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REVIEW

The Role of Renin-Angiotensin System in Prothrombotic State in Essential Hypertension

A. REMKOVÁ[1], M. REMKO[2]

[1]Department of Internal Medicine, Military Hospital, Bratislava, Slovak Republic, [2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University, Bratislava, Slovak Republic

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Summary

Rheological, haemostatic, endothelial and platelet abnormalities appear to play a role in the thrombotic complications of hypertension. This prothrombotic/hypercoagulable state in hypertension may contribute to the increased risk and severity of target organ damage. It can be induced by the activated renin-angiotensin system (RAS), with abnormalities in endothelial and platelet function, coagulation and fibrinolysis. Treatment of uncomplicated essential hypertension by RAS targeting antihypertensive therapy could result in a reversal of prothrombotic abnormalities, contributing to a reduction of thrombosis-related complications. Since angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have two distinct mechanisms of RAS interruption, it is hypothesized that each therapy might have different impact on the prothrombotic state in hypertensive patients. Some studies demonstrate a beneficial effect of both ACE inhibitors and ARBs on prothrombotic state, in addition to their efficacy to normalize elevated blood pressure. The potentially antithrombotic effect of the RAS inhibiting agents may in turn support the preservation of cardiovascular function. Available data may offer an additional explanation for the efficacy of the RAS targeting agents in the prevention of cardiovascular events in patients with atherosclerotic vascular disease.

Key words

Endothelium • Platelet • Coagulation • Fibrinolysis • Hypertension

Corresponding author

Anna Remková, Nemocnica Ministerstva obrany SR, a.s., Cesta na Červený most 1, 833 31 Bratislava 37, Slovak Republic. E-mail: remkova@gmail.com

Introduction

Hypertension is a major risk factor for thrombotic events such as myocardial infarction and stroke, reflecting a prothrombotic state that is present in hypertensive patients. A number of rheological, haemostatic, endothelial and platelet abnormalities appear to play a role in the thrombotic complications of hypertension. This prothrombotic/hypercoagulable state in hypertension may contribute to the increased risk and severity of target organ damage (Sechi *et al.* 2000, Nadar *et al.* 2004a, Spencer *et al.* 2004, Sechi *et al.* 2008, Tay and Lip 2008). Moreover, markers of a hypercoagulable state may predict subsequent cardiovascular events in hypertensives (Lip *et al.* 2002).

A growing body of evidence indicates that prothrombotic state can be induced by the activated renin-angiotensin system (RAS), which is more pronounced in hypertension. Numerous deleterious effects of angiotensin II, including vasoconstriction, sympathetic nervous activation, smooth muscle cell growth and proliferation, vascular inflammation, generation of reactive oxygen species and endothelial dysfunction are mediated through the angiotensin II type 1 (AT_1) receptor (Fig. 1). Angiotensin II opposes the effect of nitric oxide, stimulates the production of adhesion factors and plasminogen activator inhibitor-1 (PAI-1), promoting thus the risk of thrombosis. It was demonstrated that angiotensin II and aldosterone interact synergistically to increase PAI-1 production in humans (Sawathiparnich *et al.* 2003). Previous studies have

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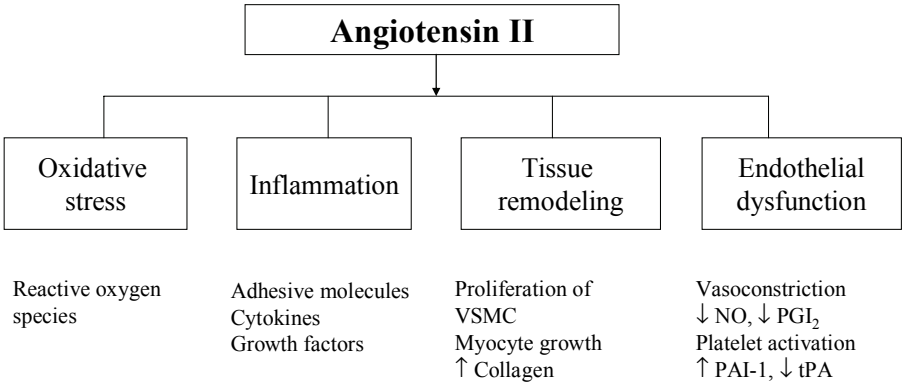

