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ORIGINAL INVESTIGATIONS

Comprehensive Cardiovascular Risk Factor Control Improves Survival

The BARI 2D Trial

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CME Objective for This Article: After reading this article, the reader should be able to: 1) understand the impact of traditional risk factors alone and in combination on prognosis among patients with type II diabetes and coronary heart disease; 2) realize that a protocol-driven approach to risk factor modification can improve risk factor control well above that usually achieved with "usual care"; and 3) understand that improvements in risk factor control are associated with reductions in mortality and cardiovascular events among patients with diabetes and coronary heart disease.

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ABSTRACT

BACKGROUND It is unclear whether achieving multiple risk factor (RF) goals through protocol-guided intensive medical therapy is feasible or improves outcomes in type 2 diabetes mellitus.

OBJECTIVES This study sought to quantify the relationship between achieved RF goals in the BARI 2D (Bypass Angioplasty Investigation Revascularization 2 Diabetes) trial and cardiovascular events/survival.

METHODS We performed a nonrandomized analysis of survival/cardiovascular events and control of 6 RFs (no smoking, non–high-density lipoprotein cholesterol <130 mg/dl, triglycerides <150 mg/dl, blood pressure [systolic <130 mm Hg; diastolic <80 mm Hg], glycosylated hemoglobin <7%) in BARI 2D. Cox models with time-varying number of RFs in control were adjusted for baseline number of RFs in control, clinical characteristics, and trial randomization assignments.

RESULTS In 2,265 patients (mean age 62 years, 29% women) followed up for 5 years, the mean ± SD number of RFs in control improved from 3.5 ± 1.4 at baseline to 4.2 ± 1.3 at 5 years ($p < 0.0001$). The number of RFs in control during the trial was strongly related to death (global $p = 0.0010$) and the composite of death, myocardial infarction, and stroke (global $p = 0.0035$) in fully adjusted models. Participants with 0 to 2 RFs in control during follow-up had a 2-fold higher risk of death (hazard ratio: 2.0; 95% confidence interval: 1.3 to 3.3; $p = 0.0031$) and a 1.7-fold higher risk of the composite endpoint (hazard ratio: 1.7; 95% confidence interval: 1.2 to 2.5; $p = 0.0043$), compared with those with 6 RFs in control.

CONCLUSIONS Simultaneous control of multiple RFs through protocol-guided intensive medical therapy is feasible and relates to cardiovascular morbidity and mortality in patients with coronary disease and type 2 diabetes mellitus. (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes [BARI 2D]; NCT00006305) (J Am Coll Cardiol 2015;66:765–73) © 2015 by the American College of Cardiology Foundation.

Reduction in cardiovascular risk factors (RFs) has contributed to lower cardiovascular event rates in the United States (1). RF control and prognosis among patients with type 2 diabetes mellitus (T2DM) have improved, but these patients remain at higher risk (2,3). Few prospective studies have addressed the effect of simultaneous control of multiple RFs in T2DM populations on cardiovascular outcomes (4,5). We hypothesized that achievement of multiple RF goals through protocol-guided intensive medical therapy is feasible and associated with improved survival and lower

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cardiovascular event rates among patients with coronary heart disease (CHD) and T2DM in the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial.

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METHODS

BARI 2D DESIGN, ENROLLMENT, AND FOLLOW-UP. The BARI 2D protocol and study results have been described previously (6–8). Briefly, this study enrolled patients with T2DM and angiographically documented stable CHD. Using a 2 × 2 factorial design, patients were randomized simultaneously to undergo cardiac treatment and glycemic control treatment strategies. The randomized cardiac treatment strategies entailed intensive medical therapy with revascularization within 4 weeks or intensive medical therapy with revascularization when clinically indicated. The randomized glycemic control strategies compared primarily insulin-sensitizing versus primarily insulin-providing treatments. The study was approved by the local institutional review boards, and subjects provided informed consent. The current post-hoc analysis includes 2,265 of the 2,368 BARI 2D patients (103 patients were missing RF information).

Target levels for RFs were adjusted as practice guidelines evolved. The final targets, collection frequency, and core laboratory status for key RFs in the BARI 2D protocol are shown in Table 1. Non-high-density lipoprotein cholesterol (non-HDL-C) rather than low-density lipoprotein cholesterol was chosen for analysis on the basis of pathophysiological and statistical considerations. Patients were followed up until their 6-year visit or December 2008, whichever came earlier.

