Online Review Article

OPEN

Experts Consensus Recommendations for the Management of Calcium Channel Blocker Poisoning in Adults

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DOI: 10.1097/CCM.0000000000002087

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

The recommendations development process was not externally funded. All workgroup members were volunteers and only in-kind donations from participating organizations helped organize the in-person meetings.

Dr. St-Onge disclosed other support (the American Academy of Clinical Toxicology gave access to "GotoMeeting" for the recommendations development process) and disclosed discussion of off-label product use (most of the medications discussed are off-labeled as it is for treatment of calcium channel blockers). Dr. Bailey disclosed discussion of off-label product use (most of the medications discussed are off-labeled as it is for treatment of calcium channel blockers poisonings). Dr. Gosselin disclosed discussion of off-label product use (lipid emulsions and insulin for the treatment of calcium channel blockers). Dr. Lavonas disclosed other support (through his employer, he provides consulting services to CytoSorbents. CytoSorbents manufactures a device capable of removing certain calcium channel blockers from human blood and has applied for Food and Drug Administration approval. He has no personal financial relationship with CytoSorbents and receives only his salary. Work on the current article was substantially complete before the relationship with CytoSorbents commenced, and the CytoSorbents technology was not considered in these recommendations) and disclosed off-label product use (Most of the therapeutic approaches discussed in these recommendations have not been reviewed by FDA for the treatment of calcium channel blocker poisoning). Dr. Juurlink disclosed other support (He has received payment for expert testimony unrelated to this study). The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Objective: To provide a management approach for adults with calcium channel blocker poisoning.

Data Sources, Study Selection, and Data Extraction: Following the Appraisal of Guidelines for Research & Evaluation II instrument, initial voting statements were constructed based on summaries outlining the evidence, risks, and benefits.

Data Synthesis: We recommend 1) for asymptomatic patients, observation and consideration of decontamination following a potentially toxic calcium channel blocker ingestion (1D); 2) as first-line therapies (prioritized based on desired effect), IV calcium (1D), high-dose insulin therapy (1D–2D), and norepinephrine and/or epinephrine (1D). We also suggest dobutamine or epinephrine in the presence of cardiogenic shock (2D) and atropine in the presence of symptomatic bradycardia or conduction disturbance (2D); 3) in patients refractory to the first-line treatments, we suggest incremental doses of high-dose insulin therapy if myocardial dysfunction is present (2D), IV lipid-emulsion therapy (2D), and using a pacemaker in the presence of unstable bradycardia or high-grade arteriovenous block without significant alteration in cardiac inotropism (2D); 4) in patients with refractory shock or who are periarrest, we recommend incremental doses of high-dose insulin (1D) and IV lipid-emulsion therapy (1D) if not already tried. We suggest venoarterial extracorporeal membrane oxygenation, if available, when refractory shock has a significant cardiogenic component (2D), and using pacemaker in the presence of unstable bradycardia or high-grade arteriovenous block in the absence of myocardial dysfunction (2D) if not already tried; 5) in patients with cardiac arrest, we recommend IV calcium in addition to the standard advanced cardiac life-support (1D), lipid-emulsion therapy (1D), and we suggest venoarterial extracorporeal membrane oxygenation if available (2D).

Conclusion: We offer recommendations for the stepwise management of calcium channel blocker toxicity. For all interventions, the level of evidence was very low. (*Crit Care Med* 2017; 45:e306–e315)

Key Words: antidotes; calcium channel blockers; cardiotoxicity; drug overdose; therapy; toxicity

Toxicity from cardiac drugs is associated with a large number of fatalities and significant morbidity (1, 2). Furthermore, the advice given by poison control centers are often not followed (2–4). Consensus recommendations were published for out-of-hospital management of calcium channel blocker (CCB) ingestion (5), but recommendations for in-hospital care have not been systematically developed.

