QRS duration is a risk indicator of adverse outcomes after MitraClip

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Abstract

Background: While QRS duration is a known marker of left ventricular (LV) function, little is known about its utility for predicting clinical prognosis after transcatheter mitral valve repair (TMVR). We investigated the association between QRS duration and one-year adverse events after TMVR with the MitraClip system.

Methods: From January 2011 through April 2019, we identified consecutive patients who underwent TMVR. Patients who had prior cardiac resynchronization therapy or a ventricular pacing rhythm were excluded. The patients were divided into two groups according to their QRS duration (<120 or ≥120 ms). Cox proportional hazard model was applied to determine the association between QRS duration and the composite outcome (all-cause mortality and re-hospitalization due to heart failure) within 1 year.

Results: A total of 348 patients were analyzed. Prolonged QRS duration (≥120 ms) was associated with an increased risk of the composite outcome (adjusted-HR 2.35, 95%CI 1.30–4.24, p = .005). There was a linear relationship between prolonged QRS duration and the increased risk of the composite outcomes. The observed association was consistent both in patients with left ventricular ejection fraction ≤35% and those with >35%. Furthermore, a QRS duration ≥120 ms was associated with lower improvement of LVEF at follow-up (adjusted-β coefficient −5.31%, 95%CI -8.17 to -2.46, p < .001).

Conclusions: Prolonged QRS duration was associated with an increased risk of mortality and re-hospitalization and less improvement of LVEF following TMVR. QRS duration could be a useful marker to predict adverse outcomes and LV function after TMVR.

KEYWORDS
left ventricular ejection fraction, MitraClip, QRS duration, transcatheter mitral valve repair

1 | BACKGROUND

Transcatheter mitral valve repair (TMVR) with MitraClip (Abbott, Santa Clara, CA, USA) has been emerging as a less invasive...
therapeutic solution for severe mitral regurgitation (MR). The COAPT trial recently reported a lower risk of heart failure hospitalization and mortality after MitraClip compared with medical therapy alone. In contrast, the MITRA-FR trial found no significant superiority of MitraClip over the control group. One reason for the different results might be an underlying myocardial condition: patients in the MITRA-FR trial were suffering from more advanced left ventricular (LV) disease with less severe MR compared with the patients in the COAPT trial. Assessing the underlying myocardial condition is a basic manner but an fundamental approach for risk stratification in patients undergoing TMVR.

QRS duration on 12-lead electrocardiography (ECG) is a readily available clinical measurement that potentially indicates the risk of adverse outcomes. Prolonged QRS duration indicates ventricular dyssynchronous contraction and relaxation, and is a marker of poor prognosis in HF with reduced ejection fraction. According to guidelines, there are clear arguments that cardiac resynchronization therapy (CRT) is recommended in patients with QRS prolongation and reduced LV ejection fraction (LVEF). However, in patients with MR, LVEF may be overestimated due to the load-dependent mechanism. Furthermore, QRS prolongation may reflect underlying myocardial damage and has recently been associated with an increased risk of adverse outcomes in various subset of HF. Nevertheless, the clinical relevance of prolonged QRS duration in patients undergoing TMVR is not thoroughly investigated.

Hence, we aimed to investigate the association of prolonged QRS duration on outcomes following TMVR. Additionally, we assessed the LV functional change concerning QRS duration during a one-year follow-up period.

2 | METHOD

2.1 | Study population

From January 2011 to March 2019, a total of 474 patients with symptomatic MR underwent TMVR with MitraClip at the University of Bonn Heart Center. All patients with symptomatic HF were considered inoperable or at high surgical risk by the institutional heart team. The therapeutic strategy was left to the discretion of the heart team after taking into account each patient's background. We excluded patients treated with CRT previously, those with ventricular pacing rhythm, and those for whom the baseline electrocardiography data was missing (Supplementary Figure 1). This study was approved by the ethics committee of the University of Bonn and was conducted in concordance with the Declaration of Helsinki.

