Renin–angiotensin system inhibitors in patients with coronary artery disease who have undergone percutaneous coronary intervention

Zhuang Xiao-Dong, Li Fei-Fei, Wen Zhan-Peng, Liao Xin-Xue and Du Zhi-Min

Abstract: The percutaneous coronary intervention (PCI) procedure has become one of the pivotal options in the treatment of coronary artery disease (CAD). Although the PCI procedure has rapidly developed in China, some concerns including in-stent restenosis and dissatisfactory long-term prognosis remain unsolved. Large-scale randomized controlled clinical trials indicate that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) can reduce all-cause mortality and recurrent cardiac events in patients with CAD. ACEIs/ARBs are recommended as a fundamental treatment in the secondary prevention of CAD and reduce in-stent restenosis after PCI. This review focuses on the role of ACEIs/ARBs in improving long-term prognosis and reducing in-stent restenosis.

Keywords: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, in-stent restenosis, percutaneous coronary intervention, prognosis

Background

Percutaneous coronary intervention (PCI) is a well-established symptomatic therapy for stable coronary artery disease (CAD). The total number of PCI procedures in China has grown from 25,000 in 2002 to 500,686 in 2014, accounting for 15–20% of all PCI procedures. It remains one of the most challenging lesions in interventional cardiology in terms of procedural success rate as well as long-term cardiac events [Chen *et al.* 2014]. Outcomes of PCI *versus* medical therapy (MT) in management of stable CAD remain controversial, with few but not all studies showing improved results in patients with ischemia. Effective MT also plays a significant role in the management of patients with PCI [Weiss and Weintraub, 2015]. The use of evidence-based pharmacotherapy might reduce the risk of secondary events in patients with established CAD [Dalal *et al.* 2015]. In addition, cardioprotective drugs, such as antiplatelet agents, beta blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and statins, should be administered according to the guidelines [O’Gara *et al.* 2013]. Despite these

advances, the morbidity and mortality rates associated with CAD are high particularly in high-risk patients. One of the reasons for this is underutilization of several effective medications, one of them being drugs that inhibit the renin–angiotensin system (RAS) [Dalal *et al.* 2015].

RAS inhibitors such as ACEIs and ARBs are being used in management of patients with cardiac diseases, such as heart failure, hypertension, and proteinuria [Ma *et al.* 2010]. In patients with CAD undergoing PCI procedures, the inhibition of RAS with ACEIs and ARBs has been associated with a reduction in both cardiovascular deaths and major nonfatal events. Recent reports also suggest the importance of RAS blockade in improving long-term prognosis and reducing in-stent restenosis (ISR) [Langeveld *et al.* 2005].

This article reviews concerns pertinent to the treatment of CAD patients and lessons learned from clinical trials regarding RAS blockade. It also focuses on the latest research in improving long-term prognosis of ISR in CAD patients through the use of RAS blockade.

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Correspondence to:

Du Zhi-Min, MD

Department of Cardiology,
the First Affiliated Hospital
of Sun Yat-sen University,
No. 58, Zhongshan Er
Road, Guangzhou 510080,
P. R. China

duzhimin@mail.sysu.edu.cn

**Zhuang Xiao-Dong, MD,
PhD**

Li Fei-Fei, MD

Wen Zhan-Peng, MD

Liao Xin-Xue, MD, PhD

Department of Cardiology,
the First Affiliated Hospital
of Sun Yat-sen University,
Guangzhou, P. R. China

Table 1. Clinical trials showing protective effect of ACEIs.

