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Out-of-hospital cardiac arrest survival outcome in patients with type 1 diabetes mellitus.

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Out-of-hospital cardiac arrest survival outcome in patients with type 1 diabetes mellitus.

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Abstract

Background: It has been estimated that 80% of cases of out-of-hospital cardiac arrest are due to cardiac causes. It is well documented that diabetes is a risk factor for conditions associated with sudden cardiac arrest including among others coronary artery disease. Type 1 diabetes (T1D) displays a 3- to 5-fold increased risk of cardiovascular disease (CVD) and death compared with the general population. This study aims to assess characteristics and outcomes of individuals with and without T1D who experienced an OHCA.

Methods: Using the Swedish Cardiopulmonary Resuscitation Registry we enrolled 54,568 cases of OHCA where cardiopulmonary resuscitation were attempted between 2010-2020. Among them, 448 patients with T1D were identified using ICD-code: E10. Survival analysis was performed using Kaplan-Meier and logistic regression. All multiple regressions were adjusted for age, sex, cause of arrest, prevalence of T1D and time to cardiopulmonary resuscitation. The outcomes were discharge status (alive vs. dead), 30 days survival and neurological outcome at discharge.

Results: Patients with pre-existing diabetes accounted for 19,9% of the study population. Crude survival rate displayed poor outcome for T1D, albeit nonsignificant. Patients with T1D had generally good neurological outcomes following OHCA, being either in category 1 (76,5%) or 2 (23,5%). Multiple regression showed T1D status had no significant association with survival after accounting for covariates, OR 0.99 (95% CI 0.96-1.02) p-value = 0.7.

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Conclusion: We conclude that people with T1D are less likely to survive following OHCA. T1D patients experience OHCA approximately 5 years younger with more cardiovascular comorbidities and less by cardiac causes.

Strengths and limitations.

A major strength of the current study is the size of the study population, with 448 patients having T1D. The study sample is representative since >95% of all cases of OHCA are recorded in the registry. The sample includes all regions in Sweden and the risk of selection bias is minimal. However, we did not have access to greater details regarding diabetes diagnosis (islet antibodies, C-peptide, etc). We based our diagnoses on ICD codes which may cause misclassification error.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality worldwide (1). The European Registry of Cardiac Arrest (EuReCa) has OHCA as the third leading cause of death in Europe (2). It has been estimated that 80% of cases of OHCA are due to cardiac causes, primarily coronary artery disease in its various forms (3). OHCA in the younger population typically has a different etiology, with trauma, intoxications and suicide attempts being much more common than in older adults and elderly. Cardiovascular diseases, including cardiomyopathies, channelopathies, myocarditis and coronary artery anomalies occur but are not common on a population level (4).

It is well documented that diabetes is a risk factor for virtually all conditions associated with sudden cardiac arrest (SCA), including coronary artery disease, myocardial infarction (MI) and heart failure (HF). Previous studies report a 2-4-fold increase in the risk of SCA in patients with diabetes (5). Type 1 diabetes (T1D) displays a 3- to 5-fold increased risk of cardiovascular disease (CVD) and death compared with the general population. Indeed, the risk for CVD and death in type 1 diabetes is doubled even with glycated hemoglobin (HbA1c) levels at or below target levels (6).

The aim of the study was to assess characteristics and outcomes of individuals with type 1 diabetes who experienced an out-of-hospital cardiac arrest, as compared with other patients experiencing an OHCA.

Methods

Data used in the study had already been collected and approved by the Ethical Review Authority, registration number 2020-02017. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

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We conducted a nationwide observational study including all cases of OHCA recorded between 2010 and 2020 in the Swedish Cardiopulmonary Resuscitation Registry (SCRR). The registry was initiated in 1990 and includes >90% of all OHCA cases where resuscitation is attempted. All ambulance organizations throughout Sweden participate in the registry, the reporting is done prospectively and uses the Utstein-based template. The annual report is available at www.shlr.registercentrum.se.

We merged the SCRR with the Patient Registry, which includes all hospital and outpatient diagnoses throughout Sweden, with 100% level of ascertainment. All diagnoses since year 2000 were assessed, allowing for a 10-year period to record diabetes and other diagnoses. In Sweden, individuals with type 1 diabetes undergo annual examinations, such that a ten 10 period should allow for an adequate level of ascertainment with regards to diabetes status. Merging the SCRR with the Patient Registry is a seamless process due to the Swedish personal identification number, which is a unique 12-digit ID assigned to all citizens.

The Patient Registry utilizes International Classification of Diseases (ICD) 10 codes. Diagnose code E10 defines type 1 diabetes (T1D), and E11 defines type 2 diabetes (T2D). Absence of any of these codes defined a non-diabetic. Presence of only E10 defined a person with type 1 diabetes, while occurrence of both E10 and E11 defined type 2 diabetes. Only diagnoses established prior to date of OHCA were assessed.

Statistical Analysis

Statistical calculations were performed using R Statistical Software (v4.2.3; R Core Team 2023). Patient baseline characteristics are described using means and medians together with appropriate measurements of dispersion. Long-term survival comparing patients with and without T1D were made using unadjusted Kaplan-Meier estimates, followed by a log-rank test. Furthermore, adjusted logistic regression evaluated a binary outcome of 30 days survival. Adjusted models included following covariates, age, sex, initial rhythm, cause of arrest and time from arrest to CPR start. Descriptive models were used for demonstrating pre-arrest comorbidities between subpopulations.

The outcomes were discharge status (alive vs. dead), 30 days survival and neurological outcome at discharge, which was classified using cerebral performance category (CPC). The CPC score is a 5-point scale, where categories 1-2 are generally considered good neurological outcome and 3 or higher equals poor neurological outcome.

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Results

Baseline characteristics

Table 1. Baseline characteristics in 54,568 patients with out of hospital cardiac arrest stratified by pre-exististence of type 1 DM

	T1D	No T1D	p	test	SMD
n	448	54120			
Group - n (%)					<0.001
Sex Women	163 (36.4)	18427 (34.1)	0.335		0.048
Patient characteristics - mean (SD)					<0.001
Age	64.39 (17.24)	69.23 (17.51)	<0.001		0.278
Cause of cardiac arrest - n (%)			<0.001		0.300
Heart disease	228 (57.6)	30158 (62.7)			
Overdose or intoxication	6 (1.5)	1381 (2.9)			
Trauma or accident	12 (3.0)	1112 (2.3)			
Pulmonary disease	14 (3.5)	2704 (5.6)			
Suffocation	10 (2.5)	1266 (2.6)			
Suicide	5 (1.3)	1098 (2.3)			
Drowning	0 (0.0)	456 (0.9)			
Other	121 (30.6)	9889 (20.6)			
Socioeconomic status - n (%)					<0.001
Region of birth			0.370		0.162
Sweden	401 (89.7)	46123 (85.6)			
Denmark Finland Norway Iceland	16 (3.6)	2976 (5.5)			
EU	12 (2.7)	1598 (3.0)			
Europe not EU	8 (1.8)	1138 (2.1)			
North America	0 (0.0)	130 (0.2)			
Asia	6 (1.3)	1301 (2.4)			
Africa	2 (0.4)	362 (0.7)			
South America	2 (0.4)	166 (0.3)			
Other	0 (0.0)	75 (0.1)			
Disposable family income - median IQR	2574.50 [1502.75, 3968.25]	2469.00 [1515.00, 3748.00]	0.353	nonnorm	0.035
Work or profession- n (%)					0.226
Unemployed	274 (69.0)	37564 (77.2)			
Educational level- n (%)			0.382		0.138
Pre gymnasium 9 years	95 (23.8)	13755 (27.9)			
Pre gymnasium 9 years	53 (13.2)	6220 (12.6)			

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Gymnasium 3 years	124 (31.0)	13770 (27.9)			
Gymnasium 3 years	58 (14.5)	6110 (12.4)			
Post gymnasium 3 years	28 (7.0)	3811 (7.7)			
Post gymnasium 3 years or longer	28 (7.0)	4191 (8.5)			
Research education	2 (0.5)	322 (0.7)			
Unknown	12 (3.0)	1169 (2.4)			
Marital status- n(%)			0.005		0.213
Not married	121 (30.0)	11225 (22.3)			
Married	162 (40.2)	22946 (45.7)			
Surviving partner	0 (0.0)	3 (0.0)			
Registered partner	0 (0.0)	16 (0.0)			
Divorced	75 (18.6)	8407 (16.7)			
Divorced partner	0 (0.0)	11 (0.0)			
Widow widower	45 (11.2)	7632 (15.2)			
Previous conditions - n (%)					<0.001
Hypertension	274 (61.2)	24183 (44.7)	<0.001		0.335
Heart failure	101 (22.5)	12316 (22.8)	0.960		0.005
Chronic ischemic heart disease	104 (23.2)	11142 (20.6)	0.190		0.064
Atrial fibrillation	74 (16.5)	11124 (20.6)	0.041		0.104
Type 2 diabetes	0 (0.0)	10423 (19.3)	<0.001		0.691
Dyslipidemia	128 (28.6)	8432 (15.6)	<0.001		0.317
Angina, including unstable angina	81 (18.1)	8263 (15.3)	0.114		0.076
Alcohol dependency	76 (17.0)	7683 (14.2)	0.109		0.076
Acute myocardial infarction	64 (14.3)	7280 (13.5)	0.656		0.024
Affective disorders	62 (13.8)	5649 (10.4)	0.024		0.104
Renal failure	68 (15.2)	5366 (9.9)	<0.001		0.159
Thrombotic stroke	33 (7.4)	4739 (8.8)	0.340		0.051
Alzheimers dementia	27 (6.0)	4059 (7.5)	0.276		0.059
Aortic stenosis	25 (5.6)	3303 (6.1)	0.718		0.022
Medications prescribed - n (%)					<0.001
Anticoagulant or antiplatelet agent ATC B01	166 (37.1)	19636 (36.3)	0.773		0.016
Beta blockers	165 (36.8)	18153 (33.5)	0.156		0.069
ACE inhibitor or ARB	201 (44.9)	17690 (32.7)	<0.001		0.252
Diuretics	144 (32.1)	14607 (27.0)	0.017		0.113
Lipid lowering drugs	165 (36.8)	12801 (23.7)	<0.001		0.290
Drugs for acid related disorders	111 (24.8)	10822 (20.0)	0.014		0.115
Calcium channel blockers	110 (24.6)	8604 (15.9)	<0.001		0.217
Other cardiovascular drugs ATC C01	55 (12.3)	6421 (11.9)	0.845		0.013
Antihypertensive drugs ATC C02	11 (2.5)	610 (1.1)	0.016		0.100

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Time of cardiac arrest- n (%)			0.001		0.206
0 to 6 am	85 (22.9)	7387 (16.4)			
1 to 6 pm	119 (32.1)	13652 (30.3)			
7 to 11 pm	68 (18.3)	8630 (19.1)			
7 to 12 am	99 (26.7)	15443 (34.2)			
Location of cardiac arrest- n (%)			0.779		0.034
Home	324 (72.6)	38574 (71.6)			
Public place	67 (15.0)	8764 (16.3)			
Other places	55 (12.3)	6553 (12.2)			
Prehospital interventions - n (%)					<0.001
Bystander CPR	240 (55.6)	28645 (55.0)	0.844		0.012
Intubation performed	131 (29.6)	15035 (28.3)	0.563		0.030
Defibrillated, any	137 (31.3)	17356 (33.4)	0.382		0.045
Defibrillated, number of attempts - mean (SD)	3.43 (3.54)	3.48 (3.16)	0.859		0.015
Adrenaline administered	371 (83.6)	42146 (78.8)	0.018		0.121
Amiodarone administered	42 (9.5)	6193 (11.8)	0.173		0.072
Critical time intervals - median (IQR)					<0.001
Time from arrest to EMS dispatch	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	0.971	nonnorm	0.082
Time from arrest to CPR start	2.00 [0.00, 10.00]	3.00 [0.00, 10.00]	0.100	nonnorm	0.065
Time from arrest to defibrillation	17.00 [11.00, 29.00]	15.00 [8.00, 24.00]	0.005	nonnorm	0.203
Time from arrest to EMS arrival	13.00 [9.00, 19.00]	13.00 [8.00, 20.00]	0.900	nonnorm	0.057
Time from EMS dispatch to arrival	10.00 [7.00, 16.00]	10.00 [7.00, 16.00]	0.737	nonnorm	0.073
Time from arrest to ROSC	15.50 [10.00, 23.75]	15.00 [9.00, 23.00]	0.392	nonnorm	0.027
Initial presentation - n (%)					<0.001
Initial rhythm			0.357		0.073
VF pVT	83 (20.9)	11083 (23.2)			
PEA	64 (16.1)	8224 (17.2)			
Asystole	251 (63.1)	28439 (59.6)			
Consciousness on EMS arrival at scene	49 (11.1)	5588 (10.6)	0.803		0.015
Breathing on EMS arrival at scene			0.604		0.068
No breathing	339 (77.2)	40852 (77.7)			
Agonal breathing	42 (9.6)	5651 (10.7)			
Normal breathing	58 (13.2)	6053 (11.5)			
Unknown	0 (0.0)	22 (0.0)			
Pulse on EMS arrival at scene	64 (15.0)	7200 (14.0)	0.614		0.028
Spontaneous circulation on hospital arrival	112 (46.1)	13823 (44.9)	0.749		0.025
Consciousness on hospital arrival	23 (9.6)	3319 (11.0)	0.551		0.047

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Witnessed cardiac	259 (59.4)	34119 (65.0)	0.018		0.115

In total, 54,568 cases of OHCA were recorded. As shown in *Table 1*, patients with type 1 diabetes prior to OHCA accounted for 448 of the cases. Patients with T1D were approximately 5 years younger, with no differences in sex. Concerning causes of cardiac arrest, 57.6% of those with T1D had heart disease as the presumed cause vs. 62.7% among others. No major differences were found with respect to location of arrest, with most cases occurring at home (72.6% in T1D vs. 71.6% among others). Being born in Sweden was more common in people with T1D (89.7% vs. 85.6%). There were difference with regars to co-existing conditions prior to OHCA, such that people with T1D had significantly more hypertension (61.2% vs. 44.7%), dyslipidemia (28.6% vs. 15.6%) and renal failure (15.2% vs. 9.9%).

T1D patients were more frequently prescribed ACE inhibitors and ARB (44.9% vs. 32.7%), lipid lowering drugs (36.8% vs. 23.7%), calcium channel blockers (24.6% vs. 15.9%) and diuretics (32.1% vs. 27.0%).

Both groups received similar rates of bystander CPR (55.6% vs. 55.0%). Patients with T1D received epinephrine at higher rates (83.6% vs. 78.8%). Critical time intervals and initial rhythm, as presented in *Table 1*, showed no significant differences between the subgroups. Patients without T1D had higher degree of witnessed arrest (65.0% vs. 59.4%).

