CLINICAL STUDY

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

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In order to examine lipids, a major treatment parameter in those with diabetes and heart disease, the authors analyzed baseline data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. The study consisted of 2368 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 low-density lipoprotein (LDL) cholesterol level <100 mg/dL. Levels of total, LDL, and non–high-density lipoprotein (HDL) cholesterol and triglycerides differed by age group (younger than 55, 55–64, and 65 years and older); they were lowest in those aged 65 years. Women had higher total, LDL, and non-HDL cholesterol values. Education was associated with lower total, LDL, and non-HDL cholesterol levels. LDL cholesterol and triglyceride values were lower in the United States and Canada. Adjustment for age, sex, education level, randomization year, and medication did not eliminate these differences. Geographic variation was seen and was not fully accounted for by demographic or treatment characteristics (all P values <.05). **Prev Cardiol.** ***2009;12:9–18.***

The prevalence of diabetes (especially type 2 diabetes, the most common form; 90% of persons with diabetes have type 2) is increasing dramatically.[1] This creates a great challenge in terms of cardiovascular disease morbidity and mortality, as rates increase 2- to 5-fold compared with the general population.[2,3] Also of concern is the higher 1-year post–myocardial infarction (MI) mortality rate associated with diabetes. Some studies note a risk of death in post-MI patients with diabetes as high as 2-fold or greater.[4] The 7-year rate of MI (fatal and nonfatal) for diabetic patients with previous MI has been reported to be 45%, or more than twice the reinfarction rate for nondiabetic patients.[3]

Dyslipidemia, especially an elevated low-density lipoprotein cholesterol (LDL-C) level, 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 elevated triglyceride and reduced high-density lipoprotein cholesterol (HDL-C) values.[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

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incidence and recurrence of cardiovascular disease. Favorable subgroup analyses for those with diabetes have been reported in a number of studies.[7,8] Furthermore, the Collaborative Atorvastatin Diabetes Study (CARDS),[8] which focused on type 2 diabetes, demonstrated a 37% reduction in coronary mortality or first cardiovascular event for those randomized to statin therapy vs placebo. Conversely, the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) trial,[9] which randomized patients with type 2 diabetes to atorvastatin 10 mg or placebo, did not find a significant reduction in the primary cardiovascular end point.

Given the high risk of recurrent events in diabetic patients with heart disease, the National Cholesterol Education Panel Adult Panel III (NCEP ATP III) in 2004 suggested an LDL-C goal as low as 70 mg/dL (1.8 mmol/L).[10] However, the management of dyslipidemia has been reported to be suboptimal.[11] Therefore, in order 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 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 vs insulin sensitization; early revascularization plus aggressive risk factor control [dyslipidemia, hypertension, smoking, and obesity] vs aggressive risk factor control alone) for patients with type 2 diabetes and documented stable coronary artery disease (CAD) in the setting of glucose management with a target hemoglobin A_{1c} value $<7.0\%$. Major objectives of this report were to describe lipid concentrations and control by key demographic groups (age, sex, country, and education) and determine to what extent the country differences are explained by use of lipid-lowering medication.

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 consisted of 2368 participants from 49 clinical sites in 6 countries. The expected mean follow up was $\geq$3.8 years. Participants ranged 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 $\geq$30% of the trial participants from minority populations. Minorities represent 40% of the US 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 data at baseline could not be obtained for 5 other participants. An additional 2 participants had complete data but were considered ineligible for this analysis due to their triglyceride levels exceeding 1000 mg/dL (11.2 mmol/L) in the presence of moderate glycemic control (hemoglobin A_{1c} $<9.0\%$) to be consistent with BARI 2D entry criteria. Of the remaining 2277 participants, 7 did not have an HDL-C value and an additional 113 with triglyceride levels $>$400 mg/dL ($>$4.5 mmol/L) did not have a calculated LDL-C value. Thus, 2157 participants with an LDL-C value, 2277 with a triglyceride value, and 2270 with an HDL-C value were included in this analysis. Availability of HDL-C data also allowed for the analysis of non-HDL-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 Eligibility Criteria

Investigators in 46 clinical sites throughout North America (United States, Canada, and Mexico), 1 in South America (Brazil), and 2 in Europe (Austria and Czech Republic) identified patients with type 2 diabetes aged 25 years and older by one of the following criteria: confirmed ($\geq$2 readings) fasting plasma glucose $>$125 mg/dL; random plasma glucose $\geq$200 mg/dL; plasma glucose $\geq$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 assess C-peptide or proinsulin and 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 $\geq$70% coronary stenosis) and at least 1 coronary vessel amenable to revascularization. Major exclusion criteria included definite need for prompt invasive intervention as determined by the attending cardiologist; prior coronary artery bypass graft or prior catheter-based intervention within the past 12 months; class III or IV congestive heart failure; creatinine $>$2.0 mg/dL; hemoglobin A_{1c} $>$13% or a need for major vascular surgery concomitant with revascularization.

