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# Control of Lipids at Baseline in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial

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## Abstract

In order to examine lipids, a major treatment goal in those with diabetes and heart disease, we analyzed baseline data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial. The study consists of 2,368 participants with Type 2 diabetes and coronary artery disease from 49 sites in 6 countries (2295 provided lipid measurements). Fifty-nine percent of participants had a LDL cholesterol <100 mg/dl. Total, LDL, and non-HDL cholesterol and triglycerides differed by age group (<55, 55–64, and 65+ years), being lowest in the 65 years old. Women had higher total, LDL, and non-HDL cholesterol. Education was associated with lower total, LDL, and non-HDL cholesterol. LDL cholesterol and triglycerides were lower in the USA and Canada. Adjustment for age, gender, education, randomization year, and medication did not eliminate these differences. Geographic variation was seen which was not fully accounted for by demographic or treatment characteristics (all p values <0.05).

## I: Introduction

The prevalence of diabetes (especially type 2 diabetes as the most common form, with 90% of persons with diabetes) is increasing dramatically (1) and creates a great challenge in terms of cardiovascular disease morbidity and mortality as rates are increased by two to five fold compared to the general population (2–3). Also of concern is the higher one-year post myocardial infarction (MI) mortality rate associated with diabetes, with some studies (4) noting

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a risk of death for post MI diabetes patients as high as 2-fold or greater. The seven-year rate of MI (fatal and nonfatal) for diabetic patients with previous MI has been reported to be 45% or over 2 times the reinfarction rate for nondiabetic patients (3).

Dyslipidemia, especially an elevated low-density lipoprotein (LDL-C), is a widely recognized major risk factor for coronary atherosclerosis and type 2 diabetes is associated with a particular lipoprotein pattern known as diabetic dyslipidemia. This pattern consists of an elevated triglyceride and reduced high density lipoprotein (HDL-C) value (5). While the LDL-C concentrations are often similar to those found in the rest of the population, the number of small dense particles is increased (6).

In recent years, several primary and secondary prevention clinical trials, utilizing varying hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), have been conducted to specifically examine the impact of modifying lipoproteins on the incidence and recurrence of cardiovascular disease (CVD). Favorable subgroup analyses for those with diabetes have been reported from a number of studies (7–8). Furthermore, the Collaborative Atorvastatin Diabetes Study (CARDS) (8), which focused on those with type 2 diabetes, demonstrated a 37% reduction in coronary mortality or first cardiovascular event for those randomized to statin therapy versus placebo. Conversely, the ASPEN trial (9), which randomized subjects with type 2 diabetes to atorvastatin 10 mg or placebo, did not find a significant reduction in the primary cardiovascular endpoint.

Given the high risk of recurrent events for diabetic subjects with heart disease, the National Cholesterol Education Panel (NCEP) Adult Panel III (ATP III) in 2004 has suggested a LDL-C goal as low as 70 mg/dl (1.8 mmol/L) (10). However, the management of dyslipidemia has been reported to be sub-optimal (11). In order, therefore, to gain further insight into the level of control in those with diabetes and angiographically documented stable coronary artery disease for which revascularization is not required for prompt control of severe or unstable angina, we have examined baseline data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. This trial was designed to determine the optimal treatment strategy (insulin provision versus insulin sensitization; early revascularization plus aggressive risk factor control (dyslipidemia, hypertension, smoking, and obesity) versus aggressive risk factor control alone) for patients with type 2 diabetes and documented stable coronary artery disease (CAD) in the setting of glucose management targeted at HbA1c < 7.0%. Major objectives of this report were to describe lipid concentrations and control by key demographic groups (age, gender, country, and education) and determine to what extent the country differences are explained by use of lipid-lowering medication.

## II: Methods

The BARI 2D protocol has been previously described in detail (12). Recruitment began on January 1, 2001 and ended on March 31, 2005. Participants had to have type 2 diabetes and ischemic heart disease. The study population consists of 2,368 participants from 49 clinical sites in six countries. The expected mean follow up is ≥3.8 years. Participants range in age from 34 to 90 years. All participants signed an institutionally approved informed consent form before randomization. In accordance with the National Institutes of Health's strong commitment to enrolling minorities in clinical trials, BARI 2D aimed to recruit ≥30% of the trial participants from minority populations. Minorities represent 40% of the USA participant cohort.

Of the 2368 randomized patients, 2295 (96.9%) had some lipid measurement from the BARI 2D Biochemistry Core Laboratory and were considered for this analysis. Basic demographic data were missing for 11 participants, and lipid therapy at baseline could not be obtained for

five other participants. An additional two participants had complete data, but were considered ineligible for this analysis due to their triglycerides exceeding 1000 mg/dl (11.2 mmol/L) in the presence of moderate glycemic control (HbA1c <9.0%) to be consistent with BARI 2D entry criteria. Of the remaining 2277 participants, seven did not have a HDL-C value and an additional 113 with triglycerides >400 mg/dl (> 4.5 mmol/L) did not have a calculated LDL-C value. Thus, 2157 participants with a LDL-C value, 2277 with a triglyceride value, and 2270 with a HDL-C value were included in this analysis. Availability of HDL-C data also allowed for the analysis of nonHDL-C, defined as total cholesterol minus HDL-C, and for the analysis of total cholesterol/HDL-C ratio in the same group of 2270 participants.

