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REVIEW ARTICLE

Is diabetes a hypercoagulable state? A critical appraisal

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Abstract Diabetes mellitus (DM), a chronic disease with an increasing incidence and prevalence worldwide, is an established risk factor for arterial cardiovascular, cerebrovascular and peripheral vascular diseases including acute myocardial infarction, stroke and peripheral artery disease. On the other hand, its role as independent risk factor for venous thromboembolism (VTE) and for cardioembolic stroke or systemic embolism (SE) in patients with atrial fibrillation (AF) is more conflicting. Venous and arterial thromboses have traditionally been regarded as separate diseases, but recent studies have documented an association between these vascular complications. Cardiovascular risk factors may contribute to unprovoked VTE, and VTE may be an early symptomatic event in patients at high cardiovascular risk, including diabetic patients. Compelling evidences suggest that DM is associated with a higher risk of development and progression of AF. Furthermore, in AF patients with a coexisting DM the risk of cardioembolic stroke/SE appeared increased. Thus, DM has been included as one of the items of the CHADS2 score and of the subsequent CHA2DS2-VASc score that have been developed to assess the arterial tromboembolic risk of AF patients. Such a high incidence of thromboembolic events observed in these clinical subsets may be attributable to the DM-related prothrombotic state due to a number of changes in primary and secondary hemostasis. Although of potential clinical interest, unfortunately, to date, no study has properly evaluated the effects of drugs used to control blood glucose levels on the risk of venous thromboembolism and arterial cardioembolic events in patients with DM.

Keywords Diabetes · Venous thromboembolism · Prothrombotic state · Glycemic control · Risk factor

Introduction

Diabetes mellitus (DM), a chronic disease with an increasing incidence and prevalence worldwide, is an established risk factor for arterial cardiovascular, cerebrovascular and peripheral vascular diseases including acute myocardial infarction, stroke and peripheral artery disease (PAD). On the other hand, its role as independent risk factor for venous thromboembolism (VTE) and for cardioembolic stroke or systemic embolism (SE) is more controversial.

Several recent studies and meta-analyses suggest that many traditional arterial cardiovascular risk factors including DM may be involved also in the pathogenesis of venous thromboembolic events, challenging the concept of arterial and venous thromboembolic diseases as two distinct entities [1].

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A proinflammatory state is very common in diabetic patients, and this condition may increase the levels of some clotting factors and impair the fibrinolytic system leading to a hypercoagulable state. However, a number of studies did not confirm these results questioning the real association between these two diseases [2–8].

Atrial fibrillation (AF) is the most frequently encountered sustained cardiac arrhythmia, with a prevalence of about 2 % in the general population [9].

Current guidelines recommend to assess the risk of cardioembolic complications of these patients using a validated clinical risk score (CHA_2DS_2-VASc score) that included also the presence of DM among the items considered [10]. However, DM did not result as an independent risk factor for stroke or SE in some studies evaluating AF patients, and the pathogenetic mechanisms increasing the risk of cardioembolic events in diabetic patients with AF are still not completely elucidated.

Due to its high prevalence, it may be of paramount importance to clarify the role of DM in these clinical settings. The presence of DM may modify the patients' risk profile, in conditions potentially at risk of VTE, and may modify the duration of anticoagulation in patients with established VTE. Furthermore, it seems critical to quantify the magnitude of the association between DM and cardioembolic events in AF patients and the pathogenetic mechanisms increasing this risk, to improve the management of these patients and to set up adequate strategies of treatment.

Thus, the aim of this review is to summarize the results of laboratory studies that evaluated potential mechanisms leading to a hypercoagulable state and the results of clinical studies that assessed the association between DM and VTE, and between DM and cardioembolic events in patients with AF. Furthermore, we searched studies that evaluated the potential role of drug therapies in the primary and secondary prevention of these diseases.

