Association Between Albuminuria and Duration of Diabetes and Myocardial Dysfunction and Peripheral Arterial Disease Among Patients With Stable Coronary Artery Disease in the BARI 2D Study

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OBJECTIVE: **To evaluate the effect of prior duration of diabetes, glycated hemoglobin level at study entry, and microalbuminuria or macroalbuminuria on the extent and severity of coronary artery disease (CAD) and peripheral arterial disease.**

PATIENTS AND METHODS: **We studied baseline characteristics of the 2368 participants of the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) study, a randomized clinical trial that evaluates treatment efficacy for patients with type 2 diabetes and angiographically documented stable CAD. Patients were enrolled from January 1, 2001, through March 31, 2005. Peripheral arterial disease was ascertained by an ankle-brachial index (ABI) of 0.9 or less, and extent of CAD was measured by presence of multivessel disease, a left ventricular ejection fraction (LVEF) of less than 50%, and myocardial jeopardy index.**

RESULTS: **Duration of diabetes of 20 or more years was associated with increased risk of ABI of 0.9 or less (odds ratio [OR], 1.54; 95% confidence interval [CI], 1.04-2.26), intermittent claudication (OR, 1.61; 95% CI, 1.10-2.35), and LVEF of less than 50% (OR, 2.03; 95% CI, 1.37-3.02). Microalbuminuria was associated with intermittent claudication (OR, 1.53; 95% CI, 1.16-2.02) and ABI of 0.9 or less (OR, 1.31; 95% CI, 0.98-1.75), whereas macroalbuminuria was associated with abnormal ABI, claudication, and LVEF of less than 50%. There was a significant association between diabetes duration and extent of CAD as manifested by number of coronary lesions, but no other significant associations were observed between duration of disease, glycated hemoglobin levels, or albumin-to-creatinine ratio and other manifestations of CAD.**

CONCLUSION: **Duration of diabetes and microalbuminuria or macroalbuminuria are important predictors of severity of peripheral arterial disease and left ventricular dysfunction in a cohort of patients selected for the presence of CAD.**

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ABI = ankle-brachial index; ACR = albumin-to-creatinine ratio; BARI 2D = Bypass Angioplasty Revascularization Investigation 2 Diabetes; CAD = coronary artery disease; CI = confidence interval; HbA_{1c} = glycated hemoglobin; LVEF = left ventricular ejection fraction; MJI = myocardial jeopardy index; OR = odds ratio; PAD = peripheral arterial disease

The association between type 2 diabetes mellitus and a higher risk of cardiovascular disease is well known.[1-3] Among other risk factors in persons with diabetes, duration of diabetes, metabolic control, and albuminuria have been associated with the higher occurrence of coronary artery disease (CAD). However, there is a paucity of data showing associations between these risk factors and the anatomic and physiologic extent and severity of CAD.

A positive association has been reported between the duration of diabetes and the risk of developing CAD[4] or peripheral arterial disease (PAD).[5] Several studies have shown an association between glycated hemoglobin (HbA_{1c}) level and higher risk of cardiovascular events.[6] Albuminuria in the presence of type 2 diabetes has also been shown to predict CAD.[7] Microalbuminuria is one of the earliest clinical findings of diabetic nephropathy. In the HOPE (Heart Outcomes Prevention Evaluation) trial,[8] the presence of microalbuminuria or macroalbuminuria was associated with increased risk of cardiovascular events in persons with and without diabetes.

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The severity and extent of CAD are directly associated with the number of circulating triglyceride-rich lipoprotein particles and inversely associated with the number of high-density lipoprotein cholesterol particles containing apolipoprotein A-I in patients with type 2 diabetes.[9,10] Studies of small sample size have shown an association between metabolic control and duration of diabetes and the severity of CAD in patients with diabetes.[11,12] Kidney function, as assessed by glomerular filtration rate[13] and macroalbuminuria,[14] has also been related to the extent and severity of CAD.

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D)[15] study included patients with type 2 diabetes and angiographically significant CAD for whom an initial strategy of medical therapy or revascularization would be appropriate. Patients were evaluated at study entry for the effect of prior duration of diabetes, HbA_{1c} level, microalbuminuria and macroalbuminuria with regard to the angiographic burden of CAD, the presence of left ventricular systolic dysfunction, and the burden of PAD as measured by the ankle-brachial index (ABI) and clinical symptoms of claudication.

