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# Gender-specific differences in return-to-spontaneous circulation and outcome after out-of-hospital cardiac arrest: Results of sixteen-year-state-wide initiatives

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## Abstract

**Aim:** Several studies reported a lower proportion of laypeople cardio-pulmonary resuscitation (CPR) in female victims of out-of-hospital cardiac arrest (OHCA). We aimed to verify how sixteen-years of state-wide initiatives impacted on gender-differences in OHCA treatment and survival.

**Methods:** All the 2481 consecutive OHCAs of presumed cardiac origin occurred between 2002 and 2018 in the Swiss Ticino Canton and in which a resuscitation was attempted, were included. Emergency medical system (EMS)-witnessed OHCAs were excluded.

**Results:** Time from call to CPR decreased from 9-min in 2002−2006 to 5-min in 2015−2018 ($p < 0.01$) and until 2014, it was longer in women. Survival to discharge increased overall from 11% in 2002−2006 to 23% in 2015−2018 ($p < 0.001$) related to telephone-assisted CPR development (period 2011−2014) and first responder and layperson recruitment via a mobile application (period 2015−2018). In males, survival increased from 12% to 25% ($p = 0.001$) with a statistically significant increase in odds of survival in 2007−2010 (OR 1.6 95%CI 1.1−2.3; $p = 0.001$), in 2011−2014 (OR 2 95%CI 1.4−2.8; $p = 0.001$), and in 2015−2018 (2.4 95%CI 1.7−3.3; $p = 0.001$) compared to 2002−2006. On the other hand, in females, survival increased from 7% to 18% ($p < 0.001$), with a corresponding increase in the odds of survival of almost 3 times from 2002−2006 to 2015−2018 time period (OR 2.9 95%CI 1.5−5.8, $p = 0.001$). No difference in survival probability was observed according to gender when adjusted for age, presenting rhythm, year-groups, OHCA location, EMS arrival time, witnessed status and laypeople-CPR.

**Conclusions:** State-wide initiatives can significantly increase the chances of survival in both male and female victims of OHCAs, by increasing the probability to receive CPR in a shorter time span.

**Keywords:** Gender-differences, Out-of-hospital cardiac arrest, Survival, Bystander, First-responder

## Introduction

Out-of-hospital cardiac arrest (OHCA) is a major health problem associated with poor outcomes.[1] Early recognition and treatment strategies that focus on rapid provision of resuscitation care and defibrillation have significantly increased survival rates after OHCA.[2] In the vast majority of developed countries, nationwide[3] or county-wide[4−6] initiatives have been undertaken to increase early recognition of OHCA, bystander-initiated cardiopulmonary resuscitation (CPR)

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http://dx.doi.org/10.1016/j.resplu.2020.100038
Received 15 July 2020; Received in revised form 1 October 2020; Accepted 1 October 2020
Available online xxx

and territorial density of public automated external defibrillators (AED). Additional nationwide initiatives to improve outcome of OHCA victims consisted in performance enhancement of the Emergency Medical System (EMS) and the creation of an efficient and effective first-responder network. Despite an overall improvement in OHCA outcome, multiple studies have reported gender differences in several aspects of OHCA pre-hospital treatment including AED-use, bystander-initiated CPR as well as in outcomes such as return-to-spontaneous circulation (ROSC) and survival with conflicting conclusions.[7–12] Gender-disparities in OHCA outcome have been associated to a lower likelihood of receiving public-AEDs and bystander-initiated CPR which has been related to perceived fears about inappropriate touching, accusation of sexual assault and fear of causing injury by bystanders.[13,14] On the other hand, gender disparities in OHCA outcome may be explained by different inclusion criteria or limitations of the studied population to selected categories, e.g. selection for shockable initial rhythm, particular age groups or etiologies (cardiac causes or both cardiac and non-cardiac causes of OHCA).[8,9] Furthermore, survival rates were often reported considering different starting points and endpoints (from OHCA to hospital admission, from hospital admission to hospital discharge), disregarding overall survival (from OHCA to hospital discharge).

Few studies assessed temporal changes of gender-disparities in outcome. Very little is known whether nationwide or state-wide initiatives undertaken to increase rates of bystander and layperson resuscitation, and improve advance care have equally benefited women and men. A low frequency of CPR before ambulance arrival (13%) and low survival to hospital discharge (7%) were identified more than 15 years ago in the Ticino Canton (Switzerland), which led to several state-wide initiatives to strengthen bystander resuscitation attempts and advanced care.[15] These strategies included 1) implementation of resuscitation training in middle class schools, as well as when acquiring a driver's license, combined with an increase in voluntary first aid training; 2) a state-wide improvement of telephone guidance from emergency dispatch centers to bystanders witnessing a cardiac arrest, including the addition of health care professionals at dispatch centers; 3) involvement of police, fire fighters, and local non-governmental organizations into a first-responder network; 4) creation of a layperson network managed by mobile application-based alert systems; 5) an annual awareness campaign supported by patients and their family testimonials; 5) a large increase in the number of automated external defibrillators located outside hospitals; 6) efforts to improve advanced care with updates of clinical guidelines including introduction of therapeutic hypothermia, and increasing focus on early revascularization.

Despite these state-wide efforts, it is unknown whether there have been changes in resuscitation attempts and improvements in gender-specific survival. To answer this question we examined temporal trends in prehospital factors directly related to cardiac arrest as well as trends in survival during the past 16 years.

