

# The fibrin network in diabetes: its role in thrombosis risk

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## KEY WORDS

atherothrombosis,  
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## ABSTRACT

Despite advances in therapy, individuals with diabetes remain at high risk of cardiovascular disease and their clinical prognosis following vascular ischemia is worse than individuals with normal glucose metabolism. Current evidence suggests that the enhanced thrombotic environment in diabetes represents a key abnormality contributing to the adverse clinical outcome following vascular occlusion in this population. Thrombus formation occurs following a complex process that encompasses both the cellular (represented by platelets) and fluid phase of coagulation, involving a large number of plasma proteins. In the current review, we discuss some of the abnormalities encountered in coagulation factor levels or activity in diabetes. In particular, we focus on the pathological processes that lead to the formation of compact fibrin networks with increased resistance to lysis. We describe current knowledge on the mechanistic pathways responsible for the increased fibrin-related thrombosis risk in diabetes and explore alternative therapeutic targets. We also briefly cover various management strategies that may help control the enhanced thrombotic milieu in this population of patients at high cardiovascular risk.

**Introduction** Diabetes mellitus is becoming the epidemic of the 21st century and the complications associated with this condition result in significant personal and financial burden. Despite advances in therapy, cardiovascular disease (CVD) remains the main cause of morbidity and mortality in patients with diabetes. Globally, 281 million men and 317 million women died of diabetes related complications in 2011, and the majority of them from CVD ([www.diabetesatlas.org/content](http://www.diabetesatlas.org/content)).

In addition to increased risk of first atherothrombotic event,<sup>1,2</sup> individuals with diabetes continue to have worse prognosis following cardiac ischemia. Studies show that regardless of the type of intervention in the acute stage, mortality following a coronary event in diabetes remains significantly higher than in individuals with normal glucose metabolism. We investigated the effect of modern treatment strategies on clinical outcome following acute coronary syndrome (ACS). Comparing 2003 with 1995, a reduction in mortality by 15% at 18 months was evident in individuals without diabetes ( $P < 0.01$ ), but only a nonsignificant reduction (4%) was documented in those with diabetes ( $P = 0.71$ ).<sup>3</sup> It could be argued that treatment has further improved over

the past decade and more up-to-date strategies may have narrowed the difference between diabetic and nondiabetic subjects. However, recent work on individuals with myocardial infarction (MI), undergoing percutaneous coronary artery intervention, has shown higher mortality in patients with diabetes compared to those without diabetes at 30 days (7.4% vs. 3.8%, respectively;  $P < 0.01$ ) and at 12 months (13.9% and 6.5%, respectively;  $P < 0.0001$ ).<sup>4</sup> Although coronary artery bypass grafting (CABG) may be superior to other forms of revascularization in diabetes,<sup>5</sup> longer-term prognosis in these patients is still poor. In 10,626 patients who had undergone CABG, mortality in individuals with diabetes remained significantly higher at 1, 5, and 10 years.<sup>6</sup> A separate study has shown that drug-eluting stents or CABG, as a treatment of multi-vessel coronary artery disease in diabetes, do not improve clinical outcome after a median follow up of 5.6 years, indicating that the type of revascularization has a limited effect on longer-term prognosis in diabetes.<sup>7</sup>

The reasons for increased mortality following cardiac ischemia in diabetes are multifactorial and include more extensive vascular pathology

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and increased thrombosis potential. The former is treated acutely with revascularization and longer-term with appropriate management of risk factors including dyslipidemia, hyperglycemia, and hypertension. Increased thrombosis potential is mainly managed with antiplatelet therapy and a largely similar approach is applied to individuals with and without diabetes. Agents that target the noncellular component of coagulation are used during the acute phase of the vascular event but rarely long term, owing to lack of evidence for the efficacy of such a strategy.

The current review addresses the abnormalities in the fluid phase of coagulation in diabetes, highlighting various mechanisms and suggesting the areas in need of clarification in order to control the enhanced thrombotic environment in this condition.

**Thrombus formation** The occlusive vascular thrombus consists of a skeleton of fibrin fibers with cellular elements embedded in this network. The formation of the thrombus results secondary to a complex interaction between the cellular arm of coagulation, represented by platelets, and the fluid phase that includes various proteins involved in both formation and breakdown of the fibrin network.<sup>8</sup> Thrombin is the pivotal enzyme in the coagulation pathway having a crucial role in both fibrin formation and platelet activation. Thrombin is generated secondary to vascular damage,<sup>9</sup> and the contact of plasma with tissue factor, by the cleavage of prothrombin by the factor Xase complex, which occurs as the result of interactions between tissue factor activated factor VII and factor X (FX).