PATIENTS AND METHODS

Study Design

The design and protocol of BARI 2D have been described in detail.[16] Briefly, BARI 2D was designed to determine the optimal therapy for patients with diabetes and established CAD in the setting of a uniform degree of glycemic control with aggressive management of dyslipidemia, hypertension, smoking, and obesity. Patients were eligible for BARI 2D if they were aged 25 years or older, had been diagnosed as having type 2 diabetes, and had angiographically documented CAD, defined as either (1) one or more significant lesions (≥50% stenosis) suitable for elective revascularization and associated with documented ischemia or (2) one or more coronary arteries with a greater than 70% narrowing in patients with classic exertional angina but no stress test.

The diagnosis of type 2 diabetes in BARI 2D was established by any 1 of the following: (1) a confirmed fasting plasma glucose level of more than 125 mg/dL (to convert to mmol/L, multiply by 0.0555), (2) a random plasma glucose level of 200 mg/dL or more, (3) a plasma glucose level of 200 mg/dL or more 2 hours after ingestion of 75 g of glucose, (4) current treatment with dietary modifications or oral agents for the control of hyperglycemia, either alone or in combination with insulin, or (5) current treatment with insulin and no previous history of diabetic ketoacidosis.

For the current analysis, only baseline data were used. Glycated hemoglobin level, known duration of diabetes, and measures of albuminuria were used as indicators of severity of disease. Metabolic control was categorized on the basis of HbA_{1c} level: good, 7.0% or less; regular, 7.1% to 8.0%; and poor, greater than 8.0%. Duration of diabetes was categorized into 5-year range groups, except for patients with durations of 20 or more years, who were included in 1 group because they represented only 13.8% of the total sample. Albuminuria was categorized to differentiate microalbuminuria and macroalbuminuria. Microalbuminuria was defined as an albumin-to-creatinine ratio (ACR) between 30.1 and 300.0 mg/g (to convert mg/g to mg/mol, multiply by 8.84), and macroalbuminuria was defined as an ACR of more than 300.0 mg/g. Urine samples sent to the study Core laboratory (Biochemistry Core Laboratory; University of Minnesota, Minneapolis, MN) were used for ACR measurements. The presence of CAD was based on angiographic data for each patient, which were collected at the Angiography Core Laboratory (Stanford University, Stanford, CA). The extent of CAD was determined by the number of coronary lesions modeled as a continuous variable, by the presence or absence of multivessel disease, and by a derived myocardial jeopardy index (MJI), which is calculated as the percentage of the distal myocardium jeopardized by lesions causing stenosis of 50% or more in any of the 3 main coronary arteries or their branches.[16] Symptoms of PAD were captured in the form of a physician assessment of intermittent claudication and data on the ABI. Underlying PAD was defined as an ABI of 0.9 or less, independent of the clinical report of symptoms of intermittent claudication.

Between January 1, 2001, and March 31, 2005, 2368 patients were enrolled in BARI 2D at 49 clinical centers throughout North America, South America, and Europe. From that number, 2000 patients had complete data required for the current analyses. For analysis of the MJI, the patient selection was restricted to those who had not had a previous revascularization (n=1544). The protocol was approved by institutional review boards at all participating institutions, and patients signed written informed consent forms.

Statistical Analyses

The 3 measures of severity of diabetes used in these analyses—HbA_{1c} level, duration of diabetes, and ACR—were each categorized to create corresponding analysis groups. Statistical comparisons between the HbA_{1c} groups (3 categories), duration-of-diabetes groups (5 categories), and ACR groups (3 categories) were performed with tests sensitive to monotonic departures (trend) from the null hypothesis of no difference among the groups. These trend tests are based on the Mantel-Haenszel χ^2 statistic (for categorical variables). Multivariate analyses were performed to examine the predictors of CAD and PAD after adjustment for the following covariables: age, sex, race, duration of diabetes, HbA_{1c} level, ACR, cumulative

TABLE 1. **Baseline Characteristics of 2000 Study Patients (Demographic Information, Diabetes, Risk Factors, and Measures of CAD and PAD)[a,b]**