Table 2. Outcomes following OHCA

	T1D	No T1D	p	test	SMD
Outcomes - n (%)					<0.001
Discharged alive	38 (37.3)	5212 (46.0)	0.094		0.179
CPC score at discharge			0.319		0.483
CPC score 1 no sequele	26 (76.5)	3346 (75.8)			
CPC score 2 mild sequele	8 (23.5)	666 (15.1)			
CPC score 3 moderate sequele	0 (0.0)	287 (6.5)			
CPC score 4 severe sequele	0 (0.0)	104 (2.4)			
Survival at 30 days	46 (10.3)	5971 (11.0)	0.661		0.025

Outcomes are shown in *Table 2*. Patients with T1D that were discharged alive in 37.3% of cases, compared with 46% of patients without T1D. Patients with T1D had generally good neurological outcomes following OHCA, being either in category 1 (76,5%) or 2 (23,5%) in the vast majority of cases, which was also true for other cases. Survival at 30 days was noted for 10.3% of those with T1D compared with 11.0% of those without T1D (p value 0.661).

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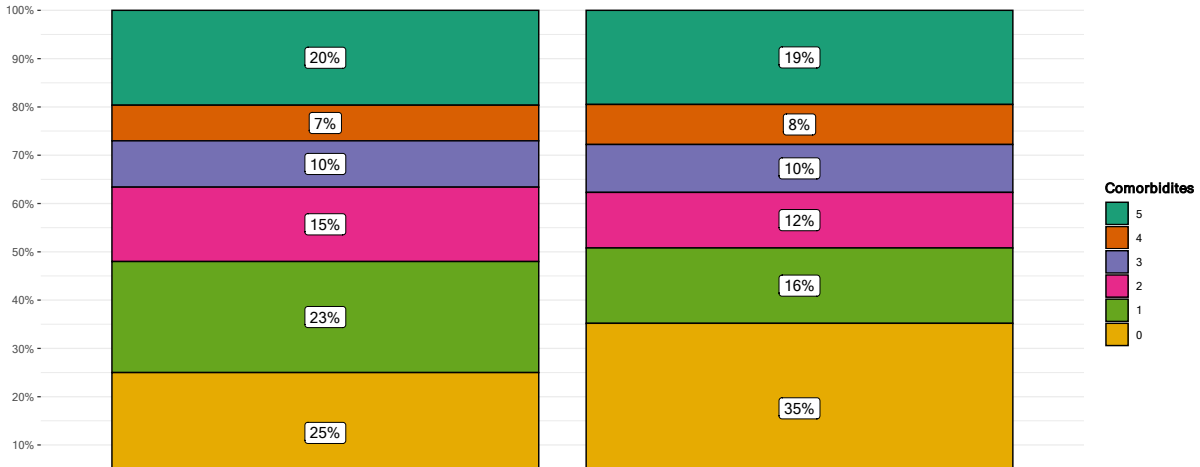
Figure 1 displays the proportion of patients with cardiovascular comorbidities; 75% of patients with T1D had at least 1 or more cardiovascular comorbidity, and at least 20% had 5 or more. Only 25% of cases with T1D were free from cardiovascular comorbidities, as compared with 35% of other cases.

Figure 1: Proportion of the number of cardiovascular comorbidities



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Survival analysis

Figure 3: Unadjusted Kaplan-Meier curve

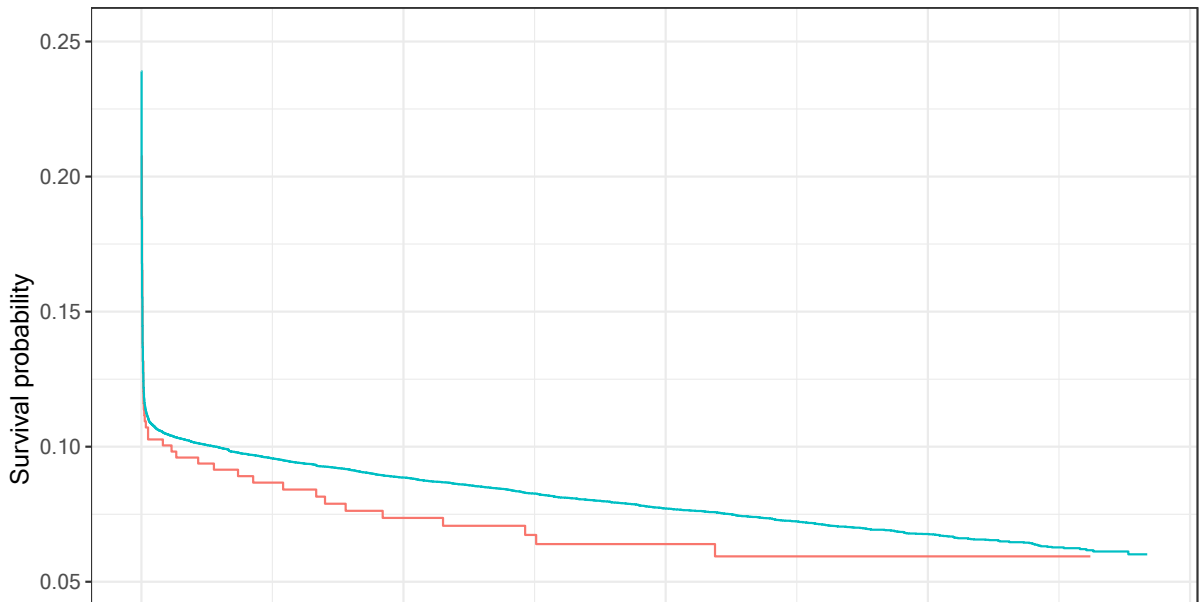

Figure 3 shows the unadjusted Kaplan-Meier curves for long-term survival. Individuals with diabetes had worse long-term survival, but the long-rank test yielded a p-value of 0,83.

Table 4: Adjusted logistic regression model

Characteristic	OR[1]	95% CI[1]	p-value
T1D			0.7
T1D	-	-	
No T1D	0.99	0.96-1.02	
Initial rhythm			<0.001
VF/pVT	-	-	
PEA	0.77	0.76-0.78	
Asystole	0.74	0.74-0.75	
Sex			0.007
Men	-	-	
Women	1.01	1.00-1.01	
Age	1.00	1.00-1.00	<0.001
Time from arrest to CPR start	1.00	1.00-1.00	<0.001

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Cause of cardiac arrest			<0.001
Heart disease	-	-	
Overdose or intoxication	0.99	0.97-1.01	
Trauma or accident	0.94	0.92-0.96	
Pulmonary disease	0.99	0.97-1.00	
Suffocation	1.00	0.98-1.01	
Suicide	0.93	0.91-0.95	
Drowning	1.01	0.98-1.04	
Other	0.97	0.97-0.98	
[1] OR = Odds Ratio, CI = Confidence Interval			

Adjusted logistic regression for 30-days survival seen in *Table 3*. Diabetes status showed no significant association with survival after accounting for age, rhythm, sex and cause of cardiac arrest. Patients with PEA and asystole had lower odds of survival compared to VF/pVT.

Discussion

This is the largest study exploring the characteristics and outcomes of people with T1D who experience an OHCA. A total of 448 cases of OHCA with T1D were studied. We show that people with T1D are 5 years younger when developing an OHCA, and they are less likely to survive to 30 days or be discharged alive. The poor outcome in T1D was evident from the crude survival rate, discharge rate and the Kaplan-Meier estimates. All these parameters pointed to the same direction, albeit with non-significant p-values.

As evident in Table 1, the prevalence of T2D was very high (19%) in the population with OHCA. In line with this, the prevalence of T1D in this study (0.8%) was higher than that in the general population (0.5%), although proportionally not as high as T2D which in this study displayed a 4-fold higher prevalence in OHCA as compared with the Swedish population (7). Thus, we do not see the excessive overrepresentation of T1D in the OHCA population. This should not be taken as evidence of a near-normal risk of OHCA in T1D for several reasons. The SCRR only includes cases in whom resuscitation was deemed reasonable by the emergency medical service (EMS), excluding all cases in whom resuscitation was deemed futile at the EMS arrival. Moreover, there may be significant competing risk that is not accounted for in this study.

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There are several other noteworthy findings. We expected T1D cases to have a higher burden of cardiac etiologies in OHCA. That was, however, not the case in this study. Cardiac etiologies were less common in T1D, as was a shockable initial rhythm. Instead, people with T1D were much more likely to experience an OHCA due to an unspecified (other) cause, compared with non-diabetics. Unfortunately, the SCRR does not detail that specific category further, but it is certainly possible that a number of those cases are dead in bed syndrome, hypoglycemic events, hyperglycemic crisis or other diabetes-related complications. The speculation that dead in bed syndrome may explain a larger proportion of OHCA cases in T1D is further corroborated by the fact that a much larger proportion of OHCAs occurred early in the morning hours in people with T1D compared with other cases (Table 1).

Moreover, we show that while individuals with T1D are 5 years younger at OHCA, they exhibit more comorbidities, as given by the fact that only 25% were free from cardiovascular conditions prior to OHCA, compared with 35% among the other individuals, which also included people with type 2 diabetes. Yet, there were no statistically significant associations between T1D and survival. We believe this is due to the sample size, which was relatively small for T1D. P-values are overly influenced by sample size, and it is reasonable to focus on the patterns in the data instead. The latter indicates rather clearly that T1D does confer worse outcomes in OHCA and worse characteristics.

While there are large studies exploring the association between T2D and OHCA outcomes, we are unaware of a study as large as the current for T1D (4)(8)(9)(10).

Moreover, this study had no exclusion criteria apart from patients with missing information on diabetes status. Previous reports have had different inclusion criteria for the study population. Some including only patients with cardiac arrest of presumed cardiac origin (9)(11)(12), whereas some included only patients that have survived to hospital admission. (13)(9). Thereby creating more homogenous groups which may enhance the comparability between the cohort groups. Making it, to some degree, easier to isolate the effect of diabetes on survival. Disregarding all pre-hospital mortality although may quarantine the effect of diabetes among survivors, also suggests predictors other than diabetes status have greater importance to pre-hospital survival.

In line with multiple prior studies, our study found initial rhythm significantly associated with both short- and long-term survival outcome. (2)(5)(14) Parry et al. reported worse outcomes in diabetes patients after OHCA but noted that the disparities were abolished by accounting for initial rhythm. Similarly, other studies, as ours, have reported lower rates of an initial shockable rhythm among diabetics and this is not explained by delays to EMS arrival (5).

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We conclude that people with T1D are 5 years younger on average, have more cardiovascular comorbidities, but with less cardiac etiologies in OHCA, and they are less likely to survive.

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Effects of pre-existing type 1 diabetes mellitus on survival outcome following out-of-hospital cardiac arrest: a registry-based observational study in Sweden.

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Abstract

Background: It has been estimated that 80% of cases of out-of-hospital cardiac arrest (OHCA) are due to cardiac causes. It is well documented that diabetes is a risk factor for conditions associated with sudden cardiac arrest including among others coronary artery disease. Type 1 diabetes (T1D) displays a 3- to 5-fold increased risk of cardiovascular disease (CVD) and death compared with the general population.

Objective: This study aims to assess characteristics and outcomes of individuals with and without T1D who experienced an OHCA.

Design: A registry-based nationwide observational study with two cohorts, patients with T1D and patients without T1D.

Setting: All emergency medical services and hospitals in Sweden were included in the study.

Participants: Using the Swedish Cardiopulmonary Resuscitation Registry we enrolled 54,568 cases of OHCA where cardiopulmonary resuscitation were attempted between 2010-2020. Among them, 448 patients with T1D were identified using ICD-code: E10.

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Methods: Survival analysis was performed using Kaplan-Meier and logistic regression. All multiple regressions were adjusted for age, sex, cause of arrest, prevalence of T1D and time to cardiopulmonary resuscitation.

Main outcome measures: The outcomes were discharge status (alive vs. dead), 30 days survival and neurological outcome at discharge.

Results: Patients with pre-existing diabetes accounted for 19,9% of the study population. Crude survival rate displayed poor outcome for T1D, albeit nonsignificant. Patients with T1D had generally good neurological outcomes following OHCA, being either in category 1 (76,5%) or 2 (23,5%). Multiple regression showed T1D status had no significant association with survival after accounting for covariates, OR 0.99 (95% CI 0.96-1.02) p-value = 0.7.

Conclusion: We conclude that T1D patients experience OHCA 5 years younger with more cardiovascular comorbidities but less by cardiac etiologies.

Strengths and limitations.

- A major strength of the current study is the size of the study population, with 448 patients having T1D.
- The study sample is representative of OHCA cases where resuscitation is attempted since >90% are recorded in the registry.
- The sample includes all regions in Sweden and the risk of selection bias is minimal.
- We did not have access to greater details regarding diabetes diagnosis, diagnoses were based on ICD codes with the risk of misclassification and coding errors.
- The Swedish Cardiopulmonary Resuscitation Registry does not include patients where resuscitation is deemed futile, a cohort that may contain patients with type 1 diabetes.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality worldwide (1). The European Registry of Cardiac Arrest (EuReCa) has OHCA as the third leading cause of death in Europe (2). It has been estimated that 80% of cases of OHCA are due to cardiac causes, primarily coronary artery disease in its various forms (3). OHCA in the younger population typically has a different etiology, with trauma, intoxications and suicide attempts being much more common than in older adults and elderly. Cardiovascular diseases, including cardiomyopathies, channelopathies, myocarditis and coronary artery anomalies occur but are not common on a population level (4).

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It is well documented that diabetes is a risk factor for virtually all conditions associated with sudden cardiac arrest (SCA), including coronary artery disease, myocardial infarction (MI) and heart failure (HF). Previous studies report a 2-4-fold increase in the risk of SCA in patients with diabetes (5). Type 1 diabetes (T1D) displays a 3- to 5-fold increased risk of cardiovascular disease (CVD) and death compared with the general population. Indeed, the risk for CVD and death in type 1 diabetes is doubled even with glycated hemoglobin (HbA1c) levels at or below target levels (6).

The aim of the study was to assess characteristics and outcomes of individuals with type 1 diabetes who experienced an out-of-hospital cardiac arrest, as compared with other patients experiencing an OHCA.

Methods

We conducted a nationwide observational study including all cases of OHCA recorded between 2010 and 2020 in the Swedish Cardiopulmonary Resuscitation Registry (SCRR), in total 54,586 patients were recorded. The registry was initiated in 1990 and includes >90% of all OHCA cases where resuscitation is attempted. Cases where resuscitation is evaluated to be futile are not included in the registry. In Sweden emergency medical services (EMS) is provided both by the responsible region (public) and by private companies. However, all ambulance organizations throughout the nation participate in the registry, the reporting is done prospectively and uses the Utstein-based template. The annual report is available at www.shlr.registercentrum.se.

We merged the SCRR with the Patient Registry, which includes both inpatient and outpatient reports throughout Sweden, with 100% level of ascertainment. It is run by the Swedish National Board of Health and Welfare with coverage since 1987. All diagnoses since year 2000 were assessed, allowing for a 10-year period to record diabetes and other diagnoses. In Sweden, individuals with type 1 diabetes undergo annual examinations, such that a 10 year period should allow for an adequate level of ascertainment with regards to diabetes status. Merging the SCRR with the Patient Registry is a seamless process due to the Swedish personal identification number, which is a unique 12-digit ID assigned to all citizens.

The Patient Registry utilizes International Classification of Diseases (ICD) 10 codes. Diagnose code E10 defines type 1 diabetes (T1D), and E11 defines type 2 diabetes (T2D). Absence of any of these codes defined a non-diabetic. Presence of only E10 defined a person with type 1 diabetes, while occurrence of only E11 or both E10 and E11 defined type 2 diabetes. Only diagnoses established prior to date of OHCA were assessed. Patients with missing data on diabetes status were excluded.

