DIHYDROPYRIDINE CCB POISONING AND ANTAGONISTS OF THE ANGIOTENSIN AXIS

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INTRODUCTION

DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKERS

- Amlodipine
- Felodipine
- Lercanidipine
- Nifedipine

- DHP CCBs perceived to have a safer pharmacological profile as they are more peripherally acting
- In Australia, amlodipine is the:

2nd

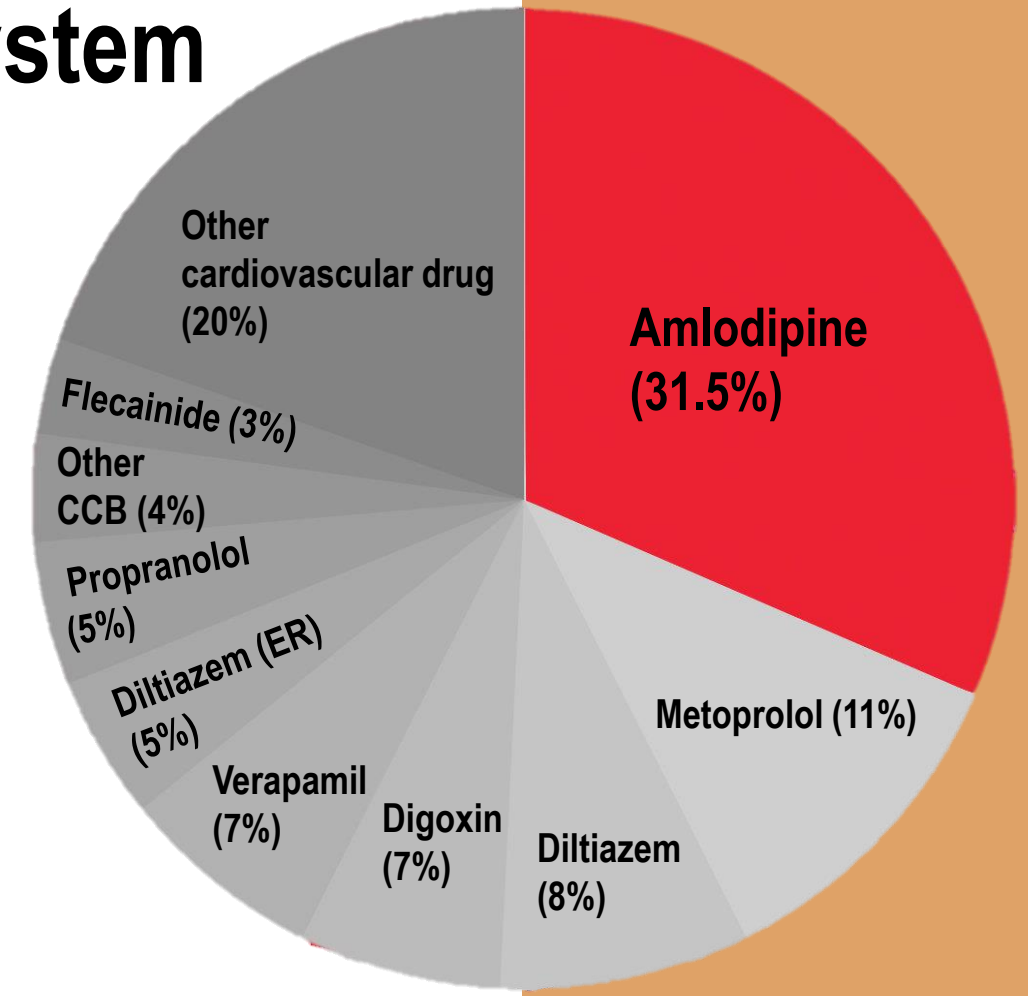
most prescribed anti-hypertensive

4th

most prescribed drug by DDD

2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System

- Amlodipine associated with the highest proportion of deaths attributed by cardiovascular drugs (80/254)



ANGIOTENSIN-II RECEPTOR BLOCKERS

- Candesartan
- Irbesartan
- Losartan
- Olmesartan
- Telmisartan
- Valsartan

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

- Perindopril
- Ramipril
- Lisinopril
- Enalapril

- Literature advocates for DHP CCBs prescribed in combination with angiotensin-II receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACEIs)

