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Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes

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ABSTRACT

Objectives To assess the current evidence on the effect of pre-arrest comorbidity on survival and neurological outcomes following out-of-hospital cardiac arrest (OHCA).

Design Systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data sources MEDLINE, Ovid Embase, Scopus, CINAHL, Cochrane Library and MedNar were searched from inception to 31 December 2018.

Eligibility criteria Studies included if they examined the association between prearrest comorbidity and OHCA survival and neurological outcomes in adult or paediatric populations.

Data extraction and synthesis Data were extracted from individual studies but not pooled due to heterogeneity. Quality of included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale.

Results This review included 29 observational studies. There were high levels of clinical heterogeneity between studies with regards to patient recruitment, inclusion criteria, outcome measures and statistical methods used which ultimately resulted in a high risk of bias. Comorbidities reported across the studies were diverse, with some studies reporting individual comorbidities while others reported comorbidity burden using tools like the Charlson Comorbidity Index. Generally, prearrest comorbidity was associated with both reduced survival and poorer neurological outcomes following OHCA with 79% (74/94) of all reported adjusted results across 23 studies showing effect estimates suggesting lower survival with 42% (40/94) of these being statistically significant. OHCA survival was particularly reduced in patients with a prior history of diabetes (four out of six studies). However, a prearrest history of myocardial infarction appeared to be associated with increased survival in one of four studies.

Conclusions Prearrest comorbidity is generally associated with unfavourable OHCA outcomes, however differences between individual studies make comparisons difficult. Due to the clinical and statistical heterogeneity across the studies, no meta-analysis was conducted. Future studies should follow a more standardised approach to investigating the impact of comorbidity on OHCA outcomes.

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INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a sudden and commonly fatal medical emergency. Although a number of patient-specific and arrest-specific factors have been identified that influence patient survival, these factors fail to fully explain the variability in outcomes. The effect of prearrest comorbidity on outcomes in patients with OHCA is poorly understood.

It has been suggested that a better understanding of the effect that comorbidity has on OHCA outcomes could lead to a number of benefits such as: improved understanding of the epidemiology of cardiac arrest, more informed end-of-life planning, improved public health policies to preemptively manage ‘at risk’ populations and improved prognostication. A number of authors have investigated the association between prearrest comorbidity and OHCA survival with some reporting comorbidity to be negatively associated with survival, while others reporting no relationship. Regarding neurological outcomes, similar variability in findings has been observed, with some authors reporting a negative relationship, while others reporting no relationship. However, despite the variability in findings and continued interest in the topic, no systematic review examining the association of prearrest comorbidity and OHCA outcomes has been conducted to date. This systematic review provides an overview of the current evidence regarding the association between prearrest comorbidity and OHCA outcomes.
patient survival and neurological outcomes following OHCA.

METHODS

Protocol
The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was followed in this systematic review.

Review question
In patients with OHCA, do preexisting chronic health conditions result in poorer survival to hospital discharge and neurological outcomes?

Eligibility criteria
To be eligible for inclusion in this systematic review, studies had to include: (1) cases of OHCA of medical aetiology, and (2) quantitative comparison between comorbidity and OHCA outcome (either survival or neurological outcome). Survival outcome could include survival to hospital discharge or 30-day survival, both being survival metrics recommended by the Utstein report. No restrictions were placed on the tool used to measure comorbidity or neurological outcome, and both adult and paediatric cases were included. No publication date or language restrictions were applied. There were no ethical requirements for inclusion in this systematic review.

All comparative study types were considered for inclusion except: (1) editorials, case studies/case reports/case series, commentaries, conference abstracts, opinion pieces and letters; (2) in-hospital cardiac arrests or arrests that occurred during interhospital transfer; (3) cardiac arrests with a primary aetiology of trauma, drug-related, drowning, electrocution or asphyxia as defined by the 2015 Utstein OHCA reporting guidelines.

Data on individual cancer sub-types were excluded as this level of detail was beyond the scope of this review. Data on prior surgeries, medication use or conditions that are congenital, idiopathic, of short duration and/or unlikely to have long term implications were not considered to constitute a comorbidity for this review.

Data sources
The databases Ovid MEDLINE, Ovid Embase, Scopus, CINAHL and Cochrane Library were searched for all eligible studies from inception to 31 December 2018. The search engine MedNar was searched until 31 December 2018 for grey literature. Reference lists from all relevant studies were searched to identify any additional studies.

Patient and public involvement
No patient or public were involved in the design or planning of this study.

Search strategy
Search terms were grouped into two broad categories of ‘OHCA’ and ‘comorbidity’ and combined using the Boolean operator ‘AND’. The search strategies for each of the databases have been provided in online supplementary appendix 1.

Study selections
Titles and abstracts were initially screened by a single author (DM) to identify potentially relevant papers. Full-text review was then performed by two authors (DM and SB) independently to identify studies that met the eligibility criteria, with disagreements resolved by a third reviewer (JF). As a subsequent check to ensure a high level of sensitivity, JF rescreened all titles and abstracts. Any papers identified from this second screen then underwent full-text review by two authors (DM and SB) and were included if they met eligibility criteria (by mutual agreement of DM and SB).

Data collection
Data were extracted by DM from the relevant studies and entered into an Excel spreadsheet. Data included information on authors, title, publication year, study location, study period, aims, study design, comorbidity, type of comorbidity measurement, patient survival and/or neurological outcome. Additionally, prehospital resuscitation factors (eg, witness status and bystander cardiopulmonary resuscitation) were extracted where available. Where a study provided relevant outcomes graphically (eg, in a forest plot) but did not provide corresponding effect estimates, the authors of those studies were contacted for additional data.

Risk of bias in individual studies
Risk of bias of individual studies was independently assessed by two authors (DM and SB) using the Newcastle-Ottawa Quality Assessment Scale for cohort studies, and any disagreements were resolved by mutual consensus.

