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Review of Novel Therapeutics in Cardiac Arrest (ReNTICA) - Systematic Review Protocol

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Travis W Murphy, MD

Abstract

Introduction

Cardiac arrest remains a common and devastating cause of death and disability worldwide. While targeted temperature management has become standard of care to improve functional neurologic outcome, few pharmacologic interventions have shown similar promise.

Methods/analysis

This systematic review will focus on prospective human studies from 2015 to 2020 with a primary focus on impact on functional neurologic outcome. Prospective studies that include pharmacologic agents given during or after cardiac arrest will be included. Study selection will be in keeping with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. If sufficient data involving a given agent are available, a meta-analysis will be conducted and compared to current evidence for therapies recommended in international practice guidelines.

Ethics and dissemination

Formal ethical approval will not be required as primary data will not be collected. The results will be disseminated through peer-reviewed publication, conference presentation and lay press.

Prospero registration number: International Prospective Register for Systematic Reviews (PROSPERO) number CRD42021230216

Article Summary

Strengths and limitations of this study

- Systematic review and meta-analysis of prospective trials investigating therapeutic agents in cardiac arrest.
- Inclusion of outcome measurements to quantify the effect of proposed therapeutic interventions on neurologic function after cardiac arrest.
- Limitation in the number of studies investigating a given therapy may diminish observed effects.
- Potential identification of therapies with positive impact on functional outcome following cardiac arrest.
- Key words: cardiac arrest, heart arrest, pharmacologic agents, functional neurologic outcome

Introduction

Cardiac arrest remains a common and often devastating cause of death and disability worldwide.[1] Outcomes are contingent on the severity of overall hypoxic-ischemic brain injury burden, which comprises primary injury during circulation standstill and ongoing secondary brain injury that occurs in the aftermath of resuscitation. Besides targeted temperature management, therapeutic options targeting improvement in neurologic outcome are scarce.[2] International practice guidelines currently recommend epinephrine/adrenaline, amiodarone and lidocaine/lignocaine.[3–5] While there is good evidence for improved survival with these medications, there is little evidence for a positive impact of these medications on functional neurologic outcomes specifically[3,5,6]. Functional neurologic outcome is less commonly the primary focus of cardiac arrest research but arguably a more granular patient-centered variable rather than rate of return of spontaneous circulation or survival. Unlike targeted temperature management, few advances have been made in pharmacologic approaches to improve functionally intact neurologic survival following cardiac arrest.[2,5,7,8] Several novel compounds have been investigated in animal studies, with some notation of effect on neurologic function, though only a small minority have made the transition from animal models into human trials.[7] The review proposed here will focus on identifying the best available data from human studies.

A similar review of the literature was performed in 2015, though this was focused on cataloging the therapies utilized and did not focus on studies that included functional outcome measurements.[8] Another recent systematic review reported the rate of translation from animal models to human trials for therapies targeted at cardiac arrest.[7] Though again, this review did not have a specific focus on functional neurologic outcome. While the review published by Lind et al. identified the large number of experimental therapies targeted at post-cardiac arrest physiology, the authors noted a relative dearth of clinical trials investigating those same therapies in humans.[7] Additionally, the review published in 2021 did not compare the effects of different pharmacologic agents.[7] The review proposed here seeks to compile the best available evidence for pharmacologic interventions that will improve functional neurologic outcomes in humans following cardiac arrest and compare this directly to current practice guidelines.

Objectives

The objective of our study is to systematically review the literature for prospective studies that evaluated the performance of pharmacologic agents used in adult cardiac arrest compared to standard resuscitation treatments currently advocated in practice guidelines. This will include studies regardless of initial cardiac rhythm and independent of the use of targeted temperature management.

Methods and Design

Population

The systematic review will focus on studies that include patients aged >15 years who have been resuscitated from cardiac arrest but are not conscious upon return of spontaneous circulation with arms for both intervention and control.

Interventions

The interventions to be evaluated include any pharmacologic agent given during cardiac arrest itself or in the immediate post-arrest period (defined as the initial 24 hours).

Comparisons
The interventions identified will be compared to current international practice guidelines and the pharmacologic agents advocated there (epinephrine/adrenaline, amiodarone, and lidocaine/lignocaine).

Outcome
The primary outcomes required of included studies will be survival and neurologic function as defined by one of the following neurologic scales: Cerebral Performance Category, modified Rankin Scale, Glasgow Outcome Scale/Glasgow Outcome Scale-Extended.

Study Design
The systematic review and meta-analysis will include prospective therapeutic studies investigating the use of a pharmacologic agent during or after cardiac arrest with a primary focus on effects on neurologic outcome. This will include systematic reviews, meta-analyses, randomized control trials, adaptive clinical trials, prospective cohort and observational studies, and non-randomized clinical trials. Studies that compare one intervention to standard ACLS resuscitation as the control will be included. The review will exclude studies without a control group using either placebo or current standard care. Retrospective studies will be excluded including retrospective cohorts, case control studies, cross sectional studies, case reports, and case series. This review has been registered on the International Prospective Register for Systematic Reviews (PROSPERO) number CRD42021230216.

Search Strategy
A three-step process will be used to identify eligible studies, including an initial search, title and abstract screening and full-text manuscript review. A professional systematic review librarian (PMW) will develop search criteria in discussion with the authors to include all relevant studies pertaining to adult, human studies of pharmacologic treatment of cardiac arrest. The databases that will be searched are PubMed, Web of Science and EMBASE from the year 2015 to 2020, inclusive. No language restrictions will be applied. Figure 1 shows an example search algorithm for PubMed. Initial deduplication will be performed using EndNote (Clarivate Analytics, Philadelphia, Pennsylvania, USA).[9]

Study Selection
Literature search results will be uploaded from EndNote and screened through DistillerSR (Evidence Partners, Ottawa, Ontario, Canada). Study titles and abstracts will be screened for relevance in duplicate, blindly and independently, by four reviewers (EA, NT, GC, MM). Eligible studies will then be assessed for quality in secondary screening through review of full-text manuscripts before data abstraction. This process will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. The PRISMA-P Checklist pertaining to this protocol is available as Supplement 1. Any conflicting remarks regarding studies will be adjudicated through discussion before inclusion in the final analysis.

Quality Assessment
Each article will undergo initial screening in parallel by two independent reviewers to minimize bias. All selected articles will be reviewed with senior authors during full-text review.

Data Extraction
Quantitative data will be extracted from studies meeting inclusion upon full-text review by a professional biostatistician (MABC). Data extracted will be specifically those pertinent to the systematic review and all others that fit into the synthesis of outcome parameters form all studies and meets the potential for inclusion in a meta-analysis. Data extraction will be independently cross-checked. Data

produced from this systematic review including the statistical code and dataset of articles screened will be published in a data repository.