Laboratory Analysis

At baseline in BARI 2D, following a minimum fast of 8 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, HDL-C, triglycerides, and calculated LDL-C. Cholesterol and triglycerides were analyzed

enzymatically,[13,14] while HDL-C was assayed after removal of apolipoprotein B–containing lipoproteins by Mg^{2+} and dextran sulphate.[15] The calculation of estimated LDL-C requires the direct measurement of total cholesterol, triglycerides, and HDL-C utilizing the Friedewald formula.[16] Data from Austria, 1 of the 2 BARI 2D European study sites, were not included in this analysis due to the absence of biochemistry core laboratory lipid data (a requirement for inclusion in this analysis).

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 were performed on the transformed variable. SAS version 9 (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

The baseline lipid profiles of the BARI 2D participants, stratified by age group, sex, postmenopausal hormone use, education level, and country are presented in Table I. When stratified by age, there was a significant decreasing trend in total cholesterol, LDL-C, triglycerides, and non-HDL-C and an increasing trend in HDL-C, in men only, with increasing age strata ($P<.01$). Significant negative correlations between each lipoprotein and age (with the exception of HDL-C in men, which was positively correlated) were seen. Women had significantly higher total cholesterol, LDL-C, and non-HDL-C concentrations than men ($P<.01$), but there was no significant difference in triglyceride concentrations by sex. Lipoprotein concentrations were not significantly different by menopausal status (data not shown), but women using postmenopausal hormone therapy, as expected, had significantly higher HDL-C concentrations ($P<.01$).

Table I also shows the lipid characteristics according to educational level. Those participants with a high school or greater education had significantly lower total cholesterol, 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 sex, participants with a high school or greater education were significantly more likely to be taking a statin ($P<.05$) or any lipid medication ($P<.01$).

Lipoprotein profiles and use of lipid medications varied significantly by country (Table I). The United States and Canada had significantly lower total cholesterol, LDL-C, and non-HDL-C ($P<.05$) than Brazil and the Czech Republic. The total cholesterol and LDL-C values in Mexico were similar to their North American neighbors, but non-HDL-C values were higher ($P<.05$). The Czech Republic and Mexico had significantly higher triglyceride concentrations ($P<.05$). 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 United States, Brazil, and Mexico ($P<.05$). Medication usage also differed by country, with participants in the United States, Canada, and Brazil significantly more likely to be taking a lipid-lowering medication, especially a statin, than participants in Mexico and the Czech Republic ($P<.05$).

Table II 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 an LDL-C <100 mg/dL (<2.6 mmol/L) and 51% had triglyceride levels <150 mg/dL (<1.7 mmol/L). More than 50% of participants in the United States, Canada, and Mexico met their respective country's LDL-C goal of <100 mg/dL (<2.6 mmol/L),[10,17,18] while <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 percentages of participants (33% and 28%, respectively) at the recommended values.[21]

Of those receiving lipid-altering medications, 67% (n=1093) had an LDL-C <100 mg/dL, while 33% (n=539) had a value >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 an LDL-C value <100 mg/dL.

The results from 4 separate stepwise linear regression models with LDL-C, triglycerides, HDL-C, and non-HDL-C as the dependent variables are presented in Table III. This analysis was performed to determine whether age, sex, 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 United States/Canada vs 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 vs other or no medication; triglycerides: fibrate, omega-3 fatty acid, niacin vs other or no medication; HDL-C: niacin,

Table I. Baseline Lipid Profiles in the BARI 2D Trial by Age Group, Sex, Postmenopausal Hormone Use, Education, and Country

