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Clinical paper

Increased 5-year risk of stroke, atrial fibrillation, acute coronary syndrome, and heart failure in out-of-hospital cardiac arrest survivors compared with population controls: A nationwide registry-based study

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Abstract

Aim: Long-term risks of stroke, atrial fibrillation, or flutter (AF), acute coronary syndrome (ACS), and heart failure (HF) among survivors of out-of-hospital cardiac arrest (OHCA) are unknown. We aimed to examine 5-year risks of these outcomes among 30-day survivors of OHCA.

Methods: Thirty-day survivors of OHCA without a prior (or within 30 days after cardiac arrest) history of stroke, AF, ACS, or HF and population controls without a prior history of these conditions were identified using Danish nationwide registries. Five-year risks of stroke, AF, ACS, and HF standardized to the distributions of age, sex, and comorbidities among OHCA survivors and controls were obtained using multivariable regression.

Results: Of 4,362 30-day OHCA-survivors, 1,051 were stroke-, AF-, ACS-, and HF-naïve and matched with controls using age, sex, and time of OHCA event. Absolute five-year risks for OHCA survivors vs. controls were for stroke: 6.3% [95% confidence interval (CI) 4.1–8.5] vs. 2.0% [1.6–2.5], AF: 7.9% [5.7–10.2] vs. 2.6% [2.1–3.1], ACS: 5.0% [3.2–6.8] vs. 1.5% [1.1–1.9], and HF: 12.7% [10.1–15.4] vs. 1.2% [0.9–1.6], respectively. Corresponding relative risks were 3.18 [95% CI 1.76–4.61] for stroke, 3.03 [1.93–4.14] for AF, 3.23 [1.69–4.77] for ACS, and 10.40 [6.57–14.13] for HF.

Conclusion: When compared with population controls, OHCA survivors had significantly increased five-year risks of incident stroke, AF, ACS, and HF.

Keywords: Out-of-hospital cardiac arrest survivors, Long-term risk, Stroke, Atrial fibrillation and atrial flutter, Acute coronary syndrome, Heart failure

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Introduction

There is a paucity of studies assessing long-term functional outcomes, including neurologic and cardiovascular outcomes, in patients surviving cardiac arrest.[1] Previous studies have largely focused on short-term survival and neurologic outcomes.[2–7] Survivors of out-of-hospital cardiac arrest (OHCA) are a selected group of patients who are younger and have less comorbid conditions relative to non-survivors. A recent cohort study of long-term survivors after OHCA found that around one-third of deaths at mean three years was due to cardiac causes.[8] The long-term risks of stroke, atrial fibrillation or flutter (AF), acute coronary syndrome (ACS), and heart failure (HF) in OHCA survivors not diagnosed with any of these conditions prior to, or during the initial post-resuscitation phase of the cardiac arrest, are unknown. Nevertheless, these disorders may greatly affect everyday function and quality of life.

The aim of this study was to examine 5-year risks of stroke, AF, ACS, and HF among 30-day survivors of OHCA in Denmark compared with age- and sex-matched population controls.

Methods

Study setting

This study was performed from June 1, 2001 to December 31, 2015 in Denmark, which covers ~43,000 km^2 and a population of 5.8 million. The emergency medical service comprises basic life support ambulances staffed with ambulance technicians and mobile advanced life support emergency care units staffed with anesthesiologists, nurses, or paramedics. The mobile emergency care units are dispatched as rendezvous with basic life support ambulances. Treatment was given in accordance with the latest resuscitation guidelines during the entire study period.[9–11]

