Diabetes, Intermittent Claudication, and Risk of Cardiovascular Events

The Framingham Study

FREDERICK N. BRAND, ROBERT D. ABBOTT, AND WILLIAM B. KANNEL

The impact of diabetes on intermittent claudication was examined in 1813 men and 2504 women with 34-yr follow-up data in the Framingham study. For both sexes, diabetes was associated with a two- to threefold excess risk of intermittent claudication compared with its absence. A pronounced excess risk was also observed in subjects on oral hypoglycemic therapy and in women receiving insulin. Although diabetes was often associated with an atherogenic-risk profile, controlling for age and several concomitant risk factors failed to eliminate the association with intermittent claudication. Those who developed both intermittent claudication and diabetes were at an especially high risk of incident cardiovascular events. In women, the risk of coronary heart disease, stroke, and cardiac failure was increased 3–4 times when diabetes and intermittent claudication occurred together compared with when either condition existed alone. In diabetic men, the presence of intermittent claudication doubled the risk of stroke, and cardiac failure was ~3 times more likely in subjects with both conditions compared with either alone. We conclude that diabetes is an important risk factor for intermittent claudication, which in turn confers a serious prognosis for subsequent cardiovascular outcomes in the patient with diabetes. *Diabetes* 38:504–509, 1989

Intermittent claudication, the main symptom of peripheral arterial disease, usually becomes manifest later in life (1). Peripheral arterial disease also occurs more frequently in the presence of diabetes, particularly diabetes of long duration (2–4). Detailed epidemiologic descriptions of the influence of diabetes on peripheral vascular disease, however, are sparse. In addition, the consequences of each condition on cardiovascular sequelae in general population samples are not well defined.

The purpose of this article is to further investigate the development of intermittent claudication among diabetic subjects, taking into account the confounding effect of several concomitant risk factors, and to examine the prognosis associated with development of intermittent claudication in the patient with diabetes. Data for this study are based on 34 yr of follow-up of the cohort of subjects originally enrolled in the Framingham study and followed biennially for the development of coronary heart disease, stroke, and cardiac failure.

MATERIALS AND METHODS

Since 1948, the Framingham study has biennially followed 5209 men and women for the development of cardiovascular disease. At the time of study entry, subjects were aged 30–62 yr. Sampling methods, response rates, and examination procedures have been described elsewhere (5,6). For this article, data were available from 18 examinations comprising 34 yr of follow-up.

In the Framingham study, a diagnosis of diabetes was based on a history of treatment with insulin or oral hypoglycemic agents, abnormal glucose tolerance tests, and casual blood glucose concentrations of ≥150 mg/dl on at least two Framingham examinations. Although the study did not include glucose tolerance tests, records of such tests were obtained from private physicians and hospitals. A glucose tolerance test was considered acceptable for study if it was taken after a 12-h fast and the ingestion of a 100-g load. The test was considered abnormal if a blood glucose concentration of ≥160 mg/dl was achieved 1 h after challenge and ≥140 mg/dl after 2 h. All subjects who exhibited characteristics of diabetes had their records carefully reviewed by study investigators before a final diagnosis was made. Those with other explanations for transiently elevated blood glucose levels were not defined as diabetic. Blood glucose was

Cholesterol 1 mM = 38.7 mg/dl	Glucose 1 mM = 18 mg/dl

From the Section of Preventive Medicine and Epidemiology, Boston University School of Medicine, Evans Research Foundation, Boston, Massachusetts; and the Statistical Resource Section, National Heart, Lung, and Blood Institute, Bethesda, Maryland.

Address correspondence and reprint requests to Frederick N. Brand, MD, The Framingham Study, 118 Lincoln Street, Framingham, MA 01701.

Received for publication 15 July 1988 and accepted in revised form 3 November 1988.

routinely determined by the method of Somogyi-Nelson (7).

The definition of intermittent claudication has been described elsewhere (6). Minimum criteria consisted of tightness or cramping discomfort in the calf, clearly provoked by walking, with rapidly increasing pain when walking quickly or uphill, and being relieved within a few minutes of rest. Interviews for symptoms of claudication were conducted by study physicians using standardized forms for uniformity of assessment. All diagnoses of intermittent claudication were confirmed by at least two study investigators.

