Treatment for calcium channel blocker poisoning: A systematic review

M. ST-ONGE,1,2,3 P.-A. DUBÉ,4,5,6 S. GOSSHELIN,7,8,9 C. GUIMONT,10 J. GODWIN,1,3 P. M. ARCHAMBAULT,11,12,13,14 J.-M. CHAUNY,15,16 A. J. FRENETTE,15,17 M. DARVEAU,18 N. LE SAGE,10,14 J. POITRAS,11,12 J. PROVENCHER,19 D. N. JUURLINK,1,20,21 and R. BLAIS7

1Ontario and Manitoba Poison Centre, Toronto, ON, Canada
2Institute of Medical Science, University of Toronto, Toronto, ON, Canada
3Department of Clinical Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada
4Department of Neurology and Neurosurgery, University of Toronto, Toronto, ON, Canada
5Department of Neurology and Neurosurgery, Queen’s University, Ottawa, ON, Canada
6Department of Medicine, McGill University, Montréal, QC, Canada
7Department of Neurology, McGill University, Montréal, QC, Canada
8Centre Hospitalier Universitaire de Montréal, Montréal, QC, Canada
9Centre de santé et services sociaux Alphonse-Desjardins (CHAU de Lévis), Lévis, QC, Canada
10Centre de santé et services sociaux Alphonse-Desjardins (CHAU de Lévis), Lévis, QC, Canada
11Divison de soins intensifs, Université Laval, Québec, QC, Canada
12Department of Family Medicine and Emergency Medicine, Université Laval, Quebec, QC, Canada
13Centre Hospitalier Universitaire de Québec, Québec, QC, Canada
14Population Health and Optimal Health Practices, Centre Hospitalier Universitaire de Québec Research Centre, Quebec, QC, Canada
15Centre antipoison du Québec, Québec, QC, Canada
16Department of Family and Emergency Medicine, University of Montreal, Montreal, QC, Canada
17Faculty of Pharmacy, University of Montreal, Montreal, QC, Canada
18Pharmacy Department, Centre de santé et services sociaux Alphonse-Desjardins (CHAU de Lévis), Lévis, QC, Canada
19Centre de santé et services sociaux Alphonse-Desjardins (CHAU de Lévis), Lévis, QC, Canada
20Sunnybrook Research Institute and Institute for Clinical Evaluative Sciences, Toronto, ON, Canada
21Departments of Medicine and Pediatrics, University of Toronto, Toronto, ON, Canada

Context. Calcium channel blocker poisoning is a common and sometimes life-threatening ingestion. Objective. To evaluate the reported effects of treatments for calcium channel blocker poisoning. The primary outcomes of interest were mortality and hemodynamic parameters. The secondary outcomes included length of stay in hospital, length of stay in intensive care unit, duration of vasopressor use, functional outcomes, and serum calcium channel blocker concentrations. Methods. Medline/Ovid, PubMed, EMBASE, Cochrane Library, TOXLINE, International pharmaceutical abstracts, Google Scholar, and the gray literature up to December 31, 2013 were searched without time restriction to identify all types of studies that examined effects of various treatments for calcium channel blocker poisoning for the outcomes of interest. The search strategy included the following Keywords: [calcium channel blockers OR calcium channel antagonist OR calcium channel blocking agent OR (amlodipine or bencyclane or bepridil or cinnarizine or felodipine or fendiline or flunarizine or gallopamil or isradipine or lidoflazine or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or prenylamine or verapamil or diltiazem)] AND [overdose OR medication errors OR poisoning OR intoxication OR toxicity OR adverse effect]. Two reviewers independently selected studies and a group of reviewers abstracted all relevant data using a pilot-tested form. A second group analyzed the risk of bias and overall quality using the STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) checklist and the Thomas tool for observational studies, the Institute of Health Economics tool for Quality of Case Series, the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines, and the modified NRCNA (National Research Council for the National Academies) list for animal studies. Qualitative synthesis was used to summarize the evidence. Of 15,577 citations identified in the initial search, 216 were selected for analysis, including 117 case reports. The kappa on the quality analysis tools was greater than 0.80 for all study types. Results. The only observational study in humans examined high-dose insulin and extracorporeal life support. The risk of bias across studies was high for all interventions and moderate to high for extracorporeal life support. High-dose insulin. High-dose insulin (bolus of 1 unit/kg followed by an infusion of 0.5–2.0 units/kg/h) was associated with improved hemodynamic parameters...
and lower mortality, at the risks of hypoglycemia and hypokalemia (low quality of evidence). Extracorporeal life support. Extracorporeal life support was associated with improved survival in patients with severe shock or cardiac arrest at the cost of limb ischemia, thrombosis, and bleeding (low quality of evidence). Calcium, dopamine, and norepinephrine. These agents improved hemodynamic parameters and survival without documented severe side effects (very low quality of evidence). 4-Aminopyridine. Use of 4-aminopyridine was associated with improved hemodynamic parameters and survival in animal studies, at the risk of seizures. Lipid emulsion therapy. Lipid emulsion was associated with improved hemodynamic parameters and survival in animal models of intravenous verapamil poisoning, but not in models of oral verapamil poisoning. Other studies. Studies on decontamination, atropine, glucagon, pacemakers, levosimendan, and plasma exchange reported variable results, and the methodologies used limit their interpretation. No trial was documented in humans poisoned with calcium channel blockers for Bay K8644, CGP 28932, digoxin, cyclodextrin, liposomes, bicarbonate, carnitine, fructose 1,6-diphosphate, PK 11195, or triiodothyronine. Case reports were only found for charcoal hemoperfusion, dialysis, intra-aortic balloon pump, Impella device and methylene blue. Conclusions. The treatment for calcium channel blocker poisoning is supported by low-quality evidence drawn from a heterogeneous and heavily biased literature. High-dose insulin and extracorporeal life support were the interventions supported by the strongest evidence, although the evidence is of low quality.

