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Atypical antipsychotic drugs and the risk of acute kidney injury: A population-based cohort study

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

ATYPICAL ANTIPSYCHOTIC DRUGS AND THE RISK OF ACUTE KIDNEY INJURY: A POPULATION-BASED COHORT STUDY

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by

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Abstract

Older adults are frequently prescribed atypical antipsychotic drugs and may be at a risk for kidney-related adverse events. This population-based retrospective cohort study examined the 90-day risk of acute kidney injury (AKI) and the potential reasons for AKI in 96,471 matched pairs of older adults who received and who did not receive a new atypical antipsychotic drug prescription from 2003 to 2011 in Ontario. Atypical antipsychotic drug use was associated with a higher risk of hospitalization with AKI (relative risk (RR) 2.06 [95% confidence interval (CI) 1.85–2.29]). The drug use was also associated with potential reasons for AKI including hypotension (RR 2.16 [95% CI 1.81–2.57]), acute urinary retention (RR 2.15 [95% CI 1.78–2.60]), and neuroleptic malignant syndrome/rhabdomyolysis (RR 1.44 [95% CI 1.06–1.96]). Residual confounding is unlikely to explain the observed associations entirely. This knowledge informs prescribing practice and may help identify a drug-induced reason for AKI.

Keywords

Atypical antipsychotic drug, acute kidney injury, hypotension, acute urinary retention, neuroleptic malignant syndrome, rhabdomyolysis, acute myocardial infarction, ventricular arrhythmia, all-cause mortality, adverse drug reaction

Dedication

I dedicate this thesis to those who believed in my dream.

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List of Abbreviations

ACE = angiotensin-converting enzyme

AKI = acute kidney injury

ARB = angiotensin II receptor blocker

CI = confidence interval

CIHI-DAD = Canadian Institute for Health Information Discharge Abstract Database

CKD = chronic kidney disease

GFR = glomerular filtration rate

HR = hazard ratio

ICD-9 = International Classification of Diseases, Ninth Revision

ICD-10 = International Classification of Diseases, Tenth Revision

NNH = number needed to harm

NSAID = non-steroidal anti-inflammatory drug

ODB = Ontario Drug Benefit

OHIP = Ontario Health Insurance Plan

OMHRS = Ontario Mental Health Reporting System

OR = odds ratio

RPDB = Ontario's Registered Persons Database

RR = relative risk

STROBE = Strengthening the Reporting of Observational Studies in Epidemiology

Chapter 1

1 Introduction

Atypical antipsychotic drugs (quetiapine, risperidone, and olanzapine) are frequently prescribed to older adults and the incidence of its use in the population continues to increase.[1,2] In many jurisdictions these drugs are used to manage behavioural symptoms of dementia, which is not an approved indication.[2–5] Safety concerns have also been raised about the use of these drugs in older adults.[3,4,6,7] Acute kidney injury (AKI; a rapid decline in kidney function) has been attributed to atypical antipsychotic drugs in several case reports.[8–12] Potential reasons for AKI include hypotension, acute urinary retention, and neuroleptic malignant syndrome/rhabdomyolysis. The antagonistic properties of atypical antipsychotic drugs against alpha-adrenergic, muscarinic acetylcholine, serotonin, and dopamine receptors contributes to the adverse effects that may cause AKI.[8–30] Acute myocardial infarction and ventricular arrhythmias have also been attributed to these drugs, and acute cardiac events can lead to hemodynamic derangements and poor renal perfusion.[31,32] However, no clinical or epidemiologic studies have quantified the risk of AKI from atypical antipsychotic drugs. This information would add to growing knowledge of potential adverse events from this drug class – the U.S. Food and Drug Administration now warns of an increased risk of death in older patients treated with these drugs versus placebo from analyses of placebo-controlled trials (averaging 10 weeks in duration).[3] We conducted a population-based retrospective matched cohort study of older adults in Ontario, Canada to characterize the 90-day risk of hospitalization with AKI associated with new atypical antipsychotic drug use versus non-use. Moreover, we explored the potential reasons by which the kidney injury may occur from the use of these drugs.

Chapter 2

2 Literature Review

2.1 Acute kidney injury (AKI)

AKI is a sudden decline in kidney function, often following insults that cause structural or functional alterations in the kidneys.[33,34] The rapid loss in kidney function results in accumulation of nitrogenous metabolic waste products including serum creatinine and urea.

Measuring changes in serum creatinine concentration is a laboratory-based clinical tool widely used to detect AKI.[35–37] AKI is defined as an absolute rise in serum creatinine concentration by 26.5 µmol/L or more within 48 hours or a relative rise by 50% or more within seven days.[37]

The population-based incidence rate of AKI is 408.5 cases per 100,000 person-years and is increasing by 10% each year.[38,39] AKI is also a frequent clinical challenge with incidence of 19.2 to 23.8 cases per 1000 hospitalizations.[40,41] The mortality rate of hospitalized patients with AKI approximates 20.3 to 28.1%.[42] AKI is associated with increased risks of developing permanent kidney failure (end-stage kidney disease) and in-hospital mortality.[40,43,44] AKI poses a financial burden to the healthcare system as patients with the kidney injury have longer length of hospital stay and higher healthcare costs.[40,43]

2.2 Risk factors for AKI

A number of demographic factors, comorbid conditions, and certain medications have been associated with AKI.

2.2.1 Age

Older age is a risk factor for AKI due to the age-related reduction in kidney function reserve and compromised ability of the kidneys to withstand acute insults.[45,46] A population-based study conducted in the U.S. observed progressively higher incidences of AKI with increasing age (less than 50 years: 78.0 cases per 100,000 person-years; 50 to 59 years: 320.0 cases per 100,000 person-years; 60 to 69 years: 814.8 cases per 100,000 person-years; 70 to 79 years: 1809.1 cases per 100,000 person-years; 80 years or older: 3545.4 cases per 100,000 person-years).[38] Moreover, a prospective cohort study of 1,411 critically ill patients showed that those aged 65 years and older were more likely to develop AKI compared to those younger than 65 years (OR 1.50 [95% CI 1.16–1.92]; $P = 0.002$).[47]

2.2.2 Sex

Previous studies have implicated male sex with a higher risk of AKI.[38,48] A population-based study of 3,787,410 U.S. adults found a higher incidence of AKI in men than women (443.1 cases per 100,000 person-years versus 330.4 cases per 100,000 person-years).[38] Bagshaw *et al.*[48] showed that men aged 65 years and older were at a significantly greater risk of intensive care unit admission with AKI compared to women of same age group (RR 2.2 [95% CI 1.5–3.2]; $P < 0.0001$).

2.2.3 Chronic kidney disease (CKD)

Measuring estimated glomerular filtration rate (GFR) is a widely used, serum creatinine-based assessment of baseline kidney function.[49] Briefly, GFR is the volume of fluid filtered through the kidney glomeruli per unit time, based on serum creatinine clearance.[50,51] A normal GFR is greater than 80 mL/min/1.73 m^2, while patients with a GFR less than 10 mL/min/1.73 m^2 frequently need ongoing dialysis treatments to maintain their life.[49,50] Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function that is prolonged for greater than three months.[49] CKD is categorized into six stages according to its severity (i.e. the degree to which GFR is reduced; stages 1, 2, 3a, 3b, 4, and 5; from less to more severe).[51]

CKD is a potent risk factor for AKI as the chronic condition leaves patients more vulnerable to acute insults to the kidneys.[37,52] A population-based surveillance performed in Alberta showed that patients with a history of CKD had a significantly higher risk of intensive care unit admission with AKI compared to patients without such a history (RR 4.9 [95% CI 3.5–6.8]; $P < 0.0001$).[48] Two retrospective cohort studies demonstrated a graded relationship between the severity of CKD and the risk of hospitalization with AKI.[53,54] Pannu *et al.*[53] demonstrated that, compared to patients with CKD Stage 3a, those with more advanced stages of CKD were more likely to develop AKI. Patients with CKD Stage 3b, 4, and 5 had ORs for hospitalization with AKI of 2.9 (95% CI 2.7–3.1), 6.2 (95% CI 5.7–6.8), and 18.3 (95% CI 16.5–20.3), respectively.[53] James *et al.*[54] had similar findings from a cohort of 920,985 patients with CKD. In their study, patients with CKD Stage 3b, 4, and 5 had respective rate ratios for hospitalization with AKI of 2.3 (95% CI 2.1–2.4), 5.6 (95% CI 5.1–6.2), and 13 (95% CI: 11–15) compared to patients with CKD Stage 3a.[54]

2.2.4 Diabetes mellitus

Diabetes mellitus, characterized by the chronic elevation of blood glucose level, is one of the leading causes of kidney disease.[55–57] The scarring of kidney nephrons in diabetes mellitus contributes to the reduction of kidney function.[55–57] A population-based surveillance study showed that adults diagnosed with diabetes mellitus had a significantly greater risk of intensive care unit admission with AKI compared to those without such a diagnosis (RR 10.3 [95% CI 7.7–13.6]; $P < 0.0001$).[48] Moreover, a case-control study that included 1,764 patients who acquired AKI and 600,820 patients who did not acquire AKI during hospitalization suggested that diabetes mellitus is a risk factor for AKI.[58] In the study, patients who developed AKI were more likely to have pre-existing diabetes mellitus compared to patients who did not develop the kidney injury (OR 2.07 [95% CI 1.86–2.30]).[58]

2.2.5 Cardiovascular disease

Normal kidney function is dependent on sufficient perfusion of the kidneys by the cardiovascular system.[33,59] Hemodynamic disturbances that arise from cardiovascular

disorders may reduce renal perfusion and lead to decline in kidney function.[33,59] Moreover, prolonged reduction in renal perfusion can lead to structural changes in the kidneys.[33,59] Bagshaw *et al.*[48] showed that adults with a history of heart disease had a significantly increased risk of intensive care unit admission with AKI compared to adults without such a history (RR 24.0 [95% CI 18.5–31.2]; $P < 0.0001$). In the same study, individuals with a history of stroke had with a significantly higher risk of AKI than those without such a history (RR 22.0 [95% CI 15.6–31.0]; $P < 0.0001$).[48] Poor left ventricular function has also been identified as a risk factor for AKI following cardiac surgery.[60] A prospective cohort study of critically ill patients demonstrated that individuals with heart failure were significantly more likely to acquire AKI compared to those without heart failure (OR 2.18 [95% CI 1.12–4.44]; $P = 0.02$).[47] A case-control study of hospitalized patients found patients who suffered AKI were more likely to have pre-existing congestive heart failure than patients who did not suffer the kidney injury (OR 9.0 [95% CI 2.1–38.9]; $P < 0.0001$).[61] Hsu *et al.*[58] performed a case-control study of 602,584 hospitalized patients and found patients who acquired AKI had higher odds of having a history of hypertension compared to patients who did not acquire the kidney injury (OR 1.41 [95% CI 1.25–1.58]).