	No.	TC, mg/dL, Mean ± SD	TG,[a] 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-C Ratio, Mean, SD	Statin, %	Statin/ Fibrate, %	Lipid Medication,[b] %
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 y	485	178±45[c]	209±177[c]	102±35[c]	35±8[c]	42±11	141±45[c]	5±2[c]	72	6	77
55–64 y	910	170±41	181±121	96±35	36±8	44±12	132±40	5±2	76	5	80
≥65 y	882	164±36	161±96	93±31	37±10	43±12	125±35	4±1	75	4	80
Correlation		−0.135[c]	−0.113[c]	−0.110[c]	0.100[c]	0.038	−0.158[c]	−0.177[c]			
Men	1598	164±39[c]	181±130	93±32[c]	36±9[c]		128±39[c]	5±2[c]	76	6[c]	80
Women	679	180±41	175±124	103±35		43±12	137±40	4±1	72	3	77
HRT Rx[e]											
No	534	179±41	168±107	104±35		42±11[c]	137±40	4±1[d]	72	3	77
Yes	65	183±35	179±94	97±31		50±15	133±35	4±1	75	3	77
Education[f]											
LHS	841	173±42[c]	181±122	99±34[c]	36±9	42±11	134±41[c]	5±1	72[d]	2[c]	76[c]
HS	1436	167±39	179±132	94±33	36±9	43±12	129±39	5±1	76	6	81
Country											
United States	1437	166±40[h]	174±123[i]	94±33[h]	36±9	43±12	128±39[k]	5±2[i]	77[i]	6[l]	82[k]
Canada	345	165±39[h]	174±134[i]	92±32[h]	38±8[j]	44±11	125±39[k]	4±1[k]	78[i]	5	82[k]
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[i]	105±35	36±8	42±10	140±40	5±1	72[i]	2	73[m]
Czech Republic[g]	64	191±42	265±236	108±30	37±10	40±10	152±43	5±2	48	2	64

Abbreviations: BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides. [a]TG log-transformed; [b]any lipid medication (statin, fibrate, niacin, bile acid sequestrant, omega-3 fish oil, cholesterol absorption inhibitor); [c]$P<.01$ between groups; [d]$P<.05$ between groups; [e]menopausal hormone replacement therapy; [f]<high school and ≥high school; [g]Prague; [h]$P<.05$ from Brazil and Czech Republic; [i]$P<.05$ from Mexico and Czech Republic; [j]$P<.05$ from United States, Mexico, and Brazil; [k]$P<.05$ from Mexico, Brazil, and Czech Republic; [l]$P<.05$ from Brazil; [m]$P<.05$ from Mexico. [TC, LDL-C, and HDL-C mg/dL × 0.02586 = mmol/L] [triglycerides mg/dL × 0.0112 = mmol/L].

Table II. BARI 2D Trial Lipid Values at Baseline by Country (% Meeting Country's Specific Goal, Overall and According to Medication Use)

	Overall		On Medication[a]		Not on Medication	
Country and Guidelines	No.	% at Goal	No.	% at Goal	No.	% at Goal
United States[b]						
LDL-C <100 mg/dL	1371	62	1078	69	293	39
Triglycerides[c] <150 mg/dL	1437	52	215	33	1222	56
Canada[d]						
LDL-C <100 mg/dL	327	64	254	74	73	32
TC/HDL-C ratio <4	340	49	279	55	61	20
LDL-C <100 mg/dL and TC/HDL-C ratio <4	327	43	270	49	57	14
Triglycerides[c] <150 mg/dL	345	53	32	41	313	54
Czech Republic[e]						
LDL-C <100 mg/dL	54	37	25	52	29	24
TC <175 mg/dL	64	33	31	39	33	27
Triglycerides[c] <150 mg/dL	64	28	11	27	53	28
Brazil[f]						
LDL-C <100 mg/dL	331	48	242	57	89	21
TC <200 mg/dL	350	71	253	79	97	53
Triglycerides[c] <150 mg/dL	350	49	10	0	340	50
HDL-C >35 mg/dL	350	55	256	55	94	53
Mexico[g]						
LDL-C <100 mg/dL	74	54	33	67	41	44
Triglycerides[c] <150 mg/dL	81	33	10	20	71	35
Overall						
LDL-C <100 mg/dL	2157	59	1632	67	525	34
Triglycerides[c] <150 mg/dL	2277	51	278	32	1999	53

Abbreviations: BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol. [a]Medication use—LDL-C: any statin, bile acid sequestrant, niacin, cholesterol absorption inhibitor; triglyceride: any fibrate, niacin, omega-3; TC: same as LDL-C; TC/HDL-C: any statin, fibrate, bile acid sequestrant, niacin, cholesterol absorption inhibitor; HDL-C: any statin, niacin, fibrate. [b]National Cholesterol Education Panel Adult Panel III; [c]American Diabetes Association; [d]2000 Canadian Guidelines; [e]European Guidelines on Cardiovascular Disease Prevention in Clinical Practice; [f]II Brazilian Guidelines Conference on Dyslipidemias; [g]official norm of the Ministry of Health of Mexico for the prevention and treatment of hypercholesterolemia (July 2003).

statin, fibrate vs other or no medication; and non-HDL-C: any lipid medication vs no lipid medication.

