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Incidence and in-hospital safety outcomes of patients undergoing percutaneous mitral valve edge-to-edge repair using MitraClip: five-year German national patient sample including 13,575 implants

Ralph S. von Bardeleben[1], MD; Lukas Hobohm[1,2], MD; Felix Kreidel[1], MD; Mir A. Ostad[1], MD; Eberhard Schulz[1], MD; Stavros Konstantinides[2,3], MD; Mareike Lankeit[2,4,5], MD; Ted Feldman[6], MD; Thomas Münzel[1,7]*, MD; Karsten Keller[2], MD

1. Heart Valve Center Mainz, Center of Cardiology, Cardiology I, University Medical Center Mainz, Mainz, Germany; 2. Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz, Mainz, Germany; 3. Department of Cardiology, Democritus University of Thrace, Alexandroupolis, Greece; 4. Department of Internal Medicine and Cardiology, Campus Virchow Klinikum (CVK), Charité – University Medicine Berlin, Berlin, Germany; 5. German Center for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany; 6. Evanston Hospital, NorthShore University Health System, Evanston, IL, USA; 7. German Center for Cardiovascular Research (DZHK), partner site Rhine Main, Mainz, Germany

R.S. von Bardeleben and L. Hobohm contributed equally to this manuscript.

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KEYWORDS

- death
- mitral regurgitation
- mitral valve repair
- transseptal

Abstract

Aims: The number of percutaneous edge-to-edge mitral regurgitation valve repairs with MitraClip implantation has increased during recent years. Published studies showed promising safety outcomes in relatively small cohorts, while results from large samples are sparse. Thus, we aimed to evaluate trends and safety outcomes in the German nationwide in-patient sample.

Methods and results: We analysed data on patients' characteristics and in-hospital safety outcomes for all percutaneous mitral valve repairs using the MitraClip technique in Germany between 2011 and 2015. Overall, 13,575 in-patients were included. The annual number of MitraClip implantations increased from 815 in 2011 to 4,432 in 2015 (β 1.00 [95% CI: 0.96-1.03], p<0.001). The in-hospital mortality (p=0.193) and major adverse cardiac and cerebrovascular events (MACCE) (p=0.183) rate remained unchanged. Important independent predictors of in-hospital mortality were heart failure (OR 1.91 [95% CI: 1.43-2.54], p<0.001), transfusion of erythrocyte concentrates (OR 9.04 [95% CI: 7.45-10.96], p<0.001), stroke (OR 6.82 [95% CI: 4.34-10.72], p<0.001), endocarditis (OR 19.52 [95% CI: 9.04-42.14], p<0.001), pulmonary embolism (OR 7.61 [95% CI: 3.44-16.81], p<0.001), pericardial tamponade (OR 14.08 [95% CI: 7.09-27.96], p<0.001) and pericardial effusion (OR 2.59 [95% CI: 1.66-4.04], p<0.001).

Conclusions: MitraClip implantations increased markedly (5.4-fold) between 2011 and 2015, with a constant in-hospital mortality and MACCE rate. Our data indicate that edge-to-edge mitral valve repair using the MitraClip technique has acceptable in-hospital safety outcomes in a real-world scenario.

**Corresponding author: Center of Cardiology, Cardiology I, University Medical Center Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany. E-mail: tmuenzel@uni-mainz.de*

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Abbreviations

ACC	American College of Cardiology
AF	atrial fibrillation/flutter
AHA	American Heart Association
DMR	degenerative mitral valve regurgitation
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
FMR	functional mitral valve regurgitation
G-DRG	German diagnosis-related groups
HF	heart failure
ICB	intracerebral bleeding
ICD-10-GM	International Classification of Diseases and Related Health Problems, 10th Revision with German Modification
LA	left atrial
LV	left ventricular
MACCE	major adverse cardiac and cerebrovascular events
MI	myocardial infarction
MR	mitral valve regurgitation
NYHA	New York Heart Association
OPS	Operationen- und Prozedurenschlüssel (surgery and procedures codes)
TRAMI	transcatheter mitral valve interventions
VHD	valvular heart disease

Introduction

Mitral valve regurgitation (MR) is the most common heart valve disease in Europe and the USA[1-3]. Its prevalence increases with age and it affects approximately 9-10% of individuals aged 75 years and older[4,5]. MR is a frequent valve disorder referred for surgical or interventional correction[2,6,7]. Significant MR is accompanied by substantial morbidity and mortality[3,4,6,8,9].

The aetiology of MR is heterogeneous with regard to the underlying pathophysiology and pathoanatomy[2,3]. In chronic primary degenerative MR (DMR), pathology of the valve leaflets is present and a subsequent correction of the MR is mostly curative. In secondary functional MR (FMR), the mitral leaflets are anatomically normal and severe left ventricular (LV)/left atrial (LA) dysfunction with LV volume/pressure overload and LV/LA enlargement, annular mitral valve dilatation and/or severe leaflet tethering prevents mitral leaflet coaptation, resulting in MR[2,7,10]. Thus, FMR is only one component of the different aspects of the disease and restoring MR itself might be beneficial, but is not the singular curative treatment approach[7,10].

Although surgical mitral valve repair is the approach recommended by the guidelines for the majority of patients with severe DMR (who are at low surgical risk), surgical treatment for high-risk patients is problematic. The treatment of FMR is still under debate because of a significant rate of recurrence and lack of clear evidence of clinical benefit[11]. Transcatheter repair for FMR patients at high surgical risk is currently under investigation in four randomised controlled trials including 288 to 749 patients each (transcatheter mitral valve interventions [TRAMI], Sentinel-EU, MITRA-FR, COAPT-US and RESHAPE-2)[5,12-17].

The current guidelines of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)[7] as well as of the American Heart Association (AHA) and the American College of Cardiology (ACC)[8] recommend consideration of percutaneous edge-to-edge procedure in high-risk patients with severe symptomatic MR and DMR in the USA, and both primary and secondary MR in most other parts of the world. Patients are eligible if they have mitral valve morphology suitable for MitraClip® (Abbott Vascular, Santa Clara, CA, USA) implantation, are judged not suitable for surgery by a "Heart Team" and have a reasonable life expectancy[7,8].

Although several studies showed promising safety outcome data in cohorts smaller than 1,000 treated patients[5,13-15], results from a real-world nationwide sample are missing. To fill this gap, we investigated trends and safety outcomes of the transcatheter-based treatment of patients with MR in the German nationwide in-patient sample.

