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Impact of type 1 diabetes mellitus on mortality rate and outcome of hospitalized patients with myocardial infarction

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ABSTRACT

Introduction: Type 1 diabetes mellitus (T1D) is associated with an increased cardiovascular risk. We aimed to investigate the influence of T1D on myocardial infarction (MI) patients' mortality.
Materials and methods: The German nationwide inpatient sample 2005–2016 was used for statistical analysis. Hospitalized MI patients were stratified for T1D and impact of T1D on in-hospital outcomes was investigated.
Results: In total, 3,307,703 hospitalizations of MI patients (37.6 % females, 56.8 % aged ≥70 years) were counted in Germany 2005–2016 and included in this analysis. In 18,625 (0.6 %) of the cases additionally T1D was coded. Overall, 410,737 (12.4 %) in-hospital deaths occurred within the investigation period. MI patients with T1D were younger (64.0 [IQR 52.0–75.0] vs. 73.0 [62.0–81.0] years, $P < 0.001$), more often female (38.7 % vs. 37.6 %, $P < 0.001$) and obese (13.2 % vs. 9.3 %, $P < 0.001$). Comorbidities like peripheral arterial (14.2 % vs. 6.4 %, $P < 0.001$) and kidney disease (38.5 % vs. 27.2 %, $P < 0.001$) were more prevalent in MI patients with T1D. T1D was an independent risk factor for in-hospital death (OR 1.23 [95%CI 1.18–1.29], $P < 0.001$), recurrent MI (OR 1.56 [95%CI 1.35–1.80], $P < 0.001$), and stroke (OR 1.75 [95%CI 1.63–1.88], $P < 0.001$). While percutaneous coronary intervention (PCI, 37.8 % vs. 42.0 %, $P < 0.001$) was less often, coronary artery bypass grafting (CABG, 7.4 % vs. 4.6 %, $P < 0.001$) was more often performed in MI patients with T1D, confirmed by regression analysis (PCI: OR 0.66 [95%CI 0.64–0.68], $P < 0.001$; CABG: OR 1.54 [95%CI 1.45–1.63], $P < 0.001$).
Conclusions: T1D represents an important and independent risk factor for mortality in MI patients. The results emphasize the high vulnerability of T1D patients who suffer from MI.

What is the novelty of the research?

a. What is already known?
- Type 1 diabetes mellitus is associated with an increased cardiovascular risk.

b. What does this study add?
- Our very large nationwide inpatient study adds findings regarding the extent in the risk for adverse outcomes in patients with myocardial infarction driven by type 1 diabetes mellitus.

c. How might these results change the direction of research or the focus of clinical practice?
- The results emphasize the high vulnerability of patients with type 1 diabetes mellitus who suffer from myocardial infarction. Patients with myocardial infarction should be monitored closely and probably should be treated more aggressively with reperfusion strategies.

d. Please write a novelty statement and unique points of your research as compared to previously published research (provide a table of comparison if necessary).
- The results of our study including more than 3 million cases of myocardial infarction revealed that type 1 diabetes mellitus represents an important and

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independent risk factor for mortality in patients suffering from myocardial infarction. The results emphasize the high vulnerability of patients with type 1 diabetes mellitus who suffer from myocardial infarction. Our study highlights important treatment differences in patients with and without type 1 diabetes mellitus who suffer from myocardial infarction.

1. Introduction

Type 1 diabetes mellitus (T1D), also known as insulin-dependent diabetes, is associated with hyperglycemia and insulin deficiency caused by an autoimmune reaction against pancreatic insulin-producing beta-cells. Most patients develop T1D at a young age and therefore T1D represents one of the most prevalent chronic childhood diseases accompanied by an increasing incidence in most countries worldwide. Living with T1D is challenging and requires frequent blood glucose controls and insulin deliveries, adequate patient education and continuous medical care [1]. T1D is a major cardiovascular risk factor due to a complex interplay of various activations in the human body like inflammation, oxidative stress and endothelial dysfunction promoting atherosclerosis and hence leading to cardiovascular diseases like myocardial infarction (MI), heart failure and ischemic stroke [2,3]. In patients with T1D cardiovascular diseases represent the main cause of death and cause affected individuals to suffer from their first cardiovascular event about 10–15 years earlier than the general population [4,5]. T1D is associated with a more than 9-fold increased risk for coronary artery disease (CAD) and a more than 6-fold increased risk for MI; remarkably, this risk is higher in female than in male patients with T1D [6]. Regarding mortality, T1D is associated with an at least 11 years reduced life expectancy [7]. Patients with T1D differ significantly from other patients suffering from atherosclerosis due to multiple reasons like vessel disease in younger age, more severe vessel affection resulting e. g. in worse manifestation of CAD and often atypical symptoms or symptom-free patients in occurrence of acute and severe diseases like MI [2,8–11]. Although, on the one hand, fortunately the risk of cardiovascular disease and associated mortality in patients with T1D decreases since the 1960s, on the other hand still a huge disparity is present between patients with T1D and the general population regarding prevalence and clinical outcome of cardiovascular diseases including CAD [2,12,13]. After MI events, especially young patients are afflicted by poor survival and this was shown to be additionally aggravated in presence of T1D [14]. Whereas risk factors for poor prognosis in patients with MI are extensively investigated in the general population and in patients with type 2 diabetes mellitus (T2D), which besides others include age, heart failure and reduced kidney function, data on T1D regarding the impact of the disease and further associated risk factors are scarce [2]. Even data regarding mortality after MI barely exist [15]. To elucidate this issue, the aim of the presents study was to investigate the influence of T1D on outcome after MI, patients' clinical profile, treatment modalities, adverse events during hospitalization and in-hospital mortality in patients suffering from MI. For this purpose, real-world data of the very large German nationwide inpatient sample were investigated analysing all hospitalizations with MI in Germany within a time period of 12 years.