Baseline characteristics	
Male	70.8
Age (y)	62.2±8.9
White, non-Hispanic	65.1
Diabetes measures	
HbA_{1c}	
≤7.0	41.6
7.1-8.0	25.0
>8.0	33.4
Duration of diabetes (y)	10.4±8.6
<5.0	33.2
5.0-9.9	23.5
10.0-14.9	17.9
15.0-19.9	11.6
≥20.0	13.8
ACR (mg protein/g creatinine)	
≤30.0	67.6
30.1-300.0	23.1
>300.0	9.3
Atherosclerotic risk factors	
Systolic blood pressure, sitting (mm Hg)	131.9±20.3
Body mass index (kg/m^2)	31.6±5.8
Total cholesterol (mg/dL)	170.3±41.3
LDL-C (mg/dL)	96.8 ±33.5
HDL-C (mg/dL)	38.2±10.3
Triglycerides (mg/dL)	182.3±132.5
Smoking status	
Never smoked	32.5
Former smoker	55.4
Current smoker	12.1
CAD measures	
No. of lesions	4.77 ±2.26
>2-Vessel disease	66.8
Abnormal LVEF, site reading	16.8
MJI among 1544 patients with no prior revascularization	46.5±24.3
PAD measures	
ABI	
Low (≤0.90)	19.1
Normal (0.91-1.30)	66.1
High (>1.30) or noncompressible	14.8
Intermittent claudication	17.4

[a] Categorical values are provided as percentage of patients and continuous values as mean ± SD. Core Laboratory values (Biochemistry Core Laboratory, University of Minnesota, Minneapolis: lipid and HbA_{1c} levels and ACR measurements; Angiography Core Laboratory, Stanford University, Stanford, CA: CAD measures) were used when available (>94% overall, >96% among 2000 study participants), and local values were used otherwise. ABI = ankle-brachial index; ACR = albumin-to-creatinine ratio; CAD = coronary artery disease; HbA_{1c} = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; MJI = myocardial jeopardy index; PAD = peripheral arterial disease.

[b] SI conversion factors: To convert HbA_{1c} values from percentage to proportion of total hemoglobin, multiply by 0.01; to convert ACR values to mg/mol, multiply by 8.84; to convert total cholesterol, LDL-cholesterol, or HDL-cholesterol values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113.

albuminuria, systolic blood pressure, total cholesterol level, high-density lipoprotein cholesterol level, and smoking status. Logistic regression models were used to assess the possible association between diabetes parameters (HbA_{1c} level, duration of diabetes, and ACR) and presence of multivessel CAD, presence of an abnormal left ventricular ejection fraction (LVEF), and measures of PAD (expressed as a dichotomy: having a low ABI, having symptoms of claudication). Data are reported as mean ± SD unless otherwise specified.

RESULTS

The 2000 patients with all required baseline data for inclusion in the current study had no clinically important differences from the overall BARI 2D cohort of 2368 patients (data not shown). Most of the randomized patients were white (non-Hispanic) (1302 [65.1%]) and male (1416 [70.8%]); mean age was 62.2±8.9 years (Table 1). A third of the patients had a diagnosis of diabetes for less than 5 years. Overall, glycemic control was acceptable at baseline; nearly 42% of patients (832) had an HbA_{1c} level of less than 7%, and two-thirds of patients (1332) had a level of 8% or less. A substantial proportion of participants demonstrated either microalbuminuria (462 [23.1%]) or macroalbuminuria (186 [9.3%]). Two-thirds of patients (1336) had multivessel CAD, and 19.1% (382) demonstrated evidence of PAD (identified by an ABI ≤0.9).

The bivariate associations between various measures of diabetes severity (HbA_{1c} level, duration of diabetes, and albuminuria) and PAD and CAD measures are shown in Table 2. Longer duration of diabetes was positively associated with higher HbA_{1c} level and ACR (Table 2). Thus, among patients with diabetes duration of less than 5 years, less than 20% (388) had either microalbuminuria or macroalbuminuria, whereas among those with diabetes duration of 20 or more years, greater than 46% (928) demonstrated such evidence. No significant associations were noted between CAD or PAD and HbA_{1c} level (Table 2). Longer duration of diabetes and a higher ACR had significant associations with symptoms of intermittent claudication, presence of more coronary lesions, and a higher frequency of abnormal LVEF, but not with abnormal ABI, CAD in more than 2 vessels, or MJI.

