BMJ Open

R_xIALTA: Pharmacist CVD Intervention for Patients with Chronic Inflammatory Diseases

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043612
Article Type:	Original research
Date Submitted by the Author:	11-Aug-2020
Complete List of Authors:	Al Hamarneh, Yazid; University of Alberta, Medicine Marra, Carlo; University of Otago, Pharmacy Gniadecki, Robert; University of Alberta, Medicine Keeling, Stephanie; University of Alberta, Rheumatology Morgan, Andrea; Foothills Medical Centre Tsuyuki, Ross; University of Alberta, Faculty of Medicine and Dentistry
Keywords:	RHEUMATOLOGY, PUBLIC HEALTH, General diabetes < DIABETES & ENDOCRINOLOGY, Hypertension < CARDIOLOGY, Cardiac Epidemiology < CARDIOLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

R_xIALTA: Pharmacist CVD Intervention for Patients with Chronic Inflammatory Diseases

Yazid N Al Hamarneh, BSc (Pharm), PhD (1), Carlo Marra, PharmD, PhD (2), Robert Gniadecki, MD, PhD (1), Stephanie O Keeling, MD (1), Andrea Morgan, BSc (Pharm) (3), Ross T Tsuyuki, BSc(Pharm), PharmD, MSc, FCSHP, FACC, FCAHS (1)

1. Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada

2. School of Pharmacy, University of Otago, Dunedin, New Zealand

3. Foothills Medical Centre, Calgary, Alberta, Canada

Corresponding author:

Yazid N. Al Hamarneh

EPICORE Centre

362 HMRC Building

University of Alberta

Edmonton, Alberta

Canada

Email: yazid.alhamarneh@ualberta.ca

Phone number: 780-492-9608

Fax: 780-492-6059

Keywords: Rheumatology, Public Health, Diabetes, Hypertension, Cardiac Epidemiology, Lipid Disorders

Abstract word count: 244

Manuscript word count: 2656

Number of Tables: 3

Number of Figures: 2

Author contributions:

Substantial contribution to study conception and design: all authors

Substantial contribution to data collection: YNA, AM, RTT

Substantial contribution to data analysis and interpretation: YNA, RTT

Drafting the article or revising it critically: all authors

Final approval of the submitted version: all authors

Acknowledgement:

None of this could have taken place without the dedication and caring of the R_xIALTA investigators, listed in descending order of recruitment:

Nader Hammoud (Shoppers Drug Mart #2326, Calgary), Nataliya Posudwvska (Calgary Co-op, Calgary), Rick Siemens (London Drugs #38, Lethbridge), Dixie Richardson (Safeway Pharmacy, Edmonton), Aileen Coutts (Calgary Co-Op, Calgary), Jan Messiha (Calgary Co-op, Calgary), Farzana Sharif (Calgary Co-Op, Calgary), Pegah Manzoori (Calgary Co-Op, Calgary), Maria James (Calgary Co-Op, Calgary), Jack Dhaliwal (Calgary Co-Op, Calgary), Derek Durocher (Shoppers Drug Mart #313, Edmonton), Leanna St. Onge, Otti Gohrbandt and Chelsey Collinge (Co-op Pharmacy, Rocky Mountain House), Aila Omar (Co-op Pharmacy, Edmonton), Diane Lazarko-Gamache (Calgary Co-Op, Calgary), Sonal Ijner (Calgary Co-Op, Calgary), Carlene Olyksen, Jelena Okuka (Meridian Pharmacy, Stony Plain), Murtaza Hassanali (Shoppers Drug Mart #371, Edmonton), Penny and Fausta (Penny and Fausta Pharmacy, Calgary).

Support:

We would like to acknowledge the generous support of the funder of R_xIALTA: Canadian Initiative for Outcomes in Rheumatology cAre (CIORA). Our funder did not have any role in the study design, collection, analysis, interpretation of the data, writing the report and the decision to submit for publication.

We would like to acknowledge the support of the Consultation and Research Services Platform at The Alberta' SPOR SUPPORT Unit in Data management and statistical services.

Significance and Innovation:

- This is the first study to assess the effect of a pharmacist-led case-finding and care on CV risk in patients with chronic inflammatory conditions in a community pharmacy setting
- The pharmacist-led case-finding and care enhanced access to CV risk assessment and care in a high-risk population, that otherwise would not have their CV risk assessed
- The pharmacist-led case-finding and care (including prescribing and ordering laboratory tests) was associated with CV risk reduction and improvement in all the individual CVD risk factors

Introduction

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.[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] Chronic inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis ankylosing spondylitis, gout, systemic lupus erythematosus and psoriasis are also increasingly being recognized as independent risk factors for CVD.[4-7] Indeed, it has been reported that the risk of myocardial infarction, heart failure and CV death among patients with chronic inflammatory disease is 2–3-fold greater than in the general population.[8-10] Such increased risk can be explained by 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]

Despite being recommended by international guidelines,[7] CV risk assessment has not been incorporated into many clinicians' daily routine.[7] In fact, reports indicate that such assessments generally only exist in larger centers for non-rheumatology patients.[11-13] Moreover, Keeling and colleagues reported that most rheumatologists, who are the main caregivers for patients with these conditions, conducted suboptimal CV risk assessments. [14] Unfortunately, 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. [7] Furthermore, many patients, especially those who are living in remote or rural areas, do not have access to family physicians. [15] These facts, combined with the benefits of early identification after the diagnosis,[16] highlight the need for new and innovative ways for assessing CV risk in this high-risk population.

Special considerations need to be taken into account when calculating CV risk in patients with chronic inflammatory diseases, as the 'classic' risk engines (such as Framingham[17]) might underestimate the overall risk,[18] since they have not been adequately evaluated in this patient population.[19,5] For example, those patients who might benefit from lipid-lowering agents may be categorized "low risk" when using the Framingham risk engine.[18] As such, it has been recommended to use a modified Framingham risk engine (multiply the overall risk by 1.5) in this patient population. [20] There is conflicting evidence in the literature regarding lipid panel measurements in patients with rheumatoid arthritis. Some studies reported that total cholesterol and LDL-cholesterol are significantly lower, while other studies reported that they are significantly higher in patients with rheumatoid arthritis when compared to the general population. [21-23] Despite the variation, it is still recommended to treat patients with rheumatoid arthritis to general population lipid targets with consideration of risk modification, such as the European League Against Rheumatism recommendations that suggest multiplying the CV risk score by a factor of 1.5 in these patients.[24-25]

Pharmacists are front line, accessible, primary healthcare professionals who see patients at risk/with chronic conditions more frequently than any other healthcare provider.[26] The efficacy of their interventions in chronic diseases including diabetes,[27] dyslipidemia,[28] hypertension,[29-32] heart failure,[33] and CVD [34-36] has been well demonstrated in the literature. Pharmacists can systematically identify patients at high risk of CVD,[36] help manage their condition, improve their medication use,[31,32,37] and assist them to achieve their treatment targets.[27-32] In addition to clinical outcomes, pharmacist interventions are also associated with high levels of patient satisfaction, improved adherence to therapy and considerable cost savings and efficient use of health care resources.[31-32,38-40] This evidence, coupled with their full scope of practice including prescribing and laboratory test monitoring, ideally position pharmacists to conduct CV risk assessment and management. Therefore, we conducted this study to determine the effect of a pharmacist-led intervention on CV risk in patients with chronic inflammatory diseases.

Methods

R_xIALTA was a non-randomized prospective pre-post-intervention study that was conducted in 17 community pharmacies across Alberta, Canada (for a list of the participating pharmacies please see the acknowledgement section). We utilized a non-randomized design because our previous work in pharmacist-led CV risk reduction[36], a 723 patient randomized trial demonstrated significant reductions in estimated cardiovascular risk, and it was felt unethical to randomize to usual care.

Patients were included if they were adults (≥18 years of age) with a physician-diagnosed chronic inflammatory condition (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, gout, systemic lupus erythematosus or psoriasis) and had at least one uncontrolled risk factor [blood pressure (≥140/90 without diabetes; ≥130/80 with diabetes)[41], LDL-cholesterol (>2.0 mmol/L)[42], A1C (>7.0%)[43], or current tobacco use]. We excluded patients if they were unwilling to participate/sign the consent form, unwilling or unable to participate in regular follow-up visits, pregnant, or experiencing a disease exacerbation (this may be indicated by current treatment with high or tapering dose of steroids), since lipid panel is most accurately measured when inflammatory diseases are stable or in remission.[5]

Recruitment

Pharmacists and pharmacy staff used the following methods to identify potential patients: 1. *Proactive case finding*: patients with physician-diagnosed chronic inflammatory conditions were identified by reviewing prescriptions of disease modifying anti-rheumatic drugs, NSAIDs, immunosuppressants, gout medications, biologics (e.g., adalimumab, infliximab, ustekinumab,

ixekizumab, secukinumab) and/or topical drugs containing calcipotriol, methotrexate with a rheumatologist or a dermatologist prescriber; 2. *Case finding via in-pharmacy posters and weekly fliers* and 3. *Case finding via bag stuffers with the above medications*.

As part of routine care, pharmacists measured the blood pressure and checked the most recent laboratory test results for the identified patients (through the provincial electronic health record). They then checked whether patients met the inclusion criteria. Those who met the inclusion criteria were considered eligible and were invited to participate in the study. Patients who agreed to participate were asked to sign a written informed consent form, then they were enrolled in the study.

The patient's physician(s) received a letter from the pharmacist to inform them that the patient agreed to participate in this study.

Intervention

All enrolled patients received: 1. Patient assessment (blood pressure measurement according to Hypertension Canada guidelines [41], waist circumference, weight and height measurements), 2. Laboratory assessment of A1C, non-fasting lipid panel (total cholesterol, LDL-cholesterol and HDL-cholesterol) and kidney function and status [creatinine (and estimated glomerular filtration rate), random urine albumin to creatinine ratio], 3. Individualized CV risk assessment and education regarding this risk using a validated interactive online tool[36] that explains the individual's CV risk, the contribution of each risk factor to the overall risk and the impact of the intervention and controlling the risk factors on the overall CV risk (https://www.epicore.ualberta.ca/epirxisk/), 4. Treatment recommendations, prescription adaptation, and prescribing where necessary to meet guideline recommended targets. Pharmacists practiced to their full scope (including prescribing medications and ordering and interpreting laboratory tests when needed), 5. Regular monthly follow-up for 6 months to check on patients' progress and provide ongoing care and motivation; and 6. Regular communication with the patient's physician(s) after each contact with the patient as per usual pharmacist practice.

Outcomes

The primary outcome was the change in CV risk over a 6-month period. CV risk is defined as the risk for future CV events (coronary heart disease [CHD], stroke, peripheral arterial disease [PAD])[7,8] as calculated by validated risk assessment equations. The CV risk was calculated using EPI·R_xISK™ Cardiovascular Risk Calculator (https://www.epicore.ualberta.ca/epirxisk/). It was estimated using the Modified Framingham[20] risk assessment equation (Framingham risk score multiplied by 1.5) for patients who have chronic inflammatory conditions without other comorbidities. If the patient had other CV risk-modifying conditions (diabetes, previous vascular disease or chronic kidney disease), risk was calculated using the Modified Framingham [20] and the most appropriate risk assessment equation based on the patient's medical history. The United Kingdom Prospective Diabetes Study (UKPDS) [44] risk assessment equation was used for those with diabetes, SMART risk assessment equation [45] was used for patients with previous vascular disease and Framingham[17] risk assessment equation was used for the ones with chronic kidney disease. If the patient had both chronic inflammatory conditions and other CV risk-modifying conditions, the risk was calculated using all the respective risk assessment equations, and the risk assessment equation estimating the highest risk was used.

The secondary outcomes were the change in individual risk factors [blood pressure (in patients with hypertension), LDL-cholesterol (in patients with dyslipidemia), A1C (in patients with diabetes) and tobacco cessation (self-reported abstinence)] over a 6-month period.

Sample size and analytical plan

Sample size

Using the information from our previous pharmacist-led CV risk reduction trial, R_xEACH[36] [Baseline CV risk (26.2%) and standard deviation (SD) (17.8)] and the following assumptions of 80% power and alpha of 0.05, 89 patients were required to detect 21% risk reduction. The sample size was inflated to 100 to to account for possible dropouts, losses to follow-up, and withdrawals of consent.

Analytical plan

Analysis was performed by using R 3.6.2 (Vienna, Austria; https://www.R-project.org/) and SAS 9.4 software (SAS Institute Inc. Cary, NC, USA).

Data were first screened to confirm that all the participating patients met the inclusion/exclusion criteria and provided informed consent. Once those conditions were confirmed, statistical analysis started.

Demographic information and clinical characteristics were analyzed using descriptive statistics. Frequency (percentage) was used for categorical variables and mean (standard derivation) for continuous variables. Statistical significance at the univariable level was assessed using Chi-square test or Fisher's exact test (when small frequencies present) for categorical variables, and T-test or Wilcoxon rank sum test (when data was heavily skewed) for continuous variables (assumption of statistics tests were checked ahead). The primary outcome was analyzed by paired T-test. Multivariable linear mixed effect models was used to adjust for centre effect and baseline characteristics. Secondary outcomes were analyzed using paired T-test and Chi-square test as appropriate.

Trial and data management was performed by EPICORE Centre

R_xIALTA was approved by the Health Research Ethics Board of the University of Alberta (Pro00072858).

Results

The study was launched in August, 2017, and the last patient was enrolled in July 2019. Follow up was completed in January 2020. We screened 126 patients, of those 103 were eligible. We enrolled 99 patients and 94 of them completed the study (Figure 1). Demographic and clinical characteristics are presented in Table 1. Mean age was 64 years (standard deviation (SD) 14.8), approximately two thirds (61%) of the participants were female and 86% were Caucasian. More than half (56%) had rheumatoid arthritis, 14% had psoriasis, 12% had psoriatic arthritis, 11% had gout, 6% had ankylosing spondylitis and 1% had systemic lupus erythematosus. Hypertension was the most commonly reported risk factor (47%), followed by dyslipidemia (45%), diabetes (13%), atherosclerotic vascular events (angina, heart attack, stroke/TIA) (11%), current tobacco use (10%) and chronic kidney disease (9%). In addition, average body mass index (BMI) was 28.2 (5.2) kg/m^2 and only 9% reported exercising for 30 minutes (or more) five or more times per week. Importantly, only 2% of participants reported that their CV risk was assessed by a healthcare provider before taking part in the study.

Table 1 baseline demographic and clinical characteristics

Characteristic		Frequency
Age	Age, years	64 +/-14.8
Sex	Female	60
Ethnicity	Aboriginal / First Nations	3
	Black	2
	Caucasian	85
	Hispanic	2
	South-Asian	1
	Other Asian	6
Inflammatory Conditions	RA	55
	Psoriasis	14
	PsA	12
	Gout	11
	AS	6
	SLE	1
Risk factors	Hypertension	47
	Dyslipidemia	45
	Diabetes	13
	Atherosclerotic vascular events	12
	Current tobacco use	11
	CKD	9
Exercise	Very active	9
	Moderately active	39
	No exercise additional to ordinary daily living	49
	Not reported	2

Physical and lab assessment	BMI, kg/m^2	28.2 +/-5.2
	Systolic BP, mmHg	136.6 +/-15.7
	Diastolic BP, mmHg	81.8 +/-11.4
	Total cholesterol, mmol/L	4.8 +/-1.3
	HDL-cholesterol, mmol/L	1.4 +/-0.5
	LDL-cholesterol, mmol/L	2.6 +/-1.1
	A1C, %	8.3 +/-1.1
	eGFR, ml/min/1.73 m^2	76.6 +/-18.5
	ACR, mg/mmol	154.7 +/-218.2

***RA: rheumatoid arthritis, PsA: psoriatic arthritis, AS: ankylosing spondylitis, SLE: systemic lupus erythematosus, CKD: chronic kidney disease**

Estimated CV risk was reduced from 25% (SD 16.1) at baseline to 19.8% (SD 14.7) after 6 months. After adjusting for baseline characteristics and centre effect, this corresponded to a 21% relative risk reduction (p <0.001) (Figure 2). In patients with hypertension, significant reductions were observed in systolic and diastolic blood pressure (Table 2). Similarly, we noted reductions in LDL-cholesterol in patients with dyslipidemia and A1C in those with diabetes (Table 2). Participants' dietary habits were also improved (p=0.02), while exercise, alcohol and tobacco use were not significantly improved.

Table 2 Changes in individual risk factors

Risk factor	Baseline	6 months	p-value
Systolic BP (n=47)	138.4 (17.9)	127.68 (10.33)	<0.001
Diastolic BP (n=47)	80.15 (13.04)	77.3 (10.12)	<0.001
LDL-cholesterol (n=45)	2.81 (1.19)	2.51 (1.13)	<0.001
A1C (n=13)	8.3 (4.68)	7.19 (1.13)	<0.001
Tobacco use (proportion)	10.3	5.2	0.4

Pharmacist interventions are listed in Table 3. Medication/dose change was the most implemented intervention (30%), followed by lifestyle education and advice (27%), patient, family members and caregivers' education about the condition and prescribed treatment (22%), follow up (12%), adherence assessment and improvement (7%) and referral to other healthcare providers (2%). There were very minimal adverse events reported during the study.