Trial	Patients	Comparator drug	Primary outcome
SAVE [Pfeffer <i>et al.</i> 1992]	2231 patients after MI (LVEF, $\leq 40\%$)	Captopril (12.5 mg/day up to 50 mg thrice daily) <i>versus</i> placebo	With captopril, the reduction in the risk for death from all causes was 19% ($p = 0.019$) and that for death from CV causes was 21% ($p = 0.014$).
TRACE [Kober <i>et al.</i> 1995]	6676 patients after MI (partial LVEF fall)	Trandolapril (1 mg/day) <i>versus</i> placebo	Trandolapril reduced the risk of CV mortality in patients with LVSD after MI (RR=0.75; $p = 0.001$)
HOPE [Yusuf <i>et al.</i> 2000]	9297 high-risk patients with CV disease (CV risk factor including diabetes)	Ramipril (10 mg/day) <i>versus</i> placebo	Ramipril reduced the risks of CV mortality (RR = 0.74; $p < 0.001$) and MI morbidity (RR = 0.68; $p < 0.001$)
EUROPA [Fox and the EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators, 2003]	13,655 patients after MI, CAD, coronary stenting	Perindopril (8 mg/day) <i>versus</i> placebo	Perindopril reduced risks of CV deaths, nonfatal MI, and cardiac arrest. The RR was 20% ($p = 0.0003$)
ACEI, angiotensin-converting enzyme inhibitor; CAD, coronary artery disease; CV, cardiovascular; LVSD, left ventricular systolic fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; RR, relative risk.			

Evidence-based summary of mechanisms of RAS inhibitors in improving the prognosis of CAD

ACEIs can reduce the incidence of cardiovascular events by various mechanisms, which act on angiotensin-converting enzymes, inhibit angiotensin II synthesis and bradykinin degradation. First, ACEIs can improve endothelial function, increase bradykinin levels and expression and activity of endothelial nitric oxide synthase, decrease the expression of smooth muscle proliferation factor, and improve endothelium-dependent vasodilation; second, ACEIs can inhibit vascular inflammation to delay the progression of atherosclerosis; and, third, these drugs can reduce metalloproteinase activation, thrombosis, improve plaque stability and fibrinolytic activity. In addition, they can antagonize proliferation and delay myocardial remodeling after myocardial infarction (MI) [Langeveld *et al.* 2005; Ferrario, 2006].

ARBs act on angiotensin II receptors (mainly AT1 receptors; valsartan has the most elective AT1/AT2 receptor affinity, 30,000:1) [Siragy, 2002]. ARBs block the function of AT1 receptors leading to an increase in blood pressure, oxidative stress, and water-sodium retention and promote the effect of AT2 receptors of antioxidative stress, antiproliferation, and remodeling [Siragy, 2002]. ARBs are similar to ACEIs in controlling blood pressure, providing a cardioprotective effect, and have fewer adverse reactions [Ma *et al.* 2010]. Both ACEIs and ARBs improve prognosis in

patients with CAD mainly by inhibiting myocardial remodeling, delaying ventricular enlargement, and reducing the incidence of heart failure, thus reducing the rate of hospitalizations, MI, mortality, etc. [Von Lueder and Krum, 2013].

Chinese and international guidelines recommend that all patients with CAD having comorbidities, including diabetes, heart failure, hypertension, and left ventricular dysfunction after MI should initiate ACEIs early and for a long period of time [Hamm *et al.* 2011; O’Gara *et al.* 2013]. Alternatively, an ARB can be used if an ACEI is contraindicated in such patients. The main clinical trials showing the protective roles of ACEIs and ARBs in cardiovascular diseases are summarized in Tables 1 and 2.

Evidence-based summary of mechanisms of RAS inhibitors in reducing ISR

The cause and mechanisms of ISR are complex and involve endothelial injury, thrombosis, proliferation of smooth muscle cells, vascular remodeling, inflammatory reaction, and release of various cytokines. ISR can be divided into four stages: (1) platelet aggregation, in which stent implantation results in mechanical endothelial damage and rapidly triggers platelet aggregation and activation; (2) inflammation, in which different types of white cells gather at the lesion location and secrete inflammatory factors within a few days to weeks; (3) proliferation, in which

Table 2. Clinical trials showing protective effect of ARBs.