In the multivariate analyses, after controlling for age, sex, race, duration of diabetes, HbA_{1c} level, ACR, cumulative albuminuria, systolic blood pressure, total cholesterol level, high-density lipoprotein cholesterol level, and smoking status, there were no associations between baseline HbA_{1c} level at study entry and measures of either PAD or CAD (Table 3). Duration of diabetes of 20 or more years (vs <5 years) was associated with increased risk of PAD (as measured by an ABI ≤0.9), intermittent claudication, and an LVEF of less than 50% (Table 3). This effect was independent of age. Compared with no albuminuria (ACR, <30 mg/g), both microalbuminuria (ACR, 30.0-300.0

TABLE 2. **Relation of PAD and Extent of CAD to Metabolic Control Estimated From HbA_{1c} Levels, Duration of Diabetes, and Albuminuria[a]**

	HbA_{1c}				Duration of diabetes (y)						Albuminuria (ACR [mg/g])			
	≤7.0 (n= 832)	7.1-8.0 (n= 500)	>8.0 (n= 668)	*P* value[b]	<5.0 (n= 666)	5.0-9.9 (n= 470)	10.0-14.9 (n= 357)	15.0-19.9 (n= 231)	≥20.0 (n= 276)	*P* value[b]	≤30.0 (n= 1354)	30.1-300.0 (n= 461)	>300.0 (n= 185)	*P* value[b]
HbA_{1c}	NA	NA	NA							<.001				<.001
≤7.0					57.4	39.6	32.2	27.7	30.8		46.2	35.4	23.2	
7.1-8.0					21.3	26.6	28.3	24.2	27.5		25.4	23.4	25.9	
>8.0					21.3	33.8	39.5	48.1	41.7		28.4	41.2	50.8	
Duration of diabetes (y)	8.3± 8.2	11.2± 8.6	12.4± 8.6	<.001	NA	NA	NA	NA	NA		9.3± 8.3	12.1± 8.9	14.4± 8.5	<.001
<5.0	45.9	28.4	21.3								39.7	23.4	11.4	
5.0-9.9	22.4	25.0	23.8								23.6	23.9	21.6	
10.0-14.9	13.8	20.2	21.1								15.6	21.5	25.4	
15.0-19.9	7.7	11.2	16.6								10.2	12.4	19.5	
≥20.0	10.2	15.2	17.2								10.9	18.9	22.2	
ACR (mg/g)				<.001						<.001	NA	NA	NA	
≤30.0	75.2	68.8	57.5		80.6	68.1	59.1	59.7	53.6					
30.1-300.0	19.6	21.6	28.4		16.2	23.4	27.7	24.7	31.5					
>300.0	5.2	9.6	14.1		3.2	8.5	13.2	15.6	14.9					
PAD measures														
ABI				.93						.29				.096
Low (≤0.9)	18.5	19.0	19.8		18.3	17.9	18.2	18.6	24.3		16.8	21.5	29.7	
Normal (0.91-1.30)	67.1	66.6	64.8		69.2	69.1	66.4	66.7	53.3		69.7	61.4	52.4	
High (>1.3) or non-compressible	14.4	14.4	15.4		12.5	13.0	15.4	14.7	22.5		13.5	17.1	17.8	
Intermittent claudication	15.3	19.8	18.1	.12	15.2	16.0	18.2	17.7	23.6	.003	14.7	21.7	25.9	<.001
CAD measures														
No. of lesions	4.70± 2.21	4.79± 2.31	4.86± 2.28	.37	4.49± 2.22	4.83± 2.19	4.84± 2.39	5.04± 2.20	5.04± 2.28	<.001	4.67± 2.21	4.89± 2.23	5.23± 2.57	.001
>2-Vessel disease	65.4	67.6	67.8	.31	64.4	66.8	66.4	70.6	69.6	.062	66.2	67.9	68.1	.45
Abnormal LVEF, site reading	16.5	17.2	16.9	.81	13.7	17.4	17.4	18.2	21.4	.004	15.1	16.9	29.2	<.001
MJI, patients with no prior revascularization	46.1± 25.1	46.1± 23.4	47.3± 24.0	.63	45.8± 24.5	46.7± 25.2	45.5± 23.2	48.7± 25.1	47.2± 23.1	.66	46.0± 24.4	47.2± 24.3	47.9± 23.6	.56

[a] Values in the cells are either percent distribution in each column category or mean values ± SD (for continuous variables). ABI = ankle-brachial index; ACR = albumin-to-creatinine ratio; CAD = coronary artery disease; HbA_{1c} = glycated hemoglobin; LVEF = left ventricular ejection fraction; MJI = myocardial jeopardy index; NA = not applicable; PAD = peripheral arterial disease.
[b] Test for trend.

mg/g) and macroalbuminuria (ACR, >300.0 mg/g) were associated with an LVEF of less than 50%, an abnormal ABI, and intermittent claudication, independent of potential confounders included in the multivariate analysis.

