

Von Willebrand Factor, Type 2 Diabetes Mellitus, and Risk of Cardiovascular Disease The Framingham Offspring Study

David S. Frankel, MD; James B. Meigs, MD, MPH; Joseph M. Massaro, PhD;
Peter W.F. Wilson, MD; Christopher J. O'Donnell, MD, MPH;
Ralph B. D'Agostino, PhD; Geoffrey H. Tofler, MD

Background—Von Willebrand factor (vWF) is inconsistently associated with cardiovascular disease (CVD). This might be explained by associations of vWF with type 2 diabetes mellitus and insulin resistance.

Methods and Results—We tested whether vWF predicted incident CVD in 3799 Framingham Offspring Study participants, and in particular, among those with type 2 diabetes mellitus or insulin resistance. During 11 years of follow-up, 351 participants developed CVD. In proportional hazards models (with adjustment for age, sex, blood pressure, smoking, body mass index, total and high-density lipoprotein cholesterol, and treatment with aspirin, insulin, antihypertensives, and lipid-lowering medications) with the lowest quartile of the vWF distribution as the referent, the hazard ratio (HR) for CVD was 0.94 in the second quartile, 0.98 in the third, and 1.32 in the highest ($P=0.04$ for trend). Additional adjustment for type 2 diabetes mellitus or insulin resistance (homeostasis model) partially attenuated the association (multivariable HRs for top quartile 1.28 and 1.21, respectively). We then stratified the models by diabetes status or the homeostasis model of insulin resistance distribution (top quartile versus lower 3 quartiles). vWF was associated with CVD among participants with diabetes mellitus (HR for top quartile relative to bottom 1.47, $P=0.04$ for trend) but not among nondiabetic participants (HR 1.15, $P=0.5$) and similarly among insulin-resistant (HR 1.50, $P=0.01$) but not insulin-sensitive (HR 1.02, $P=0.9$) participants.

Conclusions—Higher levels of vWF were associated with risk of CVD in people with type 2 diabetes mellitus or insulin resistance, which suggests that vWF may be a risk factor unique to these populations. (*Circulation*. 2008;118:2533-2539.)

Key Words: von Willebrand factor ■ diabetes mellitus ■ insulin resistance ■ cardiovascular diseases
■ epidemiology

Cardiovascular disease (CVD) accounts for $\approx 35\%$ of all deaths in the United States.¹ Major established CVD risk factors, including diabetes mellitus, hypertension, hyperlipidemia, and cigarette smoking, are found in most but not all individuals who develop CVD.^{2–4} Endothelial dysfunction is also thought to contribute to development of CVD via dysregulation of vascular tone, growth, thrombogenicity, and inflammation.⁵ Several inflammatory and hemostatic biomarkers of endothelial dysfunction have been associated with CVD, including C-reactive protein,^{6–8} interleukin-6,⁹ fibrinogen,^{10,11} fibrin D-dimer,¹² plasminogen activator inhibitor-1,¹³ and cellular adhesion molecules.^{14,15}

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Von Willebrand factor (vWF) is a large glycoprotein produced by vascular endothelial cells that mediates platelet adhesion to injured endothelium, the first step in thrombus formation. vWF also serves as the carrier protein for coagulation factor VIII.¹⁶ Given its essential role in thrombosis, as well as the possibility that vWF could serve as a biomarker of endothelial damage, the role of vWF in prediction of CVD has been studied extensively. Results have been mixed, with some finding significant associations between vWF and CVD^{17–24} and others not.^{25–30}

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From the Division of Cardiovascular Medicine (D.S.F.), Department of Medicine, University of Pennsylvania, Philadelphia, Pa; the General Medicine Division (J.B.M.) and the Cardiology Division (C.J.O.), Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston; the National Heart, Lung, and Blood Institute's Framingham Heart Study (J.M.M., C.J.O., R.B.D.), Framingham, Mass; the Division of Cardiology (P.W.F.W.), Department of Medicine, Emory University School of Medicine, Atlanta, Ga; the Department of Biostatistics (J.M.M., R.B.D.), Boston University, Boston, Mass; and the Royal North Shore Hospital (G.H.T.), Sydney, Australia.

