

# Influence of Two Different Reporting Systems on Counts of Thromboembolic and Bleeding Complications after St. Jude Medical Valve Replacement: Results from the GELIA Study

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**Background and aim of the study:** Different standards for the reporting of morbid events and different follow up techniques have a profound impact on reported morbidity after prosthetic valve replacement. Most studies follow the guidelines of The American Association of Thoracic Surgery (AATS) and The Society of Thoracic Surgeons (STS); the present authors' group has now developed an adapted Karnofsky scale which allows a more precise grading of the severity of morbid events.

**Methods:** The AATS/STS criteria and the adapted Karnofsky criteria were applied to the database of the German Experience with Low-Intensity Anticoagulation (GELIA) study. In a study population of 2,735 patients, GELIA compared three different intensities of oral anticoagulation in a prospective and randomized design. Patients registered morbid events prospectively by means of docu-

mentation cards.

**Results:** The overall rate of complications was comparable when utilizing the two classification systems. However, use of the AATS/STS criteria resulted in the counting of fewer bleeding complications, because only major bleedings were recorded. In contrast, the incidence of embolic complications was higher compared to the Karnofsky criteria because all events were counted, irrespective of their severity, while clinically insignificant (transient, reversible within 24 h) events were disregarded when using the Karnofsky grading.

**Conclusion:** The adapted Karnofsky criteria provide a precise and easily understandable framework for the assessment of complications, with equal weighting of both hemorrhagic and embolic events.

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Comparison between different prosthesis types or intensities of oral anticoagulation following the implantation of mechanical heart valves is hampered by a lack of prospective and randomized clinical trials (1-3). Therefore, conclusions are mainly based on observational follow up studies reporting the results of single valve types or intended levels of anticoagulation (intent to treat analysis). Among other factors, standardized definitions of morbid events are of paramount importance to ensure comparability among different studies (3-7). Most publications follow the classification proposed by Edmunds and associates in 1988 and updated in 1996 on behalf of The American Association for Thoracic Surgery (AATS) and The Society of Thoracic Surgeons (STS) (8,9). The present authors' group successfully employed a modified

Karnofsky scale instead, which allows a more precise grading of the severity of morbid events (4,5,10,11).

The Karnofsky scoring system was initially introduced to quantify disabilities due to cancer chemotherapy (10). After appropriate adaptation, it may however be used for the grading of disabilities of any origin. Together with a meticulous prospective follow up technique, these criteria resulted in a considerably higher incidence of complications in the present patient population (4,5). Recently, the results of the prospective and randomized multicenter German Experience with Low-Intensity Anticoagulation (GELIA) study were presented. These data compared three different levels of oral anticoagulation intensity in a study cohort of 2,735 patients (1). In order to compare the AATS/STS guidelines with the adapted Karnofsky criteria and to detect possible differences between the two, both classification systems were applied to the GELIA database. The results are presented herein; the intention was also to make the results of the GELIA study - which are originally based on the Karnofsky criteria - comparable with those of other studies.

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## Materials and methods

The design of the GELIA study and its results have been published previously (1,11). Briefly, 2,735 patients following aortic (n = 2024), mitral (n = 553) or combined aortic and mitral (n = 158) valve replacement with a St. Jude Medical (SJM) prosthesis were assigned at random to three different therapeutic ranges of oral anticoagulation. All thromboembolic and bleeding complications were graded from I to III according to the adapted Karnofsky criteria (Table I). If a morbid event could not be classified as either thromboembolic or hemorrhagic, it was entered into a third group of complications termed 'thromboembolism or bleeding complications'. Because of the increased hazard of thromboembolism early after surgery, randomization to the three different International Normalized Ratio (INR) strata was commenced three months postoperatively. To ensure that complications were registered completely, patients received documentation cards covering three-month periods in order to record events

prospectively. New documentation cards were provided by the administrative monitoring center two weeks before the end of each of the three-month periods, together with a prepaid envelope in which the previous cards were sent back. Patients' reports were cross-checked by contacting the treating physicians if more than minor (grade I) complications had occurred, or if the documentation cards had been filled out in a questionable manner.

