A Retrospective Chart Review to Assess Potentially Inappropriate Prescriptions Related to Oral NSAID, Anticoagulant, and Antiplatelet use in Two Family Medicine Teaching Clinics

by

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Abstract

Introduction: Potentially inappropriate prescriptions (PIPs) have been defined as the prescribing of medications where the risk of adverse outcomes outweighs the benefit to patients. Some medications pose a greater risk than others. Nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelets, and anticoagulants are among the top offenders for preventable drug-related ER visits, hospitalizations and deaths. Although over the counter (OTC) NSAIDs and ASA also contribute to this preventable risk, it is unclear how well these medications are documented in primary care clinics.

Methods: A literature review was conducted to determine PIPs associated with an increased risk of bleeding associated with NSAIDs, antiplatelets, and anticoagulants. Data were collected through a retrospective electronic and paper chart review for all patients prescribed a target medication in two family medicine clinics in Winnipeg, Manitoba from June 2012 to June 2013.

Results: The presence of at least one PIP was identified in 198 of 567 patients (35%). The most common PIP was the use of an oral NSAID with one or more gastrointestinal bleed risk factor without adequate gastro-protection. ASA was taken by 117 patients (20.6%) while OTC NSAIDs were taken by 36 (6.3%). OTC NSAIDs were never documented within the "medication" section of the electronic record, whereas ASA was only documented in 38 (32.5%) cases. One-hundred and eighteen out of 148 patients (79.7%) taking either OTC NSAIDs or ASA were identified as having at least one PIP. During the 12 month study period, only 34 (6%) patients received a full medication review performed by a pharmacist. Fewer patients who received a medication review had

an inappropriate prescription (27% with review, 35% without) but the difference was not statistically significant (p=0.355).

Conclusion: With over one-third of patients using NSAIDs, antiplatelets, and anticoagulants potentially inappropriately, a greater focus on improving prescribing practices with these higher-risk medications is warranted. While the contribution of non-prescription ASA and NSAIDs is known to increase one's risk of bleeding, the documentation of these products within the appropriate section in the electronic record is lacking. The documentation of these commonly taken medications is essential to provide the prescriber with all the required information when making therapeutic decisions.

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ACS – acute coronary syndrome

ADE – adverse drug event

ADR – adverse drug reaction

ALT – alanine aminotransferase

AST – aspartate aminotransferase

CABG – coronary artery bypass graft

COX-2 – cyclooxygenase-2 inhibitor

CrCl – creatinine clearance

DRM – drug related morbidity

DRP – drug related problem

EMR – electronic medical record

FMC – family medical centre

GI – gastrointestinal

H2RA – histamine 2 receptor antagonists

KMC – Kildonan Medical Centre

MI – myocardial infarction

NSAID – nonsteroidal anti-inflammatory drugs

NOAC – Novel Oral Anticoagulant

pDRM – preventable drug related morbidity

PIP – potentially inappropriate prescription

PPI – proton pump inhibitor

SCr – serum creatinine

SNRI – selective norepinephrine re-uptake inhibitor

SSRI – selective serotonin re-uptake inhibitor

Introduction

Medications have contributed to significant advances in healthcare. For example, penicillin has saved tens of millions of lives since it was introduced during World War II.[1] However, the use of medication is not without risk. The withdrawal of the cyclooxygenase 2 (COX-2) inhibitor Vioxx® (rofecoxib) from the market due to an increased risk of myocardial infarction and death reminds us of the serious risk medications can pose.[2]

Medication related problems now represent a considerable cause for emergency room visits and hospitalizations.[3,4] With the majority of these events deemed preventable,[5–7] primary care providers have the opportunity to identify these situations before they cause harm to the patient.

The underlying theme of this thesis is prescribing appropriateness. Both papers (Chapters 3 & 4) attempt to quantify the prescribing appropriateness of oral nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelets, and anticoagulants in general practice clinics, and to identify factors associated with the presence of these potentially inappropriate prescriptions (PIPs). The first paper (Chapter 3) reviews all patients prescribed an NSAID, antiplatelet, or an anticoagulant for the appropriateness of the prescriptions on 13 specified PIPs. The focus of the second paper (Chapter 4) is the role that over-the-counter (OTC) NSAIDs and ASA have on the same 13 PIPs. These papers are largely descriptive to better understand the prescribing habits of these higher-risk medications in family medicine.

Background

Terminology

Many terms have been used throughout the literature to define unwanted or unintended reactions from medications. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use defines an Adverse Drug Reaction (ADR) as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function"[8] (Figure 1). Some refer to ADRs as side effects, although this term is not recommended as it tends to minimize the injury caused by drugs.[9] An Adverse Drug Event (ADE) can be viewed as a broader term to describe injuries caused by drug use that encompass ADRs and harm resulting from medication errors.[8] Not all ADEs are caused by medication errors. For example, the case of a patient developing a rash due to an unknown allergy would not be classified as a medication error.

The term drug-related problem (DRP) is a comprehensive term that is often used in the clinical pharmacy literature. In 1990, Hepler and Strand initially defined a DRP as "an event or circumstance involving drug treatment that actually or potentially interferes with the patient's experiencing an optimum outcome of medical care."[10] By using this term, all drug related issues can be classified into one of eight categories: ADR, drug interaction, improper drug selection, untreated indication, sub therapeutic dosage, supratheraputic dosage, noncompliance and drug use without indication.[11,12]

Drug-related morbidity (DRM) occurs when a therapeutic agent fails to produce the intended therapeutic outcome, either due to treatment failure or the production of a new medical problem.[10] Consequences include physician visits, emergency room visits, hospitalizations, disability and death. Some DRM is the result of patient idiosyncrasy and is therefore unpredictable. However, a significant number may be preventable and are often the result of an unresolved DRP. In fact, at least half of the DRM that occurs may be preventable (pDRM).[5–7] Identifying the pattern of use for medications associated with pDRM can provide indicators often referred to as potentially inappropriate prescriptions (PIPs). They are often drug or disease-oriented and generally do not take into account patient preferences or the burden of comorbid disease. PIPs are intended to be used as a tool to help practitioners assess whether the benefits of a prescription outweigh the risks.

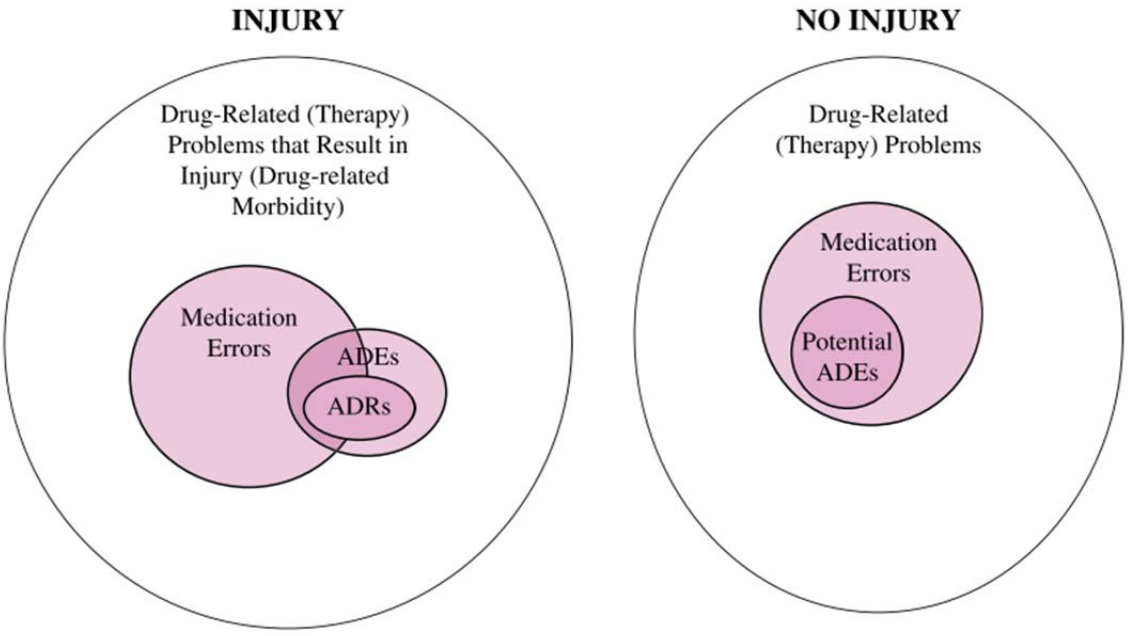

Figure 1. Visual representation of the various terms for medication related problems and their association with one another.[13] Reprinted with permission from Elsevier.

Medications Associated with Preventable Drug Related Morbidity and Mortality

Although all medications have the potential to cause harm, some medications lead to adverse events more often. Two systematic reviews provided a starting point for the identification of these higher risk medications.[14,15] The first systematic review by Thomsen et al. examined preventable ADEs (pADE) in ambulatory care.[14] The authors identified three drug groups as being responsible for almost 90% of pADEs in the ambulatory care setting: cardiovascular (e.g. antihypertensives and anticoagulants), analgesics (e.g. NSAIDs and opioids) and hypoglycemic agents (e.g. insulin and sulfonylureas). They go on to report that cardiovascular drugs are most frequently associated with pADEs and pADEs requiring hospitalization; an outcome that may be more relevant to focus on due to the seriousness of the event. Gastrointestinal toxicity resulting from a failure to prescribe prophylactic agents with NSAIDs or antiplatelet drugs was the most frequently identified adverse outcome in studies of pADEs requiring hospitalization. It was also reported that a lack of monitoring was a frequent problem leading to over/under-diuresis, hypo/hyper-glycemia, and an increased risk of bleeding. However, the authors did not provide detailed information on the frequencies of the medications implicated.

The other systematic review by Howard et al. concentrated only on medications that cause preventable admissions to the hospital.[15] Howard et al. included 9 of the 15 studies in the systematic review by Thomsen et al. The top four medication classes reported were antiplatelets (16%), diuretics (16%), NSAIDs (11%), and anticoagulants (8%). Rather than providing the most commonly reported adverse outcome, the authors described the underlying cause of the hospitalization. They were classified as either a prescribing problem, monitoring problem, or a patient adherence problem. The frequencies of these problems were fairly evenly distributed with

adherence reported as the primary cause in 33.3% of the cases, prescribing problems in 30.6%, and monitoring problems in 22.2%.

A task force was created in the Netherlands in 2009 by the Dutch Ministry of Health, Welfare and Sport to reduce the number of hospital admissions related to medications following a number of publications identifying this potentially preventable problem.[16] After a meta-analysis of two large observational trials, one of which was a retrospective cohort study and the other trial was a larger, prospective case-control study, which included over 68 000 patients in total, the task force identified very similar medications as other reviews:[14,15] vitamin K antagonists, platelet aggregation inhibitors and NSAIDs. These were acknowledged as causing the most common potentially preventable ADE, bleeding. As such, the task force provided 34 drug specific recommendations on harm reduction strategies to minimize the risk associated with these medications, the first 15 of which relate to the reduction of gastrointestinal and other bleeding. In summary, these recommendations include: regular international normalized ratio (INR) monitoring in patients prescribed warfarin including more frequent monitoring in select patients, avoidance of NSAIDs in patients at increased risk of GI toxicity or providing adequate prophylactic therapy if NSAID therapy is to be used in these patients, and adequate communication between all health care professionals involved in the care of the patient.

Based on 179 855 cases of serious, disabling, and fatal adverse drug events reported to the FDA in 2011, anticoagulants, mostly warfarin and dabigatran, were considered "the highest risk of all drug treatments," according to an ISMP report.[17] Despite being on the market for many years and having a well-known side-effect profile, adverse drug events associated with warfarin have been among the most commonly reported events to the FDA for decades.[18] The report goes on to say that dabigatran was found to have "surpassed all other regularly monitored drugs in

reports of hemorrhage, acute renal failure, and stroke."[17] This report, however, is based only on those events reported to the FDA which is voluntary and sporadic.

A six-month prospective observational study, the largest of its kind, evaluated almost 19 000 adult patients admitted to either of two English hospitals for the presence of an ADR.[19] NSAIDs, antiplatelets and anticoagulants made up 42.5% of all of the reported ADRs. It was also observed that these medications accounted for 22 of the 28 deaths during the study period indicating these medications may also be leading the way in medication related fatalities.

Analysis of death records is another way to identify high-risk medications. Unfortunately, preventability is not often assessed. One study that did assess preventability in a random selection of 1574 deceased subjects in Sweden found that 7 of the 49 fatal ADRs identified were definitely or possibly preventable; four were due to NSAIDs, two to ACE/ARBs and one to warfarin.[20] The underlying mechanism leading to the fatality in those treated with NSAIDs were GI hemorrhage in three of the four cases and renal function abnormality leading to pulmonary edema in the last case. The cause of death in the patient using warfarin was a hemorrhage leading to heart failure. Another study reviewed death certificate data from the U.S. vital statistics.[21] Within the "adverse events in therapeutic use of medications" ICD-10 code, drug-related mortality from adverse effects (as opposed to intentional overdose or poisonings) saw anticoagulants rank as the number one class of medications to cause death. An increasing trend of fatalities from 1999 to 2003 was also observed for anticoagulants within this study. The same author then analyzed the U.S. National Hospital Ambulatory Care Survey for the same years and estimated that 484,407±45,634 annual visits to US emergency departments were due to bleeding associated with the use of warfarin, which is among the drugs with the most visits.[18]

Although emergency department visits may not be as serious of an outcome as hospitalizations, it does still indicate harm to the patient and an increase in health care utilization. A literature review investigating the incidence of patients presenting to the emergency department due to a DRP found a range of 0.86-28% of visits were considered drug related.[4] Of these drug-related visits, 8.6-24.2% were deemed serious enough to require hospitalization. It is important to note that approximately 70% of these visits were considered preventable. The author reports that NSAIDs, anticonvulsants, diabetes medications, antibiotics, respiratory agents, hormones, central nervous system agents, and cardiovascular drugs were most commonly implicated as the reason for the visit.

Lastly, a prospective chart review in the Netherlands assessed preventable and non-preventable ADEs in hospitalized patients.[22] The authors reported that patients using medications affecting the blood and blood forming organs (ATC code B) had an odds ratio for experiencing a pADE of 7.06 (95% CI; 2.69-18.54), larger than any other drug class. Drugs affecting the nervous system (ATC code N) followed with an odds ratio of 4.55. Although these medications were not the sole cause of pADEs, they were major contributors.

Although NSAIDs, antiplatelets, and anticoagulants do not have the same mechanism of action, the most common adverse event associated with all of them is bleeding. Since these medications are consistently among the top offenders for leading to pADEs, and that event is most often bleeding, this led us to look at these medications collectively. Additionally, the grouping of these medications is commonly observed in clinical practice.

To summarize, gastrointestinal and other bleeding is reported as the most frequent potentially preventable ADE.[16] The medication classes implicated for this pADE are NSAIDs, antiplatelets and anticoagulants. Together, these medications account for over 35% of

preventable drug-related hospitalizations, more than any other group of drugs.[15] Furthermore, these three classes of medications are consistently reported among the most likely to result in adverse consequences leading to emergency department visits, hospitalizations and deaths.[4,14–16,23–31]

Medications have inherent risks associated with their use. However, this risk can increase or decrease based on a number of factors. Now that a group of high-risk medications has been identified (NSAIDs, antiplatelets, and anticoagulants), the following section focuses on prescribing practices that place patients at an increased risk of an ADE, namely bleeding.

