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Improving diabetes care: Multi-component Cardiovascular Disease Risk Reduction Strategies for People with Diabetes in South Asia - The CARRS Multi-center Translation Trial

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4. CONFLICT OF INTEREST STATEMENT

The authors have no financial or personal conflicts of interest.

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Abstract

Aims—Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in people with diabetes in South Asia. The CARRS translation trial tests the effectiveness, cost-effectiveness, and sustainability of a clinic-based multi-component CVD risk reduction intervention among people with diabetes in India and Pakistan.

Methods—We randomly assigned 1,146 adults with diabetes recruited from 10 urban clinic sites, to receive usual care by physicians or to receive an integrated multi-component CVD risk reduction intervention. The intervention involves electronic health record management, decision-

support prompts to the healthcare team, and the support of a care coordinator to actively facilitate patient and provider adherence to evidence-based guidelines. The primary outcome is a composite of multiple CVD risk factor control (blood glucose and either blood pressure or cholesterol, or all three). Other outcomes include control of the individual CVD risk factors, process and patient-centered measures, cost-effectiveness, and acceptability/feasibility.

Conclusion—The CARRS translation trial tests a low-cost diabetes care delivery model in urban South Asia to achieve comprehensive cardio-metabolic disease case-management of high-risk patients (clinicaltrials.gov number: NCT01212328).

Keywords

diabetes; cardiovascular risk; South Asia; translation research; healthcare delivery

1. INTRODUCTION

The greatest gains in CVD prevention are seen in subjects at high-risk for CVD, such as those with diabetes,[1] by addressing multiple risk factor targets (e.g., blood glucose, blood pressure, and blood lipids) *together*. [2-4] This is advocated by major consensus groups like the American Diabetes Association,[5] International Diabetes Federation,[6] and World Heart Federation[7]. However, achievement of recommended targets by patients with diabetes are sub-optimal in high-income countries (HICs) [8, 9] and more so in low- and middle-income regions like South Asia[10-13]. Multiple issues such as inadequately organized health systems, poor healthcare access, lack of standardized care, and challenges in patient self-management perpetuate the gaps in quality of diabetes care delivered in South Asia[10, 11, 14] - necessitating low-cost but comprehensive strategies to address the systems, organizational/provider, and patient issues[15, 16].

The CARRS (Cardiovascular Risk Reduction in South Asia) translation trial seeks to address these challenges of CVD risk factor control among patients with Type 2 diabetes in South Asia, where rigorous translational evidence is lacking.[15, 17] The study tests the feasibility, effectiveness, and cost-effectiveness of a multi-faceted intervention (physician-directed patient case-management facilitated by a non-physician care coordinator using electronic health records and decision support software) to reduce CVD risk among people with type 2 diabetes, compared to those receiving usual care. The use of care coordinators to facilitate diabetes case-management has been tested largely in HICs, showing improvements in processes of care and to some extent, intermediate biochemical outcomes (i.e., blood pressure, glycemic control).[18-20] The additional costs of case-management are counter-balanced by the *potential* to reduce emergency-room visits, hospitalization, and disease progression.[18, 21, 22] Electronic health records (EHR) provide an organized, quickly-accessible structure for storing serial patient data to monitor progress.[23] In addition, decision-support software (DSS) (e.g., providing guideline-based treatment prompts for providers) has been shown to improve process and clinical outcomes for patients in HICs. [24] Such data are sparse in low and middle-income countries. This translational trial will provide operational data for a model of integrated diabetes care in South Asia, from patient-level biochemical and quality of life indicators to clinic-level performance and policy-oriented cost-effectiveness and sustainability data.[25-27]

2. METHODS

2.1 Overview

A total of 1,146 adults with diabetes were randomly assigned to the intervention or control groups. Participants were recruited between January 2011 and June 2012 from ten urban

clinic study sites, nine in India and one in Karachi, Pakistan. The sites represent diversity in terms of clinic type (public vs. private) and geographical distribution. The Research Coordinating Center (RCC) is based in New Delhi, India. The trial is registered at clinicaltrials.gov (NCT01212328) and at Clinical Trials Registry India (CTRI/2010/091/001185).

