The role of angiotensin receptor 1 blockers in restenosis prevention after percutaneous coronary interventions

Znaczenie blokerów receptora angiotensyny 1 w zapobieganiu restenozie po przezskórnych interwencjach wieńcowych

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Atherosclerosis as systemic inflammatory fibroproliferative disease is the leading cause of death nowadays (according to the last World Health Organization report, in 2003, 16.3 million people died because of coronary, cerebrovascular or peripheral vascular disease). Despite that disease is systemic, the main adverse effects are consequences of local stenotic lesions appearing in arterial vessels with a medium and large calibre, compromising distal flow and causing ischemia. The heart and coronary arteries are main targets of atherosclerosis with most frequent results including stable angina, acute coronary syndromes, sudden cardiac death and ischemic cardiomyopathy. Medical treatment plays the basic role in symptom control and improving long-term prognosis. Unfortunately, even with maximal and optimal medical therapy, symptom control could be achieved in no more than 70% of patients, according to the most recent COURAGE results (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) [1].

In 1977, Andreas Grüntzing introduced percutaneous transluminal coronary angioplasty (PTCA), widening coronary artery stenosis with a small balloon. This resulted in a new era in coronary artery disease (CAD) treatment. The method became popular very fast, mainly because of its low invasiveness in comparison with standard coronary surgery. However, it became clear very early that the method had one significant weakness, i.e. the restenosis is about 30-50%, depending on the lesion type [2]. As a solution to this problem intravascular implantation of a stainless steel prosthesis with mesh construction was proposed, i.e. so popular coronary stent (named after Charles Stent, an English dentist, who made first tooth moulds at the end of the 19th century). At the beginning the coronary stent was proposed as a solution to acute closure appearing during balloon angioplasty (result of coronary spasm, dissection or thrombus) [3]. The first stent was implanted in 1986, but only in 1994 the stent was approved for human application. This was due to published data from BENESTENT [4] and STRESS [5] studies. They demonstrated that stents can eliminate immediate PTCA complications and decrease restenosis by 10-20%. The risk of restenosis still persists even after stent implantation and with the last generation bare metal stents (BMS) it is around 20% at 6 months. This fact stimulated researchers to reveal restenosis mechanisms and determine how to eliminate this event. There are two approaches – local and systemic medical inhibition of endothelial proliferation and synthetic activity. Thus, the drug eluting stents were created with exciting early results of zero restenosis [6]. Later it appeared that real life restenosis (except for highly selected patient populations in randomized studies) is around 5-10% with a generally accepted rate of stent thrombosis of 0.6% per year [7].

The second approach to in-stent restenosis prevention is the systemic application of drugs generally inhibiting responsible mechanisms. The systemic approach, however, brings about side effects of applied drugs. There are two groups of drugs that have a positive effect on cardiovascular mortality and can positively influence the restenotic process – HMG-CoA reductase inhibitors (statins) and angiotensin receptor 1 blockers, which are the subject matter of our further interest.

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Pathophysiological mechanisms of restenosis and the role of angiotensin receptor 1 blockers

The restenosis after PTCA is a maladaptive complex process in response to the mechanical damage caused by intervention, which mechanism is not completely understood. The main reason is the lack of a reliable animal model enabling examination of the real process of vessel healing after damage. It is important to underline that the restenosis after PTCA (30-50%), BMS (20-30%) and DES implantations is a similar process, but there are important differences. Three main mechanisms of restenosis are elastic recoil, neointima proliferation and early thrombotic formation. After balloon angioplasty the main mechanism is elastic recoil, while after stent implantation the endothelial proliferation is the leading mechanism [8]. The elastic recoil was eliminated after stent introduction. Immediately after stent implantation there is platelet and thrombin deposition around stent struts. They persist around 14-30 days after the procedure [9]. During the first three days, the local inflammatory process is activated with monocyte infiltration and differentiation to macrophages under the action of M-CSF (monocyte colony stimulating factor). They start to secrete different types of chemokines attracting different subpopulations of T lymphocytes and promoting expression of different adhesion molecules on the endothelial cell surface. Macrophages persist at the implantation place up to 3 months after the procedure. The peak T lymphocyte concentration is obtained in the 2nd and 3rd weeks and they persist there until the 6th month, sometimes even longer. The initial vessel reparation consists of thrombus organization with smooth muscle cell migration and proliferation (generally after week 2) and start to produce a large amount of extracellular matrix – mainly proteoglycans and collagen type 3, which is replaced from type 1 up to the 12th month after stenting. In fact, the main content of neointima is extracellular matrix [8, 9].

