Microparticles in Hematology: From biology to diagnostics and therapeutics

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Abstract: The present work was designed to review the literature about microparticles and their role in hematology. We found that, cell-derived microparticles had an essential role in hemostatic response and their potential as disease markers, but also their implication in a wide range of physiological and pathological processes. Microparticles derive from different cell types including platelets – the main source of microparticles – but also from red blood cells, leukocytes and endothelial cells, and they circulate in blood. In hematology, their earliest recognized and most widely accepted role is the ability to promote and support the process of blood coagulation. Consequently, there is ongoing interest in studying MPs in disorders of hemostasis and thrombosis. Both phosphatidylserine (PS) exposure and the presence of tissue factor (TF) in the MP membrane may account for their procoagulant properties, and elevated numbers of MPs in plasma have been reported in numerous prothrombotic conditions. **Conclusion:** microparticles could play an important role in the field of health and disease, especially in the field of hematology. However, it is advisable to construct future studies for examination of microparticles role in different disease states.
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1. Introduction

Normally, coagulation is a complex system initiated by endothelial injury and exposure of tissue factor and collagen which initiates a platelet plug formation at the site of injury. This leads to activation of a cascade of enzymes, which forms a fibrin clot **(Morel et al., 2009).**

Microparticles were firstly revealed in 1946 by Chargaff and West. Their trials proposed that cell free plasma encompasses a subcellular factor that stimulates clotting of blood. After twenty years in 1967, wolf defined microvesicles (MVs) as "platelet dust"; a part of plasma that owns coagulant characters when blood platelets were stored. These particles were have a size between 20 and 50 nm and a density of 1.020 to 1.025g/ml **(Wolf, 1967).** Microparticles (microvesicles) are produced by budding and subsequent separation of the plasma membrane into the extracellular pool as a consequence of dynamic reactions between phospholipid redistribution and cytoskeletal protein contraction **(Gonda et al., 2013).**

Microvesicles are key elements of hemostasis process as they directly trigger protein substances and enzymes accountable for starting the coagulation cascade. The membranes of microvesivles derived from platelet are recognized to have receptor locations for procoagulant factors IIa, Va, VII, and IXa. Also, certain microparticles also produce the phospholipid phosphatidylserine on their cell membrane, which catalyzes clotting by providing a site for the reaction to happen **(Bernimoulin et al., 2009)**.

Microparticles have a role in cancer development, the spread of viruses and pathogenic substances like HIV-1. Microvesicles have been associated with regulation of many biological processes like those associated with Alzheimer's disease and α-synuclein linked to Parkinson's disease. Thus, microparticles have absolute therapeutic role. Several therapeutic policies are under investigation. Microvesicles have been examined as possible therapeutic means for regeneration of tissue, immune responses modification and as an immunotherapy **(Chaput and Théry, 2011).**

The recognition of cell-derived particles isolated from body fluids proposed that microparticles are a hopeful source of clinically applicable and non-invasive biomarkers that permit monitoring of normal body function and diagnosis of several ailments **(Gonda et al., 2013).**

Microvesicles were examined as possible source of new biomarkers of disorders and toxicities, such as drug-induced liver damage. It has been found that liver cells produce microparticles with molecules that reflect hepatotoxicity which released to circulation **(Yang et al., 2014)**.

It is expected that, microparticles may be potent clinical instruments for new treatments by engineering the particles comprising definite level of expression of

mRNA, miRNA, or proteins in the particles, and also for great source of clinically significant biomarkers **(Gaceb et al., 2014)**.

Aim of the Work

The aim of the Study is to demonstrate the role of microparticles in hematological disorders and its diagnostic and therapeutic implications.

Hemostasis

Hemostasis is a process facilitates the person to 1) close off injured vessels, 2) maintain the blood in a fluid condition, and 3) remove clots to regain vascular integrity. The hemostatic scheme is a highly-specialized apparatus which has noticeable role in coagulation process **(Versteeg et al., 2013).**

In 1905, Morawitz, construct the first coagulation model in which thromboplastin was expressed by injured vessels to convert prothrombin into thrombin with the assistance of calcium. Thrombin then transformed fibrinogen into fibrin resulting in the development of a blood clot. However, this four-clotting factor model could not fully clarify the complex process of coagulation **(Riddel et al., 2007).**

