Inflammation – a common pathogenic factor of arterial atherosclerotic and venous thromboembolic disease

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Abstract

Inflammation is one of the basic mechanisms of arterial atherosclerotic disease, most likely also involved in the pathogenesis of venous thromboembolic disease. Various risk factors for atherosclerosis impair the vessel wall and elicit inflammatory changes resulting in the development of atherosclerosis. Subjects with advanced atherosclerosis, especially those with unstable atherosclerotic plaques reflecting profound inflammatory changes, have increased inflammatory blood markers, such ashigh-sensitivity C-reactive protein (hs-CRP), which is a nonspecific systemic indicator of inflammation, and some interleukins (interleukin-6, interleukin-8), which are among the more specific markers of inflammation of the vessel wall. Therefore, the studies have focused on improving the prediction of cardiovascular events by determining the circulating markers of inflammation. However, due to low specificity of individual indicators of inflammation, different determination methods, and close relationship between the levels of inflammatory markers and conventional risk factors, these markers have not significantly contributed to the risk estimation for cardiovascular events. Currently, the determination of hs-CRP as the most recognizable risk factor is recommended only in subjects with a medium risk for cardiovascular events, or in patients who do not have conventional risk factors, and who are at risk for other reasons, such as familial predisposition for cardiovascular events.

Recently, inflammation has been found to be involved also in the pathogenesis of venous thrombosis. In case of damage to the venous wall, inflammation is most likely the response to the injury, whereas in idiopathic (unprovoked) venous thrombosis, where there are no known risk factors present, the inflammation of the vascular wall is the primary event followed by activation of coagulation. There is a close link between inflammation and coagulation; inflammation stimulates the procoagulant activity and inhibits the endogenous fibrinolysis. Therefore, patients with a history of venous thrombosis have increased systemic markers of inflammation, hs-CRP and interleukins in particular. It is not yet clear, whether the increased systemic indicators of inflammation are the cause or the consequence of venous thrombosis. The results of our studies show that they are more likely to be the cause of prothrombotic properties of blood stimulating the development of venous thrombosis. The patients who suffered venous thrombosis have constantly elevated inflammatory markers also in the stable period of the disease (3–5 years after the diagnosis).

An increased systemic inflammatory response in an arterial atherosclerotic and venous thromboembolic disease indicates a close link between both diseases. Therefore, they may be two pathogenically similar diseases with different clinical features.

The recognition of an inflammatory basis for arterial and venous disease is important from the therapeutic point of view. Namely, until recently drugs with an anti-inflammatory effect were rather neglected in comparison to anticoagulant drugs. Aspirin has long been known to have not only anti-

platelet, but also anti-inflammatory properties, therefore it appears that aspirin might be effective in the long-term prevention of recurrence and progression of venous thrombosis.

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1. Introduction

Cardiovascular disease is, especially in the developed world, still the leading cause of morbidity and mortality in the adult population. Advanced atherosclerosis and/or thromboembolic occlusions of affected arteries and veins lead to cardiovascular events. Atherosclerotic changes develop in response to many known and less known risk factors. Venous thromboembolic events are the result of the so-called Virchow triad, which includes changes in the blood composition (resulting in increased coagulability), an injury to the blood vessel wall, and impaired blood flow (venous stasis). However, direct pathogenic mechanisms of the vascular wall impairment in venous thrombosis have not been sufficiently elucidated yet. The disease process most likely begins with impairment of the inner layers of the venous or arterial wall caused by various factors: mechanical, chemical and metabolic. Vessel wall injury is followed by an inflammatory response, which is probably the common denominator of harmful effects of exo- and endogenous factors responsible for vessel wall damage. It is well known that chronic low-grade inflammation promotes atherosclerosis. In the last several years, evidence has emerged for a key role of inflammation in venous thrombosis and thromboembolic complications. Inflammation tends to shift the hemostatic balance in favor of increased procoagulant activity of blood (1,2).

The results of studies showing a link between deep venous thrombosis (DVT), in particular idiopathic, and preclinical and clinical atherosclerosis are in favor of an interrelationship between an arterial and venous disease that share inflammation as a common pathogenic factor (3,4).

