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Insulin provision therapy and mortality in older adults with diabetes mellitus and stable ischemic heart disease: Insights from BARI-2D trial

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ABSTRACT

Importance: Optimal strategies for glucose control in very old adults with diabetes and stable ischemic heart disease (SIHD) are unclear.
Objective: To compare the effects of insulin provision (IP) therapy versus insulin sensitizing (IS) therapy for glycemic control in older (≥75 years) and younger (<75 years) adults with type II diabetes (DM) and SIHD.
Design, setting, and participants: Adults enrolled in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) were studied. The BARI 2D study population (all with type II DM and SIHD) was randomized twice: (1) between revascularization plus intensive medical therapy versus intensive medical therapy alone, and (2) between IP versus IS therapies. The primary endpoint was all-cause-mortality over five-year follow-up. In this substudy outcomes related to IP vs. IS are assessed in relation to age. Adults aged ≥75 years who received IP versus IS are compared to those <75 years who received IP versus IS. Multivariate Cox regression analysis was used to evaluate the effects of IP vs. IS on outcomes in the two age groups.
Results: 2368 subjects with SIHD and DM were enrolled in BARI 2D; 182 (8%) were ≥75 years. Compared to younger subjects, the older cohort had lower BMI, higher diuretic use, worse kidney function, and increased history of heart failure. Within the older cohort, the IP and IS subgroups were similar in respect to baseline cardiovascular risk factors, medications, and coronary artery disease severity. During follow-up, the older subjects receiving IP therapy had higher cardiovascular mortality compared to those receiving IS therapy (16% vs. 11%, $p = 0.040$). Using Cox proportional hazards analysis, the older IP subjects were at increased risk for all-cause-mortality (hazard ratio 1.89, CI 1.1–3.2, $p = 0.020$). No mortality difference between IP and IS was observed in those <75 years of age.
Conclusion and relevance: Among adults with diabetes and SIHD aged ≥75 years, IP therapy may be associated with increased mortality compared to IS therapy. Additional studies are needed to further refine optimal treatment strategies for diabetes and SIHD in old age.

1. Introduction

Older adults represent the fastest growing population in the United States. As of 2010, 15% of individuals age 65 or older had a diagnosis of diabetes mellitus (DM), with an additional 7% likely to be undiagnosed [1]. Furthermore, the number of adults ≥75 years of age with DM is expected to increase by 449% from 2005 to 2050, compared with a 220% increase in adults age 65–74 and a 200% increase in adults <65 years [2–4]. This high burden of diabetes contributes to the high prevalence of coronary heart disease in older adults, and it has been estimated that at least 68% of adults 65 years or older die from some form of heart disease [3]. Better treatment for DM in the older adult population is a vital therapeutic priority.

Contemporary treatment recommendations for DM in older adults remain largely based on expert consensus [5], reflecting a dearth of data from which to establish more definitive principles of care. Prominent differences among advisory groups underscore fundamental

Abbreviations: BARI 2D, bypass angioplasty revascularization investigation 2 diabetes; CABG, coronary artery bypass graft; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; HgbA$_{1c}$, hemoglobin A$_{1c}$; IP, insulin providing; IS, insulin sensitizing; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease.

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uncertainties regarding optimal management strategies. The American Diabetes Association expert consensus for the elderly recommends a lenient Hemoglobin A_{1c} ($HgbA_{1c}$) goal of 7–7.9% [2,6]. The American Geriatrics Society consensus report recommends initiation of pharmacotherapy with $HgbA_{1c} \geq 7.5\%$ for older adults without comorbidities, $HgbA_{1c} \geq 8.0\%$ for those with intermediate/complex comorbidities, and $HgbA_{1c} \geq 8.5\%$ for the extremely frail population with major comorbid conditions [7]. Other organizations developed statements tailoring therapy based on life expectancy, number of co-morbidities, and functional status [5].