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Correspondence to James B. Meigs, MD, MPH, General Medicine Division, Massachusetts General Hospital, 50 Staniford St, 9th Floor, Boston, MA 02114. E-mail jmeigs@partners.org

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vWF has recently been associated with insulin resistance and type 2 diabetes mellitus,^{31–33} which raises the question of whether the association between vWF and CVD is confounded by these intermediaries. Furthermore, persons with type 2 diabetes mellitus are known to have increased risk for CVD that exceeds the expected effect of associated traditional CVD risk factors.³⁴ Among participants with type 2 diabetes mellitus, insulin resistance has been associated with worse endothelial function,³³ and treatment with thiazolidinediones (insulin sensitizers) has been shown to improve endothelial function.³⁵ These observations suggest that vWF may be a risk factor for CVD unique to patients with type 2 diabetes mellitus or insulin resistance. Inconsistent observations about the relationship between vWF and CVD to date may be the result of studying patient populations with varying prevalence of diabetes mellitus and insulin resistance.

With this background in mind, we used the experience of the Framingham Offspring Study to test the hypothesis that elevated levels of vWF confer risk for new CVD after accounting for possible confounding by traditional CVD risk factors, including type 2 diabetes mellitus and insulin resistance (using the surrogate homeostasis model of insulin resistance [HOMA-IR]). We further sought to examine whether vWF is a particularly potent, independent risk factor for CVD in those with type 2 diabetes mellitus or insulin resistance.

Methods

Study Subjects

The Framingham Offspring Study is a community-based, prospective, observational study of CVD and its risk factors. It was initiated in 1971 by enrolling children of the original Framingham Heart Study cohort and the children's spouses. Members of the Offspring Cohort are white and of mixed European ancestry.³⁶ During the fifth examination cycle (1991 to 1995; the baseline examination for the present study), 3799 participants underwent a standardized medical history, physical examination, 12-lead ECG, and analysis of fasting blood samples.³⁷ We measured vWF levels in 3564 participants. Of these, we excluded 355 with CVD at baseline and 122 with missing risk factor covariate information, which left 3087 subjects for analysis. Subjects excluded for missing vWF levels or risk factor covariate information were similar to those included in the analysis ($P>0.05$ for all comparisons). The study protocol was approved by the institutional review board of the Boston University School of Medicine, and all participants provided written informed consent.

Clinical Definitions and Laboratory Methods

We measured height and weight with the subject standing in light clothes. Body mass index was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). Blood pressure values were taken as the mean of 2 measurements after the subject had been seated for at least 5 minutes. We defined diabetes mellitus as a fasting plasma glucose >125 mg/dL or treatment with glucose-lowering medication.³⁸ Those who reported smoking cigarettes regularly during the year before the examination were considered current smokers.

Subjects fasted overnight to provide a blood specimen. Samples were frozen at -80°C until assay. Laboratory methods for glucose, insulin, and lipid assays have been published previously.^{39,40} The Framingham laboratory participates in the Centers for Disease Control and Prevention's lipoprotein cholesterol laboratory standardization program. We measured insulin resistance with the homeostasis model using the following validated formula: $\text{HOMA-IR} = [\text{fasting glucose (mmol/L)} \times \text{fasting insulin } (\mu\text{U/mL})] / 22.5$.^{41,42}

vWF antigen was measured with an ELISA assay, as described previously.⁴³ Intra-assay coefficients of variation were $<3\%$ for glucose, $<10\%$ for insulin, and 8.8% for vWF.

Ascertainment of CVD

We defined CVD as coronary heart disease (myocardial infarction or angina pectoris), heart failure, stroke, or intermittent claudication, according to previously described Framingham criteria.⁴⁴ All study participants were under continuous surveillance for CVD events from baseline examination through end of follow-up in December 2006. Suspected CVD events were adjudicated by a panel of 3 experienced investigators, including a neurologist for suspected strokes, who reviewed hospital records, clinic notes, and pathology reports.