In the absence of formally recognized guidelines, we convened a workgroup of experts involved in the care of poisoned patients to develop evidence-based recommendations to guide the in-hospital management of CCB poisoning. Considering the very low level of evidence found in the literature, the workgroup agreed on developing expert consensus recommendations to propose a management approach and facilitate knowledge translation. In light of the variable pharmacokinetics among the available CCBs (6, 7), the altered pharmacokinetics following overdose (8, 9) and the loss of selectivity at very high CCB doses (10, 11), the workgroup adopted a pragmatic clinical approach and did not focus on individual agents (for complementary information concerning CCB poisoning, see **Appendix 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C94).

MATERIALS AND METHODS

Objective, Scope, Target Users, and Analytical Framework

These recommendations aimed to improve the management of CCB-poisoning and address which types of in-hospital interventions should be considered for adults with a potentially toxic ingestion of CCB. In addition to these recommendations, the workgroup would also like to emphasize the possible important role of poison centers. The workgroup (**Table 1**) was created as detailed in **Appendix 2** (Supplemental Digital Content 1, http://links.lww.com/CCM/C94), and an analytical framework illustrating the links between key questions (KQ) to be answered (**Fig. 1**) was developed (12).

The Appraisal of Guidelines for Research & Evaluation II instrument (13) provided the basis for the development of these recommendations and for the review process. The level of evidence was determined using Grading of Recommendations Assessment, Development and Evaluation (14) and the strength of recommendation using a modified Delphi like it has been used in consensus recommendations for extracorporeal treatments (**Table 2**) (Appendix 2, Supplemental Digital Content 1, http://links.lww.com/CCM/C94) (**Fig. 2**).

RESULTS

Table 2 defines the wording used for the recommendations. **Supplemental Table 1** (Supplemental Digital Content 2, http://links.lww.com/CCM/C95) (also, see **Appendix 6**, Supplemental Digital Content 1, http://links.lww.com/CCM/C94) details the rationale for each recommendation, and **Figure 3** illustrates the progression of care for key recommendations.

RECOMMENDATIONS

Therapy in Asymptomatic Patients

For the treatment of patients who ingested a potentially toxic amount of CCB, the workgroup recommends observation and consideration of decontamination following the position statements previously published jointly by the European Association of Poison Centres and Clinical Toxicologists (EAPCCT) and the American Academy of Clinical Toxicology (AACT) (16) (1D): "Based on volunteer studies, the administration of activated charcoal may be considered if a patient has ingested a potentially toxic amount of a poison (…) up to one hour previously. (…) the potential for benefit after one hour cannot be excluded."

Rationale

Based on case series (17–19), it is preferable to observe and monitor in a hospital setting for approximately 24 hours asymptomatic patients who ingested a potentially toxic amount of CCB, defined as more than a single therapeutic dose (5), to consider gastrointestinal decontamination

TABLE 1. Participating Organizations

Name	Organization (One Vote/Organization)	Expertise
Voting members		
Frank Lee Cantrell, United States	American Association of Poison Control Centres	Pharmacist
Eric Lavonas and William Kerns II, United States	American College of Medical Toxicology	Emergency physicians, medical toxicologists
Sophie Gosselin, Canada	Canadian Association of Emergency Physicians	Emergency physician, medical toxicologist
Martin Laliberté, Canada	Canadian Association of Poison Control Centres	Emergency physician, medical toxicologist
John Muscedere and Tasnim Sinuff, Canada	Canadian Critical Care Society	Critical care physicians, internists
Michael Rieder and Benoit Bailey (co-chair), Canada	Canadian Paediatric Society	Pediatricians (M.R. and B.B.), clinical pharmacologist (M.R.) and medical toxicologist (B.B.)
Philippe Hantson, Belgium	European Association of Poison Centres and Clinical Toxicologists	Critical care physician, medical toxicologist
Kurt Anseeuw, Belgium	European Society of Emergency Medicine	Emergency physician, anesthesiologist, medical toxicologist
Bruno Mégarbane, France	European Society of Intensive Care Medicine	Critical care physician, medical toxicologist
Ian Gilchrist, United States	Society of Critical Care Medicine	Critical care physician, cardiologist
Nonvoting members		
Maude St-Onge, Canada	Canadian Association of Poison Control Centres	Consensus Review Chair, emergency physician, critical care physician, medical toxicologist
David Juurlink		Epidemiologist, methodologist
Valéry Lavergne		Epidemiologist, methodologist

N.B.: A public health and medical toxicologist from Taiwan, and another medical toxicologist from United States also participated to the vote.