Study population and design

This nationwide study used a registry-based follow-up design. Thirty-day OHCA survivors who were at least 18 years of age were identified using Danish Cardiac Arrest Registry data from 2001-2015, and age- and sex-matched population controls were identified using the Danish Civil Registration System. Neither the 30-day survivors nor the population controls had preexisting stroke, AF, ACS, or HF. Furthermore, the 30-day survivors included had not received a diagnosis of stroke, AF, ACS, or HF within 30 days from OHCA. Stroke was defined from diagnosis of ischaemic stroke. Known chronic ischaemic heart disease (IHD) and previous transient ischaemic attack (TIA) was allowed. In Denmark, all residents have a unique Civil Personal Registration Number, which is used in all health care contacts as well as reported to the Danish Cardiac Arrest Registry, enabling linkage between nationwide registries.[12] Follow-up data were also obtained from these nationwide registries. Information on patients' age and sex was obtained from the Danish Civil Personal Registry, and data on the date and year of cardiac arrest were obtained from the Danish Cardiac Arrest Registry. Data on comorbidity and medication use before arrest were retrieved from the Danish National Patient Registry and the Danish National Prescription Registry and were defined based on International Classification of Diseases, Tenth Revision (ICD-10) codes and Anatomical Therapeutic Chemical Classification System (ATC) codes, respectively (Supplemental Table 1).[13,14] Comorbidity data consisted of hypertension, diabetes, chronic obstructive pulmonary disease (COPD), peripheral artery disease (PAD), IHD, TIA, and thyroid disease, and we also used information on antihypertensive drugs, antidiabetics, and selected inhalation drugs (anticholinergic and long-acting beta-agonists) from the Danish National Prescription Registry to define hypertension, diabetes, and COPD, respectively. To fulfill the definition of hypertension, at least two antihypertensive drug redemptions were required. Medication data included lipid-lowering-, antiplatelet-, and anticoagulant agents. Information on discharge diagnoses was collected for the 10 years preceding the index cardiac arrest and until day 30 post cardiac arrest; and data on prescription redemptions were collected for the last 180 days prior to the index cardiac arrest. The study was approved by the Danish Data Protection Agency. The Danish National Committee on Health Research Ethics does not require ethical approval for registry-based studies. The Danish Heart Foundation and The Danish Foundation TrygFonden provided financial support. None of these institutions have commercial interests in the field of cardiac arrest, and none of them had any influence on study design or conduct; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript for submission. The use of the Danish Cardiac Arrest Registry and other national registries used for the conduct of this study was approved by the Data Responsible Unit in the Capital Region of Denmark (P-2019–400).

Exposure

OHCA was defined as a clinical condition with resuscitation initiated either by bystanders with activation of the emergency medical system (EMS) or by EMS personnel, excluding cases with obvious late signs of death in whom resuscitation was not initiated.[7]

Outcomes

The co-primary study endpoints were stroke, atrial fibrillation or flutter, acute coronary syndrome, and heart failure from day 30 to 5 years after OHCA. The secondary endpoint was all-cause mortality. All outcomes were defined based on ICD-10 codes (Supplemental Table 1).

Statistical analysis

Characteristics are compared using counts and percentages for categorical data and medians with 25–75% percentiles for continuous data. Categorical variables were analyzed with Pearson's chi-squared test, and continuous variables were analyzed with the Mann-Whitney U-test. Five-year outcomes among 30-day OHCA survivors versus controls were depicted using Aalen-Johansen cumulative incidence estimates. Five-year outcomes were additionally compared between 30-day OHCA survivors and controls using multivariable Cox regression to obtain absolute and relative risks standardized to the age, sex, comorbidity, and pharmacotherapy distributions of the entire study population. Death was treated as a competing risk. Standardization was used to ensure that 30-day OHCA survivors and controls had similar age, sex, selected comorbidity, and pharmacotherapy distributions to examine the true impact of the patient category group on outcomes. The multivariable model included the following covariates: age, sex, hypertension, diabetes, COPD, PAD, IHD, TIA, thyroid disease, lipid-lowering-, antiplatelet-, and anticoagulant agents. Furthermore, to minimize potential bias in outcome events, sensitivity analyses were performed comparing five-year outcomes among 90-day OHCA survivors with controls. Data on cause of OHCA were pulled in accordance with previously published methods.[15] A two-sided P-

value < 0.05 was considered statistically significant. Data management and analyses were performed using SAS, version 9.4 (Cary, NC, USA) and R, version 3.6.1.