### Recruitment and Eligibity Criteria

Investigators in 46 clinical sites throughout North America (USA, Canada, Mexico), one in South America (Brazil) and two in Europe (Austria, Czech Republic) identified type 2 diabetes subjects aged 25 years and older by one of the following: confirmed (≥2 readings) fasting plasma glucose >125 mg/dl; random plasma glucose ≥200 mg/dl; plasma glucose ≥200 mg/dl 2 hours following ingestion of 75 g of glucose; current treatment with diet or oral agents for control of hyperglycemia; or current treatment with insulin and no previous history of ketoacidosis. A list of participating investigators is provided in Appendix A. Investigators were encouraged to obtain testing for C-peptide or proinsulin and for antibodies to glutamic acid decarboxylase, if a type 1 diagnosis was suspected. In addition to a diagnosis of type 2 diabetes, eligible patients must have had documented cardiac ischemia (or typical angina and ≥70% coronary stenosis) and at least one coronary vessel amenable to revascularization. Major exclusion criteria included definite need for prompt invasive intervention as determined by attending cardiologist; prior CABG or prior catheter-based intervention within the past 12 months; class III or IV congestive heart failure (CHF); creatinine >2.0 mg/dl; HbA1c >13% or a need for major vascular surgery concomitant with revascularization.

**Laboratory Analysis—**At baseline in BARI 2D, following a minimum fast of eight hours, blood for a fasting lipid profile was collected, processed for serum and frozen locally, and then sent to the Biochemistry Core Laboratory at the University of Minnesota, Minneapolis (Appendix B). The sera were analyzed for total cholesterol (TC), HDL-C, triglycerides, and calculated LDL-C. Cholesterol and triglycerides were analyzed enzymatically (13–14), while HDL-C was assayed after removal of Apo B containing lipoproteins by $Mg^{2+}$ and dextran sulphate (15). The calculation of estimated LDL-C requires the direct measurement of TC, triglycerides and HDL-C utilizing the Friedewald formula (16). Austria, one of the two Bari 2D European study sites, was not included in this analysis due to the absence of Core Lab lipid data (requirement for inclusion in this analysis).

## III: Statistical Analysis

In comparing lipid values across demographic groups, *t*-tests and ANOVA (with Bonferroni correction for multiple comparisons), where appropriate, were used to assess statistical significance. All proportions were compared with chi-square tests of general association. Pearson product-moment correlation coefficient was utilized to determine the association between lipid value and age. The simultaneous association of several demographic and clinical variables with individual lipid parameters was analyzed with standard linear regression models. Triglyceride values were log transformed and all analyses performed on the transformed variable. SAS version 9 was used for all analyses.

## IV: Results

The baseline lipid profiles of the BARI 2D participants, stratified by age group, gender, post menopausal hormone use, education level, and country are presented in Table 1. When

stratified by age, there was a significant decreasing trend in TC, LDL-C, triglycerides, non-HDL-C and an increasing trend in HDL-C, men-only, with increasing age strata ($p<0.01$). Significant negative correlations between each lipoprotein and age (with the exception of HDL-C in men, which was positively correlated) were seen. Women have significantly higher TC, LDL-C, and non-HDL-C concentrations than men ($p<0.01$), but there was no significant difference in triglyceride concentrations by gender. Lipoprotein concentrations were not significantly different by menopausal status (data not shown), but women using post menopausal hormone therapy, as expected, had significantly higher HDL-C concentrations ($p<0.01$).

Table 1 also shows the lipid characteristics according to educational level. Those participants with a high school or greater education had significantly lower TC, LDL-C, and non-HDL-C concentrations when compared with participants who did not finish high school. Triglyceride and HDL-C concentrations were similar. Although use of statin medications did not differ by age and gender, participants with a high school or greater education were significantly more likely to be taking a statin ($p<0.05$) or any lipid medication ($p<0.01$).

Lipoprotein profiles and use of lipid medications varied significantly by country (Table 1). The USA and Canada had significantly lower TC, LDL-C, and non-HDL-C ($p<0.05$) than Brazil, and the Czech Republic. The TC and LDL-C values in Mexico were similar to their North American neighbors, but non-HDL-C values were higher ($p<0.05$). Czech Republic and Mexico had significantly higher triglyceride concentrations ($p<0.05$). HDL-C concentrations were similar for women (~41 mg/dl) in all countries, but Canadian men had significantly higher HDL-C concentrations than their counterparts in the USA, Brazil and Mexico ($p<0.05$). Medication usage also differed by country, with participants in the USA, Canada, and Brazil significantly more likely to be taking a lipid lowering medication, especially a statin, than participants in Mexico and the Czech Republic ($p<0.05$).

