Patient harm from cardiovascular medications

Chariclia Paradissis (iD)**, Neil Cottrell, Ian Coombes, Ian Scott** (iD)**, William Wang and Michael Barras**

Abstract

Background: Medication harm can lead to hospital admission, prolonged hospital stay and poor patient outcomes. Reducing medication harm is a priority for healthcare organisations worldwide. Recent Australian studies demonstrate cardiovascular (CV) medications are a leading cause of harm. However, they appear to receive less recognition as 'high risk' medications compared with those classified by the medication safety acronym, 'APINCH' (antimicrobials, potassium, insulin, narcotics, chemotherapeutics, heparin). Our aim was to determine the scale and type of medication harm caused by CV medications in healthcare.

Methods: A narrative review of adult (>16 years) medication harm literature identified from PubMed and CINAHL databases was undertaken. Studies with the primary outcome of measuring the incidence of medication harm were included. Harm caused by CV medications was described and ranked against other medication classes at four key stages of a patient's healthcare journey. Where specified, the implicated medications and type of harm were investigated.

Results: A total of 75 studies were identified, including seven systematic reviews and three meta-analyses, with most focussing on harm causing hospital admission. CV medications were responsible for approximately 20% of medication harm; however, this proportion increased to 50% in older populations. CV medications were consistently ranked in the top five medication categories causing harm and were often listed as the leading cause.

Conclusion: CV medications are a leading cause of medication harm, particularly in older adults, and should be the focus of harm mitigation strategies. A practical approach to generate awareness among health professionals is to incorporate 'C' (for CV medications) into the 'APINCH' acronym.

Correspondence to:
Chariclia Paradissis
School of Pharmacy, The University of Queensland, Pharmacy Australia Centre of Excellence, 20 Cornwall Street, Woolloongabba, Brisbane, QLD 4102, Australia
c.paradissis@uq.edu.au

Pharmacy Department, Royal Brisbane and Women's Hospital, Metro North Health, Brisbane, QLD, Australia

Neil Cottrell
School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia

Ian Coombes
School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia

Pharmacy Department, Royal Brisbane and Women's Hospital, Metro North Health, Brisbane, QLD, Australia

Ian Scott
Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia

Department of Internal Medicine and Clinical Epidemiology, Princess Alexandra Hospital, Metro South Health, Brisbane, QLD, Australia

William Wang
Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia

Department of Cardiology, Princess Alexandra Hospital, Metro South Health, Brisbane, QLD, Australia

Michael Barras
School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia

Pharmacy Department, Princess Alexandra Hospital, Metro South Health, Brisbane, QLD, Australia

Plain language summary

Patient harm from cardiovascular medications
Background

- Harm from medications can cause poor patient outcomes.
- Certain medications have been identified as 'high risk' and are known to cause high rates of harm.
- 'High risk' medications are included in medication guidelines used by health professionals.
- Cardiovascular medications (e.g. blood pressure and cholesterol medications) are important and have many benefits.
- Recent studies have found cardiovascular medications to cause high rates of harm.
- Cardiovascular medication harm is often under-recognised in clinical practice.
- Some guidelines do not consider cardiovascular medications to be 'high risk'.

Method
- This review investigated the extent of harm caused by cardiovascular medications in adults across four healthcare settings:
    - (1) at the time of hospital admission;
    - (2) during hospital admission;
    - (3) after hospital; and
    - (4) readmission to hospital.
- Harm caused by cardiovascular medications was ranked against other medication classes.
- We investigated the type of cardiovascular medications to cause harm and the type of harm caused.

Results
- Seventy-five studies were reviewed across 41 countries.
- Cardiovascular medications were ranked within the top five medications to cause harm.
- Cardiovascular medications were a leading cause of harm in each healthcare setting investigated.
- Harm caused by cardiovascular medications was common in older adults (>65 years).
- Cardiovascular medications often caused preventable harm.
- Medications to treat high blood pressure and abnormal heart rhythms were the most common causes of harm.
- We reported kidney injury, electrolyte changes and low blood pressure as common types of harm.

Conclusion
- Increased focus on cardiovascular medications in clinical practice is needed.
- Health professionals need to carefully prescribe and frequently review cardiovascular medications, especially in older adults.
- Patient and health professional discussions should be based on both the benefits and harms of cardiovascular medications.
- Cardiovascular medications should be included in all 'high risk' medication guidelines.

Key points
- Medication harm is a major priority area for healthcare organisations worldwide.
- Cardiovascular medications contribute to significant medication harm (~20–50%) across both ambulatory and inpatient clinical settings.
- Adapting a medication safety acronym is recommended to generate awareness about the optimisation and rationalisation of cardiovascular medications, particularly in older adults.

Introduction
Adverse events in healthcare are defined as 'incidents in which harm resulted to a person receiving care'.[1] These events are associated with poor patient outcomes and are often preventable.[1] Medication harm is a major subset of adverse events affecting healthcare systems worldwide.[2–5] It can cause hospital admissions, longer hospital stays, increased patient morbidity and mortality and greater resource utilisation.[2–7] In Australia, the annual fiscal burden of medication harm has been estimated to be AUD$1.4 billion.[7,8] The World Health Organization has identified medication harm as a global priority and the Australian

Acronym	Expansion	Examples
A	Antimicrobials	Antibacterials: vancomycin, gentamicin
		Antifungals: amphotericin – liposomal formulation
P	Potassium and other electrolytes	Intravenous potassium, magnesium, calcium, hypertonic saline, sodium phosphate
I	Insulin	Insulin aspart, insulin glargine, insulin glulisine, neutral insulin
N	Narcotics and other sedatives	Opioids: morphine, oxycodone, fentanyl, hydromorphone
		Benzodiazepines: midazolam, clonazepam, diazepam, lorazepam
		Anaesthetic: propofol, thiopentone
C	Chemotherapeutic agents	Vincristine, methotrexate, etoposide, azathioprine, doxorubicin
H	Heparin and other anticoagulants	Low molecular weight heparins: enoxaparin, dalteparin
		Direct oral anticoagulants: rivaroxaban, dabigatran, apixaban

Figure 1. The APINCH[a] 'high risk' medication acronym.
[a]Adapted from the Australian Commission on Safety and Quality in Health Care.[12]

government lists medication safety as the country's tenth National Health Priority.[9–11]

To help clinicians recognise and mitigate medication harm, 'high alert' or 'high risk' medication lists have been promoted in clinical settings.[12–14] The most commonly acknowledged list is published by the Institute of Safe Medication Practices (ISMP).[14] 'High alert' medications are those with a heightened risk of causing devastating harm if not used correctly.[14] In Australia, there is no standard list; however, the 'APINCH' acronym (Figure 1) is widely used to advertise medication safety, encourage harm prevention strategies and raise awareness to the potential for catastrophic harm caused by certain medication classes.[12] It is not intended to be an exhaustive list and does not incorporate every medication linked to harm.[12,15]

Cardiovascular (CV) medications are among the most frequently prescribed, particularly in the older population.[16,17] Currently, 90% of Australians aged >75 years take a CV medication.[16] A strong evidence base for treating CV disorders (e.g. acute coronary syndrome and heart failure) promotes the concurrent use of multiple CV medications.[18,19] However, polypharmacy is an independent risk factor for medication harm and the older population are more susceptible to adverse drug events (ADEs).[20,21]

Local studies have identified CV medications as prominent causes of patient harm during hospital admission, and it is likely that this extends into ambulatory care.[22,23] The purpose of this narrative review was to investigate the international literature to determine the scale and type of medication harm caused by CV medications.

A contemporary review is pertinent due to the increased use of CV medications over the last three decades.[16] We sought to identify common themes, and if necessary, propose an approach to promote awareness about the safe use of these medications in clinical practice.

Methods

Data sources
Given the breadth and heterogeneity of medication harm research, a systematic review of one clinical intervention was deemed too restrictive. Instead, a narrative review exploring and evaluating the major medication harm studies was considered more appropriate to capture the extent of the issue across multiple healthcare settings. A structured literature search (see Appendix 1) based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was undertaken using PubMed and Cumulated Index to Nursing and Allied Health Literature (CINAHL) databases. Search terms such as 'adverse drug reaction', 'adverse drug event', 'adverse reaction', 'adverse event', 'medication error' and 'medication harm' were used. Citations and bibliography lists of identified articles were scanned for additional studies.

Inclusion criteria
Systematic reviews and meta-analyses, narrative reviews, case-control studies and observational cohort studies of adverse events and medication harm within both hospital and ambulatory settings were included. Included studies quantified the incidence of medication harm as a primary

outcome measure and included information about the medication classes causing harm. If systematic reviews did not specify rank of CV medications, relevant observational studies within the systematic reviews were also analysed.

Exclusion criteria

We excluded studies only investigating paediatric medication harm (<16 years of age) and those using definitions such as 'potential drug-related problems' or 'potential adverse drug events' which indicated the potential for harm, not actual patient harm. Studies investigating specific patient groups (e.g. mental health or diabetic populations) or specific medication classes (e.g. antimicrobials) were excluded. Randomised clinical trials containing adverse drug event (ADE) data about specific CV medications and conference proceedings, editorials and magazines were also excluded. To link medication harm to contemporary prescribing patterns, studies published before 1990 were excluded.