Table 3 Pharmacist interventions

Intervention	Intervention type	Proportion within an intervention (%)	Overall proportion (%)
Medication/Dose Change			30
	Medication Change	87.5	
	Dose Change	11	
	Stopping Medication	1.5	
Lifestyle education and advice			27
	Diet	47.5	
	Exercise	47.5	
	Alcohol	5	
Patient, family members and caregivers education about the condition and prescribed treatment			22
Follow up			12
Adherence assessment and improvement			7
	Encouraging patient to become more involved and monitor their condition at home regularly	40	
	Assess adherence to therapy at each encounter	20	
	Working with patient to associate taking medications with daily habits	17.5	
	Involve other healthcare professionals and work-site healthcare providers	15	
	Unit-of-dose packing	7.5	
Referral to other healthcare providers			2
	Family Physician	83.3	
	Specialist	16.7	

Discussion

Chronic inflammatory conditions increase patient's risk for CV events; however, these patients are often not receiving CV risk assessment or treatment. We hypothesized that community pharmacists could proactively and systematically screen for chronic inflammatory diseases (because of the unique medications used in these conditions), and then manage their CV risk factors. We found that a pharmacist-led care reduced the risk of major CV events by 21% ($p < 0.001$) over a 6-month period. The intervention was also associated with reductions in blood pressure, LDL-cholesterol and A1C. Such improvements are related to the following pharmacist activities: medication/dose changes, lifestyle education and advice, patient, family members and caregivers' education about the condition and prescribed treatment, follow up, adherence assessment and improvement and referral to other healthcare providers.

Our findings are consistent with the findings of the R_xEACH study, which evaluated the impact of pharmacist intervention (assessment, prescribing, and follow-up) on CV risk in patients at high risk for CVD (patients with diabetes, chronic kidney disease, established vascular disease or Framingham risk > 20%). R_xEACH reported that such intervention was associated with CV risk reduction as well as improvements in all individual risk factors.[36]

Our findings are also consistent with the findings of Semb and colleagues who reported significant CV risk reduction when a CV risk factor (lipids) was managed appropriately.[46]

Our findings highlight the importance of pharmacist prescribing, as 'medication/dose change' was the most implemented intervention. This intervention would have not been possible without having independent prescriptive authority. These findings are supported by the findings of Al Hamarneh and colleagues and Wubben and Vivian who reported that better outcomes were achieved when pharmacists had prescriptive authority.[47,48]

This study is not without limitations. As described above, the study was not a randomized controlled trial, due to ethical concerns with having a control group. We acknowledge that this reduces causal inference, however, the findings of this study are similar to the randomized R_xEACH study.[36] Since the 6-month follow-up period can be considered relatively short; it is possible that the effects of the intervention could be short lived. It is also possible, however, that greater improvements leading to larger CV risk reduction could have been observed with a longer follow up period. Pharmacists who provided the intervention also conducted the assessment and entered the information into the study online system where CV risk was calculated. This could have introduced bias; however, the study team monitored study sites

against source documents to ensure accuracy. The fact that adverse events were self-reported could have led to underreporting.

Our findings, combined with the fact that the risk of myocardial infarction, heart failure and CV death among patients with chronic inflammatory diseases is much higher than the general population,[8-10] highlight the importance of focusing on the patient as a whole, rather than only focusing on their acute complaints.

It is noteworthy that only 2% of our participants had their CV risk assessed before taking part in the study. This is consistent with the literature, as it has been reported that the levels of awareness and perceived risk of CVD is low in this patient population.[49] Gaps in care have also been reported when it comes to CV risk assessment.[7,12-14] This also highlights the importance of a systematic and proactive approach towards case-finding by pharmacists – as many patients would not know to ask for CV risk assessment. This is a unique feature of involving community pharmacists – an approach which we have used successfully in a number of areas. [28,36,50]

R_xIALTA findings add to the high-level evidence of effective pharmacist prescribing interventions in improving CV risk and individual CVD risk factors.[36,50] Such high-level evidence should encourage policy makers to broaden the scope of practice for pharmacists and pharmacy professional organizations to implement those interventions on a larger scale to seize the opportunity to enhance patient care.

To our knowledge, this is the first study to assess the effect of a pharmacist-led case-finding and care on CV risk in patients with chronic inflammatory conditions in a community pharmacy setting. We have demonstrated that pharmacist-led intervention (including prescribing) improved CV risk as well as the individual CVD risk factors. Pharmacists also improved the access to care in a high-risk population, that otherwise would not have their CV risk assessed. Implementing this on a wider scale could help addressing one of the world's major public health challenges.

Figures

Figure 1: Study flow chart

Figure 2 Change in estimated CV risk over time

Reference:

1. WHO. Cardiovascular diseases. 2017. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/ (Accessed 9/6/2020)
2. Government of Canada. Report from the Canadian Chronic Disease Surveillance System: Heart Disease in Canada, 2018. 2018. Available from: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/report-heart-disease-Canada-2018.html (Accessed 9/6/2020)
3. The Arthritis Society. Arthritis in Canada, Facts and Figures. 2020. Available from: https://arthritis.ca/about-arthritis/what-is-arthritis/arthritis-facts-and-figures (Accessed 9/6/2020)
4. Nurmohamed MT (2009) Cardiovascular risk in rheumatoid arthritis. Autoimmun Rev 8:663–667
5. Peters MJ, Symmons DP, McCarey D, et al. (2010). Evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis. 69(2):325-31.
6. Semb AG, Rollefstad S, van Riel P, et al. (2014). Cardiovascular disease assessment in rheumatoid arthritis: A guide to translating knowledge of cardiovascular risk into clinical practice. Ann Rheum Dis.
7. Schieir O, Tosevski C, Glazier RH, Hogg-Johnson S, Badley EM. Incident myocardial infarction associated with major types of arthritis in the general population: a systematic review and meta-analysis. Ann Rheum Dis. 2017; Published Online First: 22 Jan. doi: 10.1136/annrheumdis-2016-210275.
8. Maradit-Kremers H, Crowson CS, Nicola PJ, et al. (2005). Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population based cohort study. Arthritis Rheum. 52:402–11.
9. Nicola PJ, Maradit-Kremers H, Roger VL, et al. (2005). The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum. 52:412–20
10. Maradit-Kremers H, Crowson CS, Nicola PJ, et al. (2008). Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum. 52:722–32
11. Mills M, Loney P, Jamieson E, et al. (2010). A primary care cardiovascular risk reduction clinic in canada was more effective and no more expensive than usual on-demand primary care--a randomised controlled trial. Health Soc Care Community. 18(1):30-40.
12. Woodward A, Wallymahmed M, Wilding J, et al. (2006). Successful cardiovascular risk reduction in type 2 diabetes by nurse-led care using an open clinical algorithm. Diabet Med. 23(7):780-787

13. Woodward A, Wallymahmed M, Wilding J, et al. (2005). Improved glycaemic control--an unintended benefit of a nurse-led cardiovascular risk reduction clinic. Diabet Med. 22(9):1272-1274.

14. Keeling SO, Teo M, Fung D. (2011). Lack of cardiovascular risk assessment in inflammatory arthritis and systemic lupus erythematosus patients at a tertiary care center. Clin Rheumatol. 30(10):1311-1317

15. Canadian Institute for Health Information. Physicians in Canada, 2018. 2019. Available from: https://www.cihi.ca/sites/default/files/document/physicians-in-canada-2018.pdf (Accessed 9/6/2020)

16. Kremers HM, Crowson CS, Therneau TM, et al. (2008) High ten-year risk of cardiovascular disease in newly diagnosed rheumatoid arthritis patients: a population-based cohort study. Arthritis Rheum. 58:2268–2274

17. D'Agostino RB S, Vasan RS, Pencina MJ, et al. (2008). General cardiovascular risk profile for use in primary care: The framingham heart study. Circulation.117(6):743-753

18. Arts EE, Popa C, Den Broeder AA, et al. (2014). Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. Ann Rheum Dis.

19. Chung CP, Oeser A, Avalos I, *et al*. (2006). Utility of the Framingham risk score to predict the presence of coronary atherosclerosis in patients with rheumatoid arthritis. Arthritis Res Ther.8:R186.

20. Tournadre A, Mathieu S, Soubrier M. Managing cardiovascular risk in patients with inflammatory arthritis: practical considerations. Ther Adv Musculoskel Dis. 2016;8(5):180-191.

21. Semb AG, Kvien TK, DeMicco DA, et al. Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. *Arthritis & Rheumatism*. 2012;64(9): 2836-2846.

22. Liao KP, Cai T, Gainer VS, et al. Lipid and lipoprotein levels and trend in rheumatoid arthritis compared to the general population. *Arthritis Care & Research*. 2013;65(12): 2046-2050.

23. Liao KP, Liu P, Lu B, et al. Association between lipid levels and major adverse cardiovascular events in rheumatoid arthritis compared to non-rheumatoid arthritis patients. *Arthritis & Rheumatology*. 2015;67(8): 2004-2010.

24. Peters MJL, Symmons DPM, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis*. 2010;69: 325-331.

25. Rollefstad S, Kvien TK, Holme I, et al. Treatment to lipid target in patients with inflammatory joint diseases in preventative cardio-rheuma clinic. *Ann Rheum Dis* 2013;72:1968-1974.

26. Shiu JR, Simpson SH, Johnson JA, et al. (2006). Quantifying opportunities to affect diabetes management in the community. Can Pharm J. 139(3): 37-38.

27. Rothman RL, Malone R, Bryant B, et al. (2005). A randomized trial of a primary care-based disease management program to improve cardiovascular risk factors and glycated hemoglobin levels in patients with diabetes. *Am J Med*.118(3):276-84

28. Tsuyuki RT, Johnson JA, Teo K et al. (2002). A Randomized Trial of the Effect of Community Pharmacist Intervention on Cholesterol Risk Management – The Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP). Arch Intern Med. 162:1149-55

29. Carter BL, Bergus GR, Dawson JD, et al. (2008). A cluster randomized trial to evaluate physician/pharmacist collaboration to improve blood pressure control. *J Clin Hypertens (Greenwich)*. 10(4):260-27

30. McLean DL, McAlister FA, Johnson JA et al. (2008). A Randomized Trial of the Effect of Community Pharmacist and Nurse Care on Improving Blood Pressure Management in Patients with Diabetes Mellitus – Study of Cardiovascular Risk Intervention by Pharmacists-Hypertension (SCRIP-HTN). Arch Intern Med.168(21):2355-61.

31. Blenkinsopp A, Phelan M, Bourne J, et al. (2000). Extended adherence support by community pharmacists for patients with hypertension: a randomized controlled trial. International Journal of Pharmacy Practice.8:165-175.

32. Wang J, Wu J, Yang J, et al. (2011). Effect of pharmaceutical care interventions on blood pressure and medication adherence of patients with primary hypertension in China. Clinical Research and Regulatory Affairs. 1:1-6.

33. Gattis WA, Hasselblad V, Whellan DJ, et al. (1999). Reduction in heart failure events by the addition of a clinical pharmacist to the heart failure management team: results of the Pharmacist in Heart Failure Assessment Recommendation and Monitoring (PHARM) Study. *Arch Intern Med*. 159(16):1939-1945

34. Taveira TH, Wu WC, Martin OJ, et al. (2006). Pharmacist-led cardiac risk reduction model. *Prev Cardiol*.9:202-208

35. Santschi V, Chiolero A, Burnand B, et al. (2011). Impact of pharmacist care in the management of cardiovascular disease risk factors: a systematic review and meta-analysis of randomized trials. *Arch Intern Med*. 171:1441-53.

36. Tsuyuki RT, Al Hamarneh YN, Jones CA, Hemmelgarn BR. The effectiveness of pharmacist interventions on cardiovascular risk. Journal of the American College of Cardiology 2016;67(24):2847-2854. doi: 10.1016/j.jacc.2016.03.528.

37. Murray MD, Ritchey ME, Wu J, et al. (2009). Effect of a pharmacist on adverse drug events and medication errors in outpatients with cardiovascular disease. *Arch Intern Med*.169(8):757-

38. Marra C, Johnston K, Santschi V, Tsuyuki RT. 2017. Cost-effectiveness of pharmacist care for managing hypertension in Canada. *Canadian Pharmacists Journal.* 150(3):184-197

39. Al Hamarneh YN, Johnston K, Marra CA, Tsuyuki RT. Pharmacist prescribing and care improves cardiovascular risk, but is it cost-effective? A cost-effectiveness analysis of the R_xEACH study. Can Pharm J. 2019;152(4):257-266

40. Al Harmarneh YN, Lamb S, Donald M, et al. Pharmacist prescribing and care improves cardiovascular risk, but what do patients think? A substudy of the R_xEACH study. Can Pharm J. 2018; 151(4): 223–227

41. Nerenberg KA, Zarnke KB, Leung AA, et al. Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. Can J Cardiol. 2018;34(5):506-525

42. Anderson TJ, Grégoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol. 2016;32(11):1263-1282.

43. Diabetes Canada. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Canadian Journal of Diabetes. 2018; 42: S1-S326

44. Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR. The UKPDS risk engine: a model for the risk of coronary heart disease in type 2 diabetes (UKPDS 56). *Clin Sci* 2001; 101: 671-679.

45. Dorresteijn JAN, Visseren FLJ, Wassink AMJ et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study in patients with arterial disease: the SMART risk score. Heart 2013; 99:866-872.

46. Semb AG, Kvien TK, DeMicco DA, Fayyad R, Wun CC, LaRosa JC, Betteridge J, Terje R Pedersen TR, Holme I. Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. Arthritis Rheum 2012; 64:2836-46

47. Al Hamarneh YN, Hemmelgarn BR, Hassan I, Jones CA, Tsuyuki RT. The Effectiveness of Pharmacist Interventions on Cardiovascular Risk in Adult Patients with Type 2 Diabetes: The Multicentre Randomized Controlled R_xEACH Trial. Can J Diabetes. 2017;41(6):580-586.

48. Wubben DP, Vivian EM. Effects of pharmacist outpatient interventions on adults with diabetes mellitus: A systematic review. Pharmacotherapy, 2008; 28: 421-436

49. Ghosh-Swaby OR, Kuriya B. Awareness and perceived risk of cardiovascular disease among individuals living With rheumatoid arthritis is low: results of a systematic literature review. Arthritis Res Ther. 2019; 21:33-39

50. Tsuyuki RT, Houle SK, Charrois TL, et al. Randomized Trial of the Effect of Pharmacist Prescribing on Improving Blood Pressure in the Community: The Alberta Clinical Trial in Optimizing Hypertension (R_xACTION). Circulation. 2015;132(2):93-100