In this diabetic population with established coronary arteriopathy, a correlation was noted between the duration of diabetes and the presence of PAD and claudication. A significant association was also noted between the duration of diabetes and the extent of CAD as measured by the number of lesions, but only an imprecise and nonsignificant association was observed between duration of diabetes and the presence of multivessel CAD or CAD burden as measured by LVEF (Table 3).

DISCUSSION

Epidemiological and interventional studies have clearly shown that the incidence of diabetic complications increases with greater severity of diabetes (as defined by the level of HbA_{1c}) and the duration of the disease.[17-20] Despite the general correlation among the duration of diabetes, glycemic control, and the emergence of complications, susceptibility to diabetic complications varies considerably among individuals.[21] This study reexamines the association between current glycemic control and the presence of macrovascular and microvascular complications in a large patient population with type 2 diabetes and known CAD.

TABLE 3. **Odds Ratio Estimates for Various Measures of PAD and CAD, by Duration of Diabetes, Glycated Hemoglobin Level, and Urinary Excretion of Albumin[a,b]**

Measures of diabetes severity	PAD		CAD	
	ABI ≤0.9 (n=381; N=1705)[c] OR (95% CI)	Claudication (n=347; N=2000) OR (95% CI)	Multivessel disease (n=1335; N=2000) OR (95% CI)	LVEF <50% (n=336; N=2000) OR (95% CI)
Duration of diabetes (y)				
<5.0 (reference)	1.00	1.00	1.00	1.00
5.0-9.9	0.91 (0.66-1.26)	1.04 (0.74-1.45)	1.08 (0.84-1.39)	1.39 (1.00-1.95)
10.0-14.9	1.00 (0.70-1.43)	1.22 (0.85-1.74)	1.06 (0.80-1.40)	1.42 (0.98-2.05)
15.0-19.9	1.00 (0.66-1.53)	1.16 (0.76-1.77)	1.30 (0.92-1.82)	1.48 (0.97-2.26)
≥20.0	1.54 (1.04-2.26)	1.61 (1.10-2.35)	1.32 (0.96-1.82)	2.03 (1.37-3.02)
HbA_{1c} (%)				
≤7.0 (reference)	1.00	1.00	1.00	1.00
7.1-8.0	0.96 (0.71-1.31)	1.29 (0.96-1.75)	1.11 (0.87-1.42)	1.01 (0.74-1.38)
>8.0	1.02 (0.76-1.39)	1.13 (0.83-1.53)	1.09 (0.86-1.39)	0.98 (0.72-1.32)
ACR (mg/g)				
≤30.0 (reference)	1.00	1.00	1.00	1.00
30.1-300.0	1.31 (0.98-1.75)	1.53 (1.16-2.02)	1.02 (0.81-1.29)	1.18 (0.87-1.59)
>300.0	1.73 (1.15-2.59)	1.83 (1.23-2.73)	0.99 (0.69-1.41)	2.65 (1.79-3.93)
Cumulative albuminuria (ACR, >30.0 mg/g)	1.41 (1.09-1.83)	1.60 (1.24-2.07)	1.01 (0.82-1.26)	1.48 (1.13-1.92)

[a] Estimates from multivariate model adjusting for age, sex, race (white, African American, Hispanic, other), duration of diabetes, HbA_{1c} level, ACR, cumulative albuminuria, systolic blood pressure, total cholesterol level, high-density lipoprotein cholesterol level, and smoking status (none, previous, current). ABI = ankle-brachial index; ACR = albumin-to-creatinine ratio; CAD = coronary artery disease; CI = confidence interval; HbA_{1c} = glycated hemoglobin; LVEF = left ventricular ejection fraction; OR = odds ratio; PAD = peripheral arterial disease.

[b] SI conversion factor: To convert ACR values to mg/mol, multiply by 8.84.

[c] Low ABI vs normal ABI. Excluded from analysis are 295 patients with high ABI or with noncompressible vessels.

