Treatment of Calcium Channel Blocker & Beta Blocker Overdose

A presentation for HealthTrust Members

April 16, 2025

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Objectives: Pharmacists & Nurses

1. **Recall** typical clinical presentations of calcium channel and beta blocker overdoses
2. **Identify** appropriate treatment regimens for calcium channel and beta blocker overdoses depending on patient presentation
3. **Recognize** appropriate treatment targets for calcium channel and beta blocker overdoses

Objectives: Pharmacy Technicians

1. **Recall** medications that can precipitate overdose in patients taking calcium channel and beta blockers
2. **Recognize** medications commonly used to treat overdoses
3. **Identify** appropriate dosing of calcium channel blockers, beta blockers and supportive care/antidote medications

Abbreviations

- AC- activated charcoal
- AE- adverse effect
- AMS- altered mental status
- ATP- adenosine triphosphate
- AV- atrioventricular
- BB- beta blocker
- BP- blood pressure
- cAMP- cyclic AMP
- CCB- calcium channel blocker
- DHP- dihydropyridine
- g- grams
- GI- gastrointestinal
- HIET- Hyperinsulinemic euglycemic therapy
- hr- hour
- IR- immediate release
- IV- intravenous
- K- potassium
- kg- kilogram
- Mg- magnesium
- min- minute
- mL- milliliter
- NDHP- non-dihydropyridine
- Ph- phosphorus
- PO- orally
- SA- sinoatrial
- SR- sustained release
- VA-ECMO- venoarterial extracorporeal membrane oxygenation
- WBI- whole bowel irrigation

TOXIDROMES

CCBs: Pharmacology

- Block **L-type voltage-gated calcium channels**
  - Prevents intracellular calcium influx required for muscle contraction
  - **Decreased contractility**
  - **Negative inotropy, chronotropy, and dromotropy**
  - Decreased insulin secretion in pancreatic ß cells
- Specificity by class:
  - Dihydropyridines (amlodipine, nifedipine, nicardipine, nimodipine): **peripheral vascular smooth muscles**
  - Nondihydropyridines (diltiazem, verapamil): **cardiomyocytes**

Source:Alshaya OA, Alhamed A, Althewaibi S, et al. Calcium Channel Blocker Toxicity: A Practical Approach. J Multidiscip Healthc. 2022;15:1851-1862. Published 2022 Aug 30. doi:10.2147/JMDH.S374887
Source: Goldfine CE, Troger A, Erickson TB, Chai PR. Beta-blocker and calcium-channel blocker toxicity: current evidence on evaluation and management. Eur Heart J Acute Cardiovasc Care. 2024;13(2):247-253. doi:10.1093/ehjacc/zuad138

CCBs: Presentation

Hypotension	Bradycardia*	Heart block
Hyperglycemia	AMS	GI symptoms

**May have reflex tachycardia with DHP CCBs*

Onset: within 8 hours (IR), up to 24 hours (SR)

Source:Alshaya OA, Alhamed A, Althewaibi S, et al. Calcium Channel Blocker Toxicity: A Practical Approach. J Multidiscip Healthc. 2022;15:1851-1862. Published 2022 Aug 30. doi:10.2147/JMDH.S374887
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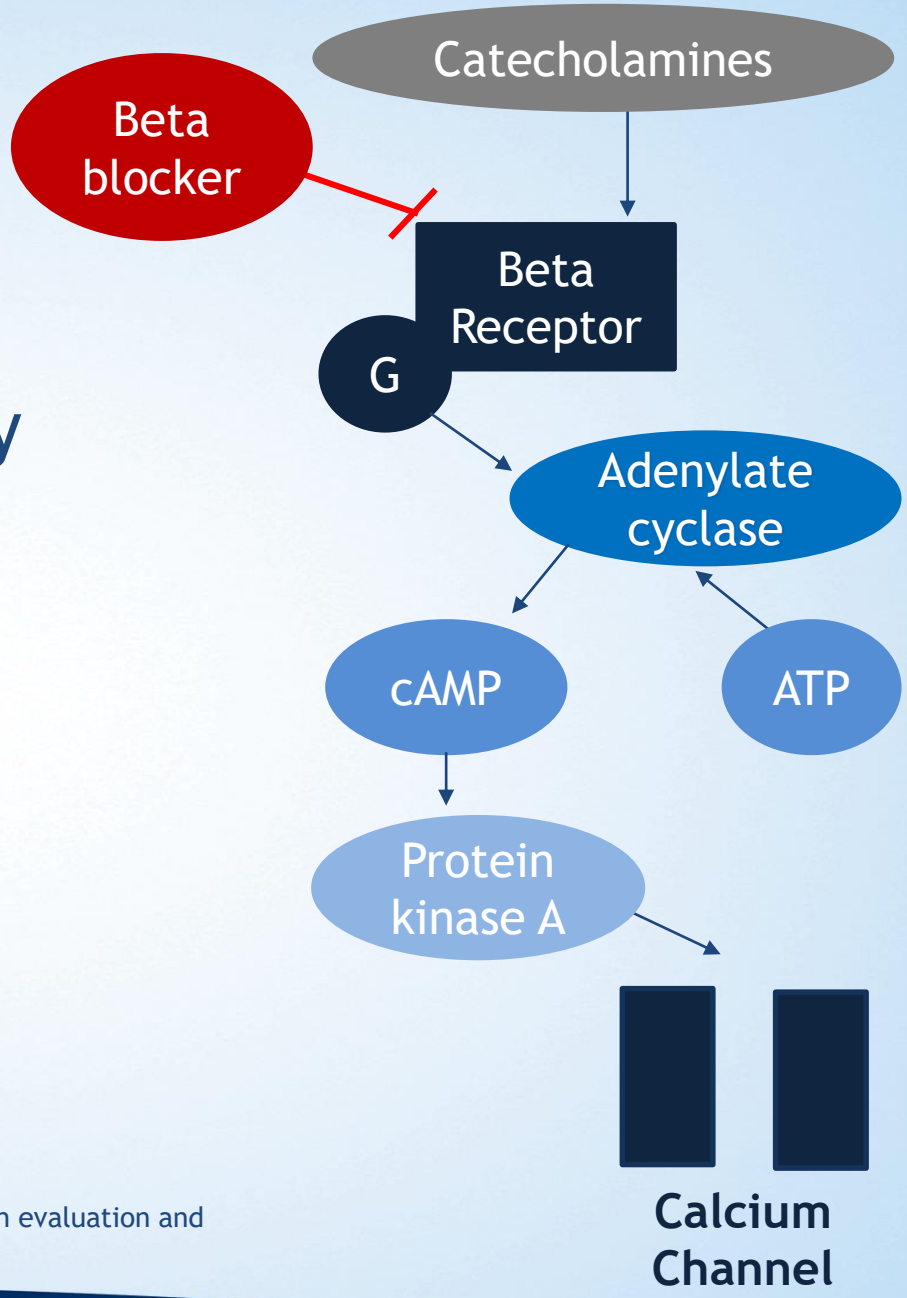
BBs: Pharmacology

