The Alberta Vascular Risk Reduction Community Pharmacy Project: R_xEACH

October 17th, 2013

Ross T. Tsuyuki, BSc(Pharm), PharmD, MSc, FCSHP, FACC
Department of Medicine, University of Alberta
Charlotte A. Jones, MD, PhD, FRCP(c)
University of British Columbia – Southern Medical Program
Brenda Hemmelgarn, MD, PhD, FRCP(c)
Department of Medicine, University of Calgary

Co-investigator:
Yazid N. Al Hamarneh, BSc(Pharm), PhD
Department of Medicine, University of Alberta

Background/Rationale

Cardiovascular disease (CVD) is the leading cause of death worldwide accounting for nearly one third of the total deaths (1). The majority (90%) of the CVD cases are caused by modifiable risk factors. These factors include tobacco smoking, hypertension, hyperlipidemia, diabetes, physical inactivity, high fat diet and obesity (2).

In Canada CVD rates have decreased drastically over the last few decades, yet it is still one of the leading causes of death (3). It also carries a financial burden on the Canadian economy with a cost close to $ 21 billion every year divided between loss of productivity and healthcare costs (3).

Despite the risks associated with the major CVD risk factors and the treatment advancement, their prevalence is still substantial in North America (4). Treatment gaps were also reported amongst such factors (5). Al Hamarneh and colleagues (2012) reported that almost 50% of the community dwelling patients with type 2 diabetes were not at their HbA1c target (6). Leiter and colleagues (2013) reported that almost half of the patients with type 2 diabetes did not achieve their HbA1c or cholesterol target, slightly more than one third achieved their blood pressure targets and only 13% achieved the composite triple target (7).

The guidelines recommend using cardiovascular risk assessment equations to guide CVD prevention and management (8). Despite being recommended by the guidelines, it has not been integrated in the clinicians' daily routine; in fact the majority of the patients attending physicians' clinics reported that they have never had a cardiovascular risk assessment (8). This indicates the need for new avenues for the patients to get their cardiovascular risk assessed.

Community pharmacists are frontline primary healthcare professionals who see patients with chronic diseases more frequently than family physicians (9); as such they are well positioned to identify patients at high risk for CVD, determine their CVD risk and assist in their disease management. The efficacy of pharmacists' intervention in chronic disease has been well demonstrated in the literature (10-15). Two of the largest randomized controlled trials in community pharmacy setting were conducted in by our group (13, 14). Both studies reported positive impact of the pharmacist intervention on the patients' lipid panel and blood pressure (13, 14).

Further studies are required to identify the kind of intervention that is suitable to help manage CVD risk factors in community pharmacy setting (15).

The Cardiovascular Strategic Care Network of Alberta Health Services is embarking on an Alberta-wide vascular risk reduction strategy, of which pharmacist interventions are a cornerstone. This strategy combined with the recent changes in the scope of pharmacy practice and remuneration in Alberta provide an opportunity for more convenient and greater access to care and reduction in CVD risk by engaging community pharmacists and their patients.

Purpose

The overall purpose of this initiative is to develop and implement a broad-based community pharmacist-initiated vascular risk reduction case-finding and intervention program based on the C-CHANGE guidelines.

Objectives

Primary objective

To evaluate the effect of a community pharmacy-based case finding and intervention program in patients at high risk for cardiovascular events on reduction in estimated risk for major cardiovascular events.

Secondary objectives

Clinical:

- Improvements in individual risk factors: LDL-cholesterol, blood pressure, HbA1c (among patients with diabetes), and smoking cessation
- Achievement of recommended cholesterol, blood pressure and glycemic control targets
- Increase in proportion of patients receiving appropriate BP, cholesterol and diabetes medication

Process:

- Increase in number of high risk patients screened for cardiovascular risk
- Assess the efficacy of various case-finding mechanisms and vulnerable patient population reach
- Assure sustainability by exploring enabling and barrier forces.
- Quality of life (using EQ5D)

Methods

Design: Randomized controlled trial with patients as the unit of randomization (Figure 1)

Setting: Community pharmacists in Alberta for recruitment and follow up, engaging both patients and family physicians

Patients/Population:

Inclusion criteria:

Adults (≥18 years of age) at high risk for cardiovascular events, including:

- Patients with diabetes
- Patients with chronic kidney disease (eGFR <60 ml/min/1.73m^2)
- Patients with established atherosclerotic vascular disease (via patient health records or self-report) including cerebrovascular disease (prior stroke or transient ischemic attack), cardiovascular disease (myocardial infarction, acute coronary syndrome, stable angina, or revascularization), or peripheral arterial disease (symptomatic and/or ankle brachial index <0.9).
- Primary prevention patients with multiple risk factors and Framingham risk score >20%
- In order to qualify for inclusion, all patients must have at least one uncontrolled risk factor (i.e., blood pressure, LDL-cholesterol, HbA1c, or current smoking)

Exclusion criteria:

- Unwilling to participate/sign consent form
- Unwilling or unable to participate in regular follow-up visits
- Pregnancy

Recruitment:

Potential participants will be approached by the pharmacist when they are picking up or dropping off their prescription. Pharmacists will check the most recent lab results for those patients in the course of routine care (using Netcare). If the patient has not had an eGFR or proteinuria test done over the last 12 months he/she will be given a request to do those tests with a copy sent to his/her family physician.

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

Patients' personal health number will be collected for long-term follow-ups. Information regarding hospitalization (length of stay and diagnosis), out patient physician visits (date, specialty and diagnosis) and out patient laboratory tests (date of laboratory test result) will be collected using the personal health number to assess the continuity of care after the end of the study."

The patient's family physician is going to receive a letter from the pharmacist to inform him/her that his/her patient agreed to participate in this study.

Randomization:
Once informed written consent is obtained, the patients will be randomized (via a centralized secure website to ensure allocation concealment) in a 1:1 ratio to either advanced care or usual care groups

Intervention:

For all the patients randomized to the advanced care group the pharmacist will complete a Comprehensive Annual Care Plan (CACP) or Standard Medication Management Assessment (SMMA), which will include:

- Patient assessment (blood pressure measurement according to CHEP guidelines, waist circumference, weight and height measurements)
- Laboratory assessment of HbA1c and lipids (if not done within 3 months)
- Individual assessment of CVD risk and education about this risk
    - Calculation of cardiovascular risk will be facilitated by an online tool in which the pharmacist enters patient demographics such as age, gender, cholesterol, blood pressure, smoking status, diabetes, etc and the system will use the appropriate risk engine based on the patient's medical history. UKPDS (16), International model to predict recurrent cardiovascular disease (17) and Framingham will be used for patients with diabetes, previous vascular disease, CKD or high Framingham risk (>20%) respectively (see appendix for risk engines score sheets). In the case where a patient has more than one co-morbidity the risk engine estimating the highest risk will be used
    - Discussion of CVD risk with the patient using the interactive online tool which explains his/her individual cardiovascular risk and targets for intervention

    - Proving the patient with education on cardiovascular risk factors and healthy lifestyle options
- Providing treatment recommendations (C-CHANGE and up to date Canadian clinical practice guidelines)
- Prescription adaptation(s), and/or prescribe where necessary to meet lipid, blood pressure and glycemic control targets and smoking cessation.
- Regular communication with the patient's family physician after each contact with the patient using the physician contact form which will be developed by the research team
- Regular follow-up with all patients a minimum of every 3-4 weeks for 3 months (Interim telephone follow-up may be performed at the discretion of the pharmacist; however telephone follow-up cannot be used for 2 consecutive visits or for the final visit (3 months).

Usual care:

Patients randomized to the usual care group will receive:

- Usual pharmacy care with no specific interventions for 3 months
- At the end of the 3 months of the usual care period, all patients will cross over to receive the advanced care outlined above for 3 months

The analysis of the results from patients who cross over from the usual care group into the advanced care group will be conducted separately on before and after design basis.

Patients' personal health number will be collected for long term follow-ups. Information regarding hospitalization (length of stay and diagnosis), outpatient physician visits (date, specialty and diagnosis) and outpatient laboratory tests (date, laboratory test result) will be collected using the personal health number to assess the continuity of care after the end of the study.

Outcomes:

Primary outcome:
The primary outcome is the difference in change in estimated cardiovascular risk between advanced care and usual care groups. Cardiovascular risk is defined as the risk for future cardiovascular events (myocardial infarction, revascularization, cardiovascular death) as calculated by validated risk engines as described above.

Secondary outcomes:

- Difference in change in individual cardiovascular risk factors between advanced care and usual care groups, including LDL-cholesterol, systolic and diastolic blood pressure, HbA1c and smoking cessation.
- Achievement of individual and the "triple target" of LDL-cholesterol $\leq$ 2.0 mmol/L, blood pressure control BP <140/90 mmHg (<130/80 in those with diabetes) and glycemic control (HbA1c $\leq$ 7.0) in advanced care compared to usual care group patients in those with diabetes.
- Difference in change in quality of life between advanced care and usual care groups

Sample size and analytical plan:

Sample size was estimated for all 4 subgroups separately (diabetes, chronic kidney disease, vascular disease and primary prevention) in order to have sufficient power to evaluate each subgroup individually.