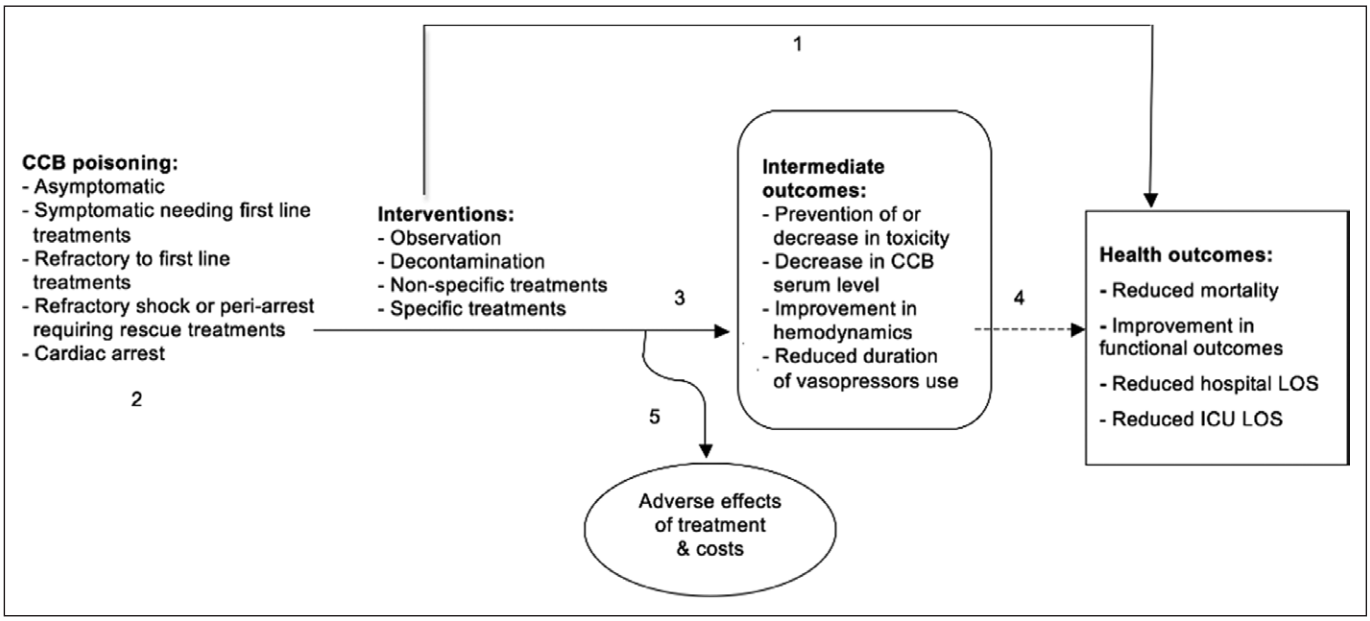

Figure 1. Analytical framework for calcium channel blocker (CCB) poisoning treatment guidelines. Key questions (KQ): 1) Is there direct evidence that one (or more than one) intervention reduces mortality (critical outcome), improves functional outcomes, reduces hospital length of stay (LOS) or reduces ICU LOS (important outcomes)? 2) Does the patient clinical presentation or type of ingestion influence the intervention(s) provided and the outcomes? 3) Does one (or more than one) intervention decrease CCB serum concentration, improve hemodynamics, or reduce the duration of vasopressor use? 4) Are the intermediate outcomes reliably associated with reduced mortality or improved functional outcomes? 5) Does one (or more than one) intervention result in adverse effects or demonstrate a lack of cost-effectiveness?