2.2 Study Participants and Visits

This study tests an intervention delivery package in people with diabetes that are currently not meeting CVD risk factor control targets based on the American Diabetes Association guidelines. To be included in the study, potential participants must have met all of the following criteria: 35 years of age, confirmed type 2 diabetes diagnosis (1999 WHO criteria), [28] poor glycemic control (glycated hemoglobin [HbA1c] $\geq 8.0\%$) AND one or both of dyslipidemia (LDL ≥ 3.36 mmol/L) or systolic hypertension (SBP ≥ 140 mmHg), irrespective of lipid- or BP-lowering medication use, respectively. [5, 29] Patients must have been willing to consent to randomization and have reasonable likelihood of following up, based on physicians' assessment.

Exclusion criteria included: type 1 diabetes mellitus, documented CVD event in the 12 months prior to recruitment, symptomatic congestive heart failure or New York Heart Association (NYHA) Class 3 or 4 effort intolerance, end-stage renal disease, transaminase >3 times upper limit of normal or active liver disease within past 2 years, malignancy or life-threatening disease with death probable in 4 years, other medications (e.g. long-term steroids, protease inhibitors) or condition (e.g., other endocrinopathy [adrenal, pituitary] that affects metabolic risk factor control, tuberculosis on treatment (based on physician's diagnosis), and any psychiatric illness or cognitive impairment, alcohol or drug abuse, history of organ transplant, BMI ≥ 45 kg/m²) that would interfere with the patient's follow-up, on an investigational drug in the last 3 months, or currently participating in other clinical trials.

Figure 1 shows how participants flow through the trial. Recruitment at each site was initiated mainly through paper/electronic health record review or during a patient's clinic visit. Potential participants were invited for two pre-randomization visits where informed consent was obtained in English or the local language depending on the patient's preference, and individuals were screened for eligibility. Screening included a brief medical history; anthropometric, blood pressure, and heart rate measurements; and urine and fasting venous blood samples for biochemical tests (glucose, HbA1c, lipid profile, creatinine, potassium, sodium, ALT, urine albumin creatinine ratio). At the randomization visit, all consenting, eligible participants underwent further baseline assessments to document history, physical examination, ECG, foot examination, eye examination, and questionnaires related to patient perceptions of illness, cost, and health-related quality of life (HRQOL).

After baseline assessment, the study staff at each clinic accessed the participant's randomization allocation from the Interactive Web Response System (IWRS), using a password-protected login provided by the RCC. The RCC developed the IWRS centrally, and it follows restricted, block randomization coding, stratified by the individual sites.

Participants will be followed for an average of 30 months (minimum 24 months), with yearly study-related measurement visits where all the assessments from baseline are repeated. Physicians will also be interviewed regarding acceptability and sustainability of the intervention. Outside the annual visits, the intervention group is encouraged to follow-up every 3-6 months (physician determines follow-up according to patients' levels of risk factor control achieved), while the control group continues visits as per existing usual care at the clinic setting. Data from these intermediate visits will be evaluated for process outcomes.

Although randomization occurs at the level of individuals, the study team has implemented a set of processes that prevent contamination. Study staff assigned to take care of study participants were restricted from coming into contact with patients before randomization. Rather, a separate “screening officer” conducted screening visits and the randomization. During follow-up visits, the care coordinators meet patients in the intervention arm in a private area and take them to the physician, while the control arm patients go directly to the physician. A separate research officer handles the data collection and input for the control arm participants.

2.3 Intervention

Participants randomized to the intervention arm receive intensive and holistic diabetes management through the following components (Figure 1): (1) *electronic health records (EHR)* with custom-designed, locally-developed, *decision-support software (DSS)* that provides prompts based on *CVD risk management algorithm-guidelines* and (2) patient *case-management* by a non-physician *care coordinator* who manages the EHR-DSS and personalizes care for each patient, following-up with them regularly and motivating them. Annual audit and feedback is also provided to the sites by the RCC to support quality assurance/control and assist with trouble-shooting.