- Antagonize **beta-adrenergic receptors**
  - In myocardial cells
  - These receptors are usually stimulated by catecholamines to open L-type calcium channels downstream
    - Entire process is inhibited in the presence of BBs
  - **Decreased contractility**
  - **Negative inotropy, chronotropy, and dromotropy**
- Additional effects due to BB **heterogeneity**



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BBs: Additional Activity

- Nonselective (B1/B2 blockade): carvedilol, labetalol, propranolol, sotalol, nadolol, pindolol
- Selective (B1 blockade): atenolol, metoprolol, esmolol, bisoprolol, acebutolol, betaxolol
- Block Na channels: carvedilol, propranolol, acebutolol
- Block K channels: sotalol, acebutolol
- Block Ca channels: carvedilol, betaxolol
- Block alpha receptors: labetalol, carvedilol
- Beta receptor agonists: acebutolol, pindolol
- Highly lipophilic: propranolol

Source: Goldfine CE, Troger A, Erickson TB, Chai PR. Beta-blocker and calcium-channel blocker toxicity: current evidence on evaluation and management. Eur Heart J Acute Cardiovasc Care. 2024;13(2):247-253. doi:10.1093/ehjacc/zuad138

BBs: Additional Activity + Presentation

- Block Na channels: QRS prolongation
- Block K channels: QTC prolongation
- Block Ca channels: Vasodilation
- Block alpha receptors: Vasodilation
- Beta receptor agonists: Vasodilation
- Highly lipophilic: CNS penetration

Source: Goldfine CE, Troger A, Erickson TB, Chai PR. Beta-blocker and calcium-channel blocker toxicity: current evidence on evaluation and management. Eur Heart J Acute Cardiovasc Care. 2024;13(2):247-253. doi:10.1093/ehjacc/zuad138

BBs: Presentation

- Hypotension
- Bradycardia
- Heart block
- Hypoglycemia
- AMS

Onset: within 6 hours (IR), up to 24 hours (SR, sotalol)

Source: Goldfine CE, Troger A, Erickson TB, Chai PR. Beta-blocker and calcium-channel blocker toxicity: current evidence on evaluation and management. Eur Heart J Acute Cardiovasc Care. 2024;13(2):247-253. doi:10.1093/ehjacc/zuad138

Evaluation

History/physical

Laboratory

- **Electrolytes**
- **Glucose**
- Renal function
- Co-ingestions
- Arterial blood gas

