Reduced pre-hospital and in-hospital survival rates after out-of-hospital cardiac arrest of patients with type-2 diabetes mellitus: an observational prospective community-based study

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Aims	Out-of-hospital cardiac arrest (OHCA) remains a major cause of death. We aimed to determine whether type-2 diabetes mellitus (T2DM) is associated with reduced pre-hospital and in-hospital survival rates after OHCA.
Methods and results	An observational community-based cohort study was performed among 1549 OHCA patients with ECG-documented ventricular tachycardia/ventricular fibrillation (VT/VF). We compared pre-hospital and in-hospital survival rates between T2DM patients and non-diabetic patients. Analyses among T2DM patients were stratified according to current T2DM treatment, used as proxy for T2DM severity. Proportions of neurologically intact survival were analysed. Pre-hospital survival rates were lower in T2DM patients ($n = 275$) than in non-diabetic patients ($n = 1274$); 48.7 vs. 55.8% (univariate $P = 0.032$). Type-2 diabetes mellitus was associated with lower pre-hospital survival [OR 0.75 (0.58−0.98); after evaluation of the risk factors, we found no relevant confounding]. Patients treated with insulin only had lower pre-hospital survival rates than patients treated with oral glucose-lowering drugs only (37.3 vs. 53.3%, univariate $P = 0.034$), partially explained by location of OHCA and EMS response time [OR_{adj} 0.62 (0.33−1.17)]. In-hospital survival rates were also lower in T2DM patients ($n = 134$) than in non-diabetic patients ($n = 711$); 40.3 vs. 57.7%, univariate $P < 0.001$. In those patients whose cause of OHCA was retrieved ($n = 771$), T2DM was significantly associated with lower in-hospital survival [OR_{adj} 0.57 (0.37−0.87)]. Neurologically intact status at discharge was similarly high among T2DM and non-diabetic patients (94.4 vs. 94.6%, $P = 0.954$).
Conclusion	T2DM is associated with lower pre-hospital and in-hospital survival rates after OHCA. Neurologically intact status at hospital discharge is high both among T2DM and non-diabetic patients.
Keywords	Diabetes mellitus • Epidemiology • Out-of-hospital cardiac arrest • Sudden cardiac arrest • Survival • Ventricular fibrillation

Introduction

Type-2 diabetes mellitus (T2DM) is a well-established risk factor for cardiovascular disease (CVD). Accordingly, T2DM is associated with a 2- to 4-fold increased risk of out-of-hospital cardiac arrest (OHCA).[1,2] Type-2 diabetes mellitus patients have been reported to have lower in-hospital survival rates (i.e. survival from hospital

admission to hospital discharge) than non-diabetic patients after OHCA (25 vs. 37%).[3] However, it is unknown whether pre-hospital survival rates (from OHCA to hospital admission) are already reduced in patients with T2DM. This information may be crucial to decide whether pre-hospital care for patients with T2DM needs improvement. Microvascular heart disease, advanced macrovascular heart disease, and cardiac autonomic dysfunction are associated

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What's new?

- Diabetes is associated with lower pre-hospital survival after out-of-hospital cardiac arrest with documented ventricular tachycardia/ventricular fibrillation.
- Among patients with diabetes, lower pre-hospital survival is explained by both type of diabetes treatment and unfavourable resuscitation parameters.
- We confirm lower in-hospital survival rates among patients with diabetes, but found a high percentage of patients with neurologically intact status at discharge from hospital.

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with T2DM and may underlie the lower survival rates after OHCA of T2DM patients.[1,2] These factors may influence myocardial infarction size, or provoke asystole during resuscitation in T2DM patients.

Survival rates are partly determined by patient characteristics; T2DM may be one such characteristic.[4] However, survival rates are also strongly determined by resuscitation parameters.[5] For instance, survival rates are higher when OHCA occurs at a public location, when an automated external defibrillator (AED) is used,[6] and when a shockable rhythm [ventricular tachycardia or ventricular fibrillation (VT/VF)] is found.[7] Thus, to establish to what extent patient characteristics determine survival, resuscitation parameters must be taken into account.

The aim of the present study was to analyse in a large prospective community-based registry whether T2DM is associated with reduced survival rates after OHCA, in particular, pre-hospital survival rates. We studied the role of T2DM as a determinant of pre-hospital and in-hospital survival rates while correcting for resuscitation parameters. To obtain supportive evidence for a possible role of T2DM, we stratified survival among patients with known T2DM according to current treatment for diabetes, used as proxy for T2DM severity.

Methods

Design and setting

We performed an observational community-based cohort study using data from ARREST (AmsteRdam REsuscitation STudies), an on-going prospective registry of OHCA in the Netherlands, in the study period June 2005 to January 2010. The study region (Noord-Holland province) contains rural and urban communities and covers 2404 km^2 with a population of 2.4 million. In collaboration with all emergency medical services (EMS) and hospitals in the study region, resuscitation parameters of all cardiopulmonary resuscitation (CPR) attempts were collected according to the Utstein recommendations.[8] Details of ARREST were described previously.[9] This study was conducted according to the principles expressed in the Declaration of Helsinki. All surviving patients gave informed consent. The Medical Ethics Committee of the Academic Medical Center, Amsterdam approved the use of data from patients who did not survive.