2. Material and methods

In the present epidemiological study, we analysed the German nationwide inpatient statistics including all hospitalized patients with MI in Germany during the observational period of the years 2005–2016 (source: Research Data Center of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005–2016, and own calculations). In Germany, patients' diagnoses are coded according to ICD-10-GM (International Classification of Diseases, 10th Revision with German Modification); in contrast, diagnostical, surgical and interventional procedures are coded with the help of OPS codes (surgery, diagnostic and procedures codes [Operationen-und Prozedurenschlüssel]). The Federal Statistical Office of Germany (Statistisches Bundesamt, Wiesbaden, Germany) gathers all treatment data from the entire inpatient cases in Germany (processed according to the diagnosis related groups [DRG] system) [16,17].

Within the present study, all hospitalization-cases of patients with MI in Germany between the years 2005 and 2016 were assessed. We identified MI patients by the diagnostic codes regarding MI (ICD-codes I21 and I22). MI patients were stratified for presence of T1D (ICD-codes E10). We compared MI patients with and without T1D regarding baseline parameters, in particular cardiovascular risk factors and cardiovascular comorbidities, use of reperfusion treatments, age as well as gender - and with special focus on occurrence of adverse in-hospital events and in-hospital case-fatality rate. In addition, we investigated time-trends on hospitalization rate, in-hospital case-fatality rate, in-hospital adverse events and reperfusion treatments.

2.1. Definitions

Obesity was defined as body mass index $\geq$30 kg/m^2 according to the recommendations of the WHO (World Health Organization) [18]. Recurrent MI was defined as recurrent MI in the first 4 weeks after a first MI. Shock as well as cardio-pulmonary resuscitation were defined according to current European guidelines [19–21].

2.2. Study endpoints and in-hospital adverse events

The primary study outcome was defined as death of all-causes during in-hospital stay (in-hospital death). Secondary study outcomes were occurrence of adverse in-hospital events such as recurrent MI (ICD-code I22), pneumonia (ICD-codes J12-J18), deep venous thrombosis and/or thrombophlebitis of the leg veins (ICD-code I80), pulmonary embolism (ICD-code I26), acute kidney injury (ICD-code N17), stroke (ischemic and hemorrhagic stroke, ICD-codes I61-64), intracerebral bleeding events (ICD-code I61), gastro-intestinal bleeding (ICD-codes K920-K922), and transfusion of blood components (OPS code 8–800).

2.3. Ethical aspects

Since in the present assessment the investigators had no direct access to data of individual patients, approval by an ethical committee and informed consent were not required, in accordance with the German law.

2.4. Statistical methods

Descriptive statistics regarding relevant patient-characteristics comparisons of MI patients with and without T1D are presented as median and interquartile range (IQR) or absolute numbers and corresponding percentages. We tested these comparisons of the continuous variables using the Mann-Whitney-U test and the comparisons of categorical variables with the Fisher's exact or the chi^2 test, as appropriate.

Total hospitalization rate for MI with T1D related to all hospitalized MI patients (with and without T1D) and relative mortality rate (case-fatality rate), recurrent MI, the usage of interventional reperfusion treatments as well as coronary artery bypass graft (CABG) and rate of adverse in-hospital events, were descriptively illustrated in figures and trends were calculated on an annual basis, and linear regression was used to assess trends over time. The results are presented as beta coefficients (β) and corresponding 95 % confidence intervals (CI).

Univariate and multivariate logistic regression models were analysed to investigate the impact of T1D on adverse in-hospital events and on in-hospital death in MI patients. Results are presented as odds ratio (OR) and 95 % CI. The multivariate regression models were adjusted for age, sex, cancer, heart failure, chronic obstructive pulmonary disease, essential arterial hypertension, acute and chronic kidney disease, atrial fibrillation/flutter, hyperlipidemia and smoking.

We selected this conservative epidemiological approach regarding the mentioned adjustment to test the widespread independence of these outstanding influencing factors on case-fatality rate during hospitalization and avoid bias regarding these parameters on outcomes. The software SPSS® (version 20.0; SPSS Inc., Chicago, Illinois, USA) was used for computerised analysis. P values of <0.05 (two-sided) were considered to be statistically significant.

3. Results

During the observational period 2005–2016, in total, 3,307,703 hospitalizations of patients with acute MI (37.6 % females, 56.8 % aged ≥70 years) were counted in Germany. All these patients, who were treated in German hospitals, were included in the present analysis. Of these treated MI patients in 2005–2016, 410,737 patients died during their hospitalization (accounting for a 12.4 % case-fatality rate). Overall, 1,007,326 (30.5 %) MI cases were additionally coded with diabetes mellitus and 18,625 (0.6 %) with T1D.

3.1. Temporal trends on hospitalization rate, case-fatality rate and MI recurrence in MI patients with type 1 diabetes mellitus

While the absolute annual numbers of MI patients increased slightly over time, absolute (β −64.0 [95%CI -95.7 to −32.3; P = 0.001) and relative numbers of MI patients with T1D decreased up to 2014 and increased later on (Fig. 1). The case-fatality rate decreased during the observational period, whereas the rate of recurrent MI was widely stable (Fig. 1). The age-dependent analysis illustrates an increase of MI cases with growing age up to the 8th decade. Although the absolute numbers of hospitalizations of MI patients with T1D increased also up to the 8th decade of life, relative numbers of MI patients with T1D decreased substantially with age. Only 7 patients with a co-prevalence of MI and T1D were counted who were aged in the first 2 decades of life. Case-fatality rate increased markedly with growing age to more than 20 % in the 9th decade and older (Fig. 1).

3.2. Comparison of MI patients with and without type 1 diabetes mellitus

MI patients with T1D were younger (64.0 [IQR 52.0–75.0] vs. 73.0 [IQR 62.0–81.0], P < 0.001), more frequently female (38.7 % vs. 37.6 %, P < 0.001) and obese (13.2 % vs. 9.3 %, P < 0.001) (Table 1).

