analysis