Potentially Inappropriate Prescriptions

Various tools can be used to quantify the inappropriateness of prescribing. A systematic review on these tools concluded that many have been produced throughout the world and that most are based either completely or partially on the "Beers Criteria."[32] By using these tools prescriptions can be classified as inappropriate by consulting a published list of medications reported as being associated with negative outcomes in certain situations. The lists are usually developed by experts who reach consensus on each situation. The resulting criteria for published potentially inappropriate prescriptions (PIPs) are supported by varying degrees of evidence. These tools have been appealing to some because they require very little or no clinical judgment on the part of the one applying the tool and can be applied to large administrative claims databases fairly quickly. Unfortunately, patient preference is not considered when using this approach. Detailed clinical data are generally absent from claims databases which remove the possibility of making individualized judgements about appropriateness.

The Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) is another tool used to identify PIPs in the elderly.[33] STOPP provides more context than the Beers list by describing clinical situations where specific drugs are, or are not, appropriate. Of the 65 explicit criteria for drugs that should be avoided, 15 are related to the use of NSAIDs, antiplatelets, or oral anticoagulants.

The use of an NSAID in patients who have one or more bleeding risk factor is most widely recognized as inappropriate.[34–39] The risk factors vary slightly, but generally include: advancing age (65 years and older), concomitant use of an anticoagulant, steroid, ASA, or a selective serotonin reuptake inhibitor, a history of peptic ulcer disease, and the presence of H. pylori infection.[34] It has been estimated that most of these risk factors at least double a patient's risk of an upper gastrointestinal event, the risks are additive, and that appropriate gastro-protective therapy can reduce the risk by approximately one-half.[40] While patient preference can play a major role on the selection of medication in clinical practice, this can be difficult to assess in this type of research setting. Therefore, we chose to follow the current standard of practice published by the American College of Gastroenterology which recommended the use of a gastro-protective agent in patients who have one or more bleeding risk factor and are using NSAID therapy.[35]

When choosing PIPs to focus our research on, we tried to draw as many as we could from previously published, validated tools. Many of our PIPs were taken from the Beers and STOPP criteria; however, we did not want to focus solely on elderly patients. Therefore, we augmented our list to include PIPs from other publications as well as evidence based guidelines (Table 1). Before adding non-validated PIPs, we wished to ensure there was a solid literature base. After reviewing the literature, we included three PIPs related to dual therapy (ASA plus an antiplatelet

or anticoagulant) or triple therapy (ASA plus an antiplatelet and an anticoagulant) that have not been previously included in published tools. Not all prescriptions for these combinations of drugs were considered inappropriate. Except for triple therapy, all of the following PIPs have a number of situations that exclude them from being considered a PIP.

The duration of dual antiplatelet therapy following stent placement or acute coronary syndrome (ACS) is an area of active research. Current evidence suggests that a patient who did not experience a stent thrombosis or another coronary event during the first 12 months following stent placement can safely discontinue one antiplatelet while continuing on low-dose ASA.[41,42] The same recommendation is made for those patients who experienced an ACS with or without stent placement. Most guidelines generally agree upon this; however, it has been observed in our practice that many patients remain on this combination far longer. Although the bleeding risk of this combination is relatively low, it is an unnecessary risk because of the little to no benefit with the combination past 12 months. Therefore, we identified the use of ASA and an antiplatelet as a PIP except: post-ACS with or without a percutaneous intervention (with or without stent placement) for up to 12 months, CABG for a non-ST segment elevation ACS for up to 12 months, or a diagnosis of atrial fibrillation with evidence of oral anticoagulant failure.

According to the 2012 American College of Chest Physicians' (CHEST) guidelines, the combination of an anticoagulant with one or more antiplatelet is rarely recommended.[43] With the evidence available at the time of writing the guidelines, the CHEST committee attempted to weigh the risk of bleeding with the risk of a thromboembolic event with the use of these medications in various situations. They concluded that the use of triple therapy (warfarin, ASA, and clopidogrel) should only be used in high thromboembolic risk patients (large anterior MI, heart failure, or atrial fibrillation) whom require a stent and should be treated for as short a

duration as possible to minimize bleeding risk. However, since then, the What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing (WOEST) trial was published in 2013, which is the only prospective trial looking at triple therapy.[44] In this trial, subjects who were randomized to the concomitant use of warfarin and clopidogrel had an annual risk of a fatal or non-fatal bleed of 19.4%.[44] This was compared to the use of triple therapy with warfarin, ASA and clopidogrel. This latter group reported an annual risk of a fatal or non-fatal bleed as high as 44.4% with no significant difference in cardiac events. Only intracranial hemorrhage rates were the same between the groups, all other outcomes including mortality favoured dual therapy. Despite the fact that this was only one, open label trial, we chose to identify all prescriptions for triple therapy as potentially inappropriate due to the apparent lack of benefit while significantly increasing one's risk of bleeding. Even if there are some situations in which this combination could be justified, it is still important to frequently identify and review these patients to ensure they are on this therapy for the shortest duration possible.

Furthermore, the 2012 CHEST guidelines only suggest the combination of warfarin and ASA in the following situations: patients with atrial fibrillation who experience an acute coronary event without stent placement, post MI in patients considered high thromboembolic risk, those with mechanical heart valves and at a low bleeding risk, and patients who experience recurrent embolism who have mitral valve stenosis or regurgitation.[43] These situations were felt to represent the patients who could benefit the most from this therapy while reducing unacceptable bleeding risks. As such, the use of warfarin and ASA was considered a PIP except in the aforementioned situations.

This review suggests that together, NSAIDs, antiplatelets, and anticoagulants make up a group of medications that lead to the most DRM when used inappropriately. Furthermore, the inappropriate use of these medications appears to be preventable. The potential costs associated with the inappropriate use of these medications, both financially and in lives, are considerable. Therefore, this research was performed to evaluate the extent of this problem within two Manitoba family practices.

Methods

Study Design

This study was designed as a cross-sectional electronic record audit to identify patients prescribed medications with a known risk of bleeding and evaluate the proportion of potentially inappropriate prescriptions for oral NSAIDs, anticoagulants and antiplatelets. This was performed using a convenience sample of two family medicine teaching clinics within Winnipeg, Manitoba.

Identification of the target population required a computer search performed within a research database which mirrors the local electronic medical record (EMR). An electronic query was run in the research database at each clinic to generate a list of patients who have received a prescription for an oral NSAID, antiplatelet agent or anticoagulant within a 12 month period (June 18th 2012-June 18th 2013). It was determined that the previous 12 months was sufficient to capture all the patients who were taking any of the index medications because patients do not receive a prescription for more than a year at a time. An initial screen of the patients included in the query output was required to ensure they are "active" patients of the clinic and received a prescription for an oral NSAID, antiplatelet and/or anticoagulant (see inclusion criteria below). Patient records were reviewed to identify the presence of the pre-determined PIPs. Data were obtained via the EMR and/or paper chart at each site. A unique identification number was assigned to each patient record to ensure confidentiality and allow the study pharmacist to return to the record, if applicable, to verify ambiguous information. The master list contained patient initials and medical record number specific to the clinic with the corresponding unique patient

identifier and was saved on a single-person access hard drive with password protection on both the drive and the digital file. All data were analyzed in an anonymous manner and was presented in aggregate. A second pharmacist reviewed the first 16 of the previously reviewed records as a quality assurance measure and to standardize the initial methodology. The detailed chart audit procedure manual can be located in Appendix A.

Inclusion Criteria

- All patients defined as "active" by the EMR as of June 18th 2013 at KMC and FMC. Active patients were defined as those currently under the care of a clinic physician.
- "Active" prescription for one or more of the following oral medications recorded in the EMR during a 12 month period (June 18th 2012-June 18th 2013). Target medications were identified using generic name and the WHO Anatomic Therapeutic Chemical (ATC) classification system.
    - NSAIDs: naproxen (M01AE02), diclofenac (M01AB05), diflunisal (N02BA11), etodolac (M01AB08), floctafenine (N02BG04), flurbiprofen (M01AE09), indomethacin (M01AB01), ketorolac (M01AB15), ketoprofen (M01AE03), piroxicam (M01AC01), meloxicam (M01AC06), mefenamic acid (M01AG01), nabumetone (M01AX01), sulindac (M01AB02), tenoxicam (M01AC02), tiaprofenic acid (M01AE11), celecoxib (M01AH01), naproxen and esomeprazole (M01AE52), diclofenac combinations (M01AB55).
    - Anticoagulants: warfarin (B01AA03), dabigatran (B01AE07), rivaroxaban (B01AF01), apixaban (B01AF02).
    - Antiplatelets: clopidogrel (B01AC04), ticagrelor (B01AC24), dipyridamole (B01AC07), prasugrel (B01AC22), ticlopidine (B01AC05).

- For comparison, higher level ATC codes for non-steroidal anti-inflammatories (M01A and N02B), antiplatelets and oral anticoagulants (B01A) were also searched.

Exclusion Criteria

- Patients on the palliative care program. Patients receiving palliative care are generally treated with comfort care as the primary goal. Although a bleed is still an important adverse outcome to prevent in these patients, they may be more willing to accept higher risks of adverse events as long as it increases their comfort.
- Patients who received an index medication for less than or equal to three days

Patient Record Identification

The electronic query set up within the EMR was limited to a 12 month period (June 18th, 2012-June 18th, 2013) and included the target prescriptions classified as "active." The study pharmacist looked for evidence that the patient was still taking the medication by reviewing the encounter notes, the most recent medication review and/or periodic health exam and in the "documents" section of the EMR. At times, it was still ambiguous whether the patient was still taking the medication or not. Therefore, some clinical judgment was required. If there was no mention of the medication being discontinued, it was assumed that the patient was currently taking the medication. For example, a patient was documented as taking a medication if they received a prescription every three months. On the other hand, a patient was no longer considered to be taking a medication if it appeared they had run out of their medication and did not receive a refill.

Preliminary review of data records revealed that documentation of OTC medications in the EMR was not done in a consistent manner. A broader search of the EMR was needed to uncover likely OTC medication use. ASA may be more frequently documented in the EMR but not always in a consistently coded manner. A patient was considered as taking ASA or OTC NSAID by either finding the medication listed under the "external medications" section, as an actual prescription, or documented within the patient's electronic record (e.g. in the patient encounter notes or documents section). All patient record notes from the last 12 months were reviewed for evidence of ASA and/or OTC NSAID use. If it was unclear or not documented as to the current status of the ASA/NSAID use, it was recorded as such.

Data Collection

A structured paper data collection form (Appendix B) was used to guide the abstraction of the following information. Medical conditions were recorded from the "Problem list" and "Medical Surgical History" sections of the electronic record and the most recent encounter for a general physical/chronic disease management.

- Patient characteristics: Age, gender, height, weight, alcohol consumption, number of prescribed medications, total number and description of specific medical conditions [hypertension, diabetes, heart failure, history of myocardial infarction (MI) and description of location to determine risk, coronary artery bypass graft, deep vein thrombosis, pulmonary embolism, transient ischemic attack, stroke (ischemic or hemorrhagic), heart valve disease/prosthetic valve (and history of embolism with heart valve disease), atrial fibrillation, renal disease (and stage), cancer and type of intervention, history of gastric or duodenal ulcer and a history of a bleed (requiring

hospitalization, hemoglobin drop of >20g/L or requiring transfusion) and date of events], limited medication list (PPIs, H2RAs, misoprostol, corticosteroids, SSRIs and SNRIs), the number of visits to the clinic within the last 12 months and whether or not the patient consulted with a pharmacist within the last year. The specific medications that were collected are those that help determine a PIP. For example, corticosteroids, SSRIs, and SNRIs increase one's bleeding risk while PPIs, H2RAs, and misoprostol reduce the bleeding risk.

- Laboratory values: Most recent SCr and estimated CrCl [(140-age)*(88.4)/SCr multiplied by 0.85 for females], platelet count, date and value of INRs for previous 12 months, abnormal renal or liver function (defined as renal transplantation, dialysis, SCr >200umol/L, ALT/AST >3 times upper limit of normal, or bilirubin >2 times upper limit of normal) and the most recent blood pressure reading.
- Calculated $CHADS_2$ and HAS-BLED score. The $CHADS_2$ is a tool used to estimate the annual risk of systemic embolism in patients with atrial fibrillation. The HAS-BLED score is a clinical tool used to estimate the annual risk of major bleeding for patients treated with warfarin.
- Prescription details for prescription oral NSAIDs, ASA, antiplatelet agent and/or anticoagulant: Generic name, indication, dose, frequency and duration.
- Generic name, dose, frequency and duration for all non-prescription NSAIDs

Potentially Inappropriate Prescription Definitions

The following prescriptions were defined as potentially inappropriate if located within a patient's record. This is not to say that all the identified prescriptions were unacceptable, just that they represented a higher risk situation to the patient over baseline and that they should be

reviewed to ensure appropriateness. All of the following PIPs are related to an increase in bleeding risk.

1. Use of ASA, antiplatelet, and an oral anticoagulant.
2. Use of an oral anticoagulant and ASA except: patients with atrial fibrillation who experience an acute coronary event without stent placement, post MI in patients considered high thromboembolic risk, those with mechanical heart valves and at a low bleeding risk, and patients who experience recurrent embolism who have mitral valve stenosis or regurgitation.
3. Use of an oral anticoagulant and ASA or an antiplatelet without adequate gastro-protection. Adequate GI protection was defined as a PPI taken regularly once or twice daily or misoprostol taken four times a day, according to the best available evidence.
4. Use of ASA and an antiplatelet except: post-ACS with or without a percutaneous intervention (with or without stent placement) for up to 12 months, CABG for a non-ST segment elevation ACS for up to 12 months, or a diagnosis of atrial fibrillation with evidence of oral anticoagulant failure.
5. Use of ASA and an antiplatelet in a patient aged 65 or older without adequate gastro-protection.
6. Use of warfarin without an INR in the past 30 days unless the INR was stable (did not require a dosage change within the last three months), in which case an INR was required within the last three months.
7. Use of an oral anticoagulant for more than three months after a first, provoked proximal deep vein thrombosis or pulmonary embolus.
8. Use of an oral anticoagulant and an oral NSAID in a patient aged 65 or older.

9. Use of oral NSAID with one or more additional GI risk factor without adequate gastro-protection. Risk factors were defined according to the American College of Gastroenterology's 2009 guideline: history of a GI ulcer, age of 65 years and older, high dose NSAID, or the concurrent use of ASA, corticosteroids, or anticoagulants.
10. Use of two or more oral NSAIDs.
11. Use of indomethacin or ketorolac in a patient aged 65 or older.
12. Use of an oral NSAID at doses above maximum recommended.
13. Use of a COX-2 and ASA or an oral anticoagulant in a patient with one or more additional GI risk factor without adequate gastro-protection.