Patient selection

Of each patient in whom a CPR attempt was undertaken by EMS personnel or lay rescuers, the ECG, recorded by AED and/or manual defibrillator, was analysed. Patients were included in this study if they had OHCA with documented VT/VF and a clear non-cardiac cause was absent (e.g. drowning, trauma, respiratory failure, or other non-cardiac causes). Hospital and EMS files were reviewed to verify a cardiac cause. Emergency medical services-witnessed OHCAs were excluded, as EMS-witness is strongly associated with increased survival rates.[10] Complete medication records in the year before OHCA were obtained from the patient's pharmacy using a standardized protocol regardless of the patient's survival status.[4,9] All medication was scored according to the Anatomical Therapeutic Chemical classification system (ATC). Two researchers checked the medication histories. Patients were excluded when medication history was incomplete or could not be retrieved, or when data on resuscitation parameters were missing.

Definitions

Type-2 diabetes mellitus was defined as the prescription of at least one glucose-lowering drug (ATC A10) within 6 months before OHCA. These patients were stratified into three categories according to medication prescriptions at OHCA date: (i) oral glucose lowering drugs (OGLDs) only; (ii) at least one OGLD plus insulin: (iii) insulin only.[1] Hospital and general practitioner records of insulin users were reviewed to determine whether the patients had type-1 diabetes mellitus (T1DM) or T2DM. Patients with T1DM were excluded from analysis, since we were unable to stratify them, as they all used only insulin.

Pre-hospital survival was defined as admission to a hospital with return of spontaneous circulation. In-hospital survival was defined as survival from hospital admission to hospital discharge. For all patients, pre-hospital and in-hospital survival rates were prospectively determined, as was neurological condition at discharge, by reviewing hospital records, using the Cerebral Performance Category (CPC) scale. Category 1 represents good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, vegetative state or coma; category 5, death.[11] Neurologically intact survival was defined as CPC 1 or 2 at hospital discharge.[4,11]

We considered the following factors as potentially confounding for the association between T2DM and survival: age, sex, pre-existing CVD, acute myocardial infarction (MI), obstructive pulmonary disease, and resuscitation parameters (OHCA at public location, bystander witnessed OHCA, bystander CPR performed, use of AED, time between emergency call and EMS arrival). Pre-existing CVD was defined as the prescription of at least one of the following CVD-drugs within 6 months before OHCA: angiotensin-2-receptor antagonists, α-adrenoceptor blockers, β-adrenoceptor blockers, calcium antagonists, diuretics, nitrates, or thrombocyte aggregation inhibitors. Obstructive pulmonary disease was defined as the prescription of at least two respiratory drugs (ATC R03) within a year before OHCA. Information on the immediate cause of VF was based on hospital records and could thus only be obtained in patients who survived to hospital admission. The immediate cause was either acute MI (ST elevation MI, non-ST elevation MI, or MI not otherwise specified) or no acute MI (any other cardiac cause).

Data analysis

The associations between T2DM and survival after OHCA were estimated with logistic regression models. Outcome measures were (i) pre-hospital survival and (ii) in-hospital survival. First, we

determined whether pre-hospital survival rates were different between patients with T2DM and non-diabetic patients. Additionally, we conducted multivariate logistic regression analysis with pre-hospital survival as the outcome measure. Secondly, we compared in-hospital survival rates by studying all patients who survived to hospital admission in whom the immediate cause of VF was diagnosed, and conducted multivariate logistic regression analysis with in-hospital survival as the outcome measure. Neurologically intact status among patients who survived to hospital discharge was compared between T2DM and non-diabetic patients.

Multivariate logistic regression analysis was performed using three models: (model 1) including all variables, (model 2) including all variables that were univariately associated with outcome, and (model 3) including all variables that changed the point estimate of the association between T2DM and outcome by ≥5%.[4,12] The change in estimate principle was used to prevent over-fitted models by filtering out variables that were in fact no confounders to the association between T2DM and outcome.[12] Interaction on a multiplicative scale between T2DM and either older age (≥75 years), sex, pre-existing CVD was estimated by including the cross-product of the two factors as a variable in the model. We performed the same analyses among patients with T2DM to investigate whether current glucose-lowering therapy determines survival rate. Results are presented as odds ratio (OR) and 95% confidence interval (CI). Continuous variables are presented as mean ± standard deviation (SD), and categorical data as absolute numbers and percentages. Differences in baseline characteristics were tested between groups using a Student's *t*-test, ANOVA, or χ^2 test where appropriate. A *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software package for Mac (SPSS for Mac, version 20.0, SPSS Inc.).

Results

Pre-hospital survival rates

To study pre-hospital survival rates, we analysed the total study cohort, which contained 1549 OHCA patients, including 275 patients with known T2DM and 1274 non-diabetic patients (*Figure 1*). Patients with T2DM were older than non-diabetic patients, and more often had pre-existing CVD (*Table 1A*). Resuscitation parameters were similar in both groups.

