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A matched case-control study to assess the association between non-steroidal anti-inflammatory drug use and thrombotic microangiopathy

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Abstract

Several case reports suggest that non-steroidal anti-inflammatory drugs (NSAIDs) may be associated with thrombotic microangiopathy (TMA). We conducted a matched case-control study with linked administrative healthcare data in Ontario, Canada to assess the relationship between TMA hospitalization and recent exposure to prescription NSAIDs versus acetaminophen (where the latter was a referent group with no known association with TMA). Cases and controls were drawn from a source population of adults who filled a prescription for NSAIDs or acetaminophen between 1996 and 2015 (restricted to adults with prescription drug benefits). Cases comprised individuals hospitalized with TMA between 1996 and 2015. Controls were matched to cases (4:1) on demographic and medical risk factors. Cases (n=38) were less likely to have received a recent prescription for NSAIDs relative to acetaminophen (adjusted odds ratio 0.37, 95% confidence interval 0.16-0.84). Results were similar in two additional analyses with alternative referent groups. Overall, the results of this study do not support a harmful association between NSAID use and TMA.

Keywords

Non-steroidal anti-inflammatory drugs, drug-induced thrombotic microangiopathy, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, acetaminophen

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Chapter 1

1 Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs), are commonly used analgesic and anti-inflammatory agents, and one of the most widely used classes of drugs in the world.[1,2] Many studies have investigated associations between NSAID use and a wide variety of adverse medical reactions. Up to 25% of all reported adverse drug events may be associated with NSAID use, and the risk of adverse drug events increases with age.[3]

Thrombotic microangiopathy (TMA) describes a rare hematological disorder characterized by thrombocytopenia (a low concentration of blood platelets) and microangiopathic hemolytic anemia (a low concentration of red blood cells due to a rupture of those cells). Several major organ systems can be damaged by TMA, including the central nervous, cardiovascular and renal systems.[4–6] Identifying drugs associated with TMA development is a relatively novel area of research. Its existence is justified by the clinical severity of the disease, the abundance of drugs that could be culprits in drug-induced TMA, the high frequency of exposure to these drugs, and the lack of understanding of drug-induced TMA etiology and pathogenesis.[7] While NSAIDs have been linked with TMA in several case reports, this potential association has yet to be investigated in analytic studies.[8–13] Therefore, we conducted a matched case-control study to assess whether a case of TMA was more likely to be associated with a prior prescription of NSAID compared to a referent prior prescription of acetaminophen. The

study sample consisted of Ontario residents who had a prescription NSAID or acetaminophen dispensed at an outpatient pharmacy between 1991 and 2015.

Chapter 2

2 Background and Literature Review

2.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of drugs used for a variety of symptoms such as pain, fever, rheumatic, and inflammatory disorders.[14–16] NSAIDs work by inhibiting prostaglandin synthesis.[17] Prostaglandins are lipid biological factors that behave similarly to hormones and carry out a great number of functions (including inflammation onset) when interacting with specific prostaglandin receptors native to different cell types.[17] Prostaglandins are derived from arachidonic acid through the action of cyclooxygenase (COX) enzymes, classified as COX-1 or COX-2. The resulting inflammation and pain alleviation is a product of terminating prostaglandin synthesis by cyclooxygenase (COX) enzymes.[14–17] Certain NSAIDs will non-selectively inhibit both COX-1 and COX-2 enzymes, while the goal of contemporary NSAIDs seem to be selective COX-2 inhibition. COX-2 is believed to be the root of inflammation and pain response while sidestepping COX-1 may mitigate unnecessary adverse gastrointestinal outcomes.[14,15,18]

NSAIDs are undisputedly among the most widely used medications in the world, with over 30 million users daily.[1,2] The adverse outcomes have the potential to affect most, if not all, major physiological systems in the human body, including cardiovascular, gastrointestinal, and renal systems.[2,19] NSAIDs are relatively inexpensive drugs on the

market to both manufacturers and consumers. However, adverse events associated with this class of drugs can be costly to the healthcare system.[2,15] Studies in the United States indicate gastrointestinal complications from NSAID use have caused over 100,000 hospitalizations, over 16,000 deaths, and over $500 million in healthcare costs.[20]

2.2 Thrombotic microangiopathy (TMA)

Thrombotic microangiopathy (TMA) has several causes and is a clinical state characterized by thrombocytopenia and microangiopathic hemolytic anemia and may also be associated with acute kidney injury, fever, and acute neurological symptoms. TMA is further classified as Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS), which share many similar clinical symptoms but can differ in their risk factors.[4–6]

2.2.1 Thrombotic thrombocytopenic purpura (TTP)

Thrombotic thrombocytopenic purpura (TTP) is a relatively severe form of TMA, with a mortality rate of up to 90% unless promptly treated with plasma exchange (PLEX).[4,21,22] The pathology of TTP can be attributed to deficiency in ADAMTS13 (A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif, member 13) protease, which cleaves von Willebrand factor into short multimers. Low ADAMTS13 activity perpetuates the presence of long multimers of von Willebrand factor, which can cause

platelets to aggregate and form clots in the small blood vessels of the body.[6,21,22] As a consequence, the features of TTP include thrombocytopenia (a consumption of platelets), neurological disorders (confusion, impaired vision, encephalopathy, coma), fever, jaundice, acute kidney injury, and heart failure. A diagnosis of TTP is supported by evidence of a severe deficiency of ADAMTS13 activity (<5%) and the presence of IgG antibody inhibitors.[21,23–26]

The estimated incidence of TTP is 2 to 11 cases per 1,000,000 persons each year.[21,22,27] The reasons for TTP may be congenital, acquired, or idiopathic. Congenital and acquired forms of TTP most often relate to ADAMTS13 deficiency.[22] There are also instances where there is no recognized cause for the TTP making it idiopathic.[21,22,27,28] Biologically, in most cases of TTP there is antibody inhibition of ADAMTS13 [29,30] The root cause of inhibitory antibodies to ADAMTS13 is not well understood. Other factors implicated in the pathogenesis of TMA include exposure to shiga-toxin, endothelial dysfunction, and drug-mediated events.[31,32]

2.2.2 Hemolytic uremic syndrome (HUS)

Hemolytic uremic syndrome (HUS) shares many clinical manifestations with TTP, but the focus is placed on acute kidney injury (which when most severe requires treatment with dialysis) and pathological infection by diarrhea-positive toxin producing bacteria (shiga-toxin and verocytoxin). A small portion of patients (roughly 10%) do not present

with diarrhea (diarrhea-negative) prior to TMA-associated symptoms, who have a worse prognosis than others who present with diarrhea.[33,34]

Diarrhea-positive HUS occurs most commonly in children, specifically those below the age of 5 years. Various sources report an annual incidence of 0.2-3.4 cases per 100,000 persons per year in Germany, up to 8 cases per 100,000 persons per year in North America, and 1.4-3.1 cases per 100,000 persons per year in Canada.[6,21,33,35–37]

2.3 Treatment of TMA disorders

Plasma exchange (PLEX) is a therapy that dramatically improves survival in TTP; for this reason there is a low threshold to start PLEX when TTP is suspected.[21,38] It is common for patients to receive multiple rounds of PLEX over several days before disease remission. Relapse, defined as reoccurrence of TTP more than 30 days from the previous episode, is observed in 20%-50% of patients.[21,26,34,39–41] It is important to identify risk factors and the root cause of TMA to effectively prevent and manage relapses.

Along with dialysis, PLEX may also be used in the treatment of HUS. Furthermore, evidence from some studies supports the use of rituximab as treatment in immune-mediated TTP. [21,33,42,43] Other treatment options include aspirin, dipyridamol, or glucocorticoids; however, patient outcomes do not seem to differ statistically or clinically with the inclusion of these drugs in the treatment regime.[44,45]

2.4 Long-term outcomes of TMA

Short-term outcomes of TMA have substantially improved with the use of PLEX therapy. Several important complications persist beyond the 6 months following TMA. First and foremost, TMA can relapse, at a rate that varies between 8%-84%, and seems to increase with increasing length of follow-up.[46,47] Roughly 10% of all deaths in the 3 years following TMA have been attributed to a TMA relapse.[32,48] Other long-term outcomes after TMA treated with plasma exchange include chronic kidney disease, hypertension, stroke, depression, preeclampsia, reduced neurocognitive function, and reduced health-related quality of life (indicated by lower physical component summary scores and/or mental component summary scores).[46,47,49–52]

2.5 Drug-induced TMA

Adverse drug events are well recognized as a potential cause of TMA.[7,53] Drug-induced thrombotic microangiopathy (DITMA) is formed under two major mechanisms. Immune-related DITMA occurs when the drug prompts the generation of antibodies that interacts with cells, eventually leading to TMA associated symptoms such as platelet aggregation.[54,55] Toxic-related DITMA is often dependent on drug dose. This type of DITMA may develop from tissue injury as a direct consequence of patients ingesting large quantities of a drug over a short period of time.[56]

DITMA occurs in both children and adults. Analyses of the Oklahoma Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome (TTP-HUS) registry suggest