The following two chapters report and discuss the results for this thesis in the format of a published manuscript. This was primarily an exploratory descriptive study; however we hypothesized that the rate of PIPs would be low relative to previous literature reports because the clinics in our study are multi-disciplinary, teaching clinics primarily staffed with health care practitioners who have advanced training. Chapter three, Assessing Prescribing of NSAIDs, Antiplatelets and Anticoagulants in Family Medicine Using Chart Review, was the original study. Our objectives for this study were to assess the prescribing appropriateness of oral NSAIDs, antiplatelets and anticoagulants in general practice clinics and to identify factors associated with the presence of these potentially inappropriate prescriptions. Using the methodology described above, all patient records included in the study were reviewed to identify any of the 13 PIPs.

The fourth chapter evolved from our consideration of the original study. OTC products appeared to merit further consideration. Once again we hypothesized that the clinics under study would have less OTC related inappropriate prescriptions than had previously been reported in the literature. Our objective for this new sub-study was to assess the contribution of OTC NSAIDs and ASA to the prescribing appropriateness of prescription oral NSAIDs, antiplatelets, and anticoagulants. This was accomplished by taking the original study population and excluding patients that were unlikely to be taking OTC NSAIDs or ASA. Although the use of these OTC products contributes to a patient's overall bleed risk, it was expected that the documentation of the products would be incomplete. Given the confines of our retrospective design, this study represented the prescribing appropriateness of the patients in whom these OTC products were documented.

Assessing Prescribing of NSAIDs, Antiplatelets and Anticoagulants in Family Medicine Using Chart Review

Abstract:

Introduction: Drug-related problems have been identified as a major contributor to ER visits, hospitalizations, and death. The most commonly implicated medications are NSAIDs, antiplatelets, and anticoagulants. Considering a significant proportion of these harms are preventable, indicators to identify risky prescribing before they lead to harm have been developed. The objective of this research is to examine the prevalence and patterns of potentially inappropriate prescriptions (PIPs) in a primary care population who are using high-risk medications.

Methods: A retrospective electronic/paper chart review was conducted within two multi-disciplinary family medicine teaching clinics to evaluate the prevalence of 13 evidence-based high-risk prescriptions. Patients were included if they were prescribed an NSAID, antiplatelet, or an anticoagulant within the 12 month period between June 2012 and June 2013.

Results: Of the 567 patients included in the review, 198 (35%) patients had received at least 1 PIP in the past year. The most common PIP was the use of an oral NSAID with one or more GI risk factor without adequate gastro-protection. Only 34 (6%) of these patients received a full medication review performed by a pharmacist. Although not statistically significant, patients who received a medication review had fewer inappropriate prescriptions (27% with review, 35% without).

Conclusion: Over one-third of the patients who were using high-risk medications were using them potentially inappropriately. Although pharmacists have been shown to reduce the amount of inappropriate prescribing, very few patients using these medications were referred to the pharmacist for a full medication review. These data suggest that there is opportunity for the

identification and assessment of these patients when prescribing or dispensing these high-risk medications.

Introduction:

Drug-related morbidity occurs when a therapeutic agent fails to produce the intended therapeutic outcome, either due to treatment failure or the production of a new medical problem.[1] Some of this morbidity is a result of patient idiosyncrasy and is therefore unpredictable. However, a significant proportion of the events may be preventable. In fact, studies suggest that at least half of the drug-related morbidity events are preventable.[2–4]

An estimation of the annual economic impact of morbidity and mortality resulting from the use of medications in ambulatory care exceeded $177 billion in the U.S.[5] Thus, improvements in the management of medications in primary care is likely to yield significant reductions in health care expenditure. Targeting the inappropriate use of medications may be one way to achieve this. Previous work from the PINCER[6] authors, the STOPP[7] and Beers[8] criteria, as well as clinical guidelines[9–11] provide evidence based indicators for the appropriate use of medications. To tackle this problem and attain the greatest return on time investment, one could consider focusing on those medications that cause the most harm.

Many publications have sought to identify medications that are most commonly associated with adverse events. NSAIDs, antiplatelets, and anticoagulants are consistently reported among the most common drugs that lead to medication related ER visits, hospitalizations, and death. Cumulatively, these medications cause the most preventable harm with bleeding being the most frequently reported event.[12–16]

The provision of pharmaceutical care is associated with reductions in inappropriate prescribing.[17,18] Pharmacists are trained to provide optimal pharmaceutical care which Cipolle and Strand define as "taking responsibility for a patient's drug-related needs and is held accountable for this commitment."[19] A recent Cochrane review reported that pharmacist interventions in community or ambulatory settings not only resulted in improvements in prescribing patterns, but also improved most clinical outcomes and patient quality of life in at least 3 subdomains.[18] The provision of pharmaceutical care in primary care has the potential to improve the quality and safety of health care to a substantial number of patients.

Measuring and monitoring the quality of health care services provides valuable information to assist in the allocation of quality improvement resources. Our objectives were to assess the prescribing appropriateness of oral NSAIDs, antiplatelets and anticoagulants in general practice clinics and to identify factors associated with the presence of these potentially inappropriate prescriptions. We hypothesized that the rate of PIPs would be low relative to previous literature reports because the clinics in our study are multi-disciplinary, teaching clinics.

Methods:

A retrospective chart review of primary care patients was conducted spanning June 2012 until June 2013. All patients prescribed an oral NSAID, antiplatelet or an anticoagulant during this 12 month period were included. The Anatomical Therapeutic Chemical (ATC) classification system developed by the World Health Organization (WHO)[20] was used to develop queries within the electronic medical record (EMR) to identify patients using any of these medications. Patients were excluded if they were receiving palliative care or took the target medication for ≤3 days (Figure 1). This study was performed within two multi-disciplinary family medicine teaching

clinics in Winnipeg, Canada. The University of Manitoba Health Research Ethics Board, as well as the local review committees, approved this study.

Data collection:

Inappropriate use of medications that are thought to lead to adverse outcomes were identified from research publications and relevant evidence based guidelines.[7–11,21] These potentially inappropriate prescriptions (PIPs) for NSAIDs, antiplatelets, and anticoagulants which increase a patient's risk of bleeding were the focus of the review and included: 1) Use of ASA, antiplatelet, and an oral anticoagulant. 2) Use of an oral anticoagulant and ASA except: patients with atrial fibrillation who experience an acute coronary event without stent placement, post MI in patients considered high thromboembolic risk, those with mechanical heart valves and at a low bleeding risk, and patients who experience recurrent embolism who have mitral valve stenosis or regurgitation. 3) Use of an oral anticoagulant and ASA or an antiplatelet without adequate gastro-protection. Adequate GI protection was defined as a PPI taken regularly once or twice daily or misoprostol taken four times a day, according to the best available evidence. 4) Use of ASA and an antiplatelet except: post-ACS with or without a percutaneous intervention (with or without stent placement) for up to 12 months, CABG for a non-ST segment elevation ACS for up to 12 months, or a diagnosis of atrial fibrillation with evidence of oral anticoagulant failure. 5) Use of ASA and an antiplatelet in a patient aged 65 or older without adequate gastro-protection. 6) Use of warfarin without an INR in the past 30 days unless the INR was stable (did not require a dosage change within the last three months), in which case an INR was required within the last three months. 7) Use of an oral anticoagulant for more than three months after a first, provoked proximal deep vein thrombosis or pulmonary embolus. 8) Use of an oral anticoagulant and an

oral NSAID in a patient aged 65 or older. 9) Use of oral NSAID with one or more additional GI risk factor without adequate gastro-protection. Risk factors were defined according to the American College of Gastroenterology's 2009 guideline: history of a GI ulcer, age of 65 years and older, high dose NSAID, or the concurrent use of ASA, corticosteroids, or anticoagulants. 10) Use of two or more oral NSAIDs. 11) Use of indomethacin or ketorolac in a patient aged 65 or older. 12) Use of an oral NSAID at doses above maximum recommended. 13) Use of a COX-2 and ASA or an oral anticoagulant in a patient with one or more additional GI bleed risk factor without adequate gastro-protection.

Although there was considerable overlap among the publications with respect to these PIPs, no publications identified the same constellation of PIPs.

Due to the adoption of electronic records early in 2012, paper charts were also reviewed to reduce the probability of transcription error propagation. Selected charts were reviewed using a data collection form developed by the authors to aid in the identification of PIPs and ensure consistency.

Analysis:

Descriptive analysis was performed on all variables in the data and all relevant data were analyzed using SPSS version 17 (IBM, Armonk, NY, USA). Univariate analysis with $\chi^2$and point-biserial correlation was used to identify significant variables associated with the risk of potentially inappropriate prescribing. The collected variables were: thromboembolic risk (prior myocardial infarction, stroke/TIA, heart failure, atrial fibrillation, prosthetic heart valve/heart valve disease, deep vein thromboembolism, or pulmonary embolism), bleeding risk (peptic ulcer disease, gastrointestinal bleed, major bleed, liver dysfunction, excess alcohol, or other non-major

bleeding), age, sex, number of concurrent medications, Charlson co-morbidity index, cancer, diabetes, number of clinic visits to a resident, nurse practitioner or physician, and a full medication review by a pharmacist. All variables were inserted into a binary, forward, stepwise multivariate logistic regression analysis to develop a model for predicting the presence of PIPs. The area under the ROC curve was analyzed as a measure of the goodness-of-fit for the regression model produced. All statistical tests were conducted in consultation with a biostatistician.

Results:

There were 11716 active patients within the two clinics, 603 (5%) patients taking the target medications were identified and 593 were included for screening after 10 patients were removed because they were no longer receiving care from either of the clinics. After excluding palliative use, non-oral medications, and use ≤ 3 days, 567 patients were included in the analysis.

The presence of at least one PIP was identified in 198 patients. This equates to 2% of the entire clinic population, or 35% of those using the targeted medications. The most common PIP was the use of an oral NSAID with one or more GI risk factor without adequate gastro-protection (68/567=12%; Table 1). Specifically in those prescribed NSAIDs, 36.6% (104/284) were potentially using them inappropriately while 59.6% (62/104) of these PIPs were due to inadequate gastro-protection. The concurrent use of 2 or more NSAIDs was identified in 6.3% (36/567) of the patients making it the second most frequently identified PIP. In total, there were 270 PIPs identified in the 567 patients with PIP number 9 accounting for over a quarter of all the PIPs (Figure 2).

The patients in this review represent an elderly, higher risk population (Table 2). The average patient was prescribed five medications and visited the office quarterly. When comparing those with PIP to those without PIP, the patients in whom a PIP was identified were older and sicker. A Charlson Comorbidity Index (CCI) above three represents an approximate doubling of mortality risk compared to a score of zero.[22] There were over twice the proportion of patients with a CCI over three in patients with a PIP (15.2% vs 6.5%).

During the 12 month study period, only 34 (6%) of these patients received a full medication review performed by a pharmacist. Fewer patients who received a medication review had an inappropriate prescription (27% with review, 35% without) but the difference was not statistically significant (p=0.355). Some PIPs resolved by means other than pharmacist intervention. For example, one-third of these prescriptions were prescribed for less than one month thereby resolving due to the short duration of the prescription. All of these prescriptions were for NSAIDs to be used short term. Further analysis revealed that patients who had a medication review had more resolved PIPs (18% with review, 13% without) but this result was also not statistically significant (p=0.429).

The number of clinic visits by a patient to either a resident, nurse practitioner, or a physician during the study period ranged from 0 to 23. No association was observed between the number of clinic visits and the presence of a PIP (r_{pbi}= -0.008; p=0.857). However, as the number of clinic visits increased, the likelihood of a pharmacist medication review decreased (r_{pbi}= -0.243; p<0.001).

Proportionately, those using a novel oral anticoagulant (NOAC; only dabigatran or rivaroxaban were prescribed) had a greater number of risk factors for bleeding than those using warfarin (Table 3). All of the patients prescribed a NOAC were 65 years of age or older and many were

co-prescribed medications that increased their risk of bleeding. Of those using dabigatran, four (25%) had a prior myocardial infarction (MI).

Polypharmacy was common in the study population with 303 (53%) patients using 5 or more prescribed medications and 62 (11%) patients using 10 or more. The combination product diclofenac and misoprostol was used in 62 (11%) patients; 20 of these 62 (32%) took an additional gastric acid suppressing agent and 2 (3%) used a dose of 800 μg per day.

The univariate analysis described thromboembolic risk, hypertension, age, number of prescribed medications, HAS-BLED score, and the Charlson Comorbidity Index as being significantly associated with the presence of a PIP. When tested together in the regression analysis, the composite of thromboembolic risk and hypertension were significant to predict the outcome of a PIP (Table 4). The area under the ROC curve test result was 0.624.

Discussion:

A substantial amount of potentially inappropriate prescribing is present in the family medicine clinics assessed in this study. There were approximately two PIPs identified per 100 patients prescribed any of the three target classes of medications throughout the entire population of the clinics. Thirty-five percent of those patients who were taking medications that increase the risk of bleeding (NSAIDs, antiplatelets and anticoagulants) were using these products in a potentially inappropriate manner.

Studies that attempt to identify inappropriate prescribing all target slightly different criteria and populations. Although an exact comparison cannot be made, one can look to publications by Morris et al. for similarities.[23] The assessment of PIPs using validated indicators in English general practices found a rate of 1%.[23] Our estimate of 2% is likely due to differences in

methodology. We were able to manually review each patient chart (electronic and paper) as opposed to relying solely on the information gathered by queries ran in the EMR. This detailed search is more time consuming but provides additional detailed information. Although we hypothesized our clinics would have more appropriate prescribing, we found insufficient evidence to support this hypothesis. However, it is also important to recognize that the wide range of approaches to the identification of PIPs in the literature make meaningful comparisons difficult. The identification of inadequate GI protection in our study is in keeping with the literature. A systematic review of preventable adverse drug events (pADEs) in ambulatory care found that gastrointestinal toxicity resulting from a failure to prescribe prophylactic agents with NSAIDs or antiplatelets was the most frequently identified adverse outcome in studies of pADEs requiring hospitalization.[24]

Pharmacists are an integral part of the primary care team whose expertise is in the improvement of medication management. Yet, only 6% of these higher risk patients were referred to receive a full medication review. The referral of a patient to receive the services of a pharmacist was non-systematic and voluntary in our multi-disciplinary clinics. In the patients that the pharmacist did review, fewer patients had PIPs overall while more had resolved PIPs. One interpretation is that pharmacists are being referred patients that do not have these PIPs to begin with. Additionally, given that a medication review was less likely as patients saw other practitioners more frequently (r_{pbi}= -0.243; p<0.001), a referral pattern that is less than optimal is suggested. Patients that visit the clinic more often usually represent complex cases that could benefit from regular pharmacist review. In light of these data, these patients may not be receiving the full extent of care offered by a multi-disciplinary clinic.

When new products come to market whose use becomes quickly widespread, especially when viable alternatives exist, it is of value to evaluate the prescribing patterns associated with these new medications. There may be some lesson to be learned from the experience with COX-2 inhibitors. These products were promoted as a safe alternative to traditional NSAIDs which, in turn, caused a rapid increased in their use.[25] The primary predictor of COX-2 use was physician preference rather than patient specific risk factors for NSAID GI toxicity.[25] With the introduction of novel oral anticoagulants that are reported to be just as effective as warfarin with less adverse events, one needs to be cautious that we do not head down the same path as with the COX-2 products.

