

## Spirolactone Does Not Prevent Restenosis After Coronary Stenting in Humans

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### Abstract

**Introduction:** In animal studies, aldosterone enhanced neointimal proliferation by increasing extracellular accumulation of collagen and potentiating the effects of angiotensin II. Spirolactone, an aldosterone antagonist, is a potent inhibitor of neointimal proliferation. We conducted a placebo-controlled, double-blind, randomised study to assess the effect of spironolactone on angiographic 6-month in-stent restenosis. **Materials and Methods:** Of the 310 randomised patients with significant coronary artery disease, 258 patients were available for analysis: 128 constituted the placebo group and 130 were assigned to receive spironolactone. Eligible patients were randomly assigned to receive a dose of 50 mg spironolactone or placebo orally twice a day for 6 months. The primary endpoint was the angiographic restenosis (>50% stenosis) rate at follow-up angiography. **Results:** At 6-month follow-up angiography after stenting, there was no difference between the 2 groups in minimal lumen diameter, percent diameter stenosis, late loss, and net gain. Angiographic restenosis occurred in 46 (35.4%) of 130 patients receiving spironolactone and 50 (39.0%) of 128 in the placebo group with an odds ratio (OR) of 0.85 with a 95% confidence interval (CI) of 0.49 to 1.46 ( $P = 0.62$ ). Restenosis rate was found in 60 (32.9%) of 182 lesions in the spironolactone group, and 61 (35.5%) of 172 lesions in the placebo group with an OR of 0.89 with a 95% CI of 0.56 to 1.42 ( $P = 0.89$ ). **Conclusions:** Spirolactone did not reduce the incidence of in-stent restenosis as compared with placebo in human, contrary to the fact that reduction of neointimal formation in animal models has been observed upon administration of spironolactone.

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**Key words:** Angiography, Coronary lesion, In-stent restenosis, Neointimal proliferation

### Introduction

High restenosis rate, which has been documented to occur in approximately 30% to 50% of cases, still remains a major concern, although percutaneous transluminal coronary angioplasty can be performed with a high initial success rate and good immediate angiographic results. Early elastic recoil, late vessel remodelling, and neointimal proliferation have been proposed as important contributors to the restenosis after coronary angioplasty.<sup>1,2</sup> Coronary stent placement has been used in order to reduce restenosis by minimising the residual stenosis and elastic recoil, and preventing late vascular remodelling.<sup>3,4</sup> Restenosis after coronary stenting is thought to be mainly due to neointimal proliferation.<sup>5</sup> The migration and proliferation of smooth muscle cells, induced by the production and release of growth factors, cytokines and extracellular matrix synthesis, result in neointimal formation and eventually represents

the restenosis.<sup>6,7</sup> With regard to neointimal formation, no orally effective agent has been definitively reported yet although several pharmacological agents have been tested in different clinical trials.<sup>8-13</sup>

Angiotensin converting enzyme (ACE) inhibitors have been shown to reduce neointimal thickening after balloon angioplasty in animal studies. This effect, which was suggested to occur by inhibiting the stimulatory effect of angiotensin II on vascular smooth cells, has not been demonstrated in humans.<sup>14-16</sup> It has been shown that aldosterone induces neointimal proliferation, increasing collagen synthesis and potentiating the effects of substances such as vasopressin, angiotensin, and noradrenaline, which have potent effects on vascular smooth cell proliferation.<sup>17-20</sup> Moreover, in an experimental study, aldosterone increased but spironolactone, an aldosterone antagonist, decreased neointimal formation after balloon denudation.<sup>21</sup> Based on

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this premise, we sought to find out whether spironolactone therapy affects in-stent restenosis rates in humans in our placebo-controlled, double-blind randomised study.

### Materials And Methods

From January 2002 to January 2003, 310 consecutive patients (Spironolactone group = 155, placebo group = 155) who met the inclusion and exclusion criteria listed below were included into the study. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki and was approved by the Institutional Ethics Committee; each patient gave a written informed consent. The baseline clinic characteristics of the patients included in this study were obtained during a 3-day screening period, including history, physical examination, 12-lead electrocardiography, echocardiography and routine laboratory evaluation.

Patients between 35 and 75 years of age with angiographically proven significant coronary artery disease (stenosis >70%), who were selected for coronary stenting in native coronary arteries, and who had not undergone previous angioplasty, were included in the study.

