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ORIGINAL RESEARCH

Epidemiology of adverse drug reactions to antihypertensive, antithrombotic and antidiabetic medications among adult inpatients at a National Referral Hospital, Uganda

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ABSTRACT

Introduction: Treatment for hypertension, thrombosis and type 2 diabetes mellitus is long term and usually requires a combination of drugs which increases the risk of adverse drug reactions (ADRs). This study aimed to establish the prevalence at admission, incidence during hospitalization and characteristics of ADRs linked to antihypertensive, antithrombotic and antidiabetic drugs among adult inpatients in Uganda.

Methods: We conducted a secondary analysis of data from a previously assembled prospective cohort study in Uganda's Mulago National Referral Hospital. We reviewed the files of inpatients who received antihypertensive, antithrombotic and/or antidiabetic medications prior to and/or during hospitalization. The modified Schumock and Thornton Preventability Scale, the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events and the World Health Organization – Uppsala Monitoring Centre seriousness criteria were used to characterize the ADRs.

Results: More than a quarter (27%, 42/155) of the inpatients experienced an ADR at admission or during hospitalization. The point prevalence of ADRs at admission was 8% (13/155) and the incidence of ADRs during hospitalization was 23% (36/155). Forty-one percent (35/86) of the ADRs were serious and the majority (59%, 51/86) were preventable.

Conclusion: One in 13 inpatients experienced an ADR on admission and one in four experienced an ADR that developed during hospitalization. Clinicians ought to prescribe medicines with lower ADR risk profile for cardiovascular and/or diabetic patients whenever possible.

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Adverse drug reaction; antidiabetic medication; antihypertensive medication; antithrombotic medication; hospital admission; Sub Saharan Africa; low- and middle-income countries; Uganda

1. Introduction

Non-communicable Diseases (NCDs) affect all countries; however, the burden of disease and death is highest in low- and middle-income countries (LMIC) [1]. Hypertension (HTN) and type 2 diabetes mellitus (T2DM) are the commonest NCDs associated with cardiovascular morbidity and mortality worldwide [1–3]. The coexistence of HTN and T2DM predisposes patients to a higher risk of cardiovascular disease, a leading cause of death globally [4,5]. Cardiovascular drugs (specifically antihypertensives and antithrombotics) and antidiabetics have significantly reduced the cardiovascular complications of uncontrolled HTN and T2DM [6–8]. However, the treatment of HTN and T2DM is often long term and usually requires a combination of two or more cardiovascular and antidiabetic medications, respectively. The long-term use and higher number of consumed cardiovascular and antidiabetic medicines increases the risk of adverse drug reactions (ADRs) [9] which could result in treatment nonadherence, increased morbidity and mortality, and higher healthcare costs [10,11].

A study conducted in China highlighted that oral antiplatelet drugs, antihypertensives and oral hypoglycemics were the most implicated for emergency ADR-related hospitalization [12]. Cardiovascular drugs have been implicated for ADRs among inpatients and outpatients in Africa and antithrombotics (anticoagulants, antiplatelets) have been most frequently linked to drug-related hospital admissions in Australia and Spain [10,13,14].

A systematic review among hospitalized older adults documented an ADR prevalence of 19%; however, none of the studies in this review were from an African setting [15]. Yet, T2DM and related cardiovascular complications have gained more importance in Africa [16]. A study in Morocco reported that 23% of all the patients on antihypertensives and antidiabetics reported negative side effects, with limited information on ADR characterization [17]. Shegena and colleagues in Uganda reported an ADR prevalence of 59% and an incidence of 106 ADRs/1000 person-days; however, these data were limited to only heart failure patients [18]. The epidemiology of ADRs linked to cardiovascular and antidiabetic medication among hospitalized patients in sub-Saharan Africa are not well documented. This study aimed to establish the prevalence at admission, incidence during hospitalization and characteristics of ADRs linked to antihypertensive, antithrombotic and

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antidiabetic drugs among adult inpatients at Mulago National Referral Hospital, Uganda.