2.2 | Electrocardiography

Standard 12-lead ECG data were obtained at baseline. The QRS duration was automatically assessed and visually controlled by the treating cardiologists. For patients with a QRS duration ≥120 ms, we further categorized the patients into three groups: (a) right bundle branch block (RBBB), (b) left bundle branch block (LBBB), and (c) intraventricular conduction delay (IVCD). The diagnosis of IVCD was based on the American Heart Association, American College of Cardiology Foundation, and Heart Rhythm Society recommendations for the standardization and interpretation of electrocardiograms.

2.3 | Echocardiography assessment

Two-dimensional transthoracic echocardiography (TTE) was scheduled at baseline, at discharge, and during the follow-up. All echocardiographic assessments were performed by independent observers blinded to clinical data and reviewed by cardiologists who were dedicated to the evaluations. LV end-systolic and end-diastolic volume and LV ejection fraction (LVEF) were measured using the biplane Simpson method. The severity of MR was graded as follows: none =0; mild =1+; moderate = 2+; moderate-to-severe =3+; severe =4+.

2.4 | TMVR with MitraClip

The TMVR procedure using a MitraClip has been described previously. All procedures were performed under general anesthesia and guided by fluoroscopy and transesophageal echocardiography. The location and number of the clips implanted were left to the discretion of the physician. Technical success and device success were defined according to the Mitral Valve Academic Research Consortium criteria (Supplemental Table 1).

2.5 | Outcome measure

The primary outcome was a composite of all-cause mortality and rehospitalization due to heart failure within 1 year. After the procedure, clinical follow-up data were collected prospectively during planned hospital visits or via telephone interviews with the patients' families or general practitioners. The secondary outcome was all-cause mortality, cardiovascular mortality, rehospitalization due to HF, and a change in LVEF (FU-LVEF – baseline-LVEF) after the TMVR procedure.

2.6 | Statistical assessment

First, a dichotomous approach was applied to separate the study cohort into patients with QRS duration <120 ms and patients with QRS duration ≥120 ms. Continuous variables with a normal distribution were analyzed by using a t-test and reported as the mean ± standard deviation, while those with a non-normal distribution were analyzed by using the Mann–Whitney U test. Categorized variables were compared by using the chi-square test or the Fisher exact test and expressed as numbers and percentages.
To estimate the event probabilities at 1 year after TMVR, we performed a survival analysis by using the Kaplan–Meier method. Then Cox proportional hazard regression models were conducted to examine the association between QRS duration and outcomes. Based on a priori knowledge, age, sex, atrial fibrillation, coronary artery disease, the etiology of MR, LVEF, logistic EuroSCORE, and device success were incorporated into the multivariable models.4-6,18

To examine the robustness of our inference, we performed several sensitivity analyses. First, we repeated the primary analysis with QRS duration as a continuous variable. Second, we depicted a loess