The potential increased risk of MI with dabigatran[26] is controversial but should still be considered when prescribing this agent. One-quarter of those using dabigatran had a history of an MI. Another concern with anticoagulants is the additive effect of bleeding when combined with other medications. Labeling of NOACs express caution with the concomitant use of medications with antiplatelet properties; yet, a greater percentage of patients taking NOACs were also taking an antiplatelet, NSAID, or serotonin modulating antidepressant compared to those using warfarin (Table 3). Considering these risk factors, and that 11% also had a history of a major bleed, the patients selected for use of a NOAC seem to be at a higher risk of bleeding than those on warfarin. This may represent the perception that NOACs are a safer alternative to warfarin. Despite the minimal number of patients identified on NOACs in this study, the concerns raised with these data is important since it is likely the use of these newer agents will only increase. If the prescribing patterns continue, we are likely to see more patients being put at risk of a bleed that is difficult to manage. When used at standard doses, dabigatran and rivaroxaban reported similar major bleeding compared to warfarin.[27,28] Although there may be a lower incidence of

intracranial bleeding with the NOACs by approximately 0.4%[27,28], this is a trade-off for other bleeding. A recent "real world" retrospective cohort trial using data from pharmacy and medical claims reported that dabigatran was associated with a significantly higher incidence of major and any bleed compared to warfarin (HR 1.58, 1.30 respectively).[29] Compound this with the lack of an antidote and relative short term experience with these medications, one should give pause prior to prescribing these new agents. Patients at an increased risk of bleeding require closer monitoring and the ability to quickly and effectively manage bleeding should it occur.

The provision of gastric protection was lacking in those who required it, and potentially inappropriate in some of those who received it. Sixty-eight patients (12%) were not prescribed adequate gastro-protection making this the most common PIP (Table 1). This comprised the majority of PIPs in those using NSAIDs.

One-third of the patients using diclofenac and misoprostol were also prescribed a PPI or ranitidine. Good quality evidence is lacking to support this dual gastric protection regimen. While 10% of these patients were using this combination for secondary ulcer prevention, it is difficult to say if this higher risk group would benefit. The only study to look at this combination found there was no difference in rebleeding, surgery, or death after 3 months with the addition of misoprostol to a PPI. However, this study was performed on patients admitted to hospital for NSAID induced acute gastrointestinal bleeding who were treated with misoprostol for up to 2 weeks.[30] With the information that is available to us at the present, this practice seems like an expensive redundancy.

The dose of misoprostol to adequately reduce the risk of ulcers is also in question. Although endoscopic evidence may suggest the use of lower doses, the only RCT that has shown a reduction in clinical ulcers used a dose of 800 μg per day.[31] In a Cochrane review of strategies to

reduce NSAID induced ulcers, Rostom et al. cautioned readers that "the practice of using lower doses of misoprostol to avoid its associated adverse effects should be questioned," due to this lack of evidence.[32] In our review, only 3% of the patients were using misoprostol at 800 μg per day. Not all of the remaining 97% of patients were considered to have a PIP because some were using the product there were no identified GI risk factors. The use of misoprostol without an indication was not identified as a PIP in our study because this would not increase the risk of bleeding.

The logistic regression analysis model, although statistically significant, can only account for a small portion of the variability observed as demonstrated by the area under the ROC curve result of 0.624 (95%CI 0.576-0.671). A result of 0.5 indicates the model does no better than chance at predicting the outcome and the lower end of the confidence interval for our model is approaching this threshold. Furthermore, the variables identified may be predicting the use of the medications, not the desired outcome. Unfortunately, these results do not support the identification of a particular high-risk subgroup and suggests that it may be more important to ensure all patients are properly using these high risk medications. Given that only 5% of the clinic population was using these medications it may be feasible to screen this overall group rather than attempting to focus on any particular subgroup.

Limitations:

As with all retrospective studies, the data collected are limited to what was documented. It is impractical to document every piece of information within the chart. Therefore, some information will undoubtedly be absent. Although we attempted to choose PIPs that were already published in the literature, we felt there were some gaps so we generated some ourselves. These

PIPs have not gone through a validation process as of yet. This research was performed within multi-disciplinary family practice centres. These clinics have more resources available to them compared to the typical family medicine clinic. One of these resources is the availability of a paid, on-site clinical pharmacist. Finally, the PIPs used within this study represent a tool to assist practitioners in assessing the appropriateness of a prescription. However, clinical practice is generally much more complex and should take into account various patient variables, including patient preference. We attempted to account for some of these variables, but there is no way to take all of this into consideration with the tool developed.

Conclusion:

Together, NSAIDs, antiplatelets, and anticoagulants are most often attributed to the cause of medication related adverse events requiring patients to seek medical care. In those patients who were prescribed these higher risk medications, 35% were using them in a potentially inappropriate manner. Although pharmacists have been shown to reduce the amount of inappropriate prescribing,[17,18] very few patients using these medications were referred to the pharmacist for a full medication review. This could represent a referral pattern that does not send the higher risk patients to the pharmacist for review. Mechanisms to enhance the referral pattern to ensure that higher risk patients are reviewed may lead to better outcomes for the patient. Alternatively, pharmacists could actively seek out these patients for review within the clinic or when dispensing these medications in the community.

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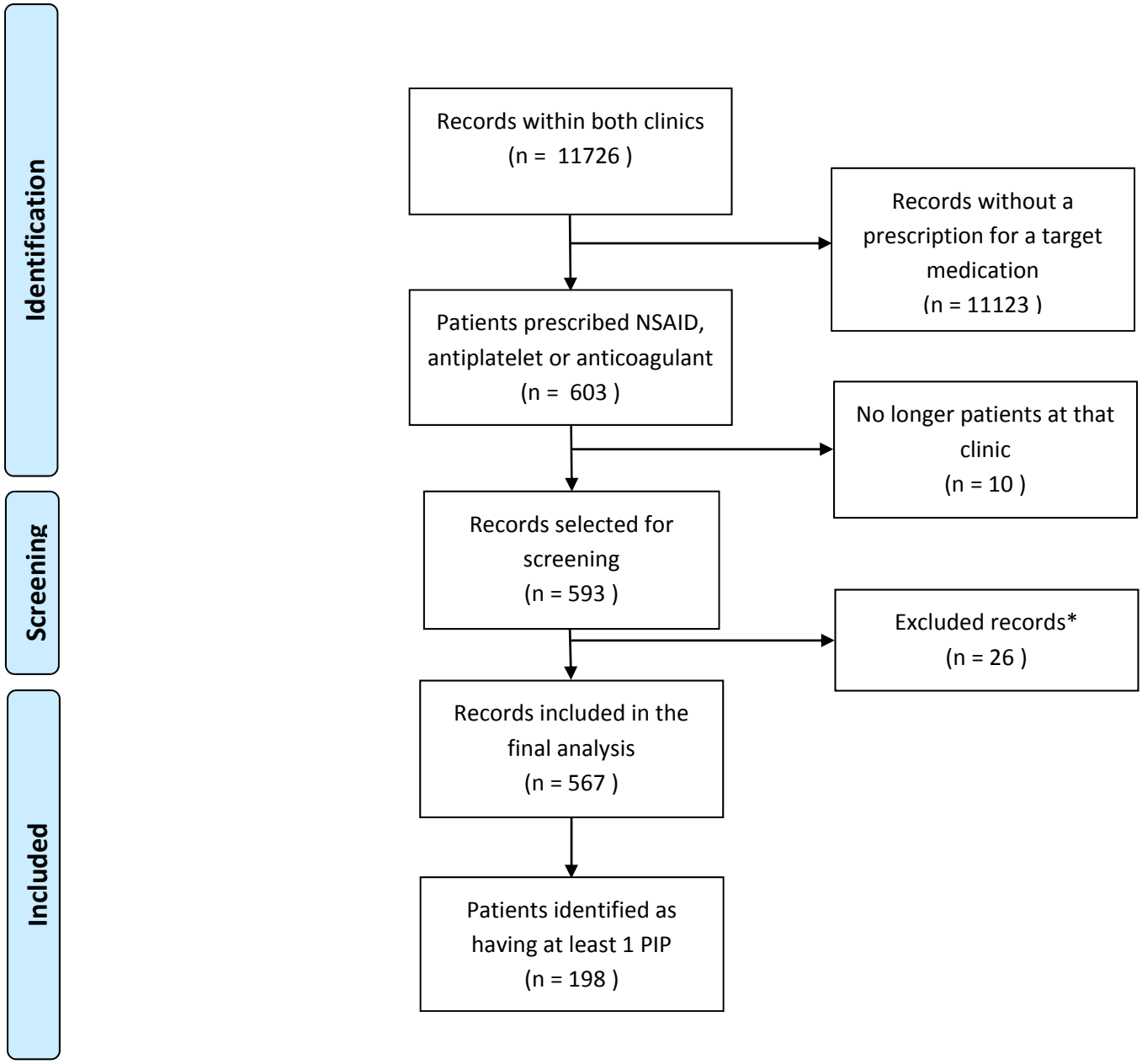

Figure 1. Flow of patient selection, review, and PIP identification

*Patients were excluded if they were receiving palliative care, using non-oral medications, or used ≤ 3 days

Table 1. Breakdown of the frequency of identified PIPs[†]

	Potentially Inappropriate Prescription	n (%)
1	Use of ASA, antiplatelet, and an oral anticoagulant	1 (0.2%)
2	Use of an oral anticoagulant and ASA*	30 (5.3%)
3	Use of an oral anticoagulant and ASA or an antiplatelet without gastro-protection	26 (4.6%)
4	Use of ASA and an antiplatelet §	35 (6.2%)
5	Use of ASA and an antiplatelet in a patient aged 65 or older without gastro-protection	18 (3.2%)
6	Use of warfarin without an INR in the past 30 days ǂ	12 (2.1%)
7	Use of an oral anticoagulant >3 months after first provoked proximal deep vein thrombosis or pulmonary embolus	4 (0.7%)
8	Use of an oral anticoagulant and an oral NSAID in a patient aged 65 or older	8 (1.4%)
9	Use of oral NSAID with 1 or more additional GI risk factor without adequate gastro-protection	68 (12%)
10	Use of 2 or more oral NSAIDs	36 (6.3%)
11	Use of indomethacin or ketorolac in a patient aged 65 or older	13 (2.3%)
12	Use of an oral NSAID at doses above maximum recommended	9 (1.6%)
13	Use of a COX-2 and ASA or an oral anticoagulant in a patient with 1 or more additional GI risk factor without adequate gastro-protection	10 (1.8%)

NSAID = nonsteroidal anti-inflammatory drug; COX-2 = cyclooxygenase-2 inhibitor; GI = gastrointestinal
*, § and ǂ indicates there are some situations in which this combination was considered appropriate

* Includes:
1. Diagnosis of atrial fibrillation and treated for ACS without stent placement for up to 12 months
2. Recurrent embolism in mitral valve stenosis or regurgitation in patients with a low bleeding risk
3. Post-ACS patients who are considered high risk for left ventricular thrombus (large anterior MI, significant heart failure or atrial fibrillation) that do not undergo stent placement for up to 3 months

§ Includes:
1. Post-ACS with or without a percutaneous intervention (± stent) for up to 12 months
2. CABG for non-ST elevation ACS for up to 12 months
3. Diagnosis of atrial fibrillation with evidence of oral anticoagulant failure

ǂ INR within the last 3 months if INR was stable (did not require adjustment for at least 3 months)

[†] Frequency of PIPs are calculated based on the 567 patients included in the analysis.

Figure 2. Proportion of individual PIPs (out of a total 270 PIPs).

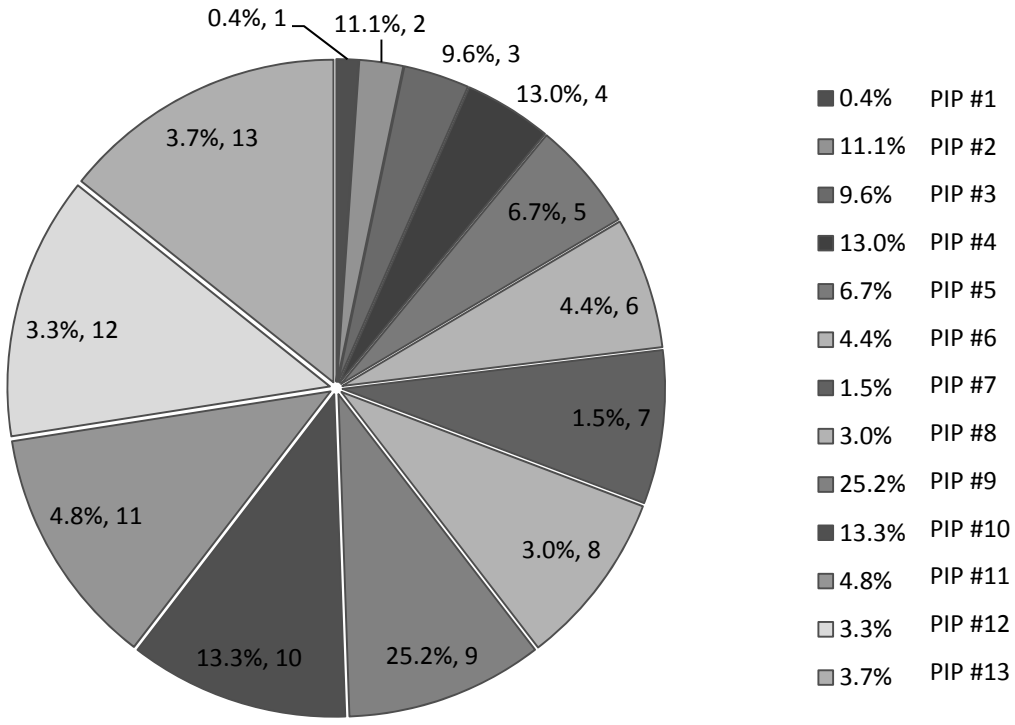

Table 2. Demographic characteristics of 567 patients with prescriptions for NSAIDs, antiplatelets, or anticoagulants

Characteristic	Total No. (%) (n=567)	With PIP (n=198)	Without PIP (n=369)
Mean age (sd)	63.6 ± 17.3	68 ± 15.7	61 ± 17.8
Age category			
<50	111 (19.6%)	29 (14.4%)	82 (22.2%)
50-64	163 (28.7%)	35 (17.7%)	128 (34.7%)
65-75	126 (22.2%)	66 (33.3%)	60 (16.3%)
>75	167 (29.5%)	67 (33.8%)	99 (26.8%)
Sex			
Male	238 (42%)	94 (47%)	144 (39%)
Female	329 (58%)	103 (52%)	225 (61%)
Median # of medications (IQR)	5 (3-7)	5.5 (4-8)	4 (3-6)
Median Charlson Comorbidity Index (IQR)	1 (0-2)	1 (0-3)	0 (0-2)
Charlson Comorbidity Index >3	54 (9.5%)	30 (15.2%)	24 (6.5%)
Creatinine Clearance, mL/Min			
<30	9 (1.6%)	3 (1.5%)	6 (1.6%)
30-50	70 (12.3%)	34 (17.2%)	36 (9.6%)
>50	307 (54.1%)	109 (55.1%)	198 (53.7%)
Not documented	181 (31.9%)	52 (26.3%)	129 (35.0%)
No. of physician/NP visits (SD)	3.7 ± 5.0	3.8 ± 3.1	3.7 ± 3.1
No. of pharmacist medication reviews	34 (6.0%)	9 (4.5%)	25 (6.8%)
Medical History			
Diabetes	105 (18.5%)	41 (20.7%)	64 (17.3%)
CVA or TIA	69 (12.2%)	33 (16.7%)	36 (7.8%)
Myocardial Infarction	93 (16.4%)	57 (28.8%)	36 (9.8%)
Peptic Ulcer Disease	18 (3.2%)	6 (3.0%)	12 (3.3%)
Atrial Fibrillation	122 (21.5%)	41 (20.7%)	81 (22.0%)
Major bleed	15 (2.6%)	7 (3.5%)	8 (2.2%)
Medications			
COX-2	59 (10.4%)	10 (5.1%)	49 (13.3%)
NSAID	284 (50.1%)	104 (52.5%)	180 (48.8%)
Antiplatelet	147 (25.9%)	101 (51.0%)	46 (12.5%)
Anticoagulant	159 (28.0%)	53 (27.8%)	108 (28.7%)
ASA	117 (20.6%)	97 (49.0%)	20 (5.4%)

COX-2=cyclooxygenase-2 inhibitor, CVA=cerebral vascular accident, NSAID=nonsteroidal anti-inflammatory, TIA=transient ischemic attack.