Keywords  Antidotes; Calcium channel blockers; Cardiotoxins; Drug overdose; Poisoning; Toxicity; Treatment

Introduction
American Poison Control Centers report cardiovascular drugs as the substance category with the third fastest rate of increase in terms of exposures. According to the National Poison Data System, calcium channel blockers (CCB) were responsible for at least 11,764 exposures and 78 deaths in 2011 in the United States. This underestimates the real burden of such poisoning. A Canadian study of CCB poisonings found that a poison control center was consulted in only 74% of cases. In order to help clinicians to best treat CCB poisoning, the development of practice guidelines on the treatment of CCB poisoning is warranted.

Therefore, the goal of this systematic review was to document and characterize the available evidence to facilitate development of guidelines following the GRADE (Grading of Recommendations Assessment, Development and Evaluation methodology) and the AGREE (Appraisal of Guidelines Research & Evaluation) II statement.

Objective
The objective of this systematic review (registry number: CRD42012002823) was to evaluate the reported effects of treatments for CCB toxicity. The primary outcomes of interest were mortality and improvement in hemodynamics. The impact of interventions on secondary outcomes, such as functional outcomes, length of stay (LOS) in hospital, LOS in intensive care unit (ICU), duration of vasopressor use, and serum CCB concentrations, was also evaluated.

Methods

Eligibility criteria

Study types
Controlled trials, observational studies, case series, animal studies, case reports, and abstracts from scientific and clinical meetings in any language, without date restriction, were included. Case reports were defined as articles pertaining to a single case, whereas articles were classified as case series when multiple cases were presented. Cohort studies were differentiated from case series based on an approach proposed by Dekkers et al.5

Participants
Studies were eligible if they involved humans or animals poisoned with any CCB. Poisoning was defined as an “exposure (...) causing or capable of causing toxicity, regardless of intent.” An adverse effect was defined as an undesirable effect of a drug taken at therapeutic doses for the appropriate indication.

Interventions
Studies with defined intervention(s) meant to improve the targeted primary and/or secondary outcomes were eligible.

Outcome measures
Studies were required to document at least one of the primary or secondary outcomes. The primary outcomes included mortality (in hospital, or at the end of experiment for animal studies) and improvement in hemodynamic parameters (heart rate, blood pressure, stroke volume, cardiac output, and peripheral vascular resistance). The secondary outcomes included functional outcomes (defined as return to functional baseline or not), LOS in ICU, LOS in hospital, duration of vasopressor use, and serum CCB concentrations. Reported adverse effects of treatments were also documented.

Search strategy
Medline/Ovid, PubMed, EMBASE, Cochrane Library, TOXLINE, and International pharmaceutical abstracts up to December 31, 2013 were searched without time restrictions. Two librarians developed the search strategy using the following Keywords: [calcium channel blockers OR calcium channel antagonist OR calcium channel blocking agent OR (amlodipine or bencyclane or bepridil or cinnarizine or felodipine or fende-line or flunarizine or gallopamil or isradipine or lido-fazine or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or prenylamine or verapamil or dil-tiazem)] AND [overdose OR medication errors OR poisoning OR intoxication OR toxicity OR adverse effect]. Conference proceedings and meeting abstracts of the EAPCCT (European Association of Poisons Centres and Clinical Toxicologists) and NACCT (North American Congress of Clinical Toxicology) (2008–2013), trial registries, and Google Scholar were also searched. Authors of selected publications were contacted.
Two independent reviewers blinded to authors and journal names selected the studies based on eligibility criteria. Disagreements were resolved by consensus or, when required, by a third reviewer. The kappa statistic was used to quantify agreement on the articles included. A data abstraction form to standardize the data collection process was used after a pilot version was tested among data abstractors with five articles related to digoxin poisoning. No significant abstraction difference was noted between abstractors. For each included study, two reviewers independently abstracted study characteristics (year of publication, authors, and study design), subjects (number, inclusion/exclusion criteria, age, gender, co-morbidities, co-ingestions, type of animal studied where applicable, sample size calculation, and weight for animal studies), treatment and control group characteristics, CCB involved (type, dose, route, and form), treatment(s) provided, outcomes, and results. To ensure uniformity, an independent individual merged the data collection into a single flow sheet.

Two independent reviewers carried out quality analysis for all of the studies except case reports. Disagreements were resolved by consensus or by a third party if required. The Cochrane risk of bias tool was not required because no controlled trials were found. The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist and the Thomas tool were used for observational studies, the Institute of Health Economics tool for case series, and the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines and the modified NRCNA (National Research Council for the National Academies) checklist for animal studies. The percent agreement was documented for each item, and the kappa statistic was calculated for each type of quality analysis tool. Qualitative synthesis was used to summarize the evidence for each outcome. A planned meta-analysis was not performed due to heterogeneity of studies, interventions, and outcomes. The search strategy identified 15,577 citations. Two reviewers selected 216 articles (Kappa on articles inclusion = 0.85, 95% CI: 0.73–0.89) (Supplementary Appendix 1, to be found at online http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827). Six full-text articles were not found because the foreign language journals were inaccessible. Professional translation was performed on 23 manuscripts. A list of the articles translated and excluded after full-text review is available upon request.

Results

No controlled trial fulfilling eligibility criteria was identified. Human observational studies were published only for high-dose insulin and extracorporeal life support. Comparative studies included observational studies evaluating two different high-dose insulin regimens and one comparing high-dose insulin to vasopressors. One human observational study compared extracorporeal life support with standard therapy.

Results of individual studies and risks of bias for medical interventions

Table 1 describes results of included articles for the interventions for which there is the highest level of evidence. A more detailed description is available online (Supplementary Appendix 2 to be found at online http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827). Published case reports for each intervention is also available online (Supplementary Appendix 3 to be found at online http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827).