Statistical Analyses

For the primary analysis, we classified subjects into quartiles of the distribution of vWF. vWF level thresholds at the first, second, and third quartile were 91.3, 120.6, and 156.6 IU/dL, respectively. We used a series of Cox proportional hazards regression models to test the hypothesis that the relationship between vWF levels and 11-year incidence of CVD is linear (ie, that higher levels of vWF are associated with increased risk of CVD) after adjustment for potentially confounding CVD risk factors. Cox models provided hazard ratios (HRs) and 95% CIs for incident CVD conditioned on baseline exposures. Models that tested linear trend in incidence of CVD across vWF quartiles were adjusted for (1) age and sex; (2) age, sex, systolic blood pressure, smoking, body mass index, total and high-density lipoprotein cholesterol, and treatment with aspirin, insulin, antihypertensive, and lipid-lowering medications; and (3) the variables in model 2 plus diabetes mellitus and HOMA-IR, individually and then combined. Given 351 CVD events, the study power at $\alpha=0.05$ to detect a HR of 1.4 across the trend of quartiles was 59.9%; for HR 1.5, it was 75.8%; for HR 1.6, it was 86.8%; and for HR 1.7, it was 93.4%. We constructed Kaplan–Meier survival curves for survival free of CVD according to quartile of the vWF distribution. We used ANOVA or Mantel–Haenszel tests of linear trend to assess differences in risk factor means (continuous risk factors) or proportions (categorical risk factors) across vWF strata. For these tests, levels of HOMA-IR were log-transformed to reduce skewness; we present untransformed means in the results.

To answer the question of whether vWF is a risk factor for CVD unique to those with type 2 diabetes mellitus or insulin resistance, in the secondary analysis, we repeated the series of Cox proportional hazards regression models stratifying subjects by the presence of diabetes versus no diabetes or by the highest quartile of the HOMA-IR distribution (which we refer to as “insulin resistant”) versus the lower 3 quartiles (“insulin sensitive”). We performed tests for first-order interaction between levels of vWF and diabetes mellitus and between levels of vWF and HOMA-IR on risk for CVD. We next constructed Kaplan–Meier survival curves for survival free of CVD according to the following 4 categories: low vWF–no diabetes, low vWF–diabetes, high vWF–no diabetes, and high vWF–diabetes. Low vWF was defined as the lower 3 quartiles of the vWF distribution. High vWF was defined as the top quartile. We constructed similar survival curves for vWF and the top quartile of HOMA-IR versus the bottom 3 quartiles. Differences in survival in the categories were tested with the Wilcoxon rank sum test.

Analyses were performed with SAS software (version 8.1, SAS Institute, Cary, NC). P values <0.05 were considered to indicate statistical significance. We reduced the level of significance (<0.2) to increase power for tests of interaction, as recommended by Selvin.⁴⁵

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

The mean age of participants was 54 years (SD 10 years), and 55% were female. Characteristics of the study subjects across

Table 1. Baseline Characteristics of 3087 Study Participants by Quartiles of the vWF Distribution

	vWF Quartile				<i>P</i> *
	1 (n=771)	2 (n=772)	3 (n=773)	4 (n=771)	
Women, %	54.6	56.9	53.3	54.5	0.6
Age, y	51.0 (9.1)	53.6 (9.6)	54.9 (9.8)	57.5 (9.7)	<0.0001
Systolic blood pressure, mm Hg	123 (17.8)	125 (18.8)	126 (18.5)	129 (20.0)	<0.0001
Current cigarette smoking, %	19.8	18.5	18.4	20.0	0.9
Body mass index, kg/m ²	26.7 (4.5)	27.2 (4.9)	27.6 (5.2)	28.0 (5.4)	<0.0001
Serum total cholesterol, mg/dL	203 (36.3)	204 (36.8)	204 (35.4)	208 (38.2)	0.02
Serum HDL cholesterol, mg/dL	51.3 (15.0)	50.9 (15.2)	49.8 (14.6)	49.7 (15.6)	0.02
Treatment with aspirin, %	54.6	55.9	53.3	51.4	0.1
Treatment with insulin, %	0.1	0.5	0.6	1.7	0.001
Treatment with antihypertensive medication, %	14.0	16.3	16.9	20.2	0.002
Treatment with lipid-lowering medication, %	3.9	5.7	6.2	6.5	0.03
Type 2 diabetes mellitus, %	2.72	4.27	5.43	8.43	<0.0001
HOMA-IR†	6.9 (4.0)	7.3 (3.9)	8.1 (5.8)	10.3 (17.5)	<0.0001

*Data shown are mean (SD) or proportions in each quartile. *P* values indicate significance for trend across quartiles of vWF. HDL indicates high-density lipoprotein.