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Material and methods

DATA SOURCE

The analyses were performed on our behalf by the Research Data Center of the Federal Statistical Office and the Statistical Offices of the federal states in Wiesbaden, Germany (DRG Statistics 2011-2015, own calculations). The aggregated statistical results were provided on the basis of SPSS codes (SPSS® software, Version 20.0; IBM Corp., Armonk, NY, USA), which we sent to the Research Data Center. For this analysis, we selected all hospitalised patients who were coded with a MitraClip procedure between 2011 and 2015.

DIAGNOSES, PROCEDURAL CODES, AND DEFINITIONS

Diagnoses are coded according to the International Classification of Diseases and Related Health Problems, 10th Revision with German Modification (ICD-10-GM) and surgical or interventional procedures according to the German Procedure Classification (Operationen- und Prozedurenschlüssel [OPS] – surgery and procedures codes). All DRG diagnoses of in-patients are collected and evaluated by the Federal Statistical Office of Germany (Statistisches Bundesamt). Thereby, we identified all hospitalised patients who were relevant for our analysis, based on the OPS code for transvenous MitraClip procedures (OPS code 5-35a.41).

STUDY SAFETY OUTCOMES

The measured safety outcomes of this study were death from any cause during the hospital stay (in-hospital death), major adverse cardiac and cerebrovascular events (MACCE, including in-hospital death, myocardial infarction [MI; ICD-code I21] and/or ischaemic stroke [ICD-code I63]), and clinically relevant bleeding events such as haemopericardium (ICD-code I31.2), intracerebral bleeding (ICB; ICD-code I61) and the need for transfusion of erythrocyte concentrates (OPS code 8-800).

ETHICAL ASPECTS

Since this study did not involve direct access to data of individual patients by the investigators, approval by an ethics

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committee and informed consent were not required, in accordance with German law.

STATISTICAL METHODS

Statistical analyses are described in **Supplementary Appendix 1**.

Results

BASELINE CHARACTERISTICS

The nationwide sample included 13,575 in-patients undergoing percutaneous mitral valve repair using the edge-to-edge MitraClip technique in Germany between 2011 and 2015. The calculated prevalence for the performance of edge-to-edge clip implantation was 3.35 per 100,000 citizens per year (over this five-year time frame). The majority of patients were male (60.0%) and the mean age was 77 years, comparable to published registry data **(Supplementary Table 1, Supplementary Table 2)**. Among these patients, 87.6% presented with dyspnoea in New York Heart Association (NYHA) Classes III/IV. Additionally, 67.3% were diagnosed with coronary artery disease, 46.0% with renal insufficiency, 30.8% with diabetes mellitus and 15.0% with chronic obstructive pulmonary disease (COPD).

NON-SURVIVORS VERSUS SURVIVORS

Comparisons of non-survivors and survivors are described in **Supplementary Appendix 2** and **Supplementary Table 1**.

PREDICTORS OF IN-HOSPITAL MORTALITY

Independent predictors of in-hospital mortality in a multivariate analysis (adjusted for sex, age and comorbidities) with an OR >1.5 were cancer, heart failure (HF), transfusion of erythrocyte concentrates, tachycardia, NYHA Class IV, stroke, endocarditis, pulmonary embolism, haemopericardium, pericardial effusion, and shock **(Table 1)**.

Table 1. Impact of baseline characteristics, comorbidities, clinical presentation and complications on in-hospital mortality.

	All patients undergoing MitraClip implantation (n=13,575; 488 patients died in-hospital [3.6%])				Multivariate (adjusted for age, sex, cancer, coronary artery disease, heart failure, COPD, arterial hypertension, renal insufficiency and diabetes mellitus)	
	Univariate		Multivariate (adjusted for age and sex)			
Parameters	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Age (years)	1.006 (0.996-1.017)	0.245	1.007 (0.996-1.018)	0.188	1.009 (0.998-1.020)	0.095
Comorbidities						
Coronary artery disease	0.864 (0.716-1.043)	0.129	0.838 (0.692-1.016)	0.072	0.800 (0.658-0.972)	0.025
Cancer	2.928 (1.919-4.467)	<0.001	2.914 (1.909-4.448)	<0.001	2.976 (1.944-4.555)	<0.001
Heart failure	2.030 (1.529-2.696)	<0.001	2.037 (1.533-2.707)	<0.001	1.906 (1.429-2.541)	<0.001
Atrial fibrillation/flutter	1.268 (1.042-1.543)	0.018	1.250 (1.025-1.526)	0.028	1.208 (0.989-1.477)	0.064
COPD	1.235 (0.974-1.564)	0.081	1.233 (0.973-1.562)	0.084	1.181 (0.930-1.499)	0.173
Renal insufficiency	1.474 (1.229-1.768)	<0.001	1.460 (1.216-1.752)	<0.001	1.381 (1.146-1.663)	<0.001
Diabetes mellitus	1.079 (0.889-1.309)	0.442	1.086 (0.895-1.319)	0.403	1.049 (0.855-1.286)	0.647
Transfusion of erythrocyte concentrates	9.276 (7.674-11.214)	<0.001	9.421 (7.786-11.399)	<0.001	9.038 (7.451-10.962)	<0.001
Clinical presentation						
Tachycardia	4.006 (3.167-5.067)	<0.001	4.151 (3.272-5.265)	<0.001	3.766 (2.962-4.790)	<0.001
NYHA Class I/II	0.268 (0.157-0.458)	<0.001	0.268 (0.157-0.457)	<0.001	0.245 (0.143-0.419)	<0.001
NYHA Class III	0.409 (0.333-0.503)	<0.001	0.408 (0.332-0.501)	<0.001	0.304 (0.246-0.376)	<0.001
NYHA Class IV	4.357 (3.622-5.241)	<0.001	4.397 (3.654-5.290)	<0.001	4.253 (3.461-5.226)	<0.001
NYHA Class III/IV	1.793 (1.436-2.239)	<0.001	1.797 (1.439-2.244)	<0.001	1.364 (0.999-1.864)	0.051
Life-threatening comorbidities/status						
Stroke	4.743 (2.670-8.425)	<0.001	4.730 (2.660-8.412)	<0.001	6.820 (4.337-10.724)	<0.001
Endocarditis	20.595 (9.689-43.776)	<0.001	21.346 (10.018-45.483)	<0.001	19.523 (9.044-42.144)	<0.001
Deep vein thrombosis and/or thrombophlebitis	2.570 (1.289-5.121)	0.007	2.539 (1.300-5.169)	0.007	2.472 (1.235-4.947)	0.011
Pulmonary embolism	7.019 (3.209-15.352)	<0.001	7.265 (3.317-15.913)	<0.001	7.608 (3.444-16.808)	<0.001
Haemopericardium	13.748 (7.021-26.922)	<0.001	13.982 (7.132-27.410)	<0.001	14.076 (7.085-27.964)	<0.001
Pericardial effusion	2.815 (1.815-4.365)	<0.001	2.839 (1.829-4.406)	<0.001	2.591 (1.664-4.036)	<0.001
Shock	36.425 (29.587-44.844)	<0.001	40.530 (32.682-50.262)	<0.001	38.735 (31.138-48.185)	<0.001