Several suspected risk factors associated with diabetes and intermittent claudication were measured at various Framingham examinations. Those considered in this article include systolic blood pressure, body mass index (kg/m^2), hematocrit, uric acid, left ventricular hypertrophy by ECG, cigarette smoking, total cholesterol, and concentrations of cholesterol in the class of high-density lipoprotein (HDL-chol), low-density lipoprotein (LDL-chol), and very-low-density lipoprotein (VLDL-chol). Procedures used to measure uric acid (8), levels of lipoprotein cholesterol (9), and the other risk factors are described elsewhere (6).

Among subjects with diabetes, risk factors were measured at the Framingham examination when diabetes was first diagnosed. For comparison with a group of nondiabetic subjects, risk factors were measured at the 10th biennial examination in those who were free of diabetes. The 10th examination was chosen so that the average age of those with and without diabetes would be similar.

Unfortunately, not all risk factors were measured at every biennial examination. Lipoprotein cholesterol levels were measured in a fasting state once from 1969 to 1971, beginning with the 10th examination. Uric acid was determined at exams 1–4 and 13. Information on the other risk factors is available from each biennial exam. In the event that information was missing, risk-factor data from the most recent exam were used.

All subjects were free of intermittent claudication at the time of risk-factor measurement. For all risk factors, age-adjusted comparisons between subjects with and without diabetes were based on analysis of covariance and logistic regression models (10).

Beginning at the examination when diabetes was first diagnosed, or the 10th exam for nondiabetic subjects, subjects without intermittent claudication were followed every 2 yr for symptoms of claudication at subsequent biennial examinations. Person-exams at risk of claudication and the number of first appearances were then combined to form age-adjusted 2-yr incidence rates among diabetic and nondiabetic subjects (10). Tests of significance and estimated relative risks of claudication, comparing subjects with and without diabetes, were based on logistic regression models for survival data analysis (11) and were adjusted for age and several other risk factors. Diabetes that developed in the course of follow-up among the sample who were nondiabetic at the 10th exam was modeled as a time-dependent covariate; i.e., individuals who developed diabetes contributed to the survival experience of the diabetic sample when their diabetes was first observed.

To determine the prognosis for additional cardiovascular events among diabetic and nondiabetic subjects and intermittent claudication, follow-up was extended to include incident cases of coronary heart disease, stroke, and cardiac failure (6). As with the incidence calculations for intermittent claudication, subjects were followed every 2 yr for a cardiovascular event, providing data for estimating age-adjusted 2-yr incidence rates. As before, tests of significance were based on logistic regression models for survival data analysis.

RESULTS

For this article, the effect of diabetes on intermittent claudication was examined in 1813 men and 2504 women. Among these groups, 318 men and 326 women had diabetes. The average age when follow-up began was virtually identical (within 1 yr) for subjects with and without diabetes for either sex. For men, the average age was 60.3 yr (8.5SD), and for women, the average was 61.0 yr (8.5SD).

Risk of intermittent claudication. Except for the oldest men, subjects with diabetes were more likely to develop intermittent claudication than those without diabetes (Table 1). Diabetic women were also more likely to develop claudication compared with those who were nondiabetic, regardless of age. Statistically significant differences occurred in men aged 50–59 and 60–69 yr and for the three age groups of women within 50–79 yr.

Men were also more likely to be victims of intermittent claudication than women for all but the oldest age group. Nondiabetic men who were aged 50–59 and 60–69 yr were at significantly greater risk of claudication compared with similarly aged women. Although the incidence of intermittent claudication increased with age up to 70 yr for all groups of

TABLE 1
Two-year incidence of intermittent claudication by age, sex, and diabetic status