Pre-hospital survival rates were lower in patients with T2DM than in non-diabetic patients in univariate analysis (*Figure 2B* and *Table 2A*). Furthermore, univariate analysis showed that age and resuscitation parameters also were determinants of pre-hospital survival (*Table 2A*). The association between pre-hospital survival rate and T2DM remained in the multivariate logistic regression analyses containing all variables (model 1), or all variables that were univariately associated with outcome (model 2), but just lost statistical significance [OR changed from 0.75 to 0.77 (model 1) and 0.78 (model 2), while 95%CI became wider]. However, none of the investigated confounders changed the point estimate of the association between T2DM and pre-hospital survival by ≥5%. Thus, multivariate regression analysis showed that patients with T2DM had a lower chance of pre-hospital survival [OR 0.75 (0.58–0.98), model 3, *Table 2A*]. There were no interactions on a multiplicative scale between T2DM and either age, sex, or pre-existing CVD.

Among patients with T2DM, patients treated with insulin only had lower pre-hospital survival rates than patients treated with OGLDs only (*Figure 2B* and *Table 3A*), but this difference did not reach statistical significance in a multivariate logistic regression model which contained confounders that were univariately associated with outcome and changed the point estimate with ≥5% (OHCA at public location, EMS response time).

In-hospital survival rates

Patients with known T2DM (*n* = 134) had lower in-hospital survival rates than non-diabetic patients (*n* = 711) regardless other patient characteristics (*Figure 2C*). To study whether this difference was explained by differences in immediate cause of OHCA (in particular, pre-existing CVD and/or acute MI), we studied in-hospital survival rates in the subgroup of patients in whom the cause was known. This subgroup contained 771 patients (patients with T2DM *n* = 117, non-diabetic patients *n* = 654), while a diagnosis was missing for 74 patients (patients with T2DM *n* = 17, non-diabetic patients *n* = 57). Patients with T2DM were older than non-diabetic patients and more often had pre-existing CVD and obstructive pulmonary disease (*Table 1B*). Resuscitation parameters were similar in both groups.

All investigated parameters, including T2DM, were univariately associated with in-hospital survival. Thus, multivariate models 1 and 2 were equal. Multivariate analysis, adjusting either for all investigated parameters (model 1 and 2) or only for parameters that changed the point estimate with ≥5% [model 3 (age, sex, pre-existing CVD, OHCA at public location)], showed that T2DM was independently associated with in-hospital survival (*Table 2B*). There were no interactions on a multiplicative scale between T2DM and age, or sex. There was a positive interaction on a multiplicative scale between T2DM and pre-existing CVD (OR 3.10, 95%CI 1.05–9.170, *P* = 0.041).

Analysis among the T2DM groups showed that patients treated with insulin only had lower in-hospital survival rates than patients treated with OGLDs only regardless other characteristics (*Figure 2C* and *Table 3B*). However, this difference did not reach statistical significance.

Time-of-onset of OHCA

Since nocturnal hypoglycaemia may have triggered OHCA, we evaluated the time of emergency call, as a proxy for the time-of-onset of OHCA, and compared this between T2DM patients and non-DM patients. However, we found no differences between groups [T2DM vs. non-DM: 12.4 vs. 11.6% (night); 28.4 vs. 28.4% (morning); 32.0 vs. 35.6% (afternoon); 27.3 vs. 24.3% (evening); *P* = 0.626, data not shown].

Discharge in neurologically intact condition

The proportion of patients with neurologically intact status at hospital discharge was comparably high among patients with T2DM and non-diabetic patients (94.4 and 94.6%, *P* = 0.954). Mean hospital admission duration was significantly longer in patients with T2DM than in non-diabetic patients (*Table 1B*).