Summary measures
We planned to use ORs to compare survival or neurological outcomes between cases with and without comorbidities. In studies that did not provide ORs, crude ORs were calculated wherever possible. Studies that provided mortality OR were converted to survival OR by calculating the reciprocal of the mortality OR for both unadjusted and adjusted values. Studies that provided statistics other than OR (eg, hazard ratios) were not included in forest plots. Where cerebral performance categories (CPC) were reported, we used CPC of 1 or 2 as an indicator of good neurological outcome. ORs for survival to hospital discharge and 30-day survival were considered equivalent and grouped together. For both survival and neurological outcomes, results were included in a forest plot only if two or more studies reported ORs on the same comorbidity. RevMan V.5.3 was used to obtain relevant figures such as forest plots. Where individual studies provided different descriptors for the same or similar comorbidity, we planned to group these where appropriate (eg, hyperlipidaemia and hypercholesterolaemia). Any results exclusively associated with an initial non-shockable cardiac arrest.
arrest rhythm were excluded. Where multiple results were reported by a single study for the same exposure but for varying subgroup (for example by initial cardiac arrest rhythm), only one set of results were utilised to prevent duplication. Given the well documented prognostic influence of specific other covariates on OHCA outcomes,\textsuperscript{4,20,21} adjusted results were preferentially used.

RESULTS

Study selection
The initial search identified 6395 citations. After removal of duplicates 3132 remained. A total of 75 potential studies were identified after title and abstract screening against inclusion/exclusion criteria. After full-text review, 29 studies were included. These results are summarised in the PRISMA flow diagram (figure 1). Of the 46 excluded studies, 24 were excluded because they did not directly document a comparison between OHCA outcome and at least one comorbid condition or did not allow for the direct calculation of such a relationship. Our search also identified two studies\textsuperscript{22,23} that conducted relevant analysis however did not report these results and were therefore excluded from this review. Our initial article search identified three papers from Taiwan\textsuperscript{24–26} with significant cohort overlap. To avoid duplication of results only the paper\textsuperscript{26} with the most comprehensive analysis of comorbidity was included within this review. Similarly, of two papers from Australia\textsuperscript{9,27} with significant cohort overlap, only one paper\textsuperscript{9} was included in the review.

Study characteristics
A summary of all included studies is provided in tables 1 and 2. Studies presented in table 1 (n=21) directly investigated the effect of comorbidity on OHCA outcome, while those in table 2 (n=8) had alternative primary aims but still provided information on the association between comorbidity and OHCA outcomes. Results from each of the individual studies are shown online supplementary tables 1 (for survival to hospital discharge outcomes) and online supplementary table 2 (for neurological outcomes). There were 18 studies conducted in Europe,\textsuperscript{3,5,10,13,15,28–40} four in the USA,\textsuperscript{8,12,41,42} three in Asia,\textsuperscript{20,26,43} two multinational studies,\textsuperscript{11,14} one in Australia\textsuperscript{9} and one in Canada.\textsuperscript{44} The number of patients enrolled in each study varied from n=6330 to n=2 47 684.\textsuperscript{41} Patient inclusion age varied between studies, with 19 studies restricted to adults (≥16 years),\textsuperscript{3,8,9,12,20,26,28,29,31,33,36–44} one\textsuperscript{10} restricted to 70 years or over, seven placing no age restrictions\textsuperscript{5,11,13,15,32,34,35} and two studies being unclear about age.\textsuperscript{14,30} Cohort recruitment points varied greatly also, with 15 studies using scene of arrest as the enrolment point,\textsuperscript{5,8–11,13,20,31–33,58–40,42,44} 6 using emergency department (ED) admission\textsuperscript{12} and 8 using hospital admission.\textsuperscript{3,14,28–30,34–41,43} Cardiac arrest aetiology was identified as either cardiac or non-traumatic in 12 studies,\textsuperscript{5,8–12,20,26,31,33,36,41} while the remaining studies either placed no restriction or were unclear. Patient clinical inclusion characteristics were highly variable between the studies. Eight studies placed no restrictions\textsuperscript{9–11,20,26,31,40,44} on inclusion criteria while 21 studies restricted inclusion to patients with one or more clinical characteristics. These clinical characteristics included such factors as initial presenting cardiac rhythm,\textsuperscript{5,8,32,34,42} whether the arrest was witnessed,\textsuperscript{33,38} Glasgow Coma Scale score after successful resuscitation,\textsuperscript{5,28,29} presence of a particular medical condition and/or admittance to a specific hospital department\textsuperscript{12} and/or certain procedures or treatments received (eg, hypothermia; coronary angiograph).\textsuperscript{3,28,43}

A number of studies had overlapping cohorts (overlapping geographical regions and recruitment dates). This included two studies from the Netherlands\textsuperscript{5,10} and two from Sweden.\textsuperscript{13,34} However, all four studies were included in this review as they differed sufficiently in inclusion criteria, study aims or recruitment period. Four studies from Denmark\textsuperscript{29,37,39,40} had overlapping cohorts but generally examined different outcomes. Where the same or similar outcomes were examined, results from only one of the studies was used in this review. A fifth Danish study\textsuperscript{7} was also included as the cohort overlap with the other four Danish studies was minimal. Three included US studies\textsuperscript{8,12,42} have a possible cohort overlap, with a fourth study\textsuperscript{41} that sourced its cohort from a nationwide inpatient sample. However, this overlap would be 20% at most and therefore it was decided to include all four studies.
Table 1  Characteristics of included studies that directly investigated the influence of comorbidity on OHCA outcomes