RF MANAGEMENT. Cardiovascular RF management followed a detailed protocol (8) and included monitoring and regular feedback on smoking cessation, dietary and exercise advice, and protocol-guided pharmacological management for dyslipidemia, hyperglycemia, and hypertension.

Of the 49,196 clinic visits in BARI 2D, a total of 47,044 (95%) had up-to-date RF information for all 6 RFs. Visit information was carried forward up to 15 months. Clinic visits were included when all 6 RFs were measured or up to date, with subjects contributing when they had available RF data.

RF MODELING. The number of RFs in control was modeled with 4 indicator variables (in control categories of 0 to 2, 3, 4, and 5 [with 6 as the reference]). RFs were in control if they met the targets listed in Table 1. In a secondary exploratory analysis, we modeled a J-shaped relationship of blood pressure (BP) and glycosylated hemoglobin (HbA_{1c}) with outcomes, as recent data suggest that overly tight control might be associated with harm (9,10). In this secondary analysis, systolic BP between 110 mm Hg and 140 mm Hg was in control and HbA_{1c} between 6.5% and 7.5% was in control. Values outside these ranges were considered out of control.

We analyzed the relationship between the number of RFs in control with all-cause death and with cardiovascular disease (CVD) events (composite endpoint of death, myocardial infarction [MI], or stroke).

STATISTICAL ANALYSIS. Baseline characteristics according to the number of baseline RFs at goal were compared by using an analysis of variance model for continuous variables or chi-square tests for categorical variables. At trial initiation, RFs were intensively monitored and medication regimens intensified to achieve RF targets, resulting in a large initial change in RF control between baseline and year 1. We determined if subsequent RF control continued to improve, was maintained, or declined from year 1 to year 5.

ABBREVIATIONS AND ACRONYMS

BP = blood pressure
CHD = coronary heart disease
CVD = cardiovascular disease
HbA_{1c} = glycosylated hemoglobin
MI = myocardial infarction
non-HDL-C = non-high-density lipoprotein cholesterol
RF = risk factor
T2DM = type 2 diabetes mellitus

TABLE 1 RF Target Levels and Collection Details

	Target	Collection Frequency	Core Laboratory
Systolic BP	<130 mm Hg	Monthly for first 6 months, quarterly thereafter	No
Diastolic BP	<80 mm Hg	Monthly for first 6 months, quarterly thereafter	No
Smoking status	Nonsmoker	Annually	No
HbA_{1c}	<7%	Baseline; months 1, 3, 6, and 20; and every 6 months thereafter	HbA_{1c} core laboratory
TG	<150 mg/dl (<1.70 mmol/l)	Baseline, 6 months, then annually	Lipid core laboratory
Non-HDL-C	<130 mg/dl (<3.37 mmol/l) Optional goal: <100 mg/dl (<2.59 mmol/l)	Baseline, 6 months, then annually	Lipid core laboratory

BP = blood pressure; HbA_{1c} = glycosylated hemoglobin; non-HDL-C = non-high-density lipoprotein cholesterol; RF = risk factor; TG = triglycerides.

The initial changes (baseline to 1 year) and subsequent changes (after year 1) were quantified by using a generalized logistic estimating equation with a continuous follow-up year and a baseline visit indicator. A significant coefficient for the baseline indicator indicated a significant first-year change. The sign and significance of the coefficient for year determined if there was continued improvement, maintenance, or degradation over the 5 years of follow-up.

Non-time-varying analyses used baseline or year 1 number of RFs in control, and time-varying RFs in control during the trial were used in a separate analysis. Cox models were used to estimate the hazard ratios and verified the proportional hazard assumption. All Cox models included baseline angiographic information (number of total lesions, Myocardial Jeopardy Index), baseline clinical and demographic information (abnormal left ventricular ejection fraction, prior revascularization, age, sex, race/ethnicity, country), and randomization assignment (insulin-sensitizing vs. insulin-providing, prompt revascularization vs. medical therapy), and revascularization strata (coronary artery bypass grafting or percutaneous coronary intervention). A Wald test determined if the number of RFs in control was significant overall.

All analyses were conducted by using SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina).