Fig. 1. Pathophysiologic effects of angiotensin II. VSMC – vascular smooth muscle cells, NO – nitric oxide, PGI_2 – prostacyclin, PAI-1 – plasminogen activator inhibitor type 1, tPA – tissue type plasminogen activator.

attempted to define the relative contribution of renin and aldosterone to the induction of the prothrombotic state. A significant relationship between plasma renin activity (PRA) and plasma aldosterone with markers of activated coagulation and decreased fibrinolytic activity was demonstrated in patients with essential hypertension. Elevated levels of PRA, aldosterone, and prothrombotic markers are associated with clinical and instrumental evidence of cardiac and renal hypertensive organ damage (Sechi *et al.* 2008).

The RAS plays an important role in the pathogenesis of atherosclerotic complications. It can influence not only vascular tone, but also disturb the balance of the haemostatic system, with abnormalities in endothelial and platelet function, coagulation and fibrinolysis (Sakata et al. 2002, Dielis et al. 2007). Therefore, it is of importance to regulate not only blood pressure (BP), but also the haemostatic system in the long-term antihypertensive therapy. From this point of view, the treatment of uncomplicated essential hypertension by RAS inhibition-based antihypertensive therapy could result in a reversal of prothrombotic abnormalities, contributing to a reduction in thrombosis-related complications.

Evidence for the protective role of some RAS targeting agents against atherothrombotic cardiovascular disease is accumulating. A precise mechanism of their ability to prevent thrombotic events is of particular interest. Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 (AT_1) receptor blockers (ARBs) effectively decrease blood pressure, but it seems that there could be some differences in clinical outcome, which may be partly related to their effect on haemostatic abnormalities. Since ACE inhibitors and ARBs have two distinct mechanisms of RAS interruption, it is hypothesized that each therapy might have different impact on the prothrombotic state in hypertensive patients.

Laboratory markers of prothrombotic state in hypertension

Laboratory markers of endothelial and platelet function, as well as markers of hypercoagulation and fibrinolytic activity can be used to document a prothrombotic state in hypertension. For example, plasma von Willebrand factor (vWF) and thrombomodulin (TM) are used as indicators of endothelial dysfunction and/or damage. Plasma β-thromboglobulin (βTG), platelet factor 4 (PF4), soluble P-selectin (sPsel) or soluble glycoprotein V (sGpV) can be measured as indicators of *in vivo* platelet activation. Plasminogen activator inhibitor type 1 (PAI-1) and tissue type plasminogen activator (tPA) antigens are used mainly as indicators of fibrinolytic activity, but partly also as markers of endothelial function. Soluble endothelial protein C receptor (sEPCR) is a new marker of hypercoagulation. Fibrinogen as a crucial component of coagulation system can be investigated as a risk factor for vascular changes. In our previous studies, a statistically significant increase of vWF, TM, βTG, sPsel, sGpV, platelet aggregation, PAI-1 antigen, tPA antigen, sEPCR and fibrinogen levels in untreated patients with the early stages of mild-to-moderate essential hypertension compared to healthy subjects was found (Remková and Kratochvílová 2002, Remková *et al.* 2008).