CI: confidence interval; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; OR: odds ratio

TRENDS BETWEEN 2011 AND 2015 AND ACROSS AGE GROUPS IN GERMANY

Total numbers of edge-to-edge MitraClip implantations increased over the five-year period (β 1.00 [95% CI: 0.96 to 1.03], p<0.001). The in-hospital mortality rate remained roughly constant at 3.1% in 2011 and 3.6% in 2015 (β 0.07 [95% CI: −0.04 to 0.19], p=0.193) **(Figure 1A, Supplementary Table 3)**, as did the MACCE rate (ß 0.06 [95% CI: −0.03 to 0.14], p=0.183) at 5.6% in 2011 and 6.8% in 2015, while age at the procedure increased significantly during this period (ß 0.06 [95% CI: 0.01-0.01], p<0.001) **(Figure 1B, Supplementary Table 3)**. Regarding age group distribution, the majority of MitraClip implantations (79.2%) were performed in patients aged between 70 and 89 years, with the lowest in-hospital mortality being between 70 and 79 years (3.1%) **(Figure 1C)**. The number of patients in NYHA Classes III/IV (ß 0.03 [95% CI: 0.04 to 0.13], p<0.001) **(Figure 2A)** increased. In-hospital stay remained unchanged at 10 days in 2011 and 10 days in 2015 (p=0.271) **(Figure 1B, Supplementary Table 3)**. While shock was more prevalent in age decades six and seven, the prevalence of renal insufficiency and the need for transfusion of erythrocyte concentrates increased with growing age **(Supplementary Figure 1)**. Of note, the transfusion of erythrocyte concentrates decreased considerably from 2011 (23.6%) to 2015 (14.7%) (ß −0.06 [95% CI: −0.25 to −0.14], p<0.001) **(Supplementary Table 3)**, whereas the rate of the safety outcomes endocarditis and stroke remained similar over the reported time frame **(Figure 2B, Supplementary Table 3)**.

The comorbidities of treated patients changed only slightly over time. We observed a small increase in the frequency of cancer, HF, atrial fibrillation/flutter (AF), COPD, renal insufficiency and peripheral artery disease over the five-year period **(Figure 2C, Supplementary Table 3)**.

Discussion

This large nationwide study included more than 13,500 MR patients treated with edge-to-edge mitral valve repair using the MitraClip technique. Previously published reports included much smaller populations, with the largest investigating 1,064 subjects[5,13-16].

It is unknown whether the aging population and improved diagnostic and treatment methods are associated with changes in the incidence, shift of patient characteristics, age and trends in safety outcomes of patients undergoing MitraClip procedures over time. A unique focus of the present study was to investigate temporal trends in prevalence, in-hospital stay, patient characteristics, safety outcomes and complications of MitraClip procedures over the five-year period between 2011 and 2015.

The key findings of our study comprise the following. 1) We observed a marked increase in the annual numbers of MitraClip procedures over this five-year period. 2) Patient characteristics shifted towards older age and a higher prevalence of HF with higher NYHA class from 2011 to 2015. 3) In-hospital mortality and the MACCE rate remained stable over time. 4) Important predictors of in-hospital death were HF, need for transfusion of erythrocyte concentrates, stroke, endocarditis, pulmonary embolism, pericardial effusion and haemopericardium, and shock. 5) The MitraClip procedures were predominantly performed in the age group between 70 and 89 years.

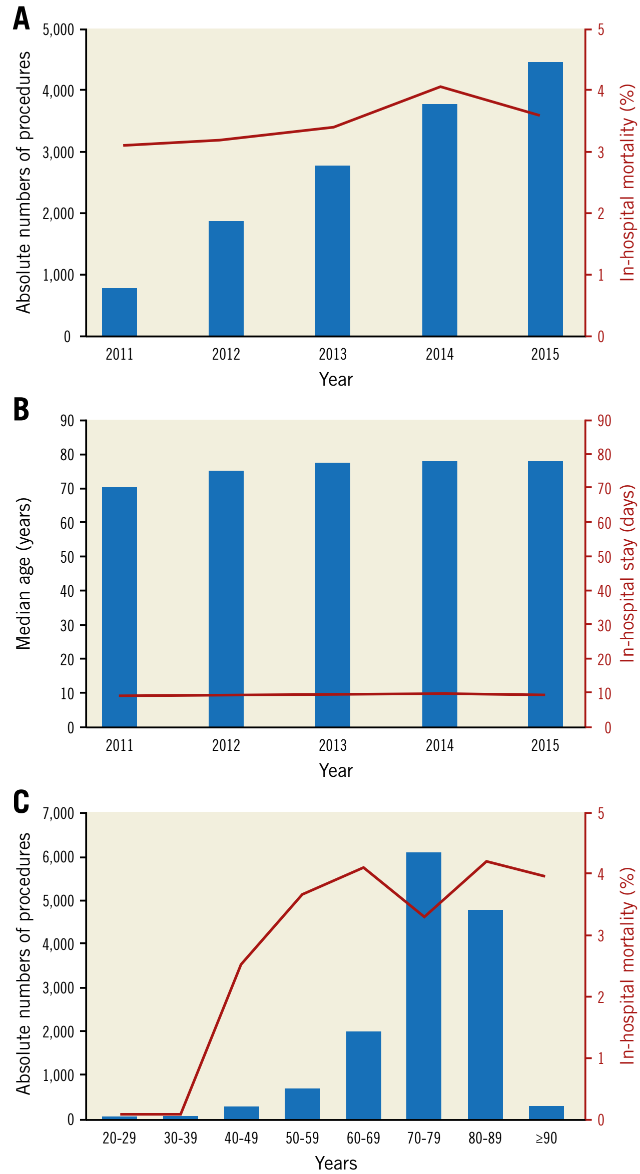

Figure 1. *Absolute annual numbers and in-hospital mortality after MitraClip implantation. A) From 2011 to 2015. B) Median age and median in-hospital stay in the years 2011-2015. C) Stratified by age group.*