| Study ID                  | Country            | Study design     | Cases     | Enrolment period | Reported outcome                        | Comorbidity                                                                 | Source of comorbidity data               | Inclusion criteria                                           | Age (years) |
|---------------------------|--------------------|------------------|-----------|------------------|------------------------------------------|----------------------------------------------------------------------------|------------------------------------------|-------------------------------------------------------------|--------------|
| Andrew et al 2017         | Australia          | Retrospective cohort | 15 953    | Jan 2007–Dec 2014| Survival to hospital discharge           | CCI=0,1,2,3,≥4, hypertension, diabetes, myocardial infarction, cerebrovascular disease, congestive heart failure, chronic obstructive disease, cancer, metastatic cancer, dementia, peripheral vascular disease, peptic ulcer, HIV/AIDS, skin ulcers, connective tissue disease. | Ambulance patient care records.          | All non-traumatic arrests with attempted resuscitation.    | ≥16          |
| Beesems et al 2015        | Netherlands        | Prospective cohort | 851       | Jan 2009–Dec 2011| Survival with good neurological outcome (CPC 1–2) | CCI ≥4.                                                                    | Patients general practitioner.           | All non-traumatic arrest patients without DNR orders and in whom resuscitation was started. | ≥70          |
| Blom et al 2013           | Netherlands        | Prospective cohort | 1172      | 2005–2008         | 30-day survival Neurological outcome at hospital discharge | Cardiovascular disease, obstructive pulmonary disease.                  | Presence of at least two condition-specific pharmacy prescriptions.          | All VF/VT OHCA of presumed cardiac aetiology in whom resuscitation was attempted. | Any          |
| Carew et al 2007          | USA                | Retrospective cohort | 1043      | Jan 1999–Dec 2003| Survival to hospital discharge           | Number of chronic conditions.                                           | Ambulance patient care records.          | All VF cardiac arrest patients who had an arrest of presumed cardiac aetiology/heart disease. | ≥18          |
| Corrada et al 2013        | Italy              | Prospective cohort | 63        | 2004–2009         | Neurological outcome at discharge        | Heart disease.                                                            | Unclear.                                | OHCA patients admitted to cardiac intensive care unit alive. | Unclear      |
| de Vreede-Swagemakers et al 1998 | Netherlands | Prospective cohort | 288       | Jan 1991–Dec 1995| Survival to hospital discharge           | Cardiac history.                                                        | Patients general practitioner.           | All OHCA where CPR was attempted by EMS and arrest was not due to trauma or intoxication or patient in terminal stage of disease. | 20–75        |
| Dickey and Adgey 1992     | Northern Ireland (UK) | Prospective cohort | 281       | Jan 1966–Dec 1987| In-hospital mortality                    | Cerebrovascular accident, myocardial infarction.                       | Unclear.                                | All OHCA patients with an initial rhythm of VF.             | Any          |
| Study ID          | Country | Study design               | Cases | Enrolment period | Reported outcome                                                                                       | Comorbidity                                                                                                                                  | Source of comorbidity data | Inclusion criteria                                      | Age (years) |
|------------------|---------|----------------------------|-------|------------------|-------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|--------------------------------------------------------|-------------|
| Dumas et al 2017 | USA     | Prospective cohort         | 1166  | Jan 2007– Dec 2013 | Survival to hospital discharge, neurological outcome at discharge (CPC)                               | CCI=0,1,2,3, atrial fibrillation, cancer, cerebrovascular accident, congestive heart disease, coronary artery disease, diabetes, gastrointestinal disease, heart disease, HIV, hypercholesterolaemia, hypertension, kidney disease, liver disease, lung disease, mental health, metabolic disease, myocardial infarction, non-cardiac history, non-neurological history, peripheral artery disease, prior cardiac arrest, tissue/ inflammatory disease, valvulopathy. | Ambulance patient care records. | Non-traumatic OHCA with initial rhythm of VF.          | ≥18         |
| Herlitz et al 1995 | Sweden  | Prospective cohort         | 488   | 1981–1992        | In-hospital mortality                                                                                   | Myocardial infarction, angina pectoris, hypertension, diabetes, congestive heart failure, cerebrovascular disease, asthema.                | Unclear.                  | All OHCA patients with initial rhythm of VF who were hospitalised alive. | Any         |
| Hirlekar et al 2018 | Sweden  | Retrospective cohort       | 12012 | 2011–2015        | 30-day survival                                                                                       | CCI=0–2, 3–4, 5–6, >6, cancer, cerebrovascular disease, chronic pulmonary disease, congestive heart failure, connective tissue disorder/ rheumatic, dementia, diabetes, diabetes (with complications), liver disease (mild), myocardial infarction, paraplegia/hemiplegia, peptic ulcer disease, peripheral vascular disease, renal disease. | National Patient Registry. | All bystander-witnessed patients with OHCA.            | ≥18         |
| Study ID   | Country                          | Study design   | Cases | Enrolment period | Reported outcome                                | Comorbidity                  | Source of comorbidity data                                      | Inclusion criteria                                                                 | Age (years) |
|-----------|----------------------------------|----------------|-------|------------------|------------------------------------------------|----------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------|-------------|
| Iqbal et al 2015 | UK                               | Prospective cohort | 174   | 2011–2013        | Neurological outcome (modified Rankin Scale, mRS) at discharge | CCI                          | National Institute for Cardiovascular Outcomes Research database. | All OHCA patients who were brought to emergency department with ROSC.       | Any         |
| Kang et al 2017 | South Korea                      | Retrospective cohort | 341   | Jan 2009 – Dec 2014 | Survival to hospital discharge, neurological outcome (CPC) | Cancer                       | Electronic medical records.                                    | All non-traumatic OHCA. Cases of hanging, intoxication and drowning were excluded. | ≥18         |
| Larsson et al 2005 | Sweden                          | Prospective cohort | 1377  | Oct 1980–Oct 2003 | Survival to hospital discharge                  | Angina pectoris, diabetes, myocardial infarction. | Hospital records and general practitioner.                    | All OHCA in whom resuscitation was attempted and patients were admitted to hospital alive. | Any         |
| Lee et al 2018 | Japan, Singapore, South Korea, Malaysia, Taiwan, Thailand UAE | Retrospective cohort | 19,044 | 2009–2012        | Survival to hospital discharge, neurological outcome at discharge (CPC) | 1, 2 or three conditions, heart disease | Hospital records, ambulance reports and ambulance dispatch records. | All non-traumatic OHCA where resuscitation was commenced and where patient's medical history was known. | Any         |
| Parry et al 2017 | Canada                          | Retrospective cohort | 10,097 | 2012–2014        | Survival to hospital discharge, neurological outcome (mRS) | Diabetes                     | In-hospital records.                                           | All OHCA's treated by ambulance services that had data on diabetes status.      | ≥18         |
| Roedl et al 2017 | Austria                         | Prospective cohort | 1068  | Jan 2005–Jan 2012 | 6-month neurological outcome (CPC)               | CCI=1,≥4, liver cirrhosis.   | Hospital screening.                                            | All OHCA patients admitted to the emergency department after ROSC.           | Any         |