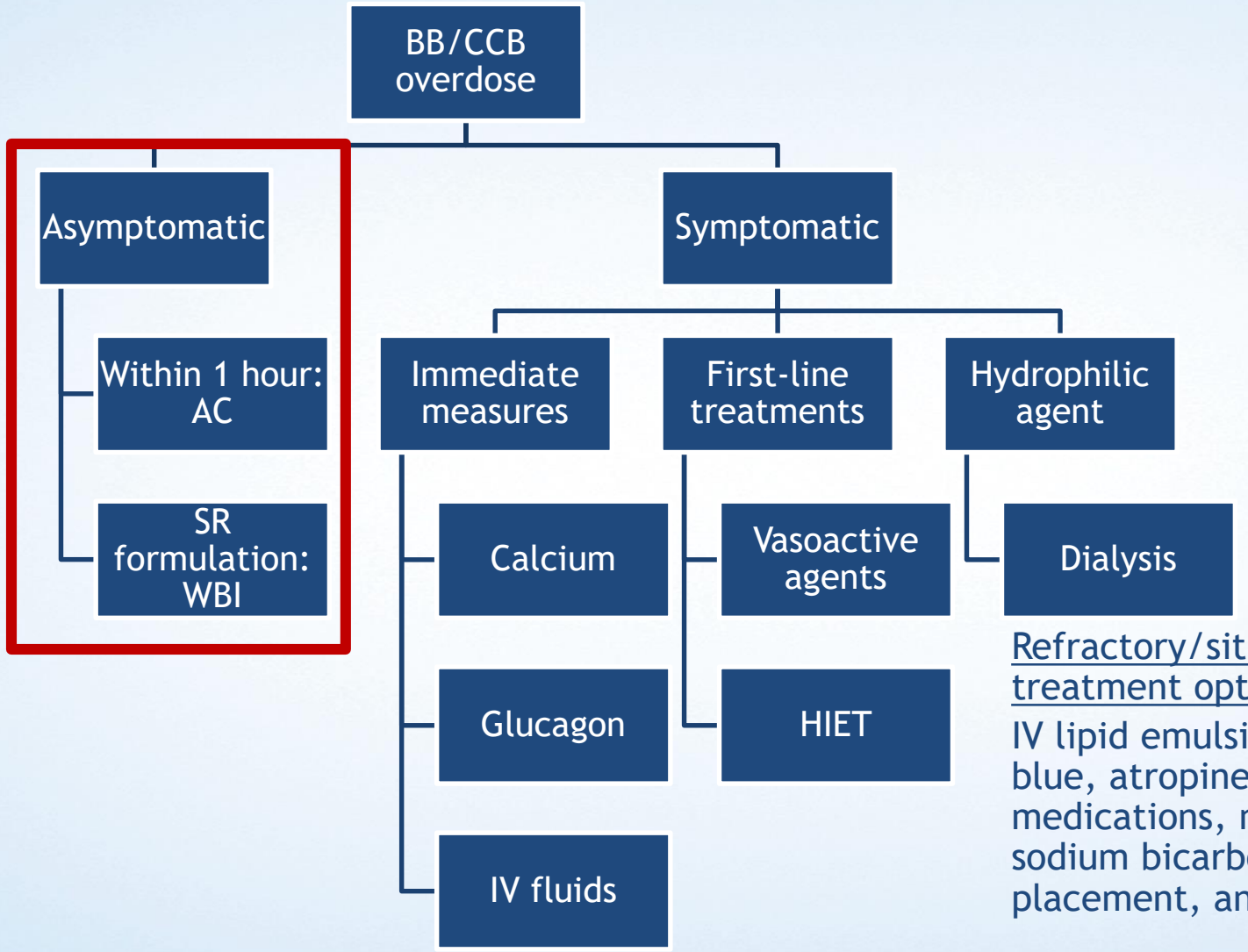
Electrocardiogram/echocardiogram

CCB vs. BB overdose

- Glucose
- **Similar presentations, similar treatment**

TREATMENT: EARLY ASYMPTOMATIC PATIENTS

Treatment Algorithm



Refractory/situational treatment options include:

IV lipid emulsion, methylene blue, atropine, seizure medications, magnesium, sodium bicarbonate, pacemaker placement, and VA-ECMO

GI Decontamination

Activated charcoal

- If within **1-2 hours** post-ingestion
- 50-100g PO x1, with or without sorbitol
- Avoid if AMS, nausea, or vomiting

Whole bowel irrigation

- If large amount of **SR product**
- Polyethylene glycol 1.5-2 L/hr through OG tube
- Continue until effluent is clear

- Not commonly used
- Observation for ~**24 hours** despite treatment chosen

Sources:Alshaya OA, Alhamed A, Althewaibi S, et al. Calcium Channel Blocker Toxicity: A Practical Approach. J Multidiscip Healthc. 2022;15:1851-1862. Published 2022 Aug 30. doi:10.2147/JMDH.S374887
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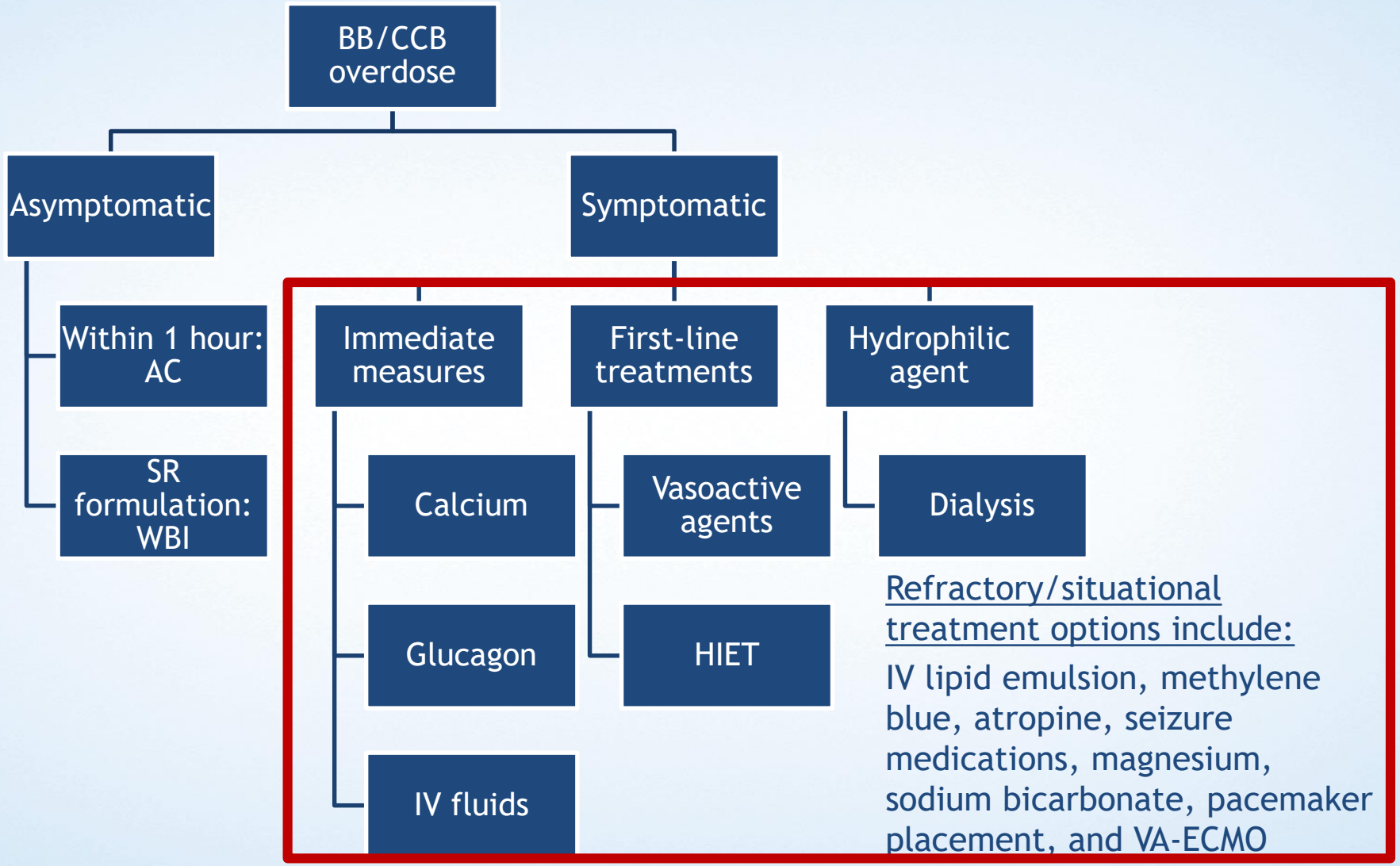
TREATMENT: INITIAL OPTIONS FOR SYMPTOMATIC PATIENTS

