Favorable Effects of Insulin Sensitizers Pertinent to Peripheral Arterial Disease in Type 2 Diabetes

Results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial

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OBJECTIVE—The aim of this manuscript was to report the risk of incident peripheral arterial disease (PAD) in a large randomized clinical trial that enrolled participants with stable coronary artery disease and type 2 diabetes and compare the risk between assigned treatment arms.

RESEARCH DESIGN AND METHODS—The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial randomly assigned participants to insulin sensitization (IS) therapy versus insulin-providing (IP) therapy for glycemic control. Results showed similar 5-year mortality in the two glycemic treatment arms. In secondary analyses reported here, we examine the effects of treatment assignment on the incidence of PAD. A total of 1,479 BARI 2D participants with normal ankle-brachial index (ABI) (0.91–1.30) were eligible for analysis. The following PAD-related outcomes are evaluated in this article: new low ABI ≤0.9, a lower-extremity revascularization, lower-extremity amputation, and a composite of the three outcomes.

RESULTS—During an average 4.6 years of follow-up, 303 participants experienced one or more of the outcomes listed above. Incidence of the composite outcome was significantly lower among participants assigned to IS therapy than those assigned to IP therapy (16.9 vs. 24.1%; $P < 0.001$). The difference was significant in time-to-event analysis (hazard ratio 0.66 [95% CI 0.51–0.83], $P < 0.001$) and remained significant after adjustment for in-trial HbA_{1c} (0.76 [0.59–0.96], $P = 0.02$).

CONCLUSIONS—In participants with type 2 diabetes who are free from PAD, a glycemic control strategy of insulin sensitization may be the preferred therapeutic strategy to reduce the incidence of PAD and subsequent outcomes.

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Peripheral arterial disease (PAD) is an atherosclerotic condition characterized by chronic occlusion of the arteries in the lower extremities. Prevalence estimates suggest that at least five million Americans have PAD (1,2). The presence of PAD is a marker of generalized systemic atherosclerosis and is associated with cardiovascular morbidity and mortality (3–8).

PAD is especially common in patients with type 2 diabetes (9). PAD progresses more rapidly (10) and leads to worse outcomes (11) in type 2 diabetic patients than nondiabetic patients. Type 2 diabetic patients with PAD have a high risk of functional impairment (12), mobility loss (13), amputation (14), and cardiovascular mortality (15).

High levels of HbA_{1c} are independently associated with increased risk of PAD in type 2 diabetes, suggesting that poor glycemic control may be a risk factor for PAD (16–19). Prior reviews have speculated that treatment with insulin sensitizers may reduce the risk of PAD in type 2 diabetic patients (20–22). However, this has never been demonstrated in a randomized controlled trial.

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial provides an opportunity to compare the effects of an insulin-sensitizing (IS) glycemic control strategy with those of an insulin-providing (IP) strategy on the incidence of PAD in a cohort of participants with type 2 diabetes and documented stable coronary artery disease (CAD). We previously demonstrated that mortality and incidence of major cardiovascular events was comparable in the glycemic control arms (23). In this article, we present the results of secondary analyses undertaken to examine the association between glycemic treatment assignment and the incidence of PAD.

RESEARCH DESIGN AND METHODS

BARI 2D trial

A detailed explanation of the BARI 2D trial has previously been published (24,25). The primary aim of the BARI 2D trial was to determine the optimal treatment for participants with type 2 diabetes and documented stable CAD. The BARI 2D trial used a 2 × 2 factorial design in which participants were assigned at random to initial elective revascularization with intensive medical therapy versus intensive medical therapy alone and simultaneously assigned at random to an IS strategy versus an IP strategy of glycemic control. All participants were treated

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medically to achieve targets of HbA_{1c} <7.0%, LDL cholesterol <100 mg/dL, and blood pressure ≤130/80 mmHg. All participants received counseling regarding smoking cessation, weight loss, and regular exercise.

BARI 2D included 49 clinical sites throughout North America, South America, and Europe and was coordinated at the University of Pittsburgh. The local institutional review boards approved the trial protocol, and all participants provided informed consent. Recruitment began in 2001 and continued until 2005; treatment continued until the 6-year visit or the last annual visit before 1 December 2008. The overall study cohort for BARI 2D consisted of 2,368 participants. The primary end point for BARI 2D was death from any cause, and the principal secondary end point was a composite of death, myocardial infarction, and stroke. Results for each of these have previously been published (23). This article reports the results of a post hoc analysis to examine PAD and related outcomes.