Results of clinical studies assessing the risk of VTE in diabetic patients

The results of clinical studies assessing this association [1, 3–8, 11–18] are summarized in Table 1. The first study reporting an association between VTE and DM was published by Hoibrateen et al. in 1998 [14]. In this case–control study, the authors assessed the role of hormonal replacement therapy as a potential risk factor for VTE in a large group of women. The prevalence of DM was significantly higher in VTE patients compared with controls. However, this was not a pre-specified end point of the study, and the authors did not adjust the results of univariate analysis for other potential confounders. Subsequently, Tsai et al. [15] assessed, in a large prospective study, the association between many different traditional risk factors and VTE. About 20,000 men and women without previous VTE were followed for a median time of 8 years. In this population, the presence of DM along with obesity was significantly associated, at multivariate analysis, with an increased risk of VTE (hazard ratio of about 1.5 for both), whereas cigarette smoking, hypertension, dyslipidemia, physical inactivity and alcohol consumption were not.

On the other hand, other case–control and cohort studies did not find a significant association between these two entities. In one case–control study focused on the association between atherosclerosis and VTE, the prevalence of DM was not significantly different in VTE patients and controls [19]. Similar results were obtained when the authors evaluated separately patients with unprovoked and provoked VTE. In a prospective cohort study including 16,608 postmenopausal women between the ages of 50 and 79 years, Cushman et al. [3] evaluated the role of estrogen plus progestin therapy as a risk factor for VTE. Again, the prevalence of DM was not significantly different in women who developed a VTE and in those who did not at univariate analysis.

In 2008, Ageno et al. [20] performed a systematic review and a meta-analysis of the literature evaluating the association between a number of traditional cardiovascular risk factors (DM, obesity, hypertension, dyslipidemia and smoking) and VTE. Twenty-one case–control and cohort studies for a total of 63,552 patients were included. Obesity and hypertension were significantly more prevalent in VTE patients compared with controls, and weighted mean high-density lipoprotein cholesterol levels were significantly lower in the former group. On the other hand, the prevalence of smoking and total and low-density lipoprotein cholesterol levels were not significantly different in the two groups. Data on the prevalence of DM were provided by nine studies for a total of about 5000 VTE patients and 50,000 controls. Prevalence of DM was significantly higher in VTE patients compared with controls with a corresponding odds ratio (OR) of 1.41 (95 % confidence interval [CI] 1.12–1.77). However, when case–control and cohort studies were considered separately, the association remained significant only in the latter group. Furthermore, due to the inherent limitations of study level meta-analyses, the authors were not able to adjust their results for potential confounders.

After the publication of the above meta-analysis, Heit et al. [11] performed a population-based case–control study evaluating the association between DM and VTE before and after adjusting for potential confounders. Using data from the Rochester Epidemiology Project resources, the authors identified 1922 patients with incident VTE over a

Table 1 Clinical studies assessing the risk of VTE in Diabetic Patients

	Study design	Study population	Main results
Prandoni [1] 2003	Case–control	299 patients with VTE 150 patients without VTE	Diabetes was present in 9.4 % of VTE patients and in 12.0 % of controls
Heit [11] 2009	Population-based Case–Control	1922 patients with VTE 2115 patients without VTE	Diabetes was present in 12 % of VTE patients and in 9.4 % of controls
Petrauskiene [13] 2005	Retrospective population-based study	302 adult patients admitted to the hospital with verified DVT or PE	The annual incidence rate of VTE among diabetic patients in the population was 432 per 100,000 individuals, and in non-diabetic individuals it was 78
Hoibraaten [14] 1999	Case–control	176 patients with VTE 352 patients without VTE	Diabetes was present in 10.3 % of VTE patients and in 4.3 % of controls
Tsai [15] 2002	Cohort	2823 patients with VTE 18645 patients without VTE	Diabetes was present in 2.09 % of VTE patients and in 1.30 % of controls
Cushman [3] 2004	Cohort	243 patients with VTE 16365 patients without VTE	Diabetes was present in 5.76 % of VTE patients and in 4.40 % of controls
Deguchi [4] 2005	Case–control	49 patients with VTE 49 patients without VTE	Diabetes was present in 1 VTE patient and no in controls
Lidegaard [5] 2002	Case–control	987 patients with VTE 4054 patients without VTE	Diabetes was present in 0.20 % of VTE patients and in 0.37 % of controls
Poulter [6] 1995	Case–control	1143 patients with VTE 2998 patients without VTE	Diabetes was present in 2.27 % of VTE patients and in 1.70 % of controls
McColl [7] 2000	Case–control	62 patients with VTE 98 patients without VTE	Diabetes has not been found in VTE patients and controls
Frederiksen [8] 2004	Cohort	208 patients with VTE 7656 patients without VTE	Diabetes was present in 4.81 % of VTE patients and in 3.0 % of controls
Vaya [16] 2011	Case–control	146 patients with VTE 150 patients without VTE	High glucose levels [OR = 2.0, 95 % CI 1.2-3.5] were significantly associated with higher VTE risk
Steffen [17] 2009	Prospective study of VTE occurrence in two population-based cohorts	359 patients with VTE 20024 patients without VTE	Diabetes was present in 30.6 % of VTE patients and in 23.6 % of controls
Di Minno [18] 2011	Case–control	323 patients with idiopathic VTE 868 patients without VTE	IFG was present in 9.6 % of idiopathic VTE patients and in 3.3 % of controls