**Platelet activation** The main role of platelets is to prevent bleeding by hemostatic thrombus formation. It is important that a balance is maintained between platelet activation and inhibition, as dysregulation of this process may lead to inappropriate thrombus formation or, conversely, it may increase bleeding risk. Vascular wall damage results in platelet adherence, aggregation, and, subsequently, activation. Adherence to the vascular matrix is mediated by a number of glycoprotein (GP) receptors (GP Ib/IX, GPVI, and GPIa), which in turn activate platelet GPIIb/IIIa complex that binds fibrinogen. Thrombin is the most potent platelet activator, which exerts its effects through binding to protease activated receptor 1 on the platelet surface. A range of other mediators including adenosine diphosphate, collagen, and thromboxane can activate the platelet through a receptor-binding event and a number of existing pharmaceutical agents act through inhibiting some of these pathways of platelet activation.<sup>10-12</sup>

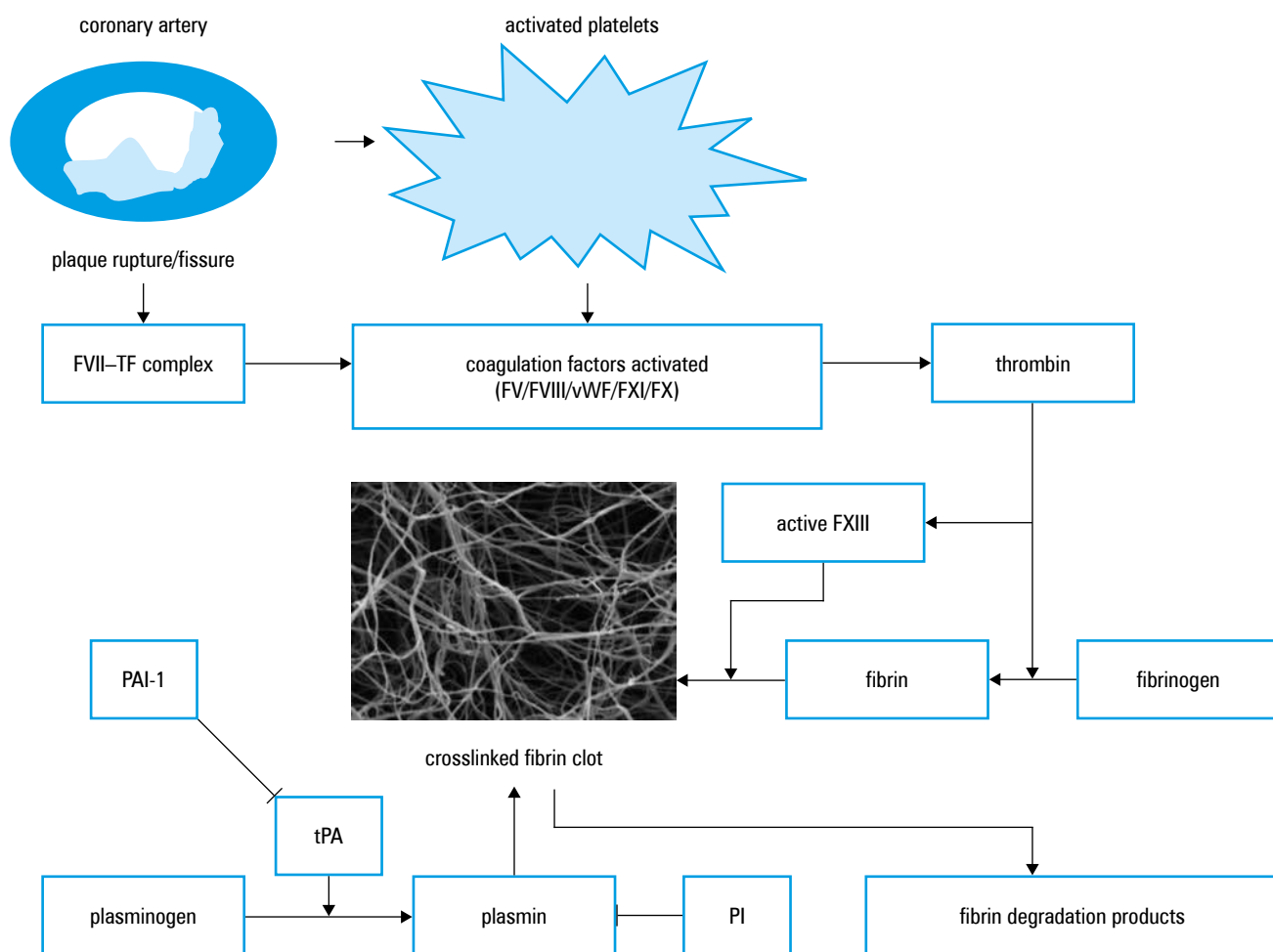
The platelet–fibrinogen interaction represents an important step in the cross-talk between the cellular and fluid phase of coagulation. During the platelet aggregation process, fibrinogen binds to platelet GPIIb/IIIa complex,

the most abundant integrin on the platelet membrane.<sup>13</sup> Resting platelet integrin does not interact with soluble fibrinogen but when platelets attach to the extracellular wall and get activated, conformational changes in GPIIb/IIIa complex (also known as integrin  $\alpha$ IIb $\beta$ 3) occur resulting in its ability to bind fibrinogen.<sup>14</sup> By means of specific binding sites on the  $\alpha$ - and  $\gamma$ -chains, 1 fibrinogen molecule can interact with 2 GPIIb/IIIa molecules, thereby having a bridging effect between the cellular components of thrombosis.

Type 2 diabetes is characterized by increased platelet activation,<sup>15</sup> thereby predisposing to thrombosis. The role of platelet activation in the enhanced thrombotic environment in diabetes is beyond the scope of the current review, which concentrates on the fluid phase of coagulation.