2. Methods

2.1. Study design and setting

The detailed methods of this study have been reported elsewhere [19]. Briefly, this was a secondary analysis of data from a previously assembled prospective cohort study of adult inpatients aged 18 years and older at Uganda's 1790-bed Mulago National Referral Hospital during November 2013 to April 2014.

2.2. Sample size estimation

During data collection of the parent prospective cohort study, 762 inpatients were screened [19] of whom 155 inpatients had received antihypertensive, antithrombotic and/or antidiabetic drugs during hospitalization and were therefore included in this analysis.

2.3. Data collection and management

We included data documented at admission and during hospitalization. The data included patient demographics, clinical conditions, ADRs and antihypertensive, antithrombotic and antidiabetic medications. The research team conducted daily assessments until discharge, transfer, death and/or loss to follow-up [20].

2.4. Identification of ADRs

We defined ADRs according to the WHO definition [21]. Clinical examination was the major approach used to identify ADRs linked to antihypertensive, antithrombotic and/or antidiabetic drugs due to limitations in timely availability of laboratory investigation results [20]. Causality of ADRs linked to antihypertensive, antithrombotic and/or antidiabetic drugs was assessed using the Naranjo ADR probability scale [22]. We defined community-acquired ADRs as those linked to preadmission use of antihypertensive, antithrombotic and/or antidiabetic drugs and hospital-acquired ADRs as those linked to hospital-initiated antihypertensive, antithrombotic and/or antidiabetic drugs during the current hospitalization. The modified Schumock and Thornton Preventability Scale was used to assess the preventability [23,24], whereas the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events evaluated severity [25] and the WHO Uppsala Monitoring Centre (UMC) criteria [21] determined the seriousness. Preventability, severity, seriousness and outcome of ADRs linked to antihypertensive, antithrombotic and/or antidiabetic drugs was determined by consensus in a committee headed by the study physician and senior clinical pharmacist.

2.5. Statistical analysis

We determined the prevalence of ADRs at hospital admission and the incidence of ADRs during hospitalization linked to antihypertensive, antithrombotic and/or antidiabetic drugs [20]. We also computed the incidence of hospital-acquired ADRs linked to antihypertensive, antithrombotic and/or antidiabetic drugs per 100 defined daily doses (DDDs) (Anatomical Therapeutic Chemical/Defined Daily Dose) [26] of each implicated cardiovascular and/or antidiabetic drug administered during hospitalization. We assessed ADRs linked to antihypertensive, antithrombotic and/or antidiabetic drugs as community-acquired or hospital-acquired; and for causality, preventability, severity, seriousness, and outcome. All statistical analyses were conducted using Stata 15.0 [27]. We determined the frequency of ADRs linked to antihypertensive, antithrombotic and antidiabetic drugs and the frequency of individual cardiovascular and antidiabetic drugs linked to ADRs among the inpatients.

2.6. Ethical clearance

The parent study obtained ethical approval from the School of Medicine Research and Ethics Committee, Makerere University College of Health Sciences (REC REF No. 2011–113), the Mulago Hospital Research and Ethics Committee (MREC 253), and the Uganda National Council for Science and Technology (HS 1151).

3. Results

3.1. Demographic and clinical characteristics of study participants

We screened 762 inpatients, of whom 155 inpatients received antihypertensive, antithrombotic and/or antidiabetic drugs during the current hospitalization and were therefore included in this analysis. The mean age of inpatients was 44 years (standard deviation, SD of 17 years). Three-fifths (61%, 94/155) of the inpatients were female, most were admitted to the medical wards (96%, 149/155) and 15% (23/155) were of known HIV-seropositive status. Nearly half (45%, 69/155) the inpatients had an admitting cardiovascular disease diagnosis without T2DM while 12% (13/155) had both cardiovascular disease and T2DM diagnoses at admission, see Table 1. Seventy-two percent (112/155) of the inpatients had admitting cardiovascular disease and/or T2DM diagnoses: 82 of 112 had cardiovascular disease (59 of 82 had HTN) and 43 of 112 had T2DM.