It is known that vWF mediates platelet adhesion to the vascular wall, platelet aggregation and serves as a plasma carrier for factor VIII. Most circulating vWF is derived from the endothelium. Blann *et al.* (1993) were

the first to describe raised vWF in essential hypertension. Now, vWF is considered to be the gold standard plasma endothelial marker, indicating a state of endothelial dysfunction/damage or activation. It has also attracted considerable interest as a predictor of cardiovascular disease (Spencer *et al.* 2004, Lee *et al.* 2005, Vischer 2006, Ceconi *et al.* 2007). Some findings in hypertension suggest that thrombomodulin, another marker of endothelial cell injury, is released into the plasma only by true endothelial cell damage during development of vascular complications and probably a certain degree of endothelial injury is necessary for its plasma increase (Okrucká-Remková *et al.* 1998, Remková *et al.* 2000, Remková and Kratochvílová, 2002).

Plasma βTG and PF4, platelet-specific proteins released from the α-granules, are established markers of platelet activity. Both sPsel and sGpV are considered to be another plasma markers of *in vivo* platelet activation. The adhesion molecule P-selectin has a role in modulating interactions between blood cells and the endothelium. It is a component of the membrane of alpha granules and dense granules of platelets, and also of the membrane of the Weibel-Palade bodies of endothelial cells. Although present on the external cell surface of both activated endothelium and activated platelets, it now seems clear that most, if not all of the measured sPsel, is of platelet origin (Blann *et al.* 2003). Increased levels of sPsel in the plasma have been demonstrated in a wide variety of acute and chronic cardiovascular and cerebrovascular disorders, including hypertension. The increased sPsel can be considered as a predictor of adverse cardiovascular events (Riondino *et al.* 1999, Blann *et al.* 2003, Nadar *et al.* 2004a,b,c, Spencer *et al.* 2004, Lee *et al.* 2005). Soluble GpV is cleaved from the platelet membrane surface by thrombin. While bound to the platelet membrane, GpV is associated with GPIb and GpIX to form the platelet GpIb-V-IX complex, which mediates platelet adhesion to the subendothelium by binding von Willebrand factor. Soluble GpV is significantly elevated in patients with atherothrombotic diseases (Blann *et al.* 2001, Wolff *et al.* 2005).

Fibrinolytic activity is determined by the balance between the levels of tPA and PAI-1, both of which are synthesized in the vascular endothelium, and endothelial injury induces an imbalance in fibrinolysis (Tomiyama *et al.* 1998). Besides endothelial cells, PAI-1 which is a strong inhibitor of fibrinolysis, is produced mainly by adipose tissue (including the liver steatosis). Among haemostatic abnormalities, an increase of PAI-1 is considered as a core feature of metabolic syndrome, and obesity is a main determinant of plasma PAI-1 concentrations (Aso *et al.* 2005). Data from the Framingham Offspring Study showed that increased PAI-1 antigen and tPA antigen levels are independently associated with hypertension (Poli *et al.* 2000). High concentrations of tPA antigen also reflect impairment of the fibrinolytic system, because most of the tPA antigen measured is complexed with PAI-1 and is inactive. These data suggest that impaired fibrinolysis may play an important role in the pathogenesis of cardiovascular disease in hypertensive patients. The mechanism by which increasing BP may result in impaired fibrinolysis is unclear, but it may be related to endothelial dysfunction. It is known that angiotensin II (*via* AT_1 receptor) stimulates the expression of PAI-1, resulting in an increase of PAI-1 release from endothelial cells (Sakata *et al.* 2002, Koh *et al.* 2004, Dielis *et al.* 2007). However, it was demonstrated that angiotensin IV, which is a metabolite of angiotensin II, can stimulate PAI-1 expression from endothelial cells (Ruiz-Ortega *et al.* 2007). Angiotensin IV has drawn a lot of attention since it exerts a wide range of distinct biological effects, including protection against cerebral ischaemia, activity at the vascular level and an involvement in atherogenesis. It is involved in the vascular inflammatory response because it regulates cell growth, activates the adhesion molecules and the cytokines. Some of these effects are AT_1 receptor-dependent but others most likely result from binding of angiotensin IV to a specific AT_4 receptor, which has recently been identified as the membrane-bound insulin-regulated aminopeptidase (IRAP). This protein appears to have multiple physiological roles that are tissue-specific. The exact mechanisms of action that mediate the angiotensin IV-induced effects following this binding are still not fully known (Ruiz-Ortega *et al.* 2007, Stragier *et al.* 2008).