Discussion

We found that patients with T2DM had lower pre-hospital survival rates than non-diabetic patients. No investigated parameter
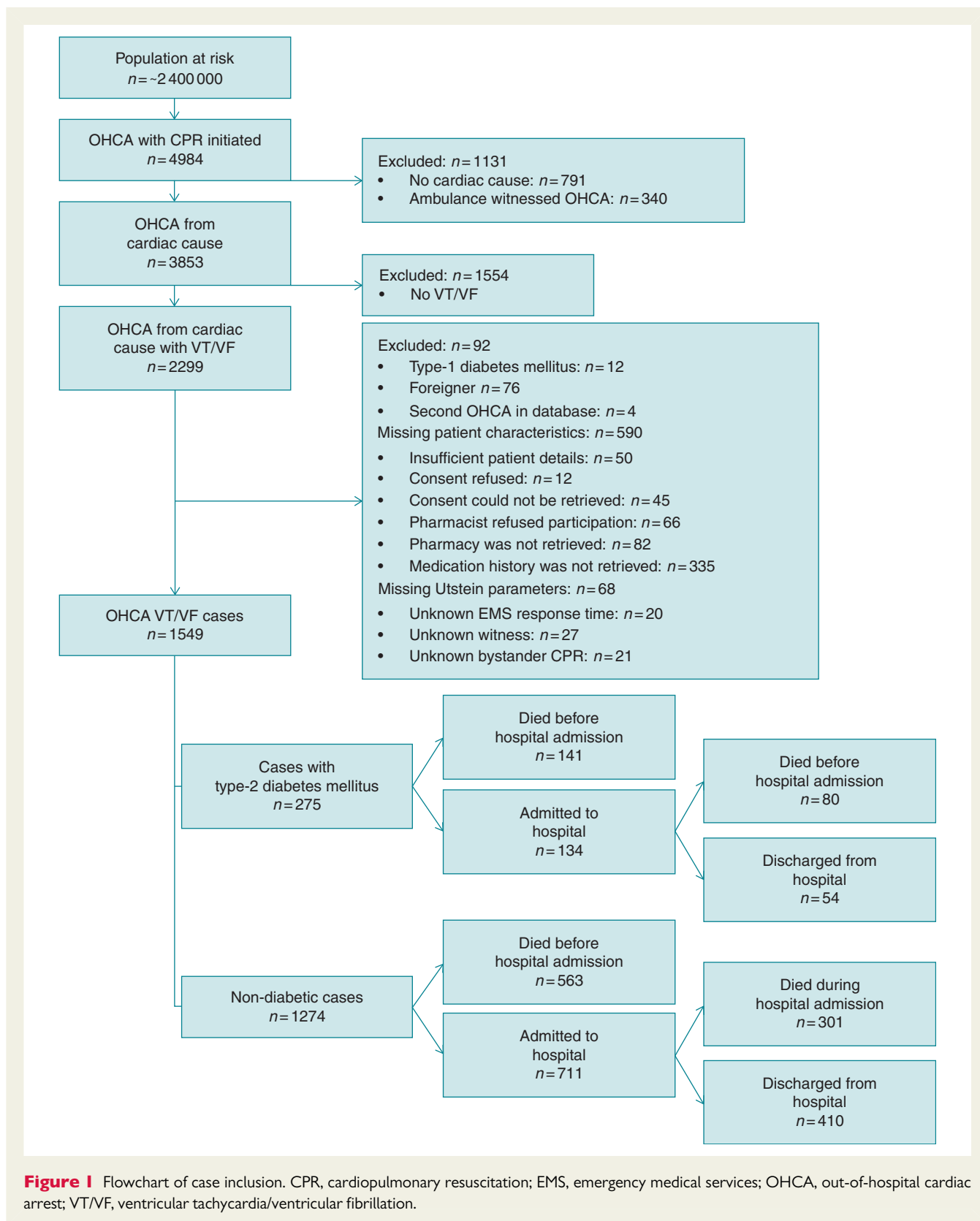
Figure I Flowchart of case inclusion. CPR, cardiopulmonary resuscitation; EMS, emergency medical services; OHCA, out-of-hospital cardiac arrest; VT/VF, ventricular tachycardia/ventricular fibrillation.

influenced the association between T2DM and lower pre-hospital survival rates in a relevant way. Moreover, patients with T2DM treated with insulin only had lower pre-hospital survival rates than patients treated with OGLDs only, but this difference lost statistical significance when resuscitation parameters (less favourable for patients treated with insulin only) were taken into account. These

Table 1 Baseline characteristics of the study population

	Patients with T2DM	Non-diabetic patients	P-value[a]	OGLD only	OGLD and insulin	Insulin only	P-value[b]
All patients (n = 1549)							
Cases, n	275	1274		165	51	59	
Mean age, years (SD)	70.4 (10.1)	66.0 (14.2)	< 0.001	70.6 (10.5)	70.1 (8.2)	70.1 (10.5)	0.929
Male sex, n (%)	223 (81.1)	985 (77.3)	0.171	130 (78.8)	41 (80.4)	52 (88.1)	0.287
Cardiovascular disease[c], n (%)	236 (85.8)	843 (66.2)	<0.001	135 (81.5)	46 (90.2)	55 (93.2)	0.060
Obstructive pulmonary disease, n (%)	52 (18.9)	193 (15.1)	0.121	26 (15.8)	10 (19.6)	16 (27.1)	0.159
Resuscitation parameters							
OHCA at public location, n (%)	93 (33.8)	464 (36.4)	0.415	63 (38.2)	17 (33.3)	13 (22.0)	0.079
Witnessed OHCA, n (%)	232 (84.4)	1081 (84.9)	0.838	139 (84.2)	43 (84.3)	50 (84.7)	0.996
Bystander CPR, n (%)	202 (73.5)	942 (73.9)	0.868	125 (75.8)	38 (74.5)	39 (66.1)	0.348
AED used, n (%)	82 (29.8)	341 (26.8)	0.303	56 (33.9)	12 (23.5)	14 (23.7)	0.187
Mean EMS response time, min (SD)	9.3 (4.1)	9.3 (3.8)	0.743	9.3 (3.8)	9.9 (4.1)	10.1 (3.4)	0.098
Patients admitted to hospital (n =771)							
Cases, n	117	654		77	22	18	
Mean age, years (SD)	70.1 (9.9)	64.4 (13.5)	<0.001	69.4 (10.4)	71.2 (9.5)	71.6 (8.4)	0.579
Male sex, n (%)	95 (81.2)	503 (76.9)	0.306	64 (83.1)	16 (72.7)	15 (83.3)	0.529
Acute MI, n (%)	67 (57.3)	394 (60.2)	0.545	42 (54.5)	12 (54.5)	13 (72.2)	0.378
Cardiovascular disease[c], n (%)	99 (84.6)	431 (65.9)	<0.001	64 (83.1)	18 (81.8)	17 (94.4)	0.449
Obstructive pulmonary disease, n (%)	23 (19.7)	76 (11.6)	0.017	12 (15.6)	5 (22.7)	6 (33.3)	0.215
Resuscitation parameters							
OHCA at public location, n (%)	56 (47.9)	294 (45.0)	0.561	42 (54.5)	8 (36.4)	6 (33.3)	0.131
Witnessed OHCA, n (%)	105 (89.7)	592 (90.5)	0.793	69 (89.6)	20 (90.9)	16 (88.9)	0.976
Bystander CPR, n (%)	91 (77.8)	517 (79.1)	0.756	63 (81.8)	14 (63.3)	14 (77.8)	0.195
AED used, n (%)	41 (35.0)	206 (31.5)	0.449	30 (39.0)	4 (18.2)	7 (38.9)	0.184
Mean EMS response time, min (SD)	8.7 (3.3)	8.8 (3.8)	0.733	8.5 (3.5)	9.2 (3.5)	9.0 (2.4)	0.643
Mean hospital admission duration[d], days (SD)	32 (21)	25 (18)	0.008	34 (22)	30 (21)	26 (12)	0.648

AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; MI, acute myocardial infarction; OGLD, oral glucose-lowering drug; OHCA, out-of-hospital cardiac arrest; SD, standard deviation; T2DM, type-2 diabetes mellitus.
[a]Comparison between T2DM and non-diabetic patients.
[b]Comparison between T2DM categories.
[c]Prescription of angiotensin-2-receptor antagonists, α-adrenoceptor blockers, β-adrenoceptor blockers, calcium antagonists, diuretics, nitrates, and/or thrombocyte aggregation inhibitors within 6 months before OHCA.
[d]Of patients who survived to hospital discharge.

findings suggest that, while reduced pre-hospital survival in patients with T2DM is importantly determined by type of T2DM treatment, it is also mediated by less favourable resuscitation parameters in patients treated with insulin only. Similarly, we found that T2DM was associated with lower in-hospital survival rates. This difference was partly explained by age, sex, and pre-existing CVD. It was also partly explained by less favourable resuscitation parameters, e.g. OHCA at non-public location. The finding that resuscitation parameters (in particular, OHCA at non-public location), partly determined both pre-hospital and in-hospital survival rates of patients with T2DM (in particular, those with severe T2DM), suggests that changes in pre-hospital resuscitation care may not fully close the gap in pre-hospital and in-hospital survival rates between patients with T2DM and non-diabetic patients.

Previous studies showed that T2DM is associated with a higher risk for sudden cardiac death and an increased all-cause and CVD mortality rate.[2,13] Few studies addressed survival of diabetic patients after OHCA.[3,14,15] However, these studies only reported in-hospital survival rates, whereas pre-hospital survival, as studied in the present study, was not reported. Moreover, disease definition differed between studies. For instance, while Larsson et al.[3] reported on all OHCA regardless of underlying rhythm, we aimed to ensure that OHCA resulted from cardiac causes by only including patients with documented VT/VF. Patients in whom only asystole was found were excluded because, in these patients, collapse could have resulted from non-cardiac causes, e.g. stroke. Still, both studies reported similar odds ratios of diabetes for in-hospital survival after OHCA. In line with our OHCA definition, Carew et al.[15] reported that survival after OHCA with VT/VF declined as the number of co-morbidities (including diabetes) increased. However, Carew et al.[15] did not investigate survival for independent comorbidities, and ambu-lance witnessed OHCAs were included in the analysis, which could
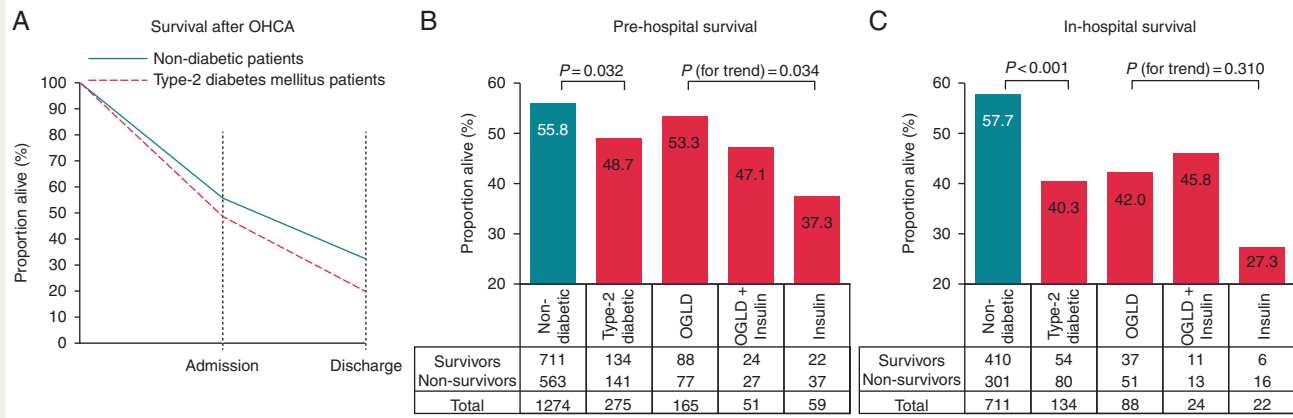
Figure 2 Survival after out-of-hospital cardiac arrest. (*A*) Survival rates of all type-2 diabetes mellitus and non-diabetic patients. (*B*) Proportions of patients (total *n* = 1549) who survived from out-of-hospital cardiac arrest to hospital admission. (*C*) Proportions of patients (total *n* = 845) who survived from hospital admission to hospital discharge after out-of-hospital cardiac arrest. OGLD, oral glucose-lowering drug; OHCA, out-of-hospital cardiac arrest.

be considered similar to in-hospital cardiac arrests, as more advanced life support is immediately available. Taken together, our study contributes the new findings that (i) T2DM is an important determinant of pre-hospital survival rate and (ii) resuscitation parameters (in particular, OHCA at public location) tend to be less favourable in patients with severe T2DM and contribute to reduction in pre-hospital and in-hospital survival rate.