3.2. Use of antihypertensive, antithrombotic and/or antidiabetic drugs

Preadmission: Nearly two-thirds of inpatients (64%, 99/155) received antihypertensive, antithrombotic and/or antidiabetic drugs during the 1-month prior to hospitalization. Almost half the inpatients (48%, 74/155) received cardiovascular drugs during the 1-month prior to hospitalization: 99% (73/74)

Table 1. Demographic and clinical characteristics of 155 hospitalized patients, Uganda.

	ADR to antihypertensive, antithrombotic/antidiabetic drugs		
Characteristic	ADR (*n* = 42)	No ADR (*n* = 113)	Total (*n* = 155)
Age in years, mean (SD)~	47 (18)	43 (16)	44 (17)
Systolic Blood Pressure in mmHg, mean (SD)*~	141 (32)	127 (28)	131 (30)
Diastolic Blood Pressure in mmHg, mean (SD)*~	88 (20)	80 (19)	82 (19)
Length of hospital stay, median (IQR)	5 (3–6)	5 (3–8)	5 (3–8)
	ADR to antihypertensive, antithrombotic/antidiabetic drugs, n [%]		
Sex			
Male	12 [28]	49 [43]	61 [39]
Female	30 [71]	64 [57]	94 [61]
Ward-type			
Medical	39 [93]	110 [97]	149 [96]
Gynaecological	3 [7]	3 [3]	6 [4]
HIV-Status			
Positive	6 [14]	17 [15]	23 [15]
Negative	36 [86]	96 [85]	132 [85]
Cardiovascular Disease/Type 2 Diabetes Mellitus Admitting Diagnoses			
Cardiovascular Disease, no Type 2 Diabetes Mellitus	23 [55]	46 [41]	69 [45]
Type 2 Diabetes Mellitus, no Cardiovascular Disease	4 [10]	26 [23]	30 [19]
Cardiovascular Disease & Type 2 Diabetes Mellitus	6 [14]	7 [6]	13 [12]
No Cardiovascular Disease/No Type 2 Diabetes Mellitus	9 [21]	34 [29]	43 [30]
Overall	**42 (27)**	**113 (73)**	**155 (100)**

ADR is adverse drug reaction; SD is standard deviation; mmHg is millimeters of mercury; IQR is interquartile range; ~Mean systolic blood pressure of inpatients who experienced ADR (versus those who did not) was significantly higher ($t = 2.501$; $p < 0.01$); Mean diastolic blood pressure of inpatients who experienced ADR (versus those who did not) is significantly higher ($t = 2.243$; $p < 0.03$); *Missing data of n = 3/762; [%] represents vertical percentages.

received antihypertensives and 22% (16/74) received antithrombotics. Fifteen of the 16 inpatients on antithrombotics also received antihypertensives. About one-fifth (22%, 34/155) of inpatients used antidiabetics in the 1-month prior to hospitalization.

During hospital stay: The majority of inpatients (92%, 142/155) received antihypertensive, antithrombotic and/or antidiabetic drugs during hospitalization. Eighty-five percent of inpatients (132/155) received cardiovascular drugs while in hospital: 90% (119/132) received antihypertensives and 19% (25/132) antithrombotics. Nineteen of 25 inpatients on antithrombotics also received antihypertensives. A quarter (26%, 41/155) of the inpatients used antidiabetics, see Table 2.

3.3. Extent of ADRs to antihypertensive, antithrombotic and/or antidiabetic drugs

Overall, 27% (42/155) of the inpatients experienced at least one ADR linked to antihypertensive, antithrombotic and/or antidiabetic drugs: 62% (26/42) of these inpatients encountered serious ADRs. The 42 inpatients experienced 86 ADRs. Three in ten (30%, 36/119) inpatients who received antihypertensives experienced ADRs linked to antihypertensives: 56% (20/36) of these inpatients encountered serious ADRs. Four of the 25 inpatients (16%) on antithrombotics experienced ADRs linked to antithrombotics: three of the four inpatients had serious ADRs. Seven of the 41 inpatients (17%) on antidiabetics experienced ADRs related to antidiabetics: all seven inpatients had serious ADRs, see Table 2. One-third (33%, 23/69; 95% CI: 22% to 46%) of inpatients with an admitting diagnosis of hypertension or thrombosis but no T2DM had ADRs linked to antihypertensive or antithrombotic drugs and about one in eight (13%, 4/30; 95% CI: 4% to 31%) with an admitting T2DM diagnosis but no hypertensive or thrombotic disease had ADRs linked to antidiabetics. Forty-six percent (6/13; 95% CI: 19% to 75%) of inpatients with either hypertensive or thrombotic disease and T2DM admitting diagnoses had ADRs linked to antihypertensive/antithrombotic/antidiabetic drugs.