**Fibrin network formation** Fibrinogen, produced in the liver, consists of 2 sets of 3 chains:  $\alpha$ ,  $\beta$ , and  $\gamma$ , linked by disulfide bonds.<sup>16</sup> Thrombin cleaves small fibrinopeptides, from  $\alpha$  and  $\beta$  chains allowing an interaction with cleaved chains from another molecule resulting in the formation of insoluble fibrin fibers that further complex together to form the fibrin network. The fibrin network is then stabilized by thrombin-activated factor XIII (FXIII). This crosslinks the  $\gamma$  chains, and, at a slower pace, the  $\alpha$  chains, thereby strengthening the fibrin clot. Moreover, FXIII crosslinks various proteins into the fibrin clot, most importantly plasmin inhibitor (PI), that greatly increases clot resistance to fibrinolysis.<sup>17</sup>

**Fibrin network breakdown** There is a fine balance between clot formation and breakdown (lysis) *in vivo*, in order to avoid widespread vascular occlusion following an external injury. Analogous to thrombin, plasmin is the pivotal enzyme in the fibrinolytic cascade. Plasmin is generated following cleavage of plasminogen by tissue plasminogen activator (tPA), and this reaction occurs 1000-fold faster in the presence of fibrin. Plasmin cleaves arginine and lysine sites on a range of molecules, and its activity is tightly controlled by PI to prevent systemic proteolysis.<sup>18</sup> Cleavage of fibrin by plasmin leads to the generation of fibrin degradation products, which can be clinically used as an indicator of a thrombotic disease. In addition to PI, other inhibitors of this pathway include plasminogen activator inhibitor 1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI). PAI-1 is the fast-acting inhibitor of tPA and is produced by endothelial cells, platelets, and adipose tissue. TAFI is found in large quantities in platelets and plasma and is activated by thrombin, a cleavage event that is much enhanced when thrombin is bound to thrombomodulin. Activated TAFI cleaves the N-terminal lysine residues from degrading fibrin fibers to prevent binding of plasminogen and tPA to fibrin, which results in the inhibition of plasmin generation and clot lysis.<sup>19</sup> The main steps in clot formation and lysis are summarized in [FIGURE 1](#).



**FIGURE 1** Fibrin clot formation and lysis. Thrombus formation results secondary to a complex interaction between the cellular arm of coagulation, represented by platelets, and the fluid phase that includes various proteins involved in both formation and breakdown of the fibrin network. Thrombin is generated following activation of various coagulation factors, and this protein supports both platelet activation and fibrin clot formation. Thrombin converts soluble fibrinogen into an insoluble network of fibrin fibers that is further strengthened by thrombin-activated factor XIII, which crosslinks the fibers and incorporates antifibrinolytic proteins into the clot, including plasminogen activator inhibitor 1. Plasmin, derived from plasminogen through the action of tissue plasminogen activator (tPA), is the main enzyme responsible for fibrin clot lysis resulting in the generation of fibrin degradation products. Abbreviations: F – factor, PAI-1 – plasminogen activator inhibitor 1, PI – plasmin inhibitor, TF – tissue factor, tPA – tissue plasminogen activator, vWF – von Willebrand factor

**Alterations in fibrin network structure and fibrinolysis in diabetes** Studies have shown that both compact fibrin networks and clots that are resistant to fibrinolysis are associated with increased risk of CVD. We discuss below the changes observed in fibrin network properties in individuals with diabetes, with a special emphasis on the role of glycemia.

**Fibrin network structure in diabetes** A number of studies have shown an increase in fibrin network density in diabetes. Jöreskog et al.<sup>20</sup> were the first to report changes in the fibrin network in individuals with type 1 diabetes. We further documented that alterations in the fibrin network structure can occur at a very early age in patients with type 1 diabetes.<sup>21</sup> The advantage of studying these patients is the ability to address the role of glycemia in the fibrin clot structure while keeping the effects of confounding factors, frequently seen in type 2 diabetes patients, to a minimum. Indeed, the relationship between glycemia and

fibrin clot properties in type 2 diabetes is less clear. One study of 20 patients with type 2 diabetes and 18 controls did not show significant differences in plasma clots between the two groups, which may be due to a small number of samples studied and the heterogeneity observed in type 2 diabetes.<sup>22</sup> The latter concept is particularly important as we have shown that the presence of micro- and/or macrovascular complications is associated with altered fibrin clot properties in type 2 diabetes.<sup>23</sup> To complicate matters, it appears that diabetes has an additional effect on clot structure in individuals with established vascular disease. Our recent study in 581 individuals with angiographically proven coronary artery disease has shown that those with diabetes (n = 148) show an increase of approximately 10% in clot maximum absorbance, indicating the formation of more compact clots.<sup>24</sup>

In order to dissect the mechanistic pathways, we studied the characteristics of clots made from plasma-purified fibrinogen of 150 patients with

type 2 diabetes and 50 healthy controls. Diabetes clots had smaller pore size, increased fiber thickness, and a number of branch points compared with controls, indicating that posttranslational modifications in fibrinogen are directly responsible for altered clot structure in diabetes.<sup>25</sup> Furthermore, hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels showed a negative correlation with pore size and a positive correlation with the number of branch points within the clots, suggesting that glycemic control has an effect on clot structure in this population.<sup>26</sup>

Therefore, current studies indicate the formation of more compact fibrin networks in individuals with both type 1 and type 2 diabetes. Altered clot structure in diabetes is evident from childhood and glycemic control appears to modulate the characteristics of the fibrin network. However, there is a great variability in fibrin networks in patients with type 2 diabetes with additional changes in clot characteristics in the presence of complications. Moreover, diabetes has an additional effect on clot structure in the presence of established CVD. This indicates that altered clot structure in diabetes is present at various stages of this condition, which may have future clinical implications.