Treatment Algorithm



Initial Treatment Options

Calcium	Glucagon	IV fluids
Vasoactive agents	High-dose insulin	Atropine
Magnesium	Sodium bicarbonate	Dialysis

Calcium

- Improves **BP and contractility**
- Calcium chloride 10%
  - 10-20mL (1-2g) every 10-20 minutes, or
  - 0.2-0.4 mL/kg/hr (0.02-0.04 g/kg/hr)
- Calcium gluconate 10%
  - 30-60mL (3-6g) every 10-20 minutes, or
  - 0.6-1.2 mL/kg/hr (0.06-0.12 g/kg/hr)
- Obtain **ionized calcium concentration** every 30-60 minutes
  - Goal: 1.5X upper limit of normal

Source: Alshaya OA, Alhamed A, Althewaibi S, et al. Calcium Channel Blocker Toxicity: A Practical Approach. J Multidiscip Healthc. 2022;15:1851-1862. Published 2022 Aug 30. doi:10.2147/JMDH.S374887

Glucagon

- **Positive inotropy and chronotropy** (bypasses blocked adrenergic receptors through direct effects on **adenylate cyclase**)
- **Bridges patients** for other treatments
- 5-10mg slow IV push followed by 1-5 mg/hr continuous infusion
  - Available in 1mg vials/syringes
- AEs- nausea, vomiting, tachyphylaxis

Source: Graudins A, Lee HM, Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. Br J Clin Pharmacol. 2016;81(3):453-461. doi:10.1111/bcp.12763

IV Fluid Resuscitation

- Improves **hemodynamic stability** in hypotensive patients
- Use early in treatment course
- 10-20 mL/kg of crystalloid
- AEs- **fluid overload**

Vasoactive Agents

- Improve hemodynamic stability
- **High doses** often necessary
  - Norepinephrine >1.25 mcg/kg/min, epinephrine >1 mcg/kg/min

Epinephrine	Norepinephrine	Milrinone	Vasopressin
• α/β • Improves both bradycardia and hypotension	• α>β • Preferred in vasodilatory shock	• PDE3 • Positive inotropy and chronotropy by bypassing adrenergic receptors	• V1/V2 • As an adjunct • Improves hypotension

Source: Alshaya OA, Alhamed A, Althewaibi S, et al. Calcium Channel Blocker Toxicity: A Practical Approach. J Multidiscip Healthc. 2022;15:1851-1862. Published 2022 Aug 30. doi:10.2147/JMDH.S374887
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High-Dose Insulin/HIET

“Hyperinsulinemic euglycemic therapy”

- Increases intracellular transport of glucose to myocardial cells
- Positive inotropy
- Decreases vasopressor requirement
- May improve survival