2. Atherosclerosis and inflammation

Inflammation plays an important role in the formation, and the progression of the disease, and in atherosclerosis-related cardiovascular complications (5,6). Therefore, atherosclerosis is defined as a chronic inflammatory disease. The identification of inflammatory changes in the vessel wall, but also of circulating inflammatory markers in blood, is important from the clinical, and in particular from the prognostic point of view. Ali: is particularly important from the clinical, but also from the prognostic …

The accumulation of lipids in the arterial wall triggers an inflammatory response (7). Increased lipid levels and mechanical stress lead to the accumulation of cholesterol and other lipids in the arterial wall reducing endothelial protective properties and inhibiting the defense mechanisms that prevent the entry of inflammatory cells in the artery wall. An impaired endothelial function followed by morphological changes of endothelial cells, lead to the synthesis of adhesion molecules on the surface of endothelial cells. Adhesion molecules crosslink with different inflammatory cells and facilitate their entry into the ar-

tery wall. The result is the activation of the inflammatory response which causes a release of various mediators, in particular the cytokines that accelerate the transit of white blood cells from blood into the intimal layer of the vessel wall. Activated macrophages accumulate large quantities of lipids and eventually transform into foam cells. Growth factors are released that encourage the reproduction and migration of vascular smooth muscle cells. Fibrinolytic enzymes, particularly metalloproteinase, degrade the connective tissue frame of the vessel wall and enable smooth muscle cells to penetrate the elastic layer that separates the intima from the media. Cholesterol-rich macrophages break down and release cholesterol and other cellular components in the intracellular space, which facilitates the inflammatory response. Further, inflammatory mediators and tissue factor are released, which is responsible for thromboembolic complications on the surface of the atherosclerotically changed vascular wall (8) The inflammatory response in the vessel wall is additionally influenced by monocyte chemoattractant protein (MCP), MCP-1 in particular (9). T-lymphocytes are activated and T-cells promote the formation of pro-inflammatory cytokines and tumor necrosis factor beta (TNF-β). In this way, the inflammation not only promotes the development of atheroma but is also responsible for acute thromboembolic complications which may lead to a heart attack, stroke or ischemic events in other organ systems.

3. Risk factors for atherosclerosis and inflammation

Risk factors for atherosclerosis elicit their adverse effects probably through the promotion of inflammation in the vessel wall. It has long been known that lipids, especially LDL cholesterol, promote the inflammatory response, which is more intense if LDL cholesterol is oxidized. Other lipoproteins such as VLDL, also promote inflammation and the development of atherosclerosis (10).

Increased blood pressure causes a mechanical vessel wall damage, whereas pathogenic factors of arterial hypertension promote inflammation. Angiotensin II has vasoconstrictive effects and promotes inflammation of the intima. Increased blood pressure promotes the release of pro-inflammatory cytokines, in particular IL-6, and adhesion molecules (VCAM-1) on the surface of endothelial cells (11). Hyperglycemia causes glycation of different molecules and also ingredients of the vessel wall, which stimulates the production of pro-inflammatory cytokines, increases oxidative stress and is the reason for the inflammatory response.

Excess body mass triggers inflammation through the accompanying risk factors of atherosclerosis, such as the increased lipids, insulin resistance, and increased blood pressure. Moreover, adipose tissue can directly stimulate the production of cytokines, such as TNF-α and IL-6 (12).

4. Blood markers of inflammation

In persons with different atherosclerotic diseases, it is possible to measure blood markers of inflammation, such as high-sensitivity C-reactive protein (hsCRP), fibrinogen, and serum amyloid-A in the earliest stages of the atherosclerotic process. These markers are present in small quantities in healthy subjects already but in case of atherosclerosis, their levels increase significantly. On the other

