Plasminogen Activator Inhibitor-1 Activity in Type 2 Diabetes
A Different Relationship With Coronary Heart Disease and Diabetic Retinopathy

Laima Brazionis, Kevin Rowley, Alicia Jenkins, Catherine Itsiopoulos, Kerin O’Dea

Background—Plasminogen activator inhibitor (PAI)-1, a key regulator of fibrinolysis, is associated with increased risk of coronary heart disease (CHD) and is a potential therapeutic target for CHD. However, the relationship between PAI-1 and the most common diabetic microvascular complication, retinopathy, is unclear. The purpose of this study was to assess the relationship between PAI-1 activity and both retinopathy and CHD in type 2 diabetes.

Methods and Results—We determined PAI-1 activity and both retinopathy (assessed by masked grading of 3-field retinal photographs) and CHD status (assessed by ECG and standard questionnaires) in 147 men and women with type 2 diabetes, mean age (SD) 64 (7) years, in a cross-sectional setting. Plasma PAI-1 activity was inversely associated with prevalent retinopathy ($P=0.006$) and severity of retinopathy ($P=0.022$), and was associated with lower risk of diabetic retinopathy, independent of major retinopathy risk factors (duration of diabetes and HbA1c) and determinants of PAI-1 (obesity and triglyceride level) (OR 0.74 [0.60 to 0.92], $P=0.006$). Conversely, higher plasma PAI-1 activity was independently associated with greater risk of CHD, after adjusting for the major CHD risk factors and determinants of PAI-1 (OR 1.31 [1.06 to 1.62], $P=0.001$).

Conclusion—These data support mounting evidence that a higher PAI-1 plasma level is independently associated with a lower risk of retinopathy but a higher risk of CHD in type 2 diabetes. (*Arterioscler Thromb Vasc Biol*. 2008;28:000-000.)

Key Words: PAI-1 activity ■ diabetic retinopathy ■ coronary heart disease ■ type 2 diabetes

It is well established that higher circulating PAI-1 levels and activity are associated with increased risk of coronary heart disease (CHD).1-3 PAI-1 levels are higher in hyperinsulinemia and type 2 diabetes, possibly related to the oxidation of LDL and insulin resistance.4 Interestingly, both types of commonly-used lipid-lowering drugs, the 3-hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase inhibitors (statins) and fibrates, have been shown to modulate plasma PAI-1 levels.10-12 In addition, genetic factors influence PAI-1.13 However, the epidemiology and clinical significance of PAI-1 in the microvascular complications of diabetes is unclear. In particular, studies of the association between PAI-1 and diabetic retinopathy have given divergent results, as shown in Table 1.

The purpose of our study was to examine the relationship between plasma PAI-1 activity and both CHD and diabetic retinopathy in community-based volunteers with type 2 diabetes and to relate our findings to the divergent results reported in earlier studies on this topic.

Materials and Methods
We recruited, via the electoral roll and media advertising, 147 community-based volunteers who had self-reported type 2 diabetes. We confirmed diabetes status biochemically, based on a fasting blood glucose value of 7 mmol/L or higher, or on the use of hypoglycemic medications. Individuals who were unable or unwilling to participate in the clinical evaluation, or who had chronic diseases (other than diabetes and cardiovascular diseases), including cancer not in remission, end-stage renal failure requiring dialysis, presence of disabling stroke, or liver disease, were excluded from the study. Pregnant women were not eligible. Sixty-eight percent of invitees who met study inclusion criteria, determined by telephone interview, participated in this study. We obtained ethics approval from the Melbourne Collaborative Cohort Study (MCCS) and Monash University and written informed consent from all participants.

We used a mydriatic retinal fundus camera (Kowa FX-500S, Japan) to take 3 50° retinal photographs per eye. Diabetic retinopathy grading was based on the validated Eurodiab protocol, in which the overall grading was that of the worse eye.14 Diabetic retinopathy grading was defined as more than 1 microaneurysm or hemorrhage. Sight-threatening retinopathy was defined as the presence of proliferative retinopathy or clinically significant macular edema. A medical retina specialist, masked to all other participant information, graded the slides on 2 separate occasions to ascertain internal validity, which was high (kappa >0.95).

Prevalent CHD was diagnosed on the basis of a self-reported history of coronary artery bypass surgery, or angioplasty for CHD, or use of nitrate medications for angina treatment, or when criteria were...
met for “probable CHD” according to the Busselton Survey\textsuperscript{15} after a resting ECG. Because of the potential role of insulin resistance as a cause of elevated concentrations of PAI-1 in type 2 diabetes, the homeostasis model assessment (HOMA) was used to derive an indicator of insulin resistance from the fasting glucose and fasting insulin concentrations.

