R$_x$IALTA: Pharmacist CVD Intervention for Patients with Inflammatory Arthritis and Psoriasis

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Background/Rationale

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide and in Canada accounting for nearly one third of the total deaths in both instances.[1-2] The majority of CVD cases are caused by modifiable risk factors such as tobacco use, obesity, hypertension, hyperlipidemia, diabetes and physical inactivity.[3] Inflammatory arthritis (IA), inclusive of rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), gout and systemic lupus erythematosus (SLE) and cutaneous psoriasis are also recognized as an independent risk factor for CVD.[4-7]

It has been reported that the risk of myocardial infarction (MI), heart failure (HF) and CV death among patients with IA is 2–3-fold greater than in the general population.[8-10] Similar numbers are reported for psoriasis. This increased CV risk reflects the combined impact of systemic inflammation, burden of traditional CVD risk factors and impact of certain medications (e.g. steroids, non-steroidal anti-inflammatories [NSAIDs], retinoids).[5,6] An elevated risk of CVD can be identified early after the diagnosis, or even in the childhood, emphasizing the need for early efforts in CV risk screening.[11]

Despite being recommended by international management guidelines,[7] CV risk assessment has not been incorporated into clinicians' daily routine.[7] Indeed, it has been reported that such assessments generally only exist in larger centers for non-rheumatology patients.[12-14] Moreover, Keeling and colleagues reported that most rheumatologists, who are the main caregivers for IA patients, conducted suboptimal CV risk assessments. [15] Similarly, patients with psoriasis are less likely to receive optimal treatment for the cardiovascular risk factors than the general population without skin disease. This gap in care is not consistently absorbed by family physicians due to lack of recognition of CV risk in these patients and competing demands of other healthcare needs (e.g. other chronic diseases, cancer, diabetes). [7]

Special considerations need to be taken into account when calculating CV risk in patients with IA and psoriasis, as the 'classic' risk engines (such as Framingham[16]) might underestimate the overall risk,[17] since they have not been adequately evaluated in this patient population.[18,5] For example, IA patients who might benefit from lipid-lowering agents may be categorized "low risk" when using the Framingham risk engine.[17] As such it has been recommended to use a modified Framingham risk engine (multiply the overall risk with 1.5) in patients with IA. [19] There is conflicting evidence in the literature regarding lipid panel measurements in patients with RA. Some studies reported that total cholesterol and LDL-cholesterol are significantly lower, while other studies reported that they are significantly higher in patients with RA when compared to the general populations. [20-22] Despite the variation, it is still recommended to treat patients with RA to general population lipid targets with consideration of risk modification (e.g., European League Against Rheumatism (EURL) 1.5 multiplicative factor).[23-24]

CV risk screening and management takes time and effort, but can be performed by other trained health professionals. As such, it has been recommended to utilize a multidisciplinary approach (integration of rheumatology, dermatology, cardiology and primary care) to support the care of IA patients.[6,25-28] Pharmacists are front line, accessible, primary healthcare professionals who see patients more frequently than any other healthcare provider.[29] The efficacy of their interventions in managing chronic diseases including osteoarthritis,[30] diabetes,[7, 31] dyslipidemia,[32] hypertension,[33,34] heart failure,[35] and CVD [36-39] has been well demonstrated in the literature. Pharmacists can systematically identify patients at high risk of CVD,[40] improve their medication use,[41] and help them achieve their treatment targets.[32,33] In addition to clinical outcomes, pharmacist involvement in patient care is associated with

improved patient satisfaction and adherence to therapy.[33,40,41] This evidence, coupled with their advanced scope of practice, ideally position pharmacists to conduct CV risk screening and management. In addition, Canadian pharmacists have access to practice guidelines for management and prevention of cardiovascular disease in the general population.[42] They also have access to the R$_x$EACH CV risk calculator, an interactive CV screening and management tool, which will help them determine CV risk, simply communicate contributing risks to patients, and show patients the impact of modifying their risks. [39]

Further studies are required to determine the feasibility of pharmacists providing CV risk screening and management for patients with chronic inflammation.

Objectives

The overall purpose of this project is for pharmacists to deliver CV risk screening and management for patients with IA and psoriasis, and determine whether such an approach results in reductions in global CV risk.

