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REPLY: Chronic Kidney Disease and Antiplatelet Therapy

A Worrying Gap Between Evidence Based Medicine and Clinical Practice

We thank Lozano and colleagues for their interest in this subject, and agree that the limited use of potent antiplatelet therapies in high-risk patients with chronic kidney disease (CKD) is a concern. In the PROMETHEUS study, prasugrel was not superior to clopidogrel, very likely on account of the selection bias for prescription of potent therapies (1). This bias in observational studies also obscures the ability to detect therapeutic toxicity with respect to bleeding, which contrasts with findings from randomized trials (2,3). In the PLATO (Platelet Inhibition and Patient Outcomes) trial, patients with CrCl <30 ml/min had significantly greater bleeding with ticagrelor than clopidogrel (23.6% vs. 14.1%) (4).

We also concur with the commentary from Gurm, especially his views regarding ticagrelor (5). However, cautious interpretation is necessary because although consistent treatment effects were observed with ticagrelor versus clopidogrel in CKD and non-CKD patients when using creatinine clearance, a treatment interaction was noted when using the more robust Modification of Diet in Renal Disease equation definition, both for the primary endpoint as well as for all-cause mortality (6). Whether or not these differences reflect a biological mechanism versus selection of higher-risk patients with renal impairment remains unclear.

Although the morbidity of bleeding cannot be underestimated, improved selection for potent therapies is warranted. This may be done with the usage of thrombotic and bleeding risk scores (7), and plausibly with a case-by-case decision for assessment of platelet reactivity for identification of CKD patients at lower risk of bleeding (8), who may then be selected for potent therapies. Future studies are necessary to examine the uptake and impact of risk scores on long-term outcomes in CKD patients.

Usman Baber, MD, MS
Jaya Chandrasekhar, MBBS, MS
***Roxana Mehran, MD**

*The Zena and Michael A. Wiener Cardiovascular Institute
The Icahn School of Medicine at Mount Sinai
One Gustave L. Levy Place
Box 1030
New York, New York 10029-6574
E-mail: Roxana.mehran@mountsinai.org

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RESEARCH CORRESPONDENCE

MitraClip in High- Versus Low-Volume Centers

An Analysis From the German TRAMI Registry

Previous studies have suggested lower rates of operative mortality for elderly patients >65 years of age undergoing mitral valve surgery in hospitals with higher annual volumes and increasing repair rates (1). Transcatheter mitral valve repair using the MitraClip

(Abbott Vascular, Santa Clara, California) has recently become an option for elderly patients with mitral regurgitation (MR) deemed inoperable or at high risk for conventional surgery (2). So far, no data exist on potential volume-outcome relationship with MitraClip therapy.

We analyzed data from 828 patients prospectively enrolled into the German multicenter TRAMI (TRAnscatheter Mitral valve Interventions) registry undergoing MitraClip implantation August 2010 and August 2013. The TRAMI registry has been described previously (3). For the present analysis participating hospitals were divided into 2 groups: the 3 top-enrolling centers performed 433 MitraClip procedures (annual procedure number 48.1 ± 13.5, range 32 to 78) during the study period and were considered "high-volume" hospitals. The remaining 395 (48%) patients underwent MitraClip implantation in 18 "low-volume" hospitals (annual procedure number 7.7 ± 10.0, range 1 to 37). Analyses were conducted using SAS statistical package version 9.3 (SAS Institute, Cary, North Carolina).

Patients undergoing MitraClip implantation in high- and low-volume centers were comparable with respect to age and risk scores (**Table 1**). The majority of patients (overall 70.2%) underwent the procedure for functional MR. However, in low-volume centers the proportion of patients with mitral valve prolapse was higher (**Table 1**). Although a minority in both groups, patients with acute cardiogenic shock were more frequent in high-volume centers (23 of 431 [5.3%] vs. 6 of 367 [1.6%]; p = 0.005).