## Methods

### *Study design and setting*

This study is a retrospective analysis of prospectively collected data in consecutive patients, aged >1year old, who suffered an OHCA between January 1st, 2002 and December 31st, 2018 in the Ticino Canton, Switzerland. All OHCAs of presumed cardiac origin, in which a resuscitation was attempted, were included. Patients with non-cardiac causes of arrest and EMS-witnessed arrests were excluded from further analysis (Fig. 1). Data are prospectively collected in compliance with the Utstein reporting guidelines for OHCA.[16] Furthermore, the study also complies with institutional guidelines, the country code of medical ethics, and has been approved by the local ethical competent authority.

### *Recording of out-of-hospital cardiac arrests*

An out-of-hospital cardiac arrest was considered when a clinical condition of cardiac arrest resulted in resuscitation efforts either by bystanders (with activation of the EMS) or by the EMS personnel. The recording of cardiac arrest cases was nearly complete because the EMS system is activated for all emergencies concerning cardiac arrests, and the definition excludes cases with obvious late signs of death (e.g., rigor mortis) for which resuscitative efforts are not initiated. Importantly, EMS personnel are required to complete a short case report for the Ticino Registry of Cardiac Arrest (TIRECA) for every OHCA. For this study, we included date; time; location of cardiac arrest

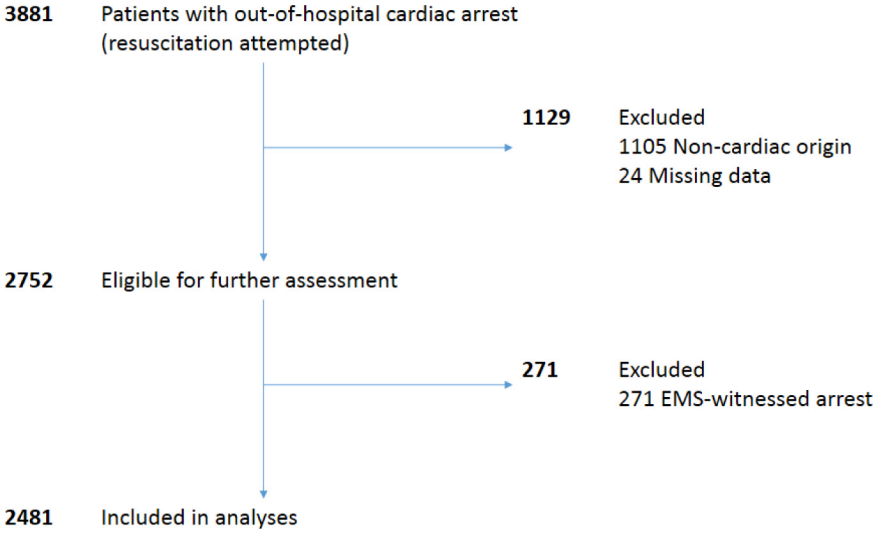


**Fig. 1 – Population selection 2002–2018.**

(private home vs public location); whether the collapse was non-witnessed, bystander-witnessed, or EMS-witnessed arrest; whether a bystander or a first responder (FR) performed CPR, defibrillated the patient, or both; first recorded heart rhythm (shockable rhythm [ventricular fibrillation or tachycardia] or non-shockable rhythm [asystole or pulseless electrical activity]); time intervals, including time from call to the EMS to layperson or FR CPR, time to the first defibrillation, time from call to ambulance arrival (EMS arrival time), and time to ROSC. Finally, survived event and survival to hospital discharge were calculated.

### *Initiatives on AED density, bystander and layperson recruitment*

In 2005 the number of public AEDs was 15 over a population of 322,276 residents; in contrast, in 2018 there were 1271 AEDs for a