TABLE 2 Baseline Characteristics

	All Patients (N = 2,265)	No. of RFs at Goal*			p Value
		0-2 RFs (n = 536)	3-4 RFs (n = 1,121)	5-6 RFs (n = 608)	
Age, yrs	62 ± 9	60 ± 8	63 ± 9	64 ± 9	<0.0001
Female	29	33	29	27	0.0730
Nonwhite race	35	37	35	36	0.1576
Geographical region					<0.0001
United States	62	51	64	69	
Canada	15	14	16	17	
Europe, South/Central America	22	35	20	15	
Clinical characteristics					
History of MI	32	28	34	32	0.0359
History of heart failure	6	5	6	8	0.1484
Cerebrovascular accident	10	9	10	9	0.8491
Prior revascularization	24	22	24	25	0.5302
No. of coronary lesions	5 ± 2	5 ± 2	5 ± 2	5 ± 2	0.0755
LVEF <50%	17	15	16	20	0.0889
Myocardial Jeopardy Index	44 ± 24	46 ± 24	45 ± 24	43 ± 24	0.1797
Diabetes duration, yrs	10 ± 9	10 ± 8	11 ± 9	10 ± 9	0.1530
History of insulin use	29	30	31	25	0.0186
Cardiovascular risk factors					
Current cigarette smoker	12	26	11	4	<0.0001
BMI	32 ± 6	32 ± 6	32 ± 6	31 ± 6	0.1368
Systolic BP, mm Hg	132 ± 20	145 ± 20	132 ± 19	120 ± 14	<0.0001
Diastolic BP, mm Hg	75 ± 11	83 ± 11	74 ± 10	68 ± 8	<0.0001
TC, mg/dl	169 ± 41	199 ± 40	170 ± 40	143 ± 25	<0.0001
HDL-C, mg/dl	38 ± 10	37 ± 10	38 ± 10	39 ± 10	0.0002
LDL-C, mg/dl	96 ± 33	117 ± 35	96 ± 33	81 ± 22	<0.0001
TG, mg/dl	181 ± 136	251 ± 167	185 ± 134	115 ± 57	<0.0001
Non-HDL-C, mg/dl	131 ± 41	162 ± 38	132 ± 39	104 ± 22	<0.0001
HbA_{1c}, %	7.6 ± 1.6	8.5 ± 1.5	7.7 ± 1.6	6.8 ± 1.3	<0.0001
Trial strata					
Insulin-sensitizing	50	50	50	50	0.9919
Early revascularization	50	45	48	56	0.0012
CABG	32	36	33	29	0.0366

Values are mean ± SD or %. To convert milligrams per deciliter to millimoles per liter, multiply by 0.02586 for cholesterol and by 0.01129 for TG. Percentages within categories shown in the table may differ from 100% due to rounding. *In the baseline table, the numbers of RFs in control are grouped as 0 to 2, 3 to 4, and 5 to 6 for ease of reading. In the analysis, the RFs are modeled as 0 to 2, 3, 4, 5, and 6 RFs in control.

BMI = body mass index; CABG = coronary artery bypass grafting; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; MI = myocardial infarction; TC = total cholesterol; other abbreviations as in Table 1.

TABLE 3 Achievement of RF Goals Over Time

	Proportion of Patients With RFs in Control (%)*				Initial Change (Baseline to Year 1) p Value	Subsequent Change (Year 1 to Year 5) p Value
	Baseline (N = 2,265)	Year 1 (n = 2,137)	Year 3 (n = 1,949)	Year 5 (n = 1,060)		
Non-HDL-C	54	70	79	82	<0.0001	<0.0001
TG	50	57	60	64	0.0005	<0.0001
Systolic BP	49	56	62	62	0.0002	0.0009
Diastolic BP	68	69	73	77	0.59	0.0002
No smoking	87	90	91	92	0.0013	0.14
HbA_{1c}	40	51	48	46	<0.0001	<0.0001
Meet all 6 goals	7	12	15	15	<0.0001	0.18

*RFs in control defined as: non-HDL-C <130 mg/dl, triglycerides <150 mg/dl, SBP <130 mm Hg, DBP <80 mm Hg, HbA_{1c} <7%, and no smoking.
DBP = diastolic blood pressure; SBP = systolic blood pressure; other abbreviations as in Table 1.