Regarding comorbidities, peripheral artery disease (14.2 % vs. 6.4 %, P < 0.001) as well as acute and chronic kidney disease (38.5 % vs. 27.2 %, P < 0.001) were more prevalent in MI patients with T1D. Driven by younger age of MI patients with T1D, atrial fibrillation/flutter (16.2 % vs. 21.8 %, P < 0.001) and chronic obstructive pulmonary disease (6.8 % vs. 8.9 %, P < 0.001) were less prevalent in MI patients with T1D (Table 1).

Fig. 2 illustrates an annual increase especially of acute and chronic kidney failure from 2005 to 2016 and an aggravation of the comorbidity burden in MI patients with T1D with growing age. Proportion of female sex was higher in older MI patients with T1D (Fig. 2).

When excluding the patients with T2D from the analysis, MI patients with T1D were still more often female, younger, more frequently obese and were more often afflicted by peripheral artery disease as well as acute and chronic kidney disease (Table S1 in the supplementary material). In contrast, MI patients with T2D were older, more often female, more frequently obese and hypertensive and revealed higher rates of

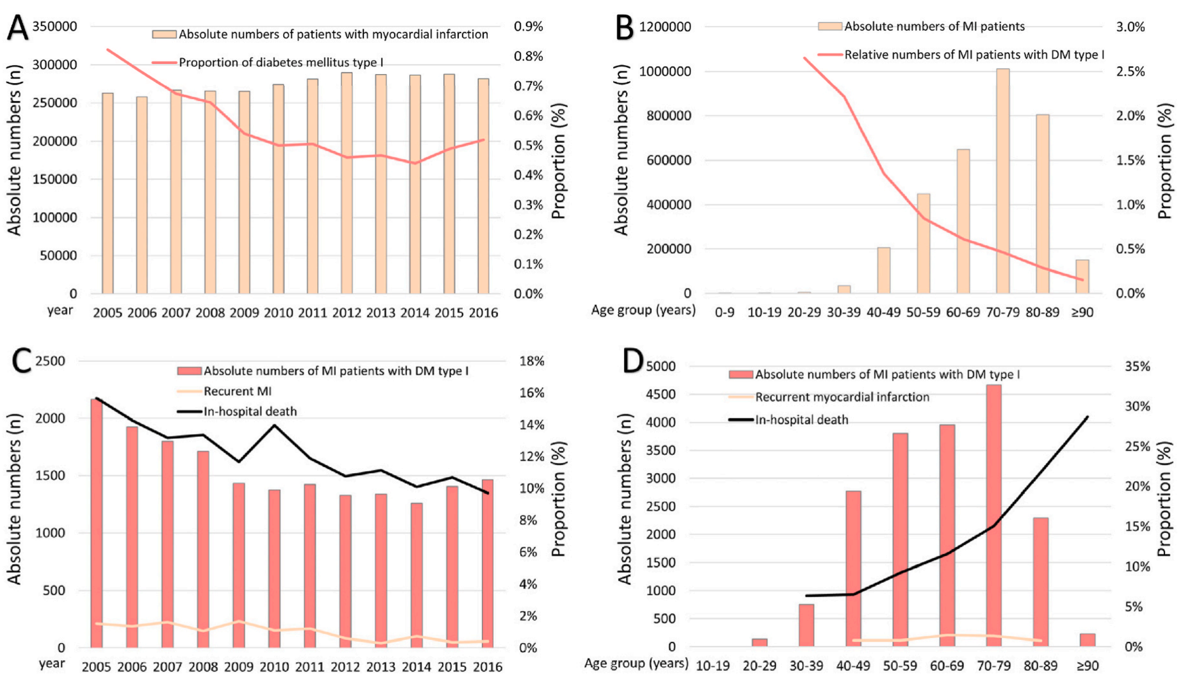

Fig. 1. Temporal trends of absolute numbers regarding hospitalizations of patients suffering from myocardial infarction, patients with type 1 diabetes mellitus suffering from myocardial infarction, relative rate of type 1 diabetes mellitus related to all patients suffering from myocardial infarction and in-hospital case-fatality rate of patients with type 1 diabetes mellitus suffering from myocardial infarction

Panel A: Temporal trends regarding absolute numbers of hospitalizations of patients with myocardial infarction (orange bars), and proportion of hospitalizations suffering from myocardial infarction with type 1 diabetes mellitus (red line) stratified for treatment year

Panel B: Temporal trends regarding absolute numbers of hospitalizations of patients with myocardial infarction (orange bars), and proportion of hospitalizations of patients suffering from myocardial infarction with type 1 diabetes mellitus (red line) stratified for age-decade

Panel C: Annual total numbers of hospitalizations of patients suffering from myocardial infarction with type 1 diabetes mellitus (red bars) and annual case-fatality rate (black line) and rate of recurrent myocardial infarction (orange line) stratified for treatment year

Panel D: Annual total numbers of hospitalizations of patients suffering from myocardial infarction with type 1 diabetes mellitus (red bars) and annual case-fatality rate (black line) and rate of recurrent myocardial infarction (orange line) stratified for age-decade.

Table 1
Patients' characteristics, medical history, presentation and outcomes of the included 3,307,703 patients suffering from myocardial infarction stratified according the presence of type 1 diabetes mellitus.