Gastrointestinal decontamination

Five human case series including two pediatric studies reported sequelae-free survival of all patients who underwent gastrointestinal decontamination (including activated charcoal, gastric lavage, and whole-bowel irrigation). Cardiac arrests following initiation of whole-bowel irrigation were documented in two case series of hemodynamically unstable patients and following gastric lavage in one case report. In all cases, complications occurred after the patient began vomiting. Given the nature of these reports, neither survival nor cardiac arrest can be attributed, with confidence, to the decontamination procedures.

High-dose insulin

High-dose insulin (intravenous (IV) bolus of 1.0 unit/kg followed by a 0.5–2.0 unit/kg/h infusion) showed an improvement in hemodynamics in one of two human observational studies, all five human case series, and all four animal studies assessing that outcome, while a survival benefit was reported in animal studies. Hypoglycemia (1 of 7 and 2 of 4 subjects) and hypokalemia (2 of 7 and 2 of 4 subjects) were reported as adverse effects in human cohort studies and case series, respectively.

Calcium

The majority of animal studies evaluating use of calcium demonstrated a reduced mortality as well as hemodynamic improvement. Human case series and case reports demonstrated inconsistent benefits, but adverse effects such as hypercalcemia were rare. The dose employed was typically an IV single dose of calcium chloride (1–5 g), sometimes followed by an infusion, or the equivalent dose in calcium gluconate.

Vasopressors

An unblinded study using a porcine model of nifedipine-induced cardiogenic shock showed no differences in mortality or hemodynamic parameters (cardiac output, blood pressure, and systemic vascular resistance), following addition of phenylephrine to high-dose insulin (10 units/kg/h). Vasopressin was reported as potentially harmful in one blinded randomized controlled trial using a swine model of verapamil poisoning, although one case series of two patients and one case report showed blood pressure improvement when added to other vasopressors. Epinephrine was associated with increased cardiac output in animal studies but hyperglycemia and
### Table 1. Results of individual studies and risks of bias.

<table>
<thead>
<tr>
<th>Source</th>
<th>Intervention</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Methodological quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observational studies</strong></td>
<td></td>
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<tr>
<td>Musselman et al. (2011)</td>
<td>HDI ± glucagon vs vaspressors only</td>
<td>20 with beta-blocker or CCB poisonings requiring vaspressors (10 in the intervention group)</td>
<td>– Hemodynamics: no significant difference in MAP (no power calculation)</td>
<td>STROBE: 6/22 Thomas tool: • Moderate: Selection bias • Weak: Cohort methods, confounders, bleeding, data collection, withdrawals, analysis, intervention integrity</td>
</tr>
<tr>
<td>Bryant et al. (2009)</td>
<td>HDI: 0.5–1.0 units/kg bolus followed by 0.5–1.0 units/kg/h infusion started preceding or shortly after vaspressors vs other form of providing HDI</td>
<td>46 poisoned with a hemodynamically unstable CCB treated with HDI (19 in the intervention group)</td>
<td>– Mortality: higher when the HDI is not provided as per the protocol</td>
<td>STROBE: 4/22 Thomas tool: • Weak: Selection bias, case–control methods, confounders, weak, data collection, withdrawals, analysis, intervention integrity</td>
</tr>
<tr>
<td>Greene et al. (2007)</td>
<td>HDI: 0.5–2.0 units/kg/h with vs without 1 unit/kg bolus</td>
<td>7 poisoned with a hemodynamically unstable CCB treated with HDI (3 in the intervention group)</td>
<td>– Mortality: 1/7 (did not receive a bolus) – Hemodynamics: increase in more than 10 mmHg Systolic blood pressure (SBP) only in the group receiving a bolus – Mean LOS in ICU, 2.7 days – Adverse effects: 1 non-clinically significant hypoglycemia (no bolus) and 2 non-clinically significant hypokalemia (1 with bolus, 1 without)</td>
<td>STROBE: 9/22 Thomas tool: • Moderate: Selection bias, confounders, blinding, withdrawals • Weak: Cohort methods, data collection, analysis, intervention integrity</td>
</tr>
<tr>
<td><strong>Case series</strong></td>
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<tr>
<td>Espinoza et al. (2013)</td>
<td>HDI: 0.5–1 units/kg bolus followed by 0.5–1 units/kg/h</td>
<td>46 poisoned with CCB</td>
<td>– Mortality: 9/46 – Adverse effects: no hypoglycemia</td>
<td>10/20 (2 unclear)</td>
</tr>
<tr>
<td>Holger et al. (2011)</td>
<td>HDI bolus with dextrose followed by 1 unit/kg/h, increasing Q15 min by 1–2 units/kg/h up to 10 units/kg/h</td>
<td>4 poisoned with amlodipine, verapamil, or diltiazem</td>
<td>– Mortality: 0/4 – Hemodynamics: vaspressors could be tapered off with HDI – LOS in ICU, 2, 3, 5, and 30 days – Adverse effects: 2/4 hypoglycemia, 2/4 hypokalemia</td>
<td>13/20 (4 unclear)</td>
</tr>
<tr>
<td>Boyer et al. (2002)</td>
<td>HDI: 0.5–1 units/kg/h</td>
<td>3 poisoned with diltiazem, amlodipine, or verapamil</td>
<td>– Mortality: 0/3 – Hemodynamics: improvement in blood pressure within 30 min – Adverse effects: hypoglycemia, hypokalemia</td>
<td>5/20 (5 unclear)</td>
</tr>
<tr>
<td>Boyer et al. (2001)</td>
<td>HDI: 0.5 units/kg/h</td>
<td>2 poisoned with amlodipine or diltiazem</td>
<td>– Hemodynamics: rapid reversal of hemodynamic collapse in both patients – Mortality: 0/3 (1 not reported) – Hemodynamics: improvement in blood pressure in all cases – LOS in hospital, 5–14 days – adverse effects: hypoglycemia</td>
<td>4/20 (4 unclear)</td>
</tr>
<tr>
<td>Yuan et al. (1999)</td>
<td>HDI: 4–70 units/h</td>
<td>4 poisoned with verapamil SR or amlodipine</td>
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</table>