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Statistical Analysis

Statistical calculations were performed using R Statistical Software (v4.2.3; R Core Team 2023). Patient baseline characteristics are described using means and medians together with appropriate measurements of dispersion. Long-term survival comparing patients with and without T1D were made using unadjusted Kaplan-Meier estimates, followed by a log-rank test. Furthermore, adjusted logistic regression evaluated a binary outcome of 30 days survival. Adjusted models included following covariates, age, sex, initial rhythm, cause of arrest and time from arrest to CPR start. Descriptive models were used for demonstrating pre-arrest comorbidities between subpopulations.

The outcomes were discharge status (alive vs. dead), 30 days survival and neurological outcome at discharge, which was classified using cerebral performance category (CPC). The CPC score is a 5-point scale, where categories 1-2 are generally considered good neurological outcome and 3 or higher equals poor neurological outcome.

Patient and Public Involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Baseline characteristics

Table 1. Baseline characteristics in 54,568 patients with out of hospital cardiac arrest stratified by pre-exististence of type 1 diabetes

	Type 1 diabetes	No type 1 diabetes	p	SMD[1]
n	448	54120		
Group - n (%)				<0.001
Sex Women	163 (36.4)	18427 (34.1)	0.335	0.048
Patient characteristics - mean (SD)				<0.001
Age	64.39 (17.24)	69.23 (17.51)	<0.001	0.278
Cause of cardiac arrest - n (%)			<0.001	0.300
Heart disease	228 (57.6)	30158 (62.7)		
Overdose or intoxication	6 (1.5)	1381 (2.9)		
Trauma or accident	12 (3.0)	1112 (2.3)		
Pulmonary disease	14 (3.5)	2704 (5.6)		
Suffocation	10 (2.5)	1266 (2.6)		

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Suicide	5 (1.3)	1098 (2.3)		
Drowning	0 (0.0)	456 (0.9)		
Other	121 (30.6)	9889 (20.6)		
Time of cardiac arrest- n (%)			0.001	0.206
0 to 6 am	85 (22.9)	7387 (16.4)		
1 to 6 pm	119 (32.1)	13652 (30.3)		
7 to 11 pm	68 (18.3)	8630 (19.1)		
7 to 12 am	99 (26.7)	15443 (34.2)		
Location of cardiac arrest- n (%)			0.779	0.034
Home	324 (72.6)	38574 (71.6)		
Public place	67 (15.0)	8764 (16.3)		
Other places	55 (12.3)	6553 (12.2)		
Prehospital interventions - n (%)				<0.001
Bystander CPR[2]	240 (55.6)	28645 (55.0)	0.844	0.012
Intubation performed	131 (29.6)	15035 (28.3)	0.563	0.030
Defibrillated, any	137 (31.3)	17356 (33.4)	0.382	0.045
Defibrillated, number of attempts - mean (SD)	3.43 (3.54)	3.48 (3.16)	0.859	0.015
Adrenaline administered	371 (83.6)	42146 (78.8)	0.018	0.121
Amiodarone administered	42 (9.5)	6193 (11.8)	0.173	0.072
Critical time intervals - median (IQR)				<0.001
Time from arrest to EMS[3] dispatch	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	0.971	0.082
Time from arrest to CPR start	2.00 [0.00, 10.00]	3.00 [0.00, 10.00]	0.100	0.065
Time from arrest to defibrillation	17.00 [11.00, 29.00]	15.00 [8.00, 24.00]	0.005	0.203
Time from arrest to EMS arrival	13.00 [9.00, 19.00]	13.00 [8.00, 20.00]	0.900	0.057
Time from EMS dispatch to arrival	10.00 [7.00, 16.00]	10.00 [7.00, 16.00]	0.737	0.073
Time from arrest to ROSC[4]	15.50 [10.00, 23.75]	15.00 [9.00, 23.00]	0.392	0.027
Initial presentation - n (%)				<0.001
Initial rhythm			0.357	0.073
Ventricular fibrillation/Pulseless ventricular tachycardia	83 (20.9)	11083 (23.2)		
Pulseless electrical activity	64 (16.1)	8224 (17.2)		
Asystole	251 (63.1)	28439 (59.6)		
Consciousness on EMS arrival at scene	49 (11.1)	5588 (10.6)	0.803	0.015
Breathing on EMS arrival at scene			0.604	0.068
No breathing	339 (77.2)	40852 (77.7)		
Agonal breathing	42 (9.6)	5651 (10.7)		
Normal breathing	58 (13.2)	6053 (11.5)		
Unknown	0 (0.0)	22 (0.0)		
Pulse on EMS arrival at scene	64 (15.0)	7200 (14.0)	0.614	0.028
Spontaneous circulation on hospital arrival	112 (46.1)	13823 (44.9)	0.749	0.025

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Consciousness on hospital arrival	23 (9.6)	3319 (11.0)	0.551	0.047
Witnessed cardiac	259 (59.4)	34119 (65.0)	0.018	0.115

Abbreviations: [1]Standard mean difference,[2]Cardiopulmonary resuscitation, [3]Emergency medical services, [4]Return of spontaneous circulation

In total, 54,568 cases of OHCA were recorded. As shown in *Table 1*, patients with type 1 diabetes prior to OHCA accounted for 448 of the cases. Patients with T1D were approximately 5 years younger, with no differences in sex. Concerning causes of cardiac arrest, 57.6% of those with T1D had heart disease as the presumed cause vs. 62.7% among others. No major differences were found with respect to location of arrest, with most cases occurring at home (72.6% in T1D vs. 71.6% among others). Being born in Sweden was more common in people with T1D (89.7% vs. 85.6%). There were difference with regars to co-existing conditions prior to OHCA, such that people with T1D had significantly more hypertension (61.2% vs. 44.7%), dyslipidemia (28.6% vs. 15.6%) and renal failure (15.2% vs. 9.9%).

T1D patients were more frequently prescribed ACE inhibitors and ARB (44.9% vs. 32.7%), lipid lowering drugs (36.8% vs. 23.7%), calcium channel blockers (24.6% vs. 15.9%) and diuretics (32.1% vs. 27.0%).

Both groups received similar rates of bystander CPR (55.6% vs. 55.0%). Patients with T1D received epinephrine at higher rates (83.6% vs. 78.8%). Critical time intervals and initial rhythm, as presented in *Table 1*, showed no significant differences between the subgroups. Patients without T1D had higher degree of witnessed arrest (65.0% vs. 59.4%).

Table 2. Outcomes following out-of-hospital cardiac arrest

	T1D[1]	No T1D	p	SMD[2]
Outcomes – n (%)				<0.001
Discharged alive	38 (37.3)	5212 (46.0)	0.094	0.179
CPC[3] score at discharge			0.319	0.483
CPC score 1 no sequele	26 (76.5)	3346 (75.8)		
CPC score 2 mild sequele	8 (23.5)	666 (15.1)		
CPC score 3 moderate sequele	0 (0.0)	287 (6.5)		
CPC score 4 severe sequele	0 (0.0)	104 (2.4)		
Survival at 30 days	46 (10.3)	5971 (11.0)	0.661	0.025

Abbreviations: [1]Type 1 diabetes, [2]Standard mean difference, [3]Cerebral performance category

Outcomes are shown in *Table 2*. Patients with T1D that were discharged alive in 37.3% of cases, compared with 46% of patients without T1D. Patients with T1D had generally good neurological outcomes following OHCA, being either in category 1 (76,5%) or 2 (23,5%) in the vast majority of

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cases, which was also true for other cases. Survival at 30 days was noted for 10.3% of those with T1D compared with 11.0% of those without T1D (p value 0.661).

Figure 1 displays the proportion of patients with cardiovascular comorbidities; 75% of patients with T1D had at least 1 or more cardiovascular comorbidity, and at least 20% had 5 or more. Only 25% of cases with T1D were free from cardiovascular comorbidities, as compared with 35% of other cases.

Figure 1: Proportion of the number of cardiovascular comorbidities

Survival analysis

Figure 2: Unadjusted Kaplan-Meier curve

Figure 2 shows the unadjusted Kaplan-Meier curves for long-term survival. Individuals with diabetes had worse long-term survival, but the long-rank test yielded a p-value of 0,83.

Table 3: Adjusted logistic regression for 30-day survival

Characteristic	OR[1]	95% CI[1]	p-value
T1D[2]			0.7
T1D	-	-	
No T1D	0.99	0.96-1.02	
Initial rhythm			<0.001
VF/pVT[3]	-	-	
PEA[4]	0.77	0.76-0.78	
Asystole	0.74	0.74-0.75	
Sex			0.007
Men	-	-	
Women	1.01	1.00-1.01	
Age	1.00	1.00-1.00	<0.001
Time from arrest to CPR[5] start	1.00	1.00-1.00	<0.001
Cause of cardiac arrest			<0.001
Heart disease	-	-	
Overdose or intoxication	0.99	0.97-1.01	
Trauma or accident	0.94	0.92-0.96	
Pulmonary disease	0.99	0.97-1.00	
Suffocation	1.00	0.98-1.01	
Suicide	0.93	0.91-0.95	
Drowning	1.01	0.98-1.04	
Other	0.97	0.97-0.98	

Abbreviations: [1] OR = Odds Ratio, CI = Confidence Interval, [2]Type 1 diabetes, [3]Ventricular fibrillation/Pulseless ventricular tachycardia, [4]Pulseless electrical activity, [5]Cardiopulmonary resuscitation

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Adjusted logistic regression for 30-days survival seen in *Table 3*. Diabetes status showed no significant association with survival after accounting for age, rhythm, sex and cause of cardiac arrest. Patients with PEA and asystole had lower odds of survival compared to VF/pVT.

Discussion

This is the largest study exploring the characteristics and outcomes of people with T1D who experience an OHCA. A total of 448 cases of OHCA with T1D were studied. We show that people with T1D are 5 years younger when developing an OHCA.

As evident in Table 1, the prevalence of T2D was very high (19%) in the population with OHCA. This high prevalence could partly be a consequence of misclassification as 3380 patients were registered with both E10 (type 1 diabetes) and E11 (type 2 diabetes), which were excluded from the T1D group. Inherently with register studies and administrative data, coding errors and misclassification is a limitation to consider. Furthermore SCRR does not have details regarding the diabetes diagnosis, we did not have acces to C-peptid, islet antibodies etc.With this is in mind, the prevalence of T1D in this study (0.8%) was higher than that in the general population (0.5%), although proportionally not as high as T2D which in this study displayed a 4-fold higher prevalence in OHCA as compared with the Swedish population (7). Thus, we do not see the excessive overrepresentation of T1D in the OHCA population. This should not be taken as evidence of a near-normal risk of OHCA in T1D. The SCRR only includes cases in whom resuscitation was deemed reasonable by the emergency medical service (EMS), excluding all cases in whom resuscitation was deemed futile at the EMS arrival.

There are several other noteworthy findings. We expected T1D cases to have a higher burden of cardiac etiologies in OHCA. That was, however, not the case in this study. Cardiac etiologies were less common in T1D, as was a shockable initial rhythm. The low rates of cardiovascular complications could partly be explained by the, over the years, more integrated and advanced patient care in Sweden improving the overall glucose control. The SCRR, however, does not provide us with further data on glycemic control. Notably though, T1D were much more likely to experience an OHCA due to an unspecified (other) cause, compared with non-diabetics. Unfortunately, the SCRR does not detail that specific category further, but it is certainly possible that a number of those cases are dead in bed syndrome, hypoglycemic events, hyperglycemic crisis or other diabetes-related complications. The

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speculation that dead in bed syndrome may explain a larger proportion of OHCA cases in T1D is further corroborated by the fact that a much larger proportion of OHCAs occurred early in the morning hours in people with T1D compared with other cases (Table 1).

Moreover, we show that while individuals with T1D are 5 years younger at OHCA, they exhibit more comorbidities, as given by the fact that only 25% were free from cardiovascular conditions prior to OHCA, compared with 35% among the other individuals, which also included people with type 2 diabetes.(Figure 1) Yet, there were no statistically significant associations between T1D and survival. We believe this is due to the sample size, which was relatively small for T1D. Although T1D exhibit worse characteristics, p-values are overly influenced by sample size and similarly, does not favor the survival analysis in this study. (Figure 2)(Table 3)
Additionally, T2D have been previously documented to negatively impact OHCA survival and its high prevalence among "No T1D" should be taken into consideration when interpreting the disparities. While there are large studies exploring the association between T2D and OHCA outcomes, we are unaware of a study as large as the current for T1D (4)(8)(9)(10).

Moreover, this study had no exclusion criteria apart from patients with missing information on diabetes status. Previous reports have had different inclusion criteria for the study population. Some including only patients with cardiac arrest of presumed cardiac origin (9)(11)(12), whereas some included only patients that have survived to hospital admission. (13)(9). Thereby creating more homogenous groups which may enhance the comparability between the cohort groups. Making it, to some degree, easier to isolate the effect of diabetes on survival. Disregarding all pre-hospital mortality although may quarantine the effect of diabetes among survivors, also suggests predictors other than diabetes status have greater importance to pre-hospital survival. Concurrently, pre-hospital mortality not accounted by the SCRR, may very well include patients suffering OHCA due to complications of diabetes.

Parry et al. reported worse outcomes in diabetes patients after OHCA but noted that the disparities were abolished by accounting for initial rhythm. In line with multiple prior studies, our study found initial rhythm significantly associated with both short- and long-term survival outcome. (Table 3)(2)(5)(14) Similarly other studies, as ours, have reported lower rates of an initial shockable rhythm among diabetics and this is not explained by delays to EMS arrival (5).

We conclude that people with T1D are 5 years younger on average, have more cardiovascular comorbidities, but with less cardiac etiologies and shockable rhythm in OHCA. Although predictors such as initial rhythm surpass that of T1D with regards to survival, it is important to further the

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knowledge of the effect it has. The risk of OHCA should not be taken as normal for this subgroup and understanding the predisposing factors may help to develop interventions for improving prevention and survival.

Ethical approval statement

Data used in the study had already been collected and approved by the Ethical Review Authority,in Sweden, registration number 2020-02017.

Data availability statement

The data supporting the findings of this study are available within the article and its supplementary material.

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Conflict of interest statement

None.

Contributors

BE and AR planned and designed the study. Acquisition of data were made by AR, AiR and AL, statistical analysis and interpretation of data were made by BE, AR, AiR, SN with input from ZM, ET, TR, OA, CD and PP. BE and AR drafted the manuscript and all authors provided critical comments and changes on drafts and read and approved the final manuscript.