Definitions and terminology

Multiple terms are often used synonymously to describe medication harm, including ADEs and adverse drug reactions (ADRs; Box 1, see Appendix 2).[24] For the purposes of this review, medication harm was defined inclusively as 'any negative patient outcome or injury, related to medication use'.[24] Classification of medications as 'high alert' *versus* 'high risk' appears to be based on the preference of international patient safety bodies. Due to the similarities between definitions, 'high alert' and 'high risk' medications were considered interchangeable for the purposes of this study.

Studies investigating medication harm have used multiple categorisations for CV medications. In this review, CV medications were classified as those that directly act on the CV system.[25] This included antihypertensives [e.g. angiotensin-converting enzyme inhibitors (ACE-Is) and calcium-channel blockers (CCBs)], diuretics (e.g. loop and thiazide diuretics), antiarrhythmics (e.g. digoxin, amiodarone), hypolipidaemics (e.g. statins, fenofibrate and ezetimibe) and antianginals (e.g. nitrates).[25] Anticoagulant and antiplatelet medications were excluded, as these medications are already widely acknowledged as high-risk medications and are a focus of pre-existing harm mitigation strategies within existing literature.[12,14,26–28] Including anticoagulants and antiplatelets in this review would detract from the focus on the harm caused by CV medications.

Analysis of studies

Studies were separated according to healthcare setting to investigate both inpatient and ambulatory populations. These included medication harm causing hospital admission, occurring during hospital stay, after discharge or in ambulatory care and readmission. If studies investigated medication harm causing hospital presentation or admission, these were separated based on whether index admissions or readmissions were investigated.

All retrieved studies were reviewed to determine the type of medication harm investigated and the incidence rate of both 'all cause' medication harm and harm caused specifically by CV medications. CV medications were then ranked comparative with other medication classes to determine if CV medications were a leading cause of harm. If specified, the types of CV medications implicated were ascertained.

Results

Study inclusion, exclusion and rationale are shown in a flow diagram included in Online Resource 1. Overall, 75 studies were included, of which 10 were systematic reviews/meta-analyses. Most studies investigated medication harm as a cause of hospital admission ($n = 42$) and five investigated both admission and inpatient medication harm. The majority of studies (not including systematic and literature reviews) were conducted in the United States (US; $n = 19$), Australia ($n = 14$) and the United Kingdom ($n = 6$; see Online Resource 2). A total of 13 studies had been included in the 10 identified systematic reviews; therefore, to prevent duplication of results, these studies were not included in tables but are referred to in the text. A broad overview of the proportion of medication harm caused by CV medications in each healthcare setting is shown in Figure 2. This figure also provides the differences between the adult (>16 years) and older person (>65 years) populations.
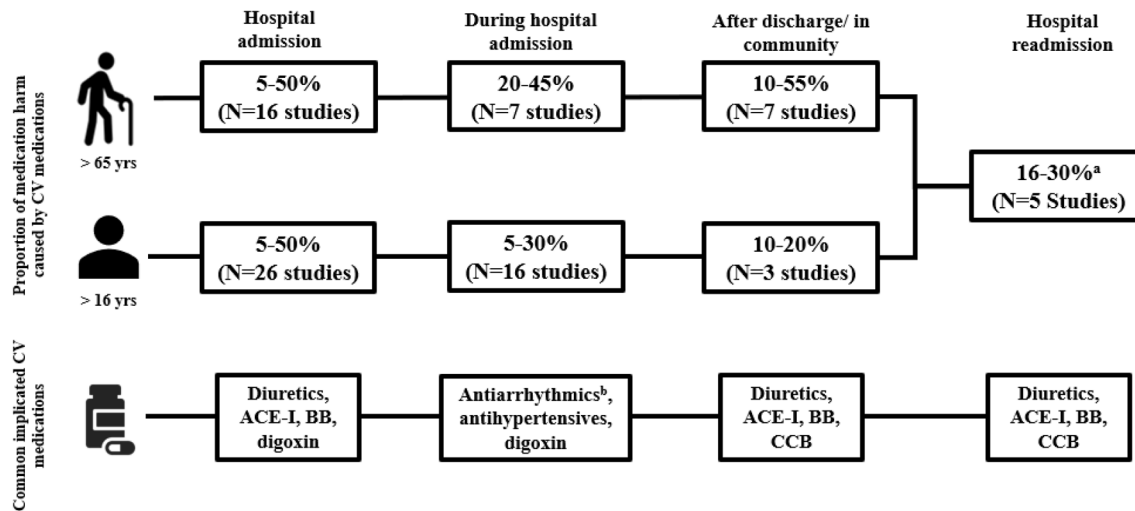
Figure 2. An overview of cardiovascular medication harm across four healthcare settings.
aRate reported for all adults, as limited literature exists for older persons.
bIncludes intravenous and oral antiarrhythmics.
ACE-I, angiotensin-converting enzyme inhibitors; BB, beta-blockers; CCBs, calcium-channel blockers; CV, cardiovascular.

CV medication harm resulting in hospital presentation or admission

Forty-two studies were identified, including six systematic reviews and one meta-analysis that examined medication harm as a cause of admission to hospital. Thirty-five studies were analysed and tabulated (Table 1). The results of the remaining seven studies are included within the systematic reviews.[29–35] The majority of studies were undertaken in general medical or aged care populations. The rate of medication harm varied, with higher rates reported in older populations (range 0.16–41.3%).[36,37]

As per Table 1, 22 studies (63%) ranked CV medications in the top three causes of medication harm. Of the remaining 13 studies, a further five categorised CV medications within the top five causes of harm and another seven were unable to be ranked but described CV medications as a leading cause of harm. The majority of studies investigating older adults [73% (*n* = 8/11)] found CV medications to be the leading cause of harm.

In Australia, Runciman *et al.*[38] found CV medications, together with anticoagulants and anti-inflammatories, as responsible for over 50% of all ADEs on admission to hospitals, and identified CV medications as prominent causes of preventable and high-impact harm. A 2019 study investigating hospitalisation due to ADRs over 13 years concluded that drugs used to treat CV diseases were the leading therapeutic category contributing to medication harm, including deaths and disabilities.[67] Similarly, international studies with high rates of CV medication harm report fatal and preventable events, longer hospital stays and substantial costs linked to this harm.[31,32,34,49,51,54]

Types of CV medications causing harm. Diuretics, antihypertensives and digoxin were most frequently identified as causes of harm.[32,34,51] Diuretics have been implicated in up to 30% of admissions due to medication harm, including renal failure and serious electrolyte imbalances.[34,39] Included within the systematic reviews of Howard *et al.*[39] and Al Hamid *et al.* is a large, prospective observational study that showed ACE-Is and beta-blockers caused 7.7% and 6.8% of ADR-related admissions, respectively.[34,40] ACE-I induced renal impairment, hypotension and angioedema, and beta-blocker induced bradycardia and heart block were common.[34] Digoxin and other antiarrhythmics were a leading cause of hospitalisation with a major US study finding 81% of emergency visits due to digoxin toxicity resulted in hospitalisation.[6,31,51]

Table 1. CV medication harm causing presentation or admission to hospital.

Author(s)	Type of study	Population/(n)	Country	Type of medication harm	Incidence	% CV medication harm	CV medications rank against other drug classes	Outcomes
Systematic reviews and meta-analysis								
Runciman et al.[38]	Review of multiple sources: SR, national data bases	Multiple data sources: refer to study	AU	ADR/ADE[a]	2–4% of admissions; 30% in ≥75 years	CV medications leading cause (% NR)	NR	Cost: >AUD$400 million per year Mortality: 27% of AE deaths in 1997–1998
Howard et al.[39]	SR of 17 POS	≥16 years/(n = 17 studies)	–	Preventable DRAs[a,b]	1.4–15.4% of admissions (3.7% median)	33% (CV) 16% (diuretics) of preventable DRAs	2nd (diuretics) 6th (BB) 7th (ACE-I) 9th (positive inotropes) 12th (CCB) 14th (nitrates)	NR
Kongkaew et al.[36]	SR of 25 POS	All patients/(n = 25 studies, 106,586 patients)	–	ADR	0.16–15.7% of admissions (5.3% median)	45.7%[c] (median in all adults) 42.5%[c] (median in older adults)	1st	Severity (reported by two studies): 3.3% and 38.1% of events were severe
Al Hamid et al.[40]	SR of ROS/POS	≥18 years/(n = 21 ADR studies, 6 ADE studies)	–	ADR and ADE[a]	ADR: 1.47% median (ROS), 12% median (POS) ADE: 12.4% median (POS)	33.9% (median) of ADRs, 42.3% (median) of ADEs	1st	Refer to study
Alhawassi et al.[41]	SR of ROS/POS	≥18 years/(n = 14 studies)	–	ADR	10.0% of admissions (median)	CV medications leading cause (% NR)	NR	NR
Oscanoa et al.[42]	SR and MA	≥60 years/(n = 42 studies)	–	ADR[a]	8.7%	BB, digoxin, ACE-I and CCB were frequently identified (% NR)	NR	NR
Literature reviews								
Roughead et al.[43]	Review of 14 studies	All patients/(n = 14 studies, 12,676 patients combined)	AU	DRA[a]	2.4–3.6% of admissions	CV medications leading cause (% NR)	NR	NR
Wiffen et al.[44]	LR of 69 studies (54 POS, 15 ROS)	All patients/ (n = 412,000)	–	ADR	3.1% of admitted patients	Digoxin (22/69), Diuretics (15/69) identified as leading cause	NR	Cost: £380 million per year