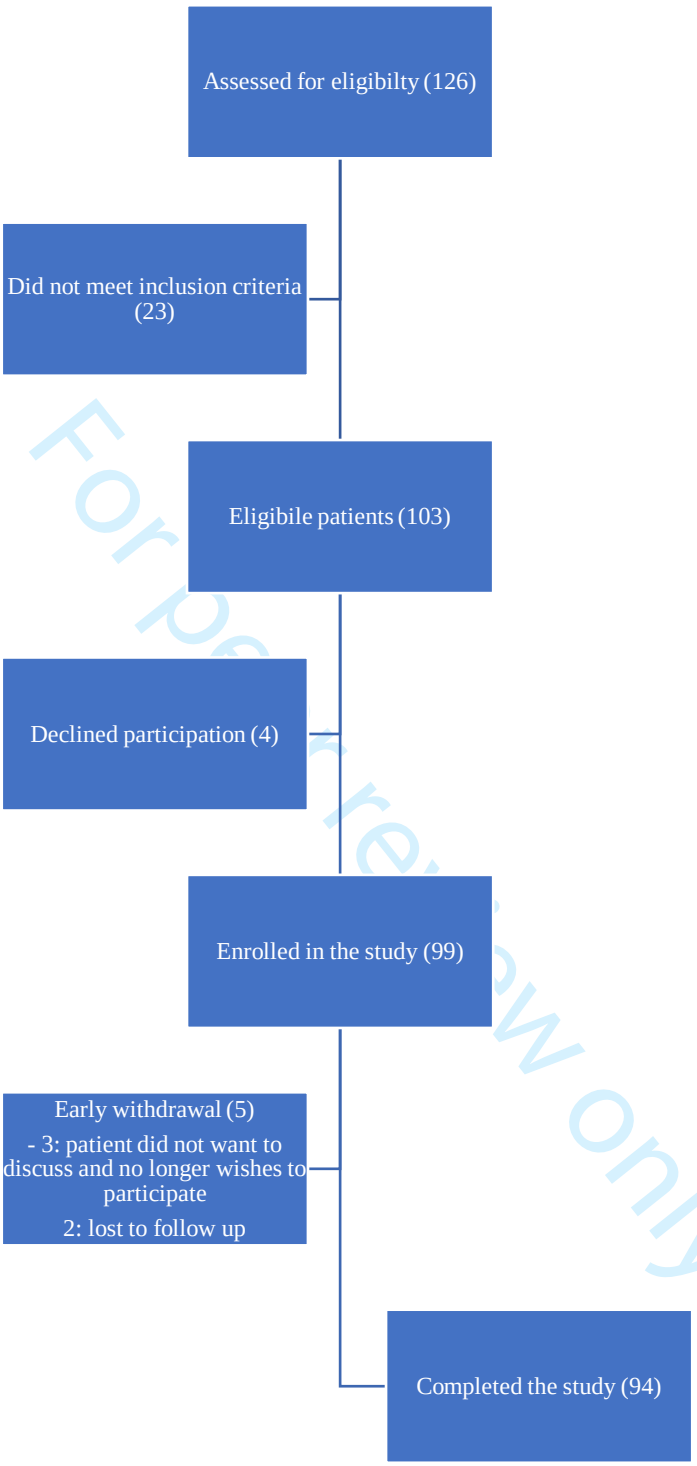


Figure 1: Study flow chart

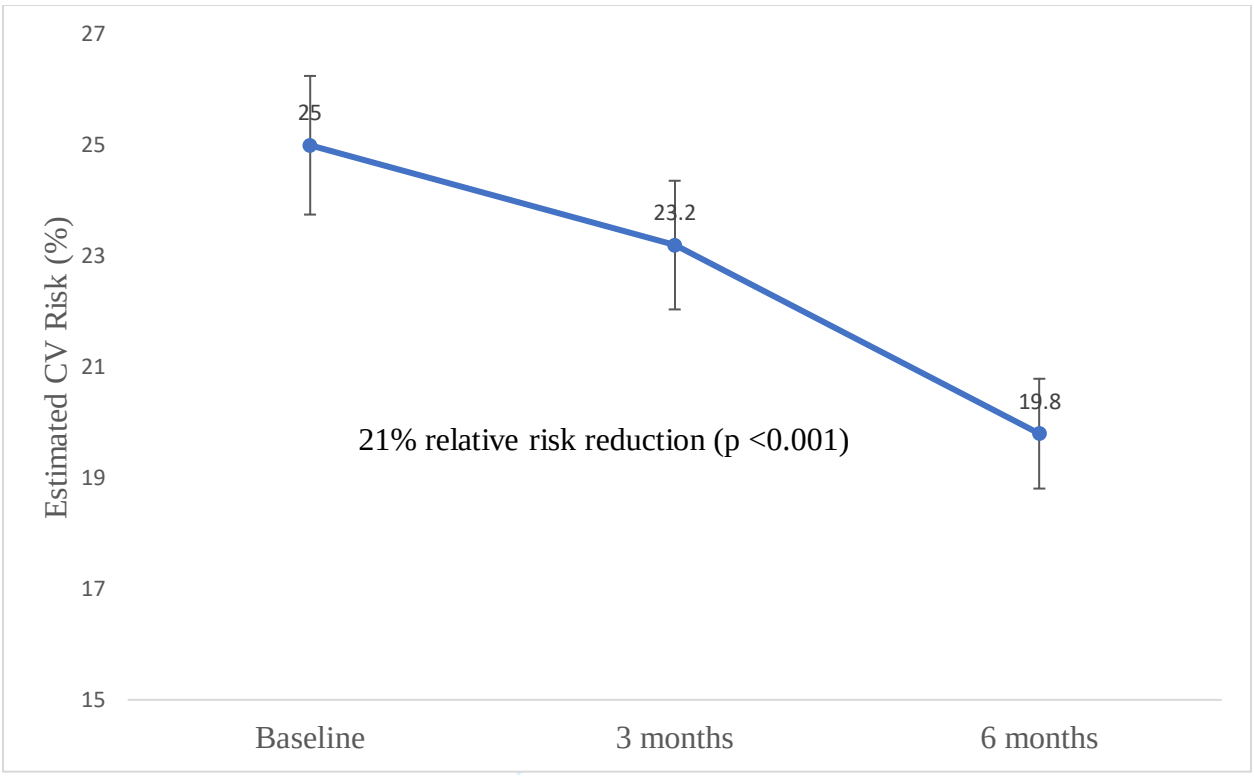


Figure 2 Change in estimated CV risk over time

BMJ Open

R_xIALTA: Evaluating the Effect of a Pharmacist-Led Intervention on CV Risk in Patients with Chronic Inflammatory Diseases in a Community Pharmacy Setting. A Prospective Pre-Post-Intervention Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043612.R1
Article Type:	Original research
Date Submitted by the Author:	01-Dec-2020
Complete List of Authors:	Al Hamarneh, Yazid; University of Alberta, Medicine Marra, Carlo; University of Otago, Pharmacy Gniadecki, Robert; University of Alberta, Medicine Keeling, Stephanie; University of Alberta, Rheumatology Morgan, Andrea; Foothills Medical Centre Tsuyuki, Ross; University of Alberta, Faculty of Medicine and Dentistry
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	RHEUMATOLOGY, PUBLIC HEALTH, General diabetes < DIABETES & ENDOCRINOLOGY, Hypertension < CARDIOLOGY, Cardiac Epidemiology < CARDIOLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

R_xIALTA: Evaluating the Effect of a Pharmacist-Led Intervention on CV Risk in Patients with Chronic Inflammatory Diseases in a Community Pharmacy Setting. A Prospective Pre-Post-Intervention Study

Yazid N Al Hamarneh, BSc (Pharm), PhD (1), Carlo Marra, PharmD, PhD (2), Robert Gniadecki, MD, PhD (1), Stephanie O Keeling, MD (1), Andrea Morgan, BSc (Pharm) (3), Ross T Tsuyuki, BSc(Pharm), PharmD, MSc, FCSHP, FACC, FCAHS (1)

1. Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada

2. School of Pharmacy, University of Otago, Dunedin, New Zealand

3. Foothills Medical Centre, Calgary, Alberta, Canada

Corresponding author:

Yazid N. Al Hamarneh

EPICORE Centre

362 HMRC Building

University of Alberta

Edmonton, Alberta

Canada

Email: yazid.alhamarneh@ualberta.ca

Phone number: 780-492-9608

Fax: 780-492-6059

Keywords: Rheumatology, Public Health, Diabetes, Hypertension, Cardiac Epidemiology, Lipid Disorders

Abstract word count: 299

Manuscript word count: 2699

Number of Tables: 3

Number of Figures: 3

Author contributions:

Substantial contribution to study conception and design: all authors

Substantial contribution to data collection: YNA, AM, RTT

Substantial contribution to data analysis and interpretation: YNA, RTT

Drafting the article or revising it critically: all authors

Final approval of the submitted version: all authors

Acknowledgement:

None of this could have taken place without the dedication and caring of the R_xIALTA investigators, listed in descending order of recruitment:

Nader Hammoud (Shoppers Drug Mart #2326, Calgary), Nataliya Posudwvska (Calgary Co-op, Calgary), Rick Siemens (London Drugs #38, Lethbridge), Dixie Richardson (Safeway Pharmacy, Edmonton), Aileen Coutts (Calgary Co-Op, Calgary), Jan Messiha (Calgary Co-op, Calgary), Farzana Sharif (Calgary Co-Op, Calgary), Pegah Manzoori (Calgary Co-Op, Calgary), Maria James (Calgary Co-Op, Calgary), Jack Dhaliwal (Calgary Co-Op, Calgary), Derek Durocher (Shoppers Drug Mart #313, Edmonton), Leanna St. Onge, Otti Gohrbandt and Chelsey Collinge (Co-op Pharmacy, Rocky Mountain House), Aila Omar (Co-op Pharmacy, Edmonton), Diane Lazarko-Gamache (Calgary Co-Op, Calgary), Sonal Ijner (Calgary Co-Op, Calgary), Carlene Olyksen, Jelena Okuka (Meridian Pharmacy, Stony Plain), Murtaza Hassanali (Shoppers Drug Mart #371, Edmonton), Penny and Fausta (Penny and Fausta Pharmacy, Calgary).

Support:

We would like to acknowledge the generous support of the funder of R_xIALTA: Canadian Initiative for Outcomes in Rheumatology cAre (CIORA). Our funder did not have any role in the study design, collection, analysis, interpretation of the data, writing the report and the decision to submit for publication.

We would like to acknowledge the support of the Consultation and Research Services Platform at The Alberta' SPOR SUPPORT Unit in Data management and statistical services.

Abstract

Patients with inflammatory conditions (e.g. inflammatory arthritis, gout, psoriasis) are at high risk for cardiovascular disease (CVD). Despite such elevated risk, their CV risk factors are sub-optimally managed.

Objective: To evaluate the effect of a pharmacist-led intervention on CV risk in patients with inflammatory conditions.

Methods:

Design: Prospective pre-post-intervention

Setting: 17 Community pharmacies across Alberta

Population: Adults with inflammatory conditions (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, gout, systemic lupus erythematosus, psoriasis vulgaris) who had at least one uncontrolled risk factor (A1C, blood pressure, LDL-cholesterol, or current tobacco users).

Intervention: All patients enrolled in the study received: physical and laboratory assessment, individualized CV risk assessment and education regarding this risk, treatment recommendations, prescription adaptation, and prescribing where necessary to meet treatment targets, regular communication with the patient's treating physician(s) and regular follow-up with all patients every month for 6 months

Outcomes: Primary: Change in estimated CV risk (risk of a major CV event in the next 10 years) after 6 months. Secondary: Change in individual risk factors [blood pressure, LDL-cholesterol, A1C and tobacco cessation] over a 6-month period

Results: We enrolled 99 patients. The median age was 66.41 years (interquartile range 57.64 – 72.79), More than half of them (61%) were female and more than three quarters (86%) were Caucasians. After adjusting for corresponding baseline values, there was a change of 24.5% in CV risk ($p<0.001$); including a change of 0.3 mmol/L in LDL-c ($p<0.001$), 10.7 mmHg in systolic blood pressure ($p<0.001$), 1.25% in A1C ($p<0.001$). There was a non-significant trend towards tobacco cessation.

Conclusion: This is the first study on CV risk reduction in patients with inflammatory conditions in a community pharmacy setting. R_xIALTA provides evidence for the benefit of pharmacist care on global cardiovascular risk reduction as well as the individual cardiovascular risk factors in patients with inflammatory conditions.

Study registration: The study was registered at Clinicaltrials.gov (NCT03152396)

Significance and Innovation:

- This is the first study to assess the effect of a pharmacist-led case-finding and care on CV risk in patients with chronic inflammatory conditions in a community pharmacy setting
- The pharmacist-led case-finding and care enhanced access to CV risk assessment and care in a high-risk population, that otherwise would not have their CV risk assessed
- The pharmacist-led case-finding and care (including prescribing and ordering laboratory tests) was associated with CV risk reduction and improvement in all the individual CVD risk factors

Introduction

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.[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] Chronic inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis ankylosing spondylitis, gout, systemic lupus erythematosus and psoriasis are also increasingly being recognized as independent risk factors for CVD.[4-7] Indeed, it has been reported that the risk of myocardial infarction, heart failure and CV death among patients with chronic inflammatory disease is 2–3-fold greater than in the general population.[8-10] Such increased risk can be explained by 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]

Despite being recommended by international guidelines,[7] CV risk assessment has not been incorporated into many clinicians' daily routine.[7] In fact, reports indicate that such assessments generally only exist in larger centers for non-rheumatology patients.[11-13] Moreover, Keeling and colleagues reported that most rheumatologists, who are the main caregivers for patients with these conditions, conducted suboptimal CV risk assessments. [14] Unfortunately, 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. [7] Furthermore, many patients, especially those who are living in remote or rural areas, do not have access to family physicians. [15] These facts, combined with the benefits of early identification after the diagnosis,[16] highlight the need for new and innovative ways for assessing CV risk in this high-risk population.

Special considerations need to be taken into account when calculating CV risk in patients with chronic inflammatory diseases, as the 'classic' risk engines (such as Framingham[17]) might underestimate the overall risk,[18] since they have not been adequately evaluated in this patient population.[19,5] For example, those patients who might benefit from lipid-lowering agents may be categorized "low risk" when using the Framingham risk engine.[18] As such, it has been recommended to use a modified Framingham risk engine (multiply the overall risk by 1.5) in this patient population. [20] There is conflicting evidence in the literature regarding lipid panel measurements in patients with rheumatoid arthritis. Some studies reported that total cholesterol and LDL-cholesterol are significantly lower, while other studies reported that they are significantly higher in patients with rheumatoid arthritis when compared to the general population. [21-23] Despite the variation, it is still recommended to treat patients with rheumatoid arthritis to general population lipid targets with consideration of risk modification, such as the European League Against Rheumatism recommendations that suggest multiplying the CV risk score by a factor of 1.5 in these patients.[24-25]

Pharmacists are front line, accessible, primary healthcare professionals who see patients at risk/with chronic conditions more frequently than any other healthcare provider.[26] The efficacy of their interventions in chronic diseases including diabetes,[27] dyslipidemia,[28] hypertension,[29-32] heart failure,[33] and CVD [34-36] has been well demonstrated in the literature. Pharmacists can systematically identify patients at high risk of CVD,[36] help manage their condition, improve their medication use,[31,32,37] and assist them to achieve their treatment targets.[27-32] In addition to clinical outcomes, pharmacist interventions are also associated with high levels of patient satisfaction, improved adherence to therapy and considerable cost savings and efficient use of health care resources.[31-32,38-40] This evidence, coupled with their full scope of practice including prescribing and laboratory test monitoring, ideally position pharmacists to conduct CV risk assessment and management. Therefore, we conducted this study to determine the effect of a pharmacist-led intervention on CV risk in patients with chronic inflammatory diseases.

Methods

R_xIALTA was a non-randomized prospective pre-post-intervention study that was conducted in 17 community pharmacies across Alberta, Canada (for a list of the participating pharmacies please see the acknowledgement section). We utilized a non-randomized design because our previous work in pharmacist-led CV risk reduction[36], a 723 patient (those with diabetes, chronic kidney disease, established vascular disease or Framingham risk >20%) randomized trial demonstrated significant reductions in estimated cardiovascular risk, and it was felt unethical to randomize this underserved high-risk population to usual care.

Patients were included if they were adults (≥18 years of age) with a physician-diagnosed chronic inflammatory condition (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, gout, systemic lupus erythematosus or psoriasis) and had at least one uncontrolled risk factor [blood pressure (≥140/90 without diabetes; ≥130/80 with diabetes)[41], LDL-cholesterol (>2.0 mmol/L)[42], A1C (>7.0%)[43], or current tobacco use]. We excluded patients if they were unwilling to participate/sign the consent form, unwilling or unable to participate in regular follow-up visits, pregnant, or experiencing a disease exacerbation (this may be indicated by current treatment with high or tapering dose of steroids), since lipid panel is most accurately measured when inflammatory diseases are stable or in remission.[5]

Recruitment

Pharmacists and pharmacy staff used the following methods to identify potential patients: 1. *Proactive case finding*: patients with physician-diagnosed chronic inflammatory conditions were identified by reviewing prescriptions of disease modifying anti-rheumatic drugs, NSAIDs,

immunosuppressants, gout medications, biologics (e.g., adalimumab, infliximab, ustekinumab, ixekizumab, secukinumab) and/or topical drugs containing calcipotriol, methotrexate with a rheumatologist or a dermatologist prescriber; 2. *Case finding via in-pharmacy posters and weekly fliers* and 3. *Case finding via bag stuffers with the above medications*.

As part of routine care, pharmacists measured the blood pressure and checked the most recent laboratory test results for the identified patients (through the provincial electronic health record). They then checked whether patients met the inclusion criteria. The pharmacists explained the study to those who met the inclusion criteria and invited them to take part. Patients who agreed to take part were asked to sign a written informed consent form. Once the signed written informed consent form was obtained the patients were enrolled in the study.

The patient's physician(s) received a letter from the pharmacist to inform them that the patient agreed to participate in this study.

Intervention

All enrolled patients received: 1. Patient assessment (blood pressure measurement according to Hypertension Canada guidelines [41], waist circumference, weight and height measurements), 2. Laboratory assessment of A1C, non-fasting lipid panel (total cholesterol, LDL-cholesterol and HDL-cholesterol) and kidney function and status [creatinine (and estimated glomerular filtration rate), random urine albumin to creatinine ratio], 3. Individualized CV risk assessment and education regarding this risk using a validated interactive online tool[36] that explains the individual's CV risk, the contribution of each risk factor to the overall risk and the impact of the intervention and controlling the risk factors on the overall CV risk (https://www.epicore.ualberta.ca/epirxisk/), 4. Treatment recommendations, prescription adaptation, and prescribing where necessary to meet guideline recommended targets. Pharmacists practiced to their full scope (including prescribing medications and ordering and interpreting laboratory tests when needed), 5. Regular monthly follow-up for 6 months to check on patients' progress and provide ongoing care and motivation; and 6. Regular communication with the patient's physician(s) after each contact with the patient as per usual pharmacist practice.

Patient and public involvement

No patient involved

Outcomes

The primary outcome was the change in CV risk over a 6-month period. CV risk is defined as the risk for future CV events (coronary heart disease [CHD], stroke, peripheral arterial disease [PAD])[7,8] as calculated by validated risk assessment equations. The CV risk was calculated using EPI·R_xISK™ Cardiovascular Risk Calculator (https://www.epicore.ualberta.ca/epirxisk/). It was estimated using the Modified Framingham[20] risk assessment equation (Framingham risk score multiplied by 1.5) for patients who have chronic inflammatory conditions without other comorbidities. If the patient had other CV risk-modifying conditions (diabetes, previous vascular disease or chronic kidney disease), risk was calculated using the Modified Framingham [20] and the most appropriate risk assessment equation based on the patient's medical history. The United Kingdom Prospective Diabetes Study (UKPDS) [44] risk assessment equation was used for those with diabetes, SMART risk assessment equation [45] was used for patients with previous vascular disease and Framingham[17] risk assessment equation was used for the ones with chronic kidney disease. If the patient had both chronic inflammatory conditions and other CV risk-modifying conditions, the risk was calculated using all the respective risk assessment equations, and the risk assessment equation estimating the highest risk was used.

The secondary outcomes were the change in individual risk factors [blood pressure (in patients with hypertension), LDL-cholesterol (in patients with dyslipidemia), A1C (in patients with diabetes) and tobacco cessation (self-reported abstinence)] over a 6-month period.