†Untransformed data.

strata of vWF are displayed in Table 1. The prevalence of common CVD risk factors rose with increasing levels of vWF. The mean level of vWF was higher in those with diabetes mellitus than in those without diabetes mellitus (146 versus 126 IU/dL, $P<0.0001$) and in those with insulin resistance than in those with normal insulin sensitivity (138 versus 122 IU/dL, $P<0.0001$).

vWF and CVD Risk

Three hundred fifty-one participants (146 women) developed new-onset CVD over a mean of 11 years of follow-up. The CVD event was myocardial infarction in 90 participants, angina pectoris in 100, heart failure in 50, stroke in 82, and intermittent claudication in 29; the cumulative incidence of CVD was 11.4%. The HR for CVD, adjusted for age and sex, increased across strata of vWF (Table 2). Increased risk associated with higher strata of vWF persisted after further adjustment for systolic blood pressure, smoking, body mass index, total and high-density lipoprotein cholesterol, and

treatment with aspirin, insulin, or antihypertensive or lipid-lowering medications (Table 2). For instance, in the latter model, with the lowest quartile as the referent, the HR for CVD was 0.94 in the second quartile, 0.98 in the third quartile, and 1.32 in the highest quartile ($P=0.04$ for trend across quartiles). With further adjustment for diabetes mellitus or HOMA-IR at baseline, the association of the top quartile of vWF with CVD was attenuated (HR 1.28, $P=0.06$ for trend and HR 1.21, $P=0.2$, respectively). Survival free of CVD decreased with increasing quartiles of the vWF distribution (Figure 1; $P<0.0001$).

We next repeated the analysis, stratifying subjects by the presence versus absence of diabetes mellitus or by the highest quartile of HOMA-IR (insulin resistant) versus the lower 3 quartiles combined (Table 3). vWF was associated with CVD among participants with diabetes mellitus (risk factor- and HOMA-IR-adjusted HR for top relative to bottom quartile 1.47, $P=0.04$ for trend across quartiles) but not among participants without diabetes mellitus (HR 1.15, $P=0.5$).

Table 2. Nested Cox Proportional Hazard Models Testing the Incidence of CVD Across Quartiles of Plasma vWF*

	vWF Quartile				<i>P</i> *
	1	2	3	4	
No. of CVD events	66	76	84	125	
Incidence density (CVD events/100 person-years)	0.76	0.89	0.98	1.59	
Model 1†	1.00	0.99 (0.71–1.38)	0.97 (0.70–1.35)	1.42 (1.05–1.93)	0.02
Model 2‡	1.00	0.94 (0.68–1.31)	0.98 (0.70–1.35)	1.32 (0.97–1.80)	0.04
Model 3A: model 2+DM	1.00	0.92 (0.66–1.29)	0.99 (0.71–1.37)	1.28 (0.94–1.74)	0.06
Model 3B: model 2+HOMA-IR	1.00	0.93 (0.67–1.29)	0.94 (0.68–1.31)	1.21 (0.89–1.65)	0.2
Model 3C: model 2+DM+HOMA-IR	1.00	0.92 (0.66–1.28)	0.96 (0.69–1.33)	1.22 (0.89–1.66)	0.1

DM indicates diabetes mellitus.

**P* values indicate significance of trend across strata of vWF.

†HRs with 95% CIs adjusted for age and sex.

‡HRs adjusted for age, sex, systolic blood pressure, smoking, body mass index, total and high-density lipoprotein cholesterol, and treatment with aspirin, insulin, antihypertensives, and lipid-lowering medications.

