

Recommendations for Reporting Morbid Events after Heart Valve Surgery

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Major reasons for the considerable heterogeneity among published results of heart valve surgery are inconsistency in follow up techniques, reporting systems and classification of adverse events. The present recommendations are intended to harmonize the presentation of clinical material in order to improve comparison of data from different sources for the analysis of pooled data. The quality of an observational study is largely, if not entirely, due to the follow up technique, which may be graded according to six categories: Self-reporting of adverse events/well-being by the patients may be classified 'excellent'; if the information is gathered and re-checked at short-term intervals. Data obtained from in-hospital or outpatient examinations by qualified examiners at least twice a year or other personal contact through qualified examiners may be regarded as 'sufficient', if the results are re-checked by contacting the treating home physician. All other follow up techniques may be regarded as inappropriate. Consequences of com-

There is considerable heterogeneity among publications reporting the results of heart valve surgery. The major reasons for this are inconsistency in follow up techniques and reporting systems (1,2), as well as the use of different classifications, for example in terms of adverse events (1,3,4).

Valid comparison of results after heart valve surgery is restricted to well-controlled studies. 'Randomized' comparisons - the 'gold standard' for clinical studies in many medical areas - may however bear a variety of sources of potential bias in the field of valve replacement surgery. Randomized studies are rare as there are various implementation difficulties to conduct and perform these investigations (5). Non-randomized

lications are entirely dependent on severity and possible sequelae. It is therefore recommended to grade any reported complication according to its severity by utilizing a score system. Embolisms are best categorized by utilizing the performance status scale. Bleeding events may be categorized according to severity as fatal, major (requiring hospital transmission with transfusion, surgery or with permanently increased disability) or minor (not requiring hospital admission, surgery or transfusion). In some cases it will remain unclear whether an event was primarily embolic or hemorrhagic. These complications should be summarized as 'not categorized'. The reporting of morbid events due to thrombosis, embolism and bleeding should go along with information regarding the quality of antithrombotic management.

The Journal of Heart Valve Disease 2005;14:1-7

studies may also be used to answer clinical questions, although extreme care should be taken not to misuse and misinterpret the data sets analyzed (1,6).

In order to interpret published data adequately, information regarding patient selection, follow up techniques and data analyses is indispensable. Moreover, any adverse event documented during follow up must be reported in an unequivocal manner.

These recommendations, prepared by the Working Group on Infection, Thrombosis, Embolism and Bleeding of the Society of Heart Valve Disease, are intended to harmonize the presentation of clinical material in order to improve the comparison of information acquired from different sources for the analysis of pooled data.

Patient enrolment for clinical trials

Patient selection may significantly bias any reported clinical outcome. For single-center studies, the selec-

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tion bias is low if all consecutive patients who give their informed consent are enrolled. The higher the percentage of patients who denied informed consent, the higher the bias. For that reason, the number and percentage of denying patients should be given in any publication.

If the statistician involved confirms that the patient cohort is large enough, the result of such a single-center follow up series may be representative for the study period and the institution where the study has been performed. If not all consecutive patients have been enrolled, the selection criteria should be specified and a significant limitation of the study announced in the respective paragraph of the publication. The start and end of enrollment (month and year) should be given. Any interruption of enrollment or an inconsistent recruitment should be indicated, along with the reasons. Progress of recruitment is best illustrated by a histogram.

Patient enrollment should be preoperative, and not at an arbitrary time interval postoperatively (e.g. 'operative survivors') as is often the case in cohort clinical trials, which therefore are of limited value. Not considering the perioperative fatalities may result in a significant study bias (1,7). If special statistical instruments (e.g. matched pair analyses) are applied, then non-consecutive patients may be used (8).

Preoperative cardiac function and co-morbidity

Preoperative cardiac function and patient co-morbidity have a significant impact on early and late outcome after heart valve surgery (9). The New York Heart Association (NYHA) classification is widely accepted to describe the patients' preoperative and postoperative clinical situation. However, this classification does not allow much differentiation, it is examiner-biased, and patients with chronic adaptation to their cardiac condition or, for example orthopedic co-morbidity, are frequently allocated to inadequate functional NYHA classes than comply with their exercise capacity (10). Authors therefore should describe the preoperative cardiac situation precisely by giving left ventricular diameters or parameters indicative of left ventricular pump function (e.g. ejection fraction, contractility reserve) or other parameters established for heart failure studies (e.g. spiroergometry data or 6-min walk test) (11).