hand, in subjects at risk of atherosclerosis, we can already detect the inflammatory blood markers which are otherwise not present in healthy subjects, such as the cytokine TNF-α and adhesion molecules. These inflammatory markers are quite reliable indicators of inflammation of the vessel wall, whereas the plasma concentrations of non-specific mediators may increase in various inflammatory processes not only in inflammation of the vessel wall. Therefore, those markers are less specific indicators of the vascular wall impairment and accompanying vascular diseases. Epidemiological studies have shown a close interrelationship between the levels of inflammatory markers in the blood and the risk of cardiovascular complications (5,6). The results of these studies have stimulated an interest in monitoring the levels of inflammatory indicators and their predictive value for cardiovascular events. Prospective epidemiological studies have shown that increased levels of various inflammatory indicators, such as cytokines (IL-6, TNF-α), adhesion molecules (ICAM-1, P-selectin, E-selectin) as well as the acute phase reactants, such as hs-CRP, fibrinogen and serum amyloid A are important predictors of cardiovascular events (13,14). The results of these studies indicate that increased levels of certain inflammatory markers (IL-6 and hs-CRP) are not only predictive of atherosclerosis but also of insulin resistance and development of type 2 diabetes (15). The monitoring of inflammatory makers permits the evaluation of the effectiveness of the preventive measures, and the treatment of risk factors in the prevention of atherosclerotic complications.

hs-CRP is one of the most investigated inflammatory markers and predictors of cardiovascular events. hs-CRP has a connecting role in the formation and activation of other inflammatory indicators, in particular the cytokines. hs-CRP stimulates the production of adhesion molecules and promotes the entry of LDL cholesterol and monocytes into the vessel wall (6). Recently, hs-CRP has received much attention because of its ability to improve the prediction of cardiovascular events in subjects who do not have classic risk factors for atherosclerosis, and has been used to measure the effectiveness of various preventive measures of atherosclerosis, in particular the effectiveness of statins (16). Numerous studies have demonstrated a link between hs-CRP and cardiovascular events. The MRFIT study (Multiple Risk Factor Intervention Trial) has demonstrated a close link between the level of hs-CRP and cardiovascular mortality in adult men (17). In the Women Heart Study, which included around 28,000 healthy women who were followed for 8 years, hs-CRP was an independent predictor of cardiovascular events. Its predictive value was greater than that of LDL cholesterol (18). In spite of numerous research findings in the field of primary prevention of atherosclerosis, the question arises as to whether the determination of hs-CRP adds the predictive value to the risk assessments based on the presence of classical risk factors. The Emerging Risk Factors Collaboration found only a limited clinical utility of hs-CRP determination due to its low specificity (19). The analysis of 52 cohort studies that included 246,669 people showed that hs-CRP or fibrinogen determination in subjects without a known cardiovascular disease and medium-high risk of cardiovascular disease could prevent only one cardiovascular event in the 10-year period in 400–500 persons screened. The predictive value of hs-CRP is limited because it is the acute phase reactant, and is increased in different inflammatory and infectious diseases. Long-term changes

in basal hs-CRP values have the highest discriminatory value in the identification of those individuals who, in spite of the absence of classical risk factors of atherosclerosis are at an increased risk of atherosclerotic cardiovascular complications. Increased hs-CRP levels have a better predictive value in subjects who are younger than 75 years, men, and individuals who have normal values of systolic blood pressure. The predictive value of hs-CRP is reduced in the presence of other risk factors of atherosclerosis. The risk assessed in Reynolds Risk Score, which in addition to the traditional risk factors also includes a family history of cardiovascular disease and hs-CRP levels shows that the hs-CRP determination only slightly contributes to the risk assessment determined solely on the basis of conventional risk factors (20). Despite the positive results of some studies and even meta-analyses about the value of hs-CRP when assessing the risk of cardiovascular events there are also numerous studies showing negative results. The results of meta-analyses of the value of cardiovascular biomarkers, which were not included in the Framingham score, showed that often the study results favored certain biomarkers and abused statistical tools to obtain positive results (21). For this reason, the hs-CRP determination in risk individuals has only a limited impact on cardiovascular risk assessment, and determination of hs-CRP in routine clinical practice is not recommended. Nevertheless, in healthy subjects who are at a medium-high risk of cardiovascular events the hs-CRP value between 1.0 and 3.0 mg/L represents a medium risk, and if the hs-CRP level is greater than 3.0 mg/L, these individuals are at high risk of cardiovascular events (22). On the other hand, there are different opinions regarding the indications for hs-CRP determination in this latter patient population, thus the latest European guidelines on the prevention of cardiovascular disease do not recommend hs-CRP determination (23).

hs-CRP has proven to be a reliable indicator of the effectiveness of the preventive and therapeutic measures that aim to reduce the risk of cardiovascular events. The JUPITER study (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) showed a concomitant proportional decrease in LDL cholesterol and hs-CRP levels. In addition, even in subjects with normal LDL cholesterol and increased hs-CRP values, statins significantly reduced the risk of cardiovascular events, which was directly proportional to the reductions of hs-CRP (24).

