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Review article

# Gender and survival after sudden cardiac arrest: A systematic review and meta-analysis☆

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ABSTRACT

*Background:* Conflicting results exist regarding the impact of gender on early survival after sudden cardiac arrest (SCA). We aimed to assess the association between female gender and early SCA survival.
*Methods:* We searched Embase, MEDLINE, EBM Reviews, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews (between 1948 and January 2014) for studies evaluating the association between gender and survival after SCA. Two independent reviewers selected studies of any design or language. Pooled odds-ratios (OR) and 95% confidence intervals (CIs) were estimated using a random-effects model. Additional sensitivity analyses and meta-regression were carried out to explore heterogeneity.
*Results:* Thirteen studies were included involving 409,323 patients. Women were more likely to present with SCA at home, less likely to have witnessed SCA, had a lower frequency of initial shockable rhythm but were more likely to receive bystander CPR. After adjustment for these differences, women were more likely to survive at hospital discharge (OR 1.1, 95% CI 1.03–1.20, $p = 0.006$, $I^2 = 61\%$). This association persisted in multiple sensitivity analyses.
*Conclusion:* This meta-analysis of observational studies demonstrates that women have increased odds of survival after SCA. Further studies are needed to address mechanisms explaining this discrepancy.
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## 1. Introduction

Despite decades of research and major investment, survival after out-of-hospital sudden cardiac arrest (SCA) remains poor, around 5%.[1] Identification of factors associated with survival is of major interest, and several prognostic factors have been described, such as bystander CPR,[1–3] initial shockable rhythm,[1,4] and early defibrillation.[5] Age is negatively associated with survival,[6–8], whereas the impact of gender remains unclear.[9]

Marked differences regarding cardiovascular disease between men and women have been described, particularly regarding genetic factors,[10] coronary artery disease,[11] cardiac arrhythmias,[12–14] or sport-related sudden death.[15,16] However, women remain underrepresented in medical research, and guidelines often extrapolate to women results from studies carried out predominantly among men. This need of specific gender studies has been repeatedly emphasized.[17,18]

In the field of SCA, striking differences have been observed in terms of prognostic factors, such as studies finding women

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to have less initial shockable rhythm[19,20] and less bystander-witnessed SCA,[19,21] two keys factors usually associated with low survival. However, some studies observed a survival advantage for women[22,23]. This apparent gender paradox have been investigated in several studies, with conflicting results.[20,21,24] To address this possible disparity, we performed a systematic review and meta-analysis to assess the extent to which female gender was associated with survival after out-of-hospital SCA.

## 2. Methods

### 2.1. Data sources and searches

We searched for studies evaluating the association between gender and survival rates at hospital discharge or at one-month after out-of-hospital SCA. We included studies in adults (subjects of ≥18 year-old) and with any design or language. Studies in children, animal studies, ex vivo and toxicological studies, duplicates, summaries, commentaries and editorials, case reports, case series, studies that did not present original data, studies including inhospital cardiac arrest, or that did not report survival rates at hospital discharge after SCA, were excluded. For studies with insufficient information, the correspondent author was contacted and in absence of response to the query, the study was eventually excluded.

A comprehensive search of several electronic databases was conducted in EMBASE (between 1988 and January 2014), Ovid MEDLINE in-process and other nonindexed citations and Ovid MEDLINE (between 1948 and January 2014), and EBM Reviews Cochrane Central Register of Controlled Trials and EBM Reviews Cochrane Database of Systematic Reviews (between 2005 and January 2014). In addition, we searched the reference lists of eligible studies and relevant reviews for additional published and unpublished data, searched by contacting several experts, and used the web search engine "Google" for abstracts, conference proceedings, and unpublished studies.

We used a combination of keywords related to:

(1) Type of exposure: "women" or "female" or "men" or "male" or "sex" or "gender".
(2) Cardiac arrest: "sudden death" or "cardiac arrest" or "out-of-hospital SCA" or "sudden cardiac death" or "sudden cardiac arrest".
(3) Outcome: "survival" or "prognosis" or "outcome".