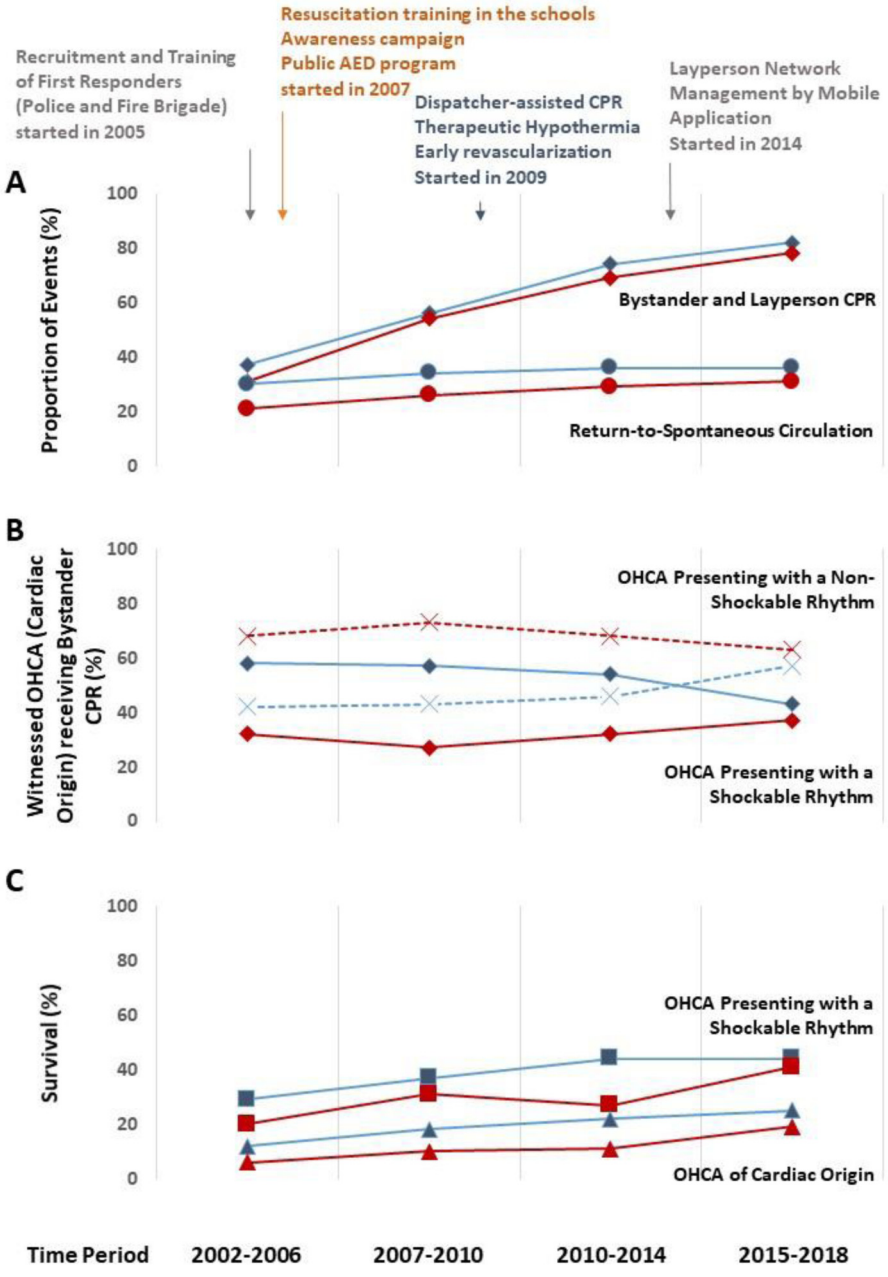


**Fig. 2 – Panel A. Proportion of bystander cardiopulmonary resuscitation (CPR) and proportion of patients with return-to-spontaneous circulation according to gender (male gender: blue line; female gender: red line), 2002–2018. Panel B. Proportion of witnessed out-of-hospital cardiac arrests (OHCA) of cardiac origin receiving a bystander or layperson CPR presenting with shockable or non-shockable rhythm according to gender (male gender: blue line; female gender: red line), 2002–2018. Panel C. Survival at discharge in out-of-hospital cardiac arrest presenting with a OHCA of cardiac origin and a shockable rhythm according to gender (male gender: blue line; female gender: red line), 2002–2018. $P<0.001$ for all changes over time; $P<0.05$ (2-sided) considered statistically significant.**