Primary objective:

The *primary objective* is to determine the effect of a pharmacist-led intervention on CV risk in patients with IA and psoriasis.

Secondary objectives:

The *secondary objectives* are to determine the effect of a pharmacist-led intervention on the following factors:
- Blood pressure
- Total cholesterol
- HDL-cholesterol
- LDL-cholesterol
- HbA1c
- Tobacco cessation (self-reported abstinence)
- Patient satisfaction

Methods

Design: A non-randomized prospective pre-post-intervention design.

Setting: 24 Calgary Co-op community pharmacies in Calgary and surrounding area

Patients/Population:

Inclusion criteria:
Adults (≥18 years of age) who have a physician-diagnosed inflammatory conditions including
- Rheumatoid arthritis

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- Psoriatic arthritis
- Ankylosing spondylitis
- Gout
- Systemic lupus erythematosus
- psoriasis vulgaris

- To be eligible for inclusion, all patients must have at least one uncontrolled risk factor (i.e., blood pressure (non-Diabetes, ≥140/90; Diabetes, ≥130/80)[43], LDL-cholesterol (>2.0 mmol/L)[44], HbA1c (>7.0%)[45], or current tobacco use)

Exclusion criteria:

Patients will be excluded if they
- Are unwilling to participate/sign consent form
- Are unwilling or unable to participate in regular follow-up visits
- Are pregnant
- Have uncontrolled IA (i.e., during a disease exacerbation – this may be indicated by current treatment with high or tapering dose of steroids) (Lipid panel is most accurately measured when IA disease is stable or in remission[5], as such patients with uncontrolled IA will be excluded)

Recruitment/Case Finding:

Pharmacists and pharmacy staff are going to use the following methods to recruit patients for the study:
- Proactive case finding
  - Patients with physician diagnosed IA will be identified via:
    - Coordinating prescriptions of disease modifying anti-rheumatic drugs (DMARDS), NSAIDs, immunosuppressants, gout medications, and/or biologics (e.g., adalimumab, infliximab) with a rheumatologist prescriber.
      - The research team has provided Calgary Co-op pharmacies with an updated list of Alberta rheumatologists
  - Patients with physician diagnosed psoriasis will be identified via coordinating prescriptions of topical drugs containing calcipotriol, methotrexate and a biologic (adalimumab, infliximab, ustekinumab, ixekizumab, secukinumab) with a dermatologist prescriber.
  - Patients using NSAIDs, DMARDs, biologics, immunosuppressants, and gout medication as well as exhibiting any of the following symptoms in their joints:
    - Pain/tenderness
    - Swelling
    - Warmth
    - Morning stiffness which lasts for more than an hour, will be referred to a family physician to confirm IA diagnosis (if they are not already diagnosed) prior to being informed about the study. Patients may also be referred to a rheumatologist as needed
  - Patients using topical medication containing calcipotriol alone or in combination with methotrexate, biologics, and acitretin, and
    - known diagnosis of psoriasis

- ▪ exhibiting scaly skin rash (will be referred to a dermatologist to confirm diagnosis)
- Case finding via in-pharmacy posters and weekly fliers
- Bag stuffers with IA medications (DMARDs, biologics, NSAIDs, immunosuppressants, gout)

If the patient meets the inclusion criteria for the study, he/she will be asked if they want to participate in the study. If the patient agrees to participate, he/she will be asked to sign a written informed consent form. After signing the consent form, the patient will be enrolled in the study.

The patient's treating physician(s) will receive a letter from the pharmacist to inform him/her that the patient agreed to participate in this study.

Figure 1 provides a visual illustration of the study procedures

Intervention:

All enrolled patients will receive the following:
- Patient assessment (blood pressure measurement according to Hypertension Canada guidelines [43], waist circumference, weight and height measurements)
- Laboratory assessment of HbA1c, non-fasting lipid panel (total cholesterol, LDL-cholesterol, HDL-cholesterol) and kidney function and status (creatinine [and estimated glomerular filtration rate], random urine albumin to creatinine ratio) (As part of the routine care, pharmacists will check the patient's most recent laboratory test results using Netcare)
- Individualized CV risk assessment and education regarding this risk (Figure 2)
    - o The validated R_xEACH CV risk calculator (Figure 2) will be utilized for baseline and subsequent risk assessment.[39] The pharmacist will enter patient demographics such as age, sex, cholesterol, blood pressure, tobacco use status, diabetes, etc and the system will use the most appropriate risk engine based on the patient's medical history. Modified Framingham[19] (Framingham risk score multiplied by 1.5) will be used to calculate risk in patients with IA. The United Kingdom Prospective Diabetes Study (UKPDS) [46], SMART risk score [47] and Framingham[16] will be used for patients with diabetes, previous vascular disease or CKD respectively. In the case where a patient has more than one co-morbidity the risk engine estimating the highest risk will be used.
    - o Patient's current CV risk will be discussed using the interactive R_xEACH CV risk calculator (Figure 2) which explains his/her individual risk and targets for intervention
    - o Education on CV risk factors and healthy lifestyle will be provided to the patient
- Treatment recommendations, prescription adaptation, and prescribing where necessary to meet treatment targets
    - o Pharmacists will practice to their full scope (including prescribing medications and ordering and interpreting laboratory tests when needed)
    - o Pharmacists will refer to other health care providers (family physicians, rheumatologist) as needed using their clinical judgement
- Regular communication with the patient's treating physician(s) after each contact with the patient

- Regular follow-up with all patients every month for 6 months to check on patients' progress and provide ongoing care and motivation
    - Pharmacists will order and interpret laboratory tests to monitor the impact of the intervention (HbA1C, lipid panel)
    - Pharmacists will refer to other health care providers (family physicians, rheumatologist) as needed using their clinical judgement

Outcomes

Primary outcome:
The *primary outcome* will be the change in CV risk over a 6-month period. Cardiovascular risk is defined as the risk for future cardiovascular events (coronary heart disease [CHD], stroke, peripheral arterial disease [PAD])[7,8] as calculated by validated risk engines.

The validated R$_x$EACH CV risk calculator[39] will be utilized to calculate CV risk. The calculator uses the most appropriate risk engine based on the patient's medical history. Modified Framingham[19] (Framingham risk score multiplied by 1.5), UKPDS [46], SMART risk score [47] and Framingham[16] will be used for patients with IA, diabetes, previous vascular disease or CKD respectively. In the case where a patient has more than one co-morbidity, the risk engine estimating the highest risk will be used.

Secondary outcomes:
The secondary outcomes will be the change over a 6-month period in:
- Blood pressure
- Total cholesterol
- HDL-cholesterol
- LDL-cholesterol
- HbA1c
- Tobacco cessation (self-reported abstinence)
- Patient satisfaction
    - The Patient Satisfaction with Pharmaceutical Care Questionnaire (PCSQ) [48] will be used to assess patients' satisfaction with the intervention. PCSQ is a validated instrument adapted for the pharmacy setting from the Patient Satisfaction Questionnaire developed by Ware and colleagues [49]. This is a self-administered instrument consisting of 20 questions answered with the 5-point Likert Scale (e.g. 5 = excellent, 1 = very poor). The data will be scored and quantified without patient identifiers. The outcome will be the mean patient satisfaction score ± standard error of the mean.

Sample size and analytical plan

Sample size:
For the primary outcome, we aim to detect a 21% relative reduction in CV risk between the pre-and-post intervention based on the findings of the R$_x$EACH study (previously completed by our group).[39] Given the expected reduction (21%), with 0.80 power, alpha of 0.05 and a SD of 17.8, the calculated sample size is 89 patients. Accounting for the risk of attrition from baseline to 6 months, we aim to recruit 100 patients.

Analytical plan:
In order to determine the change in CV risk over time, we will start by using paired t-test then use multiple regression of change in CV risk adjusting for all covariates with p<0.25.
The secondary outcomes will be analyzed using paired t-test or chi square test where appropriate, adjusting for all covariates with p<0.25.

