Management of Diabetes Following Acute Coronary Syndrome: Residual Cardiovascular Risk

PROGRAM GOAL

The goal of this program is to expand knowledge and awareness of the residual risks of cardiovascular disease following an acute coronary syndrome (ACS) event unique to patients with diabetes. This program will address knowledge, performance and competence gaps in the management of these patients by cardiologists, and educate cardiologists on how current and future treatment options may improve reduction of the residual risks of cardiovascular disease (CVD) in this patient population.

PROBLEM STATEMENT

There are a growing number of people in the United States with diabetes; the current estimate is 23.6 million people, 90% with type-2 diabetes. [Stolar 2011; Kaul 2010] Remarkably, CVD is the leading cause of death in this population, responsible for close to 70% of all deaths. [Pourcet 2006] It is not surprising then that among patients hospitalized for acute myocardial infarction (MI), 45% have known or previously undiagnosed diabetes. [Kaul 2010] Yet diabetes remains under-diagnosed. In a recent survey of patients with coronary artery disease (CAD), an oral glucose tolerance test screening uncovered previously undiagnosed diabetes or prediabetes in approximately two-thirds of the patients. [Mellbin 2010]

In ACS patients, diabetes is an independent predictor of secondary events such as reinfarction, heart failure or death. [Kaul 2010] Post-ACS morbidity or mortality attributed to CVD is significantly greater in patients with diabetes than in post-ACS patients without diabetes [Donahoe 2007] Subgroup analyses of several studies have demonstrated the significant negative influence of diabetes on CVD morbidity and mortality following ST-segment elevation MI (STEMI) (GUSTO-1) [Mak 1997] or unstable angina/non-STEMI (UA/NSTEMI) (OASIS). [Malmberg 2000].

These findings have been confirmed in more recent studies. One study (GRACE) demonstrated that hospital-case fatality following ACS was approximately twice as high in patients with diabetes as it was in patients without diabetes. [Franklin 2004] Similarly, inferior long-term outcomes with standard of care were reported in this patient population following meta-analysis of 11 TIMI study group clinical trials: the incidence of mortality was

significantly higher at 1 year following STEMI or UA/NSTEMI in patients with diabetes compared with those without diabetes. [Donahoe 2007]

Despite the significant differences in outcomes demonstrated in these clinical trials, acute and long-term management following ACS in patients with diabetes remains the same as for ACS patients without diabetes. [Donahoe 2007]

One could argue that a contributory factor is the lack of appreciation for the significant contributions diabetes makes to the residual risks of CVD post-ACS. [Personal communication with R Scott Wright, MD. Conference call on 4/20/11. Spire Learning] Cardiologists who manage ACS patients may regard diabetes as a comorbidity associated with hyperglycemia that can be easily controlled by an endocrinologist or diabetologist. [Mellbin 2010] However, the complex pathophysiologies of diabetes and CVD are intricately linked. [Mazzone 2008] Post-ACS outcomes may be improved through the use of pharmaceutical agents with multiple actions that target these risk factors. [Schneider 2006] Optimally, management of the residual risks of CVD in the post-ACS diabetes patient is a responsibility that should be shared by cardiologists and diabetologists. [Leiter 2006]

Our understanding of cardiovascular risk factors has evolved. Over a decade ago the UKPDS 23 study identified five potentially modifiable risk factors for coronary artery disease (CAD): [Turner 1998]

- Elevated low-density lipoprotein (LDL)
- Decreased high-density lipoprotein (HDL)
- Elevated blood glucose
- Elevated blood pressure
- Smoking

Since then, knowledge of the role these CVD risks factors play in diabetes has expanded to include an understanding on a molecular level of how they are directly and indirectly interlinked: [Schneider 2006; Staels 2007; Mazzone 2008; Fruchart 2008; Stolar 2011]

- Impact of diabetic dyslipidemia (elevated LDL and triglycerides, decreased HDL, often with elevated apolipoprotein B and non-HDL cholesterol) on atherosclerosis, arterial compliance and inflammation
- Impact of hyperglycemia on vascular cells (vascular dysfunction/damage) and inflammation

- Effect of chronic subclinical inflammation (systemic and cellular) on atherosclerosis, insulin resistance and impaired carbohydrate metabolism
- Coagulation disorders and impaired fibrinolysis
- Contributions of hypertension to oxidative stresses and atherosclerosis

Gap: Despite identification of risk factors and development of effective pharmaceutical interventions, the elevated incidence of death among ACS patients with diabetes continues. [Libby 2005; Chobanian 2009] Many cardiologists appear to be unaware of the clinical significance of diabetes in ACS patients and its implications for management. [Personal communication with R Scott Wright, MD. Conference call on 4/20/11. Spire Learning] Cardiologists responsible for long-term management of ACS patients with diabetes require knowledge of the complex pathophysiology of diabetes and the unique underlying mechanisms that contribute to the residual risks of CVD. Finally, these clinicians should understand how currently available and future antidiabetic agents target these risk factors.