Results

Patients and characteristics

From June 1, 2001 through December 31, 2015, resuscitation was attempted in 48,868 patients who experienced an OHCA. Of these, 4,362 (8.9%) survived the first 30 days. Among 30-day survivors, 1,063 had not been diagnosed with stroke, AF, ACS, or HF prior to OHCA, nor had they received one of these diagnoses within the first 30 days after OHCA. Twelve of these individuals could not be matched. Therefore, the final study population comprised 1,051 patients matched to a total of 5,255 population controls using age, sex, and time of OHCA event as matching variables. Table 1 shows the demographic characteristics of OHCA 30-day survivors and controls at baseline, defined as day 30 after OHCA. OHCA survivors were generally more likely to have comorbidities than controls, including IHD (22.0% vs. 1.7%, P < 0.001), PAD (4.9% vs. 1.1%, P < 0.001), hypertension (28.1% vs. 14.6%, P < 0.001), diabetes (9.5% vs. 4.1%, P < 0.001), use of lipid-lowering agents (27.6% vs. 9.5%, P < 0.001), and COPD (11.3% vs. 2.2%, P < 0.001). Among the 1,051 30-day survivors, 759 (72.2%) had a presumed cardiac cause of OHCA. Data on the presumed cause were missing in 11 (1.0%) patients.

Outcomes among 30-day survivors

Fig. 1 depicts the cumulative incidences of stroke, AF, ACS, and HF from day 30 until end of follow-up at 5 years. The standardized absolute risk of stroke beyond day 30 to 5 years of follow-up was 6.3% [95% confidence interval (CI) 4.1–8.5] vs. 2.0% [95% CI 1.6–2.5] for OHCA survivors versus controls (Fig. 2). Similarly, standardized absolute risks in OHCA survivors versus controls were 7.9% [95% CI 5.7–10.2] vs. 2.6% [95% CI 2.1–3.1] for AF, 5.0% [95% CI 3.2–6.8] vs. 1.5% [95% CI 1.1–1.9] for ACS, and 12.7% [95% CI 10.1–15.4] vs. 1.2% [95% CI 0.9–1.6] for HF, respectively (Fig. 2). As shown in Fig. 3, when standardizing for distributions of prevalent medical conditions and medications, differences in relative risks between OHCA survivors versus population controls were highly significant: stroke 3.18 [95% CI 1.76–4.61, P = 0.003], AF 3.03 [95% CI 1.93–4.14, P < 0.001], ACS 3.23 [95% CI 1.69–4.77, P = 0.005], and HF 10.40 [95% CI 6.57–14.13, P < 0.001]. Additionally, the absolute risk of mortality was significantly higher among OHCA survivors versus population controls (23.4% [95% CI 20.5–26.4] vs. 5.4 [95% CI 4.8–6.0], P < 0.001) as was the relative risk (4.35 [95 %CI 3.56–5.14], P < 0.001). Among OHCA survivors, five-year cumulative incidences of AF, ACS and HF were significantly higher among those with presumed cardiac cause of arrest; 12.9% vs. 3.2%, P < 0.001 for AF, 7.0% vs. 3.2%, P = 0.049 for ACS, and 19.4% vs. 4.6%, P < 0.001 for HF. The cumulative incidences of stroke did not significantly differ between those with a presumed cardiac cause versus those without a cardiac cause of arrest (6.7% vs. 5.3%, P = 0.69).

Sensitivity analyses

Of the 1,051 30-day survivors who were matched to population controls, 988 patients survived at least 90 days after OHCA. In a sensitivity analysis including only OHCA 90-day survivors compared with age- and sex-matched controls, differences in risks remained significant during the 5-year follow-up period. Fig. 4 illustrates event risks beyond day 90 to 5 years for OHCA survivors versus controls: 4.9% vs. 1.8% for stroke, 7.1% vs. 1.9% for AF, 3.7% vs. 1.3% for ACS, and 11.7% vs. 1.1% for HF.

Discussion

This nationwide study of 1,051 30-day survivors of OHCA and 5,255 age- and sex-matched population controls demonstrates that

Table 1 – Characteristics of OHCA 30-day survivors and age- and sex-matched controls.