Endpoint

Results of the systematic review will be grouped by drug and drug class. The primary outcomes will be survival and neurologic function as defined by one of the following neurologic scales: Cerebral Performance Category, modified Rankin Scale, Glasgow Outcome Scale/Glasgow Outcome Scale-Extended. Provided they are available in the original studies, secondary outcomes will be ICU length of stay, Ventilator days, rates of sepsis, rates of pneumonia, rate of tracheostomy, rate of acute kidney injury and need for CVVH/HD (in the hospital or afterwards). We will also include secondary outcomes of functional capacity including Barthel Index, Katz Index, Lawton-Brody Instrumental Activities of Daily Living Scale, and rates of discharge to rehab facility if included in the original studies. Any follow-up duration will be accepted as there is considerable variability in the existing literature.

Patient and Public Involvement

No patients were involved with the planning of this protocol.

Analysis

Descriptive Analysis

A narrative synthesis of the final studies included will be developed based on the different pharmacologic agents identified. The impact of each of these agents on the primary and secondary outcome mentioned above will be described in addition to a formal meta-analysis of studies using each pharmacologic agent identified.

Statistical Analysis

The primary focus of this review is to detect evidence for the impact of the pharmacologic agents identified on survival and functional neurologic outcome. As functional outcome is reported with some degree of heterogeneity, we are including three of the most widely reported functional outcome scales and not limiting to one over the others. As functional neurologic outcome is not always explicitly reported using one of these sales, we do anticipate some limitation in the ability to directly compare one agent to another. However, when available, pharmacologic agents will be compared as equitably as possible using all available outcome parameters reported in the index studies. The percentage of patients receiving a given pharmacologic agent with a favorable neurologic outcome according to each specific scale will be reported. Based on the availability of data from primary sources, subgroup analysis within cohorts treated with the same pharmacologic agent will also be performed to identify populations most likely to benefit from a given agent.

Data synthesis

Results will be presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. A PRISMA flow diagram will be used to summarize study selection. Tabulated data showing relative proportion of patients with favorable functional neurologic outcome for each pharmacologic agent will be presented. We will rank agents by proportion of favorable outcomes. For secondary outcome variables, we will present synthesized data as available in separate tables but will otherwise provide a separate narrative summary of the data available for each agent. We will produce a hierarchy of pharmacologic agents based on the quality of evidence available and degree of effects on outcome variables.

Meta-analysis
A meta-analysis of the pharmacologic agents found to have been studied with a focus on functional neurologic outcome will be performed. The results of this meta-analysis will then be compared to the best available evidence for medications recommended in practice guidelines to provide context and rank relative efficacy.

Confidence in cumulative evidence
Cochrane tools for assessment of study quality will be utilized as appropriate. (ROBINS-1 and RoB 2.0). Two independent authors will assess the risks of bias in studies considered for full-text review. Conflicts will be adjudicated with discussion and involvement of a third author (TM or CM) as necessary.

Discussion

This systematic review and meta-analysis will provide evidence for further study or use of compounds that are most likely to benefit patients following cardiac arrest in terms of functional status. The conclusions will be the result of careful accumulation of the highest-quality evidence available and will compare to current practice guidelines to place the effects in context. With a primary focus on the ability of a given pharmacologic agent to not only provide a survival benefit but protect the neurologic function of patients following cardiac arrest, this review and meta-analysis will be unique in its aim to identify agents with the greatest potential to benefit these patients.

Ethics and dissemination

No ethical or safety considerations were considered based on the nature of this review. Dissemination of findings through a peer-reviewed publication upon the conclusion of the meta-analysis.

Author Contributions

Travis Murphy: Conception and design of work, analysis, drafting of work, final approval *Garrett Snipes:* Conception and design of work, drafting of work *Muhammad Abdul Baker Chowdhury:* Conception and design of work, analysis *Patti McCall-Wright:* Conception and design of work, analysis *Elizabeth Aleong:* Analysis *Noelle Taylor:* Analysis *Maiya Messina:* Analysis *Gabriela Carrazana:* Analysis *Carolina Maciel:* Conception and design of work, analysis *Torben Becker*: Conception and design of work. All authors have reviewed and contributed to this final written manuscript.

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Competing interests statement

The authors have no competing interests.

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Figure 1. Example Search Algorithm for PubMed

PubMed

Cardiac Arrest

cardiac arrest[MeSH Terms] OR arrest, cardiopulmonary[MeSH Terms] OR heart arrest[MeSH Terms] OR deep hypothermic circulatory arrest[MeSH Terms] OR ventricular fibrillation[MeSH Terms] OR ventricular tachycardia[MeSH Terms] OR asystole[MeSH Terms] OR cardiopulmonary resuscitation[MeSH Terms] OR advanced cardiac life support[MeSH Terms] OR cardiac death[MeSH Terms] OR sudden cardiac death[MeSH Terms] OR cardiac death, sudden[MeSH Terms] OR cardiac arrest[Text Word] OR cardiopulmonary arrest[Text Word] OR heart arrest[Text Word] OR circulatory arrest[Text Word] OR ventricular fibrillation[Text Word] OR ventricular tachycardia[Text Word] OR pulseless electrical activity[Text Word] OR asystole[Text Word] OR cardiovascular arrest[Text Word] OR cardiopulmonary arrest[Text Word] OR cardiopulmonary resuscitation[Text Word] OR defibrillation[Text Word] OR advanced cardiac life support[Text Word] OR ACLS[Text Word] OR cardiac death[Text Word] OR sudden cardiac death[Text Word] OR fatal arrhythmia[Text Word] **2015:2021[pdat]**

Results 1: 57,400

AND

Survival

survival[MeSH Terms] OR mortality[MeSH Terms] OR survival[Text Word] OR mortality[Text Word] **2015:2021[pdat]**

Results 2: 705, 713

AND

Functional Outcome

glasgow outcome scale[MeSH Terms] OR glasgow outcome scale[Text Word] OR modified rankin scale[Text Word] OR cerebral performance categories score[Text Word] OR prognosis[MeSH Terms] OR disability evaluation[MeSH Terms] OR prognosis[Text Word] OR disability evaluation[Text Word] **2015:2021[pdat]**