Appropriate information regarding the patients' co-morbidity should also be given and include: (a) concomitant cardiac diseases (especially coronary artery disease); (b) concomitant non-cardiac diseases (e.g. impaired liver, kidney or lung function, diabetes); (c) previous cardiovascular events (e.g. acute myocardial

infarctions, strokes); (d) established cardiovascular risk factors (e.g. atrial fibrillation, arterial hypertension, dyslipoproteinemia, obesity, aortic enlargement, nicotine abuse); and (e) psychological disorders (e.g. depression). For grading the severity of psychological disorders, the Human Anxiety Depression Scale (HADS) may be used (12).

Follow up techniques

The quality of an observational study is largely, if not entirely, dependent upon the follow up technique, as only a sophisticated follow up may allow for a (near) complete documentation of all adverse/morbid events (1,6,13). Controlled studies have shown that when parallel to the regular follow up in an outpatient department, the same patients were sent questionnaires at 6-, 18-, and 36-month intervals, about half of those events which were transient or reversible were 'forgotten' and not mentioned on the 18- and 36-month questionnaires (6,13).

In this respect, the quality of follow up may be graded according to six categories; the respective category should be given for each follow up series.

Quality may be regarded 'excellent' for category 1 follow up technique, 'sufficient' for categories 2 and 3, 'poor' (limited value, use information with caution) for category 4, and 'inappropriate' (may not be considered for publication) for categories 5 and 6. Definitions are as follows:

Category 1: self-reporting of adverse events/well-being by the patients, information gathered and re-checked at short-term intervals (≤ 3 months); or qualified outpatient examination every three months. If patients are significantly disabled, family members or home physicians may supply the information instead.

Category 2: in-hospital or outpatient examination by a qualified examiner at least twice a year.

Category 3: other personal contact through a qualified examiner (e.g. by telephone interviews utilizing standardized questionnaire protocols) at least twice a year; the results to be re-checked by contacting the treating home physician.

Category 4: all other follow up techniques with patient contact involving a qualified examiner once or less than once a year.

Category 5: questionnaires at intervals of more than one year.

Category 6: any other follow up.

Only with patient self-reporting of complications, first described for the German Experience with Low-Intensity Anticoagulation Study (GELIA) (14), are nearly all even mild and transient complications

detected (1,15). Regular clinical examinations by qualified examiners at short-term intervals (≤ 3 months) are more costly, but probably will have the same reporting standard. With all other techniques, a more or less significant loss of information is accepted. Studies based on different follow up strategies may not be compared (as the results are incomparable!) and should not be combined in any analysis of pooled data (1).

Data collection and analysis

Data collection may be either prospective or retrospective. Retrospective collection (e.g. from clinical records) is prone to significant limitations and may produce invalid results. Any retrospective gathering of data (e.g. 'second look into the clinical records' to utilize additional data not included in the primary study protocol) should be indicated, and this limitation should be mentioned in the respective paragraph of the publication.

A prospective clinical trial requires: (a) a follow up protocol which includes full information regarding follow up techniques and time intervals as well as all parameters that are documented; and (b) the patients' informed consent to participate. Observational clinical studies often do not meet these criteria.

Data analysis should follow established statistical methods, including information of whether an intent-to-treat or an explorative data analysis has been performed. For example, if a target INR corridor for anticoagulation has been recommended, but not at least the vast majority of measurement is documented, only an intent-to-treat analysis can be performed with respect to the intensity and quality of oral anticoagulation therapy (16). If (nearly) all INR measurements have been documented and patients have been reallocated to the documented INR corridors (not to the recommended corridors!), prerequisites for an explorative data analysis are fulfilled.

Linearized rates (e.g. for complications) should not be given if the hazard for complications is non-linear. As many complications peak during the first three postoperative months, it is incorrect from a statistical point of view to give linearized hazard rates for the entire postoperative period (1,17). Instead, the period with an elevated, non-linearized risk should be mentioned separately and not be utilized for the calculation of linearized incidences (1,17).

Consequences of complications are entirely dependent on severity and possible sequelae. Counting complications without differentiating - for example between mild nose bleeding and life-threatening retroperitoneal hemorrhage - results in invalid information. It is therefore recommended that any reported complication is graded according to its severity, by uti-

lizing a score system. The performance status scale (PSS) based on the Karnofsky score (18) has been used most effectively, and seems to be appropriate for the grading of morbid events after valve surgery (3).

According to the Karnofsky criteria (18) and adapting definitions used for earlier studies (14), complications may be graded as 'mild' (grade I), 'moderate' (grade II), 'severe' (grade III), or 'fatal' (grade IV) (see Table I). If this grading scheme is used, cerebral complications and complications involving other organs must be given separately.

Categories of morbid events

Embolism

All transient or prolonged (but within ten days), fully reversible neurological symptoms are considered as embolic stroke (PSS score 00). A precise differentiation between a cardioembolic and an arterioembolic etiology is not possible by any means. If cranial computed tomography (CCT) identifies lacunary or tentorial cerebral infarction, stroke must not be considered embolic in origin.