3.4. Prevalence of ADRs to cardiovascular and/or antidiabetic drugs at admission

The prevalence of ADRs linked to antihypertensive, antithrombotic and/or antidiabetic drugs at admission was 8% (13/155): 85% (11/13) of whom had serious ADRs. About 8% (10/119) of inpatients on antihypertensives had prevalent ADRs linked to antihypertensives at admission: 80% (8/10) of whom had serious ADRs. Two of the 25 inpatients (8%) on antithrombotics had prevalent ADRs linked to antithrombotics at admission: both of whom had serious ADRs. Three in 41 inpatients (7%) on antidiabetics had prevalent ADRs linked to antidiabetics: all three of whom had serious ADRs, see Table 2.

3.5. Incidence of ADRs to cardiovascular and/or antidiabetic drugs during hospital stay

Overall: The incidence of ADRs linked to cardiovascular/antidiabetic drugs during hospitalization was 23% (36/155): 61% (22/36) of whom had serious incident ADRs. Seven of the 22 inpatients with incident serious ADRs during hospital stay had experienced prevalent serious ADRs at admission; all incident serious ADRs in these seven inpatients implicated cardiovascular/antidiabetic medications in use at admission and continued during hospital stay. A quarter (26%, 31/119) of inpatients on antihypertensives experienced incident antihypertensives-linked ADRs: 55% (17/31) of whom had serious incident ADRs. Two of the 25 inpatients (8%) on antithrombotics

Table 2. Extent of adverse drug reactions linked to cardiovascular and/or antidiabetic drugs among 155 inpatients, Uganda.

Characteristic	Proportion of inpatients with suspected ADRs, % (n/N) ~					
		Cardiovascular drugs (n = 132)				
	Cardiovascular/ Antidiabetic drugs (n = 155)	Antihypertensives/ Antithrombotics$^{\pm}$ (n = 125)	Antihypertensives (n = 119)	Antithrombotics (n = 25)	Antidiabetics (n = 41)	Antihypertensives/ Antidiabetics (n = 142)
Patient-level						
Overall ADRs	27% (42/155)	29% (36/125)	30% (36/119)	16% (4/25)	17% (7/41)	30% (42/142)
Overall serious ADRs	62% (26/42)	56% (20/36)	56% (20/36)	75% (3/4)	100% (7/7)	62% (26/42)
Prevalent ADRs	8% (13/155)	8% (10/125)	8% (10/119)	8% (2/25)	7% (3/41)	9% (13/142)
Prevalent serious ADRs	85% (11/13)	80% (8/10)	80% (8/10)	100% (2/2)	100% (3/3)	85% (11/13)
Incident ADRs	23% (36/155)	25% (31/125)	26% (31/119)	8% (2/25)	15% (6/41)	25% (36/142)
Incident serious ADRs	61% (22/36)	55% (17/31)	55% (17/31)	50% (1/2)	100% (6/6)	61% (22/36)
		Cardiovascular drugs (n = 76)				
	Cardiovascular/ Antidiabetic drugs (n = 86)	Antihypertensives/ Antithrombotics$^{\pm}$ (n = 76)	Antihypertensives (n = 73)	Antithrombotics (n = 5)	Antidiabetics (n = 10)	Antihypertensives/ Antidiabetics (n = 83)
ADR-level						
Community-acquired ADRs	31% (27/86)	30% (23/76)	30% (22/73)	40% (2/5)	40% (4/10)	31% (26/83)
Serious community-acquired ADRs	59% (16/27)	61% (14/23)	59% (13/22)	100% (2/2)	50% (2/4)	58% (15/26)
Hospital-acquired ADRs	69% (59/86)	70% (53/76)	70% (51/73)	60% (3/5)	60% (6/10)	69% (57/83)
Serious hospital-acquired ADRs	32% (19/59)	36% (19/53)	27% (14/51)	33% (1/3)	67% (4/6)	32% (18/57)