**Fibrinolysis in diabetes** Several studies have shown impaired clot lysis in diabetes and these included patients with both type 1 and type 2 diabetes.<sup>21,24,27</sup> We have shown that fibrinolytic alterations in diabetes are detected at a young age and can also be found in patients with advanced vascular complications.<sup>21,23,24</sup> While impaired fibrinolysis is generally associated with more compact fibrin networks,<sup>28</sup> this is not always the case, as increased incorporation of antifibrinolytic proteins into the clot and direct impairment in the fibrinolytic system can also modulate efficiency of fibrinolysis, which is discussed in detail below.

**Mechanisms for altered clot structure and fibrinolysis in diabetes** There are a number of factors that affect clot structure and fibrinolytic efficiency in diabetes and these include qualitative and quantitative changes in coagulation proteins.

**Clot structure** Quantitative changes in coagulation factors modulate the final ultrastructure of the clot. Most importantly, increased plasma levels of fibrinogen, commonly found in diabetes, result in the formation of more compact clots.<sup>27</sup> In addition to quantitative changes, qualitative alterations in clotting factors can affect the structure of the fibrin network. High plasma glucose mediates glycation of fibrinogen,<sup>29</sup> and clots made from glycated protein are more tightly packed. Moreover, the by-product of protein glycation, glycoaldehyde, induces posttranslational modification in fibrinogen, which impairs the fibrinolytic process.<sup>30</sup> It should be remembered that diabetes is also associated with increased oxidative stress and fibrinogen oxidation has been shown to modulate

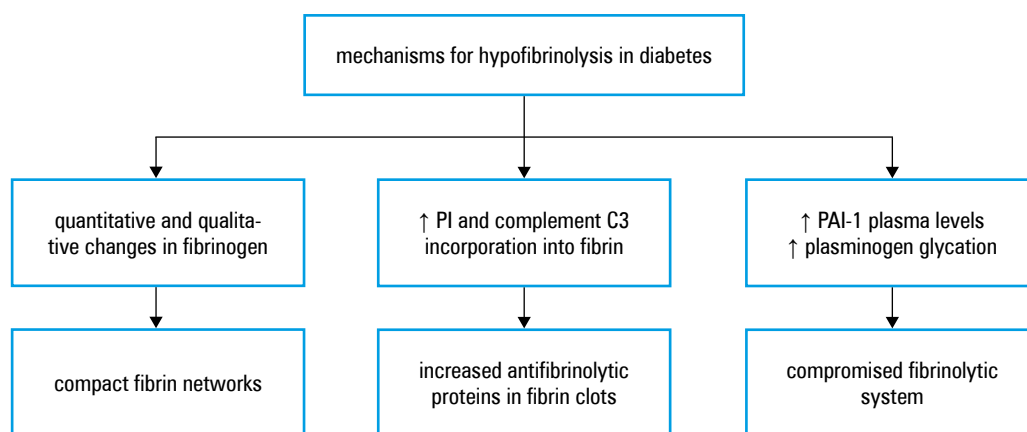
clot structure, adding another mechanism for altered clot structure in diabetes.<sup>31</sup>

If hyperglycemia has a deleterious effect on clot structure, then improving glycemic control should result in the production of less compact clots. Initial attempts at optimizing glucose control with continuous subcutaneous insulin infusion were associated with increased plasma fibrin gel porosity, but, unexpectedly, this was not related to an improvement in glycemic control as the fall in HbA<sub>1c</sub> was minor and nonsignificant.<sup>32</sup> Subsequent work from our laboratory has shown that a mean drop in HbA<sub>1c</sub> by 13 mmol/mol is associated with a decrease in plasma clot final turbidity, indicating the formation of less compact clots.<sup>21</sup> Others have demonstrated that improving glycemic control in 20 subjects with type 2 diabetes has no effect on fibrinogen levels, plasma clot porosity, or turbidity curves but it results in a small reduction in clot compaction.<sup>33</sup> A study of plasma-purified fibrinogen from the same patients has shown that improving glycemia results in variable changes in clot structure, an effect that was more obvious in a small group of 7 individuals with a larger drop in fibrinogen glycation.<sup>22</sup>

**Fibrinolysis** Changes in fibrinolysis in diabetes can be secondary to: 1) altered clot structure; 2) increased incorporation of antifibrinolytic proteins into the clot, and 3) deranged activity of the fibrinolytic system.