Glycemic control strategies

All BARI 2D participants were treated with a target HbA_{1c} <7.0%. Participants assigned to IP therapy could be treated with sulfonylureas, repaglinide, nateglinide, or insulin itself. Participants assigned to IS therapy could be treated with thiazolidinediones (glitazones) or metformin. α-Glucosidase inhibitors could be used with either treatment assignment. The trial was designed not to compare specific drugs but, rather, to compare the two mechanistically different treatment strategies. A detailed description of the BARI 2D glycemic control protocol can be found in the study by Magee et al. (26). Participants with HbA_{1c} >8.0% while taking the assigned treatment were permitted to receive the glucose-lowering drugs from the opposite treatment arm to bring HbA_{1c} within the range 7.0–8.0%. Approximately 30% of participants assigned to IS treatment also required medications from the IP arm, while 10% of participants assigned to IP treatment required medications from the IS arm. Nearly 90% of participants in both the IS group and the IP group were taking their assigned medications at 3 years (23).

Diagnosis of PAD

The following lower-extremity outcomes were analyzed: recorded decrease in ankle-brachial index (ABI) to abnormal level (ABI ≤0.9), lower-extremity revascularization, and lower-extremity amputation. This article reports incidence of each individual outcome as well as incidence of a composite PAD outcome including participants with any one of the individual outcomes. Only participants with a normal ABI (0.91–1.30) at study entry were eligible for the primary analysis in this study; the cutoff values for low, normal, and high ABI were chosen in accordance with values published in an American Diabetes Association consensus statement on PAD in diabetes. In secondary analysis, we report the incidence of lower-extremity revascularization and amputation among participants with low ABI (<0.9) at study entry.

We have previously reported the baseline prevalence and predictors of abnormal ABI in the BARI 2D trial (27). Participants with abnormal ABI at study entry were excluded from the primary analysis in this study because *1*) participants with low ABI at study entry were deemed as already having PAD and *2*) participants with high ABI and/or noncompressible arteries are likely to have arterial calcifications that would make it difficult to diagnose PAD using the ABI. Participants with a history of lower-extremity revascularization or lower-extremity amputation were also excluded from the primary analysis because of the likelihood that these participants already suffered from PAD. The algorithm for determining PAD status in this study was as follows.

Each participant's ABI was measured at study entry and annually thereafter. All ABI measurements were taken by certified technicians using a Doppler probe. Participants were asked to rest in a supine position for 5 min, after which the technician recorded the systolic blood pressure of the brachial artery of both arms and the posterior tibial artery of both ankles. The higher of the two brachial pressures was used to calculate ABI for each leg, and participants were classified according to their lowest ABI. Participants with normal ABI (0.91–1.30) at study entry were defined as incident cases of PAD if they had an ABI ≤0.9 during follow-up with a decrease of at least 0.1 from their baseline measurement.

Participants who had a lower-extremity revascularization or amputation during follow-up were included in the composite PAD outcome, even in the absence of a recorded low ABI. We acknowledge that lower-extremity revascularization and amputation may be performed for reasons other than atherosclerotic PAD, so the incidence of each outcome is reported in this article as well as the composite PAD outcome to allow reader assessment of practical implications. Intermittent claudication was not considered as an outcome because BARI 2D did not use a validated claudication questionnaire.

Statistical methods

The primary comparative analyses were performed according to the intention-to-treat principle. In addition, we performed per-protocol analyses that include only participants who remained on assigned treatment without any use of medications from the opposing treatment arm after the initial 6 months of the trial when study treatments were to be implemented and adjusted. Descriptive statistics include means ± SD and proportions; medians and interquartile ranges are presented for highly skewed data. Variables were compared between the two randomized glycemic control strategies (IS vs. IP) using *t* tests, Wilcoxon tests, and χ^2 tests for continuous, skewed continuous, and categorical data, respectively.

Kaplan-Meier estimates of the 5-year event rates were calculated for outcomes of interest, and log-rank tests were used to compare the incidence of each PAD outcome by assigned glycemic control strategy for patients with normal ABI at baseline, as described above. Time-to-event for each lower-extremity outcome was defined as time from date of randomization to the event (new low ABI, lower-extremity revascularization, or lower-extremity amputation); for the composite outcome, time to event was defined as time from date of randomization to the first event. In the absence of an event, participants were censored at their last full-protocol follow-up visit. We performed a second analysis to compare incidence of lower-extremity revascularization and amputation in patients with low ABI at baseline to assess the incidence of severe outcomes in these patients. We also calculated Kaplan-Meier event rates for the composite PAD outcome stratified by insulin use at study entry to see if the effects of assigned glycemic control strategy were consistent regardless of previous use of insulin therapy.

