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REVIEW

Are vasopressors useful in toxin-induced cardiogenic shock?

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ABSTRACT

Objective: Overdoses with cardio-depressive medications can result in toxin-induced cardiogenic shock (TICS), a life-threatening condition characterized by severe hypotension and ineffective tissue perfusion. Vasopressors are often employed in the treatment of shock to increase heart rate and blood pressure. We sought to conduct a systematic review of the literature to evaluate the effectiveness of vasopressors in improving hemodynamic function and survival in the treatment of TICS.

Data sources: We searched PubMed, EMBASE, TOXLINE, and International Pharmaceutical Abstracts.

Study selection: We included studies evaluating the use of vasopressors in humans or animals with TICS. We limited human study types to randomized controlled trials, clinical trials, observational studies, and case reports.

Data extraction: Our search yielded 913 citations and 144 of these met our inclusion criteria. 130 were human case reports and 14 were animal studies.

Data synthesis: Human case report data showed vasopressors were ineffective more often than they were partially or fully effective. In the majority of animal studies, vasopressor treatment failed to improve hemodynamic parameters and resulted in decreased survival.

Conclusions: Human case reports and controlled animal experiments lead to different conclusions about vasopressors in TICS. Most animal studies indicate that vasopressors impair hemodynamic function and increase mortality. In contrast, human case reports suggest that vasopressors are often ineffective but not necessarily harmful.

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Introduction

Overdoses with cardio-depressive medications can result in toxin-induced cardiogenic shock (TICS), a life-threatening condition characterized by severe hypotension and ineffective tissue perfusion [1]. Agents reported to cause TICS in overdose include beta blockers (BB), calcium-channel blockers (CCB), and tricyclic antidepressants (TCA). Unfortunately, overdoses with these drugs are not rare – in 2014, the American Poison Control Center responded to 24,755 BB exposures, 12,007 CCB exposures, and 10,349 TCA exposures [2].

While vasopressors are often employed in the treatment of shock to increase heart rate (HR) and blood pressure (BP), they may have undesirable effects in TICS. Their ability to increase systemic vascular resistance (SVR) could increase afterload, thereby reducing cardiac output (CO). Additionally, animal models of TICS suggest that vasopressors can induce functional ischemia and perfusion mismatch [3–5]. The goal of this paper is to conduct a systematic review of the literature to evaluate the effectiveness of vasopressors in the treatment of TICS.

Materials and methods

Search strategy

We conducted a systematic review of the literature to evaluate the effectiveness of vasopressors in treating TICS. A medical librarian performed a thorough, extensive literature search to identify articles related to the research question. Databases searched were PubMed (Web-based), EMBASE (Ovid platform), TOXLINE (Ovid platform), and International Pharmaceutical Abstracts (Ovid platform). We included conference proceedings, abstracts, and papers in the search as well as animal studies. We did not apply any language restrictions or date limits.

In PubMed, medical subject headings (MeSH) terms defined the concepts of TICS. For optimal retrieval, we supplemented all terms with relevant title and text words. We adjusted the search strategies for EMBASE, TOXLINE, and International Pharmaceutical Abstracts for the syntax appropriate for each database using a combination of thesauri and text words. Appendix A lists full search parameters. We identified published reports in peer-reviewed literature with a final search performed on 23 July 2015. Finally, we scanned bibliographies from key articles to identify additional publications.

Inclusion and exclusion criteria

Included studies evaluated the use of vasopressors in humans or animals with TICS. We limited human study types to randomized controlled trials, clinical trials, observational studies, and case reports. We excluded review articles and

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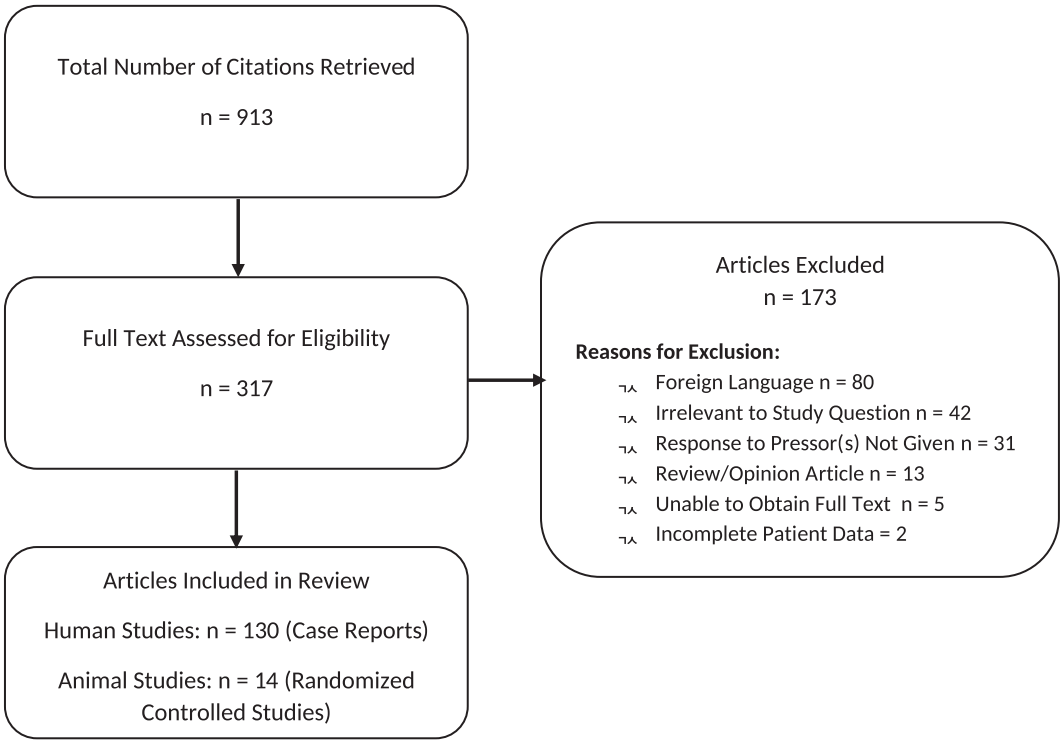

Figure 1. Diagram of study selection.

meta-analyses as they did not allow for review of primary literature. We limited animal studies to controlled experiments with clear randomization procedures. We excluded articles that did not report the clinical response to vasopressors, as they did not provide enough data to interpret treatment effectiveness. Finally, we ultimately excluded all foreign language articles due to lack of financial resources necessary for translation.

Glucagon

Glucagon is often employed in the treatment of TICS due to its positive chronotropic and inotropic effects. Mechanistically, it is not a true vasopressor as it causes vasodilation rather than vasoconstriction. However, we included it in this review because it has had a long history of use especially in BB overdose for pressor-like effects (i.e., to increase HR and bp).

Results

The combined search yielded 913 citations, which were subsequently analyzed for their relevance to the research question. Of these, 144 articles were included in the review. Among the included publications, 130 were in humans and 14 were in animals. Figure 1 shows a flow diagram of study selection.

Human studies

The only type of human data retrieved by our search was case reports. We did not find any controlled trials or observational studies.

Case reports

Case reports assessed in this review included 130 patients, ranging in age from 2.5 months to 84 years. Of these patients, 119 survived toxicity. The majority of reports described intentional drug overdose, however, there were two reports of iatrogenic toxicity and four reports of toxicity resulting from a drug–drug interaction. Drug classes most commonly implicated in TICS were CCB (77 cases) and BB (51 cases). Other drugs found in reports of TICS were TCA (11 cases), quetiapine (1 case) and amrinone (1 case). Tables 1–4 list the specific agents involved in each toxicity as well as patient characteristics and outcome. The tables also include a summary of vasopressor therapy and other pharmacologic interventions employed during treatment.

The most commonly used vasopressors were dopamine (76 cases), norepinephrine (53 cases), and epinephrine (52 cases). Less frequently used agents were vasopressin (17 cases), phenylephrine (5 cases), and terlipressin (5 cases). Glucagon was used in 73 cases. Although it is primarily an inotrope, we included dobutamine (22 cases) because it was employed for "pressor-like" effects. We did not include methylene blue in our analysis as Warrick et al. recently published a review on its use in drug-induced shock [133]. Tables 1–4 show that the specific medications and doses utilized varied greatly from case to case. Treatment often involved more than one vasopressor (85/130 cases, 65%) and vasopressors were rarely the only type of pharmacologic treatment employed (7/130 cases, 5%). Commonly used additional agents were: atropine, calcium, insulin, isoproterenol, and sodium bicarbonate. Supportive measures (e.g., fluids, oxygen) were employed ubiquitously, and are not recorded in the summary as they did not represent treatment unique to any individual case.

Table 1. Summary of human case reports of beta blocker toxicity.