More compact clots display increased resistance to fibrinolysis as previously demonstrated.<sup>28,34</sup> Therefore, the changes in clot structure outlined above can indirectly affect efficiency of the fibrinolytic process in diabetes. More recently, an additional mechanism has been described that is particularly interesting as it may have future therapeutic implications. FXIII mediates the crosslinking of various proteins into the clot to strengthen the fibrin and increase its resistance to fibrinolysis. PI represents a classic protein that is crosslinked into the fibrin clot in order to make it more resistant to lysis.<sup>35</sup> Recent work has shown that diabetes clots are characterized by increased PI incorporation into the fibrin network, representing an additional mechanism for impaired clot lysis in diabetes.<sup>36</sup> Another protein that may also be diabetes-specific is complement C3. We and others have shown that complement C3 can be detected in the fibrin clot using proteomics techniques.<sup>37,38</sup> Interestingly, C3 incorporation into the clot impairs the fibrinolytic process, which may be due to the mechanical inhibition of clot lysis secondary to the presence of C3 but may also be related to C3 acting as a substrate for plasmin.<sup>39</sup> Our studies in patients with type 1 diabetes have shown increased incorporation of C3 into diabetes clots, explaining the exaggerated antifibrinolytic response to C3 in this population.<sup>21</sup> Further work in 822 patients with type 2 diabetes has shown that C3 plasma levels are at least as good a predictor of fibrin clot lysis as PAI-1.<sup>40</sup> Interestingly, there was no correlation





**FIGURE 2** Mechanisms responsible for hypofibrinolysis in diabetes. The three main mechanisms responsible for hypofibrinolysis in diabetes include: 1) the formation of more compact clots, which increases mechanical resistance to lysis; 2) increased incorporation of antifibrinolytic proteins into the fibrin network, including plasmin inhibitor and complement C3; and 3) compromised efficacy of the fibrinolytic system through increased plasma levels of plasminogen activator inhibitor and compromised plasmin production and function secondary to increased protein glycation. Abbreviations: see [FIGURE 1](#)

between C3 and PAI-1 plasma levels, consistent with the two proteins affecting different pathways in the fibrinolytic system. Increased incorporation of PI and C3 into the fibrin clot in diabetes offers the exciting possibility of developing diabetes-specific therapies that target fibrin–PI or fibrin–C3 interactions as a means of improving the fibrinolytic efficiency in this condition, while keeping bleeding risk to a minimum.

Finally, diabetes can directly modulate the efficiency of the fibrinolytic system. It has been known for a long time that increased plasma levels of PAI-1, a characteristic of insulin-resistant states and type 2 diabetes, represent a key mechanism for impaired fibrin clot lysis in these conditions.<sup>41</sup> PAI-1 inhibits plasmin generation and levels of this protein have been repeatedly used as a surrogate marker for fibrinolytic efficiency in various research studies. More recently, however, we described a new mechanism for impaired fibrin clot lysis in diabetes that is related to increased glycation of plasminogen. N $\epsilon$ -fructosyl-lysine residue on plasminogen from type 1 diabetes individuals was increased 3-fold compared with protein purified from healthy controls, and a preferential glycation of lysines 107 and 557 within the protein was demonstrated. These sites are believed to be involved in fibrin binding and plasmin(ogen) cleavage, offering mechanistic explanations for our findings.<sup>42</sup> Indeed, we observed reduced conversion of diabetic plasminogen to plasmin and also observed reduced protein activity. These changes in plasmin(ogen) in diabetes were partly reversible with a relatively modest improvement in glycemic control, an observation that may be important clinically. Mechanisms for hypofibrinolysis in diabetes are summarized in [FIGURE 2](#).

**Glycemia, clot structure, and clinical studies** Given that high glucose levels have a deleterious effect on clot structure/fibrinolysis, it is expected

that improving glycemia reduces the risk of atherothrombotic disease. However, this has not been shown in all studies and remains an area of constant debate. The Diabetes Control and Complications Trial (DCCT) and further extension in the Epidemiology of Diabetes Interventions and Complications (EDIC) trial has shown that early glycemic control in type 1 diabetes reduces longer-term atherothrombotic complications.<sup>43</sup> Largely similar findings were documented in the UK Prospective Diabetes Study (UKPDS) with long-term follow-up of patients with newly diagnosed type 2 diabetes.<sup>44</sup> The Diabetes mellitus Insulin Glucose infusion in Acute Myocardial Infarction (DIGAMI)-1 study demonstrated that improving glycemic control following a cardiac event improves clinical outcome.<sup>45</sup> In contrast, the DIGAMI-2 study, investigating the best strategy to lower blood glucose levels following MI, failed to show a beneficial effect for tight glycemic control.<sup>46</sup> This was hardly surprising given the similar HbA<sub>1c</sub> values in the study arms and the fact that the study was underpowered. Two large studies investigating the medium-term vascular effects of tight glycemic control have shown either an absence of an effect, or quite worryingly, an increase in mortality.<sup>47,48</sup>