Table 2 compares BARI 2D participants at baseline, stratified by country, to their country's current guidelines for treating hypercholesterolemia in patients at high risk for cardiovascular disease. Overall, 59% had a LDL-C <100 mg/dl (<2.6 mmol/L) and 51% had triglycerides below 150 mg/dl (<1.7 mmol/L). Greater than 50% of participants in the USA, Canada, and Mexico met their respective country's LDL-C goal of <100 mg/dl (<2.6 mmol/L)(10, 17–18), while fewer than 50% of participants in Brazil and the Czech Republic met their recommended goals (19–20). Mean triglyceride values, regardless of country, were generally above the recommended values (21). Canada had the highest percentage of participants at or below goal (53%), while Mexico and the Czech Republic had the lowest percentage of participants (33%, 28% respectively) at the recommended values (21).

Of those on lipid-altering medications, 67% (n=1093) had a LDL-C <100 mg/dl, while 33% (n= 539) had a value above 100 mg/dl despite treatment. Twenty-four percent (n=525) of participants were not taking a lipid medication at baseline and of those, only one-third had a LDL-C value <100mg/dl.

The results from four separate stepwise linear regression models with LDL-C, triglycerides, HDL-C, and non-HDL-C as the dependent variables are presented in Table 3. This analysis was performed to determine if age, gender, medication, education, country, and year of randomization were independently associated with baseline lipid values. Age is expressed in decades and education is defined as less than high school or greater than or equal to high school. Country is categorized as USA/Canada versus others and the year of randomization as 2001/2002, 2003, or 2004/2005. Medication usage was specific to the lipoprotein disorder: LDL-C – statin, niacin, bile acid resin, cholesterol absorptive inhibitor versus other or no medication; triglycerides – fibrate, omega-3 fatty acid, niacin versus other or no medication;

HDL-C – niacin, statin, fibrate versus other or no medication; non-HDL-C – any lipid medication versus no lipid medication.

Older age, male sex, use of LDL-lowering medication, living in the USA or Canada, and being randomized in 2004/2005 compared to 2001/2002 were all associated with having lower LDL-C concentrations at baseline. The use of LDL-lowering medication produced the biggest effect ($R^2$ change 7.8%) after allowing for the effect of age and gender. In addition, it was the most significant covariate and associated with a 21 mg/dl difference in LDL-C concentrations. Beyond age, gender, and medication, there remains an effect of country and being randomized in 2004/2005, but the effect is smaller. Non-HDL-C showed similar results, but the effect of medication was diminished ($R^2$ change 3.9%). As expected, gender produced the biggest effect with HDL-C ($R^2$ change 9.1%), with HDL-specific medication having essentially no effect. Older age and being randomized in 2001/2002 was also associated with a higher HDL-C, but to a much lesser extent than gender.

Age and country were negatively associated with triglyceride value, indicating those participants who were older and lived in the USA/Canada had lower baseline triglycerides. Triglyceride-lowering medication was positively associated with baseline triglyceride concentrations, suggesting that those participants with the highest triglyceride concentrations were prescribed the triglyceride-lowering medication. Being randomized in 2004/2005 was also associated with higher triglycerides, but the association only reached borderline significance ($p<0.07$). Education level had no independent effect on lipoprotein concentrations. The total $R^2$ was low for each lipid variable indicating a large degree of unexplained variation.

Table 4 examines the LDL-C, triglyceride and HDL-C values by use of thiazolidinedione (TZD) medication (rosiglitazone or pioglitazone) stratified by concurrent statin use. Among those participants not taking a statin at baseline, TZD use was associated with higher LDL-C and non-HDL-C values. Multiple comparison analysis noted the significant differences between the Non TZD and Rosiglitazone groups ($p<0.05$). There was no difference between the Non TZD and Pioglitazone groups or the Rosiglitazone and Pioglitazone groups. This effect was not apparent in statin users.

Finally, to determine if the age effects described earlier were consistent across other major demographic groups, lipid values by age group were analyzed within country and gender (Table 5). The decline of TC, LDL-C, and non-HDL-C concentrations with increasing age was consistent across gender, but was not present in the countries outside of USA and Canada. Triglycerides fell with age in all gender and country groups, though this did not reach significance in women or in Canada.

The use of lipid-lowering medications did not vary by age group in Canada, Brazil, or the Czech Republic. However, participants 55+ years of age were significantly more likely to be prescribed a statin drug (or any lipid medication) than younger (<55 years) participants in the USA. Conversely, those aged <55 years were more likely to be taking a lipid medication in Mexico. Because of sample size, data from Czech Republic and Mexico should be cautiously interpreted.

## V. Discussion

Generally, lipids were well controlled in BARI 2D, with a mean LDL-C of 96 mg/dl (2.5 mmol/L) and triglycerides of 179 mg/dl (2.0 mmol/L), but there was room for improvement. Gender, age, country, educational level, and randomization year contributed to the differences noted at baseline.