Recently, the first evidence was offered that hypertension could contribute to the increased sEPCR levels (Remková *et al.* 2008). EPCR is a transmembrane glycoprotein restricted to the endothelium, which activates protein C *via* the thrombin-TM complex. Unlike TM, it is expressed mainly on the endothelium of large vessels. The previous studies confirm an *in vivo* function of sEPCR in the regulation of coagulation in humans (Saposnik *et al.* 2004). The release of sEPCR is inducible by inflammation and/or thrombin generation. Increased sEPCR levels may be prothrombotic (Saposnik *et al.* 2004). Lower sEPCR levels reflect a decrease of

thrombin generation. In patients free of evident inflammatory disease, plasma levels of sEPCR can be a potential marker for the prothrombotic state and a predictor of cardiovascular disease in hypertensives (Remková *et al.* 2008).

It is known that hypertensives demonstrate abnormalities of rheological function. Plasma fibrinogen and vWF are important determinants of blood viscosity and are involved in haemostasis. Elevated levels are found in patients with hypertension and there is considerable evidence indicating that they are independent predictors of cardiovascular disease. High plasma levels of fibrinogen observed in hypertensives are in agreement with a prothrombotic or hypercoagulable state in hypertension (Spencer *et al.* 2004, Remková *et al.* 2008). The highest levels of fibrinogen are found in nondipper patients with concurrent high ambulatory pulse pressure (Lee *et al.* 2005). Plasma fibrinogen is significantly related to the presence and severity of target organ damage in patients with essential hypertension and may contribute to the development of atherosclerotic disease in these patients (Sechi *et al.* 2000, 2008).

Effect of RAS inhibition on prothrombotic state in hypertension

Modern antihypertensive therapy has focused not only on BP control but also on the favorable modification of known prognostic indices, such as endothelial and platelet dysfunction or coagulation and fibrinolytic abnormalities.

In our previous study, besides a normalization of high BP in hypertensive patients, a significant decrease of plasma vWF antigen, sPsel, sGpV, PAI-1 antigen and tPA antigen level after one month of perindopril therapy, as well as a significant decrease of sEPCR and fibrinogen level after one month of telmisartan therapy was observed (Remková *et al.* 2008). This finding can document a beneficial effect of both treatment strategies on prothrombotic state in hypertensive patients.

A decrease of vWF after perindopril therapy can indicate the improvement of endothelial function in patients with hypertension. In contrary, no significant changes of vWF in hypertensives treated by telmisartan were found (Remková *et al.* 2008). This finding is supported by results of another study, in which only antihypertensive treatment by perindopril but not telmisartan was able to improve conduit artery endothelium-dependent vasodilatation (Ghiadoni *et al.* 2003). It could be hypothesized that this beneficial effect of perindopril may be related to bradykinin-dependent mechanisms (Taddei *et al.* 2002). Although many clinical studies have found that ACE inhibitors improve endothelial function, it is not clear whether ARBs have beneficial effects comparable to those of ACE inhibitors (Matsumoto *et al.* 2003). A possible vascular and anti-atherosclerotic effect of long-lasting ACE inhibition by perindopril, as shown in different experimental and other studies, was the background hypothesis for *EUROPA* study (Ferrari *et al.* 2003). The *EUROPA* study demonstrated reduction in cardiovascular mortality and myocardial infarction with ACE inhibition by perindopril in patients with coronary artery disease, including even stable patients at lower risk. The positive outcome occurred also in patients with normal blood pressure and was not related to the degree of blood pressure reduction achieved by the drug (EUROPA Trial Investigators 2003). In order to verify the mechanism of action of perindopril in secondary prevention, *PERTINENT* substudy examined the effects of perindopril on endothelial function, thrombosis, and inflammation (Ceconi *et al.* 2007). Data from *PERTINENT* suggest that long-term (1 year) ACE inhibition with perindopril 8 mg/day exerts a direct positive effect on the vascular endothelium. At baseline, vWF was at the upper limit of the normal values and even more elevated in the diabetic patients, indicating endothelial damage. Furthermore, vWF levels were correlated with prognosis, and one year of treatment with perindopril significantly reduced them independently from other risk factors. These data in patients with coronary artery disease do not provide information on whether long-term administration of perindopril is needed or whether this can be the result of an acute effect. The results of a later study demonstrate that also a short-term, i.e. one-month administration of perindopril in a half of the dose used in *EUROPA* study, has a benefit on endothelial function, even in patients with lower risk, without manifest coronary artery disease (Remková *et al.* 2008).