TABLE 2. Levels of Evidence and Strength of Recommendation

Strengths of recommendation
Level 1: Strong recommendation (appropriate by the large majority of experts with no major dissension). The desirable effects of adherence to the recommendation outweigh the undesirable effects.
In favor: "we recommend"
Against: "we recommend not to"
Level 2: Weak recommendation (appropriate by the majority of experts, but some degree of dissension exists). The desirable effects of adherence to the recommendation probably outweigh the undesirable effects.
In favor: "we suggest"
Against: "we suggest not to"
Level 3: Neutral recommendation. The course of action could be considered appropriate in the right context.
Levels of evidence
Grade A: High level of evidence. We are confident that the true effect is close to our estimate of the effect.
Grade B: Moderate level of evidence. The true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different.
Grade C: Low level of evidence. The true effect may be substantially different from our estimate of the effect.
Grade D: Very low level of evidence. Our estimate of the effect is just a guess, and it is very likely that the true effect is substantially different from our estimate of the effect.

(20–22) and to intervene with other treatments if signs of toxicity develop. The workgroup deferred the indications for, and types of, decontamination to the AACT and the EAPCCT position statement (2005) (16) instead of proposing new recommendations.

First-Line Therapy for Symptomatic Patients

For first-line therapy of symptomatic CCB-poisoned patients, the workgroup recommends the use of

- IV calcium (1D)
- High-dose insulin therapy with other first line treatment(s) if evidence of myocardial dysfunction is present (1D),
- Norepinephrine and/or epinephrine in the presence of shock (even if myocardial function has not yet been assessed), with preferential use of norepinephrine in the presence of vasodilatory shock (1D).

For the first-line therapy of symptomatic CCB-poisoned patients, the workgroup suggests the use of

- High-dose insulin therapy as a monotherapy in the presence of myocardial dysfunction (2D),
- High-dose insulin therapy in the absence of documented myocardial dysfunction if used in combination with IV fluids, calcium, and vasopressors (2D),
- Dobutamine or epinephrine in the presence of cardiogenic shock (2D),
- Atropine in the presence of symptomatic bradycardia or conduction disturbances (2D).

For the first-line therapy of symptomatic CCB-poisoned patients, the workgroup suggests not to use

- Dopamine in the presence of shock (2D),
- Vasopressin as a single vasoactive agent in the presence of documented cardiogenic shock (2D).

Rationale

The workgroup agreed that each of the treatments here mentioned could be considered as first line alone or in combination. A supplementary round of Delphi did not allow prioritization of one intervention over another. Comparative studies were rare, and more than one interventions were done concurrently in most of the studies reviewed. Therefore, the workgroup emphasized that the first-line treatments should be prioritized based on the desired effect tailored to the individual patient's clinical condition (Fig. 3; Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/CCM/C95).

The workgroup recommended IV calcium as a first-line treatment based on improvement in contractility and blood pressure observed in some case series (23–26) and animal studies (27–33). This therapy is readily available and carries little risk provided central venous or secure peripheral venous access is available. The regimen often used for the administration of 10% calcium chloride in CCB-poisoned adults is 10–20 mL (1–2 g) every 10–20 minutes or an infusion at 0.2–0.4 mL/kg/hr (0.02–0.04 g/kg/hr). When 10% calcium gluconate is given, notably to minimize peripheral vein irritation, the dose regimen frequently used is 30–60 mL (3–6 g) every 10–20 minutes or an infusion at 0.6–1.2 mL/kg/hr (0.06–0.12 g/kg/hr) (23).

Observational studies (34, 35), case series (4, 36–38), and animal studies (39–42) document an improvement in contractility, blood pressure, and a potential increase in survival with the use of high-dose insulin in CCB-poisoned patients. Considering that high-dose insulin seems to have a direct