**Table 1 – Changes in characteristics for patients during the study period according to gender.**

| | 2002/2006 | | | 2007/2010 | | | 2011/2014 | | | 2015/2018 | | | Overall | | | Missing data | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Both (684) | F (187) | M (497) | Both (601) | F (174) | M (428) | Both (601) | F (156) | M (445) | Both (595) | F (176) | M (418) | Both (2481) | F (693) | M (1788) | *N* | |
| Age | 72 [63–80] | 77 [69–83] | 70 [61–78] | 73 [63–81] | 79 [69–85] | 70 [62–78] | 74 [64–82] | 79 [70–85] | 71 [62–80] | 75 [65–83] | 77 [69–85] | 74 [64–82] | 74 [64–81] | 78 [69–85] | 71 [62–80] | 8 | <0.001 |
| Age groups | | | | | | | | | | | | | | | | 8 | <0.001 |
| <36 | 11 (1.6) | 0 (0) | 11 (2.2) | 8 (1.3) | 1 (0.6) | 7 (1.6) | 6 (1) | 0 (0) | 6 (1.3) | 7 (1.2) | 2 (1.1) | 5 (1.2) | 32 (1.3) | 3 (0.4) | 29 (1.6) | | |
| 36–64 | 185 (27.3) | 33 (17.7) | 152 (31) | 160 (26.7) | 32 (18.5) | 128 (30) | 159 (26.5) | 23 (14.7) | 136 (30.6) | 136 (22.9) | 33 (18.6) | 103 (24.6) | 640 (25.9) | 121 (17.5) | 519 (29.1) | | |
| 65–79 | 304 (44.9) | 79 (42.5) | 225 (45.8) | 262 (43.7) | 62 (35.8) | 200 (46.8) | 243 (40.4) | 57 (36.5) | 186 (41.8) | 240 (40.3) | 67 (37.8) | 173 (41.4) | 1049 (42.4) | 265 (38.3) | 784 (44) | | |
| ≥80 | 177 (26.1) | 74 (39.8) | 103 (21) | 170 (28.3) | 78 (45.1) | 92 (21.5) | 193 (32.1) | 76 (48.7) | 117 (26.3) | 212 (35.6) | 75 (42.4) | 137 (32.8) | 752 (30.4) | 303 (43.8) | 449 (25.2) | | |
| Location | | | | | | | | | | | | | | | | 8 | <0.001 |
| Home | 474 (70) | 152 (83) | 322 (65) | 384 (64) | 126 (72) | 258 (60) | 414 (69) | 118 (75) | 296 (66) | 409 (69) | 137 (77) | 272 (65) | 1681 (68) | 533 (77) | 1148 (64) | | |
| Public | 203 (30) | 32 (17) | 171 (35) | 217 (36) | 48 (28) | 169 (40) | 187 (31) | 38 (25) | 149 (34) | 185 (31) | 40 (23) | 145 (35) | 792 (32) | 158 (23) | 634 (36) | | |
| Rhythm, n (%) | | | | | | | | | | | | | | | | 0 | <0.001 |
| Shockable | 230 (34) | 44 (23) | 186 (37) | 207 (34) | 35 (20) | 172 (40) | 220 (37) | 35 (23) | 185 (41) | 182 (31) | 41 (23) | 141 (34) | 839 (34) | 155 (22) | 684 (38) | | |
| PEA | 134 (20) | 44 (23) | 90 (18) | 124 (21) | 36 (21) | 88 (20) | 127 (21) | 41 (26) | 86 (19) | 136 (23) | 37 (22) | 99 (24) | 521 (21) | 158 (23) | 363 (20) | | |
| Asystole | 290 (42) | 86 (46) | 204 (42) | 253 (42) | 96 (55) | 157 (37) | 227 (38) | 72 (46) | 155 (35) | 245 (41) | 91 (51) | 154 (37) | 1015 (41) | 345 (50) | 670 (37) | | |
| Other | 30 (4) | 13 (8) | 17 (3) | 17 (3) | 7 (4) | 10 (3) | 27 (4) | 8 (5) | 19 (5) | 32 (5) | 8 (4) | 24 (6) | 106 (4) | 36 (5) | 70 (5) | | |
| Bystander witness | 519 (76) | 136 (72) | 383 (77) | 393 (65) | 105 (60) | 288 (67) | 424 (71) | 102 (65) | 322 (72) | 394 (66) | 121 (68) | 273 (65) | 1730 (70) | 464 (67) | 1266 (71) | 0 | 0.03 |
| Lay people CPR | 243 (35) | 59 (32) | 184 (37) | 342 (57) | 94 (54) | 248 (58) | 437 (73) | 108 (69) | 329 (74) | 484 (81) | 139 (79) | 345 (83) | 1506 (61) | 400 (58) | 1106 (62) | 0 | <0.001 |
| Witnessed and CPR status | | | | | | | | | | | | | | | | 0 | 0.06 |
| Unwitnessed and no laypeople CPR | 113 (16.5) | 36 (19.2) | 77 (15.5) | 101 (16.8) | 35 (20.1) | 66 (15.5) | 59 (9.8) | 18 (11.5) | 41 (9.2) | 43 (7.2) | 12 (6.8) | 31 (7.4) | 316 (12.7) | 101 (14.6) | 215 (12) | | |
| Unwitnessed and laypeople CPR | 52 (7.6) | 15 (8.0) | 37 (7.5) | 107 (17.8) | 34 (19.5) | 73 (17.1) | 118 (19.6) | 36 (23.1) | 82 (18.4) | 158 (26.6) | 44 (24.9) | 114 (27.3) | 435 (17.5) | 129 (18.6) | 306 (17.1) | | |
| Witnessed and no laypeople CPR | 328 (47.9) | 92 (49.2) | 236 (47.5) | 158 (26.3) | 45 (25.9) | 113 (26.5) | 105 (17.5) | 30 (19.2) | 75 (16.8) | 68 (11.4) | 26 (38.2) | 42 (10.1) | 659 (26.6) | 193 (27.8) | 466 (26.1) | | |
| Witnessed and laypeople CPR | 191 (27.9) | 44 (23.5) | 147 (29.6) | 235 (39.1) | 60 (34.5) | 175 (41) | 319 (53.1) | 72 (46.1) | 247 (55.5) | 326 (54.8) | 95 (53.7) | 231 (55.3) | 1071 (43.2) | 271 (39) | 800 (44.8) | | |
| Time to first CPR | 9 [6–12] | 9 [6–12] | 8 [5–12] | 7 [3–11] | 7 [2–11] | 6 [3–10] | 5 [2–8] | 6 [2–9] | 4 [2–8] | 5 [3–8] | 5 [3–8] | 5 [3–7] | 6 [3–10] | 7 [3–10] | 6 [3–10] | 350 | 0.03 |
| FR on site, N (%) | NA | NA | NA | 115 (19) | 29 (17) | 86 (20) | 295 (49) | 71 (41) | 224 (47) | 238 (40) | 68 (45) | 170 (48) | 648 (26) | 168 (23) | 480 (27) | 1023 | 0.76 |
| FR AED use | NA | NA | NA | 19 (3) | 2 (1) | 17 (4) | 56 (9) | 10 (6) | 46 (10) | 41 (7) | 6 (3) | 35 (8) | 116 (5) | 18 (3) | 98 (5) | 0 | 0.04 |
| Time to EMS arrival | 10 [7–14] | 10 [8–14] | 9 [7–13] | 11 [8–14] | 11 [8–14] | 11 [8–15] | 10 [8–13] | 10 [8–14] | 10 [7–13] | 10 [8–13] | 10 [7–13] | 10 [8–13] | 10 [8–14] | 10 [8–14] | 10 [8–14] | 16 | 0.32 |