In early-stage hypertensive patients without microalbuminuria, which is also a marker of widespread endothelial dysfunction, only borderline changes in untreated hypertensives and no changes in plasma TM can be found during short-term treatment by perindopril or telmisartan (Remková *et al.* 2008).

Antihypertensive treatment by perindopril but not by telmisartan was reported to reduce platelet activation, with a decrease of sPsel and sGpV (Remková

et al. 2008). In the other study, normalization of BP in elderly hypertensives with an ACE inhibitor and/or a calcium antagonist resulted in a reduction in plasma levels of sPsel (Riondino *et al.* 1999). The improvement of platelet function in hypertensives treated by perindopril is in accordance with previous findings of decreased platelet aggregation in a similar group of treated patients (Okrucká-Remková *et al.* 1998). These results suggest that increased platelet activation need not be restored to normal after effective antihypertensive therapy alone (Okrucká-Remková *et al.* 1998). Indirectly, these findings can reflect a protective effect of perindopril on the vascular wall, with improvement of endothelial function. This hypothesis is likely supported by findings that perindoprilat enhances inhibition of platelet activation by human umbilical vein endothelial cells (HUVEC). Enhanced endothelial anti-platelet properties (greater amount of prostacyclin released) were able to stabilize platelets, making them less responsive to agonists in an *ex vivo* situation (Kishi *et al.* 2003). Thus, perindopril exhibited the ability to inhibit platelet aggregation by augmenting endothelial anti-platelet mechanisms. On the other hand, candesartan had no effects on inhibition of platelet aggregation by HUVEC (Kishi *et al.* 2003). Since human platelets have been demonstrated to express angiotensin II (AT_1 type) receptor, the action of ACE inhibitor on the platelets could be related to angiotensin II blockade. However, exogenous angiotensin II does not modify platelet activation (Montón *et al.* 2000). These results suggest that some RAS antagonists reduce platelet activation independently of angiotensin II involvement. Platelet activation may also be suppressed, in the presence of intact endothelial cells, through increased prostacyclin and nitric oxide (NO) release, induced by elevated bradykinin levels due to ACE inhibition. This last mechanism is absent in patients treated by ARB. Actually, telmisartan therapy failed to show any changes in platelet markers of hypertensive patients (Remková *et al.* 2008). Drugs such as RAS targeting agents possess some sympathoinhibitory effect. A subsequent reduction of catecholamine release could be a further factor for a favorable effect on platelet function in patients with essential hypertension.

The ARBs may impair the fibrinolytic system due to increased angiotensin IV, which results from an increase in angiotensin II (Sakata *et al.* 2002). The ACE inhibitors are thought to favorably affect the fibrinolytic balance by decreasing angiotensin II-mediated PAI-1 release and/or by increasing bradykinin-induced tPA release from endothelial cells (Matsumoto *et al.* 2003). Modification of the hypofibrinolytic state may have a beneficial effect on the increased cardiovascular risk in subjects with hypertension. It was reported that perindopril increases the ability of bradykinin to stimulate the release of tPA in the human coronary circulation, which is not seen with losartan (Matsumoto *et al.* 2003). According to several comparative studies, using two therapeutic regimens, ACE inhibition may have greater beneficial effects than AT_1 receptor antagonism (Matsumoto *et al.* 2003). For instance, in hypertensive postmenopausal women, the PAI-1 antigen levels were significantly decreased by trandolapril, but not by losartan therapy (Fogari *et al.* 2001a).