2.2.6 Liver disease

Liver diseases such as cirrhosis predispose patients to AKI. Reasons include decreased hyperdynamic circulation and decreased renal perfusion from blood volume depletion.[62] A prospective cohort study conducted in an intensive care setting found patients with with cirrhosis had a significantly higher odds of developing AKI compared to those without cirrhosis (OR 2.18 [95% CI 1.16–4.10]; $P = 0.01$).[47]

2.2.7 Medications

A number of commonly prescribed medications can predispose patients to AKI.[33,59,63,64] Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), diuretics, and calcium channel blockers have anti-hypertensive properties and AKI may occur with the use of these medications due to decreased renal perfusion.[64,65] Moreover, the use of ACE inhibitors and ARBs can lead to reduced GFR due to their

ability to decrease glomerular pressure by down-regulating the synthesis and activity of angiotensin II.[64,65] The use of non-steroidal anti-inflammatory drugs (NSAIDs) may also precipitate AKI.[66] NSAID-induced AKI has been reported in patients with pre-existing kidney dysfunction, congestive heart failure, hypertension, or liver disease.[67] A case-control study of 360 hospitalized patients found those who suffered AKI were significantly more likely to have used ACE inhibitors, diuretics, or NSAIDs compared to those who did not suffer the kidney injury (OR 2.0 [95% CI 1.2–3.6]; $P = 0.014$).[68]

Lipid lowering drug 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may lead to rhabdomyolysis; a severe muscle injury characterized by the breakdown of skeletal muscles.[69] The destruction of skeletal muscles results in the release of their contents, such as myoglobin, into the systemic circulation.[69] Myoglobin is nephrotoxic and may lead to AKI.[69,70] The U.S. Food and Drug Administration warned of the increased risk of myopathy associated with high dose statin based on the results of a randomized controlled trial.[71,72] In the randomized trial, 52 patients (0.9%) who received high dose statin versus one patient (0.02%) patients who received low dose statin developed myopathy.[72] In the same trial, 22 patients (0.4%) who received high dose statin versus no patient who received low dose statin developed rhabdomyolysis.[72] In chart reviews of patients hospitalized with rhabdomyolysis, statin use contributed to 4 to 13% of the muscle injury.[23,73]

2.3 Atypical antipsychotic drugs and older adults

Atypical antipsychotic drugs (quetiapine, risperidone, and olanzapine) are psychoactive medications originally approved for the treatment of schizophrenia and bipolar disorder.[74] Although their mechanism of action is not entirely clear, the antipsychotic property of the drugs has been attributed to brief blockade of dopamine receptors in the central nervous system characterized by rapid dissociation from the receptors.[75] Since their introduction in the 1990s, atypical antipsychotic drugs have largely replaced conventional antipsychotic drugs (the older class of antipsychotic drugs) due to their improved safety and efficacy profiles.[1,76] Unlike conventional antipsychotic drugs, atypical antipsychotic

drugs produce minimal extrapyramidal side effects and improve both positive and negative symptoms of psychosis.[77–79] These favourable characteristics of atypical antipsychotic drugs have been accredited to their ability to antagonize both dopamine and serotonin receptors in the central nervous system.[78,79]

In many jurisdictions, atypical antipsychotic drugs are both frequently and increasingly prescribed to older adults.[2,5] In 2002, the prevalence of antipsychotic drug prescription was 3% in Ontario residents 65 years and older and atypical antipsychotic drugs accounted for 82.5% of all antipsychotic drugs dispensed.[1] Risperidone was the most commonly prescribed atypical antipsychotic drug (56.4%), followed by olanzapine (29.6%) and quetiapine (13.9%).[1] A common, off-label use of these drugs in older adults has been the management of behavioural symptoms in dementia. In the U.S., none of the atypical antipsychotic drugs have been approved for the management of behavioural symptoms.[3] In Canada, risperidone has been the only atypical antipsychotic drug approved for the particular purpose.[4] The annual incidence of antipsychotic drug prescription among older patients with dementia has risen 20% in Ontario, from 1,512 prescriptions per 100,000 patients in 2002 to 1,813 prescriptions per 100,000 patients in 2007.[2]

2.4 Factors associated with atypical antipsychotic drug use in older adults

A number of demographic factors and comorbid conditions have been associated with atypical antipsychotic drug use.

2.4.1 Age

Previous studies of older adults have suggested patients with more advanced age are less likely to use atypical antipsychotic drugs.[80,81] A cross-sectional study of older British adults found progressive reduction in the odds of using antipsychotic drugs with respect to increasing age.[80] Adults aged between 75 and 84 years were significantly less likely to use antipsychotic drugs compared patients aged between 65 and 74 years (OR 0.61 [95%

CI 0.47–0.79]; $P < 0.05$).[80] In the same study, older adults aged 85 years and older also had significantly lower odds of using the drugs compared to adults aged between 65 and 74 years (OR 0.36 [95% CI 0.27–0.46]; $P < 0.05$).[80] Kamble *et al.*[81] found similar associations between age and antipsychotic drug use in their cross-sectional survey of U.S. long-term care residents. When compared to residents aged between 65 and 74 years, those aged between 75 and 84 years did not have a significantly lower odds of using the drugs (OR 0.93 [95% CI 0.77–1.13] $P > 0.05$).[81] However, residents aged 85 years and older were significantly less likely to use antipsychotic drugs compared to those aged between 65 and 74 years (OR 0.70 [95% CI 0.58–0.84]; $P < 0.05$).[81]

2.4.2 Sex

Previous studies of older adults showed that women were less likely to use atypical antipsychotic drugs than men.[81,82] For example, a cross-sectional study conducted in long-term care facilities showed that female residents were significantly less likely to use antipsychotic drugs compared to male residents (OR 0.80 [95% CI 0.70–0.93]; $P < 0.05$).[81] Similarly, Bronskill *et al.*[82] demonstrated that older women had a lower odds of receiving antipsychotic drugs compared to older men (OR 0.69 [95% CI 0.64–0.75]) from the analysis of 19,870 long-term care residents in Ontario.

2.4.3 Residential status

Healthcare use by older adults who reside in long-term care facilities could differ compared to those dwelling in communities.[83,84] Lindesay *et al.*[80] conducted a cross-sectional survey of adults aged 65 years and older in the U.K. and found older adults living in nursing homes were significantly more likely to use antipsychotic drugs compared to those living in residential or voluntary homes (OR 1.97 [95% CI 1.52–2.55]; $P < 0.05$). Another cross-sectional study found similar results among older Swedish adults.[85] In the study, older adults living in long-term care facilities had an increased odds of using antipsychotic drugs compared to those not living in such facilities (OR 2.72 [95% CI 1.29–5.74]).[85]

2.4.4 Dementia and mental disorders

Quetiapine, risperidone, and olanzapine have been indicated for the treatment of schizophrenia and bipolar disorder.[74] Kamble *et al.*[81] found long-term care residents with schizophrenia had a significantly higher odds of using antipsychotic drugs than residents without schizophrenia (OR 11.15 [95% CI 7.84–15.87]; $P < 0.05$). Moreover, they also showed that residents with bipolar disorder were significantly more likely to use the drugs compared to residents without the disorder (OR 3.97 [95% CI 2.52–6.24]; $P < 0.05$).[81]

Although risperidone has been the only atypical antipsychotic drug approved for the use of managing behavioural symptoms of dementia in Canada, quetiapine and olanzapine have also been widely used for this purpose.[2,4] A retrospective cohort study conducted in Ontario's long-term care facilities found older patients with a history of dementia were more likely to receive antipsychotic drugs compared to those without such a history (OR 3.52 [95% CI 3.24–3.82]).[82] Similarly, in the U.S., long-term care residents diagnosed with dementia were also significantly more likely to use antipsychotic drugs than residents without such a diagnosis (OR 2.23 [95% CI 1.94–2.57]; $P < 0.05$).[81] Also in Finland, a cross-sectional analysis of 1,987 long-term care residents showed that atypical antipsychotic drug use was more common among patients with dementia than those without dementia (28.3% versus 24.2%; $P = 0.062$).[86]

In addition to the treatment of patients with schizophrenia, bipolar disorder, or dementia, atypical antipsychotic drugs have also been used as an adjunctive treatment of major depression and anxiety disorders.[87–92] A cross-sectional survey of long-term care facilities in the U.S showed that patients with anxiety disorder were significantly more likely to use the antipsychotic drugs than those without such disorder (OR 1.70 [95% CI 1.43–2.00]; $P < 0.05$).[81] In the same study, patients who had depression also had a significantly increased odds of using antipsychotic drugs compared to those who did not have depression (OR 1.18 [95% CI 1.04–1.33]; $P < 0.05$).[81] Moreover, a British cross-sectional survey demonstrated that patients who used antidepressant drugs were significantly more likely to also use antipsychotic drugs compared to those who did not use antidepressant drugs. (OR 1.42 [95% CI 1.16–1.74]; $P < 0.05$).[80]

2.5 Atypical antipsychotic drugs and potential reasons for AKI

Potential reasons for AKI from atypical antipsychotic drug use include hypotension, acute urinary retention, neuroleptic malignant syndrome/rhabdomyolysis, and acute cardiac events (see Figure 1).

2.5.1 Hypotension

Hypotension (an abnormally low blood pressure) is a well-known cause of AKI, where decreased renal perfusion leads to reduction in kidney function and when prolonged, results in intrinsic damage to the kidneys.[33,59] The ability of atypical antipsychotic drugs to block alpha-adrenergic receptors has been postulated to result in vasodilation and a subsequent reduction in blood pressure.[78,93] Orthostatic hypotension is a type of hypotension where systolic blood pressure decreases by at least 20 mmHg and/or diastolic blood pressure declines by at least 10mmHg while transitioning from a lying to standing position.[94] Previous chart reviews of older patients have attributed orthostatic hypotension to atypical antipsychotic drug use.[95–97] For example, a chart review of 189 older patients with orthostatic hypotension attributed 5 (2.6%) cases to quetiapine use, 15 (7.9%) cases to risperidone use, and 4 (2.1%) cases to olanzapine use.[95]

Hypotension is a common adverse drug reaction observed in clinical trials of atypical antipsychotic drugs in older adults.[13–18] Sajatovic *et al.*[13] performed an analysis of data pooled from two randomized placebo-controlled trials (12 weeks in duration) that included adults aged 55 years and older with bipolar disorder. Their analysis found orthostatic hypotension in 5 out of 28 (17.9%) patients treated with quetiapine versus 1 out of 31 (3.2%) patients in the placebo group.[13] Moreover, one patient treated with quetiapine suffered unspecified kidney failure and died.[13] In an open-label, single-arm trial (13 months in duration) of quetiapine that included 184 older patients with psychosis, 28 (15.2%) patients experienced orthostatic hypotension and 32 (17.4%) patient experienced dizziness.[14] The median time to onset for orthostatic hypotension and dizziness was 18 and 15 days, respectively.[14] In another open-label, single arm trial of quetiapine involving 100 geriatric inpatients (4 weeks in duration), 9 (9.0%) patients

suffered orthostatic hypotension and 27 (27.0%) patients experienced dizziness.[15] A randomized, open-label trial (6 months in duration) allocated 27 patients to risperidone treatment and 34 patients to olanzapine treatment.[17] In the risperidone group, 3 (11.1%) patients developed orthostatic hypotension and 5 (18.5%) patients had unspecified renal adverse events.[17] In the olanzapine group, orthostatic hypotension occurred in 4 (11.8%) patients.[17] In a 12-week long open-label, single-arm study of risperidone that included 103 older patients with psychosis, orthostatic hypotension and dizziness were observed in 5 patients (4.9%) and 23 (22.3%) patients, respectively.[16] In another open-label, single-arm trial of risperidone, which followed 110 older patients with psychosis for four weeks, 6 (5.5%) patients developed orthostatic hypotension and 32 (29.1%) patients experienced dizziness.[18]

2.5.2 Acute urinary retention

Acute urinary retention is an abrupt inability to empty the bladder and this can cause AKI.[59,98] Muscarinic acetylcholine receptors are present in the urinary tract and are involved in the biological pathways of micturition.[8,98,99] Atypical antipsychotic drugs have anticholinergic properties and thus, it has been postulated in some cases that the drugs antagonize muscarinic acetylcholine receptors leading to acute urinary retention.[8] Acute urinary retention has been attributed to the use of quetiapine, risperidone, or olanzapine in case reports.[8,20,21] In the report of two older patients who developed acute urinary retention after olanzapine use, both suffered AKI.[8]

2.5.3 Neuroleptic malignant syndrome and rhabdomyolysis

Neuroleptic malignant syndrome is a serious adverse drug reaction that can occur from antipsychotic drugs. Neuroleptic malignant syndrome is characterized by altered mental status, autonomic dysfunction, extrapyramidal side effects, high fever, and elevated serum creatine kinase level.[100] Elevated creatine kinase level is a biomarker for muscle damage and may also indicate rhabdomyolysis.[69] Although the biological mechanism is not entirely clear, the sudden blockade of dopamine receptors by atypical antipsychotic drugs has been postulated to result in neuroleptic malignant syndrome.[22,30] It has been also hypothesized that, since dopaminergic neurons regulate the sympathetic nervous

system, the down-regulation of their activity by atypical antipsychotic drugs can lead to hyperactivity of the sympathetic nervous system and subsequent muscle damage.[25,26,101]