RESULTS

BASELINE CHARACTERISTICS. The mean ± SD age was 62 ± 9 years, with 29% women, 35% nonwhite, and a mean duration of T2DM of 10 years. Baseline RFs and comorbidities are detailed in Table 2. Younger patients and those outside North America had fewer RFs in control. Between 40% and 68% of patients met individual RF targets, and only 7% met all 6 RF goals (Table 3).

CHANGES IN PHARMACOLOGICAL THERAPY AND CARDIOVASCULAR RF CONTROL. The greatest change in medication use occurred within the first year (Table 4). Use of aspirin and lipid-lowering and antihypertensive drugs increased significantly over the first year and was maintained in follow-up. Changes in diabetes medications reflect the randomization to insulin-providing and insulin-sensitizing strategies and use of medications outside their randomized strategy for glucose control.

The mean number of RFs in control increased from 3.5 ± 1.4 at baseline to 4.2 ± 1.3 after 5 years ($p < 0.0001$). Except for diastolic BP, the percentage of patients at target increased between baseline and year 1 (Table 3). Improvements continued through year 5 except for smokers (maintained) and HbA_{1c} (worsened). At 5 years, >74% of patients had ≥4 RFs in control, but only 15% of patients achieved control of all 6 RFs (Figure 1). Online Table 1 displays the average values of RFs over time.

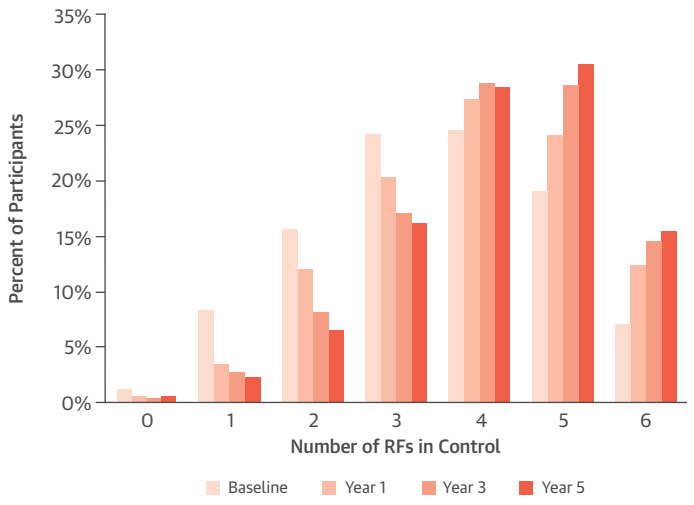
CLINICAL OUTCOMES. Mean follow-up time was 5.0 ± 1.4 years. The analysis includes 47,044 visits from 2,265 patients. There were 275 deaths, 254 incident fatal or nonfatal MIs (excluding 13 MIs before the first visit with all 6 RFs measured), 65 strokes, and 491 CVD events (excluding the previously mentioned

TABLE 4 Trial Medication Status

	Baseline (N = 2,265)	Year 1 (n = 2,137)	Year 3 (n = 1,949)	Year 5 (n = 1,060)	Initial Change (Baseline to Year 1) p Value	Subsequent Change (Year 1 to Year 5) p Value
Lipid-lowering drugs*	79	98	99	97	<0.0001	0.58
Statins	75	93	96	94	<0.0001	0.13
Antihypertensive agents	95	99	99	98	<0.0001	0.11
ACE inhibitor or ARB	77	90	91	90	<0.0001	0.26
Beta-blocker	73	87	87	87	<0.0001	0.61
Aspirin	88	92	94	92	<0.0001	0.78
Diabetes drugs†						
IS only	16	31	28	23	<0.0001	<0.0001
IP only	30	43	44	45	<0.0001	0.347
IS and IP	45	20	23	28	<0.0001	<0.0001
None	8	6	5	4	<0.0001	0.02

Values are %. *Lipid-lowering drugs include fibrates, niacin, bile acid sequestrants, omega-3 fatty acids, and cholesterol absorption inhibitors. †Insulin-sensitizing (IS) drugs included metformin and thiazolidinediones. Insulin-providing (IP) drugs included insulin and sulfonylurea. In the BARI 2D (Bypass Angioplasty Investigation Revascularization 2 Diabetes) trial, patients were randomized to initial IS or IP treatment strategies and were offered pharmacological therapy if glycosylated hemoglobin (HbA_{1c}) values were >7%. Subsequently, patients could take drugs from the other arm of the trial if HbA_{1c} values were >8%.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

FIGURE 1 Distribution of the Number of RFs in Control: Baseline to Year 5



The numbers of risk factors (RFs) in control are shown at baseline and for each year of the trial. Over time, the proportion of participants with ≥4 RFs in control increased while the proportion with fewer RFs in control declined.