Continued
| Study ID      | Country   | Study design      | Cases | Enrolment period | Reported outcome | Comorbidity                                                                                                                                                                                                 | Source of comorbidity data                                                                 | Inclusion criteria                                                                                                         | Age (years) |
|--------------|-----------|-------------------|-------|-----------------|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------|
| Salam et al 2018 | Denmark   | Prospective cohort | 666   | Jun 2002–2011   | 30-day mortality | CCI ≥1, cancer, cancer (metastatic), cerebrovascular disease, congestive heart failure, chronic kidney disease, connective tissue disease, coronary disease, dementia, diabetes, diabetes (with complications), gastric/duodenal ulcer, hemiplegia, hypercholesterolaemia, hypertension, liver disease, malignant haematological disease, acute myocardial infarction, peripheral artery disease, psychiatric disorder, pulmonary disease. | National patient registry and chart review.                                                                                  | Comatose patients (GCS<8), who were successfully resuscitated from OHCA, admitted and treated with TTM (32–36 C) for 24 hours. | ≥18          |
| Søholm et al 2015 | Denmark   | Retrospective cohort | 2527  | 2007–2011       | Survival to hospital discharge | CCI 1, 2, ≥3, cancer, cancer (metastatic), cerebrovascular disease, congestive heart failure, diabetes, diabetes (with complications), hemiplegia, ischaemic heart disease, liver disease (mild), moderate/severe liver disease, moderate/severe renal disease, peptic ulcer, peripheral vascular disease, rheumatological disease. | National Patient Registry.                                                                                                 | All OHCA of any aetiology with attempted resuscitation by EMS.                                                           | ≥18          |
| Study ID            | Country               | Study design       | Cases   | Enrolment period   | Reported outcome                          | Comorbidity                                                                                                                                  | Source of comorbidity data                        | Inclusion criteria                                                                 | Age (years) |
|---------------------|-----------------------|--------------------|---------|--------------------|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------|-------------|
| Terman et al 2015   | USA                   | Retrospective cohort | 588/558 | Jan 2005–Sept 2012 | Neurological outcome (CPC)                | CCI (continuous), CCI=1, CCI=2, AIDS, any tumour, cardiovascular disease, chronic pulmonary disease, congestive heart failure, connective tissue disease, dementia, diabetes, diabetes (with end organ damage), hemiplegia, leukaemia/lymphoma, mild liver disease, moderate/severe liver disease, moderate/severe renal disease, myocardial infarction, peptic ulcer disease, peripheral occlusive vascular disease, tumour (metastatic). | Electronic health records.                     | All non-traumatic OHCA patients that presented to the emergency department.         | ≥18         |
| Winther-Jensen et al 2016 | Europe, Australia | Post hoc analysis of clinical trial | 939     | 2010–2013          | Neurological outcome (CPC) at 6 months    | Modified CCI (mCCI); mCCI=1, mCCI=2, mCCI ≥3.                                                                 | Unclear.                                      | Comatose patients with OHCA admitted to one of 36 intensive care units with ROSC. | Unclear     |
| Winther-Jensen et al 2018 | Denmark              | Retrospective cohort | 993     | 2007–2011          | 30-day mortality Neurological outcome (CPC) at discharge | Cancer.                                                                 | National Patient Register.                    | All patients with OHCA attended to by EMS and successfully resuscitated.           | ≥18         |

CCI, Charlson Comorbidity Index; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; DNR, do not resuscitate; EMS, emergency medical services; GCS, Glasgow Coma Scale; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; TTM, therapeutic temperature management; VF, ventricular fibrillation; VT, ventricular tachycardia.
| Study ID          | Country | Study design       | Cases | Enrolment Period | Reported outcome                                                                 | Comorbidity                                                                 | Source of comorbidity data                                                                 | Inclusion criteria                                                                 | Age (years) |
|-------------------|---------|--------------------|-------|-----------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------|-------------|
| Beitland et al 2016 | Norway  | Prospective cohort | 245   | Sept 2010–Jan 2014 | Survival with good neurological outcome at 6 months.                              | Diabetes (type I) and chronic hypertension.                                  | Hospital records                                                                       | All patient with GCS <8 on admission who received TTM within 24 hours of ICU stay.        | ≥18          |
| Bro-Jeppesen et al 2012 | Denmark | Prospective cohort | 360   | Jun 2004–Dec 2010 | 30-day mortality.                                                                | No comorbidities.                                                            | Unclear                                                                                | All patients admitted to hospital with ROSC, GCS <9 and no cardiogenic shock.              | ≥18          |
| Chen et al 2017   | Taiwan  | Retrospective cohort| 5338  | 2005–2012        | Survival to hospital discharge.                                                  | CCI=1, ≥2, angina, tumour, acute myocardial infarction, cerebrovascular disease, congestive heart failure, coronary artery disease, diabetes. | Taiwan National Health Insurance database                                                                 | All non-traumatic OHCA patients admitted to the emergency department.                     | ≥18          |
| Eid et al 2017    | USA     | Cross sectional    | 247684| 1995–2013       | Neurological outcome at hospital discharge.                                      | mCCI=1, 2, 3, ≥4.                                                           | Nationwide Inpatient Survey (NIS)                                                    | All OHCA patients (non-traumatic) who achieved ROSC and were hospitalised.               | ≥18          |
| Fabbri et al 2006 | Italy   | Prospective cohort | 479   | Jul 1994–Dec 2004 | Neurological outcome at hospital discharge.                                      | Hypertension, diabetes, congestive cardiac failure, myocardial infarction.    | Unclear                                                                                | All bystander witnessed OHCA of presumed cardiac origin.                                   | ≥18          |
| Oh et al 2018     | Korea   | Retrospective cohort| 295   | Mar 2007–Dec 2013 | Neurological outcome (CPC).                                                      | Non-diabetic.                                                                | Registry and electronic records                                                      | All OHCA patients who achieved ROSC and were admitted to the emergency intensive care unit and were administered therapeutic cooling. | ≥18          |
| Sharma et al 2016 | Netherlands | Retrospective cohort | 195   | Mar 2012–Apr 2014 | Survival to hospital discharge.                                                  | Atrial fibrillation, cerebrovascular accident, congestive heart failure, diabetes, dyslipidaemia/cardiovascular conditions, hypertension, myocardial infarction, ventricular fibrillation. | Hospital records                                                                       | OHCA of cardiac presumed cardiac origin in patients that survived to emergency department admission (survived means either in ROSC or ongoing CPR). | Adults       |
Majewski D, et al. BMJ Open 2019;9:e031655. doi:10.1136/bmjopen-2019-031655