Previous chart reviews of approximately 100 patients hospitalized with rhabdomyolysis attributed 5.5 to 7.5% of the cases to quetiapine use.[23,24] A retrospective review of patients hospitalized with olanzapine overdose showed a correlation between the quantity of ingested olanzapine and the proportion of patients with creatine kinase level greater than 500 IU/L (Pearson's r = 0.91).[102] Individual cases of rhabdomyolysis have also been reported from the use of risperidone or olanzapine at therapeutic dosages and from the use of quetiapine at therapeutic dosages and due to overdose.[9–12,25–29,103,104] A common complication of rhabdomyolysis is AKI, occurring in 15 to 46% of patients who suffer the muscle breakdown (by mechanisms described in Section 2.2.7).[73,105] Several case reports have attributed AKI to the use of quetiapine, risperidone, or olanzapine where the kidney injury was mediated by neuroleptic malignant syndrome and/or rhabdomyolysis.[9–12] Another case report described the development of AKI following rhabdomyolysis induced by quetiapine overdose.[103]

2.5.4 Acute cardiac events

Acute cardiac events can result in hemodynamic instability and AKI may precipitate from such events due to decreased renal perfusion.[33,59] In a retrospective cohort study of 147,007 patients hospitalized with acute myocardial infarction, 28,545 (19.4%) of the patients developed AKI.[106] Pariente *et al.*[31] conducted a retrospective cohort study in Quebec to compare the risk of acute myocardial infarction between older patients with dementia who were initiated on antipsychotic drug therapy and those were not initiated on such a therapy. Among 10,969 antipsychotic drug users studied, 97.8% were initiated on atypical antipsychotic drugs and the drug use versus non-use was associated with a 30-day higher risk of acute myocardial infarction (HR 2.19 [95% CI 1.11–4.32]).[31]

In addition to acute myocardial infarction, ventricular arrhythmias have also been attributed to atypical antipsychotic drug use.[32] QT interval prolongation is a cardiac condition that can lead to ventricular arrhythmia and sudden cardiac death.[107] Atypical antipsychotic drugs can induce QT interval prolongation by antagonizing cardiac

potassium ion channels and thereby delaying repolarization of the heart.[108] Individual cases of QT interval prolongation have been attributed to quetiapine or risperidone use at both therapeutic dosages and due to overdose.[109–115] Ray *et al.*[32] conducted a retrospective cohort study of 279,900 U.S adults (mean age 46 years) to examine the relationship between antipsychotic drug use and sudden cardiac death. In this study, antipsychotic drug use versus non-use was associated with a significantly greater risk of sudden cardiac death (rate ratio 2.26 [95% CI 1.88–2.72]; $P < 0.001$).[32] There was a dose-dependent relationship between the dose of antipsychotic drug used and the incidence of sudden cardiac death, supporting a causal relationship between the drug use and sudden cardiac death.[32] The elevated risk of sudden cardiac death was consistently found in subgroups of quetiapine users (rate ratio 1.88 [95% CI 1.30–2.71]), risperidone users (rate ratio 2.91 [95% CI 2.26–3.76]), and olanzapine users (rate ratio 2.04 [95% CI 1.52–2.74]).[32]

2.6 Atypical antipsychotic drugs and the risk of death in older adults

In 2005, the U.S. Food and Drug Administration issued a boxed warning regarding the increased mortality associated with atypical antipsychotic drug use in older patients with dementia.[3] A boxed warning is an alert that is present on the prescribing information of a medication. The black box warning was based on the analyses of 17 placebo-controlled trials (averaging about 10 weeks in duration), which demonstrated approximately 1.6 to 1.7-fold increase in mortality rate in older patients with dementia treated with atypical antipsychotic drugs compared to patients in the placebo group.[3] The incidence of death was 4.5% in patients treated with atypical antipsychotic drugs versus 2.6% in the placebo group.[3] Later in the same year, Health Canada announced a similar warning, advising healthcare professionals of the increased mortality associated with atypical antipsychotic drug treatment.[4] Health Canada's advisory was based on 13 randomized placebo-controlled trials that showed approximately 1.6-fold increase in mortality rate in older patients with dementia treated with atypical antipsychotic drugs compared to patients in the placebo group.[4] Subsequently, a meta-analysis of 15 randomized placebo-controlled trials (10 to 12 weeks in duration) comparing atypical antipsychotic drug treatment with placebo in older patients with dementia also showed supporting evidence for the

warning.[116] The meta-analysis showed that older patients treated with atypical antipsychotic drugs were significantly more likely to die compared to those in the placebo group (OR 1.54 [95% CI 1.06–2.23]; $P < 0.01$).[116]

Several population-based observational studies have also examined the risk of death associated with atypical antipsychotic drug use in older adults.[83,84,117] Gill *et al.*[83] conducted a retrospective cohort study of older patients with dementia in Ontario to characterize the association between newly initiated atypical antipsychotic drug use and 30-day mortality at the population-level. Their study found atypical antipsychotic drug use versus non-use was associated with a higher risk of death in older patients with dementia dwelling in communities (HR 1.31 [95% CI 1.02–1.70]).[83] A similar association between the drug use and mortality was found in older patients with dementia residing in long-term care facilities (HR 1.55 [95% CI 1.15–2.07]).[83] A subsequent retrospective cohort study investigated the 30-day risk of serious events (defined as events that required hospitalization or resulted in death) associated with newly commenced atypical antipsychotic drug use in older patients with dementia.[84] This study found atypical antipsychotic drug use versus non-use was associated with an increased odds of serious events in older patients with dementia dwelling in communities (OR 3.19 [95% CI 2.77–3.68]).[84] A similar association between the drug use and serious events was found in older patients with dementia residing in long-term care facilities (OR 1.92 [95% CI: 1.68–2.21]).[84] In the U.S., Huybrechts *et al.*[117] conducted a retrospective cohort study to compare the risk of death among older long-term care residents newly initiated on different atypical antipsychotic drugs.[117] The mortality rate was 28.4 deaths per 100 person-years among quetiapine users, 36.2 deaths per 100 person-years among risperidone users, and 36.7 deaths per 100 person-years among olanzapine users within 180 days after initiation of respective atypical antipsychotic drug treatment.[117] This study found a lower risk of death in quetiapine users compared to risperidone users (HR 0.80 [95% CI 0.74–0.86]).[117] The risk of death in olanzapine users was not statistically different from that of risperidone users (HR 1.01 [95% CI 0.95–1.07]).[117]

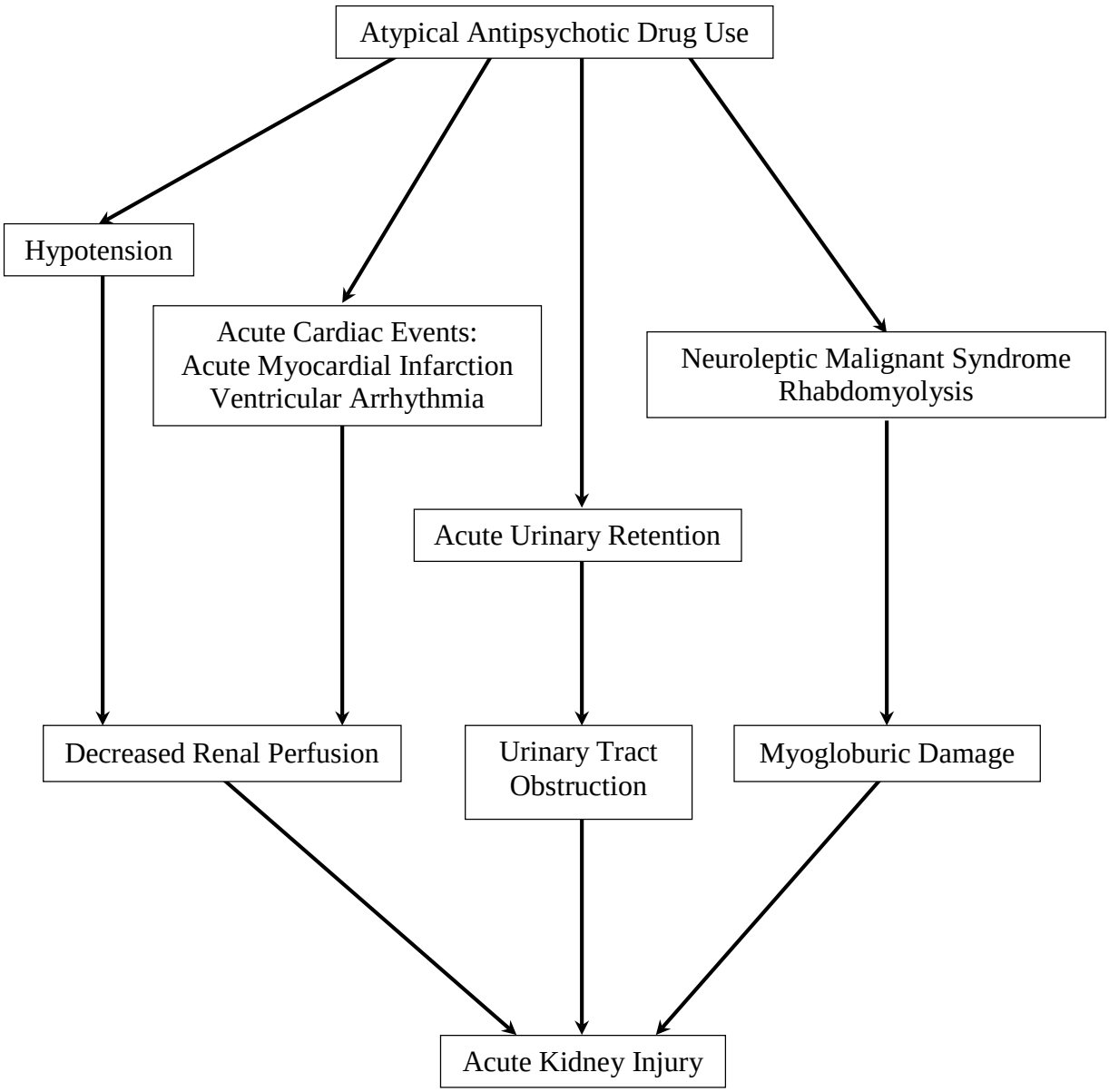

Figure 1: Putative biological mechanisms by which atypical antipsychotic drug use may lead to AKI

Chapter 3

3 Rationale and Research Questions

3.1 The need for research

Adverse drug reactions occur frequently among older adults with an incidence rate of 50.1 events per 1000 person-years.[118] Approximately 28% of the adverse drug reactions are preventable and kidney-related adverse events account for 27% of the preventable adverse events.[118,119] There currently exist genuine concerns about the safety of atypical antipsychotic drug use in older adults. For example, this class of drugs is commonly and increasingly being used for the unapproved indication of managing behavioural symptoms of dementia despite the federal warnings that advise of the risk of death associated with the drug treatment.[2–4] Determining the risk of AKI associated with atypical antipsychotic drug use will contribute to emerging knowledge regarding the safety of their use in older adults. There exist several case reports attributing AKI to atypical antipsychotic drug use, along with potential reasons why AKI may occur in this setting.[8–32] However, the association between atypical antipsychotic drug use and AKI has not been characterized in previous clinical or epidemiologic investigations. Therefore, we aimed to characterize the risk of hospitalization with AKI associated with new atypical antipsychotic drug use versus non-use. Additionally, we intended to identify potential reasons for AKI in this setting.

3.2 Research questions and hypotheses

3.2.1 Primary research question

Compared to non-use, is new atypical antipsychotic drug use associated with a higher risk of hospitalization with AKI in older adults?

Hypothesis: We hypothesize that, compared to non-use, new atypical antipsychotic drug use is associated with a higher risk of hospitalization with AKI in older adults.

3.2.2 Secondary research questions

1) Compared to non-use, is new atypical antipsychotic drug use associated with a higher risk of hospitalization with conditions that can be responsible for AKI in older adults? These five conditions are: hypotension, acute urinary retention, neuroleptic malignant syndrome/rhabdomyolysis, acute myocardial infarction, and ventricular arrhythmia. Each of these conditions will be examined separately as a secondary outcome.