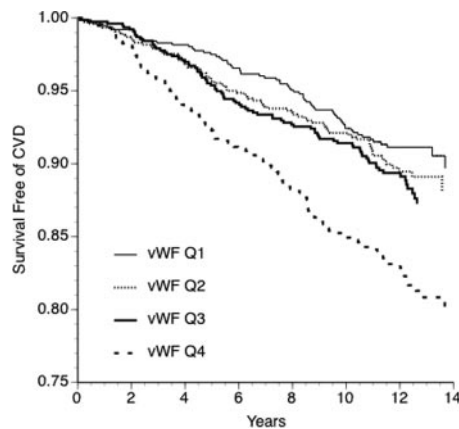


Figure 1. Kaplan–Meier curves for survival free of CVD stratified by quartile (Q) of the vWF distribution (Wilcoxon rank sum $P<0.0001$).

Similarly, vWF was associated with CVD among those with insulin resistance (risk factor– and diabetes-adjusted HR 1.50, $P=0.01$) but not among those with normal insulin sensitivity (HR 1.02, $P=0.9$). Formal testing indicated a

significant interaction between diabetes mellitus and vWF on CVD risk ($P=0.2$) and between insulin resistance and vWF on CVD risk ($P=0.08$).

In Kaplan–Meier analyses, survival free of CVD was significantly decreased in participants with high vWF and diabetes mellitus compared with the low-vWF and nondiabetes groups (Figure 2A; $P<0.0001$). A similar pattern was apparent with high vWF and high HOMA-IR (Figure 2B; $P<0.0001$). The data suggest that whereas vWF appeared to have an additive effect with diabetes mellitus and insulin resistance on CVD risk, elevated CVD risk associated with elevated vWF levels was essentially confined to those with type 2 diabetes mellitus or insulin resistance.

Discussion

Principal Findings

We observed that higher levels of vWF were associated with increased risk of new-onset CVD over 11 years of follow-up of a community-based sample. This association persisted after adjustment for traditional CVD risk factors but was weakened on accounting for the presence of type 2 diabetes

Table 3. Nested Cox Proportional Hazard Models Testing the Incidence of CVD Across Quartiles of Plasma vWF, Stratified by the Presence or Absence of Type 2 Diabetes Mellitus or Insulin Resistance

	vWF Quartiles				
	1	2	3	4	P*
Type 2 Diabetes mellitus					
No. of CVD events	7	8	11	32	...
Incidence density (CVD events/100 person-years)	3.55	2.32	2.85	6.33	...
Model 1†	1.00	0.53 (0.19–1.48)	0.82 (0.31–2.11)	1.58 (0.69–3.66)	0.02
Model 2‡	1.00	0.51 (0.18–1.49)	0.88 (0.32–2.37)	1.56 (0.64–3.78)	0.02
Model 3: model 2+HOMA-IR	1.00	0.52 (0.18–1.52)	0.86 (0.32–0.2.33)	1.47 (0.60–3.61)	0.04
No Diabetes mellitus					
No. of CVD events	59	68	73	93	...
Incidence density (CVD events/100 person-years)	0.69	0.83	0.89	1.26	...
Model 1†	1.00	1.03 (0.72–1.46)	0.97 (0.68–1.37)	1.24 (0.89–1.73)	0.2
Model 2‡	1.00	1.01 (0.71–1.44)	0.95 (0.67–1.34)	1.19 (0.85–1.66)	0.4
Model 3: model 2+HOMA-IR	1.00	1.00 (0.70–1.42)	0.93 (0.66–1.32)	1.15 (0.82–1.61)	0.5
HOMA-IR Top Quartile					
No. of CVD events	24	25	34	74	...
Incidence density (CVD events/100 person-years)	1.66	1.53	1.57	2.93	...
Model 1†	1.00	0.81 (0.46–1.42)	0.85 (0.50–1.44)	1.50 (0.94–2.39)	0.02
Model 2‡	1.00	0.77 (0.44–1.36)	0.93 (0.55–1.57)	1.50 (0.94–2.39)	0.01
Model 3: model 2+DM	1.00	0.76 (0.43–1.34)	0.93 (0.55–1.58)	1.50 (0.94–2.40)	0.01
HOMA-IR Quartiles 1–3					
No. of CVD events	42	51	50	51	...
Incidence density (CVD events/100 person-years)	0.58	0.74	0.78	0.95	...
Model 1†	1.00	1.08 (0.71–1.62)	0.97 (0.64–1.47)	1.05 (0.69–1.60)	0.9
Model 2‡	1.00	1.06 (0.70–1.60)	0.97 (0.64–1.47)	1.03 (0.67–1.58)	0.9
Model 3: model 2+DM	1.00	1.06 (0.70–1.59)	0.97 (0.64–1.47)	1.02 (0.66–1.56)	0.9