Results 3: 603,078

AND

Pharmacology

drug*[Text Word] OR drug therapy[Text Word] OR medication[Text Word] OR phamacolog*[Text Word] OR pharmaceutic*[Text Word] OR therap*[Text Word] OR injection[Text Word] OR infusion[Text Word] OR cardiovascular agents[Text Word] OR drug administration schedule[Text Word] OR therapeutics[Text Word] OR intravenous administration[Text Word] OR dose response relationship[Text Word] OR cardiovascular agents[MeSH Terms] OR therapeutics[MeSH Terms] OR drug administration

schedule[MeSH Terms] OR dose response relationship, drug[MeSH Terms] OR vasopressor agents[MeSH Terms] OR epinephrine[MeSH Terms] OR vasopressins[MeSH Terms] OR norepinephrine[MeSH Terms] OR Simendan[MeSH Terms] OR methoxamine[MeSH Terms] OR amiodarone[MeSH Terms] OR sodium channel blockers[MeSH Terms] OR lidocaine[MeSH Terms] OR lignocaine[MeSH Terms] OR procainamide[MeSH Terms] OR flecainide[MeSH Terms] OR mexiletine[MeSH Terms] OR quinidine[MeSH Terms] OR adrenergic beta blockers[MeSH Terms] OR sotalol[MeSH Terms] OR apo labetalol[MeSH Terms] OR metoprolol[MeSH Terms] OR nadolol[MeSH Terms] OR bisoprolol[MeSH Terms] OR carvedilol[MeSH Terms] OR isoproterenol[MeSH Terms] OR calcium channel blockers[MeSH Terms] OR diltiazem[MeSH Terms] OR verapamil[MeSH Terms] OR digoxin[MeSH Terms] OR isoprenaline[MeSH Terms] OR theophylline[MeSH Terms] OR aminophylline[MeSH Terms] OR magnesium[MeSH Terms] OR thrombolytic agents[MeSH Terms] OR thrombolytic drugs[MeSH Terms] OR thrombolytic therapies[MeSH Terms] OR corticosteroids[MeSH Terms] OR sodium bicarbonate[MeSH Terms] OR erythropoietin[MeSH Terms] OR crystalloid solutions[MeSH Terms] OR ascorbic acid[MeSH Terms] OR vitamin e[MeSH Terms] OR vitamin b1[MeSH Terms] OR melatonin[MeSH Terms] OR colloids[MeSH Terms] OR xenon[MeSH Terms] OR argon[MeSH Terms] OR hydrogen[MeSH Terms] OR hydrogen sulfide[MeSH Terms] OR nitric oxide[MeSH Terms] OR carbon monoxide[MeSH Terms] OR anesthetic agents[MeSH Terms] OR anesthetic drugs[MeSH Terms] OR propofol[MeSH Terms] OR ketamine[MeSH Terms] OR vasopressor[Text Word] OR epinephrine[Text Word] OR vasopressin[Text Word] OR norepinephrine[Text Word] OR levosimendan[Text Word] OR simendan[Text Word] OR methoxamine[Text Word] OR amiodarone[Text Word] OR sodium channel blockers[Text Word] OR lidocaine[Text Word] OR lignocaine[Text Word] OR procainamide[Text Word] OR flecainide[Text Word] OR mexiletine[Text Word] OR quinidine[Text Word] OR beta blocker[Text Word] OR sotalol[Text Word] OR labetalol[Text Word] OR metoprolol[Text Word] OR nadolol[Text Word] OR bisoprolol[Text Word] OR carvedilol[Text Word] OR isoproterenol[Text Word] OR calcium channel blocker[Text Word] OR diltiazem[Text Word] OR verapamil[Text Word] OR atropine[Text Word] OR atropine[MeSH Terms] OR digoxin[Text Word] OR isoprenaline[Text Word] OR theopylline[Text Word] OR magnesium[Text Word] OR thrombolytic[Text Word] OR corticosteroids[Text Word] OR sodium bicarbonate[Text Word] OR erythropoietin[Text Word] OR crystalloid[Text Word] OR colloid[Text Word] OR vitamin c[Text Word] OR ascorbic acid[Text Word] OR vitamin e[Text Word] OR vitamin b[Text Word] OR thiamine[Text Word] OR edavarone[Text Word] OR melatonin[Text Word] OR medical gas[Text Word] OR xenon[Text Word] OR argon[Text Word] OR hydrogen[Text Word] OR hydrogen sulfide[Text Word] OR nitric oxide[Text Word] OR carbon monoxide[Text Word] OR anesthetics[Text Word] OR propofol[Text Word] OR ketamine[Text Word] OR adrenergic alpha agonists[MeSH Terms] OR Adrenergic alpha-1 Receptor Antagonists[MeSH Terms] OR adrenergic beta antagonists[MeSH Terms] OR adjuvants, anesthesia[MeSH Terms] OR analgesics[MeSH Terms] OR anesthetics, dissociative[MeSH Terms] OR anesthetics, local[MeSH Terms] OR anti arrhythmia agents[MeSH Terms] OR antihypertensive agents[MeSH Terms] OR antioxidants[MeSH Terms] OR bronchodilator agents[MeSH Terms] OR cardiotonic agents[MeSH Terms] OR cardiovascular agents[MeSH Terms] OR cytochrome p 450 CYP1A2 inhibitors[MeSH Terms] OR cytochrome p 450 CYP2C9 inhibitors[MeSH Terms] OR cytochrome p 450 CYP2D6 inhibitors[MeSH Terms] OR cytochrome p 450 CYP3A inhibitors[MeSH Terms] OR enzyme inhibitors[MeSH Terms] OR excitatory amino acid antagonists[MeSH Terms] OR fibrinolytic agents[MeSH Terms] OR muscarinic antagonists[MeSH Terms] OR mydriatics[MeSH Terms] OR parasympatholytics[MeSH Terms] OR phosphodiesterase 3 inhibitors[MeSH Terms] OR potassium channel blockers[MeSH Terms] OR purinergic p1 receptor

antagonists[MeSH Terms] OR sympathomimetics[MeSH Terms] OR sympatholytics[MeSH Terms] OR vasoconstrictor agents[MeSH Terms] OR vasodilator agents[MeSH Terms] OR vitamins[MeSH Terms] OR Adrenergic alpha-Agonists[Text Word] OR Adrenergic alpha-1 Receptor Antagonists[Text Word] OR Adrenergic beta-Antagonists[Text Word] OR Adjuvants, Anesthesia[Text Word] OR Analgesics[Text Word] OR Anesthetics, Dissociative[Text Word] OR Anesthetics, Local[Text Word] OR Anti-Arrhythmia Agents[Text Word] OR Antihypertensive Agents[Text Word] OR Antioxidants[Text Word] OR Bronchodilator Agents[Text Word] OR Cardiotonic Agents[Text Word] OR Cardiovascular Agents[Text Word] OR Cytochrome P-450 CYP1A2 Inhibitors[Text Word] OR Cytochrome P-450 CYP2C9 Inhibitors[Text Word] OR Cytochrome P-450 CYP2D6 Inhibitors[Text Word] OR Cytochrome P-450 CYP3A Inhibitors[Text Word] OR Enzyme Inhibitors[Text Word] OR Excitatory Amino Acid Antagonists[Text Word] OR Fibrinolytic Agents[Text Word] OR Muscarinic Antagonists[Text Word] OR Mydriatics[Text Word] OR Parasympatholytics[Text Word] OR Phosphodiesterase 3 Inhibitors[Text Word] OR Potassium Channel Blockers[Text Word] OR Purinergic P1 Receptor Antagonists[Text Word] OR Sympathomimetics[Text Word] OR Sympatholytics[Text Word] OR Vasoconstrictor agents[Text Word] OR Vasodilator **2015:2021[pdat]**