In 1950s, many of residual substances had been defined, such as von Willebrand factor (VWF) and factors V, VII, VIII, IX, and XI (FV, FVII, FVIII, FIX, FXI). Deficiency in any of these factors was associated with bleeding disorders, such as hemophilia A (FVIII deficiency) and hemophilia B (FIX deficiency). In the 1960s, two independent sets built a model for coagulation that look like a cascade. Thus, this model was appropriately named the coagulation cascade model. The present conception of hemostasis can be summarized as follows: when vessel is injured, platelets stick to to the injured site and aggregate through interactions of platelet receptors with extracellular ligands and soluble factors namely proteins. Vascular injury-stimulated exposure of subendothelial TF creates little quantities of thrombin with multiple properties on other coagulation factors and platelets. Via multiple enforcement loops in the coagulation cascade and in platelet stimulation, large amounts of fibrin are formed stabilizing earlier formed platelet thrombi **(Versteeg et al., 2013).**

Microparticles

Microparticles (MPs) are submicron (<1μm diameter) exocytic particles, derived from cell membrane that are expressed into the circulation in vivo and created in stored blood products ex vivo. Platelets, endothelial cells, red blood cells, polymorphonuclear white blood cells, lymphocytes, and monocytes all express MPs in a firmly controlled process provoked by stimuli such as shear strain, complement activation, proapoptotic activation, or cellular injruy **(Rubin et al., 2010).**

Physiologic and pathologic procedures are accountable for micro- vesicle production in both healthy and diseased persons and the existence of these particles has proven harmful for recipients of blood transfusions **(Kozuma et al., 2011; Jy et al., 2011).**

Microvesicles typically produce antigens, and enclose cell surface proteins, cytoplasmic contents, and nuclear components from their cell of origin. These bio-particles determine their structure, characters, and transfer of biologic data **(Martinez et al., 2011).**

Microparticles have been linked to profound pro-inflammatory and procoagulant properties and have been function as essential part of normal and abnormal coagulation. They also contribute to systemic inflammation and cardiovascular, hematologic, and oncologic disease conditions **(Shah et al., 2008).**

MPs are defined as diverse, submicron (0.1–1μm) vesicles expressed from cell membranes in response to specific stimuli or due to apoptosis. They have an undamaged phospholipid membrane and produce membrane antigens specific to their cell of origin **(Tesse et al., 2006).** The working definition of a MP generally includes both the size discrimination, as well as the presence of externalized phosphatidyl-serine (PS) on the cell membrane **(Thaler et al., 2012).** New evidence supports the concept that not all MPs expose PS on their surface, and that PS content may vary depending on the cell of origin and stimulus or mechanism by which they are constructed **(Mooberry and Key, 2016).**

MPs must also be distinguished from two other bioactive vesicles expressed from cells. Exosomes are constructed particles <100 nm that are produced in endocytic multivesicular bodies and released via exocytosis. They are more similar in size than MPs, carry diverse membrane antigens, and play a vital role in the immune response **(Vlassov et al., 2012).** On the other hand, apoptotic bodies (AptB) are expressed during the latter phases of cell apoptosis. They are characteristically larger than MPs (1–3 mm), although a few may be smaller (0.5 mm). Similar to MPs, they produce PS on their surface; however, in contrast to MPs, AptB carry DNA and histones, which is one of their hallmarks **(Berda-Haddad et al., 2011).**

It should be confirmed that the term “extracellular vesicles” is increasingly being used in the scientific writings and is a term that includes MPs, exosomes, and AptB **(Raposo and Stoorvogel, 2013).** In addition, the term microvesicle is repeatedly met and in general is identical and interchangeable with the term MP **(Gyorgy et al., 2011).**

Much investigation has focused on the possible role of MPs as biomarkers of endothelial dysfunction, coagulation, inflammation and other pathological processes. Bio-markers have been formerly well-defined as characteristics that are objectively estimated and assessed as indicators of normal biological procedures, pathogenic procedures or pharmaco-logical responses to therapeutic intervention **(Al-Ismaili et al., 2011).**

As direct evaluation of biological conditions is often too invasive, or too expensive, biomarkers are of important clinical utility in identifying pathology and assessing risk of disease. In addition, because hard end points often take years to arise, biomarkers allow for early discovery of pathology and may facilitate earlier therapeutic intervention **(Burger et al., 2013).** Also, there is an increasing evidence advocates that MPs may themselves apply biological effects. MPs represent a novel and potentially significant technique of cell–cell interaction, regulating a number of physiological/ pathophysiological procedures **(Burger et al., 2013).**