Interleukins play a key role in inflammatory response to stimuli and promote the synthesis of hs-CRP and fibrinogen in the liver. Among the most known and studied anti-inflammatory interleukins there are IL-6 and IL-8, whereas IL-10 possesses an anti-inflammatory activity and reduces the inflammatory response. Interleukins and their receptors have been found in atherosclerotic plaques. It has been demonstrated that the concentration of various cytokines in plasma is positively correlated with the risk of cardiovascular events, in particular of sudden coronary artery occlusions. Similarly, IL-6 values are increased in patients with peripheral arterial occlusive disease and their concentration increases with the progression of the disease. Several prospective studies have shown that increased IL-6 levels are associated with 2–3 times higher risk of cardiovascular events compared to subjects with normal IL-6 values (25). The determination of plasma levels of certain interleukins is important because interleukins are more specific indicators of inflammation of the vessel wall than other inflammatory

markers. Their concentration in plasma is closely related to the progression of atherosclerosis and the presence of unstable atherosclerotic lesions, which are a source of cardiovascular events. Unfortunately, due to unreliable laboratory methods and many factors affecting the level of the interleukin in plasma, the determination of interleukin concentrations has not been established as a method for the assessment of risk of cardiovascular events in everyday clinical practice.

5. Inflammation and venous thromboembolic disease

Recent data indicates that inflammation is involved also in the formation of venous thrombosis (VT). The damaged vessel wall is most likely the key factor that triggers the inflammatory response in VT. On the other hand, in idiopathic (unprovoked) VT inflammation is probably the primary event which triggers the activation of the coagulation system and blood clot formation. There is a close link between inflammation and hemostasis, which includes proinflammatory cytokines, chemokines, adhesion molecules, tissue factor, platelet and endothelial cell activation, and formation of microparticles. Inflammation increases the synthesis of the factors that accelerate coagulation, and inhibits the endogenous fibrinolytic activity thus encouraging the thrombotic process and blood clot formation. Besides, inflammation damages the defense mechanisms of endothelial cells; attenuates their anticoagulant and antiplatelet properties, and inhibits the vasodilator properties (26). At the same time, the activation of the coagulation system promotes inflammation. Thrombin stimulates the synthesis and excretion of proinflammatory cytokines and growth factors. Furthermore, platelets which are activated in the context of coagulation, also promote the inflammatory response. In one of our studies, we found that the patients with idiopathic VT had increased levels of inflammatory markers compared with healthy subjects (27). Long-term follow-up after 5 years showed that in the patients with idiopathic deep VT inflammatory markers such as hs-CRP, TNF-α, and IL-6 were still elevated, while the anti-inflammatory IL-10 was significantly reduced. Additionally, we found increased markers of endothelial damage (von Willebrand factor, P-selectin) (27). These findings indicate that increased levels of inflammatory markers in VT patients are not a consequence of VT, but are probably the cause of thrombosis formation avtorja, preverita pomen. Therefore, the values of inflammatory markers in these subjects remain continuously increased. Accordingly, inflammatory markers were studied as predictors of and as diagnostic criteria for the diagnosis of VT (28,29).

Opinions about the role of hs-CRP and VT formation are divided. Two large studies investigated the role of hs-CRP in the pathogenesis of VT. In the Physicians Health Study, including more than 22,000 American physicians, plasma hs-CRP levels were not significantly associated with the incidence of venous thromboembolism (VTE). The cause for the absence of statistical significance between hs-CRP levels and the occurrence of VT was most likely due to the low incidence of VT. During a 14-year follow-up, only 101 subjects developed VT. Similarly, in the Cardiovascular Health Study no relationship between hs-CRP levels and the development of deep VT was found (28). Neither was there a difference after the incidence of VTE in relation to the quartile of hs-CRP was adjusted by age, race, and gender. However,

hs-CRP has proved to be a useful test in the diagnosis of VT.