Patients with severe congestive heart failure (ejection fraction <30%), a myocardial infarction in the preceding 2 weeks, or any other major illness, were not included in the study. Inability to follow the protocol, previous bypass surgery, significant unprotected left main artery disease, a history of cerebrovascular accident, insulin-dependent diabetes mellitus, pregnancy and hypersensitivity to spironolactone were the other exclusion criteria. Also, patients who had lesions in the vessel of less than 2 mm diameter, chronic occlusion of more than 6 months, and diffuse lesions with diameters of more than 25 mm were not included in the study.

The primary endpoint of the study was the restenosis rate after coronary stenting at follow-up angiography. Restenosis was defined as recurrent lumen diameter stenosis >50% at follow-up angiography, as determined by quantitative coronary angiography.

Stenosis was evaluated in 2 orthogonal positions for right coronary artery and 6 orthogonal positions or the branches of the left coronary artery. The orthogonal views were assessed at end-diastolic frames. Three coronary angiograms were performed for each patient: pre-angioplasty/stent, post-angioplasty/stent and at the end of 6-month follow-up period. Diameter percent stenosis was analysed by quantitative coronary angiography.

The secondary endpoint was the occurrence of major cardiac events (death, myocardial infarction, coronary bypass surgery, percutaneous reintervention) within the 6-month follow-up period.

Each patient eligible for inclusion was randomised (1:1)

to 1 of the 2 study arms 24 hours after the initial coronary angiography. Each randomised patient received a dose of 50 mg spironolactone or placebo orally twice a day for 6 months. The first dose of spironolactone or placebo was given 1 day before stenting.

The follow-up period regarding probable side effects and usage of spironolactone consisted of 5 visits. The visits took place on the first day, at the time of discharge, and in the third week, third month, and sixth month of follow-up. A physical examination was also done during the last visit; compliance with the treatment was evaluated on the third visit. In every visit, whole blood counts, serum sodium and potassium levels were also measured. Thus, both the patient and physicians remained blinded during follow-up.

Both groups were given a bolus of heparin (10,000 IU) intravenously. If the procedure lasted longer than 1 hour, an additional dose of 5000 IU heparin was injected intravenously. After a successful optimised stenting was achieved, no further heparin was administered and sheaths were removed within 6 hours. A daily dose of 100 mg aspirin and clopidogrel with a dose of 75 mg was given once a day 3 days before the procedure. The patients were asked to take aspirin indefinitely and to take clopidogrel for 4 weeks. Beta blockers, nitrates, calcium channel blockers, ACE inhibitors, and lipid-lowering drugs were prescribed if indicated.

Angioplasty/stenting was performed according to standard techniques. The technical aspects of the procedure, including the choice of stents, duration and pressure of inflation were determined by the individual operators. To achieve maximal vasodilation, each coronary angiogram was preceded by intracoronary injection of 125 µg of nitroglycerin. Balloon-expandable stents were used for both groups.

The degree of stenosis was calculated on the basis of the minimal lumen diameter (MLD) of the stenosis as compared with the reference vessel diameter. Successful stenting was defined as ≤10% residual stenosis in the target lesion poststent implantation. We defined restenosis as less than 50% luminal diameter remaining, as measured by quantitative coronary angiography at 6-month follow-up compared with the post-coronary angioplasty angiography. Acute gain was defined as the difference between MLD after and before coronary stenting, and late loss was defined as the difference between MLD after coronary stenting and at follow-up procedure. All angiographic analyses (Siemens HICOR T.O.P. Image System, Forchheim, Germany) were performed off-line by 2 cardiologists blinded to all the data of patients at our catheter laboratory.

The reproducibility of quantitative measurements was assessed by re-analysis of 30 randomly selected images. Inter- and intra-observer variability were analysed by

measurements performed by 2 independent observers and by repeated analysis of 2 separate time points 3 weeks apart, respectively.

In this study, the values for continuous data were expressed as mean  $\pm$  SD, whereas categorical data were reflected by frequencies and corresponding percentages.  $P < 0.05$  was considered statistically significant.

Dichotomous variables, such as sex and smoking, were analysed with Fisher's Exact test; however, continuous variables, such as blood cholesterol level, vessel diameter and age, were analysed with the Mann-Whitney U test. Fisher's Exact test was used to assess restenosis rates side effects, which are dichotomous variables.