25-year period and compared the prevalence of DM in this population and in a large control group matched for age, gender and length of medical history. At univariate analysis, DM was significantly more prevalent in VTE patients compared with controls with a corresponding OR of 1.32 (95 % CI 1.07, 1.63). However, after controlling for major surgery or medical illness and nursing home confinement, DM was no longer significantly associated with VTE.

Finally, two recent studies investigated the role of insulin resistance, assessed by the homeostasis model of insulin resistance (HOMA-IR), as a risk factor for VTE [21, 22] using data from the PREVEND prospective, community-based, observational cohort study (7,393 subjects followed for a median follow-up of 10.5 years) and from the EDITH hospital-based case–control study (677 patients with unprovoked VTE and 677 age- and sex-matched controls). In the first of these studies, performed by Van Schouwenburg et al. [21], high HOMA-IR was associated with increased risk of VTE after adjustment for traditional cardiovascular risk factors. However, HOMA-IR was no longer associated with VTE when BMI was added to the model. Similar results were obtained in the second study in which the unadjusted analysis showed an increased risk of unprovoked VTE associated with increasing HOMA-IR (OR 1.53, 95 % CI 1.00, 2.34 for the highest quintile of HOMA-IR compared with the first quintile), but when BMI was added in the adjusted model, HOMA-IR was no longer associated with VTE (OR 1.08; 95 % CI 0.67–1.73) [22].

Reasons for different results among the above studies are not clear. First, as previously outlined, the results of some studies were not adjusted for potential confounders. Secondly, discrepancies are, at least in part, attributable to study design. In the case–control studies, the presence of DM was generally assessed at the time of, or very close to,

the event. In the longitudinal studies, the presence of DM was evaluated at baseline and some studies considered also events that occurred after a very long follow-up. Because DM control varies during time and patients with a higher cardiovascular risk profile at baseline may have been managed more aggressively, there is a chance that its effect as potential risk factor may have been diluted at the time of the index event.

Results of clinical studies assessing the role of DM as a risk factor for stroke/SE in AF patients

Compelling data suggest that DM is associated with a higher risk of the development and progression of AF [23, 24]. In detail, a meta-analysis of seven prospective cohort studies and four case–control studies showed that DM was associated with a 40 % increase in the risk of AF compared with non-DM patients (RR: 1.39, $P < 0.001$). Interestingly, the diabetes-related risk of AF remained significant after correction for publication bias and multiple risk factors (RR 1.24, 95 % CI 1.06–1.44, vs. 1.70, 1.29–2.22, $P = 0.053$) [25]. The specific pathophysiological mechanism associated with AF occurrence in DM patients is currently unknown [26]. However, proposed mechanisms include autonomic remodeling, structural remodeling, electrical remodeling secondary to diabetes and insulin resistance. Moreover, few data are available on the role of DM-associated atrial inflammatory reaction and oxidative stress reaction in the occurrence of AF.

As outlined above, DM has been included as one of the items of the $CHADS_2$ score and of the subsequent CHA_2DS_2-VASc score that have been developed to assess the arterial tromboembolic risk of AF patients [27, 28].

In patients with a coexisting DM, the risk of cardioembolic stroke is increased with an incidence ranging between 3.6 and 8.6 % per year in different studies [29]. The significant association between diabetes and the risk of cardioembolic stroke in AF patients reported in some studies [30–33] has been challenged by other reports [34–38] (Table 2). However, by pooling together all the available data, diabetes resulted associated with a RR of 1.7 (95 % CI 1.4–2.0) for the risk of cardioembolic stroke in patients with AF [29].