(Continued)

Table 1. (continued)

Author(s)	Type of study	Population/(*n*)	Country	Type of medication harm	Incidence	% CV medication harm	CV medications rank against other drug classes	Outcomes
Angamo et al.[45]	LR of studies in developed and developing countries	≥15 years (*n* = 43 studies)	–	ADR	Developed: 6.3% (median) Developing: 5.5% (median)	CV medications identified as leading cause (% NR)	NR	Severity: Developed: 20.0% severe (median) Developing: 10.0% (median)
Observational, cohort, and cross-sectional studies								
Larmour et al.[46]	PCS	All patients/(*n* = 5623 admissions)	AU	ADR	1.6% of admissions	11.1% of ADRs	1st	Mortality: 5.6%
Stanton et al.[47]	PCS	Adult patients/ (*n* = 691)	AU	ADR	3.04% of admissions	9.5% of ADRs	4th	NR
Nelson et al.[48]	PCS	Patients admitted to ICU or internal medicine/(*n* = 452)	USA	DRA[a] (includes ADR and DTF)	DRA: 16.2% ADR: 5.3% of patients	13.2% (diuretics) 10.5% (CV) of patients with DRA	2nd 5th	NR
Jha et al.[49]	PCS	All patients/(*n* = 3238 admissions)	USA	ADE[a]	2.3% of admissions	12% of ADEs	2nd	Cost: $6.3 million per year for all ADEs Severity: 78% severe
Burgess et al.[50]	Retrospective secondary data analysis of case series	>60 years/(*n* = 43,380)	AU	ADR	0.8% of all admissions for all age-groups	17.5% of patients >60 years with ADRs	1st	NR
Passarelli et al.[51]	PCS	≥60 years admitted to internal medicine/ (*n* = 186)	Brazil	ADR	11.3% of patients	22.7% (digoxin) of ADRs causing admission	1st	LOS: increased (*p* < 0.001)
Budnitz et al.[52]	PCS	All patients/ (*n* = estimated 701,547 cases)	USA	ADE[a]	NR	7.6% of ADE hospitalisations	5th	NR
Ducharme et al.[53]	Retrospective analysis of preventability data	ADR data collected over three years at a teaching hospital/ (*n* = 475 ADRs)	USA	pADR	126 pADRs (% NR)	11.9%	4th	NR
Edwards et al.[54]	PCS	Patients ≥17 years/ (*n* = 62,064 admissions)	USA	ADE[a]	2.4% of admissions	28% of ADEs	2nd	Mortality: 3.2%
Ocampo et al.[55]	CSS	Patients ≥60 years/ (*n* = 400)	Columbia	ADE and ADR	6.8%	% NR	3rd	NR

(Continued)

Table 1. (continued)

Author(s)	Type of study	Population/(n)	Country	Type of medication harm	Incidence	% CV medication harm	CV medications rank against other drug classes	Outcomes
Ventura et al.[56]	PCS	All patients/(n = 56,031)	Italy	ADR	21.2%	% NR	3rd	NR
Budnitz et al.[6]	RCS	≥65 years/(n = estimated 99,628 cases)	USA	ADE	NR	9.8% of ADE hospitalisations	3rd	NR
Conforti et al.[57]	PCS	Patients ≥65 years/(n = 1023)	Italy	ADR	11.1% of patients	46.2% of ADRs	1st	LOS: increased (no p value reported)
Marcum et al.[58]	RCS	≥65 years veterans/(n = 6778)	USA	ADR[a]	10% of patients	CV medications identified as leading cause (% NR)	NR	NR
McLachlan et al.[59]	PCS	All general medical patients/(n = 336)	New Zealand	ADE	28.6% of admissions	23% (vasodilators), 16% (diuretics), 11% (chronotropes)	1st (vasodilators), 3rd (diuretics), 4th (chronotropes)	NR
Phillips et al.[60]	PCS	All patients/(n = 370)	AU	ADE[a,d]	16% of patients (34.7% were ADRs)	31.5% of ADEs	3rd (ACE-I) 5th (BB) 6th (diuretics) 8th (CCB)	Severity: 34.7% of ADEs were severe
Gustafsson et al.[37]	RCS	≥65 years with cognitive impairment/(n = 458)	Sweden	DRP[a,e]	DRP: 41.3% ADR: 18.8% of admissions	29.5% of DRPs (% of ADRs NR)	1st	NR
de Almeida et al.[61]	RCS	Adult patients/(n = 866)	Brazil	ADR	2.3%	14.3% of ADRs	2nd	Cost: $5698.84 per ADR hospitalisation
Paradissis et al.[22]	PCS	≥65 years admitted to internal medicine/(n = 164)	AU	ADE[a]	15.2% of patients	50% of ADEs	1st	LOS: increased (p = 0.043)
Parameswaran et al.[62]	Prospective, CSS	≥65 years admitted to hospital/(n = 1008)	AU	ADR	18.9% of admissions	23.9% of ADRs (diuretics) 16.4% (ACE-I/ARB) 7.1% (BB)	1st 2nd 3rd	Preventable: 87.2% of ADRs Mortality: 2.1% Severity: 2.1%
Poudel et al.[63]	Descriptive RCS	All patients/(n = weighted estimate 150 259 899 hospitalisations)	USA	ADE[a]	5.97–6.28% of hospitalisations	13.24% of ADEs (combined)	8th (diuretics) 11th (anti-HTN) 15th (cardiac glycosides) 17th (anti-arrhythmics) 18th (BB) 21st (antihyperlipidaemic)	LOS: increased for ADE hospitalisations (p < 0.001) Cost: increased (p < 0.001) Mortality: increased (p < 0.001)

(Continued)

Table 1. (continued)

Author(s)	Type of study	Population/[n]	Country	Type of medication harm	Incidence	% CV medication harm	CV medications rank against other drug classes	Outcomes
Ognibene et al.[64]	RCS	≥65years admitted to internal medicine/ [n = 1750]	Italy	ADR[f]	6.1% of admissions	17.6% (Diuretics)	1st	Mortality: 10.4% of ADRs Severity: 27.4% with residual disability
Schurig et al.[65]	PCS	All patients presenting to emergency/ [n = 10,174]	Germany	ADR[a]	6.5% of admissions	~19% (BB) ~17% (ACE-I)	2nd 3rd	NR
Mullan et al.[66]	RCS	≥65years with and without dementia/ [n = 228,165 admissions]	AU	MM[a,g]	4.6% of admissions	With dementia: 3.9% of MM (anti-HTN) 3.4% (BB) 2.5% (ACE-I) Without dementia: 4.7% (anti-HTN) 4.1% (BB) 2.6% (cardiac glycosides) 2.1% (diuretics) 2.0% (ACE-I)	With dementia: 4th 5th 8th Without dementia: 5th 6th 7th 8th 10th	NR
Zhang et al.[67]	Population based RCS	All patients/ [n = 315,274 ADR admissions]	AU	ADR	432.3 per 100,000 residents	4.8% of ADRs (anti-HTN) 3.9% (BB) 2.9% (cardiac stimulant)	4th 7th 9th	NR
Smeaton et al.[68]	PCS	Patients aged between 45–64years/ [n = 100]	Ireland	ADR	21%	52.2% of ADRs	1st	Preventable: 52.2% of ADRs

[a]Includes medication errors.
[b]Includes ADRs, overtreatment, under-treatment and adherence problems.
[c]Definition for CV medications incorporated antithrombotics and anticoagulants.
[d]Includes non-compliance, untreated indications, improper drug selection, sub/supratherapeutic dose, ADRs, drug interactions and drug use without indication.
[e]Includes ADR, dosage too high, dosage too low, ineffective drug, needs additional drug therapy, unnecessary drug therapy and noncompliance.
[f]Includes drug–drug interactions.
[g]Includes ADR, ADEs and medication errors.
ACE-I, angiotensin-converting enzyme inhibitor; ADE, adverse drug event; ADR, adverse drug reaction; AE, adverse events; anti-HTN, antihypertensives; ARB, angiotensin receptor blocker; AU, Australia; AUD, Australian dollars; BB, beta-blockers; CCB, calcium channel blocker; CCS, case-control study; CSS, cross-sectional study/survey; CV, cardiovascular; DRA, drug-related admission; DRP, drug-related problem; DTF, drug therapeutic failure; ICU, intensive care unit; LOS, length of stay; LR, literature review; MA, meta-analysis; MM, medication misadventure; NR, not reported; OS, observational study; pADE, preventable adverse drug event; PCS, prospective cohort study; POS, prospective observational study (includes CCS/PCSI; RCS, retrospective cohort study; ROS, retrospective observational study (includes CCS/PCSI; SR, systematic review; USA, United States of America.