5% of all TMA cases are due to drugs. However, the true incidence of DITMA is difficult to ascertain due to overlap with other prominent risk factors, the absence of appropriate diagnostic tools, and lack of understanding of pathological mechanisms.[7,53]

2.6 Drugs associated with TMA

In a systematic review of published DITMA case reports, 78 drugs were identified as a potential cause of TMA. However, the evidence only qualitatively supports 22 (28%) of these claims.[7] Drugs most commonly associated with TMA are those indicated for malaria (Quinine), cancer (gemcitabine, bevacizumab, mitomycin, oxaliplatin, pentostatin, sunitinib), immunosuppression (cyclosporine, sirolimus, tacrolimus), antibiotics (trimethoprim-sulfamethoxazole), and drugs of abuse (cocaine, ecstasy, oxymorphone).[7,53]

2.7 Risk factors for TMA

TMA occurs more commonly in women than men.[57–59] It is unclear as to why women have a higher risk of TMA, but studies with non-selective samples often show higher proportions of women with TMA as opposed to men.[57,60,61]

Malignant hypertension potentially affects TMA on two fronts: first, reduced ADAMTS13 activity has been observed in malignant hypertension, and second,

endothelium damage due to malignant hypertension may trigger release of von Willebrand factors.[62–64]

TMA is often induced in various late-stage cancers, such as prostate, breast, lung, and ovarian cancers. The pathophysiology of cancer-induced TMA is not well understood, but many similar clinical symptoms are present in both TMA and cancer, most commonly microangiopathic hemolytic anemia.[65–68]

Antibodies to ADAMTS13 may form in patients with recent transplants and in patients diagnosed with auto-immune diseases (e.g. systemic lupus erythematosus, HIV). As previously discussed, the underlying pathophysiology of TMA is not well understood.[69–73]

Fakhouri et al. found a considerable risk for TMA during pregnancy in a review published in 2010.[74] The incidence of HUS is estimated to be 1 in 25,000 pregnancies, slightly higher than the general population. However, very little is known about the pathophysiology of pregnancy related TMA, [74,75]

2.7.1 Shiga toxin-producing *Escherichia coli* infection

Shiga toxin-producing *Escherichia coli* (STEC) infections are characterized by the presence of at least one phage-encoded Shiga toxin gene (stx1 or stx2). STEC infections are associated with an array of diseases, ranging from mild gastrointestinal disturbances to clinically severe conditions, including HUS.[76] A large proportion of patients with critical STEC infections also develop conditions commonly associated with infection

such as sepsis including septic shock.[77] An English study by Byrne et al. documented 3,717 suspected cases of STEC infection between 2009 and 2012. 3,267 (90.7%) cases of infection were confirmed and 215 (6.4%) cases progressed to HUS. The HUS cases were predominately women and children, and the highest proportion of HUS cases occurred in females under the age of 14.[78] Rural residents were more likely to be infected; the incidence of STEC infections was roughly 4 fold higher in individuals residing in rural areas compared to urban residents.[78]

2.8 NSAID indications and characteristics of NSAID users

The main indications for NSAIDs are pain, inflammation, and associated diseases of an acute and chronic nature. For example, NSAIDs are commonly prescribed for patients suffering from arthritic conditions (e.g. osteoarthritis, rheumatoid arthritis) and other autoimmune diseases.[14,15,79]

Older adults are the most frequent NSAIDs users. A meta-analysis of 16 studies by Gabriel et al. found that roughly 40% of NSAID prescriptions were for patients over the age of 60.[80]

The Alabama NSAID Patient Safety Study administered surveys to understand patterns of NSAID use prescribed by 48 participating primary care physician practices. The results were published in 2007 and summarized findings based on a sample size of 404 Americans comparing black and white patients.[20] Responders were mostly women (73%) and white (68%), with a mean age of 73 years in both groups. The study found that black

NSAID users were more likely to belong to a lower socio-economic status (cut-off was selected at annual household income of $20,000). The likelihood of living in a rural residence did not differ between black and white NSAID users.[20]

While higher doses of NSAIDSs are obtained through a medical prescription, several lower dose NSAIDs can be purchased over-the-counter without a prescription. A study of 229 447 French patients described and compared the characteristics of over-the-counter and prescription NSAID users. About 52% of patients in the study received at least one prescription for a NSAID. Compared to over-the-counter NSAID users, prescription strength NSAID users were older (mean age 39.9 vs. 47.4), and were more likely to have at least one long-term illness (18.9% vs. 27.6) (conditions considered as long-term illnesses included stroke, severe arterial hypertension, coronary artery disease, severe heart failure, arrhythmia, heart valve disease, and congenital heart defects). Both groups had similar portions of women (56.7% versus 53%).[81]

Chapter 3

3 Rationale

3.1 TMA association with NSAID usage

We performed a comprehensive review of the literature to summarize the current state of evidence regarding the association between TMA and NSAID exposure. We used the bibliographic databases Pubmed, EMBASE, Google Scholar, and Web of Science. Our search strategy for each database is described in appendix A. We identified 8 case reports suggesting a possible link between TMA and NSAID usage.

Several generic methods have been used to assess the quality of reports to gain insight into the potential causality of an adverse drug event (e.g. Naranjo, Jones). No measure has been shown to better than the others, and in most cases the measure results in a conclusion that the drug has a ‘possible’ or ‘probable’ chance of causing the adverse drug event.[82,83]

In our case, we evaluated the quality of the 8 case reports using an existing framework to assess drug-induced TMA (see appendix B). The results of this appraisal are found in table 1. In summary, TMA development was linked to Ibuprofen in 4 cases.[8–10,84] None of the 4 patients reported exposure to other risk factors for TMA, and exhibited telltale signs of TMA including hemolytic anemia, a low platelet count, acute kidney injury, an altered mental state, and low ADAMTS13 levels. Another published case report study of a 58-year old woman described a possible link between ketorolac trometamol and TMA.[12] One

case report published by Trice et al. attributed TMA development in a 64-year old man to treatment with D-penicillamine (an antibiotic); however, the patient had received naproxen (an NSAID) prior to receiving D-penicillamine.[85] The NSAIDs diclofenac and pranoprofen were each reported to be associated with TMA in two separate case reports.[13,86] In a review of DITMA, Al-Nouri et al. listed 2 case reports of ibuprofen and ketorolac under immune-mediated TMA in their supplementary table S3.[7] These case reports were captured within the scope of our literature review.

Beyond the published literature, we searched the European Database and Suspected Adverse Drug Reaction Reports, which records reports from the European Economic Areas (EEA). Collectively, there were a total of 54 cases of TMA with an NSAID identified as a suspected cause. Ibuprofen accounted for the majority of these cases (40), followed by diclofenac (12) and naproxen (2). The age of these patients ranged from less than 1 year to over the age of 65. We also searched (i) Health Canada's Canada Vigilance Program database and (ii) the Food and Drug Administration's Adverse Event Reporting System (FAERS) database, but these searches did not yield any reports. We recognize we have may have missed potentially reports of interest within these databases, given our limited level of access and difficulties with how the data are organized.

We contacted manufacturers of NSAIDs (Pfizer, Novartis, and Bayer) via telephone and/or e-mail to inquire whether they had any documented cases of TMA associated with their NSAID drugs. Whenever a valid response was received, we were simply referred to publicly available information that we had already reviewed.

It appears the current evidence supporting an association between NSAIDs and TMA is limited to case report studies. While case reports are helpful in detecting novel events and are hypothesis generating, they are limited in eliciting cause and effect relationships, and they are also limited by several forms of bias and poor generalizabilitys.[87] We were unable to perform an in-depth review of two of the eight reports due to language barriers (one report was written in Italian and one report was written in Spanish) and limited access to full articles (the articles were published in 1974 and 1989). The reports have been referenced in more recent case reports but a detailed analysis of the reports was not made.

Five of the remaining six studies reviewed did not document an alternative condition or drug exposure which could have led to TMA, and it was not clear from the report whether discontinuation of the NSAID (or a reduced dose of NSAID) was followed by an improvement in TMA symptoms.

None of the case reports provided information as to whether reintroduction of a NSAID after a TMA episode resulted in a TMA reoccurrence.

Furthermore, the potential pathophysiologic mechanism by which of NSAIDs may cause TMA is not well understood. Some have hypothesized that the potential association between TMA and NSAID lies within the formation of autoantibodies against ADAMTS13.[84]

Thus, an important gap exists in the literature with respect to the possible link between NSAIDs and TMA.

3.2 Research objective and hypothesis

This study was conducted to investigate whether a TMA hospitalization was more likely to be associated with a recent prior prescription for NSAID compared to a recent prior prescription of acetaminophen, the latter being the referent drug with no known association with TMA. To address this objective, we conducted a retrospective matched case-control study using health administrative data in the province of Ontario. Given the current state of evidence, we hypothesized that exposure to NSAIDs, relative to acetaminophen, would be associated with a higher incidence of TMA.

Table 1.