There are a number of explanations for these contradictory findings when addressing fibrin-related thrombosis risk. First, the effect of glycemia on fibrin network structure is only apparent with very high glucose levels and perhaps only a modest improvement in glycemia is required for the reduction of fibrin-related thrombosis risk. Therefore, a drop in HbA<sub>1c</sub> from 75 to 65 mmol/mol will have a significant effect on thrombosis risk that is not seen following a reduction in HbA<sub>1c</sub> levels from 65 to 55 mmol/mol. Second, HbA<sub>1c</sub> is a poor marker of glycemia as it fails to take into account fluctuations in glucose levels, which can be prothrombotic.<sup>49</sup> Third, several

pieces of evidence have indicated that hypoglycemia, which HbA<sub>1c</sub> fails to capture, is prothrombotic and may have a role in the adverse clinical outcome in diabetes. Previous work has shown that acute hypoglycemia is associated with a rise in PAI-1 levels<sup>50</sup> and an increase in factor VIII coagulation activity coupled with accelerated thrombin generation.<sup>51</sup> Our ex-vivo studies using hypoglycemia clamp studies in patients with diabetes have shown that low blood glucose levels are associated with hypofibrinolysis, measured using the validated turbidimetric assays.<sup>52</sup> Moreover, this thrombotic effect of hypoglycemia can persist for 1 week following the event, adding an important dimension to our understanding of the impact of hypoglycemia on thrombosis risk.<sup>53</sup> The above findings may explain improved clot porosity after continuous subcutaneous insulin infusion, despite no improvement in HbA<sub>1c</sub>, as this treatment is typically associated with less hypoglycemic episodes.<sup>32</sup>

Therefore, clinical studies investigating the effects of glycemia on cardiovascular event and thrombosis risk should not only rely on HbA<sub>1c</sub> but should take into account glucose variability and hypoglycemia,<sup>54</sup> which will only be possible using continuous glucose monitoring. With the development of new continuous glucose devices, a more sophisticated approach to monitoring glycemia is now a real possibility that should be explored in future cardiovascular studies in diabetes.

**Role of hypoglycemic agents in thrombosis risk in diabetes** We have mentioned above that type 2 diabetes is a heterogeneous condition with a large number of variables that may affect CVD risk. One set of these variables is introduced by the type of treatment used to address hyperglycemia in these individuals.

Metformin is usually used as first-line therapy in subjects with type 2 diabetes and the UKPDS has demonstrated that use of this agent is associated with reduced risk of ischemic heart disease in overweight patients.<sup>55</sup> This is further supported by observational data from the REACH registry including 19,691 patients.<sup>56</sup> The mechanisms for reduced cardiovascular events in metformin users may be related, at least in part, to the effects of this agent on the fibrin network, reviewed elsewhere.<sup>27</sup>

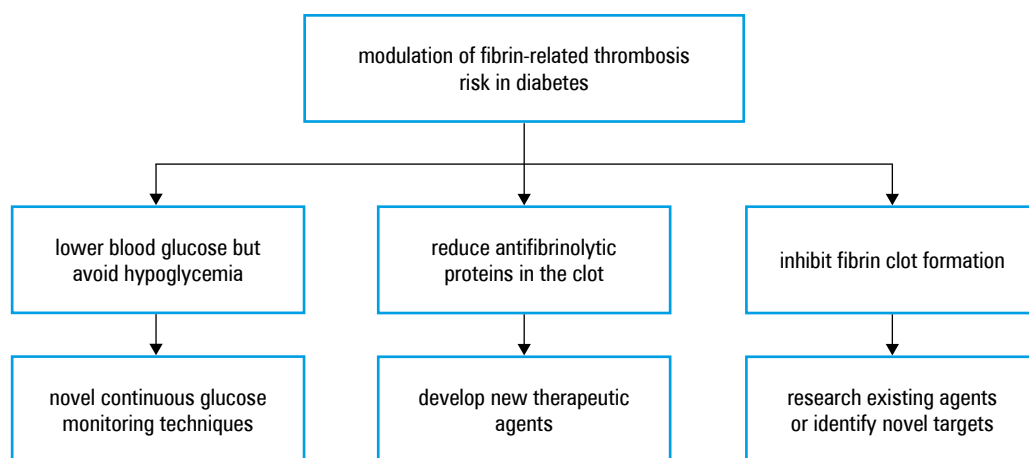
Thiazolidinediones are peroxisome proliferator-activated receptor  $\gamma$  stimulators and directly affect insulin resistance, the key pathogenic mechanism in diabetes. Thiazolidinediones can lower fibrinogen and PAI-1 levels, which reduces thrombosis potential and improves fibrinolysis.<sup>57-60</sup> Furthermore, these agents can delay intraarterial thrombus formation and modulate progression of atherothrombotic lesions.<sup>61-63</sup> In the PROactive trial, pioglitazone failed to show a benefit for a complex primary endpoint but was associated with a reduction in the prespecified secondary endpoint (all-cause mortality, nonfatal MI, and stroke).<sup>64</sup> However, there was an increase in heart

failure making the cardiac protective role of this agent debatable. In a controversial meta-analysis, rosiglitazone was found to increase the risk of cardiovascular events in diabetes,<sup>65</sup> which subsequently resulted in withdrawal of this agent from the European market. The promising effects of glitazones on various cardiovascular risk factors did not translate clinically into meaningful vascular protection and the use of rosiglitazone was associated with apparent harm, although the data are far from conclusive. This clearly demonstrates that reliance on surrogate markers is not enough to assess the clinical efficacy of a drug, for which outcome studies are required.