To help clarify strategies for optimal care in very old adults with DM and stable ischemic heart disease (SIHD), we studied the population enrolled in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. While BARI 2D focused primarily on the utility of revascularization in addition to intensive medical therapy compared to intensive medical therapy alone for adults with type DM and SIHD, the protocol also randomized subjects between insulin providing (IP) versus insulin sensitizing (IS) therapies. Insulin provision entails various forms of insulin as well as medications that promote insulin secretion (e.g., sulfonylureas and non-sulfonylurea secretagogues) whereas insulin sensitizing medications increase overall efficacy of existing insulin. In this study, we compared the IP vs. IS treatment groups in adults aged ≥75 versus <75 years. All-cause mortality as well as the composite endpoint of death, myocardial infarction (MI), and stroke were assessed. Differences in circulating insulin levels and health status were also evaluated in the IP versus IS treatment groups in relation to age (≥75 vs <75 years).

2. Methods

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study enrolled adults with type II DM and SIHD from January 2001 to March 2005. The complete BARI 2D protocol and the main trial results have been published previously [8,9]. Inclusion criteria included: age ≥25 years; type II DM diagnosed via medical record review or plasma glucose measurements; at least 1-vessel coronary artery disease (CAD) able to be revascularized; documented typical angina with ≥70% stenosis in at least one of the major epicardial arteries or a positive stress test; and good candidates for PCI or coronary artery bypass grafting (CABG). Exclusion criteria included necessity for urgent revascularization; left main coronary artery disease; $HgbA_{1c} > 13.0\%$; fasting triglycerides >1000 mg/dl (in the presence of moderate glycemic control with $HgbA_{1c} < 9.0\%$); chronic steroid use; creatinine level >2.0 mg/dl; New York Heart Association (NYHA) functional class III or IV; hepatic dysfunction; or prior CABG or PCI within the past year [8]. Enrollees underwent coronary angiography, and were then randomized into one of two treatment groups: prompt revascularization (PR) with intensive medical therapy or Intensive medical therapy alone.

BARI-2D subjects were also randomized between IP versus IS therapies. Insulin provision medications included sulfonylurea drugs, repaglinides, and other approved meglitinides and insulin itself. Insulin sensitizing medications included biguanides (metformin) and thiazolidinediones (TZD). $HgbA_{1c}$ was monitored for six years or until December 1, 2008, with <7.0% designated as the target level. HbA_{1c} levels of 7.0–7.4% were considered acceptable provided patients were free of microvascular complications of diabetes, including retinopathy, neuropathy, and/or nephropathy. In addition, HbA_{1c} levels of 7.5–8.0% were considered appropriate for patients who began the study with a significantly elevated HbA1c despite prior management with multiple medications. For each treatment strategy, an algorithm for changes in the treatment regimen was implemented when there was a failure of HbA_{1c} to improve within 1–2 months.

Patients in the IS group could receive IP drugs, and patients in the IP group could receive IS drugs if the glycated hemoglobin level could not otherwise be maintained below 8.0%. Following randomization, patients were seen once a month for the first 6 months and then 4 times per year for the 5-year duration of the study.

2.1. Statistical analysis

Baseline demographic, clinical, and health outcome data were analyzed by age groups (≥75 versus <75 years) and by treatment groups (IP versus IS). Participants were followed for 5 years. Pre-specified clinical outcomes included all-cause mortality, major adverse cardiovascular events (MACE, defined as a composite of death, MI, and stroke), cardiac death, cardiovascular death, and subsequent CABG or PCI. Continuous variables were reported as medians with interquartile range (IQR) and categorical variables as proportions. Comparisons were made using the Wilcoxon rank sum test, Student's *t-test*, and Pearson chi-square test, as appropriate.

Separate Cox regression models were used to evaluate the association of DM treatment strategy with clinical outcomes in the older (≥75 years) cohort. Clinical variables with an association of $p < 0.20$ with mortality were selected and included in the model along with the assigned treatment strategies. These variables include: DM treatment (IP vs. IS), prompt revascularization, significant proximal left anterior descending artery disease, serum creatinine, left ventricular ejection fraction <50%, moderate to strenuous physical activity, and circulating insulin levels. Kaplan-Meier survival analysis and log-rank statistics were assessed within each age group to evaluate the effect of DM treatment (IP vs. IS) on survival. Finally, forward stepwise selection methods with a $p < 0.10$ entry criterion were utilized to create a parsimonious model. Mean (SD) circulating insulin levels (IU/dL) for all individuals randomized to IP versus IS group were calculated at yearly intervals. For longitudinal data analysis, the significance of the change over time was determined based on a p for trend using a random intercept linear mixed effects model [10]. Two-sided p values were considered statistically significant when <0.05. All analyses were performed using Stata 13.0 software (Stata Corporation, College Station, TX).