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

Age and country were negatively associated with triglyceride value, indicating that participants who were older and lived in the United States/Canada had lower baseline triglyceride values. Use of triglyceride-lowering medication was positively associated with baseline triglyceride concentrations, suggesting that 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 ($P<.07$). 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 IV examines the LDL-C, triglyceride, and HDL-C values by use of thiazolidinedione (TZD) medication (rosiglitazone or pioglitazone) stratified by concurrent statin use. Among participants not

Table III. The Association of Baseline Demographic Variables and Lipid Values in the BARI 2D Trial

	Coefficient Estimate	Total R^2	R^2 Change	*P* Value
LDL-C, mg/dL (n=2157)				
Age (10 years older)	−3.94		1.2	<.01
Female	8.73		1.9	<.01
Use of LDL-C–lowering drug[a]	−20.72		7.8	<.01
High school education	−0.92		0.2	.56
United States/Canada	−7.86		0.5	<.01
Randomized in 2003 vs 2001/2002	0.75			.67
Randomized in 2004/2005 vs 2001/2002	−3.40		0.3	.06
		11.9		
Triglycerides (log of mg/dL)[c] n=2277				
Age (10 years older)	−0.07		1.3	<.01
Female	−0.02		0.0	.54
Use of triglyceride-lowering drug[b]	0.34		3.1	<.01
High school education	−0.01		0.3	.73
United States/Canada	−0.15		1.2	<.01
Randomized in 2003 vs 2001/2002	0.05			.15
Randomized in 2004/2005 vs 2001/2002	0.06		0.2	.07
		6.1		
HDL-C, mg/dL (n=2270)				
Age (10 years older)	0.80		0.7	<.01
Female	6.76		9.1	<.01
Use of HDL-C–raising drug[d]	0.58		0	.25
High school education	−0.23		0	.63
United States/Canada	0.02		0.1	.97
Randomized in 2003 vs 2001/2002	−1.70			<.01
Randomized in 2004/2005 vs 2001/2002	−2.12		0.7	<.01
		10.6		
Non-HDL-C, mg/dL (n=2270)				
Age (10 years older)	−6.86		2.5	<.01
Female	7.91		1.1	<.01
Use of any lipid drug	−17.79		3.9	<.01
High school education	−1.09		0.4	.56
United States/Canada	−11.08		0.8	<.01
Randomized in 2003 vs 2001/2002	1.93			.36
Randomized in 2004/2005 vs 2001/2002	−2.01		0.2	.34
		8.9		

Abbreviations: BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. [a]Statin, niacin, bile acid resin, cholesterol absorptive inhibitor; [b]fibrate, omega-3 fatty acid, niacin; [c]log-transformed; [d]niacin, statin, fibrate.

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 ($P<.05$). 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 whether the age effects described earlier were consistent across other major demographic groups, lipid values by age group were analyzed within country and sex (Table V). The decline of total cholesterol, LDL-C, and non-HDL-C concentrations with increasing age was consistent across sexes but was not present in the countries outside of the United States and Canada. Triglycerides fell with age in all sex 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 aged 55 and older were significantly more likely to have a statin drug (or any lipid medication) prescribed than younger (younger than 55) participants in the United States. Conversely, those younger than 55 years were more likely to be taking a lipid medication in Mexico. Because of sample size, data from the Czech Republic and Mexico should be cautiously interpreted.