CV medication harm occurring during hospital stay

A total of 23 inpatient studies were found, including one systematic review, two meta-analyses, 16 observational studies and three literature reviews. Twenty-one studies were analysed and tabulated and the results of the remaining two studies are included within the systematic reviews (Table 2).[2,69] There were wide variations in the reported rates of inpatient medication harm (2–46% of patients).[51,70,71] This may be attributed to the different methodologies used to identify harm and to the different patient populations studied. Studies investigating older adults reported higher rates of harm compared with those including all age groups.[22,51,71,72]

CV medications were found to be one of the top five medications to cause harm during admission, and the prevalence of CV medication harm increased in older populations (Table 2).[2,4,5,22,44,51,57,69–72,74,76,83] A meta-analysis and systematic review found CV medications were the second and third most frequently implicated medications in inpatient ADEs and ADRs, respectively.[74] In addition, CV medications were the fourth most frequently involved drug class in fatal ADRs after antithrombotics, sedatives and antineoplastics.[74] Another literature review found CV medications to be implicated in causing 17.9% of preventable ADEs and recommended that they be a high-priority focus for harm prevention strategies.[70]

In the Harvard Medical Practice Study, 3.7% of 30,195 patients experienced harm, with medications responsible for 19% of harm.[4] CV medications were the fourth highest cause (8.5%) of ADEs.[4] Antihypertensives, classified separately, were the seventh highest cause (5.0%).[4] In the Quality in Australian Health Care Study, CV medications were implicated in causing 20% ($n = 46$) of 230 ADEs of which, 13% resulted in permanent disability.[5] Events caused by CV medications were the most highly preventable.[5]

Two studies investigated medication harm in critical care.[75,82] A scoping review of 30 studies investigated medications as contributors to clinical deterioration or the need for critical care.[75] Sedatives, analgesics and CV medications were most commonly implicated, although the quality of evidence was low due to small sample sizes and few primary medication-related outcomes.[75] A Columbian study investigating ADRs as a cause of admission to the intensive care unit (ICU) found antiplatelet drugs (bleeding) and renin–angiotensin-receptor-blocking drugs (renal impairment) were most frequently responsible for harm.[82]

Type of CV medication causing harm. Of the studies that delineated CV medications, antiarrhythmics, antihypertensives (e.g. beta-blockers, ACE-I) and diuretics were common causes of medication harm.[22,44,74,76] Notably, digoxin was frequently implicated, likely a result of its narrow therapeutic range.[44,76,84] Diuretics and antihypertensives have been reported to cause up to 33% and 17% of medication harm events, respectively.[57,71] Renal impairment and electrolyte imbalances caused by these medications were frequent, and in severe cases, led to ICU admission and a prolonged length of hospital stay.[22,44,51,71,82]

CV medication harm after discharge from hospital

The transition of patients from hospital raises safety challenges due to the risk of medication harm.[85–88] Ten studies, one systematic review and nine observational studies, investigated medication harm after discharge or in ambulatory care. This included a systematic review and observational studies with a post discharge follow-up period of up to 365 days, and observational studies conducted in outpatient departments, multispecialty clinics or a community setting (e.g. residential/continuing care facilities and general practitioners). Six studies were analysed and included in Table 3 as the remaining four observational studies were encompassed within the systematic review.[87–90] An examination of all adverse events in 400 general medical patients after discharge, found that ADEs accounted for the majority (66%) of events.[91] However, similar to medication harm on/during hospital admission, there was a wide variation in rates, with the highest rates reported in older populations (0.4–51.2%).[88,92]

CV medications were a leading cause of harm post discharge. Most studies found approximately one in five medication harm events were caused by CV medications, increasing in some studies to over half of events among older patients.[88–90,92,95–97] The aforementioned systematic review of patients

Table 2. CV medication harm within hospitals.

Author	Type of study	Patient population/(n)	Country	Type of medication harm	Incidence	% medication harm caused by CV medications	CV medications ranked against other drug classes	Outcomes
Systematic reviews and meta-analyses								
Beijer et al.[73]	MA	All patients/(n=68 studies, 123,794 admissions)	–	ADR[a]	4.9% of admissions (mean)	CV identified in 38 studies	NR	Preventable: 28.9% (mean) from 12 studies
Alhawassi et al.[41]	SR of POS/ROS	≥18years/(n=14 studies)	–	ADR	11.5% (median)	CV medications identified as leading cause (% NR)	NR	NR
Laatikainen et al.[74]	MA and SR of nine studies	All patients/(n=9 studies, 46,626 patients)	–	ADE[a] ADR FADR	ADEs: 21.6% (mean) ADRs: 23.4% (mean) FADRs: 9.6% (mean)	16% of ADEs 20% of ADRs 9% of FADR (from three studies)	2nd 3rd 4th	Preventable: 12.0–75% Severity: 9.6% fatal (mean from 3 studies)
Literature reviews								
Wiffen et al.[44]	LR of 69 studies (54 POS and 15 ROS)	All patients/(n=412,000)	–	ADR	3.7% of inpatients	Digoxin (22 studies) Diuretics (15 studies) identified as leading cause of harm (% NR)	NR	Cost: £380 million
Kanjanarat et al.[70]	LR of 10 studies	All patients/(n=10 studies, 117,259 patients)	–	pADE[a]	1.8% (median)	17.9% of pADEs	1st	NR
Levkovich et al.[75]	Scoping LR	Hospitalised patients/(n=12 studies)	–	Emergency call/respiratory arrest	5–37% of deteriorations	CV medications identified as leading cause (% NR)	NR	NR
Observational/cohort and case-control studies								
Leape et al.[4]	RCS	All patients/(n=30,195)	USA	AEs (including drug complications)[a]	19% of adverse events	8.5% of drug complications	4th	Severity: 14.1% caused serious disability
Wilson et al.[5]	RCS	All patients/(n=14,000 admissions)	AU	AEs including drug related[a]	10.8% of AEs	11.6% (CV) 8.2% (antihypertensive) of drug-related AEs	3rd (CV) 6th (anti-HTN)[b]	Mortality: 8%, Severity: 17% caused permanent disability
Classen et al.[76]	Matched CCS	All patients/(n=1580 cases and 20,197 controls)	USA	ADE[a]	2.43% of patients	NR	2nd (digoxin)	Cost: increase of $2262 linked with ADE (p<0.001) Severity: 5.8% severe, 3.5% fatal LOS: increased (p<0.01)

(Continued)

Table 2. (continued)

Author	Type of study	Patient population/(n)	Country	Type of medication harm	Incidence	% medication harm caused by CV medications	CV medications ranked against other drug classes	Outcomes
Doucet et al.[77]	PCS	≥70 years admitted to geriatric unit/(n = 2814)	France	ADE	15.2%	43.7% of ADEs	1st	NR
Al-Tajir et al.[78]	PCS	All patients/(n = 736 ADE reports)	UAE	ADE	NR	16.5%	3rd	Preventable: 13.8% of ADEs
Passarelli et al.[51]	PCS	≥60 years admitted to internal medicine/(n = 186)	Brazil	ADR	46.2% of patients	11.8% (diuretics) 7.6% (captopril) of ADRs	1st (diuretics) 2nd (captopril)	LOS: increased (p < 0.001)
Cecile et al.[72]	RCS	Patients ≥65 years/(n = 823)	France	ADE[a,c]	13.6% of patients	23.2% (CV) 15.2% (diuretics) of ADEs[c]	1st (CV) 4th (diuretics)	NR
Trivalle et al.[79]	Randomised prospective trial	Patients ≥65 years/(n = 576)	France	ADE[a]	223 ADEs identified	19.8% of ADEs	1st	NR
Morimoto et al.[80]	PCS	Patients ≥15 years/(n = 3459 admissions)	Japan	ADE	21% of patients	5.1% of ADEs	5th	Mortality: 1.6% of ADEs Severity: 4.9% life threatening
Conforti et al.[57]	PCS	Patients ≥65 years/(n = 1023)	Italy	ADR	25% of patients	32.4% of ADRs	1st (diuretics)	LOS: increased (no p value reported)
O'Connor et al.[71]	PCS	Patients ≥65 years/(n = 513)	Ireland	ADR	26% of patients	25% (diuretics) 17% (anti-HTN) of ADRs	1st (diuretics) 4th (anti-HTN)	Severity: 24% were severe
Parikh et al.[81]	RCS	All patients/(n = 57,205)	AU	ADE[a]	0.7% of admissions	9% of ADEs	4th	NR
Paradissis et al.[22]	RCS	Patients ≥65 years/(n = 164)	AU	ADE[a]	7.3% of patients	44% of ADEs	1st	LOS: increased (p = 0.043)
Rojas-Velandia et al.[82]	RCS	Patients admitted to ICU/(n = 697 patients)	Colombia	ADR	11.0% of patients	33.3%	2nd	Preventable: 44% of ADRs
Robb et al.[83]	RCS	All patients/(n = 2659)	New Zealand	ADE/MRH[a,d]	28% of patients[e]	5.4% of MRH	5th (furosemide) 8th (metoprolol)	Severity: 1.6% permanent disability or death, 2.4% required an intervention to sustain life

[a]Includes medication errors.
[b]n.b. leading drug type was 'other'.
[c]Includes ADEs causing admission; inpatient rate not separated in analysis.
[d]terms used interchangeably.
[e]Includes ADEs causing admission, readmission and inpatient ADEs.
ADE, adverse drug event; ADR, adverse drug reaction; AE, adverse events; antiHTN, antihypertensives, AU, Australia; CCS, case-control study; CV, cardiovascular; FADR, fatal ADR; ICU, intensive care unit; LOS, length of stay; LR, literature review; MA, meta-analysis; MRH, medication-related harm; NR, not reported; OS, observational study; pADE, preventable ADE; pADR, preventable ADR; PCS, prospective cohort study; POS, prospective observational study (includes PCS/CCS/cross-sectional study); RCS, retrospective cohort study; ROS, retrospective observational study (includes RCS/CCS/cross sectional study; SR, systematic review; USA, United States of America.