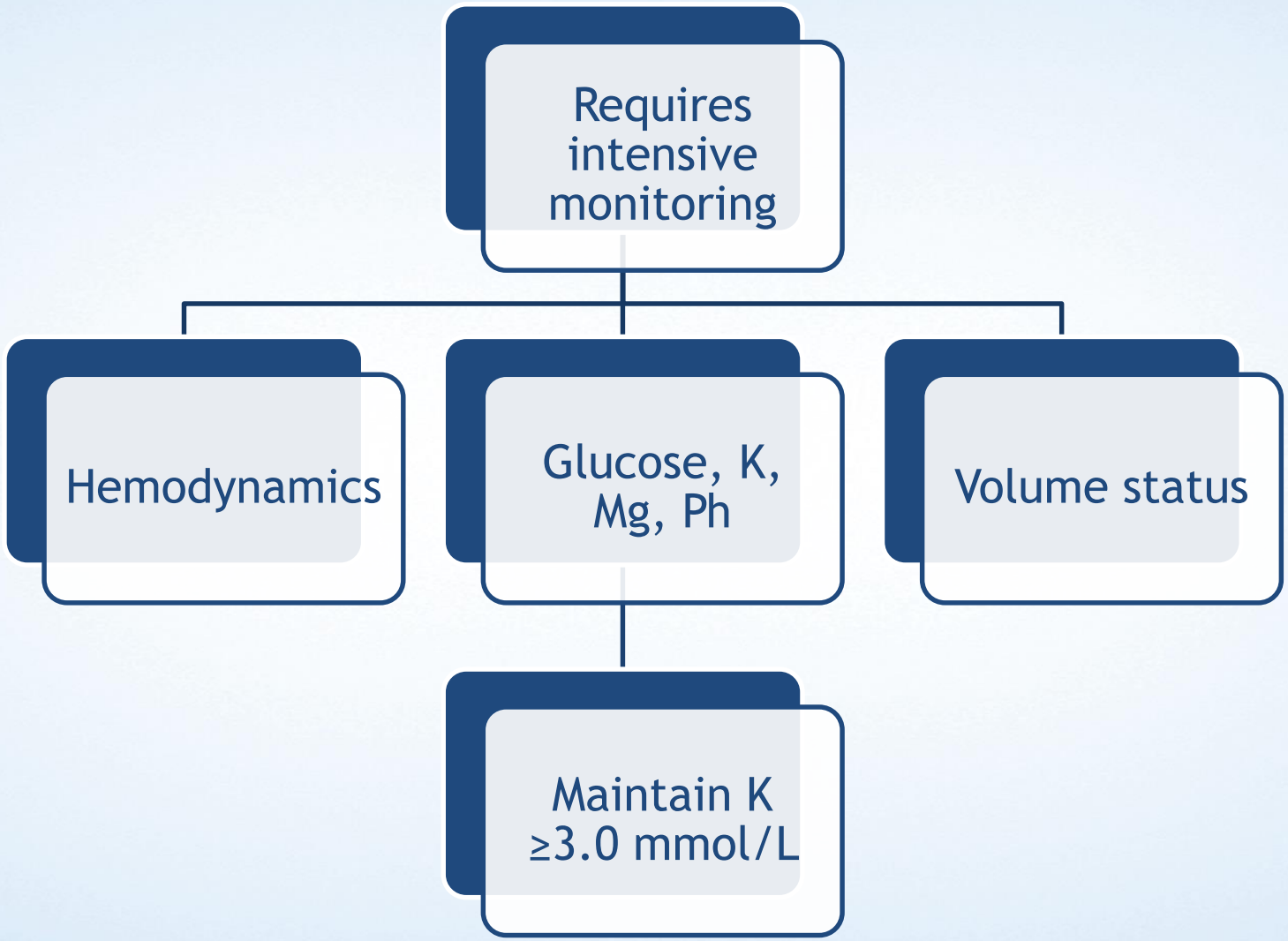
Source: Krenz JR, Kaakeh Y. An Overview of Hyperinsulinemic-Euglycemic Therapy in Calcium Channel Blocker and ß-blocker Overdose. Pharmacotherapy. 2018;38(11):1130-1142. doi:10.1002/phar.2177

High-Dose Insulin/HIET

- High-dose **regular insulin:**
  - 1 U/kg bolus, then
  - 1 U/kg/hr up to 10 U/kg/hr
  - Commonly available as **1 U/mL (100 unit) bags**, but may need higher concentration or volume
- Administered with **dextrose** as needed for euglycemia
  - Monitor glucose every 30 minutes initially, then every 60 minutes
    - Goal **glucose >100 mg/dL**
  - Dextrose infusions or high concentration dextrose pushes

Source: Krenz JR, Kaakeh Y. An Overview of Hyperinsulinemic-Euglycemic Therapy in Calcium Channel Blocker and ß-blocker Overdose. Pharmacotherapy. 2018;38(11):1130-1142. doi:10.1002/phar.2177

High-Dose Insulin/HIET



Atropine

- Used in symptomatic **bradycardia** and conduction abnormalities
- 0.5-1mg every 3-5 minutes as needed
- Often **ineffective**
  - Could be diagnostic as it will often not work in CCB/BB overdose patients

Source: St-Onge M, Anseeuw K, Cantrell FL, et al. Experts Consensus Recommendations for the Management of Calcium Channel Blocker Poisoning in Adults. Crit Care Med. 2017;45(3):e306-e315. doi:10.1097/CCM.0000000000002087

Agent-Specific Treatment

- Sodium channel blockade
  - BBs (**carvedilol, propranolol, acebutolol**)
  - Widened QRS +/- monomorphic ventricular tachycardia
  - Treatment: **sodium bicarbonate**
- Potassium channel blockade
  - BBs (**sotalol, acebutolol**)
  - Prolonged QTc interval +/- torsades de pointes
  - Treatment: **magnesium**
- High lipophilicity
  - **Propranolol**
  - Seizures
  - Treatment: **benzodiazepines**, additional seizure medications

Source: Goldfine CE, Troger A, Erickson TB, Chai PR. Beta-blocker and calcium-channel blocker toxicity: current evidence on evaluation and management. Eur Heart J Acute Cardiovasc Care. 2024;13(2):247-253. doi:10.1093/ehjacc/zuad138