Table IV. TZD Use by Baseline Lipid Profile for Participants in the BARI 2D Trial With and Without Statins

	No TZD (n=1338)	Rosiglitazone (n=199)	Pioglitazone (n=163)	*P* Value
With Statin				
TC, mg/dL	163/158	163/157	163/159	NS
Triglycerides, mg/dL[a]	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
HDL-C, mg/dL (women)	43/41	43/41	43/42	NS
Non-HDL-C, mg/dL	125/119	124/121	124/120	NS
	No TZD (n=505)	Rosiglitazone (n=33)	Pioglitazone (n=36)	*P* Value
Without Statin				
TC, mg/dL	184/179	204/203[b]	196/190	<.01
Triglycerides, mg/dL[a]	186/155	212/172	167/132	NS
LDL-C, mg/dL	112/111	128/128[b]	123/121	<.05
HDL-C, mg/dL (men)	35/33	34/32	36/34	NS
HDL-C, mg/dL (women)	42/40	50/51	46/40	NS
Non-HDL-C, mg/dL	147/144	168/163[b]	155/147	<.05

Abbreviations: BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TZD, thiazolidinediones. Data are mean/median. [a]Triglycerides log-transformed [TC, LDL-C, and HDL-C mg/dL × 0.02586 = mmol/L] [triglycerides mg/dL × 0.0112 = mmol/L]; [b]no TZD vs rosiglitazone (<0.05). The difference in the "without statin" group is restricted to "no TZD" vs "rosiglitazone" ($P<.05$) (multiple comparison *P* value).

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. Sex, age, country, education level, and randomization year contributed to the differences noted at baseline.

Women had significantly higher total cholesterol, 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 that men received more aggressive treatment. This disparity in dyslipidemic treatment has been noted previously. A 2005 study[22] found that women with diabetes and confirmed coronary artery disease were less likely than men to be taking aspirin or to have their hemoglobin A_{1c}, blood pressure, or lipids controlled to recommended levels. The authors suggested that these differences in clinical treatment may contribute to the 30-year age-adjusted increase in coronary heart disease mortality previously noted in women with diabetes.[23] It has also been suggested that since women have higher HDL-C concentrations, physicians may be convinced they are protected and not in need of aggressive lipid therapy.[22] 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 total cholesterol, LDL-C, and triglycerides and an increasing trend in HDL-C (in 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 to be 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 (65 years or older) had lower hemoglobin A_{1c} values, an older age at onset of diabetes, and a lower body mass index 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 ($P<.05$). A recent study by Safford and associates[25] that 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

Table V. BARI 2D Trial Baseline Lipid Profiles: Age Groups by Sex and Country

	No.	TC, mg/dL	TG,[a] mg/dL	LDL-C, mg/dL	HDL-C, mg/dL		Non-HDL-C, mg/dL	TC/HDL-C Ratio	Statin, %	Any Lipid Drug, %
					Men	Women				
	2277	169±40	179±128	96±33	36±9	43±12	131±40	5±1	75	79
Men										
<55 y	338	175±46[b]	217±177[b]	99±35[b]	35±8[b]		140±46[b]	5±2[b]	73	79
55–64 y	658	165±39	184±124	93±33	36±8		129±39	5±2	78	81
≥65 y	602	158±35	158±35	90±30	37±10		121±34	4±1	76	80
Women										
<55 y	147	184±41[c]	193±174	107±34[c]	42±11		142±41[c]	5±1[c]	69	71
55–64 y	252	183±44	172±114	105±38	44±12		139±44	4±1	72	78
≥65 y	280	175±38	168±98	99±32	43±12		132±37	4±1	74	80
Countries										
United States										
<55 y	295	179±45[b]	198±157[b]	104±36[b]	35±9	42±11	141±45[b]	5±1[b]	69[b]	75[b]
55–64 y	559	166.3±39.7	175.2±122.4	93.8±34.0	35±9	45±13	128±39	5±2	82	86
≥65 y	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 y	74	169±42[b]	203±204	95±33[b]	37±7	41±11	131±43[b]	5±2[b]	77	84
55–64 y	145	170±42	174±122	98±35	38±8	46±13	131±42	4±1	75	81
≥65 y	126	155±31	158±85	83±25	39±9	44±11	115±30	4±1	81	83
Mexico										
<55 y	23	179±54	272±165[c]	91±26	30±5	31±8	148±54	6±2[b]	70[c]	70
55–64 y	38	178±35	218±102	100±34	36±8	35±6	142±32	5±1	45	55
≥65 y	20	175±34	164±67	102±24	39±8	40±13	135±31	5±1	30	35
Brazil										
<55 y	86	178±39	210±132[b]	103±33	34±7[b]	41±10	142±38	5±1	78	80
55–64 y	135	177±45	188±111	103±38	35±7	42±9	139±44	5±1	69	70
≥65 y	129	181±39	157±76	109±33	39±10	42±10	141±38	5±1	72	72
Czech Republic[c]										
<55 y	7	222±66	537±550[c]	108±49	30±4	46±9	187±68	7±3	57	57
55–64 y	33	188±40	236±142	107±28	37±8	42±13	149±41	5±2	52	64
≥65 y	24	185±34	226±143	109±28	40±13	36±7	147±34	5±1	42	67

Abbreviations: BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides. Data are mean ± SD.
[a]Triglycerides log-transformed; [b]$P<.01$; [c]$P<.05$. [TC, LDL-C, and HDL-C mg/dL × 0.02586 = mmol/L] [triglycerides mg/dL × 0.0112 = mmol/L].