In our preliminary research, all the site physicians reported a large patient load and shortage of personnel. Although having an EHR-DSS system would be helpful, the physicians would not realistically use it because of time constraints. Thus, the non-physician care coordinator is a vital part of this trial’s intervention to manage the EHR and deliver DSS prompts to the physician to improve treatment decision-making and support patient care. Case-management has been shown to be most effective when care coordinators can adjust medications without physician approval.[30] In this trial, we opted for a low-cost strategy by employing care coordinators with less training (maximum Bachelor’s degree) and therefore no prescriptive powers. Instead, the care coordinators can influence physician prescribing by conveying the software-generated algorithmic decision-making treatment prompts to the physicians. The system ensures physician adherence to guidelines by requiring documented justification for not following the prompts. With basic training and physician and algorithm guidance, the intervention’s care coordinators manage and monitor patient follow-up using the EHR-DSS and promote patient self-management, thereby facilitating care in fragmented health systems.

2.3.2 Electronic health record-decision support software (EHR-DSS) and CVD risk management algorithm-guidelines—The EHR-DSS was designed by a competitively selected Delhi-based e-health software company, with significant input from the research team for specifications and iterative testing at a local diabetes clinic that is not involved in the study. The software facilitates case-management with the following functions:

- stores all electronic health records and patient self care activities/habits, integrating all laboratory and consultation reports in one easily accessible portal to monitor participant progress;
- provides decision-support prompts of guideline-recommended processes of care (e.g. treatment plan, laboratory tests, screenings);
- allows scheduling of appointments for patients and reminders to staff for follow-up calls/tests;

- automatically sends out reminders to patients for clinic visit appointments and motivational text messages, and reminders to care coordinators for follow-up items; and
- collects process data for the trial participants (i.e., documenting clinical activities in terms of prescriptions, intensification of therapy, advice given, etc).

The evidence-based CVD risk management algorithm-guidelines are the basis of the decision-support software (Supplementary Material 1). They were developed by a multi-disciplinary team led by members of the study steering committee, with feedback from site investigators. The algorithm-guidelines follows current internationally-accepted evidence (primarily the ADA Standards of Care), with adaptations to increase relevance to the South Asian population.[5, 29] It provides recommendations for blood glucose, blood pressure, and lipid control, processes of care (aspirin use; ACE-inhibitor use; regular eye, foot, and urine testing), and lifestyle recommendations (smoking cessation, alcohol control, diet, physical activity). Refer to Supplementary Material 2 for an example of the DSS prompts print-out.

The care coordinator has login-access to the DSS-enabled EHR only for the intervention group that he/she manages. The research officer has access to a simple EHR only for the control arm participants that he/she manages. The site investigators are provided with view-only permission (no editing rights) to review case report form completion and any completed serious adverse event (SAE) forms for further action. The RCC has open access to both intervention and control group data for monitoring and analysis purposes.

2.3.3 Non-physician care coordinator—The non-physician care coordinators were recruited locally by each Site Investigator, and are provided a competitive salary by the study. The qualifications for the care coordinator are: (1) registered nurse, social worker, or dietician OR minimum of 12th grade pass plus 2 years of health care experience, (2) strong inter-personal, motivational, and organizational skills, (3) basic computer application knowledge and (4) willingness to stay for the full duration of the trial of approximately 3 years.

Each site's care coordinator manages the participants randomized to the intervention arm. To ensure that contamination does not occur, the care coordinator does not have any connection with people randomized to the control arm. The work of the care coordinator is a combination of interactions with the clinical team and personalized follow-up care for intervention participants. Figure 2 offers a detailed diagram of care coordinator functions and points out where the EHR-DSS is used in the clinic setting. The care coordinator:

- fully manages the EHR-DSS for (a) data-entry of intervention group participant's, (b) communication of DSS management prompts to the physician at consultation via print-out or electronic display, and (c) updating participant treatment plans after each consultation;
- during consultation, assists the physician in devising a tailored follow-up plan for patients, accounting for routine and motivation (but not permitted to make prescriptive or treatment plan changes);
- facilitates participant follow-up, referral, treatment, and investigation appointments through reminders via text-message sent from the EHR and phone calls;
- encourages and motivates participants to better self-manage risk factors (e.g., obtaining medications, adherence to daily therapy, lifestyle modification, and follow-up) by providing the appropriate guidance and tools for behavior-change and addressing any access issues (e.g., transport, delivery of medications);

- prompts earlier attention of intervention group patient's needs/progress to the treating physician (e.g. eliciting a prescription without waiting for the patient's next clinic appointment); and
- manages the intervention group's trial data collection, documentation, and communication with the RCC.