Sample size and analytical plan

Sample size

Using the information from our previous pharmacist-led CV risk reduction trial, R_xEACH[36] [Baseline CV risk (26.2%) and standard deviation (SD) (17.8)] and the following assumptions of 80% power and alpha of 0.05, 89 patients were required to detect 21% risk reduction. The sample size was inflated to 100 to to account for possible dropouts, losses to follow-up, and withdrawals of consent.

Analytical plan

Analysis was performed by using R 3.6.2 (Vienna, Austria; https://www.R-project.org/) and SAS 9.4 software (SAS Institute Inc. Cary, NC, USA).

Data were first screened to confirm that all the participating patients met the inclusion/exclusion criteria and provided informed consent. Once those conditions were confirmed, statistical analysis started.

Demographic information and clinical characteristics were analyzed using descriptive statistics. Frequency (percentage) was used for categorical variables and mean (standard derivation) for continuous variables. Statistical significance at the univariable level was assessed using Chi-square test or Fisher's exact test (when small frequencies present) for categorical variables, and T-test for continuous variables (assumption of statistics tests were checked ahead). The primary outcome was analyzed by paired T-test. Multivariable linear mixed effect models was used to adjust for centre effect and baseline characteristics. Secondary outcomes were analyzed using paired T-test and Chi-square test as appropriate.

Trial and data management was performed by EPICORE Centre

R_xIALTA was registered at Clinicaltrials.gov (NCT03152396) and approved by the Health Research Ethics Board of the University of Alberta (Pro00072858).

Results

The study was launched in August, 2017, and the last patient was enrolled in July 2019. Follow up was completed in January 2020. We screened 126 patients, of those 103 were eligible. We enrolled 99 patients and 94 of them completed the study (Figure 1). Demographic and clinical characteristics are presented in Table 1. Mean age was 64 years (standard deviation (SD) 14.8), approximately two thirds (61%) of the participants were female and 86% were Caucasian. More than half (56%) had rheumatoid arthritis, 14% had psoriasis, 12% had psoriatic arthritis, 11% had gout, 6% had ankylosing spondylitis and 1% had systemic lupus erythematosus. Hypertension was the most commonly reported risk factor (47%), followed by dyslipidemia (45%), diabetes (13%), atherosclerotic vascular events (angina, heart attack, stroke/TIA) (12%),

current tobacco use (11%) and chronic kidney disease (9%). In addition, average body mass index (BMI) was 28.2 (5.2) kg/m^2 and only 9% reported exercising for 30 minutes (or more) five or more times per week. Importantly, only 2% of participants reported that their CV risk was assessed by a healthcare provider before taking part in the study.

Table 1 baseline demographic and clinical characteristics

Characteristic		**Frequency**	**Percentage**
Age (Mean, SD)	Age, years	64	14.8
Sex	Female	60	61%
Ethnicity	Aboriginal / First Nations	3	3%
	Black	2	2%
	Caucasian	85	86%
	Hispanic	2	2%
	South-Asian	1	1%
	Other Asian	6	6%
Inflammatory Conditions	RA	55	56%
	Psoriasis	14	14%
	PsA	12	12%
	Gout	11	11%
	AS	6	6%
	SLE	1	1%
Risk factors	Hypertension	47	47%
	Dyslipidemia	45	45%
	Diabetes	13	13%
	Atherosclerotic vascular events	12	12%
	Current tobacco use	11	11%

	CKD	9	9%
Exercise	Very active	9	9%
	Moderately active	39	39%
	No exercise additional to ordinary daily living	49	50%
	Not reported	2	2%
Alcohol use	None	38	38%
	1-2/day	40	41%
	>2 drinks/day	14	14%
	1-3 drinks/week	5	5%
	Not reported	2	2%
Dietary habits	No specific diet	85	86%
	Low sugar	3	3%
	Low salt	7	7%
	Low saturated fat	1	1%
	High fruit/vegetables	6	6%
	Other	2	2%
Physical and lab assessment (Mean, SD)	BMI, kg/m^2	28.2	5.2
	Systolic BP, mmHg	136.6	15.7
	Diastolic BP, mmHg	81.8	11.4
	Total cholesterol, mmol/L	4.8	1.3
	HDL-cholesterol, mmol/L	1.4	0.5
	LDL-cholesterol, mmol/L	2.6	1.1
	A1C, %	8.3	1.1

	eGFR, ml/min/1.73 m^2	76.6	18.5
	ACR, mg/mmol	154.7	218.2

***RA: rheumatoid arthritis, PsA: psoriatic arthritis, AS: ankylosing spondylitis, SLE: systemic lupus erythematosus, CKD: chronic kidney disease, SD: Standard deviation, eGFR: estimated glomerular filtration rate, ACR: Random albumin to creatinine ratio**

Estimated CV risk was reduced from 25% (SD 16.1) at baseline to 19.8% (SD 14.7) after 6 months. After adjusting for baseline characteristics and centre effect, this corresponded to a 24.5% relative risk reduction [6 (95% confidence interval (4.6 – 7.4)] p <0.001) (Figure 2). In patients with hypertension, significant reductions were observed in systolic and diastolic blood pressure (Table 2). Similarly, we noted reductions in LDL-cholesterol in patients with dyslipidemia and A1C in those with diabetes (Table 2). Participants' dietary habits were also improved (p=0.02), while exercise, alcohol and tobacco use were not significantly improved.

Table 2 Changes in individual risk factors

Risk factor	Baseline	6 months	Difference (95% confidence interval)	P-value
Systolic BP (n=47)	138.4 (17.9)	127.7 (10.33)	10.7 (10 to 12.66)	<0.001
Diastolic BP (n=47)	80.2 (13.04)	77.3 (10.12)	2.9 (1.9 to 3.9)	<0.001
Total Cholesterol (n=45)	4.96 (1.439)	4.60 (1.25)	0.36 (0.32 to 0.40)	<0.001
LDL-cholesterol (n=45)	2.81 (1.19)	2.51 (1.13)	0.3 (0.25 to 0.35)	<0.001
HDL-cholesterol (n=45)	1.43 (0.52)	1.47 (0.51)	0.04 (0.05 to 0.01)	<0.001
A1C (n=13)	8.3 (1.07)	7.05 (0.95)	1.25 (0.6 to 1.9)	<0.001
BMI	28.2	28.3	0.1 (-0.24 to 0.11)	0.4551
Tobacco use (proportion)	10.3	5.2	N/A	0.2619

Pharmacist interventions are listed in Figure 3. Medication/dose change was the most implemented intervention (30%) (Table 3), followed by lifestyle education and advice (27%), patient, family members and caregivers' education about the condition and prescribed treatment (22%), follow up (12%), adherence assessment and improvement (7%) and referral to other healthcare providers (2%). There were very minimal adverse events reported during the study.

Table 3 Medication use and changes

	Proportion of patients taking the medications for				
Medication Frequency	Diabetes	Dyslipidemia	Hypertension	Inflammatory Conditions	Vascular Disease
Baseline					
0	89.1	77.2	67.4	5.4	91.3
1	6.5	21.7	13	35.9	8.7
2	4.4	1.1	14.1	30.4	0
3	0	0	3.3	13.1	0
4	0	0	1.1	13	0
5	0	0	1.1	1.1	0
6	0	0	0	1.1	0
6-months					
0	86.5	63.5	59.5	4.1	93.2
1	5.4	33.8	21.6	33.8	6.8
2	4.1	2.7	13.5	29.7	0
3	4	0	4.1	14.9	0
4	0	0	1.3	13.5	0
5	0	0	0	2.7	0
6	0	0	0	1.3	0

Discussion

Chronic inflammatory conditions increase patient's risk for CV events; however, these patients are often not receiving CV risk assessment or treatment. We hypothesized that community pharmacists could proactively and systematically screen for chronic inflammatory diseases (because of the unique medications used in these conditions), and then manage their CV risk factors. We found that a pharmacist-led care reduced the risk of major CV events by 24.5% ($p < 0.001$) over a 6-month period. The intervention was also associated with reductions in blood pressure, LDL-cholesterol and A1C. Such improvements are related to the following pharmacist activities: medication/dose changes, lifestyle education and advice, patient, family members and caregivers' education about the condition and prescribed treatment, follow up, adherence assessment and improvement and referral to other healthcare providers.

Our findings are consistent with the findings of the R_xEACH study, which evaluated the impact of pharmacist intervention (assessment, prescribing, and follow-up) on CV risk in patients at high risk for CVD (patients with diabetes, chronic kidney disease, established vascular disease or Framingham risk > 20%). R_xEACH reported that such intervention was associated with CV risk reduction as well as improvements in all individual risk factors.[36]

Our findings are also consistent with the findings of Semb and colleagues who reported significant CV risk reduction when a CV risk factor (lipids) was managed appropriately.[46] They also highlight the importance of pharmacist prescribing, as 'medication/dose change' was the most implemented intervention. This intervention would have not been possible without having independent prescriptive authority. These findings are supported by the findings of Al Hamarneh and colleagues and Wubben and Vivian who reported that better outcomes were achieved when pharmacists had prescriptive authority.[47,48]

This study is not without limitations. As described above, the study was not a randomized controlled trial, due to ethical concerns of randomizing this high risk underserved population to usual care after proving that the intervention is effective. We acknowledge that this reduces causal inference, however, the findings of this study are similar to the randomized R_xEACH study.[36] Since the 6-month follow-up period can be considered relatively short; it is possible that the effects of the intervention could be short lived. It is also possible, however, that greater improvements leading to larger CV risk reduction could have been observed with a longer follow up period. Pharmacists who provided the intervention also conducted the assessment and entered the information into the study online system where CV risk was calculated. This could have introduced bias; however, the study team monitored study sites against source documents to ensure accuracy. The fact that adverse events were self-reported could have led to underreporting.

Our findings, combined with the fact that the risk of myocardial infarction, heart failure and CV death among patients with chronic inflammatory diseases is much higher than the general population,[8-10] highlight the importance of focusing on the patient as a whole, rather than only focusing on their acute complaints.

It is noteworthy that only 2% of our participants had their CV risk assessed before taking part in the study. This is consistent with the literature, as it has been reported that the levels of awareness and perceived risk of CVD is low in this patient population.[49] Gaps in care have also been reported when it comes to CV risk assessment.[7,12-14] This also highlights the importance of a systematic and proactive approach towards case-finding by pharmacists – as many patients would not know to ask for CV risk assessment. This is a unique feature of involving community pharmacists – an approach which we have used successfully in a number of areas. [28,36,50]

R_xIALTA findings add to the high-level evidence of effective pharmacist prescribing interventions in improving CV risk and individual CVD risk factors.[36,50] Such high-level evidence should encourage policy makers to broaden the scope of practice for pharmacists and pharmacy professional organizations to implement those interventions on a larger scale to seize the opportunity to enhance patient care.

To our knowledge, this is the first study to assess the effect of a pharmacist-led case-finding and care on CV risk in patients with chronic inflammatory conditions in a community pharmacy setting. We have demonstrated that pharmacist-led intervention (including prescribing) improved CV risk as well as the individual CVD risk factors. Pharmacists also improved the access to care in a high-risk population, that otherwise would not have their CV risk assessed. Implementing this on a wider scale could help addressing one of the world's major public health challenges.

Figures

Figure 1 Study flow chart

Figure 2 Change in estimated CV risk over time

Figure 3 Pharmacist interventions

Contributorship statement:

Substantial contribution to study conception and design: YNA, RG, SK, CM, AM, RTT

Substantial contribution to data collection: YNA, AM, RTT

Substantial contribution to data analysis and interpretation: YNA, RTT

Drafting the article or revising it critically: YNA, RG, SK, CM, AM, RTT

Final approval of the submitted version: YNA, RG, SK, CM, AM, RTT

Acknowledgement:

None of this could have taken place without the dedication and caring of the R_xIALTA investigators, listed in descending order of recruitment:

Nader Hammoud (Shoppers Drug Mart #2326, Calgary), Nataliya Posudwvska (Calgary Co-op, Calgary), Rick Siemens (London Drugs #38, Lethbridge), Dixie Richardson (Safeway Pharmacy, Edmonton), Aileen Coutts (Calgary Co-Op, Calgary), Jan Messiha (Calgary Co-op, Calgary), Farzana Sharif (Calgary Co-Op, Calgary), Pegah Manzoori (Calgary Co-Op, Calgary), Maria James (Calgary Co-Op, Calgary), Jack Dhaliwal (Calgary Co-Op, Calgary), Derek Durocher (Shoppers Drug Mart #313, Edmonton), Leanna St. Onge, Otti Gohrbandt and Chelsey Collinge (Co-op Pharmacy, Rocky Mountain House), Aila Omar (Co-op Pharmacy, Edmonton), Diane Lazarko-Gamache (Calgary Co-Op, Calgary), Sonal Ijner (Calgary Co-Op, Calgary), Carlene Olyksen, Jelena Okuka (Meridian Pharmacy, Stony Plain), Murtaza Hassanali (Shoppers Drug Mart #371, Edmonton), Penny and Fausta (Penny and Fausta Pharmacy, Calgary).

Funding statement:

We would like to acknowledge the generous support of the funder of R_xIALTA: Canadian Initiative for Outcomes in Rheumatology cAre (CIORA) (Grant number: 2015-001). Our funder did not have any role in the study design, collection, analysis, interpretation of the data, writing the report and the decision to submit for publication.

We would like to acknowledge the support of the Consultation and Research Services Platform at The Alberta' SPOR SUPPORT Unit in Data management and statistical services (Grant number N/A).

Competing interests: None

Data sharing statement: Data can be shared upon reasonable requests

Reference:

1. WHO. Cardiovascular diseases. 2017. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/ (Accessed 9/6/2020)
2. Government of Canada. Report from the Canadian Chronic Disease Surveillance System: Heart Disease in Canada, 2018. 2018. Available from: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/report-heart-disease-Canada-2018.html (Accessed 9/6/2020)
3. The Arthritis Society. Arthritis in Canada, Facts and Figures. 2020. Available from: https://arthritis.ca/about-arthritis/what-is-arthritis/arthritis-facts-and-figures (Accessed 9/6/2020)
4. Nurmohamed MT (2009) Cardiovascular risk in rheumatoid arthritis. Autoimmun Rev 8:663–667
5. Peters MJ, Symmons DP, McCarey D, et al. (2010). Evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis. 69(2):325-31.
6. Semb AG, Rollefstad S, van Riel P, et al. (2014). Cardiovascular disease assessment in rheumatoid arthritis: A guide to translating knowledge of cardiovascular risk into clinical practice. Ann Rheum Dis.
7. Schieir O, Tosevski C, Glazier RH, Hogg-Johnson S, Badley EM. Incident myocardial infarction associated with major types of arthritis in the general population: a systematic review and meta-analysis. Ann Rheum Dis. 2017; Published Online First: 22 Jan. doi: 10.1136/annrheumdis-2016-210275.
8. Maradit-Kremers H, Crowson CS, Nicola PJ, et al. (2005). Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population based cohort study. Arthritis Rheum. 52:402–11.
9. Nicola PJ, Maradit-Kremers H, Roger VL, et al. (2005). The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum. 52:412–20
10. Maradit-Kremers H, Crowson CS, Nicola PJ, et al. (2008). Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum. 52:722–32
11. Mills M, Loney P, Jamieson E, et al. (2010). A primary care cardiovascular risk reduction clinic in canada was more effective and no more expensive than usual on-demand primary care--a randomised controlled trial. Health Soc Care Community. 18(1):30-40.
12. Woodward A, Wallymahmed M, Wilding J, et al. (2006). Successful cardiovascular risk reduction in type 2 diabetes by nurse-led care using an open clinical algorithm. Diabet Med. 23(7):780-787

13. Woodward A, Wallymahmed M, Wilding J, et al. (2005). Improved glycaemic control--an unintended benefit of a nurse-led cardiovascular risk reduction clinic. Diabet Med. 22(9):1272-1274.

14. Keeling SO, Teo M, Fung D. (2011). Lack of cardiovascular risk assessment in inflammatory arthritis and systemic lupus erythematosus patients at a tertiary care center. Clin Rheumatol. 30(10):1311-1317

15. Canadian Institute for Health Information. Physicians in Canada, 2018. 2019. Available from: https://www.cihi.ca/sites/default/files/document/physicians-in-canada-2018.pdf (Accessed 9/6/2020)

16. Kremers HM, Crowson CS, Therneau TM, et al. (2008) High ten-year risk of cardiovascular disease in newly diagnosed rheumatoid arthritis patients: a population-based cohort study. Arthritis Rheum. 58:2268–2274

17. D'Agostino RB S, Vasan RS, Pencina MJ, et al. (2008). General cardiovascular risk profile for use in primary care: The framingham heart study. Circulation.117(6):743-753

18. Arts EE, Popa C, Den Broeder AA, et al. (2014). Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. Ann Rheum Dis.

19. Chung CP, Oeser A, Avalos I, *et al*. (2006). Utility of the Framingham risk score to predict the presence of coronary atherosclerosis in patients with rheumatoid arthritis. Arthritis Res Ther.8:R186.

20. Tournadre A, Mathieu S, Soubrier M. Managing cardiovascular risk in patients with inflammatory arthritis: practical considerations. Ther Adv Musculoskel Dis. 2016;8(5):180-191.

21. Semb AG, Kvien TK, DeMicco DA, et al. Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. *Arthritis & Rheumatism*. 2012;64(9): 2836-2846.

22. Liao KP, Cai T, Gainer VS, et al. Lipid and lipoprotein levels and trend in rheumatoid arthritis compared to the general population. *Arthritis Care & Research*. 2013;65(12): 2046-2050.

23. Liao KP, Liu P, Lu B, et al. Association between lipid levels and major adverse cardiovascular events in rheumatoid arthritis compared to non-rheumatoid arthritis patients. *Arthritis & Rheumatology*. 2015;67(8): 2004-2010.