STATEMENT OF NEEDS

Cardiologists need to recognize the impact of diabetes on residual cardiovascular risks following ACS.

Cardiologists generally regard diabetes as a simple disorder in carbohydrate metabolism. With an increased recognition of the significant impact of diabetes on multiple systems that contribute to cardiovascular disease, cardiologists will have a better appreciation of the need for targeted interventions in their post-ACS patients with diabetes.

Cardiologists need to implement evidence-based treatments that target multiple residual risk factors for CVD in post-ACS patients with diabetes.

Cardiologists typically have not kept abreast of recent developments in pharmaceutical options for the management of diabetes. In the past decade, there have been a number of studies that advanced our understanding of regimens that can reduce residual cardiovascular risks in patients with diabetes and established CVD. By gaining a greater understanding of how specific agents can target CVD risk factors, cardiologists may choose interventions that will improve the outcomes of their post-ACS patients with diabetes.

TARGET AUDIENCE

- Cardiologists

LEARNING OBJECTIVES

At the conclusion of this educational program, participants should be able to:

1. Recognize the impact of residual cardiovascular risks in post-ACS patients with diabetes on CVD morbidity and mortality
2. Realize the residual risk factors for CVD following ACS that are unique to patients with diabetes, and comprehend how they interact to contribute to the progression of CVD.
3. Apply evidence-based multifactorial treatment strategies to reduce the unique risks of CVD in post-ACS patients with diabetes.
4. Assess the potential of future treatments that reduce the risk of cardiovascular morbidity and mortality in patients with diabetes following ACS.

Planning Worksheet Grid

Gap	Type of Gap	Needs That Will Address Gap	Learning Objective(s) That Will Address Gap and Need	Results That Will be Measured	Method That Will be Used
Cardiologists are unaware of the clinical significance of diabetes in ACS patients and its implications for management [Personal communication with R Scott Wright, MD. Conference call on 4/20/11. Spire Learning]	Knowledge, Performance, Competence	Cardiologists need to recognize the impact of diabetes on residual cardiovascular risks following ACS	Recognize the impact of residual cardiovascular risks in post-ACS patients with diabetes on CVD morbidity and mortality	1) Responses to vignette questions regarding the management of post-ACS patients with diabetes 2) Plans to change patient management in their clinical practice	1) Posttest to be completed at end of program 2) Commitment to change assessment to be completed 3 months post-program
			Realize the residual risk factors for CVD following ACS that are unique to patients with diabetes, and comprehend how they interact to contribute to the progression of CVD		
		Cardiologists need to implement evidence-based treatments that target multiple residual risk factors for CVD in post-ACS patients with diabetes	Apply evidence-based multifactorial treatment strategies to reduce the unique risks of CVD in post-ACS patients with diabetes		
			Assess the potential of future treatments that reduce the risk of cardiovascular morbidity and mortality in patients with diabetes following ACS		

PROPOSED AGENDA

10 minutes — Overview of residual cardiovascular risks unique to patients with diabetes following ACS

- Clinical variables that increase residual risk: eg, atherosclerosis in multiple vascular beds (other than coronaries), diabetic dyslipidemia, hypertension, hyperglycemia, chronic subclinical inflammation, coagulation disorders, excess abdominal weight /girth [Mazzone 2008; Bhatt *JAMA* 2010; Anderson *Circulation* 2011;]
- Clinical impact of residual risks in post-ACS patients with diabetes on relative risks (versus patients without diabetes) of all-cause mortality, mortality associated with cardiovascular events or macrovascular morbidities

20 minutes — The mechanistic processes and interrelationships of CVD risk factors that contribute to residual cardiovascular risks in patients with diabetes [Robenson 2005; Schneider 2006; Staels 2007; Mazzone 2008; Fruchart 2008; Judge 2010; Stolar 2011]