Perhaps the best-recognized character of MPs is their capability to encourage coagulation. MPs are increased in hypercoagulative diseases and this association is probably a result of their active contribution in the coagulation process. The procoagulative characters of MPs are mainly attributed to their physical properties with two specific surface characters thought to be accountable for this procoagulant action. First, the externalization of anionic phospholipids (predominantly phosphatidyl-serine) results in a negatively charged surface; this negatively charged surface permits for interaction with cationic fields in clotting substances, the subsequent assembly of coagulation factors and eventually thrombin formation. The externalization of phosphatidylserine is supposed to be a character of all types of MPs and is a strong promoter of coagulation. Secondly, certain factors of MPs have been found to express tissue factor on their surface **(Owens and Mackman, 2011).**

Tissue factor is a serious constituent of the early phases of coagulation where it constitutes a complex with Factor VII/VIIa, eventually leading to the beginning of coagulation. The surface release of tissue factor has been stated in monocyte and endothelial cell-derived MPs, whereas platelet MPs are not supposed to release tissue factor **(Kasthuri et al., 2012).** It is unclear to what degree MPs contribute to coagulation in vivo; however, an in vitro analysis of platelet MPs recently detected that their surfaces were 50–100 times more procoagulant than those of activated platelets **(Giacomazzi et al., 2016).**

Microparticles in hemostasis

1.1. Role of MPs in coagulation and fibrinolysis

According to their parent cells, MPs harbor membrane and cytoplasmic constituents involved in a range of biological methods **(Lacroix et al., 2013).**

1.2. Procoagulant potential of MPs

The procoagulant characters of MPs rely chiefly on the release of anionic phosphor-lipids, particularly PS, and of TF, the chief cellular stimulator of the clotting system. During MP production, the loss of asymmetrical membrane spreading of phospholipids leads to the externalization of PS at the external leaflet of the cellular membrane. Due to its negative charge, PS upsurges the procoagulant potential by assisting the assembly of calcium-dependent coagulation factors on the MP surface, thus allowing tenase and/or prothrombinase complex formation followed by thrombin generation **(Owens and Mackman, 2011).** MPs harboring both PS and TF have the uppermost level of procoagulant action. Certainly, TF is the receptor for FVII/VIIa, which in turn stimulates both FX and FIX to start blood coagulation. Different mechanisms that may control TF action on MPs have been suggested, such as post-translational alterations or low- (also encrypted) vs. high-activity conformational conditions. This proposes that TF-releasing MPs from different cellular sources may have different procoagulant actions **(Witkowski et al., 2016).** In human disorders, the impact of MPs initiating from endothelial cells to the circulating pool of TF+ MPs has previously been recognized in sickle cell anemia and sepsis. Moreover, these MPs encourage TF release of monocytes after binding and, thus, contribute in the amplification of procoagulant cellular responses **(Aras et al., 2004).**

Cancer MPs represent another set of procoagulant MPs. Cultured human tumor cell lines of different origins release variable amounts of TF and express highly procoagulant cancer MPs in their supernatant **(Date et al., 2013).**

1.3. Anticoagulant functions of MPs

Apart from their well-recognized procoagulant actions, platelet-, leukocyte-, endothelial- and cancer-derived MPs harbor a different anticoagulant factors, reflecting the pro-/ anticoagulant characters of their parent cells. The TF–FVIIa complex is controlled by tissue factor pathway inhibitor (TFPI), which is principally manufactured by endothelial cells and circulated in blood to stop unsuitable activation of coagulation. Thus, one can theorize that some of the TF–VIIa complexes harbored by MPs will be inhibited by circulating TFPI **(Lacroix et al., 2013).** The release of TFPI itself has been demonstrated in MPs from endothelial cells, monocytes, cancer cells, and

circulating MPs from patients with acute myocardial infarction and diabetes **(Tsimerman et al., 2012).** Thus, it is likely that the equilibrium between TF and TFPI on MPs affects their thrombogenicity and varies in different disease conditions compared with healthy subjects. This balance reflects the hypercoagulable condition and could be beneficial in classifying thrombotic risk **(Nomura et al., 2015).** Another regulatory mechanism by which EMPs and MoMPs are thought to counteract thrombin production is the release of the anticoagulant receptors thrombomodulin (TM) and the endothelial cell protein C receptor (EPCR). PMPs have also been found to accelerate factor Va inactivation by stimulated protein C. In addition, it has been established that MPs may also expose fibrinolytic characters, thereby complementing their procoagulant action **(Briens et al., 2016).**