24. Peters MJL, Symmons DPM, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis*. 2010;69: 325-331.

25. Rollefstad S, Kvien TK, Holme I, et al. Treatment to lipid target in patients with inflammatory joint diseases in preventative cardio-rheuma clinic. *Ann Rheum Dis* 2013;72:1968-1974.

26. Shiu JR, Simpson SH, Johnson JA, et al. (2006). Quantifying opportunities to affect diabetes management in the community. Can Pharm J. 139(3): 37-38.

27. Rothman RL, Malone R, Bryant B, et al. (2005). A randomized trial of a primary care-based disease management program to improve cardiovascular risk factors and glycated hemoglobin levels in patients with diabetes. *Am J Med*.118(3):276-84

28. Tsuyuki RT, Johnson JA, Teo K et al. (2002). A Randomized Trial of the Effect of Community Pharmacist Intervention on Cholesterol Risk Management – The Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP). Arch Intern Med. 162:1149-55

29. Carter BL, Bergus GR, Dawson JD, et al. (2008). A cluster randomized trial to evaluate physician/pharmacist collaboration to improve blood pressure control. *J Clin Hypertens (Greenwich)*. 10(4):260-27

30. McLean DL, McAlister FA, Johnson JA et al. (2008). A Randomized Trial of the Effect of Community Pharmacist and Nurse Care on Improving Blood Pressure Management in Patients with Diabetes Mellitus – Study of Cardiovascular Risk Intervention by Pharmacists-Hypertension (SCRIP-HTN). Arch Intern Med.168(21):2355-61.

31. Blenkinsopp A, Phelan M, Bourne J, et al. (2000). Extended adherence support by community pharmacists for patients with hypertension: a randomized controlled trial. International Journal of Pharmacy Practice.8:165-175.

32. Wang J, Wu J, Yang J, et al. (2011). Effect of pharmaceutical care interventions on blood pressure and medication adherence of patients with primary hypertension in China. Clinical Research and Regulatory Affairs. 1:1-6.

33. Gattis WA, Hasselblad V, Whellan DJ, et al. (1999). Reduction in heart failure events by the addition of a clinical pharmacist to the heart failure management team: results of the Pharmacist in Heart Failure Assessment Recommendation and Monitoring (PHARM) Study. *Arch Intern Med*. 159(16):1939-1945

34. Taveira TH, Wu WC, Martin OJ, et al. (2006). Pharmacist-led cardiac risk reduction model. *Prev Cardiol*.9:202-208

35. Santschi V, Chiolero A, Burnand B, et al. (2011). Impact of pharmacist care in the management of cardiovascular disease risk factors: a systematic review and meta-analysis of randomized trials. *Arch Intern Med*. 171:1441-53.

36. Tsuyuki RT, Al Hamarneh YN, Jones CA, Hemmelgarn BR. The effectiveness of pharmacist interventions on cardiovascular risk. Journal of the American College of Cardiology 2016;67(24):2847-2854. doi: 10.1016/j.jacc.2016.03.528.

37. Murray MD, Ritchey ME, Wu J, et al. (2009). Effect of a pharmacist on adverse drug events and medication errors in outpatients with cardiovascular disease. *Arch Intern Med*.169(8):757-

38. Marra C, Johnston K, Santschi V, Tsuyuki RT. 2017. Cost-effectiveness of pharmacist care for managing hypertension in Canada. *Canadian Pharmacists Journal.* 150(3):184-197

39. Al Hamarneh YN, Johnston K, Marra CA, Tsuyuki RT. Pharmacist prescribing and care improves cardiovascular risk, but is it cost-effective? A cost-effectiveness analysis of the R_xEACH study. Can Pharm J. 2019;152(4):257-266

40. Al Harmarneh YN, Lamb S, Donald M, et al. Pharmacist prescribing and care improves cardiovascular risk, but what do patients think? A substudy of the R_xEACH study. Can Pharm J. 2018; 151(4): 223–227

41. Nerenberg KA, Zarnke KB, Leung AA, et al. Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. Can J Cardiol. 2018;34(5):506-525

42. Anderson TJ, Grégoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol. 2016;32(11):1263-1282.

43. Diabetes Canada. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Canadian Journal of Diabetes. 2018; 42: S1-S326

44. Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR. The UKPDS risk engine: a model for the risk of coronary heart disease in type 2 diabetes (UKPDS 56). *Clin Sci* 2001; 101: 671-679.

45. Dorresteijn JAN, Visseren FLJ, Wassink AMJ et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study in patients with arterial disease: the SMART risk score. Heart 2013; 99:866-872.

46. Semb AG, Kvien TK, DeMicco DA, Fayyad R, Wun CC, LaRosa JC, Betteridge J, Terje R Pedersen TR, Holme I. Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. Arthritis Rheum 2012; 64:2836-46

47. Al Hamarneh YN, Hemmelgarn BR, Hassan I, Jones CA, Tsuyuki RT. The Effectiveness of Pharmacist Interventions on Cardiovascular Risk in Adult Patients with Type 2 Diabetes: The Multicentre Randomized Controlled R_xEACH Trial. Can J Diabetes. 2017;41(6):580-586.

48. Wubben DP, Vivian EM. Effects of pharmacist outpatient interventions on adults with diabetes mellitus: A systematic review. Pharmacotherapy, 2008; 28: 421-436

49. Ghosh-Swaby OR, Kuriya B. Awareness and perceived risk of cardiovascular disease among individuals living With rheumatoid arthritis is low: results of a systematic literature review. Arthritis Res Ther. 2019; 21:33-39

50. Tsuyuki RT, Houle SK, Charrois TL, et al. Randomized Trial of the Effect of Pharmacist Prescribing on Improving Blood Pressure in the Community: The Alberta Clinical Trial in Optimizing Hypertension (R_xACTION). Circulation. 2015;132(2):93-100

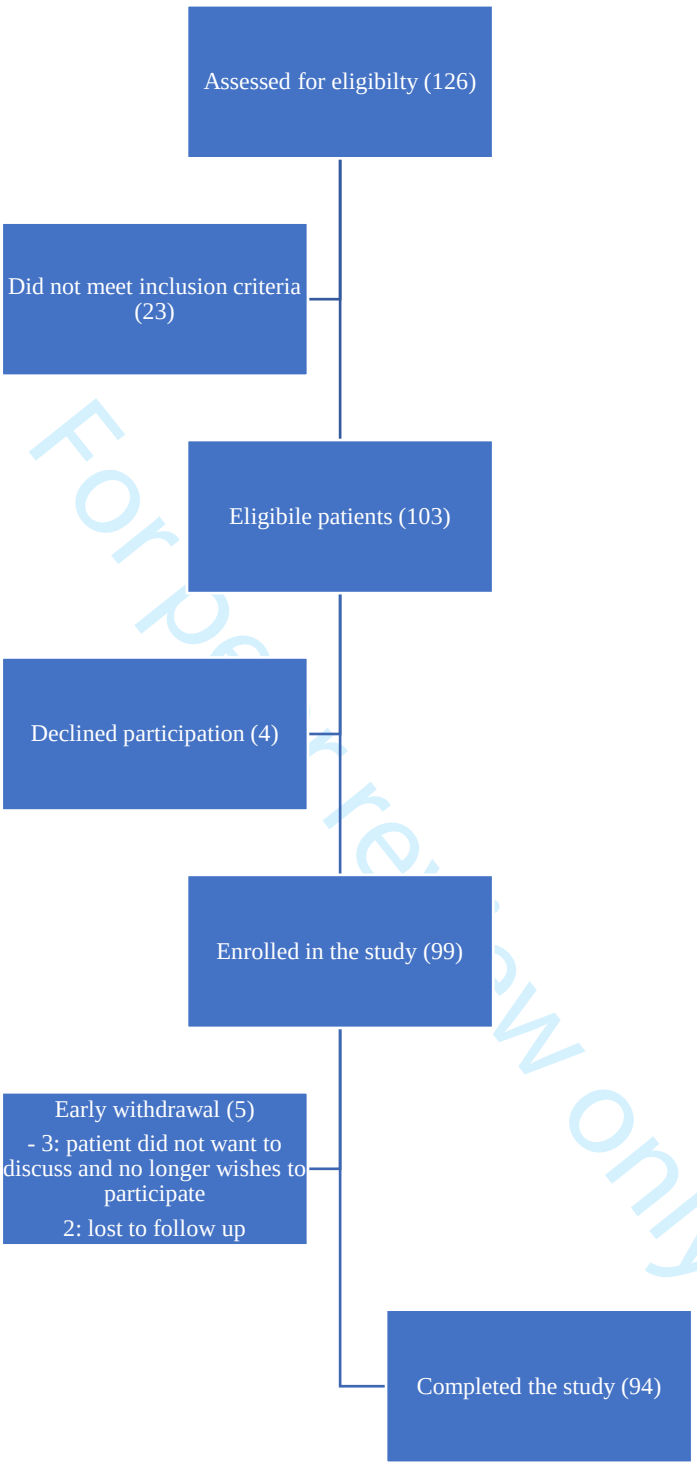


Figure 1: Study flow chart

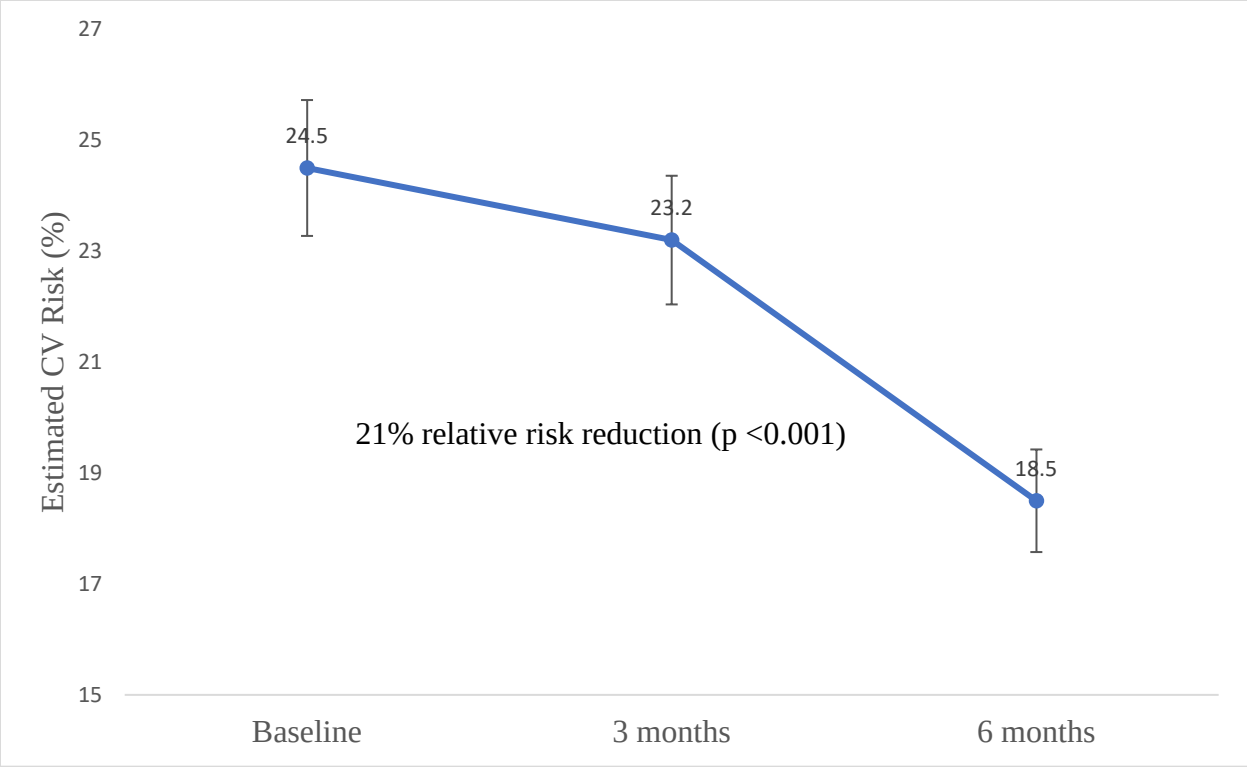
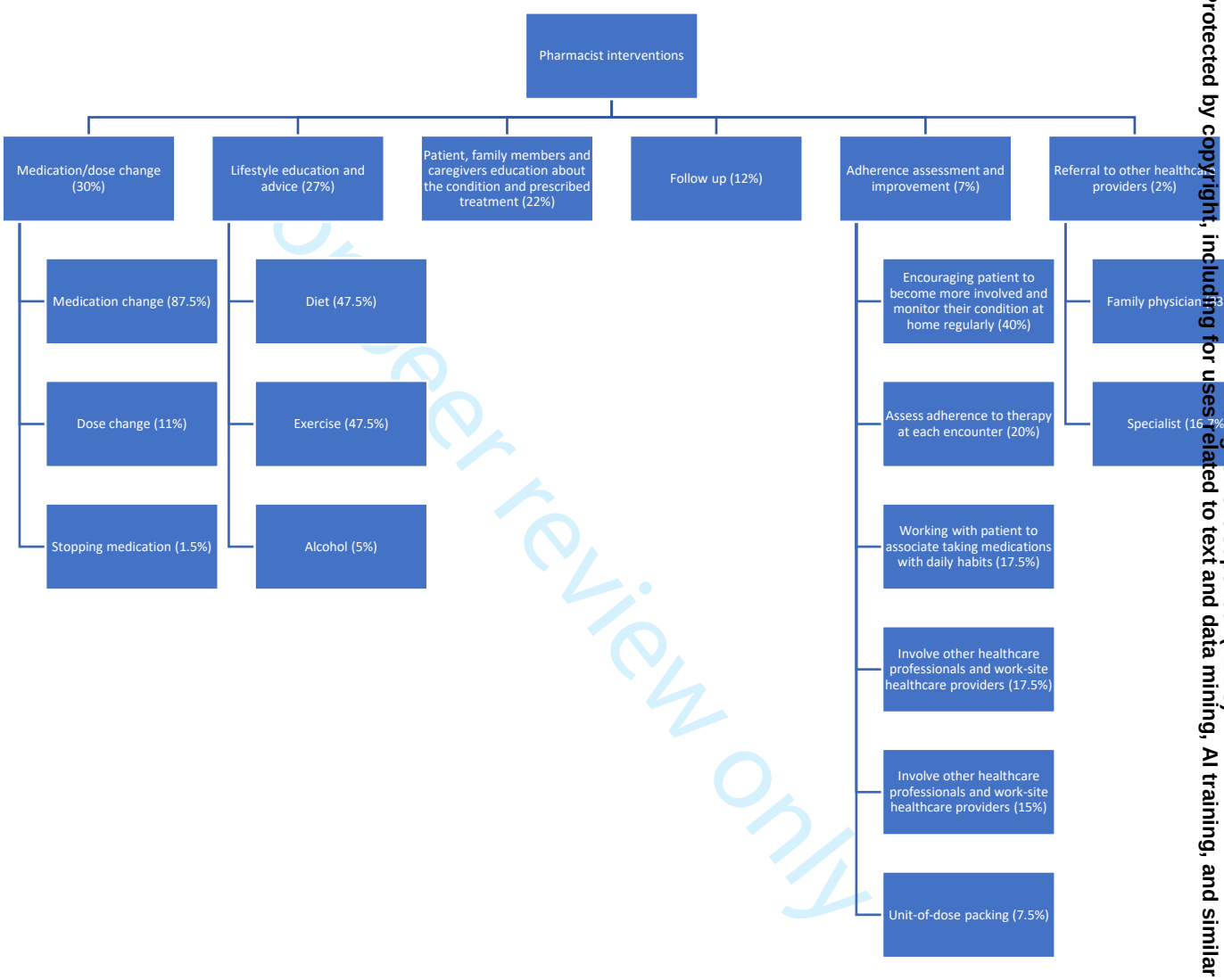


Figure 2 Change in estimated CV risk over time



TREND Statement Checklist

Paper Section/ Topic	Item No	Descriptor	Reported?	Pg #
Title and Abstract				
Title and Abstract	1	Information on how unit were allocated to interventions	Yes	3
		Structured abstract recommended	Yes	3
		Information on target population or study sample	Yes	3
Introduction			Yes	5-6
Background	2	Scientific background and explanation of rationale	Yes	5-6
		Theories used in designing behavioral interventions		
Methods				
nts	3	Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	Yes	6
		Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	Yes	6-7
		Recruitment setting	Yes	6
		Settings and locations where the data were collected	Yes	6
Interventions	4	Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:	Yes	7
		○ Content: what was given?	Yes	7
		○ Delivery method: how was the content given?	Yes	7
		○ Unit of delivery: how were the subjects grouped during delivery?	Yes	7
		○ Deliverer: who delivered the intervention?	Yes	7
		○ Setting: where was the intervention delivered?	Yes	7
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	Yes	7
		○ Time span: how long was it intended to take to deliver the intervention to each unit?	Yes	7
		○ Activities to increase compliance or adherence (e.g., incentives)	N/A	
Objectives	5	Specific objectives and hypotheses	Yes	6
Outcomes	6	Clearly defined primary and secondary outcome measures	Yes	8
		Methods used to collect data and any methods used to enhance the quality of measurements	Yes	6-7
		Information on validated instruments such as psychometric and biometric properties	N/A	
Sample Size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	Yes	8
Assignment Method	8	Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	N/A	
		Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)	N/A	
		Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	N/A	