**Table 2 – Changes in outcome for patients during the study period.**

| | 2002/2006 | | | 2007/2010 | | | 2011/2014 | | | 2015/2018 | | | Overall | | | Missing data | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Both (684) | F (187) | M (497) | Both (601) | F (174) | M (428) | Both (601) | F (156) | M (445) | Both (595) | F (176) | M (418) | Both (2481) | F (693) | M (1788) | *N* | |
| Survived event | 192 (28) | 40 (21) | 152 (30) | 192 (32) | 45 (26) | 147 (34) | 206 (34) | 45 (29) | 161 (36) | 206 (35) | 55 (31) | 151 (36) | 796 (32) | 185 (27) | 611 (34) | 0 | 0.01 |
| Time to ROSC | 25 [19–35] | 28 [18–46] | 25 [20–34] | 26 [18–35] | 26 [17–36] | 26 [18–35] | 24 [19–32] | 26 [18–32] | 24 [19–31] | 25 [19–33] | 25 [17–30] | 25 [18–35] | 25 [18–34] | 26 [18–33] | 25 [19–34] | 0 | 0.84 |
| Discharge survival | 74 (11) | 13 (7) | 61 (12) | 95 (16) | 17 (10) | 78 (18) | 115 (19) | 18 (11) | 97 (22) | 137 (23) | 32 (18) | 105 (25) | 421 (17) | 80 (11) | 341 (19) | 0 | <0.001 |
| CPC at discharge | | | | | | | | | | | | | | | | 70 | 0.49 |
| 1–2 | 57 (79.2) | 9 (69.2) | 48 (81.4) | 79 (90.8) | 17 (100) | 62 (88.6) | 99 (95.2) | 16 (100) | 83 (94.3) | 80 (90.9) | 16 (94.1) | 64 (90.1) | 315 (89.7) | 58 (92.1) | 257 (89.2) | | |
| 3–4 | 15 (20.8) | 4 (30.8) | 11 (18.6) | 8 (9.2) | 0 (0) | 8 (11.4) | 5 (4.8) | 0 (0) | 5 (5.7) | 8 (9.1) | 1 (5.9) | 7 (9.9) | 36 (10.3) | 5 (7.9) | 31 (10.8) | | |

population of 353,709 residents. Since 2005, 108,547 resident people have been trained in BLS and AED use, corresponding to 30% of local population). As of December 31st 2018, 3400 resident people had completed a BLS-D course and became part of the layperson network; of these, 2712 persons are laypersons and 688 are off-duty physicians, nurses, or CPR course trainers.

### *First responder network*

Unlike many other Swiss Cantons, in the Ticino Canton a two-tier first responder network exists. One tier is made up by police, border inspectors and the fire brigade. The activity of this group of first responders started on January 1st, 2006 (Fig. 2). Each first responder is trained and certified following the standard ERC BLS/AED course. A second tier is represented by a very large group of adult volunteers who are trained and certified following the standard ERC BLS/AED course. The layperson network is activated only in case the OHCA scene is safe and their relative distance to OHCA is shorter than ambulance arrival as estimated by a smartphone application.[17,18] The mobile application was launched on June 1st 2014 (Fig. 2), and its functionality has been described previously.[17,18] Registration of a layperson takes place via an online database in which they can enter their contact information including mobile phone number and specifications of their BLS certificate. Biannual retraining is required.

### *Definitions*

Survived event was defined as ROSC with a palpable pulse sustained until arrival at the emergency department and transfer of care to medical staff at the receiving hospital. This definition corresponds to the Utstein-style guideline.[16] A bystander was defined as an individual who witnessed the collapse or who found the person unresponsive and activated the EMS system. Modifiable factors were defined as factors that, in theory, could be altered by public health or organizational initiatives/interventions to improve care and outcomes for OHCA patients.[19] We considered modifiable factors in pre-hospital organization bystander intervention, first-responder and layperson intervention and time to initiate CPR and/or defibrillate the patient. Non-modifiable in the pre-hospital setting were defined as patient or arrest characteristics which cannot be altered by any public health intervention or improvements in the systems of care (age, witnessed status, initial heart rhythm).

### *Statistical analysis*

All analyses were performed using Stata 15.1 (StataCorp, College Station, TX, USA). A 2-sided $p<0.05$ was considered statistically significant. Continuous data are reported as mean and standard deviation, median and quartiles when appropriate. Categorical data are reported as counts and percent. The studied population was divided in 4 time periods (2002–2006, 2007–2010, 2010–2014, 2015–2018), i.e. according to the year in which the OHCA occurred. These 4 time periods corresponded to the introduction or launch of state-wide initiatives (Fig. 1) which were considered relevant to increase outcome of OHCA victims. CPR proportion, survived event and survival to hospital discharge were calculated for each time period and then compared. Univariable logistic regression analysis was performed to compare the characteristics and outcomes between males and females. A multivariable logistic regression analysis was performed to assess whether gender was an independent predictor

of survival at discharge. Potential confounders to be included in the model were selected based on biological plausibility and data reported in previous studies. They were: year group of the OHCA's occurrence (as a categorical variable), the victim's age group (as a categorical variable), presenting rhythm (shockable or not), a combination of witnessed status and laypeople initiated CPR, OHCA location (home vs public) and EMS arrival time.