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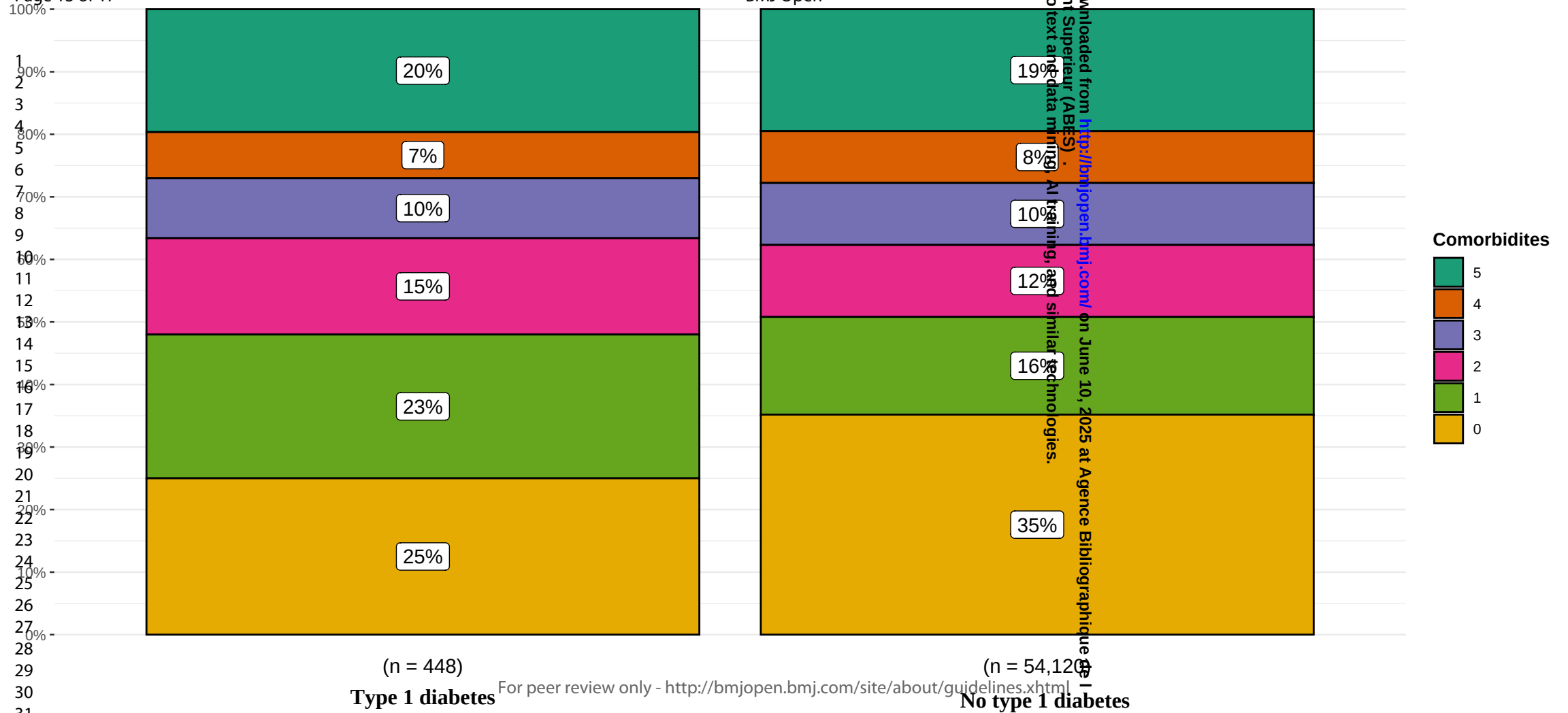

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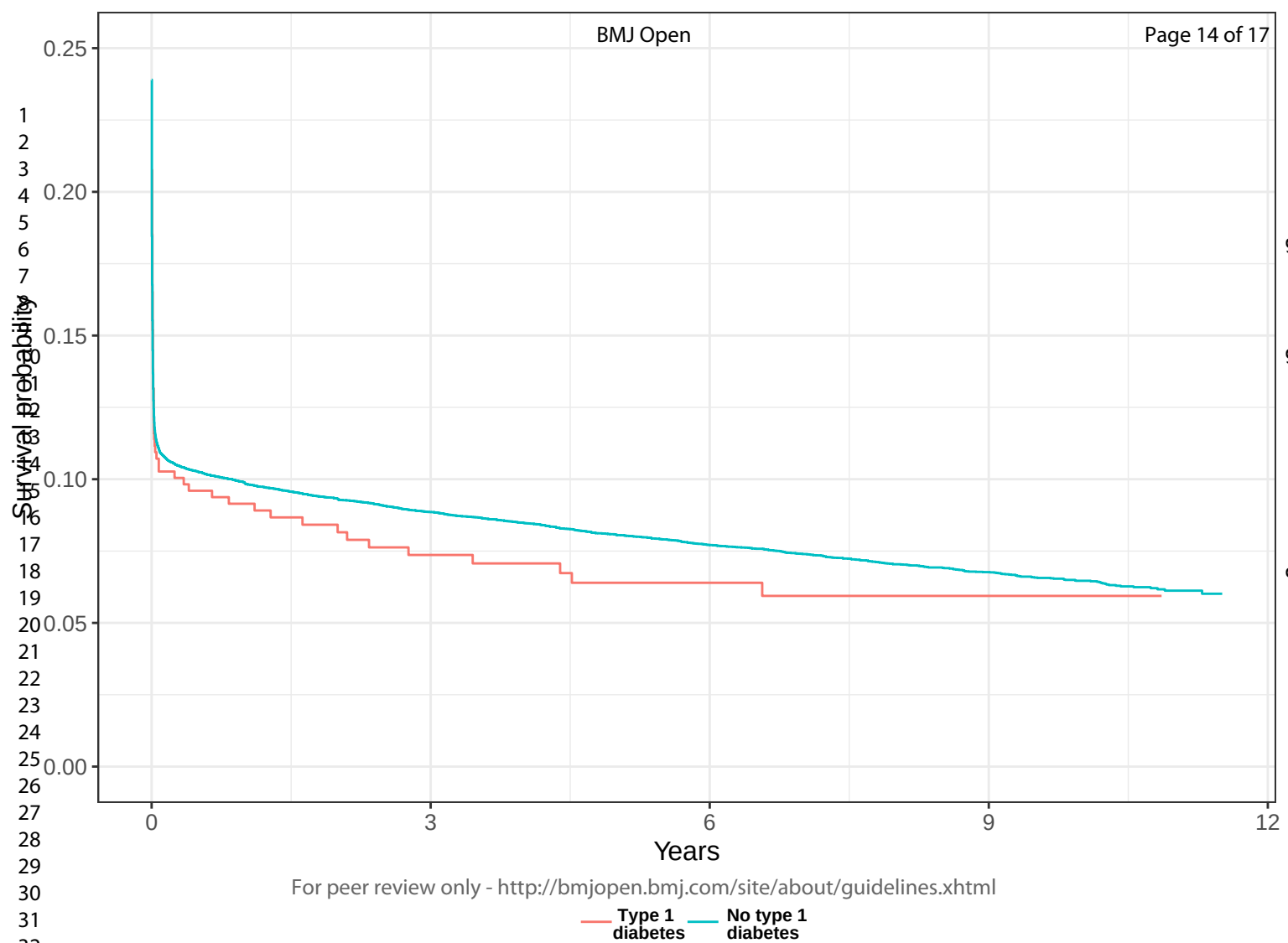

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Supplementary table 1. Baseline characteristics in 54,568 patients with out of hospital cardiac arrest stratified by pre-exististence of type 1 diabetes				
	Type 1 diabetes	**No type 1 diabetes**	**p**	**SMD[1]**
Socioeconomic status - n (%)				<0.001
Region of birth			0.370	0.162
Sweden	401 (89.7)	46123 (85.6)		
Denmark Finland Norway Iceland	16 (3.6)	2976 (5.5)		
EU	12 (2.7)	1598 (3.0)		
Europe not EU	8 (1.8)	1138 (2.1)		
North America	0 (0.0)	130 (0.2)		
Asia	6 (1.3)	1301 (2.4)		
Africa	2 (0.4)	362 (0.7)		
South America	2 (0.4)	166 (0.3)		
Other	0 (0.0)	75 (0.1)		
Disposable family income - median IQR[2]	2574.50 [1502.75, 3968.25]	2469.00 [1515.00, 3748.00]	0.353	0.035
Work or profession- n (%)				0.226
Unemployed	274 (69.0)	37564 (77.2)		
Educational level- n (%)			0.382	0.138
Pre gymnasium 9 years	95 (23.8)	13755 (27.9)		
Pre gymnasium 9 years	53 (13.2)	6220 (12.6)		
Gymnasium 3 years	124 (31.0)	13770 (27.9)		
Gymnasium 3 years	58 (14.5)	6110 (12.4)		
Post gymnasium 3 years	28 (7.0)	3811 (7.7)		
Post gymnasium 3 years or longer	28 (7.0)	4191 (8.5)		
Research education	2 (0.5)	322 (0.7)		
Unknown	12 (3.0)	1169 (2.4)		
Marital status- n(%)			0.005	0.213
Not married	121 (30.0)	11225 (22.3)		
Married	162 (40.2)	22946 (45.7)		
Surviving partner	0 (0.0)	3 (0.0)		
Registered partner	0 (0.0)	16 (0.0)		
Divorced	75 (18.6)	8407 (16.7)		
Divorced partner	0 (0.0)	11 (0.0)		
Widow widower	45 (11.2)	7632 (15.2)		
Previous conditions - n (%)				<0.001
Hypertension	274 (61.2)	24183 (44.7)	<0.001	0.335
Heart failure	101 (22.5)	12316 (22.8)	0.960	0.005
Chronic ischemic heart disease	104 (23.2)	11142 (20.6)	0.190	0.064
Atrial fibrillation	74 (16.5)	11124 (20.6)	0.041	0.104
Type 2 diabetes	0 (0.0)	10423 (19.3)	<0.001	0.691
Dyslipidemia	128 (28.6)	8432 (15.6)	<0.001	0.317

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Angina, including unstable angina	81 (18.1)	8263 (15.3)	0.114	0.076
Alcohol dependency	76 (17.0)	7683 (14.2)	0.109	0.076
Acute myocardial infarction	64 (14.3)	7280 (13.5)	0.656	0.024
Affective disorders	62 (13.8)	5649 (10.4)	0.024	0.104
Renal failure	68 (15.2)	5366 (9.9)	<0.001	0.159
Thrombotic stroke	33 (7.4)	4739 (8.8)	0.340	0.051
Alzheimers dementia	27 (6.0)	4059 (7.5)	0.276	0.059
Aortic stenosis	25 (5.6)	3303 (6.1)	0.718	0.022
Medications prescribed - n (%)				<0.001
Anticoagulant or antiplatelet agent ATC[3] B01	166 (37.1)	19636 (36.3)	0.773	0.016
Beta blockers	165 (36.8)	18153 (33.5)	0.156	0.069
ACE inhibitor or ARB	201 (44.9)	17690 (32.7)	<0.001	0.252
Diuretics	144 (32.1)	14607 (27.0)	0.017	0.113
Lipid lowering drugs	165 (36.8)	12801 (23.7)	<0.001	0.290
Drugs for acid related disorders	111 (24.8)	10822 (20.0)	0.014	0.115
Calcium channel blockers	110 (24.6)	8604 (15.9)	<0.001	0.217
Other cardiovascular drugs ATC C01	55 (12.3)	6421 (11.9)	0.845	0.013
Antihypertensive drugs ATC C02	11 (2.5)	610 (1.1)	0.016	0.100

Abbreviations: [1]Standard mean difference, [2]Interquartile range, [3]Anatomical Therapeutic Chemical Classification System

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1-2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*3-4*
Bias	9	Describe any efforts to address potential sources of bias	3-4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		© Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-6/supplementary table
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	6-7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		© If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Effects of pre-existing type 1 diabetes mellitus on survival outcome following out-of-hospital cardiac arrest: a registry-based observational study in Sweden.

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Effects of pre-existing type 1 diabetes mellitus on survival outcome following out-of-hospital cardiac arrest: a registry-based observational study in Sweden.

Berkan Eken[1], Araz Rawshani, Aidin Rawshani, Zacharias Mandalenakis, Erik Thunström, Antros Louca, Petur Petursson, Oskar Angerås, Sadek Nadhir, Christian Dworeck, Truls Råmunddal

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Abstract

Background: It has been estimated that 80% of cases of out-of-hospital cardiac arrest (OHCA) are due to cardiac causes. It is well documented that diabetes is a risk factor for conditions associated with sudden cardiac arrest including among others coronary artery disease. Type 1 diabetes (T1D) displays a 3- to 5-fold increased risk of cardiovascular disease (CVD) and death compared with the general population.

Objective: This study aims to assess characteristics and survival outcomes of individuals with and without T1D who experienced an OHCA.

Design: A registry-based nationwide observational study with two cohorts, patients with T1D and patients without T1D.

Setting: All emergency medical services and hospitals in Sweden were included in the study.

Participants: Using the Swedish Cardiopulmonary Resuscitation Registry, we enrolled 54,568 cases of OHCA where cardiopulmonary resuscitation were attempted between 2010-2020. Among them, 448 patients with T1D were identified using ICD-code: E10.

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Methods: Survival analysis was performed using Kaplan-Meier and logistic regression. Multiple regression were adjusted for age, sex, cause of arrest, prevalence of T1D and time to cardiopulmonary resuscitation.

Main outcome measures: The outcomes were discharge status (alive vs. dead), 30 days survival and neurological outcome at discharge.

Results: No significant differences in patients discharged alive with T1D 37,3% vs, 46% among others. No difference in neurological outcome. Kaplan-Meier curves yielded no significant difference in long-term survival. Multiple regression showed no significant association with survival after accounting for covariates, OR 0.99 (95% CI 0.96-1.02) p-value = 0.7. Baseline characteristics indicate T1D patients to be 5 years younger at OHCA ocurrence. T1D had proportionally fewer cases of heart disease as cause of arrest (57.6% vs. 62.7%) however with more cardiovascular comorbidities.

Conclusion: We conclude, with current sample size, that there is no statistically significant difference in long or short-term survival between patients with and without T1D.

Strengths and limitations.

- The study sample is representative of OHCA cases where resuscitation is attempted since >90% are recorded in the registry.
- The sample includes all regions in Sweden and the risk of selection bias is minimal.
- The sample size is relatively small, with 448 T1D patients.
- We did not have access to greater details regarding diabetes diagnosis, diagnoses were based on ICD codes with the risk of misclassification and coding errors.
- The Swedish Cardiopulmonary Resuscitation Registry does not include patients where resuscitation is deemed futile, a cohort that may contain patients with type 1 diabetes.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality worldwide (1). The European Registry of Cardiac Arrest (EuReCa) has OHCA as the third leading cause of death in Europe (2). It has been estimated that 80% of cases of OHCA are due to cardiac causes, primarily coronary artery disease in its various forms (3). OHCA in the younger population typically has a different etiology, with trauma, intoxications and suicide attempts being much more common than in older adults and elderly. Cardiovascular diseases, including cardiomyopathies, channelopathies, myocarditis and coronary artery anomalies occur but are not common on a population level (4).

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It is well documented that diabetes is a risk factor for virtually all conditions associated with sudden cardiac arrest (SCA), including coronary artery disease, myocardial infarction (MI) and heart failure (HF). Previous studies report a 2-4-fold increase in the risk of SCA in patients with diabetes (5). Type 1 diabetes (T1D) displays a 3- to 5-fold increased risk of cardiovascular disease (CVD) and death compared with the general population. Indeed, the risk for CVD and death in type 1 diabetes is doubled even with glycated hemoglobin (HbA1c) levels at or below target levels (6).