Because of the unexpected high number of mild (grade I) bleedings (e.g. small hematomas or bleedings from the gums), comparison with the AATS/STS criteria was confined to those complications classified as grade II and grade III by the GELIA (adapted Karnofsky) criteria. This decision was made because the inclusion criteria for minor complications were fundamentally different between the two reporting systems (vide infra). In addition, complications were classified as minor only if they were transient and fully reversible within 24 h, and therefore of no/low clinical significance. Results for each valve position are pre-

Table I: Grading of thrombotic, thromboembolic and hemorrhagic complications in the German Experience with Low-Intensity Anticoagulation (GELIA) study according to the Karnofsky criteria.

Score	PSS score*	Karnofsky criteria Criteria for neurological symptoms	Adapted GELIA grading Criteria for other organs	Grade
I	00	Transient, reversible within 6 h	Symptoms observed and treated by the patient himself	I
	00	Transient, reversible within 24 h		
II	00	Prolonged, reversible within 10 days	Symptoms observed by the patient and treated in an outpatient mode	II
	00	Significantly prolonged, but completely reversible		
	10-20 30-40	Prolonged, partly reversible, minimal functional impairment persisting Prolonged, partly reversible, but some sequelae		
III	50-60	Prolonged, limiting functional impairment persisting	Symptoms leading to hospitalization	III
	70-90	Severe permanent impairment (severe handicap, persistent hospitalization/institutional care)		
	90-100	Direct/indirect fatal complication (as well as any prosthetic valve thrombosis or thromboembolism/bleeding complication necessitating surgical intervention or blood transfusion, regardless of PSS score)		

\*Modified performance status scale (PSS), which allows grading of persistent disabilities.

Table II: Cross-tabulation showing overall thromboembolic and bleeding events according to the GELIA study criteria (rows) and the AATS/STS guidelines (columns) after aortic valve replacement (n = 2,024).

GELIA classification*	AATS/STS classification				
	Embolism	Bleeding	Thrombosis	Not reported <sup>‡</sup>	
Embolism (TE)	14	-	1	2	17 (0.33)
Bleeding (BL)	-	74	-	60	134 (2.61)
TE or BL	9	-	-	-	9 (0.18)
Not classified <sup>†</sup>	35	1	-	-	-
Total AATS/STS	58 (1.13)	75 (1.46)	1 (0.02)	-	Total GELIA

Values in parentheses are percentages.

Table III: Cross-tabulation showing overall thromboembolic and bleeding events according to the GELIA study criteria (rows) and the AATS/STS guidelines (columns) after mitral valve replacement (n = 553).

GELIA classification*	AATS/STS classification				
	Embolism	Bleeding	Thrombosis	Not reported <sup>‡</sup>	
Embolism (TE)	10	-	-	-	10 (0.78)
Bleeding (BL)	-	22	-	10	32 (2.49)
TE or BL	1	-	-	-	1 (0.08)
Not classified <sup>†</sup>	20	-	1	-	-
Total AATS/STS	31 (2.41)	22 (1.71)	1 (0.08)	-	Total GELIA

Values in parentheses are percentages.

Table IV: Cross-tabulation showing overall thromboembolic and bleeding events according to the GELIA study criteria (rows) and the AATS/STS guidelines (columns) after aortic and mitral valve replacement (n = 158).

GELIA classification*	AATS/STS classification				
	Embolism	Bleeding	Thrombosis	Not reported <sup>‡</sup>	
Embolism (TE)	2	-	-	-	2 (0.52)
Bleeding (BL)	-	8	-	4	12 (3.15)
TE or BL	-	-	-	-	- (0.00)
Not classified <sup>†</sup>	2	-	-	-	-
Total AATS/STS	4 (1.05)	8 (2.09)	- (0.00)	-	Total GELIA

Values in parentheses are percentages.

\*Includes all serious (grade II and III) complications according to the GELIA (adapted Karnofsky) criteria, excluding time periods in which the patient deliberately left the randomized INR range (exclusion period).

<sup>†</sup>According to the GELIA protocol, all of these events are reported but excluded in the analysis of serious complications. However, they are accounted for in the AATS/STS classification. This category includes a total of 22 cerebral ischemic complications which fall into grade I complications according to the GELIA criteria, five events which occurred during excluded periods, and 32 possible transient ischemic attacks not classified as such in GELIA.