Drug	Age and sex	Amount ingested	Co-ingestion	Lab confirmation	Survived?	Vasopressor treatments	Other pharmacologic treatment	Reference #
Propranolol	47 yr F	Unknown (serum level on admission 2462 ng/mL)	None	Y	Y	Dopamine (15 mcg/kg/min), norepinephrine (12 mcg/min)	Atropine (8 mg), isoproterenol (32 mcg/min)	[6]
Acebutolol, labetalol	24 yr F	9600 mg; 7200 mg	Trimipramine	Y	Y	Dopamine (50–200 mcg/kg/min)	Atropine (1 mg), isoproterenol (30–1600 mcg/min)	[7]
Metoprolol	19 yr F	7500 mg	None	N	Y	Epinephrine (0.05–0.1 mg)	Prenalterol (420 mg)	[8]
Esmolol	11 yr F	Received 12.5 mg esmolol over 1–2 mins (iatrogenic)	None	N/A	Y	Epinephrine (2.1 mg)	Atropine (2 mg)	[9]
Metoprolol	42 yr F	Unknown	Phenobarbital and dilantin	N	Y	Dopamine (20–50 mcg/kg/min), dobutamine (20–40 mcg/kg/min), epinephrine (2.5–66 mcg/min, 0.5 mg × 2, 0.25 mg × 12)		[10]
Acebutolol	32 yr F	4000 mg	Alcohol (amount unknown, blood level 3.35 g/L)	Y	Y	Dopamine (10–20 mcg/kg/min)	Isoproterenol (0.3 mcg/kg/min)	[11]
Labetalol	37 yr F	800 mg	None	N/A	Y	Dopamine 20 mcg/kg/min, phenylephrine 67–100 mcg/min	Glucagon 4 mg/h, amrinone 5–15 mcg/kg/min	[12]
Propranolol	20 yr F	2000 mg	Alcohol	Y	Y	Dopamine (0.5–5 mg/min)	Atropine (1 mg), isoproterenol (4–20 mcg/min), glucagon (3 mg bolus, 5 mg/h infusion)	[13]
Propranolol	17 yr F	3880 mg	None	Y	Y	Epinephrine (0.5 mg), dopamine (5–20 mcg/kg/min)	Sodium bicarb (50 mEq), glucose (25 g), naloxone (0.8 mg), atropine (1 mg), calcium chloride (10%, 5 mL), isoproterenol (8 mcg/min), glucagon (3 mg, then 5 mg/h)	[14]
Propranolol	17 yr F	8000 mg	None	Y	Y	Epinephrine (2 mg), dopamine (>25 mcg/kg/min), norepinephrine (>30 mcg/min), dobutamine (>25 mcg/min)	Atropine (1 mg), glucagon (10 mg total in boluses, then 5 mg/h)	[15]
Propranolol	40 yr F	Unknown, up to 4800 mg	None	Y	Y	Epinephrine (1 mg × 2), dopamine (10–15 mcg/kg/min)	Naloxone, isoproterenol (2 mcg/min), glucagon (6 mg, then 2 mg/h)	[16]
Atenolol	20 yr F	1800–2500 mg	HCTZ, fluoxetine, diazepam	Y	Y	Epinephrine (0.4–0.7 mcg/kg/min)	Flumazenil (1 mg), glucagon (5 mg, then 4 mg/h), calcium chloride (1g × 2, then 125 mg/h)	[17]
Labetalol	43 yr F	5600–7000 mg	Prednisone, azathioprine, doxepin, temazepam, arginine	N	Y	Epinephrine (total dose received 174 mg), dopamine (1000 mcg/min), dobutamine (250 mg)	Atropine (0.6 mg), isoprenaline (200 mcg), glucagon (2 mg), calcium (10 mmol)	[18]
Acebutalol	38 yr M	20 g	None	Y	N	Epinephrine (1 mg), dopamine (40–60 mcg/kg/min), dobutamine (80 mcg/kg/min)	Atropine (1 mg), isoproterenol (10 mcg/min)	[19]
Propranolol	31 yr F	3600 mg	Ethanol	Y	Y	Dopamine (5–15 mcg/kg/min)	Diazepam (10 mg), atropine (1 mg), glucagon (3 mg × 2), insulin (20 units), sodium bicarb (8.4%), 20% intralipid (1000 mL)	[20]
Oxprenolol	27 yr F	Unknown, plasma level 9.5 mg/L	None	Y	Y	Dopamine		[21]
Nebivolol	48 yr M	Unknown	Ethanol, possibly diazepam, and cocaine	N	Y	Epinephrine (1 mg × 2)	Calcium (18 mEq), atropine (1 mg × 2), 20% intralipid, insulin (100 units, then 21 units/kg/h)	[22]
Oxprenolol	62 yr M	Unknown, plasma level 3100 ng/mL	Diazepam	Y	Y	Epinephrine (1/1000 3 mL, then infusion)	Isoprenaline, calcium gluconate (20 mL), sodium bicarb (100 mL), atropine (0.6 mg), glucagon (10 mg, then 2 mg/h)	[23]

(*continued*)

Table 1. Continued

Drug	Age and sex	Amount ingested	Co-ingestion	Lab confirmation	Survived?	Vasopressor treatments	Other pharmacologic treatment	Reference #
Sotalol	70 yr M	3000–4000 mg	Enalapril	N	Y	Dopamine (7.5 mcg/kg/min)	Atropine (1 mg × 3), glucagon (3 mg), isoproterenol (4 mcg/min), lidocaine	[24]
Atenolol	39 yr M	1500–2000 mg	Ethanol	N	Y	Dopamine (20 mcg/kg/min), norepinephrine,	Atropine (1 mg), glucagon (12 mg, then 10 mg/h), calcium chloride (3 g), isoproterenol (5 mcg/min)	[25]
Oxprenolol	16 yr F	8000 mg	None	Y	Y	Dopamine (10 mcg/kg/min)	Glucagon (10 mg × 3, then 10 mg/h), isoprenaline (10 mcg/min)	[26]
Propranolol	24 yr F	3120 mg	Ethanol	Y	N	Epinephrine, dopamine, norepinephrine	Isoprenaline, glucagon (4 mg), isoproterenol (1 mg)	[27]
Propranolol	54 yr M	Unknown, up to 2000 mg	Ethanol	N	Y	Dopamine (400–800 mcg/min)	Naloxone, thiamine, atropine (1 mg), glucagon (5 mg, then 5 mg/h)	[28]
Propranolol	20 yr F	2000 mg	Acetaminophen, codeine, doxylamine	Y	Y	Epinephrine (1 mg × 2, then 25 mcg/mL)	Atropine (1.2 mg), isoprenaline (200 mcg bolus, then 20 mcg/min), glucagon (9 mg, 6 mg)	[29]
Carvedilol	54 yr F	1050 mg	Zopiclone	Y	Y	Dopamine (10 mcg/kg/min)	Glucagon (10 mg, then 2 mg/h)	[30]
Atenolol	50 yr M	1000 mg	None	Y	Y	Norepinephrine (13 mcg/min)	Atropine (2 mg × 2), glucagon (1 mg, 2mg × 4, then 1–5 mg/h), isoproterenol (60 mcg/min)	[31]
Nadolol	57 yr F	Unknown, plasma level 1.25 nmol/L	None	Y	Y	Dopamine (10 mcg/kg/min), norepinephrine (16 mcg/kg/min)	Atropine, calcium chloride, glucagon (2 mg, then 2–4 mg/h)	[32]
Labetalol	19 yr F	16 g	None	Y	Y	Dopamine (2 mcg/kg/min)	Furosemide (40 mg)	[33]
Carvediolol	84 yr M	375 mg	Simvastatin	Y	Y	Dopamine (10 mcg/kg/min)	Glucagon (3 mg × 6)	[34]
Metoprolol	55 yr W	10 g	None	Y	Y	Epinephrine	Atropine, calcium gluconate, enoximone (0.5 mg/kg bolus, then 15 mcg/kg/min), glucagon	[35]
Labetalol	25 yr M	6000 mg	Ethanol	N	Y	Dobutamine	Atropine, isoprenaline, glucagon (10 mg, then 4 mg/h)	[36]
Metoprolol	23 yr F	up to 15.2 g	None	N	Y	Epinephrine (600 mcg/h), dopamine (10 mcg/kg/min)	Calcium gluconate, glucagon (1 mg)	[37]
Propranolol	28 yr M	3000 mg	None	N	Y		Atropine (0.4 mg/kg), isoprenaline (0.55–1.1 mcg/kg/min), glucagon (10 mg × 2)	[38]
Propranolol	29 yr F	3200 mg	None	N	Y		Glucagon (7.5 mg bolus, then 5 mg/h)	[39]
Metoprolol	19 yr M	10,000 mg	None	Y	Y		Sodium bicarb, metaraminol (7 mg, 3 mg), glucagon (6 mg), furosemide	[40]
Propranolol	37 yr F	800 mg	Imipramine, diazepam	N	Y		Isoproterenol (2 mg), glucagon (10 mg)	[41]
Atenolol	53 yr F	Unknown	None	Y	Y		Atropine (3.6 mg) glucagon (10 mg × 2), prenalterol (5 mg × 8)	[42]
Propranolol	55 yr F	Unknown	Amitriptyline	N	Y		Naloxone (0.4 mg), atropine (0.6 mg), glucagon (1 mg, 4 mg, 10 mg)	[43]
Propranolol	27 yr F	3200 mg	None	N	Y		Glucagon (7.5 mg, then 2.5 mg/h)	[44]
Oxprenolol	58 yr M	20 mg	None	N	Y		Glucagon (2 mg), atropine (1.2 mg), isoprenaline (5–40 mcg/min), calcium gluconate (10% 10 mL)	[45]

yr: years of age; M: male; F: female; Y: yes; N: no. Doses are listed in the table unless they were not provided by the article. Drugs are listed as they appeared in the article (e.g., "calcium" vs. "Calcium gluconate", "isoproterenol" vs. "isoprenaline").

Table 2. Summary of human case reports of calcium-channel blocker toxicity.