To date, controversial results have been reported in both experimental and clinical studies about the effect of ARBs (with different pharmacokinetic and pharmacodynamic properties) on fibrinolysis, with some studies showing no influence and others a reduction or even an increase of PAI-1 levels (Fogari *et al.* 2001b, Erlinger *et al.* 2002, Koh *et al.* 2004, Dielis *et al.* 2007). The reason for these differences is not clear, but it might be related to the different inhibitory characteristic of the various ARBs. One possible explanation for the lack of effect on fibrinolysis by some ARBs might be that receptor subtypes other than AT_1 mediate the effect of angiotensin II on endothelial PAI-1 expression. In fact, there have also been conflicting findings on the effects of ACE inhibitors on fibrinolysis. In general, they may result from the study population and design, such as drug dosage etc. (Sakata *et al.* 2002). It was shown that perindopril enhances fibrinolysis (with a decrease of PAI-1 as well as tPA antigens), but telmisartan does not attenuate fibrinolysis in essential hypertension (Remková *et al.* 2008). These different effects of each drug on fibrinolysis appear to be associated with the changes in angiotensin metabolites. The results are in accordance with findings of other authors, showing that levels of PAI-1 antigen are reduced after antihypertensive treatment with perindopril (Erdem *et al.* 1999, Fogari *et al.* 2002). On the other hand, it was reported that expression of PAI-1 was *in vitro* attenuated by telmisartan in cultured mesangial cells, possibly owing to its lipophilic and antioxidant properties (Shao *et al.* 2007).