In a large European survey, it was shown that approximately half of the patients with severe MR were not referred for surgery[18]. Patient characteristics which were independently associated with a decision not to operate the MR were lower LV ejection fraction, non-ischaemic aetiology, older age, higher Charlson comorbidity index, and grade three MR[18]. Correspondingly, our results confirm a marked increase of the annual numbers of MitraClip procedures as a less invasive method for MR repair has become available for these high-risk patients **(Figure 1A)**. Thus, in future it has to be

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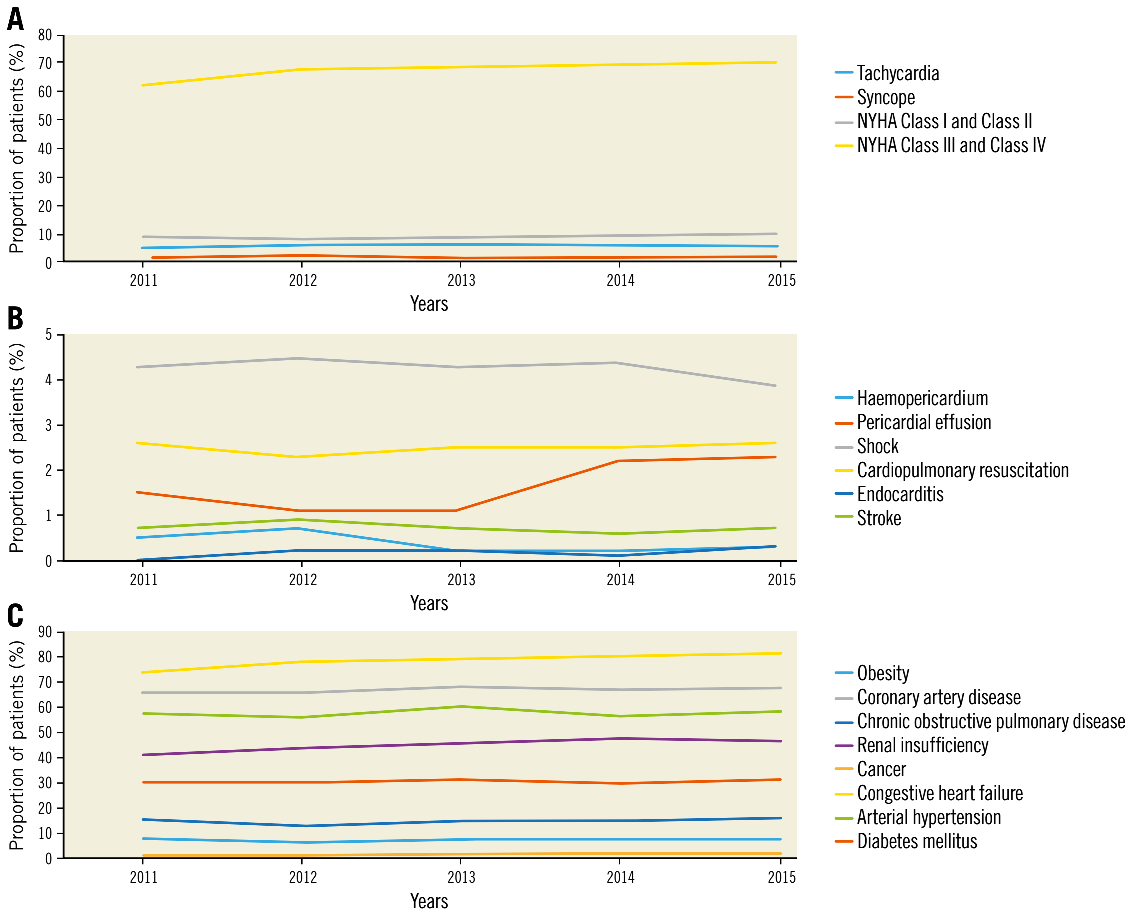

Figure 2. *Trends regarding comorbidities, clinical parameters/signs of haemodynamic compromise and more severe mitral valve regurgitation (end-stage disease), and complications from 2011-2015. A) Clinical parameters/signs of haemodynamic compromise and more severe mitral valve regurgitation (end-stage disease). B) Complications. C) Comorbidities.*

expected that the procedural number of percutaneous edge-to-edge valve repairs will increase markedly.

COMPARISON OF TRAMI AND TCVT WITH THE GERMAN NATIONWIDE SAMPLE – BASELINE AND COMORBIDITIES

The TRAMI registry represents the largest previously reported cohort of patients treated with MitraClip[5]. Patient age and days of in-hospital stay are comparable to the German nationwide in-patient sample. Acute kidney injury is known to be a predictor of subsequent mortality after a transcatheter valve repair, which could be based on contrast- or drug-induced nephropathy, atheroemboli or renal hypofusion[19]. The TRAMI registry[5] showed more renal insufficiency (65.5%) compared to the TCVT registry[15] (30.5%) and the German nationwide sample (46.0%) **(Supplementary Table 2)**. Notably, renal insufficiency was identified as a predictor (OR 1.38 [95% CI: 1.15-1.66], p<0.001) of in-hospital death in our study[5]. Rudolph et al showed that patients in NYHA Class IV had considerably higher mortality than patients in lower NYHA classes[20]. NYHA Classes III/IV were present in 89.0% of all patients in TRAMI and 85.5% in the TCVT registry and therefore comparable with the German nationwide sample with 87.6%. NYHA Class IV was found to be an important predictor of in-hospital mortality in our study. Both the TRAMI registry and the German nationwide sample showed that patients undergoing MitraClip implantation in real-world practice are older and sicker than in the selected EVEREST trial cohort, with German nationwide sample patients having older age and with more being in NYHA Classes III/IV[5,12-14].