## Results

A total of 2481 patients with OHCA were included in the final study population (Fig. 1). Patient-related and cardiac arrest–related characteristics are reported in Table 1. Patients' outcome is reported in Table 2. Female patients represented one-third of the entire study cohort. Compared to men, women were significantly older (on average 6.7 years) and the OHCA occurred more frequently at home. Over the 16-year study period, there was a progressive increase in the mean age of men, whereas the mean age of the female population remained nearly unchanged.

### *Witnessed status and bystander resuscitation attempt*

Altogether, 70% of the patients had a bystander-witnessed arrest, with a modest significant annual fluctuation. An OHCA was less frequently witnessed in women (Table 1). The overall proportion of a first responder performing a CPR significantly improved over time from 35% to 81% ($p<0.001$); there was no difference between the genders in the proportion of first responders on site (Fig. 2). Use of AED progressively increased year-after-year from 3% to 10% ($p<0.01$), but still remained lower in women (Table 1).

### *First recorded heart rhythm and time interval*

The proportion of patients with a shockable rhythm was 34% for the entire study period, with a modest variation over time (Table 1 and Fig. 2). Women more frequently had a non-shockable rhythm with a non-significant trend reduction over time (Fig. 2). The time from a bystander call to BLS initiation either by bystander or first responder, was reduced over time from 9 min (IQR 6–12) in 2002–2006 to 5 min (IQR 3–8) in 2015–2018 ($p<0.01$); up until 2014, the time from a call to BLS initiation was consistently longer in women (Table 1). However, after the introduction of the automatic management of lay responder network by a mobile application-based alert system in 2014 (Fig. 2), there was a significant reduction in the time to CPR in both women and men (Table 1). The median time interval from recognition of cardiac arrest to ambulance arrival was 10 min (IQR 7–14) in 2002–2006, which did not vary over time and was similar for both genders (Table 1).

### *First recorded heart rhythm in witnessed OHCA receiving a CPR before ambulance arrival*

Over a 16-year-long period, the proportion of patients with shockable rhythm showed a progressive decrease in the subset of witnessed OHCAs receiving bystander CPR (Fig. 2). In the period 2002–2006, there were 52% of the cases of witnessed shockable OHCA receiving a bystander CPR, whereas in the period 2015–2018 there were 41%. The change was particularly evident in men, whereas in women the proportion of non-shockable rhythm only slightly reduced.

**Table 3 – Multivariable logistic regression analysis of the probability of survival to hospital discharge according to gender adjusted for confounding factors. The model was derived considering the patients who had all the variables included in the model available (2457 out of a total of 2481). CPR: cardio pulmonary resuscitation.**

| Survival at discharge | Odds ratio | 95% CI | P value |
|---|---|---|---|
| Gender | | | |
| F | 1.0 | | |
| M | 1.13 | 0.8–1.5 | 0.43 |
| Age groups | | | |
| <36 | 7.3 | 3–17.7 | <0.001 |
| 36–64 | 3.17 | 2.2–4.5 | <0.001 |
| 65–79 | 1.7 | 1.2–2.4 | 0.003 |
| ≥80 | 1.0 | | |
| Year groups | | | |
| 2002/2006 | 1.0 | | |
| 2007/2010 | 1.9 | 1–2.7 | 0.001 |
| 2011/2014 | 2.2 | 1–3.2 | <0.001 |
| 2015/2018 | 3.7 | 2.6–5.4 | <0.001 |
| Shockable rhythm | | | |
| No | 1.0 | | |
| Yes | 5 | 3–6.4 | <0.001 |
| Witnessed and CPR status | | | |
| Unwitnessed and no laypeople CPR | 1.0 | | |
| Unwitnessed and laypeople CPR | 0.88 | 0.5–1.5 | 0.659 |
| Witnessed and no laypeople CPR | 1.35 | 0.8–2.3 | 0.248 |
| Witnessed and laypeople CPR | 1.99 | 1.2–3.2 | 0.005 |
| EMS arrival time | 0.4 | 0.3–0.5 | <0.001 |
| Location | | | |
| Home | 1.0 | | |
| Public | 1.7 | 1.3–2.2 | <0.001 |

### *Proportion of patients with return-to-spontaneous circulation, and survival at discharge*

The overall proportion of patients with a survived event increased from 28% to 35% ($p=0.01$) over a 16-year-period. During the 16-year-period, survival on arrival at hospital of male patients increases from 30% to 36% ($p=0.07$) whereas in females patients this same item increased from 21% to 31% ($p=0.03$) (Table 2).

### *Changes in survival to hospital discharge following state-wide initiatives*

The overall survival to hospital discharge increased from 11% in the period 2002–2006 to 23% in the period 2015–2018 ($p<0.001$). In male patients, the survival at discharge increased from 12% in 2002–2006 to 25% in 2015–2018 ($p=0.001$) (Fig. 2), with a statistically significant increase in odds of survival in 2007–2010 (OR 1.6 95% CI 1.1–2.3; $p<0.001$), in 2011–2014 (OR 2 95%CI 1.4–2.8; $p<0.001$) and in 2015–2018 (OR 2.4 95%CI 1.7–3.3; $p<0.001$) compared to 2002–2006. These time-periods correspond to the development of the telephone-assisted CPR as well as to the launch of the mobile APP for the FRs and layperson recruitment, respectively. On the other hand, in females, survival increased from 7% in 2002–2006 to 18% in 2015–2018 ($p<0.001$) (Table 2 and Fig. 2), with a corresponding increase in the odds of survival of almost 3 times from 2002–2006 compared to 2015–2018 (OR 2.9 95%CI 1.5–5.8, p 0.001).