Such a high incidence of thromboembolic events observed in this clinical subset may be attributable to the DM-related prothrombotic state. Indeed, DM predisposes to thrombosis by means of several mechanisms that will be discussed in the "pathophysiological mechanisms" paragraph. In addition, the presence of a concomitant diabetic neuropathy may mask the cardiac symptoms of AF, making it more difficult to be diagnosed. This may determine a delay in the establishment of an appropriate anti-arrhythmic and/or antithrombotic treatment and, in turn, leads to a further increase in the thrombotic risk.

Potential pathophysiological mechanisms of the DM-related hypercoagulable state

As previously underlined, in the last years several epidemiological studies suggested that DM is an independent risk for deep vein thrombosis and pulmonary embolism [11–13] and stroke and SE in patients with AF.

Further confirming and extending these data, recent evidence suggests that primary hemostasis (endothelial function and platelet activation/aggregation) and secondary hemostasis (coagulation and fibrinolysis) may be involved in both arterial and venous thrombosis [2, 39] (Table 3).

Several different factors contribute to the prothrombotic state reported in DM, including chronic low-grade inflammation, primary hemostasis changes, increased levels of clotting factors, impaired fibrinolysis, enhanced oxidative stress and decreased expression of protector endothelial factors [40].

Platelet reactivity has been widely studied in diabetic patients because of its known association with cardiovascular risk. However, most alterations documented may also be associated with venous thromboembolism [41].

Although diabetes impacts on a wide series of pathways regulating platelet function, the cornerstone is represented by increased platelet reactivity.

In detail, hyperglycemia is responsible for increased Ca++ mobilization from intracellular storage pools, resulting in increased intracellular Ca++ levels [42]. In parallel, non-enzymatic glycation of platelet membrane proteins may result in enhanced expression of some receptors (P-selectin, glycoprotein Ib-IX and IIb/IIIa) crucial for platelet function [41].

All these changes determine the enhanced sensitivity of platelet to aggregating agents (arachidonic acid, thrombin, collagen, adenosine diphosphate, epinephrine, collagen) that leads to increased platelet aggregation, consumption and, ultimately, accelerated thrombopoiesis of more reactive young platelets [43]. This latter phenomenon is further potentiated by hyperinsulinemia which has some direct effects on the endomitotic cycle of megakaryocytes, leading to the production of hyperreactive, larger platelets [44].

Furthermore, a decreased platelet membrane fluidity due to the glycation of membrane proteins is reported in diabetic patients, and it is associated with a hyperreactivity of platelets to thrombin [45]. Interestingly, some ex vivo studies documented that spontaneous platelet aggregation is often reported in patient with diabetes, and this phenomenon correlates with the concentration of glycated hemoglobin (HbA1c) [46].

Table 2 Clinical studies assessing the risk of stroke/SE in AF Diabetic Patients

	Study design	Study population	Main results
Laupacis [30] 1994	Pooled data from 5 RCT	1593 patients with AF without antithrombotic treatment (Annual rate of stroke = 4.5 %)	Diabetes [RR = 1.7] was significantly associated with stroke risk
Hart [31] 1999	Pooled data from 3 RCT	130 patients with ischemic stroke 1882 patients without ischemic stroke	Diabetes was present in 22 % of ischemic stroke patients and in 15 % of controls
Wang [32] 2003	Prospective, community-based, observational cohort	111 patients with ischemic stroke 768 patients without ischemic stroke	Diabetes [RR = 1.98, 95 % CI 1.25-3.13] was significantly associated with stroke risk
AFI [33] 1998	Pooled data from 3 RCT	78 patients with ischemic stroke 988 patients without ischemic stroke	Diabetes [RR = 1.7, 95 % CI 1.00-2.8] was significantly associated with stroke risk
Seidl [34] 1998	Population-based cohorts	22 patients with embolic events 169 patients without embolic events	At multivariate analysis, diabetes was not independent predictor of embolic risk
SPAF III [35] 1998	Prospective cohort study	39 patients with embolic events 853 patients without embolic events	At multivariate analysis, diabetes was not independent predictor of embolic risk
Petersen [36] 1990	Prospective cohort study	25 patients with embolic events 311 patients without embolic events	Diabetes was not independent predictor of embolic risk
Aronow [37] 1998	Prospective cohort study	162 patients with ischemic stroke 150 patients without ischemic stroke	Diabetes [RR = 0.83, 95 % CI 0.56-1.22] was not significantly associated with stroke risk
Stollberger [38] 2004	Prospective cohort study	83 patients with embolic events 326 patients without embolic events	Diabetes [RR = 1.37, 95 % CI 0.79-2.36] was not significantly associated with stroke risk