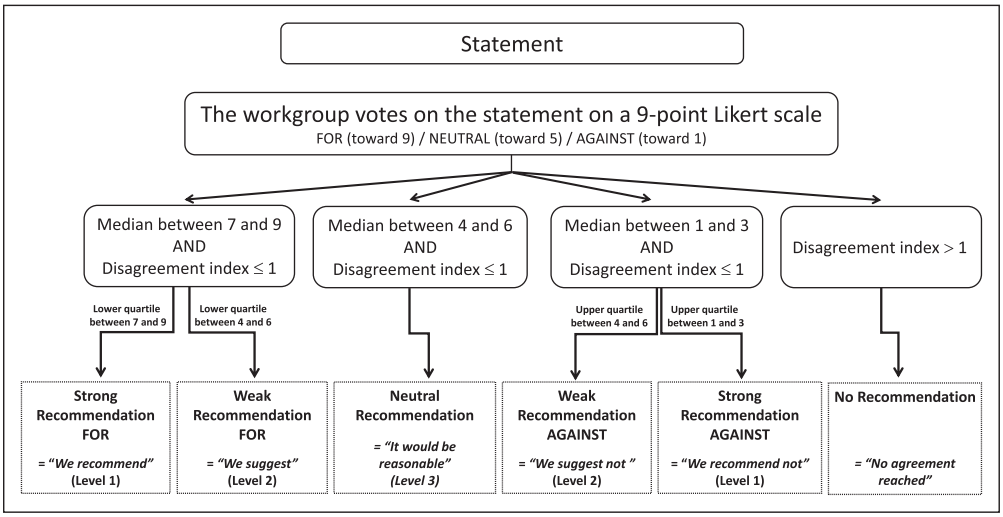

Figure 2. Voting process for recommendations.

positive inotropic effect (39, 42), the workgroup recommended its use in the face of documented myocardial dysfunction, but still suggested if myocardial dysfunction is not documented because case series documented hemodynamic improvement even with dihydropyridines poisoning (19). Despite the fact that high-dose insulin requires intensive monitoring, its benefits were thought to outweigh the risks such as hypoglycemia, hypokalemia, or volume overload (4). The proposed dose regimen of high-dose insulin (regular insulin) includes a bolus of 1 U/kg followed by an infusion of 1 U/kg/hr with maintenance of euglycemia with a dextrose infusion as needed and close monitoring of serum potassium. Because titration of high-dose insulin to response up to 10 U/kg/hr is supported only by case series, the workgroup suggests to use this dosage only for patients who do not respond to first-line therapies (43).