Case reports (see Supplementary Appendix to be found at online http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827): – Improvement in hemodynamics reported in 18 cases60,63,157–167,173,174,176,178,179 – No improvement in hemodynamics reported in 3 cases76,168,172 – Adverse effects: Volume overload in 1 case167 and hypoglycemia reported in 1 case175

(Continued)
### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Animal studies</th>
<th>ARRIVE guidelines and Modified NRCNA</th>
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<tbody>
<tr>
<td><strong>Engebretsen et al. (2010) [36]</strong></td>
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<tr>
<td>Group 1: NS</td>
<td></td>
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<tr>
<td>Group 2: HDI, 2 units/kg/h, increased Q10 min by 2 units/kg/h and max 10 units/kg/h</td>
<td></td>
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<tr>
<td>Group 3: HDI and phenylephrine</td>
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<tr>
<td>15 Yorkshire pigs poisoned with nitroprusside of 0.0125 mcg/kg/min until 25% of baseline Mean arterial pressure (MAP) X Cardiac output (CO)</td>
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<tr>
<td>– Mortality: 4/5 deaths in group 1 compared to 1/5 in group 2 and no death in group 3</td>
<td>ARRIVE: 18/20 NRCNA: 8/16</td>
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<tr>
<td>– Hemodynamics: groups 2–3 had significant improvement in MAP compared to group 1, but no significant difference in hemodynamics between groups 2 and 3</td>
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<tr>
<td>– Adverse effects: hypoglycemia and hypokalemia</td>
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<tr>
<td><strong>Kline et al. (1997) [37]</strong></td>
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<tr>
<td>Group 1: NS</td>
<td></td>
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<tr>
<td>Group 2: epinephrine</td>
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<tr>
<td>Group 3: glucagon</td>
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<tr>
<td>Group 4: HDI, 1000 nU/min, with dextrose</td>
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<tr>
<td>20 Mongrel dogs randomized with intraportal verapamil infusion of 0.04 mg/kg/min × 1 h then 0.08 mg/kg/min × 1 h then 0.1 mg/kg/min × 1 h then 0.2 mg/kg/min until death</td>
<td></td>
</tr>
<tr>
<td>– Hemodynamics: significant improvement in heart rate and blood pressure compared to all other groups</td>
<td>ARRIVE: 17/20 NRCNA: 9/16</td>
</tr>
<tr>
<td><strong>Kline et al. (1996) [38]</strong></td>
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<tr>
<td>Group 1: NS</td>
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<tr>
<td>Group 2: HDI</td>
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<tr>
<td>Group 3: HDI without verapamil toxicity</td>
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<tr>
<td>18 Mongrel dogs randomized with intraportal verapamil infusion of 0.04 mg/kg/min × 1 h then 0.08 mg/kg/min × 1 h then 0.1 mg/kg/min until death</td>
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</tr>
<tr>
<td>– Hemodynamics: significant improvement in myocardial contractile function independent of glucose transport compared to normal saline</td>
<td>ARRIVE: 15/20 NRCNA: 7/16</td>
</tr>
<tr>
<td><strong>Kline et al. (1993) [39]</strong></td>
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<tr>
<td>Group 1: NS</td>
<td></td>
</tr>
<tr>
<td>Group 2: epinephrine</td>
<td></td>
</tr>
<tr>
<td>Group 3: glucagon</td>
<td></td>
</tr>
<tr>
<td>Group 4: HDI, 4 units/min ± dextrose and potassium</td>
<td></td>
</tr>
<tr>
<td>24 Mongrel dogs poisoned with verapamil infusion of 0.1 mg/kg/min until 50% reduction of MAP for 30 min, then infusion at 1 mg/kg/h until 4 h or death</td>
<td></td>
</tr>
<tr>
<td>– Mortality: 6/6 in group 1, 2/6 in group 2, 3/6 in group 3, 0/6 in group 4 (significant)</td>
<td>ARRIVE: 11/20 NRCNA: 6/16</td>
</tr>
<tr>
<td>– Hemodynamics: improvement in groups 2 and 4</td>
<td></td>
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<tr>
<td>– Adverse effects: increased lactate and hyperglycemia with epinephrine, hyperglycemia followed by hypoglycemia with glucagon</td>
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</tbody>
</table>
### Observational studies

<table>
<thead>
<tr>
<th>Study</th>
<th>ECLS (mean duration)</th>
<th>Events</th>
<th>STROBE and Thomas’ tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masson et al. (2012)</td>
<td>ECLS (mean duration of 6 days ± 2.9 days) vs not ECLS</td>
<td>62 cardiac arrests or severe shock secondary to poisoning (16 CCB including verapamil and diltiazem)</td>
<td>Mortality: 9/11 without ECLS compared to 23/41 with ECLS (patients in severe shock) and 0/7 without ECLS vs 3/3 with ECLS (patients in cardiac arrest) (significant difference)</td>
</tr>
<tr>
<td>Daubin et al. (2009)</td>
<td>ECLS (mean duration of 4.5 days ± 2.4 days)</td>
<td>17 patients with persistent cardiac arrest or severe shock secondary to poisoning refractory to conventional therapy (4 CCB poisonings with verapamil)</td>
<td>Mortality: 4/17 deaths</td>
</tr>
<tr>
<td>Mégarbané et al. (2007)</td>
<td>ECLS (5–108 h, mean duration of 56 h)</td>
<td>12 prolonged out-of-hospital cardiac arrests secondary to poisoning (2 CCB, verapamil)</td>
<td>Mortality: survival 50% at 24h and 25% at hospital discharge but not of the CCB poisoning survived</td>
</tr>
<tr>
<td>Babatasi et al. (2001)</td>
<td>ECLS (48–71 h, mean duration 59.25 ± 2 h)</td>
<td>6 cardiac arrests secondary to a cardiotoxic drug (2 CCB with verapamil)</td>
<td>Mortality: 2/6</td>
</tr>
</tbody>
</table>