Table I. Restenosis predictors – modified from [18]

• Patient-related factors
- Previous restenosis in another segment
- Diabetes
- Acute coronary syndrome PCI
- Low ejection fraction (< 40%)
• Lesion characteristics and procedure-related factors
- Vessel diameter
- Lesion/stent length
- Multiple/overlapping stents
- Minimal lumen diameter before stent implantation
- Minimal lumen diameter after stent implantation
- Ostial lesions
- Saphenous vein grafts
- Chronic total occlusions
- Bifurcation lesions

The main predictors (clinical and procedural) are shown in Table I. Angiotensin II has a basic role in proliferative answer of vessel wall injury mainly through the activation of type 1 receptors. By platelets activation and increasing plasminogen activator inhibitor-1 (PAI-1) the local thrombus formation and inflammatory response is potentiated. The described mechanisms suggest that all drugs acting on vessel wall tissue and blocking inflammatory and proliferative processes should influence the restenosis process. It is logical that angiotensin converting enzyme inhibitors (ACE-I) attract the attention of medical community. Unfortunately, the results from ACE-I application were highly disappointing [19, 20]. Surprisingly and in contradiction to theoretical expectations, as well as to the results of animal experiments, the restenosis with ACE-I was almost double (mean 40% in different studies vs. 20% in controls). Repeatability of the results in all large randomized studies in more than 1000 patients means that this is not an accidental finding. This is true for balloon angioplasty, shown in MERCATOR and MARCATOR studies, but also for bare metal stent implantation studies [10, 11]. The reason for this fact is unclear: it is possible that there is a role of bradikinine as well as by-pass phenomenon with consequent rebound effect.

In contrast with ACE-I, the blockers of angiotensin 1 receptors, so called sartans, have an unequivocal effect. The results of different studies are summarized in Table II. There are several important facts that must be underlined: first, there is a different effect on restenosis of different drugs. The clear positive effect is demonstrated only for valsartan, which is dose-dependent: from 19% (39% in a placebo group) to 0% in females taking 320 mg valsartan in the VALVACE study [12, 15, 19]. In patients after myocardial infarction randomized to valsartan and losartan, the restenosis was significantly lower in the valsartan group [17]. All published trials with candesartan still have a neutral effect on restenosis [13, 16, 18]. There are important details of these studies: the dosage was relatively low and far from the effective dose having an effect in animal experiments. Moreover, neither of the randomized studies with candesartan achieved a pre-determined number of necessary patients for hypothesis proof, for example the AACHEN study recruits only half of pre-determined number. It is possible that the necessary tissue concentration for endothelial proliferation inhibition is much higher in comparison with those in valsartan. An indirect proof of this hypothesis is that in all intravascular ultrasound (IVUS) controlled studies there is a minimal, but significant reduction of neointima formation in comparison with placebo [13, 14, 16, 18]. Other important differences between the studies are patient populations, types of stent implanted and study timing. The impressive 7.3% restenosis, reported by Peters et al. are achieved with very high doses of valsartan (320 mg) in a patient cohort with complex lesions, almost 70% of acute coronary