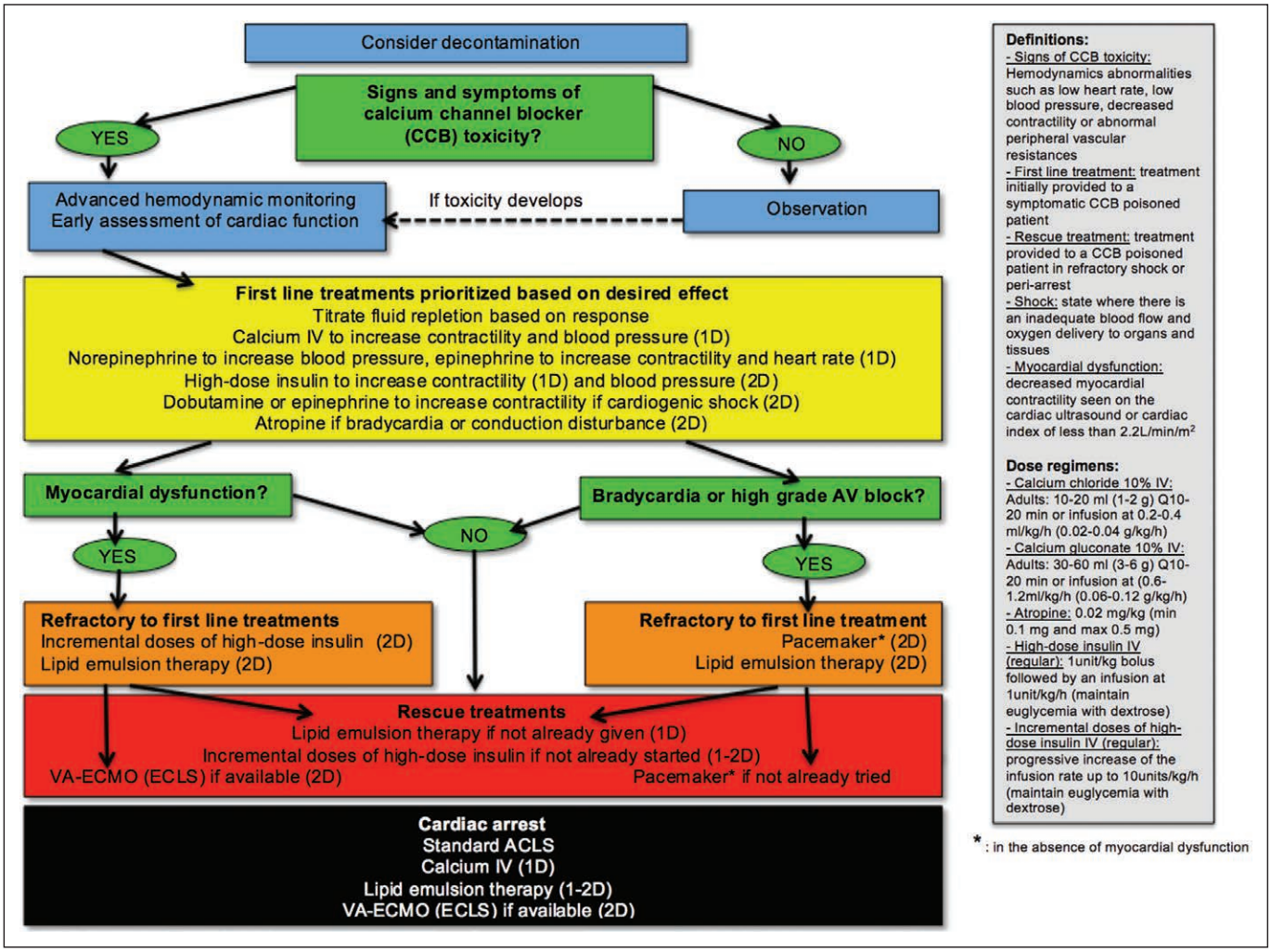

Figure 3. Progression of care for key recommendations. ACLS = advanced cardiac life-support, CCB = calcium channel blocker, ECLS = Extracorporeal Life Support, VA-ECMO = venoarterial extracorporeal membrane oxygenation.

The selection of vasopressors should be guided by the type of shock. Based on mechanism of action, the workgroup recommended the use of norepinephrine to increase blood pressure in vasoplegic shock or if myocardial function has not yet been assessed (30, 32, 44). The use of epinephrine is also recommended for a CCB-poisoned patient in shock to increase contractility and heart rate (30, 32, 39). In the presence of confirmed myocardial dysfunction, clinicians can also use dobutamine (44). High infusion rates of vasopressors and inotropes may be required (44).

Based on inconsistent hemodynamic improvement in case series (23–25), the workgroup suggest not to use dopamine. The use of vasopressin alone was discouraged due to lack of efficacy and worsened survival in animal models (45, 46). The workgroup could not make recommendations regarding the use of vasopressin as an adjunct to other vasopressors as there is little documented clinical experience. No agreement was reached for the use of phenylephrine in CCB-poisoned patients.

In situations in which there is symptomatic bradycardia or conduction disturbances, the workgroup suggested using atropine at a dose regimen of 0.5 mg every 3–5 minutes for few doses if needed. This suggestion is supported based on considerations that the therapy may temporarily help, is easily accessible, is inexpensive, and is associated with few risks (30, 32).

Although fluid resuscitation is commonly used, no formal recommendation was made because no fluid repletion studies were found specifically for CCB poisoning. Nonetheless, the workgroup considered fluid administration as a first-line therapy and continued administration as long as the patient demonstrates evidence of fluid responsiveness (e.g., hemodynamic improvement based on hemodynamic parameters and monitoring devices such as echocardiography after receiving 10–20 mL/kg of crystalloid over 10–15 min).

Therapy for Patients Refractory to First-Line Treatments

For the therapy of CCB-poisoned patients refractory to first-line treatments, the workgroup suggests the use of

- Incremental doses of high-dose insulin therapy (up to 10 U/kg/hr) if evidence of myocardial dysfunction is present (2D),
- Pacemaker in the presence of unstable bradycardia or high-grade AV block, without significant alteration in cardiac inotropism (2D),
- IV lipid-emulsion therapy (2D).