1.4. MP-dependent fibrinolytic potential

The innovation of fibrinolytic action harbored by MPs additional adds to their involvement in the regulation of the hemostatic equilibrium. This fibrinolytic action is connected to the evidence of molecular equipment that classifies MPs as an efficient support for plasmin production. Plasminogen action is highly controlled by the functions of both activators and inhibitors, which limits the spreading of proteolytic actions on dedicated surfaces (fibrin, extra-cellular matrix, and definite cell membranes). Only two serine proteases, urokinase (u-PA) and tissue-type plasminogen activator (t-PA), can stimulate plasminogen into plasmin **(Chapin and Hajjar, 2015).** u-PA binds to a definite cellular receptor (u-PAR, CD87) that is released at the surface of monocytes, T cells, neutrophils, endothelial cells, epithelial cells, smooth muscle cells, and fibroblasts, whereas t-PA is mainly formed by neurons, microglial cells, endothelium, and smooth muscle cells. The binding of t-PA to fibrin significantly rises its affinity for plasminogen (10009 to 15009); however, other cell surface receptors, such as annexin II, have been recognized as potential co-factors for plasmin creation **(Weisel and Litvinov, 2017).** Recent information showed that the whole molecular panel desirable for an efficient plasmin production is exposed on MPs originating from white blood cells, endothelial and tumor cells. On the other hand, platelet and erythrocyte MPs, the major MP subpopulations, are devoid of such action **(Lacroix and Dignat-George, 2013).** Plasmin production is a highly-regulated procedure controlled by an equilibrium between activators and inhibitors. The existence of tPA in a complex with its inhibitor PAI-1 was found in purified EMPs and MPs extracted from patients with thrombotic thrombocytopenia purpura or systemic lupus **(Lacroix et al., 2012).** Other plasmin inhibitors linked with MPs were defined such as PAI-2 in MPs from the placenta **(Guller et al., 2010)** or α2-macroglobulin in the MPs of patients with deep venous thrombosis **(Ramacciotti et al., 2010).**

3.6. Role of MPs in arterial and venous thrombosis

3.6.1. Arterial thrombosis

Different studies have evaluated the participation of MPs in the beginning and creation of a platelet thrombus in animal models. One of the existing views attributes a key role to MoMPs as a significant source of circulating TF in arterial thrombosis **(Furie and Furie, 2008).**

In the laser damage model of arteriolar thrombosis, a minimal damage is stimulated in the vessel wall. This model uses a focused ablative laser beam to stimulate thrombosis in the cremaster circulation of living mice. The dye laser stimulates endothelial cells, leading to the construction of a platelet thrombus that is dependent on the production of thrombin through the activation of the TF pathway **(Atkinson et al., 2010).** A fast buildup of TF and fibrin is observed upstream of the platelet-rich thrombus, proposing a recruitment of TF+ MPs to the thrombus. These MPs were recognized as initiating from monocytes. Actually, when expressed in the bloodstream, MoMPs accumulate at the site of thrombus production and share in the production of fibrin. The exposure of PSGL-1 at the surface of MoMPs was accountable for their accumulation at the site of thrombus production through interactions with P-selectin expressed at the surface of activated platelets. Exogenously primed and labeled MoMPs quickly accumulate, with a peak at 60 s, at the site of the laser injury in comparison with TF+ monocytes that adhere to a platelet thrombus in only 3–5 min post-damage **(Khan et al., 2016).**

The interaction between PSGL-1 and P-selectin likely exerts a key role in the enrollment of TF+ MoMPs to the site of thrombosis. Monocytes may not be the exclusive source of TF+ MPs in the production of an arterial thrombus. Low-TF mice containing bone marrow from WT givers established larger thrombi with increased values of fibrin at the site of laser-stimulated injury in comparison with thrombi performed in low-TF mice. On the other hand, WT mice containing low-TF bone marrow had smaller thrombi containing less fibrin in comparison with that detected in wild-type mice. These results specify that myeloid cells and/or MPs may contribute in the production of a platelet thrombus by bearing TF **(Lacroix et al., 2013).**

