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TITLE

CHOLESTABETES Quality Enhancement Research Initiative (QuERI) in the Dyslipidemia Management Strategy Involving Combination Therapy in High Risk Patients who have not achieved LDL targets recommended by the 2012 CCS Lipid Guidelines and the Lipid Chapter of the 2013 CDA Guidelines.

CHOLESTABETES Program: **CHOLEST**erol lowering in type 2 di**ABETES**

Protocol CHRC 2014

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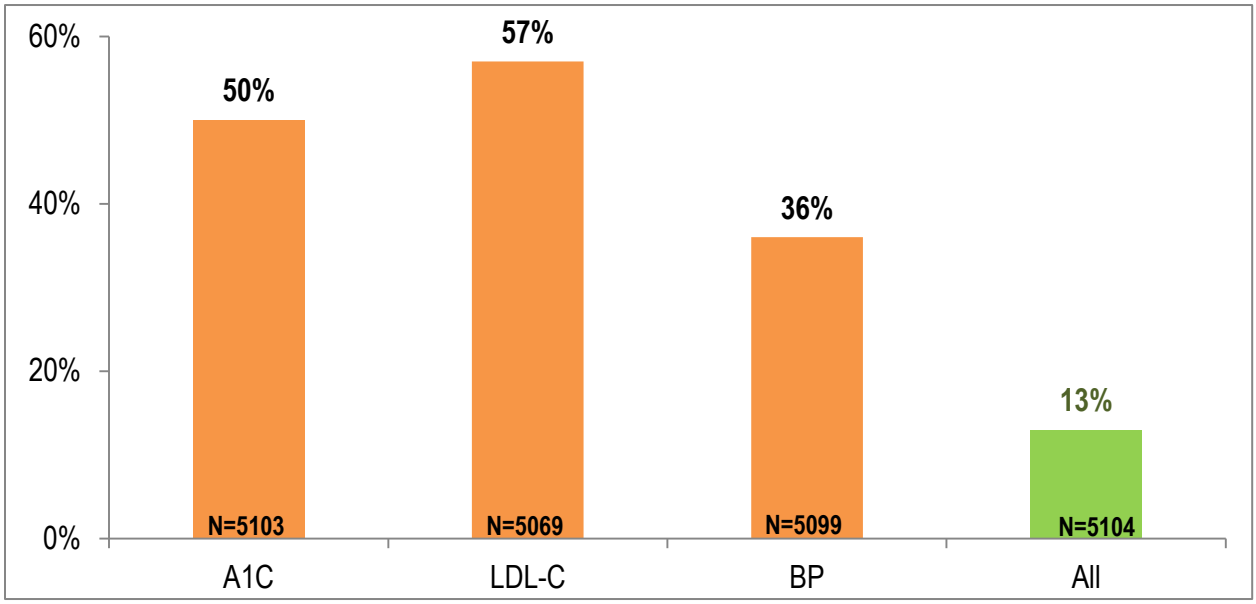
CHOLESTABETES PROGRAM SYNOPSIS