PREDICTORS OF IN-HOSPITAL MORTALITY IN THE GERMAN NATIONWIDE SAMPLE

The rate of MACCE is higher in the German nationwide in-patient sample compared to TRAMI **(Supplementary Table 2)**[5]. These differences were possibly driven by including patients from only high-volume centres in TRAMI. The German nationwide sample represents a real-world sample, which includes MitraClip implantations from every high-volume as well as low-volume centre in Germany.

The current guidelines recommend the use of antithrombotic and antiplatelet treatment after MitraClip implantation due to a possible risk of thrombus formation with embolic risk of stroke[7,21]. Studies have reported a stroke rate of 1.1% after transcatheter MitraClip implantation[13,22], which was higher compared with the TRAMI registry (0.8%)[5] and the German nationwide sample (0.7%). Stroke was found to be a strong predictor of in-hospital death in our cohort. It is well known that bleeding and blood transfusion after transcatheter valve procedures have been strongly associated with mortality[23]. Our study showed a higher bleeding and transfusion rate compared to the EVERST-II cohort[24], the ACCESS-EU study[14], the TCVT registry[15] and the TRAMI registry[5]. We demonstrated that transfusion of blood constitutes a strong predictor of in-hospital death. This is the first nationwide study sample reporting predictors of in-hospital safety outcomes and thus a head-to-head comparison of our results to other studies is not feasible. However, predictors of in-hospital mortality were tested in a multivariable analysis and were in line with one-year mortality predictors from the TRAMI registry[5]. Cancer and tachycardia were identified as predictors of in-hospital mortality in our study. Periprocedural and post-procedural conditions such as pericardial effusion, haemopericardium, endocarditis and shock were also identified as strong predictors of in-hospital mortality. In our study, AF was not an independent predictor of in-hospital mortality, which is in accordance with the study of Velu et al[25]; the authors reported that AF was also not an independent predictor of long-term mortality[25].

TRENDS IN MITRACLIP IMPLANTATION

While the current study revealed a marked increase in MitraClip implantations over this five-year period, the in-hospital mortality and the MACCE rate remained stable.

There was a significant shift towards higher age and higher prevalence of HF with higher NYHA class from 2011 to 2015 **(Supplementary Table 3)**. This might indicate an increasing number of patients with FMR since HF as well as NYHA Class IV are typical attributes of FMR. We can only speculate about this coherence, since we could not distinguish between FMR and DMR aetiology in the nationwide sample data. Among patients with HF and FMR, two large trials reported divergent results. While the MITRA-FR trial[12] indicated that FMR patients with HF revealed no significant prognostic benefit as a result of MitraClip implantation additional to optimal drug therapy compared to optimal drug therapy alone after one-year follow-up, the larger COAPT-US trial[17] reported a significant benefit of additional MitraClip implantation in addition to optimal drug therapy regarding hospitalisation for HF and all-cause mortality after a two-year follow-up.

Germany is one of the leading countries regarding MitraClip implantations worldwide and, in contrast to other European countries, the German health insurance system provided reimbursement for both DMR and FMR following the ESC VHD guidelines of 2012 and 2017. Over recent years, experience with the MitraClip system has increased markedly, and both younger and more critical patients with severe MR have been treated with MitraClip, resulting in distinctly increased numbers of MitraClip implantations. In particular, the number of MitraClip procedures in old patients at high surgical risk has increased substantially.

In-hospital mortality and MACCE rates did not decrease, probably due to patients of a higher age and with more comorbidities being treated. MitraClip procedures were predominantly performed in the age group between 70 and 89 years, whereas patients <70 years still remain in the minority. While shock was more prevalent in age decades six and seven, the prevalence of important comorbidities increased with advancing age **(Supplementary Figure 1)**.

Limitations

There are limitations to our study that require consideration. The analysis is based on ICD discharge codes, which might have led to incomplete data due to underreporting/undercoding. As mentioned above, we could not distinguish between FMR and DMR aetiology. Therefore, the focus of our study was on clear endpoints such as in-hospital death and complications (MACCE among others) which are very unlikely to be miscoded or not coded. This study includes in-hospital results and cannot address long-term outcomes.

Conclusions

The use of MitraClip implantation increased 5.4-fold from 2011 to 2015, with a constant in-hospital mortality and MACCE rate despite increasing patient age and frequency of comorbid conditions. Our data indicate that MitraClip implantations have acceptable in-hospital safety outcomes in a real-world scenario.

Impact on daily practice

Our data indicate that MitraClip procedures have acceptable in-hospital safety outcomes in a real-world scenario. Moreover, our study underlines that periprocedural haemopericardium, and also pericardial effusion and transfusion of erythrocyte concentrates have to be considered as independent predictors of in-hospital death.

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Conflict of interest statement

R.S. von Bardeleben reports having received consultancy and lecture honoraria from Abbott Structural Heart, Boehringer Ingelheim, Cardiac Dimensions, Edwards Lifesciences, GE Health Systems and Philips Healthcare. L. Hobohm reports having received lecture honoraria from MSD. F. Kreidel reports having received consultancy and lecture honoraria from Abbott, Cardiac Implants, and Edwards Lifesciences. E. Schulz reports lecture honoraria from Edwards Lifesciences and Medtronic. S. Konstantinides reports having received consultancy and lecture honoraria from Bayer, Boehringer Ingelheim, Daiichi Sankyo, MSD and Pfizer – Bristol-Myers Squibb, and institutional grants from Actelion, Bayer, Boehringer Ingelheim, Daiichi Sankyo and Pfizer – Bristol-Myers Squibb. M. Lankeit reports having received consultancy and lecture honoraria from Actelion, Bayer, Daiichi Sankyo, MSD and Pfizer – Bristol-Myers Squibb, and research funding from B.R.A.H.M.S./Thermo Fisher Scientific. T. Feldman reports research grants and honoraria from Abbott, BSC and Edwards Lifesciences. T. Münzel is PI of the DZHK (German Center for Cardiovascular Research), partner site Rhine-Main, Germany. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Statistical methods.

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Supplementary Figure 1. Trends in baseline comorbidities and complications across age groups.

Supplementary Table 1. Baseline characteristics, medical history and presentation of the patients undergoing percutaneous mitral valve repair using edge-to-edge MitraClip implantation.

Supplementary Table 2. Comparison across the TRAMI registry, the TCVT registry and the German nationwide in-patient sample.