Characteristic	OHCA survivors (n = 1051)	Controls (n = 5255)	P-value
Age, median [25%-75%]	56 [42–67]	56 [42–67]	>0.99
Male sex, n (%)	697 (66.3)	3485 (66.3)	>0.99
Ischaemic heart disease, n (%)	231 (22.0)	91 (1.7)	<0.001
Peripheral artery disease, n (%)	52 (4.9)	59 (1.1)	<0.001
Transient ischaemic attack, n (%)	8 (0.8)	13 (0.2)	0.02
Hypertension, n (%)	295 (28.1)	215 (4.1)	<0.001
Diabetes, n (%)	100 (9.5)	215 (4.1)	<0.001
Chronic obstructive pulmonary disease, n (%)	119 (11.3)	117 (2.2)	<0.001
Chronic kidney disease, n (%)	37 (3.5)	33 (0.6)	<0.001
Malignant disease, n (%)	63 (6.0)	163 (3.1)	<0.001
Hypothyroidism, n (%)	38 (3.6)	95 (1.8)	<0.001
Hyperthyroidism, n (%)	11 (1.0)	32 (0.6)	0.17
Aspirin therapy, n (%)	315 (30.0)	335 (6.4)	<0.001
$P2Y_{12}$ inhibitor therapy, n (%)	134 (12.7)	17 (0.3)	<0.001
Clopidogrel, n (%)	86 (8.2)	17 (0.3)	<0.001
Ticagrelor, n (%)	38 (3.6)	0 (0.0)	<0.001
Prasugrel, n (%)	10 (1.0)	0 (0.0)	<0.001
Warfarin therapy, n (%)	45 (4.3)	30 (0.6)	<0.001
Novel/direct oral anticoagulant therapy, n (%)	13 (1.2)	5 (0.1)	<0.001
Lipid-lowering drug therapy, n (%)	290 (27.6)	497 (9.5)	<0.001

Characteristics are compared using median and 25–75% percentiles for continuous data totals and percentages for categorical data.