Trial	Patients	Comparator Drug	Primary Outcome
VALUE [Julius <i>et al.</i> 2006]	15,245 high-risk hypertensive patients	Valsartan (80–160 mg/day) <i>versus</i> amlodipine (5–10 mg/day)	No difference was observed in the rates of cardiovascular mortality and morbidity (primary endpoint); valsartan can reduce the incidence of new-onset diabetes (OR = 0.78; $p = 0.034$)
Val-HeFT [Cohn <i>et al.</i> 2001]	5010 patients with heart failure (NYHA class II–IV)	Valsartan (160 mg twice daily) <i>versus</i> placebo	Valsartan reduced the risk of composite endpoint of mortality (RR = 0.87; $p = 0.009$)
VALIANT [Pfeffer <i>et al.</i> 2003]	14,703 patients after MI	Valsartan (20 mg/day–160 mg twice daily) <i>versus</i> valsartan (20 mg/day–80 mg twice daily) + captopril (6.25 mg/day–50 mg thrice daily) <i>versus</i> captopril (6.25 mg/day–50 mg thrice daily)	No difference was observed in the mortality rate in high-risk patients after MI (HR [valsartan group <i>versus</i> captopril group] = 1.00; $p = 0.98$)
OPTIMAAL [Dickstein and Kjekshus, 2002]	5477 high-risk patients after AMI (heart failure, left ventricular dysfunction)	Losartan (50 mg/day) <i>versus</i> captopril (50 mg thrice daily)	The rate of all-cause mortality was higher in the losartan group than that in the captopril group (RR = 1.13); however, this was not statistically significant ($p = 0.07$)
ONTARGET [ONTARGET Investigators <i>et al.</i> 2008]	25,620 patients with cardiovascular disease and diabetes mellitus	Telmisartan (80 mg/day) <i>versus</i> ramipril (10)	Telmisartan reduced the risk of composite endpoint of death from cardiovascular causes and was noninferior to ramipril (RR = 1.01); the revascularization rate was equivalent to that with ramipril (RR = 1.03)
CHARM [Pfeffer <i>et al.</i> 2003]	7601 patients with LVEF	Candesartan (32 mg/day) <i>versus</i> placebo	Candesartan reduced the risk of cardiovascular mortality (HR = 0.88; $p = 0.012$)
AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OR, odds ratio; RR, relative risk.			

vascular smooth muscle cells (VSMCs) migrate, proliferate, and produce neointima to repair injured vessels; and (4) remodeling, in which neointima rich in cells turn into plaques of rich extracellular matrix [Kraitzer *et al.* 2008].

Studies show that RAS is involved in platelet aggregation, thrombosis, and VSMC proliferation [Burnier and Brunner, 2000]. A large number of AT1 receptors are distributed in the VSMCs at restenosis sites, and angiotensin II can promote the proliferation of VSMCs DNA synthesis [Daemen *et al.* 1991]. The effect of angiotensin-II-mediated AT 2 receptor stimulation include antiproliferation/inhibition of cell growth, cell differentiation, tissue repair, and apoptosis [Burnier and Brunner, 2000]. Groenewegen and colleagues showed that angiotensin II can promote angiogenesis in rats after stent implantation [Groenewegen *et al.* 2008]. Valsartan was also found to reduce the proliferation of neointima in rats with balloon injury [Li

et al. 2014]. Ohtani and colleagues showed that valsartan can reduce neointima formation and ISR in macaques after stent implantation [Ohtani *et al.* 2006]. These fundamental studies have shown that ARBs can reduce the occurrence of restenosis. Similar conclusions were drawn from several clinical trials [Peters *et al.* 2001, 2005; Peters, 2008; Yoshikawa *et al.* 2009]. However, the role of ACEIs in reducing the incidence of restenosis is still controversial. Meurice and colleagues showed that treatment with ACEIs significantly increased the incidence of ISR ($p = 0.018$) in patients with deletion (DD) genotype [Meurice *et al.* 2001]. However, Guneri and colleagues showed that treatment with ACEIs may reduce the incidence of ISR in type 2 diabetic patients with D allele (DD or insertion/deletion [ID]) [Guner *et al.* 2005]. Therefore, the role of ACEIs in reducing the incidence of restenosis needs to be studied further. The evidence on the role of ARBs in reducing ISR is summarized in Table 3.

Table 3. Research summary of RASi reduction in ISR.