13 MIs). The 5-year Kaplan-Meier total mortality rate was 11%, and the rate of CVD events was 22%.

OUTCOMES RELATED TO RF CONTROL AT BASELINE AND YEAR 1. Among the 2,169 patients with baseline RF data, there was no relationship between the number of RFs in control at baseline and subsequent death (hazard ratios between 0.8 and 1.1; p = 0.36) or CVD events (hazard ratios between 1.0 and 1.3; p = 0.22). In contrast, RF control at year 1 was strongly related to both outcomes after adjusting for the number of RFs in control at baseline. Participants with 0 to 2 RFs in control had approximately twice the risk of death and 1.7 times the risk of the composite outcome compared with participants with 6 RFs in control (Table 5).

TABLE 5 Hazard Ratios for Death and CVD Events According to Number of RFs in Control at Year 1 and Time-Varying*

	Death†			Death/MI/Stroke†		
	HR	95% CI	p Value	HR	95% CI	p Value
No. of RFs at goal at year 1 (n = 1,994) time to first event after year 1						
0–2	2.1	1.2–3.7	0.0069	1.7	1.1–2.6	0.0199
3	1.7	1.0–2.8	0.0366	1.3	0.9–2.0	0.1589
4	1.1	0.7–1.8	0.7443	0.8	0.5–1.2	0.2118
5	1.1	0.7–1.8	0.7311	0.8	0.6–1.3	0.3929
6	1.0	Reference	—	1.0	Reference	—
Global p value			0.0056			<0.0001
No. of RFs at goal, time-varying RF control (n = 2,265) time to first event after randomization						
0–2	2.0	1.3–3.3	0.0031	1.7	1.2–2.5	0.0043
3	1.3	0.9–2.0	0.2092	1.2	0.8–1.6	0.4071
4	1.1	0.8–1.7	0.6685	1.2	0.9–1.6	0.3239
5	0.8	0.5–1.2	0.2858	0.9	0.7–1.3	0.574
6	1.0	Reference	—	1.0	Reference	—
Global p value			0.0010			0.0035

*RFs in control defined as: non-HDL-C <130 mg/dl, TG <150 mg/dl, SBP <130 mm Hg, DBP <80 mm Hg, HbA_{1c} <7%, and no smoking. †Cox models adjusted for: baseline number of RFs in control, number of total lesions, abnormal LVEF, Myocardial Jeopardy Index, prior revascularization, age, sex, race/ethnicity, country, and trial strata.

CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; MI = myocardial infarction; other abbreviations as in Tables 1, 2, and 3.

OUTCOMES RELATED TO TIME-VARYING RFs IN CONTROL DURING THE TRIAL. The number of RFs in control during the trial was strongly related to death (global p = 0.0010) and CVD event (global p = 0.0035) after adjusting for the number of baseline RFs in control (Table 5). Patients with 0 to 2 RFs in control during follow-up were twice as likely to die as those with 6 RFs in control with similar results for CVD events. The model suggested a J-shape: patients with 6 RFs in control had nonsignificantly higher risks of death and the composite endpoint compared with patients with 5 RFs in control.

EXPLORATORY ANALYSIS TO LOOK FOR POTENTIAL HARMS OF INTENSIVE BP AND GLUCOSE CONTROL. Table 6 displays hazard ratios as a function of the number of RFs in control, with systolic BP and HbA_{1c} ranges modified to reflect less stringent control. The uptick in risk with 6 RFs in control compared with 5 RFs in control was no longer evident, suggesting that aggressive control of systolic BP or HbA_{1c} is associated with increased risk. Hazard ratios associated with 0 to 2, 3, 4, and 5 RFs in control were consistently higher than in the main analysis (Central Illustration). Results were consistent with variations in the modified target ranges (Online Table 2). In analyses stratified according to cardiac randomization group, those randomly assigned to revascularization within 4 weeks exhibited a trend of larger benefit of RF control. However, the interaction between the treatment assignment and the number of RFs in control was not significant for either outcome (Online Table 3).