Case report evaluation for NSAID associated TMA				
NSAID	Citation	Year published	Patient sex and age in years	Level of evidence[1]
Diclofenac	Claros González I, Baños Gallardo M, Casal Alvarez F, Argüelles Toraño M. Systemic thrombotic microangiopathy secondary to diclofenac. *Med Clínica*. 1989;92(10):396.	1989	Male, middle aged	5
Ibuprofen	Catizone L, Santoro A, Scialfa G, Cagnoli L, Fabbri L. Thrombotic thrombocytopenic purpura due to administration of Ibuprofen. *Minerva Nefrol*. 1974;21(6):439-444.	1974	Female, 55	5
Ibuprofen	Schoenmaker NJ, Weening JJ, Krediet RT. Ibuprofen-induced HUS. *Clin Nephrol*. 2007;68(3):177-178.	2007	Female, 44	2
Ibuprofen	Oregel KZ, Ramdial J, Glück S. Nonsteroidal Anti-inflammatory Drug Induced Thrombotic	2013	Male, 21	2

	Thrombocytopenic Purpura. *Clin Med Insights*. 2013;6:19-22. doi:10.4137/CMBD.S12843.			
Ibuprofen	Benmoussa J, Chevenon M, Nandi M, Forlenza TJ, Nfonoyim J. Ibuprofen-induced thrombotic thrombocytopenic purpura. *Am J Emerg Med*. 2016;34(5):942.e5-e7. doi:10.1016/j.ajem.2015.10.044.	2016	Male, 37	2
Ketorolac Tromethamine	Randi ML, Tison T, Luzzatto G, Girolami A. Haemolytic uraemic syndrome during treatment with ketorolac trometamol. *BMJ*. 1993;306(6871):186.	1993	Female, 58	2
Naproxen	Trice JM, Pinals RS, Plitman GI. Thrombotic thrombocytopenic purpura during penicillamine therapy in rheumatoid arthritis. *Arch Intern Med*. 1983;143(7):1487-1488. doi:10.1001/archinte.1983.00350070215039.	1983	Male, 64	3

Pranoprofen	Okura H, Hino M, Nishiki S, et al. Recurrent hemolytic uremic syndrome induced by pranoprofen. *Rinsho Ketsueki*. 1999;40(8):663-666.	1999	Female, 25	2

[1] Case reports are given a level from 1 to 5 depending on how many causal criteria the case fulfills; 1 = definite evidence of a causal relationship, 2 = probable, 3 = possible, 4 = unlikely, 5 = unsuitable for review. A more detailed explanation is provided in appendix B.

Chapter 4

4 Methods

4.1 Study design and setting

We conducted a retrospective matched case-control study using administrative data in the province of Ontario, linked at the Institute of Clinical Evaluative Sciences (ICES). Cases (individuals who were hospitalized for TMA between 1996 and 2015) and controls (described below) were identified from a source population of Ontario residents who (i) were prescribed NSAIDS or acetaminophen between 1996 and 2015 and (ii) had universal drug coverage during this time (in Ontario, universal drug coverage is granted to Ontario residents who are older than age 65, to those living in a long-term-care facility or a home for special care, and to those enrolled in the Home Care program, the Trillium Drug Program, Ontario Works, or the Ontario Disability Support Program). We selected this study design given TMA is a rare disease.

This study was conducted according to a pre-specified protocol, which was approved by the Research Ethics Board at the Sunnybrook Health Sciences Centre in Toronto, Ontario. The reporting of the study adheres to the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) guideline (appendix C).

4.2 Data sources

This study was conducted using administrative healthcare databases linked at the ICES Western site in London, Ontario. The study was conducted primarily using the following four databases:

1) Registered Persons Database

The Registered Persons Database (RPDB) is a population-based registry managed by the Ministry of Health and Long-Term Care (MOHLTC) in Ontario, Canada. The RPDB is essentially a comprehensive listing of the unique health numbers that have been issued to individuals eligible for coverage since its conception, and the purpose of the database is to direct publicly funded health care services covered under the Ontario Health Insurance Plan. When new RPDB data arrive at ICES, information regarding a potential patient's identity is removed and each unique health number is encrypted into an anonymous identifier, the ICES Key Number (IKN). The IKN is a unique identifier that is used to link patient data across databases in ICES. We used the RPDB database to obtain demographic information including a patient's date of birth, sex, income categories (sorted into 5 quintiles in order of ascending income levels), urban or rural residence status, and date of death.

2) Ontario Drug Benefit

The Ontario Drug Benefit (ODB) Program is a publicly funded program that provides financial assistance for medication costs. The ODB records all outpatient drug

prescriptions dispensed to patients who are eligible for this program, specifically, Ontario residents aged 65 years and older, those living in a long-term-care facility or a home for special care, and those enrolled in the Home Care program, the Trillium Drug Program, Ontario Works, or the Ontario Disability Support Program. We used this database to ascertain exposures to any of our study drugs and to any baseline medications.

3) Canadian Institute for Health Information – Discharge Abstracts Database

The Canadian Institute for Health Information – Discharge Abstract Database (CIHI-DAD) contains patient-level demographic, diagnostic, medical procedural, and other administrative information (e.g. physician responsible for the patient) for hospitals across Ontario. The structure of the database allows an assignment of up to a maximum of 25 diagnoses allocated to a single hospitalization event. Diagnoses made prior to 2002 are recorded using the International Classification of Diseases, ninth revision (ICD-9). Since then the tenth revision of the coding has been used to record diagnosis information. We used this database to identify all diagnoses of TMA from 1991 to the latest update, which includes up to March of 2015. We also used this database to ascertain information on baseline comorbidities.

4) Ontario Health Insurance Plan

The Ontario Health Insurance Plan (OHIP) database contains medical service claims made by healthcare professionals, including physicians, for patients who are residents of

Ontario. Ontario physicians are reimbursed for the services they are documented as providing to specific patients on specific days. The OHIP database records information such as the type of service provided, diagnostic information, the healthcare professional that provided the service, the patient who received the service, the date the claim was filed, and the associated fee code. It is estimated that 95% of physicians in Ontario utilize OHIP as their source of income. We used this database to identify any patients who received plasma exchange treatments between July 1991 to March 2015.

4.3 Patient population selection

Patients who had at least one prescription for an NSAID or acetaminophen dispensed through Ontario Drug Benefit (ODB) between July 1991 and March 2015 formed the study base for this case-control study. The data was subsequently linked to the Registered Persons Database (RPDB) and all patients with an invalid or missing value under the variables age, sex, or health card number (patient identifying number) were excluded. Next, we identified all hospitalizations with TMA through linkage to Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD). As we were interested in new (de novo) episodes of TMA, we excluded patients with evidence of a TMA diagnosis or patients who received plasma exchange preceding July 1, 1996. The remaining patients consisted of cases with a hospitalization diagnosis of TMA as defined from CIHI-DAD (codes presented in appendix D), and potential controls that did not have a hospitalization diagnosis of TMA as defined from CIHI-DAD.

4.4 Index date

Cases were assigned an index date representative of the initial date of their hospitalization for TMA. Index dates fell between July 1, 1996 and March 31, 2015. Since the remaining patients were not diagnosed with TMA, we sampled the distribution of index dates from the case population and randomly assigned index dates to the remaining non-TMA patients based on the same distribution of index dates as cases

4.5 Study population

4.5.1 Cases

We identified all available Ontario patients from our study base with a hospital admission diagnosis of TMA between July 1, 1996 and March 31, 2015 (codes presented in appendix D). Patients were restricted to their first admission to a hospital with TMA diagnosis within our accrual period, and the initial hospitalization with a TMA diagnosis served as the index date for cases.

4.5.2 Controls

All individuals from our study base without a TMA diagnosis during our accrual period were eligible to be selected as controls. Since patients without TMA did not have a date of diagnosis to serve as an index date, we randomly assigned an index date to the pool of potential controls based on the distribution of index dates in cases.

Matching is defined as the pairing of cases and controls based on pre-specified characteristics in order to form similar, if not identical matched sets with respect to said characteristics.[88] The purpose of matching in case-control studies is to increase a study's efficiency by ensuring similarity in the distribution of variables between cases and controls, in particular, the distribution of potential confounders.[88,89] We matched 4 controls per case based on the following characteristics: age (± 2 years), sex, index date (<6 months), rural residence (population less than 10,000), neighborhood income quintile, and conditions and drugs associated with a higher risk of TMA: malignant hypertension, systemic lupus erythematosus, HIV, sepsis, and use of quetiapine, tacrolimus, sirolimus, cyclosporine, clopidogrel, and ticlopidine.

4.5.3 Exposure

We were interested in patients who had a past prescription of NSAIDs or a past prescription for acetaminophen, an analgesic drug used for a similar indication but not suspected to be associated with TMA.