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 total cholesterol, LDL-C, and non-HDL-C concentrations. Although triglyceride and HDL-C concentrations were similar, these patients were likely to receive lipid treatment. 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 better health status and care utilization among the more educated. A study conducted in the Netherlands showed that persons 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 lower LDL-C and HDL-C levels and higher triglyceride values. 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 ATP III report,[10] which recommends an 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 have reported the adverse impact of TZD treatment on blood lipids in type 2 diabetes.[29–31] In BARI 2D, participants taking a TZD who did not receive statin therapy had higher LDL-C concentrations than participants not taking a TZD (Table IV). Prior research has also shown that treatment with the TZD pioglitazone shows a beneficial effect on triglycerides and a less detrimental effect on LDL-C than does rosiglitazone.[29–31] That finding was confirmed at this baseline examination, but the addition of statin therapy eliminated this difference, indicating that 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 trial 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 an LDL-C–lowering medication at baseline. Of those on medication, 33% (n=531) had an LDL-C value $\geq$100 mg/dL. Suboptimal dosages of statin medications may help explain this inadequate effect. This has been demonstrated by Baessler and colleagues[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 triglyceride 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 participants were healthier than the general population with diabetes and coronary artery disease. Because 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 sex-related disparity was also apparent, as men were treated more aggressively than women with statin/fibrate combinations. In addition, those with a higher education level, and presumably higher socioeconomic class, had more favorable lipid profiles compared with those who were less educated. It therefore appears that greater efforts to reduce socioeconomic and sex-related disparities in the management of lipid disorders in high-risk patients are needed.

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APPENDIX

Bari 2d Lipid Methodologies

The Cobas FARA analyzer (Roche Diagnostics) was in use at the Biochemistry Core Laboratory for measurement of lipid concentrations when BARI 2D began. This analyzer remained in use through December 2004. In January 2005 lipid analyses were moved to the Hitachi 911 analyzer (Roche Diagnostics). In June 2007 lipid analyses were moved to the Roche/Hitachi Modular P analyzer (Roche Diagnostics).

BARI 2D lipids are analyzed as endpoint reactions in which the absorbance change at 505 nm is measured photometrically at 37°C.

Cholesterol concentration is determined by a double enzyme (cholesterol esterase, cholesterol oxidase) reaction that yields hydrogen peroxide as one of its products. In the presence of peroxidase, 4-aminophenazone and phenol a colored product is produced and is measured at 505 nm without sample blank.

The triglycerides concentration is measured using a glycerol-blanked method in a two-step procedure that first inactivates endogenous free glycerol prior to quantitation. This reaction is followed by the enzymatic hydrolysis of triglycerides and determination of the liberated glycerol by an enzymatic color reaction and is measured at 505 nm.

The high density lipoprotein fraction is measured by determining its cholesterol content. The HDL-cholesterol fraction is separated from other lipoprotein fractions by precipitation of the non-HDL fractions with divalent cations (Mg^{2+}) and polyanions (dextran sulfate). The HDL-cholesterol fraction remains in the supernatant and is measured as described previously for total cholesterol.

The calculation of estimated low density lipoprotein cholesterol (LDLCholesterol) requires values derived from the measurement of cholesterol, triglycerides and high density lipoprotein cholesterol (HDLC) utilizing the Friedewald formula:

Estimated LDLCholesterol = Total Cholesterol – (HDLCholesterol + estimated VLDLCholesterol), where estimated VLDLCholesterol = triglycerides/5.

Once Cholesterol, Triglycerides and HDLCholesterol values are available, LDLCholesterol is automatically calculated by the MiSys laboratory information system. NOTE: LDLCholesterol cannot be estimated when triglycerides exceed a concentration of 400 mg/dL.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Supplemental Appendix S-1: Bari 2d investigators.

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