Procedure (113.3 ± 58.4 min vs. 95.3 ± 49.2 min; p < 0.001) and fluoroscopy times (28.3 ± 20.3 min vs. 30.0 ± 83.3 min; p < 0.001) were significantly shorter in high-volume centers. Hospital stay was also shorter at high-volume centers (median 9.0 days [interquartile range (IQR): 6.0 to 15.0 days] vs. 8.0 days [IQR: 6.0 to 13.0 days]; p < 0.001). At discharge, rates of residual moderate (16.0% vs. 28.4%) or severe (2.0% vs. 6.5%) MR were lower in high-volume centers (p < 0.001). In-hospital complications and mortality rates, and rehospitalization for heart failure, need for post-procedural mitral valve surgery, and mortality at 1 year were similar in the 2 groups with better functional New York Heart Association functional class at 1 year among patients at high-volume centers (**Table 1**). Quality of life as measured by the EQ-5D-3L questionnaire and self-rated health status by the EQ visual analogue scale was similar in high- and low-volume centers (EQol-D5-3L score: 0.9 [IQR: 0.7 to 0.9] vs. 0.8 [IQR: 0.7 to 0.9]; p = 0.42; EQ visual analogue scale: 60 [IQR: 50 to 70] vs. 55 [IQR: 50 to 70]).

TABLE 1 Comparison of High- and Low-Volume Centers (Overall Cohort)

	High-Volume Centers (n = 433)	Low-Volume Centers (n = 395)	p Value
Baseline data			
Age, yrs	75.0 ± 8.8	75.7 ± 8.2	0.37
Female	156/433 (36.0)	171/395 (43.3)	0.033
Logistic EuroSCORE, %	22.8 ± 14.9	26.3 ± 21.5	0.18
Logistic EuroSCORE >20%	198/393 (50.4)	185/354 (52.3)	0.61
Previous bypass surgery	112/432 (25.9)	89/367 (24.3)	0.59
Atrial fibrillation	173/432 (40.0)	181/370 (48.9)	0.012
Left ventricular ejection fraction <30%	142/417 (34.1)	114/360 (31.7)	0.65
NYHA functional class ≥III	374/433 (86.4)	341/370 (92.2)	0.009
Decompensated heart failure (within last 6 months)	247/429 (57.6)	194/355 (54.6)	0.41
Functional MR	308/419 (73.5)	207/315 (65.7)	0.022
Mitral valve prolapse	74/362 (20.4)	113/308 (36.7)	<0.001
In-hospital outcomes			
Mortality	11/433 (2.5)	7/394 (1.8)	0.45
Neurological events			
Stroke	4/432 (0.9)	3/352 (0.9)	0.91
TIA	5/432 (1.2)	3/352 (0.9)	0.67
Myocardial infarction	0	0	–
Major access and vascular complications	8/431 (1.9)	3/352 (0.9)	0.24
Major bleeding complications	34/431 (7.9)	24/352 (6.8)	0.57
Acute kidney injury			
without need for dialysis	2/433 (0.5)	4/395 (1.0)	0.35
with new dialysis at discharge	5/430 (1.2)	3/354 (0.8)	0.66
Arrhythmias	17/433 (3.9)	2/395 (0.5)	<0.001
1-yr outcomes			
Mortality	93/418 (22.2)	59/331 (17.8)	0.13
NYHA functional class III/IV	89/264 (33.7)	88/218 (40.4)	0.048
Rehospitalization during 1 yr	203/305 (66.6)	161/261 (61.7)	0.23
for heart failure	43/203 (21.2)	37/161 (23.0)	0.68
Mitral valve surgery	5/228 (2.2)	5/208 (2.4)	0.92

Values are mean ± SD or n/N (%).

EuroSCORE = European System for Cardiac Operative Risk Evaluation; MR = mitral regurgitation; NYHA = New York Heart Association; TIA = transient ischemic attack.

For patients undergoing MitraClip implantation for functional MR (70.2% of the overall cohort), procedure times were again shorter and residual MR at discharge was less in high-volume hospitals (**Table 2**). Yet similar to the overall cohort, rates of in-hospital complications as well as short-term and midterm mortality were not different between high- and low-volume centers.

