# Effectiveness of Pharmacist Interventions on Cardiovascular Risk in Patients With CKD: A Subgroup Analysis of the Randomized Controlled $R_x$EACH Trial

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**Background:** Affecting a substantial proportion of adults, chronic kidney disease (CKD) is considered a major risk factor for cardiovascular (CV) events. It has been reported that patients with CKD are underserved when it comes to CV risk reduction efforts.

**Study Design:** Prespecified subgroup analysis of a randomized controlled trial.

**Setting & Participants:** Adults with CKD and at least 1 uncontrolled CV risk factor were enrolled from 56 pharmacies across Alberta, Canada.

**Intervention:** Patient, laboratory, and individualized CV risk assessments; treatment recommendations; prescription adaptation(s) and/or initiation as necessary; and regular monthly follow-up for 3 months.

**Outcomes:** The primary outcome was change in estimated CV risk from baseline to 3 months after randomization. Secondary outcomes were change between baseline and 3 months after randomization in individual CV risk factors (ie, low-density lipoprotein cholesterol, blood pressure, and hemoglobin $A_{1c}$), risk for developing end-stage renal disease, and medication use and dosage; tobacco cessation 3 months after randomization for those who used tobacco at baseline; and the impact of rural versus urban residence on the difference in change in estimated CV risk.

**Measurements:** CV risk was estimated using the Framingham, UK Prospective Diabetes Study, and international risk assessment equations depending on the patients' comorbid conditions.

**Results:** 290 of the 723 participants enrolled in $R_x$EACH had CKD. After adjusting for baseline values, the difference in change in CV risk was 20% ($P < 0.001$). Changes of 0.2 mmol/L in low-density lipoprotein cholesterol concentration ($P = 0.004$), 10.5 mm Hg in systolic blood pressure ($P < 0.001$), 0.7% in hemoglobin $A_{1c}$ concentration ($P < 0.001$), and 19.6% in smoking cessation ($P = 0.04$) were observed when comparing the intervention and control groups. There was a larger reduction in CV risk in patients living in rural locations versus those living in urban areas.

**Limitations:** The 3-month follow-up period can be considered relatively short. It is possible that larger reduction in CV risk could have been observed with a longer follow up period.

**Conclusions:** This subgroup analysis demonstrated that a community pharmacy–based intervention program reduced CV risk and improved control of individual CV risk factors. This represents a promising approach to identifying and managing patients with CKD that could have important public health implications.

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A substantial proportion of Canadian adults (~1 in 10) are living with chronic kidney disease (CKD),[1] defined as a reduction in kidney function (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 $m^2$) or markers of kidney damage (albuminuria with albumin excretion ≥ 3 mg/mmol or abnormalities in urine sediment or renal imaging) for more than 3 months.[2] CKD is associated with a high burden of comorbid conditions and adverse outcomes,[3] including increased cardiovascular (CV) risk.[4] Suboptimal treatment has been reported in patients with CKD and has been associated with increased risk for progression to end-stage renal disease (ESRD).[5] Identification and management of patients at early stages of CKD is therefore pivotal for slowing the progression of kidney dysfunction, preventing or delaying the development of ESRD, and reducing CV events.

CV disease (CVD) is the most common cause of death in patients with CKD,[6] accounting for ~40% of overall deaths.[2] Clinical guidelines recommend using CV risk assessment equations to guide CVD prevention and management,[7] and it is now recommended that CKD should be included as part of this assessment.[8,9] Despite these recommendations, risk assessment has not become part of many clinicians' daily routine. Indeed, most patients attending physicians' clinics report never having had a CV risk assessment.[7]

As primary care professionals who see patients with chronic diseases frequently,[10] pharmacists are well positioned to identify patients with CKD,[11] determine their CV risk, and assist in their disease management. The efficacy of pharmacists' interventions in chronic disease has been well documented in the literature.[12-20] Moreover, pharmacists in Alberta, Canada, can order and interpret laboratory tests, conduct medication management assessment, and prescribe medications. This advanced scope of practice for pharmacists, combined with the fact that >95% of patients

with CKD are cared for in primary care settings without input from a nephrologist,[21] provides a unique opportunity for the use of this innovative community-based care model to aid in the identification and management of these high-risk patients.