Figure 2 shows the adjusted effect of individual time-varying RF control status entered simultaneously into the same model on the outcomes of death and CVD events. Significant RFs for death included smoking, high non-HDL-C, systolic BP (too low), and HbA_{1c} (too high). For CVD events, high non-HDL-C and systolic BP outside the target range (too low and too high) were significant predictors. When using a stepwise algorithm to identify the significant RFs, non-HDL-C and systolic BP outside the target range remained in the model (Online Table 4).

DISCUSSION

To our knowledge, this study is the first among patients with T2DM and CHD to show a strong association between the number of RFs below predetermined target levels and clinical outcomes. These observational data suggest that patients with CHD and T2DM require multiple RF interventions, including management of systolic BP and HbA_{1c}, to avoid undertreatment and overtreatment.

RF control among patients with T2DM and CHD has improved, but treatment targets in effect during BARI 2D are often not achieved (3). The level of RF control at baseline in BARI 2D was comparable to that of a contemporary National Health and Nutrition Examination Survey cohort (3). Consistent with other trials that included patients with diabetes and CHD (4,5,11,12), BARI 2D data show that RF treatment goals are achievable by using evidence-based, protocol-guided therapy with dedicated personnel.

Prospective data on the benefits of multifactorial intervention in patients with diabetes are sparse. The Steno-2 study compared outcomes in patients with T2DM randomized to receive intensive management of multiple RFs versus usual care. Patients with intensively managed RFs had a 53% reduction in the 7-year risk for CVD events and a 46% reduction in mortality after post-trial follow-up to 13 years (4,5). The study was small (160 patients) and not designed

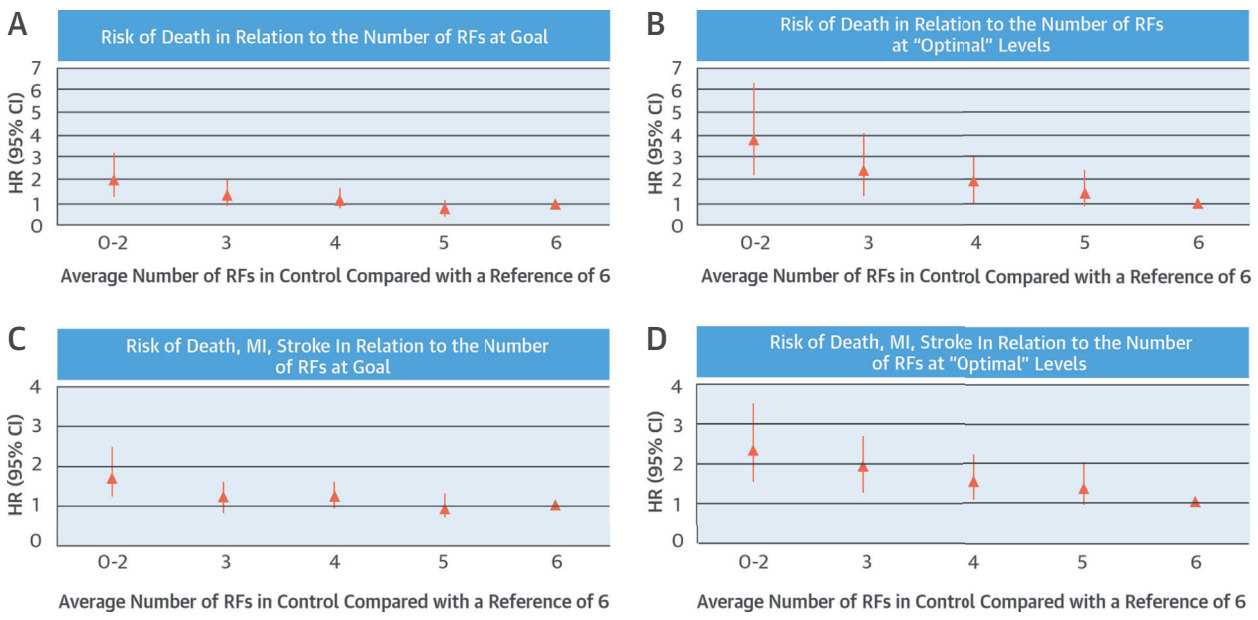
TABLE 6 Hazard Ratios for Death and CVD Events According to Number of RFs In Control/Within Target Range*