TREND Statement Checklist

Blinding (masking)	9	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed.	
Unit of Analysis	10	Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community) **(Yes, 9)**	Yes
		If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis) **N/A**	
Statistical Methods	11	Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data **(Yes, 9)**	
		Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis **(N/A)**	
		Methods for imputing missing data, if used **(N/A)**	
		Statistical software or programs used **(Yes, 9)**	
Results			
Participant flow	12	Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended) **(Yes, Figure 1)**	
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study **(Yes, 9-10)**	
		○ Assignment: the numbers of participants assigned to a study condition **(N/A)**	
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention **(N/A)**	
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition **(Yes, Figure 1)**	
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition **(Yes, 10)**	
		Description of protocol deviations from study as planned, along with reasons **(N/A)**	
Recruitment	13	Dates defining the periods of recruitment and follow-up **(Yes, 10)**	
Baseline Data	14	Baseline demographic and clinical characteristics of participants in each study condition **(Yes, Table 1)**	
		Baseline characteristics for each study condition relevant to specific disease prevention research **(N/A)**	
		Baseline comparisons of those lost to follow-up and those retained, overall and by study condition **(N/A)**	
		Comparison between study population at baseline and target population of interest **(N/A)**	
Baseline equivalence	15	Data on study group equivalence at baseline and statistical methods used to control for baseline differences **(N/A)**	

Numbers analyzed	16	Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible **(Yes, Table 1)** Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses **(N/A)**		
comes and		For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision **(Yes, table 2)**		
		Inclusion of null and negative findings **(N/A)**		
		Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any **(N/A)**		
Ancillary analyses	18	Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory **(N/A)**		
Adverse events	19	Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals) **(Yes, 10)**		
DISCUSSION				
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	Yes	14
		Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	N/A	
		Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	N/A	
		Discussion of research, programmatic, or policy implications	N/A	
Generalizability	21	Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues		
Overall	22	General interpretation of the results in the context of current evidence	Yes	14-15

TREND Statement Checklist

From: Des Jarlais, D. C., Lyles, C., Crepaz, N., & the Trend Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of Public Health*, 94, 361-366. For more information, visit: http://www.cdc.gov/trendstatement/

BMJ Open

R_xIALTA: Evaluating the Effect of a Pharmacist-Led Intervention on CV Risk in Patients with Chronic Inflammatory Diseases in a Community Pharmacy Setting. A Prospective Pre-Post-Intervention Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043612.R2
Article Type:	Original research
Date Submitted by the Author:	16-Feb-2021
Complete List of Authors:	Al Hamarneh, Yazid; University of Alberta Marra, Carlo; University of Otago, Pharmacy Gniadecki, Robert; University of Alberta, Medicine Keeling, Stephanie; University of Alberta, Rheumatology Morgan, Andrea; Foothills Medical Centre Tsuyuki, Ross; University of Alberta, Faculty of Medicine and Dentistry
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	RHEUMATOLOGY, PUBLIC HEALTH, General diabetes < DIABETES & ENDOCRINOLOGY, Hypertension < CARDIOLOGY, Cardiac Epidemiology < CARDIOLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

R_xIALTA: Evaluating the Effect of a Pharmacist-Led Intervention on CV Risk in Patients with Chronic Inflammatory Diseases in a Community Pharmacy Setting. A Prospective Pre-Post-Intervention Study

Yazid N Al Hamarneh, BSc (Pharm), PhD (1), Carlo Marra, PharmD, PhD (2), Robert Gniadecki, MD, PhD (1), Stephanie O Keeling, MD (1), Andrea Morgan, BSc (Pharm) (3), Ross T Tsuyuki, BSc(Pharm), PharmD, MSc, FCSHP, FACC, FCAHS (1)

1. Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada

2. School of Pharmacy, University of Otago, Dunedin, New Zealand

3. Foothills Medical Centre, Calgary, Alberta, Canada

Corresponding author:

Yazid N. Al Hamarneh

EPICORE Centre

362 HMRC Building

University of Alberta

Edmonton, Alberta

Canada

Email: yazid.alhamarneh@ualberta.ca

Phone number: 780-492-9608

Fax: 780-492-6059

Keywords: Rheumatology, Public Health, Diabetes, Hypertension, Cardiac Epidemiology, Lipid Disorders

Abstract word count: 299

Manuscript word count: 3048

Number of Tables: 2

Number of Figures: 3

Author contributions:

Substantial contribution to study conception and design: all authors

Substantial contribution to data collection: YNA, AM, RTT

Substantial contribution to data analysis and interpretation: YNA, RTT

Drafting the article or revising it critically: all authors

Final approval of the submitted version: all authors

Acknowledgement:

None of this could have taken place without the dedication and caring of the R_xIALTA investigators, listed in descending order of recruitment:

Nader Hammoud (Shoppers Drug Mart #2326, Calgary), Nataliya Posudwvska (Calgary Co-op, Calgary), Rick Siemens (London Drugs #38, Lethbridge), Dixie Richardson (Safeway Pharmacy, Edmonton), Aileen Coutts (Calgary Co-Op, Calgary), Jan Messiha (Calgary Co-op, Calgary), Farzana Sharif (Calgary Co-Op, Calgary), Pegah Manzoori (Calgary Co-Op, Calgary), Maria James (Calgary Co-Op, Calgary), Jack Dhaliwal (Calgary Co-Op, Calgary), Derek Durocher (Shoppers Drug Mart #313, Edmonton), Leanna St. Onge, Otti Gohrbandt and Chelsey Collinge (Co-op Pharmacy, Rocky Mountain House), Aila Omar (Co-op Pharmacy, Edmonton), Diane Lazarko-Gamache (Calgary Co-Op, Calgary), Sonal Ijner (Calgary Co-Op, Calgary), Carlene Olyksen, Jelena Okuka (Meridian Pharmacy, Stony Plain), Murtaza Hassanali (Shoppers Drug Mart #371, Edmonton), Penny and Fausta (Penny and Fausta Pharmacy, Calgary).

Support:

We would like to acknowledge the generous support of the funder of R_xIALTA: Canadian Initiative for Outcomes in Rheumatology cAre (CIORA). Our funder did not have any role in the study design, collection, analysis, interpretation of the data, writing the report and the decision to submit for publication.

We would like to acknowledge the support of the Consultation and Research Services Platform at The Alberta' SPOR SUPPORT Unit in Data management and statistical services.

Abstract

Patients with inflammatory conditions are at high risk for cardiovascular disease (CVD). Despite such elevated risk, their CV risk factors are sub-optimally managed.

Objective: To evaluate the effect of a pharmacist-led intervention on CV risk in patients with inflammatory conditions.

Methods:

Design: Prospective pre-post-intervention

Setting: 17 Community pharmacies across Alberta

Population: Adults with inflammatory conditions (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, gout, systemic lupus erythematosus, psoriasis vulgaris) who had at least one uncontrolled risk factor (A1C, blood pressure, LDL-cholesterol, or current tobacco users).

Intervention: All patients enrolled in the study received: physical and laboratory assessment, individualized CV risk assessment and education regarding this risk, treatment recommendations, prescription adaptation, and prescribing where necessary to meet treatment targets, regular communication with the patient's treating physician(s) and regular follow-up with all patients every month for 6 months

Outcomes: Primary: Change in estimated CV risk (risk of a major CV event in the next 10 years) after 6 months. Secondary: Change in individual risk factors [blood pressure, LDL-cholesterol, A1C and tobacco cessation] over a 6-month period

Results: We enrolled 99 patients. The median age was 66.41 years (interquartile range 57.64 – 72.79), More than half of them (61%) were female and more than three quarters (86%) were Caucasians. After adjusting for age, sex and ethnicity and centre effect, there was a reduction of 24.5% in CV risk ($p<0.001$); including a reduction of 0.3 mmol/L in LDL-c ($p<0.001$), 10.7 mmHg in systolic blood pressure ($p<0.001$), 1.25% in A1C ($p<0.001$). There was a non-significant trend towards tobacco cessation.

Conclusion: This is the first study on CV risk reduction in patients with inflammatory conditions in a community pharmacy setting. R_xIALTA provides evidence for the benefit of pharmacist care on global cardiovascular risk reduction as well as the individual cardiovascular risk factors in patients with inflammatory conditions.

Study registration: The study was registered at Clinicaltrials.gov (NCT03152396)

Significance and Innovation:

- This is the first study to assess the effect of a pharmacist-led case-finding and care on CV risk in patients with chronic inflammatory conditions in a community pharmacy setting
- The pharmacist-led case-finding and care enhanced access to CV risk assessment and care in a high-risk population, that otherwise would not have their CV risk assessed
- The pharmacist-led case-finding and care (including prescribing and ordering laboratory tests) was associated with CV risk reduction and improvement in all the individual CVD risk factors

Introduction

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.[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] Chronic inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis ankylosing spondylitis, gout, systemic lupus erythematosus and psoriasis are also increasingly being recognized as independent risk factors for CVD.[4-7] Indeed, it has been reported that the risk of myocardial infarction, heart failure and CV death among patients with chronic inflammatory disease is 2–3-fold greater than in the general population.[8-10] Such increased risk can be explained by 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]

Despite being recommended by international guidelines,[7] CV risk assessment has not been incorporated into many clinicians' daily routine.[7] In fact, reports indicate that such assessments generally only exist in larger centers for non-rheumatology patients.[11-13] Moreover, Keeling and colleagues reported that most rheumatologists, who are the main caregivers for patients with these conditions, conducted suboptimal CV risk assessments. [14] Unfortunately, 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. [7] Furthermore, many patients, especially those who are living in remote or rural areas, do not have access to family physicians. [15] These facts, combined with the benefits of early identification after the diagnosis,[16] highlight the need for new and innovative ways for assessing CV risk in this high-risk population.

Special considerations need to be taken into account when calculating CV risk in patients with chronic inflammatory diseases, as the 'classic' risk engines (such as Framingham[17]) might underestimate the overall risk,[18] since they have not been adequately evaluated in this patient population.[19,5] For example, those patients who might benefit from lipid-lowering agents may be categorized "low risk" when using the Framingham risk engine.[18] As such, it has been recommended to use a modified Framingham risk engine (multiply the overall risk by 1.5) in this patient population. [20] There is conflicting evidence in the literature regarding lipid panel measurements in patients with rheumatoid arthritis. Some studies reported that total cholesterol and LDL-cholesterol are significantly lower, while other studies reported that they are significantly higher in patients with rheumatoid arthritis when compared to the general population. [21-23] Despite the variation, it is still recommended to treat patients with rheumatoid arthritis to general population lipid targets with consideration of risk modification, such as the European League Against Rheumatism recommendations that suggest multiplying the CV risk score by a factor of 1.5 in these patients.[24-25]

Pharmacists are front line, accessible, primary healthcare professionals who see patients at risk/with chronic conditions more frequently than any other healthcare provider.[26] The efficacy of their interventions in chronic diseases including diabetes,[27] dyslipidemia,[28] hypertension,[29-32] heart failure,[33] and CVD [34-36] has been well demonstrated in the literature. Pharmacists can systematically identify patients at high risk of CVD,[36] help manage their condition, improve their medication use,[31,32,37] and assist them to achieve their treatment targets.[27-32] In addition to clinical outcomes, pharmacist interventions are also associated with high levels of patient satisfaction, improved adherence to therapy and considerable cost savings and efficient use of health care resources.[31-32,38-40] This evidence, coupled with their full scope of practice including prescribing and laboratory test monitoring, ideally position pharmacists to conduct CV risk assessment and management. Therefore, we conducted this study to determine the effect of a pharmacist-led intervention on CV risk in patients with chronic inflammatory diseases.

Methods

R_xIALTA was a non-randomized prospective pre-post-intervention study that was conducted in 17 community pharmacies across Alberta, Canada (for a list of the participating pharmacies please see the acknowledgement section). We utilized a non-randomized design because our previous work in pharmacist-led CV risk reduction[36], a 723 patient (those with diabetes, chronic kidney disease, established vascular disease or Framingham risk >20%) randomized trial demonstrated significant reductions in estimated cardiovascular risk, and it was felt unethical to randomize this underserved high-risk population to usual care.

Patients were included if they were adults (≥18 years of age) with a physician-diagnosed chronic inflammatory condition (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, gout, systemic lupus erythematosus or psoriasis) and had at least one uncontrolled risk factor [blood pressure (≥140/90 without diabetes; ≥130/80 with diabetes)[41], LDL-cholesterol (>2.0 mmol/L)[42], A1C (>7.0%)[43], or current tobacco use]. We excluded patients if they were unwilling to participate/sign the consent form, unwilling or unable to participate in regular follow-up visits, pregnant, or experiencing a disease exacerbation (this may be indicated by current treatment with high or tapering dose of steroids), since lipid panel is most accurately measured when inflammatory diseases are stable or in remission.[5]

Recruitment

Pharmacists and pharmacy staff used the following methods to identify potential patients: 1. *Proactive case finding*: patients with physician-diagnosed chronic inflammatory conditions were identified by reviewing prescriptions of disease modifying anti-rheumatic drugs, NSAIDs,

immunosuppressants, gout medications, biologics (e.g., adalimumab, infliximab, ustekinumab, ixekizumab, secukinumab) and/or topical drugs containing calcipotriol, methotrexate with a rheumatologist or a dermatologist prescriber; 2. *Case finding via in-pharmacy posters and weekly fliers* and 3. *Case finding via bag stuffers with the above medications*.

As part of routine care, pharmacists measured the blood pressure and checked the most recent laboratory test results for the identified patients (through the provincial electronic health record). They then checked whether patients met the inclusion criteria. The pharmacists explained the study to those who met the inclusion criteria and invited them to take part. Patients who agreed to take part were asked to sign a written informed consent form. Once the signed written informed consent form was obtained the patients were enrolled in the study.

The patient's physician(s) received a letter from the pharmacist to inform them that the patient agreed to participate in this study.

Intervention

All enrolled patients received: 1. Patient assessment (blood pressure measurement according to Hypertension Canada guidelines [41], waist circumference, weight and height measurements), 2. Laboratory assessment of A1C, non-fasting lipid panel (total cholesterol, LDL-cholesterol and HDL-cholesterol) and kidney function and status [creatinine (and estimated glomerular filtration rate), random urine albumin to creatinine ratio], 3. Individualized CV risk assessment and education regarding this risk using a validated interactive online tool[36] that explains the individual's CV risk, the contribution of each risk factor to the overall risk and the impact of the intervention and controlling the risk factors on the overall CV risk (https://www.epicore.ualberta.ca/epirxisk/), 4. Treatment recommendations, prescription adaptation, and prescribing where necessary to meet guideline recommended targets. Pharmacists practiced to their full scope (including prescribing medications and ordering and interpreting laboratory tests when needed), 5. Regular monthly follow-up for 6 months to check on patients' progress and provide ongoing care and motivation; and 6. Regular communication with the patient's physician(s) after each contact with the patient as per usual pharmacist practice.

Patient and public involvement

No patient involved

Outcomes

The primary outcome was the change in CV risk over a 6-month period. CV risk is defined as the risk for future CV events (coronary heart disease [CHD], stroke, peripheral arterial disease [PAD])[7,8] as calculated by validated risk assessment equations. The CV risk was calculated using EPI·R_xISK™ Cardiovascular Risk Calculator (https://www.epicore.ualberta.ca/epirxisk/). It was estimated using the Modified Framingham[20] risk assessment equation (Framingham risk score multiplied by 1.5) for patients who have chronic inflammatory conditions without other comorbidities. If the patient had other CV risk-modifying conditions (diabetes, previous vascular disease or chronic kidney disease), risk was calculated using the Modified Framingham [20] and the most appropriate risk assessment equation based on the patient's medical history. The United Kingdom Prospective Diabetes Study (UKPDS) [44] risk assessment equation was used for those with diabetes, SMART risk assessment equation [45] was used for patients with previous vascular disease and Framingham[17] risk assessment equation was used for the ones with chronic kidney disease. If the patient had both chronic inflammatory conditions and other CV risk-modifying conditions, the risk was calculated using all the respective risk assessment equations, and the risk assessment equation estimating the highest risk was used.

The secondary outcomes were the change in individual risk factors [blood pressure (in patients with hypertension), LDL-cholesterol (in patients with dyslipidemia), A1C (in patients with diabetes) and tobacco cessation (self-reported abstinence)] over a 6-month period.

Sample size and analytical plan

Sample size

Using the information from our previous pharmacist-led CV risk reduction trial, R_xEACH[36] [Baseline CV risk (26.2%) and standard deviation (SD) (17.8)] and the following assumptions of 80% power and alpha of 0.05, 89 patients were required to detect 21% risk reduction. The sample size was inflated to 100 to to account for possible dropouts, losses to follow-up, and withdrawals of consent.

Analytical plan

Analysis was performed by using R 3.6.2 (Vienna, Austria; https://www.R-project.org/) and SAS 9.4 software (SAS Institute Inc. Cary, NC, USA).

Data were first screened to confirm that all the participating patients met the inclusion/exclusion criteria and provided informed consent. Once those conditions were confirmed, statistical analysis started.

Demographic information and clinical characteristics were analyzed using descriptive statistics. Frequency (percentage) was used for categorical variables and mean (standard derivation) for continuous variables. Statistical significance at the univariable level was assessed using Chi-square test or Fisher's exact test (when small frequencies present) for categorical variables, and T-test for continuous variables (assumption of statistics tests were checked ahead). The primary outcome was analyzed by paired T-test. Multivariable linear mixed effect models was used to adjust for centre effect, age, sex and ethnicity.. Secondary outcomes were analyzed using paired T-test and Chi-square test as appropriate.