Rationale

In patients refractory to the first-line treatments, the workgroup considered therapies supported by a limited number of case series and associated with a moderate risk. The workgroup kept therapies associated with higher risks for rescue treatments. Therefore, in the presence of myocardial dysfunction, the workgroup suggested to titrate high-dose insulin infusion rates up to 10 U/kg/hr to improve inotropy and facilitates the use of carbohydrates by the myocardium (43) with a dextrose infusion to maintain euglycemia if needed. Pacing has been associated with frequent capture and pacing problems. However, there may be hemodynamic improvement in patients presenting with unstable bradycardia or high-grade AV block (47–50). To avoid spending time on a therapy that involves risk and may not be effective, the workgroup suggested to attempt transcutaneous pacing first. If transcutaneous pacing is effective, IV pacing can be instituted when clinically appropriate.

Based on possible hemodynamic improvement documented in animal studies (51–53), case series (54, 55) and case reports (56, 57), the workgroup also suggested the use of lipid-emulsion therapy. However, this is not recommended earlier in therapy in the absence of cardiac arrest, given the inconsistent response and the concern of potentially increasing the absorption of medications still present in the gastrointestinal tract by changing the distribution of the CCB. This concern was reported in an animal study only published as an abstract at the time of analysis showing worse outcomes (58) with an oral model of CCB poisoning. The workgroup felt that there were insufficient data to recommend a specific dose regimen of lipid-emulsion therapy. The dose most commonly used is 1.5 mL/kg of 20% lipid emulsion administered as a bolus, repeated up to twice as needed until clinical stability is achieved, and followed by an infusion of 0.25 mL/kg/min for 30–60 minutes (59). The Food and Drug Administration fixed a maximum total dose administered per 24 hour of 12.5 mL/kg (60).

Therapy for Patients in Refractory Shock or Periarrest

For the therapy of CCB-poisoned patients in refractory shock or periarrest despite increasing doses of inotropes and vasopressors, the workgroup recommends the following as rescue treatments:

- Incremental doses of high-dose insulin therapy (up to 10 U/kg/hr) if evidence of myocardial dysfunction is present if not administered previously (1D),
- Lipid-emulsion therapy if not administered previously (1D)

For the therapy of CCB-poisoned patients in refractory shock or periarrest, the workgroup suggests, as rescue treatments, the use of

- Incremental doses of high-dose insulin therapy (up to 10 U/kg/hr) even in the absence of myocardial dysfunction if not administered previously (2D),
- VA-ECMO in presence of cardiogenic shock in centers where the treatment is available (2D),
- Pacemaker in the presence of unstable bradycardia or high-grade AV block, without significant alteration in cardiac inotropy if not tried previously (2D).

Rationale

Given the high risk of mortality in patients with severe refractory shock or periarrest, the workgroup members considered therapies with less evidence and/or greater risks. Therefore, incremental doses of high-dose insulin therapy are suggested even if no myocardial dysfunction has been documented (43) and the use of lipid-emulsion therapy is recommended in that situation (52,53,55–57).

Given the risk of mortality in severely poisoned patients and the potential survival benefit demonstrated in an observational study conducted in experienced centers (61),

the workgroup members suggested venoarterial extracorporeal membrane oxygenation (VA-ECMO), which allows gas exchange and hemodynamic support, while blood is pumped from the venous to the arterial side, as a rescue therapy in CCB-poisoned patients presenting with cardiogenic shock or mixed shock involving a significant cardiogenic part in centers where the treatment is available. In this clinical scenario, the workgroup concluded that the benefits outweigh the risks of limb ischemia, bleeding, or thrombosis. The members were neutral with regard to the use of the Impella catheter (Abiomed, Danvers, MA) or other ventricular-assisted devices as potential alternatives to VA-ECMO as there is simply insufficient clinical or research experience (62).

Therapy for Patients in Cardiac Arrest

For therapy of CCB-poisoned patients in cardiac arrest, the workgroup recommends, in addition to standard advanced cardiac life-support provided to nonpoisoned patients, the use of

- IV calcium, even if previously administered (1D),
- Lipid-emulsion therapy if not administered previously (1D).

For therapy of CCB-poisoned patients in cardiac arrest, the workgroup suggests the use of

- Lipid-emulsion therapy, even if previously administered (2D),
- VA-ECMO in centers where the treatment is available (2D).