We determined plasma PAI-1 activity as follows: A fasting (12 h/overnight) sample of blood was drawn from the antecubital vein of subjects using a multi-sample needle into a precooled sodium citrate evacuated siliconized plastic collection tube (Greiner Labortechnik) in a 9:1 ratio of blood to citrate. Blood was drawn from rested and seated subjects to minimize subject stress. We used minimal venocclusion to prevent activation of hemostatic factors and collected blood within a 2-hour window (8 to 10 AM) to minimize the effects of diurnal variation in PAI-1 levels. There were no nightshift workers in our study sample. Within 30 min of collection, blood was

<table>
<thead>
<tr>
<th>Authors and Year</th>
<th>Design</th>
<th>Country</th>
<th>No. of Subjects</th>
<th>PAI-1 Characteristic</th>
<th>Association Between Plasma PAI-1 and Any Retinopathy</th>
<th>Other Associations With PAI-1 Including CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zietz et al, 2006</td>
<td>Cc</td>
<td>Germany</td>
<td>570</td>
<td>Genotype</td>
<td>No association</td>
<td>*Rare PAI-1 genotype associated with PDR</td>
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<tr>
<td>Funk et al, 2005</td>
<td>CH</td>
<td>Austria</td>
<td>147</td>
<td>Genotype</td>
<td>No association</td>
<td>*4G/4G genotype associated with PDR</td>
</tr>
<tr>
<td>Erem et al, 2005</td>
<td>CH</td>
<td>Turkey</td>
<td>40</td>
<td>Plasma concentration</td>
<td>Positive (antigen)</td>
<td>Nephropathy neuropathy associated with PAI-1</td>
</tr>
<tr>
<td>Zietz et al, 2004</td>
<td>Cc</td>
<td>Germany</td>
<td>547</td>
<td>Plasma conc. genotype</td>
<td>No association</td>
<td>PAI-1 level and genotype not associated</td>
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<td>Santos et al, 2003</td>
<td>CH</td>
<td>Brazil</td>
<td>210</td>
<td>Genotype</td>
<td>No association</td>
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<tr>
<td>Leurs et al, 2003</td>
<td>CH</td>
<td>Netherlands</td>
<td>46</td>
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</tr>
<tr>
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<td>Slovenia</td>
<td>204</td>
<td>Genotype</td>
<td>No association</td>
<td></td>
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<td>Czechoslovakia</td>
<td>25</td>
<td>Plasma concentration</td>
<td>No association</td>
<td></td>
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<td>Tarnow et al, 2000</td>
<td>CH</td>
<td>Denmark</td>
<td>390</td>
<td>Plasma concentration</td>
<td>No association</td>
<td></td>
</tr>
<tr>
<td>Kato et al, 2000</td>
<td>CH</td>
<td>Japan</td>
<td>47</td>
<td>Plasma concentration</td>
<td>Positive (antigen)*</td>
<td>Only for PDR</td>
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<tr>
<td>Simpson et al, 1999</td>
<td>CH</td>
<td>UK</td>
<td>16</td>
<td>Plasma platelet concentration</td>
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<td>Only for PDR</td>
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<tr>
<td>Telejko et al, 1998</td>
<td>CH</td>
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<td>38</td>
<td>Plasma activity</td>
<td>No association</td>
<td>Higher activity in nephropathy, neuropathy, CHD</td>
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<td>Japan</td>
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<td>Genotype</td>
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<td>Association with macrovascular disease</td>
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<td>Plasma activity</td>
<td>No association (activity)</td>
<td>Association with PAI-1 4G allele</td>
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<tr>
<td>Maser et al, 1997</td>
<td>Cc</td>
<td>USA (EDC study)</td>
<td>454</td>
<td>Plasma tPA/PAI-1 complex</td>
<td>Not reported</td>
<td>Associated with higher PA/PAI-1 complex</td>
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<td>Grant et al, 1996</td>
<td>L</td>
<td>USA</td>
<td>10</td>
<td>Retinal capillary PAI-1 antigen</td>
<td>Positive (antigen)</td>
<td>With either plasma PAI-1 antigen or retinopathy</td>
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<td>Mansfield et al, 1995</td>
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<td>UK</td>
<td>135</td>
<td>Plasma concentration</td>
<td>Inverse (antigen)</td>
<td>For PDR</td>
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<tr>
<td>Mansfield et al, 1994</td>
<td>CH</td>
<td>UK</td>
<td>123</td>
<td>Genotype</td>
<td>No association</td>
<td></td>
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<td>Cho et al, 1994</td>
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<td>Korea</td>
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<td>Plasma concentration</td>
<td>Inverse (antigen)*</td>
<td></td>
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<td>CH</td>
<td>Japan</td>
<td>53</td>
<td>Plasma concentration</td>
<td>No association</td>
<td></td>
</tr>
</tbody>
</table>