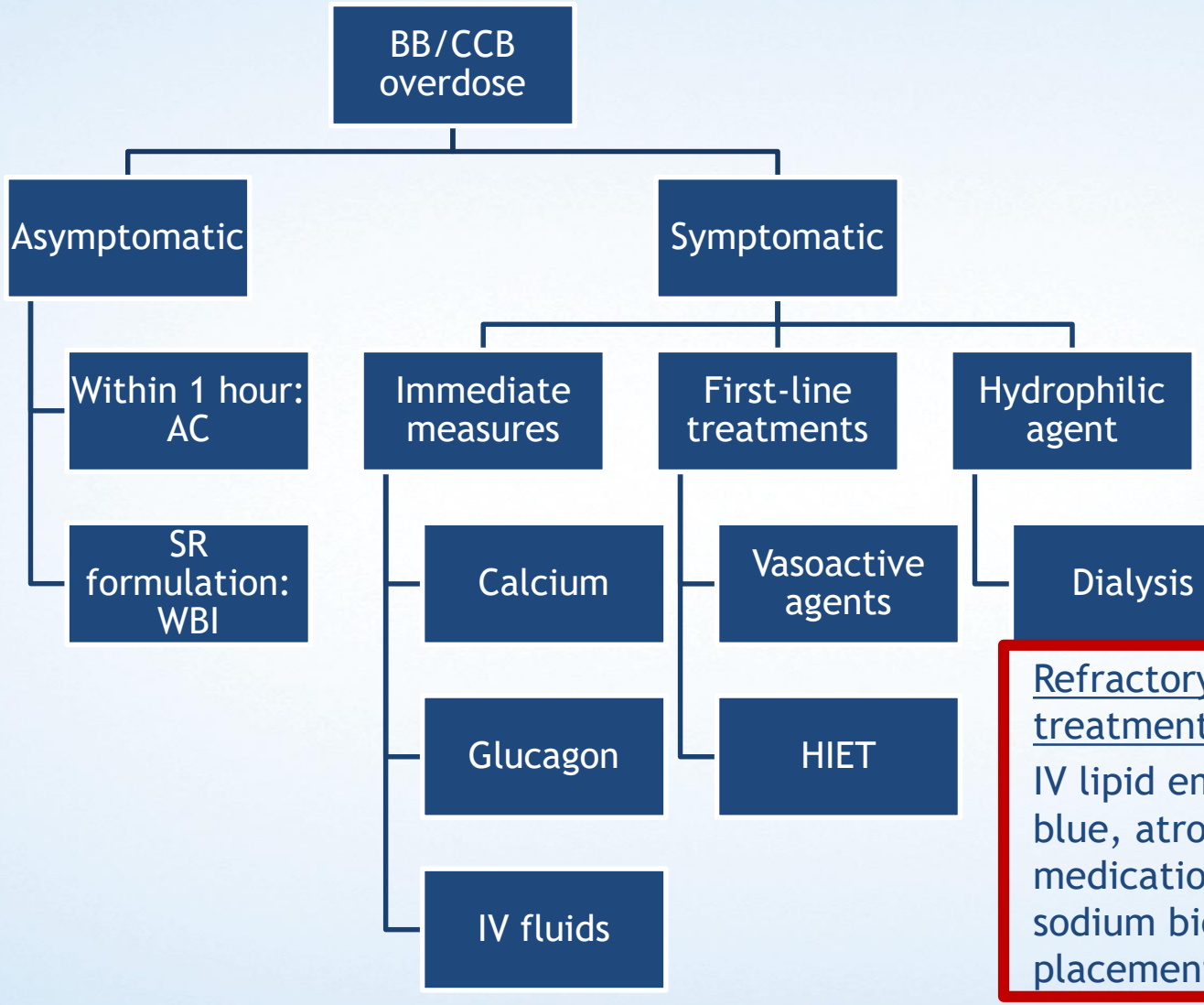
Dialysis

- Used in **life-threatening** cases
- Not recommended for CCB overdose
- Only useful in select BB overdose: **atenolol, nadolol, acebutolol, and sotalol**
- HD preferred
- Continue until clinical improvement (HR, BP, perfusion, vasopressor requirements)

Source: Bouchard J, Shepherd G, Hoffman RS, et al. Extracorporeal treatment for poisoning to beta-adrenergic antagonists: systematic review and recommendations from the EXTRIP workgroup. Crit Care. 2021;25(1):201. Published 2021 Jun 10. doi:10.1186/s13054-021-03585-7
Source: Wong A, Hoffman RS, Walsh SJ, et al. Extracorporeal treatment for calcium channel blocker poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol (Phila). 2021;59(5):361-375. doi:10.1080/15563650.2020.1870123

TREATMENT: REFRACTORY TO FIRST-LINE AGENTS

Treatment Algorithm



Refractory/situational treatment options include:

IV lipid emulsion, methylene blue, atropine, seizure medications, magnesium, sodium bicarbonate, pacemaker placement, and VA-ECMO

Refractory Treatment Options

- Titration of current treatments
- IV lipid emulsion
- Methylene blue
- Pacemaker
- ECMO

IV lipid emulsion

- **Minimal positive evidence**
- Used in lipophilic medications: **propranolol, verapamil**
- 20% lipid emulsion
  - 1.5 mL/kg once or twice, THEN
  - 0.25 mL/kg/min for 30-60 minutes
  - Maximum total daily dose: 12.5 mL/kg