Rationale

Studies looking specifically at CCB-poisoned patients in cardiac arrest are scarce. Most recommendations other than use of VA-ECMO are extrapolated from studies conducted in severely ill patients not in cardiac arrest. Therefore, the workgroup emphasized the importance of aggressive resuscitation with the previously mentioned modalities. Consequently, the workgroup members recommended the use of IV calcium and lipid-emulsion therapy at the same dose regimen described earlier. Furthermore, a second dose of lipid-emulsion therapy overall is suggested even if the patient already received a bolus before the cardiac arrest.

Concerning the use of VA-ECMO in experienced centers, observational studies and case reports have demonstrated a survival benefit in cardiac arrest patients (61, 63–67). The workgroup members estimated that the benefit of saving a life outweighs the risks of initiating such invasive therapy as long as there is a reasonable chance of surviving without significant deficit. The workgroup recognized that a long period of low flow may be associated with poorer outcomes, but the evidence is unclear regarding the time to declare futility.

The rationale for not recommending or suggesting other treatments such as glucagon or methylene blue is available in **Appendix 7** (Supplemental Digital Content 1, http://links.lww.com/CCM/C94). A description of values and preferences, the result of the review process, and the planned implementation and revisions are available in Appendix 2 (Supplemental Digital Content 1, http://links.lww.com/CCM/C94).

TABLE 3. Participating Organizations That Endorsed the Recommendations After an Internal Review Process Based on the AGREE II Instrument

American Association of Poison Control Centres
American College of Medical Toxicology
Canadian Association of Emergency Physicians[a]
Canadian Association of Poison Control Centres
Canadian Critical Care Society
Canadian Paediatric Society
European Association of Poison Centres and Clinical Toxicologists
European Society of Emergency Medicine
European Society of Intensive Care Medicine
Society of Critical Care Medicine

[a]Endorsed the submitted article to *Critical Care Medicine* and will review the accepted article.

DISCUSSION

The target population for these recommendations includes CCB-poisoned adults. However, given the paucity of literature for the treatment of CCB-poisoned children and the absence of evidence that children respond differently than adults to CCB poisoning, the workgroup believes that it is reasonable to apply the recommendations to the pediatric population.

Even if articles were found to answer some KQs (1–5), the overall evidence available to develop these recommendations was of very low quality. Many interventions had only been studied for surrogate outcomes. With the exception of VA-ECMO for cardiotoxicant poisonings, the use of and costs associated with these resources had not been described (KQ5) (Fig. 1) (68). Hence, many questions within our proposed analytic framework remain unanswered (Fig. 1). These represent potential areas for future research.

First, comparative studies should be conducted to identify which intervention improves intermediate and health outcome (KQ 1, 3, and 4) for each specific class of CCB (KQ 2) with acceptable adverse effects and cost (KQ 5). Second, observational studies should identify prognostic factors, which is particularly imperative in severe cases that may potentially require VA-ECMO (KQ 2). Third, scientists should conduct clinical trials to identify factors associated with favorable responses to high-dose insulin therapies (KQ 2). Prospective, controlled clinical trials are needed to evaluate currently recommended antidotes or to assess new ones (KQ 1, 3, 4, and 5) (**Table 3**).

CONCLUSION

Those recommendations have been developed to help improve current treatment of CCB-poisoned patients by reducing physician practice variation. The workgroup also identified potential areas for future research.

ACKNOWLEDGMENTS

For his participation to the workgroup and for reviewing the article, we would like to thank David H. Jang, medical toxicologist and emergency physician for the Department of Emergency Medicine, NYU School of Medicine. For his initial participation to the workgroup and for reviewing the article, we would like to thank Reza Afshari, Immediate Past President of Asia Pacific Association of Medical Toxicology, BC Center for Disease Control. For reviewing the article, we would like to thank the Canadian Critical Care Trials Group. For sharing unpublished data from their work, we would like to thank Pierre-André Dubé, Chantal Guimont, Jesse Godwin, Patrick Archambault, Jean-Marc Chauny, Anne-Julie Frenette, Martin Darveau, Natalie Lesage, Julien Poitras, Joanne Provencher, and René Blais, co-authors of a previously published systematic review (19).

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