Age (yr)	Diabetic men		Nondiabetic men*		Diabetic women		Nondiabetic women	
	Rate/1000	*n*/person-exams	Rate/1000	*n*/person-exams	Rate/1000	*n*/person-exams	Rate/1000	*n*/person-exams
<50	15.6	2 of 128	0.0	0 of 95	9.1	1 of 110	0.0	0 of 128
50–59	18.1†	8 of 441	4.8	12 of 2506	12.3‡	5 of 405	4.1	14 of 3375
60–69	32.5§	24 of 738	10.8‖	43 of 3987	26.2§	19 of 724	6.2	38 of 6143
70–79	17.0	8 of 470	11.3¶	27 of 2389	15.7†	9 of 575	4.9	21 of 4286
>79	0.0	0 of 75	3.4	2 of 593	5.0	1 of 201	3.6	5 of 1386

n = number of events at risk of occurring.
* $P < .01$, significant age effect on the incidence of intermittent claudication in nondiabetic men who were <80 yr old.
† $P < .01$, ‡ $P < .05$, § $P < .001$, excess risk compared with nondiabetic subjects in the same age and sex group.
‖ $P < .05$, ¶ $P < .01$, excess risk compared with nondiabetic women in the same age group.

TABLE 2
Age-adjusted mean risk factors

Risk factor	Men		Women	
	Diabetic (n = 318)	Nondiabetic (n = 1495)	Diabetic (n = 326)	Nondiabetic (n = 2178)
Blood glucose (mg/dl)	146.8 ± 75.8*	87.4 ± 16.7	134.3 ± 68.0*	85.9 ± 16.4
Systolic blood pressure (mmHg)	145.0 ± 23.0*	136.9 ± 21.6	149.2 ± 28.2*	139.6 ± 24.4
Body mass index (kg/m^2)	27.4 ± 3.9*	26.0 ± 3.4	28.0 ± 6.4*	25.4 ± 4.3
Hematocrit (%)	46.6 ± 4.1*	45.2 ± 3.6	43.9 ± 4.1*	41.9 ± 3.5
Uric acid (mg/dl)	5.3 ± 1.3*	4.9 ± 0.9	4.4 ± 1.1*	3.9 ± 0.8
Left ventricular hypertrophy (%)	6.3 ± 24.3*	1.7 ± 13.1	5.9 ± 24.0*	1.8 ± 13.3
Cigarette use (%)	35.6 ± 48.0†	43.0 ± 49.5	32.3 ± 46.3	33.6 ± 47.3
Total cholesterol (mg/dl)	223.1 ± 42.5	223.4 ± 40.4	248.2 ± 49.2	243.6 ± 44.3
HDL-chol (mg/dl)	42.1 ± 12.5*	46.1 ± 13.1	53.0 ± 16.6*	57.6 ± 15.4
LDL-chol (mg/dl)	138.2 ± 39.9	143.1 ± 36.7	155.9 ± 42.7	156.1 ± 38.9
VLDL-chol (mg/dl)	37.3 ± 28.4*	30.1 ± 21.5	33.1 ± 23.5*	27.9 ± 18.6

Values are means ± SD. HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol; VLDL-chol, very-low-density lipoprotein cholesterol.
*$P < .001$, †$P < .05$, vs. nondiabetic subjects.

subjects, a significant effect of age was observed in only nondiabetic men <80 yr.

The differences in the incidence of intermittent claudication between men and women was greater for those with diabetes compared with those without diabetes for individuals <70 yr, with less apparent influences due to gender and diabetes occurring in those who were older (Table 1). Interaction effects on the incidence of intermittent claudication involving age, sex, and diabetes, however, were not statistically significant.

Compared with nondiabetic individuals, those with diabetes had significantly higher levels of systolic blood pressure, hematocrit, uric acid, and VLDL-chol and had lower concentrations of HDL-chol (Table 2). Those with diabetes were also significantly heavier and more likely to have left ventricular hypertrophy than those without diabetes. Neither total cholesterol nor LDL-chol showed any relationship to diabetic status. Although subjects with diabetes were less likely to smoke cigarettes than those without diabetes, a significant difference was noted only in men.