For the diabetes subgroup, we used the information from Song and Brown (2004) (baseline risk of 21.5%) (19) and the following assumptions 80% power and alpha of 0.05 to calculate the sample size. A sample size of 400 patients is required to detect a 15% difference in the relative reduction of cardiovascular risk between advanced care and usual care groups.

For the chronic kidney disease subgroup, we used the demographic and clinical information (age, gender, hypertension, cholesterol and diabetic status) from Manns *et al* (2012) (20) and the CVD risk calculator from D'Agostino *et al* (2008) (18) and the following assumptions 80% power and alpha of 0.05 to calculate the sample size. A sample size of 260 patients is required to detect a 15% difference in the relative reduction of cardiovascular risk between advanced care and usual care groups.

For the vascular disease subgroup, we used the demographic and clinical information (age, gender, smoking status, diabetic status, etc) and the CVD risk calculator from Wilson *et al* (2012) (17) and the following assumptions 80% power and alpha of 0.05 to calculate the sample size. A sample size of 300 patients is required to detect a 15% difference in the relative reduction of cardiovascular risk between advanced care and usual care groups.

For the primary prevention subgroup, we used the information from Simmons *et al* (2009) (baseline risk of 22.3%) (21) and the following assumptions 80% power and alpha of 0.05 to calculate the sample size. A sample size of 220 patients is required to detect a 15% difference in the relative reduction of cardiovascular risk between advanced care and usual care groups

We then added together these subgroups for a total sample size of 1180 patients is required to detect a 15% difference in the relative reduction of cardiovascular risk between advanced care and usual care groups amongst all subgroups.

Analytical plan:

All analyses will be conducted on intention to treat basis. In the case of missing data, a last observation carried forward approach will be used.
The primary outcome will be analyzed using ANCOVA , adjusting for all covariates with $p<0.25$ between groups.
The secondary outcomes will be analyzed using ANCOVA, t-test or chi square test where appropriate, adjusting for all covariates with $p<0.25$ between groups.

Trial and Data Management will be done by EPICORE Centre

Feasibility

Remuneration*:* Pharmacists will submit to Alberta Health for remuneration of baseline (Comprehensive Annual Care Plan or Standard Medication Management Assessment) and follow-up visits. In the case of patients who are not eligible, the same fee will be provided to the pharmacist by the study.

- We will work with the Alberta Pharmacists Association to develop a simple method to bill Alberta Health for these services

Training*:* Training will be developed by the research team and provided at face-to-face regional meetings. Additional online training will be available using materials from major organizations (CTFPHC, CPhA, Hypertension Canada, Canadian Diabetes Association). Those materials will include the following:

- Case finding
- CVD risk calculation and communication
- CKD treatment and management based on the CKD Clinical Pathway developed for Primary Care and adapted for pharmacists
- Hypertension treatment and management
- Cholesterol treatment and management
- Diabetes treatment and management
- Smoking cessation
- Diet and lifestyle management
- Preparing CACP and SMMA
- Obtaining your PRAC ID

A hotline will be made available for the participating pharmacists where they will be put in touch with one of our experts depending on the kind of question they have. This expert will help the interested pharmacist address his/her problem/concern.

Case finding facilitators identified by the pharmacies will also be trained on case finding and recruitment methods.

Pharmacy Recruitment: We will recruit pharmacies through the Alberta College of Pharmacists and Alberta Pharmacists Association who have agreed to send communications to all licensed pharmacists and call for Expressions of Interest. Pharmacies and pharmacists will be selected based upon their track record in innovative patient care initiatives, commitment of in-kind resources (e.g., pharmacist and technician time), and service provided to vulnerable populations (e.g., rural, elderly, South Asians, Aboriginal, etc.).

Online patient enrollment and education: We will develop an online patient registration system where pharmacists can screen and enroll patients. The system will prompt for the presence of diabetes, vascular disease, serum creatinine, cholesterol, blood pressure, age , smoking status, and gender and use the appropriate risk calculator to determine the patients' risk for cardiovascular events.