Trial and data management was performed by EPICORE Centre

R_xIALTA was registered at Clinicaltrials.gov (NCT03152396) and approved by the Health Research Ethics Board of the University of Alberta (Pro00072858).

Results

The study was launched in August, 2017, and the last patient was enrolled in July 2019. Follow up was completed in January 2020. We screened 126 patients, of those 103 were eligible. We enrolled 99 patients and 94 of them completed the study (Figure 1). Demographic and clinical characteristics are presented in Table 1. Mean age was 64 years (standard deviation (SD) 14.8), approximately two thirds (61%) of the participants were female and 86% were Caucasian. More than half (56%) had rheumatoid arthritis, 14% had psoriasis, 12% had psoriatic arthritis, 11% had gout, 6% had ankylosing spondylitis and 1% had systemic lupus erythematosus. Hypertension was the most commonly reported risk factor (47%), followed by dyslipidemia (45%), diabetes (13%), atherosclerotic vascular events (angina, heart attack, stroke/TIA) (12%),

current tobacco use (11%) and chronic kidney disease (9%). In addition, average body mass index (BMI) was 28.2 (5.2) kg/m^2 and only 9% reported exercising for 30 minutes (or more) five or more times per week. Importantly, only 2% of participants reported that their CV risk was assessed by a healthcare provider before taking part in the study.

Table 1 baseline demographic and clinical characteristics

Characteristic		Frequency	Percentage
Sex	Female	60	61
Ethnicity	Aboriginal / First Nations	3	3
	Black	2	2
	Caucasian	85	86
	Hispanic	2	2
	South-Asian	1	1
	Other Asian	6	6
Inflammatory Conditions	RA	55	56
	Psoriasis	14	14
	PsA	12	12
	Gout	11	11
	AS	6	6
	SLE	1	1
Risk factors	Hypertension	47	47
	Dyslipidemia	45	45
	Diabetes	13	13
	Atherosclerotic vascular events	12	12
	Current tobacco use	11	11
	CKD	9	9
Exercise	Very active	9	9
	Moderately active	39	39
	No exercise additional to ordinary daily living	49	50
	Not reported	2	2
Alcohol use	None	38	38
	1-2/day	40	41
	>2 drinks/day	14	14
	1-3 drinks/week	5	5
	Not reported	2	2
Dietary habits	No specific diet	85	86
	Low sugar	3	3
	Low salt	7	7

	Low saturated fat	1	1
	High fruit/vegetables	6	6
	Other	2	2
Characteristic		**Mean**	**Standard Deviation**
Age	Age, years	64	14.8
Physical and lab assessment	BMI, kg/m^2	28.2	5.2
	Systolic BP, mmHg	136.6	15.7
	Diastolic BP, mmHg	81.8	11.4
	Total cholesterol, mmol/L	4.8	1.3
	HDL-cholesterol, mmol/L	1.4	0.5
	LDL-cholesterol, mmol/L	2.6	1.1
	A1C, %	8.3	1.1
	eGFR, ml/min/1.73 m^2	76.6	18.5
	ACR, mg/mmol	154.7 (Median)	77.5-231.8 (IQR)

***RA: rheumatoid arthritis, PsA: psoriatic arthritis, AS: ankylosing spondylitis, SLE: systemic lupus erythematosus, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, ACR: Random albumin to creatinine ratio, IQR: Interquartile Range**

Estimated CV risk was reduced from 25% (SD 16.1) at baseline to 19.8% (SD 14.7) after 6 months. After adjusting for age, sex, ethnicity and centre effect, such reduction corresponded to a 24.5% relative risk reduction [6 (95% confidence interval (4.6 – 7.4)] p <0.001) (Figure 2). In patients with hypertension, significant reductions were observed in systolic and diastolic blood pressure (Table 2). Similarly, we noted reductions in LDL-cholesterol in patients with dyslipidemia and A1C in those with diabetes (Table 2). Participants' dietary habits were also improved (p=0.02), while exercise, alcohol and tobacco use were not significantly changed.

Table 2 Changes in individual risk factors

Risk factor	Baseline	6 months	Difference (95% confidence interval)	P-value
Systolic BP (n=47)	138.4 (17.9)	127.7 (10.3)	10.7 (10 to 12.6)	<0.001
Diastolic BP (n=47)	80.2 (13)	77.3 (10.1)	2.9 (1.9 to 3.9)	<0.001
Total Cholesterol (n=45)	5 (1.4)	4.6 (1.3)	0.4 (0.3 to 0.4)	<0.001
LDL-cholesterol (n=45)	2.8 (1.2)	2.5 (1.1)	0.3 (0.3 to 0.4)	<0.001
HDL-cholesterol (n=45)	1.4 (0.5)	1.5 (0.5)	0.1 (0.1 to 0.2)	<0.001
A1C (n=13)	8.3 (1.1)	7.1 (1)	1.2 (0.6 to 1.9)	<0.001
BMI	28.2 (5.2)	28.3 (5.3)	0.1 (-0.2 to 0.1)	0.5
Tobacco use (proportion)	10.3	5.2	N/A	0.3

Pharmacist interventions are listed in Figure 3. Medication/dose change was the most implemented intervention (30%), followed by lifestyle education and advice (27%), patient, family members and caregivers' education about the condition and prescribed treatment (22%), follow up (12%), adherence assessment and improvement (7%) and referral to other healthcare providers (2%). There were very minimal adverse events reported during the study.

Discussion

Chronic inflammatory conditions increase patient's risk for CV events; however, these patients are often not receiving CV risk assessment or treatment. We hypothesized that community pharmacists could proactively and systematically screen for chronic inflammatory diseases (because of the unique medications used in these conditions), and then manage their CV risk factors. We found that a pharmacist-led care reduced the risk of major CV events by 24.5% (p <0.001) over a 6-month period. The intervention was also associated with reductions in blood pressure, LDL-cholesterol and A1C. Such improvements are related to the following pharmacist activities: medication/dose changes, lifestyle education and advice, patient, family members and caregivers' education about the condition and prescribed treatment, follow up, adherence assessment and improvement and referral to other healthcare providers.

Our findings are consistent with the findings of the R_xEACH study, which evaluated the impact of pharmacist intervention (assessment, prescribing, and follow-up) on CV risk in patients at high risk for CVD (patients with diabetes, chronic kidney disease, established vascular disease or Framingham risk > 20%). R_xEACH reported that such intervention was associated with CV risk reduction as well as improvements in all individual risk factors.[36]

Our findings are also consistent with the findings of Semb and colleagues who reported significant CV risk reduction when a CV risk factor (lipids) was managed appropriately.[46] They also highlight the importance of pharmacist prescribing, as 'medication/dose change' was the most implemented intervention. This intervention would have not been possible without having independent prescriptive authority. These findings are supported by the findings of Al Hamarneh and colleagues and Wubben and Vivian who reported that better outcomes were achieved when pharmacists had prescriptive authority.[47,48]

This study is not without limitations. As described above, the study was not a randomized controlled trial, due to ethical concerns of randomizing this high risk underserved population to usual care after proving that the intervention is effective. We acknowledge that this reduces causal inference, however, the findings of this study are similar to the randomized R_xEACH study.[36] Since the 6-month follow-up period can be considered relatively short; it is possible that the effects of the intervention could be short lived. It is also possible, however, that greater improvements leading to larger CV risk reduction could have been observed with a longer follow up period. Pharmacists who provided the intervention also conducted the assessment and entered the information into the study online system where CV risk was calculated. This could have introduced bias; however, the study team monitored study sites against source documents to ensure accuracy. The fact that adverse events were self-reported could have led to underreporting.

Our findings, combined with the fact that the risk of myocardial infarction, heart failure and CV death among patients with chronic inflammatory diseases is much higher than the general population,[8-10] highlight the importance of focusing on the patient as a whole, rather than only focusing on their acute complaints.

It is noteworthy that only 2% of our participants had their CV risk assessed before taking part in the study. This is consistent with the literature, as it has been reported that the levels of awareness and perceived risk of CVD is low in this patient population.[49] Gaps in care have also been reported when it comes to CV risk assessment.[7,12-14] This also highlights the importance of a systematic and proactive approach towards case-finding by pharmacists – as many patients would not know to ask for CV risk assessment. This is a unique feature of involving community pharmacists – an approach which we have used successfully in a number of areas. [28,36,50]

R_xIALTA findings add to the high-level evidence of effective pharmacist prescribing interventions in improving CV risk and individual CVD risk factors.[36,50] Such high-level evidence should encourage policy makers to broaden the scope of practice for pharmacists and pharmacy professional organizations to implement those interventions on a larger scale to seize the opportunity to enhance patient care.

To our knowledge, this is the first study to assess the effect of a pharmacist-led case-finding and care on CV risk in patients with chronic inflammatory conditions in a community pharmacy setting. We have demonstrated that pharmacist-led intervention (including prescribing) improved CV risk as well as the individual CVD risk factors. Pharmacists also improved the access to care in a high-risk population, that otherwise would not have their CV risk assessed. Implementing this on a wider scale could help addressing one of the world's major public health challenges.

Figures

Figure 1 Study flow chart

Figure 2 Change in estimated CV risk over time

Figure 3 Pharmacist interventions

Contributorship statement:

Substantial contribution to study conception and design: YNA, RG, SK, CM, AM, RTT

Substantial contribution to data collection: YNA, AM, RTT

Substantial contribution to data analysis and interpretation: YNA, RTT

Drafting the article or revising it critically: YNA, RG, SK, CM, AM, RTT

Final approval of the submitted version: YNA, RG, SK, CM, AM, RTT

Acknowledgement:

None of this could have taken place without the dedication and caring of the R_xIALTA investigators, listed in descending order of recruitment:

Nader Hammoud (Shoppers Drug Mart #2326, Calgary), Nataliya Posudwvska (Calgary Co-op, Calgary), Rick Siemens (London Drugs #38, Lethbridge), Dixie Richardson (Safeway Pharmacy, Edmonton), Aileen Coutts (Calgary Co-Op, Calgary), Jan Messiha (Calgary Co-op, Calgary), Farzana Sharif (Calgary Co-Op, Calgary), Pegah Manzoori (Calgary Co-Op, Calgary), Maria James (Calgary Co-Op, Calgary), Jack Dhaliwal (Calgary Co-Op, Calgary), Derek Durocher (Shoppers Drug Mart #313, Edmonton), Leanna St. Onge, Otti Gohrbandt and Chelsey Collinge (Co-op Pharmacy, Rocky Mountain House), Aila Omar (Co-op Pharmacy, Edmonton), Diane Lazarko-Gamache (Calgary Co-Op, Calgary), Sonal Ijner (Calgary Co-Op, Calgary), Carlene Olyksen, Jelena Okuka (Meridian Pharmacy, Stony Plain), Murtaza Hassanali (Shoppers Drug Mart #371, Edmonton), Penny and Fausta (Penny and Fausta Pharmacy, Calgary).

Funding statement:

We would like to acknowledge the generous support of the funder of R_xIALTA: Canadian Initiative for Outcomes in Rheumatology cAre (CIORA) (Grant number: 2015-001). Our funder did not have any role in the study design, collection, analysis, interpretation of the data, writing the report and the decision to submit for publication.

We would like to acknowledge the support of the Consultation and Research Services Platform at The Alberta' SPOR SUPPORT Unit in Data management and statistical services (Grant number N/A).

Competing interests: None

Data sharing statement: Data can be shared upon reasonable requests

Reference:

1. WHO. Cardiovascular diseases. 2017. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/ (Accessed 9/6/2020)
2. Government of Canada. Report from the Canadian Chronic Disease Surveillance System: Heart Disease in Canada, 2018. 2018. Available from: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/report-heart-disease-Canada-2018.html (Accessed 9/6/2020)
3. The Arthritis Society. Arthritis in Canada, Facts and Figures. 2020. Available from: https://arthritis.ca/about-arthritis/what-is-arthritis/arthritis-facts-and-figures (Accessed 9/6/2020)
4. Nurmohamed MT (2009) Cardiovascular risk in rheumatoid arthritis. Autoimmun Rev 8:663–667
5. Peters MJ, Symmons DP, McCarey D, et al. (2010). Evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis. 69(2):325-31.
6. Semb AG, Rollefstad S, van Riel P, et al. (2014). Cardiovascular disease assessment in rheumatoid arthritis: A guide to translating knowledge of cardiovascular risk into clinical practice. Ann Rheum Dis.
7. Schieir O, Tosevski C, Glazier RH, Hogg-Johnson S, Badley EM. Incident myocardial infarction associated with major types of arthritis in the general population: a systematic review and meta-analysis. Ann Rheum Dis. 2017; Published Online First: 22 Jan. doi: 10.1136/annrheumdis-2016-210275.
8. Maradit-Kremers H, Crowson CS, Nicola PJ, et al. (2005). Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population based cohort study. Arthritis Rheum. 52:402–11.
9. Nicola PJ, Maradit-Kremers H, Roger VL, et al. (2005). The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum. 52:412–20
10. Maradit-Kremers H, Crowson CS, Nicola PJ, et al. (2008). Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum. 52:722–32
11. Mills M, Loney P, Jamieson E, et al. (2010). A primary care cardiovascular risk reduction clinic in canada was more effective and no more expensive than usual on-demand primary care--a randomised controlled trial. Health Soc Care Community. 18(1):30-40.
12. Woodward A, Wallymahmed M, Wilding J, et al. (2006). Successful cardiovascular risk reduction in type 2 diabetes by nurse-led care using an open clinical algorithm. Diabet Med. 23(7):780-787

13. Woodward A, Wallymahmed M, Wilding J, et al. (2005). Improved glycaemic control--an unintended benefit of a nurse-led cardiovascular risk reduction clinic. Diabet Med. 22(9):1272-1274.

14. Keeling SO, Teo M, Fung D. (2011). Lack of cardiovascular risk assessment in inflammatory arthritis and systemic lupus erythematosus patients at a tertiary care center. Clin Rheumatol. 30(10):1311-1317

15. Canadian Institute for Health Information. Physicians in Canada, 2018. 2019. Available from: https://www.cihi.ca/sites/default/files/document/physicians-in-canada-2018.pdf (Accessed 9/6/2020)

16. Kremers HM, Crowson CS, Therneau TM, et al. (2008) High ten-year risk of cardiovascular disease in newly diagnosed rheumatoid arthritis patients: a population-based cohort study. Arthritis Rheum. 58:2268–2274

17. D'Agostino RB S, Vasan RS, Pencina MJ, et al. (2008). General cardiovascular risk profile for use in primary care: The framingham heart study. Circulation.117(6):743-753

18. Arts EE, Popa C, Den Broeder AA, et al. (2014). Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. Ann Rheum Dis.

19. Chung CP, Oeser A, Avalos I, *et al*. (2006). Utility of the Framingham risk score to predict the presence of coronary atherosclerosis in patients with rheumatoid arthritis. Arthritis Res Ther.8:R186.

20. Tournadre A, Mathieu S, Soubrier M. Managing cardiovascular risk in patients with inflammatory arthritis: practical considerations. Ther Adv Musculoskel Dis. 2016;8(5):180-191.

21. Semb AG, Kvien TK, DeMicco DA, et al. Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. *Arthritis & Rheumatism*. 2012;64(9): 2836-2846.

22. Liao KP, Cai T, Gainer VS, et al. Lipid and lipoprotein levels and trend in rheumatoid arthritis compared to the general population. *Arthritis Care & Research*. 2013;65(12): 2046-2050.

23. Liao KP, Liu P, Lu B, et al. Association between lipid levels and major adverse cardiovascular events in rheumatoid arthritis compared to non-rheumatoid arthritis patients. *Arthritis & Rheumatology*. 2015;67(8): 2004-2010.

24. Peters MJL, Symmons DPM, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis*. 2010;69: 325-331.

25. Rollefstad S, Kvien TK, Holme I, et al. Treatment to lipid target in patients with inflammatory joint diseases in preventative cardio-rheuma clinic. *Ann Rheum Dis* 2013;72:1968-1974.

26. Shiu JR, Simpson SH, Johnson JA, et al. (2006). Quantifying opportunities to affect diabetes management in the community. Can Pharm J. 139(3): 37-38.

27. Rothman RL, Malone R, Bryant B, et al. (2005). A randomized trial of a primary care-based disease management program to improve cardiovascular risk factors and glycated hemoglobin levels in patients with diabetes. *Am J Med*.118(3):276-84

28. Tsuyuki RT, Johnson JA, Teo K et al. (2002). A Randomized Trial of the Effect of Community Pharmacist Intervention on Cholesterol Risk Management – The Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP). Arch Intern Med. 162:1149-55

29. Carter BL, Bergus GR, Dawson JD, et al. (2008). A cluster randomized trial to evaluate physician/pharmacist collaboration to improve blood pressure control. *J Clin Hypertens (Greenwich)*. 10(4):260-27

30. McLean DL, McAlister FA, Johnson JA et al. (2008). A Randomized Trial of the Effect of Community Pharmacist and Nurse Care on Improving Blood Pressure Management in Patients with Diabetes Mellitus – Study of Cardiovascular Risk Intervention by Pharmacists-Hypertension (SCRIP-HTN). Arch Intern Med.168(21):2355-61.

31. Blenkinsopp A, Phelan M, Bourne J, et al. (2000). Extended adherence support by community pharmacists for patients with hypertension: a randomized controlled trial. International Journal of Pharmacy Practice.8:165-175.

32. Wang J, Wu J, Yang J, et al. (2011). Effect of pharmaceutical care interventions on blood pressure and medication adherence of patients with primary hypertension in China. Clinical Research and Regulatory Affairs. 1:1-6.