Authors investigated thrombus formation and fibrin production in CX3CR1-GFP mice. These mice coexpressed the green fluorescent protein with the receptor CX3CR1, such that monocytes and their MPs,

macrophages, dendritic cells, and natural killer cells are fluorescently tagged. Unexpectedly, no fluorescent signal was detected at the site of laser-stimulated damage consistent to an accumulation of GFP-tagged MoMPs. Thus, further trials are required to settle the involvement of endogenous circulating MoMPs in thrombus production **(Darbousset et al., 2012).** When using the ferric chloride damage model, thrombus production could be reliant on both production of thrombin by the coagulation waterfall and exposure of the subendothelial matrix. The relative significance of one pathway to the other is dependent on the tissue studied and the condition used. Characteristically, when a filter paper soaked with 10% ferric chloride is applied for 5 min on the mesentery, this paper leads to the production of a platelet thrombus that is reliant on the interaction of platelets with collagen. When a 7.5% FeCl3 is applied for 3 min on the mesentery, the production of the platelet thrombus was independent of the interaction of platelets with collagen but was dependent on the production of thrombin **(Estevez et al., 2016).** Excitingly, **Geddings et al. (2016)** stated that the time to complete thrombotic occlusion was considerably longer in CD36-null mice when compared to wild-type mice when the grade of vascular oxidative injury in the carotid artery FeCl3 damage model was negligible. However, it is significant to note that the study of thrombus production in mesenterial veins of mice is mostly not a dedicated mouse model reflecting arterial thrombosis.

CD36 is an 88000-MW essential membrane protein released on platelets, micro-vascular endothelium, muscle cells, lipid cells, and the specialized epithelium and could interact with PS. In vitro, MPs equipped from human endothelial cells bound to CD36 were released at the surface of platelets. This binding stimulated platelets. In thrombi shaped in the carotid artery, the relative grade of accumulation of EMPs was decreased in CD36-null mice when compared to wild-type mice. Altogether, these findings indicate that EMPs may also exert a significant role in arterial thrombosis by accumulating at the site of thrombus production through CD36 **(Lacroix et al., 2013).**

3.6.2. Venous thrombosis

The main model used to investigate the participation of MPs in venous thrombosis is the inferior vena cava (IVC) ligation model. **Ramacciotti et al. (2009)** verified that in this model, the injection of MPs positively influences the weight of the formed thrombus. **Mege et al. (2016)** revealed that the infusion of MPs isolated from human pericardial blood following cardiac surgery increases thrombus production in a model of IVC, with a positive association between the thrombus weight and TF exposure on MPs. TF appears to play a significant role in different venous thrombosis models: low-TF mice had smaller thrombi than WT mice in the IVC ligation model, and a TF-dependent fibrin accumulation was revealed using a rabbit model in which a collagen-coated thread was inserted in the jugular vein. In addition, another study revealed a key role of both neutronphils and monocytes in thrombus production in a deep venous thrombosis mouse model, challenging the real effect and role of MPs in venous thrombosis **(von Bruhl et al., 2012).**

When expressed in the bloodstream, cancer-cell-derived MPs but not their parental cells aggregate at the site of damage and increase the size of a platelet-rich thrombus. Excitingly, authors detected that, endogenous cancer-cell-derived microparticles tagged using GFP- transfected cancer cells leave the site of tumor production, circulate in the bloodstream, and accumulate at the site of thrombus production through the P-selectin/PSGL-1 pathway **(Lacroix et al., 2013).**

3.7. Role of MPs as biomarkers in thrombotic diseases

The clinical importance of MP discovery in the circulation can be viewed as the consequence of a dynamic equilibrium between MP production and clearance. Over the past years, different studies have measured circulating MP values from different cell types in healthy and diseased subjects. Previous reviews of the literature recognized that MP levels are increased in a wide range of arterial and venous thrombotic diseases, with an exciting association between MP values and disease physiopathology, activity, or progression **(Viera et al., 2012; Reitsma et al., 2012).**

Although it is likely that MPs contribute in disease severity, due to their prothrombotic potential, it still unknown whether MPs are causally involved in the prediction of cardiovascular disorders or are exclusively a result of the underlying pathology and are just a marker of increased risk. Although a wide range of clinical trials has investigated the link between MP levels and cardiovascular risk such as endothelial dysfunction, diabetes, or hypertension **(Lacroix et al., 2013).**

3.8. Arterial thrombosis

Platelet MPs, which are the most copious in blood circulation, were described to be higher in transient ischemic stroke and coronary artery disorders **(Lukasik et al., 2013).** Increased levels of platelet MPs were linked with high-risk score of coronary heart disease in healthy men **(Ueba et al., 2010).** Interestingly, **Sinning et al. (2011)** stated that the value of circulating CD31+/annexin V+ MPs is an

independent predictor of cardiovascular events in patients with stable coronary artery disease.