| TABLE 1 | Baseline characteristics |
|---------------------|--------------------------|
| **QRS duration**    | **QRS duration**         | **p**  |
| **<120 ms**         | **≥120 ms**              |       |
| **(n = 243)**       | **(n = 105)**            |       |
| Age (year), mean ± SD | 78 ± 8                  | 79 ± 7 | .27 |
| Sex, n (%)          | 132 (53.9)               | 78 (74.3) | <.001 |
| Body mass index (kg/m²), mean ± SD | 25.9 ± 4.7 | 26.2 ± 5.3 | .61 |
| **Comorbidities, n (%)** |                      |       |
| Hypertension        | 173 (71.2)               | 78 (74.3) | .65 |
| Diabetes            | 62 (25.5)                | 31 (29.5) | .52 |
| Chronic kidney disease | 149 (61.3)            | 70 (66.7) | .41 |
| Coronary artery disease | 131 (53.9)          | 78 (74.3) | <.001 |
| Previous myocardial infarction | 69 (28.4)       | 49 (46.7) | .001 |
| Atrial fibrillation | 181 (74.5)               | 77 (73.3) | .93 |
| Chronic obstructive pulmonary disease | 53 (21.8) | 18 (17.1) | .40 |
| Prior percutaneous coronary intervention | 94 (38.7) | 51 (48.6) | .11 |
| Prior coronary artery bypass graft | 48 (19.8) | 34 (32.4) | .02 |
| Prior ICD implantation | 25 (10.3)              | 23 (21.9) | .007 |
| Logistic EuroSCORE, mean ± SD | 17.0 ± 13.0         | 22.8 ± 16.1 | <.001 |
| NT-pro-BNP (pg/ml), median (IQR) | 2,504 [1158–6,375] | 3,399 [1739–5,839] | <.001 |
| NYHA functional scale III/IV, n (%) | 194 (79.9) | 76 (72.4) | .16 |
| Transthoracic echocardiography at enrollment, mean ± SD |                      |       |
| LV end-diastole volume (ml) | 123.0 ± 56.1        | 152.3 ± 75.1 | <.001 |
| LV end-systole volume (ml) | 63.5 ± 44.9         | 85.8 ± 54.1 | <.001 |
| LVEF (%) | 51.0 ± 15.0 | 45.6 ± 14.6 | .002 |
| Left atrium volume (ml) | 117.7 ± 78.6 | 109.5 ± 54.7 | .40 |
| Mitral regurgitation ≥3+, n (%) | 220 (90.5) | 97 (92.4) | .73 |
| Effective regurgitation orifice area (cm²), mean ± SD | 0.30 ± 0.11 | 0.32 ± 0.14 | .15 |
| Etiology of MR, n (%) |                      |       |
| Degenerative | 122 (51.7) | 38 (37.3) | .045 |
| Functional | 94 (39.8) | 54 (52.9) |       |
| Mixed | 20 (8.5) | 10 (9.8) |       |
| Medications, n (%) |                      |       |
| β-Blocker | 204 (84.3) | 86 (83.5) | .98 |
| ACE-I | 112 (46.3) | 48 (46.6) | .99 |
| ARB | 71 (29.3) | 24 (23.3) | .31 |
| ACE-I or ARB | 181 (74.8) | 80 (68.0) | .23 |
| Mineralocorticoid receptor antagonist | 135 (55.8) | 58 (56.3) | .99 |

Abbreviations: ACE-I, Angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; HF, heart failure; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; SD, standard deviation; TMVR, transcatheter mitral valve repair; TRPG, tricuspid regurgitation pressure gradient.
curve for the incidence rate of the primary outcome concerning QRS duration. Third, we also analyzed associations between QRS duration and outcomes, stratified by LVEF (≤35%, >35%) and the etiology of MR. Finally, we estimated the event probabilities of each QRS morphology (i.e., RBBB, LBBB, IVCD).

Additionally, in order to assess the association of QRS duration with the LVEF change, we used a multivariable linear regression model. According to the previous literature, age, sex, atrial fibrillation, coronary artery disease, the etiology of MR, LVEF, and LV end-diastolic volume were forced into the multivariable model. Two-tailed p values <.05 were considered statistically significant. All statistical analyses were performed using EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

3 RESULTS

Data of 348 patients were analyzed (Supplementary Figure 1). Among all the patients, the mean age was 78 years, and 56% were male. The mean LVEF was 49.4%, LV end-diastolic volume was 131.9 mL, EROA was 0.30 ± 0.12 cm², and an NYHA class III/IV was reported in 270 patients (77.6%). QRS duration ≥120 ms was identified in 105 (30.2%) patients (RBBB, n = 39; LBBB, n = 49; IVCD, n = 17). The following variables were more prevalent in patients with QRS duration ≥120 ms, including male, coronary artery disease, higher NT-pro-brain natriuretic peptide (NT-pro-BNP), larger LV volumes, lower LVEF, and functional MR (Table 1), as compared with patients with QRS duration <120 ms. According to guidelines, eight patients had been considered as a potential candidate for CRT implantation. Taking into account the patient background (Supplemental Table 2), the final therapeutic strategy had been left to the discretion of the institutional heart team.