Results 4: 2, 723, 077

Combined Results 1+2+3+4: 4308

Date: December 7, 2020

Figure 1. Example Search Algorithm for PubMed

PubMed

Cardiac Arrest

cardiac arrest[MeSH Terms] OR arrest, cardiopulmonary[MeSH Terms] OR heart arrest[MeSH Terms] OR deep hypothermic circulatory arrest[MeSH Terms] OR ventricular fibrillation[MeSH Terms] OR ventricular tachycardia[MeSH Terms] OR asystole[MeSH Terms] OR cardiopulmonary resuscitation[MeSH Terms] OR advanced cardiac life support[MeSH Terms] OR cardiac death[MeSH Terms] OR sudden cardiac death[MeSH Terms] OR cardiac death, sudden[MeSH Terms] OR cardiac arrest[Text Word] OR cardiopulmonary arrest[Text Word] OR heart arrest[Text Word] OR circulatory arrest[Text Word] OR ventricular fibrillation[Text Word] OR ventricular tachycardia[Text Word] OR pulseless electrical activity[Text Word] OR asystole[Text Word] OR cardiovascular arrest[Text Word] OR cardiopulmonary arrest[Text Word] OR cardiopulmonary resuscitation[Text Word] OR defibrillation[Text Word] OR advanced cardiac life support[Text Word] OR ACLS[Text Word] OR cardiac death[Text Word] OR sudden cardiac death[Text Word] OR fatal arrhythmia[Text Word] **2015:2021[pdat]**

Results 1: 57,400

AND

Survival

survival[MeSH Terms] OR mortality[MeSH Terms] OR survival[Text Word] OR mortality[Text Word] **2015:2021[pdat]**

Results 2: 705, 713

AND

Functional Outcome

glasgow outcome scale[MeSH Terms] OR glasgow outcome scale[Text Word] OR modified rankin scale[Text Word] OR cerebral performance categories score[Text Word] OR prognosis[MeSH Terms] OR disability evaluation[MeSH Terms] OR prognosis[Text Word] OR disability evaluation[Text Word] **2015:2021[pdat]**

Results 3: 603,078

AND

Pharmacology

drug*[Text Word] OR drug therapy[Text Word] OR medication[Text Word] OR phamacolog*[Text Word] OR pharmaceutic*[Text Word] OR therap*[Text Word] OR injection[Text Word] OR infusion[Text Word] OR cardiovascular agents[Text Word] OR drug administration schedule[Text Word] OR therapeutics[Text Word] OR intravenous administration[Text Word] OR dose response relationship[Text Word] OR cardiovascular agents[MeSH Terms] OR therapeutics[MeSH Terms] OR drug administration

schedule[MeSH Terms] OR dose response relationship, drug[MeSH Terms] OR vasopressor agents[MeSH Terms] OR epinephrine[MeSH Terms] OR vasopressins[MeSH Terms] OR norepinephrine[MeSH Terms] OR Simendan[MeSH Terms] OR methoxamine[MeSH Terms] OR amiodarone[MeSH Terms] OR sodium channel blockers[MeSH Terms] OR lidocaine[MeSH Terms] OR lignocaine[MeSH Terms] OR procainamide[MeSH Terms] OR flecainide[MeSH Terms] OR mexiletine[MeSH Terms] OR quinidine[MeSH Terms] OR adrenergic beta blockers[MeSH Terms] OR sotalol[MeSH Terms] OR apo labetalol[MeSH Terms] OR metoprolol[MeSH Terms] OR nadolol[MeSH Terms] OR bisoprolol[MeSH Terms] OR carvedilol[MeSH Terms] OR isoproterenol[MeSH Terms] OR calcium channel blockers[MeSH Terms] OR diltiazem[MeSH Terms] OR verapamil[MeSH Terms] OR digoxin[MeSH Terms] OR isoprenaline[MeSH Terms] OR theophylline[MeSH Terms] OR aminophylline[MeSH Terms] OR magnesium[MeSH Terms] OR thrombolytic agents[MeSH Terms] OR thrombolytic drugs[MeSH Terms] OR thrombolytic therapies[MeSH Terms] OR corticosteroids[MeSH Terms] OR sodium bicarbonate[MeSH Terms] OR erythropoietin[MeSH Terms] OR crystalloid solutions[MeSH Terms] OR ascorbic acid[MeSH Terms] OR vitamin e[MeSH Terms] OR vitamin b1[MeSH Terms] OR melatonin[MeSH Terms] OR colloids[MeSH Terms] OR xenon[MeSH Terms] OR argon[MeSH Terms] OR hydrogen[MeSH Terms] OR hydrogen sulfide[MeSH Terms] OR nitric oxide[MeSH Terms] OR carbon monoxide[MeSH Terms] OR anesthetic agents[MeSH Terms] OR anesthetic drugs[MeSH Terms] OR propofol[MeSH Terms] OR ketamine[MeSH Terms] OR vasopressor[Text Word] OR epinephrine[Text Word] OR vasopressin[Text Word] OR norepinephrine[Text Word] OR levosimendan[Text Word] OR simendan[Text Word] OR methoxamine[Text Word] OR amiodarone[Text Word] OR sodium channel blockers[Text Word] OR lidocaine[Text Word] OR lignocaine[Text Word] OR procainamide[Text Word] OR flecainide[Text Word] OR mexiletine[Text Word] OR quinidine[Text Word] OR beta blocker[Text Word] OR sotalol[Text Word] OR labetalol[Text Word] OR metoprolol[Text Word] OR nadolol[Text Word] OR bisoprolol[Text Word] OR carvedilol[Text Word] OR isoproterenol[Text Word] OR calcium channel blocker[Text Word] OR diltiazem[Text Word] OR verapamil[Text Word] OR atropine[Text Word] OR atropine[MeSH Terms] OR digoxin[Text Word] OR isoprenaline[Text Word] OR theopylline[Text Word] OR magnesium[Text Word] OR thrombolytic[Text Word] OR corticosteroids[Text Word] OR sodium bicarbonate[Text Word] OR erythropoietin[Text Word] OR crystalloid[Text Word] OR colloid[Text Word] OR vitamin c[Text Word] OR ascorbic acid[Text Word] OR vitamin e[Text Word] OR vitamin b[Text Word] OR thiamine[Text Word] OR edavarone[Text Word] OR melatonin[Text Word] OR medical gas[Text Word] OR xenon[Text Word] OR argon[Text Word] OR hydrogen[Text Word] OR hydrogen sulfide[Text Word] OR nitric oxide[Text Word] OR carbon monoxide[Text Word] OR anesthetics[Text Word] OR propofol[Text Word] OR ketamine[Text Word] OR adrenergic alpha agonists[MeSH Terms] OR Adrenergic alpha-1 Receptor Antagonists[MeSH Terms] OR adrenergic beta antagonists[MeSH Terms] OR adjuvants, anesthesia[MeSH Terms] OR analgesics[MeSH Terms] OR anesthetics, dissociative[MeSH Terms] OR anesthetics, local[MeSH Terms] OR anti arrhythmia agents[MeSH Terms] OR antihypertensive agents[MeSH Terms] OR antioxidants[MeSH Terms] OR bronchodilator agents[MeSH Terms] OR cardiotonic agents[MeSH Terms] OR cardiovascular agents[MeSH Terms] OR cytochrome p 450 CYP1A2 inhibitors[MeSH Terms] OR cytochrome p 450 CYP2C9 inhibitors[MeSH Terms] OR cytochrome p 450 CYP2D6 inhibitors[MeSH Terms] OR cytochrome p 450 CYP3A inhibitors[MeSH Terms] OR enzyme inhibitors[MeSH Terms] OR excitatory amino acid antagonists[MeSH Terms] OR fibrinolytic agents[MeSH Terms] OR muscarinic antagonists[MeSH Terms] OR mydriatics[MeSH Terms] OR parasympatholytics[MeSH Terms] OR phosphodiesterase 3 inhibitors[MeSH Terms] OR potassium channel blockers[MeSH Terms] OR purinergic p1 receptor