Overall, these changes lead to an increased platelet activation and to overproduction of 11-dehydro-thromboxane which, in turn, mediates further platelet activation and aggregation [47].

In parallel, the low-grade inflammatory status determines an enhanced generation of reactive oxygen species and of 8-iso-PGF2α, a further marker of platelet activation [48].

Diabetes, by determining an increased concentration of von Willebrand factor, of vascular cell adhesion molecule and E-selectin, is associated with an impaired endothelial cell function [49]. In addition, in patients with diabetes, the glycation of nitric oxide synthase (NOS) leads to a decreased production of nitric oxide, a potent endothelial cell-derived vasodilator that inhibits platelet aggregation [50]. Thus, vascular dilatory mechanisms and inhibition of platelet activation are impaired in patients with diabetes. Such alteration is further amplified by a concomitant decrease in prostacyclin production by vascular endothelium [51].

Diabetic subjects exhibit increased polyol pathway, intracellular formation of glycation end products, activation of protein kinase C isoforms and hexosamine pathway overactivity, which lead to an overproduction of reactive oxygen (ROS) [52], and such an increased oxidative stress is able to induce further endothelial cell damage [53, 54]. Moreover, hyperglycemia promotes the impairment of the antioxidant systems such as reduced glutathione (GSH) [52]. In addition, oxidative stress-induced endothelial cell damage is associated with the elevation of several markers such as VWF and endothelin-1 that contribute to the prothrombotic state found in diabetes.

In addition to all these well-known mechanisms, a recent study described more than 300 platelet-derived prothrombotic proteins (e.g., secretogranin III, cyclophilin A and calumenin) overexpressed in diabetic patients and associated with a thrombotic risk [55].

Moving to secondary hemostasis, plasma levels of many clotting factors are elevated in DM, and also impairment of the natural anticoagulant system has been reported.

Some general information about a hypercoagulable state in diabetic patients derives from the demonstration of shorter PT (prothrombin time) and PTT (partial thromboplastin time) in this clinical setting [56].

More specific studies showed that tissue factor (TF) levels are elevated in diabetic patients partly due to its

Table 3 Mechanisms of hemostasis dysfunction in diabetic patients

Primary hemostasis	
Endothelial dysfunction	↓ NO
	↑ ICAM-1
	↑ VCAM-1
	↑ Tissue factor
	↑ IL-1
	↑ TNF-α
	↑ MCP-1
	↑ Endothelin-1
	↑ NF-kB
Platelet hyperreactivity	↓ NO
	↑ P-selectin
	↑ TXA2
	↑ intracellular Ca ++
	↑ GpIIb/IIIa
	↑ Gp Ib/IX
	↑ 8-iso-PGF2α
	Accelerated thrombopoiesis
Secondary hemostasis	
Impaired coagulation	↑ vW factor
	↑ TF
	↑ Fibrinogen
	↑ Factor VII
	↑ Factor VIII
	↑ Factor XI
	↑ Factor XII
	↑ Kallikrein
	↓ Protein C
	↓ ATIII
Impaired fibrinolysis	↑ PAI-1
	↓ TPA activity

release by adipocytes and by inflammatory macrophages, partly through a direct effect of glucose and hyperinsulinemia [57]. In addition, TF levels can be indirectly influenced through the formation of advanced glycation end products and reactive oxygen species which activate NFkB, leading to TF production [58].

Always investigating the extrinsic pathway, increased levels of Factor VII (FVII) have been reported in patients with the metabolic syndrome and hyperglycemia seems to have an independent effect on FVII levels [59]. Furthermore, increased levels of FVII have been reported by patients with diabetic complications such as microalbuminuria, a well-known marker of cardiovascular risk [60].