Women had significantly higher TC, LDL-C and non-HDL-C concentrations than their male counterparts. There was no difference in statin usage between men and women. However, there was a significant difference in combination therapy (statin+fibrate) suggesting men received more aggressive treatment. This disparity in dyslipidemic treatment has been noted previously. A recent study (22) found women with diabetes and confirmed CAD were less likely than men to be taking aspirin or have their HbA1c, blood pressure or lipids controlled to recommended levels. The authors suggested these differences in clinical treatment may contribute to the 30-year age-adjusted increase in CHD mortality previously noted in women with diabetes (23). It has also been suggested (22) that since women have higher HDL-C concentrations, physicians may be convinced they are protected and not in need of aggressive lipid therapy. However, the protective effect of increased HDL-C in diabetes has been questioned as some evidence indicates a reduction in its antiatherogenic properties (24)

There was a decreasing trend in TC, LDL-C, and triglycerides and an increasing trend in HDL-C (men only) with increasing age. A likely contributor to this better lipid profile in the older population is survivor bias. As statin use was similar across all age groups and the younger age groups were more likely to be taking combination therapy (statin+fibrate), the age pattern is unlikely due to medication bias. A likely factor is the probability that dyslipidemia is more prominent in the younger participants and accounts for their having concomitant heart disease and diabetes (and thus BARI 2D eligibility) whereas in the older participants, this combination of events is more likely to be age related and thus less dependent on dyslipidemia. The older participants (≥65years) had lower HbA1c values, an older age of onset of diabetes, lower body mass index (BMI) and were more likely to exercise regularly and not smoke which may have also affected their baseline lipid values (data not shown).

There was no difference in the use of lipid-lowering medication by age in Canada, Brazil, and the Czech Republic, but the oldest participants in Mexico, were less likely to receive treatment for their lipids ($p<0.05$). A recent study by Safford et al. (25), which examined the disparities in the use of lipid lowering medications, noted similar results. Older participants were less likely to receive lipid lowering medications, despite the increased risk that diabetes confers. These findings are troubling, especially as a recent meta-analysis, examining the efficacy and safety of statin use in older adults (26), demonstrated that older individuals benefit from treatment with lipid medications. It is possible that many physicians believe that lipid lowering medications are not well tolerated in older individuals and place increased emphasis on diet and exercise.

Education demonstrated a significant impact on the lipid values of participants. High school graduates had lower TC, LDL-C and non-HDL-C concentrations. Although TG and HDL-C concentrations were similar, they were likely to receive treatment for their lipids. Education level has been used widely as an indicator of socioeconomic status because of its relationship to income, occupation and social status (27). Many studies have documented the better health status and care utilization among the more educated. A study conducted in the Netherlands showed that subjects with diabetes and less education utilized fewer services related to diabetes care (28), which could partially explain some of our lipid differences. Access to care and lack of health insurance may also be causative factors.

Being randomized into BARI 2D in 2004/2005, as compared to randomization in 2001/2002, was associated with a lower LDL-C and HDL-C and higher triglycerides. Although this association only reached borderline significance for LDL-C and triglycerides, it is consistent with more intensive LDL-C therapy by physicians in response to the NCEP Report (10), which recommends a LDL-C of <70 mg/dl in very high risk patients. Our results also suggest that physicians may not be treating beyond LDL-C, as exemplified by the negative and positive association of later randomization with HDL-C and triglycerides respectively. These

associations may be a reflection of increased weight and unhealthy lifestyles that go unaddressed by physicians.

Several studies (29–31) have reported the adverse impact of TZD treatment on blood lipids in type 2 diabetes. In BARI 2D, participants taking a TZD, but not prescribed statin therapy, had higher LDL-C concentrations than participants not taking a TZD (Table 4). Prior research (29–31) has also shown that treatment with the TZD pioglitazone shows a beneficial effect on triglycerides and a less detrimental effect on LDL-C than rosiglitazone. That finding was confirmed at this baseline examination, but the addition of statin therapy eliminated this difference, indicating the negative effect of TZD therapy on lipids may be counteracted with the addition of statin therapy. However, the dose of statin needed to neutralize the effect will vary and is dependent upon the statin prescription.

Despite overwhelming clinical trials evidence showing the benefits of lipid-lowering medication in high-risk coronary artery disease patients, only 76% (n=1632) of BARI 2D participants were taking a LDL-C lowering medication at baseline. Of those on medication, 33% (n=531) had a LDL-C value at or above 100 mg/dl. Suboptimal dosages of statins medications may help explain this inadequate effect. This has been demonstrated by Baessler (32) in a community-based study of post-MI patients. He reported that only 11% of the patients were being treated with optimal statin therapy, while 43.4% were treated suboptimally and 45.7% were untreated.

Fasting status may have been a limitation in this analysis, although the LDL-C and triglycerides patterns are largely confirmed by non-HDL-C which is unaffected by fasting status. Although mandated in the study protocol, fasting status was not recorded on the data collection forms. Consequently, it may not always have been rigorously applied and could account for the large standard deviations associated with some of the triglyceride values. It is also possible that BARI 2D subjects were healthier than the general population with diabetes and coronary artery disease. As participation in the trial was dependent upon a physician's referral, physicians may have been more likely to recommend their healthier patients.