T1D indicates type 1 diabetes; T2D, type 2 diabetes; ND, nondiabetic; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; C, cross-sectional; H, hospital-based; c, community-based; P, prospective; L, laboratory; EDC, epidemiology of diabetes complications. *Association only with proliferative retinopathy.
centrifuged (GS-6R Centrifuge, Beckman Instruments Inc) gently (10 min at 4°C at 2000g) to not activate platelets. As platelets are a rich source of PAI-1 and increased platelet-derived PAI-1 activity has been demonstrated, plasma was aspirated from the middle layer to prevent contamination by platelet debris (platelet-poor plasma [PPP]) and recentrifuged (10 min at 4°C at 3000g) to obtain platelet-free plasma (PFP). Importantly, platelet PAI-1 is rapidly inactivated and so may increase PAI-1 antigen concentrations in blood considerably more than PAI-1 activity. Hence we assessed PAI-1 activity in platelet-poor plasma. The samples were immediately frozen and stored at −70°C until assayed for PAI-1 activity (in duplicate) on the ACL TOP instrument using a commercial kit and controls from Behring (PAI-1 test kit #OWOA-Cat No. 2586). The reference range is 0 to 3.5 Inhibitory units (U)/mL plasma. The assay, conducted by Southern Health pathology laboratory, is sensitive to PAI-1 (endothelial PAI) and PAI-2 (placental PAI) and had an interassay CV of 7.7% at 2.6 U/mL and 7.3% at 4.1 U/mL.

Plasma glucose concentrations were analyzed using an automatic analyser (Hitachi model 705) and a commercial enzymatic kit (Boehringer Mannheim GmbH Diagnostica) by the glucose oxidase method. Glucose concentrations were calibrated against calibration serum for automated systems (Boehringer Mannheim; CV normal range [5.5 to 7.5 mmol/L] was 3.7%, pathological range [12 to 16 mmol/L] was 2.7%). Plasma cholesterol and triglyceride concentrations were analyzed with an automatic analyser (Hitachi model 705) using a commercial enzymatic kit (Boehringer Mannheim GmbH Diagnostica). Urinary albumin concentration, in a 24-hour urine sample collected the day before venipuncture, was measured using immunonephelometry (Kallestadt QM300 or Beckman 360 Array nephelometers; interassay CV was 3% to 5%). Urinary creatinine concentration was measured using an alkaline picrate method (Olympus AU800 autoanalyser; interassay CV was 2%). The urinary albumin to creatinine ratio was calculated as albumin (mg)/creatinine (mmol). We used SPSS Version 13 for Windows (SPSS Inc) software to perform statistical analyses. The data were cross-sectional observations. Descriptive statistics for the exposure and outcome variables were obtained, and the distribution for continuous variables was defined. PAI-1 data were not normally distributed and so were log-transformed before multivariate analysis. Associations between retinopathy or CHD and continuous variables were assessed by ANOVA for variables with homogeneous variances or the Mann-Whitney-Wilcoxon test when variances were nonhomo- geneous. Associations between categorical variables were analyzed with χ² tests. Both variables with probability values <0.25 in univariate analyses and known risk factors for diabetic retinopathy and CHD were dropped by binomial logistic regression analysis to determine the best predictors of diabetic retinopathy and CHD. Poor predictors of retinopathy and CHD were removed to arrive at models that best predicted retinopathy and CHD in type 2 diabetes. The fit of each model was tested, and the Nagelkerke $R^2$ approximation was provided for final logistic regression models. $P<0.05$ was considered statistically significant.

**Results**

**Prevalence Data and Descriptive Statistics**

Diabetic retinopathy, defined as more than one microaneu- rysm or hemorrhage (validated Eurodiab protocol), was present in 29.3% (n=43) of diabetic subjects, who had a mean (95% CI) age of 64 (63 to 65) years. CHD was diagnosed in 27.3% of diabetic subjects (n=40). Severe (sight-threatening retinopathy) was present in 5.4% (n=8). The median (interquartile range) plasma PAI-1 activity was 3.0 (2.0 to 5.2) U/mL and within the reference range (0 to 3.5U/mL). In this sample of older individuals with type 2 diabetes, gender was not associated with plasma PAI-1 activity, diabetic retinopathy, or CHD ($P=0.480$, $P=0.492$, $P=0.433$, respectively).