2.5 Sample Size

The primary outcome is the between-group difference in proportions achieving multiple risk factor control targets (glycemic control *plus* either control of blood pressure or blood lipids, or both). Relative to the control group, we hypothesize that 40% more participants in the intervention group will, on average, achieve multiple CVD risk factor control targets (at least HbA1c < 7.0% AND one of SBP < 130 mmHg OR LDL-cholesterol < 3.36 mmol/L [<1.81 mmol/L if history of CVD event] [5]). The sample size calculations (OpenEpi Software [31], methodology from Kesley et al. [32]) were estimated based on conservative proportions of the sample populations (intervention [28%] and control [20%]) reaching multiple risk factor control, with 20% allowance for loss to follow-up and/or missing data, a 5% alpha, and 80% power, resulting in a minimum $n=1120$ participants. This sample size also permits detection of 10% greater proportion of the intervention group achieving the secondary outcomes of individual targets, compared to the control group. Although the study has not been powered for CVD event and/or mortality reduction, we anticipate that the data we collect will be useful for putatively planning an extension of this trial to detect clinically significant CVD and/or mortality endpoints.

2.6 Study Measures

A full listing of the study measures is provided in Table 1. All patient-related quantitative study measures are collected and entered into the EHR using the case report forms. We will utilize the process data collected to more closely understand participants' treatment responses and follow-up care adherence patterns. To evaluate sustainability, we are examining the incremental cost-effectiveness of the intervention, at each site and cumulatively. Costs of care and resource utilization questions have been integrated into the participant baseline assessments, and will also be derived from secondary clinic data assessed by RCC staff during the site initiation, annual monitoring, and close-out visits. During monitoring visits, the RCC staff-person will conduct in-depth interviews regarding acceptability and sustainability of the intervention with 1-2 site physicians to assess study progress and challenges. Participants who drop out of the study will also be followed to explore reasons for discontinuing involvement.

2.8 Statistical Analysis

2.8.1 Quantitative Analysis—Quantitative data analysis will be performed using SAS 9.1 (SAS Institute, Cary, North Carolina) or STATA 9.0 (Statacorp, Texas). A two-sided significance level of 5% will be used for all statistical inference. All data analysis will be conducted according to the intention-to-treat principle. Baseline differences between intervention and control groups will be assessed using chi-square tests for the categorical outcomes and t-tests/Wilcoxon rank-sum tests for the continuous outcomes. Recruitment and retention of trial participants will be assessed by examining: number eligible to be randomized, number enrolling in the study, and dropout from regular testing at the completion of 30 months. Baseline and close-out differences between the groups will be assessed using McNemar's tests for categorical outcomes (proportion achieving the primary outcome of multiple risk factor targets and secondary outcomes of single risk factor targets). Differences in changes in HRQOL scores (EQ-5D, HUI-3) and diabetes treatment satisfaction between baseline and the end of follow-up will be compared using an analysis of

covariance including the baseline value as a covariate. Effectiveness of the intervention comparing multiple time points for between-group and/or within-group differences will be performed using generalized estimating equation (GEE) for categorical and continuous outcomes. Tests for heterogeneity across sites, age groups, genders, and baseline disease severity will be applied.

We acknowledge that clustering may arise since individuals may be seen by the same physician at each site and recognize that this violates the assumption of independence in regression analysis, creating downward bias in standard error estimates and producing erroneously significant results. We will adjust for this possibility using robust standard error estimation techniques—with either SAS or STATA software—that correct for the non-independence of observations. In the event that there is an interest in identifying a coordinator effect, we will use simple multi-level models which can include dummy variables for characteristics of the physician/coordinator and draw out any significant effects of seeing a particular coordinator (relative to a referent coordinator) on individual outcomes. We believe testing at an adequate number of sites, with an adequately powered sample size, sufficient number of care coordinators and using the appropriate statistical methods, will allow us to exclude the possibility that the effects shown can be attributed to one person.