Drug	Age and sex	Amount ingested	Co-ingestion	Lab confirmation	Survived?	Vasopressor treatment	Other pharmacological treatment	References #
Verapamil (SR)	73 yr F	2880 mg	Temazepam 60 mg	Y	Y	Dobutamine (5 mcg/kg/min), dopamine (2–16 mcg/kg/min)	Atropine (2 mg), calcium chloride (1 g), sodium bicarb (54 mEq), glucagon (5 mg, then 2–4 mg/h)	[46]
Diltiazem	73 yr M	4800 mg	None	Y	Y	Dopamine (10–40 mcg/kg/min), epinephrine (1 mg, then 0.2–0.6 mcg/kg/min)	Calcium gluconate (2 g), atropine (1.2 mg), isoprenaline (0.4 mg), glucagon (1 mg × 2),	[47]
Diltiazem (SR)	42 yr F	Unknown, "two handfuls" of 180 mg tablets	None	N	Y	Dopamine (5–50 mcg/kg/min), norepinephrine, dobutamine	Atropine (0.5 mg × 4), calcium chloride (2g × 2), insulin (5 units), glucagon (10 mg)	[48]
Verapamil	22 yr M	Unknown, up to 16,000 mg	None	Y	Y	Dobutamine (32 mcg/kg/min), dopamine (3.5–5 mcg/kg/min), norepinephrine (20 mcg/min)	Calcium chloride (2 g), glucagon (1 mg)	[49]
Verapamil	31 yr M	8000 mg	None	Y	N	Epinephrine (1 mg, then infusion), dopamine	Calcium chloride (2 g × 5), diazepam (5 mg), atropine (2 mg), glucagon (4 mg)	[49]
Verapamil	38 yr F	2400 mg	None	N	Y	Dopamine (5–30 mcg/kg/min), epinephrine (0.8 mcg/kg/min)	Orciprenalin (0.5 mg), calcium gluconate (10%, 20 mL)	[50]
Verapamil (SR)	23 yr M	4800 mg	Cocaine	N	Y	Dobutamine, dopamine	Naloxone, calcium chloride (2 g), isoproterenol, glucagon (5 mg/h)	[51]
Verapamil	16 yr F	8000 mg	None	N	Y	Dopamine (15–20 mcg/kg/min)	Calcium gluconate (2 g), sodium bicarbonate (60 mEq), isoproterenol (2–4 mcg/min), amrinone (6 mcg/kg/min)	[52]
Nifedipine	59 yr M	900 mg	None	N	Y	Dopamine (10–25 mcg/kg/min)	Lidocaine (100 mg), calcium chloride (1 g × 3, then 10 mg/h), atropine (1 mg)	[53]
Nifedipine	50 yr M	620 mg	Mexiletine (12.4 g), nitroglycerine	N	Y	Epinephrine (1 mg, then 0.6 mcg/kg/min), dopamine (>40 mcg/kg/min), phenylephrine (1.3 mcg/kg/min)	Midazolam, atropine (1 mg), calcium gluconate (2 g)	[54]
Verapamil	41 yr M	6800 mg	None	N	Y	Dopamine (5–20 mcg/kg/min), norepinephrine (2–4 mcg/min)	Calcium chloride (1 g)	[55]
Amlodipine	42 yr M	1000 mg	Chlorthalidone (3000 mg), mefenamic acid (3000 mg), ethanol	Y	Y	Dobutamine, norepinephrine, terlipressin	Calcium gluconate, insulin	[56]
Verapamil	22 yr F	2400 mg	None	Y	Y	Dopamine	Atropine (0.5 mg), isoproterenol, calcium chloride (2 g), insulin (5 units, then 0.1 mg/kg/h)	[57]
Amlodipine	11 mo. M	10–45 mg	Benazepril (40–180 mg)	Y	N	Epinephrine (0.1 mg × 3, then 0.65 mg/h)	Atropine (0.2 mg × 2), sodium bicarb (20 mEq × 2), calcium gluconate (100 mg), insulin (4 units, then 10 units/h)	[58]
Lercanidipine (SR)	49 yr M	560 mg	None	N	Y	Norepinephrine (0.235 mcg/kg/min)	Calcium chloride (10%, 10 mL), insulin (0.5 units/kg/h), glucagon (10 mg),	[59]
Amlodipine, Nitrendipine	34 yr F	300 mg, 600 mg	None	Y	Y	Dopamine (4.9 mcg/kg/min), norepinephrine (60 mcg/kin), angiotensin II (5–15 mcg/min)	Calcium gluconate (1 g)	[60]
Amlodipine	63 yr F	70 mg	Oxazepam (plasma level 5.25 ug/mL)	Y	N	Dopamine (15 mcg/kg/min), norepinephrine (0.3 mcg/kg/min, 400–600 ng/kg/min), epinephrine (50 mg, then 20 mg/h)	Calcium gluconate (2 g), insulin (4 units/h), glucagon (10 mg/h)	[61]
Amlodipine	50 yr F	770 mg	Losartan (16.64 g)	N	Y	Norepinephrine (0.1–0.25 mcg/kg/min), vasopressin (0.02 units/h), epinephrine (0.24 mcg/kg/min)	Metaraminol, calcium gluconate (10%, 20 mL then 3 mL/kg/h), glucagon (10 mg bolus, then 0.12 units/h), insulin (800 units/h)	[62]

(*continued*)

Table 2. Continued

Drug	Age and sex	Amount ingested	Co-ingestion	Lab confirmation	Survived?	Vasopressor treatment	Other pharmacological treatment	References #
Diltiazem (SR)	16 yr F	12 g	None	Y	Y	Epinephrine (0.1–0.4 mcg/kg/min, 50 mg total), norepinephrine (1 mg/kg/h)	Glucagon (1 mg), calcium chloride (1 g), isoprenaline	[63]
Felodipine	61 yr M	140 mg	None	N	Y	Epinephrine (20 mg/h), norepinephrine (15 mg/h), terlipressin (0.05 mcg/kg/min)	Calcium gluconate (10%, 10 mL)	[64]
Amlodipine	16 yr F	500 mg	None	N	Y	Dopamine (10 mcg/kg/min), norepinephrine (2 mcg/kg/min)	Insulin (0.5 units/kg/h), levosimendan	[65]
Diltiazem	38 yr F	900 mg	Ethanol	Y	Y	Dopamine (7.5 mcg/kg/min)	Calcium gluconate (10 g), atropine (0.5 mg)	[66]
Diltiazem	50 yr M	5880 mg	Ethanol	N	Y	Dopamine (2.5–5 mcg/kg/min)	Calcium gluconate (10%, 20 mL)	[67]
Amlodipine	25 yr F	900 mg	Olmesartan (3600 mg), HCTZ (1125 mg)	N	Y	Norepinephrine (180 mcg/min), dopamine (50 mcg/kg/min), vasopressin (0.06 units/min), phenylephrine (200 mcg/min)	Glucagon (6.6 mg), calcium chloride (infusion), insulin (8–40 units/h)	[68]
Nifedipine	54 yr F	300 mg	Ethanol	N	Y	Dopamine (400 mg)	Calcium gluconate (10%, 20 mL)	[69]
Verapamil	73 yr F	3600 mg	Suicide attempt, arrived to ED 1.5 hours after. BP 95/41 HR 70 bpm.	Y	Y	Dopamine (10–20 mcg/kg/min), norepinephrine (0.4 mg/kg/min)		[70]
Verapamil (SR)	49 yr F	5800 mg	Captopril (1500 mg), glyburide (65 mg)	N	Y	Dopamine (18 mcg/kg/min), norepinephrine (35 mcg/min)	Atropine, sodium bicarb, calcium chloride (13 g), insulin (0.1 units/kg bolus, then 0.25 units/kg/h)	[71]
Amlodipine	11 mo. M	90 mg	None	N	Y	Dopamine, epinephrine	Calcium gluconate (0.5 mEq/kg/h), insulin (0.5 units/kg/h)	[72]
Nifedipine	13 yr F	Unknown, up to 180 mg	Clonidine (unknown, up to 0.6 mg)	N	Y	Dopamine (5 mcg/kg/min)	Atropine (1 mg), calcium chloride (500 mg), glucagon (5 mg, then 3 mg/h)	[73]
Amlodipine	24 yr F	280 mg	None	N	Y	Dopamine, norepinephrine	Calcium gluconate (10%, 30 mL, then 10 mL/h), glucagon (3 mg, then 3 mg/h), insulin (25 units, then 20 units/h)	[74]
Verapamil	78 yr F	80 mg	None	Y	Y	Dobutamine (40 mcg/kg/min), norepinephrine 15 mcg/min)	Calcium gluconate (10%, 20 mL)	[75]
Verapamil	40 yr M	Unknown, up to 3600 mg	Ethanol, carbamazepine, oxycodone	Y	Y	Norepinephrine (10–120 mcg/min), epinephrine (5–30 mcg/min), vasopressin (0.03 units/min), phenylephrine (225 mcg/min)	20% lipids (200 mL), glucagon (5 mg, then 5 mg/h), calcium chloride (4 g, then 0.2 mL/kg/h), insulin (1–1.6 units/kg/h)	[76]
Diltiazem	45 yr M	4200 mg	Clinoril	Y	Y	Dopamine (28–30 mcg/kg)	Calcium chloride (10%, 4 g), atropine (1 mg)	[77]
Nifedipine (ER)	2 yr F	200 mg	None	Y	N	Epinephrine (10.8 mg total)	Atropine (2.7 mg), calcium gluconate (940 mg total), glucagon (1 mg), amrinone (1300 mg), sodium bicarb (12 mEq)	[78]
Nifedipine (ER)	14 mo. F	10 mg	None	Y	N	Epinephrine (11.5 mg total), norepinephrine (0.3 mg)	Calcium gluconate (940 mg), calcium chloride (500 mg), glucagon (1.5 mg), sodium bicarb (40 mEq)	[78]
Diltiazem (CD)	18 yr F	14.94 g	None	Y	Y	Dopamine (20–50 mcg/kg/min), epinephrine (2 mg), norepinephrine	Atropine (4 mg), sodium bicarb (100 mEq), calcium gluconate (4 g), glucagon (5 mg)	[79]
Nifedipine (ER)	59 yr M	Unknown, up to 2700 mg	Ethanol	N	Y	Norepinephrine (4–96 mcg/min)	Calcium gluconate (20 mL), glucagon (1 mg × 4, then 4 mg/h)	[80]
Verapamil (SR)	33 yr M	12 g	None	N	N	Dopamine (10–20mcg/kg/min), epinephrine (2–20 mcg/kg/min)	Atropine (1 mg), calcium chloride (6 g), isoproterenol (>5 mcg/kg/min)	[81]

(*continued*)