More severe/more prolonged cerebral complications (PSS 10-100) are considered embolic stroke only, if other etiologies (especially cerebral hemorrhage) have been excluded by applying adequate imaging techniques (e.g. CCT or MR scans) at adequate time intervals (see Table I).

Systemic embolism is considered if contemptuous clinical signs and symptoms indicative of organ-specific ischemia are present. In cases where an embolic complication cannot be differentiated from hemorrhage clinically, an embolic complication is likely if an (in)complete obstruction of the respective artery can be documented (e.g. using Doppler ultrasound techniques), or a bleeding has been ruled out by utilizing adequate imaging techniques. Complications with unclear etiologies should be categorized as described below (see 'Not categorized').

Thrombosis

Prosthetic valve thrombosis (PVT) or thrombus formation adjacent to a valve corrected surgically or by a catheter-based intervention is likely, if adequate imaging techniques (initially transesophageal echocardiography; TEE) demonstrate new appearance of 'masses' attached to the respective sites in the absence of clinical signs and symptoms of an infection. PVT may be either obstructive or non-obstructive, depending on the presence or absence of limited motion of the occluder(s), if other pathologies such as pannus or vegetation can be excluded (19). Obstruction is likely if transprosthetic gradients are increased, as measured by Doppler echocardiography. PVT may also result in

Table I: Grading the severity of thrombotic, thromboembolic and hemorrhagic complications. For neurological symptoms, criteria given by Karnofsky and Burchenai (18) were adapted and the performance status scale (PSS) modified. The PSS allows grading of transient and persistent disabilities.

Severity score	PSS score	Criteria for neurological symptoms	Criteria for other organs
I	00	Transient, reversible within 24 h	Symptoms observed for >24 h and treated by the patient him/herself
II	00	Prolonged, reversible within 10 days	Symptoms observed by the patient and treated in an outpatient mode, completely reversible
	00	Prolonged for >10 days, but completely reversible	Symptoms observed by the patient and treated in an outpatient mode, no more than mild sequelae which do not limit the patient during any day-to-day activities
	10-20	Prolonged, partly reversible, minimal functional impairment persisting	
III	30-40	Prolonged, partly reversible; some sequelae which do not limit the patient during any day-to-day activities	Symptoms leading to hospitalization, limiting functional impairment persisting/sequelae
	50-60	Prolonged, limiting functional impairment persisting	
	70-90	Severe permanent impairment (severe handicap, persistent hospitalization or institutional care) or prosthetic valve thrombosis, thromboembolic/bleeding complications necessitating surgical intervention or blood transfusion, regardless of PSS score	
IV	100		Direct/indirect fatal complication

increased or reduced intraprosthetic regurgitation. Limited occluder motion may be demonstrated by cinefluoroscopy or TEE. Obstructive PVT is also likely if the acoustic behavior of occluder opening and closure clicks change (20,21).

Bleedings

A bleeding complication is obvious if observed by the patient him/herself (e.g. nose bleeding, hematuria). Cerebral hemorrhage can be differentiated precisely from embolic stroke only when applying (timely) adequate imaging techniques. If other than cerebral bleedings are supposed, straightforward diagnostic imaging tools should be used routinely today, so that the number of definite unclear cases (see 'Not categorized') should be low.

Bleeding events can be categorized according to severity (22) as:

fatal (if documented on convincing clinical evidence or at autopsy);

major: requiring hospital admission with transfusion, surgery or being accompanied by permanent sequelae; or

minor: those that are transient and do not require hospital admissions, surgery or transfusion (e.g. nasal, gingival, subcutaneous, hematuria).

Not categorized

In some cases it will remain unclear as to whether an event was primarily embolic or hemorrhagic. Some guidelines (4) count such unclear events as 'thromboembolism'. However, there is evidence nowadays that most patients - for example, with cerebral events of unknown etiology - have cerebral bleedings rather than embolism, when CCT scans are performed (21). This has major clinical implications: If in a clinical series with a certain prosthetic valve a high number of cerebral events are recorded and the prosthetic device - according to older definitions (4) - is regarded as 'high thrombogenic' because all these events are counted as 'embolic', then a more intensive anticoagulation may be recommended. However, the high complication rate may not be due to thromboembolism but rather to cerebral bleedings. The adequate therapeutic measure would then be to reduce the intensity of anticoagulation. Therefore, it is strongly recommended not to mix up complications of unclear origin but to summarize them as 'not categorized'.