- Hyperglycemia: impact on vascular cells (endothelium, vascular smooth muscles), pro-inflammatory cells
- Diabetic dyslipidemia: impact on arterial compliance, activation of inflammation, atherogenic role
- Subclinical inflammation: atherosclerosis, insulin resistance, impaired carbohydrate metabolism, role of adipose tissue inflammation

20 minutes — Evidence-based studies for reducing risks of CVD in post-ACS patients with diabetes

- Recent guidelines for management of cardiovascular risks in patients with diabetes:
  - ACCF/AHA [Anderson 2011]

    - 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [Chobanian 2003]
    - NCEP/ATP III [Grundy 2004]
    - AACE [AACE 2007]
    - ADA [Bloomgarden 2010; ADA 2011]
- Impact of standard of care agents on CVD morbidity and mortality in clinical trials that target CVD risks in patients with long-standing diabetes, diabetes with established CAD or history of CVD events
    - Studies that address diabetic dyslipidemia: 4S [4S 1994], LIPID [Tonkin 1998], AFSAPS/TexCAPS [DOWNS 1999], GDDS [Wanner 2005], CTT [Baigent 2005], TNT [LaRosa 2005], ACCORD [Ginsberg 2010]
    - Studies of glycemic control: SYMPHONY/SYMPHONY 2 [McGuire 2004], ACCORD [Gerstein 2008], ADVANCE [Patel 2008], VADT [Duckworth 2009]
    - Studies of blood pressure control: ADVANCE [Patel 2007], ACCORD [Cushman 2010], INVEST [Cooper-DeHoff 2010]
- Current treatment options with potentially pleiotropic mechanisms that address residual CVD risk in patients with diabetes [Schneider 2006; Opie 2011; Stolar 2011]
    - Metformin, thiazolindinediones, incretins
    - Statins, fibrates
    - Angiotensin inhibitors
    - Antithrombotics

15 minutes	Theoretical, preclinical and clinical bases for future treatment options currently in development that target residual risks of CVD in patients with diabetes • Preclinical studies: a balanced dual PPAR α/γ agonist decreases lipolysis and cytokine production from inflamed adipocytes [Dzyakanchuk 2010] • Impact of PPAR agonists on CVD residual risk factors [Pourcet 2006; Fiévet 2009] • Strategies for the development of PPAR agonists [Cavender *Am J Cardiovasc Drugs* 2010; Cavender *Eur J Cardiovasc Prev Rehabil* 2010] • Dual, balanced peroxisome proliferator-activated α/γ agonists (SYNCHRONY) [Henry 2009; Study NCT01042769 2011]
15 minutes	Interactive case presentations • Post-ACS patient with diabetes and dyslipidemia • Post-ACS patient with diabetes and uncontrolled HbA1C • Post-ACS patient with diabetes and metabolic syndrome
10 minutes	Conclusions and Q&A

Abbreviations
4S: Scandinavian Simvastatin Survival Study
ACCF: American College of Cardiology Foundation
ACCORD: Action to Control Cardiovascular Risk in Diabetes
AACE: American Association of Clinical Endocrinologists
ACS: acute coronary syndrome
ADA: American Diabetes Association
ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study
AHA: American Heart Association

CAD: coronary artery disease
CTT: Cholesterol Treatment Trialists
CVD: cardiovascular disease
GDDS: German Diabetes and Dialysis Study
GRACE: Global Registry of Acute Coronary Events
GUSTO-1: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries
HDL: high-density lipoprotein
INVEST: International Verapamil SR-Trandolapril Study
LDL: low-density lipoprotein
LIPID: Long-Term Intervention with Pravastatin in Ischaemic Disease
MI: myocardial infarction
NCEP ATP III: National Cholesterol Education Program, Adult Treatment Panel III
OASIS: Organization to Assess Strategies for Ischemic Syndromes
REACH: Reduction of Atherothrombosis for Continued Health
SYMPHONY: Sibrafiban Versus Aspirin to Yield Maximum Protection From Ischemic Heart Events Postacute Coronary Syndromes
SYNCHRONY: A Study of Aleglitazar in Patients With Type 2 Diabetes
STEMI: ST-segment elevation MI
TIMI: Thrombolysis in Myocardial Infarction
TNT: Treating to New Targets
UA/NSTEMI: unstable angina/non-STEMI
UKPDS: United Kingdom Prospective Diabetes Study
VADT: Veterans Affairs Diabetes Trial

Listed below are the names of potential faculty.

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