| Study ID          | Country       | Study design   | Cases | Inclusion criteria                                                                 | Comorbidity | Reported outcome | Enrolment period | Source of comorbidity data | Risk of bias within studies |
|-------------------|---------------|----------------|-------|-----------------------------------------------------------------------------------|--------------|------------------|-----------------------|---------------------------|-----------------------------|
| Søholm et al 2014 | Denmark       | Prospective cohort | 1016  | All OHCA of any aetiology where patient was either in ROSC or had ongoing CPR on emergency department admission. | CCI          | 30-day mortality | 2007–2011            | Hospital records         | Generally, the quality of studies varied greatly in regards to selection criteria and comparability. More specifically, most studies were found to be of high risk of bias with respect to comparability (ie, adjustment for confounders) and representativeness of the exposed cohort with no single study scoring well in both categories (online supplementary table 3). The majority of studies ascertained comorbidity data from hospital records however many were not clear on the type of hospital record (eg, patient clinical records or hospital billing/statistical records) or whether the record referred to prior hospitalisations or treatments. Only 12 studies obtained history from sources that could be considered to have a low risk of exposure ascertainment bias. All studies were judged to be of low risk of bias with respect to selection of non-exposed cohort and follow-up length. |

## Results of individual studies

The relevant results of individual studies are reported under each of the corresponding outcome subheadings ‘Survival to hospital discharge’ and ‘Neurological outcomes after OHCA’. A request for additional data was sent to the authors of two studies with data subsequently being provided for one of these studies.

### Survival to hospital discharge

Comorbidity and survival to hospital discharge/30-day survival results were provided by 19 studies. Of these, six studies used the Charlson Comorbidity Index (CCI) as a predictor of survival. The use of CCI scores varied greatly, with some studies comparing individual CCI scores and others comparing ranges of CCI. Fifteen studies examined the presence or absence of individual comorbid conditions as the predictor of survival.

#### Adjusted survival to hospital discharge results

There were 15 studies that provided a total of 71 adjusted analyses on the association between comorbidity and survival to hospital discharge. Three studies found statistically significant decreased survival in all CCI models (where $\text{CCI} > 0$). Two studies found that survival was not statistically different in those with a CCI $\geq 1$ (compared with $\text{CCI}=0$) although these studies restricted their cohort to patients either successfully resuscitated and admitted to hospital or admitted to the ED. Another paper found that only higher CCI scores showed significant negative relationships. Three studies demonstrated monotonic trends, whereby each increase in CCI (ie, increased comorbidity), was associated with a further reduction in survival. Most individual comorbidities were predictive of lower survival. Four out of six studies found statistically significant lower survival to hospital discharge in patients with a prearrest history of diabetes. One out of four studies demonstrated that a history of myocardial infarction (MI)
was associated with higher survival after OHCA (mortality HR: 0.80 CI: 0.68 to 0.94). One of two studies showed a slight, but non-significant, survival benefit in patients with peripheral vascular disease (figure 2). One of two studies that looked at a prearrest history of angina pectoris showed a statistically significant increase in survival to hospital discharge. Looking more broadly at heart disease and survival following OHCA, two studies found no significant relationship, while another found a statistically significant negative association with survival. Three studies reported on the effect of cancer on survival to hospital discharge with all three studies finding no significant effect on survival. One study that looked at the relationship between the number of comorbid conditions and survival found that an increasing cumulative number of comorbidities resulted in decreased survival (figure 3). Finally, a single study found that patients with no prearrest comorbidity were significantly more likely to survive to hospital discharge than those with prearrest comorbidity.

Unadjusted results for survival to hospital discharge

There were 17 studies that reported a total of 97 unadjusted analyses on the association between comorbidity and survival to hospital discharge. Individual papers reported between 1 and 22 unadjusted results for a variety of comorbidity measures. Of all reported unadjusted results across these 17 studies, 51% (49/97) showed a statistically significant reduction in survival to hospital discharge for individuals who had a prearrest comorbidity while 4% (4/97) showed significantly higher survival. Of the remaining 44/97 non-significant results, 86% (38/44) had point estimates indicating reduced survival. Forest plots for unadjusted survival outcomes have been provided as supplementary figures (online supplementary figure 1 and online supplementary figure 2).

Neurological outcomes after OHCA

The effect of prearrest comorbidity on neurological outcome following OHCA was reported in 16 studies. One study provided functional outcomes after hospital discharge, but was not included in this section as the neurological outcomes could not be deduced from the paper. Eleven studies measured neurological outcome at discharge, four studies measured it at 6 months, and one study assessed at both discharge and 12 months. Comorbidity was assessed using the CCI in six of the studies and a modified version of the CCI was used by an additional paper. The remaining nine studies used the presence or absence of individual comorbidity as the predictor.
and the other defining it as a mRS of 0–2. Of the two remaining studies, one defined good outcome as patients discharged alive without International Classification of Diseases codes indicating coma, permanent anoxic brain injury or persistent vegetative state and the other study defined good outcome using the Overall Performance Categories scores of 1 or 2.

**Adjusted results**

A total of 23 adjusted analyses relating to the association between comorbidity and neurological outcome following OHCA were reported by 11 studies. In comparison with CCI=0, a CCI=1 was significantly associated with a poorer neurological outcome in three studies (figure 4) while two other studies found no significant relationship. Similarly, CCI=2 (relative to CCI=0) was significantly associated with a poorer neurological outcome in three studies; while another study found no significant relationship. A 2016 study showed effect estimates for the modified CCI=2 favouring a good neurological outcome, although this was not significant. Two studies found that a CCI ≥4 was associated with poor neurological outcomes; however, this was statistically significant in only one of these studies. Five studies reported individual comorbid conditions in relation to neurological outcomes (online supplementary table 2).