Supplementary Table 3. Trends in total numbers of MitraClip procedures, patient characteristics, complications and safety outcomes over the five-year period.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/150th_issue/298

Supplementary data

Supplementary Appendix 1. Statistical methods

We compared in-hospital survivors versus non-survivors. Descriptive statistics for relevant baseline comparisons are provided as median and interquartile range (IQR), or as absolute numbers and corresponding percentages. We tested the continuous variables using the Mann-Whitney U test and categorical variables with Fisher's exact test or the chi^2 test, as appropriate.

For analyses of the annual trends from 2011 to 2015, the absolute numbers of all MitraClip procedures, the relative mortality rate and safety outcomes, length of in-hospital stay, and also patients' clinical presentation and comorbidities were calculated annually, and linear regressions were used to test regarding an increase/decrease in these parameters. The results were presented as beta (β) and corresponding 95% confidence intervals (CI). The same parameters were analysed for the trend analyses regarding patients' life decades.

Univariate and multivariate logistic regression models were performed to investigate the impact of age, comorbidities, clinical presentation and safety outcomes/adverse in-hospital events on the in-hospital mortality. The results were presented as odds ratios (OR) and corresponding 95% CIs. Multivariate logistic regression models, testing the independence of predictors for in-hospital mortality, were adjusted in model I for age and sex and in model II for age, sex, cancer (ICD-codes C00-C97), coronary artery disease (ICD-code I25), heart failure (ICD-code I50), chronic obstructive pulmonary disease (ICD-code J44), renal insufficiency (comprising diagnosis of chronic renal insufficiency stages three to five with glomerular filtration rate <60 ml/min/1.73 m^2; ICD-codes N18.3, N18.4 and N18.5), essential arterial hypertension (ICD-code I10) and diabetes mellitus (ICD-codes E10-E14).

SPSS software, Version 20.0 (IBM Corp., Armonk, NY, USA) was used for computerised analysis. P-values of <0.05 (two-sided) were considered to be statistically significant.

Supplementary Appendix 2. Supplementary results

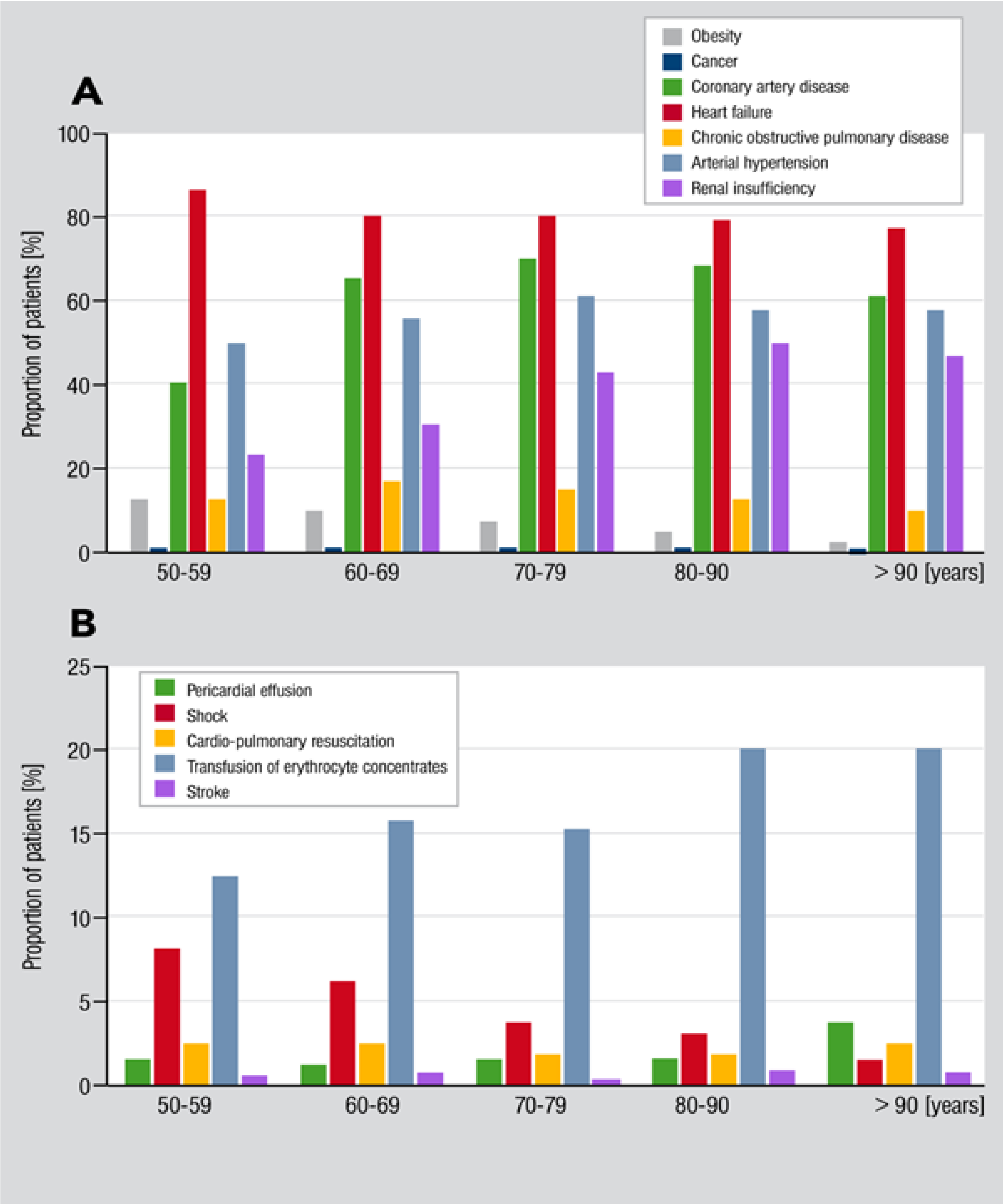
Non-survivors versus survivors

Non-survivors and survivors had similar age (78 [IQR 71-78] vs. 77 [71-82] years, $p=0.184$); non-survivors more frequently showed comorbidities including cancer (5.1% vs. 1.8%, $p<0.001$), renal insufficiency (55.3% vs. 45.7%, $p<0.001$), atrial fibrillation/flutter (69.7% vs. 30.3%, $p=0.017$) and heart failure (88.7% vs. 79.5%, $p<0.001$). Survivors were more often diagnosed with essential arterial hypertension (58.3% vs. 48.6%, $p<0.001$). Clinical parameters such as NYHA Classes III/IV (96.5% vs. 87.3%, $p<0.001$) and signs of haemodynamic compromise such as tachycardia (19.7% vs. 5.8%, $p<0.001$) and shock (49.0% vs. 2.6%, $p<0.001$) were observed more frequently in non-survivors **(Supplementary Table 1)**.