- An interactive educational graphic will be developed to show patients their risk for cardiovascular events as well as show them how modest modification of their risk factors reduce their risk

Partners:

- Merck Canada: funding for the pharmacist training
- HWAP Project (Drs. Hemmelgarn, Manns, Tonelli, Tsuyuki): This project, funded by Alberta Health is focusing on cardiovascular risk reduction in rural patients with CKD. We will share training and data management resources.
- Pharmacy chains and independents: a call for Expressions of Interest was sent out in March 2013. Participating pharmacies will be expected to "bring something to the table" such as pharmacist/technician time and a strong commitment to the study (possibly consider pre-recruitment lists of potential participants or participant numbers).
- Cardiovascular and Stroke Strategic Care Network, Alberta Health Services: some limited funding for study coordination and data management for the overall study

What This Study Adds:

This is the first large scale study on global cardiovascular risk reduction in community pharmacy setting.

It has a public health importance since we have a special focus on vulnerable populations such as rural, South Asian, Aboriginal and can reach patients who don't or can't see a family physician

We will use several innovative methods to capture patients at high risk for cardiovascular disease. We will pay unique attention to case finding, this is the *sine qua non* of chronic disease management – without good case finding, interventions are worthless.

We are capitalizing on the Alberta Health framework for pharmacy services and will provide evidence for its benefit (these data are not available for most funded Alberta Health programs) to help providing sustainable interventions in community pharmacy setting.

Timelines:

- March – June 2013: Finalize study protocol, implementation planning, meeting with partners, agreements signed
- May – August 2013: preparation of study materials, training of pharmacists and technicians
- June 2013: research ethics board submission
- September 2013: Study launch meetings, first patient enrolled
- May 2014: End of recruitment.
- August 2014: Last advanced care patients followed up.
- November 2014: Final follow-up of usual care group patients crossed over to receive the intervention
- August - November, 2014: Data analysis and report writing
- December 2014: Wrap-up investigators' meeting,
- March 2015: presentation at the American College of Cardiology meeting, Media release of result

Reference:

1. WHO. Cardiovascular diseases (2013). Available online from http://www.who.int/mediacentre/factsheets/fs317/en/ accessed on 29-04-2013

2. Schenck-Gustafsson K. Risk factors for cardiovascular disease in women. Maturitas 2009; 63(3):186-190

3. Heart and Stroke Foundation. Statistics (2013). Available online from http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3483991/k.34A8/Statistics.htm accessed on 29-4-2013

4. Lim SS, Vos T, Flaxman AD et al. A comparative assessment of burden of disease injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the global burden of disease study 2010. Lancet. 2012; 380:2224-2260

5. Zillich AJ, Sutherland JM, Kumbera PA, Carter BL. Hypertension outcomes through blood pressure monitoring and evaluation by pharmacists (HOME study). J Gen Intern Med. 2005; 20:1091-1096.

6. Al Hamarneh YN, Rosenthal M, Tsuyuki RT, Glycemic control in community dwelling patients with type 2 diabetes. Can Pharm J. 2012; 145: 68-69 e1.

7. Leiter LA, Berard L, Bowering CK, et al. Type 2 diabetes mellitus management in Canada: Is it improving? Can J Diabetes. 2013; (37): 82-89.

8. Grover SA, Lowensteyn I. The challenges and benefits of cardiovascular risk assessment in clinical practice. Can J Cardiol 2011; 27: 481-487.

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

10. Vivian EM. Improving blood pressure control in a pharmacist-managed hypertension clinic. Pharmacotherapy. 2001; 21:1337-44.

11. Scott DM, Boyd ST, Stephan M et al. Outcomes of pharmacist-managed diabetes care services in a community health centre. Am J Health-Syst Pharm. 2006; 63:2116-22.

12. Sanchi SR, Chiolero A, Burnand B et al. Impact of Pharmacist Care in the Management of Cardiovascular Disease Risk Factors. Arch Intern Med. 2011; 171(16): 1441-1453.

13. Tsuyuki RT, Johnson JA, Teo KK et al. 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. 2002;162:1149-1155.

14. McLean DL, McAlister FA, Johnson JA et al. 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. 2008;168(21):2355-2361.

15. Santschi V, Chiolero A, Burnand B, Colosimo AL, Paradis G. Impact of pharmacist care in the management of cardiovascular disease risk factors: a systematic review and meta-analysis of randomized trials. Arch Intern Med 2011; 171(16):1441-1453.

16. 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.

17. Wilson PWF, D'Agostino R, Bhatt DL et al. An international model to predict recurrent cardiovascular disease. Am J Med 2012; 125:695-703.