**Unadjusted results**

Eleven studies provided a total of 31 unadjusted analyses on the association between comorbidity and neurological outcomes following OHCA. Individual studies reported between 1 and 14 unadjusted results for a variety of comorbidity measures. Of all reported unadjusted results across these 11 studies, 29% (9/31) of results showed statistically significant poorer neurological outcomes for individuals who had a prearrest comorbidity while 3% (1/31) showed a statistically significant positive neurological outcome. Of the remaining 21 non-significant results, 62% (13/21) had point estimates indicating poorer neurological outcomes. Forest plots for unadjusted neurological outcomes have been provided as online supplementary figure 3.

**DISCUSSION**

This review identified 29 studies that examined the association between OHCA outcome and prearrest comorbidity. To our knowledge, this is the first systematic review to assess the association between prearrest comorbidity on both survival and neurological outcomes in patients with OHCA. We identified only one other systematic review, from 2013, that overlapped the scope of our review, with several important differences. This other review was restricted to patients over 70 years of age, did not examine neurological outcomes and considered comorbidity as one of a number of predictors of survival (ie, it did not focus specifically on comorbidity). This previous review identified only a single paper that examined comorbidity as a predictor for survival, and concluded that more studies on comorbidity and survival were needed.

Our review found that generally the presence of prearrest comorbidity among patients with OHCA was associated with decreased survival to hospital discharge. Of the 15 included studies that presented adjusted analyses for survival to hospital discharge, 38% (27/71) reported a statistically significant negative association between comorbidity and survival, while only 3% (2/71) found a significant positive association. Furthermore, of the 42/71 remaining non-significant analyses, 62% (26/42) had point estimates indicating reduced survival, further demonstrating an overall pattern of poorer survival outcomes. Additionally, increased levels of comorbidity burden, measured using the CCI, were generally associated with a trend of decreasing survival (figure 3). With reference to individual comorbid conditions, a history of diabetes was associated with statistically significant reduced rates of survival in four of six studies. Despite this, no meta-analysis could be conducted between any of the studies as a result of significant clinical heterogeneity. As such, we believe the use of prearrest comorbidity as a prognostic tool for OHCA survival is unlikely to be useful which is consistent with the International Liaison Committee on Resuscitation statement.

In contrast, a patient’s prearrest history of MI was shown to be suggestive of increased survival to hospital discharge in three out of four studies reporting on the condition, with one of the studies reporting statistically significant results. Furthermore, one of two studies found that patients with a history of angina, a condition with a similar underlying pathology to MI, had statistically increased odds of survival. The reasons for these apparent survival benefits are unclear, however it has been suggested that certain medications such as statins, routinely prescribed to patients with these conditions, may be responsible for this effect.

The presence of prearrest comorbidity was generally associated with worse neurological outcome after OHCA. A total of 23 adjusted neurological outcome results were reported across 11 studies of the 29 included studies. Overall, 56% (13/23) of these adjusted results showed that individuals with prearrest comorbidity had statistically poorer neurological outcomes while no results
reported statistically positive neurological outcomes. Of the remaining 10 non-significant results, 80% (8/10) had point estimates indicating reduced neurological outcome. As with survival, we found similar variation in results between studies. When looking at cumulative comorbidity burden using CCI there was no corresponding pattern between increasing CCI and increasing odds of poorer neurological outcome. Furthermore, there was greater variation in results between studies examining neurological outcome by corresponding CCI level (figure 4) than for survival. We suspect this discrepancy could be explained by the fact that CCI is a mortality risk indicator and therefore may be ineffective in assessing the effect of comorbidity burden on neurological outcomes.

Limitations

Limitations of included studies

A number of limitations within the studies included in this review were identified. First, a large proportion of studies did not stipulate specific health conditions, instead using broad descriptors such as ‘heart history’ or ‘respiratory disease’. This ultimately made it difficult to interpret results, since many different diseases could fall within those broad descriptions. Second, many of the included studies did not adequately quantify the severity of the comorbidities within their cohorts. This was particularly noteworthy in conditions that can have a large range of physiological presentations and mortality risks such as diabetes or liver disease. Some studies did attempt to account for this. Some dichotomised conditions by severity, such as those that stratified diabetes as either ‘diabetes’ or ‘diabetes with complications’. One study attempted to account for comorbidity severity by using the Sequential Organ Failure Assessment scores, while others adjusted for comorbidity severity using the CCI. Given the CCI was designed to predict 1 year mortality risk based on the presence of a predefined list of comorbid conditions, we believe it is an acceptable tool that assesses both the number of comorbidities and severity of those conditions and recommend its use in future studies on comorbidity and OHCA survival. Third, a number of authors only reported comorbidities that were found to be significantly associated with survival which resulted in a high risk of reporting bias. Lastly, the vast majority of studies were vague regarding the completeness of patient medical histories and/or only focused on a limited number of conditions. The use of incomplete or inaccurate patient history may result in large variability between studies as seen in patients with peptic ulcer disease (figure 2). This was identified as a major risk of bias in the majority of studies. Furthermore, three studies obtained prearrest comorbidity history from ambulance patient care record forms alone. Comorbidity data from ambulance records may be ascertained by paramedics from a variety of sources including bystander reports and/or current patient medications which are likely to be inaccurate or incomplete.

A high degree of clinical heterogeneity was found between studies which is consistent with findings of other related OHCA systematic reviews. A substantial source of clinical heterogeneity resulted from participant recruitment and inclusion criteria. Some studies included all participants in OHCA, while others specified eligibility criteria such as witnessed arrest or shockable initial rhythm. Others only recruited participants that reached specific resuscitation milestones such as ROSC, survival to ED or hospital admission. Furthermore, a number of studies only included patients with specific acute or chronic complications/conditions or those meeting specific eligibility criteria for clinical interventions. Ultimately, this heterogeneity made it inappropriate to compare outcomes between studies and prevented a meta-analysis from being conducted. This review highlights a clear need for a more standardised approach in reporting of comparative observational OHCA studies to enable the true effect of comorbidity on outcomes to be determined. Achieving this would require standardised patient study recruitment start and end points, consistent inclusion criteria, complete comorbidity histories and uniform statistical outcome reporting. To allow for future meta-analysis in observational OHCA studies we also suggest the development of a standardised guide for statistical adjustment for arrest and resuscitation factors.