Table 3. Comparison of characteristics that increase the propensity for bleeding with NOACs and warfarin

	NOAC n (%) (n = 18)	Warfarin n (%) (n = 143)
DM	4 (22)	33 (23)
History of PUD	0	4 (3)
History of GI bleed	1 (6)	11(8)
Age ≥65	18 (100)	114 (80)
Prior major bleed	2 (11)	5 (3)
Weight ≤60kg	3 (17)	13 (9)
CrCl <30	0	7 (5)
Antiplatelet (inc. ASA)	6 (33)	24 (17)
NSAID	2 (11)	7 (5)
Steroid	0	2 (1)
SSRI	2 (11)	7 (5)
SNRI	1 (6)	5 (3)
Liver dysfunction	0	1 (<1)
Excess alcohol (≥8 drinks per week)	1 (6)	5 (3)

NOAC=novel oral anticoagulant, DM=diabetes mellitus, PUD=peptic ulcer disease, GI=gastrointestinal, NSAID=nonsteroidal anti-inflammatory, SSRI=selective serotonin reuptake inhibitor, SNRI=selective norepinephrine reuptake inhibitor

Table 4. Logistic regression model of variables predicting PIPs using SPSS

				95% CI	
Variable	Wald	p Value	Exp (B) (odds ratio)	Low	High
Thrombo-embolic risk	8.684	0.003	1.761	1.21	2.57
Hypertension	7.847	0.005	1.713	1.18	2.50
Constant	643186	0.000		NA	

AUC = 0.624 (95% CI 0.576 to 0.671)
HL Goodness of fit test: p=0.589

High Risk Use of OTC NSAIDs and ASA in Family Medicine: A Retrospective Chart Review

Abstract:

Introduction: Complications associated with the use of NSAIDs, antiplatelet agents, and anticoagulants are among the top causes of preventable drug-related ER visits, hospitalizations and deaths. Although over the counter (OTC) NSAIDs and ASA also contribute to this preventable risk, it is unclear how well these medications are documented in primary care records. If OTC NSAID and ASA use is overlooked, the overall risk of bleeding may be underestimated.

Methods: A retrospective electronic/paper chart review was conducted to evaluate the prevalence of 13 evidence-based high-risk prescriptions and the contribution of OTC NSAIDs and ASA to these potentially inappropriate prescriptions (PIPs).

Results: Of the 148 patients included in the review, ASA was taken by 117 patients (79%) while OTC NSAIDs were taken by 36 (24%). OTC NSAIDs were never documented within the "medication" section of the electronic record, whereas ASA was documented in 65 (56%) cases. Eighty percent (118/148) taking either OTC NSAIDs or ASA were identified as having at least one PIP. Although these OTC medications contributed to an increase in bleeding risk, it was unknown whether these PIPs were addressed by the family medicine clinics or the community pharmacy.

Conclusion: OTC NSAIDs and ASA are widely available and are commonly taken without the knowledge of the prescriber. These medications contribute to the overall risk of bleeding. Although documentation of these medications is essential to provide the prescriber with all the required information when making therapeutic decisions, it was infrequently done in these

clinics. Review and documentation of OTC NSAIDs and ASA use should be part of all relevant patient encounters when prescribing NSAIDs, antiplatelets and anticoagulants.

Introduction:

Many studies have attempted to identify patterns of medication use that leads to an increase in the risk of adverse outcomes.[1–4] These have been termed potentially inappropriate prescriptions (PIPs). Despite the potential for poor outcomes with PIPs, they are still commonly prescribed.[2] Unfortunately, many of the publications fail to take into account use of over-the-counter (OTC) medications. Without accounting for these medications, risk is generally underestimated. In 2005, Wilcox et al. estimated that 23 million Americans use nonsteroidal anti-inflammatory drugs (NSAIDs) on a daily basis and that one quarter used them inappropriately.[5]

NSAIDs, antiplatelets, and anticoagulants are often acknowledged as the causative factor leading to medication-related emergency room visits, hospitalizations and death.[6–10] The Dutch HARM-Wrestling Task Force was commissioned to identify, and make recommendations to reduce, the most common adverse drug events (ADEs).[9] Bleeding associated with vitamin K antagonists, platelet aggregation inhibitors, and NSAIDs were the most frequent ADEs identified. Some NSAIDs, including ASA, are widely available without a prescription in many countries. This presents a unique problem in that OTC medications are often omitted from patient records.[11,12] Our objective was to assess the contribution of OTC NSAIDs and ASA to the prescribing appropriateness of prescription oral NSAIDs, antiplatelets, and anticoagulants.

Study population:

All patients prescribed an oral NSAID, antiplatelet or an anticoagulant during the 12 month study period from June 2012 until June 2013 within two multi-disciplinary family medicine teaching clinics in Winnipeg, Canada were included. Queries within the electronic medical record (EMR) were conducted to identify patients by using the Anatomical Therapeutic Chemical (ATC) classification system developed by the World Health Organization (WHO).[13] Patients were excluded if they were receiving palliative care or took the target medication for ≤3 days. This study focused on patients who were using OTC NSAIDs or ASA. The University of Manitoba Health Research Ethics Board, as well as the local review committees, approved this study.

Data collection:

We conducted a retrospective chart review of primary care patients within the period from June 2012 until June 2013. Both clinics utilize the same EMR which assures consistent formatting of records. Due to the recent adoption of electronic records, paper charts were also reviewed to reduce the probability of transcription error propagation. Selected charts were reviewed using a data collection form developed by the authors to aid in the identification of PIPs and ensure consistency. Detailed review of the charts was performed by the study pharmacist (KH) with the first 16 charts also reviewed by a clinical pharmacist (CD). This step was performed as a quality assurance measure to standardize the initial methodology.

Documentation of OTC products were defined as being either: prescribed by the clinic physician/resident/nurse practitioner, found within the "External Prescriptions" section (the

section to document OTCs or those medications prescribed from a provider outside the clinic), or "Other" (recorded in notes, consults, histories or other parts of the record).

Methods:

Inappropriate prescribing criteria were identified from research publications and relevant evidence based guidelines.[14,4,15–17,1] These were amalgamated to produce 13 PIPs for NSAIDs, antiplatelets, and anticoagulants which increase a patient's risk of bleeding: 1) Use of ASA, antiplatelet, and an oral anticoagulant. 2) Use of an oral anticoagulant and ASA except: patients with atrial fibrillation who experience an acute coronary event without stent placement, post MI in patients considered high thromboembolic risk, those with mechanical heart valves and at a low bleeding risk, and patients who experience recurrent embolism who have mitral valve stenosis or regurgitation. 3) Use of an oral anticoagulant and ASA or an antiplatelet without adequate gastro-protection. Adequate GI protection was defined as a PPI taken regularly once or twice daily or misoprostol taken four times a day, according to the best available evidence. 4) Use of ASA and an antiplatelet except: post-ACS with or without a percutaneous intervention (with or without stent placement) for up to 12 months, CABG for a non-ST segment elevation ACS for up to 12 months, or a diagnosis of atrial fibrillation with evidence of oral anticoagulant failure. 5) Use of ASA and an antiplatelet in a patient aged 65 or older without adequate gastro-protection. 6) Use of warfarin without an INR in the past 30 days unless the INR was stable (did not require a dosage change within the last three months), in which case an INR was required within the last three months. 7) Use of an oral anticoagulant for more than three months after a first, provoked proximal deep vein thrombosis or pulmonary embolus. 8) Use of an oral anticoagulant and an oral NSAID in a patient aged 65 or older. 9) Use of oral NSAID with one or more additional GI

risk factor without adequate gastro-protection. Risk factors were defined according to the American College of Gastroenterology's 2009 guideline: history of a GI ulcer, age of 65 years and older, high dose NSAID, or the concurrent use of ASA, corticosteroids, or anticoagulants. 10) Use of two or more oral NSAIDs. 11) Use of indomethacin or ketorolac in a patient aged 65 or older. 12) Use of an oral NSAID at doses above maximum recommended. 13) Use of a COX-2 and ASA or an oral anticoagulant in a patient with one or more additional GI bleed risk factor without adequate gastro-protection.

Analysis:

Descriptive analysis was performed on all variables in the data and all relevant data were analyzed using SPSS version 17 (IBM, Armonk, NY, USA). Univariate analysis with $\chi^2$and point-biserial correlation was used to identify significant variables associated with the risk of potentially inappropriate prescribing. Variables included in the analysis were: thromboembolic risk (prior myocardial infarction or established coronary artery disease, stroke/TIA, heart failure, atrial fibrillation, prosthetic heart valve/heart valve disease, deep vein thromboembolism, or pulmonary embolism), bleeding risk (peptic ulcer disease, gastrointestinal bleed, major bleed, liver dysfunction, excess alcohol, or other non-major bleeding), age, sex, number of concurrent medications, Charlson co-morbidity index, cancer, diabetes, number of clinic visits to a resident, nurse practitioner or physician, and a full medication review by a pharmacist. All variables were inserted into a forward stepwise binary multivariate logistic regression analysis to develop a global model for predicting the presence of PIPs. The area under the ROC curve was analyzed as a measure of the goodness-of-fit for the regression model produced. All statistical tests were conducted in consultation with a biostatistician.

Results:

From 11716 active patients within the two clinics, 593 patients taking the target medications were identified (Figure 1). After excluding palliative use, non-oral medications, and use ≤ 3 days, 567 patients were remaining. Non-prescription ASA and NSAID use was then identified in 148 of the 567 patients; ASA was reported as being taken by 117 patients (79%) while OTC NSAIDs were taken by 36 (24%).

Demographic and disease characteristics are presented in Table 2. The patients were similar between the two clinics with respect to these characteristics and the combined population of the clinics was used in the overall analysis. The majority of the population was seniors 65 years of age and older while over half were male. The study population represented patients at an elevated cardiovascular risk, with almost half of the patients having a history of a myocardial infarction and close to one-third having diabetes. A history of peptic ulcer disease, GI bleed or a major bleed was observed in seven (5%), ten (7%) and five (3%) patients, respectively.

A total of 176 PIPs were identified in 148 patients. One-hundred and eighteen patients had one or more PIPs (80%). The majority of patients (60%) had only one PIP while 40 (34%) had two PIPs (Figure 2). The potentially inappropriate use of ASA and clopidogrel tied as the most prevalent PIP along with the use of an oral NSAID with one or more GI bleed risk factors without adequate GI protection (23%, Table 1). Adequate GI protection was considered to be a PPI taken regularly once or twice daily or misoprostol taken four times a day. The inappropriate use of an oral anticoagulant and ASA was the second most common medication issue identified (14%).

Of the patients taking ASA, almost half were documented outside of the standard prescribing section of the EMR, and 32% were only documented in the "Other" sections which are unlikely to be consulted prior to prescribing new agents. All of the known OTC NSAID use was contained within the "Other" sections.

The concomitant use of a prescription NSAID, OTC NSAID and ASA was observed in 4 patients while 25 patients used both a prescription NSAID and an OTC NSAID (Table 3). Other potential drug interactions of concern were the use of novel anticoagulants or celecoxib with ASA. This review found that 8 patients were using celecoxib and ASA; two such patients were using the ASA for secondary MI prevention. Five patients used dabigatran with an OTC NSAID or ASA with a diagnosis of atrial fibrillation and only one patient having a history of a myocardial infarction.

With regard to the risk of experiencing a PIP, a number of logistic regression analysis models were tested using multiple independent variables. The only statistically significant variable was the composite variable of thromboembolic risk factors (prior myocardial infarction, stroke/TIA, heart failure, atrial fibrillation, prosthetic heart valve/heart valve disease, deep vein thromboembolism, or pulmonary embolism; $p=0.048$). The presence of a thromboembolic risk factor more than doubled the odds of experiencing a PIP (OR 2.28; 95% CI 1.01-5.15). The area under the curve (AUC) for the calculated ROC curve was 0.597.

Discussion:

The PIPs presented in this paper represent situations which place the patient at an increased risk of bleeding with little to no added therapeutic benefit. This review indicates that potentially inappropriate prescribing of high risk medications in these two primary care clinics is

problematic. In the overall population of 11726 active patients between the two clinics, only 118 (1%) were identified as having a PIP that was mostly due to OTC use. However, in patients who were actually prescribed NSAIDs, antiplatelets, or anticoagulants the rate was 21% (118 of 567 patients using target medications). In patients that were using OTC NSAIDs or ASA, the rate of PIP was 80% (118 of 148 patients).

Most of the research in this area focuses on slightly different criteria to assess for inappropriate prescribing. We, too, selected some criteria that were not present in other studies making a direct comparison with these data difficult. In a study by Koffeman et al., OTC NSAID use was assessed in 264 high risk patients within four general practice offices in the Netherlands.[18] The high risk group was selected based on age, pre-existing disease (heart failure, chronic kidney disease, peptic ulcer, stroke, myocardial infarction, severe rheumatoid arthritis, diabetes), or co-prescription (anticoagulant, ASA, corticosteroid, or selective serotonin reuptake inhibitor). The authors reported that 13% of patients who were at an elevated risk of ADE used an OTC NSAID. The high risk population we chose to focus on were those who were prescribed either an NSAID, antiplatelet or an anticoagulant and using an OTC NSAID or ASA. When comparing the rate of PIP in our high risk population to that of Koffeman et al., we found the prevalence to be 21%. This higher rate is likely due to the greater number of PIPs we focused on. Despite the differences in methodology of this study compared to ours, the rate of potentially inappropriate use in our clinic is higher which is not what we hypothesized would happen. Our clinics are not performing particularly well when patients are using OTC NSAIDs or ASA.

We suspect that we have not captured all OTC NSAID and ASA use. Documentation of OTC medications is known to be deficient.[11] Due to the likelihood of OTC omission from the medical

record, both the rate of PIPs and contribution of OTC NSAIDS and ASA to inappropriate prescribing are likely to be an underrepresentation of the true risk.

Primary healthcare providers rely on their patients as the source of information for OTC medication use. With a wide array of medications available without a prescription, many of which are marketed under more than one name brand and contain labeling that is challenging to read, many patients can become confused. In many cases, the EMR is not well designed to capture OTC products. This culminates in a situation which fosters uncertainty.