While there are large studies exploring the association between T2D and OHCA outcomes, we are unaware of a study as large as the current for T1D. Often conjoined in similar studies, T2D and T1D are, however, significantly different. T1D is generally characterized with insulin deficiency emanating from immune-associated destruction of insulin-producing pancreatic beta cells. (7) While T2D is a progressive metabolic disease developing insulin resistance with an eventual failure of pancreatic beta cells. (8) Although the outcome for both is characterized with hyperglycemia, the respective type may often be burdened with different comorbidities requiring different sets of treatment.

The aim of the study was to assess characteristics and outcomes of individuals with type 1 diabetes who experienced an out-of-hospital cardiac arrest, as compared with other patients experiencing an OHCA.

Methods

We conducted a nationwide observational study including all cases of OHCA recorded between 2010 and 2020 in the Swedish Cardiopulmonary Resuscitation Registry (SCRR), in total 54,586 patients were recorded. The registry was initiated in 1990 and includes >90% of all OHCA cases where resuscitation is attempted. Cases where resuscitation is evaluated to be futile are not included in the registry. In Sweden emergency medical services (EMS) is provided both by the responsible province (public) and by private companies. However, all ambulance organizations throughout the nation participate in the registry. Reporting is done prospectively and uses the Utstein-based template. The annual report is available at www.shlr.registercentrum.se.

We merged the SCRR with the Patient Registry, which includes both inpatient and outpatient reports throughout Sweden, with 100% level of ascertainment. It is run by the Swedish National Board of Health and Welfare with coverage since 1987. All diagnoses since year 2000 were assessed, allowing for a 10-year period to record diabetes and other diagnoses. In Sweden, individuals with type 1 diabetes undergo annual examinations, such that a 10-year period should allow for an adequate level of ascertainment with regards to diabetes status. Merging the SCRR with the Patient Registry is a

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seamless process due to the Swedish personal identification number, which is a unique 12-digit ID assigned to all citizens.

The Patient Registry utilizes International Classification of Diseases (ICD) 10 codes. Diagnose code E10 defines type 1 diabetes (T1D), and E11 defines type 2 diabetes (T2D). Absence of any of these codes defined a non-diabetic. Presence of only E10 defined a person with type 1 diabetes, while occurrence of only E11 or both E10 and E11 defined type 2 diabetes. Only diagnoses established prior to date of OHCA were assessed.

Statistical Analysis

Statistical calculations were performed using R Statistical Software (v4.2.3; R Core Team 2023). Patient baseline characteristics are described using means and medians together with appropriate measurements of dispersion. Long-term survival comparing patients with and without T1D were made using unadjusted Kaplan-Meier estimates, followed by a log-rank test. Furthermore, adjusted logistic regression evaluated a binary outcome of 30 days survival. Adjusted models included following covariates: age, sex, initial rhythm, cause of arrest and time from arrest to CPR start. Descriptive models were used for demonstrating pre-arrest comorbidities between subpopulations.

The outcomes were discharge status (alive vs. dead), 30 days survival and neurological outcome at discharge, which was classified using cerebral performance category (CPC). The CPC score is a 5-point scale, where categories 1-2 are generally considered good neurological outcome and 3 or higher equals poor neurological outcome.

Patient and Public Involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Baseline characteristics

Table 1
Baseline characteristics in 54,568 patients with out-of-hospital cardiac arrest stratified by pre-exististence of type 1 diabetes.

	Type 1 diabetes	No type 1 diabetes	p

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n	448	54120	
Group - n (%)			
Sex Women	163 (36.4)	18427 (34.1)	0.335
Patient characteristics - mean (SD)			
Age	64.39 (17.24)	69.23 (17.51)	<0.001
Cause of cardiac arrest - n (%)			<0.001
Heart disease	228 (57.6)	30158 (62.7)	
Overdose or intoxication	6 (1.5)	1381 (2.9)	
Trauma or accident	12 (3.0)	1112 (2.3)	
Pulmonary disease	14 (3.5)	2704 (5.6)	
Suffocation	10 (2.5)	1266 (2.6)	
Suicide	5 (1.3)	1098 (2.3)	
Drowning	0 (0.0)	456 (0.9)	
Other	121 (30.6)	9889 (20.6)	
Time of cardiac arrest- n (%)			0.001
0 to 6 am	85 (22.9)	7387 (16.4)	
1 to 6 pm	119 (32.1)	13652 (30.3)	
7 to 11 pm	68 (18.3)	8630 (19.1)	
7 to 12 am	99 (26.7)	15443 (34.2)	
Location of cardiac arrest- n (%)			0.779
Home	324 (72.6)	38574 (71.6)	
Public place	67 (15.0)	8764 (16.3)	
Other places	55 (12.3)	6553 (12.2)	
Prehospital interventions - n (%)			
Bystander CPR[1]	240 (55.6)	28645 (55.0)	0.844
Intubation performed	131 (29.6)	15035 (28.3)	0.563
Defibrillated, any	137 (31.3)	17356 (33.4)	0.382
Defibrillated, number of attempts - mean (SD)	3.43 (3.54)	3.48 (3.16)	0.859
Adrenaline administered	371 (83.6)	42146 (78.8)	0.018
Amiodarone administered	42 (9.5)	6193 (11.8)	0.173
Critical time intervals - median (IQR)			
Time from arrest to EMS[2] dispatch	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	0.971
Time from arrest to CPR start	2.00 [0.00, 10.00]	3.00 [0.00, 10.00]	0.100
Time from arrest to defibrillation	17.00 [11.00, 29.00]	15.00 [8.00, 24.00]	0.005
Time from arrest to EMS arrival	13.00 [9.00, 19.00]	13.00 [8.00, 20.00]	0.900
Time from EMS dispatch to arrival	10.00 [7.00, 16.00]	10.00 [7.00, 16.00]	0.737
Time from arrest to ROSC[3]	15.50 [10.00, 23.75]	15.00 [9.00, 23.00]	0.392
Initial presentation - n (%)			
Initial rhythm			0.357
Ventricular fibrillation/Pulseless ventricular tachycardia	83 (20.9)	11083 (23.2)	

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Pulseless electrical activity	64 (16.1)	8224 (17.2)	
Asystole	251 (63.1)	28439 (59.6)	
Consciousness on EMS arrival at scene	49 (11.1)	5588 (10.6)	0.803
Breathing on EMS arrival at scene			0.604
No breathing	339 (77.2)	40852 (77.7)	
Agonal breathing	42 (9.6)	5651 (10.7)	
Normal breathing	58 (13.2)	6053 (11.5)	
Unknown	0 (0.0)	22 (0.0)	
Pulse on EMS arrival at scene	64 (15.0)	7200 (14.0)	0.614
Spontaneous circulation on hospital arrival	112 (46.1)	13823 (44.9)	0.749
Consciousness on hospital arrival	23 (9.6)	3319 (11.0)	0.551
Witnessed cardiac	259 (59.4)	34119 (65.0)	0.018

Abbreviations: [1]Cardiopulmonary resuscitation, [2]Emergency medical services, [3]Return of spontaneous circulation

In total, 54,568 cases of OHCA were recorded. As shown in *Table 1*, patients with type 1 diabetes prior to OHCA accounted for 448 of the cases. Patients with T1D were approximately 5 years younger, with no differences in sex. Concerning causes of arrest, 57.6% of those with T1D had heart disease as the presumed cause vs. 62.7% among others. No major differences were found with respect to location of arrest, with most cases occurring at home (72.6% in T1D vs. 71.6% among others). Being born in Sweden was more common in people with T1D (89.7% vs. 85.6%). There were differences with regards to co-existing conditions prior to OHCA, such that people with T1D had significantly more hypertension (61.2% vs. 44.7%), dyslipidemia (28.6% vs. 15.6%) and renal failure (15.2% vs. 9.9%).

T1D patients were more frequently prescribed ACE inhibitors and ARB (44.9% vs. 32.7%), lipid lowering drugs (36.8% vs. 23.7%), calcium channel blockers (24.6% vs. 15.9%) and diuretics (32.1% vs. 27.0%).(Supplementary table 1)

Both groups received similar rates of bystander CPR (55.6% vs. 55.0%). Patients with T1D received epinephrine at higher rates (83.6% vs. 78.8%). Critical time intervals and initial rhythm, as presented in *Table 1*, showed no significant differences between the subgroups. Patients without T1D had higher degree of witnessed arrest (65.0% vs. 59.4%).

Table 2
Outcomes following out-of-hospital cardiac arrest.

	T1D[1]	No T1D	p
Outcomes – n (%)			
Discharged alive	38 (37.3)	5212 (46.0)	0.094
CPC[2] score at discharge			0.319

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CPC score 1 no sequele	26 (76.5)	3346 (75.8)	
CPC score 2 mild sequele	8 (23.5)	666 (15.1)	
CPC score 3 moderate sequele	0 (0.0)	287 (6.5)	
CPC score 4 severe sequele	0 (0.0)	104 (2.4)	
Survival at 30 days	46 (10.3)	5971 (11.0)	0.661
Abbreviations: [1]Type 1 diabetes, [2]Cerebral performance category			

Outcomes are shown in *Table 2*. Patients with T1D that were discharged alive in 37.3% of cases, compared with 46% of patients without T1D. Patients with T1D had generally good neurological outcomes following OHCA, being either in category 1 (76,5%) or category 2 (23,5%), This was also true for patients without T1D. Survival at 30 days was noted for 10.3% of those with T1D compared with 11.0% of those without T1D.

Figure 1 displays the proportion of patients with cardiovascular comorbidities; 75% of patients with T1D had at least 1 or more cardiovascular comorbidity, and at least 20% had 5 or more. Only 25% of cases with T1D were free from cardiovascular comorbidities, as compared with 35% of other cases.

Figure 1: Proportion of the number of cardiovascular comorbidities

Survival analysis

Figure 2: Unadjusted Kaplan-Meier curve

Figure 2 shows the unadjusted Kaplan-Meier curves for long-term survival. Individuals with T1D showed no significant difference in long-term survival outcome. Log-rank test yielded a p-value of 0,83.

Table 3: Adjusted logistic regression for 30-day survival

Characteristic	OR[1]	95% CI[1]	p-value
T1D[2]			0.7
T1D	-	-	
No T1D	0.99	0.96-1.02	
Initial rhythm			<0.001
VF/pVT[3]	-	-	
PEA[4]	0.77	0.76-0.78	
Asystole	0.74	0.74-0.75	
Sex			0.007
Men	-	-	
Women	1.01	1.00-1.01	
Age	1.00	1.00-1.00	<0.001

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Time from arrest to CPR[5] start	1.00	1.00-1.00	<0.001
Cause of cardiac arrest			<0.001
Heart disease	-	-	
Overdose or intoxication	0.99	0.97-1.01	
Trauma or accident	0.94	0.92-0.96	
Pulmonary disease	0.99	0.97-1.00	
Suffocation	1.00	0.98-1.01	
Suicide	0.93	0.91-0.95	
Drowning	1.01	0.98-1.04	
Other	0.97	0.97-0.98	

Abbreviations: [1] OR = Odds Ratio, CI = Confidence Interval, [2]Type 1 diabetes, [3]Ventricular fibrillation/Pulseless ventricular tachycardia, [4]Pulseless electrical activity, [5]Cardiopulmonary resuscitation

Adjusted logistic regression for 30-days survival seen in *Table 3*. T1D status showed no significant association with survival after accounting for age, initial rhythm, sex and cause of cardiac arrest. Patients with PEA and asystole had lower odds of survival compared to VF/pVT.

Discussion

A total of 448 cases of OHCA with coexisting T1D were studied. There was no statistically significant difference in long or short-term survival between patients with and without T1D. We show that people with T1D are 5 years younger when developing an OHCA. The cause of arrest was comparatively less by heart disease in the T1D group. (Table 1) No significant difference could be seen in the proportion of discharged alive with T1D having 37,3% vs, 46% among other cases. Both cohort groups exhibited good neurological outcome, the majority being in either CPC category 1 or 2. (Table 2).

As evident in Table 1, the prevalence of T1D in this study (0.8%) was higher than that in the general population (0.5%). Although proportionally not as high as T2D, which in this study (19%) displayed a 4-fold higher prevalence in OHCA as compared with the Swedish population (9). Thus, we do not see the excessive overrepresentation of T1D in the OHCA population. This should not be taken as evidence of a near-normal risk of OHCA in T1D. Previous study reports the risk of death among T1D from any cause and from cardiovascular complications, to be twice that of the general population. Even with glycemic control on target. (10)

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In line with previous studies we expected T1D cases to have a higher burden of cardiac etiologies in OHCA. That was, however, not the case in this study. Cardiac etiologies were less common in T1D. The lower rates of cardiovascular complications likely reflect the advancements on integrated patients care with chronic diseases, improvements in patient education in addition to management and early treatment of cardiovascular risk factors. (11) Notably though, T1D were much more likely to experience an OHCA due to an unspecified (other) cause, compared with non-diabetics. Unfortunately, the SCRR does not detail that specific category further, but it is certainly possible that a number of those cases are dead in bed syndrome, hypoglycemic events, hyperglycemic crisis or other diabetes-related complications. The speculation that dead in bed syndrome may explain a larger proportion of OHCA cases in T1D is further corroborated by the fact that a much larger proportion of OHCAs occurred early in the morning hours in people with T1D compared with other cases (Table 1).

Moreover, we show that while individuals with T1D are 5 years younger at OHCA, they exhibit more comorbidities. Only 25% were free from cardiovascular conditions prior to OHCA compared with 35% among the other individuals, also including people with T2D. (Figure 1) Indicating the debilitating nature of T1D at a younger age. Yet, there were no statistically significant associations between T1D and survival. We believe this is due to the sample size, which was relatively small for T1D. Although T1D exhibit worse characteristics, p-values are overly influenced by sample size and accordingly, does not favor the survival analysis in this study. (Figure 2)(Table 3)
Additionally, we did not accurately represent the general population by excluding T2D from the control group. Although the expected variance in survival that would materialize by exclusion probably is, marginal and remaining statistically insignificant, T2D have been previously documented to negatively impact OHCA survival. Its high prevalence among “No T1D” should be taken into consideration when interpreting the disparities. (4)(12)(13)(14)
The high prevalence of T2D could partly be a consequence of an inherent limitation with register studies and administrative data, coding errors and misclassification. The SCRR does not provide us with details regarding the diabetes diagnosis, making us rely on ICD-codes. A total of 3380 patients were registered with both E10 (type 1 diabetes) and E11 (type 2 diabetes) and consequently, were excluded from the T1D group.

Moreover, this study had no exclusion criteria. Previous reports have had different inclusion criteria for the study population. Some including only patients with cardiac arrest of presumed cardiac origin (13)(15)(16), whereas some included only patients that have survived to hospital admission. (17)(13). Thereby creating more homogenous cohort groups and making it, to some degree, easier to isolate the effect of diabetes on survival. Disregarding all pre-hospital mortality although may quarantine the effect of diabetes among survivors, also suggests predictors other than diabetes status have greater importance to pre-hospital survival. Parry et al. reported worse outcomes in patients with diabetes after

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OHCA but noted that the disparities were abolished by accounting for initial rhythm. (5) In accordance with preceding studies, our study found initial rhythm significantly associated with both short- and long-term survival outcome. (Table 3)(2)(18) Similarly, our study found lower rates of initial shockable rhythm among diabetics, not explained by delays to emergency medical service (EMS) arrival.(5)

In opposition though, a major limitation of this study remains, the SCRR only includes cases in whom resuscitation was deemed reasonable by the EMS, excluding all cases in whom resuscitation was deemed futile at the EMS arrival. It is possible that pre-hospital mortality not accounted by the SCRR, may include patients suffering OHCA due to complications of diabetes. Thus, conflicting our ability to draw causal interference.