Table 3. CV medication harm after hospital discharge and in ambulatory care.

Author	Type of study	Patient population/ (n =)	Country	Type of medication harm	Incidence	% of medication harm caused by CV medications	CV medication ranked against other drug classes	Outcomes
Systematic review								
Parekh et al.[92]	SR of 8 POS/ROS	≥65 years/(n = 8 studies, 10,945 patients combined)	–	ADRs and ADEs[a]	0.4–51.2% of patients	18.8–55.7% of events	1st	Preventable: 35–59%
Observational studies								
Gandhi et al.[93]	PCS	Outpatients/ (n = 1202)	USA	ADE[a]	25%	9% (BB) 8% (ACE-I) of ADEs	2nd 3rd	Severity: 3.6% Preventable: 3.0%
Gurwitz et al.[90]	RCS	Outpatients ≥65 years/ (n = 27,617)	USA	ADE	50.1 events per 1000 person-years	24.5%	1st	Severity: 38% serious, life threatening or fatal
Carnovale et al.[94]	PCS	≥65 years/(n = 1073 cases)	Italy	ADR[a]	NR	7.8% of ADRs	6th	Severity: 18% of ADRs were serious Preventable: 7.3%
Mann et al.[95]	RCS	≥18 years admitted to Hospital at Home service/ (n = 50)	USA	ADE[a]	22% of patients	21.4% of ADEs	2nd (diuretics)	Preventable: 7.1%
Parekh et al.[96]	PCS	≥65 years/ (n = 1280)	England	MRH[a,b]	37%	22.4% (anti-HTN), 12.2% (diuretics) of MRH	1st (anti-HTN) 3rd (diuretics)	Severity: 1.0% fatal, 2.2% life threatening Preventable: 14%

[a]Includes medication errors.
[b]Includes ADR, medication errors or harm caused by non-adherence.
ACE-I, angiotensin converting enzyme inhibitors; ADE, adverse drug event; ADR, adverse drug reaction; AE, adverse events; anti-HTN, antihypertensives; BB, beta-blockers; CV, cardiovascular; ME, medication error; MRH, medication-related harm; NR, not reported; OS, observational study; pADE, preventable adverse drug event; PCS, prospective cohort study; POS, prospective observational study; RCS, retrospective cohort study; ROS, retrospective observational study; SR, systematic review; USA, United States of America.

greater than 65 years of age found that CV medications were the leading cause of ADRs and ADEs, implicated in 18.8–55.7% of events.[92] Within the review, a 1999 study found that the number of newly prescribed medications at the time of discharge was a significant risk factor for medication harm.[97] CV medications were the most commonly prescribed medications at the time of discharge, a potential reason for the high rates of harm in this group (18.8%).[97]

Types of CV medications causing harm. Medication harm was most frequently attributed to anti-hypertensives which included diuretics, ACE-Is, beta-blockers and CCBs.[87,88,93] Harm caused by these medications was deemed highly preventable, causing 40.5% of preventable ADEs.[88] They were also implicated in causing 42% of serious ADEs.[93] While the high prevalence of harm caused by CV medications may simply reflect their high prescribing rates, one study found that, after correcting for this factor, CV medications still contributed to excess harm.[93]

Readmission caused by CV medication harm
While a number of studies investigated medication harm that caused readmission, most of these

studies were summarised in one systematic review.[86] This review of 19 studies showed a wide variation in the reported incidence of medication harm causing readmission (3–64%).[86] The mean readmission rate caused by medication harm at 30 days and 12 months was found to be approximately 20% (range 7–61%).[86] CV medications were frequent causes of preventable readmissions in six studies within the systematic review, causing as many as 30% of ADR readmissions.[20,86,98,99] Diuretics causing renal impairment were common and, in severe cases, were linked with death.[86,98] Postural hypotension, arrhythmias and peripheral oedema caused by ACE-Is/diuretics, beta-blockers and CCBs, respectively, were also reported.[98,100]

Discussion

This review identified CV medications as a leading cause of medication harm, consistent with results reported from recent, local studies.[22,23] Irrespective of clinical setting, approximately one in five medication harm events were found to be caused by CV medications and they were also ranked within the top five classes of medications to cause harm. Antihypertensives, diuretics and antiarrhythmics (e.g. digoxin) were most frequently implicated. The latter is consistent with a 2014 study that found that despite decreasing rates of digoxin prescribing, emergency presentations due to toxicity remained high, with >5000 visits estimated annually in the US.[101]

CV medications and the ageing population

An emergent theme was that older persons are particularly susceptible to CV medication harm, as shown in Figure 2.[17] This class accounted for greater than 50% of all events reported in some studies, and studies specifically involving older patients are summarised in Online Resource 3.[22,62,96] Similar to the findings for all adults, antihypertensives, such as diuretics and ACE-Is, and antiarrhythmics, were frequently implicated (Figure 2).

As the population ages and the prevalence of CV disease increases, harm caused by CV medications will likely increase. As a result of the ageing process, body systems undergo a progressive decline in physiological functioning, including the CV, pulmonary and renal systems.[102] This results in altered pharmacokinetics/pharmacodynamics of medications which clinicians must consider when managing CV medications.[17,102]

The importance of individualising and rationalising therapy in older adults is essential for patient care. A number of deprescribing tools have been developed and incorporate CV medications.[103–105] The application of decision support is particularly prudent in frail older persons in whom risks of medications often outweigh their benefits.[106,107] Of particular interest is optimising the use of antihypertensives by using agreed treatment goals, absolute CV disease risk and appropriate blood-pressure target levels.[107] Knowing when to review or deprescribe CV medications in older patients is challenging in light of the strong evidence base for these medications in reducing CV disease risk.[108] However, it is imperative to note that most clinical trials have not included the frail and multimorbid older patients who are frequently encountered in routine clinical practice.[109,110] It is important to recognise that deprescribing is indeed concordant with ethical principles when serving patient-centred interests (i.e. beneficence, non-maleficence, autonomy, and justice).[111]

The under-representation of multimorbid, older adults, the focus of drug approval processes on efficacy and the lack of long-term efficacy and data on harm in clinical trials of CV medications has been described in the literature.[110,112,113] These factors result in a discrepancy between the incidence, type and severity of harm reported in clinical trials and that reported in clinical practice (post-marketing).[112] While the benefits of CV medications are widely acknowledged, a recent push for active pharmacovigilance programmes and deprescribing in patients with CV diseases has emphasised the need to recognise the harms linked with CV medications.[110,112,113] Patient–clinician interactions should allow for informed treatment decisions about the benefits and harms of CV medications.[110,114] In addition, opportunities for rationalisation through withdrawal or dose reduction should be considered regularly with a focus on realistic treatment goals.[110,114] The studies included in this review are representative of real-world treatment populations, and the findings support the need for

emphasis to be placed on the rationalisation of antihypertensives and other CV medications, particularly within older populations.

The implications of CV medication harm

While it is acknowledged that CV medications have a fundamental role in the reduction of major CV endpoints, such as morbidity and mortality, the harm caused by these medications should not be overlooked. Although medication harm, such as electrolyte imbalance and renal impairment caused by antihypertensives, can be potentially reversible and may not be considered severe, the findings of this review highlighted that these events are linked with poor outcomes. The included studies reported life-threatening events, admissions to the ICU, prolonged hospital stays and in some cases, fatal events, caused by antihypertensives and diuretics.[22,34,39,44,51,71,82,88,98] Although underexplored, this medication harm has the potential to cause both unwanted physical and psychological ramifications for patients due to the distress associated with hospitalisation and intensive care stays.[115] Many studies also found a high proportion of preventable medication harm events to be caused by CV medications.[5,62,70,77,88,98] The resultant financial impact and consumption of healthcare resources due to potentially avoidable hospital presentations and prolonged length of hospital stays should also be considered when measuring the magnitude of the harm. For patients where withdrawal of CV medications is not indicated (see above), prudent dose selection and stringent monitoring following guideline driven dose adjustments is warranted to reduce the risk of medication harm.

In this review, we wanted to investigate CV medication harm from an international perspective. The studies included in this review (including those within the systematic and literature reviews) were conducted across six continents including: North America, Europe, Australia/Oceania, South America, Asia and Africa, from 41 countries. This highlights that CV medication harm is a global challenge and does not discriminate across healthcare settings or healthcare systems worldwide. The World Health Organization's third global patient safety challenge 'Medication without harm' has paved the way to improve medication harm from a global perspective.[9] The findings of this review suggest that improving CV medication harm should be prioritised along with other 'high risk' medications.

High risk medications

In responding to the high prevalence of medication harm, lists of 'high risk/alert' medications have been formulated. These include medications associated with an increased risk of patient harm, particularly if prescribed, dispensed or administered erroneously.[14] The lists are commonly promoted in hospitals to raise awareness about medication safety.