Details of the search strategy are provided in Appendix 1.

### 2.2. Study selection

Two independent reviewers (W.B. and H.M.) screened all abstracts and titles to identify potentially eligible studies. The full text of these potentially eligible studies was then screened to determine the eligibility of the study for the review and meta-analysis. Inter-rater agreement was assessed at each step of selection, using kappa statistic.[25] Kappa indicates level of agreement, ranging from 0 (no agreement) to 1 (perfect agreement). According to previous standards[26] we considered very good agreement for kappa value between 0.81 and 1. Disagreements regarding eligibility were resolved by consensus with the help of a third reviewer (E.M.).

### 2.3. Quality assessment

This meta-analysis complies with the preferred reporting items of Meta-Analyses of Observational Studies in Epidemiology (MOOSE).[27] We selected relevant risk of bias indicators from the Newcastle-Ottawa Scale[28] and the Cochrane risk of bias tool (www.cochrane.org/resources/handbook). According to the Newcastle-Ottawa quality assessment scale, we evaluated three components (selection of cases, comparability of cohorts, and assessment of outcome), and we complied with the Cochrane risk of bias tool, assessing risk of bias regarding outcome (here, survival assessment). Finally, we evaluated three components related with survival after SCA (the validation of SCA occurrence from cardiac origin, survival assessment, and the extent of adjustment for confounders). Concerning the validation of SCA occurrence from cardiac origin, we considered the diagnosis to be most valid if it was based on Utstein criteria as well as clinical, laboratory, electrocardiographic, medical imaging or autopsy criteria (0 was given in the absence of valid criteria). For cases reported in SCA registries, we considered the diagnosis as previously adjudicated. Regarding the quality assessment of the outcome (survival), it was judged on the basis of record linkage, adequate follow-up (at least to hospital discharge or at one-month) and a small loss to follow up (less than 10%). For the adjustment for confounders, 0 was given if no adjustment or insufficient adjustment has been made (no adjustment for age, initial rhythm or witness). One point was given if adjustments on age and initial rhythm and witnessed status had been made. If an additional adjustment was made, either for bystander cardiopulmonary resuscitation or for location or for another adjustment, a score of 2 was given. If a study had validation of SCA from cardiac origin, proper assessment of survival and adjustment on age and initial rhythm, it was deemed to be of low risk of bias. Quality indicators are presented in Appendix 2.

### 2.4. Data extraction

Data extraction was performed using a standardized form that included a full description of the study characteristics, cardiac arrest description (occurrence at home, bystander-witnessed, bystander CPR, initial shockable rhythm), outcome (survival at hospital discharge or survival at one-month), effect size measurement, and the type of adjustments performed (age, gender, initial rhythm, witnessed status, cardio-pulmonary resuscitation, location, other adjustment). The authors were contacted in case of uncertainty about the data. Data extraction was performed in duplicate by 2 reviewers (W.B. and H.M.) and then compared. In case of discordance, a third reviewer (E.M.) facilitated a consensus. The most adjusted measure of association was extracted from studies that presented multiple adjusted estimates.

### 2.5. Data synthesis and analysis

We decided a priori to use the random-effects model as described by DerSimonian and Laird to pool outcomes across studies.[29] This model was chosen because of the significant anticipated heterogeneity between studies in terms of population and methods. The random-effects model is the most conservative approach in this setting because it incorporates within and between-study heterogeneity. Outcomes were reported as odds ratios (OR) and 95% confidence intervals (CIs) as the relative measure of association. Statistical heterogeneity across the studies was evaluated using the $I^2$ statistic to quantify inconsistency among studies that is not attributable to chance. $I^2$ values of 25% or less, 50%, and 75% or more represent low, moderate, and high inconsistency, respectively.[30] Sources of heterogeneity were assessed in meta-regression, with mixed effects regression using unrestricted maximum likelihood. In meta-regression, dependent variable was the log odds ratio of survival in every study, and the independent variables were population baseline characteristics (rates of occurrence at home, bystander-witnessed SCA, bystander-CPR and

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