We conclude, with the current sample size, that there is no statistically significant association between T1D and survival after OHCA. People with T1D are on average 5 years younger and have more cardiovascular comorbidities. T1D patients present with less cardiac etiologies and shockable rhythm in OHCA. Although predictors such as initial rhythm surpass that of T1D with regards to survival, the risk of SCA remains higher among T1D. Further knowledge may encourage the development of interventions and guidelines improving prevention and survival in this population. Perhaps future research could elucidate a potential association with T1D and survival after OHCA using a larger sample size, or compare the survival among T1D and T2D.

Ethical approval statement

Data used in the study had already been collected and approved by the Ethical Review Authority,in Sweden, registration number 2020-02017.

Data availability statement

The data supporting the findings of this study are available within the article and its supplementary material.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest statement

None.

Contributors

BE and AR planned and designed the study. Acquisition of data were made by AR, AiR and AL, statistical analysis and interpretation of data were made by BE, AR, AiR, SN with input from ZM, ET, TR, OA, CD and PP. BE and AR drafted the manuscript and all authors provided critical comments and changes on drafts and read and approved the final manuscript.

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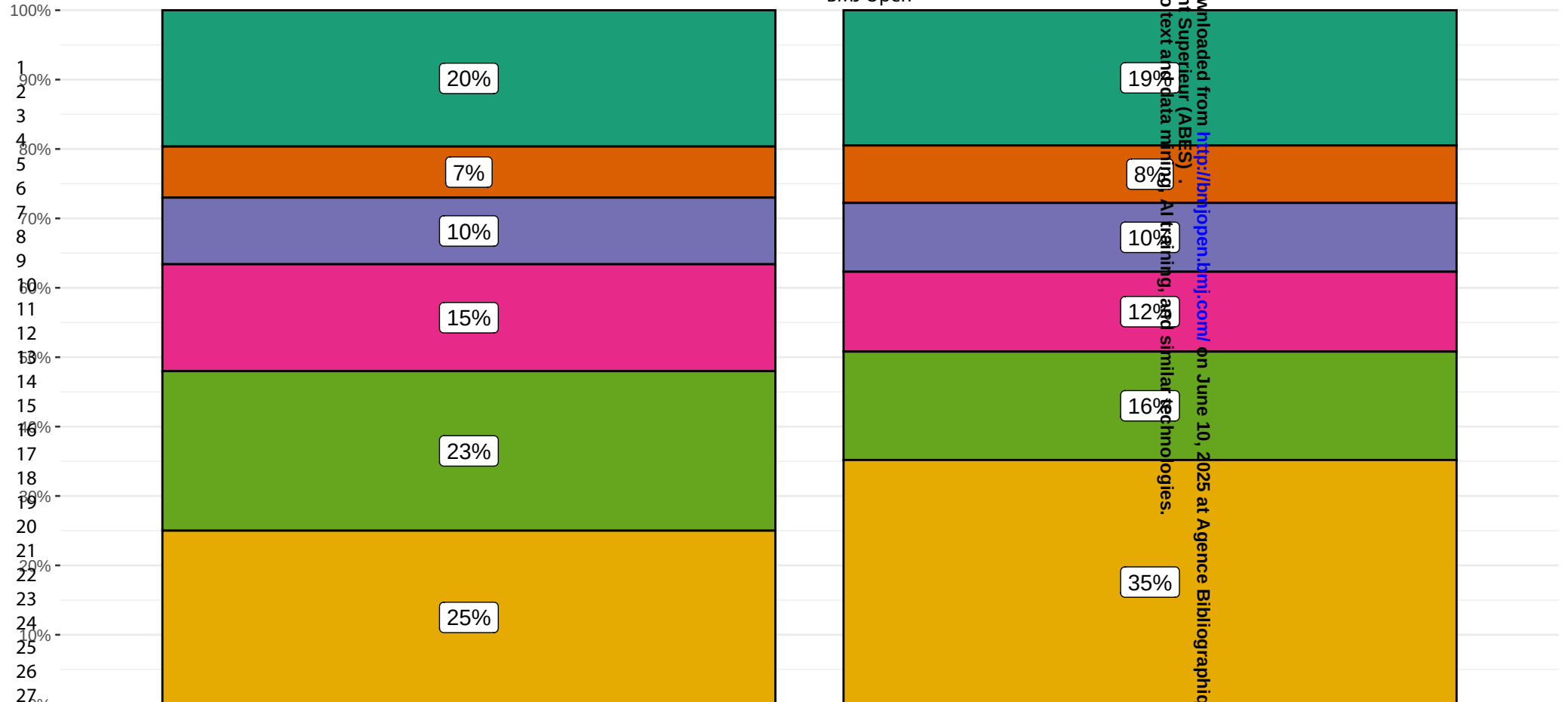

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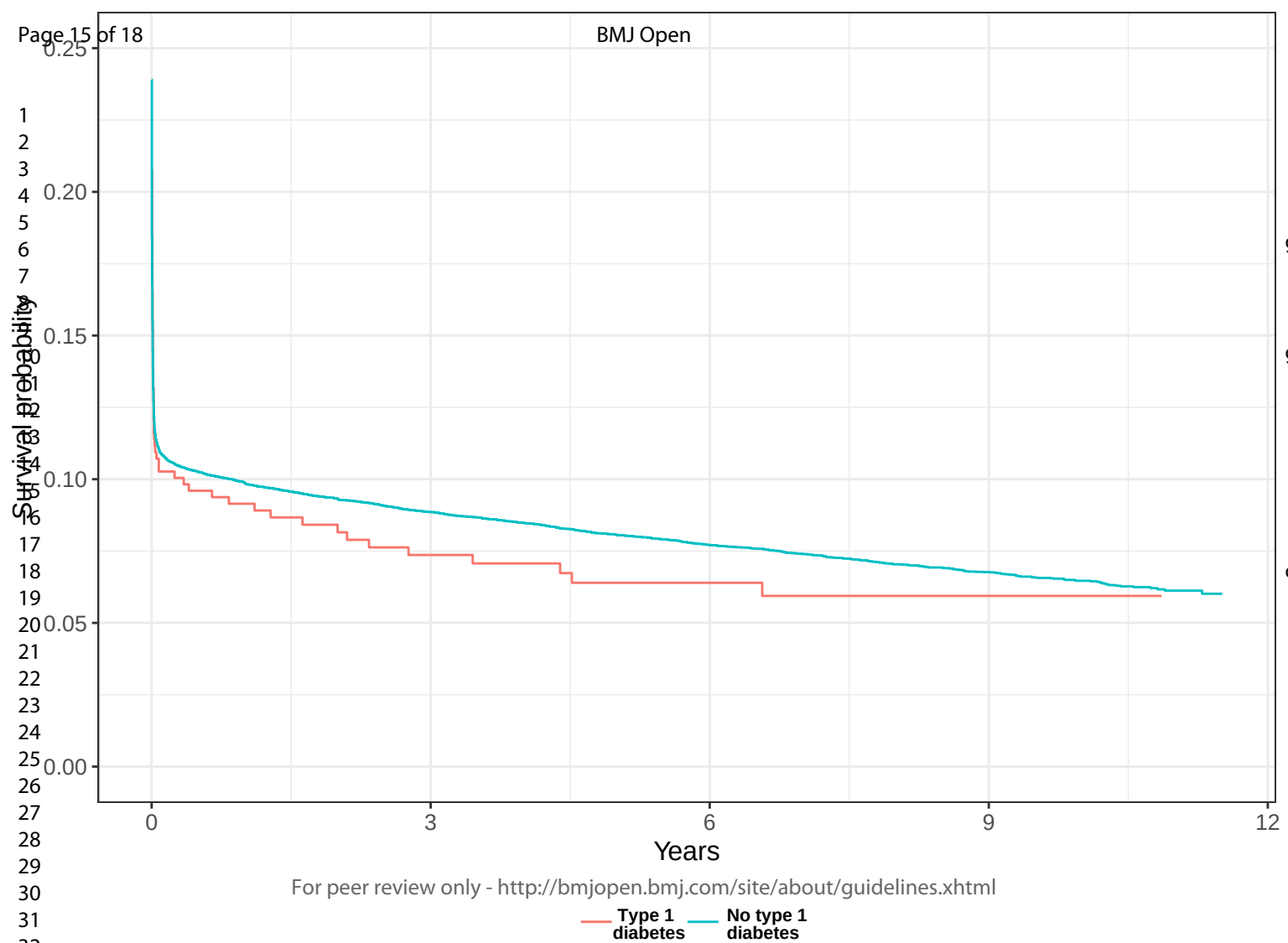

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Supplementary table 1
Baseline characteristics in 54,568 patients with out of hospital cardiac arrest stratified by pre-exististence of type 1 diabetes.

	Type 1 diabetes	No type 1 diabetes	p
Socioeconomic status - n (%)			
Region of birth			0.370
Sweden	401 (89.7)	46123 (85.6)	
Denmark Finland Norway Iceland	16 (3.6)	2976 (5.5)	
EU	12 (2.7)	1598 (3.0)	
Europe not EU	8 (1.8)	1138 (2.1)	
North America	0 (0.0)	130 (0.2)	
Asia	6 (1.3)	1301 (2.4)	
Africa	2 (0.4)	362 (0.7)	
South America	2 (0.4)	166 (0.3)	
Other	0 (0.0)	75 (0.1)	
Disposable family income - median IQR[1]	2574.50 [1502.75, 3968.25]	2469.00 [1515.00, 3748.00]	0.353
Work or profession- n (%)			
Unemployed	274 (69.0)	37564 (77.2)	
Educational level- n (%)			0.382
Pre gymnasium 9 years	95 (23.8)	13755 (27.9)	
Pre gymnasium 9 years	53 (13.2)	6220 (12.6)	
Gymnasium 3 years	124 (31.0)	13770 (27.9)	
Gymnasium 3 years	58 (14.5)	6110 (12.4)	
Post gymnasium 3 years	28 (7.0)	3811 (7.7)	
Post gymnasium 3 years or longer	28 (7.0)	4191 (8.5)	
Research education	2 (0.5)	322 (0.7)	
Unknown	12 (3.0)	1169 (2.4)	
Marital status- n(%)			0.005
Not married	121 (30.0)	11225 (22.3)	
Married	162 (40.2)	22946 (45.7)	
Surviving partner	0 (0.0)	3 (0.0)	
Registered partner	0 (0.0)	16 (0.0)	
Divorced	75 (18.6)	8407 (16.7)	
Divorced partner	0 (0.0)	11 (0.0)	
Widow widower	45 (11.2)	7632 (15.2)	
Previous conditions - n (%)			
Hypertension	274 (61.2)	24183 (44.7)	<0.001
Heart failure	101 (22.5)	12316 (22.8)	0.960
Chronic ischemic heart disease	104 (23.2)	11142 (20.6)	0.190
Atrial fibrillation	74 (16.5)	11124 (20.6)	0.041

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Type 2 diabetes	0 (0.0)	10423 (19.3)	<0.001
Dyslipidemia	128 (28.6)	8432 (15.6)	<0.001
Angina, including unstable angina	81 (18.1)	8263 (15.3)	0.114
Alcohol dependency	76 (17.0)	7683 (14.2)	0.109
Acute myocardial infarction	64 (14.3)	7280 (13.5)	0.656
Affective disorders	62 (13.8)	5649 (10.4)	0.024
Renal failure	68 (15.2)	5366 (9.9)	<0.001
Thrombotic stroke	33 (7.4)	4739 (8.8)	0.340
Alzheimers dementia	27 (6.0)	4059 (7.5)	0.276
Aortic stenosis	25 (5.6)	3303 (6.1)	0.718
Medications prescribed - n (%)			
Anticoagulant or antiplatelet agent ATC[2] B01	166 (37.1)	19636 (36.3)	0.773
Beta blockers	165 (36.8)	18153 (33.5)	0.156
ACE inhibitor or ARB	201 (44.9)	17690 (32.7)	<0.001
Diuretics	144 (32.1)	14607 (27.0)	0.017
Lipid lowering drugs	165 (36.8)	12801 (23.7)	<0.001
Drugs for acid related disorders	111 (24.8)	10822 (20.0)	0.014
Calcium channel blockers	110 (24.6)	8604 (15.9)	<0.001
Other cardiovascular drugs ATC C01	55 (12.3)	6421 (11.9)	0.845
Antihypertensive drugs ATC C02	11 (2.5)	610 (1.1)	0.016
Abbreviations: [1]Interquartile range, [2]Anatomical Therapeutic Chemical Classification System			

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1-2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*3-4*
Bias	9	Describe any efforts to address potential sources of bias	3-4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		© Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-6/supplementary table
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	6-7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		© If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Effects of pre-existing type 1 diabetes mellitus on survival outcome following out-of-hospital cardiac arrest: a registry-based observational study in Sweden.

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Secondary Subject Heading:	Emergency medicine, Diabetes and endocrinology, Cardiovascular medicine
Keywords:	Cardiopulmonary Resuscitation, General diabetes < DIABETES & ENDOCRINOLOGY, Out-of-Hospital Cardiac Arrest

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Effects of pre-existing type 1 diabetes mellitus on survival outcome following out-of-hospital cardiac arrest: a registry-based observational study in Sweden.

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Abstract

Background: It has been estimated that 80% of cases of out-of-hospital cardiac arrest (OHCA) are due to cardiac causes. It is well documented that diabetes is a risk factor for conditions associated with sudden cardiac arrest. Type 1 diabetes (T1D) displays a 3- to 5-fold increased risk of cardiovascular disease (CVD) and death compared with the general population.

Objective: This study aims to assess characteristics and survival outcomes of individuals with and without T1D who experienced an OHCA.

Design: A registry-based nationwide observational study with two cohorts, patients with T1D and patients without T1D.

Setting: All emergency medical services and hospitals in Sweden were included in the study.

Participants: Using the Swedish Cardiopulmonary Resuscitation Registry, we enrolled 54,568 cases of OHCA where cardiopulmonary resuscitation were attempted between 2010-2020. Among them, 448 patients with T1D were identified using ICD-code: E10.

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Methods: Survival analysis was performed using Kaplan-Meier and logistic regression. Multiple regression was adjusted for age, sex, cause of arrest, prevalence of T1D and time to cardiopulmonary resuscitation.

Main outcome measures: The outcomes were discharge status (alive vs. dead), 30 days survival and neurological outcome at discharge.

Results: There were no significant differences in patients discharged alive with T1D 37,3% vs, 46% among cases without T1D. There was also no difference in neurological outcome. Kaplan-Meier curves yielded no significant difference in long-term survival. Multiple regression showed no significant association with survival after accounting for covariates, OR 0.99 (95% CI 0.96-1.02), p-value = 0.7. Baseline characteristics indicate that T1D patients were 5 years younger at OHCA occurrence and had proportionally fewer cases of heart disease as the cause of arrest (57.6% vs. 62.7%).