antagonists[MeSH Terms] OR sympathomimetics[MeSH Terms] OR sympatholytics[MeSH Terms] OR vasoconstrictor agents[MeSH Terms] OR vasodilator agents[MeSH Terms] OR vitamins[MeSH Terms] OR Adrenergic alpha-Agonists[Text Word] OR Adrenergic alpha-1 Receptor Antagonists[Text Word] OR Adrenergic beta-Antagonists[Text Word] OR Adjuvants, Anesthesia[Text Word] OR Analgesics[Text Word] OR Anesthetics, Dissociative[Text Word] OR Anesthetics, Local[Text Word] OR Anti-Arrhythmia Agents[Text Word] OR Antihypertensive Agents[Text Word] OR Antioxidants[Text Word] OR Bronchodilator Agents[Text Word] OR Cardiotonic Agents[Text Word] OR Cardiovascular Agents[Text Word] OR Cytochrome P-450 CYP1A2 Inhibitors[Text Word] OR Cytochrome P-450 CYP2C9 Inhibitors[Text Word] OR Cytochrome P-450 CYP2D6 Inhibitors[Text Word] OR Cytochrome P-450 CYP3A Inhibitors[Text Word] OR Enzyme Inhibitors[Text Word] OR Excitatory Amino Acid Antagonists[Text Word] OR Fibrinolytic Agents[Text Word] OR Muscarinic Antagonists[Text Word] OR Mydriatics[Text Word] OR Parasympatholytics[Text Word] OR Phosphodiesterase 3 Inhibitors[Text Word] OR Potassium Channel Blockers[Text Word] OR Purinergic P1 Receptor Antagonists[Text Word] OR Sympathomimetics[Text Word] OR Sympatholytics[Text Word] OR Vasoconstrictor agents[Text Word] OR Vasodilator **2015:2021[pdat]**

Results 4: 2, 723, 077

Combined Results 1+2+3+4: 4308

Date: December 7, 2020

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Review of Novel Therapeutics in Cardiac Arrest (ReNTICA) - Systematic Review Protocol

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Secondary Subject Heading:	Cardiovascular medicine, Neurology, Patient-centred medicine
Keywords:	CLINICAL PHARMACOLOGY, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Neurological injury < NEUROLOGY, THERAPEUTICS, Adult cardiology < CARDIOLOGY, ACCIDENT & EMERGENCY MEDICINE

Review of Novel Therapeutics in Cardiac Arrest (ReNTICA) - Systematic Review Protocol

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Word Count: 2109/4000

Travis W Murphy, MD

Abstract

Introduction

Cardiac arrest remains a common and devastating cause of death and disability worldwide. While targeted temperature management has become standard of care to improve functional neurologic outcome, few pharmacologic interventions have shown similar promise.

Methods/analysis

This systematic review will focus on prospective human studies from 2015 to 2020 available in PubMed, Web of Science and EMBASE with a primary focus on impact on functional neurologic outcome. Prospective studies that include pharmacologic agents given during or after cardiac arrest will be included. Study selection will be in keeping with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. If sufficient data involving a given agent are available, a meta-analysis will be conducted and compared to current evidence for therapies recommended in international practice guidelines.

Ethics and dissemination

Formal ethical approval will not be required as primary data will not be collected. The results will be disseminated through peer-reviewed publication, conference presentation and lay press.

Prospero registration number: International Prospective Register for Systematic Reviews (PROSPERO) number CRD42021230216

Article Summary

Strengths and limitations of this study

- Systematic review and meta-analysis of prospective trials investigating therapeutic agents in cardiac arrest.
- Inclusion of outcome measurements to quantify the effect of proposed therapeutic interventions on neurologic function after cardiac arrest.
- Limitation in the number of studies investigating a given therapy may diminish observed effects.
- Potential identification of therapies with positive impact on functional outcome following cardiac arrest.

Introduction

Cardiac arrest remains a common and often devastating cause of death and disability worldwide.[1] Outcomes are contingent on the severity of overall hypoxic-ischemic brain injury burden, which comprises primary injury during circulation standstill and ongoing secondary brain injury that occurs in the aftermath of resuscitation. Aside from targeted temperature management, therapeutic options targeting improvement in neurologic outcome are scarce and recent data has cast doubt on even this guideline-recommended therapy.[2,3] International practice guidelines currently recommend epinephrine/adrenaline, amiodarone and lidocaine/lignocaine.[4–6] While there is good evidence for improved survival with these medications, there is little evidence for a positive impact of these medications on functional neurologic outcomes specifically[4,6,7]. Functional neurologic outcome is less commonly the primary focus of cardiac arrest research but arguably a more granular patient-centered variable rather than rate of return of spontaneous circulation or survival. Unlike targeted temperature management, few advances have been made in pharmacologic approaches to improve functionally intact neurologic survival following cardiac arrest.[2,6,8,9] Several novel compounds have been investigated in animal studies, with some notation of effect on neurologic function, though only a small minority have made the transition from animal models into human trials.[8] The review proposed here will focus on identifying the best available data from human studies and report on therapies that may not have been explicitly mentioned in international guidelines to date.