Overall, TF and FVII initiate the thrombotic process, resulting in thrombin generation and, subsequently, in the conversion of fibrinogen into a three-dimensional network of fibrin fibers, which forms the skeleton of the blood clot.

The chronic low-grade inflammation state is able to stimulate Factor VIII and von Willebrand factor expression from endothelial cells, via the overexpression of several cytokines (including TNF-α and IL-6) [61]. More in detail, the oxidative stress can modify functional properties of von Willebrand factor, leading to a prothrombotic tendency [62].

All these changes lead to alterations in end products of the coagulation cascade (i.e., thrombin and fibrinogen).

Thrombin generation is enhanced in both type 1 and in type 2 diabetes, and it is proportional to the degree of glycemic control [63]. The generation of thrombin in patients with diabetes is likely to be dependent by increased activity of factor Xa, a key component of the prothrombinase complex, which includes Factor Xa, Va and II and is assembled on phospholipid membranes [64]. The activity of this complex is mirrored by plasma concentrations of prothrombin fragment 1.2, a cleavage product of prothrombin. Increased concentrations of prothrombin fragment 1.2 in blood are seen in diabetic patients, clearly suggesting a prothrombotic state in this clinical setting. The increase in fibrinogen levels reported in diabetes can be secondary to a series of mechanisms. First, the diabetes-related inflammatory state can influence fibrinogen levels. Adipose tissue and macrophages produce cytokines (i.e., IL-6, IL-1 and TNF-α) which may induce the production of fibrinogen by the liver [65]. In addition, insulin resistance and glucose levels seem to directly impact on fibrinogen levels [65], whose concentrations are correlated with insulin and proinsulin levels also in healthy subjects [66].

As a further mechanism, oxidative stress, by modifying functional properties of fibrinogen, increases thrombotic risk in diabetic patients.

As to natural anticoagulant system, some in vitro studies suggested that hyperglycemia is able to induce a transition of antithrombin to a form with low affinity for heparin. In addition, hyperglycemia induces the formation of intracellular antithrombin microaggregates, leading to type I antithrombin deficiency [67].

Always evaluating natural anticoagulants, some data suggest that acute hyperglycemia is associated with a reduction in protein C levels [68].

Besides changes in clotting factor levels, patients with diabetes also exhibit impaired fibrinolysis that can be exerted at different levels. Some data suggest that, in the presence of hyperglycemia, glycation of fibrinogen leads to changes in clot structure that decrease plasmin generation and increase resistance to lysis [69].

One of the most widely recognized alterations reported in diabetic patients is increased plasminogen activator inhibitor type 1 (PAI-1) concentration and activity [70]. Indeed, both the low-grade inflammatory state and hyperinsulinemia are able to increase liver synthesis of

PAI-1 [71]. In detail, a series of cytokines and mediators (tumor growth factor-β, tumor necrosis factor-α, interleukin-1 and CRP), known to be increased in patients with type 2 diabetes, are able to induce the release of PAI-1 from adipose tissue and from endothelial cells [72]. Furthermore, the diabetes-mediated oxidative stress, by increasing the generation of oxygen free radicals, leads to an enhanced PAI-1 synthesis by several cells and may further potentiate the cytokine-stimulated PAI-1 synthesis [73].

In parallel, insulin, insulin-like growth factor (IGF)-1 and insulin precursors (proinsulin and proinsulin split products) are able to further stimulate PAI-1 synthesis [74]. Moreover, elevated concentrations of glucose can increase elaboration of PAI-1 by endothelial cells and by vascular smooth muscle cells in culture [74]. Thus, among all people who have syndromes of insulin resistance, those who have diabetes are particularly prone to impairment of the fibrinolytic system [75]. In patients with diabetes, in addition to hyperglycemia, hyperinsulinemia and increased concentrations of proinsulin [76], altered lipid metabolism and increased accumulation of visceral fat seem to contribute to elevated concentrations of PAI-1 [77]. On the other hand, some clinical studies showed increased t-PA levels in subjects with impaired glucose tolerance and diabetes [78]. Although such increase in the main mediator of fibrinolysis could be thought beneficial, some studies demonstrated that this can be just an epiphenomenon of raised PAI-1 levels [79]. Very recently, a number of studies demonstrated that diabetic patients had higher levels of complement C3, an inflammatory protein, and that this protein directly compromises fibrin clot lysis in type 1 and type 2 diabetes independently of PAI-1 [80, 81]. Overall, the impairment of fibrinolytic balance may contribute to acceleration of atherosclerosis and may predispose to acute thrombotic events, such as those that underlie precipitation of acute coronary syndromes [82].