Limitations of this review

This review had several limitations. First, while every effort was made to identify all relevant studies in our search we acknowledge that some relevant studies may have been inadvertently missed. Second, as the definition of comorbidity covers a broad range of conditions and severity, a set of criteria was developed to determine what would constitute ‘comorbidity’ for this review (see methods section). Where studies were vague or broad in their identification of comorbid conditions, clinical judgement was used to group conditions that we believed are the same or similar. Third, comorbidities were only included in forest plots if adjusted results were available from at least two studies that provided relevant ORs. Many studies provided results for both individual comorbid conditions as well as CCI. Ultimately this meant that the same patient populations may have been used in both results. Additionally, this review only used survival to hospital discharge/30-day survival as the measure for survival and did not report shorter or longer term outcomes.

Lastly, this review predominately utilised adjusted results to reduce the effects that patient-specific and arrest-specific resuscitation factors would have on the variability of results between studies. However, the list of adjustment factors varied greatly between studies (online supplementary table 1 and online supplementary table 2), with some only adjusting for one or two resuscitation factors while others adjusted for multiple prearrest/periarrest/postarrest factors. Despite this, given the clinical variability between studies we believe these results still
CONCLUSIONS

Despite variability between studies and reported outcomes, it appears that prearrest comorbidity is generally associated with both lower survival and poorer neurological outcomes following OHCA. Survival to hospital discharge was found to be particularly negatively associated with a prearrest history of diabetes. Few studies had point estimates of a positive association between comorbidity and survival, with the most consistent result being for MI (three of four studies having point estimates of a positive association, although only one statistically significant association). There were high levels of clinical heterogeneity between studies which precluded meta-analyses of results. Given our findings, we believe using comorbidity as a prognostication tool for determining OHCA outcomes is unlikely to be useful.

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REFERENCES

1 Chambertain D. Predictors of survival from out-of-hospital cardiac arrest. Heart 2010;96:1786–9.
2 Sandroni C, Cavallaro F, Callaway CW, et al. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part I: patients treated with therapeutic hypothermia. Resuscitation 2013;84:1324–38.
3 Salam I, Thomsen JH, Kjaergaard J, et al. Importance of comorbidities in comatose survivors of shockable and nonshockable out-of-hospital cardiac arrest treated with target temperature management. Scand Cardiovasc J 2018;52:133–40.
4 Sasson C, Rogers MA, Dahl J, et al. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2010;3:63–81.
5 Blom MT, Warner MJ, Bardai A, et al. Reduced in-hospital survival rates of out-of-hospital cardiac arrest victims with obstructive pulmonary disease. Resuscitation 2013;84:569–74.
6 Hallstrom AP, Cobb LA, Yu BH. Influence of comorbidity on the outcome of patients treated for out-of-hospital ventricular fibrillation. Circulation 2010;121:9322.
7 van de Gild EMM, van Munster BC, van de Wetering FT, et al. Pre-arrest predictors of survival after resuscitation from out-of-hospital cardiac arrest in the elderly: a systematic review. BMC Geriatr 2013;13:68.
8 Dumas F, Blackwood J, White L, et al. The relationship between chronic health conditions and outcome following out-of-hospital ventricular fibrillation cardiac arrest. Resuscitation 2017;120:71–6.
9 Andrew E, Nehme Z, Bernard S, et al. The influence of comorbidity on survival and long-term outcomes after out-of-hospital cardiac arrest. Resuscitation 2017;110:42–7.
10 Beesems SG, Blom MT, van der Pas MHA, et al. Comorbidity and favorable neurologic outcome after out-of-hospital cardiac arrest in patients of 70 years and older. Resuscitation 2015;94:33–9.
11 Lee MH, Fook-Chong S, Wai W, et al. Effect of known history of heart disease on survival outcomes after out-of-hospital cardiac arrests. Emerg Med Australas 2018;30:67–76.
12 Termann SW, Shields TA, Humé B, et al. The influence of age and chronic medical conditions on neurological outcomes in out-of-hospital cardiac arrest. Resuscitation 2015;89:169–76.
13 Larsson M, Thorén A-B, 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.
14 Winther-Jensen M, Kjaergaard J, Nielsen N, et al. Comorbidity burden is not associated with higher mortality after out-of-hospital cardiac arrest. Scand Cardiovasc J 2016;50:305–10.
15 Iqbal MB, Al-Hussaini A, Rosser G, et al. Predictors of survival and favorable functional outcomes after an out-of-hospital cardiac arrest in patients systematically brought to a dedicated heart attack center (from the Harefield cardiac arrest study). Am J Cardiol 2015;115:730–7.
16 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.
17 Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals developed as a collaboration between the American Heart Association, the European Resuscitation Council, the Australian and New Zealand Council on resuscitation, heart and stroke Foundation of Canada, InterAmerican heart Foundation, resuscitation Council of southern Africa, resuscitation Council of Asia; and the American heart association emergency cardiovascular care Committee and the Council on cardiopulmonary, critical care, perioperative and resuscitation. Circulation 2015;132:1286–300.
18 Anon. A randomized clinical study of cardiopulmonary-cerebral resuscitation: design, methods, and patient characteristics. Brain resuscitation clinical trial I study Group. Am J Emerg Med 1986;4:72–86.
19 The Cochrane Collaboration. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, 2014.
20 Kang SB, Kim KS, Suh GJ, et al. Long-term survival of out-of-hospital cardiac arrest patients with malignancy. Am J Emerg Med 2017;35:1457–61.
21 Mathiesen WT, Bjersel CA, Kvasley JT, et al. Effects of modifiable prehospital factors on survival after out-of-hospital cardiac arrest in rural versus urban areas. Crit Care 2018;22.
22 Patel AA, Arabi AR, Alzaeem H, et al. Clinical profile, management, and outcome in patients with out of hospital cardiac arrest: insights from a 20-year regional cardiac arrest registry. Crit Care 2016;20:373–81.
23 Geri G, Savary G, Legriel S, et al. Influence of body mass index on the prognosis of patients successfully resuscitated from out-of-hospital cardiac arrest treated by therapeutic hypothermia. Resuscitation 2016;109:49–55.
24 Wang C-Y, Wang J-Y, Chang C-Y, et al. The secular trends in the incidence rate and outcomes of out-of-hospital cardiac arrest in Taiwan--a nationwide population-based study. PLoS One 2015;10:e0122675.
25 Lai C-Y, Lin F-H, Chu H, et al. Survival factors of hospitalized out-of-hospital cardiac arrest patients in Taiwan: a retrospective study. PLoS One 2018;13:e0219185.
26 Chen Y-C, Hung M-S, Chang C-H, et al. Major interventions are associated with survival of out of hospital cardiac arrest patients—a population based survey. Signa Vitae 2017;13:108–15.10.22514/SV.132.112017.17
27 Nehme Z, Nair R, Andrew E, et al. Effect of diabetes and pre-hospital blood glucose level on survival and recovery after out-of-hospital cardiac arrest. Crit Care Resusc 2016;18:69–77.
28 Beitland S, Nakstad EP, Staaersen H, et al. Impact of acute kidney injury on patient outcome in out of hospital cardiac arrest: a prospective observational study. Acta Anaesthesiol Scand 2016;60:1170–81.
29 Bro-Jeppesen J, Kjaergaard J, Wanscher M, et al. Emergency coronary angiography in comatose cardiac arrest patients: do real-life experiences support the guidelines? Eur Heart J Acute Cardiovasc Care 2012;1:291–301.