TITLE	CHOLESTABETES Quality Enhancement Research Initiative (QuERI) in the Dyslipidemia Management Strategy Involving Combination Therapy in High Risk Patients who have not achieved LDL-C targets recommended by the 2012 CCS Lipid Guidelines and 2013 Lipid Chapter in the CDA Diabetes Guidelines **CHOLESTABETES** Program: **CHOLEST**erol lowering in type 2 di**ABETES**
PROGRAM DESCRIPTION	Observational quality enhancement initiative – provides guideline-based management strategies and feedback to physicians caring for patients who have not yet achieved guideline-recommended LDL-C and A1C targets in patients with T2DM. The decision to follow the recommendations are left to the physician's discretion; once decision to achieve Guidelines recommended target is made, the physician is offered to follow an evidence based algorithm in the dual achievement of LDL-C targets with combination strategies and A1C targets through optimization of metformin therapy.
PRIMARY OBJECTIVE	**To access the impact of combination therapy and A1C optimization algorithm strategies in achieving dual LDL-C and A1C targets in patients with T2DM after 24±6 weeks**
SECONDARY OBJECTIVES	1. To compare the percent of patients achieving the LDL-C target after 24±6 weeks of treatment optimization 2. To compare the percent of patients achieving the A1C target after 24±6 weeks of treatment optimization 3. To evaluate the safety and tolerability of LDL-C lowering combination therapy 4. To evaluate the safety and tolerability of A1C optimization therapy 5. To compare the impact of earlier initiation of combination therapy on time to achievement of LDL-C and A1C targets and on the proportion of patients achieving LDL-C and A1C target at Visit 2 and Visit 3 6. To assess the association between treatment and changes in other lipid fractions (TC, TG, HDL-C and non HDL-C) during the 24±6 week period 7. To assess A1C response in relation to use of once daily metformin therapy
PROGRAM DESIGN AND DURATION	This is a multi-center program conducted over 24±6 weeks. "High-risk" patients with type 2 diabetes, not at LDL-C or A1C target despite optimal statin and metformin therapy, will be enrolled. Eligible patients that agree to participate will be treated in order to achieve the recommended target for LDL-C and A1C providing that this treatment is in the best interest of the patient.
PATIENT POPULATION	Approximately 375 eligible patients will be enrolled in the program by approximately 75 participating physicians. Eligible patients will include both male and female adults with a diagnosis of hypercholesterolemia and diabetes who are defined as being "high-risk" (40 years of age or older or younger than 40 with other sources of risk as per the CDA Guidelines) Patients will be included if they are not at target for LDL-C (≥ 2.0 mmol/L) and not at target for A1C (≥ 7.0% and <9.0%) while on: a. Optimal Statin therapy (e.g. Atorvastatin ≥ 20 mg, Rosuvastatin ≥ 10 mg, Simvastatin ≥ 40 mg) b. Optimal Metformin therapy (e.g. ≥ 1500 mg / day)
MEDICATIONS	Patients will be prescribed commercially available medications by their physicians according to a treatment strategy which they have been randomized to and which they believe is in the best interest of the patient and in compliance with the 2012 CCS Lipid and the Lipid Chapter of the 2013 CDA Guidelines.

PROGRAM BACKGROUND AND OVERVIEW

Lowering of the total and LDL cholesterol (LDL-C) has been shown to be the key step in lowering the risk of cardiovascular morbidity and mortality in patients at risk [1]. Despite clear guidelines for the targets for achieving LDL-C [2, 3], up to 50% of high-risk patients continue to not be at target [4-6] and may therefore benefit from further optimization of their therapy.

Recent survey by the Canadian Heart Research Centre [6] among 479 Canadian physicians involving over 5,000 patients with type 2 diabetes mellitus has revealed an even greater care-gap in the comprehensive care of high-risk patients whereby only 13% of patients achieved a triple target of glycemic, LDL-C, and blood pressure control (Figure below).



Given these data and the need for greater control of these risk factors, this program aims to identify challenges Canadian physicians experience in managing patients with diabetes and to provide the decision making support to the physicians in their desire to achieve guidelines recommended targets.

This program is an observational prospective registry of high-risk patients with diabetes complemented by knowledge translation through clinical decision making support imbedded into the electronic case report form. Thus, this program is a quality enhancement research initiative (QuERI) with two parallel streams: knowledge translation to achieve quality of care enhancement and data collection on challenges faced by Canadian physicians as part of the research initiative.

The program will emphasize guideline-based management strategies through feedback to physicians caring for patients who have not yet achieved guideline-recommended LDL-C and A1C targets in patients with diabetes. The decision to follow the recommendations is left to the physician's discretion. Once a decision to achieve Guidelines recommended target is made, the physician may then choose to follow an evidence based algorithm in the dual achievement of LDL-C and A1C targets utilizing treatment combination strategies.

PROGRAM OBJECTIVES

Primary Objective:

- To assess the impact of combination therapy and A1C optimization algorithm strategies in achieving dual LDL-C and A1C targets in patients with T2DM after 24±6 weeks.

Secondary Objectives:

1. To compare the percent of patients achieving the LDL-C target after 24±6 weeks of treatment optimization
2. To compare the percent of patients achieving the A1C target after 24±6 weeks of treatment optimization
3. To evaluate the safety and tolerability of LDL-C lowering combination therapy
4. To evaluate the safety and tolerability of A1C optimization therapy
5. To compare the impact of earlier initiation of combination therapy on time to achievement of LDL-C and A1C targets and on the proportion of patients achieving LDL-C and A1C target at Visit 2 and Visit 3
6. To assess the association between treatment and changes in lipid profile (TC, TG, HDL-C and non HDL-C) during the 24±6 -week period
7. To assess A1C response in relation to use of once daily metformin therapy.

PROGRAM DESIGN AND DURATION

This is a multi-center, management-oriented program conducted over 24±6 weeks. High-risk patients, not at LDL-C or A1C target despite optimal statin and metformin therapy will be enrolled.