No correlation was found between CAD burden and HbA_{1c} level at study entry, perhaps reflecting the inadequacy of a single HbA_{1c} measurement at study entry to reflect lifetime glycemic control. This lack of association may also reflect the weaker influence of hyperglycemia relative to lipid level and blood pressure control on coronary outcomes, as suggested in UKPDS (UK Prospective Diabetes Study), ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), and Steno 2 trials.[22-25]

One possible explanation for these findings is that the population selected was relatively homogenous in angiographic severity of CAD. The exclusion criteria eliminated persons with high-grade proximal lesions of the left main coronary artery or of left main coronary artery–equivalent anatomy; on the basis of known survival data, it was deemed inappropriate to randomize these patients to medical therapy rather than revascularization. The inclusion criteria required that participants have angiographically significant obstructive lesions of the proximal or medium-sized coronary vessels that could reasonably be treated with either revascularization or medical therapy.

A potential surrogate marker for the severity of vascular disease in diabetes is the presence of albuminuria.[26] In contrast to HbA_{1c} level, microalbuminuria and macroalbuminuria showed a significant correlation with both claudication and ABI of 0.9 or less and with CAD measured by the number of coronary lesions and percentage of patients with LVEF abnormalities (Table 2). Our observation confirms the well-described association of albuminuria as a marker of future cardiovascular events,[27]cardiac death, or nonfatal myocardial infarction[28] and shows the importance of microalbuminuria as a marker of CAD severity.

Of note is the finding that the HbA_{1c} values significantly correlated with the severity of albuminuria (Table 2). Although the emergence of proteinuria requires years of poor glycemic control, short-term changes in blood glucose values can also alter the rate of urinary protein excretion.[29] The correlation of the duration of diabetes and the presence of albuminuria (Table 2) is in agreement with the known association between microvascular complications and the duration of diabetes.[19] The presence of proteinuria is a marker of both CAD and PAD (Table 3) and is itself dependent on other risk factors, such as hypertension and diabetic nephropathy, but it is not dependent on lipid levels.[30] In our data, HbA_{1c} level correlated with albuminuria, and albuminuria correlated with the burden of CAD and PAD, but HbA_{1c} level did not directly correlate with the burden of CAD and PAD. This finding for people with type 2 diabetes in BARI 2D contrasts with the findings in patients with type 1 diabetes in DCCT/EDIC

(Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study). In patients with type 1 diabetes, the difference in HbA_{1c} level between intensive and conventional treatment groups explained the beneficial effect of intensive treatment on CAD and PAD.[31]

CONCLUSION

In a population of patients with stable CAD, duration of diabetes is associated with a higher prevalence of microalbuminuria and myocardial dysfunction. Peripheral arterial disease and further deterioration of myocardial function are seen when diabetes duration exceeds 20 years. Longer duration of diabetes and especially macroalbuminuria portend a greater number of coronary lesions. The large number of patients included in BARI 2D adds to the relevance of this study, as do the specific objective measures of structural changes indicative of the severity of CAD and PAD. Microalbuminuria, an early marker of nephropathy, can also be considered a marker of more severe CAD, and its diagnosis must be a primary goal in the care of a patient with type 2 diabetes. Whether patients with PAD, albuminuria, or both achieve similar benefits with either initial medical therapy or revascularization in the BARI 2D clinical trial remains to be seen.

REFERENCES

1. Mueller HS, Cohen LS, Braunwald E, et al; TIMI Investigators. Predictors of early morbidity and mortality after thrombolytic therapy of acute myocardial infarction: analyses of patient subgroups in the Thrombolysis in Myocardial Infarction (TIMI) trial, phase II. *Circulation*. 1992;85(4):1254-1264.

2. Natali A, Vichi S, Landi P, Severi S, L'Abbate A, Ferrannini E. Coronary atherosclerosis in type II diabetes: angiographic findings and clinical outcome. *Diabetologia*. 2000;43(5):632-641.

3. Melidonis A, Dimopoulos V, Lempidakis E, et al. Angiographic study of coronary artery disease in diabetic patients in comparison with nondiabetic patients. *Angiology*. 1999;50(12):997-1006.

4. Hu FB, Stampfer MJ, Solomon CG, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. *Arch Intern Med*. 2001;161(14):1717-1723.

5. Al-Delaimy WK, Merchant TA, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Effect of type 2 diabetes and its duration on the risk of peripheral arterial disease among men. *Am J Med*. 2004;116(4):236-240.

6. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med*. 2004;141(6):421-431.

7. de Zeeuw D, Parving HH, Henning RH. Microalbuminuria as an early marker for cardiovascular disease. *J Am Soc Nephrol*. 2006 Aug;17(8):2100-2105. Epub 2006 Jul 6.