Gliptins and glucagon-like peptide 1 (GLP-1) analogues are relatively new hypoglycemic agents and current evidence suggests that gliptins have a neutral effect on cardiovascular risk, whereas studies with GLP-1 analogues are yet to be reported.<sup>66-68</sup>

Finally, insulin-treated patients with type 2 diabetes are at greater risk of cardiovascular events compared with noninsulin-treated subjects, which may simply reflect longer disease duration with a consequent increase in the risk of complications.<sup>69</sup> In healthy individuals, insulin has an antithrombotic effect but the converse is true in the presence of insulin resistance secondary to enhanced platelet activation and increased plasma levels of fibrinogen and PAI-1.<sup>27</sup>

**Modulation of fibrin-related thrombosis risk in diabetes** Despite the increased thrombotic environment in diabetes, the antithrombotic treatment in these individuals remains largely similar to that in individuals with normal glucose metabolism and relies on the use of antiplatelet agents. However, the coagulation system involves a cellular and fluid phase and rather than extreme suppression of 1 pathway, mild suppression of both pathways may offer a clinical advantage through maximizing the benefit and minimizing the bleeding risk. There are clinical precedents to such an approach as studies have shown that the use of lower doses of multiple antihypertensive agents is associated with better outcome than using the maximum dose of a single agent, which subsequently filtered through into clinical guidelines.<sup>5</sup> Therefore, the authors believe that a combined approach targeting platelets and the fibrin network will offer the best protection against repeated vascular ischemia. Fortunately, we are not alone in our thinking as a “dual pathway” inhibition has been recently proposed.<sup>70</sup> One difficulty in targeting the fibrin network is the complexity involved in this system. Earlier studies have shown that warfarin, which inhibits production of certain coagulation factors thus affecting fibrin network formation, can reduce the risk of arterial thrombotic events. However, use of this agent for atherothrombosis has been difficult to implement owing to a nonspecific mode of action, narrow therapeutic window, need for frequent testing, and increased bleeding risk.<sup>71,72</sup> Newer and



**FIGURE 3** Modulation of fibrin-related thrombosis risk to reduce atherothrombosis in diabetes. Optimizing glycemic control, by lowering blood glucose levels while avoiding hypoglycemia, will prevent the formation of compact fibrin clots and will facilitate the fibrinolytic process. Developing agents that inhibit the incorporation of antifibrinolytic proteins, including plasmin inhibitor and complement C3, into the fibrin clot represents a novel, diabetes-specific, approach to reduce the risk of thrombosis in this condition. Finally, existing agents that inhibit the formation of fibrin clot should be tested in studies that are adequately powered to address their efficacy in patients with diabetes.

more specific agents, including direct thrombin and FX inhibitors, have shown a more consistent effect and their use in diabetes is briefly discussed below.

**Bivalirudin** Bivalirudin is a direct thrombin inhibitor. In the Acute Catheterization and Urgent Intervention Triage Strategy trial (ACUTITY), a subgroup analysis of diabetes subjects showed that bivalirudin use was associated with similar ischemic events compared with the combination of GPIIb/IIIa inhibitors (GPIs) plus heparin (7.9% and 8.9%, respectively;  $P = 0.40$ ) but with far less major bleeding (3.7% and 7.1%, respectively;  $P < 0.001$ ), resulting in a clear net clinical benefit.<sup>73</sup> In the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, which enrolled 3602 patients, diabetes subjects ( $n = 593$ ) treated with bivalirudin had reduced mortality at 30 days compared with the combination of GPI and unfractionated heparin (2.1% and 5.5%, respectively;  $P = 0.04$ ). Bleeding complications were lower in the bivalirudin compared with the GPI/heparin combination group (2.5% and 7.1%, respectively;  $P = 0.01$ ), although no difference in mortality was demonstrated at 12 months (14.2% and 16.2%, respectively;  $P = 0.4$ ).<sup>74</sup> Therefore, bivalirudin is recommended for clinical use in diabetes subjects with ACS, particularly in those who have high bleeding risk. Given the heterogeneity of patients with diabetes, more research is needed to clarify the type of individuals who would benefit most from this therapy.

**Fondaparinux** Fondaparinux binds reversibly to antithrombin III, indirectly inhibiting FX activity. OASIS 5, a noninferiority study, enrolled 20,078 patients with unstable angina and non-ST-elevation MI and showed lower mortality

in fondaparinux-treated individuals compared with those receiving low-molecular-weight heparin (LMWH) at both 30 days and 6 months with a significantly lower bleeding rate.<sup>75</sup> OASIS 6 investigated 12,092 patients with ST-elevation MI, who underwent thrombolysis or percutaneous coronary intervention, and showed that fondaparinux was superior to LMWH in those who had thrombolysis or conservative management, whereas the opposite was true in individuals undergoing percutaneous coronary intervention.<sup>76</sup> Although diabetes patients constituted 25% of the patients in OASIS 5 and 18% of those in OASIS 6, no data were provided in this subgroup of patients and it is unclear whether diabetes has an effect on response to fondaparinux therapy.