Table 2. Continued

Drug	Age and sex	Amount ingested	Co-ingestion	Lab confirmation	Survived?	Vasopressor treatment	Other pharmacological treatment	References #
Amlodipine	13 yr W	300 mg	Ethanol, barbituates	N	Y	Norepinephrine (0.1–0.4 mcg/kg/min), epinephrine (0.1 mcg/kg/min)		[82]
Amlodipine	34 yr M	Unknown	Diazepam, temazepam, citalopram, anti-freeze	N	Y	Norepinephrine (80 mcg/min), epinephrine (42 mcg/min), vasopressin (0.053 units/min)	Intralipid (12 mL/kg)	[83]
Amlodipine	58 yr M	500 mg	Ethanol, ramipril, doxazosin	N	Y	Norepinephrine (1.33 mg/min), vasopressin (4 units/h)	Metaraminol (30 mg/h), calcium gluconate (10%, 10 mL), insulin (0.5–10 units/kg/h), ketamine (100 mg, then 500 mg/h)	[84]
Nifedipine (ER)	14 yr F	350 mg	None	N	Y	Dopamine (10–20 mcg/kg/min), norepinephrine (0.3 mcg/kg/min)	Calcium chloride (10%, 18.3 mg/kg)	[85]
Diltiazem	17 yr F	1200 mg	Dipyridamole	N	Y	Epinephrine (1 mg), dopamine (10 mcg/kg/min)	Atropine (0.6 mg), calcium chloride (1 g), isoprenaline (4 mg/h)	[86]
Verapamil (SR)	41 yr F	19.2 g	None	N	Y	Norepinephrine (0.3–0.75 mcg/kg/min), epinephrine (0.02–0.04 mcg/kg/min), vasopressin (0.04–0.05 units/min)	Isoproterenol, calcium, insulin (40 units/h), intralipid 20% (100 mL, then 0.5 mL/kg/h)	[87]
Verapamil	17 yr F	Unknown	None	Y	N	Dopamine (1 mg/min)	Atropine (1.8 mg), isoprenaline (200 mcg, then 270 mcg/min), calcium gluconate (10%, 20 mL)	[88]
Verapamil	39 yr F	Unknown, at least 1200 mg	None	Y	Y	Dopamine (2.5 mcg/kg/min), dobutamine (40 mcg/kg/min)	Glucagon (10 mg), prenalterol (10 mg), atropine (1.2 mg), calcium gluconate (10%, 240 mL), isoprenaline (5 mg, then 2–15 mcg/min)	[89]
Nifedipine (SR)	57 yr F	Unknown	"Sleeping pills"	N	N	Epinephrine (6 mg/h), norepinephrine (9.6 mg/h), vasopressin (2.4 units/h)	Calcium, glucagon (5 mg), insulin (100 units/h)	[90]
Amlodipine	42 yr M	500 mg	None	N	Y	Dopamine (20 mcg/kg/min), norepinephrine (20 mcg/min), terlipressin (2–3 mcg/min), epinephrine (20 mcg/min)	Calcium gluconate (3 g), glucagon (5 mg, then 5 mg/h), insulin	[91]
Amlodipine (ER)	34 yr F	30 mg	None	N	Y	Dopamine (20 mcg/kg/min), dobutamine (10 mcg/kg/min), norepinephrine (14 mcg/kg/min)	Glucagon (5 mg), insulin (0.5 units/kg/h)	[92]
Diltiazem (ER)	48 yr M	Unknown	None	N	Y	Dopamine (20 mcg/kg/min), dobutamine (10 mcg/kg/min)	Calcium gluconate (4 g), insulin (0.5 units/kg/h)	[92]
Amlodipine	50 yr M	500 mg	Lisinopril, HCTZ	N	Y	Dopamine (30 mcg/kg/min), norepinephrine (60 mcg/kg/min), vasopressin (6 units/h), epinephrine (5 mcg/min)	Calcium gluconate, glucagon, insulin (2 units/kg/h), fat emulsion, methylene blue	[93]
Verapamil	11 mo. F	400 mg	None	N	Y	Dopamine (13 mcg/kg/min)	Phenobarbital (110 mg total), calcium chloride (10%, 2 mL), isoproterenol (1.2 mcg/kg/min)	[94]
Nifedipine	14 mo. F	800 mg	None	N	Y	Epinephrine, dopamine (5 mcg/kg/min)	Atropine, sodium bicarb, calcium chloride	[95]
Verapamil	41 yr M	4800–6400 mg	Diclofenac, thiamine, cyanocobalamin, pyridoxine, timolol	Y	Y	Epinephrine (12.5 mg, then 2.8 mcg/kg/min), dopamine (1.67–3 mcg/kg/min)	Atropine (9.5 mg, 8.5), orciprenaline (2 mg), glucagon (30 mg), calcium (11.5 mmol), theophylline (0.48 g)	[96]
Verapamil	18 yr M	3200 mg	TMP–SMX, dipyridamole, amoxicillin	Y	Y	Dopamine (95 mcg/kg/min)	Isoproterenol (0.2–0.5 mcg/kg/min), atropine (1 mg), calcium gluconate (10%, 0.5 mg), glucagon (1 mg), fentanyl, lorazepam	[97]
Nifedipine	27 yr M	900 mg	Furosemide	N	Y		Calcium chloride (1 g × 2), glucagon (0.5 mg, 10 mg)	[98]

(*continued*)

Table 2. Continued

Drug	Age and sex	Amount ingested	Co-ingestion	Lab confirmation	Survived?	Vasopressor treatment	Other pharmacological treatment	References #
Diltiazem (ER)	50 yr M	6700 mg	HCTZ	N	Y		Calcium gluconate (1 g 10% bolus, then 4.65 mEq infusion), atropine (0.5 mg × 2), glucagon (10 mg)	[99]
Verapamil (SR)	30 yr F	3600 mg	None	N	Y		Calcium chloride (2 g), atropine (1 mg), glucagon (14 mg, then 5 mg/h), amrinone (1 mg/kg bolus, then 6 mcg/kg/min)	[100]
Verapamil (SR)	79 yr F	480 mg QD	Erythromycin	N	Y	Dopamine	Calcium	[101]
Verapamil	53 yr M	4800 mg	Allopurinol, ethanol	N	Y	Dobutamine 20 mcg/kg/h	Calcium chloride (6 g), atropine (2 mg), isoprenaline (100 mcg),	[102]
Verapamil (SR)	76 yr F	180 mg QD	Telithromycin	N	Y	Dopamine (17 mcg/kg/min), norepinephrine (3 mcg/kg/min)		[103]
Amlodipine	68 yr M	300 mg	Metformin, ethanol	Y	Y	Norepinephrine (13–80 mcg/min)	Glucagon (5 mg), calcium gluconate, insulin (80 units, then up to 640 units/h), dextrose (50% 80 mL), sodium bicarb, intralipid (20%), L–carnitine (6 g, then 1 g every 4 h)	[104]
Amlodipine	43 yr M	560 mg	Ethanol, citalopram, fluoxetine, perindopril, ASA, APAP	N	Y	Norepinephrine (0.83 mcg/kg/min), epinephrine (0.16 mcg/kg/min)	Glucagon (10 mg), calcium gluconate (10% 30 mL), metaraminol (2 mg, then 1 mcg/kg/min)	[105]
Amlodipine	20 yr F	420 mg	None	N	Y	Epinehprine (5 mg/hr)	Succinylcholine (90 mg), hypnomidate, fentanyl (250 mcg), calcium gluconate (10% 20 mL, then 2g/h), insulin (1 unit/kg bolus, then 0.5 units/kg infusion), dextrose (50 g)	[106]
Diltiazem	71 yr F	145 mg IV	None	N	Y	Dopamine (5 mg/kg/min)	Calcium chloride (1g), glucaon (5 mg, then 2 mg/h)	[107]
Felodipine	16 yr F	280 mg	Doxazosin, cinnarizine, bendroflumethiazide, flucoxacillin, ethanol	N	Y	Epinephrine (2 mg then 0.62 mcg/kg/min), norepinephrine (0.62 mcg/min), vasopressin (0.025 units/kg/h)	Calcium chloride (10% 10 mL), ILE (20% 15 mL/kg/h), glucagon (10 mg, 5 mg)	[108]

yr: years of age; mo: months of age; M: male; F: female; Y: yes; N: no. Doses are listed in the table unless they were not provided by the article. Drugs are listed as they appeared in the article (e.g., "calcium" vs. "calcium gluconate", "isoproterenol" vs. "isoprenaline").

Table 3. Summary of human case reports in dual beta blocker/calcium-channel blocker toxicity.