When OTC use is documented, it is often contained in a part of the medical record that is easily overlooked. We found approximately 1/3 of the known ASA use, and all of the OTC NSAID use could have been missed by the practitioner at the time of prescribing. Because the documentation of these medications is not in an area easily reviewed by the practitioner at the time of prescribing, a PIP could be generated without the prescriber realizing it. The exceptionally high rate of PIPs seen in this study confirms the importance of adequate documentation. Additionally, many EMR programs have decision support tools that alert prescribers to drug interactions, but this function is ineffective if the drugs are not contained in the "medications" area. Greater diligence is required from primary care providers to systematically identify and document these OTC products to improve the quality of prescribing.

COXIBs are marketed as a safer alternative to traditional NSAIDs with respect to adverse GI events. That benefit, however, is lost with the concomitant use of ASA or an anticoagulant.[19,20] The only possible justification for this combination is for patients who require ASA for secondary cardiovascular prevention and an NSAID. This review found that 8 patients were using celecoxib and ASA, only two of which were using ASA for secondary prevention. This

treatment should be questioned as there are alternative therapies available that have equivalent efficacy and are more cost effective.

The risk of bleeding has been a concern in studies of dabigatran.[21] The use of OTC NSAIDs or ASA combined with dabigatran would be expected to increase this risk. We observed this combination in 5 study patients. One of these patients was using ticagrelor, dabigatran, ASA and OTC naproxen. Canadian labeling of dabigatran indicates that its use with ASA is not recommended for the prevention of stroke in patients with atrial fibrillation due to the apparent lack of additional benefit while almost doubling the risk of major bleeding.

Risk factors associated with future thromboembolic events have some predictive value for PIPs. However, this likely represents a risk factor more for the use of the medications themselves rather than the outcome of a PIP. Furthermore, the ROC curve produced indicated that the resulting regression model has poor predictive power. This suggests that there is a subset of patients with a very small, but statistically significant increase in the risk of PIPs. Practically, the poor predictive power of this model does not offer much that is usable to identify higher risk patients in clinical practice. As such, given the risk of bleeding, care should be taken in prescribing NSAIDs, antiplatelets, and anticoagulants particularly in patients that may also be using OTC NSAIDs and ASA.

Limitations:

The study reflects the practice at these multi-disciplinary, family medicine teaching clinics which includes a clinical pharmacist as a care provider. It is possible that other clinics with less support may have poorer outcomes.

All retrospective reviews have limitations and rely on the information that is recorded. Without interviewing the patient it could not be confirmed whether the medications were or were not taken; it had to be inferred from the information gathered from the chart. The data presented was dependent on what was available within the records. Additionally, chart notes were ambiguous at times allowing for some degree of interpretation by the study pharmacist.

Conclusion:

OTC NSAIDs and ASA are widely available and are commonly taken without the knowledge of the prescriber. These medications contribute to the overall risk of bleeding. Documentation of these medications in an area of the medical record that is commonly reviewed is essential to provide the prescriber with all the required information when making therapeutic decisions. This step is often overlooked which can lead to serious drug interactions.

Despite the well-known risks associated with these medications, they are still being used in a fashion that increases that risk to a large portion of patients. The information gained from this research can be used to guide prescribing improvement programs in the future. Additionally, improvements on the EMRs are warranted to address the limited capacity to adequately capture OTC products.

Bottom-line: Review and documentation of OTC NSAIDs and ASA use should be part of all relevant patient encounters when prescribing or dispensing NSAIDs, antiplatelets and anticoagulants.

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Conflicts of interest: There are no conflicts of interest to declare.

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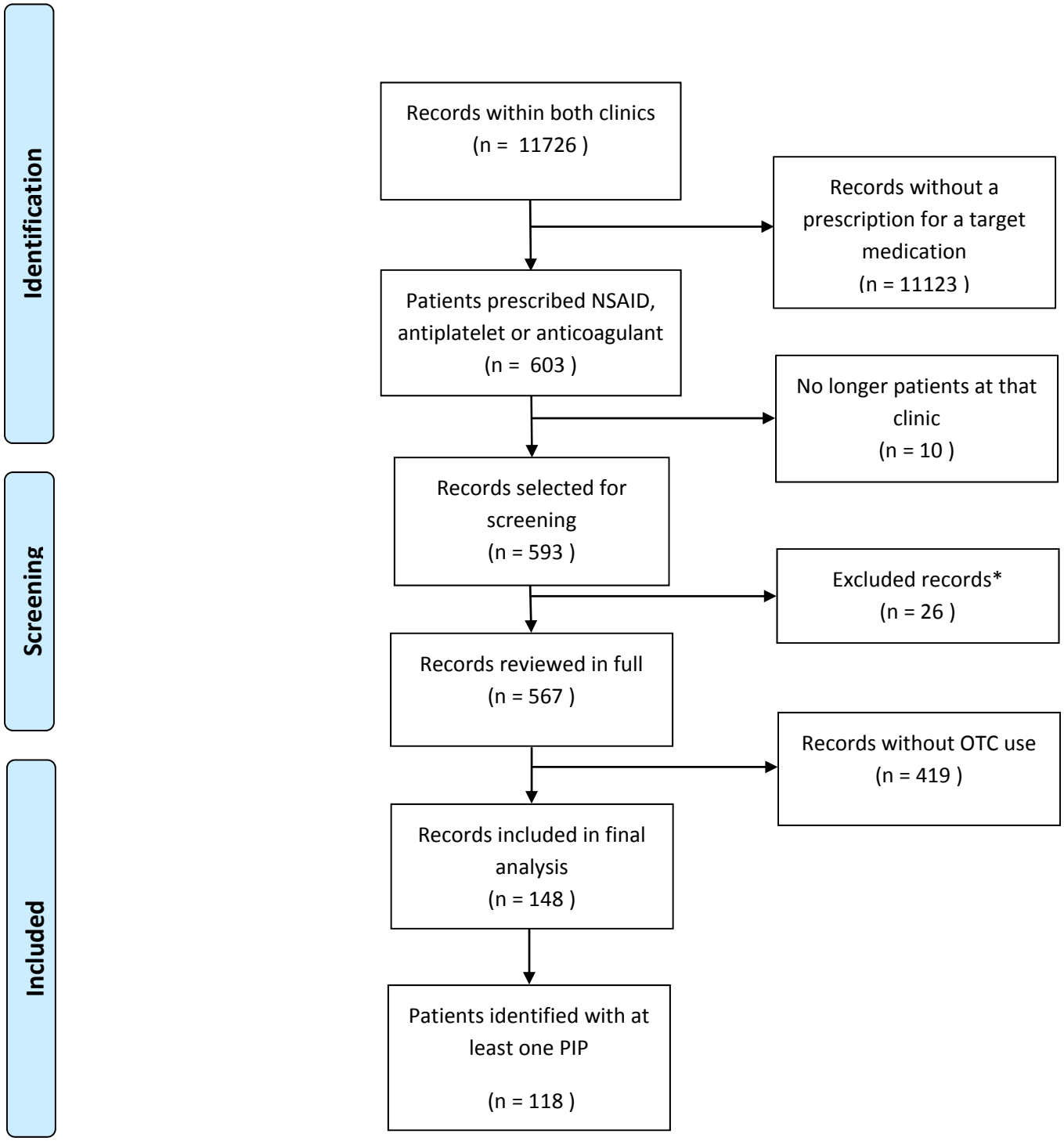

Figure 1. Flow diagram describing patient selection

*Patients were excluded if they were receiving palliative care, using non-oral medications, or used ≤ 3 days

Table 1. Frequency of PIPs identified in the study population

	Potentially Inappropriate Prescription	n (%)
1	Use of ASA, antiplatelet, and an oral anticoagulant	1 (0.7%)
2	Use of an oral anticoagulant and ASA*	25 (17%)
3	Use of an oral anticoagulant and ASA or an antiplatelet without gastro-protection	20 (14%)
4	Use of ASA and an antiplatelet §	34 (23%)
5	Use of ASA and an antiplatelet in a patient aged 65 or older without gastro-protection	18 (12%)
6	Use of warfarin without an INR in the past 30 days ǂ	1 (0.7%)
7	Use of an oral anticoagulant >3 months after first provoked proximal deep vein thrombosis or pulmonary embolus	0
8	Use of an oral anticoagulant and an oral NSAID in a patient aged 65 or older	5 (3%)
9	Use of oral NSAID with 1 or more additional GI bleed risk factor without adequate gastro-protection	34 (23%)
10	Use of 2 or more oral NSAIDs	23 (16%)
11	Use of indomethacin or ketorolac in a patient aged 65 or older	6 (4%)
12	Use of an oral NSAID at doses above maximum recommended	1 (0.7%)
13	Use of a COX-2 and ASA or an oral anticoagulant in a patient with 1 or more additional GI bleed risk factor without adequate gastro-protection	8 (5%)

NSAID = nonsteroidal anti-inflammatory drug; COX-2 = cyclooxygenase-2 inhibitor; GI = gastrointestinal
*, § and ǂ indicates there are some situations in which this combination was considered appropriate

* Excludes:
1. Diagnosis of atrial fibrillation and treated for ACS without stent placement for up to 12 months
2. Recurrent embolism in mitral valve stenosis or regurgitation in patients with a low bleeding risk
3. Post-ACS patients who are considered high risk for left ventricular thrombus (large anterior MI, significant heart failure or atrial fibrillation) that do not undergo stent placement for up to 3 months

§ Excludes:
1. Post-ACS with or without a percutaneous intervention (± stent) for up to 12 months
2. CABG for non-ST elevation ACS for up to 12 months
3. Diagnosis of atrial fibrillation with evidence of oral anticoagulant failure

ǂ INR within the last 3 months if INR was stable (did not require adjustment for at least 3 months)

Table 2. Demographic and clinical patient characteristics	
Characteristic	**No. (%) of patients**
Age	
Mean (SD)	67 ± 16
65 years or older	90 (61%)
75 years or older	61 (41%)
Sex	
Male	79 (53%)
Female	69 (47%)
Estimated creatinine clearance (mL/min)	
<50	31 (21%)
≥50	82 (55%)
Not documented within last 12 mos.	35 (24%)
Median number of medications (IQR)	6 (4-9)
Median Charlson Comorbidity Index (IQR)	1 (0-3)
Charlson Comorbidity Index >3	24 (16.2%)
No. of physician/NP visits (SD)	4.5 (8.3)
No. of pharmacist medication reviews	9 (6.0%)
Medical history	
MI	60 (41%)
CVA	16 (11%)
TIA	13 (9%)
DM	39 (26%)
PUD	7 (5%)
GI bleed	10 (7%)

CVA=cerebrovascular accident, DM=diabetes mellitus, GI=gastrointestinal, MI=myocardial infarction, PUD=peptic ulcer disease, TIA=transient ischemic attack.

Figure 2. Number of PIPs per patient in those identified with PIPs. There were a total of 176 PIPs in 148 patients.

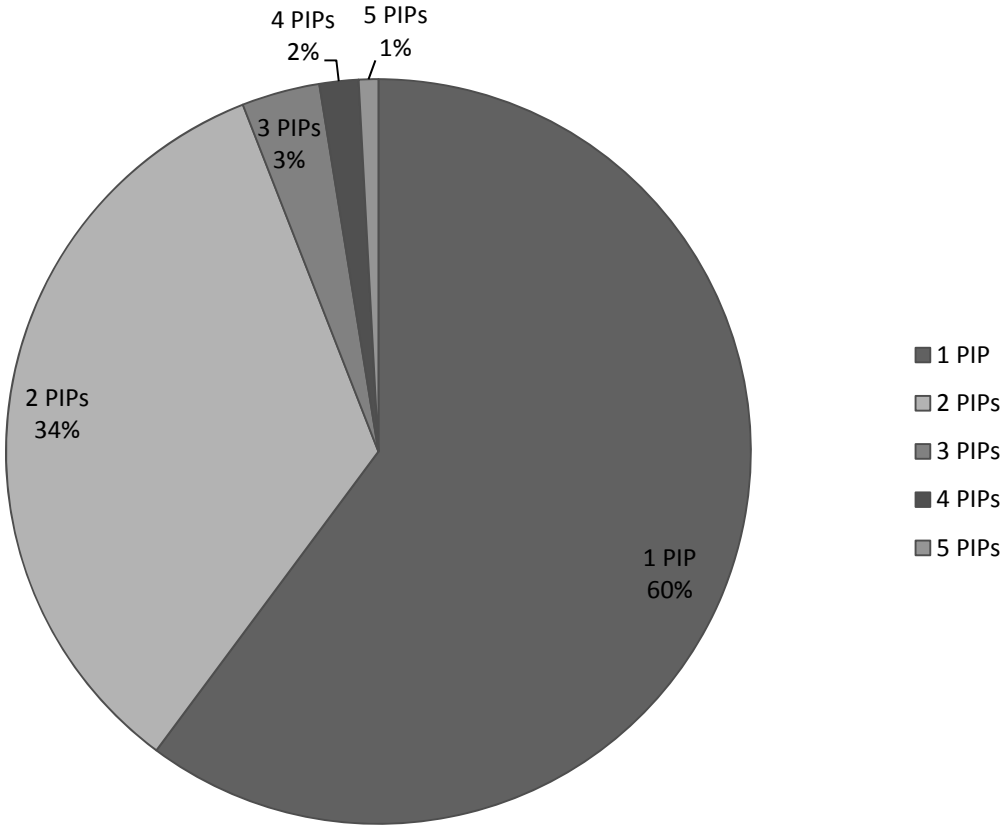

Table 3. Frequencies of triple and dual use of prescription and OTC NSAID or ASA (n=148)

Triple use	Rx NSAID, OTC NSAID and ASA	4
Dual use	Rx NSAID and OTC NSAID	25
	Rx NSAID and ASA	44
	OTC NSAID and ASA	1

Conclusion

Upon review of the literature, NSAIDs, antiplatelets, and anticoagulants appear to lead to the most preventable harm caused by the inappropriate use of medications. Although other medications are sometimes reported as frequently as some of these medications individually (e.g. diuretics), combined they make up the largest group.[15] It was felt that these medications all have similar adverse events, namely bleeding, so it was justified to combine these classes of medications. Additionally, the Dutch task force publication that identified bleeding (caused by these medications) as the most common preventable ADE, reinforced this decision.[16] Once this was determined, it was then required to identify ways in which these medications were being used that would increase their risk of bleeding. These situations, termed PIPs, were taken from publications such as the "Beers Criteria," the "STOPP Criteria," and clinical practice guidelines.[35–37,39,43,45] All PIPs related to the inappropriate use of these medications leading to bleeding were included in the review.

Some of the PIPs included in this research are unique. We believe that dual antiplatelet therapy, combination ASA and an anticoagulant, and triple therapy are of high enough risk that they deserve to be identified by health care professionals. Dual antiplatelet therapy was the third most common PIP identified in our study. Although the other new PIPs were not as common, they still represent a significant concern that future researchers should focus on.

This retrospective chart review was designed to describe the prescribing appropriateness of NSAIDs, antiplatelets and anticoagulants in two family medicine teaching clinics. It is among the first studies to utilize the clinic-based electronic medical records to evaluate the

appropriateness of prescribing in family practice clinics in Manitoba, Canada. This is an emerging field of research with many studies expected to follow.