We looked at patients who were exposed to either one, mutually exclusive exposures, to minimize confounding by indication. For the purposes of this study, patients prescribed an NSAID were classified as “exposed”, while patients prescribed an acetaminophen were classified as “unexposed”. Index dates served as the point in time from when we looked back in time to ascertain exposure, where the drug supply period of the most recently dispensed NSAID or acetaminophen overlapped with the index date. The window of time in which we ascertained drug exposure was defined by the variable “day supply” in ODB, extended by 50%. For example, if a patient had received a prescription for 30 days worth of drug supply for NSAID or acetaminophen, we would look to see if they had been hospitalized with TMA within 45 days (30 days + 50%) of the date of prescription. Given the way we constructed the study sample to efficiently pull data from our data sources, it was expected we would have a substantial number of patients with no evidence of an NSAID or acetaminophen dispensed just prior to the index date (i.e. they had an NSAID or acetaminophen filled between July 1996 and March 2015, but this was well before or after their index date); such patients were excluded from analysis.

Patients with evidence of both an NSAID and acetaminophen were excluded from the analysis so that we could compare mutually exclusive groups.

4.6 Baseline characteristics

Baseline characteristics were assessed using ICD-9 and ICD-10 codes within the five years prior to the index date, with the exception of primary care physician visits being assessed in the year prior to the index date (but not in the 30-day period before the index date to avoid physician encounters possibly related to the TMA; database codes used to define characteristics are presented in supplementary appendix 2). Baseline outpatient drug use was ascertained in 120-day period before the index date, as in Ontario the maximum day supply for a dispensed drug is 100 days.

4.7 Comorbidity indices

Comorbidity can be referred to as the simultaneous existence of disease conditions other than the disease or outcome of interest. Comorbidity indices are designed to reflect comorbid burden, which can be used to predict mortality or adjust for as potential confounders in epidemiological studies.[90,91] We considered implementing the Charlson Comorbidity Index and the John Hopkins Aggregated Diagnostic Groups. The Charlson Comorbidity Index measures general comorbidity based on the presence of a combination of diseases for a specific patient. Patients receive scores corresponding to a diagnosed

disease, the cumulative scores of all relevant diagnosed diseases represents their individual Charlson Comorbidity Index. A score of 1 is assigned to the following conditions: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, and diabetes. A score of 2 is assigned to the following conditions: hemiplegia, moderately severe renal disease, diabetes with organ damage, any tumors within the last 5 years, lymphoma, and leukemia. A score of 3 is assigned to moderately severe liver disease. Finally, patients diagnosed with acquired immune deficiency syndrome (AIDs) or metastasized tumors are assigned a score of 6. [90–93] John Hopkins Aggregated Diagnostic Groups features 32 diagnostic clusters called aggregated diagnostic groups (ADGs), and each disease is categorized into one of the 32 clusters based on: duration of the condition, severity of the condition, disease etiology, diagnostic certainty, and specialty care involvement. Similarly, all baseline conditions are categorized and a cumulative score is derived to represent risk of mortality.[94] Both techniques have been modified to utilize ICD codes for scoring.[91,94] Austin et al. published a study in 2011 that showed superior performance in model discrimination and calibration for John Hopkins ADG scores as compared to the Charlson Comorbidity Index.[95] This study was performed using the same Ontario datasets analyzed in our study. For this reason we decided to use the John Hopkins ADG score for this study.

4.8 Statistical analysis

We assessed balance of baseline characteristics between case and control groups using hypothesis testing and standardized differences. Hypothesis testing operates on the null hypothesis that there are no critical differences between one group over another in terms of a specific treatment or condition. With respect to baseline assessment, we are testing if there is evidence to refute the null hypothesis (i.e. if there are indeed differences in means or proportions between cases and controls) across our selected baseline characteristics.[96] The p-value is widely used in hypothesis testing and describes the probability of obtaining an observation as large as the observed, had the null hypothesis been true. A p-value of <0.05 can represent considerable evidence against the null hypothesis.[97] Another method we used to compare baseline characteristics is the standardized difference. The standardize difference statistic measures differences between group means with respect to pooled standard deviation. A value of greater than 10% or 0.01 can be interpreted as a meaningful difference between two compared groups.[98–100] We initially considered using standardized differences for its advantageous properties over hypothesis testing in studies with large sample sizes, however, this was not an issue with the current study.[99,100] Therefore, we selected to report p-values over standardize differences. We implemented generalized estimating equations (GEE) to assess baseline balance between cases and controls.[101]

Logistic regression is fundamentally used to model the relationship between a binary dependent variable and a series of independent variables, but the method can be tailored to fit the nature of the data that is to be analyzed.[102,103] We used conditional logistic

regression to obtain odds ratios, which provides an effect estimate of the likelihood of having a recent prescription for an NSAID among patients who were hospitalized with TMA (binary dependent variable) relative to acetaminophen. Conditional logistic regression is commonly selected as the statistical analysis when matching is done in a case control study.[104] The main reason for this selection is to provide an estimate that is less susceptible to the effects of sparse data created by forming multiple strata of matched pairs as seen in our study.[105]

We conducted all analyses using SAS version 9.3 (SAS institute, Cary, North Carolina, USA, 2008)

4.9 Additional analyses

We repeated the analysis with the referent drug hydromorphone instead of acetaminophen. The purpose of this analysis was to replicate the results of the primary analysis, as agreement between the two would increase our confidence in the findings. There is no known association between hydromorphone and TMA.

Another consideration is that some NSAIDs (i.e. ibuprofen) are readily accessible over the counter and without a physician's prescription. Exposure to over the counter non-prescription NSAID use in the referent group would reduce differences in exposure between our comparison groups and reduce our ability to detect a higher risk of TMA with NSAIDs if an association had indeed existed. This is described as contamination bias, where the patients in the acetaminophen group were inadvertently exposed to

NSAIDs, thus diminishing the difference in outcomes between the two exposures.[106] To limit the risk of contamination bias we repeated the analysis with the referent drug as an ACE-inhibitor instead of acetaminophen, as we expected less over the counter NSAID use in the setting of ACE-inhibitor use (as using both drugs together is often avoided).

Chapter 5

5 Results

5.1 Source population and selection of cases and controls

The steps in patient selection are summarized in Figure 1. In brief, the source population consisted of 3,598,154 individuals who had evidence of a prescription dispensed for either a study NSAID or acetaminophen at least once anytime between July 1991 and March 2015, but after we excluded those with invalid or missing age, sex, and Ontario health card numbers. Next, we excluded 28 individuals with a TMA diagnosis prior to July 1996. Another 3,673 individuals were excluded due to their receipt of plasma exchange (939 prior to 1996; after the index date was assigned, 2,734 recipients of plasma exchange prior to 6 months before their index date). Of the remaining population of patients (n=3,598,154), we excluded 3,344,893 patients because their index date did not fall within the duration of their day supply extended by 50% (i.e. they had their NSAID or acetaminophen dispensed well before or after their index date), and we excluded 18,282 patients who had an index day fall within the duration of supply of both a study NSAID and acetaminophen. The patient population prior to matching consisted of 44 cases and 231,234 potential controls. Patients were ‘hard’ matched on binary variables and for categorical variables (i.e. case and control must have same output). Ultimately, we were able to match 38 cases of TMA to 152 controls without TMA (1:4) for a final study population of 190 patients.

We performed some descriptive analyses to understand the clinical context of this 38 TMA cases. To comply with privacy regulations for minimizing the chance of patient identification, cells between 1-5 patients are suppressed (reported as ≤5). Cells with a value of 0 are reported, as there is no one who could be identified. The TMA cases occurred across 28 different hospitals in Ontario. Within 90 days of their index hospital admission, 16 of 38 cases (42%) received at least one treatment with PLEX, 6 of 38 (16%) received at least one treatment with dialysis, ≤5 (≤ 13%) of 38 were admitted to an intensive care unit, and ≤5 (≤ 13%) of 38 died.

5.2 Baseline characteristics

A comparison of baseline characteristics in cases and controls is presented in Table 2. The average age of patients was 67, and women accounted for two-thirds of the study sample. Given that we matched on several baseline characteristics, cases and controls were similar on most characteristics (p-value > 0.05). However, there were observed differences between cases and controls on the number of visits to a primary care physician in the year prior to the patient's index date, and on the John Hopkins Aggregated Diagnosis Group Score.

5.3 Primary analysis

19 cases (50%) were exposed to an NSAID and 19 cases (50%) were exposed to acetaminophen.

The results of the regression analyses comparing TMA among patients prescribed NSAIDs vs. acetaminophen are presented in Table 3. Patients who were hospitalized with TMA were less likely to have received NSAIDs compared to acetaminophen (odds ratio [OR] 0.32, 95% confidence interval [CI] 0.15 – 0.68). Adjusting for baseline characteristics that differed between cases and controls did not meaningfully change this result (table 3; OR 0.37, 95% CI 0.16 – 0.84).

5.4 Additional Analyses

We wanted to determine if the reintroduction of NSAIDs after a TMA episode resulted in reoccurrence of the TMA. We found that of the 19 cases that had NSAIDs prior to their first TMA episode, 8 (42.1%) received a repeat prescription for NSAIDs in the year following their TMA-associated discharge date. None of these patients had a re-hospitalization with TMA in the 30 days after the follow-up prescription.