Drug	Age and sex	Amount ingested	Coingestion	Lab confirmation	Survived?	Vasopressor treatments	Other pharmacologic treatments	Reference #
Atenolol, nifedipine, lacidipine	36 yr M	10,000 mg, unknown, unknown	Alcohol, sertraline, fluoxetine	Y	Y	Dopamine (50–300 mcg/kg/min), epinephrine (2.3–15 mcg/kg/min), vasopressin (0.03 units/min)	Sodium bicarb, calcium chloride (40 mL), insulin (0.7–1.5 units/kg/h), glucagon (5 mg, then 5 mg/h)	[109]
Bisoprolol, amlodipine	59 yr M	560 mg, 300 mg	Chlorothiazide	N	Y	Dobutamine (20 mcg/kg/min), dopamine (20 mcg/kg/min), norepinephrine (1 mcg/kg/min), terlipressin (1 mg BID)	Milrinone (1 mcg/kg/min), glucagon (0.2 mg/h)	[110]
Bisoprolol, diltiazem	32 yr M	200 mg, 5040 mg	Simvastatin	N	Y	Epinephrine (1.4 mcg/kg/min), norepinephrine (1.4 mcg/kg/min), dobutamine (10 mcg/kg/min), vasopressin (0.03 units/min),	Calcium gluconate (10%, 30 mL), 20% fat emulsion (1.5 mL/kg), insulin (0.25 mcg/kg/h), glucagon (50–150 mcg/kg/h), methylene blue (2 mg/kg)	[111]
Atenolol, amlodipine	69 yr F	Unknown	None	N	Y	Norepinephrine (1 mcg/kg/min), dopamine (20 mcg/kg/min), vasopressin (0.8 units/min)	Calcium chloride, insulin, glucagon, methylene blue (1 mg/kg bolus, then infusion 1 mg/kg/h)	[112]
Bisoprolol, diltiazem (SR)	57 yr F	Unknown	Candesartan/HCTZ, acetaminophen/ caffeine/codeine, dimenhydrinate, ethanol	Y	Y	Norepinephrine, vasopressin, dopamine	Calcium chloride (3 g), lipid emulsion (1.5 mL/kg, then 0.25 mL/kg/min), glucagon (5 mg × 2, then 5 mg/h)	[113]
Atenolol, nifedipine	45 yr F	Unknown	None	Y	Y	Epinephrine (0.8–1 mcg/kg/min)	Atropine, calcium gluconate (7.5 mg), insulin (5 units/h), glucagon (7.5 mg/h)	[114]
Atenolol, diltiazem (SR)	19 yr M	Unknown, Unknown	Venlafaxine, irbesartan/ HCTZ, clozapine, setraline	Y	Y	Epinephrine (200 mcg, then 25 mcg/min), norepinephrine (20 mcg/min), vasopressin (0.04 units/min)	Calcium gluconate (3 g, then infusion), sodium bicarb (100 mmol), metaraminol (5 mg), atropine, glucagon (3 mg)	[115]
Bisoprolol, amlodipine, nifedipine	66 yr M	450 mg, 300 mg, 600 mg	Doxazosin, torsamide, aspirin, ibuprofen	Y	Y	Norepinephrine (10 mcg/kg/min), dobutamine (10 mcg/kg/min), vasopressin (0.03 units/min)	Calcium gluconate (10%, 40 mL), insulin (1 unit/kg bolus, then 1 unit/kg/h), lipid emulsion 20% (250 mL), glucagon (5 mg × 3)	[116]
Metoprolol, verapamil	54 yr M	Unknown, Toxicity due to concomittant iatrogenic metoprolol and verapamil	None	N	Y	Epinephrine (30 mcg, then 2 mcg/min), dopamine 10 mcg/kg/min, dobutamine 5 mcg/kg/min	Atropine (1 mg), calcium chloride, glucagon (1, 2, 3 mg boluses then 10 mg/h)	[117]
Metoprolol, verapamil (SR)	78 yr F	100 mg, 240 mg	None	N	Y	Dobutamine (30 mcg/kg/min), dopamine (30 mcg/kg/min)	Atropine 4 mg, calcium chloride	[118]
Metoprolol, nifedipine	45 yr F	4200 mg, 1120 mg	Prazosin	Y	Y		Calcium chloride (10% 10 mL), insulin 6 units/h, dextrose 6 g/h, glucagon (3 mg, 6 mg, then 9 mg/h)	[119]

yr : years of age; mo: months of age; M: male; F: female; Y: yes; N: no. Doses are listed in the table unless they were not provided by the article. Drugs are listed as they appeared in the article (e.g., "Calcium" vs. "calcium gluconate", "isoproterenol" vs. "isoprenaline").

Table 4. Summary of human case reports of other toxicities (tricyclic antidepressants, quetiapine, and amrinone).

Drugs	Age and sex	Amount ingested	Coingestion	Laboratory confirmation	Survived?	Vasopressor treatments	Other pharmacologic treatments	Reference #
Dothiepin	36 yr F	Unknown, serum level 2.5 mg/L	None	Y	Y	Epinephrine (2 mg/h), dobutamine (3–5 mcg/kg/min), dopamine (2.5 mcg/kg/min)	Diazepam, etomidate, glucagon (1 mg, 2 mg, 10 mg × 2)	[120]
Amitriptyline, imipramine	47 yr F	Unknown	Ethanol	Y	Y	Dopamine (16 mcg/kg/min), norepinephrine (15 mcg/min)	Physostigmine (2 mg), dextrose (25 g), naloxone (0.4 mg), sodium bicarb 50 mEq	[121]
Amitriptyline	41 yr F	11.25 g	Diclofenac	Y	Y	Epinephrine (1 mg × 6, then 1 mcg/kg/min), norepinephrine (2 mcg/kg/min), terlipressin (1 mg)	Amiodarone 150 mg, sodium bicarb (8.4%, 200 mL)	[122]
Amitriptyline	56 yr M	Unknown	None	N	Y	Norepinephrine (20 mcg/min), vasopressin (0.04 units/min)	Sodium bicarb (400 mEq), lorazepam (48 mg total), lidocaine (3 mg/min), midazolam (5 mg)	[123]
Amitriptyline	14 yr F	1050 mg	None	Y	Y	Dopamine 10 mcg/kg/min, norepinephrine 8 mcg/kg/min	Diazepam (4 mg), physostigmine (2 mg), phenobarbital (100 mg), magnesium sulfate (250 mg/kg)	[124]
Amitriptyline	37 yr F	750 mg	Perphenazine	Y	Y	Dopamine (10–30 mcg/kg/min)	Physostigmine (4 mg × 2), lidocaine (100 mg, then 4 mg/min), sodium bicarb (50 mEq)	[125]
Nortriptyline	52 yr F	5000 mg	None	Y	Y	Norepinephrine	Sodium bicarb (44.6 mEq), midazolam (1 mg, then 2 mg/h)	[126]
Nortriptyline	29 yr F	8 g	None	N	Y	Domapine (20 mcg/kg/min), norepinephrine (22 mcg/min)	Sodium bicarb (8.4%, 200 mL), NaCl (7.5% 200 mL)	[127]
Amitriptyline	30 yr F	up to 5000 mg	None	N	Y	Dopamine		[128]
Amitriptyline	65 yr F	Unknown	Citalopram	Y	Y	Epinephrine (1 mg), norepinephrine (8–40 mcg/min), vasopressin (4 units/h)	Dextrose 50%, insulin (10 units, 80 units, then up to 600 units/h), glucagon (6.5 mg)	[129]
Amitriptyline	77 yr M	Unknown	None	Y	Y	Dopamine 10 ug/kg/min	Isoprenaline, prenalterol (10 mg, 5 mg, 1.4 mcg/kg/min), hydrocortisone (1 g), insulin (12 units), digoxin (0.5 mg)	[130]
Amrinone	40 yr F	Unknown	None	Y	Y	Epinephrine (2.5 mg), norepinephrine (0.7 mcg/kg/min)		[131]
Quetiapine	2.5 mo F	180–198 mcg/kg/min IV	N/A	Y	N	Epinephrine (0.44–5 mcg/kg/min, then 10 mcg/kg bolus × 3), dobutamine (30 mcg/kg/min), phenylephrine (20 mcg/kg bolus, then 15 mcg/kg/min infusion)	Calcium chloride, sodium bicarb	[132]

yr: years of age; mo: months of age; M: male; F: female; Y: yes; N: no. Doses are listed in the table unless they were not provided by the article. Drugs are listed as they appeared in the article (e.g., "calcium" vs. "calcium gluconate", "isoproterenol" vs. "isoprenaline").

Tables 5–8 list the effectiveness of each individual vasopressor in improving hemodynamic function (BP and HR), following a format created by Olson et al. in their review on CCB toxicity [5]. This format was chosen as it provided a consistent way to evaluate and record the subjective, heterogeneous data provided by the case reports. Clinical responses were grouped into one of four categories: detrimental (−), not effective (0), partially effective (+) or effective (++). Interventions were deemed detrimental if they caused clinical deterioration that could not otherwise be attributed to the usual course of toxicity alone. Interventions in the not effective category had no appreciable clinical effect. Included in this group are treatments after which the patient continued to deteriorate clinically consistent with the course of intoxication. Partially effective interventions only partly reversed the negative cardiovascular manifestations of toxicity, fully reversed only one aspect (e.g., HR or BP), or only reversed cardiovascular toxicity in combination with other agents. Effective interventions were those that fully reversed all of the major cardiovascular manifestations of toxicity. Table 9 shows a summary of each vasopressor's overall effectiveness (in all overdose types).

Table 5. Summary of the effectiveness of vasopressors and glucagon in improving hemodynamic function in beta blocker toxicity.

	−	0	+	++
Catecholamine vasopressors				
Dobutamine		10, 15, 18, 36	19	
Dopamine		6, 7, 10, 13, 14, 15, 16, 18, 19, 20, 26, 27, 32	7, 11, 12, 25, 27, 28, 30, 33, 34	21
Epinephrine		9, 10, 14, 15, 16, 18, 19, 23, 27, 29, 35	8, 12, 17, 22, 35	10, 18
Norepinephrine		15, 31, 32	25, 27	6
Phenylephrine			12	
Non-catecholamine vasopressors				
Vasopressin				
Other				
Glucagon		15, 18, 20, 24, 26, 27, 29, 31, 42, 43, 45	12, 14, 16, 17, 25, 26, 28, 30, 34, 35, 40	13, 23, 31, 32, 36, 37, 38, 39, 41, 43, 44

Format adapted from Olson et al. [5]. Clinical responses were grouped into four categories: effective (++), partially effective (+), not effective (0), or detrimental (−). Effective interventions fully reversed all major cardiovascular manifestations of toxicity. Interventions listed here are those that were thought to be primarily responsible for the patient's clinical recovery at that time. Partially effective interventions may have: (1) partially improved cardiovascular function, but did not return it to normal, (2) only restored one parameter to normal, or (3) restored cardiovascular status to normal only in conjunction with other treatments. Interventions listed as not effective were those that either did not produce any appreciable clinical effect or resulted in the patient continuing to deteriorate in a manner consistent with the course of BB intoxication. Detrimental interventions caused clinical deterioration that could not be attributed to the normal course of BB toxicity alone. Interventions can appear in more than one category if they were unsuccessful at one dose but successful at another. Numbers on the chart correspond to article reference number.

Table 6. Summary of the effectiveness of vasopressors and glucagon in improving hemodynamic function in calcium-channel blocker toxicity.