Conclusion: We conclude, with current sample size, that there is no statistically significant difference in long-term or short-term survival between patients with and without T1D following OHCA.

Strengths and limitations.

- The study sample is representative of OHCA cases where resuscitation is attempted since >90% are recorded in the registry.
- The sample includes all regions in Sweden and the risk of selection bias is minimal.
- The sample size is relatively small, with 448 T1D patients.
- We did not have access to greater details regarding diabetes diagnosis; diagnoses were based on ICD codes with the risk of misclassification and coding errors.
- The Swedish Cardiopulmonary Resuscitation Registry does not include patients for whom resuscitation is deemed futile, excluding a cohort that may contain patients with type 1 diabetes.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality worldwide (1). The European Registry of Cardiac Arrest (EuReCa) identifies OHCA as the third leading cause of death in Europe (2). It has been estimated that 80% of cases of OHCA are due to cardiac causes, primarily coronary artery disease in its various forms (3). OHCA in the younger population typically has different

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etiologies, trauma, intoxications and suicide attempts being much more common than in older adults and elderly. Cardiovascular diseases, including cardiomyopathies, channelopathies, myocarditis and coronary artery anomalies, do occur but are not common at a population level (4).

It is well documented that diabetes is a risk factor for virtually all conditions associated with sudden cardiac arrest (SCA), including coronary artery disease, myocardial infarction (MI) and heart failure (HF). Previous studies have reported a 2-4-fold increase in the risk of SCA in patients with diabetes (5). Type 1 diabetes (T1D) exhibits a 3- to 5-fold increased risk of cardiovascular disease (CVD) and death compared to the general population. Indeed, the risk for CVD and death in type 1 diabetes is doubled even with glycated hemoglobin (HbA1c) levels at or below target levels (6).

While there are large studies exploring the association between T2D and OHCA outcomes, we are unaware of a study as large as the current one for T1D. Often conjoined in similar studies, T2D and T1D are, however, significantly different. T1D is generally characterized with insulin deficiency emanating from immune-mediated destruction of insulin-producing pancreatic beta cells. (7) In contrast, T2D is a progressive metabolic disease marked by insulin resistance and eventual failure of pancreatic beta cells. (8) Although the outcome for both conditions is characterized with hyperglycemia, each type is often burdened with different comorbidities requiring disitinct treatment approaches.

The aim of the study was to assess characteristics and outcomes of individuals with T1D who experienced an out-of-hospital cardiac arrest, compared to patients without T1D experiencing an OHCA.

Methods

We conducted a nationwide observational study including all cases of OHCA recorded between 2010 and 2020 in the Swedish Cardiopulmonary Resuscitation Registry (SCRR); in total 54,586 patients were recorded. The registry was initiated in 1990 and includes more than 90% of all OHCA cases where resuscitation is attempted. Cases where resuscitation is deemed futile are not included in the registry. In Sweden, emergency medical services (EMS) are provided both by the respective province (public) and by private companies. However, all ambulance organizations throughout the nation participate in the registry. Reporting is done prospectively and uses the Utstein-based template. The annual report is available at www.shlr.registercentrum.se.

We merged the SCRR with the Patient Registry, which includes both inpatient and outpatient reports throughout Sweden. The Patient Registry is managed by the Swedish National Board of Health and

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Welfare, with coverage since 1987, and currently achievies a 100% level of ascertainment. All diagnoses since year 2000 were assessed, allowing for a 10-year period to record diabetes and other diagnoses. In Sweden, individuals with type 1 diabetes undergo annual examinations, such that a 10-year period should allow for an adequate level of ascertainment with regards to diabetes status. Merging the SCRR with the Patient Registry is a seamless process due to the Swedish personal identity number, a unique 12-digit ID assigned to all citizens.

The Patient Registry utilizes International Classification of Diseases (ICD) 10 codes. Diagnosis code E10 defines type 1 diabetes (T1D), and E11 defines type 2 diabetes (T2D). The absence of any of these codes defined a non-diabetic. Presence of only E10 defined a person with type 1 diabetes, while the occurrence of only E11 or both E10 and E11 defined type 2 diabetes. Only diagnoses established prior to date of OHCA were assessed.

Statistical Analysis

Statistical calculations were performed using R Statistical Software (v4.2.3; R Core Team 2023). Patient baseline characteristics are described using means and medians together, along with appropriate measurements of dispersion. Long-term survival comparisons between patients with and without T1D were made using unadjusted Kaplan-Meier estimates, followed by a log-rank test. Furthermore, adjusted logistic regression evaluated the binary outcome of 30 days survival. Adjusted models included following covariates: age, sex, initial rhythm, cause of arrest and time from arrest to CPR start. Descriptive models were used to demonstrate pre-arrest comorbidities between subpopulations.

The outcomes were discharge status (alive vs. dead), 30-day survival and neurological outcome at discharge, which was classified using cerebral performance category (CPC). The CPC score is a 5-point scale, where categories 1-2 are generally considered good neurological outcome, and 3 or higher indicates a poor neurological outcome.

Patient and Public Involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

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Results

Baseline characteristics

Table 1
Baseline characteristics in 54,568 patients with out-of-hospital cardiac arrest stratified by pre-exististence of type 1 diabetes.

	Type 1 diabetes	No type 1 diabetes	p
n	448	54120	
Group - n (%)			
Sex Women	163 (36.4)	18427 (34.1)	0.335
Patient characteristics - mean (SD)			
Age	64.39 (17.24)	69.23 (17.51)	<0.001
Cause of cardiac arrest - n (%)			<0.001
Heart disease	228 (57.6)	30158 (62.7)	
Overdose or intoxication	6 (1.5)	1381 (2.9)	
Trauma or accident	12 (3.0)	1112 (2.3)	
Pulmonary disease	14 (3.5)	2704 (5.6)	
Suffocation	10 (2.5)	1266 (2.6)	
Suicide	5 (1.3)	1098 (2.3)	
Drowning	0 (0.0)	456 (0.9)	
Other	121 (30.6)	9889 (20.6)	
Time of cardiac arrest- n (%)			0.001
0 to 6 am	85 (22.9)	7387 (16.4)	
1 to 6 pm	119 (32.1)	13652 (30.3)	
7 to 11 pm	68 (18.3)	8630 (19.1)	
7 to 12 am	99 (26.7)	15443 (34.2)	
Location of cardiac arrest- n (%)			0.779
Home	324 (72.6)	38574 (71.6)	
Public place	67 (15.0)	8764 (16.3)	
Other places	55 (12.3)	6553 (12.2)	
Prehospital interventions - n (%)			
Bystander CPR[1]	240 (55.6)	28645 (55.0)	0.844
Intubation performed	131 (29.6)	15035 (28.3)	0.563
Defibrillated, any	137 (31.3)	17356 (33.4)	0.382
Defibrillated, number of attempts - mean (SD)	3.43 (3.54)	3.48 (3.16)	0.859
Adrenaline administered	371 (83.6)	42146 (78.8)	0.018
Amiodarone administered	42 (9.5)	6193 (11.8)	0.173
Critical time intervals - median (IQR)			
Time from arrest to EMS[2] dispatch	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	0.971
Time from arrest to CPR start	2.00 [0.00, 10.00]	3.00 [0.00, 10.00]	0.100

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Time from arrest to defibrillation	17.00 [11.00, 29.00]	15.00 [8.00, 24.00]	0.005
Time from arrest to EMS arrival	13.00 [9.00, 19.00]	13.00 [8.00, 20.00]	0.900
Time from EMS dispatch to arrival	10.00 [7.00, 16.00]	10.00 [7.00, 16.00]	0.737
Time from arrest to ROSC[3]	15.50 [10.00, 23.75]	15.00 [9.00, 23.00]	0.392
Initial presentation - n (%)			
Initial rhythm			0.357
Ventricular fibrillation/Pulseless ventricular tachycardia	83 (20.9)	11083 (23.2)	
Pulseless electrical activity	64 (16.1)	8224 (17.2)	
Asystole	251 (63.1)	28439 (59.6)	
Consciousness on EMS arrival at scene	49 (11.1)	5588 (10.6)	0.803
Breathing on EMS arrival at scene			0.604
No breathing	339 (77.2)	40852 (77.7)	
Agonal breathing	42 (9.6)	5651 (10.7)	
Normal breathing	58 (13.2)	6053 (11.5)	
Unknown	0 (0.0)	22 (0.0)	
Pulse on EMS arrival at scene	64 (15.0)	7200 (14.0)	0.614
Spontaneous circulation on hospital arrival	112 (46.1)	13823 (44.9)	0.749
Consciousness on hospital arrival	23 (9.6)	3319 (11.0)	0.551
Witnessed cardiac	259 (59.4)	34119 (65.0)	0.018
Abbreviations: [1]Cardiopulmonary resuscitation, [2]Emergency medical services, [3]Return of spontaneous circulation			

In total, 54,568 cases of OHCA were recorded. As shown in *Table 1*, patients with type 1 diabetes prior to OHCA accounted for 448 of the cases. Patients with T1D were approximately 5 years younger, with no differences in sex. Concerning causes of arrest, 57.6% of those with T1D had heart disease as the presumed cause vs. 62.7% among patients without T1D. No major differences were found with respect to the location of arrest, with most cases occurring at home (72.6% in T1D vs. 71.6%). Being born in Sweden was more common in people with T1D (89.7% vs. 85.6%). There were differences regarding co-existing conditions prior to OHCA, such that people with T1D had significantly more hypertension (61.2% vs. 44.7%), dyslipidemia (28.6% vs. 15.6%), and renal failure (15.2% vs. 9.9%).

T1D patients were more frequently prescribed angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) (44.9% vs. 32.7%), lipid lowering drugs (36.8% vs. 23.7%), calcium channel blockers (24.6% vs. 15.9%), and diuretics (32.1% vs. 27.0%).(Supplementary table 1)

Both groups received similar rates of bystander CPR (55.6% vs. 55.0%). Patients with T1D received epinephrine at higher rates (83.6% vs. 78.8%). Critical time intervals and initial rhythm, as presented

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in *Table 1*, showed no significant differences between the subgroups. Patients without T1D had a higher degree of witnessed arrest (65.0% vs. 59.4%).

Table 2
Outcomes following out-of-hospital cardiac arrest.

	T1D[1]	No T1D	p
Outcomes – n (%)			
Discharged alive	38 (37.3)	5212 (46.0)	0.094
CPC[2] score at discharge			0.319
CPC score 1 no sequele	26 (76.5)	3346 (75.8)	
CPC score 2 mild sequele	8 (23.5)	666 (15.1)	
CPC score 3 moderate sequele	0 (0.0)	287 (6.5)	
CPC score 4 severe sequele	0 (0.0)	104 (2.4)	
Survival at 30 days	46 (10.3)	5971 (11.0)	0.661
Abbreviations: [1]Type 1 diabetes, [2]Cerebral performance category			

Outcomes are shown in *Table 2*. Patients with T1D that were discharged alive in 37.3% of cases, compared to 46% of patients without T1D. Patients with T1D had generally good neurological outcomes following OHCA, with 76.5% classified as category 1 and 23.5% as category 2. This was also true for patients without T1D. Survival at 30 days was noted for 10.3% of those with T1D compared to 11.0% of those without T1D.

Figure 1 displays the proportion of patients with cardiovascular comorbidities; 75% of patients with T1D had at least 1 or more cardiovascular comorbidity, and at least 20% had 5 or more. Only 25% of cases with T1D were free from cardiovascular comorbidities, as compared to 35% among cases without T1D.

Figure 1: Proportion of the number of cardiovascular comorbidities

Survival analysis

Figure 2: Unadjusted Kaplan-Meier curve

Figure 2 shows the unadjusted Kaplan-Meier curves for long-term survival. Individuals with T1D showed no significant difference in long-term survival outcome. The log-rank test yielded a p-value of 0,83.

Table 3: Adjusted logistic regression for 30-day survival

Characteristic	OR[1]	95% CI[1]	p-value

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T1D[2]			0.7
T1D	-	-	
No T1D	0.99	0.96-1.02	
Initial rhythm			<0.001
VF/pVT[3]	-	-	
PEA[4]	0.77	0.76-0.78	
Asystole	0.74	0.74-0.75	
Sex			0.007
Men	-	-	
Women	1.01	1.00-1.01	
Age	1.00	1.00-1.00	<0.001
Time from arrest to CPR[5] start	1.00	1.00-1.00	<0.001
Cause of cardiac arrest			<0.001
Heart disease	-	-	
Overdose or intoxication	0.99	0.97-1.01	
Trauma or accident	0.94	0.92-0.96	
Pulmonary disease	0.99	0.97-1.00	
Suffocation	1.00	0.98-1.01	
Suicide	0.93	0.91-0.95	
Drowning	1.01	0.98-1.04	
Other	0.97	0.97-0.98	

Abbreviations: [1] OR = Odds Ratio, CI = Confidence Interval, [2]Type 1 diabetes, [3]Ventricular fibrillation/Pulseless ventricular tachycardia, [4]Pulseless electrical activity, [5]Cardiopulmonary resuscitation

Adjusted logistic regression for 30-day survival is presented in *Table 3*. T1D status showed no significant association with survival after accounting for age, initial rhythm, sex, and cause of cardiac arrest. Patients with PEA and asystole had lower odds of survival compared to VF/pVT.

Discussion

A total of 448 cases of OHCA with pre-existing T1D were studied. There was no statistically significant difference in long-term or short-term survival between patients with and without T1D. We found that people with T1D are, on average, 5 years younger when experiencing an OHCA. The cause of arrest was comparatively less attributed to heart disease among cases with T1D. (Table 1) No significant difference could be seen in the proportion of discharged alive, with T1D patients at 37.3% compared to 46% among cases without T1D. Both cohort groups exhibited good neurological outcome, with the majority being catergorized as either CPC category 1 or 2. (Table 2).

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As evident in Table 1, the prevalence of T1D in this study (0.8%) was higher than that in the general population (0.5%), although proportionally not as high as T2D, which in this study (19%) showed a 4-fold higher prevalence in OHCA compared to the Swedish population (9). Thus, we do not see an excessive overrepresentation of T1D in the OHCA population. This should not be taken as evidence of a near-normal risk of OHCA in T1D. A previous study reports the risk of death among individuals with T1D, from any cause and from cardiovascular complications, is twice that of the general population, even with glycemic control on target. (10)

In line with previous studies, we expected T1D cases to have a higher burden of cardiac etiologies in OHCA. However, that was not the case in this study. Cardiac etiologies were less common in T1D. The lower rates of cardiovascular complications likely reflect the advancements on integrated patient care for chronic diseases, improvements in patient education, and the management and early treatment of cardiovascular risk factors. (11) Notably, T1D cases were much more likely to experience an OHCA due to an unspecified (other) cause, compared with non-diabetics. Unfortunately, the SCRR does not provide further details on this specific category, but it is possible that a number of these cases are dead-in-bed syndrome, hypoglycemic events, hyperglycemic crisis, or other diabetes-related complications. The speculation that dead-in-bed syndrome may explain a larger proportion of OHCA cases in T1D is further supported by the fact that a significantly larger proportion of OHCAs occurred early in the morning hours in people with T1D compared to cases without T1D. (Table 1).