Parameters	MI patients without type 1 diabetes mellitus (n = 3,289,078; 99.4 %)	MI patients with type 1 diabetes mellitus (n = 18,625; 0.6 %)	P-value
Age	73.0 (62.0–81.0)	64.0 (52.0–75.0)	<0.001
Age ≥70 years	1,872,150 (56.9 %)	6736 (36.2 %)	<0.001
Female sex[a]	1,235,833 (37.6 %)	7203 (38.7 %)	0.002
In-hospital stay (days)	7.0 (4.0–12.0)	9.0 (4.0–17.0)	<0.001
Traditional cardiovascular risk factors			
Obesity	304,638 (9.3 %)	2453 (13.2 %)	<0.001
Diabetes mellitus	988,701 (30.1 %)	18,625 (100.0 %)	<0.001
Essential arterial hypertension	1,808,136 (55.0 %)	10,407 (55.9 %)	0.014
Hyperlipidemia	1,270,395 (38.6 %)	6647 (35.7 %)	<0.001
Comorbidities			
Peripheral artery disease	210,579 (6.4 %)	2654 (14.2 %)	<0.001
Heart failure	1,207,005 (36.6 %)	7062 (37.8 %)	0.001
Cancer	122,855 (3.7 %)	665 (3.6 %)	0.237
Atrial fibrillation/flutter	716,216 (21.8 %)	3021 (16.2 %)	<0.001
Chronic obstructive pulmonary disease	293,854 (8.9 %)	1271 (6.8 %)	<0.001
Sleep apnoea	38,872 (1.2 %)	302 (1.6 %)	<0.001
Acute and chronic kidney disease	895,454 (27.2 %)	7164 (38.5 %)	<0.001
Interventional and surgical reperfusion treatments			
Cardiac catheter	1,816,790 (55.2 %)	9849 (52.9 %)	<0.001
Percutaneous coronary intervention	1,383,048 (42.0 %)	7032 (37.8 %)	<0.001
Bare metal stent	577,008 (17.5 %)	2299 (12.3 %)	<0.001
Drug eluting stent	728,106 (22.1 %)	4251 (22.8 %)	0.024
Bioresorbable vascular scaffold	8272 (0.3 %)	50 (0.3 %)	0.645
Coronary-artery bypass graft	152,740 (4.6 %)	1376 (7.4 %)	<0.001
Intensive care unit	1,024,420 (31.1 %)	7138 (38.2 %)	<0.001
Adverse events during hospitalization			
In-hospital death	408,418 (12.4 %)	2319 (12.5 %)	0.890
Cardio-pulmonary resuscitation	205,956 (6.3 %)	1492 (8.0 %)	<0.001
Recurrent myocardial infarction	21,400 (0.7 %)	194 (1.0 %)	<0.001
Pneumonia	382,036 (11.6 %)	2629 (14.1 %)	<0.001
Deep venous thrombosis and/or thrombophlebitis	22,376 (0.7 %)	109 (0.6 %)	0.115
Pulmonary embolism	22,529 (0.7 %)	127 (0.7 %)	0.959
Acute kidney injury	205,088 (6.2 %)	1762 (9.5 %)	<0.001
Shock	226,482 (6.9 %)	1628 (8.7 %)	<0.001
Stroke (ischemic or hemorrhagic)	94,575 (2.9 %)	789 (4.2 %)	<0.001
Transient ischemic attack	15,252 (0.5 %)	85 (0.5 %)	0.883
Intracerebral bleeding	9317 (0.3 %)	93 (0.5 %)	<0.001
Gastro-intestinal bleeding	47,595 (1.4 %)	291 (1.6 %)	0.189
Hemopericardium	4033 (0.1 %)	21 (0.1 %)	0.701
Transfusion of blood constituents	416,896 (12.7 %)	3695 (19.8 %)	<0.001

[a] Information available for 3,307,574 patients.

peripheral artery disease, heart failure, atrial fibrillation/flutter as well as acute and chronic kidney disease than MI patients without diabetes mellitus of both types (Table S2 in the supplementary material).

When comparing MI patients with T1D and vs. MI patients with T2D, MI patients with T1D were younger, less often female, but revealed a higher prevalence of peripheral artery disease (Table S3 in the supplementary material).

3.3. Differences in performed revascularization treatments between MI patients with and without type 1 diabetes mellitus

Interventional reperfusion strategies like cardiac catheter (52.9 % vs. 55.2 %, P < 0.001) and percutaneous coronary intervention (37.8 % vs. 42.0 %, P < 0.001) were less often performed in MI patients with T1D. Bare metal stents (12.3 % vs. 17.5 %, P < 0.001) were also less often used in MI patients with T1D, whereas drug eluting stents (22.8 % vs. 22.1 %, P = 0.024) were slightly more often implanted in MI patients with T1D and CABG was more often performed in patients with T1D (7.4 % vs. 4.6 %, P < 0.001) (Table 1). These study results remained widely stable when MI patients with T2D were excluded from the analysis (Table S1 in the supplementary material).

Temporal annual trends in the used reperfusion strategies revealed an increase of cardiac catheterization, percutaneous coronary intervention and implantation of drug eluting stents in MI patients with T1D, whereas the conduction of CABG surgeries was widely unchanged over the investigated time period. However, the use of reperfusion treatments decreased with growing age (Fig. 3).

Presence of T1D was independently associated with an underuse of cardiac catheterization (OR 0.691 [95%CI 0.670–0.713], P < 0.001) and percutaneous coronary intervention (OR 0.659 [95%CI 0.638–0.680)], P < 0.001) in MI patients as well as lower implantation rates of all investigated stent subtypes after adjustment for age, sex and comorbidities. In contrast, T1D was associated with increased usage of CABG (OR 1.538 [95%CI 1.454–1.627], P < 0.001) (Table 2).

When focusing on the comparison of MI patients with and without T2D (excluding MI patients with T1D), cardiac catheterization, percutaneous coronary intervention as well as implantation of bare metal stents and drug eluting stents were all more often used in MI patients without T2D, whereas CABG surgery was also more frequently performed in MI patients with T2D (Table S2 in the supplementary material). The comparison of MI patients with T1D versus MI patients with T2D showed that in MI patients with T1D slightly more often cardiac catheterization, drug eluting stent implantation and CABG surgery were performed (Table S3 in the supplementary material).

3.4. Differences in adverse in-hospital events between MI patients with and without type 1 diabetes mellitus

Direct comparison between both groups showed a non-significant slightly higher case-fatality rate in MI patients with T1D compared to MI patients without T1D (12.5 % vs. 12.4 %, P = 0.890). In contrast, the adverse events recurrent myocardial infarction (1.0 % vs. 0.7 %, P < 0.001), cardio-pulmonary resuscitation (8.0 % vs. 6.3 %, P < 0.001), pneumonia (14.1 % vs. 11.6 %, P < 0.001), shock (8.7 % vs. 6.9 %, P < 0.001), stroke (4.2 % vs. 2.9 %, P < 0.001), acute kidney injury (9.5 % vs. 6.2 %, P < 0.001) and necessity of transfusion of blood constituents (19.8 % vs. 12.7 %, P < 0.001) were more prevalent in MI patients with T1D (Table 1).