After age adjustment, subjects with diabetes had a threefold excess risk ($P < .001$) of intermittent claudication compared with those without diabetes (Table 3). Risk ratios were greater for women than men. Based on the risk-factor comparisons described in Table 2, relative risks were estimated after additional adjustment for systolic blood pressure, body mass index, hematocrit, uric acid, HDL-chol, VLDL-chol, and the use of cigarettes. After risk-factor adjustment, the excess risk of intermittent claudication in diabetic subjects was somewhat reduced, but it remained significant ($P < .01$). The rate of intermittent claudication in diabetic subjects was twice the rate for those without diabetes, taking other risk factors into account.

Although intermittent claudication was strongly related to diabetes, the elevated risk did not appear to be altered by its duration (Table 4). There was no apparent or significant trend in the incidence of intermittent claudication for either men or women across levels of diabetes duration ranging from <6 to ≥18 yr.

The incidence of intermittent claudication was further examined in relation to the use of diabetic medication. Without exception, the incidence of claudication was lowest for the nondiabetic subjects (Table 5). After adjusting for the risk factors, diabetic men on oral hypoglycemic therapy had the highest rate of intermittent claudication, significantly higher than those without diabetes ($P < .05$). For women, the highest rates of diabetes occurred among those receiving insulin or oral agents, more than tripling the rate experienced by those without diabetes ($P < .01$). There were no significant differences among the rates of intermittent claudication for the treated and untreated diabetic men and women after risk-factor adjustment.

Prognosis. Among subjects with diabetes, a prognostic comparison was made between those with and without in-

TABLE 3
Age-adjusted 2-yr incidence and estimated relative risks of intermittent claudication

	2-yr incidence				Estimated relative risk			
	Diabetic		Nondiabetic		Age adjusted		Risk-factor adjusted*	
	Rate/1000	n/person-exams	Rate/1000	n/person-exams	Rate/1000	95% CI	Rate/1000	95% CI
Men	22.9	42 of 1852	8.8	84 of 9570	2.7†	(1.8, 3.9)	2.0‡	(1.2, 3.3)
Women	17.3	35 of 2015	5.1	78 of 15,318	3.4†	(2.3, 5.1)	2.4‡	(1.4, 4.2)

n = number of patients at risk; CI, confidence interval.
*Adjusted for age, systolic blood pressure, body mass index, hematocrit, uric acid, high-density and very-low-density lipoprotein cholesterol, and the use of cigarettes.
†$P < .001$, ‡$P < .01$, excess risk compared with nondiabetic subjects.

TABLE 4
Age-adjusted 2-yr incidence of intermittent claudication by duration of diabetes

Duration of diabetes (yr)	Men		Women	
	Rate/1000	*n*/person-exams	Rate/1000	*n*/person-exams
<6	19.7	10 of 509	16.4	9 of 534
≥6 and <12	18.4	10 of 544	21.4	12 of 579
≥12 and <18	24.9	7 of 280	17.0	5 of 324
≥18	20.9	2 of 95	18.1	2 of 129
Unknown	30.8	13 of 424	14.0	7 of 449

Duration of diabetes and incidence of intermittent claudication were not significantly related. *n* = number of patients at risk.

termittent claudication. For both men and women, each cardiovascular event occurred more frequently in the presence of diabetes associated with intermittent claudication (Table 6). In the presence of both conditions, coronary heart disease was the most common cardiovascular manifestation. Although not statistically significant, diabetic women with intermittent claudication experienced coronary heart disease, stroke, and cardiac failure more often than similarly afflicted men.

For diabetic men, the risk of stroke was doubled in the presence of intermittent claudication compared with men with diabetes alone ($P < .05$). Risk of cardiac failure was nearly 3 times more common in subjects with both diabetes and intermittent claudication compared with either diabetes alone ($P < .001$) or intermittent claudication alone ($P < .01$).

In women, the risk of each cardiovascular event was significantly increased in coexistent diabetes and intermittent claudication compared with the presence of either condition. There was a three- to fourfold excess of coronary events and cardiac failure ($P < .001$) in those with both conditions. Stroke was nearly 3 times more common when diabetes and intermittent claudication coexisted ($P < .01$ vs. diabetes alone and $P < .05$ vs. intermittent claudication alone).