Other study reported that the levels of TF+ MPs, most likely derived from stimulated monocytes and macrophages, are increased in subjects with cardiovascular diseases. In acute coronary syndromes, MP-dependent TF (MP-TF) activity was found to be increased in patients with acute coronary syndromes, increasing after angioplasty and continuing increased in patients who failed to achieve thrombolysis **(Huisse et al., 2009).** This discovery proposes that this failure may include a supply of circulating TF+ MPs to the thrombus. CD11b+ leukocyte MPs were linked with repeated cardiovascular events in acute coronary syndromes **(Faille et al., 2011).** On the other hand, a few prospective studies revealed that, the EMP level is an independent predictor of major adverse cardiovascular events and mortality. **Nozaki et al. (2009)** revealed that the plasma levels of EMPs could independently expect future cardiovascular events. Finally, **Amabile et al. (2012)** revealed that, the EMP level is a strong independent predictor of severe cardiovascular consequence including fatal myocardial infarction, stroke, acute pulmonary edema, and sudden cardiac death.

3.9. Venous thrombosis

Most of the trials on MPs and venous thromboembolism (VTE) have been done in patients with cancer or mouse model of cancer because tumor cells express high quantities of TF+ MPs in vitro, and it is well known that patients with cancer have a considerably increased risk of developing VTE events **(Date et al., 2013). Wang et al. (2012)** determined the role of tumor-derived TF in thrombosis. The activation of the coagulation system observed was due to the existence of human TF. However, remarkably, < 5% of the TF action was linked with circulating MPs. These results propose that the main source of TF involved in the systemic activation of the blood coagulation cascade was the tumor by itself. This study may reveal the complexity of the mechanisms involved in arterial and venous cancer-linked thrombosis. The cancer cell lines studied, the way of discovery and characterizing MPs, the localization of the tumor, and the use of human or mouse cancer cells in wild-type or nude mice are all important variables that affect the physiopathology of the disease. However, it is significant to know that cancer-cell-derived MPs are probably not the exclusive resources of developing a procoagulant/ prothrombotic condition leading to cancer-associated thrombosis. The majority of the clinical studies found increased levels of TF+ MPs and MP-TF activity in cancer patients with VTE compared with those without VTE **(Campello et al., 2011; Manly et al., 2010).** However, there is a lack of large prospective clinical trials that clearly analyze the predictive value of MPs for future VTE. A small number of studies in patients with pancreatic cancer verified the predictive value of MP-TF action, whereas another one in patients with multiple myeloma did not find such link **(Auwerda et al., 2011).** In a comparable way, MP-TF action was not found to be linked to future VTE in pancreatic, gastric, colorectal, and brain cancer; however, a strong link of MP-TF activity with mortality was found in pancreatic cancer **(Thaler et al., 2012).** A third study revealed that higher levels of TF+ MPs identified a subgroup of patients with cancer at a substantially higher risk of developing VTE**.** Remarkably, low molecular weight heparin resulted in a trend toward a decreased rate of VTE in such patients with cancer **(Zwicker et al., 2013).**

Although chemotherapy has been reported to further elevate the risk of VTE, MP-TF action in treated patients does not seem to correlate with a higher risk of VTE **(Mukherjee et al., 2010).** Another study proposes that MP procoagulant activity can be used to predict VTE **(van Doormaal et al., 2012).** The association between MPs and non-cancer-related VTE is less well investigated. Two retrospective studies revealed that EMPs are increased in antiphospho-lipid syndrome patients with thrombosis or in patients with acute VTE. In addition, several but not all studies stated that MP-TF action correlates with the risk of VTE **(Steppich et al., 2011; Bucciarelli et al., 2012; Devalet et al., 2014).**

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