The ISMP list of 'high alert' medications is the most comprehensive and frequently used worldwide.[14] It is updated regularly based on medication error reports, medication harm literature and consensus from practitioners and safety experts.[14] The latest list consists of 21 different medication classes, with CV medications accounting for 19.0% of the listed medications.[14]

A standardised list is important to remind clinicians of the risk of medication harm. In Australia, the current 'high risk' medications are within the acronym, 'APINCH' (Figure 1), which has been widely adopted nationwide.[12] It differs from the ISMP list in that it does not incorporate CV medications, such as antiarrhythmics (e.g. amiodarone), inotropes (e.g. digoxin) and adrenergic antagonists (e.g. beta-blockers).[12–14]

The omitted 'C' in APINCH

In addition to the evidence for contributing to harm, there are other clinical reasons CV medications should be considered 'high risk'. First, many CV medications require well-defined protocols to guide administration and often can only be prescribed by skilled staff. Second, 'high risk' medicines are defined as 'medicines that have an increased risk of causing significant patient harm or death if they are misused or used in error'.[13] This criteria would apply to intravenously administered antiarrhythmics, such as digoxin, metoprolol and amiodarone.[116] Third, CV medication harm largely affects older populations who account for most hospital admissions and are particularly vulnerable to medication harm.[36,50,117] Additionally, harm is prevalent across all healthcare settings and our findings suggest patients newly prescribed CV medications during hospital

admission are at risk of medication harm in ambulatory care.[92,97] This emphasises the need for clinicians to consider harm mitigation strategies at the time of discharge such as home medication reviews, additional follow-up general practitioner visits and 'high-risk' discharge clinics.

Given the results of our review, we propose that CV medications are brought to the forefront by incorporating 'C' into the 'APINCH' acronym. 'CAPINCH' or 'APINCH-C' would serve as a prompt to optimise the use of CV medications throughout hospitalisation, including at the time of discharge. We acknowledge that this may be a different application of the 'APINCH' acronym to what was originally intended. However, the addition of 'C' would provide a practical and timely initiative to generate awareness about the harm caused by CV medications.

Limitations

There are some limitations to this review. Medication harm literature is vast and heterogeneous, and studies differ in terminology and methodology which makes it difficult to compare studies.[24] Additionally, the breadth and exploratory nature of the research across four healthcare settings did not meet the explicit criterion for a systematic approach, such as PRISMA. Therefore, a narrative review was undertaken and consequently, some relevant studies may not have been included. To account for this, we employed a structured search strategy using elements of PRISMA (e.g. medical subject headings, abstract/title screening) with a focus on the major studies incorporating definitions that matched our medication harm definition. To aid in transparency, we distinguished between study design and definitions used throughout this review. Similarly, the classification of drug classes differed between studies. For example, some studies included antithrombotics (e.g. aspirin) as a CV medication.[36] As our focus was on medications directly acting on the CV system, antithrombotics were excluded; however, some studies did not specify what was included within the CV medication class. It should be noted that antiplatelets are not incorporated within the 'APINCH' acronym.[12] Due to the important role these medications play in practice, antiplatelets could be a potential focus for future reviews of medication harm. Finally, it is acknowledged that medication harm can be precipitated by drug–drug and drug–disease interactions and from medication omission (e.g. non-compliance). Unless it was specified by the authors of the study, we were unable to discern whether these underlying factors were major contributors to medication harm.

Conclusion

CV medications are frequently implicated in causing harm across all healthcare settings. A common theme was the high prevalence of harm in older adults, which leads to morbidity and hospital utilisation. A practical method for socialising the risk would be to adapt a well-accepted safety acronym.

Author contributions

CP, MB, IC and NC were involved in the conception and planning of the manuscript. CP researched, analysed and wrote the manuscript under the guidance of MB, IC and NC. MB, IC, NC, IS and WW reviewed and edited the manuscript. IS and WW provided medical expertise in the analysis and presentation of results and discussion points.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Code availability

Not applicable

ORCID iDs

Chariclia Paradissis https://orcid.org/0000-0001-9449-6761

Ian Scott https://orcid.org/0000-0002-7596-0837

Availability of data and material

All data included and analysed for this research are incorporated within the manuscript and supplementary files provided. These published works were obtained from PubMed and CINAHL databases.

Supplemental material

Supplemental material for this article is available online.

References

1. Australian Institute of Health and Welfare. *Australia's health 2018.* Australia's health series no. 16. AUS 221. Canberra: AIHW, 2018.

2. Bates DW, Cullen DJ, Laird N, *et al*. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA* 1995; 274: 29–34.

3. Davis P. Adverse events in New Zealand public hospitals I: occurrence and impact. *N Z Med J* 2002; 115: U271.

4. Leape LL, Brennan TA, Laird N, *et al*. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* 1991; 324: 377–384.

5. Wilson RM, Runciman WB, Gibberd RW, *et al*. The quality in Australian health care study. *Med J Aust* 1995; 163: 458–471.

6. Budnitz DS, Lovegrove MC, Shehab N, *et al*. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med* 2011; 365: 2002–2012.

7. Roughead L, Semple S and Rosenfeld E. *Literature review: medication safety in Australia.* Sydney: Australian Commission on Safety and Quality in Health Care, 2013.

8. Roughead EE, Semple JS and Rosenfeld JE. The extent of medication errors and adverse drug reactions throughout the patient journey in acute care in Australia. *Int J Evid Based Healthc* 2016; 14: 113–122.

9. World Health Organization. The third WHO global patient safety challenge: medication without harm, https://www.who.int/patientsafety/medication-safety/en/ (2019, accessed 29 August 2019).

10. Pharmaceutical Society of Australia. Medicine safety to be the 10th National Health Priority area, https://www.psa.org.au/ (2019, accessed 30 July 2020).

11. The Hon Greg Hunt MP. Doorstop interview about the COAG health ministers meeting, https://www.health.gov.au/ministers/the-hon-greg-hunt-mp/media/doorstop-interview-about-the-coag-health-ministers-meeting (2019, accessed 30 July 2020).

12. Australian Commission on Safety and Quality in Health Care. APINCHS classification of high risk medicines, https://www.safetyandquality.gov.au/our-work/medication-safety/high-risk-medicines/apinchs-classification-high-risk-medicines (2019, accessed 8 November 2019).

13. Australian Commission on Safety and Quality in Health Care. High risk medicines, https://www.safetyandquality.gov.au/our-work/medication-safety/high-risk-medicines (2019, accessed 12 December 2019).

14. Institute for Safe Medication Practices. High-alert medications in acute care settings, https://www.ismp.org/recommendations/high-alert-medications-acute-list (2018, accessed 10 September 2019).

15. Clinical Excellence Commission. High-risk medicines, http://www.cec.health.nsw.gov.au/patient-safety-programs/medication-safety/high-risk-medicines/A-PINCH (2019, accessed 8 November 2019).

16. Australian Institute of Health and Welfare. Medicines for cardiovascular disease. Cat. no. CVD 80. Canberra: AIHW, 2017.

17. Holbeach E and Yates P. Prescribing in the elderly. *Aust Fam Physician* 2010; 39: 728–733.

18. Chew DP, Scott IA, Cullen L, *et al*. National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. *Heart Lung Circ* 2016; 25: 895–951.

19. Ali Raza J and Movahed A. Use of cardiovascular medications in the elderly. *Int J Cardiol* 2002; 85: 203–215.

20. Ruiz B, Garcia M, Aguirre U, *et al*. Factors predicting hospital readmissions related to adverse drug reactions. *Eur J Clin Pharmacol* 2008; 64: 715–722.

21. Wang Y, Singh S and Bajorek B. Old age, high risk medication, polypharmacy: a 'trilogy' of risks in older patients with atrial fibrillation. *Pharm Pract (Granada)* 2016; 14: 706.

22. Paradissis C, Coombes ID, Donovan P, *et al*. The type and incidence of adverse drug events in ageing medical inpatients and their effect on

length of hospital stay. *J Pharm Pract Res* 2017; 47: 347–354.

23. Falconer N, Barras M, Abdel-Hafez A, *et al*. *Prioritising patients at high-risk of medication harm: Development and validation of risk prediction models [dissertation]*. University of Queensland, Brisbane, Australia, 2019.

24. Falconer N, Barras M, Martin J, *et al*. Defining and classifying terminology for medication harm: a call for consensus. *Eur J Clin Pharmacol* 2019; 75: 137–145.

25. Australian medicines handbook online [Internet]. Adelaide (S. Australia): Australian Medicines Handbook Pty Ltd, 2020. Cardiovascular drugs, https://amhonline.amh.net.au/chapters/cardiovasculardrugs?menu=banner (2020, accessed 30 July 2020).

26. Guerrouij M, Uppal CS, Alklabi A, *et al*. The clinical impact of bleeding during oral anticoagulant therapy: assessment of morbidity, mortality and post-bleed anticoagulant management. (Report). *J Thromb Thrombolysis* 2011; 31: 419.

27. Piazza G, Nguyen TN, Cios D, *et al*. Anticoagulation-associated adverse drug events. *Am J Med* 2011; 124: 1136–1142.

28. Budnitz DS, Shehab N, Kegler SR, *et al*. Medication use leading to emergency department visits for adverse drug events in older adults. *Ann Intern Med* 2007; 147: 755–765.