Logistic regression analyses demonstrated an independent association between T1D and increased case-fatality (OR 1.232 [95%CI 1.176–1.290], P < 0.001) as well as most adverse in-hospital events in MI patients. T1D was afflicted with an increased risk for recurrent MI (OR 1.561 [95%CI 1.354–1.800], P < 0.001), cardio-pulmonary resuscitation (OR 1.154 [95%CI 1.093–1.218], P < 0.001), stroke (OR 1.749 [95%CI 1.627–1.880], P < 0.001), intracerebral bleeding (OR 1.652 [95%CI 1.345–2.029], P < 0.001) and necessity of transfusion of blood constituents (OR 1.642 [95%CI 1.582–1.705], P < 0.001) (Table 3). Remarkably, T1D was not an independent risk factor for increased acute kidney injury in multivariate logistic regression analysis. In regards of the age-dependent impact of T1D on case-fatality, we identified an independent association of T1D with case-fatality in older MI patients (Table S4 of the supplementary material).

Regarding time-trends, the annual proportion of pneumonia and acute kidney injury increased from 2005 to 2016, while most other

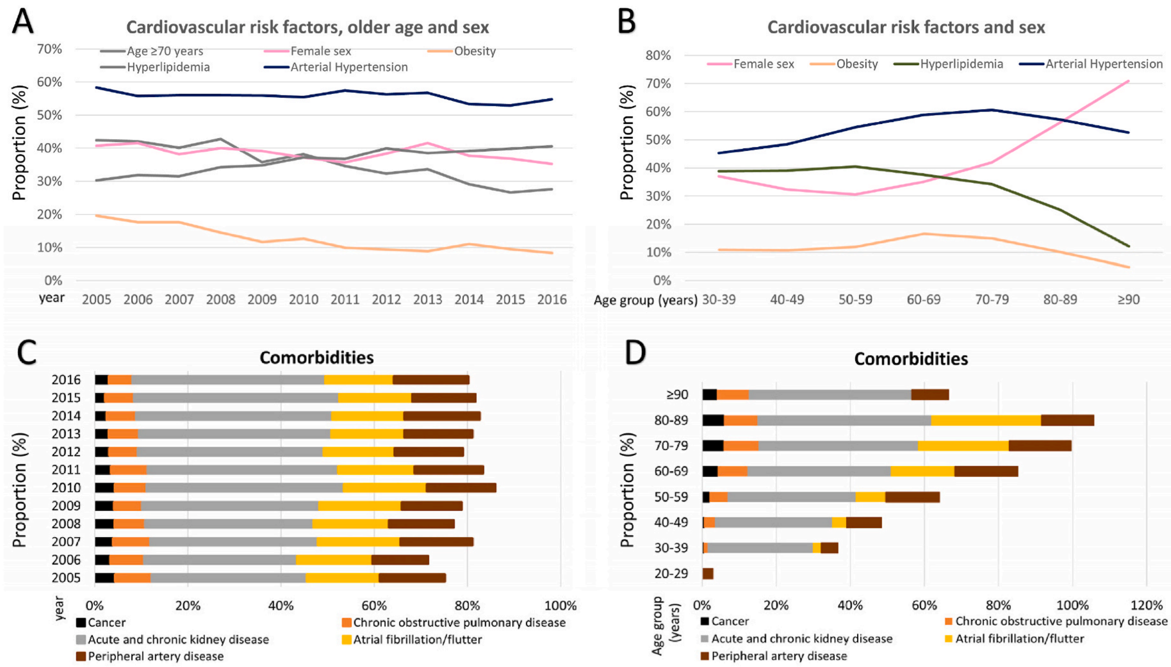

Fig. 2. Temporal trends regarding sex distribution, cardiovascular risk factors and comorbidities of patients suffering from myocardial infarction with type 1 diabetes mellitus

Panel A: Temporal trends regarding proportions of female (pink bars) patients suffering from myocardial infarction with type 1 diabetes mellitus and cardiovascular risk factors stratified for treatment year

Panel B: Temporal trends regarding proportions of female (pink bars) patients suffering from myocardial infarction with type 1 diabetes mellitus and cardiovascular risk factors stratified for age-decade

Panel C: Temporal trends regarding proportion of comorbidities of patients suffering from myocardial infarction with type 1 diabetes mellitus stratified for treatment year

Panel D: Temporal trends regarding proportion of comorbidities of patients suffering from myocardial infarction with type 1 diabetes mellitus stratified for age-decade.

adverse in-hospital events remained widely unchanged over the years. Necessity regarding transfusion of blood constituents was highest in the 7th to 9th decades of life and adverse in-hospital events comprising stroke, pneumonia and acute kidney injury increased markedly with age (Fig. 4).

After excluding MI patients with T2D from the analysis, in-hospital case-fatality was higher in MI patients with T1D compared to patients without diabetes mellits (12.5 % vs. 12.1 %, $P = 0.125$) (Table S1 in the supplementary material). In this analysis, T1D represented an independent risk factor for death in patients suffering from MI (multivariate logistic regression: OR 1.255 [95%CI 1.195–1.317], $P < 0.001$).

In addition, also T2D had a significant impact on survival of MI patients. The case-fatality of MI patients with T2D was higher than the case-fatality of MI patients without diabetes mellitus of both types T2D (13.1 % vs. 12.1 %, $P < 0.001$) (Table S2 in the supplementary material). The case-fatality rate was lower in MI patients with T1D in comparison to those with T2D (12.5 % vs. 13.1 %, $P = 0.006$) (Table S3 in the supplementary material), while the logistic regression analyses identified a significant and independent impact of T1D on death in MI patients with diabetes mellitus (MI patients with T1D vs. those with T2D as the reference: multivariate logistic regression: OR 1.259 [95%CI 1.203–1.318], $P < 0.001$).