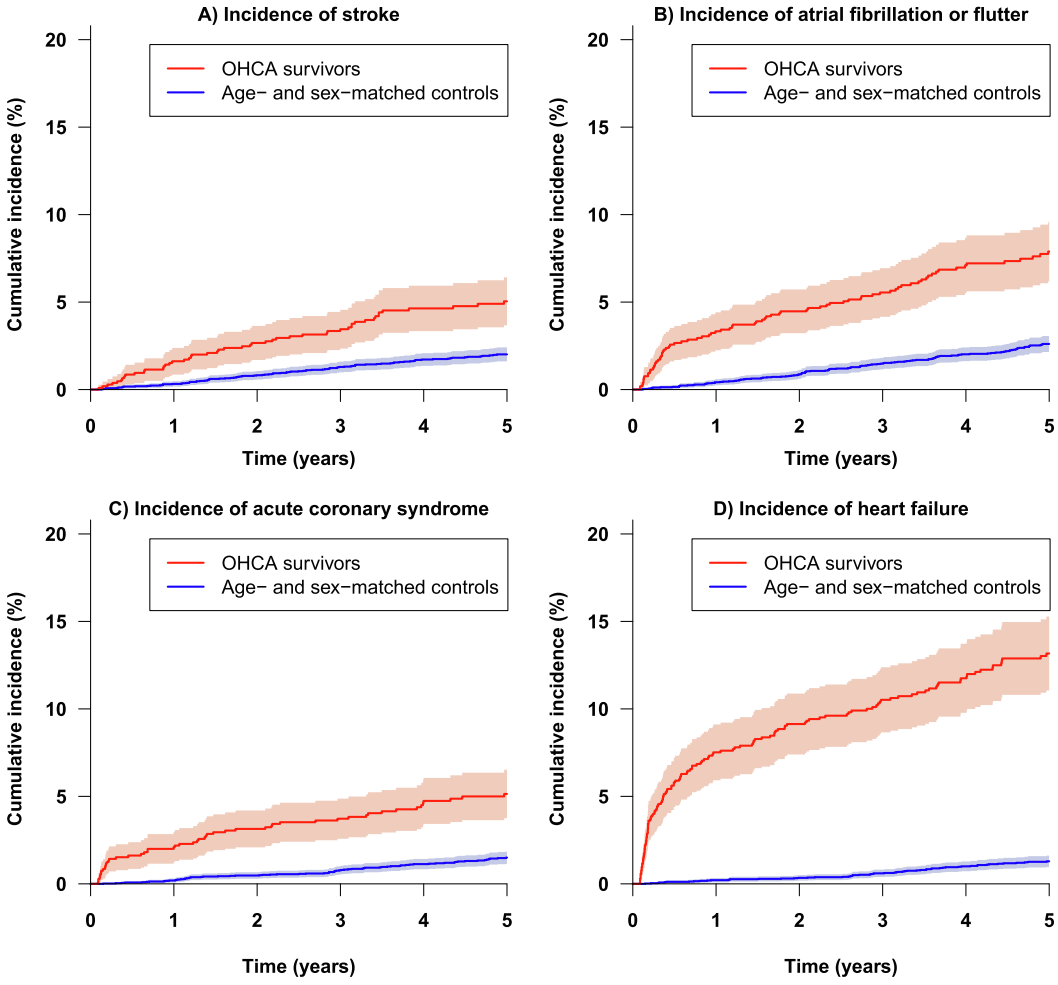

Fig. 1 – Cumulative incidence of stroke (A), atrial fibrillation or flutter (B), acute coronary syndrome (C) and heart failure (D) in OHCA survivors and age- and sex-matched population controls from day 30 to 5 years.

from post-arrest day 30 and until 5 years of follow-up the incident risks of stroke, AF, ACS, and HF were significantly increased in 30-day survivors from OHCA compared with population controls. Results were consistent when only considering 90-day OHCA survivors. The fact that long-term incident risks of ACS and HF were higher among OHCA survivors is not surprising as ~70% of all patients with OHCA have IHD. Accordingly, our data showed that 72% of the OHCA patients had a presumed cardiac cause of arrest. As expected, all-cause mortality was also significantly higher among all OHCA survivors, and five-year cumulative incidences of AF, ACS and HF were higher among patients with a presumed cardiac cause of arrest.

Previous studies of outcomes after cardiac arrest have mainly focused on survival to hospital discharge and have shown improved survival over time in patients who experienced OHCA or in-hospital cardiac arrest (IHCA). The improvement in survival was associated with updates in treatment recommendations in contemporary resuscitation guidelines.[16,17] Additionally, the presence of moderate and severe pre-arrest left ventricular systolic dysfunction seems to be associated with lower rates of survival to hospital discharge compared with normal or nearly normal left ventricular function in patients surviving IHCA.[18]

Both short-term and long-term survival after OHCA have substantially improved over time, and more data on long-term survivors are warranted.[15,19] Neurological outcomes in long-term survivors from OHCA have been extensively studied.[2–7] In contrast, only few studies have focused on long-term cardiovascular risk in these individuals. A Danish study of 897 OHCA survivors found that patients with AF had significantly higher 180-day mortality, primarily driven by cardiac causes and multiple-organ failure. The authors concluded that the presence of AF may identify a particularly vulnerable subpopulation.[20] A Spanish cohort study including 201 OHCA survivors found that 33.3% of deaths at mean 3 years were due to cardiac causes. Furthermore, 26.4% of patients were readmitted to the hospital due to cardiac causes, with heart failure and stroke being the most frequent reasons.[8] Finally, in a Canadian population-based cohort study, the authors followed 1,591 OHCA patients who survived until hospital discharge for up to 3 years. In that study, prior myocardial infarction, heart failure, or arrhythmia were not significantly associated with increased hazards for mortality.[21] Although the data derived from these studies are not directly comparable with ours, they summarize some of the current knowledge on cardiovascular disease in long-term survivors of OHCA. Overall, our results of increased five-year risks of all studied outcomes would advocate for

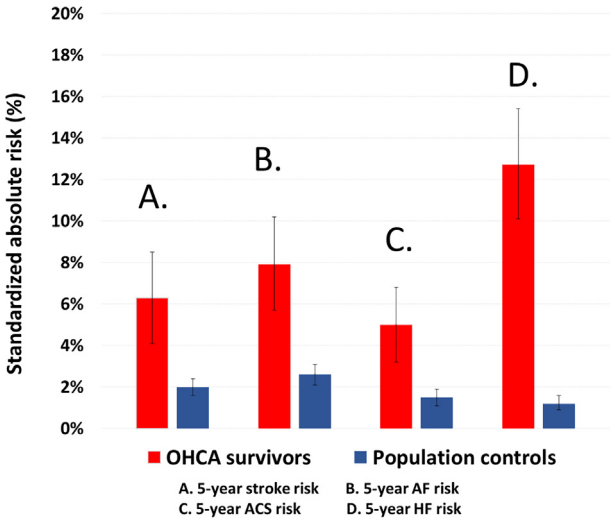

Fig. 2 – Standardized absolute risk of stroke (A), atrial fibrillation or flutter (B), acute coronary syndrome (C) and heart failure (D) in OHCA survivors and age- and sex-matched population controls, standardizing the outcome risks between groups to the distribution of age, sex, selected comorbidity (ischaemic heart disease, hypertension, diabetes, chronic obstructive pulmonary disease, thyroid diseases, chronic kidney disease, cancer) and pharmacotherapy (lipid-lowering agents, antiplatelets, anticoagulants) from day 30 to 5 years.