29. Chan M, Nicklason F and Vial J. Adverse drug events as a cause of hospital admission in the elderly. *Intern Med J* 2001; 31: 199–205.

30. Hallas J, Gram LF, Grodum E, *et al*. Drug related admissions to medical wards: a population based survey. *Br J Clin Pharmacol* 1992; 33: 61–68.

31. McDonnell PJ and Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. *Ann Pharmacother* 2002; 36: 1331–1336.

32. Mjorndal T, Boman MD, Hagg S, *et al*. Adverse drug reactions as a cause for admissions to a department of internal medicine. *Pharmacoepidemiol Drug Saf* 2002; 11: 65–72.

33. Onder G, Pedone C, Landi F, *et al*. Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA). *J Am Geriatr Soc* 2002; 50: 1962–1968.

34. Pirmohamed M, James S, Meakin S, *et al*. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; 329: 15–19.

35. Wawruch M, Zikavska M, Wsolova L, *et al*. Adverse drug reactions related to hospital admission in Slovak elderly patients. *Arch Gerontol Geriatr* 2009; 48: 186–190.

36. Kongkaew C, Noyce PR and Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. *Ann Pharmacother* 2008; 42: 1017–1025.

37. Gustafsson M, Sjolander M, Pfister B, *et al*. Drug-related hospital admissions among old people with dementia. *Eur J Clin Pharmacol* 2016; 72: 1143–1153.

38. Runciman WB, Roughead EE, Semple SJ, *et al*. Adverse drug events and medication errors in Australia. *Int J Qual Health Care* 2003; (15 Suppl. 1): i49–i59.

39. Howard RL, Avery AJ, Slavenburg S, *et al*. Which drugs cause preventable admissions to hospital? A systematic review. *Br J Clin Pharmacol* 2007; 63: 136–147.

40. Al Hamid A, Ghaleb M, Aljadhey H, *et al*. A systematic review of hospitalization resulting from medicine-related problems in adult patients. *Br J Clin Pharmacol* 2014; 78: 202–217.

41. Alhawassi TM, Krass I, Bajorek BV, *et al*. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. *Clin Interv Aging* 2014; 9: 2079–2086.

42. Oscanoa TJ, Lizaraso F and Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. *Eur J Clin Pharmacol* 2017; 73: 759–770.

43. Roughead EE, Gilbert AL, Primrose JG, *et al*. Drug-related hospital admissions: a review of Australian studies published 1988-1996. *Med J Aust* 1998; 168: 405–408.

44. Wiffen P, Gill M, Edwards J, *et al*. Adverse drug reactions in hospital patients: a systematic review of the prospective and retrospective studies. In: *Database of Abstracts of Reviews of Effects (DARE): quality-assessed reviews*. York, UK: Centre for Reviews and Dissemination (UK), 2002, pp.1–14.

45. Angamo MT, Chalmers L, Curtain CM, *et al*. Adverse-drug-reaction-related hospitalisations in developed and developing countries: a review

of prevalence and contributing factors. *Drug Saf* 2016; 39: 847–857.

46. Larmour I, Dolphin RG, Baxter H, *et al.* A prospective study of hospital admissions due to drug reactions. *Aust J Hosp Pharm* 1991; 21: 90–95.

47. Stanton LA, Peterson GM, Rumble RH, *et al.* Drug-related admissions to an Australian hospital. *J Clin Pharm Ther* 1994; 19: 341–347.

48. Nelson KM and Talbert RL. Drug-related hospital admissions. *Pharmacotherapy* 1996; 16: 701–707.

49. Jha AK, Kuperman GJ, Rittenberg E, *et al.* Identifying hospital admissions due to adverse drug events using a computer-based monitor. *Pharmacoepidemiol Drug Saf* 2001; 10: 113.

50. Burgess CL, Holman CD and Satti AG. Adverse drug reactions in older Australians, 1981-2002. *Med J Aust* 2005; 182: 267–270.

51. Passarelli MC, Jacob-Filho W and Figueras A. Adverse drug reactions in an elderly hospitalised population: inappropriate prescription is a leading cause. *Drugs Aging* 2005; 22: 767–777. 2005/09/15. DOI: 10.2165/00002512-200522090-00005

52. Budnitz DS, Pollock DA, Weidenbach KN, *et al.* National surveillance of emergency department visits for outpatient adverse drug events. *JAMA* 2006; 296: 1858–1866.

53. Ducharme MM and Boothby LA. Analysis of adverse drug reactions for preventability. *Int J Clin Pract* 2007; 61: 157–161.

54. Edwards DB, Heisler M, Guidry J, *et al.* Adverse drug events leading to admission at a community nonteaching hospital. *J Clin Outcomes Manag* 2007; 14: 389–394. Article.

55. Ocampo JM, Chacón JA, Gómez JF, *et al.* Adverse drug reactions and adverse drug events in elderly patients consulting a hospital emergency unit. *Colomb Med* 2008; 39: 135–146.

56. Ventura MT, Laddaga R, Cavallera 'P, *et al.* Adverse drug reactions as the cause of emergency department admission: focus on the elderly. *Immunopharmacol Immunotoxicol* 2010; 32: 426–429.

57. Conforti A, Costantini D, Zanetti F, *et al.* Adverse drug reactions in older patients: an Italian observational prospective hospital study. *Drug, Healthcare and Patient Safety* 2012; 4: 75.

58. Marcum ZA, Amuan ME, Hanlon JT, *et al.* Prevalence of unplanned hospitalizations caused by adverse drug reactions in older veterans. *J Am Geriatr Soc* 2012; 60: 34–41.

59. McLachlan CY, Yi M, Ling A, *et al.* Adverse drug events are a major cause of acute medical admission. *Intern Med J* 2014; 44: 633–638.

60. Phillips AL, Nigro O, Macolino KA, *et al.* Hospital admissions caused by adverse drug events: an Australian prospective study. *Aust Health Rev* 2014; 38: 51–57.

61. De Almeida SM, Romualdo A, De Abreu Ferraresi A, *et al.* Use of a trigger tool to detect adverse drug reactions in an emergency department. *BMC Pharmacol Toxicol* 2017; 18: 71.

62. Parameswaran Nair N, Chalmers L, Bereznicki BJ, *et al.* Adverse drug reaction-related hospitalizations in elderly Australians: a prospective cross-sectional study in two Tasmanian hospitals. *Drug Saf* 2017; 40: 597–606.

63. Poudel DR, Acharya P, Ghimire S, *et al.* Burden of hospitalizations related to adverse drug events in the USA: a retrospective analysis from large inpatient database. *Pharmacoepidemiol Drug Saf* 2017; 26: 635–641.

64. Ognibene S, Vazzana N, Giumelli C, *et al.* Hospitalisation and morbidity due to adverse drug reactions in elderly patients: a single-centre study. *Intern Med J* 2018; 48: 1192–1197.

65. Schurig AM, Bohme M, Just KS, *et al.* Adverse Drug Reactions (ADR) and emergencies. *Dtsch Arztebl Int* 2018; 115: 251–258.

66. Mullan J, Burns P, Mohanan L, *et al.* Hospitalisation for medication misadventures among older adults with and without dementia: a 5-year retrospective study. *Australas J Ageing* 2019; 38: e135–e141.

67. Zhang H, Du W, Gnjidic D, *et al.* Trends in adverse drug reaction-related hospitalisations over 13 years in New South Wales, Australia. *Intern Med J* 2019; 49: 84–93. 2018/10/04. DOI: 10.1111/imj.14134.

68. Smeaton T, McElwaine P, Cullen J, *et al.* A prospective observational pilot study of adverse drug reactions contributing to hospitalization in a cohort of middle-aged adults aged 45–64 years. *Drugs Ther Perspect* 2020; 36: 123–130.

69. Davies EC, Green CF, Taylor S, *et al.* Adverse drug reactions in hospital in-patients: a

prospective analysis of 3695 patient-episodes. *PLoS One* 2009; 4: e4439.

70. Kanjanarat P, Winterstein AG, Johns TE, *et al*. Nature of preventable adverse drug events in hospitals: a literature review. *Am J Health Syst Pharm* 2003; 60: 1750–1759.

71. O'Connor MN, Gallagher P, Byrne S, *et al*. Adverse drug reactions in older patients during hospitalisation: are they predictable? *Age Ageing* 2012; 41: 771–776.

72. Cecile M, Seux V, Pauly V, *et al*. Adverse drug events in hospitalized elderly patients in a geriatric medicine unit: study of prevalence and risk factors. *Rev Med Interne* 2009; 30: 393–400.

73. Beijer HJ and de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci* 2002; 24: 46–54.

74. Laatikainen O, Miettunen J, Sneck S, *et al*. The prevalence of medication-related adverse events in inpatients-a systematic review and meta-analysis. *Eur J Clin Pharmacol* 2017; 73: 1539–1549.

75. Levkovich BJ, Bingham G, Jones D, *et al*. Understanding how medications contribute to clinical deterioration and are used in rapid response systems: a comprehensive scoping review. *Aust Crit Care* 2019; 32: 256–272.

76. Classen DC, Pestotnik SL, Evans RS, *et al*. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1997; 277: 301–306.

77. Doucet J, Jego A, Noel D, *et al*. Preventable and non-preventable risk factors for adverse drug events related to hospital admissions in the elderly. *Clin Drug Investig* 2002; 22: 385–392.