DM indicates diabetes mellitus.

* P values indicate significance of trend across strata of vWF.

†HRs with 95% CIs adjusted for age and sex.

‡HRs adjusted for age, sex, systolic blood pressure, smoking, body mass index, total and HDL cholesterol, and treatment with aspirin, insulin, antihypertensives, and lipid-lowering medications.

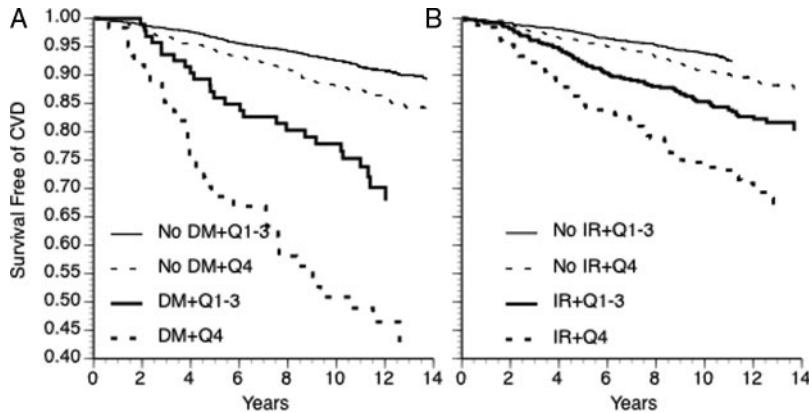


Figure 2. Kaplan-Meier curves for survival free of CVD according to the following strata: A, No diabetes-low vWF; no diabetes-high vWF; diabetes-low vWF; diabetes-high vWF (Wilcoxon rank sum $P < 0.0001$). B, Insulin sensitive-low vWF; insulin sensitive-high vWF; insulin resistant-low vWF; insulin resistant-high vWF ($P < 0.0001$). Low vWF is defined as the lower 3 quartiles of the vWF distribution. High vWF is the top quartile. Insulin sensitive is defined as the lower 3 quartiles of HOMA-IR. Insulin resistant is the top quartile. DM indicates diabetes mellitus; Q, quartile; and IR, insulin resistance.

mellitus or insulin resistance. Further examination showed that elevated vWF was associated with CVD only in participants with diabetes mellitus or insulin resistance. This observation may explain past inconsistencies in the literature linking vWF to CVD and suggests that vWF may be a CVD risk factor that is particularly prominent in type 2 diabetes mellitus and insulin resistance.

Possible Mechanisms

Under physiological conditions, vWF is produced by vascular endothelium and plays an important role in hemostasis. Under pathological conditions, vWF serves as a biomarker of endothelial damage and dysfunction.^{46,47} Endothelial dysfunction is a systemic disorder that leads to atherosclerosis and CVD.⁴⁸

We found that insulin resistance and diabetes mellitus attenuated the association between elevated vWF and increased risk of CVD, which points to these as potential mediators. Elevated levels of vWF have been associated with increased risk of development of type 2 diabetes mellitus.³¹ Furthermore, vWF has been associated with insulin resistance both in those with and those without diabetes mellitus.^{32,33} Thus, participants with elevated vWF tend to be insulin resistant and at elevated risk of developing diabetes mellitus, and on this basis, they could be at elevated risk for developing CVD.