   Hypothesis: We hypothesize that, compared to non-use, new atypical antipsychotic drug use is associated with a higher risk of hospitalization with each of the conditions that can be responsible for AKI in older adults.

2) Compared to non-use, is new atypical antipsychotic drug use associated with a higher risk of all-cause mortality in older adults?

   Hypothesis: We hypothesize that, compared to non-use, new atypical antipsychotic drug use is associated with a higher risk of all-cause mortality in older adults.

Chapter 4

4 Methods

4.1 Study design and setting

We conducted a population-based retrospective matched cohort study of older adults using linked healthcare administrative databases in Ontario. Approximately 1.8 million adults aged 65 years and older reside in Ontario.[120] Older residents of Ontario have comprehensive, universal healthcare that covers outpatient drug prescriptions, physician services, and hospitalizations under a single-payer healthcare system.

We conducted this study according to a pre-specified protocol that was approved by the research ethics board at Sunnybrook Health Sciences Centre in Toronto, Ontario. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (see Appendix A for checklist).[121]

4.2 Data sources

We used following six healthcare administrative databases housed at the Institute for Clinical Evaluative Sciences to ascertain drug exposure, covariate information, and outcome data:

1) Ontario Drug Benefit (ODB) Database

   The ODB database stores records of all outpatient drug prescriptions dispensed to patients aged 65 years and older in Ontario with a high level of accuracy (overall error rate of less than 1%).[122] We used this database to ascertain exposure to atypical antipsychotic drugs and baseline medication use. We also acquired information on patient residential status (community-dwelling or long-term care) and medical specialty of the physicians who prescribed atypical antipsychotic drugs.

2) Ontario's Registered Persons Database (RPDB)

We used RPDB to attain information on patient demographics (age, sex, and vital status), income (categorized into quintiles of average neighbourhood income), and location of residence (urban or rural). Moreover, we used the vital status information captured by this database to ascertain the outcome of all-cause mortality.

3) Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD)

CIHI-DAD contains diagnostic and procedural information on all hospitalizations occurred in Ontario. A maximum of 25 unique diagnosis codes (for example, codes for AKI, hypotension, or acute urinary retention) can be assigned to each hospitalization. The hospital diagnosis codes were based on the International Classification of Diseases, Ninth Revision (ICD-9) codes prior to 2002 and ICD-10 codes since 2002. We used both ICD-9 and ICD-10 codes to determine baseline comorbid conditions (detailed in Appendix B). We used ICD-10 codes exclusively to determine hospitalized outcomes as the cohort entry of the patients commenced in 2003 (detailed in Appendix C).

4) Ontario Health Insurance Plan (OHIP) Database

The OHIP database stores information on physician claims on inpatient and outpatient services using fee codes. We used the information captured by the database to identify baseline comorbid conditions in addition to the diagnostic information attained from CIHI-DAD.

5) Ontario Mental Health Reporting System (OMHRS) Database

The OMHRS database contains demographic and health information on patients admitted to adult mental health beds in Ontario. The diagnosis codes used record health conditions in this database were based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (detailed in Appendix B). In addition to CIHI-DAD and OHIP database, we used the diagnostic information stored in this database to determine baseline psychiatric comorbid conditions.

6) Cerner and Gamma-Dynacare Laboratory Databases

A subpopulation of patients in Southwestern Ontario had outpatient serum creatinine and urine dipstick protein measurements available before cohort entry and was in the catchment area of 12 hospitals in which linked serum creatinine laboratory measurements were available through these laboratory datasets.[123] We used the information to assess baseline kidney function and to ascertain the outcome of AKI defined using serum creatinine values.

All six databases have been repeatedly used to study health outcomes including adverse drug reactions in previous studies.[83,84,124–128]

4.3 Patients

We accrued all adults aged 66 years and older in Ontario who were dispensed a new oral outpatient prescription for an atypical antipsychotic drug (quetiapine, risperidone, or olanzapine) between June 2003 and December 2011 to the drug user group. The date of this prescription served as the 'index date' for the drug users. We then randomly assigned an index date to all Ontario residents 66 years and older who were not dispensed a prescription for any antipsychotic drug (according to the index date of the drug users) and accrued them to the non-user group. For example, if more drug users were accrued between 2005 and 2006, a larger proportion of nonusers would be randomly assigned an index date between 2005 and 2006. We excluded the following patients from both groups: (1) those with prescriptions for any antipsychotic drug in the 180 days prior to their index date to ensure the drug users were newly prescribed, (2) those who were discharged from a hospital in the two days before their index date to ensure the drug users were newly initiated on an atypical antipsychotic drug in an outpatient setting and the non-users had the potential to be newly initiated on such a drug in an outpatient setting, and (3) those with an evidence of end-stage kidney disease (since the development of AKI is no longer relevant). From the drug user group, we excluded individuals who received a prescription for more than one type of antipsychotic drug on their index date to

compare mutually exclusive groups in subgroup analysis. From the non-user group, we excluded individuals without any outpatient medication dispensed in the 90 days prior to their index date to ensure that the non-users could have been prescribed a drug in Ontario.

4.4 Matching

The Consolidated Standards of Reporting Trials statement defined selection bias as a "systematic error in creating intervention groups, causing them to differ with respect to prognosis. That is, the groups differ in measured or unmeasured baseline characteristics because of the way in which participants are selected for the study or assigned to their study groups."[129] In randomized controlled trials, random allocation of treatment reduces selection bias as the method, on average, distributes both measured and unmeasured baseline factors similarly to the groups being compared.[130,131] However, in cohort studies, the exposure status is not randomly determined and thus, the exposed and unexposed groups can differ in baseline characteristics that may affect the outcome.[131] Consequently, cohort studies are susceptible to selection bias and this form of bias can lead to confounding.[131,132] Koepsell and Weiss[133] stated "confounding occurs in epidemiologic research when the measured association between an exposure and disease occurrence is distorted by an imbalance between exposed and non-exposed persons in regard to one or more other risk factors for the disease." Matching is a method used to reduce selection bias by forming exposed and unexposed groups that are similar with respect to baseline characteristics that may affect the outcome.[134] Therefore, we used the method of matching to minimize selection bias and to control for potential confounding.

Propensity score matching allowed us to form a matched set of patients in the drug user and non-user groups with similar probability of receiving an atypical antipsychotic drug (the propensity score) conditional on observed baseline covariates.[135,136] Following the guidance provided by recent methodological studies, we incorporated the following three types of variables into the propensity score[136–138]: (1) variables that are associated with atypical antipsychotic drug use, (2) risk factors for AKI, and (3) variables that are associated with both atypical antipsychotic drug use and AKI. We estimated the

propensity score using a multivariable logistic regression model that included following 27 covariates: age (per year); sex (men or women); year of cohort entry (2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, or 2011); residential status (community-dwelling or long-term care); evidence of dementia (yes or no), schizophrenia or other psychotic disorder (yes or no), bipolar disorder (yes or no), major depression and/or anxiety disorder (yes or no), chronic kidney disease (yes or no), cerebrovascular disease (yes or no), chronic liver disease (yes or no), congestive heart failure (yes or no), coronary artery disease (yes or no), diabetes mellitus (yes or no), hypertension (yes or no), and peripheral vascular disease (yes or no); the use of anticonvulsant (yes or no), antidepressant (yes or no), cholinesterase inhibitor (yes or no), lithium (yes or no), ACE inhibitor or ARB (yes or no), beta-adrenergic antagonist (yes or no), calcium channel blocker (yes or no), NSAID excluding aspirin (yes or no), potassium sparing diuretic (yes or no), non-potassium sparing diuretic (yes or no), and statin (yes or no).

Subsequently, we matched a non-user to each drug user on the following 12 characteristics: the logit of the propensity score (within caliper of ± 0.2 standard deviations[139]); age (within two years); sex; index date (within six months); residential status (community-dwelling or long-term care); evidence of dementia (yes or no), schizophrenia or other psychotic disorder (yes or no), bipolar disorder (yes or no), major depression and/or anxiety disorder (yes or no), CKD (yes or no); a recently dispensed medication from a pharmacy in the catchment area of linked hospital-based laboratory measurements (yes or no)[123]; availability of serum creatinine measurement in the year prior to the index date (yes or no). We matched the patients without replacement and using greedy matching technique. Patients who were not matched successfully were excluded from our analysis. Previously, it has been shown that optimal matching does not perform better than greedy matching in forming balanced groups.[140] Greedy matching was preferred over optimal matching for the purpose of computing efficiency.

4.5 Baseline characteristics

We assessed baseline comorbid conditions in the five years prior to the index date and medication use in the 180 days prior to the index date of each atypical antipsychotic drug user and non-user (see Appendix B for coding information). For the subpopulation of patients whose laboratory measurements were available, we assessed their kidney function in the year prior to their index date.

4.6 Outcomes

We followed patients for 90 days after the index date to assess the pre-specified outcomes. We elected for the 90-day follow-up period to (1) focus on short-term adverse outcomes, (2) avoid potential crossovers among different types of atypical antipsychotic drugs that may occur with longer periods of follow-up, and (3) mimic the duration of follow-up where safety outcomes were reported in clinical trials of atypical antipsychotic drug treatment in older adults.[3,4,116] The primary outcome was hospitalization with AKI. The secondary outcomes were potential reasons for AKI (hospitalization with hypotension, hospitalization with acute urinary retention, hospitalization with neuroleptic malignant syndrome/rhabdomyolysis, hospitalization with acute myocardial infarction, and hospitalization with ventricular arrhythmia), and all-cause mortality. Hospital diagnosis codes used to ascertain the outcomes are presented in Appendix C. Because up to 25 diagnosis codes can be assigned per hospitalization, patients with codes for several study outcomes were accounted under each outcome present.

In our validation study, the hospital diagnosis code for AKI in Ontario identified a median (interquartile range) absolute increase in serum creatinine of 98 μmol/L (43 to 200 μmol/L) from the most recent measured value prior to hospitalization, whereas its absence identified a median (interquartile range) increase of 6 μmol/L (IQR −4 to 20 μmol/L).[141] Patients hospitalized with AKI might or might not have the hospital diagnosis code recorded. The code was more likely to be present for patients with more severe forms of AKI, indicated by larger increases in serum creatinine.[141] When compared

against the reference standard of increases in serum creatinine, the specificity of the code was greater than 95%.[141] However, the sensitivity of the code ranged from 22 to 66% with the metric being lower for milder forms of AKI and thus, the code underestimated the true incidence of AKI.[141] Therefore, in the subpopulation of patients whose serum creatinine measurements were available, we examined AKI defined as an absolute increase in serum creatinine concentration of 27 μmol/L or greater or a relative increase by 50% or more from the most recently measured serum creatinine concentration in the year prior to the patient's index date (on the basis of the Acute Kidney Injury Network staging system).[35]

The known validity of hospital diagnosis codes for secondary outcomes is presented in Appendix C. Using reabstracted information written in a patient's chart as the reference standard, the hospital diagnosis code for hypotension and acute urinary retention had a sensitivity of 72% and 86% and positive predictive value of 39% and 48%, each respectively.[142] Using the same reference standard, one of the two codes for acute myocardial infarction had a sensitivity of 89% and positive predictive value of 87%.[142] The codes for neuroleptic malignant syndrome/rhabdomyolysis and ventricular arrhythmia have not been validated in our region and are not expected to be sensitive. However, there was no reason to suspect differential misclassification of these diagnosis codes between atypical antipsychotic drug users and non-users. Another secondary outcome was all-cause mortality and the corresponding code has been found to be highly accurate for identifying death with a sensitivity of 94% and specificity of 100%.[143]

We considered examining the robustness of our findings using tracer outcomes (also referred to as falsification end-points).[144,145] Tracer outcomes are those outcomes that are hypothesized to be causally unrelated to the exposure; the presence of an association between the exposure and tracer outcome would suggest that the observed associations in the study may be confounded.[144] However, after detailed review, we elected against this given the wide range of adverse effects reported with atypical antipsychotic drugs.