Although the risk of new cardiovascular events was often significantly more common when diabetes and intermittent claudication coexisted than in the presence of one condition, the effect of diabetes and intermittent claudication was not significantly enhanced by the other. Sex-specific interactions were also statistically insignificant, a possible consequence of small numbers.

Compared with nondiabetic subjects, the risk of each cardiovascular event was significantly higher in those with diabetes, intermittent claudication, or both ($P < .05$). The only exception occurred in women with intermittent claudication alone, where the rate of coronary heart disease exceeded the rate for women without diabetes and intermittent claudication, although the comparison failed to achieve statistical significance.

DISCUSSION

As with most observational studies, findings from Framingham may be influenced by selective survival experiences or by the often healthier predisposition of individuals who volunteer for medical evaluation. Unfortunately, the effect of these influences cannot be evaluated for this article. Nevertheless, results from Framingham are consistent with other studies that have demonstrated that intermittent claudication and degenerative vascular disease is not uncommon in diabetic men and women <60 yr old relative to those without diabetes (12–14).

Some evidence suggests that duration of diabetes is also an important contributor to the development of macrovascular complications, including coronary heart disease and peripheral atherosclerotic disease, although details are controversial (2–4,15–20). Although duration of diabetes in Framingham was not predictive of intermittent claudication, it appears that severity of diabetes is important. Evidence suggests that subjects with diabetes in need of control by oral agents had the highest rates of intermittent claudication. Women receiving insulin were also at especially high risk. In addition, despite having lower levels of blood glucose, the

TABLE 5
Age-adjusted mean blood glucose levels and 2-yr incidence of intermittent claudication in diabetic subjects by diabetes medication

	Diabetes medication			Without diabetes
	None	Insulin	Oral agents	
Men				
Blood glucose (mg/dl)	146.0 ± 73.5	186.3 ± 93.5*	127.2 ± 60.3†	87.4 ± 16.7‡
2-yr incidence				
Age adjusted	14.0	29.8	31.6†	8.8§
Risk-factor adjusted‖	13.3	12.0	23.8	9.8¶
n/person-exams at risk	12 of 857	11 of 389	19 of 606	84 of 9570
Women				
Blood glucose (mg/dl)	141.1 ± 73.3	153.7 ± 83.2	117 ± 47.6#	85.9 ± 16.4‡
2-yr incidence				
Age adjusted	8.8	29.8†	18.6	5.1§
Risk-factor adjusted‖	11.0	25.0	18.2	6.0**
n/person-exams at risk	7 of 800	14 of 458	14 of 757	78 of 15,318

*$P < .001$, †$P < .05$, #$P < .01$, vs. untreated subjects.
‡$P < .001$ vs. diabetic groups.
§$P < .001$, **$P < .01$, vs. subjects receiving insulin or oral agents.
¶$P < .05$ vs. subjects receiving oral agents.
‖Adjusted for age, systolic blood pressure, body mass index, hematocrit, uric acid, high-density lipoprotein and very-low-density lipoprotein cholesterol, blood glucose, and the use of cigarettes.

TABLE 6
Two-year age-adjusted incidence of coronary heart disease, stroke, and cardiac failure

	Coronary heart disease		Stroke		Cardiac failure	
	Rate/100	*n*/person-exams	Rate/100	*n*/person-exams	Rate/100	*n*/person-exams
Men						
Diabetic with intermittent claudication	8.1*	13 of 163	5.3†‡	14 of 245	7.5†§	20 of 251
Diabetic only	6.2†	83 of 1417	2.6‖	41 of 1741	2.7†	43 of 1748
Intermittent claudication only	7.9	23 of 261	3.4†	20 of 468	2.6‖	16 of 494
Neither condition	4.0	321 of 8102	1.4	129 of 9198	1.3	117 of 9391
Women						
Diabetic with intermittent claudication	15.6†¶	15 of 98	6.7†#	13 of 189	9.2†¶	17 of 179
Diabetic only	5.2†	81 of 1631	2.7†	50 of 1917	3.3†	58 of 1867
Intermittent claudication only	3.6	11 of 274	2.5‖	13 of 401	2.5‖	12 of 414
Neither condition	2.1	286 of 13,870	1.1	158 of 14,773	0.9	128 of 14,974

n = number of events at risk of occurring.
*$P < .05$, †$P < .001$, ‖$P < .01$, vs. neither condition.
‡$P < .05$ vs. diabetic only.
§$P < .001$ vs. diabetic only and $P < .01$ vs. intermittent claudication only.
¶$P < .001$ vs. diabetic or intermittent claudication only.
#$P < .05$ vs. diabetic only and $P < .05$ vs. intermittent claudication only.