- ARB or ACEI overdose is relatively benign – low reports of significant toxicity

OBJECTIVES

- To compare the effect of a DHP CCB overdose with ARBs/ACEIs versus DHP CCB overdoses alone.
- We hypothesised that combined overdoses of DHP CCBs and ACEIs/ARBs synergistically cause more toxicity

METHODS

- Retrospective review of NSW PIC database and SEATS, HATS, PATS toxicology units from Jan 2016 to July 2019

INCLUSION:

- >14 years of age
- Exceeding maximum dose of DHP CCB

Amlodipine >10mg

Felodipine >20mg

Lercanidipine >20mg

Nifedipine IR >80mg CR >120mg

EXCLUSION:

- Co-ingestion with non-DHP CCB or other vasodilators

PRIMARY OUTCOMES

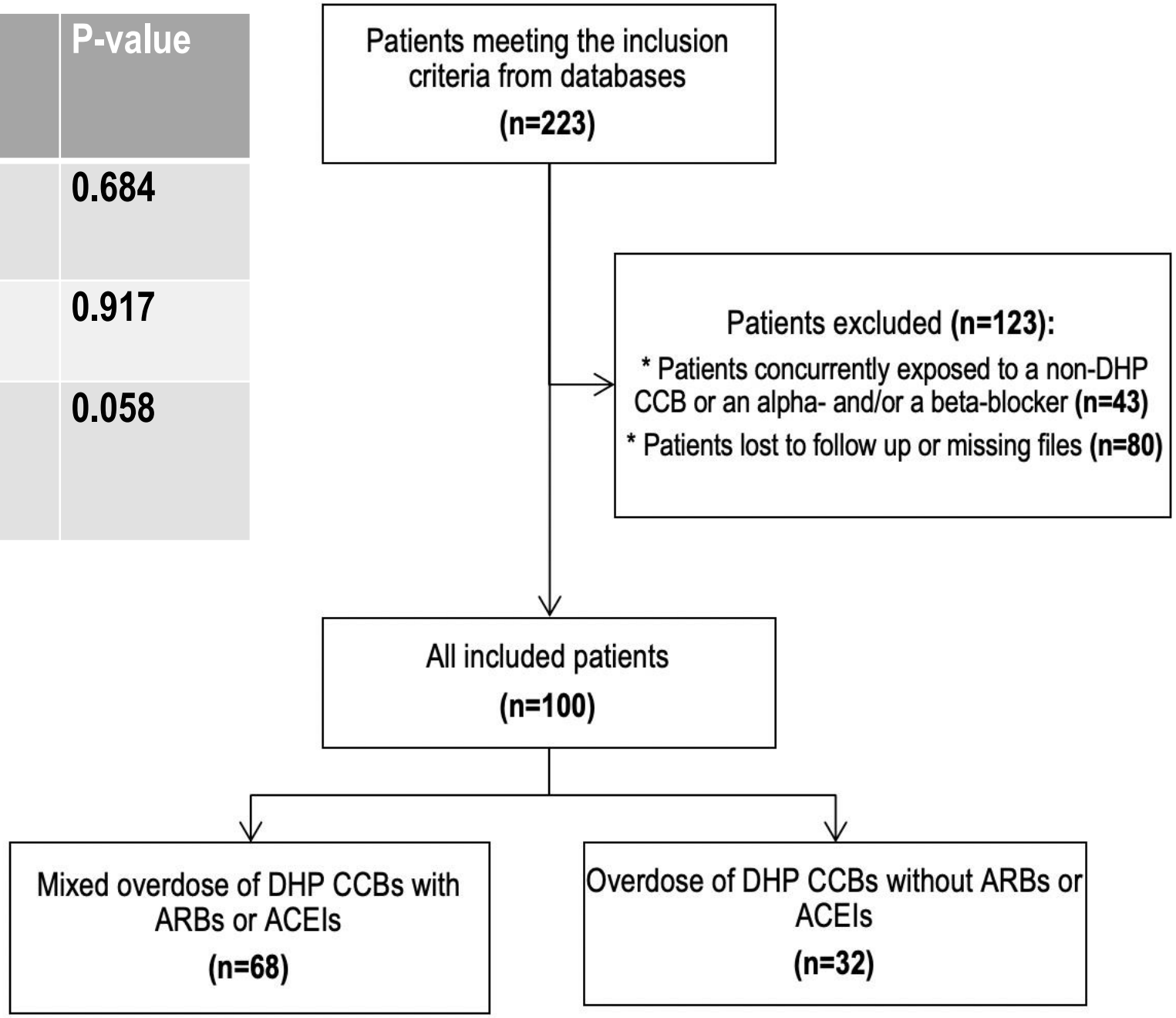
- Hypotension
- Lowest SBP and MAP
- Heart rate