We recently published results of a multicenter randomized controlled trial[18] reporting that a community pharmacy–based case finding and intervention program led to a 21% reduction in CV risk over a 3-month period when compared to usual care. In this prespecified substudy, we evaluate the effect of this intervention on estimated CV risk in the subset of patients with CKD because CVD is the most common cause of death in this patient population.[6] Previous work conducted by our group showed that CVD risk factors are among the top 5 comorbid conditions in patients with CKD[3] and that 95% of this population are cared for in the community without nephrologist input.[21] These findings, combined with the facts that early stages of CKD are often asymptomatic[11] and a large proportion of community-dwelling patients with CKD are underdiagnosed and undertreated[22] highlight the care gaps in this highly vulnerable population. Such gaps indicate the need to implement and evaluate innovative models of care.

## Methods

### Overview

This prespecified subgroup analysis was conducted as a part of "The Alberta Vascular Risk Reduction Community Pharmacy Project: $R_x$EACH."[18] The CKD subgroup was identified a priori as being a high-risk group of interest. The original protocol was developed for patients with CKD only (Item S1, available as online supplementary material). This was later expanded to include other high-risk groups and additional funds were sought to undertake a larger trial, which ultimately became $R_x$EACH.[18] The study aimed to evaluate the effect of a community pharmacy–based case finding and intervention program on estimated CV risk in patients at high risk for CV events.[18] $R_x$EACH was a randomized controlled trial (with the patient as the unit of randomization) conducted in 56 community pharmacies across Alberta, Canada.[18]

### Patient Population

With respect to this subgroup, patients were eligible if they were adults (≥18 years of age) who had CKD and at least 1 uncontrolled risk factor (ie, blood pressure [≥140/90 or ≥130/80 mm Hg if the patient had diabetes], low-density lipoprotein [LDL] cholesterol concentration [>2 mmol/L], hemoglobin $A_{1c}$ [$HbA_{1c}$] concentration [>7%], or current tobacco use [self-reported]). CKD was defined as having at least 1 of the following: 2 consecutive eGFRs both < 60 mL/min/1.73 $m^2$ over a 3-month period and/or 2 consecutive random urine albumin-creatinine ratios (ACRs) both ≥ 3 mg/mmol over a 3-month period and/or at least 1 ACR ≥ 30 mg/mmol.

Patients were excluded if they were unwilling to sign the consent form/participate, unwilling or unable to participate in regular follow-up visits, or pregnant (same exclusion criteria as $R_x$EACH).[18]

### Recruitment

Pharmacists systematically identified potential participants by focusing on target prescriptions for diabetes (eg, metformin), hypertension (eg, angiotensin-converting enzyme inhibitors), dyslipidemia (eg, statins), and previous vascular events (eg, antiplatelet agents and anticoagulants). As part of routine care, pharmacists checked the most recent laboratory test results for those patients (through the provincial electronic health record). Pharmacists then checked whether patients met the inclusion criteria (which include having at least 1 elevated risk factor). Those who met the inclusion criteria were considered eligible and were invited to participate in the study. $R_x$EACH was approved by the research ethics boards of the University of Alberta (Pro 00041644) and University of Calgary (REB 13-0751) and registered at ClinicalTrials.gov (study number NCT01979471).

Once written informed consent was obtained, patients were randomly assigned (by using a centralized secure website to ensure allocation concealment) in a 1:1 ratio to either the intervention or control group.

Pharmacists used the CKD Clinical Pathway (www.CKDpathway.ca)[23] to screen for CKD using eGFR and ACR. Results of tests performed in the prior 12 months were used if available and were ordered by the pharmacist if not. Test results for eGFR and ACR were entered into the CKD Clinical Pathway to confirm the presence of CKD. Participants were also asked if they had a previous diagnosis of CKD.

Patients with CKD were further categorized as "known" CKD (defined as having test results showing decreased kidney function [as defined above] and a previous diagnosis of CKD as reported by the patient [confirmed by laboratory results from the provincial electronic health record] and/or pharmacist knowledge/awareness of a previous CKD diagnosis [confirmed by the provincial electronic health record][11]) or "previously unrecognized" CKD (defined as having no previous diagnosis of CKD as reported by the patient or pharmacist and no laboratory confirmation of CKD [as defined in the preceding][11]).

### Intervention

Patients randomly assigned to the intervention group received a Medication Therapy Management consultation from their pharmacist. This included: (1) patient assessments: blood pressure,[24] waist circumference, weight and height measurements; (2) laboratory assessments: $HbA_{1c}$ and lipid profile (if not done within 3 months); and (3) individualized CV risk assessment: risk calculation, education, and discussion of this risk using an interactive online tool (https://www.epicore.ualberta.ca/rxeach/)