2.8.2 Cost-effectiveness—Cost-effectiveness will be calculated on Microsoft Excel (2010) by assessing the incremental cost-effectiveness ratio (ICER), which equals $(\text{Mean Cost}_{\text{intervention}} - \text{Mean Cost}_{\text{control}}) / (\text{Mean Effect}_{\text{intervention}} - \text{Mean Effect}_{\text{control}})$. The numerator represents intervention versus control group *net costs* (only patient care costs, not investigator time and planning efforts, plus out-of-research costs to the clinic and patients). Unit costs of resources in the first year of the trial will be derived from secondary sources (e.g., clinic records, research budget). The denominator represents the net “effectiveness” of outcomes, which include the following: (1) primary outcome (multiple risk factor control) using a composite CVD risk score (e.g. Framingham), (2) secondary outcomes (individual risk factors), and (3) HRQOL (EQ-5D, HUI-3,). Thus, we will be calculating cost per unit of each of these outcomes at 30 months.

The ICERs for each clinic will be compared taking into account clinic heterogeneity, and a collective ICER for the trial as a whole will be determined. Confidence intervals will be calculated using bootstrap methods. In addition, sensitivity analyses will be performed in order to examine societal effects of key parameters on CE ratios (e.g. different wage rates or market value of intervention components). A discount rate of 5% will be used to adjust for inflation over the study years.

2.8.3 Qualitative Analysis—Qualitative data from the audio-taped physician interviews on sustainability and feasibility of the intervention will be analyzed using MAXqda (2007) software. Analysis of the textual data will follow the grounded theory methodology whereby key themes are identified inductively from the textual data. These themes will then be compared using structured comparisons to identify specific issues relevant to the intervention and control groups as well as sub-groups of participants.

2.9 Training and Quality Assurance/Control

Training for all site study staff was standardized and held in a central location (RCC in New Delhi). The RCC staff then visited each site for on-site setup and training 1 month prior to initiation of recruitment. Each site was provided with a manual of procedures, a study laptop to access the EHR-DSS via a desktop icon, and blood pressure monitors. Study site staff were trained regarding use of EHR-DSS and all study procedures were reviewed with the investigators, care coordinator, and research officer, using mock-patients and patient data.

The care coordinators received additional training to promote patient self-management including basic diabetes pathophysiology, diabetes care requirements, warning signs, and behavioral change tools. The care coordinators and research officers were tested on the protocol using the teach-back methodology against a pre-defined checklist. All manuals and training materials were created by the research team, with review by the investigators and subject-experts, and tested for clarity and comprehensiveness before finalization and use.

On-site monitoring visits by an RCC staff-person will occur on an annual basis, along with a final close-out visit. The RCC provides annual audit and feedback to all the site teams regarding their progress and areas for improvement.

2.10 Participant safety and confidentiality

The intervention (a CVD risk reduction delivery strategy) is not the same as implementing a new drug or invasive procedure, so risks to participants are considered minimal. However, appropriate precautions are being taken to avoid inflicting harm or risk to participants and ensuring their confidentiality. Patients are asked about adverse and serious adverse events at every visit, and the Site Investigator is responsible for ensuring accurate and timely reporting of these for each patient. In addition, a data safety and monitoring board is in place and conducts annual reviews of trial progress and patient outcomes. The study has been approved by all site Ethics Committees, Emory University's Institutional Review Board, PHFI's Independent Ethics Committee, and India's Health Ministry Screening Committee. All study staff involved in the trial are trained in human subjects protection (CITI program), safe measurement and data collection, and standard confidentiality procedures.

3. DISCUSSION

There are no published clinical trials of integrated CVD risk reduction intervention in South Asia, but reviews of studies in HICs show favorable results for non-physician case-management [33] and equivocal results regarding electronic decision support.[24] Moreover, these mostly small, single-strategy studies with short test periods have tended to focus on intermediate or surrogate endpoints and had limited evaluation of cost-effectiveness and sustainability. For these reasons, we sought to comprehensively assess an integrated and multidimensional CVD risk reduction intervention tailored for the context of South Asia. This trial introduces integrated case-management by a care coordinator who manages an EHR equipped with DSS tools: guideline-based treatment prompts for providers and patient reminders. Further, the trial intervention intends to improve the provider's adherence to intensive patient management and empower better self-management among patients.