an enhanced focus on long-term preventive interventions in OHCA survivors. Long-term survival after OHCA has improved significantly, and so the results of the current study were somewhat expected. However, the scarcity of research data makes our study clinically impactful. No guidelines on the preventive strategy directed towards these long-term survivors are currently available. Our study implies that randomized controlled trials focusing on long-term prevention are warranted to clarify whether screening and treatment of risk factors in this patient population could improve long-term survival even further.

Due to the unique Civil Personal Registration Number given to each Danish citizen allowing linkage between medical data and follow-up registries, lost-to-follow-up was extremely low. Furthermore, by using nationwide registries, we minimized the risk of selection bias associated with geographic differences in patient- and cardiac arrest-related characteristics. However, the study had some limitations. First, as with all observational study designs, our results should be interpreted as associations, with no direct inferences regarding causality. Although patients who suffered an OHCA appeared to be sicker at baseline compared with population controls, standardised regression analysis is a robust method for obtaining adjusted estimates in such settings, i.e., the overall between-group variation is diminished, and the need for a control group with comparable cardiovascular disease is omitted. Nevertheless, we cannot rule out the presence of unrecognized underlying comorbidities, nor did we have information on the severity of the conditions that were in fact registered or of peri-arrest factors of potential prognostic importance, e.g., presenting rhythm, left ventricular function, and estimated glomerular filtration rate. The increased risks of cardiac events that we demonstrated may constitute truly increased risks for OHCA survivors, but because events are diagnoses retrieved from national, administrative registries, they may also represent preexisting underlying conditions that simply were not registered until after the cardiac arrest. Furthermore, we cannot rule out that some of the diagnoses in patients hospitalized for more than 30 days may be related to the index cardiac arrest but not registered until discharge. Although bias in outcome events is possible, we attempted to minimize this through sensitivity analyses assessing outcomes among 90-day survivors. Still, individuals with OHCA may have been subject to more frequent medical visits, enabling more efficient detection of incident cardiovascular events, potentially leading to some extent of surveillance bias. Importantly, most of the diagnostic codes used in the present study have been previously validated.[22]

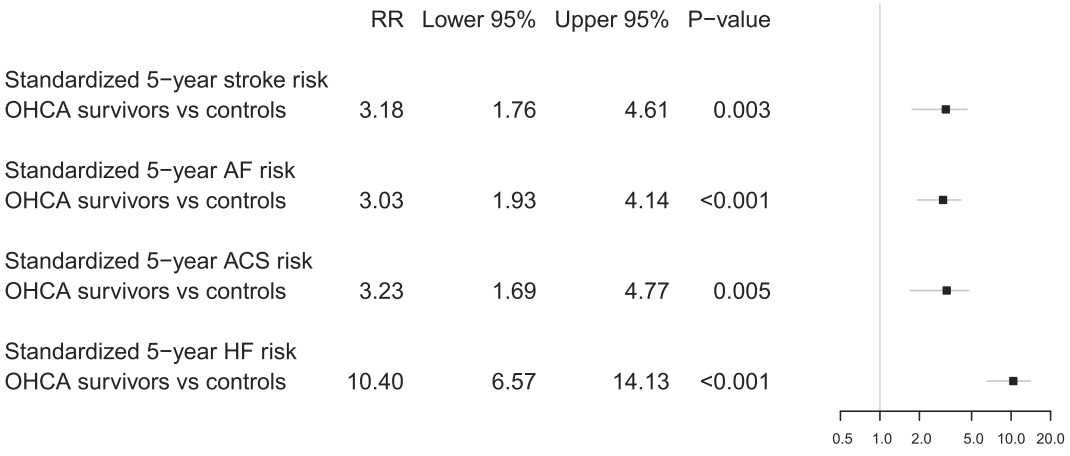

Fig. 3 – Analyses of OHCA 30-day survivors vs. population controls, standardizing the outcome risks between groups to the distribution of age, sex, selected comorbidity (ischaemic heart disease, hypertension, diabetes, chronic obstructive pulmonary disease, thyroid diseases, chronic kidney disease, cancer) and pharmacotherapy (lipid-lowering agents, antiplatelets, anticoagulants).