group treated with oral agents had a higher risk than those with untreated diabetes. A different conclusion was reached in a study of diabetes and treadmill-elicited intermittent claudication (21). In the latter report, however, investigators attributed their findings to differences in patient age. When an age correction was introduced, however, the insulin-dependent subjects had a 6–12% higher prevalence of peripheral vascular disease. The drawback of this study was a lack of age- and sex-matched control subjects.

In non-insulin-dependent diabetes, clinical signs of occlusive peripheral arterial disease are also exhibited more frequently than in subjects without diabetes. Such signs may include lower-limb calcification on X-ray or the absence of an arterial pulse at one or more locations (22). Subjects with diabetes seem to experience restricted perfusion of the arteries between the knee and ankle and less disease of aortic-iliac vessels than subjects with peripheral vascular disease who are nondiabetic (23,24). Circulatory problems that lead to gangrene, ulcers, and amputations are also not uncommon in diabetic individuals. Such events were too infrequent in the Framingham sample to be carefully examined.

In this article, diabetes was also strongly associated with other cardiovascular risk factors. Subjects with diabetes had higher levels of systolic blood pressure, hematocrit, uric acid, and VLDL-chol. Diabetic individuals also tended to be more obese and have lower concentrations of HDL-chol and were more likely to have left ventricular hypertrophy. Despite the strong relationship between diabetes and the preceding risk factors, diabetes was a significant independent contributor to the incidence of intermittent claudication. As a result, the underlying mechanism and metabolic derangements by which diabetes predisposes to premature or extensive peripheral arterial disease remain unclear and appear to be unexplained by known risk factors for atherosclerosis.

This article further demonstrates that the risk of each cardiovascular event is even greater when diabetes coexists with intermittent claudication. The joint effect of both conditions appears to be particularly strong in women, where the incidence of new cardiovascular events exceeded the rates experienced by men. Among survivors of a myocardial infarction in the Framingham sample, diabetes in women was also associated with a more severe prognosis compared with men for recurrent infarction or fatal coronary heart disease.

The issue of the influence of diabetic control on cardiovascular complications has been debated extensively without resolution. The major difficulty is that practical or accurate methods of monitoring the control of diabetes are not available. Studies in the United States have failed to show that strict control of diabetes prevents the development of peripheral vascular disease or improves the prognosis for coronary heart disease, stroke, and cardiac failure (21). Apparently, however, an aggressive multifactorial approach to controlling hypertension, obesity, blood glucose, and other cardiovascular risk factors is the most sensible way to reduce cardiovascular disease risk in the presence of diabetes or intermittent claudication. The Framingham data further suggest that such attempts may have their greatest potential for an improved prognosis when both diabetes and intermittent claudication occur together.

ACKNOWLEDGMENTS

This study was supported in part by National Institutes of Health Contracts NO1-HV-92922 and NO1-HV-52971.