Stratified analyses demonstrated that vWF is a risk factor for development of CVD only in participants with insulin resistance or diabetes mellitus, which suggests that these conditions exacerbate the endothelial dysfunction and prothrombotic state associated with risk for CVD events. Among people with diabetes mellitus, insulin resistance has been associated with worse endothelial function,³³ and treatment with thiazolidinediones (insulin sensitizers) has been shown to improve endothelial function.³⁵ A vicious circle may exist whereby endothelial dysfunction promotes insulin resistance and diabetes mellitus, both of which in turn worsen endothelial function, accelerating atherosclerosis and the onset of clinical CVD. More severe endothelial dysfunction and hemostatic imbalance may be key atherogenic factors that account for the consistently observed, traditional risk factor-adjusted, as-yet-unexplained 2- to 4-fold excess risk for CVD seen in type 2 diabetes mellitus.³⁴

Strengths and Limitations

Unlike prior studies that found inconsistent relationships between vWF and CVD, we attempted to dissect the complex relationship between elevated vWF, insulin resistance, and diabetes mellitus in promoting CVD. Additional strengths include studying a large, community-based sample assessed with standardized clinical measures and biomarker assays with good precision. Of interest, increased risk for CVD appeared to be confined to the top quartile of vWF; the HRs of the intermediate quartiles compared with the lowest quartile were all ≈ 1 . We only performed a test for linear trend across the quartiles, because that was the a priori specified statistical analysis; however, future studies may search for a threshold effect of vWF on CVD incidence. Other limitations include those of biomarker interpretation. As a biomarker, elevated levels of vWF represent both endothelial dysfunction and hemostatic imbalance. It is not possible from the present study to determine which has primacy in the actual mechanisms hypothesized to link vWF with new cases of CVD in people with diabetes mellitus or insulin resistance. In addition, we only had 1 baseline measure of vWF; evidence exists that levels of biomarkers may vary over time in response to disease progression and treatment.⁴⁹ However, misclassification by vWF level is likely to be random, and thus, the effect is to produce an underestimate of the magnitude of the association of vWF levels with CVD risk. Generalizability of the study also is limited to white European-descent populations.

Conclusions

We found that elevated levels of vWF were associated with increased risk of CVD in a community-based sample, even after accounting for traditional CVD risk factors. This association was attenuated by adjustment for type 2 diabetes mellitus or insulin resistance, and elevated levels of vWF were a particularly potent, independent risk factor in participants with diabetes mellitus or insulin resistance, which supports a role in the pathogenesis of atherosclerosis and CVD in these populations. If the present findings can be confirmed in other populations, endothelial dysfunction/hemostatic dysfunction might represent a novel therapeutic target for prevention of CVD in people with type 2 diabetes mellitus or insulin resistance.

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Disclosures

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CLINICAL PERSPECTIVE

We tested whether elevated levels of the hemostatic and vascular dysfunction biomarker von Willebrand factor predicted incident cardiovascular disease in a community sample over 11 years of longitudinal follow-up, and in particular, among those with type 2 diabetes mellitus or insulin resistance (measured with the homeostasis model). After adjustment for age, sex, blood pressure, smoking, body mass index, total and high-density lipoprotein cholesterol, and treatment with aspirin, insulin, antihypertensives, and lipid-lowering medications, the hazard ratio for cardiovascular disease was 1.32 in the highest quartile of the von Willebrand factor distribution relative to the lowest ($P=0.04$ for trend). Additional adjustment for type 2 diabetes mellitus or insulin resistance somewhat weakened the association. We stratified the models by diabetes status or the top quartile of the homeostasis model of insulin resistance distribution (“insulin resistant”) versus the lower 3 quartiles. Von Willebrand factor was associated with cardiovascular disease among participants with diabetes mellitus ($P=0.04$ for trend) but not among nondiabetics ($P=0.5$) and similarly among insulin-resistant ($P=0.01$) but not insulin-sensitive ($P=0.9$) participants. Elevated levels of von Willebrand factor were an independent risk factor for cardiovascular disease, especially in people with diabetes mellitus or insulin resistance, in whom endothelial or hemostatic dysfunction may be a novel therapeutic target for prevention of cardiovascular disease.