The role of hs-CRP in the diagnosis of VTE in individuals with suspected VTE has been investigated in several studies. Thomas and co-workers aimed at finding whether increased hs-CRP values would be useful in the identification of VTE (hs-CRP was defined as increased if the values were greater than 10 mg/L). The sensitivity of the increased hs-CRP value was 100 %, and specificity only 52 %, the positive predictive value was 56 %, and the negative predictive value 100 %. Their results indicated that low or normal hs-CRP values could be used for the exclusion of VTE in patients with suspected VTE, however, this was not confirmed in subsequent studies by Wong and co-workers (29). Hence, it has been concluded that hs-CRP values do not allow to confirm or to exclude the diagnosis of VTE in patients with clinical suspicion of this disease.

Inflammatory markers in VT include cytokines (interleukins, lymphokines, monokines), TNF-α, growth factors and alpha interferons. Interleukins, especially IL-6, followed by IL-8, and IL-10, were the most frequently studied in patients with VT.. Most of the research was done in patients with an acute VT. Van Aken noted that patients who had at least two episodes of VT had significantly higher values of IL-6 and IL-8 (30). The same group of researchers came to similar findings in the Leiden Thrombophilia Study (LTS). This study included 474 patients with VT and the same number of healthy subjects. It was found that patients had significantly higher IL-8 values, and that 90 % higher values of interleukin as compared to healthy subjects were related to 1.9 times higher risk, whereas a 99 % increase in IL-8 compared to control subjects was associated with a 6-fold higher risk of developing VT (31). The additional analysis of the LTS study confirmed IL-6, IL-8, and TNF-α to be ranked among the independent risk factors for VT (32). On the contrary, IL-10 was shown to have a protective role: individuals with higher IL-10 values were at a lower risk of VT compared to individuals with lower IL-10 values (2). Prehod A group of Dutch researchers observed interleukin values in the acute phase of VT, at the time of the first diagnosis and five days later. At the time of diagnosis, they found increased levels of IL-6, IL-8, and hs-CRP, whereas five days later the IL-6 and hs-CRP values were already significantly reduced, therefore they have concluded that inflammation is a consequence and not a cause of VT. The authors considered the reduction of clinical symptoms to be accompanied by a reduction of inflammatory markers. However, the reduction of inflammatory markers within five days after the onset of acute VT could also result from heparin treatment. Namely, heparin has been shown to possess an anti-inflammatory activity (33).

The prognostic importance of inflammatory markers, of interleukins in particular, was studied in a Norwegian prospective study (HUNT 2 – The Nord-Trøndelag Health Study). + ref Blood samples for inflammatory markers were taken from 66,140 healthy subjects; it was found that the levels of inflammatory markers (IL-1b, IL-6, IL-8, IL-10, and IL-12) did not differ from the subjects who developed VT during a three-year follow-up period when compared with the samples taken from people who were similar to the cases but had no thrombosis. On the basis of these results the authors have concluded that there is no evidence to support the hypothesis that increased inflammatory markers would be a risk factor of developing VT and that the alteration in the inflamma-

tory profile after VT is more likely to be the result and not the cause of VT (34). However, the flow of the study was the lack of data on inflammatory markers immediately (days or weeks) before the occurrence of thrombosis.

In our study, we found that the patients with idiopathic deep VT had increased levels of IL-6, and IL-8, and TNF- α also five years after the initial event. This indicates an increased inflammatory response present in a stable period (up to 5 years), suggesting that VT is not only an episodic event but a chronic condition which is accompanied by long-term systemic inflammatory changes. Although we did not have data about the levels of inflammatory markers immediately before the development of VT, the results of our study and data from other studies imply that this long-term increased inflammatory response is the cause of VT, and not caused by VT. A chronic inflammatory response could be explained by the processes taking place in the thrombosed vein directly after an acute event. The acute occlusion is certainly accompanied by inflammation, followed by a breakdown of a blood clot and/or connective tissue organization. Inflammatory cells are present in both later processes and are probably responsible for maintaining the inflammatory process in the venous wall. VT is only rarely followed by a complete healing of the vessel wall and a total restitution of physiological conditions through a previously thrombosed vein. This is probably also one of the reasons why individuals with VT have long-term increased markers of inflammation.

Inflammation plays an important, perhaps even a decisive role, in recanalization of venous thrombotic occlusions. The relationship between the elevated systemic markers of inflammation (IL-6) and resolution of the blood clot that is associated with the occurrence of the postthrombotic syndrome, was described by Dutch authors (35).