4. Discussion

In the present study, more than 3.3 million hospitalizations of MI patients who were treated between 2005 and 2016 in Germany were included to investigate the influence of T1D on comorbidities, adverse events, usage of reperfusion procedures and in-hospital death. The findings of the present analysis let us draw the following conclusions: First, while the rate of MI patients with T1D decreased until 2014 and increased thereafter again, in-hospital death of MI patients with T1D decreased during the observational period and the occurrence of recurrent MI remained widely unchanged. Certainly, in-hospital mortality as well as the rate of recurrent MI were still considerably higher in MI patients with than in those without T1D. Second, although MI patients with T1D were significantly younger (in the median 9 years), this patient group presented with an aggravated micro- and macrovascular comorbidity profile including a higher prevalence of peripheral artery disease and chronic kidney injury. Third, presence of T1D in patients with MI was associated with lower usage of interventional and higher rates of surgical reperfusion treatment strategies, although the conduction of invasive strategies increased within the investigation period. In this context, higher age was accompanied by higher rates of interventional procedures in patients with T1D. Fourth, T1D was identified as an independent risk factor for adverse events like recurrent MI, stroke, intracerebral bleeding as well as in-hospital death. Fifth, taken the findings together, in all patients who suffered from MI, individuals with T1D represented a small (namely 0.6 % of all MI cases in the present study), but highly vulnerable patient-group with aggravated morbidity and mortality.

Management of myocardial infarction in patients with T1D is challenging and implicates various difficulties, but data regarding this issue are scarce and most of the available studies focus on T2D [22]. However, although manifold improvements proceeded in the treatment of MI in the past decades, patients with diabetes mellitus are still associated with increased mortality and risk for heart failure, stroke and recurrent MI [22–24]. Both, hypo- and hyperglycemia were shown to be accompanied by negative clinical effects in MI patients with diabetes mellitus, and strict glucose management was associated with reduced heart inflammation and remodelling as well as increased regenerative potential of the myocardium during acute infarction [22,25,26]. Otherwise, findings

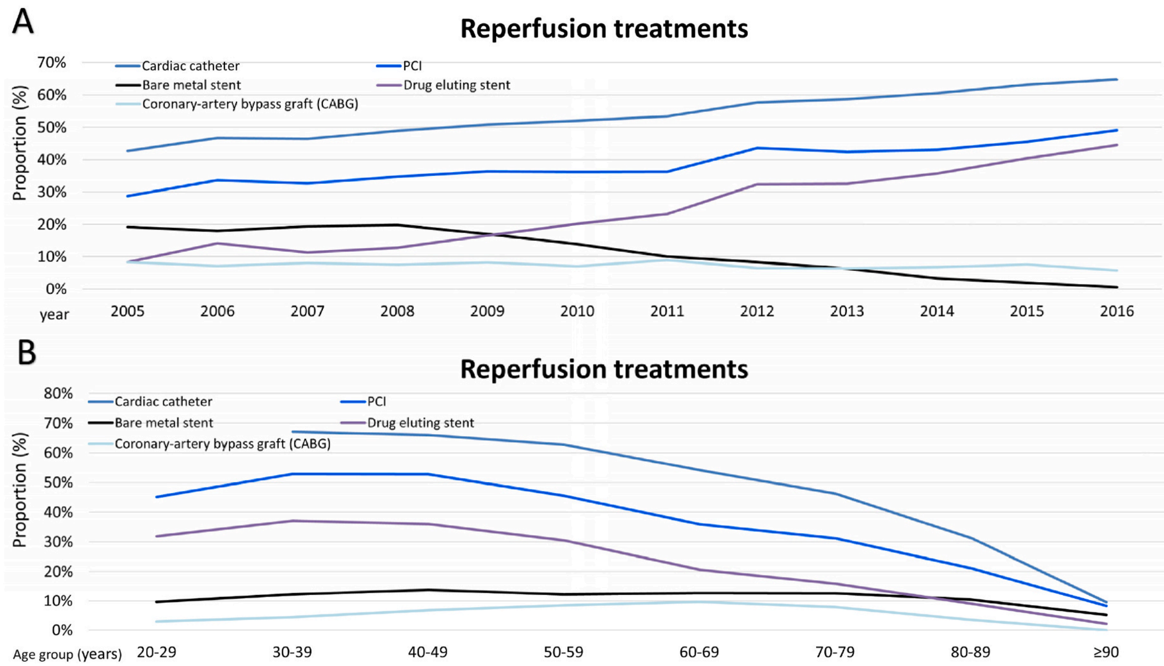

Fig. 3. Temporal trends regarding reperfusion treatments in patients suffering from myocardial infarction with type 1 diabetes mellitus
Panel A: Temporal trends regarding cardiac catheter (dark blue line), percutaneous coronary intervention (navy blue line), coronary artery bypass graft surgery (light grey line), as well as stent implantations of drug eluting stent implantation (purple line] and bare metal stent implantation (grey line) in patients suffering from myocardial infarction with type 1 diabetes mellitus stratified for treatment year
Panel B: Temporal trends regarding cardiac catheter (dark blue line), percutaneous coronary intervention (navy blue line), coronary artery bypass graft surgery (light grey line), as well as stent implantations of drug eluting stent implantation (purple line] and bare metal stent implantation (grey line) in patients suffering from myocardial infarction with type 1 diabetes mellitus stratified for age-decade.

Table 2
Impact of type 1 diabetes mellitus on usage of different interventional and surgical reperfusion treatments in patients hospitalized for myocardial infarction (univariate and multivariate logistic regression model).