A similar review of the literature was performed in 2015, though this was focused on cataloging the therapies utilized and did not focus on studies that included functional outcome measurements.[9] Another recent systematic review reported the rate of translation from animal models to human trials for therapies targeted at cardiac arrest.[8] Though again, this review did not have a specific focus on functional neurologic outcome. While the review published by Lind et al. identified the large number of experimental therapies targeted at post-cardiac arrest physiology, the authors noted a relative dearth of clinical trials investigating those same therapies in humans.[8] Additionally, the review published in 2021 did not compare the effects of different pharmacologic agents.[8] The review proposed here seeks to compile the best available evidence for pharmacologic interventions that will improve functional neurologic outcomes in humans following cardiac arrest and compare this directly to current practice guidelines.

Objectives

The objective of our study is to systematically review the literature for prospective studies that evaluated the performance of pharmacologic agents used in adult cardiac arrest compared to standard resuscitation treatments currently advocated in practice guidelines. This will include studies regardless of initial cardiac rhythm and independent of the use of targeted temperature management.

Methods and Design

Population

The systematic review will focus on studies that include patients aged >15 years who have been resuscitated from cardiac arrest but are not conscious upon return of spontaneous circulation with arms for both intervention and control.

Interventions

The interventions to be evaluated include any pharmacologic agent given during cardiac arrest itself or in the immediate post-arrest period (defined as the initial 24 hours).

Comparisons

The added benefit of the interventions identified will be compared to current international practice guidelines and the pharmacologic agents advocated there (epinephrine/adrenaline, amiodarone, and lidocaine/lignocaine).

Outcome

The primary outcomes required of included studies will be survival and neurologic function as defined by one of the following neurologic scales: Cerebral Performance Category, modified Rankin Scale, Glasgow Outcome Scale/Glasgow Outcome Scale-Extended.

Study Design

The systematic review and meta-analysis will include prospective therapeutic studies investigating the use of a pharmacologic agent during or after cardiac arrest with a primary focus on effects on neurologic outcome. This will include systematic reviews, meta-analyses, randomized control trials, adaptive clinical trials, prospective cohort and observational studies, and non-randomized clinical trials. Studies that compare one intervention to standard resuscitation as the control will be included. No minimum number of included subjects will be required. The review will exclude studies without a control group using either placebo or current standard care. Retrospective studies will be excluded including retrospective cohorts, case control studies, cross sectional studies, case reports, and case series. This review has been registered on the International Prospective Register for Systematic Reviews (PROSPERO) number CRD42021230216.

Search Strategy

A three-step process will be used to identify eligible studies, including an initial search, title and abstract screening and full-text manuscript review. A professional systematic review librarian (PMW) will develop search criteria in discussion with the authors to include all relevant studies pertaining to adult, human studies of pharmacologic treatment of cardiac arrest. The databases that will be searched are PubMed, Web of Science and EMBASE from the year 2015 to 2020, inclusive. No language restrictions will be applied. Figure 1 shows an example search algorithm for PubMed. Initial deduplication will be performed using EndNote (Clarivate Analytics, Philadelphia, Pennsylvania, USA).[10]

Study Selection

Literature search results will be uploaded from EndNote and screened through DistillerSR (Evidence Partners, Ottawa, Ontario, Canada). Study titles and abstracts will be screened for relevance in duplicate, blindly and independently, by four reviewers (EA, NT, GC, MM) and adjudicated by a senior author (TM, CM). Eligible studies will then be assessed again for inclusion and for quality in secondary screening through review of full-text manuscripts before data abstraction. This process will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. The PRISMA-P Checklist pertaining to this protocol is available as Supplement 1. Any conflicting remarks regarding studies will be adjudicated through discussion before inclusion in the final analysis.

Quality Assessment

Each article will undergo initial screening in parallel by two independent reviewers to minimize bias. All selected articles will be reviewed with senior authors during full-text review. Cochrane tools for assessment of study quality will be utilized as appropriate. (ROBINS-1 and RoB 2.0). Two independent

authors will assess the risks of bias in studies considered for full-text review in order to determine feasibility of a meta-analysis. Conflicts will be adjudicated with discussion and involvement of a third author (TM or CM) as necessary.

Data Extraction

Quantitative data will be extracted from studies meeting inclusion upon full-text review by a professional biostatistician (MABC). Data extracted will be specifically those pertinent to the systematic review and all others that fit into the synthesis of outcome parameters from all studies and meets the potential for inclusion in a meta-analysis. This will include demographics, characteristics of cardiac arrest, medications administered, and outcome parameters as well as any data that are available across all included studies. Data extraction will be independently cross-checked by a senior author and discrepancies resolved through discussion with other senior authors. Data produced from this systematic review including the statistical code and dataset of articles screened will be published in a data repository.

Endpoint

Results of the systematic review will be grouped by drug and drug class. The primary outcomes will be survival and neurologic function as defined by one of the following performance scales: Cerebral Performance Category, modified Rankin Scale, Glasgow Outcome Scale/Glasgow Outcome Scale-Extended. Provided they are available in the original studies, secondary outcomes will be ICU length of stay, Ventilator days, rates of sepsis, rates of pneumonia, rate of tracheostomy, rate of acute kidney injury and need for CVVH/HD (in the hospital or afterwards). We will also include secondary outcomes of functional capacity including Barthel Index, Katz Index, Lawton-Brody Instrumental Activities of Daily Living Scale, and rates of discharge to rehab facility if included in the original studies. Any follow-up duration will be accepted as there is considerable variability in the existing literature.

Patient and Public Involvement

No patients were involved with the planning of this protocol.

Analysis

Descriptive Analysis

A narrative synthesis of the final studies included will be developed based on the different pharmacologic agents identified. The impact of each of these agents on the primary and secondary outcome mentioned above will be described in addition to a formal meta-analysis of studies using each pharmacologic agent identified.

Statistical Analysis

The primary focus of this review is to detect evidence for the impact of the pharmacologic agents identified on survival and functional neurologic outcome. As functional outcome is reported with some degree of heterogeneity, we are including three of the most widely reported functional outcome scales and not limiting to one over the others. As functional neurologic outcome is not always explicitly reported using one of these sales, we do anticipate some limitation in the ability to directly compare one agent to another. However, when available, pharmacologic agents will be compared as equitably as possible using all available outcome parameters reported in the index studies. The percentage of patients receiving a given pharmacologic agent with a favorable neurologic outcome according to each specific scale will be reported. Based on the availability of data from primary sources, subgroup analysis

within cohorts treated with the same pharmacologic agent will also be performed to identify populations most likely to benefit from a given agent.

Data synthesis

Results will be presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. A PRISMA flow diagram will be used to summarize study selection. Tabulated data showing relative proportion of patients with favorable functional neurologic outcome for each pharmacologic agent will be presented. We will rank agents by proportion of favorable outcomes. For secondary outcome variables, we will present synthesized data as available in separate tables but will otherwise provide a separate narrative summary of the data available for each agent. We will produce a hierarchy of pharmacologic agents based on the quality of evidence available and degree of effects on outcome variables.