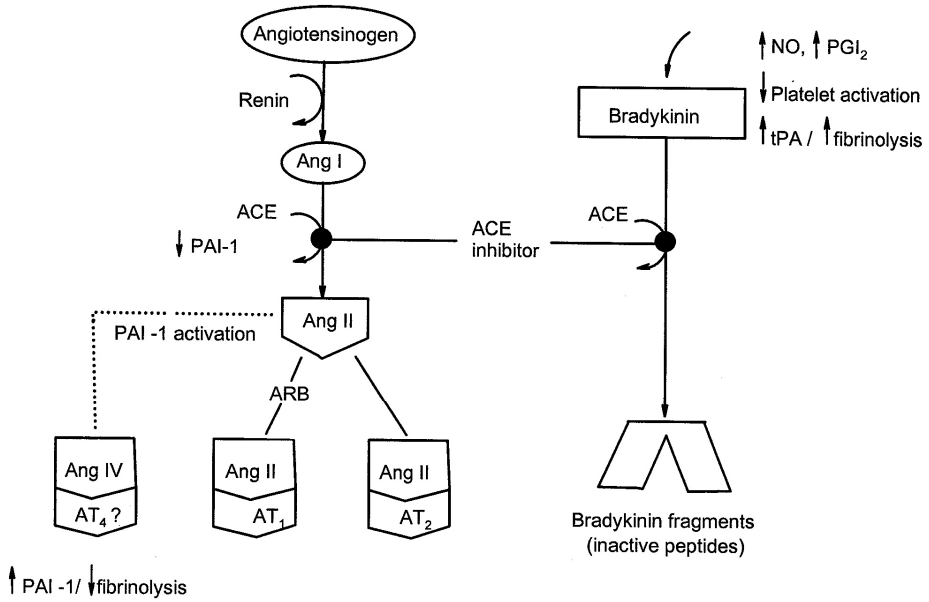

Fig. 2. The effect of ACE inhibitors and angiotensin II (AT_1) receptor blockers (ARB) on haemostasis. ACE – angiotensin converting enzyme, Ang – angiotensin, PAI-1 – plasminogen activator inhibitor type 1, tPA – tissue plasminogen activator, NO – nitric oxide, PGI_2 – prostacyclin. The accumulation of bradykinin due to ACE inhibition induces NO and PGI_2 release with antiplatelet effect and tPA release with increase of fibrinolysis. This mechanism is absent in ARBs. Inhibition of Ang II formation due to ACE inhibition decreases PAI-1 release. In contrary, ARBs through the increase of Ang IV stimulate PAI-1 release, followed by a decrease of fibrinolysis.

According to a finding of decreased sEPCR due to telmisartan therapy, it is probably possible to improve the prothrombotic state in hypertensive patients (Remková *et al.* 2008). The mechanism of this effect is not clear; but because the EPCR is expressed mainly on the endothelium of large arteries, a speculation about the improvement of their functional properties can arise as explanation.

Previous studies examining the influence of therapeutic intervention on fibrinogen plasma levels have shown conflicting results. For example, treatment with either irbesartan or atenolol (Makris *et al.* 2000) and with telmisartan (Remková *et al.* 2008) in hypertensive patients was associated with a significant decrease in the levels of fibrinogen, but no changes of fibrinogen were observed in 20 subjects with insulin resistance after telmisartan administration (Nagel *et al.* 2006). In another studies in hypertensive patients, plasma fibrinogen levels were reduced by perindopril (Fogari *et al.* 1998) but not by losartan (Fogari *et al.* 1998, Li-Saw-Hee *et al.* 2001). On the other hand, no changes of fibrinogen level were found in another studies in hypertensive patients after treatment by enalapril (Li-Saw-Hee *et al.* 2001) or perindopril (Remková and Kratochvíľová 2000, Remková *et al.* 2008). It has not yet been determined whether the decrease in fibrinogen levels, whenever observed, is related directly to BP reduction or is associated with coexisting properties of the drugs used. It has been suggested that it may result from hemodilution caused by vasodilating agents or by a decrease in red cell rigidity (Makris *et al.* 2000). The supposed mechanisms of the effect of therapy by RAS inhibiting agents on prothrombotic state are shown in Figure 2.

There is only scarce information about the effect of other RAS targeting agents, i.e. aldosterone receptor antagonists and renin inhibitor on haemostatic markers in hypertension. Spironolactone through mineralocorticoid receptor antagonism prevents the effect of activation of the RAS on PAI-1 antigen in normotensive subjects and improves fibrinolytic balance in hypertensive subjects. In hypertensive patients, spironolactone significantly decreased PAI-1 antigen (Ma *et al.* 2005). In experimental chronic heart failure model, spironolactone added to an ACE inhibitor trandolapril beneficially modulates the balance of nitric oxide and superoxide anion formation (Bauersachs *et al.* 2002). In a similar experimental model, monotherapy with ACE inhibitor trandolapril or with selective aldosterone receptor antagonist eplerenone partially reduced the increased platelet activation, which was completely reduced to basal levels by combination therapy (Schäfer *et al.* 2003).

Table 1. The effect of renin-angiotensin system (RAS) targeting agents on prothrombotic state in hypertensive patients. ACE – angiotensin converting enzyme, ARBs – angiotensin II receptor blockers, PAI-1 – plasminogen activator inhibitor type 1, tPA – tissue type of plasminogen activator, sEPCR – soluble endothelial protein C receptor.