33. Gattis WA, Hasselblad V, Whellan DJ, et al. (1999). Reduction in heart failure events by the addition of a clinical pharmacist to the heart failure management team: results of the Pharmacist in Heart Failure Assessment Recommendation and Monitoring (PHARM) Study. *Arch Intern Med*. 159(16):1939-1945

34. Taveira TH, Wu WC, Martin OJ, et al. (2006). Pharmacist-led cardiac risk reduction model. *Prev Cardiol*.9:202-208

35. Santschi V, Chiolero A, Burnand B, et al. (2011). Impact of pharmacist care in the management of cardiovascular disease risk factors: a systematic review and meta-analysis of randomized trials. *Arch Intern Med*. 171:1441-53.

36. Tsuyuki RT, Al Hamarneh YN, Jones CA, Hemmelgarn BR. The effectiveness of pharmacist interventions on cardiovascular risk. Journal of the American College of Cardiology 2016;67(24):2847-2854. doi: 10.1016/j.jacc.2016.03.528.

37. Murray MD, Ritchey ME, Wu J, et al. (2009). Effect of a pharmacist on adverse drug events and medication errors in outpatients with cardiovascular disease. *Arch Intern Med*.169(8):757-

38. Marra C, Johnston K, Santschi V, Tsuyuki RT. 2017. Cost-effectiveness of pharmacist care for managing hypertension in Canada. *Canadian Pharmacists Journal.* 150(3):184-197

39. Al Hamarneh YN, Johnston K, Marra CA, Tsuyuki RT. Pharmacist prescribing and care improves cardiovascular risk, but is it cost-effective? A cost-effectiveness analysis of the R_xEACH study. Can Pharm J. 2019;152(4):257-266

40. Al Harmarneh YN, Lamb S, Donald M, et al. Pharmacist prescribing and care improves cardiovascular risk, but what do patients think? A substudy of the R_xEACH study. Can Pharm J. 2018; 151(4): 223–227

41. Nerenberg KA, Zarnke KB, Leung AA, et al. Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. Can J Cardiol. 2018;34(5):506-525

42. Anderson TJ, Grégoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol. 2016;32(11):1263-1282.

43. Diabetes Canada. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Canadian Journal of Diabetes. 2018; 42: S1-S326

44. Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR. The UKPDS risk engine: a model for the risk of coronary heart disease in type 2 diabetes (UKPDS 56). *Clin Sci* 2001; 101: 671-679.

45. Dorresteijn JAN, Visseren FLJ, Wassink AMJ et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study in patients with arterial disease: the SMART risk score. Heart 2013; 99:866-872.

46. Semb AG, Kvien TK, DeMicco DA, Fayyad R, Wun CC, LaRosa JC, Betteridge J, Terje R Pedersen TR, Holme I. Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. Arthritis Rheum 2012; 64:2836-46

47. Al Hamarneh YN, Hemmelgarn BR, Hassan I, Jones CA, Tsuyuki RT. The Effectiveness of Pharmacist Interventions on Cardiovascular Risk in Adult Patients with Type 2 Diabetes: The Multicentre Randomized Controlled R_xEACH Trial. Can J Diabetes. 2017;41(6):580-586.

48. Wubben DP, Vivian EM. Effects of pharmacist outpatient interventions on adults with diabetes mellitus: A systematic review. Pharmacotherapy, 2008; 28: 421-436

49. Ghosh-Swaby OR, Kuriya B. Awareness and perceived risk of cardiovascular disease among individuals living With rheumatoid arthritis is low: results of a systematic literature review. Arthritis Res Ther. 2019; 21:33-39

50. Tsuyuki RT, Houle SK, Charrois TL, et al. Randomized Trial of the Effect of Pharmacist Prescribing on Improving Blood Pressure in the Community: The Alberta Clinical Trial in Optimizing Hypertension (R_xACTION). Circulation. 2015;132(2):93-100

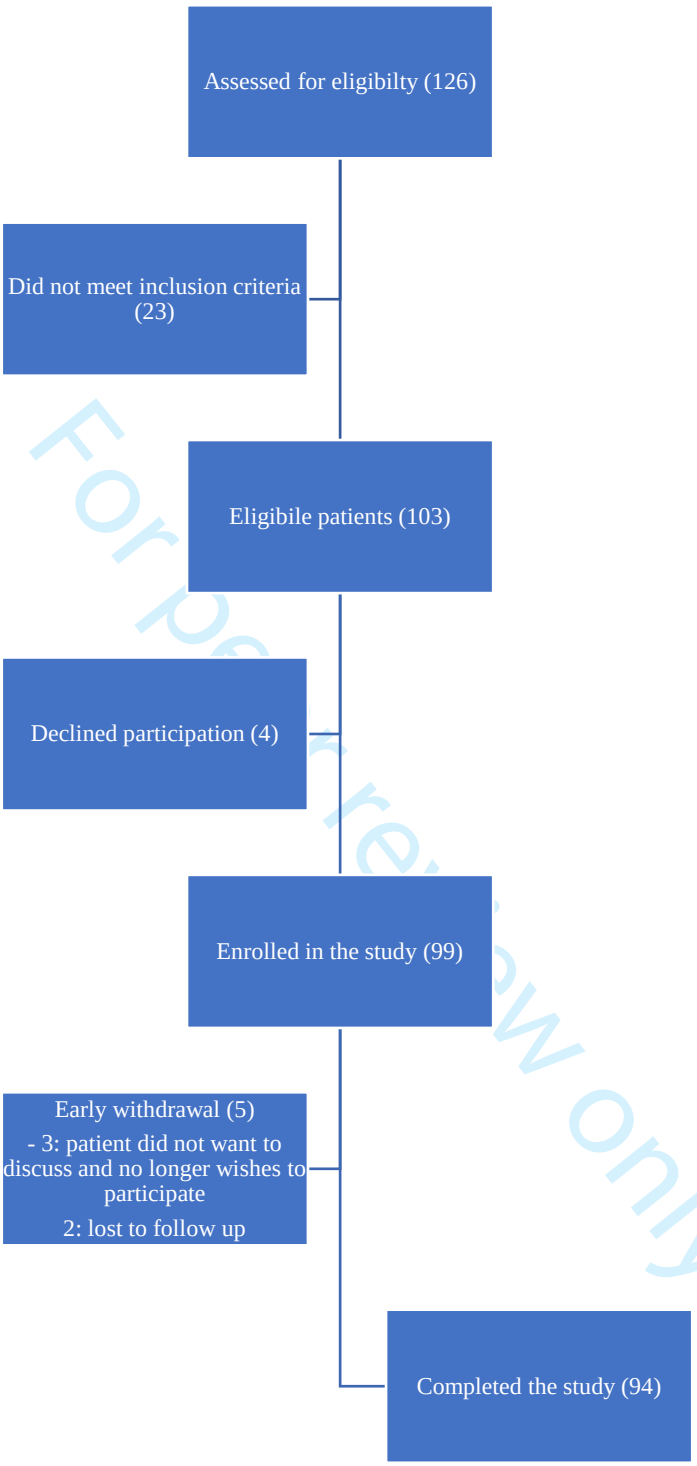


Figure 1: Study flow chart

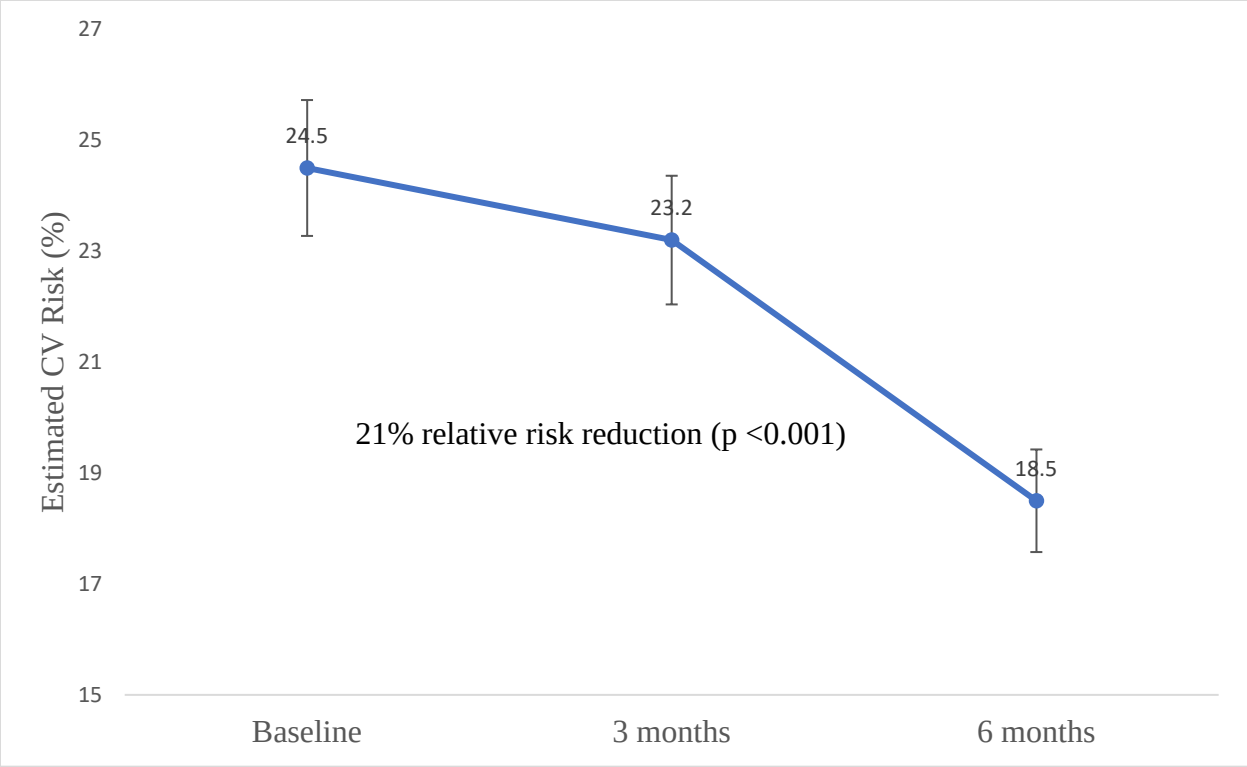
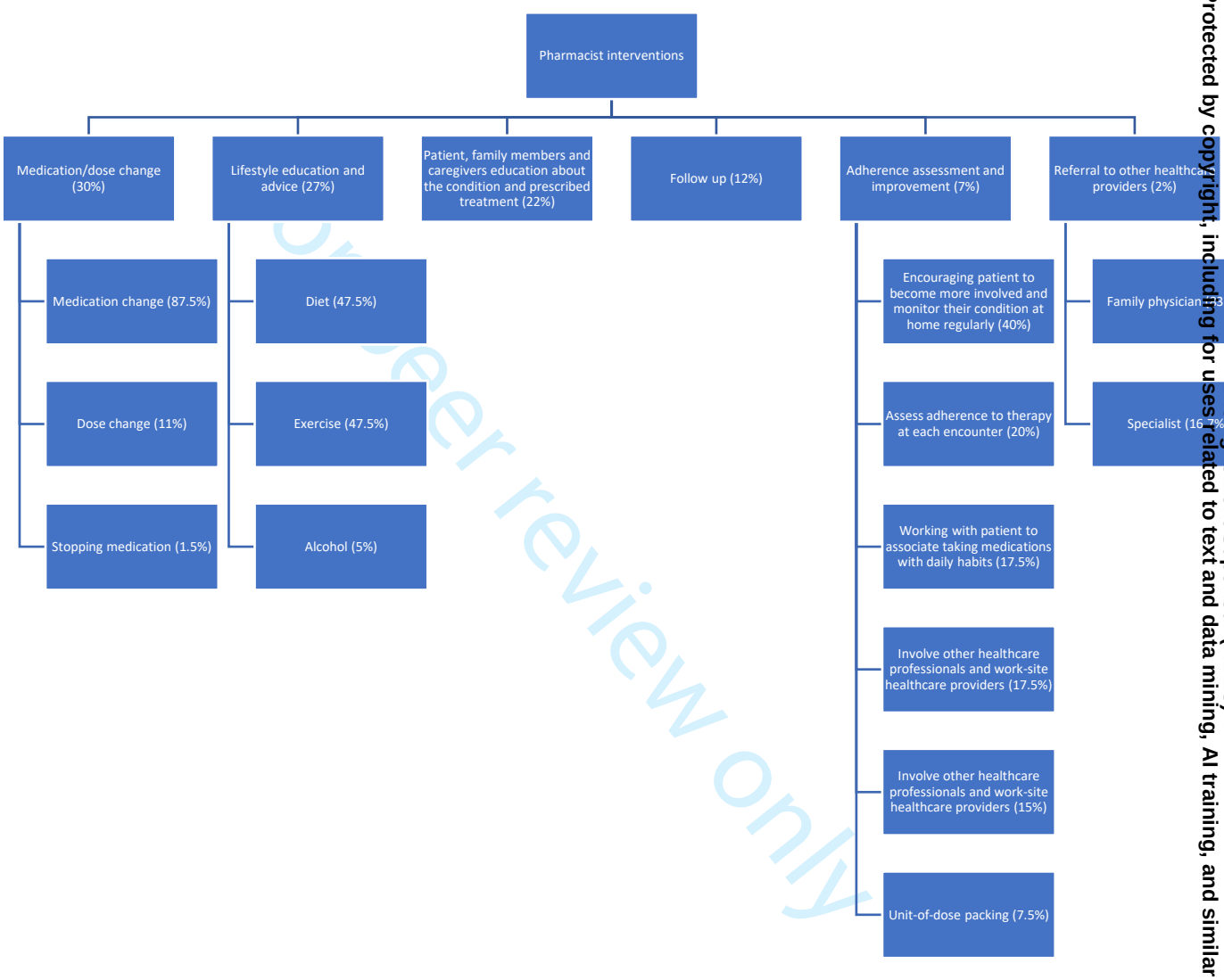


Figure 2 Change in estimated CV risk over time



TREND Statement Checklist

Paper Section/ Topic	Item No	Descriptor	Reported?	Pg #
Title and Abstract				
Title and Abstract	1	Information on how unit were allocated to interventions	Yes	3
		Structured abstract recommended	Yes	3
		Information on target population or study sample	Yes	3
Introduction			Yes	5-6
Background	2	Scientific background and explanation of rationale	Yes	5-6
		Theories used in designing behavioral interventions		
Methods				
nts	3	Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	Yes	6
		Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	Yes	6-7
		Recruitment setting	Yes	6
		Settings and locations where the data were collected	Yes	6
Interventions	4	Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:	Yes	7
		○ Content: what was given?	Yes	7
		○ Delivery method: how was the content given?	Yes	7
		○ Unit of delivery: how were the subjects grouped during delivery?	Yes	7
		○ Deliverer: who delivered the intervention?	Yes	7
		○ Setting: where was the intervention delivered?	Yes	7
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	Yes	7
		○ Time span: how long was it intended to take to deliver the intervention to each unit?	Yes	7
		○ Activities to increase compliance or adherence (e.g., incentives)	N/A	
Objectives	5	Specific objectives and hypotheses	Yes	6
Outcomes	6	Clearly defined primary and secondary outcome measures	Yes	8
		Methods used to collect data and any methods used to enhance the quality of measurements	Yes	6-7
		Information on validated instruments such as psychometric and biometric properties	N/A	
Sample Size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	Yes	8
Assignment Method	8	Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	N/A	
		Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)	N/A	
		Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	N/A	

TREND Statement Checklist

Blinding (masking)	9	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed.	
Unit of Analysis	10	Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community) **(Yes, 9)**	Yes
		If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis) **N/A**	
Statistical Methods	11	Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data **(Yes, 9)**	
		Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis **(N/A)**	
		Methods for imputing missing data, if used **(N/A)**	
		Statistical software or programs used **(Yes, 9)**	
Results			
Participant flow	12	Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended) **(Yes, Figure 1)**	
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study **(Yes, 9-10)**	
		○ Assignment: the numbers of participants assigned to a study condition **(N/A)**	
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention **(N/A)**	
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition **(Yes, Figure 1)**	
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition **(Yes, 10)**	
		Description of protocol deviations from study as planned, along with reasons **(N/A)**	
Recruitment	13	Dates defining the periods of recruitment and follow-up **(Yes, 10)**	
Baseline Data	14	Baseline demographic and clinical characteristics of participants in each study condition **(Yes, Table 1)**	
		Baseline characteristics for each study condition relevant to specific disease prevention research **(N/A)**	
		Baseline comparisons of those lost to follow-up and those retained, overall and by study condition **(N/A)**	
		Comparison between study population at baseline and target population of interest **(N/A)**	
Baseline equivalence	15	Data on study group equivalence at baseline and statistical methods used to control for baseline differences **(N/A)**	

Numbers analyzed	16	Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible **(Yes, Table 1)** Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses **(N/A)**		
comes and		For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision **(Yes, table 2)**		
		Inclusion of null and negative findings **(N/A)**		
		Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any **(N/A)**		
Ancillary analyses	18	Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory **(N/A)**		
Adverse events	19	Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals) **(Yes, 10)**		
DISCUSSION				
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	Yes	14
		Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	N/A	
		Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	N/A	
		Discussion of research, programmatic, or policy implications	N/A	
Generalizability	21	Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues		
Overall	22	General interpretation of the results in the context of current evidence	Yes	14-15

TREND Statement Checklist

From: Des Jarlais, D. C., Lyles, C., Crepaz, N., & the Trend Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of Public Health*, 94, 361-366. For more information, visit: http://www.cdc.gov/trendstatement/