Meta-analysis

A meta-analysis of the pharmacologic agents found to have been studied with a focus on functional neurologic outcome will be performed. The results of this meta-analysis will then be compared to the best available evidence for medications recommended in practice guidelines to provide context and rank relative efficacy.

Discussion

This systematic review and meta-analysis will provide evidence for further study or use of compounds that are most likely to benefit patients following cardiac arrest in terms of functional status. The conclusions will be the result of careful accumulation of the highest-quality evidence available and will compare to current practice guidelines to place the effects in context. With a primary focus on the ability of a given pharmacologic agent to not only provide a survival benefit but protect the neurologic function of patients following cardiac arrest, this review and meta-analysis will be unique in its aim to identify agents with the greatest potential to benefit these patients.

Ethics and dissemination

No ethical or safety considerations were considered based on the nature of this review. Dissemination of findings through a peer-reviewed publication upon the conclusion of the meta-analysis.

Author Contributions

Travis Murphy: Conception and design of work, analysis, drafting of work, final approval *Garrett Snipes:* Conception and design of work, drafting of work *Muhammad Abdul Baker Chowdhury:* Conception and design of work, analysis *Patti McCall-Wright:* Conception and design of work, analysis *Elizabeth Aleong:* Analysis *Noelle Taylor:* Analysis *Maiya Messina:* Analysis *Gabriela Carrazana:* Analysis *Carolina Maciel:* Conception and design of work, analysis *Torben Becker*: Conception and design of work. All authors have reviewed and contributed to this final written manuscript.

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Competing interests statement

The authors have no competing interests.

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Figure 1. Example Search Algorithm for PubMed

PubMed

Cardiac Arrest

cardiac arrest[MeSH Terms] OR arrest, cardiopulmonary[MeSH Terms] OR heart arrest[MeSH Terms] OR deep hypothermic circulatory arrest[MeSH Terms] OR ventricular fibrillation[MeSH Terms] OR ventricular tachycardia[MeSH Terms] OR asystole[MeSH Terms] OR cardiopulmonary resuscitation[MeSH Terms] OR advanced cardiac life support[MeSH Terms] OR cardiac death[MeSH Terms] OR sudden cardiac death[MeSH Terms] OR cardiac death, sudden[MeSH Terms] OR cardiac arrest[Text Word] OR cardiopulmonary arrest[Text Word] OR heart arrest[Text Word] OR circulatory arrest[Text Word] OR ventricular fibrillation[Text Word] OR ventricular tachycardia[Text Word] OR pulseless electrical activity[Text Word] OR asystole[Text Word] OR cardiovascular arrest[Text Word] OR cardiopulmonary arrest[Text Word] OR cardiopulmonary resuscitation[Text Word] OR defibrillation[Text Word] OR advanced cardiac life support[Text Word] OR ACLS[Text Word] OR cardiac death[Text Word] OR sudden cardiac death[Text Word] OR fatal arrhythmia[Text Word] **2015:2021[pdat]**

Results 1: 57,400

AND

Survival

survival[MeSH Terms] OR mortality[MeSH Terms] OR survival[Text Word] OR mortality[Text Word] **2015:2021[pdat]**

Results 2: 705, 713

AND

Functional Outcome

glasgow outcome scale[MeSH Terms] OR glasgow outcome scale[Text Word] OR modified rankin scale[Text Word] OR cerebral performance categories score[Text Word] OR prognosis[MeSH Terms] OR disability evaluation[MeSH Terms] OR prognosis[Text Word] OR disability evaluation[Text Word] **2015:2021[pdat]**

Results 3: 603,078

AND

Pharmacology

drug*[Text Word] OR drug therapy[Text Word] OR medication[Text Word] OR phamacolog*[Text Word] OR pharmaceutic*[Text Word] OR therap*[Text Word] OR injection[Text Word] OR infusion[Text Word] OR cardiovascular agents[Text Word] OR drug administration schedule[Text Word] OR therapeutics[Text Word] OR intravenous administration[Text Word] OR dose response relationship[Text Word] OR cardiovascular agents[MeSH Terms] OR therapeutics[MeSH Terms] OR drug administration schedule[MeSH Terms] OR dose response relationship, drug[MeSH Terms] OR vasopressor agents[MeSH Terms] OR epinephrine[MeSH Terms] OR vasopressins[MeSH Terms] OR norepinephrine[MeSH Terms] OR Simendan[MeSH Terms] OR methoxamine[MeSH Terms] OR amiodarone[MeSH Terms] OR sodium channel blockers[MeSH Terms] OR lidocaine[MeSH Terms] OR lignocaine[MeSH Terms] OR procainamide[MeSH Terms] OR flecainide[MeSH Terms] OR mexiletine[MeSH Terms] OR quinidine[MeSH Terms] OR adrenergic beta blockers[MeSH Terms] OR sotalol[MeSH Terms] OR apo labetalol[MeSH Terms] OR metoprolol[MeSH Terms] OR nadolol[MeSH Terms] OR bisoprolol[MeSH Terms] OR carvedilol[MeSH Terms] OR isoproterenol[MeSH Terms] OR calcium channel blockers[MeSH Terms] OR diltiazem[MeSH Terms] OR verapamil[MeSH Terms] OR digoxin[MeSH Terms] OR isoprenaline[MeSH Terms] OR theophylline[MeSH Terms] OR aminophylline[MeSH Terms] OR magnesium[MeSH Terms] OR thrombolytic agents[MeSH Terms] OR thrombolytic drugs[MeSH Terms] OR thrombolytic therapies[MeSH Terms] OR corticosteroids[MeSH Terms] OR sodium bicarbonate[MeSH Terms] OR erythropoietin[MeSH Terms] OR crystalloid solutions[MeSH Terms] OR ascorbic acid[MeSH Terms] OR vitamin e[MeSH Terms] OR vitamin b1[MeSH Terms] OR melatonin[MeSH Terms] OR colloids[MeSH Terms] OR xenon[MeSH Terms] OR argon[MeSH Terms] OR hydrogen[MeSH Terms] OR hydrogen sulfide[MeSH Terms] OR nitric oxide[MeSH Terms] OR carbon monoxide[MeSH Terms] OR anesthetic agents[MeSH Terms] OR anesthetic drugs[MeSH Terms] OR propofol[MeSH Terms] OR ketamine[MeSH Terms] OR vasopressor[Text Word] OR epinephrine[Text Word] OR vasopressin[Text Word] OR norepinephrine[Text Word] OR levosimendan[Text Word] OR simendan[Text Word] OR methoxamine[Text Word] OR amiodarone[Text Word] OR sodium channel blockers[Text Word] OR lidocaine[Text Word] OR lignocaine[Text Word] OR procainamide[Text Word] OR flecainide[Text Word] OR mexiletine[Text Word] OR quinidine[Text Word] OR beta blocker[Text Word] OR sotalol[Text Word] OR labetalol[Text Word] OR metoprolol[Text Word] OR nadolol[Text Word] OR bisoprolol[Text Word] OR carvedilol[Text Word] OR isoproterenol[Text Word] OR calcium channel blocker[Text Word] OR diltiazem[Text Word] OR verapamil[Text Word] OR atropine[Text Word] OR atropine[MeSH Terms] OR digoxin[Text Word] OR isoprenaline[Text Word] OR theopylline[Text Word] OR magnesium[Text Word] OR thrombolytic[Text Word] OR corticosteroids[Text Word] OR sodium bicarbonate[Text Word] OR erythropoietin[Text Word] OR crystalloid[Text Word] OR colloid[Text Word] OR vitamin c[Text Word] OR ascorbic acid[Text Word] OR vitamin e[Text Word] OR vitamin b[Text Word] OR thiamine[Text Word] OR edavarone[Text Word] OR melatonin[Text Word] OR medical gas[Text Word] OR xenon[Text Word] OR argon[Text Word] OR hydrogen[Text Word] OR hydrogen sulfide[Text Word] OR nitric oxide[Text Word] OR carbon monoxide[Text Word] OR anesthetics[Text Word] OR propofol[Text Word] OR ketamine[Text Word] OR adrenergic alpha agonists[MeSH Terms] OR Adrenergic alpha-1 Receptor Antagonists[MeSH Terms] OR adrenergic beta antagonists[MeSH Terms] OR adjuvants, anesthesia[MeSH Terms] OR analgesics[MeSH Terms] OR