Markers	RAS inhibiting agents	Effect	Mechanism
Endothelial function	ACE inhibitors	Beneficial (benazepril -Tomiyama *et al.* 1998, perindopril - Erdem *et al.* 1999, Ghiadoni *et al.* 2003, Ceconi *et al.* 2007, Remková *et al.* 2008, quinapril - Hlubocká *et al.* 2002) or neutral (cilazapril - Trifiletti *et al.* 1997)	Bradykinin-dependent mechanism
	ARBs	Neutral (losartan - Matsumoto *et al.* 2003, telmisartan - Ghiadoni *et al.* 2003, Remková *et al.* 2008)	Bradykinin-dependent mechanism is absent
Platelet function	ACE inhibitors	Beneficial (perindopril - Okrucká *et al.* 1998, Riondino *et al.* 1999, Kishi *et al.* 2003, Remková *et al.* 2008, trandolapril - Schäfer *et al.* 2003) or neutral (cilazapril -Trifiletti *et al.* 1997, quinapril - Hlubocká *et al.* 2002)	Enhanced endothelial antiplatelet properties (increased prostacyclin and nitric oxide release) induced by elevated bradykinin levels
	ARBs	Neutral (candesartan - Kishi *et al.* 2003, telmisartan - Remková *et al.* 2008)	This mechanism is absent
Fibrinolysis	ACE inhibitors	Beneficial (benazepril - Tomiyama *et al.* 1998, perindopril - Erdem *et al.* 1999, Fogari *et al.* 2002, Matsumoto *et al.* 2003, Remková *et al.* 2008, trandolapril - Fogari 2001a, quinapril - Sakata 2002) or neutral (cilazapril - Trifiletti *et al.* 1997)	Inhibition of angiotensin II-mediated PAI-1 release and/or stimulation of bradykinin induced tPA release from endothelial cells
	ARBs	Neutral (losartan - Fogari *et al.* 2001a, Fogari *et al.* 2001b, Matsumoto *et al.* 2003, valsartan, irbesartan - Fogari *et al.* 2001b, eprosartan -Dielis *et al.* 2007, telmisartan - Remková *et al.* 2008) or even harmful (candesartan - Fogari *et al.* 2001b, losartan - Sakata *et al.* 2002, Erlinger *et al.* 2002, Koh *et al.* 2004)	Increased angiotensin IV (due to angiotensin II increase) and its effect on endothelial PAI-1 expression and increase of PAI-1 levels
Fibrinogen	ACE inhibitors	Neutral (perindopril - Remková and Kratochvíľová 2000, Remková *et al.* 2008, enalapril - Li-Saw-Hee *et al.* 2001) or even beneficial (perindopril - Fogari *et al.* 1998)	Unknown mechanism, probably hemodilution due to vasodilation or decrease in blood cell regidity
	ARBs	Neutral (losartan - Fogari *et al.* 1998, Li-Saw-Hee *et al.* 2001, telmisartan - Nagel *et al.* 2006) or even beneficial (irbesartan - Makris *et al.* 2000, telmisartan - Remková *et al.* 2008)	
Other sEPCR	ACE inhibitors	Neutral (perindopril - Remková *et al.* 2008)	
	ARBs	Beneficial (telmisartan - Remková *et al.* 2008)	Unknown mechanism (improved function of large arteries?)

In vitro effects of a renin inhibitor aliskiren on a total of 33 biomarkers of platelet activity, coagulation and fibrinolysis were assessed in subjects with multiple risk factors for vascular disease. In the therapeutic concentration, aliskiren does not affect haemostatic markers *in vitro* (Serebruany *et al.* 2008). It is suggested that antithrombotic properties of aliskiren should be explored further in an *ex vivo* clinical setting.

In conclusions, available data may offer an additional explanation for the efficacy of the RAS targeting agents in the prevention of cardiovascular events in patients with atherosclerotic vascular disease (Table 1). Some studies demonstrate a beneficial effect of both ACE inhibitors and ARBs on prothrombotic state, in addition to their efficacy to normalize elevated BP. Despite the results of these studies, the possible role of blood pressure lowering effect on prothrombotic state should be always kept in mind. The potentially antithrombotic effect of the RAS targeting agents may in turn support the preservation of cardiovascular function.

Conflict of Interest

There is no conflict of interest.

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