We tried to find an explanation why T2DM patients were less often at a public location when OHCA occurred. Since nocturnal hypoglycaemia can cause VF,[16] we compared the time of OHCA between T2DM and non-DM patients, but we found no differences between groups. Therefore, we think that nocturnal hypoglycaemia does not explain the observation that patients with T2DM less often had OHCA at a public location. However, it has been hypothesized that patients suffering OHCA at non-public locations have more advanced disease.[17] Our observations that patients using insulin only were more often at a non-public location at the time of the OHCA, and more often had COPD, although not significantly different, may support this hypothesis.

We suggest some possible explanations for our finding that T2DM is an important determinant of reduced pre-hospital and in-hospital survival rate. First, the risk for microvascular and macrovascular complications in patients with T2DM increases as T2DM progresses.[1] Accordingly, T2DM is associated with larger MI sizes and reduced reperfusion.[18] These factors are both associated with increased mortality after acute MI (the most common cause of OHCA) and may partially explain the lower survival rates of patients with diabetes.[18] We aimed to address this issue by analysis among patients who survived to hospital admission in whom the immediate cause of OHCA was known. In this analysis, we adjusted additionally for acute MI. Although we found that acute MI was univariately associated with lower rate of survival to discharge, additional adjustment for acute MI did not relevantly change the association between T2DM and lower survival. We were unable to obtain MI size and this analysis could also not be performed in a pre-hospital setting as there were no diagnoses available for patients who did not

survive to hospital admission. Secondly, metabolic derangements of patients with T2DM after OHCA (e.g. increased blood glucose variability leading to hyperglycaemia and/or hypoglycaemia) may contribute to reduced in-hospital survival rate. Hyperglycaemia is often present early after OHCA, and increased blood glucose variability frequently occur in an intensive care unit population. Both factors are associated with poor in-hospital survival rates.[19] Hyperglycaemia and increased blood glucose variability during treatment after OHCA may be more often present in patients with T2DM than in non-diabetic patients.

Our observations may implicate that the gap in survival rates between patients with T2DM and non-diabetic patients may be closed in two ways. First, improvement of pre-hospital survival rate in patients with T2DM may be achieved by pre-hospital or in-community treatment to reduce risk for OHCA and to increase survival rate. Moreover, patients with T2DM treated with insulin had less favourable resuscitation parameters, notably less often OHCA at a public location. The survival disadvantage of patients who suffer OHCA at a non-public location may be resolved by granting them better access to treatments that increase survival after OHCA that occurs at a public location, e.g. AED. One way to achieve this could be to implement a text message alert system in the EMS dispatch system, which alerts lay rescuers in the vicinity of the OHCA patient to perform CPR and/or direct them to the nearest AED, to achieve early defibrillation.[20] Secondly, optimizing glucose homeostasis after OHCA in patients T2DM may reduce mortality at intensive care unit and may thereby improve in-hospital survival.[19] Future studies aimed at establishing the factors that contribute to decreased in-hospital survival of patients with T2DM and/or decreased pre-hospital survival of patients with T2DM after OHCA are recommended.

A major strength of this study is that ARREST is specifically designed to study the determinants and outcomes of OHCA. This ensured that OHCA diagnosis was accurate, and that a cardiac cause of OHCA was proved by the presence of VT/VF on the ECG and the analysis of general practitioner/hospital records. Moreover,