6. A connecting role of inflammation in the pathogenesis of arterial and venous vascular disorders

The association between arterial atherosclerotic and venous thromboembolic disease was first suggested by studies where inflammation was recognized as one of the basic pathogenic mechanisms. Several studies found a link between VT and preclinical atherosclerosis, such as asymptomatic atherosclerotic plaques in carotid arteries and endothelial dysfunction observed in both diseases (4,36). Moreover, atherosclerosis as well as VTE, share many common risk factors for which inflammation represents the common denominator of its harmful action on the vessel wall (37).

The risk factors for atherosclerosis and VTE are both classical and non-conventional. For example, increasing age increases the risk of both diseases, increased body weight is related to increased risk of VTE and atherosclerosis. Recent data have shown that hypercholesterolemia as one of the most important risk factors for atherosclerosis increases the risk of VTE, and also increased blood pressure and hyperhomocysteinemia are positively correlated with VTE (38). Significantly related to VTE are mainly metabolic risk factors for atherosclerosis, such as obesity, hypertriglyceridemia and reduced HDL-cholesterol (39). A significant risk factor for both diseases is also the metabolic syndrome which is involved in the pathogenesis of atherosclerosis and VTE via inflammation and increased levels of plasminogen-activator inhibitor (40).

7. Inflammation as a challenge for new therapeutic approaches in cardiovascular diseases

Although it has long been known that atherosclerosis is a chronic inflammatory disease, little attention was given to the anti-inflammatory treatment of atherosclerosis. Low-dose aspirin and certain other antiplatelet agents prescribed to patients at risk for atherosclerosis for several decades, but the main focus for the prescription of these drugs has been their antiplatelet and antithrombotic activity and not their anti-inflammatory effects. Recently, anti-inflammatory effects have been recognized in some drugs that primarily do not possess an anti-inflammatory activity, such as statins. The JUPITER trial (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial) has shown that the preventive effects of statins are linearly associated with their anti-inflammatory effects, therefore, they are effective in subjects who have normal LDL cholesterol levels but increased hs-CRP levels. Their anti-inflammatory effect has been associated with a reduction in the levels of inflammatory mediators, hs-CRP in particular, regardless of the changes in the cholesterol level (41). This indicates that in the prevention and treatment of atherosclerosis more attention should be paid to anti-inflammatory actions and the selection of drugs that have a more pronounced anti-inflammatory effect.

For the acute treatment of deep vein thrombosis (DVT), anticoagulant drugs have proved to be more effective than aspirin. On the other hand, several studies have reported that aspirin and perhaps other drugs with anti-inflammatory effects as well, if prescribed to patients with a history of DVT for the long-term prevention of DVT, may reduce DVT recurrence (42). In a randomized, placebo-controlled study it has been shown that the treatment with 100 mg aspirin daily after the discontinuation of anticoagulant therapy (6 to 8 months after the DVT diagnosis) reduces the risk of DVT recurrence for up to 40 %. There is also evidence that statins, the basic antiatherosclerotic drugs, may also reduce the risk of VTE. Their preventive effect on the risk of DVT has been supposed based on the cholesterol-independent, parallel (pleiotropic) effect of statins, particularly the anti-inflammatory effects (43). Similarly, the results of two meta-analyses have pointed to the effectiveness of statins in the prevention of VTE, specifically in subjects with high hs-CRP and normal lipid values (44,45). Likewise, the INSPIRE collaboration (International Collaboration of Aspirin Trials for Recurrent Venous Thromboembolism) has concluded that aspirin after anticoagulation treatment reduces the overall risk of VTE recurrence by more than one third in a broad cross-section of patients with a first unprovoked VTE, without significantly increasing the risk of bleeding (46).

Based on these facts the question arises whether a combination of anticoagulant and anti-inflammatory drugs in the acute phase of DVT treatment might be more effective than anticoagulant drugs alone. The administration of aspirin, which has anti-inflammatory effects, together with anticoagulant drugs in the acute phase of DVT might improve the recanalization of thrombotic venous occlusions and thereby prevent the development of postthrombotic syndrome, which is known to be more common in case of chronically occluded veins, and dramatically reduces patients quality of life.

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