The institutional review board at the University of Miami approved the study. All data analyses were conducted on the public use datasets obtained from the National Heart, Lung, and Blood Institute BioLINCC data repository.

3. Results

Of the 2368 subjects enrolled in the BARI 2D study, the $HgbA_{1c}$ (median, [IQR]) prior to randomization was 7.3% (6.4, 8.5) with a duration of DM prior to randomization of 8.6 years (3.7, 15.2). Among these subjects, 1176 were randomized to intensive medical therapy plus revascularization, while 1192 were randomized to receive only intensive medical therapy. In addition, 1185 were randomized to IP and 1183 subjects were randomized to IS. At the 3-year follow-up, the most frequently used drugs in the insulin-provision group were insulin (60.7%) and sulfonylurea (52.0%); in the insulin-sensitization group, the most frequently used drugs were metformin (74.6%) and a TZD (62.1%).

Of the 2368 subjects, 182 (8%) were ≥75 years of age. Table 1 summarizes baseline characteristics in the older vs. younger groups. Compared to younger patients, older patients were more likely to have a history of cerebrovascular accident, prior heart failure, reduced ejection fraction, and higher use of diuretics (Table 1). While the distribution of most anti-diabetic drugs at baseline (including TZD, sulfonylureas, and insulin) was similar between younger and older groups, older subjects were less likely to be on biguanide therapy (43% vs. 55%, $p = 0.002$). Older subjects also had longer duration of DM (10 vs. 8 years, $p < 0.001$) and higher median creatinine (1.2 vs. 1.0 mg/dl, $p < 0.001$) (Table 1). The distribution of prompt revascularization with intensive medical therapy vs intensive medical therapy alone was similar by IP vs. IS therapies. There were no differences in use of glucose lowering agents (prior to randomization) by type of diabetes treatment in BARI 2D (Supplementary Table 1). In the entire cohort, there was no difference in mortality between IP vs. IS groups. Age greater than or equal to 75 years was a predictor of mortality (HR 2.6, $p < 0.001$; p for interaction = 0.083). Within the older group, those randomized to IP therapy were more likely to be male, and to have higher use of diuretics, worse kidney function, and higher circulating insulin levels compared to those treated with IS therapy. Measures of baseline physical function, regular exercise, and Duke Activity Status Index were similar by type of diabetes therapy (Table 2).

Within the older cohort, unadjusted comparisons of IP vs. IS treatments showed trends of increased all-cause mortality (41% vs. 29%, $p = 0.083$) and cardiac death (15% vs. 7%, $p = 0.071$). Similarly, within the older cohort IP vs. IS was associated with increased risks of major adverse cardiovascular events (MACE) (53% vs. 38%, $p = 0.045$) and cardiovascular death (16% vs. 11%, $p = 0.040$). However, there were no significant differences between IP vs. IS with respect to need for CABG, PCI, or subsequent procedures (Supplementary Fig. 1; Supplementary Table 2).

Unadjusted Cox proportional hazards analysis among subjects ≥75 years also showed a trend towards increased risk for all-cause mortality in the IP vs. IS groups (hazard ratio [HR] 1.65, confidence interval [CI] 0.99–2.72, $p = 0.050$). Other univariate predictors of increased mortality risk were left ventricular ejection fraction (LVEF) <50% (HR 2.78, CI 1.66–4.67, $p < 0.001$) and serum creatinine (HR 2.87, CI 1.26–6.51, $p < 0.011$). After multivariable adjustment, a step-wise forward regression model showed that both IP (HR 1.89, $p = 0.020$), serum creatinine

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