4.7 Statistical analyses

We compared baseline characteristics between atypical antipsychotic drug users and non-users using standardized differences. This metric describes differences between group means with respect to pooled standard deviation and indicates a meaningful difference if greater than 0.10 (10%).[136,146,147] The use of standardized differences has been recommended over that of statistical hypothesis testing (using *P* values) for assessing balance in baseline characteristics between propensity score matched groups.[148–150] The standardized difference is not influenced by sample size and thus, one can compare the balance in the unmatched sample to that in the matched sample.[149,150]

We measured the risk for the primary and secondary outcomes in both absolute and relative terms. We calculated absolute risk differences and 95% CIs using a method that accounts for matching.[151] Absolute risk difference was further expressed as the number needed to harm (NNH; 1/absolute risk difference), a measure that indicates how many patients need to receive an atypical antipsychotic drug to cause harm to one patient who otherwise would not have been harmed. NNH was calculated for ease of interpretation and not to imply causality. We used conditional logistic regression to estimate ORs and 95% CIs for the primary and secondary outcomes by using the non-user group as the referent group.

We repeated the analysis of the primary outcome (hospitalization with AKI) in four pre-specified subgroups: (1) evidence of CKD (present or absent), (2) antipsychotic drug type (quetiapine, risperidone, or olanzapine), (3) antipsychotic drug dose (high dose or low dose; high dose defined by a higher than median daily dose for the matched cohort [quetiapine >25 mg/day, risperidone >0.5 mg/day, and olanzapine >2.5 mg/day]), and (4) residential status (community-dwelling or long-term care). Each matched set of the drug users and non-users were included in subgroups defined by the antipsychotic drug type and dose based on the characteristics of the drug users.

CKD was identified using an algorithm of hospital diagnosis codes validated in our region for older adults.[152] The algorithm identified patients with a median (interquartile range) estimated GFR of 38 mL/min/1.73 m^2 (27 to 52 mL/min/1.73 m^2), whereas its

absence identified patients with a median (interquartile range) estimated GFR of 69 mL/min/1.73 m^2 (56 to 82 mL/min/1.73 m^2).[152] The algorithm for CKD had a sensitivity of 32% and specificity of 94% using an estimated GFR of 45 mL/min/1.73 m^2 as the referent standard.[152] Due to its limited sensitivity, the algorithm underestimated the true prevalence of CKD.[152]

All ORs were interpreted as RRs, which was appropriate given the observed incidence of the study outcomes (less than 10%). We performed all analyses using SAS version 9.2 (SAS Institute, Cary, North Carolina, USA, 2008).

Chapter 5

5 Results

5.1 Cohort characteristics

5.1.1 Unmatched cohort

Cohort selection is presented in Figure 2 and baseline characteristics of the unmatched and matched cohorts are presented in Table 1. Prior to matching, we identified 122,610 atypical antipsychotic drug users and 1,204,613 non-users. The drug users were older than the non-users and were more likely to be female and reside in long-term care facilities. The users were more likely to be diagnosed with dementia, schizophrenia or other psychotic disorder, bipolar disorder, major depression and/or anxiety disorder, chronic kidney disease, cerebrovascular disease, congestive heart failure, and coronary artery disease compared to the non-users. Moreover, the drug users were more likely to use anticonvulsants, antidepressants, cholinesterase inhibitors, and lithium. The drug users were less likely to use ACE inhibitors or ARBs and statins compared to the non-users (Table 1). Information on income was not available for 676 (0.6%) drug users and 4,380 (0.4%) non-users. Location of residence could not be ascertained for 234 (0.2%) drug users and 1,142 (0.1%) non-users.

5.1.2 Matched cohort

After matching, 96,471 pairs of atypical antipsychotic drug users and non-users remained in the cohort. The two groups were well balanced showing no meaningful difference in the 29 baseline characteristics measured: age, sex, income, year of cohort entry, location of residence, residential status, 12 comorbid conditions, and use of 11 medications (Table 1). The mean age was 81 years, 64.6% of patients were women and 23.9% resided in long-term care facilities. More than half of patients (53.9%) had a diagnosis of dementia. 7.6% of patients were diagnosed with schizophrenia or other psychotic disorder and 4.9% was diagnosed with bipolar disorder. A diagnosis of major depression and/or anxiety

disorder was made on 18.9% of patients. The most frequently prescribed atypical antipsychotic drug was risperidone (45.3%), followed by quetiapine (35.9%) and olanzapine (18.8%). The median (interquartile range) daily dose for quetiapine was 25 (25–50) mg/day, for risperidone was 0.5 (0.3–0.6) mg/day, and for olanzapine was 2.5 (2.5–5.0) mg/day. The prescriber information was not available for 10.7% of the atypical antipsychotic drug users. When the prescriber information was available (89.3% of the drug users), general practitioners (82.0%) were the most frequent prescribers of atypical antipsychotic drugs, followed by psychiatrists (7.1%) and geriatricians (4.7%). Income could not be ascertained for 448 (0.5%) drug users and 386 (0.4%) non-users. Location of residence could not be identified for 177 (0.2%) drug users and 109 (0.1%) non-users.

Baseline characteristics of patients from the subpopulation in Southwestern Ontario with available serum creatinine measurements are presented in Table 2. Within the matched cohort, there were 1,442 pairs of atypical antipsychotic drug users and non-users were from the subpopulation. The two groups were well balanced showing no meaningful differences in the 29 baseline characteristics including age, sex, income, year of cohort entry, location of residence (urban or rural), residential status (community-dwelling or long-term care), 10 comorbid conditions, use of 10 medications, baseline serum creatinine concentration, estimated GFR, and urine dipstick protein (Table 2). However, the drug users were more likely to have a diagnosis of cerebrovascular disease than the non-users (7.0% versus 4.4%; standardized difference = 0.11). The number of patients with bipolar disorder, use of lithium, and estimated GFR less than 15 mL/min/1.73m^2 was too few (less than five) and were not reported for reasons of patient privacy.

5.2 Main analysis

The primary outcome was 90-day hospitalization with AKI, assessed with a hospital diagnosis code and with serum creatinine values. The 90-day incidence of hospitalization with AKI assessed with a hospital diagnosis code in the atypical antipsychotic drug user group was 1.06% (1,022 events) and in the non-user group was 0.52% (500 events). Atypical antipsychotic drug use versus non-use was associated with a greater risk of

hospitalization with AKI (RR 2.06 [95% CI 1.85–2.29]; absolute risk difference 0.54% [95% CI 0.46%–0.62%]; NNH 185 [95% CI 161–216]). In the subpopulation where AKI was assessed using serum creatinine values, the 90-day incidence of hospitalization with AKI in atypical antipsychotic drug user group was 1.46% (21 events) and in the non-user group was 0.55% (8 events). Atypical antipsychotic drug use versus non-use was associated with an increased risk of hospitalization with AKI (RR 2.63 [95% CI 1.16–5.93]; absolute risk difference 0.90% [95% CI 0.17%–1.63%]; NNH 111 [95% CI 61–585]) (see Section 4.6 for the serum creatinine-based definition of AKI).

The potential reasons for AKI assessed with hospital diagnosis codes are considered as secondary outcomes and are presented in Table 3. Atypical antipsychotic drug use versus non-use was associated with a 90-day higher risk of hospitalization with hypotension (RR 2.16 [95% CI 1.81–2.57]), acute urinary retention (RR 2.15 [95% CI 1.78–2.60]), neuroleptic malignant syndrome/rhabdomyolysis (RR 1.44 [95% CI 1.06–1.96]), acute myocardial infarction (RR 1.34 [95% CI 1.19–1.51]), and ventricular arrhythmia (RR 1.72 [95% CI 1.37–2.14]). Another secondary outcome investigated was all-cause mortality and is also presented in Table 3. Atypical antipsychotic drug use versus non-use was associated with a 90-day higher risk of all-cause mortality (RR 2.68 [95% CI 2.56–2.81]).

5.3 Subgroup analysis

The four subgroup analyses performed are presented in Table 4. The presence of CKD did not influence the relative association between atypical antipsychotic drug use and hospitalization with AKI (Interaction $P = 0.15$). The absolute risk difference in the incidence of hospitalization with AKI between the drug users and non-users was greater in patients with CKD (1.82% [95% CI 1.23%–2.41%]) compared to patients without CKD (0.44% [95% CI 0.37%–0.52%]). The association between atypical antipsychotic drug use and hospitalization with AKI was not modified by antipsychotic drug type (Interaction $P = 0.13$) nor by antipsychotic drug dose (Interaction $P = 0.49$). The risk of hospitalization with AKI associated with atypical antipsychotic drug use versus non-use

was higher in community-dwellers (RR 2.37 [95% CI 2.08–2.71]) than in long-term care residents (RR 1.53 [95% CI 1.27–1.85]) (Interaction $P < 0.001$).

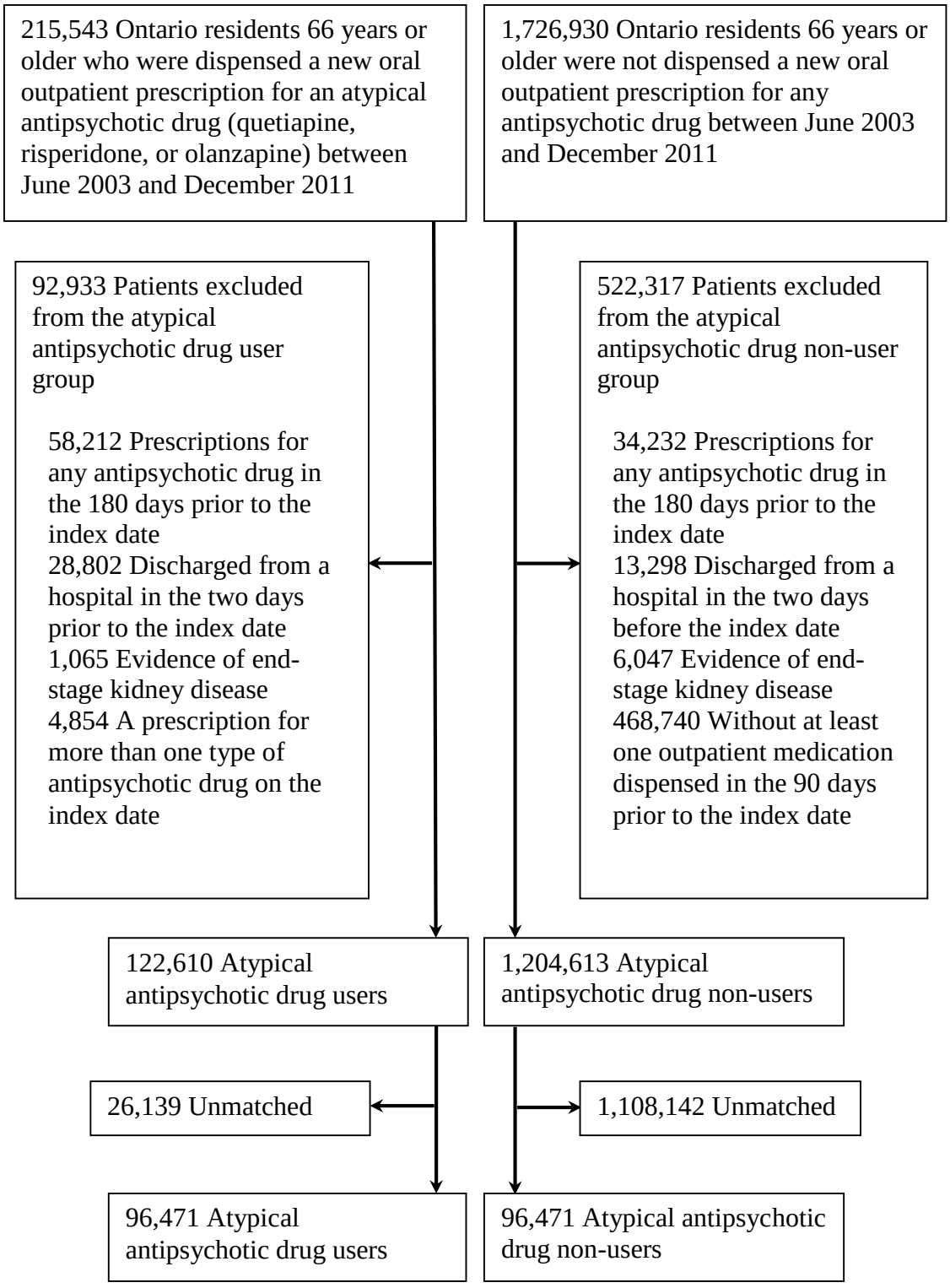

Figure 2: Cohort selection

Table 1: Baseline characteristics of atypical antipsychotic drug users and non-users[a]