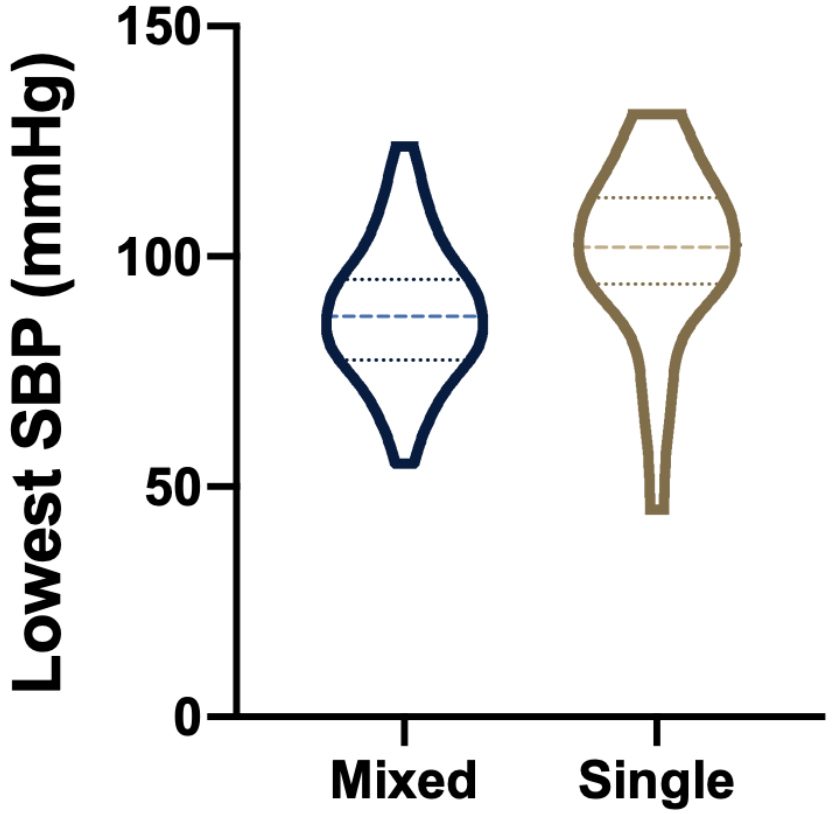
SECONDARY OUTCOMES

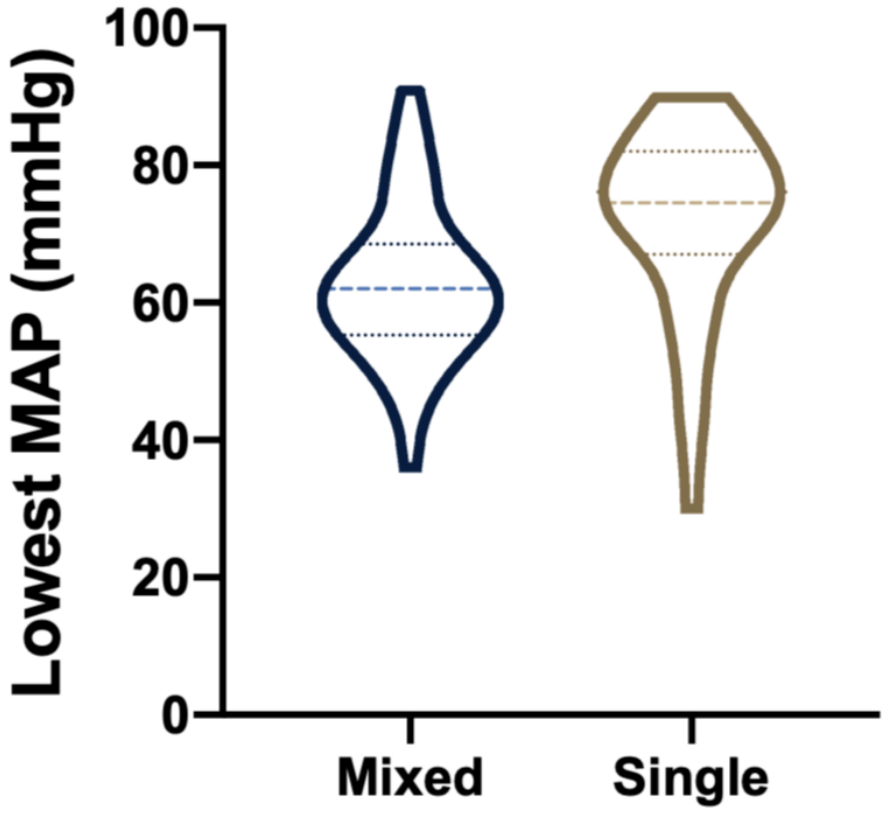
- Fluid, antidote, vasopressor requirements
- ICU admission
- Length of stay