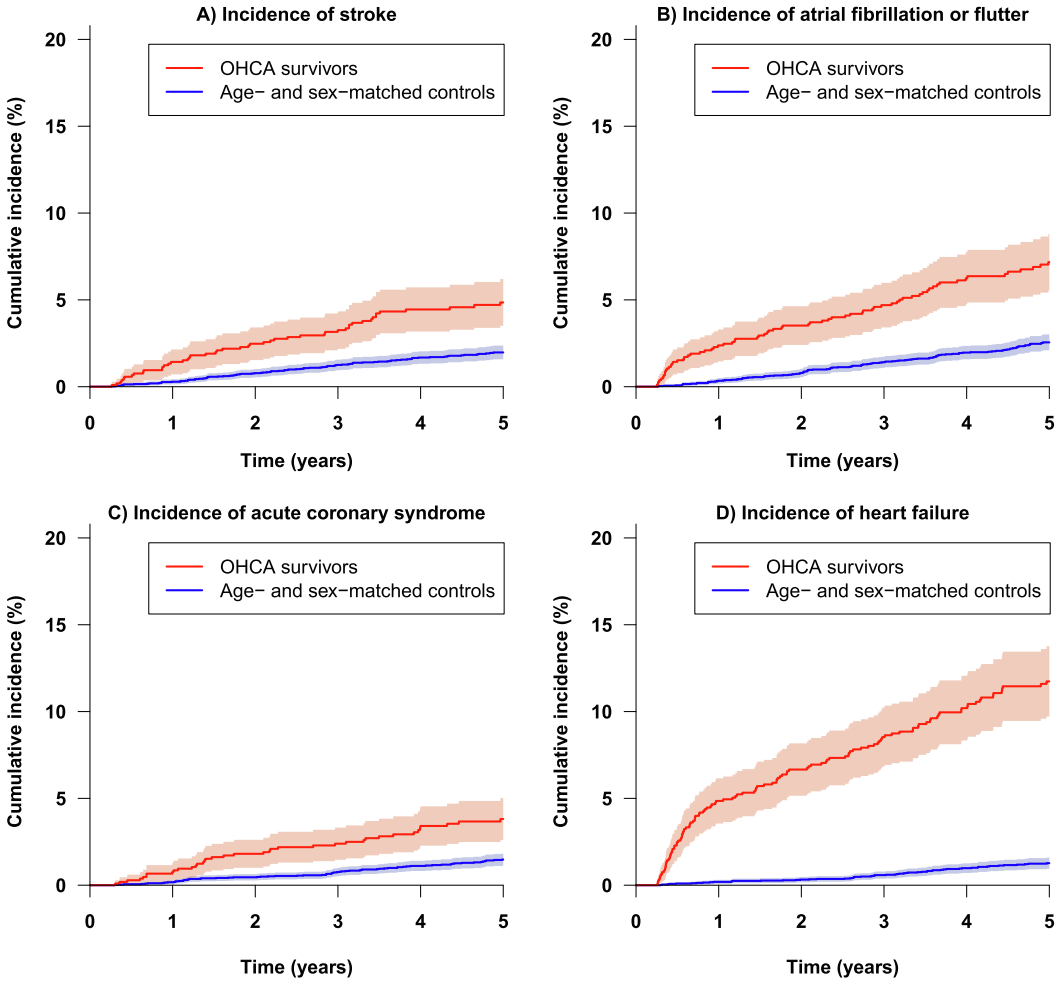

Fig. 4 – Cumulative incidence of stroke (A), atrial fibrillation or flutter (B), acute coronary syndrome (C) and heart failure (D) in OHCA survivors and age- and sex-matched population controls from day 90 to 5 years.

Conclusions

In conclusion, we demonstrated increased five-year risks of stroke, AF, ACS, and HF in survivors of OHCA compared with population controls. These results indicate that OHCA survivors continue to remain at high risk for cardiovascular events. Therefore, clinical attention and preventive measures are warranted to potentially improve long-term cardiovascular outcomes.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.10.024.

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