Country differences are apparent at baseline and may partly reflect use of effective lipid-lowering medication. Caution is advised, however, in interpreting the data, given the varying sample sizes. Residual differences, beyond medication usage, remain and merit further evaluation. A gender disparity was also apparent as men were treated more aggressively than women with statin and fibrate combinations. In addition, those with a higher education level, and presumably higher socioeconomic class, had more favorable lipid profiles compared to those who were less educated. It therefore appears that greater efforts to reduce socioeconomic and gender-related disparities in the management of lipid disorders in high risk patients are needed.

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**Table 1**

Baseline Lipid Profiles in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial by Age groups, Gender, Post-Menopausal Hormone Use, Education and Country

| | n | TC (mg/dl) Mean, SD | Trig* (mg/dl) Mean, SD | LDL-C (mg/dl) Mean, SD | HDL-C (mg/dl) Mean, SD | | Non-HDL-C (mg/dl) Mean, SD | TC/HDL Ratio Mean, SD | Statin (%) | Statin+ fibrate (%) | Lipid Med † (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Total | 2277 | (n=2277) | (n=2277) | (n=2157) | (n=2270) | | (n=2270) | (n=2270 | | | |
| | | | | | Men | Women | | | | | |
| | | 169 ± 40 | 179 ± 128 | 96 ± 33 | 36 ± 9 | 43 ± 12 | 131 ± 40 | 5 ± 1 | 75 | 5 | 79 |
| Age Groups | | | | | | | | | | | |
| < 55 yrs | 485 | 178 ± 45‡ | 209 ± 177 ‡ | 102 ± 35 ‡ | 35 ± 8‡ | 42 ± 11 | 141 ± 45 ‡ | 5 ± 2‡ | 72 | 6 | 77 |
| 55–64 yrs | 910 | 170 ± 41 | 181 ± 121 | 96 ± 35 | 36 ± 8 | 44 ± 12 | 132 ± 40 | 5 ± 2 | 76 | 5 | 80 |
| >= 65 yrs | 882 | 164 ± 36 | 161 ± 96 | 93 ± 31 | 37 ± 10 | 43 ± 12 | 125 ± 35 | 4 ± 1 | 75 | 4 | 80 |
| Correlation | | −0.135‡ | −0.113 ‡ | −0.110 ‡ | 0.100 ‡ | 0.038 | −0.158 ‡ | −0.177‡ | | | |
| | | | | | | | | | | | |
| Men | 1598 | 164 ± 39‡ | 181 ± 130 | 93 ± 32 ‡ | 36 ± 9 ‡ | | 128 ± 39‡ | 5 ± 2 ‡ | 76 | 6‡ | 80 |
| Women | 679 | 180 ± 41 | 175 ± 124 | 103 ± 35 | | 43 ± 12 | 137 ± 40 | 4 ± 1 | 72 | 3 | 77 |
| HRT Rx // | | | | | | | | | | | |
| No | 534 | 179 ± 41 | 168 ± 107 | 104 ± 35 | | 42 ± 11‡ | 137 ± 40 | 4 ± 1§ | 72 | 3 | 77 |
| Yes | 65 | 183 ± 35 | 179 ± 94 | 97 ± 31 | | 50 ± 15 | 133 ± 35 | 4 ± 1 | 75 | 3 | 77 |
| | | | | | | | | | | | |
| Education ¶ | | | | | | | | | | | |
| LHS | 841 | 173 ± 42 ‡ | 181 ± 122 | 99 ± 34‡ | 36 ± 9 | 42 ± 11 | 134 ± 41‡ | 5 ± 1 | 72 § | 2 ‡ | 76‡ |
| HS | 1436 | 167 ± 39 | 179 ± 132 | 94 ± 33 | 36 ± 9 | 43 ± 12 | 129 ± 39 | 5 ± 1 | 76 | 6 | 81 |
| | | | | | | | | | | | |
| Country | | | | | | | | | | | |
| USA | 1437 | 166 ± 40** | 174 ± 123†† | 94 ± 33** | 36 ± 9 | 43 ± 12 | 128 ± 39§§ | 5 ± 2†† | 77†† | 6 // // | 82§§ |
| Canada | 345 | 165 ± 39** | 174 ± 134†† | 92 ± 32** | 38 ± 8‡‡ | 44 ± 11 | 125 ± 39§§ | 4 ± 1§§ | 78†† | 5 | 82§§ |
| Mexico | 81 | 177 ± 40 | 220 ± 122 | 98 ± 29 | 35 ± 8 | 37 ± 10 | 142 ± 39 | 5 ± 1 | 48 | 6 | 54 |
| Brazil | 350 | 179 ± 41 | 182 ± 107†† | 105 ± 35 | 36 ± 8 | 42 ± 10 | 140 ± 40 | 5 ± 1 | 72†† | 2 | 73¶¶ |
| Czech Republic # | 64 | 191 ± 42 | 265 ± 236 | 108 ± 30 | 37 ± 10 | 40 ± 10 | 152 ± 43 | 5 ± 2 | 48 | 2 | 64 |