We used the active comparator (reference group) acetaminophen in this study, to reduce concerns about confounding by indication. However, this has implications for the interpretation of study results. For example, patients who were hospitalized with TMA were less likely to have received NSAIDs compared to acetaminophen (odds ratio [OR]

0.32, 95% confidence interval [CI] 0.15 – 0.68). This can be interpreted in several ways, including that NSAIDs are ‘protective’ in preventing TMA, acetaminophen is ‘harmful’ in causing TMA, acetaminophen is more ‘harmful’ than NSAIDs in causing TMA, or acetaminophen is less ‘beneficial’ than NSAIDS in preventing TMA, although most of these possibilities are not supported by our underlying understanding of the biology of TMA. However, to consider the results in other contexts we repeated the analysis twice with either hydromorphone or angiotensin converting enzyme inhibitors (ACE-I) (and not acetaminophen) as the reference group.

5.4.1 Hydromorphone comparator group

A new data cut was performed for this analysis to create a source population consisting of individuals with an evidence of prescription filling for NSAIDs or hydromorphone. The exclusions and cohort selection methods were as done for the primary analysis, comparing NSAIDs to acetaminophen. Ultimately, fewer than six cases were exposed to hydromorphone, which precluded us from presenting the results of this analysis due to privacy considerations; however, there was no observed association between NSAID use and TMA when the referent group was hydromorphone. The limited statistical power of this analysis meant the estimate was likely not precise enough to be considered meaningful.

5.4.2 Angiotensin-converting enzyme inhibitor (ACE-I) comparator group

This supplementary analysis was done to reduce concerns about over-the-counter NSAID use in the control group (as NSAIDs are often avoided in the setting of ACE-I use). In a similar fashion to our other supplementary analysis, a new data cut was performed in order to create a source population of patients with evidence of a prescription filled for NSAIDs or ACE-Is. The exclusions and cohort selection methods were identical to that of the primary analysis, comparing NSAIDs to acetaminophen. The figures and tables corresponding to patient selection, baseline characteristics, and analysis output can be found in appendix E, F, and G respectively.

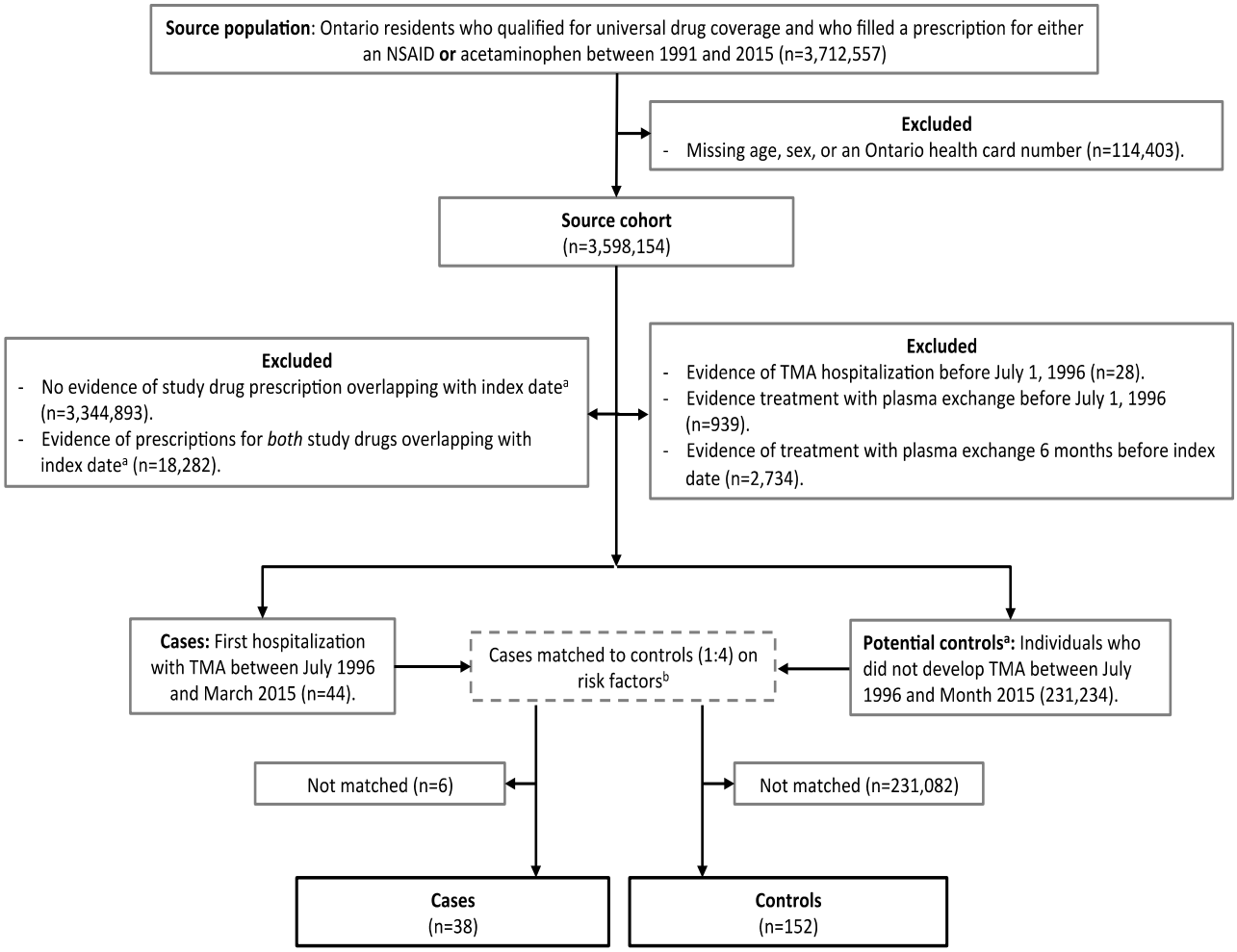
In brief, the source population consisted of 3,442,246 individuals. Patients with a past diagnosis for TMA (n=80), and history of evidence for plasma exchange (n=3,392) were excluded. In ascertaining exposure, it was determined that 2,858,914 individuals were not exposed to either class of study drugs and 49,896 individuals were exposed to both classes of study drugs simultaneously. Exposure definitions were as done for the primary analysis. After matching, the final study population consisted of 84 cases matched to 336 controls.

The mean age of patients in the study population was 73. Females accounted for roughly 60% of the study population.

There was no observed association between NSAID use and TMA when the referent group was ACE-I (odds ratio 0.82, 95% CI 0.45-1.49; selection, baseline characteristics

and outcomes presented in appendices 3, 4 and 5, respectively). We performed an analysis adjusting for differences in baseline characteristics (more specifically: cancer, osteoarthritis, rheumatoid arthritis, John Hopkin's ADG score and primary care physician visits), but did not observe a meaningful change in the results (odds ratio 0.72, 95% CI 0.38-1.37).

Figure 1. Flow diagram of patient selection with acetaminophen as the referent group



[a]Controls were assigned an index date randomly based on the distribution of index dates in case patients
[b]age (± 2 years), sex, index date (<6 months), rural residence (population less than 10,000), neighborhood income quintile, and conditions and drugs associated with a higher risk of TMA: malignant hypertension, systemic lupus erythematosus, HIV, sepsis, and use of quetiapine, tacrolimus, sirolimus, cyclosporine, clopidogrel, and ticlopidine.
Abbreviations: **NSAID**: non-steroidal anti-inflammatory drugs, **TMA**: thrombotic microangiopathy

Table 2. Baseline characteristics for patients prescribed NSAIDs or acetaminophen with and without thrombotic microangiopathy (cases and controls, respectively)

	Controls (n=152)	**Cases (n=38)**	**P-value**
Demographics			
Age, no. (%)			
Median (IQR)	71 (65-79)	71 (61-78)	
Mean ± SD	67 ± 16.11	67 ± 16.75	0.47
16 - 34	9 (5.9%)	≤5	0.23
35 - 44	8 (5.3%)	≤5	
45- 54	7 (4.6%)	≤5	
55 - 64	11 (7.2%)	≤5	
65 - 74	61 (40.1%)	15 (39.5%)	
75 - 84	45 (29.6%)	9 (23.7%)	
≥ 85	11 (7.2%)	≤5	
Women, no. (%)	96 (63.2%)	24 (63.2%)	1.0
Rural residence[2], no. (%)	32 (21.1%)	8 (21.1%)	1.0
Socioeconomic status[3], no. (%)			
Quintile 1	28 (18.4%)	7 (18.4%)	1.0
Quintile 2	52 (34.2%)	13 (34.2%)	1.0