Parameter	Mixed ingestion (n=68)	Single ingestion (n=32)	P-value
Median Age (yrs)	54 (IQR 45-61)	52 (IQR 35-67)	0.684
Number of Females	39 (57%)	18 (56%)	0.917
Defined Daily Dose of DHP CCB	22 (IQR 10-40)	13 (IQR 7-30)	0.058

RESULTS







Parameter	DHP CCB with ACEI/ARB (n=68)	DHP CCB without ACEI/ARB (n=32)	P-value
Lowest SBP (mmHg)	87 (IQR 79 – 95)	102 (IQR 94 – 112)	<0.0001
Lowest MAP (mmHg)	62 (IQR 56 – 68)	75 (IQR 69 – 82)	<0.0001

RESULTS

PREDICTORS FOR LOWEST SBP/MAP:

- Mixed ingestion (negative)
- DDD (negative)
- Age (positive)

Rate of BRADYCARDIA was significantly higher in mixed group

(22% vs 3%, p=0.018)

HYPOTENSION was 3.9 times more likely in the mixed group vs the single group

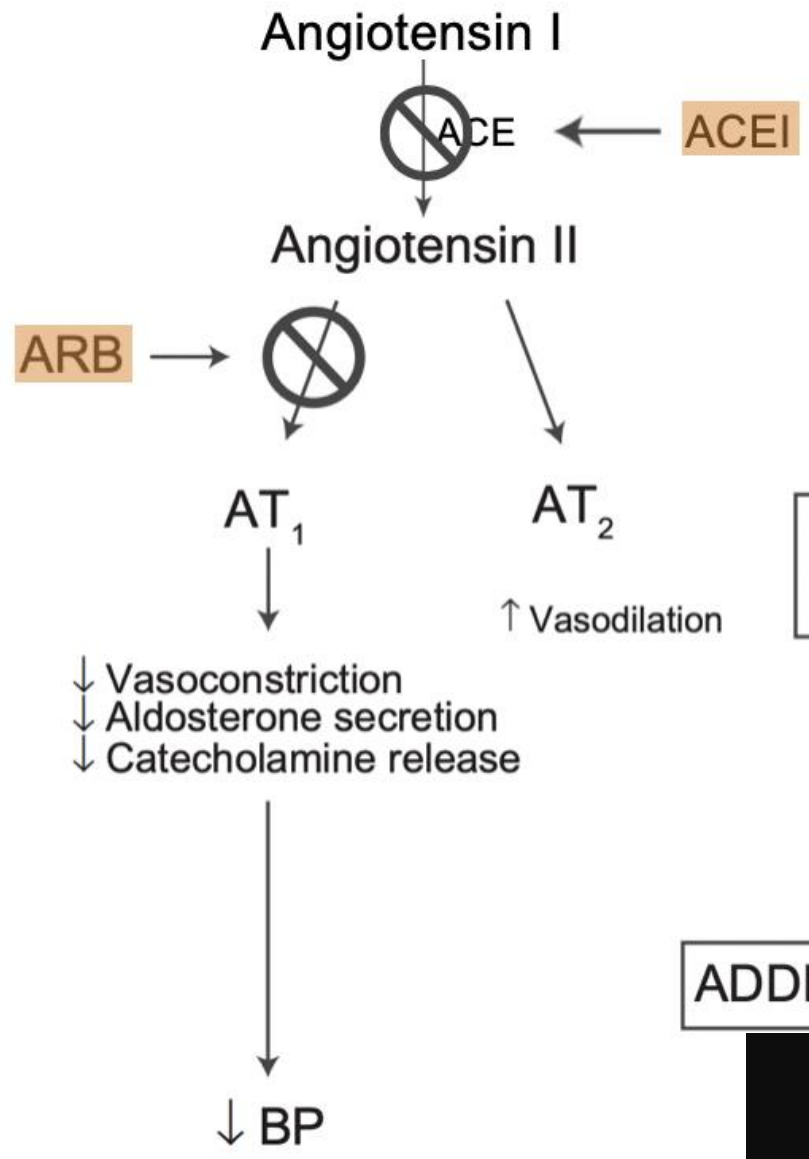
(95% CI:1.4-11)