*Triglycerides log transformed

†any lipid medication (statin, fibrate, niacin, bile acid sequestrant, omega-3 fish oil, cholesterol absorption inhibitor)

‡ p<0.01 between groups

§ p<0.05 between groups

// menopausal hormone replacement therapy

¶ < high school, ≥ high school

# Prague

** p<0.05 from Brazil & Czech Republic

†† p<0.05 from Mexico & Czech Republic

‡‡ p<0.05 from USA, Mexico & Brazil

§§ p<0.05 from Mexico, Brazil & Czech Republic

/// p<0.05 from Brazil

¶¶ p<0.05 from Mexico; [Total cholesterol, LDL cholesterol, and HDL cholesterol mg/dl * 0.02586 = mmol/L][Triglycerides mg/dl * 0.0112 = mmol/L]

**Table 2**

BARI 2D Lipid Values at Baseline by Country (percent meeting country's specific goal, overall, and according to medication use)

| Country and Guidelines | Overall | | On medication* | | Not on medication | |
|---|---|---|---|---|---|---|
| | N | % at goal | N | % at goal | N | % at goal |
| **USA**† | | | | | | |
| LDL-C < 100 mg/dl | 1371 | 62 | 1078 | 69 | 293 | 39 |
| Triglycerides‡ < 150 mg/dl | 1437 | 52 | 215 | 33 | 1222 | 56 |
| **Canada**§ | | | | | | |
| LDL-C < 100 mg/dl | 327 | 64 | 254 | 74 | 73 | 32 |
| TC/HDL-C <4 | 340 | 49 | 279 | 55 | 61 | 20 |
| LDL-C<100 mg/dl AND TC/HDL-C<4 | 327 | 43 | 270 | 49 | 57 | 14 |
| Triglycerides‡ < 150 mg/dl | 345 | 53 | 32 | 41 | 313 | 54 |
| **Czech Republic** // | | | | | | |
| LDL-C < 100 mg/dl | 54 | 37 | 25 | 52 | 29 | 24 |
| TC <175 mg/dl | 64 | 33 | 31 | 39 | 33 | 27 |
| Triglycerides‡ < 150 mg/dl | 64 | 28 | 11 | 27 | 53 | 28 |
| **Brazil**¶ | | | | | | |
| LDL-C < 100 mg/dl | 331 | 48 | 242 | 57 | 89 | 21 |
| TC <200 mg/dl | 350 | 71 | 253 | 79 | 97 | 53 |
| Triglycerides‡ < 150 mg/dl | 350 | 49 | 10 | 0 | 340 | 50 |
| HDL-C >35 mg/dl | 350 | 55 | 256 | 55 | 94 | 53 |
| **Mexico** # | | | | | | |
| LDL-C < 100 mg/dl | 74 | 54 | 33 | 67 | 41 | 44 |
| Triglycerides‡ < 150 mg/dl | 81 | 33 | 10 | 20 | 71 | 35 |
| **Overall** | | | | | | |
| LDL-C < 100 mg/dl | 2157 | 59 | 1632 | 67 | 525 | 34 |
| Triglycerides‡ <150 mg/dl | 2277 | 51 | 278 | 32 | 1999 | 53 |

*Medication use: LDL-C-any statin, bile acid sequestrant, niacin, cholesterol absorption inhibitor; Triglyceride-any fibrate, niacin, omega-3; Total Cholesterol (TC)-same as LDL-C; TC/HDL-C-any statin, fibrate, bile acid sequestrant, niacin, cholesterol absorption inhibitor; HDL-C-any statin, niacin, fibrate

†NCEP ATP III

‡American Diabetes Association



*Prev Cardiol*. Author manuscript; available in PMC 2010 January 1.

[§] 2000 Canadian Guidelines

[//] European Guidelines on Cardiovascular Disease Prevention in Clinical Practice

[¶] II Brazilian Guidelines Conference on Dyslipidemias

[#] Official norm of the Ministry of Health of Mexico for the prevention and treatment of hypercholesterolemia, July, 2003

**Table 3**

The association of baseline demographic variables and lipid values in the Bypass Revascularization Investigation 2 Diabetes (BARI 2D) Trial