Inter- and intra-observer measurement reproducibility was calculated for minimal lumen diameter. Wilcoxon Signed Rank test was used to test whether the difference was statistically different from zero. Also, the measurements were evaluated by the Pearson correlation coefficient for lumen area.

## Results

Of the 310 randomised patients, the finally evaluable population included 258 patients: 130 assigned to receive active treatment and 128 constituting the placebo group. No severe complications during stenting, including the occurrence of myocardial infarction, urgent coronary artery bypass graft surgery, or death during the hospital stay, occurred. Failed coronary stenting, according to the study protocol, was encountered in 30 patients (14 in the spironolactone group and 16 in the placebo group). Moreover, 5 patients (3 in the treatment group and 2 in the placebo group), who had long dissections of  $>30$  mm

during the coronary angioplasty procedure, were excluded from the analyses. Four patients in the spironolactone group and 3 in the placebo group were also excluded from the analyses due to lack of compliance. Another 4 patients who were eligible for follow-up in the placebo group declined a 6-month follow-up coronary angiography. Six patients, 4 in the spironolactone group and 2 in the placebo group, died of acute ST-elevation myocardial infarction and lethal arrhythmia during the study period. In total, a total number of 52 patients (25 in the spironolactone and 27 in the placebo group) were excluded from the study.

The total number of stents for stenoses evaluated in the study was 354, 182 in the spironolactone and 172 in the placebo group. One stenosis occurred in 178 patients, 64 patients had 2 stenoses and 16 patients had 3 stenoses. A mean of 1.4 stenoses were performed per patient.

The baseline clinical and demographic characteristics of 258 patients being randomised are shown in the Table 1. All the baseline clinical characteristics of the 2 groups were evenly distributed and both treatment arms were absolutely comparable. The locations of the target lesions in the coronary arteries were the left anterior descending or one of its side branches, the left circumflex artery and the right coronary artery. The right coronary artery was frequent in the spironolactone group whereas the left circumflex artery was frequent in the placebo group. There were no group differences in the major types of lesions (A, B, C) (Table 2).

The results of angiographic assessment of the target lesion are shown in Table 3. There were no significant differences between the spironolactone and placebo groups in mean percent diameter stenosis and minimal lumen

Table 1. The Clinical and Demographic Characteristics of Patients

	Spironolactone (130)	Placebo (128)	P value
Age (y)	54.9 $\pm$ 10.9	55.7 $\pm$ 10.5	ns**
Males (%)	71.4	73.1	ns*
Unstable angina pectoris (%)	24.7	21.8	ns*
Diabetes (%)	21.4	18.9	ns*
Previous MI (%)	67.6	71.5	ns*
Hypertension (%)	32.4	28.3	ns*
Smoking (%)	38.7	35.3	ns*
Body mass index (kg/m <sup>2</sup> )	26.8 $\pm$ 3.1	25.5 $\pm$ 2.9	ns**
NHYA class	2.4 $\pm$ 0.4	2.5 $\pm$ 0.4	ns**
Total cholesterol (mg/dL)	232 $\pm$ 43	227 $\pm$ 47	ns**
Triglyceride (mg/dL)	191 $\pm$ 58	183 $\pm$ 59	ns*
Fibrinogen	286 $\pm$ 53	278 $\pm$ 62	ns**
Aspirin	87	85	ns*
ACE inhibitors	44	41	ns*
Calcium channel blockers	31	34	ns*
Nitrates	68	72	ns*
Statins	57	62	ns*

\*Fisher's Exact  $\chi^2$  test. \*\*Mann-Whitney U test. Values are expressed as mean  $\pm$  SD unless otherwise noted. MI: myocardial infarction; NHYA: New York Heart Association; ns: not significant

Table 2. Baseline Target Lesion Characteristics

	Spironolactone (n = 182)	Placebo (n = 172)	P value**
Lesion location			
LAD n (%)	78 (43)	70 (41)	ns*
LCX n (%)	18 (9.8)	36 (21)	0.01*
RCA n (%)	86 (47)	66 (38)	0.02*
Lesion type			
A n (%)	62 (34)	57 (33)	ns*
B n (%)	99 (54)	96 (56)	ns*
C n (%)	21 (12)	19 (11)	ns*
No. of diseased vessels			
1 (n = patient x 1) (%)	87 (48)	91 (53)	ns*
2 (n = patient x 2) (%)	68 (34 x 2) (37)	60 (30 x 2) (35)	ns*
3 (n = patient x 3) (%)	27 (9 x 3) (15)	21 (7 x 3) (12)	ns*

\* It is analysed with Fisher's Exact  $\chi^2$  test.