Participating physicians will enroll patients meeting all inclusion criteria and having none of the exclusion criteria at Visit 1 (Screening). Eligible patients that agree to participate and sign an informed consent will be treated according to their physicians in order to achieve the recommended target for LDL-C and A1C providing that this treatment is in the best interest of the patient.

After enrollment there are two additional time frames where data will be captured as part of routine patient care: 14±6 weeks and 24±6 weeks and only when the repeat blood work is performed and is available prior to Visit 2 and Visit 3 as per Canadian guideline recommendations. The patient may be seen as often as clinically required by their physician.

All patients will have vital signs measured and lab values reviewed at Visit 1 (Screening/ Baseline) and treatment optimized. At Visit 2 (14±6 weeks) patients with LDL-C > 2.0 mmol/L will be treated in order to achieve the recommended target of LDL-C <2.0 mmol/L and A1C target providing that this treatment is in the best interest of the patient. At the final Visit 3 (24±6 weeks) patients with LDL-C >2.0 mmol/L will be treated in order to achieve the recommended target of LDL<2.0 mmol/L and A1C targets (as per the CDA guidelines) providing that this treatment is in the best interest of the patient. Following Visit 3 physicians will continue to treat these patients according to their best clinical judgment.

PATIENT POPULATION

Approximately 375 eligible patients across Canada will be enrolled in the program by approximately 75 participating Canadian physicians.

Inclusion Criteria (all of the criteria must be present):

1. Male and female patients older than 18 years of age
2. Diagnosis of hypercholesterolemia and type 2 diabetes mellitus (CDA definition)
3. High risk for cardiovascular disease defined as one of:
    - 10-year risk of cardiovascular event ≥20% based on the Framingham risk score
    - Prior diagnosis of CAD (PCI, CAMG, MI, stenosis > 50% on angiogram)
    - Prior diagnosis of CeVD (TIA, CVA, Carotid disease on ultrasound > 50%)
    - Prior history of abdominal aortic aneurysm surgery
    - Prior history of PAD (AFB, stent, or ABI <0.7 with symptoms of intermittent claudication)
4. LDL-C > 2.0 mmol/L despite on optimal statin therapy (e.g. Atorvastatin ≥ 20 mg, Rosuvastatin ≥ 10 mg, Simvastatin ≥ 40 mg)
5. A1C > 7% and < 9% on optimal metformin therapy (e.g. ≥ 1500 mg / day)
6. Patient's Consent to participate

Exclusion Criteria (none of the criteria present)

1. Patients with clinically significant concomitant illness or co-morbid condition (e.g. cancer)
2. Liver, muscle or kidney abnormalities (e.g. compromises patient management according to physician)
3. Secondary causes of hypercholesterolemia (e.g. hypothyroidism, nephrotic syndrome)
4. Contraindications or intolerance to combination therapy

PROGRAM STEPS

Participating physicians will be provided a feedback on the results of their management at the time of their completion of the e-CRF during or following the scheduled visits. The feedback will be based on available guidelines, published data and clinical rationale.

Clinical rationale for LDL-C and A1C reduction management will be based on calculation of an average expected LDL-C reduction with each step and includes considerations of:

- statin dose,
- niacin effect on worsening glycemia,
- fibrates lack of effect on lowering LDL-C
- colesevelam and ezetimibe effect on lower LDL-C to similar degree and colesevelam additional effect on lowering A1C

Visit 1

Visit 1: Management Considerations when LDL-C is not at target

1. Add colesevelam or ezetimibe based on the clinical rationale

Visit 1: Management Considerations when A1C is not at target

1. Consider trying to increase adherence by switching to Glumetza (once daily metformin) if relevant
2. Increase metformin dose if on < 2000 mg
3. Consider adding another agent: *Acarbose, Basal Insulin, Colesevelam, DPP-4 inhibitor, GLP-1 Receptor Agonist, SGLT2 Inhibitor, Sulfonylurea, Thiazolinedione*

Visit 2

Visit 2: Management Considerations when LDL-C is not at target

1. Add colesevelam or ezetimibe based on the clinical rationale

Visit 2: Management Considerations when A1C is not at target

1. Switch to once daily Glumetza
2. Add another agent: *Acarbose, Basal Insulin, Colesevelam, DPP-4 inhibitor, GLP-1 Receptor Agonist, SGLT2 Inhibitor, Sulfonylurea, Thiazolinedione*

Visit 3

Visit 3: Management Considerations when LDL-C is not at target

1. Add colesevelam if not already on it
2. Add ezetimibe if not already on it

Visit 3: Management Considerations when A1C is not at target

1. Ensure patient is on 3 antihyperglycemic agents maximized for adherence:

PROGRAM DATA AND TIMELINES

Program data points are summarized in the Table below.
All of the program data points may not be available.

