ELSEVIER

Journal of Diabetes and Its Complications 19 (2005) 80–87

Journal of Diabetes and its Complications

Hyperglycemia and its effect after acute myocardial infarction on cardiovascular outcomes in patients with Type 2 diabetes mellitus (HEART2D) Study design

Zvonko Milicevic[a,*], Itamar Raz[b], Krzysztof Strojek[c], Jan Skrha[d], Meng H. Tan[e], John W. Wyatt[e], Scott D. Beattie[e], David C. Robbins[e]

[a]*Eli Lilly and Company, Vienna, Austria*
[b]*Department of Endocrinology, Hadassah Hospital, Ein Kerem, Jerusalem, Israel*
[c]*Department and Clinic of Internal Diseases and Diabetology, Silesian School of Medicine, Zabrze, Poland*
[d]*Department of Internal Medicine, Charles University, Prague, Czech Republic*
[e]*Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, USA*

Received 5 February 2004; received in revised form 17 May 2004; accepted 21 June 2004

Abstract

Objective: Cardiovascular (CV) disease is the major cause of death in patients with diabetes. Up to 40% of patients with Type 2 diabetes mellitus (T2DM) who survive an initial myocardial infarction (MI) suffer a recurrent event within 2 years, the majority of which are fatal. One independent risk factor for cardiovascular disease (CVD) may be postprandial blood glucose (PPBG) excursions. The HEART2D study seeks to determine the effect that PPBG control has on cardiovascular outcomes in patients who suffered an MI within the 21 days before study enrollment. **Research design and methods:** Approximately 1355 patients with T2DM with recent MI will be entered in this multicenter study of about 3.0-year duration. Using infarct severity and peri-infarct treatment as randomization factors, patients will be assigned to one of two insulin treatment strategies: (1) *postprandial strategy*: premeal insulin lispro with basal insulin at bedtime if needed (NPH insulin), targeting 2-h PPBG ≤7.5 mmol/l or (2) *basal strategy*: insulin (NPH insulin twice daily or insulin glargine once daily; or premixed human insulin (70% NPH/30% regular; 30/70) twice daily), targeting fasting and premeal blood glucose (BG; ≤6.7 mmol/l). Both groups will aim for a target hemoglobin AlC (AlC) of <7%. **Anticipated results:** The anticipated difference in PPBG (~2.0 to 2.5 mM) between strategies is expected to demonstrate a 15% to 18.5% relative risk reduction in CV events for the postprandial strategy. **Conclusion:** This study may provide practical insights into the clinical management of patients with diabetes who have an increased risk of recurrent CV events and death.

Keywords: Type 2 diabetes mellitus; Myocardial infarction; Glycemia; Cardiovascular outcomes; Postprandial metabolism; Cardiovascular disease

1. Introduction

Myocardial infarction (MI), stroke, peripheral vascular disease, and cardiovascular (CV) death occur at least two to three times more frequently in patients with diabetes compared with nondiabetic patients with similar risk factors (de Vegt et al., 1999; Haffner, Lehto, Ronnemaa, Pyorala, & Laakso, 1998; Kuller et al., 2000; Stamler, Vaccaro, Neaton,

Abbreviations: Blood glucose (BG); Cardiovascular (CV); Cardiovascular disease (CVD); Cardiac care unit (CCU); Hemoglobin AlC (AlC); Left ventricular ejection fraction (LVEF); Myocardial infarction (MI); Postprandial blood glucose (PPBG); Type 2 diabetes mellitus (T2DM).

* Corresponding author. Eli Lilly Regional Operations, Vienna, Austria. Tel.: +43 1 711 78 236; fax: +43 1 711 78 259.
E-mail address: milicevic_zvonko@lilly.com (Z. Milicevic).

1056-8727/05/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.jdiacomp.2004.06.003

& Wentworth, 2001; Wingard & Barrett-Connor, 1995). CV events contribute to morbidity in approximately 70% of people with Type 2 diabetes mellitus (T2DM; Gu, Cowie, & Harris, 1971). Patients with T2DM and previous MI have the highest risk of mortality and morbidity. These individuals have a higher risk of CV death, nonfatal MI, and stroke when compared with matched, nondiabetic individuals (Haffner et al., 1998; Malmberg et al., 1995).