Trial and Data Management will be done by EPICORE Centre

Project team and Feasibility

Arthritis is a very common problem in Alberta, with more than one in ten adults (15.3%) reporting having a type of arthritis in Canadian Health surveys. [50] With this high proportion of patients, we do not anticipate challenges with recruitment. Indeed, when prescriptions for DMARDs and biologics were coordinated with prescribing rheumatologists 1300 patients were identified within the 24 Co-op pharmacies who agreed to participate. As such we do not anticipate any issues in achieving our sample size of 100. Our team has extensive track records in conducting similar studies and have had success in pharmacist recruitment.[12, 32, 34] With expertise in rheumatology, cardiology, pharmacy and primary care, our team is well positioned to conduct this study. Principal Investigator, **Dr. Ross Tsuyuki**, B.Sc.(Pharm.), Pharm.D., M.Sc, is Professor in the Division of Cardiology, Faculty of Medicine at the University of Alberta. He has pioneered interventional studies in community pharmacies examining cardiac risk reduction and the improvement of cardiovascular outcomes. Co-PI, **Dr. Carlo Marra** B.Sc.(Pharm.), Pharm.D., Ph.D., Professor and Dean with the School of Pharmacy, University of Otago is dedicated to expanding the scope of practice of pharmacists. He has vast experience in conducting pharmacy practice studies in rheumatology, and expertise in health outcomes and patient satisfaction research. As a methodologist (Ph.D. in epidemiology and health outcomes), he will co-lead the analytical components of the study. **Dr. Yazid Al Hamarneh,** B.Sc. (Pharm), Ph.D, is the scientific officer of the Alberta SPOR SUPPORT Unit Consultation and Research Services Platform. He has conducted interventional studies in community pharmacy setting with special focus on cardiovascular risk reduction and cardiovascular risk factors. **Dr. Stephanie Keeling**, MD, MSc, FRCP(C) is a rheumatologist and Associate Professor at the University of Alberta. She has conducted a cardiovascular risk reduction clinic for IA patients for over five years and will provide her clinical expertise in IA to support this project, including the development of the intervention and pharmacist training. **Dr Robert Gniadecki, MD, PhD, DMSci** is a professor of dermatology and director of the Division of Dermatology at the University of Alberta. He conducted numerous studies focused on psoriasis comorbidities, cardiovascular risk factors in psoriasis and effect of therapy on cardiovascular morbidity and mortality.

Timelines

Study Year	Year 1 02/17 - 12/17				Year 2 01/18 - 12/18			
Calendar Year Quarters	*Q1*	*Q2*	*Q3*	*Q4*	*Q1*	*Q2*	*Q3*	*Q4*

Ethics, finalize intervention & develop database	▓							
Training and recruitment	▓	▓						
Data collection		▓	▓	▓	▓	▓		
Data analysis						▓	▓	
Synthesis & KT								▓

What This Study Adds

This is the first study to assess the effect of a pharmacist-led intervention on CV risk in patients with IA in the community pharmacy setting. It has a public health importance since it will provide CV risk assessment for a high risk population who otherwise will not receive such service.[15] As well, it improves access to care in patients who are not affiliated with a family physician or those who see their family physician infrequently. Indeed, it has been reported that pharmacists see patients with chronic conditions more frequently than any other healthcare professional.[29] As frontline professionals, pharmacists can be the first port of call to bring those patients back into the healthcare system.