	Univariate regression model		Multivariate regression model[a]	
	OR (95 % CI)	P-value	OR (95 % CI)	P-value
Cardiac catheter	0.909 (0.884–0.936)	<0.001	0.691 (0.670–0.713)	<0.001
Percutaneous coronary intervention	0.836 (0.811–0.861)	<0.001	0.659 (0.638–0.680)	<0.001
Bare metal stent	0.662 (0.634–0.691)	<0.001	0.608 (0.582–0.636)	<0.001
Drug eluting stent	1.040 (1.005–1.077)	<0.001	0.863 (0.833–0.894)	<0.001
Bioresorbable vascular scaffold	1.068 (0.808–1.410)	0.645	0.742 (0.561–0.981)	0.036
Coronary-artery bypass graft	1.638 (1.550–1.731)	<0.001	1.538 (1.454–1.627)	<0.001

[a] Adjusted for age, sex, cancer, heart failure, chronic obstructive pulmonary disease, essential arterial hypertension, acute and chronic kidney disease, atrial fibrillation/flutter, hyperlipidemia and smoking.

Table 3
Impact of type 1 diabetes mellitus on the different adverse in-hospital events in patients hospitalized for myocardial infarction (univariate and multivariate logistic regression model).

	Univariate regression model		Multivariate regression model[a]	
	OR (95 % CI)	P-value	OR (95 % CI)	P-value
In-hospital death	1.003 (0.960–1.048)	0.890	1.232 (1.176–1.290)	<0.001
Cardio-pulmonary resuscitation	1.304 (1.236–1.375)	<0.001	1.154 (1.093–1.218)	<0.001
Recurrent myocardial infarction	1.607 (1.394–1.853)	<0.001	1.561 (1.354–1.800)	<0.001
Pneumonia	1.251 (1.200–1.303)	<0.001	1.382 (1.323–1.443)	<0.001
Deep venous thrombosis or thrombophlebitis	0.859 (0.712–1.038)	0.116	0.843 (0.698–1.019)	0.077
Pulmonary embolism	0.995 (0.836–1.186)	0.959	0.990 (0.830–1.180)	0.908
Acute kidney injury	1.571 (1.496–1.651)	<0.001	0.922 (0.873–0.974)	0.004
Shock	1.295 (1.231–1.363)	<0.001	1.073 (1.018–1.130)	0.008
Stroke (ischemic or hemorrhagic)	1.494 (1.391–1.605)	<0.001	1.749 (1.627–1.880)	<0.001
Intracerebral bleeding	1.767 (1.439–2.168)	<0.001	1.652 (1.345–2.029)	<0.001
Gastro-intestinal bleeding	1.081 (0.962–1.214)	0.189	1.192 (1.060–1.339)	0.003
Transfusion of blood constituents	1.705 (1.645–1.768)	<0.001	1.642 (1.582–1.705)	<0.001

[a] Adjusted for age, sex, cancer, heart failure, chronic obstructive pulmonary disease, essential arterial hypertension, acute and chronic kidney disease, atrial fibrillation/flutter, hyperlipidemia and smoking.

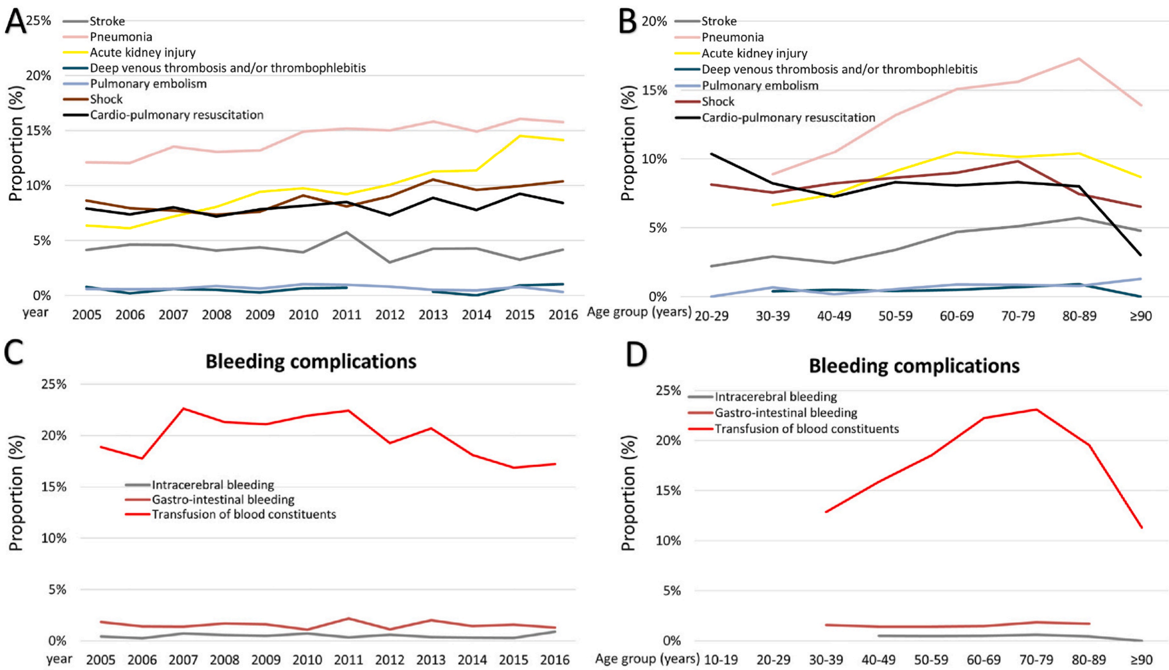

Fig. 4. Temporal trends regarding adverse in-hospital events in patients suffering from myocardial infarction with diabetes mellitus
Panel A: Temporal trends regarding adverse in-hospital events in patients suffering from myocardial infarction with type 1 diabetes mellitus stratified for treatment year
Panel B: Temporal trends regarding adverse in-hospital events in patients suffering from myocardial infarction with type 1 diabetes mellitus stratified for age-decade
Panel C: Temporal trends regarding bleeding events in patients suffering from myocardial infarction with type 1 diabetes mellitus stratified for treatment year
Panel D: Temporal trends regarding bleeding events in patients suffering from myocardial infarction with type 1 diabetes mellitus stratified for age-decade.