Quintile 3 + 4[5]	40 (26.4%)	10	1.0
Quintile 5	32 (21.1%)	8 (21.1%)	1.0
Primary care physician visits, no. (%)			
Median (IQR)	19 (5-15)	14 (7-23)	
Mean ± SD	12 ± 11.98	19 ± 17.06	<0.05
0 - 2	16 (10.5%)	≤5	
3 - 4	20 (13.2%)	≤5	
5 - 6	24 (15.8%)	≤5	<0.05
7 - 8	14 (9.2%)	≤5	
9 - 10	15 (9.9%)	≤5	<0.05
≥ 11	63 (41.4%)	23 (60.5%)	
Comorbidities, no. (%)			
John Hopkins Aggregated Diagnosis Group Score, no. (%)			
Median (IQR)	12 (9-15)	14 (12-16)	
Mean ± SD	12 ± 3.77	14 ± 3.43	<0.05
≤ 9	44 (28.9%)	10 (26.3%)[5]	
10 - 12	41 (27%)		
13 - 15	42 (27.6%)	14 (36.8%)	<0.05
≥ 16	25 (16.4%)	14 (36.8%)	
Malignant hypertension	≤5	≤5	-
Systemic lupus erythematosus	≤5	≤5	-
Cancer[5]	Suppressed	≤5	1.0
Renal transplant	≤5	≤5	-

Osteoarthritis	12 (7.9)	≤5	0.59
Rheumatoid arthritis	12 (7.9)	≤5	0.56
HIV	≤5	≤5	1.0
Sepsis	≤5	≤5	1.0
Medications, no. (%)			
Quinine	≤5	≤5	-
Quetiapine	≤5	≤5	-
Tacrolimus	≤5	≤5	-
Sirolimus	≤5	≤5	-
Cyclosporine	≤5	≤5	-
Clopidogrel	≤5	≤5	-
Ticlopidine	≤5	≤5	-

[1]no.: Number, IQR: interquartile range, SD: Standardized difference, NSAIDs: Non-steroidal anti-inflammatory drugs.
[2]Rural residence is defined as population < 10,000.
[3]Quntiles are ranked from lowest to highest (i.e. Quintile 1 = lowest, Quintile 5 = highest).
[4]P-values are calculated using generalized estimating equations to account for the non-independent correlation structure.
[5]Cells are combined or suppressed to avoid reporting numbers ≤5.

Table 3. The association between NSAID use and thrombotic microangiopathy, with acetaminophen as a reference group. Odds ratios derived from a conditional logistic regression model

	Cases of TMA (n=38)	Controls (n=152)	Odds Ratio (95% confidence interval)	
			Unadjusted	Adjusted[1]
Acetaminophen	19 (50%)	37 (24%)	1.0 (referent)	1.0 (referent)
NSAIDs[2]	19 (50%)	115 (76%)	0.32 (0.15 – 0.69)	0.37 (0.16 – 0.84)

[1]Adjusted analysis included the variables John Hopkin's ADG score and primary care physician visits.
[2]NSAIDs: Non-steroidal anti-inflammatory drugs.

Chapter 6

6 Discussion

6.1 Interpretation of study results

There are over 30 million daily users of NSAIDs worldwide, and there is some evidence from case-report studies that patients who present with TMA have a recent history of NSAID use.[1,2] We conducted this matched case-control study to better understand whether NSAID use is associated with a higher risk of hospitalization for TMA. We found that cases with TMA were less likely to have had a recent prescription for NSAIDS relative to acetaminophen. More specifically, we observed that the case patients were nearly 3 times (OR: 0.37) less likely to be exposed to an NSAID relative to acetaminophen. Furthermore, this association was statistically significant (95% CI: 0.16 – 0.84). We found no association between NSAID use and TMA when we examined two alternate reference groups. For example, when we compared NSAIDs to ACE-inhibitors, we observed no significant association [OR of 0.72 (95% CI: 0.38 – 1.37)]. Ultimately, we were unable to provide any evidence to support a harmful association between NSAIDs and TMA.

Our findings prompted us to re-examine the case reports.[7–10,12,13,85] The most common reason the reports suggested NSAIDs as the cause of TMA was simply because there was no other identified cause present. Furthermore, no research to date provides a strong biological basis for a higher risk of TMA with NSAIDs. This would indicate that, at the

very least, NSAIDs are not associated with a higher risk of TMA, which is consistent with our findings.

None of the case reports addressed the topic of re-introduction of an NSAID after an episode of TMA. It would be concerning if NSAID use after a TMA episode resulted in TMA reoccurrence. In our study, we found that 8 (42.1%) exposed cases received a repeat prescription for NSAIDs in the year following their TMA-associated discharge date. No patient was re-hospitalized with TMA in the 30 days after the follow-up NSAID prescription. Thus, these data do not support avoiding NSAID use in patients with a prior history of TMA.

6.2 Strengths and limitations

Since TMA is a rare event (< 1 per 100,000)[21,22,27], our use of large healthcare databases in the largest province in Canada was opportune as we captured all TMA cases for the entire province of Ontario over two decades. Methodologically, the case-control design is considered to be stronger than the case-series design and weaker than the cohort study design, but we chose to implement the case-control design for this rare disease in order to identify all available cases and maximize statistical power[107] To our knowledge, our study is the first study to explore an association between NSAIDs and TMA using population-based administrative data.

However, as with all observational studies, our results are subject to residual confounding. Even though we controlled for many well-known risk factors for TMA and

important indications of NSAID use, not all the characteristics are well-coded in our data sources, which were collected for the primary purpose of healthcare administration rather than research. To the best of our knowledge, the ICD-9 and ICD-10 codes for TMA have not yet been validated in any setting. Generally, codes representing administrative data are typically highly specific, and vary widely in sensitivity.[108]

The clinical severity of TMA warrants immediate diagnosis and prompt treatment. Most patients who develop TMA would present to hospital due to acute illness. To reduce the risk of early mortality, treatment is initiated in hospital upon an early suspicion of TMA.[30,109,110] Without treatment most TMA is fatal. It remains possible that some TMA goes undiagnosed in routine care, where a patient dies before a diagnosis is made (either before or during a hospitalization). It is an inherent limitation of this study that such cases of TMA were not assessed.[30]

Other consequences that are inevitably associated with the use of administrative data affected how we defined our outcomes, comorbid conditions, and overall selection of patients. Furthermore, our data only informs us as to whether the patients had an oral prescription dispensed, which does not necessarily equate to drug ingested.

One of the biggest challenges in the design of a case-control study is selecting the appropriate patient population to draw cases and controls.[111] We conducted a case-control study within a population of patients exposed to common pain-indicated drugs, which would have eliminated some uncertainty around the source we sampled our cases and controls. However, this approach is not without its flaws. The results obtained from such a case-control study cannot discriminate an association between the two exposures.[112]

Using the results of this study as an example, we obtained a statistically significant odds ratio that suggests an association exists between NSAIDs and TMA, and this association was protective. On the other hand, the result can also be interpreted as a harmful association between acetaminophen and TMA. More research is required before any conclusions may be drawn regarding the protective association of NSAIDs or the harmful association with acetaminophen. Nevertheless, our hypothesis had been that a harmful association would exist between NSAIDs and TMA, with no prior reason to believe acetaminophen use alters TMA risk. A case-control study of pharmacological contraceptives presented in Weiss and Koepsell, 2014 utilized a similar study design.[112] The study consisted of entirely oral contraceptive users. However, elements of such a case-control study is commonly found in nested case-control studies, which is differentiated by the use of incidence-density sampling in selecting matched controls.[113]

It is important to note that the study is susceptible to inadequate power to detect a true effect. Larger sample sizes are generally necessary to accurately ascertain a suspected difference between comparator groups, which is closer to the true effect with increasing power.[114] However, it is also important to note that low power can increase the chance of observing a statistically significant effect where in truth none had existed.[115] The effect estimate in our primary analysis was statistically significant (95% CI did not cross 1, or the estimate of no difference in effect). However, the confidence interval was quite wide (0.16 – 0.84). Wide confidence intervals are a telling feature that the estimates lack precision and that an analysis likely suffers from low power.[116]

Another limitation of our study, on the topic of small sample size, is in how we can control for potential confounders. While we may have deferred to a method of selecting

confounders based on significance level of each variable (e.g. forward selection, backwards elimination, or a hybrid method)[117], we recognized that we were limited by our small sample size and placed more reliance on matching to ensure that the distribution of potential confounders were similar between cases and controls. Nonetheless, we attempted to control for all potential confounders within the constraints of a relatively small sample size.

While we included patients of all ages, the majority of information gathered from the Ontario Drug Benefit database was limited to patients older than age 65. This was apparent in the median age (71) of our cohort. Therefore, our results may not generalize to younger age groups.

6.3 Conclusion and future directions

In conclusion, the results of this study did not provide evidence supporting a harmful association between NSAIDs and TMA.

Historically, case reports and small observational studies have been key to advancing TMA treatments. Initial observations of TMA symptoms were largely reported in isolated cases, dating as far back as 1925. Since then there have been a series of studies with small sample sizes ($n<15$) noting the efficacy of various treatments, until the literature began to converge on the success of plasma exchange therapy, eventually leading to a randomized control trial of 102 TMA patients; this trial clearly demonstrated the superiority of plasma exchange therapy compared to plasma infusion.[118] Convincing

results from case reports and small observational studies are important for hypothesis generation and set the precedence for clinical trials. We also believe in the value of observational studies for identifying strong candidates for biological studies on the etiology, pathogenesis, and pathophysiology of TMA. Therefore, additional studies on DITMA in different populations and/or settings could provide further evidence of an potential association between NSAIDs and TMA, generate hypotheses for future studies, and strengthen the current state of evidence which consists predominately of case reports.