	Unmatched			Matched		
	Users (n=122,610)	**Non-Users (n=1,204,613)**	**Standardized Difference[b]**	**Users (n=96,471)**	**Non-Users (n=96,471)**	**Standardized Difference[b]**
Demographics						
Age, mean (SD), years	81 (8)	76 (7)	0.74	81 (8)	81 (8)	0.00
Women	77,508 (63.2)	687,831 (57.1)	0.12	62,326 (64.6)	62,326 (64.6)	0.00
Income quintile[c]						
1 (low)	27,282 (22.3)	234,967 (19.5)	0.07	21,347 (22.1)	20,704 (21.5)	0.01
2	25,465 (20.8)	253,463 (21.0)	0.00	20,189 (20.9)	19,813 (20.5)	0.01
3 (middle)	23,838 (19.4)	234,892 (19.5)	0.00	18,866 (19.6)	18,649 (19.3)	0.01
4	23,106 (18.8)	235,555 (19.6)	0.02	18,159 (18.8)	18,497 (19.2)	0.01
5 (high)	22,243 (18.1)	241,356 (20.0)	0.05	17,462 (18.1)	18,422 (19.1)	0.03
Year of cohort entry						
2003–2004	26,712 (21.8)	229,290 (19.0)	0.07	19,561 (20.3)	19,582 (20.3)	0.00
2005–2006	29,640 (24.2)	272,475 (22.6)	0.04	22,501 (23.3)	22,523 (23.3)	0.00
2007–2008	25,286 (20.6)	251,863 (20.9)	0.01	19,979 (20.7)	19,882 (20.6)	0.00
2009–2010	26,795 (21.9)	289,588 (24.0)	0.05	22,281 (23.1)	22,323 (23.1)	0.00
2011	14,177 (11.6)	161,397 (13.4)	0.05	12,149 (12.6)	12,161 (12.6)	0.00
Rural residence[d]	15,811 (12.9)	172,157 (14.3)	0.04	12,288 (12.7)	13,400 (13.9)	0.04
Long-term care	37,598 (30.7)	32,457 (2.7)	0.81	23,063 (23.9)	23,063 (23.9)	0.00
Comorbid conditions[e]						
Dementia	73,839 (60.2)	90,115 (7.5)	1.81	51,983 (53.9)	51,983 (53.9)	0.00
Schizophrenia or other psychotic disorder	15,263 (12.4)	14,095 (1.2)	0.79	7,322 (7.6)	7,322 (7.6)	0.00
Bipolar disorder	9,673 (7.9)	11,413 (0.9)	0.56	4,769 (4.9)	4,769 (4.9)	0.00
Major depression and/or anxiety disorder	27,250 (22.2)	74,960 (6.2)	0.61	18,239 (18.9)	18,239 (18.9)	0.00

Table 1 (continued)

Chronic kidney disease	10,341 (8.4)	70,440 (5.8)	0.11	6,819 (7.1)	6,819 (7.1)	0.00
Cerebrovascular disease	9,079 (7.4)	28,550 (2.4)	0.30	6,178 (6.4)	6,145 (6.4)	0.00
Chronic liver disease	4,020 (3.3)	36,398 (3.0)	0.01	3,080 (3.2)	3,054 (3.2)	0.00
Congestive heart failure	24,999 (20.4)	134,486 (11.2)	0.28	18,662 (19.3)	19,641 (20.4)	0.03
Coronary artery disease[f]	50,601 (41.3)	420,958 (34.9)	0.13	38,976 (40.4)	40,071 (41.5)	0.02
Diabetes mellitus[g]	20,435 (16.7)	208,112 (17.3)	0.02	15,919 (16.5)	16,720 (17.3)	0.02
Hypertension[h]	84,209 (68.7)	883,364 (73.3)	0.10	66,913 (69.4)	68,829 (71.3)	0.04
Peripheral vascular disease	2,587 (2.1)	17,790 (1.5)	0.05	1,888 (2.0)	2,089 (2.2)	0.01
Medication use[i]						
Anticonvulsant	14,457 (11.8)	45,907 (3.8)	0.39	9,606 (10.0)	10,764 (11.2)	0.04
Antidepressant	31,278 (25.5)	85,243 (7.1)	0.66	20,481 (21.2)	21,638 (22.4)	0.03
Cholinesterase inhibitor	36,347 (29.6)	25,683 (2.1)	1.41	22,457 (23.3)	20,081 (20.8)	0.06
Lithium	1,324 (1.1)	1,317 (0.1)	0.22	599 (0.6)	531 (0.6)	0.01
ACE inhibitor or ARB	54,674 (44.6)	617,052 (51.2)	0.13	43,908 (45.5)	45,249 (46.9)	0.03
Beta-adrenergic antagonist	37,391 (30.5)	365,976 (30.4)	0.00	29,574 (30.7)	30,216 (31.3)	0.01
Calcium channel blocker	33,166 (27.0)	344,285 (28.6)	0.03	26,607 (27.6)	27,499 (28.5)	0.02
NSAID (excluding aspirin)	20,720 (16.9)	220,395 (18.3)	0.04	16,626 (17.2)	16,587 (17.2)	0.00
Potassium sparing diuretic	7,998 (6.5)	69,486 (5.8)	0.03	6,243 (6.5)	6,590 (6.8)	0.01
Non-potassium sparing diuretic	41,896 (34.2)	355,874 (29.5)	0.10	32,567 (33.8)	33,832 (35.1)	0.03
Statin	41,975 (34.2)	539,520 (44.8)	0.21	34,019 (35.3)	34,523 (35.8)	0.01

Table 1 (continued)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; NSAID, Non-steroidal anti-inflammatory drug; SD, standard deviation

[a]Data are presented as the number (percentage) of patients, unless otherwise reported.

[b]Standardized difference describes differences between group means with respect to pooled standard deviation and indicates a meaningful difference if greater than 0.10 (10%).[146,147,150]

[c]Income was not available for 676 (0.6%) drug users and 4,380 (0.4%) non-users in the unmatched cohort and 448 (0.5%) drug users and 386 (0.4%) non-users in the matched cohort.

[d]Location of residence was not available for 234 (0.2%) drug users and 1,142 (0.1%) non-users in the unmatched cohort and 177 (0.2%) drug users and 109 (0.1%) non-users in the matched cohort.

[e]Comorbid conditions in the 5 years preceding the index date were considered.

[f]Coronary artery disease includes diagnoses of angina and receipt of coronary artery bypass graft surgery and percutaneous coronary intervention.

[g]Diabetes mellitus and were defined by use of any diabetic medication in the 6 months preceding the index date.

[h]Hypertension was defined by use of any antihypertensive medication in the 6 months preceding the index date.

[i]Medication use in the 180 days preceding the index date were considered.

Table 2: Baseline characteristics of atypical antipsychotic drug users and non-users in the subpopulation with available serum creatinine measurements (Matched)[a]

	Users (n=1,442)	Non-Users (n=1,442)	Standardized Difference[b]
Demographics			
Age, mean (SD), years	79 (7)	80 (7)	0.01
Women	938 (65.0)	938 (65.0)	0.00
Income quintile[c]			
1 (low)	333 (23.1)	312 (21.6)	0.04
2	270 (18.7)	278 (19.3)	0.02
3 (middle)	287 (19.9)	279 (19.3)	0.02
4	224 (15.5)	235 (16.3)	0.02
5 (high)	287 (19.9)	302 (20.9)	0.02
Year of cohort entry			
2003–2004	173 (12.0)	176 (12.2)	0.01
2005–2006	319 (22.1)	317 (22.0)	0.00
2007–2008	315 (21.8)	323 (22.4)	0.01
2009–2010	404 (28.0)	400 (27.7)	0.01
2011	231 (16.0)	226 (15.7)	0.01
Rural residence[d]	163 (11.3)	167 (11.6)	0.01
Long-term care	177 (12.3)	177 (12.3)	0.00
Comorbid conditions[e]			
Dementia	614 (42.6)	614 (42.6)	0.00
Schizophrenia or other psychotic disorder	42 (2.9)	42 (2.9)	0.00
Bipolar disorder[f]	…	…	…
Major depression and/or anxiety disorder	286 (19.8)	286 (19.8)	0.00
Chronic kidney disease	48 (3.3)	48 (3.3)	0.00
Cerebrovascular disease	101 (7.0)	63 (4.4)	0.11
Chronic liver disease	62 (4.3)	49 (3.4)	0.05

Table 2 (continued)

Congestive heart failure	281 (19.5)	281 (19.5)	0.00
Coronary artery disease[g]	559 (38.8)	593 (41.1)	0.05
Diabetes mellitus[h]	269 (18.7)	272 (18.9)	0.01
Hypertension[i]	1,081 (75.0)	1,096 (76.0)	0.02
Peripheral vascular disease	23 (1.6)	22 (1.5)	0.01
Medication use[j]			
Anticonvulsant	97 (6.7)	127 (8.8)	0.08
Antidepressant	399 (27.7)	413 (28.6)	0.02
Cholinesterase inhibitor	254 (17.6)	225 (15.6)	0.05
Lithium[f]	…	…	…
ACE inhibitor or ARB	714 (49.5)	732 (50.8)	0.02
Beta-adrenergic antagonist	506 (35.1)	505 (35.0)	0.00
Calcium channel blocker	435 (30.2)	422 (29.3)	0.02
NSAID (excluding aspirin)	265 (18.4)	246 (17.1)	0.03
Potassium sparing diuretic	119 (8.3)	120 (8.3)	0.00
Non-potassium sparing diuretic	515 (35.7)	533 (37.0)	0.03
Statin	571 (39.6)	585 (40.6)	0.02
Kidney function[k]			
Baseline serum creatinine concentration, median (IQR), µmol/L	83 (69–103)	82 (68–100)	0.01
Estimated GFR, median (IQR), mL/min/1.73m^2 [l]	64 (50–80)	66 (50–79)	0.02
Estimated GFR			
≥60 mL/min/1.73m^2	824 (57.1)	870 (60.3)	0.07
45-59 mL/min/1.73m^2	346 (24.0)	336 (23.3)	0.02
30-44 mL/min/1.73m^2	209 (14.5)	179 (12.4)	0.06
15-29 mL/min/1.73m^2	58 (4.0)	53 (3.7)	0.02
<15 mL/min/1.73m^2 [f]	…	…	…
Urine dipstick protein[m]			

Table 2 (continued)

negative	146 (73.4)	153 (69.9)	0.08
0.3g/L or more	53 (26.6)	66 (30.1)	0.08

Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; IQR, interquartile range; NSAID, Non-steroidal anti-inflammatory drug; SD, standard deviation

[a]Data are presented as the number (percentage) of patients, unless otherwise reported.

[b]Standardized difference describes differences between group means with respect to pooled standard deviation and indicates a meaningful difference if greater than 0.10 (10%).[146,147,150]

[c]Income was not available for 41 (2.8%) drug users and 36 (2.5%) non-users.

[d]Location of residence was not available for less than five drug users and was available for all non-users.

[e]Comorbid conditions in the 5 years preceding the index date were considered, respectively.

[f]Number of patients with bipolar disorder, use of lithium, and estimated GFR <15mL/min/1.73m^2 were too few (less than five) and were not available for the reasons of patient privacy.

[g]Coronary artery disease includes diagnoses of angina and receipt of coronary artery bypass graft surgery and percutaneous coronary intervention.

[h]Diabetes mellitus and were defined by use of any diabetic medication in the 6 months preceding the index date.

[i]Hypertension was defined by use of any antihypertensive medication in the 6 months preceding the index date.

[j]Medication use in the 180 days preceding the index date were considered.

[k]Baseline serum creatinine measurements were taken as a routine care at a median (IQR) of 83 (32-183) and 119 (50-208) days prior to the index date for the drug user and non-user groups, respectively.