~ADRs is Adverse Drug Reactions; $^{\pm}$At patient-level, 19 inpatients received both antihypertensives and antithrombotics while at ADR-level, 2 ADRs were linked to both antihypertensives and antithrombotics. Eleven inpatients experienced 15 prevalent serious ADRs at admission. The 15 serious ADR-drug pairs were: fever-captopril; jaundice-efavirenz, captopril; dizziness-insulin; headache-nifedipine, captopril; palpitations-lisinopril; easy fatiguability-lisinopril, carvedilol; abdominal pain/distention-digoxin, frusemide; vomiting-nifedipine, captopril, spironolactone; vomiting-glibenclamide, metformin; headache-clopidogrel, carvedilol; diarrhea-digoxin; reduced appetite-metformin, glibenclamide; itchy rash with numbness of lower swollen limbs-ethambutol/isoniazid, carvedilol; palpitations-carvedilol, tenofovir/lamivudine/efavirenz; dizziness-lisinopril, carvedilol, spironolactone.

Table 3. Individual antihypertensive, antithrombotic and antidiabetic drugs implicated in the 86 adverse drug reactions among 42 of 155 inpatients, Uganda.

Drug class, individual drug	No. of ADRs	No. of community-acquired ADRs	No. of hospital-acquired ADRs	DDDs received during current hospitalization	No. of patients who used drug in hospital	No. of hospital-acquired ADRs/100 DDDs	95% CI of hospital-acquired ADRs/100 DDDs
Cardiovascular drugs							
Antihypertensives							
Captopril	27	17	10	72.1	48	14	8–22
Carvedilol	22	11	11	19.9	26	55	45–65
Nifedipine	19	8	11	75.3	31	15	9–24
Frusemide	14	5	9	209.0	57	4	1–10
Digoxin	6	3	3	17.0	11	18	11–27
Amlodipine	5	2	3	86.0	17	3	0–9
Hydralazine	5	3	2	2.0	10	103	-
Lisinopril	5	4	1	28.0	1	4	1–10
Bendroflumethiazide	4	3	1	14.0	5	7	3–14
Spironolactone	2	1	1	71.7	25	1	0–5
Propranolol	2	0	2	14.8	15	14	8–22
Labetalol	2	1	1	0.7	2	150	-
Anticoagulants							
Cardiac Acetylsalicylic Acid	4	2	2	11.5	17	17	10–26
Clopidogrel	1	0	1	0.5	1	188	-
Warfarin	1	0	1	16.7	6	6	2–13
Antidiabetics							
Glibenclamide	7	4	3	4.0	5	75	65–83
Metformin	5	3	2	17.5	13	11	6–19
Insulin	4	1	3	82.3	34	4	1–10

had incident antithrombotics-linked ADRs: one of whom had a serious ADR. Six of 41 inpatients (15%) on antidiabetics experienced incident antidiabetics-linked ADRs: all six of whom had serious ADRs, see Table 2.

Individual drugs: The most consumed individual drugs during hospital stay were furosemide (209 defined daily doses, DDDs), amlodipine (86 DDDs), insulin (82.3 DDDs), nifedipine (75.3 DDDs) and captopril (72.1 DDDs), among others. The incidence of hospital-acquired ADRs standardized by DDDs for drugs used by ≥16 inpatients was as follows: carvedilol (55 ADRs/100 DDDs), cardiac acetylsalicylic acid (17 ADRs/100 DDDs), nifedipine (15 ADRs/100 DDDs) and captopril (14 ADRs/100 DDDs), see Table 3. The incidence of serious hospital-acquired ADRs linked to individual drugs used by ≥16 inpatients was 23% (7/31) for nifedipine, 19% (5/26) for carvedilol, 13% (6/48) for captopril, 9% (5/57) for frusemide, 4% (1/

Table 4. Incidence of hospital-acquired adverse drug reactions linked to individual antihypertensive, antithrombotic and antidiabetic drugs among 155 inpatients, Uganda.