	Death†			Death/MI/Stroke†		
	HR	95% CI	p Value	HR	95% CI	p Value
0–2	3.8	2.2–6.5	<0.0001	2.4	1.6–3.6	<0.0001
3	2.4	1.4–4.1	0.0009	2.0	1.3–2.8	0.00011
4	1.9	1.1–3.0	0.0142	1.6	1.1–2.3	0.0163
5	1.5	0.9–2.4	0.1365	1.4	1.0–2.1	0.0709
6	1.0	Reference	–	1.0	Reference	–
Global p value			<0.0001			0.0005

*RFs in-control defined as: non-HDL-C <130 mg/dl, TG <150 mg/dl, 110 mm Hg < SBP <140 mm Hg, DBP <80 mm Hg, 6.5% < HbA_{1c} <7.5%, and no smoking. Note redefinition of target range for SBP and HbA_{1c} in this exploratory analysis. †Cox models adjusted for baseline number of RFs in control, number of total lesions, abnormal LVEF, Myocardial Jeopardy Index, prior revascularization, age, sex, race/ethnicity, country, and trial strata.

Abbreviations as in Tables 1, 2, 3, and 5.

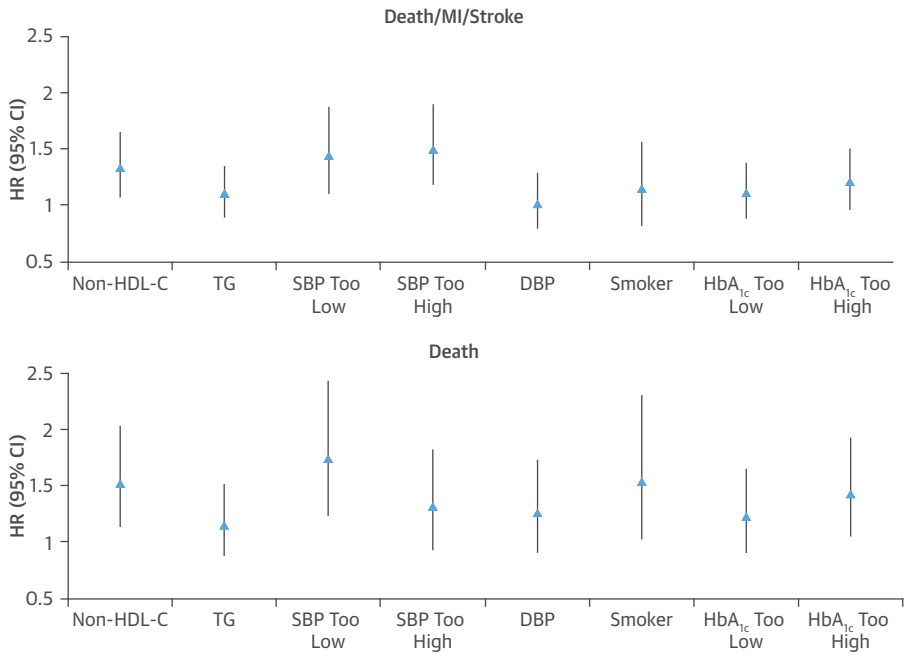
CENTRAL ILLUSTRATION Cardiac RF Control Improves Survival and Reduces Cardiovascular Events



Bittner, V. et al. J Am Coll Cardiol. 2015; 66(7):765–73.

The number of risk factors (RFs) in control is plotted **(A and B)** against mortality and **(C and D)** against cardiovascular disease events. In panels **A** and **C**, RFs in control are defined on the basis of the BARI 2D (Bypass Angioplasty Investigation Revascularization 2 Diabetes) trial protocol (main analysis). A J-shape is evident: patients with 6 RFs in control have a numerically higher risk of events than those with 5 RFs in control. In panels **B** and **D**, "optimal ranges" are defined for systolic and diastolic blood pressures and glycosylated hemoglobin. A J-shape is no longer evident, and the risk gradient comparing 6 versus 0 to 2 RFs in control is steeper. CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

FIGURE 2 Hazard Associated With Individual RFs Out of Control/Out of Target Range