from epigenetic studies support the hypothesis of the hyperglycemic memory assuming end organ damage caused by dysglycemia to be irreversible and hence query the potency of glucose management within the setting of MI to improve clinical outcome as well as structural or functional effects on the diabetic heart [22,27,28]. These discrepancies emphasize the quandary of recent data, highlighting the need for further studies on glucose management in patients with MI, and considering the narrow availability of data especially in patients with T1D. Nevertheless, new technologies allowing continuous glucose monitoring which are already applied by people with both types of diabetes mellitus maybe promising tools to also improve management of people with diabetes mellitus in the setting of MI [22]. Remarkably, our study indicates for an underuse of interventional treatment strategies in MI patients with T1D. Regarding outcome, although the risk of T1D patients for cardiovascular disease declined within the past decades, a substantial peril remains compared to the risk of the general population [12,13]. A nationwide study from Norway comprising a 27 years observation period revealed a nine-fold elevated risk for acute MI in patients with T1D compared to matched controls [29] and in a meta-analysis a 6.4-fold elevated risk for MI was found [6]. Even at an age of <40 years a 5- to 10-fold increased risk for CAD events was reported [30]. In our present study, in-hospital mortality of MI patients with T1D was 12.5 % and did not differ from patients without T1D, who were in median 9 years older. The regression analysis revealed that after adjustment for age, sex and comorbidities, T1D is a crucial and independent risk factor for in-hospital death in patients with MI. Remarkably, the impact of T1D on case-fatality was observed especially in older patients and was even more pronounced than the effect of T2D. In accordance with previously published studies, our study results might illustrate that T1D attenuates the protective effect of female sex on cardiovascular risk, especially in a premenopausal age group of women [31–33]. This may also be a reason for over-representation of female gender in the T1D group. In this context, it is important to notice that our study included only the short observational period of the in-hospital stay, but a marked burden of T1D becomes firstly apparent and emerges in the following time after discharge. A recent study by Smidtslund et al. [2] on first-ever MI patients revealed poor survival of those with T1D with only 71 % survivors after 30 days, 62 % after 1 year and only 42 % of patients were alive 5 years after their first MI. In this study, T1D patients were comparably as young as in our assessment (52.4 ± 9.56 years) and 73.9 % of the included patients died during the median post-MI follow-up of 3.07 years. Data from Poland also showed less invasive procedures and higher mortality in MI patients with T1D [34]. Similar results on mortality were found by Kerola et al. [15] who additionally reported a significantly higher risk for recurrent MI, stroke and heart failure hospitalizations in T1D patients after MI [5]. In an interesting, large study by Sethupathi et al. [35] on data from the United States National Inpatient Sample outcome of acute MI was assessed in patients with T1D, T2D and without diabetes mellitus. The authors found similar results to our study with increased risk for major adverse cardiac and cerebrovascular events, all-cause mortality, major bleeding and lower performance rates of percutaneous coronary intervention in patients with T1D compared to individuals without diabetes mellitus. Of special interest, bleeding events and transfusion of blood units were elevated in our study in the T1D cohort although rates of atrial fibrillation were lower in this group, and unfortunately no reason for bleeding could be identified as appropriate explanation, whereas we had no information about medication as possible cause for higher bleeding risk. In the literature, bleeding risk after MI in T1D is scarcely described and also the authors of the aforementioned study did not discuss possible reasons for higher major bleeding events in T1D after MI, hence highlighting the fact that this issue is under-investigated and requires further attention. As a further vital finding of their study, lowest rate of revascularization was exposed in patients with T1D even in comparison to T2D [35]. Aiming to improve outcome of patients with T1D who suffer from MI, the identification of risk factors for morbidity and mortality are crucial [36]. Several risk factors were identified for elevated mortality in individuals with T1D following MI: patients with T1D suffer from more severe CAD compared to the general population including left main or multi-vessel disease, and mortality was shown to be increased by the number of affected vessels [5,37]. Besides manifestation of CAD, an impaired kidney function was identified as a vast risk factor for mortality in MI patients with T1D [2]. Regarding sex, women with T1D seem not to have protective features concerning acute MI and suffer from MI at the same age as men; in contrast, risk for mortality was even elevated in women with T1D suffering from acute MI [38,39].

Today the key strategy in avoiding cardiovascular diseases in patients with T1D remains an optimal prevention and best possible treatment of cardiovascular risk factors besides optimized diabetes therapy. In the setting of MI, T1D is associated with less revascularization and worse clinical outcome. Hence, there is much work to do for several reasons. Guideline targets of cardiovascular risk factors are often not met in T1D patients presenting with acute MI [40], requiring optimisation of medical care including continuous medical monitoring of patients with T1D to best possibly treat the primary disease especially focusing on low HbA1c levels [41]. Cardiovascular risk factors and comorbidities like renal impairment or damage of other end organs need to be prevented and early discovered to improve therapy and outcome [42]. Data are rare regarding management and complications of T1D in occurrence of MI calling for further investigation efforts to improve therapy strategies of these patients. In this context, medical professions in daily routine need to be aware that MI patients with T1D remain an especially vulnerable patient group that requires enhanced medical attention during and after the cardiovascular event.

5. Limitations

There are some limitations that merit consideration: First, the study results are based on ICD as well as OPS discharge codes of hospitalized patients, which might lead to an under-reporting/under-coding. Second, we can only provide data from the timeframe of hospitalization and have no data about later follow-ups. Third, data regarding disease duration of T1D are not available in the German nationwide inpatient statistics. Forth, no data regarding anticoagulation treatments are available in the German nationwide inpatient statistics.

6. Conclusions

Patients with T1D suffering from MI are associated with higher risk for clinical adverse events, lower usage rate of reperfusion strategies and higher in-hospital mortality compared to individuals without diabetes mellitus. Besides optimized diabetes therapy with avoidance of high HbA1c levels and with usage of continuous glucose monitoring, guideline targeted treatment of cardiovascular risk factors is the most important strategy regarding outcome improvement of T1D patients before and after suffering from MI. This vulnerable patient group therefore requires continuous medical consultation with optimal treatment of cardiovascular risk factors and accompanying diseases as well as best possible post-MI care with secondary prevention strategies.

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Declaration of competing interest

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Appendix A. Supplementary data

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