Source: Lavonas EJ, Akpunonu PD, Arens AM, et al. 2023 American Heart Association Focused Update on the Management of Patients With Cardiac Arrest or Life-Threatening Toxicity Due to Poisoning: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2023;148(16):e149-e184. doi:10.1161/CIR.0000000000001161
Source: Alshaya OA, Alhamed A, Althewaibi S, et al. Calcium Channel Blocker Toxicity: A Practical Approach. J Multidiscip Healthc. 2022;15:1851-1862. Published 2022 Aug 30. doi:10.2147/JMDH.S374887

IV lipid emulsion

- May increase absorption of medication still in the GI tract
- May interfere with laboratory testing and/or ECMO
- May cause pancreatitis or sudden cardiovascular collapse
- May sequester other lipophilic medications patient is requiring

Source: Lavonas EJ, Akpunonu PD, Arens AM, et al. 2023 American Heart Association Focused Update on the Management of Patients With Cardiac Arrest or Life-Threatening Toxicity Due to Poisoning: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2023;148(16):e149-e184. doi:10.1161/CIR.0000000000001161
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Methylene Blue

- Used in **refractory vasodilatory shock**
- Nitric oxide synthase inhibitor
- 1-2 mg/kg over 15 minutes followed by 1 mg/kg/hr continuous infusion (maximum 7 mg/kg)
- AEs- blue/green discoloration, methemoglobinemia, hemolytic anemia, arrhythmias, respiratory collapse, serotonin syndrome

Source: Alshaya OA, Alhamed A, Althewaibi S, et al. Calcium Channel Blocker Toxicity: A Practical Approach. J Multidiscip Healthc. 2022;15:1851-1862. Published 2022 Aug 30. doi:10.2147/JMDH.S374887

Pacemaker

- For **unstable bradycardia** or high-grade AV block
- Capture is often difficult
  - Transvenous more successful than transcutaneous

Source: St-Onge M, Anseeuw K, Cantrell FL, et al. Experts Consensus Recommendations for the Management of Calcium Channel Blocker Poisoning in Adults. Crit Care Med. 2017;45(3):e306-e315. doi:10.1097/CCM.0000000000002087

VA-ECMO

- "Venoarterial extracorporeal membrane oxygenation"
- Used in **cardiogenic shock**
- Allows hemodynamic support while drug is metabolized
- AEs- limb ischemia, bleeding, thrombosis

Source: St-Onge M, Anseeuw K, Cantrell FL, et al. Experts Consensus Recommendations for the Management of Calcium Channel Blocker Poisoning in Adults. Crit Care Med. 2017;45(3):e306-e315. doi:10.1097/CCM.0000000000002087