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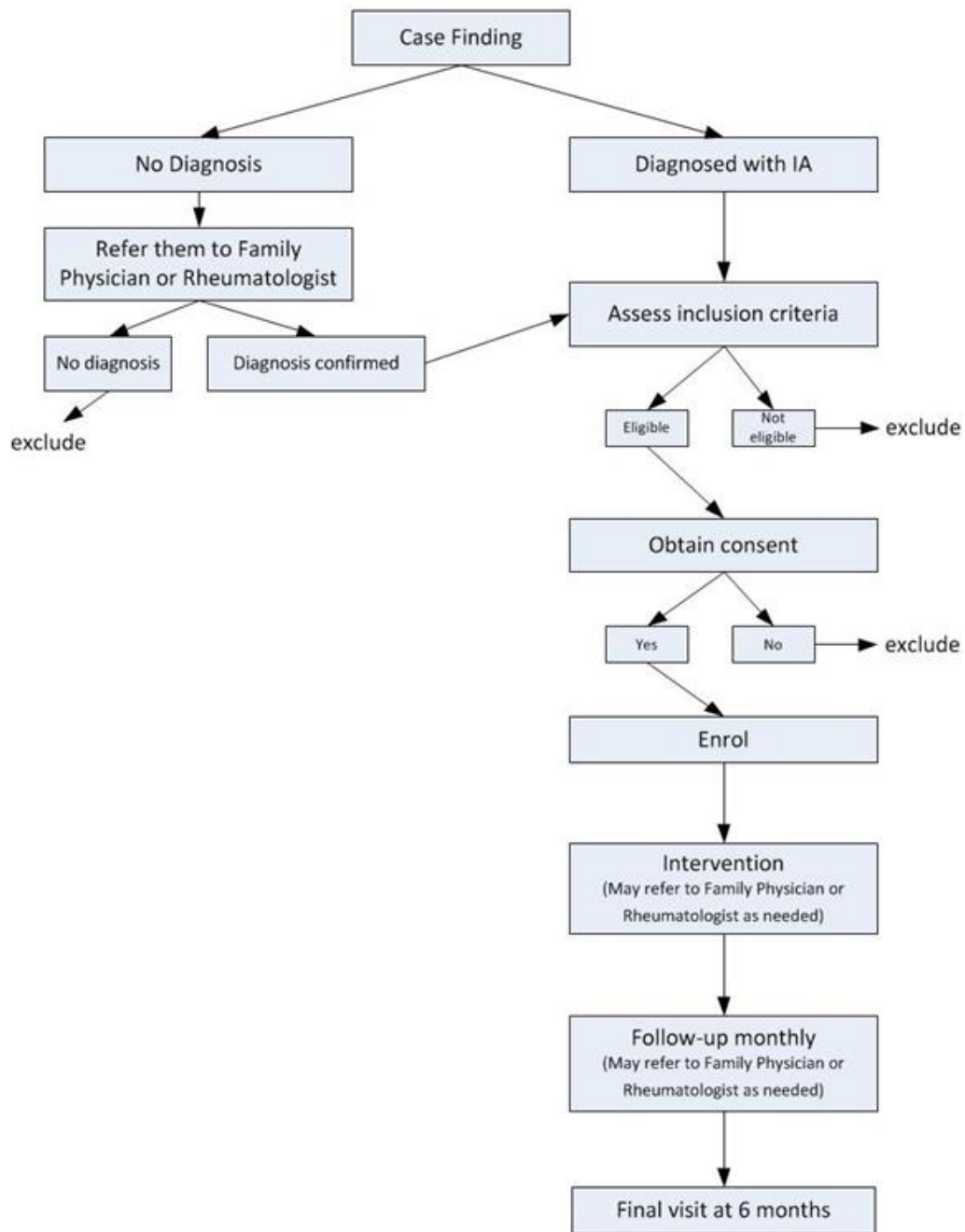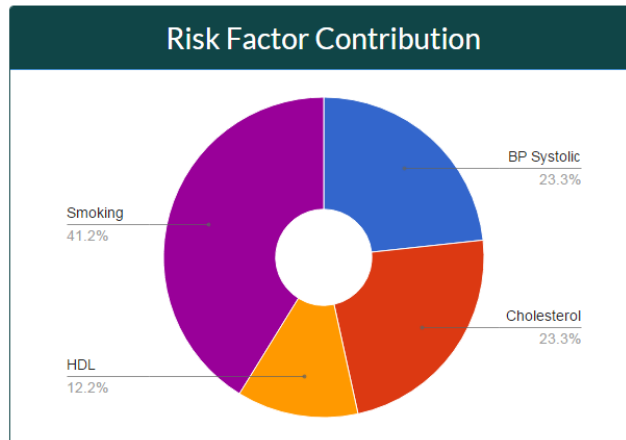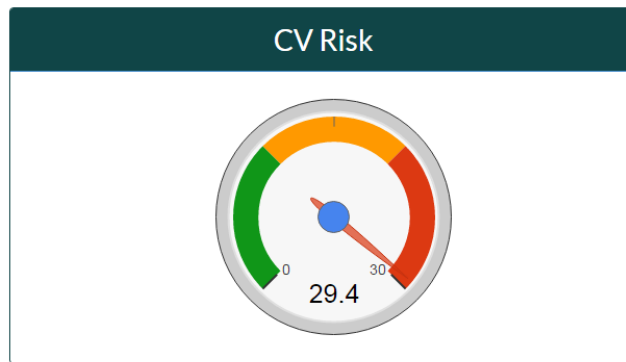
Figure 1: Visual illustration of the study procedures

Figure 2: RxEACH CV risk calculator