Table II. Result of different studies

	Patient number and characteristics	Drug used	Follow-up [months]	Lesion types	Reference vessel diameter, [mm]	Stent type	TLR [%] TLI [%]	Commentary
Val-PREST Peters et al. [12]	n = 200, randomized	valsartan 80 mg (n = 99)	6 months, angiography – QCA, 80%	B2/C	2.71 mm	first generation BMS	TLR: valsartan – 19.2% control – 38.6% TLI: valsartan – 21.1% control – 28.7%	In diabetics group – TLR valsartan 25%, control 44%. High risk population – 36% diabetics; 69% ACS patients; LLL – valsartan 0.52 ± 0.16 vs. 1.08 ± 0.55 mm in controls.
ISHIN Wakeyama et al. [13]	n = 136, randomized	candesartan 16 mg (n = 43), candesartan + probucol (8 mg + 500 mg) (n = 44), placebo (n = 45)	6 months, angiographic control – QCA, 82%, IVUS	A/B1	2.9 mm	third generation BMS	TLR: candesartan – 26% placebo – 27% candesartan + probucol – 11%	LLL – candesartan 1.33 ± 0.56 mm/placebo 1.45 ± 0.54 mm/ candesartan + probucol 1.03 ± 0.59 mm.
Yoshida et al. [14] (n = 25)	n = 50, randomized	candesartan 4-12 mg, placebo (n = 25)	6 months, angiographic control – QCA, IVUS	B2/C < 50%	2.9 mm	second generation BMS	TLR: candesartan – 13.3% placebo – 24.1% TLI: candesartan – 16.7% placebo – 24.1%	Differences in TLR and TLI rates are non-significant! There is a significant difference in the volume of neointima proliferation – candesartan – 34.2 ± 16.6 ml; placebo 52.3 ± 32.6 ml.
VALVACE Peters et al. [15]	n = 700, EF < 50% ACE inhibitor; EF > 50% valsartan	valsartan (n = 456) acute coronary syndrome patients (n = 336) ACE inhibitor (n = 244)	6 months, angiographic control – QCA, 89% followed	B2/C	2.68 mm	third generation BMS	TLR: valsartan – 19.5% ACE inhibitor – 34.5% diabetics: valsartan – 24% ACE inhibitor – 43% ACS: valsartan – 14% ACE inhibitor – 43% TLI: valsartan – 7% ACE inhibitor – 22% STEMI: valsartan – 3% ACE inhibitor – 8%	There is no significant difference in restenosis in patients with stable coronary disease (26.5/27.5%); LLL: valsartan – 0.4 ± 0.11 mm; ACE inhibitor – 1.13 ± 0.26 mm; there is a powerful effect of valsartan in all high risk groups.
AACHEN Radke et al. [16]	n = 120, randomized, exclusion criteria – diabetics, ACS patients, long lesions > 20 mm	candesartan 16 mg	6 months angiographic control, QCA – 78%, IVUS – 64%	A/B1	2.9 mm	second generation BMS	TLR: candesartan – 8% placebo – 7%	The study was planned to recruit 230 patients, but stopped at n = 120! Very low follow-up rate for such type of study. The patients are low-risk. No difference in angiographic parameters.