### *Survival probability in different age groups according to gender*

Results of the multivariable logistic analysis to assess predictors of survival is shown in Table 3. Young patients showed a 6-fold greater probability to survive than 80-year old or older patients (Table 3). When adjusted according to age, presenting rhythm, year-groups of OHCA's occurrence, OHCA location, EMS arrival time, witnessed status and CPR-initiated by laypeople, no significant difference in survival probability was observed according to gender (OR 1.13, 95 % CI 0.8−1.5 in males). Interaction tests showed a significant interaction of the age-group with the victim gender (p=0.019) and for the EMS arrival time and gender (p=0.016); in contrast, no interaction between the other variables (year group, shockable rhythm and witness/ laypeople CPR) with the victim gender was noted.

### *New onset of anoxic brain damage in survivors*

Overall, 10 % of the survivors were diagnosed with a significant anoxic brain damage (CPC 3−4) at discharge, without significant differences among gender over time.

## Discussion

This study of OHCA patients in urban and rural areas in the Ticino Canton aimed at evaluating gender-related differences in bystander, first- and lay-responders intervention over a decade and how these differences related to outcome. Our state-wide study has had several major findings: 1) survival rates more than doubled over a 16-year-long period and in an equal proportion in male and female patients which is probably the result of multiple initiatives implemented; 2) a major improvement of survival rates in both men and women with shockable and non-shockable rhythm was observed in the subsequent years after the introduction of a mobile application for the management of first-responders and lay-responders; 3) in the subset of witnessed OHCAs receiving bystander CPR, the proportion of women presenting with a shockable rhythm increased significantly; 4) after taking non-modifiable gender-related differences into account (age, witnessed status, laypeople CPR, initial rhythm and EMS arrival time), survival significantly increased over time and in a similar amount in both men and women.

Our findings contribute to clarify how modifiable and non-modifiable factors influenced the outcome of women suffering an OHCA during a two-decade-period in relation to state-wide activities. Taken together, our observations suggest that multiple state-wide initiatives contributed to increase survival in equal proportion in men and women, probably by mitigating the effect of non-modifiable factors responsible for the difference in survival, which nevertheless play a predominant role in this difference in survival between males and females. Our results may have implications in the manner in which gender-related differences should be addressed in modern resuscitation era in order to increase survival in both men and women.

The large temporal increase in bystander and layperson CPR in conjunction with the large increase in number of patients reaching a stable spontaneous circulation and then, reaching the hospital alive, is a strong indicator of the improvements made in pre-hospital setting. Our study results are confirmatory of the large literature evidence about the key role played by bystanders and survival with improved neurological outcome of OHCA victims.[2,20] As shown in Wissenberg et al.[3] in Denmark in the period 2001−2010, a significant increase in survival following OHCA and a major reduction in new onset of anoxic brain damage was associated with a concomitant increase in bystander CPR. As in the Danish cohort, we observed an increase in survival of patients having a shockable rhythm for a similar historical period and of comparable duration (10 years). Indeed, in Denmark 30-day survival increased from 10 % in 2001 to 30 % in 2010, whereas in Ticino it increased from 15 % in 2005 to 41 % in 2014.[15]

OHCA bystanders plays a key role in increased OHCA survival by providing CPR and facilitating early activation of the first responder network with an early call to the EMS dispatch center. In the Ticino Canton area, once the EMS dispatcher confirms the OHCA and scene's safety, the layperson network is immediately activated via the mobile application. The automatic alert of both network arms (first responders and laypersons) has the obvious advantage to target people able to perform CPR and to dispatch them to the OHCA location, thus reducing the time from collapse to initiation of resuscitation manoeuvres with a positive effect on survival rates as shown in the present study. Although our study design does not allow to conclusively indicate which specific factors have contributed most to the increase in ROSC achievement, survived event and then in survival to hospital discharge, the change in survival rate of women compared to men may provide some insights.

In line with other more recent observational studies,[7] we noticed a smaller increase in the overall non adjusted survival in women compared to men despite a similar increase in bystander CPR or CPR/ AED use. As in the Goto et al. study,[7] we observed that women experienced their OHCA at home more frequently than men (77 % vs 64 %), and were on average 6 years older than men. Considering that in the Ticino Canton, the average life expectancy is 86 years of age for women and 82 years of age for men,[21] it is likely that − at the time of OHCA − women are more frequently on a single-person household compared to men. This society scenario finds significant similarities in Goto et al.,[7] who also reported, in a nationwide observational study, that women having OHCA more frequently lived in rural areas (25.7 % vs. 24.9 %), possibly alone (unwitnessed OHCA: 63.7 % in women and 59.7 % in men), and were on average 6 years older than men (80.3 years vs. 74.3 years). That may well explain the slightly lower bystander witnessed OHCA we recorded, and the longer time to initiate CPR in women than in men we observed. Whether the lower proportion of witnessed OHCA and consequently of lower bystander CPR in women may result in the observed substantial proportion of female patients with non-shockable heart rhythm is speculative, but supported by some physiopathological reasoning and by our findings. Even if the initial rhythm is a ventricular tachycardia or ventricular fibrillation, the delay in CPR or AED use would naturally evolve to asystole or to a very low amplitude ventricular fibrillation, a rhythm with very low probability to be converted into sinus rhythm.[22] Unlike many other registries, time to first CPR and time to first responder arrival is well documented in our registry due to systematic phone call analysis and use of the mobile application, which exactly monitors the time from alert to arrival on target. On average, time to CPR initiation in our cohort was 1 min longer in women than in men. It is well known that each minute delay in CPR/defibrillation reduces the likelihood of survival by approximately 8%−10%. Consistent with this scenario is the reported lower rate of a non-shockable rhythm in women, and the lower likelihood of return to spontaneous circulation in women, which on average was 7%−8% lower in women than in men. Additional explanations for inadequate or late recognition of OHCA in women were proposed, e.g. lack of awareness that OHCA may strike women