### Case series

<table>
<thead>
<tr>
<th>Study</th>
<th>ECLS (mean duration)</th>
<th>Events</th>
<th>Institute of Health Economics tool for quality of case series and quality of reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daubin et al. (2009)</td>
<td>ECLS (mean duration of 4.5 days ± 2.4 days)</td>
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<td>13/20 (2 unclear)</td>
</tr>
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<td>15/20 (3 unclear)</td>
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<td>9/20 (9 unclear)</td>
</tr>
</tbody>
</table>

Case reports (see online Appendix to be found at online http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827):

- Survival without neurologic or cardiac deficit reported in 7 cases
- Death reported in 2 cases
- Adverse effects: Bleeding in 1 case and leg amputation reported in 1 case

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<table>
<thead>
<tr>
<th>Case series</th>
<th>Calcium gluconate bolus received calcium</th>
<th>5/7 poisoned with CCB receiving calcium</th>
<th>– Mortality: 1/5</th>
<th>6/20 (2 unclear)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Konca et al. (2013)</td>
<td>Calcium gluconate bolus followed by an infusion at 10 mg/h</td>
<td>2 poisoned with amlopidine</td>
<td>– Mortality: 0/2</td>
<td>9/20 (13 unclear)</td>
</tr>
<tr>
<td>Supradip and Mrinal (2008)</td>
<td>Calcium chloride or gluconate infusion to maintain a calcemia of 4 mmol/L</td>
<td>7 poisoned with diltiazem, verapamil, or nifedipine</td>
<td>– Hemodynamics: no change in case 1 and deterioration in case 2</td>
<td>– LOS in hospital: 5 and 10 days</td>
</tr>
<tr>
<td>Karti et al. (2002)</td>
<td>Calcium chloride, 10%, 10 and 20 ml, IV administered to 4/7 patients</td>
<td>2 poisoned with verapamil SR</td>
<td>– Mortality: 0/2</td>
<td>7/20 (5 unclear)</td>
</tr>
<tr>
<td>Howarth et al. (1994)</td>
<td>Calcium chloride, 1–3 g, IV administered to 4/7 patients</td>
<td>2 poisoned with verapamil</td>
<td>– Hemodynamics: no improvement</td>
<td>– Hemodynamics: atropine was effective only after calcium administration</td>
</tr>
<tr>
<td>Parikka et al. (1993)</td>
<td>Calcium chloride IV 1–5 g IV</td>
<td>2 poisoned with verapamil</td>
<td>– Mortality: 0/2</td>
<td>9/20 (3 unclear)</td>
</tr>
<tr>
<td>Ramoska et al. (1993)</td>
<td>Calcium, 4.5–95.2 mmol, IV (23/113 received calcium)</td>
<td>2 poisoned with verapamil</td>
<td>– Hemodynamics: no change in case 1, blood pressure improvement in case 2</td>
<td>7/11 increased their heart rate, 16/20 increased their blood pressure</td>
</tr>
<tr>
<td>Bausch et al. (1991)</td>
<td>Calcium received in 1/4 patient</td>
<td>4 fatal poisonings with diltiazem</td>
<td>– Mortality: 0/2</td>
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<tr>
<td>Roper et al. (1993)</td>
<td>Calcium chloride, 1–5 g IV</td>
<td>3 poisoned with verapamil (1 had also nifedipine)</td>
<td>– Mortality: 0/2</td>
<td>3/20 (3 unclear)</td>
</tr>
<tr>
<td>Howowitz and Rhee (1989)</td>
<td>Calcium chloride IV</td>
<td>2 poisoned with verapamil</td>
<td>– Mortality: 0/2</td>
<td>8/20 (4 unclear)</td>
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<tr>
<td>Henry et al. (1985)</td>
<td>Calcium chloride, 1–2 g IV</td>
<td>2 poisoned with verapamil</td>
<td>– Mortality: 0/2</td>
<td>7/20 (3 unclear)</td>
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<tr>
<td>Jaeger et al. (1984)</td>
<td>Calcium gluconate IV</td>
<td>11 poisoned with verapamil</td>
<td>– Adverse effects: 1 case had more arrhythmias</td>
<td>2/20 (6 unclear)</td>
</tr>
</tbody>
</table>

**Case reports (see online appendix):**
- Improvement in hemodynamics reported in 19 cases
- No improvement in hemodynamics reported in 2 cases
- Adverse effects: Hypercalcemia reported in 1 case

| Group 1: NS                  | Group 2: levosimendan                  | 60 Wistar rats (6 groups of 10) poisoned with verapamil, 6 mg/kg/h, until 50% decrease in MAP then 4 mg/kg/h | – Mortality 0/10–1/10 as opposed to 1/10–2/10 in the other groups | ARRIVE: 16/20 NRCNA: 5/16 |
| Group 2: levosimendan + 4-AP | Group 3: levosimendan and calcium chloride | 35 Wistar rats (5 groups of 7) poisoned with verapamil, 6 mg/kg/h, until 50% decrease in MAP then 4 mg/kg/h | – Hemodynamics: improvement in cardiac output and blood pressure | ARRIVE: 16/20 NRCNA: 5/16 |
| Group 5: calcium chloride    | Group 6: levosimendan and calcium chloride | 35 Wistar rats (5 groups of 7) poisoned with verapamil, 6 mg/kg/h, until 50% decrease in MAP then 4 mg/kg/h | – Mortality 1/7 in group 2 and 0/7 in group 5 as opposed to 5/7 in group 1 | ARRIVE: 16/20 NRCNA: 5/16 |