**Factor Xa inhibitors** Rivaroxaban and apixaban are inhibitors of factor Xa and are currently in clinical use but mainly for protection from venous and embolic thrombotic events. The Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51 trial randomized 15,526 patients to rivaroxaban (2.5 mg bid or 5 mg bid) or placebo in addition to antiplatelet therapy.<sup>77</sup> The primary endpoint of a composite of death from cardiovascular causes, MI, or stroke was reduced with both doses of rivaroxaban. However, the rate of major bleeding was increased creating doubts about the net clinical benefit. In a further subanalysis of 665 patients who suffered an MI following randomization, rivaroxaban was shown to reduce spontaneous MI compared with placebo (4.4% and 5.7%, respectively;  $P = 0.01$ ), an effect that was dose-dependent.<sup>78</sup> Diabetes patients have not been fully investigated, but a preliminary analysis suggests that this group may benefit less from the addition of rivaroxaban to existing antiplatelet therapy, compared with the non-diabetic population.<sup>77</sup> However, this analysis does

not have the necessary power to provide accurate information. Therefore, further investigation is needed to study such an approach in patients with diabetes, particularly those with higher risk.

A common theme emerging from the vast amount of clinical research in ACS is the relative absence of studies targeting the population with diabetes, despite the altered thrombotic environment in these individuals. Most studies rely on a subgroup analysis to understand the effects of an antithrombotic treatment on vascular prevention in diabetes, and these analyses are usually underpowered and unable to provide concrete conclusions. Moreover, patients with diabetes are not always captured (some studies report very low prevalence) or appropriately characterized. This makes the interpretation of the results problematic and future studies will require close collaboration between cardiologists and diabetologists in order to incorporate the diabetes question into study design. This will hopefully help to better understand response of diabetes patients to antithrombotic therapy, which in turn will allow to devise alternative treatment strategies to improve the poor prognosis following a vascular ischemic event in this population. **FIGURE 3** summarizes potential interventions in diabetes aimed at modulating fibrin-related thrombosis risk.

**Conclusions** Individuals with diabetes are at high risk of a cardiovascular event, and their outcome following vascular ischemia remains worse than that of patients with normal glucose metabolism. One reason for this poor prognosis is related to an enhanced thrombotic milieu secondary to increased platelet activation as well as quantitative and qualitative changes in coagulation factors resulting in the formation of compact fibrin networks that are difficult to lyse.

Antiplatelet therapy represents a cornerstone in the management of the increased thrombotic environment in patients with vascular ischemia. However, several pieces of evidence suggest that therapy targeting the fibrin network may offer additional benefit, and some agents have shown particular promise in diabetes. Unfortunately, studies continue to largely ignore the altered thrombotic environment in diabetes and the possible need for a different antithrombotic regimen in this population is yet to be appropriately investigated.

It should be acknowledged that there are several difficulties associated with understanding the efficacy of antithrombotic therapy in diabetes. First, studies investigating novel agents or regimens are not usually adequately powered to analyze diabetes subjects separately and the results are often inconclusive. Second, the diagnosis of diabetes does not always follow strict criteria; therefore, a significant number of diabetes patients are missed, which may bias the results. Third, diabetes is a heterogeneous condition and not a single clinical entity; therefore, cardiovascular risk can vary greatly between individuals,

depending on diabetes duration, presence of various complications, and type of hypoglycemic therapy used. Studies have rarely taken this point into account, making data interpretation problematic.

Taken together, current evidence indicates that diabetes subjects have an enhanced thrombotic environment and may thus require a different and bespoke antithrombotic therapy following a vascular event. This calls for future studies that would concentrate on investigating the optimal antithrombotic strategy in patients with diabetes, particularly in those with established vascular disease.

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# Sieć fibrynowa w cukrzycy a ryzyko zakrzepowe

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## SŁOWA KLUCZOWE

cukrzyca, fibryna,  
fibrynoliza, glikemia,  
miażdżycza, zakrzepica

## STRESZCZENIE

Mimo postępów w leczeniu, chorzy na cukrzycę są wciąż obciążeni większym ryzykiem chorób układu krążenia, a rokowanie po epizodach niedokrwienych jest u nich gorsze niż u pacjentów z prawidłowym metabolizmem glukozy. Dostępne dane sugerują, że stan prozakrzepowy w cukrzycy stanowi główne zaburzenie przyczyniające się w tej populacji do gorszego rokowania w chorobach związanych z niedrożnością naczyń. Skrzeplina powstaje w toku złożonych procesów obejmujących fazę komórkową (płytki krwi) i humoralną, obejmującą dużą liczbę białek osocza. W niniejszym przeglądzie omówiono niektóre zaburzenia dotyczące stężenia lub aktywności czynników krzepnięcia w cukrzycy. W szczególności skupiono się na procesach patologicznych prowadzących do powstania zbitej sieci fibrynowej o podwyższonej oporności na lizę. Opisano aktualny stan wiedzy na temat patomechanizmów odpowiedzialnych za zwiększone ryzyko zakrzepicy związane z fibryną występujące w cukrzycy i omówiono alternatywne cele terapeutyczne. Omówiono też w skrócie różne strategie postępowania, które mogą być pomocne w kontroli stanu prozakrzepowego w tej populacji obciążonej zwiększonym ryzykiem sercowo-naczyniowym.

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