<sup>‡</sup>Events reported as serious complications in GELIA but not routinely reported in the AATS/STS classification. This category includes 74 grade II bleedings that did not require hospitalization or transfusion. There are also two grade II thromboembolic complications, which, according to the AATS/STS guidelines, would be categorized as prosthetic valve endocarditis.

sented as cross-tabulations containing the number of complications according to the GELIA criteria in the rows and those according to the AATS/STS criteria in the columns (Tables II-IV).

## Results

Tables II-IV are cross-tabulations containing the number of thromboembolic and bleeding complications according to both reporting systems following aortic, mitral and aortic plus mitral valve replacement. Categories of complications differ as the category 'thromboembolism or bleeding complications' is included in the GELIA classification only (to account for events with unclear etiologies) and the category 'valve thrombosis' in the AATS/STS classification only. The respective numbers of events collected in these categories, however, are small. Whereas the total number of events is comparable, the incidence of thromboembolic complications is higher using the AATS/STS criteria, as they require any embolic event to be recorded, irrespective of its severity or etiology. In contrast, minor embolic events are reported as grade I complications in the GELIA classification system (Table I), but are disregarded in this comparison, as they are by definition without clinical importance. On the other hand, the rate of bleeding complications is lower with the AATS/STS criteria, because hemorrhagic events have to necessitate transfusion or to cause death, hospitalization or permanent injury to be considered (8,9). As a consequence, all GELIA classification grade II bleedings which do not fulfill these conditions are ignored.

## Discussion

Reliable and complete documentation of complications is of major importance for the proper assessment of risks associated with different types of prosthetic cardiac valves or intensities of oral anticoagulation (3-7). Apart from standardized definitions of morbid events, the quality of data collection deserves particular attention (7). If data are collected retrospectively and the follow up intervals are too long (i.e. more than 12 months for follow up visits or more than six months for mailed questionnaires), a significant number of transient complications will inevitably be missed (6,12). At worst, the study with the most incomplete follow up will yield the best results (3,6). The design of the GELIA study was unique for its rigorous follow up regime, which resulted - in conjunction with its graduation of the severity of complications according to a modified Karnofsky scale - in a remarkably high rate of minor bleeding complications. The overall rate of minor (grade I) bleedings in the GELIA study popula-

tion was as high as 22.2% per patient-year (1). This result was in line with the findings of a previous non-randomized study of SJM heart valve recipients with a similar follow up design published 10 years ago, in which complication rates were also higher than those usually reported for the SJM prosthesis (4,5).

The adapted Karnofsky criteria allow a more precise differentiation of morbid events into three categories, with equal weighting of thromboembolic and bleeding complications (4,5,10,11). In contrast, the AATS/STS guidelines account for embolic complications of all severities, whereas bleeding complications are disregarded unless they are major (i.e. they necessitate transfusion or cause death, hospitalization or permanent injury) (8,9). In the opinion of the present authors, the definitions set up by the AATS/STS guidelines introduce a bias which results in an under-reporting of hemorrhagic events and over-reporting of prosthetic valve-related embolic events. The majority of minor strokes, however, may neither be prosthetic valve-related nor even cardiogenic in origin (13). Even though minor (grade I) complications according to the GELIA criteria were deliberately excluded from the comparative analysis, the imbalance between thromboembolism and bleedings in the AATS/STS classification in comparison to the GELIA classification is easily illustrated by the higher rate of embolic complications and the lower rate of bleeding complications, because even a proportion of intermediate (grade II) bleedings according to the GELIA protocol are disregarded. To allow for the mutual interplay between thrombosis, embolism and bleeding, the computation of a combined index of these complications has been proposed (3,14). While this index would facilitate the definition of an optimum INR range minimizing the net complication rate, it would not allow insight any to be gained into the interaction between anticoagulation and thromboembolism.

*In conclusion*, the transformation of complication rates of the GELIA study from the Karnofsky classification into the AATS/STS classification not only allows comparisons to be drawn with previous studies, but also illustrates the risks and merits of the two sets of criteria, as well as the importance of proper data collection and definition of morbid events for the quality of clinical trials.

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