	Incidence of hospital-acquired adverse drug reactions			
Adverse Drug Reaction	Serious, % (n/N)	Non-serious, % (n/N)	Total, % (n/N)	95% CI of Total
Cardiovascular drugs				
Antihypertensives				
Carvedilol	19% (5/26)	23% (6/26)	42% (11/26)	23% – 63%
Nifedipine	23% (7/31)	13% (4/31)	35% (11/31)	19% – 55%
Captopril	13% (6/48)	8% (4/48)	21% (10/48)	10% – 35%
Frusemide	9% (5/57)	7% (4/57)	16% (9/57)	7% – 28%
Digoxin	18% (2/11)	9% (1/11)	27% (3/11)	6% – 61%
Amlodipine	0% (0/17)	18% (3/17)	18% (3/17)	4% – 43%
Hydralazine	20% (2/10)	0% (0/10)	20% (2/10)	3% – 56%
Lisinopril	50% (1/2)	0% (0/2)	50% (1/2)	1% – 99%
Spironolactone	4% (1/25)	0% (0/25)	4% (1/25)	0% – 20%
Propranolol	13% (2/15)	0% (0/15)	13% (2/15)	2% – 40%
Bendroflumethiazide	20% (1/5)	0% (0/5)	20% (1/5)	0% – 72%
Labetalol	50% (1/2)	0% (0/2)	50% (1/2)	1% – 99%
Anticoagulants				
Cardiac Aspirin	6% (1/17)	0% (1/17)	12% (2/17)	1% – 36%
Clopidogrel	100% (1/1)	0% (0/1)	100% (1/1)	3% – 100%
Warfarin	17% (1/6)	0% (0/6)	17% (1/6)	0% – 64%
Antidiabetics				
Glibenclamide	60% (3/5)	0% (0/5)	60% (3/5)	15% – 95%
Metformin	15% (2/13)	0% (0/13)	15% (2/13)	2% – 45%
Insulin	9% (3/34)	0% (0/34)	9% (3/34)	2% – 24%

25) for spironolactone, 0% (0/17) for amlodipine, 6% (1/17) for cardiac acetylsalicylic acid and 9% (3/34) for insulin, see Table 4.

3.6. Community-acquired and hospital-acquired ADRs

Community-acquired ADRs: At the *ADR-level*, nearly one-third (31%, 27/86) of ADRs were community-acquired: 59% (16/27) were serious. Thirty percent (22/73) of ADRs linked to antihypertensives were community-acquired: 59% (13/22) were serious ADRs. Two of the five ADRs linked to antithrombotics were community-acquired: both were serious ADRs. Four of the 10 ADRs linked to antidiabetics were community-acquired: two were serious, see Table 2.

Hospital-acquired ADRs: More than two-thirds (69%, 59/86) of ADRs were hospital-acquired: 32% (19/59) were serious ADRs. Twenty-seven percent (14/51) of the ADRs linked to antihypertensives were serious, one of the three ADRs linked to antithrombotics was serious and four of the six ADRs linked to antidiabetics were serious, see Table 2.

3.7. Causality, seriousness and preventability of ADRs

Overall, 37% (32/86) of the ADRs were probable or definite. Forty-one (35/86) percent of the ADRs were serious and the majority (59%, 51/86) were preventable: one ADR linked to antidiabetics was fatal (preventable hospital-acquired hypoglycemia associated with glibenclamide); one ADR linked to antithrombotics was life-threatening (non-preventable community-acquired epigastric pain associated with tenofovir/lamivudine/efavirenz and cardiac acetylsalicylic acid); 31% (11/35) caused or prolonged hospitalization; and 9% (3/35) caused disability., see Table 5 & S1.

Table 5. Causality, seriousness, severity, outcome and preventability of 86 adverse drug reactions associated with the use of antihypertensive, antithrombotic and antidiabetic drugs among 42 inpatients, Uganda.