	−	0	+	++
Catecholamine vasopressors				
Dobutamine		46, 49, 56, 75, 89, 92(1,2)	48, 51, 102	
Dopamine	46	47, 48, 49(2), 50, 52, 53, 55, 60, 61, 65, 68, 70, 71, 72, 73, 74, 77, 79, 81, 85, 86, 88, 89, 91, 92(1,2), 93, 96	49(1), 51, 53, 54, 57, 66, 67, 69, 77, 94, 96, 97, 101, 107	95
Epinephrine		49(2), 54, 58, 61, 62, 63, 64, 72, 76, 78(1,2), 79, 81, 82, 83, 86, 87, 91, 93, 96, 105, 106, 107	54, 63, 90, 96, 107	47, 50
Norepinephrine		56, 60, 61, 62, 64, 65, 68, 71, 74, 75, 76, 78(2), 79, 80, 82, 83, 84, 87, 91, 92(1), 93, 104, 105	48, 49(1), 55, 59, 63, 68, 70, 85, 90, 107	
Phenylephrine		76	54, 68	
Non-catecholamine vasopressors				
Angiotensin II				60
Vasopressin		62, 76, 83, 84, 87, 93	68, 90, 107	
Terlipressin		91		56, 64
Other				
Glucagon		47, 48, 49(2), 51, 61, 62, 63, 73, 74, 76, 78(1,2), 79, 89, 91, 92(1), 93, 96, 97, 100, 104, 107, 108	49(1), 59, 68, 80, 90, 99, 105	46, 98, 107

Format adapted from Olson et al. [5]. Clinical responses were grouped into four categories: effective (++), partially effective (+), not effective (0), or detrimental (−). Effective interventions fully reversed all major cardiovascular manifestations of toxicity. Interventions listed here are those that were thought to be primarily responsible for the patient's clinical recovery at that time. Partially effective interventions may have: (1) partially improved cardiovascular function, but did not return it to normal, (2) only restored one parameter to normal, or (3) restored cardiovascular status to normal only in conjunction with other treatments. Interventions listed as not effective were those that either did not produce any appreciable clinical effect or resulted in the patient continuing to deteriorate in a fashion consistent with the course of BB intoxication. Detrimental interventions caused clinical deterioration that could not be attributed to the normal course of BB toxicity alone. Interventions can appear in more than one category if they were unsuccessful at one dose but successful at another. Numbers on the chart correspond to article reference number.

Table 7. Summary of the effectiveness of vasopressors and glucagon in improving hemodynamic function in dual beta blocker/calcium-channel blocker toxicity.

	–	0	+	++
Catecholamine vasopressors				
Dobutamine		110, 116, 118	111, 117	
Dopamine		109, 110, 112, 113, 118	117	
Epinephrine		109	111, 114, 115, 117	
Norepinephrine		110, 112, 113	111, 115, 116	
Phenylephrine				
Non-catecholamine vasopressors				
Vasopressin		109, 112, 113	111, 115, 116	
Terlipressin			110	
Other				
Glucagon		109, 110, 112, 113, 116	111, 114, 115, 117, 119	

Format adapted from Olson et al. [5]. Clinical responses were grouped into four categories: effective (++), partially effective (+), not effective (0), or detrimental (−). Effective interventions fully reversed all major cardiovascular manifestations of toxicity. Interventions listed here are those that were thought to be primarily responsible for the patient's clinical recovery at that time. Partially effective interventions may have: (1) partially improved cardiovascular function, but did not return it to normal, (2) only restored one parameter to normal, or (3) restored cardiovascular status to normal only in conjunction with other treatments. Interventions listed as not effective were those that either did not produce any appreciable clinical effect or resulted in the patient continuing to deteriorate in a fashion consistent with the course of BB intoxication. Detrimental interventions caused clinical deterioration that could not be attributed to the normal course of BB toxicity alone. Interventions can appear in more than one category if they were unsuccessful at one dose but successful at another. Numbers on the chart correspond to article reference number.

Table 8. Summary of the effectiveness of vasopressors and glucagon in improving hemodynamic function in tricyclic antidepressant, quetiapine, and amrinone toxicities.

	–	0	+	++
Catecholamine vasopressors				
Dobutamine		132[A]	120	
Dopamine		121, 127, 128	120, 124, 145, 130	
Epinephrine		129, 131[Q], 132[A]	120, 122	
Norepinephrine			122, 126	121, 124
Phenylephrine		132[A]		
Non-catecholamine vasopressors				
Vasopressin		129		123
Terlipressin				122
Other				
Glucagon		129	120	

Format adapted from Olson et al. [5]. Clinical responses were grouped into four categories: effective (++), partially effective (+), not effective (0), or detrimental (−). Effective interventions fully reversed all major cardiovascular manifestations of toxicity. Interventions listed here are those that were thought to be primarily responsible for the patient's clinical recovery at that time. Partially effective interventions may have: (1) partially improved cardiovascular function, but did not return it to normal, (2) only restored one parameter to normal, or (3) restored cardiovascular status to normal only in conjunction with other treatments. Interventions listed as not effective were those that either did not produce any appreciable clinical effect or resulted in the patient continuing to deteriorate in a manner consistent with the course of BB intoxication. Detrimental interventions caused clinical deterioration that could not be attributed to the normal course of BB toxicity alone. Interventions can appear in more than one category if they were unsuccessful at one dose but successful at another. Numbers on the chart correspond to article reference number. Q: quetiapine toxicity; A: amrinone toxicity; and all others are TCA toxicities.

In respect to the most commonly used vasopressors, dopamine was the only one noted to have a detrimental effect on hemodynamic status (1 case). It was ineffective (49/76 cases, 64%) more often than it was partially effective (28/76 cases, 37%) or fully effective (2/76 cases, 3%). The next most commonly used vasopressors, norepinephrine, and epinephrine, were also ineffective (33/53 cases, 62% and 38/52 cases, 73%, respectively) more often than partially effective (17/53 cases, 32% and 16/52 cases, 31%, respectively), or fully effective (3/53 cases, 6% and 4/52 cases, 8%, respectively). Glucagon too was more often ineffective (40/73 cases, 55%) than partially effective (24/73 cases, 33%) or fully effective (14/73 cases, 19%).

Table 9 illustrates that the commonly used vasopressors (dopamine, norepinephrine, and epinephrine) were partially effective in about one-third of the cases in which they were used (31–37%), and were fully effective in <10% of cases. Commenting on the effectiveness of the remaining vasopressors is difficult, as they were studied in less than half as many cases. Table 9 also summarizes their overall effectiveness.

Table 9. Overall effectiveness of each vasopressor and glucagon in all human case reports of toxin-induced cardiogenic shock.

Agent	–	0	+	++
Dopamine 76 cases	1 (1%)	49 (64%)	28 (37%)	2 (3%)
Norepinephrine 53 cases	0 (0%)	33 (62%)	17 (32%)	3 (6%)
Epinephrine 52 cases	0 (0%)	38 (73%)	16 (31%)	4 (8%)
Dobutamine 22 cases	0 (0%)	15 (68%)	7 (32%)	0 (0%)
Vasopressin 17 cases	0 (0%)	10 (59%)	6 (35%)	1 (6%)
Phenylephrine 5 cases	0 (0%)	2 (40%)	3 (60%)	0 (0%)
Terlipressin 5 cases	0 (0%)	1 (20%)	1 (20%)	3 (60%)
Glucagon 73 cases	0 (0%)	40 (55%)	24 (33%)	14 (19%)

Format adapted from Olson et al. [5]. Clinical responses were grouped into four categories: effective (++), partially effective (+), not effective (0), or detrimental (−). Effective interventions fully reversed all major cardiovascular manifestations of toxicity. Interventions listed here are those that were thought to be primarily responsible for the patient's clinical recovery at that time. Partially effective interventions may have (1) partially improved cardiovascular function, but did not return it to normal, (2) only restored one parameter to normal, or (3) restored cardiovascular status to normal only in conjunction with other treatments. Interventions listed as not effective were those that either did not produce any appreciable clinical effect or resulted in the patient continuing to deteriorate in a fashion consistent with the course of BB intoxication. Detrimental interventions caused clinical deterioration that could not be attributed to the normal course of BB toxicity alone. Interventions can appear in more than one category if they were unsuccessful at one dose but successful at another.

Animal studies

We included 14 controlled animal studies examining vasopressors in TICS in this review. Seven studies were models of BB toxicity (three on pigs, two on dogs, and two on rats) and seven studies were models of CCB toxicity (five on dogs and two on pigs).

Studies on BB toxicity

Table 10 summarizes the animal studies involving BB toxicity. Each study evaluated propranolol toxicity. Propranolol infusions used to achieve and maintain toxicity ranged from 0.125 to 0.5 mg/kg/min, and one study used a single 10 mg/kg bolus. In these studies, vasopressors were compared to treatment with insulin (three studies) and/or glucagon (four studies) [134–139]. Vasopressors used included epinephrine (three studies), vasopressin (two studies),

Table 10. Summary of animal studies examining the effectiveness of vasopressors in beta blocker toxicity.