Overall, technical success was achieved in 324 patients (93.1%). At the time of discharge from the hospital, echocardiographic data were available for 307 patients. Device success rate tended to be lower in patients with QRS duration <120 ms compared with patients with ≥120 ms (86.4% vs. 93.3%, p = .07). There was no significant difference between the groups with regard to the postprocedural MR grades (1.4 ± 0.9 vs. 1.4 ± 0.9, p = .97) or the mean trans-mitral pressure gradient (4.2 ± 1.8 vs. 4.0 ± 1.9, p = .59) (Table 2).

3.1 Primary analysis for the composite outcome

Overall, 33 patients died, and 27 patients experienced rehospitalization due to HF during the first year of follow-up. Compared
with patients with QRS duration <120 ms, the event-free survival rate was significantly lower in patients with QRS duration ≥120 ms (85.3% vs. 70.2%, log-rank p = .001: Figure 1). QRS duration ≥120 ms was significantly associated with an increased risk of the primary outcome (HR 2.33, 95%CI 1.37–3.95, p = .002) and remained significant after adjusting for predefined covariates (adjusted-HR 2.35, 95%CI 1.30–4.24, p = .005) (Table 3, Supplemental Table 3). Similarly, QRS duration ≥120 ms was associated with an increased risk of all-cause mortality (adjusted-OR 1.01, 95%CI 1.00–1.02, p = .02). Loess spline for the primary outcome (Figure 2) showed a steady increase up to QRS duration =150 ms. The sensitivity analyses stratified by LVEF are depicted in Supplemental Figure 2. LVEF did not influence the event-free survival rate in patients with QRS duration <120 ms and ≥120 ms (LVEF ≤35%: 85.5% vs. 70.4%; LVEF >35%: 85.2% vs. 70.2%). After adjusting for predefined covariates, the directions of the association between QRS prolongation and increased risk of outcomes were consistent among the sub-stratification by LVEF or the etiology of MR (Supplemental Table 4). Furthermore, regarding the QRS morphology, the event-free survival rate was the lowest in patients with LBBB (61.6%). The clinical prognosis in patients with RBBB (75.6%) and those with IVCD (80.2%) were still numerically worse than those with QRS duration <120 ms (85.3%) (Supplemental Figure 3).

### 3.3 LV functional response to TMVR

Among the study population, follow-up echocardiography was available in 184 (53%) patients. A QRS duration ≥120 ms was associated with low improvement of LVEF (adjusted-β coefficient −5.31%, 95% CI −8.17 to −2.46, p < .001). Figure 3 depicts the follow-up LVEF of each group subclassified according to their QRS duration and baseline LVEF. The follow-up LVEF differed significantly (p < .001) among the groups. Regardless of the subgroup of baseline LVEF, patients with a QRS duration ≥120 ms had lower follow-up LVEF compared with patients with a QRS duration <120 ms.

### 4 DISCUSSION

With the debate ongoing regarding the prognostic impact of the MitraClip system based on two landmark randomized controlled trials, there is a critical need to identify patients who will benefit from the
procedure. In this analysis of 348 patients who underwent TMVR with the MitraClip system, we found that prolonged QRS duration was associated with an increased risk of mortality and rehospitalization within the first year after MitraClip. Furthermore, QRS prolongation was associated with less improvement in LVEF at follow-up.

Our finding of the association between QRS duration and clinical prognosis after TMVR is in line with earlier studies of HF patients. Prolonged QRS has been shown to be a marker of poor prognosis in patients with HF and reduced LVEF.7 Our findings build off of these earlier studies11 and extend their results by demonstrating that prolonged QRS duration is linked to an increased risk of an adverse outcome after TMVR.