Table II. continued

	Patient number and characteristics	Drug used	Follow-up [months]	Lesion types	Reference vessel diameter, [mm]	Stent type	TLR [%] TLI [%]	Commentary
Iwata et al. [17]	n = 138 retrospective patients with stable CAD n = 40 post MI patients randomized to valsartan or losartan	valsartan (n = 45); losartan (n = 55); controls (n = 38); post-MI: valsartan (n = 20); losartan (n = 20)	6 months angiographic control, QCA	B/C	> 3.5 mm in retrospective cohort; > 3.0 mm in randomized group	third generation BMS	TLR: controls – 27% losartan – 19% valsartan – 10% (p = 0.05 according to controls) Randomization group: TLR: valsartan – 15% losartan – 40% TLI: valsartan – 10% losartan – 35%	LLL: valsartan – 0.4 mm losartan – 0.7 mm very low patient number Valsartan advantage according to angiographic data and long term follow-up.
CAIRP Kramer et al. [18]	n = 206, randomized	candesartan 16 mg (n = 107) placebo (n = 99)	6 months angiographic control, QCA, 1/3 IVUS controlled	all types	two groups > 2.75 mm and < 2.75 mm	third generation BMS	TLR: candesartan – 30.6% placebo – 28.4% TLI: candesartan – 18.1% placebo – 16.3%	there is significant difference in minimal lumen diameter in group with RVD < 2.75 mm – candesartan - 1.39 vs. 1.18 mm in placebo group.
Peters [19]	n = 450, registry type, 1 : 1 patient allocation for two tested dose regimes	valsartan 160 vs. 320 mg	6 months angiographic control, QCA, 82%	B2/C	2.63 mm	third generation BMS	TLR: 7.3% (ACS – 7.2% stable CAD – 7.5%) TLI: 4.3%	LLL – 0.37 ± 0.3 mm; in 27% of patients with high dose, 320 mg, it was necessary to reduce the dose to 240 or 160 mg; in females with high dose regime the restenosis was 0%.

Abbreviations: TLR – target lesion restenosis, TLI – target lesion intervention, LLL – late lumen loss, QCA – quantitative coronary analysis

syndromes and more than 30% diabetics [19]. This is a high risk population with active inflammation. These types of patients were actually excluded from other trials with sartans. It is remarkable that in a group with stable angina the restenosis is actually the same as in controls (around 26%). Additionally, the studies with valsartan were performed in patients with a relatively small calibre – mean 2.7 mm. The rest of the studies are performed in patients with larger reference diameters – 2.9-3.5 mm. The late lumen loss in valsartan groups is between 0.4-0.5 mm, while in other studies the late lumen loss is between 0.7-1.2 mm. This demonstrates the fact of more intensive neointima proliferation inhibition. It is interesting to note that in a recently published CAIRP study (with candesartan), the positive effect on neointima proliferation was observed only in a group with reference diameters below 2.75 mm [18]. The vessels with a median and small calibre (below 3 mm) have a propensity for more intensive inflammation and it seems logical to suppose that exactly these patients will have good results [19]. It must be taken into account the stent types used in different studies. The best results are reported actually with the last generation bare metal stents, with a small stent strut thickness. This is a factor for inflammatory reaction decrease, because of stent metal/artery surface ratio [20, 21]. Even in this situation it was demonstrated that valsartan had an effect, decreasing the clinical restenosis rates from 23% to 7.3% with high dosage schemes (160-320 mg).

Conclusions and future directions

On the basis of the recent studies it could be concluded that sartans have a class effect on decreasing neointima proliferation. The substantial clinical effect, i.e. significant decrease of clinical restenosis rates is demonstrated only for valsartan. According to the current guidelines recommendation classification, it could be given class IIA for application of valsartan after BMS implantation in patients with treated type B2 and C lesions, acute coronary syndromes and vessels below 2.75 mm reference diameter. Additional data are necessary to prove that such

a recommendation could be given for candesartan. Taking into account the risk of late stent thrombosis with DES implantation, good results, at least with valsartan, it will be helpful to perform a study comparing DES and BMS plus sartans performance. Moreover, the last combination, at least theoretically, will decrease bleeding risks, as it is not necessary to make the patient to take clopidogrel for more than one month. The economic impact must also be taken into account: the price of DES plus one-year clopidogrel is considerably higher than that of BMS plus sartan. The sartans have almost no side effects and could be safely applied. It must be underlined that neither European, nor American guideline even mentions anything about ACE-I application in patients after stenting despite plenty of data demonstrating their negative effect in this patient group. In this situation, even if we accept the neutral effect of sartans on restenosis they represent a reasonable alternative in the first 6 months after stent implantation, especially in patients with hypertension and diabetes.

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