Complications and case fatality rate

In non-survivors, stroke (2.9% vs. 0.6%, $p<0.001$), endocarditis (2.5% vs. 0.1%, $p<0.001$), pulmonary embolism (1.6% vs. 0.2%, $p<0.001$) and pericardial effusion (9.2% vs. 1.7%, $p<0.001$) were observed more often compared to the survivors **(Supplementary Table 1)**. Regarding bleeding complications, non-survivors considerably more often had intracerebral bleeding (1.6% vs. 0.2%, $p<0.001$), haemopericardium (2.7% vs. 0.2%, $p<0.001$) and received more transfusions of erythrocyte concentrates (62.9% vs. 15.5%, $p<0.001$) compared to survivors. Non-survivors underwent prolonged post-procedural mechanical ventilation (70.5% vs. 16.9%, $p<0.001$) and cardiopulmonary resuscitation (34.4% vs. 1.3%, $p<0.001$) more often than survivors. The overall in-hospital mortality rate was 3.6% **(Supplementary Table 1)**.

Supplementary Figure 1. Trends in baseline comorbidities (A) and complications (B) across age groups.



Supplementary Table 1. Baseline characteristics, medical history and presentation of the 13,575 patients undergoing percutaneous mitral valve repair using edge-to-edge MitraClip implantation (cumulative data of the years 2011-2015).

Parameters	**Non-survivors (n=488; 3.6%)**	**Survivors (n=13,087; 96.4%)**	***p*-value**
Age (years)	78 (71-78)	77 (71-82)	0.184
Sex (female)	187 (38.6%)	5,239 (40.0%)	0.480
In-hospital stay (days)	**21 (11-36)**	**10 (7-17)**	**<0.001**
Obesity	35 (7.2%)	982 (7.5%)	0.852
Comorbidities			
Cancer	**25 (5.1%)**	**237 (1.8%)**	**<0.001**
Coronary artery disease	313 (64.1%)	8,824 (67.4%)	0.140
Heart failure	**433 (88.7%)**	**10,404 (79.5%)**	**<0.001**
Atrial fibrillation/flutter	**340 (69.7%)**	**148 (30.3%)**	**0.017**
Chronic obstructive pulmonary disease	2,043 (4.3%)	1,956 (14.9%)	0.080
Thrombophilia	**3 (0.6%)**	**17 (0.1%)**	**0.033**
Essential arterial hypertension	**237 (48.6%)**	**7,636 (58.3%)**	**<0.001**
Renal insufficiency	**270 (55.3%)**	**5,975 (45.7%)**	**<0.001**
Diabetes mellitus	158 (32.4%)	4,023 (30.7%)	0.455
Peripheral artery disease	**50 (10.2%)**	**924 (7.1%)**	**0.010**
Clinical parameters			
Tachycardia	**96 (19.7%)**	**754 (5.8%)**	**<0.001**
Syncope	8 (1.6%)	142 (1.1%)	0.263

NYHA Classes I and II	**14 (3.5%), n/N=14/401**	**1,297 (12.7%), n/N=1,297/10,212**	**<0.001**
NYHA Classes III and IV	**387 (96.5%), n/N=387/401**	**8,915 (87.3%), n/N=8,915/10,212**	**<0.001**
Shock	**239 (49.0%)**	**336 (2.6%)**	**<0.001**
Bleeding complications			
Intracerebral bleeding	**8 (1.6%)**	**12 (0.1%)**	**<0.001**
Haemopericardium	**13 (2.7%)**	**26 (0.2%)**	**<0.001**
Transfusion of erythrocyte concentrates	**307 (62.9%)**	**2,023 (15.5%)**	**<0.001**
Safety outcomes			
Mechanical ventilation	**344 (70.5%)**	**2,261 (16.9%)**	**<0.001**
Cardiopulmonary resuscitation	**168 (34.4%)**	**171 (1.3%)**	**<0.001**
Adverse in-hospital events	**488 (100.0%)**	**2,284 (17.5%)**	**<0.001**
MACCE	**488 (100.0%)**	**419 (3.2%)**	**<0.001**
Stroke	**14 (2.9%)**	**81 (0.6%)**	**<0.001**
Endocarditis	**12 (2.5%)**	**16 (0.1%)**	**<0.001**
Pulmonary embolism	**8 (1.6%)**	**31 (0.2%)**	**<0.001**
Deep vein thrombosis and/or thrombophlebitis	**9 (1.8%)**	**95 (0.7%)**	**0.013**
Pericardial effusion	**23 (9.2%)**	**226 (1.7%)**	**<0.001**

MACCE: major adverse cardiac and cerebrovascular events; NYHA: New York Heart Association

10,613

Supplementary Table 2. **Comparison across the TRAMI registry, the TCVT registry and the German nationwide in-patient sample.**

Parameters	TRAMI n=749	TCVT n=628	German nationwide sample n=13,575
Age (years)	76 (71-81)	74±9.7	77 (71-82)
Sex (female)	289 (38.6%)	232 (36.9%)	5,426 (40.0%)
In-hospital stay (days)	9 (6-15)	5 (3-7)	10 (7-17)
Comorbidities			
Coronary artery disease	424 (78.1%)	194 (30.9%)	9,137 (67.3%)
Chronic obstructive pulmonary disease	160 (22.3%)	121 (19.3%)	2,043 (15.0%)
Renal insufficiency	468 (65.5%)	192 (30.5%)	6,245 (46.0%)
Diabetes mellitus	226 (31.4%)	175 (27.9%)	4,181 (30.8%)
Clinical parameters			
NYHA Classes III-IV	646 (89.0%)	537 (85.5%)	9,302 (87.6%), n/N=9,302/10,613
MACCE (death, MI and stroke)			

MACCE	22 (3.1%)	NA	907 (6.7%)
In-hospital death	18 (2.4%)	18 (2.9%)	488 (3.6%)
Myocardial infarction	0 (0.0%)	0 (0%)	382 (2.8%)
Stroke	6 (0.8%)	1 (0.2%)	95 (0.7%)
Non-MACCE			
TIA	6 (0.8%)	NA	28 (0.2%)
Severe bleeding/transfusion	50 (7.0%)	70 (11.2%)	2,330 (17.2%) *
Haemopericardium	12 (1.7%)	7 (1.1%)	39 (0.3%)

*transfusion of erythrocyte concentrates during the in-hospital stay.