Effects on risk of clinical events of drugs used in the management of diabetic patients

To date, no study has been planned to properly evaluate the effects of drugs used to control blood glucose in diabetic patients on the risk of developing a VTE. However, over the last years a number of studies provided data on the potential beneficial effect of other agents frequently used in the management of these patients.

Statins are the best-studied and most powerful cholesterol lowering drugs and are frequently used in diabetes. Their therapeutic benefits in reducing cardiovascular risk are not completely explained by low-density lipoprotein cholesterol lowering only, thus suggesting that other mechanisms are involved. Potential vascular protective effects of statins include increased nitric oxide bioavailability, atherosclerotic plaque stabilization, regulation of angiogenesis, reduction in the inflammatory response and antithrombotic properties. A number of clinical studies and a recent large meta-analysis suggest that the use of statins may reduce the risk of VTE [83].

Likewise, antiplatelet drugs and in particular aspirin are frequently used in the primary and secondary prevention of arterial cardio- and cerebrovascular events in diabetic patients. Low-dose aspirin seems to be an effective treatment for the primary prevention of venous thromboembolism in high-risk surgical patients [84]. Moreover, two recent randomized controlled trials and a pooled analysis of these two trials suggested an efficacy of aspirin also in preventing VTE recurrences after a first thromboembolic event [85–87]. However, no study has specifically evaluated the efficacy of statins and aspirin therapy in preventing VTE in the population of diabetic patients.

Vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) are highly effective in reducing the risk of cardioembolic complications in AF patients, and in reducing the risk of VTE recurrence in patients with acute DVT or PE [10, 88, 89]. To date, no study has demonstrated a different efficacy of VKAs in diabetic patients in these settings. In a recent meta-analysis focused on patients with AF, DOACs appeared effective and safe as VKAs both in diabetic and in non-diabetic patients [90]. Conversely, diabetes resulted independently associated with major bleeding in a large cohort of patients treated with VKAs for AF [91]. Furthermore, in a secondary analysis of the ARISTOTLE study, a large RCT, that included AF patients treated with VKA or with apixaban, the presence of diabetes slightly but significantly increased the risk of major bleeding complications [92]. Guidelines on the management of VTE included diabetes among the potential risk factors for bleeding in patients on antithrombotic therapy [89]. However, there are no studies that demonstrated an increased risk of bleeding in VTE patients treated with VKA or with DOACs.

In a recent study on a large population of Taiwanese diabetic patients, metformin use independently protected the diabetic patients from new-onset AF [93]. This reduction appeared to be related to the attenuation of atrial cell tachycardia-induced myolysis and oxidative stress mediated by the use of metformin.

Furthermore, in a small randomized controlled trial, the use of pioglitazone seems to be associated with a lower incidence of permanent AF in DM patients with persistent AF [94]. This therapy appeared to lower the procollagen type I carboxy-terminal peptide that may contribute to its inhibitory effect on the advanced glycation end products potentially improving the prognosis of DM patients with persistent AF. Unfortunately, to date, evidences on the role

of a strict glycemic control (with specific diets and/or with glucose-lowering therapies) in reducing the incidence of stroke and SE in diabetic patients with AF are lacking. Thus, other studies are warranted to better clarify the role of these therapies in this setting.

Conclusions

In the last few years, several studies have evaluated the role of DM as a potential risk factor for VTE and for stroke/SE in diabetic patients with AF. Evidence from laboratory studies showed many potential pathophysiological mechanisms to explain these associations. On the other hand, findings of clinical studies are more conflicting and there are few data (if any) on the efficacy in reducing these complications with drugs habitually used in the glycemic control of diabetic patients. Thus, further high-quality prospective studies are warranted to better clarify the nature and the magnitude of these associations.

Conflict of interest The authors declare that they have no conflict of interest.

Human and Animals rights disclosure This article does not contain any study with human or animal subjects performed by any of the authors.

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