78. Al-Tajir GK and Kelly WN. Epidemiology, comparative methods of detection, and preventability of adverse drug events. *Ann Pharmacother* 2005; 39: 1169–1174.

79. Trivalle C, Cartier T, Verny C, *et al*. Identifying and preventing adverse drug events in elderly hospitalised patients: a randomised trial of a program to reduce adverse drug effects. *J Nutr Health Aging* 2010; 14: 57–61.

80. Morimoto T, Sakuma M, Matsui K, *et al*. Incidence of adverse drug events and medication errors in Japan: the JADE study. *J Gen Intern Med* 2011; 26: 148–153.

81. Parikh S, Christensen D, Stuchbery P, *et al*. Exploring in-hospital adverse drug events using ICD-10 codes. *Aust Health Rev* 2014; 38: 454–460.

82. Rojas-Velandia C, Ruiz-Garzon J, Moscoso-Alcina JC, *et al*. Characterization of adverse drug reactions causing admission to an intensive care unit. *Br J Clin Pharmacol* 2017; 83: 1134–1140.

83. Robb G, Loe E, Maharaj A, *et al*. Medication-related patient harm in New Zealand hospitals. *N Z Med J* 2017; 130: 21–32.

84. Cohen MR. *Medication errors*. 2nd ed. Washington, DC: American Pharmacists Association, 2007.

85. Australian Pharmaceutical Advisory Council. *Guiding principles to achieve continuity in medication management*. Canberra: Commonwealth of Australia, 2005.

86. El Morabet N, Uitvlugt EB, Van den Bemt BJF, *et al*. Prevalence and preventability of drug-related hospital readmissions: a systematic review. *J Am Geriatr Soc* 2018; 66: 602–608.

87. Hanlon JT, Pieper CF, Hajjar ER, *et al*. Incidence and predictors of all and preventable adverse drug reactions in frail elderly persons after hospital stay. *J Gerontol A Biol Sci Med Sci* 2006; 61: 511–515.

88. Kanaan AO, Donovan JL, Duchin NP, *et al*. Adverse drug events after hospital discharge in older adults: types, severity, and involvement of Beers Criteria Medications. *J Am Geriatr Soc* 2013; 61: 1894–1899.

89. Forster AJ, Murff HJ, Peterson JF, *et al*. Adverse drug events occurring following hospital discharge. *J Gen Intern Med* 2005; 20: 317–323.

90. Gurwitz JH, Field TS, Harrold LR, *et al*. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003; 289: 1107–1116.

91. Forster AJ, Murff HJ, Peterson JF, *et al*. The incidence and severity of adverse events affecting patients after discharge from hospital. *Ann Intern Med* 2003; 138: 161.

92. Parekh N, Ali K, Page A, *et al*. Incidence of medication-related harm in older adults after hospital discharge: a systematic review. *J Am Geriatr Soc* 2018; 66: 1812–1822.

93. Gandhi TK, Weingart SN, Borus J, *et al*. Adverse drug events in ambulatory care. *N Engl J Med* 2003; 348: 1556–1564.

94. Carnovale C, Gentili M, Fortino I, *et al.* The importance of monitoring adverse drug reactions in elderly patients: the results of a long-term pharmacovigilance programme. *Expert Opin Drug Saf* 2016; 15: 131–139.

95. Mann E, Zepeda O, Soones T, *et al.* Adverse drug events and medication problems in "Hospital at Home" patients. *Home Health Care Serv Q* 2018; 37: 177–186.

96. Parekh N, Ali K, Stevenson JM, *et al.* Incidence and cost of medication harm in older adults following hospital discharge: a multicentre prospective study in the UK. *Br J Clin Pharmacol* 2018; 84: 1789–1797.

97. Gray SL, Mahoney JE and Blough DK. Adverse drug events in elderly patients receiving home health services following hospital discharge. *Ann Pharmacother* 1999; 33: 1147–1153.

98. Davies EC, Green CF, Mottram DR, *et al.* Emergency re-admissions to hospital due to adverse drug reactions within 1 year of the index admission. *Br J Clin Pharmacol* 2010; 70: 749–755.

99. Zhang M, Holman CD, Preen DB, *et al.* Repeat adverse drug reactions causing hospitalization in older Australians: a population-based longitudinal study 1980-2003. *Br J Clin Pharmacol* 2007; 63: 163–170.

100. Crispo JAG, Thibault DP and Willis AW. Adverse drug events as a reason for adult hospitalization: a nationwide readmission study. *Ann Pharmacother* 2019; 53: 557–566.

101. See RI, Shehab RN, Kegler SS, *et al.* Emergency department visits and hospitalizations for digoxin toxicity: United States, 2005 to 2010. *Circ Heart Fail* 2014; 7: 28–34.

102. Mangoni AA and Jackson S. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004; 57: 6–14.

103. O'Mahony D, O'Sullivan D, Byrne S, *et al.* STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015; 44: 213–218.

104. Fick DM, Semla TP, Beizer J, *et al.* American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015; 63: 2227–2246.

105. Scott IA, Hilmer SN, Reeve E, *et al.* Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med* 2015; 175: 827.

106. Nyborg G, Straand J and Brekke M. Inappropriate prescribing for the elderly--a modern epidemic? *Eur J Clin Pharmacol* 2012; 68: 1085–1094.

107. Scott IA, Hilmer SN and Le Couteur DG. Going beyond the guidelines in individualising the use of antihypertensive drugs in older patients. *Drugs Aging* 2019; 36: 675–685.

108. Goyal P, Anderson TS, Bernacki GM, *et al.* Physician perspectives on deprescribing cardiovascular medications for older adults. *J Am Geriatr Soc.* Epub ahead of print 11 September 2019. DOI: 10.1111/jgs.16157.

109. Naganathan V. Cardiovascular drugs in older people. *Aust Prescr* 2013; 36: 190–194.

110. Krishnaswami A, Steinman MA, Goyal P, *et al.* Deprescribing in older adults with cardiovascular disease. *J Am Coll Cardiol* 2019; 73: 2584–2595.

111. Reeve E, Denig P, Hilmer SN, *et al.* The ethics of deprescribing in older adults. *J Bioeth Inq* 2016; 13: 581–590.

112. Garattini S, Garattini S, Bertele' V, *et al.* Benefits, benefits, once more benefits... with no risk? Stop overlooking the harms of medicines. *Eur J Clin Pharmacol* 2018; 74: 373–375.

113. Rossello X, Pocock SJ and Julian DG. Long-term use of cardiovascular drugs: challenges for research and for patient care. *J Am Coll Cardiol* 2015; 66: 1273–1285.

114. Morgan DJ, Scherer LD and Korenstein D. Improving physician communication about treatment decisions: reconsideration of "Risks vs Benefits". *JAMA* 2020; 324: 937–938.

115. Rose L, Muttalib F and Adhikari NKJ. Psychological consequences of admission to the ICU: helping patients and families. *JAMA* 2019; 322: 213–215.

116. Saedder E, Brock B, Nielsen L, *et al.* Identifying high-risk medication: a systematic literature review. *Eur J Clin Pharmacol* 2014; 70: 637–645.

117. Australian Institute of Health and Welfare. *Australian hospital statistics*. Health Services Series no. 90. Cat. no. HSE 225. 90 ed. Canberra: AIHW, 2019.

Appendix 1

Example search strategy for manuscript 'Patient harm from cardiovascular medications'

Manuscript title Patient harm from cardiovascular medications

Authors Paradissis, C; Coombes I; Cottrell, W.N.; Scott, I; Wang, W and Barras, M

Date 5 November 2020

Database PubMed

Search

(((((((((("Inpatients"[Mesh])) OR "Ambulatory Care"[Mesh:NoExp]) OR "Patient Discharge"[Mesh]) OR "Patient Readmission"[Mesh]) OR "Outpatients"[Mesh]) OR "Patient Admission" [Mesh]) OR (hospital*[Title/Abstract] AND (discharge*[Title/Abstract] OR admission*[Title/Abstract] OR readmission*[Title/Abstract] OR re-admission*[Title/Abstract] OR inpatient* [Title/Abstract]) OR (outpatient*[Title/Abstract] OR ambulatory[Title/Abstract]))) AND ((((((((("adverse drug reaction*"[Title/Abstract]) OR ("adverse drug event*" [Title/Abstract])) OR ("adverse reaction*" [Title/Abstract])) OR ("medication harm"[Title/Abstract])) OR ("medication related harm"[Title/Abstract])) OR ("medication-related harm"[Title/Abstract])) OR ("medication error*"[Title/Abstract])) OR ("adverse event*"[Title/Abstract]))) OR ("Drug-Related Side Effects and Adverse Reactions" [Mesh:NoExp]))) NOT (paediatric OR pediatric OR child OR children)

Filters Date restriction: 1990–present.

Number of results 14, 926.

Appendix 2

Box 1. Medication harm definitions and terminology.[a].

Acronym	Definition
ADE	Any untoward medical occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relation to the treatment
ADR	A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man
ME	Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer

[a]Based on definitions from the World Health Organization. ADE, adverse drug event; ADR, adverse drug reaction; ME, medication error.