Reference	Design	Animal	Toxicity	Treatment	Results: survival	Results: hemodynamics
[133]	Randomized, controlled	Pig ($n = 15$)	Propranolol	INS, INS + NE, NE + E	Survival time significantly decreased for NE + E (0.1 h) compared to INS (1.9 h) and INS + NE (2.9 h).	Mean decrease in PBrO2 lower for INS + NE (0.4 mmHg/h) compared to INS alone (10.4 mmHg/h)
[134]	Randomized, controlled	Pig ($n = 10$)	Propranolol	INS vs. V + E	Survival rate significantly decreased for V/E vs. INS ($p < 0.001$). 5/5 INS pigs survived the 4 hour duration of the experiment while 0/5 V + E pigs survived. All V + E pigs died within 90 minutes.	INS: maintenance of MAP over time, increase in HR, decrease in SVR, dramatic increase in CO. V + E: increase in MAP 30 min into resuscitation, followed by significant decrease until death. SVR similar; peaked at 30 min, fell until death. CO and HR fell continuously after onset. Vasopressor effects of V/E depress CO and contribute to death
[135]	Randomized, controlled	Pig ($n = 16$)	Propranolol	V vs. G	No significant differences in survival rate (p=0.81). 0/8 G pigs & 1/8 V pigs survived.	No significant differences overall in cardiac parameters; initially higher SBP/MAP in V for first hour
[136]	Randomized, controlled	Canine ($n = 18$)	Propranolol	INS vs. G vs. E	Survival rate for INS greater than E (p<0.02) and G (p<0.05). 6/6 INS pigs survived, 4/6 G pigs survived, and 1/6 E pigs survived.	INS had improved cardio/hemodynamics, increased myocardial glucose uptake, and decreased serum K+ E had transient improvement in contractility and SBP, but refractory toxicity HR: G elicited greatest chronotropic effects; neither E nor INS changed HR.
[137]	Randomized, controlled	Rat ($n = 50$)	Propranolol	G vs. DOP vs. G + DOP	Survival time not improved by any treatment, but significantly reduced with DOP/G combination (p<0.05). G 251 mins, DOP 235 min, G + DOP 188 mins when G started first and 197 min when DOP started first.	All treatment groups: Hemodynamics (HR, MAP) initially improved, but this was transient and did not translate to improved survival.
[138]	Randomized, controlled	Rat ($n = 30$)	Propranolol	ISO vs. ISO + G vs. ISO + DOP	Survival time not improved by any treatment, but significantly reduced with ISO/DOP combination (p<0.05). ISO 255 min, ISO + G 254 min, ISO + DOP 204 min.	ISO/DOP: HR and MAP transiently increased, but then decreased significantly compared to control and other treatment groups. Sharp decrease in MAP likely cause of death.
[139]	Randomized, controlled	Canine ($n = 18$)	Propranolol	G vs. AM	Not evaluated (duration of monitoring was 31 min).	CO: G increased vs. control at 1, 6, 11 min; AM increased at 1 min (p=0.05) HR: higher for G vs. AM & control at all time periods (1–31 min) (p=0.05). AM had no difference vs. control. dP/dt max: G increased vs. control at 6 and 11 min; AM increased at 11 min (p=0.05). MAP: no difference vs. control for G or AM.

INS: insulin; NE: norepinephrine; E: epinephrine; V: vasopressin; G: glucagon; A: amrinone; PBrO2: cerebral perfusion; MAP: mean arterial pressure; HR: heart rate; SVR: systemic vascular resistance; CO: cardiac output; SBP: systolic blood pressure; dP/dt: rate of left ventricle pressure change.

dopamine (two studies), and norepinephrine (one study). Glucagon was compared to amrinone in one study [139].

Survival was an outcome parameter in six studies examining vasopressors. In five of six studies, survival was statistically reduced for animals receiving vasopressors (norepinephrine, epinephrine, vasopressin, or dopamine) compared to other treatment groups [4,134,137,138]. The remaining study found no significant survival difference with a vasopressor (vasopressin) [136]. Mean arterial pressure (MAP) was evaluated in four studies. In all studies, there was an initial improvement in MAP that then decreased until death [4,135,136,138]. Systolic blood pressure (SBP) was measured in four studies. In all studies, vasopressor treatment (vasopressin + epinephrine, vasopressin, epinephrine, dopamine) gave an initial increase in SBP that then fell for the remainder of the experiment [4,135–137]. HR was evaluated in four studies. In two studies, vasopressor treatment (epinephrine or vasopressin + epinephrine) had no effect on

HR [135,137]. In the other two studies, HR transiently improved with dopamine but then decreased until death [4,138].

Notably, a recent study by Katzung et al. evaluated the effect of vasopressors on cerebral perfusion (PBrO2) as their primary outcome and cardiovascular parameters (CO and MAP) and survival as their secondary outcomes in a porcine model of BB toxicity [134]. They found that adding norepinephrine to maximized high-dose insulin improved brain perfusion once MAP dropped and remained <50 mmHg. However, if norepinephrine + epinephrine were used without prior inotropic support of high-dose insulin, the group died so rapidly that researchers were unable to collect data on brain perfusion prior to death [134]. Addition of norepinephrine to insulin when MAP dropped and remained <50 mmHg suggested a trend to decreased cardiovascular mortality, but this trend was not statistically significant.

Glucagon was evaluated in five studies. Its impact on survival was evaluated in four studies. In two studies survival was not significantly different than saline control [136,138], in one study survival was significantly decreased compared to insulin [137], and in one study combination glucagon and dopamine reduced survival compared to saline control [4]. Glucagon's effect on HR was evaluated in five studies. In four studies, glucagon increased HR compared to other treatment groups [4,137–139], while in one study it had no difference vs. vasopressin [136]. MAP was evaluated in three studies. In two studies there was no difference compared to saline control [4,139] and in the third study there was no difference compared to vasopressin [136]. SBP and CO were evaluated in two studies. In one study, both CO and SBP were statistically increased with glucagon compared to control [139]. In the other study, there was no difference in CO or SBP for glucagon vs. vasopressin [136].

Studies on CCB toxicity

Table 11 summarizes animal studies involving CCB toxicity. One study evaluated nifedipine toxicity, while the others were models of verapamil toxicity. In studies of verapamil toxicity, infusion doses used to induce and maintain toxicity ranged from 0.017 to 0.2 mg/kg/min and one study used a single 15 mg/kg bolus. Vasopressors used in these studies included epinephrine (three studies), vasopressin (two studies), and phenylephrine (one study). The effect of vasopressor treatment on survival was evaluated in four studies. One study found statistically reduced survival (epinephrine vs. insulin) [145], one found a trend toward decreased survival (vasopressin vs. saline control) [142], and the remaining two studies found no survival difference (epinephrine vs. saline control, and phenylephrine + insulin vs. insulin alone) [140,143]. The effect on MAP was evaluated in three studies. In two studies, vasopressin did not improve MAP compared to saline control [141,142]. In the remaining study MAP improved with phenylephrine + insulin compared to control, but was not statistically different from insulin alone [140]. The effect on HR was evaluated in three studies. In all three studies, treatment with a vasopressor (epinephrine, phenylephrine) leads to no difference in HR vs. control [3,140,143]. Cardiac index (CI) was examined in two studies. In one study, adding phenylephrine to insulin improved CI compared to saline control but not compared to insulin alone [140], while in the other study vasopressin worsened CI compared to saline control [142].

Glucagon was evaluated in four studies. Its impact on survival was evaluated in two of four studies. In both studies, survival was significantly lower in glucagon groups compared to insulin groups [143,145]. HR was evaluated in three studies. In all three studies glucagon increased HR compared to other treatment groups [3,143,145]. Its effects on MAP and SBP were evaluated in one study each, and it had no significant impact on either [3,144].

The metabolic effects of vasopressors in CCB toxicity were examined by Kline et al. in three studies [3,143,145]. Although the heart normally uses free fatty acids (FFA) for energy, Kline et al. found that verapamil toxicity induces a metabolic switch in which FFA oxygenation is impaired and the heart becomes dependent on carbohydrates as its primary energy source [143]. Insulin was found to facilitate carbohydrate metabolism and increase myocardial lactate uptake and mechanical efficiency of the heart. Epinephrine and glucagon prevented this metabolic shift and increased FFA consumption, resulting in reduced myocardial mechanical efficiency and decreased survival [142].

Discussion

Evaluating the effectiveness of vasopressors in the treatment of TICS is challenging, given that the only available evidence is of low quality (human case reports and animal data). Drawing definitive conclusions is difficult if not impossible. However, a notable finding of this review is that there seems to be a discrepancy between the existing human and animal data. Collectively, animal data does not support the use of vasopressors. They have not been shown to sustainably improve hemodynamic parameters or increase survival. Multiple studies demonstrated negative effects on hemodynamic parameters and increased mortality even compared to saline. Conversely in human case reports, vasopressors were simply ineffective in most cases.

An example highlighting this discrepancy can be seen in the conflicting results regarding vasopressor treatment in the recent studies by Katzung et al. and Levine et al. [134,146]. Katzung et al. conducted a controlled, blinded animal study using propranolol and three different pharmacologic regimens with invasive monitoring of brain perfusion and cardiovascular parameters. Levine et al. performed a retrospective chart review of human case reports involving verapamil and diltiazem. In these cases, different drugs and doses were ingested and patients received numerous different drug therapies. The data from Levine et al. were not obtained in a controlled setting, and invasive monitoring was not done or at least not reported. Given these differences in design, it is nearly impossible to compare the two studies.

When considering the discrepancy in effectiveness of vasopressors between human and animal data, additional

Table 11. Summary of animal studies examining the effectiveness of vasopressors in calcium-channel blocker toxicity.