as often as men[14] and the possibility that women themselves do not recognize the urgency of sentinel complaints during acute MI (a common trigger of OHCA), as they may have more equivocal complaints such as fatigue, syncope, vomiting, and neck/jaw pain compared to men. Therefore, home surveillance system using wearable garments, smartwatch technology, or smart wearable ECG monitors in single household women, especially at a certain age, may represent a possible technological solution to reduce the time to EMS alert and/or to activation of layperson network or first-responders.

When we restricted our analysis to the subset of witnessed OHCA receiving bystander CPR, we observed a striking divergent trend for women and men. During the last 4 years, we observed a reduction of non-shockable rhythm in women, whereas there was an increase in non-shockable rhythm in men. The increase in shockable rhythm in women was temporally related to the introduction of the layperson network, and resulted in major improvement of survival in women. In contrast, the reduction of shockable rhythm in men despite high rate of bystander CPR and a well-performing first responder and layperson network is somehow puzzling. This novel trend for men follows a reported increase in non-shockable rhythm in western countries.[23] This change might be related to a subtle incremental role played by unmodifiable factors over modifiable factors as indicated by the aging of the male population – on average 4 years (period 2015–2018 compared to the past periods).

Multiple studies have consistently reported differences in OHCA care between women and men, thus resulting in poorer outcome in women in the crude analysis.[7–12] However, when the survival was adjusted for non-modifiable factors (age, witnessed status, initial heart rhythm), there was no difference between women and men. This is also in line with the study by Blom et al.,[11] as they did not observe any difference in survival according to patient gender with shockable rhythm, and by Goto et al.,[7] who used hierarchical propensity score matching indicating no differences between women and men in the 1-month survival and neurologically intact survival in a nationwide, population-based observational study. Our results were also in line with those by Bray et al.,[12] who pointed out that no gender differences were observed in survival to hospital discharge after adjustment for known predictors of survival (age, witnessed arrest, bystander CPR, year of arrest, rural location, public location, EMS response time). However, our study also helps to understand how state-wide initiatives may improve OHCA survival independently of gender, emphasizing the major importance to consider long-term trend when assessing gender-specific differences in OHCA outcome.

The main limitation is that our study is observational in nature, thus we cannot exclude the presence of uncontrolled confounders which may have affected our results. However, we adjusted our analysis for the most common factors with prognostic relevance according to recent literature.[16,24] In this context, the state-wide initiatives overlapped in time, and although supportive, they offer no direct causal link between initiatives and outcomes. Secondly, we were able to only analyse a limited number of covariates without data on several important factors: the quality of CPR given, type of CPR (compression-only CPR versus conventional), advanced treatment provided, including therapeutic hypothermia, revascularization, etc. Although the overall proportion of missing data was small, it was as high as 17 % for CPC at hospital discharge; therefore, we used survival to hospital discharge without the evaluation of neurological status as endpoint. Finally, considering the structure of our registry, we were not able to calculate the percentage of patients who received an attempted resuscitation over time.

## Conclusions

We observed an increase in survival following OHCA that was significantly associated with a concomitant increase in bystander and/or first-responder and layperson intervention. Both genders benefited from these and other state-wide initiatives as indicated by a similarly large increase in the likelihood to return to spontaneous circulation, and survival. The survival difference was mostly explained by non-modifiable factors, in particular, by a lower proportion of shockable rhythm. Finally in the most recent years, an alarming trend toward increase in non-shockable rhythm in men has been noticed which needs further assessment.

## Credit author statement

AA, MLC and EB were responsible for Conceptualization, Methodology and writing the original draft. GMDF and TM reviewed and edited the manuscript. CK was responsible for formal analysis. CB and RC were responsible for data curation.

## Disclosures

Angelo Auricchio is a consultant to Boston Scientific, Backbeat, Biosense Webster, Cairdac, Corvia, Microport CRM, EPD-Philips, Radcliffe Publisher. He received speaker fees from Boston Scientific, Medtronic, and Microport. He participates in clinical trials sponsored by Boston Scientific, Medtronic, EPD-Philips. He has intellectual properties with Boston Scientific, Biosense Webster, and Microport CRM.

## Conflict of interest

No other conflict of interest to disclose.

## Funding

The present study was realized thanks to a grant from the Swiss Heart Foundation. Grant n° FF18018 “Lay people involvement in out-of-hospital cardiac arrest resuscitation: strategies for improvement and impact on survival”.

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