8. Gerstein HC, Mann JF, Yi Q, et al; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*. 2001;286(4):421-426.

9. Tkác I, Kimball BP, Lewis G, Uffelman K, Steiner G. The severity of coronary atherosclerosis in type 2 diabetes mellitus is related to the number of circulating triglyceride-rich lipoprotein particles. *Arterioscler Thromb Vasc Biol*. 1997;17(12):3633-3638.

10. Syvänne M, Pajunen P, Kahri J, et al. Determinants of the severity and extent of coronary artery disease in patients with type-2 diabetes and in nondiabetic subjects. *Coron Artery Dis*. 2001;12(2):99-106.

11. Ravipati G, Aronow WS, Ahn C, Sujata K, Saulle LN, Weiss MB. Association of hemoglobin A_{1c} level with the severity of coronary artery disease in patients with diabetes mellitus. *Am J Cardiol*. 2006 Apr;97(7):968-969. Epub 2006 Feb 13.

12. Saleem T, Mohammad KH, Abdel-Fattah MM, Abbasi AH. Association of glycosylated haemoglobin level and diabetes mellitus duration with the severity of coronary artery disease. *Diab Vasc Dis Res*. 2008;5(3):184-189.

13. Abaci A, Şen N, Yazici H, et al. Renal dysfunction is the most important predictor of the extent and severity of coronary artery disease in patients with diabetes mellitus. *Coron Artery Dis*. 2007;18(6):463-469.

14. Liu JE, Robbins DC, Palmieri V, et al. Association of albuminuria with systolic and diastolic left ventricular dysfunction in type 2 diabetes: the Strong Heart Study. *J Am Coll Cardiol*. 2003;41(11):2022-2028.

15. BARI 2D Study Group. Baseline characteristics of patients with diabetes and coronary artery disease enrolled in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *Am Heart J*. 2008 Sep;156(3):528-536, 536.e1-536.e5. Epub 2008 Jul 31.

16. Botas J, Stadius ML, Bourassa MG, et al; BARI Investigators. Angiographic correlates of lesion relevance and suitability for percutaneous transluminal coronary angioplasty and coronary artery bypass grafting in the Bypass Angioplasty Revascularization Investigation study (BARI). *Am J Cardiol*. 1996;77(10):805-814.

17. Candido R, Srivastava P, Cooper ME, Burrell LM. Diabetes mellitus: a cardiovascular disease. *Curr Opin Investig Drugs*. 2003;4(9):1088-1094.

18. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12 year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16(2):434-444.

19. Stratton IM, Adler AI, Neil HA, et al. Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405-412.

20. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). *BMJ*. 2001;322(7277):15-18.

21. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33*)* [published correction appears in *Lancet.* 1999;354(9178):602]. *Lancet*. 1998;352(9131):837-853.

22. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of microvascular and microvascular complications in Type 2 diabetes: UKPDS 38 [published correction appears in *BMJ.* 1999;318(7175)29]. *BMJ*. 1998;317(7160):703-713.

23. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008 Jun 12;358(24):2545-2559. Epub 2008 Jun 6.

24. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008 Jun 12;358(24):2560-2572. Epub 2008 Jun 6.

25. Gaede P, Lund-Anderson H, Parving HH, Pederson O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med*. 2008;358(6):580-591.

26. Miettinen H, Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Proteinuria predicts stroke and other atherosclerotic vascular disease events in nondiabetic and non-insulin-dependent diabetic subjects. *Stroke*. 1996;27(11):2033-2039.

27. Gerstein HC, Mann JFE, Yi Q, et al; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*. 2001;286(4):421-426.

28. Young LH, Wackers FJT, Chyun DA, et al; DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes. The DIAD Study: a randomized controlled trial. *JAMA*. 2009;301(15):1547-1555.

29. Parving HH, Noer I, Deckert T, et al. The effect of metabolic regulation on microvascular permeability to small and large molecules in short-term juvenile diabetics. *Diabetologia*. 1976;12(2):161-166.

30. Jager A, Kostense PJ, Ruhé HG, et al. Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: five-year follow-up of the Hoorn Study. *Arterioscler Thromb Vasc Biol*. 1999;19(3):617-624.

31. Nathan DM, Cleary PA, Backlund JY, et al; Diabetes control and complications trial/Epidemiology of diabetes interventions and complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353(25):2643-2653.