LOWEST HEART RATE was significantly lower in mixed group

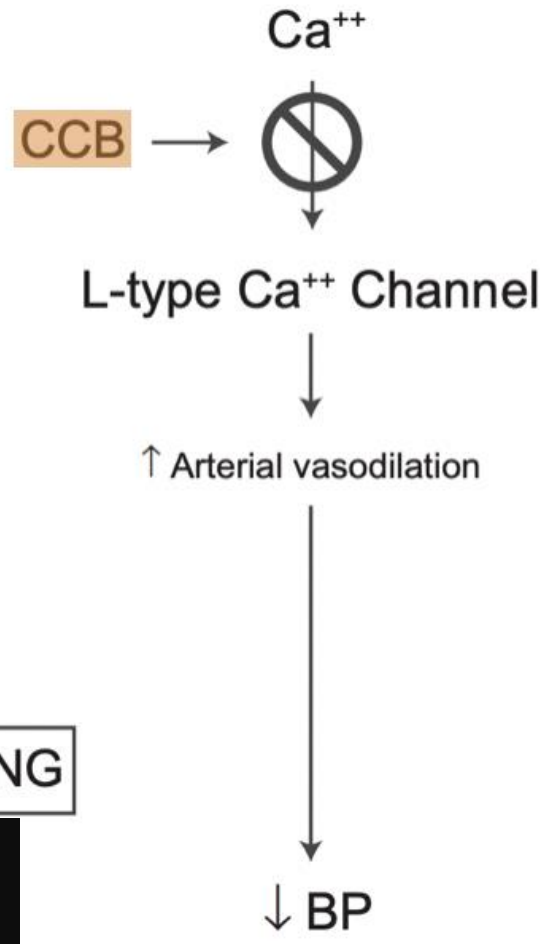
(70 vs 80bpm, p=0.001)

Parameter	DHP CCB with ACEI/ARB (n=68)	DHP CCB without ACEI/ARB (n=32)	P-value	Odds Ratio (95% CI)
Number Received Activated Charcoal	7 (10%)	5 (16%)	0.444	0.62 (0.18 – 2.1)
Number Received IV Fluids	63 (93%)	22 (69%)	0.002	5.7 (1.8 – 19)
Number Received Antidote or Vasopressors	24 (35%)	5 (16%)	0.043	2.9 (1.004 – 8.6)
Number of ICU Admissions	18 (26%)	6 (19%)	0.399	1.6 (0.55 – 4.4)
Length of Stay	1.3 (IQR 0.7-2.2)	0.9 (IQR 0.5-1.6)	0.101	-
Deaths	0	0	-	-

ARB/ACEI Mechanism of Action



CCB Mechanism of Action



Complementary actions

ADDITIVE BP LOWERING

1 + 1 > 2

CONCLUSION

- DHP CCB act synergistically with ACEI/ARB in overdose
- Mixed overdose associated with more hypotension and a lower lowest SBP/MAP than single overdose, requiring more fluids, antidotes and vasopressors

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