**Animal studies**

**ARRIVE guidelines and Modified NRCNA**
<table>
<thead>
<tr>
<th>Study</th>
<th>Group Details</th>
<th>Animals</th>
<th>Mortality</th>
<th>Hemodynamics</th>
</tr>
</thead>
</table>
| Strubelt and Diederich (1990) | Group 1: NS  
Group 2: dopamine  
Group 3: norepinephrine  
Group 4: isoproterenol  
Group 5: polygeline  
Group 6: calcium chloride | 31 Wistar rats (in 6 groups) poisoned with nisoldipine, 0.1 mg/kg/min | − Mortality: 152% improvement in survival with group 6 (138 min vs 54.7 min ± 11.1 min)  
− Hemodynamics: normalization of cardiac output and MAP | ARRIVE: 12/20  
NRCNA: 5/16 |
| Gay et al. (1986) | Group 1: calcium chloride  
Group 2: isoproterenol  
Group 3: atropine  
Group 4: epinephrine  
Group 5: norepinephrine  
Group 6: dopamine  
Group 7: phenylephrine  
Group 8: 4-AP | 23 Mongrel dogs poisoned with verapamil bolus, 0.72 mg/kg, followed by an infusion of 0.11 mg/kg/min | − Hemodynamics: calcium increased aortic pressure and left ventricular pressure | ARRIVE: 11/20  
NRCNA: 6/16 |
| Strubelt and Diederich (1986) | Rats:  
Group 1: NS  
Group 2: calcium chloride, 5 mg/kg/min  
Group 3: calcium chloride, 10 mg/kg/min  
Group 16: calcium chloride and isoproterenol  
Rabbits:  
Group 1: NS  
Group 2: calcium chloride  
Group 5: calcium chloride and isoproterenol | 95 Wistar rats (in 16 groups) poisoned with nifedipine, 0.2 mg/kg/min  
21 bastard rabbits (in 5 groups) poisoned with nifedipine, 0.2 mg/kg/min | − Mortality: 100% improvement with calcium, isoproterenol, or dopamine in rats, survival also improved with calcium in rabbits, but not with isoproterenol or dopamine  
− Hemodynamics: improvement in cardiac output and blood pressure with calcium | ARRIVE: 13/20  
NRCNA: 4/16 |
| Strubelt (1984) | Group 1: calcium  
Group 2: epinephrine  
Group 3: dopamine  
Group 4: norepinephrine  
Groups 5-6: isoproterenol  
Group 7: orciprenaline  
Group 8: pithaladrenalin  
Group 9: angiotensin amide  
Group 10: atropine  
Group 11: haemacel | 80 Wistar rats (in 11 groups) poisoned with verapamil, 0.15 mg/kg/min | − Mortality: tripled with calcium chloride and vasopressors  
− Hemodynamics: calcium increased the blood pressure and LV dp/dt but not heart rate as opposed to vasopressors | ARRIVE: 11/20  
NRCNA: 5/16 |
| Wesseling et al. (1983) | Group 1: NS  
Group 2: calcium levulcate, 0.4 ml of 10%  
Group 3: 4-aminopyridine, 1mg/kg, after the drop in SBP | 12 rabbits (in 3 groups) poisoned with verapamil, 30 mg/kg/h, until the SBP drops by one-third | − Mortality: no difference | ARRIVE: 10/20  
NRCNA: 7/16 |

(Continued)
Table 1. (Continued)

<table>
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<tr>
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<tr>
<td>Levine et al. (2013)</td>
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<tr>
<td>Konca et al. (2013)</td>
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</table>
Case reports (see online Appendix to be found at online http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827):  
- Improvement in hemodynamics reported in most reported cases²,8,11,19,191,192–194 except²,190,195  
- Adverse effects: None reported

| Animal studies | Group 1: NS | Group 2: HDI, 2 units/kg/h, increased Q10 min 2 units/kg/h ad max 10 units/kg/h | 15 Yorkshire pigs poisoned with nifedipine, 0.0125 mcg/kg/min, until 25% of baseline MAP X CO | – Mortality: 4/5 deaths in group 1, 1/5 in group 2, and no death in group 3  
– Hemodynamics: significant improvement in MAP compared to group 1 and no significant difference in hemodynamics between groups 2 and 3, the addition of phenylephrine did not make a difference  
– Adverse effects: hypoglycemia and hypokalemia | ARRIVE: 18/20  
NRCNA: 8/16 |
| Barry et al. (2005)³⁹ | Group 1: NS | Group 2: vasopressin, 0.01 units/kg/min | 18 swine (9 per group) | – Mortality: 4/8 in the vasopressin group vs 2/10 in the control group (p = 0.32)  
– Hemodynamics: no significant improvement in MAP, cardiac output, or systemic vascular resistance | ARRIVE: 18/20  
NRCNA: 9/16 |
| Sztajnkrycer et al. (2004)²²⁸ | Group 1: NS | Group 2: vasopressin, 0.004 units/kg/min, increasing to 0.01 units/kg/min then 0.04 units/kg/min Q 20 min | 12 dogs (6 per group) | – Mortality: 0/6 in the vasopressin group vs 2/6 in the control group  
– Hemodynamics: no significant difference | ARRIVE: 15/20  
NRCNA: 6/16 |
| Stone et al. (1996)³⁶ | Group 1: NS | Group 2: glucagon, Group 3: glucagon and phenylephrine, 100–180 µg/min | 18 Mongrel dogs (6 per group) | – Mortality: 2/6 deaths in group 1 vs none in the other groups  
– Hemodynamics: increase in MAP in group 3 compared to group 1, increase in cardiac output in groups 2–3  
– Mortality: 2/6 deaths in group 1 vs none in the other groups  
– Hemodynamics: increase in MAP in group 3 compared to group 1, increase in cardiac output in groups 2–3  
– Adverse effects: increased lactate and glyceria with epinephrine | ARRIVE: 15/20  
NRCNA: 6/16 |
| Kline et al. (1993)³⁹ | Group 1: NS | Group 2: epinephrine, Group 3: glucagon | 24 Mongrel dogs | – Mortality: 0/6 in the vasopressin group vs 2/6 in the control group  
– Hemodynamics: no significant difference | ARRIVE: 11/20  
NRCNA: 6/16 |
| Strubelt and Diederich (1990)²² | Group 1: NS | Group 2: dopamine, Group 3: norepinephrine, Group 4: isoproterenol, Group 5: polyeptide, Group 6: Calcium chloride | 31 Wistar rats (in 6 groups) poisoned with nisoldipine, 0.1 mg/kg/min | – Mortality: 135% improvement in survival in group 2 (129.2 min vs 54.7 min +/− 11.1 min), 75.6 min vs 54.7 min in group 3, 187% improvement in group 4 (157 min vs 54.7 min)  
– Hemodynamics: groups 2–4 showed an increase in blood pressure, cardiac output and stroke volume, group 3 showed an increase in resistances  
– Epinephrine, norepinephrine, dopamine, and high doses of phenylephrine increase cardiac output; AO and LV dp/dt increased | ARRIVE: 12/20  
NRCNA: 5/16 |
| Gay et al. (1986)¹³ | Group 1: calcium chloride | Group 2: isoproterenol, Group 3: atropine, Group 4: epinephrine, Group 5: norepinephrine, Group 6: dopamine, Group 7: phenylephrine, Group 8: 4-AP | 23 Mongrel dogs poisoned with verapamil bolus, 0.72 mg/kg, followed by an infusion of 0.11 mg/kg/min | – Mortality: 4/5 deaths in group 1, 1/5 in group 2, and no death in group 3  
– Hemodynamics: significant improvement in MAP compared to group 1 and no significant difference in hemodynamics between groups 2 and 3, the addition of phenylephrine did not make a difference  
– Adverse effects: hypoglycemia and hypokalemia | ARRIVE: 18/20  
NRCNA: 8/16 |