| | Coefficient Estimate | Total $R^2$ | $R^2$ Change | P value |
|---|---|---|---|---|
| | LDL-C Cholesterol (mg/dl) n=2157 | | | |
| Age (10 years older) | −3.94 | | 1.2 | <0.01 |
| Female Gender | 8.73 | | 1.9 | <0.01 |
| Use of LDL-lowering drug* | −20.72 | | 7.8 | <0.01 |
| High School Education | −0.92 | | 0.2 | 0.56 |
| USA/Canada | −7.86 | | 0.5 | <0.01 |
| Randomized 2003 vs 2001/2002<br>Randomized 2004/2005 vs 2001/2002 | 0.75<br>−3.40 | | 0.3 | 0.67<br>0.06 |
| | | 11.9 | | |
| | Triglycerides (log of mg/dl)‡ n=2277 | | | |
| Age (10 years older) | −0.07 | | 1.3 | <0.01 |
| Female Gender | −0.02 | | 0.0 | 0.54 |
| Use of Trig-lowering drug† | 0.34 | | 3.1 | <0.01 |
| High School Educ | −0.01 | | 0.3 | 0.73 |
| USA/Canada | −0.15 | | 1.2 | <0.01 |
| Randomized 2003 vs 2001/2002<br>Randomized 2004/2005 vs 2001/2002 | 0.05<br>0.06 | | 0.2 | 0.15<br>0.07 |
| | | 6.1 | | |
| | HDL-C Cholesterol (mg/dl) n=2270 | | | |
| Age (10 years older) | 0.80 | | 0.7 | <0.01 |
| Female Gender | 6.76 | | 9.1 | <0.01 |
| Use of HDL-raising drug§ | 0.58 | | 0 | 0.25 |
| High School Education | −0.23 | | 0 | 0.63 |
| USA/Canada | 0.02 | | 0.1 | 0.97 |
| Randomized 2003 vs 2001/2002<br>Randomized 2004/2005 vs 2001/2002 | −1.70<br>−2.12 | | 0.7 | <0.01<br><0.01 |
| | | 10.6 | | |
| | Non-HDL-C (mg/dl) n=2270 | | | |
| Age (10 years older) | −6.86 | | 2.5 | <0.01 |
| Female Gender | 7.91 | | 1.1 | <0.01 |
| Use of any lipid drug | −17.79 | | 3.9 | <0.01 |
| High School Education | −1.09 | | 0.4 | 0.56 |
| USA/Canada | −11.08 | | 0.8 | <0.01 |
| Randomized 2003 vs 2001/2002 | 1.93<br>−2.01 | | 0.2 | 0.36<br>0.34 |

| | Coefficient Estimate | Total $R^2$ | $R^2$ Change | P value |
|---|---|---|---|---|
| Randomized 2004/2005 vs 2001/2002 | | | | |
| | | 8.9 | | |

*(statin, niacin, bile acid resin, cholesterol absorptive inhibitor)

†(fibrate, omega-3 fatty acid, niacin)

‡log-transformed

§(niacin, statin, fibrate)

**Table 4**

Thiazolidinediones (TZDs) Medication Use by Baseline Lipid Profile for Participants in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial With and Without Statin

| | **No TZD n=1338** | **Rosiglitazone n=199** | **Pioglitazone n=163** | **p value** |
|---|---|---|---|---|
| | | | | |
| | | **With Statin** | | |
| TC (mg/dl) | 163 , 158 | 163 , 157 | 163 , 159 | NS |
| Trig (mg/dl)‡ | 177 , 147 | 186 , 148 | 167 , 131 | NS |
| LDL-C (mg/dl) | 91 , 87 | 89 , 87 | 89 , 86 | NS |
| HDL-C (mg/dl) men | 36 , 35 | 38 , 36 | 37 , 37 | NS |
| women | 43 , 41 | 43 , 41 | 43 , 42 | NS |
| Non-HDL-C (mg/dl) | 125 , 119 | 124 , 121 | 124 , 120 | NS |
| | | | | |
| | **NoTZD** n=505 | **Rosiglitazone** n=33 | **Pioglitazone** n=36 | |
| | | | | |
| | | **Without Statin** | | |
| TC (mg/dl) | 184 , 179 | 204 , 203 § | 196 , 190 | <0.01 |
| Trig (mg/dl)‡ | 186 , 155 | 212 , 172 | 167 , 132 | NS |
| LDL-C (mg/dl) | 112 , 111 | 128 , 128 § | 123 , 121 | <0.05 |
| HDL-C (mg/dl) men | 35 , 33 | 34 , 32 | 36 , 34 | NS |
| women | 42 , 40 | 50 , 51 | 46 , 40 | NS |
| Non-HDL-C (mg/dl) | 147 , 144 | 168 , 163 § | 155 , 147 | <0.05 |
| | | | | |

Data are means, median

* p <0.01

† p<0.05

‡ triglycerides log-transformed [Total cholesterol, LDL cholesterol, and HDL cholesterol mg/dl * 0.02586 = mmol/L][Triglycerides mg/dl * 0.0112 = mmol/L]

§ No TZD vs Rosiglitazone (<0.05)