18. D'Agostino RB, Vasan RS, Pencina MJ et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. Circulation 2008; 117:743-753.

19. Song SH, Brown PM. Coronary heart disease risk assessment in diabetes mellitus: comparison of UKPS risk engine with Framingham risk assessment function and its clinical implications. Diabet Med 2004; 21:238-245.

20. Manns B, Tonelli M, Culleton B et al. A cluster randomized trial of enhanced eGFR prompt in chronic kidney disease. Clin J Am Soc Nephrol 2012; 7:565-572.

21. Simmons RK, Coleman RL, Price HC et al. Performance of the UK prospective diabetes study risk engine and the Framingham risk equation in estimating

cardiovascular disease in the epic-norfolk cohort. Diabetes Care 2009; 32:708-713.

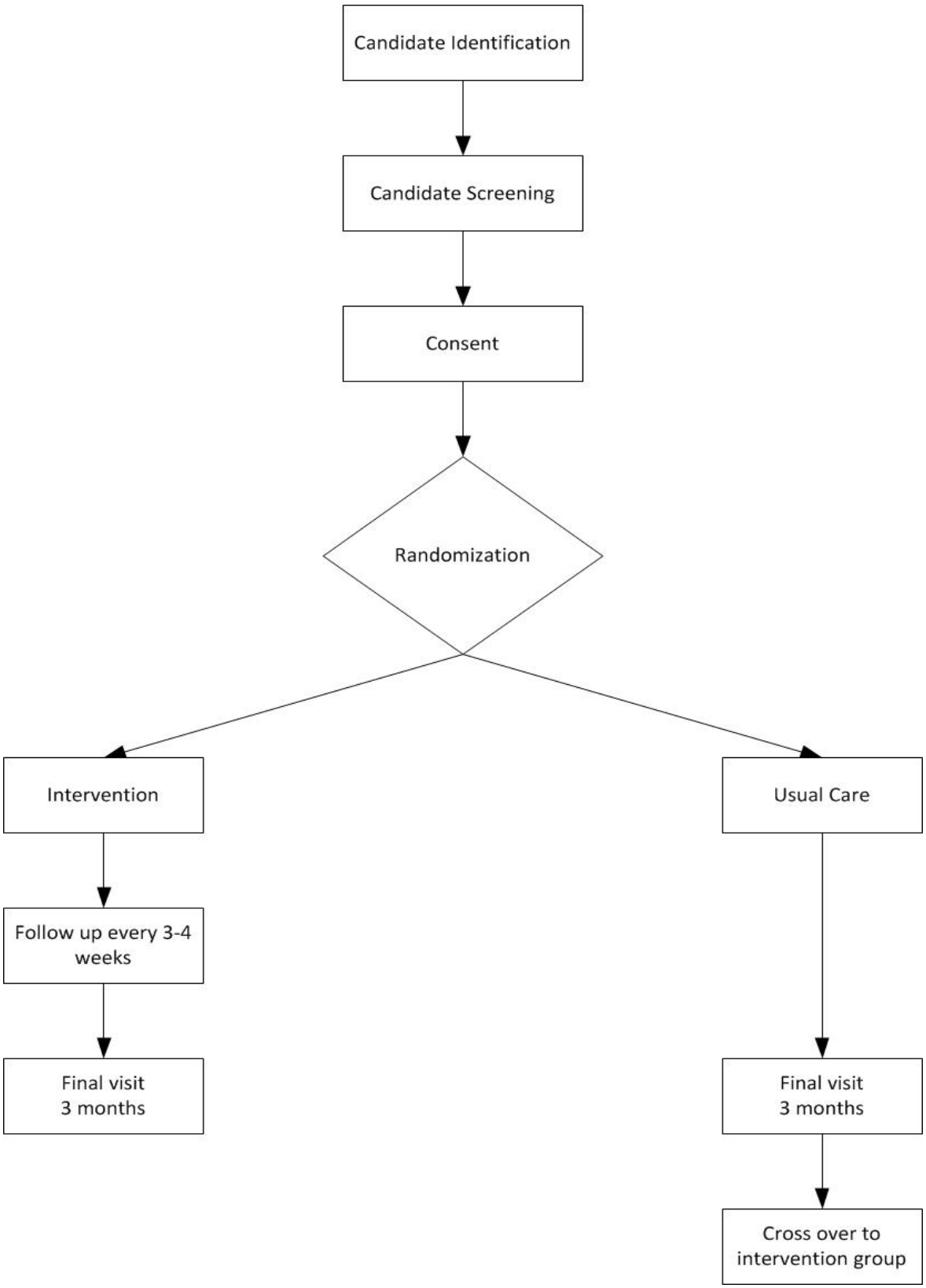

Figure 1 R_xEACH overview

Appendix
Risk Engines score sheets which will be used in the study

Abbreviations	Definitions/values
AGE	Age in years at diagnosis of diabetes
SEX	1 for female; 0 for male
AC	1 for Afro-Caribbean; 0 for Caucasian or Asian-Indian
SMOK	1 for a current smoker, of tobacco in any form, at diagnosis of diabetes; 0 otherwise
H	HbA_{1c} (%), mean of values for years 1 and 2
SBP	Systolic blood pressure (mmHg), mean of values for years 1 and 2
LR	Total cholesterol/HDL cholesterol ratio, mean of values for years 1 and 2

Parameter	Interpretation	Estimate	95% confidence interval
q_0	Intercept	0.0112	0.0082–0.014
β_1	Risk ratio for one year of age at diagnosis of diabetes	1.059	1.05–1.07
β_2	Risk ratio for female sex	0.525	0.42–0.63
β_3	Risk ratio for Afro-Caribbean ethnicity	0.390	0.19–0.59
β_4	Risk ratio for smoking	1.350	1.11–1.59
β_5	Risk ratio for 1% increase in HbA_{1c}	1.183	1.11–1.25
β_6	Risk ratio for 10 mmHg increase in systolic blood pressure	1.088	1.04–1.14
β_7	Risk ratio for unit increase in logarithm of lipid ratio	3.845	2.59–5.10
d	Risk ratio for each year increase in duration of diagnosed diabetes	1.078	1.05–1.11

UKPDS Risk engine score sheet