(Continued)
Increasing lactate were noted as adverse effects. Dopamine and norepinephrine infusions showed improved survival and hemodynamics in animal studies, but results were inconsistent in case series. No significant ischemic complications were noted with high doses of vasopressors in a case series of 48 patients. In animal studies, the use of isoproterenol or atropine showed occasional improvement in hemodynamics. In one human case series of three patients and one case report, patients who received isoproterenol had improved heart rate and blood pressure.

**Glucagon**

Improvement in heart rate and cardiac output was observed with glucagon (IV bolus of 3 mg, followed by an infusion of 3 mg/h) in two of three animal studies, but in only one of the three human case series. Cardiac output was not measured in case series. Hyperglycemia and vomiting were side effects observed in six case reports.

**Lipid emulsion therapy**

In an animal model of IV verapamil toxicity, the administration of 20% lipid emulsion (IV bolus of 6.2–18.6 ml/kg) was associated with improvement in hemodynamics and survival. However, there was no significant improvement or an increased mortality in two animal studies using an oral verapamil toxicity model. One available human case series of five patients demonstrated 60% mortality when using this antidote compared to a lower mortality reported in retrospective studies of CCB poisoning (6% reported by St-Onge et al. in 2012). Importantly, the mortality reported in observational studies with this treatment included CCB ingestions regardless of severity, whereas the case series published by Geib et al. only included severe cases. In one case report, adverse effects such as hypertriglyceridemia and hypoxemia were observed with lipid emulsion when used at exceptionally high doses (2 L). Hyponatremia, extreme lipemia, and inability to obtain reliable complete blood count, arterial blood gas, or electrolyte levels were also noted in one case report.

**4-Aminopyridine**

Animal studies and human case series showed survival and hemodynamic benefit with 4-aminopyridine. Seizures were observed in two animal studies.

**Levosimendan**

Animal studies and a small case series suggested a hemodynamic benefit for levosimendan, although seizures were observed in both patients. One of four animal studies used higher doses of verapamil to induce toxicity, resulting in increased mortality.

**Results of individual studies and risks of bias for mechanical interventions**

**Extracorporeal life support**

The use of extracorporeal life support was associated with a survival benefit in patients with severe shock or cardiac arrest.
secondary to cardiotoxic poisonings. In the observational study published by Masson et al., extracorporeal life support was associated with a lower mortality when initiated in a group of 14 patients compared to conventional therapies provided to a group of 48 patients (48% vs. 86%) after adjustment for Simplified Acute Physiology Score (SAPS) II and beta-blocker intoxication. Most human case series reported positive functional outcomes in the majority of survivors. However, some patients experienced limb ischemia (10% in the observational study and 0–50% in the case series), thrombosis (2% in the observational study and 0–12% in the case series), or hemorrhage (5% in the observational study and 0–12% in the case series).

**Pacemaker**

Results were inconsistent on the success of temporary pacemakers in achieving capture and improving hemodynamics in human case series and case reports. Pacing and capture problems were identified even with transvenous pacemakers. However, hemodynamic improvement was observed most of the time when capture was successful and no adverse effect has been reported.

**Results of individual studies and risks of bias for interventions for which only small case series, case reports, or animal studies are available**

The use of amrinone did not show a benefit in animal studies, although human case reports using another phosphodiesterase inhibitor (enoximone) observed an increase in inotropy and a decrease in vasopressor requirement. One human case series and two case reports suggested use of plasma exchange to decrease verapamil concentrations and improve hemodynamics. One human case series of three patients suggested the use of extracorporeal albumin dialysis to improve hemodynamics without a clear impact on the serum CCB concentrations. Only human case reports were found for charcoal hemoperfusion, continuous venous venous hemodiafiltration, insertion of an intra-aortic balloon pump, Impella device, and methylene blue. Animal studies showed conflicting results for the use of carnitine. Finally, only animal studies were found for the following interventions: Bay K 8644 and CGP 28932, digoxin, cycloedextrin, sanguamadex, liposomes, bicarbonate, fructose 1,6-diphosphate, PK11195 and triiodothyronine.