**Table 5**

BARI 2D Baseline Lipid Profiles: Age groups by Gender and Country

| | n | TC (mg/dl) | Trig* (mg/dl) | LDL-C (mg/dl) | HDL-C (mg/dl) | | non-HDL-C (mg/dl) | TC/HDL ratio | Statin (%) | Any Lipid Drug (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2277 | 169 ± 40 | 179 ± 128 | 96 ± 33 | Men | Women | | 5 ± 1 | 75 | 79 |
| | | | | | 36 ± 9 | 43 ± 12 | 131 ± 40 | | | |
| Men <55 yrs | 338 | 175 ± 46† | 217 ± 177† | 99 ± 35† | 35 ± 8† | | 140 ± 46† | 5 ± 2† | 73 | 79 |
| 55–64 yrs | 658 | 165 ± 39 | 184 ± 124 | 93 ± 33 | 36 ± 8 | | 129 ± 39 | 5 ± 2 | 78 | 81 |
| >= 65 yrs | 602 | 158 ± 35 | 158 ± 35 | 90 ± 30 | 37 ± 10 | | 121 ± 34 | 4 ± 1 | 76 | 80 |
| Women <55 yrs | 147 | 184 ± 41‡ | 193 ± 174 | 107 ± 34‡ | 42 ± 11 | | 142 ± 41‡ | 5 ± 1‡ | 69 | 71 |
| 55–64 yrs | 252 | 183 ± 44 | 172 ± 114 | 105 ± 38 | 44 ± 12 | | 139 ± 44 | 4 ± 1 | 72 | 78 |
| >= 65 yrs | 280 | 175 ± 38 | 168 ± 98 | 99 ± 32 | 43 ± 12 | | 132 ± 37 | 4 ± 1 | 74 | 80 |
| **Countries** | | | | | | | | | | |
| USA <55 yrs | 295 | 179 ± 45† | 198 ± 157† | 104 ± 36† | 35 ± 9 | 42 ± 11 | 141 ± 45† | 5 ± 1† | 69† | 75† |
| 55–64 yrs | 559 | 166.3, 39.7 | 175.2, 122.4 | 93.8, 34.0 | 35 ± 9 | 45 ± 13 | 128 ± 39 | 5 ± 2 | 82 | 86 |
| >= 65 yrs | 583 | 160.6, 35.8 | 160.3, 100.3 | 90.5, 30.0 | 36 ± 9 | 43 ± 12 | 122 ± 34 | 4 ± 1 | 78 | 83 |
| Canada <55 yrs | 74 | 169 ± 42† | 203 ± 204 | 95 ± 33† | 37 ± 7 | 41 ± 11 | 131 ± 43† | 5 ± 2† | 77 | 84 |
| 55–64 yrs | 145 | 170 ± 42 | 174 ± 122 | 98 ± 35 | 38 ± 8 | 46 ± 13 | 131 ± 42 | 4 ± 1 | 75 | 81 |
| >= 65 yrs | 126 | 155 ± 31 | 158 ± 85 | 83 ± 25 | 39 ± 9 | 44 ± 11 | 115 ± 30 | 4 ± 1 | 81 | 83 |
| Mexico <55 yrs | 23 | 179 ± 54 | 272 ± 165‡ | 91 ± 26 | 30 ± 5 | 31 ± 8 | 148 ± 54 | 6 ± 2† | 70‡ | 70 |
| 55–64 yrs | 38 | 178 ± 35 | 218 ± 102 | 100 ± 34 | 36 ± 8 | 35 ± 6 | 142 ± 32 | 5 ± 1 | 45 | 55 |
| >= 65 yrs | 20 | 175 ± 34 | 164 ± 67 | 102 ± 24 | 39 ± 8 | 40 ± 13 | 135 ± 31 | 5 ± 1 | 30 | 35 |
| Brazil <55 yrs | 86 | 178 ± 39 | 210 ± 132† | 103 ± 33 | 34 ± 7† | 41 ± 10 | 142 ± 38 | 5 ± 1 | 78 | 80 |
| 55–64 yrs | 135 | 177 ± 45 | 188 ± 111 | 103 ± 38 | 35 ± 7 | 42 ± 9 | 139 ± 44 | 5 ± 1 | 69 | 70 |
| >= 65 yrs | 129 | 181 ± 39 | 157 ± 76 | 109 ± 33 | 39 ± 10 | 42 ± 10 | 141 ± 38 | 5 ± 1 | 72 | 72 |
| Czech‡ Republic <55 yrs | 7 | 222 ± 66 | 537 ± 550‡ | 108 ± 49 | 30 ± 4 | 46 ± 9 | 187 ± 68 | 7 ± 3 | 57 | 57 |
| 55–64 yrs | 33 | 188 ± 40 | 236 ± 142 | 107 ± 28 | 37 ± 8 | 42 ± 13 | 149 ± 41 | 5 ± 2 | 52 | 64 |

| | n | TC (mg/dl) | Trig* (mg/dl) | LDL-C (mg/dl) | HDL-C (mg/dl) | | non-HDL-C (mg/dl) | TC/HDL ratio | Statin (%) | Any Lipid Drug (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| >= 65 yrs | 24 | 185 ± 34 | 226 ± 143 | 109 ± 28 | 40 ± 13 | 36 ± 7 | 147 ± 34 | 5 ± 1 | 42 | 67 |

Data are means ± SD

* triglycerides log-transformed

† p<0.01

≠ p<0.05; [Total cholesterol, LDL cholesterol, and HDL cholesterol mg/dl * 0.02586 = mmol/L][Triglycerides mg/dl * 0.0112 = mmol/L]