Step	Factor	Next CV event: factors and points	CV event points	CV death: factors and points	CV death points
1	Sex	Man Woman 1 0		Man Woman 1 0	
2	Age, years	20–24 25-29 30-34 35-39 40–44 45-49 50–54 0 1 2 3 4 5 6 55–59 60-64 65-69 70–74 75-79 80–84 85-89 7 8 9 10 11 12 13		20–24 25-29 30-34 35-39 40–44 45-49 50–54 0 1 2 3 4 5 6 55–59 60-64 65-69 70–74 75-79 80–84 85-89 7 8 9 10 11 12 13	
3	Smoking	No Yes 0 2		No Yes 0 1	
4	Diabetes mellitus	No Yes 0 2		No Yes 0 2	
5	BMI < 20 kg/m^2	No Yes 0 2		No Yes 0 2	
6	Number of vascular beds	One Two Three 2 4 6		One Two Three 1 2 3	
7	CV event in past year	No Yes 0 2		No Yes 0 1	
8	Congestive heart failure	No Yes 0 3		No Yes 0 4	
9	Atrial fibrillation	No Yes 0 2		No Yes 0 2	
10	Statin therapy	No Yes 0 –2		No Yes 0 -1	
11	ASA therapy	No Yes 0 -1		No Yes 0 -1	
12	Eastern Europe or Middle East	No Yes 0 2		No Yes 0 1	
13	Japan or Australia	No Yes 0 -2		No Yes 0 -3	
14		Next CV event points total		CV death points total	

An international model to predict recurrent cardiovascular disease score sheet

Males

Points	Age, y	HDL	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic
−2		60+		<120			
−1		50–59					
0	30–34	45–49	<160	120–129	<120	No	No
1		35–44	160–199	130–139			
2	35–39	<35	200–239	140–159	120–129		
3			240–279	160+	130–139		Yes
4			280+		140–159	Yes	
5	40–44				160+		
6	45–49						
7							
8	50–54						
9							
10	55–59						
11	60–64						
12	65–69						
13							
14	70–74						
15	75+						
Points allotted							Total

Females

Points	Age, y	HDL	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic
−3				<120			
−2		60+					
−1		50–59			<120		
0	30–34	45–49	<160	120–129		No	No
1		35–44	160–199	130–139			
2	35–39	<35		140–149	120–129		
3			200–239		130–139	Yes	
4	40–44		240–279	150–159			Yes
5	45–49		280+	160+	140–149		
6					150–159		
7	50–54				160+		
8	55–59						
9	60–64						
10	65–69						
11	70–74						
12	75+						
Points allotted							Total

Framingham risk engine score sheet