30 Corrada E, Mennuni MG, Grieco N, et al. Neurological recovery after out-of-hospital cardiac arrest: hospital admission predictors and one-year survival in an urban cardiac network experience. Minerva Cardioangiol 2013;61:451–60.

31 de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, et al. Factors associated with temporal trends in survival and comorbidity. Ann Emerg Med 2015;65:523–31.

32 Dickey W, Adgey AA. Mortality within hospital after resuscitation from out-of-hospital cardiac arrest and unsuccessful resuscitation after out-of-hospital cardiac arrest and out-of-hospital cardiac arrest survivors with liver cirrhosis. Eur J Prev Cardiol 2014;21:619–38.

33 Eidsmo AS, Bratland F, Pedersen PA, et al. The impact of statin treatment on survival for in-hospital cardiac arrest. J Investig Med 2017;65:689–93.

34 Fabbri A, Marchesini G, Spada M, et al. Monitoring intervention programmes for out-of-hospital cardiac arrest in a mixed urban and rural setting. Resuscitation 2015;88:150–7.

35 Friedl K, Wallmüller C, Drolz A, et al. Outcome of in- and out-of-hospital cardiac arrest survivors with liver cirrhosis. Ann Intensive Care 2017;7:103.

36 Sharma AS, Pilis RWM, Weerwind PW, et al. Out-of-hospital cardiac arrest: the prospect of E-CPR in the Maastricht region. Netherlands Heart Journal 2016;24:120–6.

37 Soholm H, Bro-Jeppesen J, Lippert FK, et al. Resuscitation of patients suffering from sudden cardiac arrests in nursing homes is not futile. Resuscitation 2014;85:369–75.

38 Hiriakar G, Jonsson M, Karlsson T, et al. Comorbidity and survival in out-of-hospital cardiac arrest. Resuscitation 2018;133:118–23.

39 Winther-Jensen M, Kjaergaard J, Hassager C, et al. Cancer is not associated with higher short or long-term mortality after successful resuscitation from out-of-hospital cardiac arrest when adjusting for prognostic factors. Eur Heart J Acute Cardiovasc Care 2018;2048872618794090.

40 Soholm H, Hassager C, Lippert F, et al. Factors associated with successful resuscitation after out-of-hospital cardiac arrest and temporal trends in survival and comorbidity. Ann Emerg Med 2015;65:523–31.

41 Eid SM, Abouergi MS, Albaeni A, et al. Survival, expenditure and disposition in patients following out-of-hospital cardiac arrest: 1995–2013. Resuscitation 2017;113:13–20.

42 Carew HT, Zhang W, Rea TD. Chronic health conditions and survival after out-of-hospital ventricular fibrillation cardiac arrest. Heart 2007;93:728–31.

43 Oh SJ, Kim JJ, Jang JH, et al. Age is related to neurological outcome in patients with out-of-hospital cardiac arrest (OHCA) receiving therapeutic hypothermia (th). Am J Emerg Med 2018;36:243–7.

44 Parry M, Danielson K, Brennenstuhl S, et al. The association between diabetes status and survival following an out-of-hospital cardiac arrest: a retrospective cohort study. Resuscitation 2017;113:21–6.

45 Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

46 Nolan JP, Neumar RW, Adrie C, et al. Post-Cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognosis. A scientific statement from the International Liaison Committee on resuscitation; the American heart association emergency cardiovascular care Committee; the Council on cardiovascular surgery and anesthesia; the Council on cardiopulmonary, perioperative, and critical care; the Council on clinical cardiology; the Council on stroke. Resuscitation 2008;79:350–79.

47 Hung S-W, Chu C-M, Su C-F, et al. Effect of preceding medications on resuscitation outcome of out-of-hospital cardiac arrest. J Investig Med 2017;65:689–93.

48 Khoury Abdulla R, Kheder E, Yeow R, et al. The impact of statin therapy on survival for in-hospital cardiac arrest. J Investig Med 2017;65:e4.

49 Rahimi K, Majoni W, Merhi A, et al. Effect of statins on ventricular tachyarrhythmia, cardiac arrest, and sudden cardiac death: a meta-analysis of published and unpublished evidence from randomized trials. Eur Heart J 2012;33:1571–81.

50 Whitehead L, Perkins GD, Clarey A, et al. A systematic review of the outcomes reported in cardiac arrest clinical trials: the need for a core outcome set. Resuscitation 2015;88:150–7.

51 Shah KSV, Shah ASV, Bhopal R. Systematic review and meta-analysis of out-of-hospital cardiac arrest and race or ethnicity: black US populations fare worse. Eur J Prev Cardiol 2014;21:619–38.