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Appendices

Appendix A: Search strategy summary

Database	Search strategy
Pubmed	1. Search (((Anti-Inflammatory Agents, Non-Steroidal) OR NSAID*)) 2. Search ((((Thrombotic Microangiopathy) OR Microangiopathies, Thrombotic) OR Microangiopathy, Thrombotic)) 3. Search (thrombotic thrombocytopenic purpura) OR TTP 4. Search (hemolytic uremic syndrome) OR HUS 5. 2 OR 3 OR 4 6. 1 AND 5
Embase	1. Thrombotic microangiopathy.mp. OR thrombotic thrombocytopenic purpura/ 2. Hemolytic uremic syndrome/ 3. NSAID.mp. OR nonsteroidal anti-inflammatory agent/ 4. 1 OR 2 5. 3 AND 4
Google Scholar	Keyword search using “thrombotic microangiopathy”, “thrombotic thrombocytopenic purpura”, “hemolytic uremic syndrome”, “non-steroidal anti-inflammatory”,

	and any alternative representations (e.g. NSAID).
Web of Science	1. TI=thrombotic thrombocytopenic purpura 2. TI=Hemolytic uremic syndrome 3. TS=Thrombotic microangiopathy 4. TS=NSAID 5. TS=non-steroidal anti-inflammatory 6. 1 OR 2 OR 3 7. 4 OR 5 8. 6 AND 7

Appendix B:

Criteria for evaluation of reports[1]	
1. Clinical or pathologic diagnostic criteria for TMA were present	
2. Clinically apparent causes of clinical/pathologic criteria other than TMA and causes of TMA other than drug toxicity were excluded **AND** the suspected drug was the only drug taken or other drugs were continued or restarted	
3. TMA resolved or improved when suspected drug stopped or dose reduced (kidney injury may persist)	
4. TMA worsened after suspected drug discontinued **OR** TMA recurred without subsequent drug exposure	
Levels of evidence for an association of the NSAID induced TMA	
Evidence Level	Criteria met

Level 1 Definite	1, 2, and 3
Level 2 Probable	1 and 2
Level 3 Possible	1
Level 4 Unlikely	1 and 4
Level 5[2] Not suitable for review due to any one of following:	
1. No individual patient data reported	
2. Insufficient patient data for assessment	
3. Diagnostic criteria for TMA (1) was not met	
4. Inappropriate drug dose or non-therapeutic use	
5. Drug etiology neither proposed or discussed	
6. Combination drug etiology proposed	

[1]Criteria for evaluation for this study is based on the criteria for evaluation used in Al-Nouri et al.[7] for toxic-mediated drug induced TMA. Criteria for immune-mediate drug induced TMA was not utilized due to the differences in indication and pharmacological action between NSAIDs and drugs which are speculated and/or suspected to cause TMA through an immune-mediated mechanism (e.g. quinine).

[2]We did not limit our literature search by language. Therefore, reports with an available English title and reports that were referenced via other literature were included and reviewed them according to these criteria, where possible. We were unable to review reports without access to full article.

Appendix C: The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary	Title page, abstract, methods	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.	Title page, abstract, methods

		of what was done and what was found		RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	
Introduction					
Background rationale	2	Explain the scientific background and	Introduction		Introduction

		rationale for the investigation being reported			
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction		Introduction
Methods					
Study Design	4	Present key elements of study design early in the paper	Methods		Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods		Methods

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional*	Methods	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and	Methods

		study - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Methods, table 2, Appendix D	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Methods, table 2, appendix D
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	Appendix D, Methods		Appendix D, Methods

		one group			
Bias	9	Describe any efforts to address potential sources of bias	Methods, Results		Methods, Results
Study size	10	Explain how the study size was arrived at	Figure 1		Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Methods, table 2		Methods, table 2
Statistical methods	12	(a) Describe all statistical methods,	Methods, results, table 2, and table 3		Methods, results, table 2, and table 3

		including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls			

		was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors	Methods

				should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods: data sources
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers	Figure 1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection)	Figure 1

		potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and	Figure 1, table 2, methods		Figure 1, table 2, methods

		potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in	Table 3		Table 3

		each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
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	Table 3, results		Table 3, results

		they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Results		Results
Discussion					

Key results	18	Summarise key results with reference to study objectives	Results		Results
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	Discussion	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion
Interpretation	20	Give a cautious overall interpretation	Discussion		Discussion

		of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			Discussion
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the	Acknowledgements		Acknowledgements

		original study on which the present article is based			
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	ICES data is not available to the public as it contains personal medical information

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Appendix D: Codes

Coding definitions for cohort build and baseline characteristics		
Variable	Database	Codes
Cohort Selection		
TMA	CIHI-DAD	ICD-9: "4466" ICD-10: "M311"
Plasma Exchange	OHIP	"G272", "G277", "G278", "G290"
NSAIDs	ODB	CELECOXIB, DICLOFENAC, DICLOFENAC SODIUM, DICLOFENAC SODIUM & MISOPROSTOL, DIFLUNISAL, ETODOLAC, FENOPROFEN CALCIUM, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, KETOROLAC TROMETHAMINE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PIROXICAM, ROFECOXIB, SULINDAC, TIAPROFENIC ACID, TOLMETIN SODIUM, VALDECOXIB

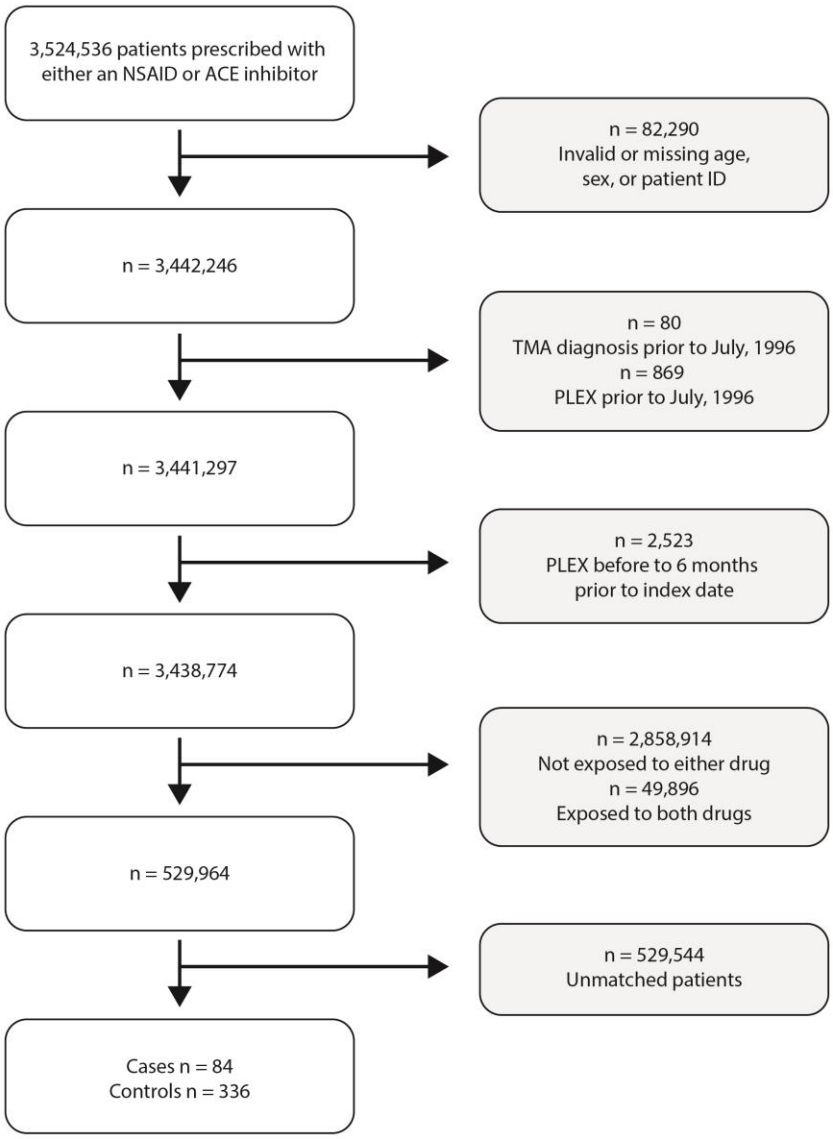
Acetaminophen	ODB	ACETAMINOPHEN & CODEINE PHOSPHATE, ACETAMINOPHEN & CAFFEINE & CODEINE PHOSPHATE
Dilaudid	ODB	HYDROMORPHONE, HYDROMORPHONE HCL
ACE inhibitors	ODB	BENAZEPRIL CHLOROHYDRATE, BENAZEPRIL HCL, CAPTOPRIL, CILAZAPRIL, ENALAPRIL SODIUM, FOSINOPRIL, FOSINOPRIL SODIUM, LISINOPRIL, PERINDOPRIL TERT.BUTYLAMINE, QUINAPRIL, RAMIPRIL, TRANDOLAPRIL
Baseline comorbidities		
Cancers	CIHI-DAD OHIP	ICD9 (CIHI-DAD): "150", "154", "155", "157", "162", "174", "175", "185", "203", "204", "205", "206", "207", "208", "2303", "2304", "2307", "2330", "2312", "2334" IDC10 (CIHI-DAD): "971", "980", "982", "984", "985", "986", "987", "988", "989", "990", "991", "993", "C15", "C18", "C19", "C20", "C22", "C25", "C34", "C50", "C56", "C61", "C82", "C83", "C85", "C91", "C92", "C93", "C94", "C95", "D00", "D05", "D010", "D011", "D012", "D022", "D075"