REFERENCES

1. Kannel WB, Brand FN: Cardiovascular risk factors in the elderly. In *Principles of Geriatric Medicine*. Anders R, Bierman EI, Hazzard WR, Eds. New York, McGraw-Hill, 1985, p. 104–19
2. Semple R: Diabetes and peripheral arterial disease. *Lancet* 1:1064–68, 1953
3. Herzstein J, Weinroth LA: Arteriosclerotic peripheral vascular disease in diabetes. *Arch Intern Med* 76:34–38, 1945
4. Pearl FL, Kandel A: Peripheral vascular status of one hundred unselected patients with diabetes. *Arch Surg* 39:86–96, 1939
5. Dawber TR, Kannel WB, Lyell LP: An approach to longitudinal studies in a community: the Framingham Study. *Ann NY Acad Sci* 107:539–56, 1963
6. Cupples A, D'Agostino RB: *Some Risk Factors Related to the Annual Incidence of Cardiovascular Disease and Death Using Pooled Repeated Biennial Measurements. Framingham Heart Study: 30-Year Follow-Up*. Washington, DC, Natl. Inst. of Health, 1987 (DHHS publ. no. 87-2703)
7. Nelson N: A photometric adaptation of the Somogyi method for the determination of glucose. *J Biol Chem* 153:375–80, 1944
8. Jacobsen BM: The uric acid in the serum of gouty and non-gouty individuals: determination by Folin's recent method and its significance in the diagnosis of gout. *Ann Intern Med* 11:1277–95, 1938
9. Abbott RD, Garrison RJ, Wilson PWF, Epstein FH, Castelli WP, Feinleib

M, Larue C: Joint distribution of lipoprotein cholesterol classes: the Framingham Study. *Arteriosclerosis* 3:260–72, 1983
10. Lane PW, Nelder JA: Analysis of covariance and standardization as instances of prediction. *Biometrics* 38:613–21, 1982
11. Wu M, Ware J: On the use of repeated measurements in regression analysis with dichotomous responses. *Biometrics* 35:513–21, 1979
12. Vyden JK, Thorner J, Takano K, Groseth-Dittich MF, Perlow R, Swan HJC: Metabolic and cardiovascular abnormalities in patients with peripheral arterial disease. *Am Heart J* 190:703–708, 1975
13. Reunanen A, Takkunen R, Aromaa A: Prevalence of intermittent claudication and its effect on mortality. *Acta Med Scand* 211:249–55, 1982
14. Dry TG, Hines EA Jr: The role of diabetes in the development of degenerative vascular disease; with special reference to the incidence of retinitis and periferal neuritis. *Ann Intern Med* 14:1893–902, 1941
15. Melton LJ III, Macken KM, Palumbo PJ, Elveback LR: Incidence and prevalence of clinical peripheral vascular disease in a population-based cohort of diabetic patients. *Diabetes Care* 3:650–54, 1980
16. Janka HU, Standl E, Mehnert H: Peripheral vascular disease in diabetes mellitus and its relation to cardiovascular risk factors: screening with the Doppler ultrasonic technique. *Diabetes Care* 3:207–13, 1980
17. West KM, Ahuja MMS, Bennett PH, Czyzyk A, Mateo A, Decosta O, Fuller JH, Grab B, Grabauskas V, Jarrett RJ, Kosaka K, Keen H, Krolewski AS, Miki E, Schliak V, Teuscher A, Watkins PJ, Stober JA: The role of circulating glucose and triglyceride concentrations and their interactions with other "risk factors" as determinants of arterial disease in nine diabetic population samples from the WHO multinational study. *Diabetes Care* 6:361–69, 1983
18. Christensen NJ: Spontaneous variations in resting blood flow postischemic peak flow and vibratory perception in the feet of diabetics. *Diabetologia* 5:171–78, 1969
19. Kramer DW, Perilstein PK: Peripheral vascular complications in diabetes mellitus: a survey of 3,600 cases. *Diabetes* 7:384–87, 1958
20. Nathan DM, Singer DE, Godine JE, Perlmuter LC: Non-insulin dependent diabetes in older patients. *Am J Med* 81:837–42, 1985
21. Beach KW, Strandness DE Jr: Arteriosclerosis obliterans and associated risk factors in insulin-dependent and non-insulin-dependent diabetes. *Diabetes* 29:882–88, 1980
22. Klimt CR, Knatterud GL, Meinert CL, Prout TE: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. I. Design, methods and baseline results. *Diabetes* 19 (Suppl. 2):747–83, 1970
23. Strandness DE Jr, Priest RE, Gibbons GE: Combined clinical and pathologic study of diabetic and nondiabetic peripheral arterial disease. *Diabetes* 13:366–72, 1964
24. Conrad MC: Large and small artery occlusion in diabetes and non-diabetes with severe vascular disease. *Circulation* 36:83–91, 1967