[l]Estimated GFR was calculated using the CKD-EPI equation[153]: $141 \times \min([\text{Serum creatinine concentration in } \mu\text{mol/L}/88.4]/k,1)^a \times \max([\text{serum creatinine concentration in } \mu\text{mol/L}/88.4]/k,1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]; k=0.7 if female and 0.9 if male; a=-0.329 if female and -0.411 if male; min=the minimum of serum creatinine concentration/k or 1; max=the maximum of serum creatinine concentration/k or 1. Information on race was not available in our data sources and all patients were assumed not to be of African Canadian race; African Canadians represented less than 5% of the population of Ontario in 2006.[154]

[m]Urine dipstick protein measurements were available for 199 drug users and 219 non-users.

Table 3: Potential reasons for AKI and all-cause mortality in atypical antipsychotic drug users and non-users

	Events, No (%)		Relative Risk (95% CI)	Absolute Risk Difference (95% CI), %	NNH (95% CI)
	Users (*n*=96,471)	Non-Users (*n*=96,471)			
Potential reasons for AKI[a]					
Hypotension	393 (0.41)	182 (0.19)	2.16 (1.81–2.57)	0.22 (0.17–0.27)	457 (374–588)
Acute urinary retention	340 (0.35)	158 (0.16)	2.15 (1.78–2.60)	0.19 (0.14–0.23)	530 (427–698)
Neuroleptic malignant syndrome/rhabdomyolysis	101 (0.10)	70 (0.07)	1.44 (1.06–1.96)	0.03 (0.01–0.06)	3112 (1704–17963)
Acute myocardial infarction	629 (0.65)	471 (0.49)	1.34 (1.19–1.51)	0.16 (0.10–0.23)	611 (433–1036)
Ventricular arrhythmia	211 (0.22)	123 (0.13)	1.72 (1.37–2.14)	0.09 (0.05–0.13)	1096 (779–1849)
All-cause mortality					
All-cause mortality	6,688 (6.93)	2,658 (2.76)	2.68 (2.56–2.81)	4.18 (3.99–4.37)	24 (23–25)

Abbreviations: AKI, acute kidney injury; CI, confidence interval; NNH, number need to harm

[a]Events (and the proportion of patients with an event) were assessed using hospital diagnosis codes. The true event rate is underestimated for some outcomes as the codes for the outcomes have high specificity, but low sensitivity. Similarly, NNH is underestimated for this reason.

Table 4: The association between atypical antipsychotic drug use and hospitalization with AKI, examined in subgroups defined by evidence of CKD, antipsychotic drug type, antipsychotic drug dose, and residential status

	No. with Events/No. at Risk (%)[a]		Relative Risk (95% CI)	Interaction Test (*P* value)	Absolute Risk Difference (95% CI), %	NNH (95% CI)
	Users	Non-Users				
Evidence of CKD						
CKD	280/6,819 (4.11%)	156/6,819 (2.29%)	1.82 (1.49–2.22)	0.15	1.82 (1.23–2.41)	55 (41–82)
No CKD	742/89,652 (0.83%)	344/89,652 (0.38%)	2.16 (1.90–2.46)		0.44 (0.37–0.52)	225 (194–269)
Antipsychotic Drug Type						
Quetiapine	379/34,672 (1.09%)	202/34,672 (0.58%)	1.89 (1.59–2.24)	0.13	0.51 (0.38–0.65)	196 (155–267)
Risperidone	468/43,693 (1.07%)	232/43,693 (0.53%)	2.04 (1.74–2.39)		0.54 (0.42–0.66)	185 (152–237)
Olanzapine	175/18,106 (0.97%)	66/18,106 (0.36%)	2.65 (2.00–3.52)		0.60 (0.43–0.77)	166 (130–230)
Antipsychotic Drug Dose[b]						
High dose	386/34,089 (1.13%)	180/34,089 (0.53%)	2.16 (1.81–2.59)	0.49	0.60 (0.47–0.74)	165 (135–213)
Low dose	636/62,382 (1.02%)	320/62,382 (0.51%)	2.00 (1.75–2.29)		0.51 (0.41–0.60)	197 (166–244)
Residential Status						
Community dwelling	740/73,408 (1.01%)	316/73,408 (0.43%)	2.37 (2.08–2.71)	< 0.001	0.58 (0.49–0.66)	173 (151–203)
Long-term Care	282/23,063 (1.22%)	184/23,063 (0.80%)	1.53 (1.27–1.85)		0.42 (0.24–0.61)	235 (164–414)

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; NNH, number need to harm

[a]Acute kidney injury (AKI) (and the proportion of patients with AKI) were assessed using a hospital diagnosis code. The true event rate of AKI is underestimated for some outcomes as the code for AKI has high specificity, but low sensitivity. Similarly, NNH is underestimated for this reason.

[b]High dose was defined as: >25 mg/day quetiapine, >0.5mg/day risperidone, and >2.5mg/day olanzapine and low dose was defined as: ≤25 mg/day quetiapine, ≤0.5mg/day risperidone, and ≤2.5 mg/day olanzapine.

Chapter 6

6 Discussion

6.1 Summary and interpretation of study results

Although previous case reports have attributed AKI to atypical antipsychotic drug use, their relationship had not been investigated.[8–12] In this retrospective matched cohort study of older adults, we followed new atypical antipsychotic drug users and non-users for 90 days to characterize the risk of AKI associated with the initiation of atypical antipsychotic drug use. We demonstrated that newly initiated atypical antipsychotic drug use versus non-use was associated with a higher risk of hospitalization with AKI in older adults.

Although the precise mechanism of AKI from these drugs requires further elucidation, our results suggest that hypotension, acute urinary retention, neuroleptic malignant syndrome/rhabdomyolysis, and acute cardiac events might have biologically mediated the observed association between the drug use and AKI. First, AKI might have developed from decreased renal perfusion.[13–18,33,59,78,93,95–97] The drugs have the ability to induce hypotension by antagonizing alpha-adrenergic receptors which are involved in the regulation of vascular contractility.[78,93] Furthermore, it is plausible that the hemodynamic derangements and decreased renal perfusion that resulted from acute cardiac events might have precipitated AKI.[31–33,59,106–115] Second, acute urinary retention induced by the drugs might have led to AKI.[8,20,21,59,98,99,155] The drugs are able to block muscarinic acetylcholine receptors, which are present in the urinary tract and involved in micturition.[8,98,99] Lastly, AKI might have occurred from the structural damage incurred by the myoglobin released from damaged muscles in patients suffering neuroleptic malignant syndrome/rhabdomyolysis following the drug use.[9–12,22–30,101–104] The ability for the drugs to suddenly block dopamine receptors have been postulated to explain this adverse effect.[22,30] The down-regulation of the dopaminergic neurons could have also resulted in the hyperactivity of the sympathetic nervous system and resultant muscle damage.

Patients with CKD are especially predisposed to AKI.[37,52–54] In our study, the absolute risk difference in the incidence of hospitalization with AKI between atypical antipsychotic drug users and non-users were greater in patients with CKD compared to those without CKD. Patients with CKD should be warned about the potential risk of AKI and be closely monitored when commenced on atypical antipsychotic drug therapy.[37,48,52–54]

The association found between atypical antipsychotic drug use and AKI was consistent in patients who received quetiapine, risperidone, or olanzapine.

The antipsychotic drug dose did not influence the association between the drug use and AKI. A possible explanation for this observation would be that the starting dose was used to define high dose versus low dose in our study. Since dose titration is a common therapeutic strategy in older patients, the starting dose is unlikely to represent the end-dose.[78] An alternative speculation would be that the rate of dose titration rather than the absolute amount of dose influences the development of AKI.

While an association between atypical antipsychotic drug use and hospitalization with AKI was observed in both community-dwellers and long-term care residents, the association was more pronounced in community-dwellers. This finding is consistent with a previous study that found the risk of short-term serious events associated with atypical antipsychotic drug use to be higher in community-dwellers than in long-term care residents.[84] A possible explanation for this finding is less surveillance following treatments in older adults residing in the community compared to those living in long-term care facilities.

Our findings expand on accumulating evidences that have advised caution in the use of atypical antipsychotic drugs in older adults.[3,4,31,32,83,84,116] In our study, atypical antipsychotic drug use versus non-use was also associated with a higher risk of all-cause mortality. This finding supports the federal advisory of the U.S. and Canada that warns of the risk of death associated with the drug use in older patients with dementia.[3,4] In our observational study, the 90-day incidence of death was 6.9% in the drug users versus 2.8% in the non-users. These rates similar to those presented by the U.S. Food and Drug

Administration from the analyses of placebo-controlled trials that included older patients (averaging 10 weeks in duration).[3] In their analysis, the incidence of death was 4.5% in the drug-treated group versus 2.6% in the placebo group.[3] The association between atypical antipsychotic drug use and short-term mortality has also been evidenced in a meta-analysis of randomized placebo-controlled trials (10 to 12 weeks in duration) and a previous population-based cohort study.[83,116]

In our observational study, the incidence of hospitalization with hypotension was 0.41% in the atypical antipsychotic drug user group and 0.19% in the non-user group (i.e. RR of 2.16 [95% CI 1.81–2.57]). In the analysis of two randomized placebo-controlled trials that included patients aged 55 years and older, the incidence of orthostatic hypotension was 5.5-fold higher in patients treated with an atypical antipsychotic drug compared to patients in the placebo group.[13] Unlike our observational study, which used a hospital diagnosis code to identify hypotension (a code which is expected to be insensitive and to detect only severe forms of hypotension), the incidence of orthostatic hypotension in the analysis of two randomized trials was 17.9% (5 out of 28 patients) in the drug-treated group versus 3.2% (1 out of 31 patients) in the placebo group.[13]

6.2 Study strengths and limitations

Our study has several strengths. To our knowledge, this is the first population-based study that characterized the risk of AKI associated with atypical antipsychotic drug use. Furthermore, our study explored potential reasons why AKI may develop from the drug use. The population-based associations observed in our study were supported by the known biological effects of the drugs.[8–30] The use of provincial healthcare administrative data on universal prescription drug coverage allowed us to accrue a large, representative sample of older adults who received atypical antipsychotic drugs. This enabled us to estimate the risk of less common but serious adverse drug events with high levels of precision and generalizability. Many previous population-based studies that examined the safety of atypical antipsychotic drugs in older adults only included those with dementia.[31,83,84,128] In comparison, the inclusion of older patients with a variety of mental

disorders (schizophrenia or other psychotic disorder, bipolar disorder, and major depression and/or anxiety disorder) enabled the study results to be applicable to a wider range of patients. Finally, we employed a 'new user' design, which allows observational studies to mimic clinical trials in that patients are immediately followed from the time of treatment initiation.[156] This method enabled us to reduce potential bias that may arise from accruing prevalent drug users who have survived initial periods of the pharmacotherapy.[156]

Experimental studies provide the strongest evidence for whether or not an exposure has an effect on the risk of a disease.[157] However, clinical trials are costly and the relatively small number of patients enrolled in the trials makes the estimation of risk for relatively rare adverse drug events difficult.[131,158] Large observational studies can complement the findings of clinical trials by enabling the investigation of uncommon but important adverse drug events with adequate statistical power. Moreover, these observational studies can include vulnerable groups of patients who may be excluded from clinical trials and better reflect what occurs in routine clinical settings where treatments and monitoring are less regulated than in clinical trials.[31,32,83,159,160]

A major concern of observational studies is the non-random distribution of exposure; in the case of our study, atypical antipsychotic drug use. The two groups being compared may be different on several characteristics including those that are risk factors for the outcomes of interest such as AKI.[133] Despite achieving similarity in 29 baseline characteristics measured in the drug users and non-users, the concern for residual confounding cannot be eliminated, as there may be other unmeasured patient characteristics that differ between the drug user and non-user groups that may influence the risk of AKI. However, we propose residual confounding is unlikely to explain the entire observed association between the drug use and AKI in this study for several reasons. First, the association is supported by numerous case reports and the known biological effects of these drugs.[8–30] It is difficult to conceive that a particular cause of AKI, such as neuroleptic malignant syndrome/rhabdomyolysis, in the 90-day follow-up (a risk observed in the present study) was not related to new atypical antipsychotic drug use.[9–12,22–30] Second, the magnitude of the effect size was robust, with most point

estimates of RRs being greater than two. Even if the risk estimates are partly attenuated after accounting for unmeasured confounders, the results would still suggest that atypical antipsychotic drug-induced AKI is an important adverse drug event at the population-level given the high prevalence and increasing incidence of prescriptions for the drugs in older adults.[1,2]