MACCE: major adverse cardiac and cerebrovascular events; NYHA: New York Heart Association; TIA: transient ischaemic attack

Supplementary Table 3. **Trends in total numbers of MitraClip procedures, patient characteristics, complications and safety outcomes over the 5-year period.**

Year	2011	2012	2013	2014	2015	ß (95% CI)	*p*-value
MitraClip procedures	**815**	**1,865**	**2,726**	**3,737**	**4,432**	**0.999 (0.964 to 1.033)**	**<0.001**
Sex (female)	329 (40.4%)	720 (38.6%)	1,066 (39.1%)	1,477 (39.5%)	1,834 (41.4%)	0.016 (-0.003 to 0.081)	0.069
Age at procedure (years)	**76 (71-81)**	**76 (70-81)**	**77 (71-82)**	**77 (71-82)**	**78 (72-82)**	**0.058 (0.006 to 0.010)**	**0.0001**
In-hospital stay (days)	10 (7-17)	10 (7-18)	10 (7-18)	11 (7-18)	10 (7-17)	-0.001 (-0.003 to 0.001)	0.271
Obesity	65 (8.0%)	121 (6.5%)	206 (7.6%)	280 (7.5%)	345 (7.8%)	0.008 (-0.039 to 0.118)	0.329
Comorbidities							
Cancer	**10 (1.2%)**	**26 (1.4%)**	**54 (2.0%)**	**77 (2.1%)**	**95 (2.1%)**	**0.020 (0.026 to 0.326)**	**0.022**
Coronary artery disease	536 (65.8%)	1,226 (65.7%)	1,859 (68.2%)	2,505 (67.0%)	3,011 (67.9%)	0.013 (-0.011 to 0.078)	0.136
Heart failure	**602 (73.9%)**	**1,459 (78.2%)**	**2,158 (79.2%)**	**3,004 (80.4%)**	**3,614 (81.5%)**	**0.045 (0.086 to 0.189)**	**0.0001**
Atrial fibrillation/flutter	**508 (62.3%)**	**1,191 (63.9%)**	**1,710 (62.7%)**	**2,452 (65.6%)**	**2,911 (65.7%)**	**0.023 (0.016 to 0.102)**	**0.008**
Chronic obstructive pulmonary disease	**126 (15.5%)**	**245 (13.1%)**	**406 (14.9%)**	**558 (14.9%)**	**708 (16.0%)**	**0.018 (0.004 to 0.119)**	**0.037**

Essential arterial hypertension	468 (57.4%)	1,048 (56.2%)	1,650 (60.5%)	2,118 (56.7%)	2,589 (58.4%)	0.004 (-0.033 to 0.051)	0.662
Renal insufficiency	**334 (41.0%)**	**818 (43.9%)**	**1,242 (45.6%)**	**1,781 (47.7%)**	**2,070 (46.7%)**	**0.030 (0.031 to 0.114)**	**0.001**
Diabetes mellitus	248 (30.4%)	566 (30.3%)	853 (31.3%)	1,122 (30.0%)	1,392 (31.4%)	0.005 (-0.031 to 0.058)	0.551
Peripheral artery disease	**38 (4.7%)**	**141 (7.6%)**	**184 (6.7%)**	**267 (7.1%)**	**344 (7.8%)**	**0.020 (0.014 to 0.174)**	**0.022**
Clinical parameters							
Tachycardia	45 (5.5%)	116 (6.2%)	178 (6.5%)	241 (6.4%)	270 (6.1%)	0.001 (-0.079 to 0.091)	0.889
Syncope	6 (0.7%)	32 (1.7%)	33 (1.2%)	30 (0.8%)	49 (1.1%)	-0.010 (-0.310 to 0.086)	0.267
Shock	35 (4.3%)	83 (4.5%)	117 (4.3%)	165 (4.4%)	175 (3.9%)	-0.007 (-0.146 to 0.060)	0.411
Bleeding complications/transfusion of erythrocyte concentrates							
Haemopericardium	4 (0.5%)	7 (0.7%)	6 (0.2%)	9 (0.2%)	13 (0.3%)	-0.158 (0.545 to 0.228)	0.421
Transfusion of erythrocyte concentrates	192 (23.6%)	347 (18.6%)	524 (19.2%)	615 (16.5%)	652 (14.7%)	-0.060 (-0.249 to -0.140)	**0.0001**
Safety outcomes							
In-hospital death	25 (3.1%)	59 (3.2%)	94 (3.4%)	149 (4.0%)	161 (3.6%)	0.074 (-0.037 to 0.185)	0.193
Cardiopulmonary resuscitation	21 (2.6%)	42 (2.3%)	67 (2.5%)	94 (2.5%)	115 (2.6%)	0.005 (-0.094 to 0.171)	0.573

Adverse in-hospital events	151 (18.5%)	380 (20.4%)	563 (20.7%)	808 (21.6%)	870 (19.6%)	0.003 (-0.048 to 0.054)	0.909
MACCE	46 (5.6%)	117 (6.3%)	182 (6.7%)	259 (6.9%)	303 (6.8%)	0.056 (-0.027 to 0.139)	0.183
Stroke	6 (0.7%)	17 (0.9%)	18 (0.7%)	24 (0.6%)	30 (0.7%)	-0.092 (-0.340 to 0.155)	0.465
Endocarditis	0 (0.0%)	4 (0.2%)	5 (0.2%)	5 (0.1%)	14 (0.3%)	0.366 (-0.090 to 0.821)	0.116
Deep vein thrombosis and/or thrombophlebitis	5 (0.6%)	13 (0.7%)	15 (0.6%)	30 (0.8%)	41 (0.9%)	0.186 (-0.051 to 0.423)	0.123
Pulmonary embolism	3 (0.4%)	6 (0.3%)	6 (0.2%)	9 (0.2%)	15 (0.3%)	0.022 (-0.365 to 0.408)	0.913
Pericardial effusion	12 (1.5%)	21 (1.1%)	31 (1.1%)	81 (2.2%)	104 (2.3%)	0.315 (0.161 to 0.469)	0.315

CI: confidence interval; MACCE: major adverse cardiac and cerebrovascular events; NYHA: New York Heart Association