**Clinical and Demographic Characteristics of Subjects**

Lower PAI-1 activity was significantly associated with diabetic retinopathy (Table 2). Diabetic retinopathy was also associated with a longer duration of diabetes, higher HbA1c and systolic and pulse blood pressure levels, use of hypoglycemic medications, and the urinary albumin to creatinine ratio (ACR). Mean plasma triglyceride and cholesterol levels were not associated with diabetic retinopathy in univariate analyses. Only older age and lower HDL-cholesterol levels were significantly associated with prevalent CHD (Table 2). Lower PAI-1 activity was also associated with sight-threatening diabetic retinopathy ($P=0.022$).

**Potential Confounders of PAI-1 Activity Levels**

Higher PAI-1 activity was associated with many factors, including higher BMI and waist circumference, insulin resistance (HOMA), higher fasting plasma insulin and triglyceride concentrations, higher total to HDL cholesterol ratio, shorter duration of diabetes, and younger age, but not albumin excretion rate or statin or fibrate use. In multivariate linear regression analysis the strongest predictors of higher PAI-1 activity, adjusted for potential confounders (the aforementioned factors and known determinants of PAI-1), were higher BMI, higher fasting plasma triglyceride concentration, and younger age (data not shown).

**Predictors of Diabetic Retinopathy and CHD**

A longer duration of diabetes, lower plasma PAI-1 activity, and hypertriglyceridemia (plasma triglyceride levels >2.0 mmol/L) were all identified as independent predictors of diabetic retinopathy, after adjusting for the major determinants of retinopathy (HbA1c and duration of diabetes) and potential confounders of PAI-1. Table 3 model 1 demonstrates that the odds of retinopathy decreased significantly with increasing PAI-1 activity and that the univariate testing of the relationship between triglycerides and diabetic retinopathy (Table 2) was (inversely) confounded by PAI-1.

A similar protocol for multivariate analysis of CHD, identified higher PAI-1 activity and a lower HDL-cholesterol level as independent predictors of CHD, after adjusting for CHD risk factors, such as age. Table 3 model 2 demonstrates that the odds of CHD increased with increasing PAI-1 activity and that the univariate testing of the relationship between PAI-1 and CHD (Table 2) was (inversely) confounded by age and HDL-cholesterol.

**Discussion**

We sought to investigate the relationship between PAI-1 and 2 major complications of diabetes, CHD and retinopathy, to better interpret the inconclusive findings of previous studies. We observed that higher plasma PAI-1 activity was independently associated with a lower risk of diabetic retinopathy, after adjusting for retinopathy risk factors and determinants of PAI-1. Conversely, we observed that higher plasma PAI-1 activity was associated with a higher risk of CHD, independent of established CHD risk factors and determinants of PAI-1, such as use of statins or fibrates.
Many complex mechanisms may link lower PAI-1 activity to diabetic retinopathy. Endothelial dysfunction is a prime candidate\(^18\); The relative excess of tissue plasminogen activator (tPA) may also contribute to diabetic retinopathy via impairment of cell-cell communication and neuronal degeneration\(^19\) and retinal toxicity.\(^20\) Moreover, a protective role for PAI-1 is recognized,\(^22\) with hypertriglyceridemia being associated with both more severe diabetic retinopathy and diabetic nephropathy. In addition, increased production of reactive oxygen species and inflammation may contribute to lower PAI-1 in diabetic retinopathy.\(^23\)

Disparate observations between studies (Table 1) may in part relate to differences in subject characteristics, sample handling, and inadequate sample size (where no association was observed). However, study design and methodological factors are a major reason for the observed differences. Many different PAI-1 exposures were assessed; some studies evaluated PAI-1 genotype, whereas others evaluated PAI-1 activity or antigen levels in platelet-poor plasma or platelets, and these do not correlate well with each other.\(^24\)\(^25\) However, PAI-1 antigen level and activity correlate strongly, and so studies using these PAI-1 exposures may be comparable. Indeed, our PAI-1 activity findings were consistent with those of 3 antigen studies (Table 1).