Table 2 Odds ratios for survival of the study population

	Pre-hospital survival		ORᵃ	95%CI	ORᵇ	95%CI	ORᶜ	95%CI	ORᵈ	95%CI
All patients (n = 1549)	**Yes (n = 845)**	**No (n = 704)**								
T2DM, n (%)	134 (15.9)	141 (20.0)	0.75	0.58–0.98	0.77	0.59–1.02	0.78	0.59–1.02	0.75	0.58–0.98
Mean age, years (SD)	65.9 (13.4)	67.9 (13.9)	0.99	0.98–0.996	0.99	0.98–0.999	0.99	0.99–1.00		
Male sex, n (%)	646 (76.4)	562 (79.8)	0.82	0.64–1.05	0.71	0.55–0.91				
Cardiovascular diseaseᵉ, n (%)	586 (69.3)	493 (70.0)	0.97	0.78–1.20	1.15	0.90–1.46				
Obstructive pulmonary disease, n (%)	125 (14.8)	120 (17.0)	0.85	0.64–1.11	0.99	0.74–1.31				
Resuscitation parameters										
OHCA at public location, n (%)	364 (43.1)	193 (27.4)	2.00	1.62–2.48	1.83	1.45–2.29	1.75	1.40–2.19		
Witnessed OHCA, n (%)	756 (89.5)	557 (79.1)	2.24	1.69–2.98	2.05	1.53–2.75	2.07	1.54–2.77		
Bystander CPR, n (%)	648 (76.7)	496 (70.5)	1.38	1.10–1.73	1.19	0.93–1.54	1.17	0.91–1.51		
AED used, n (%)	258 (30.5)	165 (23.4)	1.44	1.14–1.80	1.27	0.99–1.62	1.28	1.00–1.64		
Mean EMS response time, min (SD)	8.8 (3.7)	9.8 (4.0)	0.93	0.90–0.96	0.93	0.91–0.96	0.93	0.91–0.96		
	In-hospital survival									
Patients admitted to hospital (n = 771)ᶠ	**Yes (n = 463)**	**No (n = 308)**								
T2DM, n (%)	54 (11.7)	63 (20.5)	0.51	0.35–0.76	0.56	0.36–0.88	0.56	0.36–0.88	0.57	0.37–0.87ᵍ
Mean age, years (SD)	62.5 (12.7)	69.4 (12.8)	0.96	0.95–0.97	0.96	0.95–0.98	0.96	0.95–0.98	0.96	0.95–0.98
Male sex, n (%)	377 (81.4)	221 (71.8)	1.73	1.23–2.43	1.63	1.10–2.41	1.63	1.10–2.41	1.75	1.20–2.56
Acute MI, n (%)	237 (51.2)	224 (72.7)	0.39	0.29–0.54	0.34	0.24–0.48	0.34	0.24–0.48	0.32	0.23–0.45
Cardiovascular diseaseᵉ, n (%)	291 (62.9)	239 (77.6)	0.49	0.35–0.68	0.62	0.42–0.92	0.62	0.42–0.92	0.62	0.42–0.90
Obstructive pulmonary disease, n (%)	45 (9.7)	54 (17.5)	0.51	0.33–0.78	0.72	0.45–1.16	0.72	0.45–1.16		
Resuscitation parameters										
OHCA at public location, n (%)	241 (52.1)	109 (35.4)	1.98	1.47–2.67	1.54	1.10–2.15	1.54	1.10–2.15	1.65	1.20–2.28
Witnessed OHCA, n (%)	434 (93.7)	263 (85.4)	2.56	1.57–4.19	2.33	1.35–4.01	2.33	1.35–4.01		
Bystander CPR, n (%)	385 (83.2)	223 (72.4)	1.88	1.33–2.67	1.28	0.85–1.93	1.28	0.85–1.93		
AED used, n (%)	167 (36.1)	80 (26.0)	1.61	1.17–2.21	1.50	1.04–2.17	1.50	1.04–2.17		
Mean EMS response time, min (SD)	8.4 (3.5)	9.4 (4.0)	0.93	0.90–0.97	0.92	0.88–0.97	0.92	0.88–0.97		

Abbreviations as in *Table 1*, CI, confidence interval; OR, odds ratio.
ᵃUnadjusted.
ᵇModel 1: adjusted for all confounders.
ᶜModel 2: adjusted for confounders that were univariately associated with outcome.
ᵈModel 3: adjusted for confounders that changed the point estimate with ≥5%.
ᵉPrescription of angiotensin-2-receptor antagonists, α-adrenoceptor blockers, β-adrenoceptor blockers, calcium antagonists, diuretics, nitrates, and/or thrombocyte aggregation inhibitors within 6 months before OHCA.
ᶠIncluded patients are patients of whom the cause of OHCA could be retrieved (acute MI or no acute MI), diagnosis was missing in 74 patients (T2DM, n = 17; non-DM, n = 57).
ᵍAmong all patients who survived to hospital admission (n = 845) OR was 0.57 (0.38–0.84) adjusted for age, sex, cardiovascular disease, location of OHCA.

our findings are representative for the community at large, because our previous studies have indicated that, with our patient inclusion method, we miss only a small proportion of all OHCA cases in our study region.[9]

Some limitations of our study should be discussed. Misclassification in the diagnosis of T2DM may have occurred, since some patients with T2DM may only be treated with diet. However, we consider this a minor limitation as general practitioner guidelines in the Netherlands advise treatment with OGLD within 3 months if diet has limited effect. Similarly, our diagnosis of CVD was based on the prescription of certain CVD drugs within 6 months before OHCA. Other definitions, e.g. the use of anti-arrhythmic drugs, may lead to different classifications. Still, it may be assumed that patients with a recognized high cardiac risk profile will use at least one of the drugs in the categories of our definition. Exclusion criteria might have an impact on the population analysed. For example, we were unable to retrieve the medication history of all patients. However, as such patients were randomly distributed between the T2DM and non-diabetes groups, this may only have a small impact on the population analysed. Lastly, these analyses were performed *post-hoc* in an existing registry with medication data of OHCA-VF patients. Residual confounding may persist from factors that were not available for analysis (e.g. poor kidney function, obesity).

Table 3 Odds ratios for survival of patients with T2DM

	Pre-hospital survival		OR[a]	95%CI	OR[b]	95%CI
All patients with T2DM (*n* = 275)	**Yes (*n* = 134)**	**No (*n* = 141)**				
OGLD only, *n* (%)	88 (65.7)	77 (54.6)	1		1	
OGLD and insulin, *n* (%)	24 (17.9)	27 (19.1)	0.78	0.42−1.46	0.85	0.44−1.62
Insulin only, *n* (%)	22 (16.4)	37 (26.2)	0.52	0.28−0.96	0.62	0.33−1.17
	In-hospital survival					
Patients with T2DM admitted to hospital	**Yes (*n* = 54)**	**No (*n* = 80)**				
OGLD only, *n* (%)	37 (68.5)	51 (63.8)	1			
OGLD and insulin, *n* (%)	11 (20.4)	13 (16.3)	1.17	0.47−2.89		
Insulin only, *n* (%)	6 (11.1)	16 (20.0)	0.52	0.19−1.45		

Abbreviations as in *Tables 1* and *2*.
[a]Unadjusted.
[b]Adjusted for confounders that were univariately associated with outcome and changed the point estimate with ≥5% (OHCA in public, EMS response time).