\*\* Statistical difference was defined at the  $P < 0.05$  level.

LAD: left anterior descending artery; LCX: Left circumflex coronary artery; RCA: right coronary artery

diameter before and after stenting. Moreover, the mean percent diameter stenosis at follow-up was not different in both groups ( $34.3 \pm 16.2\%$  in spironolactone group;  $36.6 \pm 14.2\%$  in placebo group,  $P = 0.32$ ). Minimal lumen diameter at follow-up angiography was  $1.63 \pm 0.52$  mm in the spironolactone group and  $1.52 \pm 0.43$  mm in the placebo group ( $P = 0.33$ ). The lumen diameter of the reference segment of the spironolactone group at follow-up was not different from the placebo group ( $2.9 \pm 0.75$  vs.  $2.8 \pm 0.71$  mm,  $P = 0.40$ ). The initial gain was  $1.77 \pm 0.52$  mm in the spironolactone group and  $1.73 \pm 0.60$  mm in the placebo group ( $P = 0.35$ ). Late loss was  $0.96 \pm 0.68$  mm in the spironolactone group and  $0.95 \pm 0.74$  mm in the placebo group ( $P = 0.54$ ). Net gain was also similar in both groups ( $0.81 \pm 0.66$  mm in the spironolactone group;  $0.78 \pm 0.63$  mm in the placebo group,  $P = 0.44$ ).

At 6-month follow-up, the restenosis rate was 35.4% (46/130) in the spironolactone group and 39.0% (50/128) in the placebo group. We found an odds ratio (OR) of 0.85 with a 95% confidence interval (CI) of 0.49-1.46 ( $P = 0.62$ ). According to target lesion, restenosis rate was found 32.9% (60/182) in the spironolactone group, and 35.5% (61/172) in the placebo group and an OR of 0.89 with a 95% CI of 0.56 to 1.42 ( $P = 0.89$ ). Repeat in-stent angioplasty was required in 44 target lesions in the spironolactone group and 47 in the placebo group ( $P = 0.46$ ). One patient in each group underwent coronary bypass surgery. Thus, target lesion revascularisation was performed in 45 (24.7%) of 182 lesions in the spironolactone and 48 (27.9%) of 172 lesions in the placebo group ( $P = 0.43$ ).

Quantitative measurements were highly reproducible. The correlation coefficient between repeated measurements of the same observer (intra-observer variability) was 0.98; the mean difference was  $0.13 \pm 1.22$  ( $P = 0.49$ ). For

Table 3. Quantitative Coronary Angiographic Measurements of Target Lesion

	Spironolactone (n = 182)	Placebo (n = 172)	P value
Stent length (mm)			
	$17.9 \pm 4.3$	$19.5 \pm 4.7$	0.36*
%DS			
Before stenting	$82.5 \pm 6.5$	$83.4 \pm 7.4$	0.24*
After stenting	$6.5 \pm 1.8$	$7.1 \pm 2.0$	0.55*
F/U angiography	$34.3 \pm 16.2$	$36.6 \pm 14.2$	0.32*
Minimal LD (mm)			
Before stenting	$0.82 \pm 0.34$	$0.74 \pm 0.39$	0.38*
After stenting	$2.59 \pm 0.65$	$2.47 \pm 0.53$	0.24*
F/U angiography	$1.63 \pm 0.52$	$1.52 \pm 0.43$	0.33*
Reference LD (mm)			
Before stenting	$3.0 \pm 0.68$	$2.9 \pm 0.81$	0.41*
After stenting	$3.0 \pm 0.73$	$2.8 \pm 0.67$	0.39*
F/U angiography	$2.9 \pm 0.75$	$2.8 \pm 0.71$	0.40*
Initial gain (mm)	$1.77 \pm 0.52$	$1.73 \pm 0.60$	0.35*
Late loss (mm)	$0.96 \pm 0.68$	$0.95 \pm 0.74$	0.54*
Net gain (mm)	$0.81 \pm 0.70$	$0.78 \pm 0.63$	0.44*

\*It is analysed with Mann-Whitney U test

DS: diameter stenosis; LD: lumen diameter; F/U: follow-up

measurements performed by 2 independent observers, the correlation coefficient was 0.97; the mean difference was  $0.19 \pm 1.35$  ( $P = 0.32$ ).