This research was only able to identify potentially inappropriate or "high-risk" prescriptions, which is separate from inappropriate. This distinction becomes important because of the complexities within clinical practice. Some medically complex patients may benefit from treatment with high-risk prescriptions, yet it is important to frequently review these patients. Targets, such as PIPs, are therefore needed to enable health care practitioners to systematically identify, and review, high-risk prescribing.

We found that inappropriate prescribing is still occurring despite the well-known risks associated with NSAIDs, antiplatelets, and anticoagulants. We had expected that clinical data would help to predict PIPs; unfortunately, our resulting model was unreliable in its ability to predict this outcome (AUC = 0.624). As such, it seems as though it is the medications themselves that are the risk and the prescribing of any of these medications could serve as a flag for patient review. This reinforces the notion of a systematic method for capturing and preventing these high-risk prescriptions on a regular basis.

The use of OTC ASA and NSAIDs represent a major source of PIPs in this study. The gap in documentation of relevant non-prescription medicines keeps the prescriber ignorant of this increased risk. The inclusion of OTC products in the medication section of the EMR, however, may not be enough to resolve this issue. The clinical decision support tools within the EMR may not recognize all OTC products and will not function if placed with the "external medications" section. Future efforts should concentrate interventions on these areas which could considerably improve the quality of care a patient receives.

This research has identified that there is room for improvement in the prescribing of NSAIDs, antiplatelets, and anticoagulants in family medicine. The inclusion of a pharmacist as part of the family medicine team may help to reduce PIPs; yet, the referral pattern to the pharmacist was less than optimal. With this knowledge, quality improvement programs can be developed to focus on these areas resulting in improvements in the quality of care to a large number of patients. Perhaps academic detailing sessions that focus on this issue should be targeted to both community pharmacists and physicians to address this problem at both ends of the ambulatory care spectrum.

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Appendix A

Chart Audit Procedure Manual

"A Retrospective Chart Review to Assess Potentially Inappropriate Prescriptions Related to Oral NSAID, Anticoagulant and Antiplatelet use in Two Family Medicine Teaching Clinics"

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Seven Oaks, Kildonan Medical Centre (KMC)
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Chart Abstraction Process (Data Collection)

Confidentiality
Confidentiality of the patient medical records must be observed at all times. The chart of a patient that may be known by the person conducting the chart review must be reviewed by

another team member or, if known to both members of the team, omitted. Patient charts that are actual staff members of the practice or members of their family are to be omitted.

A. ACCURO REPORTING

Step 1: Create a report for each of the following medications prescribed during the following time period: June 18, 2012 to June 18, 2013

- naproxen (M01AE02)
- etodolac (M01AB08)
- ketorolac (M01AB15)
- ketoprofen (M01AE03)
- piroxicam (M01AC01)
- tiaprofenic acid (M01AE11)
- diclofenac (M01AB05)
- floctafenine (N02BG04)
- prasugrel (B01AC22)
- meloxicam (M01AC06)
- mefenamic acid (M01AG01)
- diflunisal (N02BA11)
- flurbiprofen (M01AE09)
- indomethacin (M01AB01)
- sulindac (M01AB02)
- nabumetone (M01AX01)
- tenoxicam (M01AC02)
- celecoxib (M01AH01)
- warfarin (B01AA03)
- dabigatran (B01AE07)
- rivaroxaban (B01AF01)
- apixaban (B01AF02)
- clopidogrel (B01AC04)
- ticagrelor (B01AC24)
- dipyridamole (B01AC07)
- ticlopidine (B01AC05)
- naproxen and esomeprazole (M01AE52)
- diclofenac combinations (M01AB55)

1. Go to “Reports” in the menu bar across the top ➔ “Alerts (Query Builder)”
2. “Alert Definition”
    a. Choose [FMC “All Active Clients”] For KMC site choose [KMC “All Active Clients”]
    b. Click “copy” button and rename the Query OR Create New Query (red “+“ sign)
    c. Office: FMC, status “active”
3. Categories
    a. EMR ➔ Prescription
    b. Remove status “active” from rule
    c. Click “new” or green “+” sign
        i. select “classification” – from drop down menu
        ii. insert ATC code
    d. Click “New” or green “+” sign➔Start date type of constraint
        i. Select “between” dates from drop down menu
        ii. Enter 06/18/2012 – 06/18/2013
        iii. “Update Rule”
    e. Demographics ➔File number
        i. “Update Rule”

N.B.
- click on the “pencil” at the top to edit the query manually
- Choose “Patient Records ONLY” if you get multiple results for one patient

4. Run Report ➔ All Patients ➔ Fields to Display (include chart # by double clicking) ➔ Run
5. Alert Matches ➔ Select charts you want
    a. At bottom, “Export” to excel as a .CSV file (name by medication)
    b. For instructions on saving the file - See Appendix 1 “Saving Exported reports via Citrix”
    c. When saving the report, make sure you delete all identifying information except **Patient Initials and Clinic Chart #**
    d. delete duplicate records
    e. Make sure to password protect the document

STEP 2 - A report for each medication will be run. All identified charts will be screened.

STEP 3 – Review charts for inclusion/exclusion

1. Record the initials and clinic chart# on the “Master List”
2. Evaluate for Inclusion/Exclusion
    a. Review the encounter notes for an indication that the patient is on the Palliative Care Program
3. If excluded – indicate reason
4. If included – assign a unique identifier

<u>Patient charts are eligible for inclusion</u> if they are currently under the care of a clinic physician and have an active prescription for any of the previously listed medications at any point between July 18, 2012 and July 18, 2013.

Patient charts are excluded if they are receiving palliative care or have only taken the index medication for less than four days.

All screened patients will be recorded on the Master List and assigned a Screening ID. If the patient does not meet the above inclusion criteria, this should be recorded on the Master List (giving them a Screening ID and indicating their non-eligibility and the reason for it) and go on to the next chart. Once an eligible chart is found this patient is assigned a Unique Participant Code.

If the patient meets criteria for inclusion, they will also be given a Unique Participant Code (Patient ID, ranging from A1-A750 for FMC and B1-B750 for KMC) in sequential order on the Master List (along with a screening ID and the eligible box ticked Yes). The Unique Participant Code is then entered on the top left-hand corner of the Data Capture Sheet, along with the site ID (FMC = A or KMC = B) and the date the data was collected. No other patient identifying information should be entered on the Data Capture Sheet.

For validation purposes, some charts will need to be accessed a second time by the Co-PIs. Therefore the Master List will contain Patient Initials and Clinic Chart Number. **This list must be saved on a single-person access drive (H: drive) on the hospital server (SBGH/SOGH) within a password protected file.**

B. Data Collection

Review the chart and fill out the "Data Capture Sheet". Keep completed forms in locked cabinet within the clinic when not in use.

Step 1 – Enter the Unique Participant Code and site ID (FMC = A or KMC = B) on the top left hand corner

Step 2 – Enter the Demographic Data

Step 3 – Enter data elements from chart

- Go to "medications" tab to obtain prescription information and double click on the prescription
- Go to "External Medications" on the medical band
- Go to the "Encounter note" to obtain clinical details
- Go to "History of Medical Problems" on the medical band to record relevant diagnoses
- Go to "virtual chart" to obtain laboratory results/scanned documents
- Number of currently prescribed medications excludes: topical creams/ointments/lotions, short term medications (e.g. antibiotics), prn medications (e.g. nitroglycerin spray) and vaginal estrogen cream. PRN medications are defined as those used ≤3 days per week. Included are: inhalers, nasal sprays, eye drops, topical patches and OTCs (if prescribed; except saline).

Step 4 – Assess chart for potentially inappropriate prescriptions

- Only a dose of 200 mcg misoprostol qid has evidence of clinical PUD reductions. As such, only this dose will be considered adequate gastro-protection. Additionally, the dose of a PPI must be at least a once daily dose of a standard dose to be considered adequate gastro-protection

- If OTC ASA and/or NSAID usage unsure/not documented, assessment for PIPs assumed the patient was not taking the medications

N.B.
-If there is any ambiguity in the chart, the reviewer will request a second review to be performed by either CD or JF.
-A second pharmacist will also review the first 20 record, then a random selection of records to ensure quality data abstraction.

C. Excel Data Entry
- Data entry is outlined in the codebook (available upon request).

D. Data Cleaning
- identify and correct errors made during data entry
- correct typos, spelling errors, remove duplicates

E. Data Validation
- check that data is sensible and possible
- compare data against applicable rules
- identify inappropriate or out of range values
Data Validation in Excel - Full Tutorial at: http://www.contextures.com/xlDataVal01.html

F. Data Verification
- Check that data is entered correctly and that there are no transcription errors
- confirm that missing data is indeed missing
- Verify a sample of DCSs with charts
- Compute percent accuracy overall and for subsections (demographics, diagnostics, and surgical procedures)
- Goal: 95% accuracy - Identify sections falling below 80% accuracy for full verification
- Verify all missing information if possible
-Second pharmacist will perform this duty on the first 20 charts and a random selection throughout (time permitting)

Appendix B

Data Collection/Capture Sheet

Protocol Title: A Retrospective Chart Review to Assess Potentially Inappropriate Prescriptions Related to oral NSAID, Oral Anticoagulant and Antiplatelet use in Two Family Medicine Teaching Clinics.

Data to be collected on paper and subsequently entered into a computer spread sheet

Date Data collected: _____ Collected by:_____

Data Elements to be collected:

Demographic data:

Age: _____ Gender: _____ Height_____ Weight:_____

# of prescribed medications:_____ Charlson Comorbidity Index: _____

Data elements from chart:

(Q1) Traditional oral NSAID: Yes ☐ No ☐
(Q2) Selective oral NSAID: Yes ☐ No ☐
(Q3) Oral anticoagulant: Yes ☐ No ☐
(Q4) Oral antiplatelet agent: Yes ☐ No ☐
(Q4a) ASA: Yes ☐ No ☐ Unclear ☐ Not documented ☐
(Q4b) If Yes, ASA documented in: prescribed meds ☐ external meds ☐ other ☐ _____
(Q4c) Non-prescription oral NSAID? Yes ☐ No ☐ Unclear ☐ Not documented ☐

Q5

Index Drug Name-Rx and OTC (generic)	**Dose/ Frequency/weekly use** eg: 500 mg bid 3d /wk.	**Date Prescribed & Duration**	**Indication**

Q6

Co-prescribed drugs (PPI, H2RA, misoprostol, corticosteroids)	**Dose/ Frequency/weekly use** eg: 500 mg bid 3d /wk.	**Date Prescribed & Duration**	**Indication**

(Q7) History of MI? Yes ☐ No ☐ Date and description of MI:_____

(Q7a) Patient treated with: PCI ☐ CABG ☐ Medical therapy ☐
(Q7b) No stent? ☐ Drug eluting stent? ☐ subtype_____ Bare metal stent? ☐
(Q7c) Stent insertion: < 6 months? ☐ 6-12 months? ☐ > 1 yr ago ☐

Medical hx question		Yes	No	Date	Medical hx question		Yes	No	Date
Q8	TIA				**Q16**	PUD			
Q9	Stroke				**Q17**	Other bleed			
Q9a	subtype:				**Q17a**	Describe:			
Q10	diabetes				**Q18**	GI bleed			
Q11	HTN				**Q19**	Major bleed			
	reading:				Defined as: requiring hospitalization, transfusion or resulted in a hemoglobin drop of >20g/L, ICH				
Q12	HF				**Q20**	Atrial fibrillation			
Q13	PE				**Q21**	prosthetic valve			
Q14	DVT				**Q22**	heart valve dz			
Q15	Cancer				**Q22a**	recurrent embolism with valve dz			
Q15a	active chemo								
	If Yes, treatment:								

(Q23) Estimated CrCl: ☐ < 30 mL/min ☐ 30-50 mL/min ☐ > 50 mL/min
☐ No SCr recorded within last 12 months

(Q24) Registered with Manitoba Renal Program? Yes ☐ No ☐
(Q24a) If Yes, renal transplant ☐ pre-dialysis ☐ dialysis ☐ (hemo ☐ peritoneal ☐)

(Q25) Platelet count documented within last 12 months? Yes ☐ No ☐ value:_____

(Q26) Liver dysfunction? Yes ☐ No ☐ Not documented ☐
(Q26a) ALT >3xULN Yes ☐ No ☐
(Q26b) AST >3xULN Yes ☐ No ☐
(Q26c) bilirubin >2xULN Yes ☐ No ☐

(Q27) Alcohol consumption ≥8 drinks per week? Yes ☐ No ☐ Not documented ☐

(Q28) $CHADS_2$ Score: _____ HAS-BLED score: _____ N/A ☐

(Q29) How many clinic visits has the patient had within the last 12 months? _____

(Q30) Pharmacist consult within the last year? Yes ☐ No ☐
(Q30a) If Yes, before or after index medication initiated? _____

If taking traditional (e.g. naproxen) or selective NSAID (e.g. celecoxib):

(Q31) Age ≥ 65? Yes ☐ No ☐

(Q32) History of uncomplicated peptic/duodenal ulcer disease? Yes ☐ No ☐

(Q33) Concomitant corticosteroid? Yes ☐ No ☐

(Q34) Concomitant oral anticoagulant? Yes ☐ No ☐

(Q35) Concomitant ASA? Yes ☐ No ☐

(Q36) If Yes to 1 or 2 of Q31-35, is patient taking PPI ☐ misoprostol ☐ H2Blocker ☐
If Yes PPI/misoprostol, proceed to Q37
(Q36a) Is patient using celecoxib? Yes ☐ No ☐ If No, PIP#9; proceed to Q37
(Q36b) If Yes to Q36a, is patient taking ASA/anticoagulant in addition to 1 other previously mentioned risk factor? Yes ☐ No ☐ If Yes, PIP #13

(Q37) Does patient have a history of complicated PUD (perforation/obstruction/bleed) OR yes to >2 of Q31-35? Yes ☐ No ☐ If No, proceed to Q38
(Q37a) If Yes to Q37, is patient taking celecoxib AND PPI/misoprostol? Yes ☐ No ☐
If No, PIP #9

(Q38) Taking 2 NSAIDs (excluding ASA)? Yes ☐ No ☐ If Yes, PIP #10

(Q39) Taking above maximum recommended dose? Yes ☐ No ☐ If Yes, PIP #12
(some maximum doses/day of common NSAIDs: indomethacin 200mg, diclofenac 200mg, ketorolac 40mg x7days max, ibuprofen 2.4-3.2g, naproxen 1-1.5g, celecoxib 400mg)

(Q40) Taking Indomethacin or Ketorolac AND Age ≥ 65? Yes ☐ No ☐ If Yes, PIP# 11

(Q41) Concomitant OAC AND Age ≥ 65? Yes ☐ No ☐ If Yes, PIP#8

If taking oral anticoagulant:

(Q42) Was an INR performed within the last month? Yes ☐ No ☐ N/A (Using NOAC) ☐
(Q42a) If No, was INR performed in the last 3 months? Yes ☐ No ☐
(Q42b) Was INR stable (defined as an INR that did not require adjustment for at least three months)?
Yes ☐ No ☐
If INR not recorded within the last month (or 3 months if patient meets criteria) PIP #6

(Q43) Concomitant clopidogrel? Yes ☐ No ☐ Other antiplatelet? _____
(Q43a) Age ≥ 65 Yes ☐ No ☐ If No, proceed to Q44
(Q43b) If Yes to Q43a, is patient taking: PPI ☐ Misoprostol ☐ H2Blocker ☐
If No PPI/misoprostol, PIP# 5

(Q44) Concomitant ASA, clopidogrel and warfarin? Yes ☐ No ☐ If Yes, PIP# 1
Other anticoagulant? _____ Other antiplatelet? _____

(Q45) Use for first provoked DVT/PE for longer than 3 months? Yes ☐ No ☐ If Yes, PIP #7

(Q46) Concomitant ASA? (excluding those on triple therapy) Yes ☐ No ☐ If Yes, PIP #2
(Except in the following situations: i.) Diagnosis of atrial fibrillation and treated for ACS without stent placement for up to 12 months. ii) Recurrent embolism in mitral valve stenosis or regurgitation in patients with a low bleeding risk. iii) Post-ACS patients who are considered high risk for left ventricular thrombus [large anterior MI, significant heart failure or atrial fibrillation] that do not undergo stent placement for up to 3 months. iv) Mechanical valves if at low bleeding risk for an indefinite duration.)