3.1 Challenges in developing and implementing the trial intervention

Developing and linking DSS management prompts to the CVD risk reduction algorithm-guidelines required numerous iterations of testing between the study and software design teams. With feedback from site physicians, the EHR-DSS is calibrated to provide generic diabetes management prompts but enough discretion for physicians to personalize care for individual patients. Clinic site teams were also involved in integrating the care-coordinator/EHR-DSS functions in their setting and workflow (e.g., timing, location, use of laptop vs. printing records). This involvement of local clinic staff facilitated the seamless incorporation of the intervention into each clinic's existing setup, without major system overhaul or neglecting patient focus. The key duties of the care coordinator remained the same across sites, though the education qualifications of each care coordinator varied due to availability.

3.2 Design strengths

The trial is the first of its kind for LMICs, testing a comprehensive and multi-faceted CVD risk reduction intervention strategy. The trial is rigorously designed, factoring in adequate duration of follow-up, minimization of biases, and cost-effectiveness evaluations.

In designing and implementing the trial with the goal of maximizing the validity and generalizability of our results, the following decisions were made:

- The choice of individual over cluster randomization was justified by: (a) high risk of bias in cluster randomization - in particular, since quality of care is being assessed, it is unlikely that health care providers will cooperate to being controls (they are likely to refuse consent) as this will undermine their practices. (b) The intervention is multi-faceted (structured guidelines, decision support system, reminders, care coordinator) and these elements will be tailored to suit the needs of the individual. Individual randomization is therefore appropriate for personalized care packages. (c) Outcomes (achieving risk factor control targets, quality of care indicators, health-related quality of life and any unforeseen incident events, morbidity and mortality) are all measured at the individual level. (d) Individual randomization, in relative terms, has benefit with respect to the sample size and power derived from this design over cluster randomization, and will minimize bias.
- To avoid contamination between the intervention and control groups, the Research Officer assigned for data collection for control group participants will never meet control group patients in the interim between visits or assist in clinic visits for intervention arm participants. Similarly, the care coordinator will solely manage intervention arm patients and never transfer any information to or meet control group patients.
- The study incorporates low-cost approaches (e.g., use of generic medication and less expensive testing methods) in the algorithm-guidelines for the decision-support management prompts to providers so that the cost of contact with healthcare for the participant is appropriate and not unnecessarily burdensome.
- The EHR-DSS has been designed to be simple, easy-to-use with low-cost features (e.g., text message reminder systems, updates to guidelines, technical support), so that it is suitable for use in developing countries (and South Asia specifically). The trial sites will continue to have access to the EHR-DSS after completion of the trial.
- The study will cover only study-related investigations (baseline, annual, and closeout visits) free of cost. All the investigations and treatment costs in between are borne by the participants as per the norms at the respective clinics. This is to ensure the translation trial resembles real life.

Based on our experience, we caution that although EHR-DSS and non-physician care coordinator models of chronic disease care seems replicable in other LMIC settings, we recommend considering appropriate contextual customization before widespread implementation. From challenges in infrastructure (e.g., clinics might not have reliable internet/computer access) to difficulties in recruitment or availability of clinic resources (e.g., clinic staff, investigators, nurses), we observed that involving local clinic site staff early can help to integrate the model of care into contextual norms and help identify workarounds (e.g., sealed envelope randomization when power is unavailable for the IWRS) to the challenges presented. This trial seeks to maximize the responsibilities of auxiliary health workers (non-physician trained care coordinator) and minimize other clinic resource use. We aim to create an integrated chronic diseases care model that can be translated and

implemented in other clinic settings with minimal influence of the research-specific resources, staff, and investigators.