In addition to the potential for residual confounding, our study has several other shortcomings. The absolute risk difference for some outcomes was underestimated because the hospital diagnosis codes for some conditions were insensitive.[141,142] To address this concern for the primary outcome of AKI, we supplemented our findings and observed consistent results in a subpopulation with available serum creatinine measurements. We generalize our findings only to older adults, as reliable drug data was not available on patients under age 65 in our data sources. Although younger patients may be expected to have improved resistance to AKI, it is worth noting that the doses of atypical antipsychotic drugs used in younger patients are also generally higher than of those used in older patients.[74] Moreover, our findings may be only applicable to the use of quetiapine, risperidone, and olanzapine; the most commonly used atypical antipsychotic drugs in Ontario.[1,2] However, it remains prudent to use other atypical antipsychotic drugs cautiously as well (such as aripiprazole, ziprasidone, and paliperidone) as federal warnings for increased mortality extend to the entire drug class.[3,4,155,161–169]

6.3 Study implications

Our results suggest that AKI may result from atypical antipsychotic drug use and that the kidney injury may be mediated by hypotension, acute urinary retention, neuroleptic malignant syndrome/rhabdomyolysis, acute cardiac events. We propose the study results are sufficiently compelling that they should be acted on to help prevent adverse drug events. There should be judicious use of atypical antipsychotic drugs for managing behavioural symptoms of dementia, as the adverse effects of the drugs can offset potential benefits.[170,171] Using these drugs for the management behavioural symptoms of

dementia are not an approved indication by regulatory authorities (with the exception of risperidone in Canada).[3,4] Patients with CKD may be at the highest absolute risk of AKI from use of these drugs. When an atypical antipsychotic drug is initiated, patients, especially those with CKD, can be informed about the potential adverse effects of the drug. Preventative measures may include monitoring for a decrease in urine output, performing a bladder scan to check for retention of urine, and measuring serum creatinine and blood pressure in follow-up. If a patient does present to medical attention with AKI, this drug class can be considered as a potential cause of the kidney injury so that it can be discontinued to promote resolution.

6.4 Recommendations for future studies

Future studies are warranted to better characterize the risk of AKI associated with atypical antipsychotic drug use including potential reasons for the kidney injury. Future studies may benefit by employing improved tools to measure the outcomes, such as blood pressure measurement for the assessment of hypotension or post-void residual urine measurement for the assessment of acute urinary retention. Moreover, future studies should further investigate the association between the drug use and the outcomes by including younger drug users and newly emerging atypical antipsychotic drugs such as aripiprazole.

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Appendices

Appendix A: STROBE checklist[121]

	Item No	Recommendation	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Chapter 1, 2, 3, Figure 1
Objectives	3	State specific objectives, including any pre-specified hypotheses	Chapter 3
Methods			
Study design	4	Present key elements of study design early in the paper	Chapter 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Chapter 4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Chapter 4, Figure 2
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Chapter 4, Figure 2, Appendix B
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Chapter 2, Chapter 4, Appendix B, Appendix C
Data sources/measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Chapter 4, Appendix B, Appendix C
Bias	9	Describe any efforts to address potential sources of bias	Chapter 4, Chapter 6

Study size	10	Explain how the study size was arrived at	Chapter 4; based on availability of the data
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Chapter 4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Chapter 4
		(b) Describe any methods used to examine subgroups and interactions	Chapter 4
		(c) Explain how missing data were addressed	Not applicable
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	Not applicable
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Chapter 5, Figure 2
		(b) Give reasons for non-participation at each stage	Chapter 4, Figure 2
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Chapter 5, Table 1, Table 2
		(b) Indicate number of participants with missing data for each variable of interest	Chapter 5, Table 1, Table 2
		(c) Summarize follow-up time (e.g. average and total amount)	Chapter 5, Table 3
Outcome data	15	Report numbers of outcome events or summary measures over time	Chapter 5, Table 3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were	Chapter 5, Table 3

		included	
		(b) Report category boundaries when continuous variables were categorized	Chapter 4
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Chapter 5, Table 3, Table 4
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Chapter 5, Table 4
Discussion			
Key results	18	Summarize key results with reference to study objectives	Chapter 6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Chapter 6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Chapter 6
Generalizability	21	Discuss the generalizability (external validity) of the study results	Chapter 6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Acknowledgments

Appendix B: Coding definitions for demographics and comorbid conditions

Variable	Database	Code
Age	RPDB	
Sex	RPDB	
Income (neighbourhood income quintiles)	Statistics Canada	
Location of residence	Statistics Canada	
Residential status	ODB	
Dementia	CIHI-DAD	ICD-9 2900, 2901, 2903, 2904, 2908, 2909, 2948, 2949, 3310, 3311, 3312, 2941, 797 ICD-10 F065, F066, F068, F069, F09, F00, F01, F02, F03, F051, G30, G31, R54
	OMHRS	DSM-IV 29040, 29041, 29042, 29043, 29120, 29282, 29410, 29411, 29480, 78090
	OHIP	290, 331, 797
Schizophrenia or other psychotic disorder	CIHI-DAD	ICD-9 2950, 2951, 2952, 2953, 2954, 2955, 2956, 2957, 2958, 2959, 2970, 2971, 2972, 2973, 2978, 2979, 2980, 2981, 2983, 2984, 2988, 2989 ICD-10 F060, F062, F105, F107, F115, F117, F125, F127, F135, F137, F145, F147, F155, F157, F165, F167, F175, F177, F185, F187, F195, F197, F200, F201, F202, F203, F204, F205, F206, F208, F209, F220, F228, F229, F230, F231, F232, F233, F238, F239, F24, F250, F251, F252, F258, F259, F28, F29
	OMHRS	DSM-IV 29130, 29150, 29211, 29212, 29381, 29382, 29510, 29520, 29530, 29540, 29560, 29570, 29590, 29710, 29730, 29880, 29890
	OHIP	291, 292, 295, 297, 298, Q021
Bipolar disorder	CIHI-DAD	ICD-9 2960, 2961, 2964, 2965, 2966, 2967, 2968 ICD-10 F300, F301, F302, F308, F309, F310, F311, F312, F313, F314, F315, F316, F317, F318, F319
	OMHRS	DSM-IV 29600, 29601, 29602, 29603, 29604, 29605, 29606, 29640, 29641, 29642, 29643, 29644, 29645, 29646, 29650, 29651, 29652, 29653, 29654, 29655, 29656, 29660, 29661, 29662, 29663, 29664, 29665, 29666, 29670, 29680, 29689
	OHIP	296, Q020

Major depression and/or anxiety disorder	CIHI-DAD	ICD-9 2962, 2963, 3000, 3002, 3003, 3004, 3091, 311 ICD-10 F063, F064, F320, F321, F322, F323, F328, F329, F330, F331, F332, F333, F334, F338, F339, F341, F400, F401, F402, F408, F409, F410, F411, F412, F413, F418, F419, F420, F421, F422, F428, F429, F430, F431
	OMHRS	DSM-IV 29189, 29284, 29289, 29383, 29384, 29620, 29621, 29622, 29623, 29624, 29625, 29626, 29630, 29631, 29632, 29633, 29634, 29635, 29636, 30000, 30001, 30002, 30021, 30022, 30023, 30029, 30030, 30040, 30113
	OHIP	311
Chronic kidney disease	CIHI-DAD	ICD-9 4030, 4031, 4039, 4040, 4041, 4049, 582, 583, 580, 581, 584, 585, 586, 587, 5880, 5888, 5889, 5937 ICD-10 E102, E112, E132, E142, I12, I13, N08, N18, N19
	OHIP	403, 585
Cerebrovascular disease	CIHI-DAD	ICD-9 434, 436, 431, 4358, 4359 ICD-10 H341, I630, I631, I632, I633, I634, I635, I638, I639, I629, I64, G45, I61
Chronic liver disease	CIHI-DAD	ICD-9 4561, 4562, 070, 5722, 5723, 5724, 5728, 573, 7824, V026, 2750, 2751, 7891, 7895, 571 ICD-10 B16, B17, B18, B19, I85, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77
	OHIP	571, 573, 070, Z551, Z554
Congestive heart failure	CIHI-DAD	ICD-9 425, 5184, 514, 428 ICD-10 I500, I501, I509, I255, J81 CCP 4961, 4962, 4963, 4964 CCI 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR
	OHIP	428, R701, R702, Z429
Coronary artery disease	CIHI-DAD	ICD-9 410 412, 413, 414, 4292, 4295, 4296, 4297 ICD-10 I20, I21, I22, I23, I24, I25, Z955, Z958, Z959, R931, T822 CCP 4801, 4802, 4803, 4804, 4805, 481, 482, 483

		CCI 1IJ26, 1IJ27, 1IJ54, 1IJ57, 1IJ50, 1IJ76
	OHIP	410, 412, 413, R741, R742, R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448
Diabetes mellitus	ODB	
Hypertension	ODB	
Peripheral vascular disease	CIHI-DAD	ICD-9 4402, 4408, 4409, 5571, 4439, 444 ICD-10 I700, I702, I708, I709, I731, I738, I739, K551 CCP 5125, 5129, 5014, 5016, 5018, 5028, 5038 CCI 1KA76, 1KA50, 1KE76, 1KG26, 1KG50, 1KG57, 1KG76MI, 1KG87
	OHIP	R787, R780, R797, R804, R809, R875, R815, R936, R783, R784, R785, E626, R814, R786, R937, R860, R861, R855, R856, R933, R934, R791, E672, R794, R813, R867, E649
Prescribing physician	ODB	

CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; ODB, Ontario Drug Benefit; OHIP, Ontario Health Insurance Plan; OMHRS, Ontario Mental Health Reporting System; RPDB, Ontario's Registered Persons Database

Appendix C: Coding definitions for hospitalized outcomes

Outcome	Database	Code
Primary outcome		
Acute kidney injury[a]	CIHI-DAD	ICD-10 N17
Secondary outcomes		
Hypotension[b]	CIHI-DAD	ICD-10 I95
Acute urinary retention[b]	CIHI-DAD	R33
Neuroleptic malignant syndrome/rhabdomyolysis	CIHI-DAD	ICD-10 G210, M628, T796
Acute myocardial infarction[c]	CIHI-DAD	ICD-10 I21, I22
Ventricular arrhythmia	CIHI-DAD	ICD-10 I460, I469, I470, I472, I4900, I4901, CCI 1HZ09JAFS, 1HZ09JAJF, 1HZ30JN, 1HZ30JY
All-cause mortality[d]	RPDB	Vital status field

Abbreviations: CCI, Canadian Classification of Health Interventions; CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; ICD-10, International Classification of Diseases, Tenth Revision; RPDB, Ontario's Registered Persons Database

[a]Validation of the code for acute kidney injury was performed on approximately 39 000 hospitalizations with linked laboratory measurements for serum creatinine. See Methods section for a description of the validation.[141]

[b]Using reabstracted information written in a patient's chart as the reference standard, the code for hypotension and acute urinary retention has a sensitivity of 72% and 86%, and positive predictive value of 39% and 48%, respectively.[142] This is a poor reference standard compared to patient blood pressure measurements and post-void residual urine volumes.

[c]Code I21 (most responsible diagnosis) has a sensitivity of 89% and positive predictive value of 87%.[142]

[d]All-cause mortality has a sensitivity of 94% and specificity of 100%.[143]

Curriculum Vitae

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Hwang YJ, Shariff SZ, Gandhi S, Wald R, Clark E, Fleet JL, Garg AX. Validity of the International Classification of Diseases, Tenth Revision code for acute kidney injury in elderly patients at presentation to the emergency department and at hospital admission. *BMJ Open* 2012;2(6):1–11.