Cox proportional hazards models were used to estimate hazard ratios (HRs) and associated 95% CIs for IS strategy with IP as the reference group. Time to event was defined in the same fashion as that described above. A second model was constructed with in-trial HbA_{1c} included as a time-varying covariate,

updated at the time of each new ABI measurement, to determine whether potential differences between IS and IP strategy were attenuated by adjustment for glycemic control. The effects of assigned cardiovascular treatment strategy and the interaction between the assigned glycemic control strategy and cardiovascular treatment strategy were also tested. *P* values <0.05 were considered statistically significant; no adjustment was made for multiple comparisons.

RESULTS—The BARI 2D study population consisted of 2,368 participants with type 2 diabetes and stable CAD. Only participants with normal ABI at study entry and no history of PAD were selected for this paper's primary analysis. 889 participants were excluded because of history of PAD, missing baseline ABI, or abnormal baseline ABI, leaving 1,479 BARI 2D participants eligible for this analysis (Fig. 1). The participants excluded from this analysis were generally older, heavier, and more likely to be smokers; had higher systolic blood pressure, higher pulse pressure, and a longer duration of diabetes; and were more likely to have renal dysfunction at study entry than those included in this analysis (data not shown). Since many of the participants excluded from this analysis had a history of PAD, this is consistent with expectations.

Participants included in the intention-to-treat analysis were age 61.9 ± 8.0 years old; 72% were male and 15% were black. The distribution of baseline lipid values, blood pressure, glycemic control, and renal function were similar between the assigned glycemic treatment groups (Table 1). The mean ABI at study entry was 1.10 in the IS group and 1.09 in the IP group ($P = 0.23$). There were no significant differences in major baseline demographic or clinical characteristics between the assigned glycemic treatment groups.

Incidence of the composite PAD outcome was significantly lower in the IS arm than in the IP arm (16.9 vs. 24.1%, $P < 0.001$; event rates for all intention-to-treat comparisons in Supplementary Table 1). On the time-to-event curve, the difference becomes noticeable after 3 years and increases during longer follow-up (Fig. 2). With each clinical outcome examined separately, participants assigned to IS therapy had a significantly lower rate of low ABI (16.5 vs. 22.7%, $P < 0.001$) and amputation (0.1 vs. 1.6%, $P = 0.002$) and a moderately lower rate of lower-extremity revascularization (1.1 vs. 2.6%, $P = 0.07$) than those assigned to IP therapy. Among participants with low ABI at baseline, we observed no significant difference between the IS arm and IP arm in risk of lower-extremity revascularization (7.7 vs. 6.7%, $P = 0.68$) or lower-extremity amputation (3.4 vs. 7.2%, $P = 0.08$).

The lower risk of PAD and related outcomes in participants assigned to IS therapy was also significant in time-to-event analyses using Cox models (HR for IS vs. IP therapy for composite outcome = 0.66 [95% CI 0.51–0.83], $P < 0.001$) (Table 2). The effects of glycemic control strategy were partially attenuated by adjustment for in-trial HbA_{1c}; however, even with adjustment for in-trial HbA_{1c}, there was a significantly lower risk of PAD in participants assigned to IS therapy (adjusted HR for IS vs. IP therapy for composite outcome = 0.76 [0.59–0.96], $P = 0.02$). None of the PAD outcomes were associated with assigned cardiovascular treatment strategy, and no interactions between glycemic control and cardiovascular treatment strategies were statistically significant ($P > 0.10$ for all).

Among participants in the per-protocol analysis, there were significant baseline differences between the glycemic control arms in average duration of diabetes, proportion using insulin at study entry, and HbA_{1c} (Supplementary Table 2) but not in other risk factors such as age, smoking, race, or baseline ABI. As in intention-to-treat analyses, the results generally favor IS therapy for each outcome (incidence of composite outcome 12.4 vs. 26.0%, $P < 0.001$; event rates for all per-protocol comparisons shown in Supplementary Table 3). The effects of IS therapy are also significant in per-protocol analyses when using time-to-event analyses (HR for IS vs. IP therapy for composite outcome = 0.44 [95% CI 0.31–0.62], $P < 0.001$) (Supplementary Table 4). As in the intention-to-treat analyses, the effect of glycemic control strategy is partially attenuated by adjustment for in-trial HbA_{1c} in the per-protocol analysis but still significant (adjusted HR for IS vs. IP therapy for composite outcome = 0.54 [0.37–0.79], $P = 0.002$).