Conclusion

Patients with T2DM have both reduced pre-hospital and in-hospital survival rates after OHCA. This is explained both by type of T2DM treatment and by less favourable resuscitation parameters. Survival gains may be achieved by improvements in both pre-hospital and in-hospital post-resuscitation care of patients with T2DM. Neurologically intact status at hospital discharge is high in both patient groups.

References

1. Nathan DM. Initial management of glycemia in type 2 diabetes mellitus. *N Engl J Med* 2002;**347**:1342−9.
2. Jouven X, Lemaître RN, Rea TD, Sotoodehnia N, Empana JP, Siscovick DS. Diabetes, glucose level, and risk of sudden cardiac death. *Eur Heart J* 2005;**26**:2142−7.
3. Larsson M, Thorén AB, Herlitz J. A history of diabetes is associated with an adverse outcome among patients admitted to hospital alive after an out-of-hospital cardiac arrest. *Resuscitation* 2005;**66**:303−7.
4. Blom MT, Warnier MJ, Bardai A, Berdowski J, Koster RW, Souverein PC et al. Reduced in-hospital survival rates of out-of-hospital cardiac arrest victims with obstructive pulmonary disease. *Resuscitation* 2013;**84**:569−74.
5. Iwami T, Nichol G, Hiraide A, Hayashi Y, Nishiuchi T, Kajino K et al. Continuous improvements in 'chain of survival' increased survival after out-of-hospital cardiac arrests: a large-scale population-based study. *Circulation* 2009;**119**:728−34.
6. Berdowski J, Blom MT, Bardai A, Tan HL, Tijssen JGP, Koster RW. Impact of onsite or dispatched automated external defibrillator use on survival after out-of-hospital cardiac arrest. *Circulation* 2011;**124**:2225−32.
7. Herlitz J, Bang A, Gunnarsson J, Engdahl J, Karlson BW, Lindqvist J et al. Factors associated with survival to hospital discharge among patients hospitalised alive after out of hospital cardiac arrest: change in outcome over 20 years in the community of Göteborg, Sweden. *Heart* 2003;**89**:25−30.
8. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. *Resuscitation* 2004;**63**:233−49.
9. Blom MT, Van Hoeijen DA, Bardai A, Berdowski J, Souverein PC, De Bruin ML et al. Genetic, clinical and pharmacological determinants of out-of-hospital cardiac arrest: rationale and outline of the AmsteRdam REsuscitation Studies (ARREST) registry. *Open Heart* 2014;**1**:e000112.
10. Rea TD, Cook AJ, Stiell IG, Powell J, Bigham B, Callaway CW et al. Predicting survival after out-of-hospital cardiac arrest: role of the Utstein data elements. *Ann Emerg Med* 2010;**55**:249−57.
11. Herlitz J, Ekstrom L, Wennerblom B, Axelsson A, Bang A, Holmberg S. Prognosis among survivors of prehospital cardiac arrest. *Ann Emerg Med* 1995;**25**:58−63.
12. Greenland S. Modeling and Variable Selection in Epidemiologic Analysis. *Am J Public Heal* 1989;**79**:340−9.
13. Laukkanen JA, Mäkikallio TH, Ronkainen K, Karppi J, Kurl S. Impaired fasting plasma glucose and type 2 diabetes are related to the risk of out-of-hospital sudden cardiac death and all-cause mortality. *Diabetes Care* 2013;**36**:1166−71.
14. Herlitz J, Ekström L, Wennerblom B, Axelsson A, Bang A, Holmberg S. Hospital mortality after out-of-hospital cardiac arrest among patients found in ventricular fibrillation. *Resuscitation* 1995;**29**:11−21.
15. Carew HT, Zhang W, Rea TD. Chronic health conditions and survival after out-of-hospital ventricular fibrillation cardiac arrest. *Heart* 2007;**93**:728−31.
16. Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. *Nat Rev Endocrinol* 2014;**10**:711−22.
17. Weisfeldt ML, Everson-Stewart S, Sitlani C, Rea T, Aufderheide TP, Atkins DL et al. Ventricular tachyarrhythmias after cardiac arrest in public versus at home. *N Engl J Med* 2011;**364**:313−21.
18. Alegria JR, Miller TD, Gibbons RJ, Yi Q-L, Yusuf S. Infarct size, ejection fraction, and mortality in diabetic patients with acute myocardial infarction treated with thrombolytic therapy. *Am Heart J* 2007;**154**:743−50.
19. Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, DeVries JH. Glucose variability is associated with intensive care unit mortality. *Crit Care Med* 2010;**38**:838−42.
20. Zijlstra JA, Stieglis R, Riedijk F, Smeekes M, Van der Worp WE, Koster RW. Local lay rescuers with AEDs, alerted by text message, contribute to early defibrillation in a Dutch out-of-hospital cardiac arrest dispatch system. *Resuscitation* 2014;**85**:1444−9.