3.3 Conclusion

Given the continued growth of the diabetes epidemic, integrated CVD risk reduction intervention models to achieve guideline recommended care among high-risk diabetes patients are urgently needed. The CARRS Trial will demonstrate whether an integrated, multi-factorial intervention consisting of EHR-DSS (which simplifies tracking patient's health records) and non-physician care coordinator, is an optimal diabetes care delivery package.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. CARRS Translation Trial Schematic: design, participant flow and study measures
HbA1c=glycated hemoglobin, SBP=systolic blood pressure, LDLc=low density lipoprotein cholesterol, Ht=height, Wt=weight, WC=waist circumference, BP=blood pressure, HR=heart rate, FBG=fasting blood glucose, ECG=electrocardiogram, DSS=decision-support software

Figure 2. Intervention arm: care coordinator functions and electronic health record/decision-support software interactions for patient case-management

txt msg = text message, call = phone call, DSS=decision-support software, EHR= electronic health records, CC=care coordinator

1. CC checks EHR to track which patients have upcoming visits. CC sends reminder (text message or phone call) to patient to visit clinic and get needed lab tests done for visit evaluation.
2. During clinic visit, CC first takes the patient's intake (history, labs, measurements) and enters the information into the EHR to patient-specific DSS prompts.
3. CC takes patient to physician and conveys the patient's status and the treatment DSS prompts to the physician. Physician conducts any exam, updates the plan accounting for the DSS prompts, and provides patient education and needed prescriptions/referrals. The CC updates the response to the DSS prompts (accepted or rejected) and treatment plan in the EHR, including any reminders to schedule.
4. CC checks EHR to track and send patient reminders for referrals, lab tests, or pharmacy.

5. CC checks EHR to track and send patient reminders for self-care and motivation.

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Table 1
Study measures and correlating data collection source for CARRS Translational Trial
collected at baseline, every 12 months, and close-out

Study Measure	Details	Data collection source
Demographics (only baseline)	age, sex, education, occupation, income, language, religion	EHR
History (only baseline)	medical, family CVD/diabetes history	EHR
Medications	glucose/blood pressure/lipid lowering, and others	EHR
CVD risk-factors (behavioral)	adherence to diet, exercise, blood-glucose testing, medications, foot care; tobacco use; alcohol use; stress level (modified SDSCA) [34]	EHR
CVD risk-factors (biochemical)	FBG, HbA1c, BP, lipid profile (every 12 mo)	EHR
Anthropometrics	weight, height, waist circumference	
Care processes (provider-patient cross-check)	preventive screenings (eye-dilated pupil funduscopy, foot/neurological exam, urine-albumin:creatinine ratio, heart-ECG & heart/lung exam)	EHR
	prescriptions for CVD risk factor control (glucose, BP, and lipid-lowering meds) and prevention (ASA, ACEi/ARB use); diabetes education; follow-up information	EHR
	frequency of: visits, FBG/HbA1c/lipid/BP testing, preventive screenings, diabetes education, dental exam	EHR
Adverse events	hospitalizations, ER visits, out-patient visits, surgery/revascularization, limb amputation, infections, * renal failure/dialysis/transplant	EHR, (AE/SAE)
Patient-centered outcomes	Short quality of life (EQ5D) [35], general quality of life (HUI-3) [36], treatment satisfaction (DTSQ) [37]	EHR
Sustainability/acceptability	physician perspectives of trial	Qualitative interview
Cost-effectiveness	out-patient and in-patient costs of care from patients and provider/clinic	eCRF & clinic records

ACEi=ACE-inhibitor; AE/SAE=adverse event, serious adverse event; ARB= Angiotensin Receptor Blocker; ASA=aspirin; BP=blood pressure; ECG=electrocardiogram; FBG=fasting blood glucose; HbA1c=glycated hemoglobin; SDSCA=Summary of Diabetes Self-Care Activities; EQ-5D = European Quality of Life 5 Dimensions; HUI-3 = Health Utility Index Mark 3; DTSQ = Diabetes Treatment Satisfaction Questionnaire; eCRF=electronic case report form (specific forms in EHR); B=baseline

* *Infections to capture:* UTI, skin infections, lower respiratory tract infections/physician-diagnosed pneumonia; any serious infections requiring hospitalization and/or parenteral antibiotics