		Frequency of suspected ADR, n (%)			
Assessment	Category	Overall	Antihypertensives	Antithrombotics	Antidiabetics
Causality	Possible	54 (63)	48 (66)	2 (40)	6 (60)
	Probable or definite	32 (37)	25 (34)	3 (60)	5 (40)
Seriousness	Yes	35 (41)	27 (37)	3 (60)	6 (60)
	Caused death	1 (3)	0 (0)	0 (0)	1 (1)
	Life-threatening	1 (3)	0 (0)	1 (33)	0 (0)
	Caused or prolonged hospitalization	11 (31)	10 (37)	1 (33)	1 (17)
	Caused disability	3 (9)	2 (7)	0 (0)	1 (17)
	Required intervention to prevent damage	17 (49)	13 (48)	1 (33)	3 (50)
	Other medically significant condition	2 (6)	2 (7)	0 (0)	0 (0)
	No	51 (59)	46 (63)	2 (40)	4 (40)
Severity	Mild	30 (35)	24 (33)	1 (20)	5 (50)
	Moderate	42 (49)	40 (55)	3 (60)	1 (10)
	Severe or life-threatening	14 (16)	9 (12)	1 (20)	4 (40)
Outcome	Resolved	50 (58)	43 (59)	3 (60)	5 (50)
	Ongoing	36 (42)	30 (41)	2 (40)	5 (50)
Preventability	Preventable	51 (59)	44 (60)	1 (20)	7 (70)
	Non-preventable	35 (41)	29 (40)	4 (80)	3 (30)

3.8. Frequency of the commonest ADRs linked to antihypertensive, antithrombotic and/or antidiabetic drugs and the drugs most implicated

The commonest ADRs linked to cardiovascular drugs were headache (17%), vomiting (9%), epigastric pain (8%), palpitations (8%) and dizziness (6%), among others. The commonest ADRs linked to antidiabetics were hypoglycemia (26%), diarrhea (21%), abdominal pain (16%) and paresthesia (11%), among others, see **S1 & S2**. The commonest serious ADRs were headache (23%), palpitations (11%), dizziness (9%) and vomiting (9%), see **Table S1**. The most frequently implicated cardiovascular drugs were captopril (15%), carvedilol (13%) and nifedipine (12%). Glibenclamide (4%) and metformin (4%) were the most frequently implicated antidiabetics, see **S33.9 System Organ Class and pharmacological drug class**

Gastrointestinal disorders (31%, 27/86), nervous system disorders (24% (21/86) and cardiac disorders (12%, 10/86) were the most frequent system organ classes, see **S4**. Almost three-quarters (31/42) of the inpatients with ADRs had antihypertensives-linked ADRs only. Also, ADRs linked to antihypertensives were the most frequent (83%), see **S5**.

4. Discussion

In a cohort of 155 inpatients on antihypertensive, antithrombotic and antidiabetic drugs, more than a quarter (27%, $n = 42$) experienced an ADR at admission or during hospitalization of whom more than half had serious ADRs (62%, 26/42). The point prevalence of ADRs at admission was 8% (13/155): more than three quarters (85%, 11/13) of them had serious ADRs. The incidence of ADRs linked to cardiovascular/antidiabetic drugs during hospitalization was 23% (36/155); 61% (22/36) of them had serious ADRs. Three in ten (30%, 36/119) inpatients who received antihypertensives experienced ADRs linked to antihypertensives: 17% (20/119) had serious ADRs. Seven of the 41 inpatients (17%) on antidiabetics experienced ADRs related to antidiabetics: all seven inpatients had serious ADRs. Some inpatients experienced multiple ADRs that is why 42 inpatients experienced 86 ADRs. Overall, only 37% (32/86) of the ADRs were probable or definite. Forty-one (35/86) percent of the ADRs were serious and the majority (59%, 51/86) were preventable. Overall captopril was linked to most of the ADRs (27/84) and carvedilol had the highest incidence (55 ADRs/100 DDDs) of hospital-acquired ADRs standardized by DDDs considering drugs used by ≥16 inpatients. A third of the ADRs (31%, 27/86) affected the gastrointestinal system.