SUMMARY

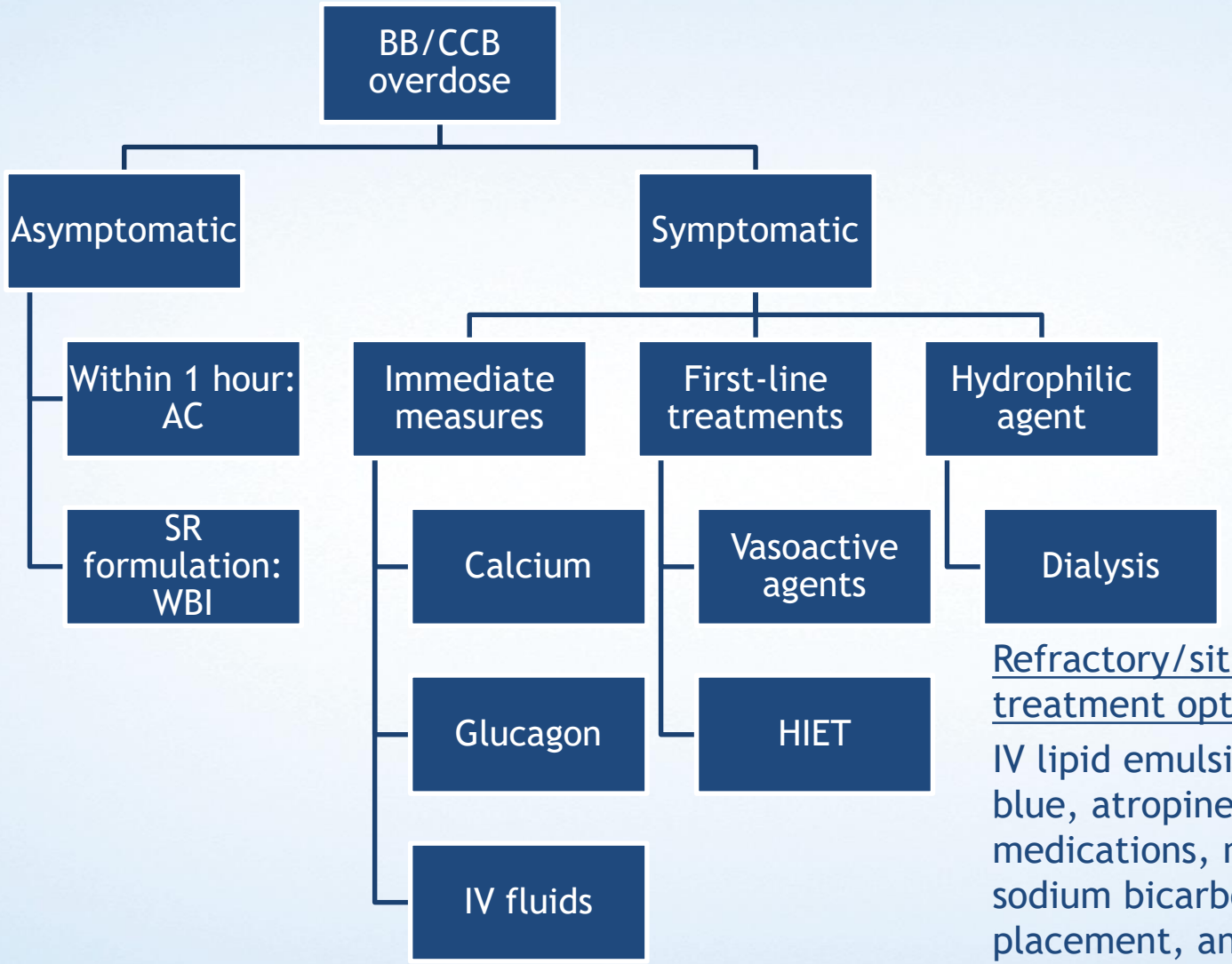
CCB and BB Overdose

- Present with **hypotension and bradycardia**
- Asymptomatic patients should be observed for 24 hours
  - **Activated charcoal** can be given within 1 hour of ingestion
  - **Whole bowel irrigation** can be considered for SR formulations
- **Calcium, glucagon, and IV fluids** can stabilize the patient initially

CCB and BB Overdose

- High doses of **vasoactive agents** are often necessary
  - **Norepinephrine, epinephrine, vasopressin, or milrinone** are preferred
  - Methylene blue can be considered in refractory cases
- **Hyperinsulinemic euglycemic** therapy decreases vasopressor requirements and may improve survival
  - Administer with **dextrose**
- Options for specific populations or refractory treatment include atropine, lipid emulsion, dialysis, VA-ECMO, or pacemaker placement

Treatment Algorithm



Refractory/situational treatment options include:

IV lipid emulsion, methylene blue, atropine, seizure medications, magnesium, sodium bicarbonate, pacemaker placement, and VA-ECMO

ASSESSMENT QUESTIONS: PHARMACISTS & NURSES

Assessment Question 1:

Which of the following best represents the hemodynamic presentation of a calcium channel blocker or beta blocker overdose:

A. Hypertensive and tachycardic

B. Normotensive and bradycardic

C. Hypotensive and bradycardic

D. Hypotensive and tachycardic

Assessment Question 1: Answer

Which of the following best represents the hemodynamic presentation of a calcium channel blocker or beta blocker overdose:

~~A. Hypertensive and tachycardic~~

~~B. Normotensive and bradycardic~~

C. Hypotensive and bradycardic

~~D. Hypotensive and tachycardic~~

Assessment Question 2:

Which of the following options is an appropriate initial treatment regimen of a suspected calcium channel blocker or beta blocker overdose:

A. Norepinephrine and methylene blue

B. Glucagon, calcium chloride, and IV fluids

C. Glucagon, calcium gluconate, and IV lipid emulsion

D. Hemodialysis

Assessment Question 2: Answer

Which of the following options is an appropriate initial treatment regimen of a suspected calcium channel blocker or beta blocker overdose:

~~A. Norepinephrine and methylene blue~~

B. Glucagon, calcium chloride, and IV fluids

~~C. Glucagon, calcium gluconate, and IV lipid emulsion~~

~~D. Hemodialysis~~

Assessment Question 3:

Which of the following would you expect after a patient is treated with first-line options, high-dose insulin, and vasoactive agents:

A. Decreased blood pressure

B. Decreased heart rate

C. Negative inotropy and/or chronotropy

D. Positive inotropy and/or chronotropy

Assessment Question 3: Answer

Which of the following would you expect after a patient is treated with first-line options, high-dose insulin, and vasoactive agents:

~~A. Decreased blood pressure~~

~~B. Decreased heart rate~~

~~C. Negative inotropy and/or chronotropy~~

D. Positive inotropy and/or chronotropy

ASSESSMENT QUESTIONS: PHARMACY TECHNICIANS

Assessment Question 1:

Which of the following medications can cause a calcium channel blocker or beta blocker overdose:

A. Lisinopril

B. Amlodipine

C. Metformin

D. Furosemide

Assessment Question 1: Answer

Which of the following medications can cause a calcium channel blocker or beta blocker overdose:

~~A. Lisinopril~~

B. Amlodipine

~~C. Metformin~~

~~D. Furosemide~~

Assessment Question 2:

Which of the following medications can be used to treat a calcium channel blocker or beta blocker overdose:

A. High-dose insulin

B. Metoprolol

C. Nicardipine

D. Nitroglycerin

Assessment Question 2: Answer

Which of the following medications can be used to treat a calcium channel blocker or beta blocker overdose:

A. High-dose insulin

~~B. Metoprolol~~

~~C. Nicardipine~~

~~D. Nitroglycerin~~

Assessment Question 3:

Which of the following options demonstrates an appropriate dosing regimen for the associated treatment:

A. Glucagon 0.05g once

B. Calcium gluconate 3g once

C. Lorazepam 100mg as needed for seizures

D. Lactated ringers 5 liter bolus once

Assessment Question 3: Answer

Which of the following options demonstrates an appropriate dosing regimen for the associated treatment:

~~A. Glucagon 0.05g once~~

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Thank you!

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