The increased incidence of cardiovascular disease (CVD) in patients with diabetes cannot be solely explained by classical CV risk factors such as dyslipidemia, smoking, or hypertension (Adler et al., 2000; Koskinen et al., 1992; Lehto et al., 1997; Pyorala et al., 1997). Patients with diabetes suffer increased mortality and CV morbidity even after adjustment for all known risk factors (Kannel & McGhee, 1979). While hyperglycemia seems to be a central pathological marker of diabetes and associated risks, there are no prospective studies showing convincing benefits of lowering blood glucose (BG) on macrovascular disease (Duckworth, McCarren, & Abraira, 2001; The DCCT Research Group, 1993; UKPDS Group, 1983). Previous studies not focused on CV outcomes have had insufficient statistical power to fully investigate this hypothesis. Thus, several fundamental questions of clinical importance remain to be answered. Does a therapy that effectively lowers the total glycemic exposure (i.e., hemoglobin AlC [AlC]) improve overall macrovascular disease outcomes in diabetes independent of other risk factors? Furthermore, do the various components (fasting, preprandial, or postprandial periods) of the daily BG profile carry different risks for chronic complications and macrovascular disease? If so, should these periods of glycemic exposure be treatment targets to minimize the risk of disease progression? If there is a benefit from good glycemic control, must the intervention begin during the acute stages of MI?

In numerous epidemiological studies (Balkau et al., 1998; Rodriguez et al., 1996; Temelkova-Kurktschiev et al., 2000; The DECODE Study Group, 1999a), postprandial blood glucose (PPBG) correlates with the risk of CV complications. The DECODE study showed that postprandial hyperglycemia is an independent risk factor for CVD (The DECODE Study Group, 1999b). Other studies have shown that AlC, as a measure of total glycemic exposure, correlates with the risk of macrovascular complications, but to a lesser extent than PPBG does (Laakso & Seppo, 1998; The DECODE Study Group, 1999a).

The postprandial state in T2DM is characterized by early-phase hypoinsulinemia and reduced clearance of meal-related glucose and fat (postprandial lipemia). Numerous metabolic abnormalities may also occur, including prolonged hyper-free-fatty acidemia, reduced vascular reactivity, production of an oxidative state (Ceriello, 1998), and accumulation of advanced glycation end products (Beisswenger et al., 2001). In addition, postprandial lipemia and large fluctuations in PPBG concentrations may be responsible for other mechanisms contributing to the occurence of complicated CVD (stroke and MI), including transient hypertension caused by adrenergic stimulation (Marfella et al., 2000), abnormalities of repolarization of the myocardial tissue (Marfella et al., 2000), and a hypercoagulatory postprandial state brought about by abnormalities in concentration and/or activity of coagulation factors (Ceriello et al., 1996).

Because both early postprandial hypoinsulinemia and hyperglycemia may be a common pathogenic denominator of these CV abnormalities, restoring near-normal daily insulin concentrations may correct many of these. In the HEART2D study, we will test the hypothesis whether this form of diabetes treatment that targets abnormalities of the postmeal period reduces excess CV mortality and morbidity in patients with T2DM and recent MI.

2. Methods

2.1. Primary objective

The primary objective of the HEART2D study is to demonstrate a difference between two glucose-lowering treatment strategies on the time until the first recurrent event in patients with T2DM (Alberti & Zimmet, 1998) and recent MI. The primary and secondary CV outcomes are shown in Table 1.

2.2. Study design

This study will use an open-label, randomized, two-arm parallel group design. Approximately 1355 patients with T2DM and acute MI will be assigned to receive one of two treatments: preprandial or basal insulin (twice a day neutral-protamine human insulin or once a day insulin glargine). The study consists of the following three periods: (1) entry/lead-in period of approximately 2.5 weeks; (2) randomization; and (3) outpatient follow-up period of at least 1.5 to at least 3.5 years, during which patients will receive one of the two treatments (Fig. 1). Prior to study entry, patients with T2DM will be evaluated according to inclusion and exclusion criteria (Table 2). The ethical review boards of the participating centers approved the protocol and the informed consent document for the study. Patients will be required to give written informed consent to participate, and the study will be conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines.

2.3. Patient entry

Patients with acute MI will enter the study within 18 days after admission to the cardiac care unit (CCU). During the lead-in period, before randomization, patients will be treated with a conventional insulin regimen, including oral antihyperglycemic agents, as determined by the investigator. A dietician will discuss the dietary plan with the patient and