The present analysis is the first to evaluate volume-outcome relationship in 828 "real-world" MitraClip patients and suggested better efficiency (shorter procedure times) and higher procedural success (lower rates of post-procedural moderate or severe MR) as well as shorter hospital stays in high-volume centers, likely as a result of better practical experience with the procedure (4). Despite these differences, the acute and midterm outcomes of patients undergoing MitraClip implantation at high-volume centers were not different from those

TABLE 2 Comparison of High- and Low-Volume Centers (Patients With Functional MR Only)

	High-Volume Centers (n = 308)	Low-Volume Centers (n = 207)	p Value
Baseline data			
Age, yrs	74.5 ± 8.2	74.8 ± 7.5	0.82
Females	107/308 (34.7)	89/207 (43.0)	0.059
Logistic EuroSCORE, %	22.2 ± 14.9	26.9 ± 23.0	0.038
Logistic EuroSCORE >20%	146/303 (48.2)	109/203 (53.7)	0.22
Previous bypass surgery	89/308 (28.9)	53/204 (26.0)	0.47
Atrial fibrillation	129/308 (41.9)	105/207 (50.7)	0.048
Left ventricular ejection fraction <30%	109/300 (36.3)	84/205 (41.0)	0.16
NYHA functional class ≥III	269/308 (87.3)	190/207 (91.8)	0.11
Decompensated heart failure (within last 6 months)	174/305 (57.0)	106/199 (53.3)	0.40
Procedure times (min)	99.9 ± 51.0	110.9 ± 59.8	0.047
Fluoroscopy times (min)	29.6 ± 21.2	36.4 ± 113.0	<0.001
In-hospital outcomes			
Mortality	6/308 (1.9)	5/207 (2.4)	0.72
Neurological events			
Stroke	1/307 (0.3)	1/204 (0.5)	0.77
TIA	4/307 (1.3)	1/204 (0.5)	0.36
Myocardial infarction	0	0	–
Major access and vascular complications	8/431 (1.9)	3/352 (0.9)	0.24
Major bleeding complications	23/306 (7.5)	11/203 (5.4)	0.35
Acute kidney injury			
without need for dialysis	2/308 (0.6)	3/207 (1.4)	0.36
with new dialysis at discharge	5/306 (1.6)	2/205 (1.0)	0.53
Moderate/severe MR at discharge	43/294 (14.7)	79/202 (39.1)	<0.001
Length of hospital stay, days	9 (7–16)	7 (5–11)	<0.001
1-yr outcomes			
Mortality	60/301 (19.9)	34/177 (19.2)	0.85
NYHA functional class III/IV	67/197 (34.0)	43/117 (36.8)	0.62
Rehospitalization during 1 yr	160/223 (71.7)	84/139 (60.4)	0.025
for heart failure	35/160 (21.9)	21/84 (25.0)	0.58
Mitral valve surgery	4/164 (2.4)	2/110 (1.8)	0.78

Values are mean ± SD, n/N (%), or median (interquartile range).
Abbreviations as in Table 1.

patients treated at low(er)-volume centers. This is in contrast to that reported for patients undergoing surgical mitral valve repair, where higher hospital volume was associated with better outcomes (1). Nevertheless, the lower rates of relevant post-procedural MR were associated with better functional New York Heart Association functional class at 1 year, although patients' quality of life was not different between high- and low-volume centers.

Finally, our analyses indicated that MitraClip therapy appears to be safe with procedural mortality rates in the lower single-digit numbers even in the high-risk patients undergoing this procedure at both high- and low-volume centers. It is possible that the modest sample size of the present analysis together with small number of events might have lacked the statistical power to detect relevant differences in acute outcomes between high- and low-volume centers. Midterm outcomes appeared to be largely related to the underlying comorbid conditions and the disease as mirrored by high rates of rehospitalizations (66%) within 1 year in both groups. Our data suggest that more research in larger cohorts with extended follow-up are needed before making policy implications.

Our analysis was limited by its observational character. Centers were arbitrarily differentiated into high- and low-volume centers based on the number of patients enrolled into the registry. Level of training, efficiency of the heart team, and variability of intra-procedural imaging could not be evaluated in this study.

*Holger Eggebrecht, MD
Rajendra H. Mehta, MD, MS
Edith Lubos, MD
Peter Boekstegers, MD
Joachim Schofer, MD
Horst Sievert, MD
Taoufik Ouarrak
Jochen Senges, MD
Wolfgang Schillinger, MD
Axel Schmermund, MD

*Cardioangiological Center Bethanien
Im Prüfling 23
60389 Frankfurt
Germany
E-mail: h.eggebrecht@ccb.de

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