Program Data Points			
Evaluation	**Visit 1**	**Visit 2**	**Visit 3**
1. Informed Consent	x		
2. Eligibility verification	x		
3. Patient ID assignment	x		
4. Demographics (age, gender)	x		
5. Functional Assessment / Symptoms	x	x	x
6. Co-morbidities and Medical History	x		
7. Vital signs including body weight	x	x	x
8. Medications to date	x	x	x
9. Cholesterol panel	x	x	x
10. Glycemic assessment	x	x	x
11. Other Lab Values if abnormal • AST • ALK PHOS • Creatinine • e-GFR • ACR	x	x	x
12. New prescription	x	x	x

INFORMED CONSENT AND ETHICS

This PROGRAM is to be conducted according to globally accepted standards of Good Clinical Practice (International Committee on Harmonization guidelines, May 1996), US 21 CFR Part 50 – Protection of Human Subjects, and Part 56 – Institutional Review Boards, the Declaration of Helsinki and all local regulations.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for all formal approval of the program conduct. The decision of the EC/IRB concerning the conduct of the program will be made in writing to the Investigator and a copy of this decision will be provided to the Canadian Heart Research Centre (CHRC) before commencement of this program.

The program will not be monitored by regular site visits and telephone calls to the Investigator by the CHRC or its representatives.

INFORMED CONSENT FORM (ICF)

Before they agree to participation in this program, all patients will be provided with sufficient information in the form of an Informed Consent. This document will be submitted for approval to the EC/IRB along with the protocol. A statement of approval should be provided before commencement of the program.

The formal consent of all patients must be obtained (whether written or witnessed, according to the local regulations) before they undergo any program-specific procedures.

The ICF will be approved by the same IRB that approves this protocol. Each ICF will comply with the Health Canada regulations and local regulatory requirements. The patient will receive a copy of the signed informed consent form; the original shall be kept on file by the investigator.

SAFETY ASSESSMENT

Only approved and marketed medications will be recommended or used by the physicians participating in this program. Accordingly, completion and reporting of any adverse or serious adverse events will be left to the discretion of the practicing physician and in accordance with local provincial and federal regulations.

STATISTICAL ANALYSIS

The data entered will be validated according to pre-specified validation plan as part of quality assurance/ quality control. Descriptive analysis of demographic variables, physical exam, medical history and treatment profile will be performed for baseline and each observation as appropriate. Continuous variables will be summarized as median and interquartile range (IQR) and categorical variables as absolute frequency and proportion (n[%]). Confidence Intervals (95%) will be calculated for descriptive and comparative purposes. The association between prespecified end-points and recorded variables will be assessed using multivariable logistic regression analysis. A multivariate analysis will be utilized to assess the impact of treatment on primary outcome.

The sample size of 375 patients will allow an initial assessment of the feasibility of this approach towards supporting the physicians' decision making.

RECORDS, REPORTS AND POLICY

The CHRC will provide a program document binder for all required documents and a checklist of all records to be retained.

All information about the program is considered confidential, including the clinical protocol, case-report forms, and information developed during the conduct of the program. This confidential information shall remain the sole property of the CHRC, shall not be disclosed to others without prior consent from the CHRC, and shall not be used except in the performance of this program.

To allow the use of the information derived from this program and to ensure compliance with current regulations, participating physicians must provide the CHRC with complete test results and all data developed in this program within 30 days of completion of 6 month follow up of enrolled patients. The information obtained during this program may be made available to other physicians conducting similar studies and to the Therapeutics Protection Directorate of Canada and the United States Food and Drug Administration or other regulatory agencies.

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this program will be maintained by the participating physicians and made available for direct inspection by authorized persons. Investigator(s)/institution(s) will permit program-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons.

The participating physician will ensure that the program center file is maintained as required by applicable local regulations.

REFERENCES

1. Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. Lancet 2005;366:1267-78.

2. Anderson, Todd J. et al; 2012 Update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult Canadian Journal of Cardiology , Volume 29 , Issue 2 , 151 – 167

3. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2013;37(suppl 1):S1-S212.

4. Yan AT, Yan RT, Tan M, et al. Contemporary management of dyslipidemia in high-risk patients: targets still not met. Am J Med 2006;119:676-83.

5. Hackam DG, Leiter LA, Yan AT, et al. Missed opportunities for secondary prevention of cardiovascular disease in Canada. Can J Cardiol 2007;23:1124-30.

6. L.A. Leiter et al; Canadian Journal of Diabetes, vol. 37, 2013, p. 82-89.