Several plausible mechanisms linking QRS duration to clinical prognosis can be suggested. One explanation could be related to advanced cardiovascular disease. Patients with prolonged QRS duration were more likely to have multiple cardiac comorbidities (e.g., coronary artery disease or impaired LV function), which may contribute to their worse clinical prognosis.23 Alternatively, a plausible mechanism of observed association is related to underlying myocardial damage.10 Various stressors (e.g., age, ischemia) lead to cause myocardial fibrosis24 as well as damage the cardiac conduction system.25,26 Indeed, patients with QRS prolongation presented a higher rate of functional etiology of MR, as confirmed by the higher rate of history of myocardial infarction and larger LV volumes. However, the association between QRS prolongation and clinical outcomes was consistently observed among the stratification by the etiology of MR.

The association of QRS prolongation and worse clinical outcomes is not limited in patients with reduced LVEF. The results of our analyses showed the utility of QRS duration as a prognostic marker to identify subjects at higher risk of adverse outcomes, regardless of the LVEF sub-classification. Likewise, Joseph et al. reported that QRS duration is an independent marker of clinical prognosis in patients with preserved LVEF.12 Besides, assuming the load-depending mechanism of LV, LVEF alone cannot accurately reflect potential LV systolic function in patients with MR. Indeed, in the present study, longer QRS duration was associated with lower LVEF during the follow-up. Patients with prolonged QRS duration exhibited even a decline of LVEF, as compared with patients with normal-range QRS duration. Earlier studies have indicated that CRT may help patients with a wide range of LVEF.27,28 Therefore, in patients with prolonged QRS duration, CRT treatment might be chosen over TMVR or added during the follow-up after TMVR, even if the LVEF value was above the criterium for CRT from the guidelines.

Also, the QRS morphology may be another important measurement of the 12-ECG to assess clinical prognosis. We found that patients with LBBB experienced the worst clinical outcome. However, evidence from two meta-analyses indicates that after accounting for QRS duration, QRS morphology did not seem to influence the effect of CRT[Cleland, 2013 #227;Linde, 2018 #231].

4.1 Study limitations

First, a selection bias cannot be ruled out. Current guidelines recommend CRT treatment for patients with QRS ≥130 ms prior to TMVR if
they have reduced LVEF (≤35%).22 That is, the observed association between prolonged QRS duration and worse prognosis might be affected by the lack of CRT treatment in eight patients who had been potential candidates for CRT implantation according to guidelines (Supplemental Table 2).22 However, the association of prolonged QRS duration with outcomes remained significant after adjusting for baseline characteristics. Furthermore, consistent findings among several sensitivity analyses support the validity of our findings. Second, due to the retrospective design of the study and at local site follow-up, the number of follow-up echocardiography was limited. Third, the current study only assessed a single cohort of TMVR patients, without any control group. Further studies are needed to investigate the prognostic impact of a TMVR procedure with the MitraClip system according to their QRS duration.

5 | CONCLUSIONS

In patients with severe MR, prolonged QRS duration is associated with an increased risk of mortality and heart failure rehospitalization after TMVR. The association was consistently observed among the sub-stratifications by LVEF and etiology of MR. Additionally, a longer QRS duration was associated with lower LVEF during the follow-up. Our findings suggest that QRS duration is a conventional, but simple and useful marker to identify subgroups who are at higher risk of outcomes following TMVR.

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CONFLICT OF INTERESTS

Nickenig G, and Sinning JM report having received speaker honoraria and research grants from Medtronic, Boston Scientific, Edwards Lifesciences, and Abbott. Weber M has received lecture or proctoring fees from Abbott, Boehringer-Ingelheim, Edwards Lifesciences, Neochord, Pfizer and Servier. The other authors report no conflicts of interest. Sugiura A, Tabata N, Goto T, Öztürk C, Lin M, and Zimmer S have no conflict of interest. Nickenig G and Sinning JM have received speaker honoraria and research grants from Medtronic, Boston Scientific, Edwards Lifesciences, and Abbott.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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