Researcher and year	Drug	Animals or patients	Outcomes	Conclusion
Basic research				
[Groenewegen <i>et al.</i> 2008]	Candesartan	Rats with stent implantation	Neointimal area was increased in angiotensin II group ($0.88 \text{ mm}^2 \pm 0.21$) <i>versus</i> control group ($0.66 \text{ mm}^2 \pm 0.16$) ($p < 0.05$)	Angiotensin II can promote neointimal proliferation in rats after stenting
[Li <i>et al.</i> 2014]	Valsartan	Balloon-injured rat's vascular intima	Valsartan reduced intimal thickness (intimal thickness 29.32 ± 9.15) <i>versus</i> control (91.66 ± 10.45) ($p < 0.01$)	Valsartan reduced vascular endothelial cell proliferation and neointimal hyperplasia after balloon injury in rats
[Ohtani <i>et al.</i> 2006]	Valsartan	Macaques with stent implantation	Valsartan compared with control reduced new neointimal area ($p < 0.01$) and the incidence of ISR ($p < 0.01$)	Valsartan compared with control reduced new neointimal area and the incidence of ISR
Clinical research				
[Peters <i>et al.</i> 2001]	Valsartan <i>versus</i> placebo	200 patients with B2/C complex lesions after PTCA balloon dilatation and bare metal stent placement	ISR rate: Valsartan group, 19.2% <i>versus</i> control group, 38.6% ($p < 0.005$) Re-intervention rate: Valsartan group, 12.1% <i>versus</i> control group, 28.7% ($p < 0.005$)	Valsartan reduced the rates of ISR and revascularization with complex coronary artery disease after PCI
[Peters <i>et al.</i> 2005]	Valsartan <i>versus</i> ACEI	623 patients with stable disease after B2/C bare metal stent placement	ISR rate after PCI: Valsartan group, 14.0% <i>versus</i> ACEI group, 43.0% ($p < 0.0001$)	Valsartan reduced the rate of ISR, with ACS and MACE compared with ACEI
[Peters, 2008]	Valsartan 80 mg/day <i>versus</i> valsartan 160–320 mg/day	450 patients with B2/C bare metal stent placement	ISR rate: Valsartan 80 mg/day, 19.5% <i>versus</i> valsartan 160–320 mg/day, 7.3% ($p < 0.01$) TLR/TVR rate: Valsartan 80 mg/day, 9.0% <i>versus</i> valsartan 160–320 mg/day, 4.3% ($p < 0.01$)	High-dose valsartan (160–320 mg/day) compared with routine dose of valsartan (80 mg/day) reduced the rates of ISR restenosis, TVR, and MACE with complex coronary artery disease after PCI
[Yoshikawa <i>et al.</i> 2009]	ARB <i>versus</i> statins <i>versus</i> ARB+statins	330 patients with coronary stent implantation	ISR rate: ARB, 31.2%, <i>versus</i> statins, 33.3%, <i>versus</i> ARB+statins, 19.1% ($p < 0.05$) TLR was necessary in ARB group (26.0%) <i>versus</i> statin group (26.3%) <i>versus</i> ARB + statin group (14.2%) ($p < 0.05$)	ARB+statins can reduce the incidences of ISR and TLR
ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndromes; ARB, angiotensin II receptor blocker; ISR, in-stent restenosis; MACE, major adverse cardiovascular events; PTCA, percutaneous transluminal coronary angioplasty; PCI, percutaneous coronary intervention; RASi, renin-angiotensin system inhibitor; TLR, target lesion revascularization; TVR, target vascular revascularization.				

Summary

Moran and colleagues forecasted that the incidence of cardiovascular diseases in China will double from 2010 to 2030 due to ageing and growth of the population and increasing major cardiovascular risk factors will also accelerate this rate of increase [Moran *et al.* 2010]. PCI has been

widely used as one of the most crucial therapies of CAD and ISR is a major drawback of PCI. RAS plays a fundamental role in maintaining vascular function and its dysfunction results in cardiovascular disease. RAS inhibitors such as ACEIs and ARBs are used extensively for the treatment of cardiac disease. Likewise, RAS could play a role

in the pathophysiology of ISR. Studies have shown that RAS inhibitors could improve prognosis in patients after MI and reduce ISR. The mechanism relates to improved endothelial function, increased bradykinin levels, reduced expression of VSMC proliferation factors, inhibition of inflammation, reduced thrombosis, etc. This makes RAS inhibitors an appealing approach for the reduction of ISR. However, more research is needed to determine a standardized administration of ACEIs/ARBs after a PCI procedure.

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Conflict of interest statement

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