This study documented a period prevalence of 27% which is similar to the 31% reported in the United Kingdom (UK) [30]. It is known that patients in LMIC have poor health-seeking habits so cardiovascular/antidiabetic drugs are not commonly used compared to the UK population where there is overuse of medicines as preventive interventions for chronic conditions [30]. The medications produce symptoms by altering gastrointestinal physiology, causing tissue toxicity and damage and change the intestinal microbiota [28]. Our study reported a prevalence of 30% of ADRs among antihypertensive inpatients which is consistent with the prevalence of 26% reported in Australia [29]. The prevalence of ADRs among diabetic patients in our study (17%) was higher than the 12% documented in Indian outpatients [31]. The difference could be because our study was carried out among inpatients who were possibly more critically ill and more likely to experience ADRs. To note is that the majority of ADRs at admission were serious (85%) which is consistent with findings from a study among emergency patients in China where 94% of the ADRs were serious [12].

More than a quarter of all the ADRs affected the gastrointestinal system. This is comparable with previous studies [18,31,32]. Cardiovascular and antidiabetic drugs can affect the whole gastrointestinal tract including changes in gastrointestinal motility, gastric emptying, nutrient absorption, and antimicrobial associated colitis [33]. This study also revealed that more than half (59%) the ADRs were preventable and this proportion is comparable with what other studies have reported [18,29]. The preventable nature of the ADRs calls for attention by the healthcare team involved in prescribing for the patients. It demonstrates the need for ADR prevention strategies among these inpatientsfor example, limit the prescription of drugs with very high ADR risk, discontinue unnecessary drugs, provide patient counseling, conduct medication reviews and ensure appropriate dose and drug monitoring [12,34].

Captopril, carvedilol, nifedipine and furosemide accounted for most of the adverse reactions. These are the same drugs observed in Nigeria among antihypertensive patients [11]. This could be because calcium channel blockers, beta blockers and captopril are first-line drugs used in the management of different stages of hypertension; hence are commonly prescribed in LMIC [35]. Furosemide is indicated for the management of hypertension in patients with fluid overload secondary to heart failure, diabetes and chronic renal disease [36].

This study had important limitations: 1) the sample size was not adequate to determine the factors associated with ADRs and antihypertensive, antithrombotic and/or antidiabetic drugs among inpatients; 2) it was conducted at a national referral hospital which admits critically ill patients. Therefore, it is not appropriate to generalize these findings to the larger population; 3) the majority of suspect ADRs were detected by patient reports and on clinical examination rather than by laboratory investigations, which could have underestimated the measurement of ADRs. The strengths of this study were as follows: 1) previously, most studies were among adults aged 60 years and older [15,29,30,37]. However, the average age of inpatients in this study was 44 years which shows that ADRs are of great concern in the younger population in our setting; 2) the prospective nature of this study enabled us to gather more complete information at admission and during daily assessment of the ADRs directly from the inpatients. Moreover, consensus agreement on ADR causality was reached in a committee headed by the ward-based study physician and senior clinical pharmacist.

5. Conclusion

The current study showed that one in four inpatients reported an ADR on admission or during hospitalization. One in 13 inpatients experienced an ADR at admission and

one in five experienced an ADR during hospitalization linked to a cardiovascular and/or antidiabetic drug. More than three-quarters of the ADRs at admission were serious and overall, more than half of the ADRs were preventable. The gastrointestinal system was the most affected by ADRs. Whenever possible, clinicians should prescribe medicines with lower ADR risk profiles for cardiovascular and/or diabetic patients. This will reduce the burden of serious ADRs reported at admission and during hospitalization and obviate the associated unnecessary economic burden. Patients should be counseled on known ADRs so that there is timely detection and reporting of these reactions. Increased awareness of drug-related ADRs among cardiovascular and/or diabetic patients could lead to early detection and minimization of ADR-associated harms.

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Declaration of interests

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Ethical approval

Ethical approval was obtained from the School of Medicine Research and Ethics Committee, Makerere University College of Health Sciences (REC REF No. 2011–113), the Mulago Hospital Research and Ethics Committee (MREC 253), and the Uganda National Council for Science and Technology (HS 1151). Voluntary participation of the inpatients (≥18 years) was sought through provision of written informed consent

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