Insulin treatment at study entry was associated with greater risk of the composite PAD outcome (patients on insulin 26.3% vs. patients not on insulin 18.5%, $P = 0.01$). There was a significant difference in risk for the composite PAD outcome between the glycemic control arms regardless of whether participants were receiving insulin at study entry (Supplementary Fig. 1). The incidence of PAD was lower in the IS arm among participants receiving insulin at study entry (IS 20.7% vs. IP 31.9%, $P = 0.01$) and also those not receiving insulin at study entry (IS 15.6% vs. IP 21.3%, $P = 0.01$). The difference in PAD incidence between the IS arm and the IP arm tended to emerge earlier for participants on insulin at study entry.

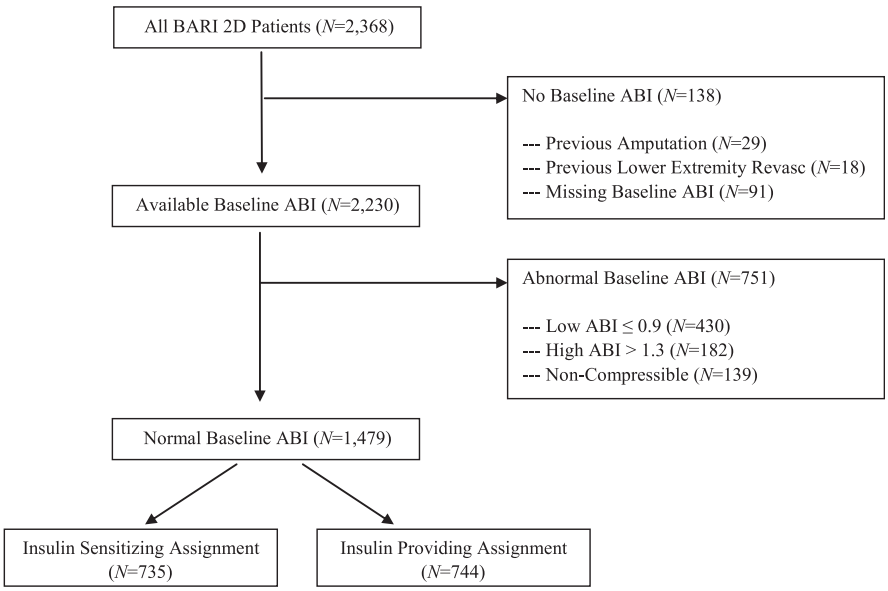

Figure 1—*Flowchart of ABI measurements available in all BARI 2D patients* (N = *2,368). Revasc, revascularization.*

CONCLUSIONS—In a large cohort of participants with stable CAD and type

Table 1—*Baseline characteristics of BARI 2D patients with normal ABI at study entry (N = 1,479) by assigned glycemic control strategy*

	Assigned glycemic control strategy		
	IS	IP	*P*
N	735	744	
Age at study entry (years)	61.8, 8.9	62.0, 8.7	0.68
Sex (male), %	71.7	71.9	0.92
Race (black), %	16.2	14.5	0.37
BMI (kg/m^2)	31.6, 5.9	31.4, 5.6	0.48
Current smoker, %	11.7	11.4	0.87
Cholesterol (mg/dL)	166.7, 41.0	170.2, 39.6	0.11
LDL (mg/dL)	94.4, 33.0	96.7, 31.8	0.18
HDL (mg/dL)	37.6, 9.6	38.2, 10.1	0.25
Triglycerides (mg/dL)**	146 (99–217)	152 (108–220)	0.37
Systolic BP (mmHg)	130.9, 18.7	130.0, 19.1	0.39
Diastolic BP (mmHg)	75.0, 11.0	74.3, 10.6	0.26
Pulse pressure (mmHg)	55.9, 15.1	55.7, 14.7	0.78
CRP (μg/mL)**	2.1 (1.0–5.7)	2.2 (1.0–5.2)	0.72
Number of vessels >50% stenosis			
0/1	37.6	32.4	0.07
2	33.2	38.7	
3	29.1	28.8	
Proximal LAD >50% stenosis	12.1	15.2	0.08
Left ventricular ejection fraction	57.6, 10.7	58.1, 10.7	0.42
Baseline ABI	1.10, 0.10	1.09, 0.11	0.23
Duration of diabetes (years)	9.4, 8.0	9.9, 8.2	0.25
HbA_{1c}, % (mmol/mol)	7.6 (60), 1.6	7.7 (61), 1.6	0.10
Diabetic peripheral neuropathy*	50.8%	49.2%	0.75
eGFR**	77.6 (63.8–91.5)	76.6 (64.2–91.5)	0.93
eGFR <60, %	19.8	18.8	0.62
ACR (mg/g)**	10.7 (4.8–42.4)	10.8 (5.2–34.6)	0.80
Albuminuria			
No albuminuria (ACR <30), %	70.0	72.8	0.49
Microalbuminuria (30 < ACR < 300), %	22.6	20.1	
Macroalbuminuria (ACR >300), %	7.4	7.1	
Diabetes medications at study entry			
Insulin, %	25.6	25.7	0.97
Sulfonylurea, %	53.4	53.4	0.99
Metformin, %	55.9	55.8	0.98
Thiazolidinediones, %	20.6	17.2	0.10