Multivariable-adjusted hazard ratios (HRs) (95% confidence intervals [CIs]) are shown for individual risk factors (RFs) out of target range. RFs in control/in target range for this exploratory analysis were defined as: non-high-density lipoprotein cholesterol (non-HDL-C) <130 mg/dl, triglycerides (TG) <150 mg/dl, 110 mm Hg < systolic blood pressure (SBP) <140 mm Hg, diastolic blood pressure (DBP) <80 mm Hg, 6.5% < glycosylated hemoglobin (HbA_{1c}) < 7.5%, and no smoking. Cox models were adjusted for number of total lesions, abnormal left ventricular ejection fraction, Myocardial Jeopardy Index, prior revascularization, age, sex, race/ethnicity, country, and trial strata. MI = myocardial infarction.

to link observed benefits to achievement of specific treatment targets. Howard et al. (13) observed benefits of tighter cholesterol and BP targets on carotid atherosclerosis in SANDS (Stop Atherosclerosis in Native Diabetics Study) but acknowledged a greater rate of adverse events associated with tighter BP control (13). Concerns were raised about the increased mortality associated with "aggressive" treatment of hyperglycemia among patients with T2DM in ACCORD (Action to Control Cardiovascular Risk in Diabetes Study) (9). Long-term follow-up in INVEST (International Verapamil SR/Trandolapril Study) suggested small but significant increases in mortality among patients with diabetes and CHD who achieved systolic BP <130 mm Hg compared with less stringent control (130 to 140 mm Hg) (14).

In the present study, the number of RFs in control at baseline was not related to study outcomes. In contrast, the number of RFs in control after 1 year of comprehensive medical intervention was strongly related to subsequent mortality and CVD events. Potential explanations for this observation include the potency of pharmacological interventions initiated after randomization (statins and antihypertensive agents), which diminishes the prognostic value of baseline RFs and greater statistical power to show an effect of better RF control during follow-up when more patients have good RF control. Given that RF control at BARI 2D entry was comparable to the U.S. population with diabetes (3), these data suggest that, with appropriate resource allocation, similar improvements in prognosis could be achieved among subjects with diabetes in the general population.

Using BARI 2D treatment targets, patients with 0 to 2 RFs under control had twice the risk of mortality and a 70% greater risk of death or CVD event during follow-up compared with those who had 6 RFs under control. These analyses also suggest that there is a plateau of benefit at 5 RFs under control, with a small increase in risk among those who had 6 RFs under control. Our exploratory analyses (including sensitivity analyses using 2 different ranges of "ideal" BP and HbA_{1c}) suggest that overcontrol of systolic BP, but not HbA_{1c}, could mediate this phenomenon.

STRENGTHS AND LIMITATIONS. BARI 2D represents a contemporary cohort of patients with T2DM, well characterized at baseline, with 5-year longitudinal assessment of RFs, and with adjudicated cardiovascular and mortality outcomes. Our statistical analysis has important strengths: first, it captured the cardiovascular and mortality risks associated with the number of RFs below target levels over the entire follow-up period; second, it assessed the risk associated with changes in RF status incorporating baseline RF status; third, it adjusted for important confounders; and lastly, it explored the risk associated with BP and HbA_{1c} within a target range.

We acknowledge some limitations. First, subjects enrolled in the BARI 2D study represent a selected population of subjects with T2DM, angiographically documented stable CHD with revascularizable lesions, and myocardial ischemia who were followed up at tertiary care centers. Second, although we expressed outcomes as a function of RF control, we were unable to distinguish benefits that accrued through pleiotropic effects of medications used to achieve RF control from benefits that accrued due to the actual level of each RF achieved. Finally, in our exploratory analysis, "overcontrol" of BP was associated with worse outcomes. Given the design of this post-hoc analysis, we are unable to distinguish between declines in BP due to intensified treatment as opposed to declines that occurred as a consequence of developing ill health. Our conclusion should thus be interpreted with caution and requires verification in specifically designed prospective trials.

CONCLUSIONS

Protocol-guided therapy with specific treatment targets can improve control of multiple RFs, which relates to survival and future clinical events among patients with CHD and T2DM.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with T2DM and coronary artery disease, achievement of RF targets is related to cardiovascular events and mortality.

TRANSLATIONAL OUTLOOK: Additional studies are needed to define optimal target levels for systolic BP and HbA_{1c} for patients with T2DM.

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KEY WORDS blood pressure, cholesterol, coronary heart disease, diabetes mellitus, glycosylated hemoglobin A, smoking

APPENDIX For supplemental Methods and tables, please see the online version of this article.

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