		OHIP DX: "203", "204", "205", "206", "207", "208", "150", "154", "155", "157", "162", "174", "175", "183", "185"
Kidney transplant	CORR OHIP	CORR: RECIPIENT_TREATMENT dataset [Treatment_Code]: 171 [Treatment_Date] [Transplanted_Organ_Type_Code][1-3]: "10", "11", "12", "18", "19" CCP: "6759" CCI: "1PC85" OHIP feecode: "S435", "S434"
Rheumatoid arthritis		ICD9: "714" ICD10: "M05", "M06" OHIP Dx: "714"

Osteoarthritis	CIHI-DAD	ICD9: "715" ICD10: "M15", "M150", "M151", "M152", "M153", "M154", "M158", "M159"
Malignant hypertension	CIHI-DAD	ICD9: "4010" ICD10: "I101"
Systemic lupus erythematosus	CIHI-DAD	ICD9: "7100" ICD10: "M320", "M321", "M328", "M329"
HIV	CIHI-DAD OHIP	ICD9 (CIHI-DAD): "042", "043", "044", "176" ICD10 (CIHI-DAD): "B24", "Z21", "C46" OHIP DX: "042", "043", "044"
Sepsis	CIHI-DAD	ICD9: "0031", "0362", "0380", "0381", "0382", "0383", "03840", "038.41", "03842", "03843", "03844", "03849", "0388", "0389" ICD10: "A40", "A41"

TMA: Thrombotic microangiopathy, NSAIDs: non-steroidal anti-inflammatory drugs, ICD: International Classification of Diseases, CIHI-DAD: Canadian Institute for Health Information – Discharge Abstract Database, OHIP: Ontario Health Insurance Plan, CORR: Canadian Organ Replacement Register, CCI: Canadian Classification of Health Interventions, CCP: Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures, ACE: angiotensin-converting enzyme, HIV: Human Immunodeficiency Vir

Appendix E: Flow diagram of patient selection with angiotensin-converting enzyme inhibitors as referent group



Appendix F: Baseline characteristics for patients prescribed NSAIDs[1] or ACE-inhibitors[1] with and without thrombotic microangiopathy (cases and controls, respectively)

	Controls (n=336)	**Cases (n=84)**	**P-value[4]**
Demographics			
Age, no. (%)			
Median (IQR)	74 (68-81)	74 (67-82)	
Mean ± SD	73 ± 10.4	73 ± 11.13	0.22
≤ 17	21 (6.3%)[5]	0	0.41
18 - 44		0	
35 - 44		≤5	
16 - 54		≤5	
55 - 64	20 (6%)	7 (8.3%)	
65 - 74	140 (41.7%)	37 (44%)	
75 - 84	112 (33.3%)	22 (26.2%)	
≥ 85	43 (12.8%)	13 (15.5%)	
Female, no. (%)	200 (59.5%)	50 (59.5%)	1.0
Rural location, no. (%)[2]	56 (16.7%)	14 (16.7%)	1.0
Socioeconomic status, no. (%)[3]			
Quintile 1	72 (21.4%)	18 (21.4%)	1.0
Quintile 2	56 (16.7%)	14 (16.7%)	1.0

Quintile 3	56 (16.7%)	14 (16.7%)	1.0
Quintile 4	72 (21.4%)	18 (21.4%)	1.0
Quintile 5	80 (23.8%)	20 (23.8%)	1.0
Primary care physician visits, no. (%)			
Median (IQR)	8 (5-13)	12 (7-19)	
Mean ± SD	11 ± 11.26	16 ± 14.23	<0.01
0	16 (4.8%)	≤5	
1 - 2	34 (10.1%)	8 (9.5%)	<0.01
3 - 4	54 (16.1%)	≤5	
5 - 6	54 (16.1%)	6 (7.1%)	
7 - 8	37 (11%)	9 (10.7%)	
9 - 10	38 (11.3%)	9 (10.7%)	<0.01
≥ 11	103 (30.7%)	47 (56%)	
Comorbidities, no. (%)			
John Hopkins ADG Score, no. (%)			
Median (IQR)	11 (8-14)	13.5 (11-16)	
Mean ± SD	11 ± 4.19	13 ± 3.68	<0.01
≤ 9	122 (36.3%)	12 (14.3%)	
10 - 12	92 (27.4%)	23 (27.4%)	
13 - 15	62 (18.5%)	22 (26.2%)	<0.01
≥ 16	60 (17.9%)	27 (32.1%)	
Malignant hypertension	≤5	≤5	-
Systemic lupus erythematosus	≤5	≤5	-

Cancer	32 (9.5%)	12 (14.3%)	<0.01
Renal transplant	≤5	≤5	-
Osteoarthritis	11 (3.3%)	≤5	<0.01
Rheumatoid arthritis	18 (5.4%)	9 (10.7%)	<0.01
HIV[1]	≤5	≤5	1.0
Sepsis	Suppressed[5]	≤5	1.0
Medications, no. (%)			
Quinine	≤5	≤5	-
Quetiapine	≤5	≤5	-
Tacrolimus	≤5	≤5	-
Sirolimus	≤5	≤5	-
Cyclosporine	≤5	≤5	-
Clopidogrel	≤5	≤5	-
Ticlopidine	≤5	≤5	-

[1]no.: Number, IQR: interquartile range, SD: Standardized difference, NSAIDs: non-steroidal anti-inflammatory drugs, ACE: angiotensin-converting enzyme, HIV: Human immunodeficiency virus
[2]Rural residence is defined as population < 10,000
[3]Quntiles are ranked from lowest to highest (i.e. Quintile 1 = lowest, Quintile 5 = highest)
[4]P-values are calculated using generalized estimating equations
[5]cells are combined or suppressed to avoid reporting numbers ≤5

Appendix G: The association between NSAID use and thrombotic microangiopathy, with ACE inhibitors as a reference group. Odds ratios derived from a conditional logistic regression model.

	Cases of TMA n=84	**Controls n=336**	**Odds Ratio (95% confidence interval)**	
			Unadjusted	**Adjusted[1]**
ACE inhibitors[2]	66 (79%)	253 (75%)	1.0 (referent)	1.0 (referent)
NSAIDs[2]	18 (21%)	83 (25%)	0.82 (0.45-1.49)	0.72 (0.38-1.37)

1Adjusted analysis included the following variables: cancer, osteoarthritis, rheumatoid arthritis, John Hopkin's ADG score and primary care physician visits

[2]NSAIDs: Non-steroidal anti-inflammatory drugs, ACE: angiotensin-converting enzyme

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- Thejeel, B, Garg, AX, Clark, WF, **Liu, AR**, Iansavichus, AV, Hildebrand, AM. Long-Term Outcomes of Thrombotic Microangiopathy Treated with Plasma Exchange: A Systematic Review. *American Journal of Hematology*. **Published**

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- Ahmed A. Al-Jaishi, Matthew J. Oliver, **Aiden R. Liu**, Amit X. Garg, Joyce C. Zhang, Sonia M. Thomas, Louise M. Moist. Complication rates of the arteriovenous fistula: a systematic review. (Study Protocol) PROSPERO 2014:CRD42014010444 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014010444 **Published**

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- Kidney Week 2015, San Diego, California, Long-Term Outcomes of Thrombotic Microangiopathy Treated with Plasma Exchange: A Systematic Review. **Accepted Abstract**
- 11th Annual Kidney Clinical Research Day, Victoria Hospital, London Health Sciences Centre, Increased Risk of Adverse Renal Outcome Following Polyethylene Glycol Bowel Preparation Compared to Sodium Picosulfate, **Oral Presentation**
- Canadian Society of Epidemiology and Biostatistics Conference, Hilton Meadowvale Missisauga, Risk of adverse renal events with polyethylene glycol compared to picosalax, **Poster Presentation**

2014

- 10th Annual Kidney Clinical Research Day, Victoria Hospital, London Health Sciences Centre, Reporting of propensity score method: a methodological review of the top five Nephrology journals, **Oral Presentation**
- Ontario Biology Day 2014, University of Toronto Mississauga Campus, Phenotypic response to inhibition of meridional growth in adult *Arbacia punctulata,* **Poster Presentation**