### Table 3. Logistic Regression Models of Predictors of Diabetic Retinopathy and CHD Status

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Diabetic Retinopathy Status</th>
<th>CHD Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent (n = 107)</td>
<td>Present (n = 40)</td>
</tr>
<tr>
<td>Age, y</td>
<td>63 (62–64)</td>
<td>65 (62–67)</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>71</td>
<td>77</td>
</tr>
<tr>
<td>PAI-1 activity*, U/ml</td>
<td>3.2 (2.2–5.6)</td>
<td>2.5 (1.4–2.5)</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>10.0 (9.5–10.5)</td>
<td>10.8 (9.9–11.6)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.9 (7.6–8.2)</td>
<td>8.8 (8.3–9.3)</td>
</tr>
<tr>
<td>Diabetes duration*, y</td>
<td>9 (5–12)</td>
<td>12 (7–22)</td>
</tr>
<tr>
<td>Hypoglycemic Mx, %</td>
<td>64</td>
<td>88</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>71</td>
<td>77</td>
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</tr>
<tr>
<td>Hypoglycemic Mx, %</td>
<td>64</td>
<td>88</td>
</tr>
</tbody>
</table>

Data are means (95% CI) for normally-distributed data or *median (interquartile range) for nonparametric data.
P values are Pearson Chi-square for categorical data or ANOVA for normally-distributed and Mann–Whitney for nonparametric continuous data.
BMI indicates body mass index; BP, blood pressure; ACR, albumin creatinine ratio; HDL, high-density lipoprotein.

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Hypertriglyceridemia is defined as plasma triglyceride concentration greater than 2 mmol/L. HDL indicates high density lipoprotein; OR, odds ratio.
diabetic multiple-field photo-documentation protocol and masked grading of the slides, whereas other studies used clinical records, ophthalmoscopy, or nonmydriatic single-field photography, with or without masked grading. Mydriatic multiple-field retinal photography is the most sensitive method for the classification of diabetic retinopathy. Furthermore, whereas most studies were hospital-based, several, including this study, were community-based and so able to capture a broader and more diverse range of lifestyle exposures and outcomes. This increased our ability to detect underlying associations. In addition, we measured risk factors (clinically or biochemically) to determine vascular risk status, whereas some studies relied on self-report and did not adjust for known confounders, such as smoking. Consequently, residual confounding may have limited some studies more than others and may have also impacted on our observations.

Our study had a number of strengths. Our findings were consistent with established associations, such as that between PAI-1 activity and CHD, indicating the design and sample size were appropriate for the detection of these effects. Similarly, because a statistically significant association was identified between retinopathy and PAI-1 activity, the study was adequately powered to detect that effect. The lack of an association between PAI-1 activity and overt nephropathy may have related to several factors, including the small number of nephropathy cases (13 cases with AER > 200 μg/min) in our community-based participants, the use of diabetic rather than nondiabetic controls, different diagnostic criteria for diabetes determination, or to different definitions of renal disease. Consistency in blood sample collection and handling reduced bias in the dataset and circadian variation in PAI-1 activity. Outcome measures were based on validated protocols, and we used face-to-face interviews to reduce the likelihood of reporting errors in the collection of clinical, demographic, and lifestyle data. Finally, whereas previous studies have investigated the relationship between PAI-1 and either the microvascular or macrovascular complications of diabetes, few studies have examined the relationship of PAI-1 to both the microvascular and macrovascular complications of diabetes.

The main limitation of this study was its cross-sectional design, which precludes causal inferences. Potential confounding was reduced but not eliminated by attention to appropriate statistical techniques. Certain genetic polymorphisms for PAI-1 have been identified in specific population groups, such as Pima Indians. However, the prevalence of the genetic polymorphisms associated with PAI-1 have been shown to be similar for individuals with low PAI-1 activity and a bleeding tendency and healthy controls with significantly higher PAI-1 activity. Nevertheless, our lack of polymorphism data are an acknowledged limitation of this study that future studies should address. Because it has been demonstrated that the ratio of PAI-1 activity to antigen concentrations can differ in people with type 2 diabetes compared with nondiabetic individuals, future studies of the relationship between PAI-1 and diabetes complications should measure both PAI-1 activity and antigen concentrations.

In conclusion, our observations suggest the relationship between fibrinolysis and vascular disease may depend on the unique characteristics of each vascular bed. The clinical implications are important for the management of type 2 diabetes. Unlike fish oils, which may increase PAI-1 activity, antithrombotic (or thrombolytic) therapies that lower plasma PAI-1 levels to prevent or attenuate chronic macrovascular disease and supplements that modulate fibrinolysis, such as ginkgo biloba may inadvertently promote retinal bleeding in type 2 diabetes.

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Disclosures

None.

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