Reference	Design	Animal	Toxicity	Treatment	Results: survival	Results: hemodynamics	Results: metabolic effects
[3]	Randomized, controlled	Pig ($n = 15$)	Nifedipine	INS vs. INS + PHE	Survival rate was not different between groups (p=0.32). 4/5 INS pigs survived, 5/5 INS + PHE pigs survived.	Addition of PHE did not improve cardiovascular parameters (CI, HR MAP, SVR)	Not evaluated.
[140]	Randomized, controlled, blinded	Pig ($n = 18$)	Verapamil	V	Trend for decreased survival rate with V vs. control (p=0.32) 4/8 V pigs survived, 8/10 control pigs survived.	No statistical difference in MAP V vs. control (p=0.70)	Not evaluated.
[141]	Randomized, controlled	Canine ($n = 12$)	Verapamil	V	Survival not evaluated in the study.	Escalating doses of V worsened CI and failed to return MAP to within 20% of baseline. No significant difference in MAP for escalating V vs. control.	Not evaluated.
[142]	Randomized, controlled	Canine ($n = 20$)	Verapamil	INS vs. E vs. G	Survival not evaluated statistically. INS had longest survival time (360 +/− 51 min). G was longer than control (208 +/− 45 min vs. 149 +/− 28 min), while E was shorter (125 +/− 34 min). INS only treatment to significantly increase lethal dose of verapamil vs. control ($p<0.05$)	INS only treatment to improve *E*max and SBP vs. control ($p<0.05$). Improved LV efficiency and decreased Tau vs. all other treatments ($p<0.05$). E and G decreased LV efficiency vs. control ($p<0.05$). E decreased Tau vs. control ($p<0.05$). No difference for *E*max, +/− d*P*/d*t*, HR, LV work, SBP, or CABF. G improved HR & +d*P*/d*t* vs. control ($p<0.05$). No difference for *E*max, −d*P*/d*t*, Tau, LV work, SBP, or CABF.	INS increased lactate usage vs. control and reduced free fatty acid usage vs. all other groups ($p<0.05$). E increased free fatty acid usage vs. control; decreased glucose and lactate uptake vs. all other treatments ($p<0.05$). Net negative shift of lactate implying development of functional ischemia. G increased free fatty acid & myocardial oxygen uptake vs. control ($p<0.05$).
[143]	Randomized, controlled	Canine ($n = 30$)	Verapamil	INS vs. E vs. G vs. CaCl2	INS improved survival rate vs. all other groups ($p<0.05$). 6/6 INS, 2/4 EPI, 0/3 G, and 0/3 $CaCl_2$ pigs survived duration of experiment. No significant difference in survival rate for E, G, $CaCl_2$ vs. control.	INS improved *E*max and CABF vs. all other treatments ($p<0.05$). G increased HR vs. all other treatments ($p<0.05$). E produced more frequent ventricular and junctional tachycardia than INS $p<0.05$	INS increased myocardial uptake of glucose & lactate vs. all other groups ($p<0.05$).
[144]	Randomized, controlled	Canine ($n = 15$)	Verapamil	G	Not evaluated statistically. 8/8 G and 5/7 control dogs survived.	G increased CO at 45 and 60 min and HR at 30, 45, and 60 min ($p<0.05$). No difference for MAP or TPR.	Not evaluated.
[145]	Randomized, controlled	Canine ($n = 24$)	Verapamil	INS vs. E vs. G	INS had increased survival compared to E and G ($p<0.05$). 6/6 INS, 2/6 E, 0/6 G dogs survived to end of experiment.	INS and E had similar hemodynamic parameters throughout, but INS had significantly greater LVDP, CABF, and *E*max ($p<0.05$)	E caused persistent hyperglycemia and increased arterial lactate vs. other groups ($p<0.05$).

INS: insulin; PHE: phenylephrine; V: vasopressin; E: epinephrine; G: glucagon; CaCl2: calcium chloride; CI: cardiac index; HR: heart rate; MAP: mean arterial pressure; SVR: systemic vascular resistance; *E*max: ventricular end-systolic maximum elastance; SBP: systolic blood pressure; LV: left ventricle; Tau: time required for left ventricular pressure to decay 50% from end-systole to first deflection of left ventricle filling; d*P*/d*t* = rate of left ventricle pressure change; CABF: coronary artery blood flow; CO: cardiac output; TPR: total peripheral resistance; LVDP: left ventricular diastolic pressure.

considerations should be made. In the majority of human TICS cases evaluated (over 90%), the patient survived. Treatment failures are likely underreported, as they do not have as much potential to influence clinical practice. Another possible explanation for the apparent lack of detrimental effect of vasopressors in humans is that pulmonary artery catheters (PACs) are no longer commonly used in emergency medicine or critical care. Frequently, providers use only BP and HR with no further physiological data such as CO or SVR to monitor patients and treatment effectiveness. Consequently, adverse effects of vasopressors are more likely to go undetected. Clinicians either note a "lack of effect" or assume the patient just succumbed to overdose instead of considering that vasopressors potentially hastened death. Non-invasive alternatives to PACs, such as ultrasound, echocardiography, and waveform monitoring, should be considered to help guide treatment [147].

This discordance in the data is problematic for the clinician. While animal studies generally do not support the use of vasopressors and suggest harm, the findings of those studies are not completely translatable to human practice and available human data are limited to case reports. Additional human data regarding the effectiveness of vasopressors in TICS could possibly be obtained by searching the AMCT ToxIC database, as well as other international population poison databases.

Limitations

Notable limitations of this study include the body of data evaluated. It is possible that certain databases were missed, however, the literature search was conducted by professional medical librarian staff for completeness. Additionally, foreign language articles could not be translated and therefore had to be excluded. Furthermore, as this paper focuses on the drug classes most frequently implicated in TICS (BB, CCB, and TCA) it does not include a robust discussion of other drugs with the potential to cause TICS.

Another limitation is the type of data evaluated. There were no randomized, controlled clinical trials in humans assessing the research question, so the only resources available were case reports and animal studies. Animal models may not accurately reflect human overdose. Case reports are also problematic considering the heterogeneity in patient characteristics and treatments employed. Additionally, given the brevity of information provided, treatment efficacy is subjective and up to reviewer interpretation. In the case reports evaluated, we considered treatments to be effective if they were the primary agent responsible for restoring hemodynamic function. However, patients were almost always receiving multiple treatment modalities, so it is possible that improvement and survival were ultimately attributable to other or multiple agents. Finally, animal models of BB induced TICS all used propranolol to induce toxicity. Propranolol's sodium channel blockade may result in neurotoxicity and cardiovascular toxicity significantly different from other BB and CCBs.

Conclusions

While human case reports suggest that vasopressors are often ineffective but not necessarily harmful in TICS, controlled animal studies indicate that vasopressors impair hemodynamic function and increase mortality. In cases of mild intoxication it may not make a difference, which pharmacologic agent is used. This may be the reason why most patients survive in case reports of TICS. Likewise in extremely lethal overdoses, no pharmacologic agent may be able to increase survival and in these cases, advanced extracorporeal methods need to be considered. However, if the numerous animal studies are accurate, then we actually could be harming patients with our treatment choices. With drug overdose deaths now exceeding deaths from breast cancer and from motor vehicle accidents, it is time for toxicology and critical care medicine to find a way to carry out good quality studies in humans [148,149].

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Appendix A: Search strategy keywords

Toxicity search string
(Toxicity OR Shock OR Poison induced shock OR Poisoning OR poison OR overdose)

Calcium channel blocker search string
(Calcium channel blockers OR calcium channel antagonist OR calcium channel blocking agent) AND (Phenylalkylamine OR Verapamil OR Gallopamil OR Fendiline OR Benzothiazepine OR Diltiazem OR Dihydropyridine OR Amlodipine OR Felodipine OR Nicardipine OR Nifedipine OR Aranidipine OR Azelnidipine OR Barnidipine OR Benidipine OR Cilnidipine OR Clevidipine OR Isradipine OR Efonidipine OR Lacidipine OR Lercanidipine OR Manidipine OR Nilvadipine OR Nimodipine OR Nisoldipine OR Nitrendipine OR Pranidipine OR Bepridil OR Flunarizine OR Fluspirilene OR Mibefradil)

Beta blocker search string
(Adrenergic beta-antagonists OR Beta Adrenergic Antagonists OR Beta Blocker OR Beta Antagonist OR Beta channel Blocking agent) AND (Acebutolol OR Atenolol OR Bisoprolol OR Carvedilol OR Esmolol OR Labetalol OR Metoprolol OR Nadolol OR Nebivol OR Sotalol OR Betaxolol

OR Bucindolol OR Butoxamine OR Carteolol OR Celiprolol OR Oxprenolol OR Penbutolol OR Pindolol OR Timolol)

Tricyclic antidepressant search string
(Antidepressant agents, tricyclic AND Tricyclic Antidepressants) AND (Imipramine OR Clomipramine OR Desipramine OR Dibenzepin OR Lofepramine OR Nortriptyline OR Protriptyline OR Amitriptyline OR Amitriptylinoxide OR Amoxapine OR Butriptyline OR Demexiptiline OR Dimetacrine OR Dosulepin OR Doxepin OR Imipraminoxide OR Melitracene OR Metapramine OR Nitroxazepine OR Noxiptiline OR Pipofezine OR Propizepine OR Quinupramine OR Amineptine OR Iprindole OR Opipramol OR Tianeptine OR Trimipramine)

Treatment search strings
Combined vasopressor search
(Vasopressor Agents OR Vasopressors OR Vasoconstrictor Agents) AND (Vasopressor OR Vasopressin OR Epinephrine OR Dopamine OR Dobutamine OR Phenylephrine OR Norepinephrine)

Glucagon
Methylene blue
Beta adrenergic agonist
(Isoprenaline OR Isoproterenol)

Phosphodiesterase inhibitor
(Phosphodiesterase Inhibitors OR Phosphodiesterase 4 Inhibitors OR Phosphodiesterase 3 Inhibitors OR Phosphodiesterase 5 Inhibitors OR 1-Methyl-3-isobutylxanthine) OR (Caffeine OR aminophylline OR IBMX OR paraxanthine OR pentoxifylline OR theobromine OR theophylline OR PDE1 inhibitor OR vinpocetine OR PDE2 inhibitor OR EHNA OR BAY 60-7550 OR Oxindole OR PDE3 inhibitor OR inamrinone OR milrinone OR enoximone OR anagrelide OR cilostazol OR pimobendan OR PDE4 inhibitor OR mesembrine OR rolipram OR ibudilast OR piclamilast OR luteolin OR drotaverine OR roflumilast OR apremilast OR PDE 5 inhibitor OR sildenafil OR tadalafil OR vardenafil OR udenafil OR avanafil OR dipyridamole OR icariin OR 4-methylpiperazine OR pyrazolo pyrimidin-7-1 OR PDE7 inhibitor OR PDE10 inhibitor OR papaverine)