**Synthesis of results**

**Mortality**

High-dose insulin (IV bolus of 1 unit/kg followed by an infusion of 0.5–2.0 units/kg/h) initiated before or shortly after vasopressors was associated with survival improvement. In animal studies (rats and rabbits), calcium, epinephrine, dopamine, noradrenaline, and 4-aminopyridine were associated with reduced mortality. Based on human case series, only calcium and dopamine were associated with reduced mortality. Most human studies did not report a survival benefit with atropine, glucagon, pacemaker, levsimendan, or plasma exchange. Animal studies did not report any survival benefit either with atropine in a rat model, glucagon in a dog model, or levsimendan in a rat model. Animal studies (two murine models and one dog model, all of them of moderate methodological quality) suggested that lipid emulsion improves survival in an IV model of verapamil poisoning. That was not confirmed in two oral models of verapamil poisoning.

**Impact on functional outcomes**

Functional outcomes were only reported in two case series involving extracorporeal life support in humans. Daubin et al. observed that all survivors in their sample were discharged without cardiovascular or neurological sequelae. Mégurbanne et al. reported that three patients treated with extracorporeal life support were symptom-free after one year. However, in isolated case reports, one patient was discharged to a long-term care facility and another underwent leg amputation.

**Impact on other outcomes**

Only one observational study concerning high-dose insulin studied the impact on LOS in ICU or hospital, but did not find significant differences in patients who received the therapy. However, no power calculation was done.
Risk of bias across studies

Observational studies

The interobserver agreement on the STROBE checklist scoring was excellent for observational studies (kappa: 0.90; 95% CI: 0.82–0.99). Percent agreement for each element varied from 67 to 100%, with the exception of the criterion related to the mention of a specific hypothesis, on which observers frequently disagreed. The high-dose insulin studies reported between 4 and 10 of 22 elements in the STROBE checklist, while the extracorporeal life support study reported 17 of 22. Clear eligibility criteria and reports of data collection methods for high-dose insulin studies, sample size calculation, statistical methods, reported bias, and limitations were often missing from observational studies. The application of the Thomas tool resulted in 67% or higher agreement. However, observers disagreed on selection bias and data quality. Relevant confounders such as comorbidities were poorly described in all studies. Adherence to the high-dose insulin protocol was often variable. Therefore, the integrity of the intervention (defined as the degree to which it is implemented as planned or intended) was considered weak for high-dose insulin.

Case series

The interobserver agreement with the Institute of Health Economics tool for Quality of Case Series and Quality of reporting was substantial (kappa: 0.80; 95% CI: 0.76–0.84). Percent agreement was higher than 88% when judging the quality of the statistical tests used (which were generally descriptive) and follow-up rates. Case series scored 10/20 or less except for two of three articles involving extracorporeal life support (13/20 and 15/20), one of four high-dose insulin case series scored 13/20, and one of ten vasopressors case series scored 14/20. It was often unclear whether several case series were collected in different centers, or participants were recruited consecutively, or there was loss to follow-up. A very small number of studies were conducted prospectively with outcomes measured a priori and with adverse events reported.

Animal studies

The interobserver agreement for the use of the ARRIVE guidelines for animal studies was excellent (kappa: 0.90; 95% CI: 0.88–0.92). Percent agreement for each item varied from 80 to 100%. All studies obtained a score of 10/20–18/20 except for one related to calcium use (5/20), two related to lipid emulsion (7/20–8/20), and one related to carnitine (8/20). The studies’ relevance to human biology was unclear and details concerning the randomization procedure, sample size calculation, and husbandry conditions were often missing. When using the modified NRCNA list, the interobserver agreement was still excellent (kappa: 0.98; 95% CI: 0.96–0.99) and the percent agreement remained higher than 88% for all items. All studies obtained a score between 4/16 and 9/16. The weaknesses identified by the NRCNA list included use of unanesthetized animals, lack of blood concentration measurements, intervention tested in only one species, oral CCB administration, autopsy not conducted, lack of allocation concealment, and blinded assessment.

As expected, the risk of bias with case reports was high. Risk of bias across studies was high for all interventions and high to moderate for extracorporeal life support. Appendix 4 (to be found at online http://informahealthcare.com/doi/abs/10.3109/15563650.2014.965827) lists risk of bias across studies for each intervention. The risk of publication bias was estimated to be high, considering inherent risk with case reports.

Limitations

The evidence for treatment of CCB poisoning derives from a highly biased and heterogeneous literature. Important limitations were identified in the majority of studies. Different analysis tools have been used to assess the risk of bias with transparency, but to our knowledge this is the first time that these tools have been used in toxicology. For many interventions (high-dose insulin, extracorporeal life support, calcium, dopamine, norepinephrine, epinephrine, and 4-aminopyridine), results were consistent across different study types. Inconsistency among studies arose from differences in interventions, populations, and outcome measures. Moreover, head-to-head comparisons of treatments were infrequent, making it difficult to evaluate the comparability of treatments. Based upon the published literature, few valid inferences can be drawn about the relative merits of one intervention over another.

The search strategy was designed to be as inclusive as possible, including a search of the gray literature. Some articles identified by title could not be retrieved, but these were primarily case reports and it is unlikely that they would have influenced the overall findings.

Conclusions

This systematic review found a low level of evidence supporting the use of high-dose insulin and extracorporeal life support, and a very low level of evidence supporting the use of calcium, dopamine, norepinephrine, and epinephrine for the treatment of CCB poisoning. This systematic review focused on important outcomes for decision-making in managing patients poisoned with CCB. Controlled clinical trials involving vasopressors, calcium, high-dose insulin, and extracorporeal life support should be performed.

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Declaration of interest

The authors have no conflict of interest or financial disclosure. All authors have provided permission to publish the manuscript. Dr Maude St-Onge takes responsibility for the paper as a whole and all authors contributed substantially to its revision.

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Supplementary material available online

Supplementary Appendices 1–4.