Data are mean, SD, or percentages unless otherwise indicated. Asterisks next to variable names denote which variables are presented as median (quartile 1–quartile 3). ACR, albumin-to-creatinine ratio; BP, blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LAD, left anterior descending. *Diabetic peripheral neuropathy assessed using Michigan Neuropathy Screening Instrument (clinical score ≥2). **Triglycerides, estimated glomerular filtration rate, albumin-to-creatinine ratio, and C-reactive protein are presented as median (quartile 1–quartile 3) because of their skewed distribution.

2 diabetes, participants assigned to IS therapy experienced significantly fewer cases of incident PAD than participants assigned to IP therapy over an average of 4.6 years of clinical follow-up. The difference in PAD risk between the glycemic control arms was significant regardless of assigned cardiovascular treatment strategy and consistent in both intention-to-treat analyses and per-protocol analyses. The results also favored IS therapy for patients receiving insulin at study entry as well as those not receiving insulin at study entry. This is the first randomized controlled trial to demonstrate that treatment with IS agents reduces the risk of incident PAD in participants with type 2 diabetes.

The reduction in risk of amputation or revascularization with IS therapy was not as pronounced for patients with low ABI at baseline, although the incidence of each outcome was still lower for patients assigned to IS therapy than for patients assigned to IP therapy. This could be explained in two ways. First, perhaps IS therapy does have a benefit for these patients, but there was insufficient sample size to detect an effect in the subgroup with low ABI at study entry. Alternatively, it is possible that the benefit of IS therapy on peripheral outcomes is lessened in patients with existing PAD because the disease in the lower extremities has advanced beyond "prevention" of the atherosclerotic process in this vascular bed.

The only previous study to demonstrate a similar result is the PROactive trial, which found that treatment with pioglitazone versus placebo resulted in a moderate decrease in the rate of leg revascularizations and amputations among participants free from PAD at study entry (28). Notably, the BARI 2D results demonstrate an even stronger benefit of IS therapy in this population. This may be explained by the shorter follow-up time in PROactive (3 years) than BARI 2D (5 years), since the BARI 2D results showed that the treatment benefit of IS therapy began to emerge around 3 years and progressively increased thereafter. It could also be a result of moderate differences in treatment protocol; PROactive randomly assigned patients to pioglitazone or placebo in the setting of continued additional diabetes therapy, whereas BARI 2D assigned patients to an IS strategy or to an IP strategy.

One potential mechanism through which IS treatment may have reduced the risk of PAD incidence in BARI 2D is better glycemic control; we have previously reported that participants assigned to IS had lower HbA_{1c} than participants assigned to IP during BARI 2D follow-up (29). However, the treatment difference reported here was significant after adjustment for in-trial HbA_{1c}, suggesting that IS therapy conferred a benefit beyond better glycemic control.

Furthermore, previous trials of intensive glucose-lowering therapy have not demonstrated a consistent reduction in macrovascular outcomes. The Veterans Affairs Diabetes Trial (VADT), the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial all failed to demonstrate that intensive glucose-lowering therapy reduced the risk of macrovascular outcomes (30–32). With that in mind, the BARI 2D results are particularly encouraging because the decreased risk of