Hemorrhagic transformation of a cerebral infarction complicates the matter further. Hemorrhagic infarction has no mass effect and is classified as HI-1 if small petechiae are documented on CCT along the margin of infarction, and HI-2 if hemorrhage is confluent within

the infarcted area. A parenchymal hematoma (which is a primary cerebral bleeding) has a mass effect (23). Hemorrhagic conversion can also be defined as 'mild' (speckled or mottled) with indistinct margins or 'large' (homogeneous signal consistent with blood, within the area of infarction or with a mass effect). Experienced neuroradiologists or neurologists with CCT training may distinguish hemorrhagic transformation of acute ischemic stroke from primary cerebral bleedings (24), which should limit the number of 'not categorized' events.

Infective endocarditis

For definition (e.g. early versus late prosthetic valve endocarditis), diagnosis and reporting complications, the detailed guidelines of the ESC Task Force should be followed (25). These will not be summarized here, but are available online (www.escardio.org).

Malfunction of mechanical valve prostheses

Besides PVT, malfunction of valve prostheses may be caused by entrapment of the occluder, obstruction of the bloodstream by pannus (tissue ingrowth), sutures or cardiac structures (e.g. inappropriate sizing of the prosthesis) and infective vegetations ('non-structural dysfunction'). This category includes all new, permanent or transient events. All clinically documented obstructions are reported in accordance with this definition as 'thrombosis', which tends to result in excessive reporting because non-thrombotic obstructions are also regarded as PVT if the etiology cannot be differentiated accurately.

Signs of prosthesis malfunction are incomplete opening of any origin, non-thrombotic obstruction, high intraprosthetic regurgitation of any origin (e.g. interference with sutures, strands, etc.) or periprosthetic regurgitation. An abnormal transprosthetic pressure loss is best indicated by the opening area of the index prosthesis (peak and mean gradients may also be given) (26). Irregular movements of occluders or unsimultaneous movements of the occluders in bileaflet prostheses are most often flow-related and a result of prosthesis orientation chosen by the surgeon, and do not indicate malfunction in the majority of cases.

An abnormal intraprosthetic volume loss exceeding the technical closing volume plus leakage flow is difficult to quantify (27). Doppler and/or angiographic parameters may be given.

Mechanical dysfunction of a prosthesis

A mechanical dysfunction is any mechanical failure of parts of the prosthetic device (e.g. leaflet escape, strut fracture, intermittent occluder obstruction due to lipid adsorption).

Dysfunction of a biological prosthesis (degeneration)

Structural valve deterioration (SVD) in bioprostheses is time-dependent and characterized by tissue degeneration and dystrophic calcification. Non-calcific-related cusp tears, leaflet disruption and increased stiffness are the most significant modes of failure (28,29). Bioprosthesis dysfunction is considered if valve opening becomes restricted (stenotic) or valve closure regurgitant (insufficiency). Doppler echocardiography is the technique of choice to assess these hemodynamic consequences. The degeneration of bioprosthetic valves is enhanced by young age, possibly pregnancy, and any etiology causing calcification, including renal failure and hyperparathyroidism.

Freedom from primary tissue failure may be different in the aortic and mitral positions. Hence, data should be given separately (30,31).

Especially in homografts/freeform valves, the hemodynamic performance of the substitute should be assessed at discharge and at six months postoperatively, eventually to allow for a differentiation between poor surgical technique and structural failure.

Intravascular hemolysis

Intravascular hemolysis should be regarded as a complication if serum lactate dehydrogenase (LDH) - the prototypic indicator for hemolysis - is elevated to twice or more the normal value (32). Intravascular hemolysis that requires intermittent blood transfusion (decompensated anemia) should be considered a severe complication.

All non- (prosthetic) valve-related deaths

Fatal complications which do not fit the aforementioned categories should be grouped into a separate category structured as follows: clear cases subdivided into cardiac (but not valve-related) and non-cardiac fatalities; unclear cases including all sudden deaths which should be listed separately.

Anticoagulation management

Reporting morbid events due to thrombosis, embolism and bleeding should go along with information regarding the quality of the antithrombotic (anticoagulant) management (33). The following information is indispensable:

Antithrombotic drugs used (anticoagulants and antiplatelet drugs), dosage and laboratory control techniques.

Quality of anticoagulation including home monitoring, target INR and INR stability (15,34-39).

In conclusion, the authors of these recommendations appreciate that the high standards recommended for the most efficient follow up and correct reporting of morbid events after valve replacement surgery may not always be achievable, for example in Third World countries. Scientific investigations (e.g. observational clinical trials) that do not meet established standards may also contain information worth publishing, if those limitations are clearly pointed out. Furthermore, the recommendations for reporting morbid events after heart valve surgery are intended to be discussed and improved until they eventually become 'guidelines'.

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