anesthetics, dissociative[MeSH Terms] OR anesthetics, local[MeSH Terms] OR anti arrhythmia agents[MeSH Terms] OR antihypertensive agents[MeSH Terms] OR antioxidants[MeSH Terms] OR bronchodilator agents[MeSH Terms] OR cardiotonic agents[MeSH Terms] OR cardiovascular agents[MeSH Terms] OR cytochrome p 450 CYP1A2 inhibitors[MeSH Terms] OR cytochrome p 450 CYP2C9 inhibitors[MeSH Terms] OR cytochrome p 450 CYP2D6 inhibitors[MeSH Terms] OR cytochrome p 450 CYP3A inhibitors[MeSH Terms] OR enzyme inhibitors[MeSH Terms] OR excitatory amino acid antagonists[MeSH Terms] OR fibrinolytic agents[MeSH Terms] OR muscarinic antagonists[MeSH Terms] OR mydriatics[MeSH Terms] OR parasympatholytics[MeSH Terms] OR phosphodiesterase 3 inhibitors[MeSH Terms] OR potassium channel blockers[MeSH Terms] OR purinergic p1 receptor antagonists[MeSH Terms] OR sympathomimetics[MeSH Terms] OR sympatholytics[MeSH Terms] OR vasoconstrictor agents[MeSH Terms] OR vasodilator agents[MeSH Terms] OR vitamins[MeSH Terms] OR Adrenergic alpha-Agonists[Text Word] OR Adrenergic alpha-1 Receptor Antagonists[Text Word] OR Adrenergic beta-Antagonists[Text Word] OR Adjuvants, Anesthesia[Text Word] OR Analgesics[Text Word] OR Anesthetics, Dissociative[Text Word] OR Anesthetics, Local[Text Word] OR Anti-Arrhythmia Agents[Text Word] OR Antihypertensive Agents[Text Word] OR Antioxidants[Text Word] OR Bronchodilator Agents[Text Word] OR Cardiotonic Agents[Text Word] OR Cardiovascular Agents[Text Word] OR Cytochrome P-450 CYP1A2 Inhibitors[Text Word] OR Cytochrome P-450 CYP2C9 Inhibitors[Text Word] OR Cytochrome P-450 CYP2D6 Inhibitors[Text Word] OR Cytochrome P-450 CYP3A Inhibitors[Text Word] OR Enzyme Inhibitors[Text Word] OR Excitatory Amino Acid Antagonists[Text Word] OR Fibrinolytic Agents[Text Word] OR Muscarinic Antagonists[Text Word] OR Mydriatics[Text Word] OR Parasympatholytics[Text Word] OR Phosphodiesterase 3 Inhibitors[Text Word] OR Potassium Channel Blockers[Text Word] OR Purinergic P1 Receptor Antagonists[Text Word] OR Sympathomimetics[Text Word] OR Sympatholytics[Text Word] OR Vasoconstrictor agents[Text Word] OR Vasodilator **2015:2021[pdat]**

Results 4: 2, 723, 077

Combined Results 1+2+3+4: 4308

Date: December 7, 2020

Figure 1. Example Search Algorithm for PubMed

Cardiac Arrest

cardiac arrest[MeSH Terms] OR arrest, cardiopulmonary[MeSH Terms] OR heart arrest[MeSH Terms] OR deep hypothermic circulatory arrest[MeSH Terms] OR ventricular fibrillation[MeSH Terms] OR ventricular tachycardia[MeSH Terms] OR asystole[MeSH Terms] OR cardiopulmonary resuscitation[MeSH Terms] OR advanced cardiac life support[MeSH Terms] OR cardiac death[MeSH Terms] OR sudden cardiac death[MeSH Terms] OR cardiac death, sudden[MeSH Terms] OR cardiac arrest[Text Word] OR cardiopulmonary arrest[Text Word] OR heart arrest[Text Word] OR circulatory arrest[Text Word] OR ventricular fibrillation[Text Word] OR ventricular tachycardia[Text Word] OR pulseless electrical activity[Text Word] OR asystole[Text Word] OR cardiovascular arrest[Text Word] OR cardiopulmonary arrest[Text Word] OR cardiopulmonary resuscitation[Text Word] OR defibrillation[Text Word] OR advanced cardiac life support[Text Word] OR ACLS[Text Word] OR cardiac death[Text Word] OR sudden cardiac death[Text Word] OR fatal arrhythmia[Text Word] **2015:2021[pdat]**

Results 1: 57,400

AND

Survival

survival[MeSH Terms] OR mortality[MeSH Terms] OR survival[Text Word] OR mortality[Text Word] **2015:2021[pdat]**

Results 2: 705, 713

AND

Functional Outcome

glasgow outcome scale[MeSH Terms] OR glasgow outcome scale[Text Word] OR modified rankin scale[Text Word] OR cerebral performance categories score[Text Word] OR prognosis[MeSH Terms] OR disability evaluation[MeSH Terms] OR prognosis[Text Word] OR disability evaluation[Text Word] **2015:2021[pdat]**

Results 3: 603,078

AND

Pharmacology

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Combined Results 1+2+3+4: 4308

Date: December 7, 2020

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page Number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	6
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	6
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Fig. 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	4
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5-6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/a
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	4

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.