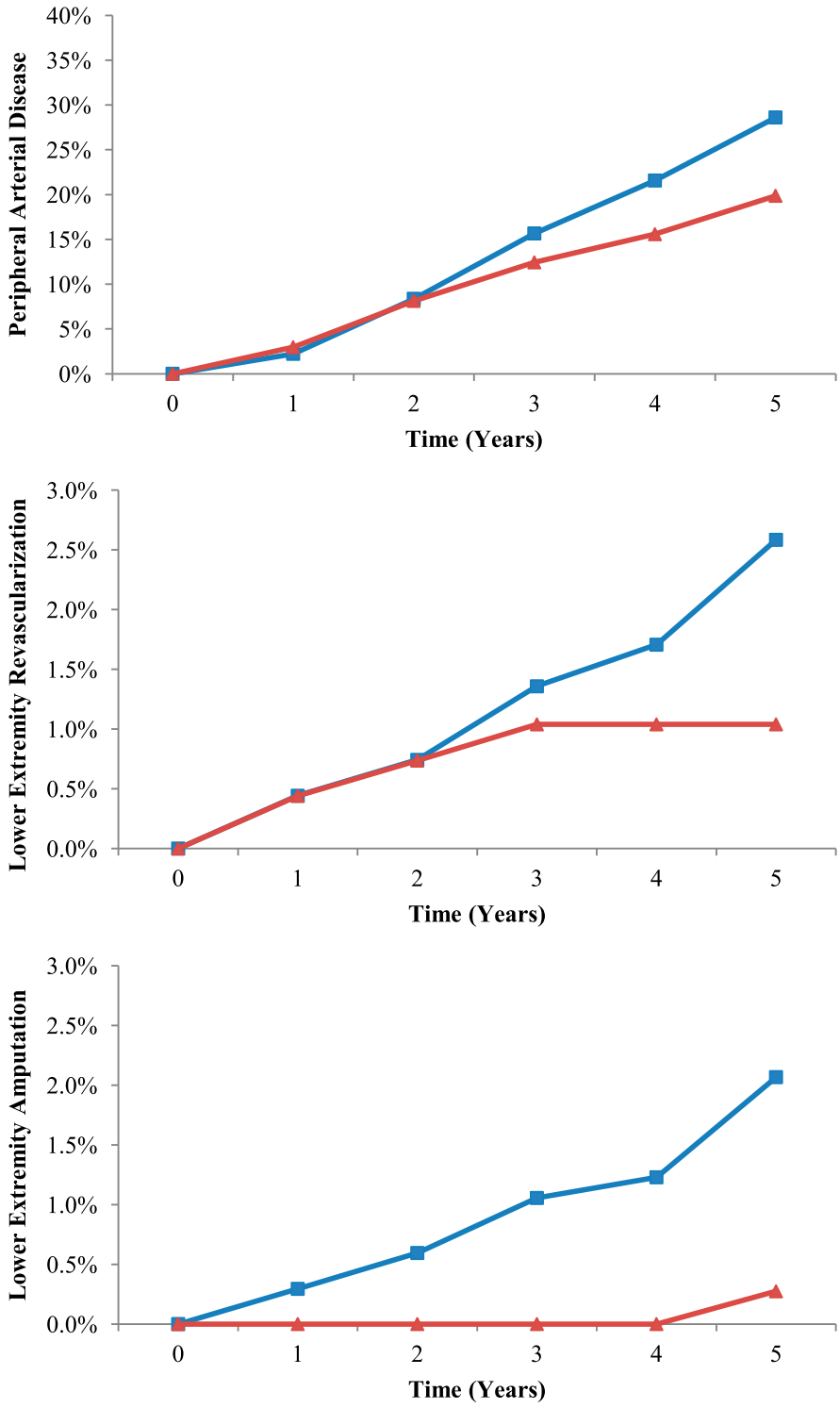

Figure 2—*Cumulative incidence of PAD and related outcomes by assigned glycemic control strategy.*

PAD in participants assigned to IS therapy was significant even while adjusting for in-trial glycemic control, suggesting that improvements in macrovascular outcomes may be achieved by changing the mechanistic approach rather than targeting a lower HbA_{1c}.

A second plausible mechanism of the reduced PAD risk with IS therapy may be the anti-inflammatory effects of t thiazolidinediones used in the BARI 2D trial, which may retard atherosclerosis development and progression (33,34). We have previously reported that the IS strategy led to changes in biomarker profiles indicative of a profibrinolytic, antithrombotic, and anti-inflammatory state (29). This could contribute to the lower incidence of PAD in the IS group. While thiazolidinediones have been shown to induce and maintain the regression of carotid intima-media thickness in participants with type 2 diabetes (35), to our knowledge no previous study has reported an effect on PAD. However, because the BARI 2D trial was designed to examine mechanistically different treatment strategies rather than individual drugs, we cannot say for certain whether thiazolidinediones alone were responsible for the reduction in PAD risk.

It is also plausible that the observed results reflect a harmful effect of IP therapy rather than a protective benefit of IS therapy. Hyperinsulinemia has long been a known risk factor for atherosclerosis, although the causality of the relationship is controversial, and the mechanism is unclear. One study suggests that hyperinsulinemia may promote atherosclerosis by promoting macrophage foam cell accumulation (36). However, this is not clearly established; further research is needed to determine the potential atherogenic effects of insulin.