(Q46a) If Yes to Q47, is patient taking: PPI ☐ Misoprostol ☐ H2Blocker ☐
If No PPI/misoprostol PIP #3

(Q47) Concomitant tNSAID AND Age ≥ 65? Yes ☐ No ☐ If Yes, PIP#8

(Q48) Concomitant NSAID or celecoxib and other risk factors (as per Q31-37) Yes ☐ No ☐

If Yes, PIP#9/13

If patient is taking antiplatelet agent:

(Q48) Concomitant ASA, clopidogrel and warfarin? Yes ☐ No ☐ If Yes, PIP# 1
Other anticoagulant? _____ Other antiplatelet? _____

(Q49) Concomitant warfarin? (excluding those on triple therapy) Yes ☐ No ☐ If ASA, PIP#2
(Q49a) If Yes to Q49, is patient taking: PPI ☐ Misoprostol ☐ H2Blocker ☐
If No PPI/misoprostol PIP# 3

(Q50) Concomitant ASA and clopidogrel? Yes ☐ No ☐ If Yes, PIP #4
Other antiplatelet? _____

(Except in the following situations: i.) Post-ACS with or without a percutaneous intervention (± stent) for up to 12 months. ii.) CABG for non-ST elevation ACS for up to 12 months. iii.) Diagnosis of atrial fibrillation with evidence of oral anticoagulant failure.)

(Q50a) Age ≥ 65 Yes ☐ No ☐
(Q50b) If Yes to Q50a, is patient taking: PPI ☐ Misoprostol ☐ H2Blocker ☐
If No PPI/misoprostol PIP #5

Summary:

Presence of current PIP? Yes ☐ No ☐ Presence of past PIP? Yes ☐ No ☐

PIP #

PIP #	Resolved how? (was it identified? did the prescription expire?)

Appendix C

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS
Research Ethics Boards

P126 - 770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Telephone 204-789-3255
Fax 204-789-3414

HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Mr. K. Hamilton	UofM / Pharmacy	HS16565 (H2013:316)
APPROVAL DATE: August 20, 2013	**EXPIRY DATE:** August 20, 2014	
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. C. Davis		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE;
NA	A Retrospective Chart Review to Assess Potentially Inappropriate Prescriptions Related to Oral NSAID, Anticoagulant and Antiplatelet Use in two Family Medicine Teaching Clinics
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: UofM Internal Funds	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
July 30, 2013	August 8, 2013

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date

Protocol:

Proposal received August 8, 2013

Consent and Assent Form(s):

Other:

Data Collection/Capture Sheet received August 8, 2013

CERTIFICATION

The above named research study/project has been reviewed in a ***delegated manner*** by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION

The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

John Arnett, PhD. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone**: (204) 789-3255/ **Fax:** (204) 789-3414

P126 - 770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Telephone 204-789-3255
Fax 204-789-3414

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS Research Ethics Boards

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF FINAL APPROVAL FOR AMENDMENTS AND ADDENDUMS

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Mr. K. Hamilton	UofM / Pharmacy	HS16565 (H2013:316)
HREB MEETING DATE (If applicable):	**APPROVAL DATE:** October 17, 2013	
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. C. Davis		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
NA	A Retrospective Chart Review to Assess Potentially Inappropriate Prescriptions Related to Oral NSAID, Anticoagulant and Antiplatelet Use in two Family Medicine Teaching Clinics
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: UofM Internal Funds	

REMINDER: THE CURRENT HREB APPROVAL FOR THIS STUDY EXPIRES: August 20, 2014

REVIEW CATEGORY OF AMENDMENT:	Full Board Review ☐	Delegated Review ☒
Submission Date of Investigator Documents: October 9, 2013	**HREB receipt date of Documents:** October 10, 2013	

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date

Protocol:

Amendment per report received October 10, 2013

Consent and Assent Form(s):

Other:

Data Collection/Capture Sheet — October 10, 2013

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the amendment to the research study/project named on this ***Certificate of Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. The amendment and documents listed above were granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION

The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulation of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. This amendment is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

John Arnett, PhD. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone**: (204) 789-3255/ **Fax:** (204) 789-3414

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS
Research Ethics Boards

P126 - 770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Telephone 204-789-3255
Fax 204-789-3414

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF FINAL APPROVAL FOR AMENDMENTS AND ADDENDUMS

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Mr. K. Hamilton	UofM / Pharmacy	HS16565 (H2013:316)
HREB MEETING DATE (If applicable):	**APPROVAL DATE:** December 19, 2013	
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. S. Bugden		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
NA	A Retrospective Chart Review to Assess Potentially Inappropriate Prescriptions Related to Oral NSAID, Anticoagulant and Antiplatelet Use in two Family Medicine Teaching Clinics
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: UofM Internal Funds	

REMINDER: THE CURRENT HREB APPROVAL FOR THIS STUDY EXPIRES: August 20, 2014

REVIEW CATEGORY OF AMENDMENT:	Full Board Review ☐	Delegated Review ☒
Submission Date of Investigator Documents: December 12, 2013	**HREB receipt date of Documents:** December 12, 2013	

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date

Protocol:

Amendment per report received December 12, 2013

Consent and Assent Form(s):

Other:

Data Collection/Capture Sheet — November 20, 2013

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the amendment to the research study/project named on this ***Certificate of Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. The amendment and documents listed above were granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION

The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulation of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. This amendment is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

John Arnett, PhD. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone**: (204) 789-3255/ **Fax:** (204) 789-3414

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Telephone 204-789-3255
Fax 204-789-3414

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS
Research Ethics Board

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF ANNUAL APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Mr. K. Hamilton	UofM/Pharmacy	HS16565 (H2013:316)
HREB MEETING DATE (If applicable):	**APPROVAL DATE:** January 27, 2015	**EXPIRY DATE:** **August 20, 2015**
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. S. Bugden		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
NA	A Retrospective Chart Review to Assess Potentially Inappropriate Prescriptions Related to Oral NSAID, Anticoagulant and Antiplatelet Use in two Family Medicine Teaching Clinics
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: UofM Internal Funds	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
January 22, 2015	January 27, 2015

REVIEW CATEGORY OF ANNUAL REVIEW: **Full Board Review** ☐ **Delegated Review** ☒

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name(if applicable)	Version(if applicable)	Date

Annual approval

*Annual approval implies that the most recent **HREB approved** versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc. are approved.*

Consent and Assent Form(s):

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the annual study status report for the research study/project named on this ***Certificate of Annual Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. Annual approval was granted by the Chair or Acting Chair, UM HREB, per the response to the conditions of approval outlined during the initial review (full board or delegated) of the annual study status report.

HREB ATTESTATION

The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE

The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of annual approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

John Arnett, PhD., C. Pysch.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone**: (204) 789-3255/ **Fax:** (204) 789-3414

Hôpital St-Boniface Hospital

409 Taché Ave, Winnipeg MB Canada R2H 2A6

Research Review Committee
Approval Form

Principal Investigator:	**Mr. K. Hamilton**
RRC Reference Number:	**RRC/2013/1339**
Date:	**August 27, 2013**
Protocol Title:	**A Retrospective Chart Review to Assess Potentially Inappropriate Prescriptions Related to Oral NSAID, Anticoagulant and Antiplatelet use in Two Family Medicine Teaching Clinics**

The following is/are approved for use:

- **Proposal, Version reviewed at the RRC meeting held on August 7, 2013**
- **Data Collection/Capture Sheet, Version reviewed at the RRC meeting held on August 7, 2013**

The above was approved by Dr. B. Ramjiawan, Co-Chairperson, Research Review Committee (RRC), St. Boniface Hospital, on behalf of the Committee. As the recommendations by the Research Review Committee have been met, final approval is now granted.

As a reminder any changes to the study Protocol and/or Informed Consent Form must be reported to the Research Review Committee along with any other documents required as per Standard Operating Procedures for Clinical Investigators. The Research Review Committee must be notified regarding discontinuation or study closure.

Should you require assistance during any stage of your research project, please do not hesitate to contact the St. Boniface Hospital Office of Clinical Research (204-258-1044).

The Research Review Committee wishes you much success with your study.

Sincerely yours,

[redacted]

Dr. B. Ramjiawan
Co-Chairperson, Research Review Committee
St. Boniface Hospital

Please quote the above reference number on all correspondence.
Inquiries should be directed to the RRC Secretary
Telephone: (204) 235-3623 **Fax**: (204) 237-9860
R1004 – 409 Taché, Winnipeg, MB, Canada R2H 2A6

SEVEN OAKS
General Hospital

Contact Information
(T) 204.631.3834, (F) 204.632.9539

Office of the Research Director
Approval Form

August 27, 2013

Principal Investigator: Kevin Hamilton, BSP, Masters of Pharmacy (Candidate)
Dr. Christine Davis, Assistant Professor, U of M

Study Title: ***A Retrospective Chart Review to Assess Potentially Inappropriate Prescriptions Related to Oral NSAID, Anticoagulant and Antiplatelet use in Two Family Medicine Teaching Clinics***

The above has been evaluated and approved by Dr. Paul Komenda, Medical Research Director for Seven Oaks General Hospital/Wellness Institute.

We wish you success with your study. Should you have any questions, please do not hesitate to contact us.

Sincerely,

[redacted]

Christine Bencharski
Research Admin
Seven Oaks General Hospital

[redacted]

Paul Komenda MD, FRCPC, MHA, CHE
Assistant Professor of Medicine
University of Manitoba
Director of Research
Seven Oaks General Hospital

cc:
Dr. Ricardo Labato Da Faria, CMO, SOGH
Dr. Tunji Fatoye, KMC Unit Director

Winnipeg Regional Health Authority / Office régional de la santé de Winnipeg
Caring for Health / À l'écoute de notre santé

200 – 1155 Concordia Avenue
Winnipeg, Manitoba
R2K 2M9 CANADA

September 11, 2013

Mr. Kevin Hamilton
Faculty of Pharmacy
University of Manitoba
750 McDermot Avenue
Winnipeg, MB R3E 0T5

Dear Mr. Hamilton:

Re: "A Retrospective Chart Review to Assess Potentially Inappropriate Prescriptions Related to Oral NSAID, Anticoagulant and Antiplatelet Use in Two Family Medicine Teaching Clinics" – WRHA Reference No: 2013-034

We are pleased to inform you that your research access request for the above-named study has been approved by the Winnipeg Regional Health Authority (WRHA) Research Review.

As this is a retrospective audit, the work can be done in the *Community Accuro Research Stage* database for the FMC and KMC clinics, and not in the live production database used by FMC and KMC clinics. Sandra Mann (CSIS) will need to verify that the current *Research Stage* database fits the study's time frame and, if an update to the *Research Stage* database (if needed) can be done without impacting another study underway.

An account request will need to be made to Manitoba eHealth for access to the EMR - the role requested needs to be that of researcher (this gives view only privileges). It should also stipulate access to the *Community Accuro Research Stage* database for FMC and KMC clinics only. Sandra Mann (CSIS) will ensure the account is set up correctly and she should be copied on the request made to MB e-Health for a research account. Once the research account is established, data analysts from CSIS can begin to work with you and Dr. Christine Davis to develop the query for the data needed answer your research questions.

Your research access is also approved pending confirmation that the following conditions are met or agreed to:

- You, your co-investigators, and your research assistants comply with the relevant privacy legislation as indicated below.

  [X] *The Personal Health Information Act*

  [ ] *The Freedom of Information and Protection of Privacy Act*

  [ ] *The Personal Health Information Act* and *The Freedom of Information and Protection of Privacy Act*

- **In the event that your REB approval expires before the completion of this project, please copy us on your Application for Renewal and please send us an updated copy of the Renewal Approval once received by REB;**
- You complete and return the attached Confidentiality Agreement(s) to Judy Dyrland, Concordia Hip & Knee Institute, WRHA, 200 – 1155 Concordia Avenue, Winnipeg, MB R2K 2M9;
- You submit to our attention any significant changes in your proposal prior to implementation or any significant changes during the course of the study;
- You submit a summary of the final results of the study to the WRHA and provide us with a copy of any publications arising from the study;
- It is an expected courtesy that WRHA will be given a minimum of five working days advance notice of publication or presentation of results with policy implications, in order to be prepared for public response;
- You agree to be accountable for appropriate storage and elimination of material.
- You agree to acknowledge the WRHA and/or affiliated organizations in any peer-reviewed publications of the results of this study.

Thank you for selecting the Winnipeg Regional Health Authority as the site to conduct your research. Please let us know should you encounter any site-related difficulties during the course of your study.

We extend best wishes for successful completion of your study.

Yours Sincerely,

[redacted]

Dr. Colleen J. Metge, BSc (Pharm), PhD
Director, Research and Evaluation Unit
Chair, WRHA Research Review Committee
Winnipeg Regional Health Authority

cc. Ms. Arlene Wilgosh, President and CEO, WRHA
Dr. John Arnett, Chair, HREB

Encl: ***PHIA Agreement***

family medical centre
5th floor, 400 tache avenue. winnipeg, manitoba, canada r2h 3e1
Tel: (204) 237-2863
Fax: (204) 231-2648

August 30, 2013

Re: "A Retrospective Chart Review to Assess Potentially Inappropriate Prescriptions Related to Oral NSAID, Anticoagulant and Antiplatelet use in Two Family Medicine Teaching Clinics"

Dear Members of the REB:

This letter is in support of the study, "A Retrospective Chart Review to Assess Potentially Inappropriate Prescriptions Related to Oral NSAID, Anticoagulant and Antiplatelet use in Two Family Medicine Teaching Clinics" to take place at Family Medical Centre and Kildonen Medical Centre. It will be implemented by Kevin Hamilton, BSP and Dr. Christine Davis, Pharm. D.

The study will examine prescribing practices at these clinics and has the potential both to improve patient care and enhance the learning of our Family Medicine residents. The clinics will provide the space necessary to complete the project and will allow access both to our electronic medical records and paper charts if necessary.

Please consider approval of this worthwhile project.

Sincerely,

[redacted]

Gerald Konrad MD
Unit Director, Family Medical Centre

Hôpital St-Boniface Hospital