Moreover, we show that while individuals with T1D are, on average, 5 years younger at OHCA occurrence, they exhibit more comorbidities. Only 25% were free from cardiovascular conditions prior to OHCA compared to 35% among individuals without T1D, including those with T2D. (Figure 1) This indicates the debilitating nature of T1D at a younger age. Yet, there were no statistically significant associations between T1D and survival. We believe this is due to the relatively small sample size of T1D cases. Although T1D patients exhibit worse characteristics, p-values are overly influenced by sample size and, accordingly, do not favor the survival analysis in this study. (Figure 2)(Table 3)

Additionally, we did not accurately represent the general population by excluding T2D from the control group. The expected variance in survival that would materialize due to this exclusion is marginal and remains statistically insignificant; however, T2D has been previously documented to negatively impact OHCA survival. Its high prevalence among cases without T1D should be taken into consideration when interpreting the disparities. (4)(12)(13)(14)

The high prevalence of T2D could partly be a consequence of an inherent limitation with register studies and administrative data, predominantly, coding errors and misclassification. The SCRR does not provide us with details regarding the diabetes diagnosis, making us rely on ICD-10 codes. A total

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of 3380 patients were registered with both E10 (type 1 diabetes) and E11 (type 2 diabetes) and consequently were excluded from the T1D group.

This study had no exclusion criteria. Previous reports have had different inclusion criteria for the study population. Some studies included only patients with cardiac arrest of presumed cardiac origin (13)(15)(16), while others included only patients that have survived to hospital admission. (17)(13). These criteria aimed to create more homogenous cohort groups, making it easier to isolate the effect of diabetes on survival. However, disregarding all pre-hospital mortality may not only confound the effect of diabetes among survivors but also suggests predictors other than diabetes status have greater importance for pre-hospital survival. Parry et al. reported worse outcomes in patients with diabetes following OHCA but noted that these disparities were absent upon accounting for initial rhythm. (5) Consistent with prior investigations, our study found the initial rhythm to be significantly associated with both short- and long-term survival outcome. (Table 3)(2)(18) Similarly, our analysis found lower rates of initial shockable rhythm among diabetics, which were not explained by delays in emergency medical service (EMS) arrival.(5)

A major limitation of this study remains: the SCRR only includes cases in which resuscitation was attempted, excluding all cases in which resuscitation was deemed futile upon EMS arrival. It is possible that pre-hospital mortality not accounted for by the SCRR may include patients suffering OHCA due to complications of diabetes, thus conflicting our ability to draw causal inference.

We conclude that, with the current sample size, there is no statistically significant association between T1D and survival following OHCA. People with T1D are, on average, 5 years younger and have more cardiovascular comorbidities. T1D patients present with fewer cardiac etiologies and shockable rhythm in OHCA. Although predictors such as initial rhythm are more significant than T1D with regards to survival, the risk of SCA remains higher among T1D. Further knowledge may encourage the development of interventions and guidelines to improve prevention and survival in this population.

Future research could potentially elucidate a significant association between T1D and survival following OHCA with a larger sample size. Additionally, comparing the survival rates between T1D and T2D patients could provide further insights.

Ethical approval statement

Data used in the study had already been collected and approved by the Ethical Review Authority,in Sweden, registration number 2020-02017.

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Data availability statement

The data supporting the findings of this study are available within the article and its supplementary material.

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Conflict of interest statement

None.

Contributors

BE and AR planned and designed the study. Acquisition of data were made by AR, AiR and AL, statistical analysis and interpretation of data were made by BE, AR, AiR, SN with input from ZM, ET, TR, OA, CD and PP. BE and AR drafted the manuscript and all authors provided critical comments and changes on drafts and read and approved the final manuscript.

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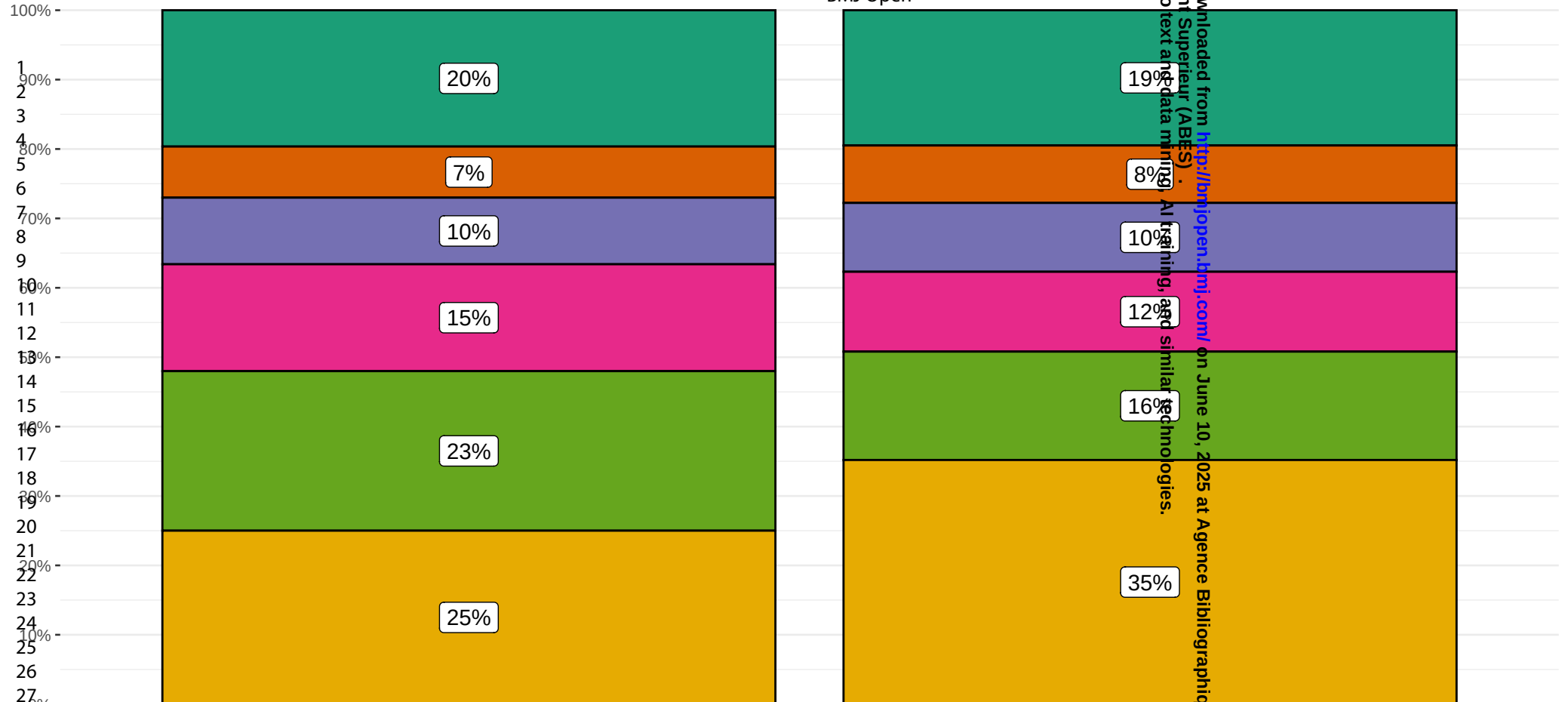

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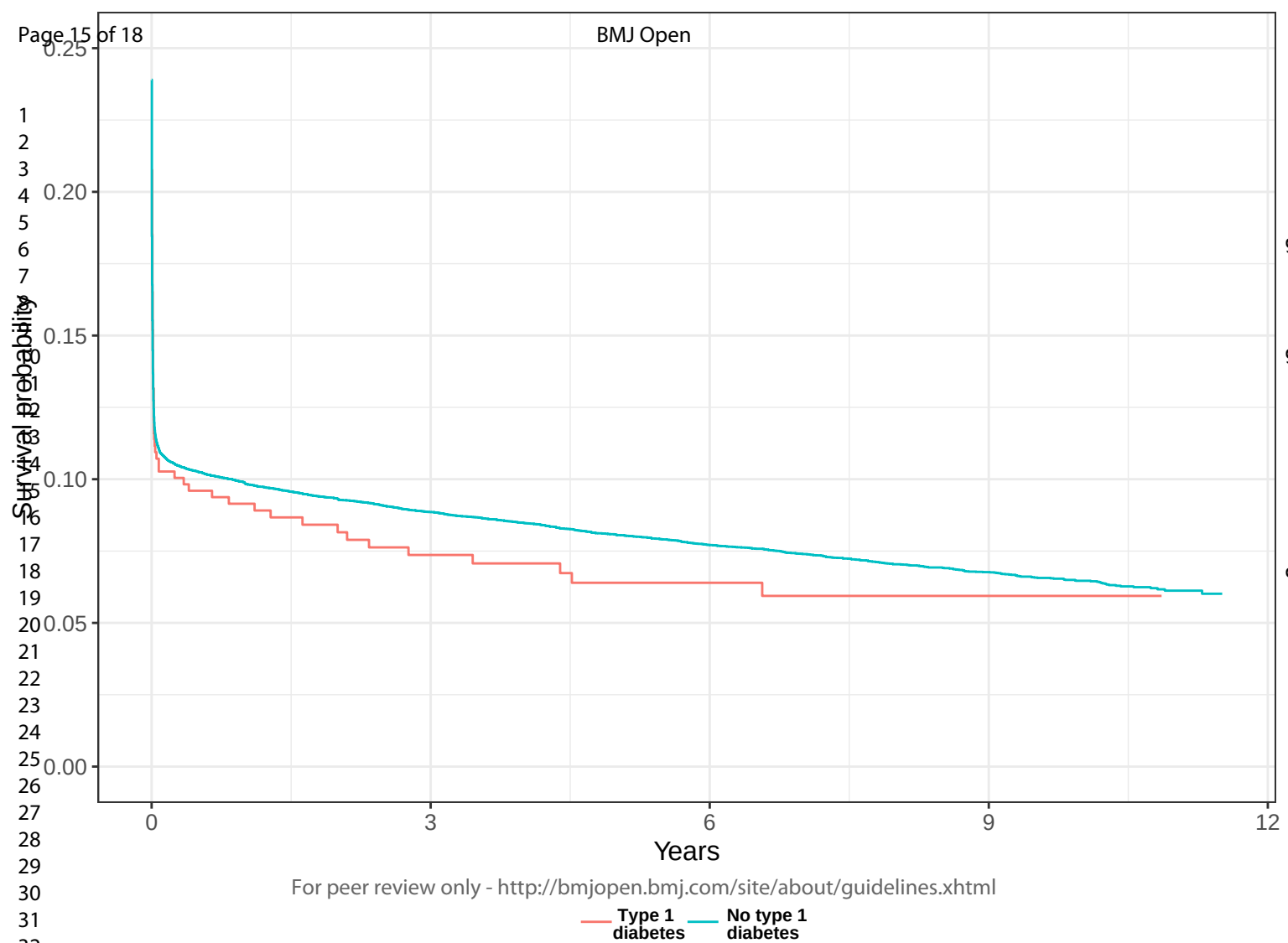

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Supplementary table 1
Baseline characteristics in 54,568 patients with out of hospital cardiac arrest stratified by pre-exististence of type 1 diabetes.

	Type 1 diabetes	No type 1 diabetes	p
Socioeconomic status - n (%)			
Region of birth			0.370
Sweden	401 (89.7)	46123 (85.6)	
Denmark Finland Norway Iceland	16 (3.6)	2976 (5.5)	
EU	12 (2.7)	1598 (3.0)	
Europe not EU	8 (1.8)	1138 (2.1)	
North America	0 (0.0)	130 (0.2)	
Asia	6 (1.3)	1301 (2.4)	
Africa	2 (0.4)	362 (0.7)	
South America	2 (0.4)	166 (0.3)	
Other	0 (0.0)	75 (0.1)	
Disposable family income - median IQR[1]	2574.50 [1502.75, 3968.25]	2469.00 [1515.00, 3748.00]	0.353
Work or profession- n (%)			
Unemployed	274 (69.0)	37564 (77.2)	
Educational level- n (%)			0.382
Pre gymnasium 9 years	95 (23.8)	13755 (27.9)	
Pre gymnasium 9 years	53 (13.2)	6220 (12.6)	
Gymnasium 3 years	124 (31.0)	13770 (27.9)	
Gymnasium 3 years	58 (14.5)	6110 (12.4)	
Post gymnasium 3 years	28 (7.0)	3811 (7.7)	
Post gymnasium 3 years or longer	28 (7.0)	4191 (8.5)	
Research education	2 (0.5)	322 (0.7)	
Unknown	12 (3.0)	1169 (2.4)	
Marital status- n(%)			0.005
Not married	121 (30.0)	11225 (22.3)	
Married	162 (40.2)	22946 (45.7)	
Surviving partner	0 (0.0)	3 (0.0)	
Registered partner	0 (0.0)	16 (0.0)	
Divorced	75 (18.6)	8407 (16.7)	
Divorced partner	0 (0.0)	11 (0.0)	
Widow widower	45 (11.2)	7632 (15.2)	
Previous conditions - n (%)			
Hypertension	274 (61.2)	24183 (44.7)	<0.001
Heart failure	101 (22.5)	12316 (22.8)	0.960
Chronic ischemic heart disease	104 (23.2)	11142 (20.6)	0.190
Atrial fibrillation	74 (16.5)	11124 (20.6)	0.041

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Type 2 diabetes	0 (0.0)	10423 (19.3)	<0.001
Dyslipidemia	128 (28.6)	8432 (15.6)	<0.001
Angina, including unstable angina	81 (18.1)	8263 (15.3)	0.114
Alcohol dependency	76 (17.0)	7683 (14.2)	0.109
Acute myocardial infarction	64 (14.3)	7280 (13.5)	0.656
Affective disorders	62 (13.8)	5649 (10.4)	0.024
Renal failure	68 (15.2)	5366 (9.9)	<0.001
Thrombotic stroke	33 (7.4)	4739 (8.8)	0.340
Alzheimers dementia	27 (6.0)	4059 (7.5)	0.276
Aortic stenosis	25 (5.6)	3303 (6.1)	0.718
Medications prescribed - n (%)			
Anticoagulant or antiplatelet agent ATC[2] B01	166 (37.1)	19636 (36.3)	0.773
Beta blockers	165 (36.8)	18153 (33.5)	0.156
ACE inhibitor or ARB	201 (44.9)	17690 (32.7)	<0.001
Diuretics	144 (32.1)	14607 (27.0)	0.017
Lipid lowering drugs	165 (36.8)	12801 (23.7)	<0.001
Drugs for acid related disorders	111 (24.8)	10822 (20.0)	0.014
Calcium channel blockers	110 (24.6)	8604 (15.9)	<0.001
Other cardiovascular drugs ATC C01	55 (12.3)	6421 (11.9)	0.845
Antihypertensive drugs ATC C02	11 (2.5)	610 (1.1)	0.016
Abbreviations: [1]Interquartile range, [2]Anatomical Therapeutic Chemical Classification System			

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1-2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*3-4*
Bias	9	Describe any efforts to address potential sources of bias	3-4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		© Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-6/supplementary table
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	6-7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		© If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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