To date, no pharmacologic therapies have proven to reduce the risk of incident PAD in type 2 diabetic patients. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study has reported lower amputation rates in patients assigned to treatment with fenofibrate versus placebo; however, PAD status at study entry was not reported for the FIELD results, so we are uncertain whether these findings extend to incident cases of PAD (37). For patients with PAD, current American College of Cardiology/American Heart Association guidelines recommend aggressive management of atherosclerotic risk factors to reduce future cardiovascular events (38). Exercise conditioning (39) and smoking cessation (40) have proven beneficial effects for those with PAD, but these are generally recommended for all type 2 diabetic patients regardless of their effects on PAD risk. Notably, while all participants in BARI 2D received intensive medical therapy, counseling regarding smoking cessation, and regular exercise, treatment with IS agents still resulted in fewer cases of incident PAD than treatment with IP agents.

One potential limitation of this research is the composition of the BARI 2D population, which was restricted to patients with documented CAD suitable for elective revascularization and type 2

Table 2—*Effects of assigned glycemic control strategy on lower-extremity outcomes* (N = *1,479*)

		Unadjusted			Adjusted for in-trial HbA_{1c}		
Outcome	Events (*n*)	HR*	95% CI	*P*	HR*	95% CI	*P*
PAD	303	0.66	0.51–0.83	<0.001	0.76	0.59–0.96	0.02
Incident low ABI	290	0.68	0.54–0.85	0.001	0.73	0.57–0.93	0.002
Lower-extremity revascularization	25	0.47	0.20–1.09	0.08	0.58	0.24–1.37	0.22
Lower-extremity amputation	13	0.08	0.01–0.63	0.02	0.12	0.02–0.91	0.04

HR, hazard ratio. *Hazard ratios are for IS arm vs. IP arm (reference group).

diabetes. Given that both of these conditions are independently associated with PAD, the BARI 2D population is at very high risk for PAD, and therefore, the findings from this research may not extend to those at lower risk. Further study will be needed to determine whether IS medications offer the same benefit to lower-risk patients. Additional limitations include the fact that individual drugs cannot be evaluated because of the trial design, which assigned patients to a mechanistic treatment strategy rather than a specific drug, and the lack of a standardized claudication questionnaire, which might have resulted in the diagnosis of a few more PAD cases during follow-up.

In summary, we have reported that an IS strategy for glycemic control resulted in fewer incident PAD cases, lower-extremity revascularizations, and lower-extremity amputations than treatment with IP agents in type 2 diabetic patients. The difference between glycemic treatment arms remained significant with adjustment for in-trial HbA_{1c}, suggesting that insulin sensitizers confer a benefit independent of glycemic control. Our results suggest that treatment of type 2 diabetic patients with insulin sensitizers might reduce the morbidity and treatment cost of PAD in this population.

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A.D.A. performed statistical analyses and wrote the manuscript. J.D.A., K.S.-T., and A.D.F. contributed to discussion and reviewed and edited the manuscript. M.S.L. contributed to statistical analysis. L.V.B., I.P.-S., and J.-C.T. reviewed and edited the manuscript. M.M.B. contributed to statistical analysis and discussion and reviewed and edited the manuscript. A.D.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation 2004;110:738–743
2. Allison MA, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. Am J Prev Med 2007;32:328–333
3. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381–386
4. Newman AB, Sutton-Tyrrell K, Vogt MT, Kuller LH. Morbidity and mortality in hypertensive adults with a low ankle/arm blood pressure index. JAMA 1993;270:487–489
5. O'Hare AM, Katz R, Shlipak MG, Cushman M, Newman AB. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. Circulation 2006;113:388–393
6. Sutton-Tyrrell K, Venkitachalam L, Kanaya AM, et al. Relationship of ankle blood pressures to cardiovascular events in older adults. Stroke 2008;39:863–869
7. Criqui MH, Ninomiya JK, Wingard DL, Ji M, Fronek A. Progression of peripheral arterial disease predicts cardiovascular disease morbidity and mortality. J Am Coll Cardiol 2008;52:1736–1742
8. Criqui MH, McClelland RL, McDermott MM, et al. The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2010;56:1506–1512
9. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care 2003;26:3333–3341
10. Palumbo PJ, O'Fallon WM, Osmundson PJ, Zimmerman BR, Langworthy AL, Kazmier FJ. Progression of peripheral occlusive arterial disease in diabetes mellitus. What factors are predictive? Arch Intern Med 1991;151:717–721
11. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. Diabetes Care 2001;24:1433–1437
12. Dolan NC, Liu K, Criqui MH, et al. Peripheral artery disease, diabetes, and reduced lower extremity functioning. Diabetes Care 2002;25:113–120
13. Brach JS, Solomon C, Naydeck BL, et al.; Cardiovascular Health Study Research Group. Incident physical disability in people with lower extremity peripheral arterial disease: the role of cardiovascular disease. J Am Geriatr Soc 2008;56:1037–1044
14. Adler AI, Boyko EJ, Ahroni JH, Smith DG. Lower-extremity amputation in diabetes. The independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. Diabetes Care 1999;22:1029–1035
15. Leibson CL, Ransom JE, Olson W, Zimmerman BR, O'fallon WM, Palumbo PJ. Peripheral arterial disease, diabetes, and mortality. Diabetes Care 2004;27:2843–2849
16. Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ, Holman RR. UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. Diabetes Care 2002;25:894–899

17. Muntner P, Wildman RP, Reynolds K, Desalvo KB, Chen J, Fonseca V. Relationship between HbA1c level and peripheral arterial disease. Diabetes Care 2005;28:1981–1987
18. Selvin E, Wattanakit K, Steffes MW, Coresh J, Sharrett AR. HbA1c and peripheral arterial disease in diabetes: the Atherosclerosis Risk in Communities study. Diabetes Care 2006;29:877–882
19. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141:421–431
20. Jude EB, Eleftheriadou I, Tentolouris N. Peripheral arterial disease in diabetes—a review. Diabet Med 2010;27:4–14
21. Marso SP, Hiatt WR. Peripheral arterial disease in patients with diabetes. J Am Coll Cardiol 2006;47:921–929
22. Norgren L, Hiatt WR, Dormandy JA, et al.; TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007;33(Suppl. 1):S1–S75
23. Frye RL, August P, Brooks MM, et al.; BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360:2503–2515
24. Brooks MM, Frye RL, Genuth S, et al.; Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial Investigators. Hypotheses, design, and methods for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. Am J Cardiol 2006;97(12A):9G–19G
25. Bypass Angioplasty Revascularization Investigation 2 Diabetes 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; 156:528–536.e1-5
26. Magee MF, Isley WL; BARI 2D Trial Investigators. Rationale, design, and methods for glycemic control in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. Am J Cardiol 2006;97(12A):20G–30G
27. Singh PP, Abbott JD, Lombardero MS, et al.; Bypass Angioplasty Revascularization Investigation 2 Diabetes Study Group. The prevalence and predictors of an abnormal ankle-brachial index in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Diabetes Care 2011;34:464–467
28. Dormandy JA, Betteridge DJ, Schernthaner G, Pirags V, Norgren L; PROactive investigators. Impact of peripheral arterial disease in patients with diabetes—results from PROactive (PROactive 11). Atherosclerosis 2009;202:272–281
29. Sobel BE, Hardison RM, Genuth S, et al.; BARI 2D Investigators. Profibrinolytic, antithrombotic, and antiinflammatory effects of an insulin-sensitizing strategy in patients in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Circulation 2011;124:695–703
30. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
31. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
32. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
33. Patel CB, De Lemos JA, Wyne KL, McGuire DK. Thiazolidinediones and risk for atherosclerosis: pleiotropic effects of PPar γ agonism. Diab Vasc Dis Res 2006;3:65–71
34. Staels B, Fruchart JC. Therapeutic roles of peroxisome proliferator-activated receptor agonists. Diabetes 2005;54:2460–2470
35. Yamasaki Y, Katakami N, Furukado S, et al. Long-term effects of pioglitazone on carotid atherosclerosis in Japanese patients with type 2 diabetes without a recent history of macrovascular morbidity. J Atheroscler Thromb 2010;17:1132–1140
36. Park YM, R Kashyap S, A Major J, Silverstein RL. Insulin promotes macrophage foam cell formation: potential implications in diabetes-related atherosclerosis. Lab Invest 2012;92:1171–1180
37. Rajamani K, Colman PG, Li LP, et al.; FIELD study investigators. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. Lancet 2009;373:1780–1788
38. Gandhi S, Weinberg I, Margey R, Jaff MR. Comprehensive medical management of peripheral arterial disease. Prog Cardiovasc Dis 2011;54:2–13
39. Hiatt WR, Regensteiner JG, Hargarten ME, Wolfel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. Circulation 1990;81:602–609
40. Chi YW, Jaff MR. Optimal risk factor modification and medical management of the patient with peripheral arterial disease. Catheter Cardiovasc Interv 2008;71:475–489