## Discussion

In this randomised, double-blind and placebo-controlled study, we found that the effect of spironolactone, an aldosterone antagonist, on in-stent restenosis was not statistically different from placebo in humans. This result does not support the hypothesis of the animal study.<sup>21</sup>

Neointimal formation has been demonstrated to be a major causative mechanism of in-stent restenosis.<sup>22</sup> The underlying mechanisms, representing the fundamental sequence of neointimal formation, are smooth muscle cell migration, proliferation, and extracellular matrix formation.<sup>7</sup> Previous studies have shown that mineralocorticoid receptors can be found in vascular smooth muscle cells.<sup>23,24</sup> In this regard, aldosterone administration causes extracellular accumulation of collagen, one of the main components in neointimal formation.<sup>17</sup> Moreover, aldosterone potentiates the effects of various humoral factors such as noradrenalin, angiotensin II, and vasopressin, having powerful effects on the proliferation of vascular smooth muscle cells.<sup>25-28</sup> In a study conducted on rabbits by Van Belle et al,<sup>21</sup> it was shown that aldosterone caused an increase in neointimal formation whereas spironolactone inhibited neointimal formation after aortic and iliac balloon denudations. Moreover, Ward et al<sup>29</sup> revealed that eplerenone, another aldosterone antagonist, suppressed constructive remodelling and collagen accumulation after

angioplasty was performed on porcine coronary arteries. In light of these findings, we considered that spironolactone would reduce the rate of in-stent restenosis.

In the current study comparing spironolactone and placebo for in-stent restenosis rate, baseline characteristics of both groups were the same. There were also no significant differences between 2 groups with regards to stent types, diameters, lengths, and average inflation pressures. It is evident that the majority of restenosis due to neointimal formation occurs within the first 3 months following angioplasty and stenting, and occurrence of restenosis after 3 to 6 months is rare.<sup>30</sup> Considering these data, we prolonged our treatment protocol to the sixth month after stenting. However, we could not demonstrate any favourable effect on the in-stent restenosis rate with spironolactone as compared with placebo.

In-stent restenosis due to neointimal formation is a multifactorial process in which many growth factors can play a role.<sup>31,32</sup> Although the role of aldosterone in causing neointimal formation has been demonstrated, it may not be strong enough on its own to modulate restenosis. Besides, a variety of other factors can result in neointimal formation.

In contrast to the present study, the previous one was conducted on animals in which the effects of aldosterone antagonist on neointimal formation were evaluated after only balloon angioplasty. An interesting consideration is whether neointimal formation resulting from balloon injury alone differs from the injury by oversized stents. Vascular injury caused by percutaneous revascularisation is regarded as the initiating phenomenon, eventually leading to restenosis. First, it was suggested that there is a proportional relationship between the degree of vessel injury depth and the subsequent degree of neointimal formation.<sup>32</sup> Occurrence of neointimal formation after stenting could be predicted as being greater than that which follows balloon angioplasty alone since vessel wall damage is more often caused by oversized stents than angioplasty alone. Second, angioplasty alone can result in a large dissection. After coronary stent placement, each strut of stent buried into the vessel can cause various degrees of injury and stimulate neointimal formation.<sup>34</sup> These differences can be responsible for the ineffectiveness of the methods, reducing neointimal formation after angioplasty alone, to the in-stent restenosis.

One of the major properties of neointimal formation which occurs after coronary stenting is that the duration of mitotic activity after stenting is longer than angioplasty alone.<sup>34</sup> In this regard, we prolonged spironolactone administration until control angiography at 6 month follow-up. However, this prolonged drug administration could not achieve favourable results.

In conclusion, in the present randomised, placebo-controlled study, spironolactone did not reduce the incidence

of in-stent restenosis as compared with placebo in humans, in disagreement with the fact that reduction of neointimal formation in animal models has been observed upon administration of spironolactone.

#### REFERENCES

1. Forrester JS, Fishbein M, Helfant R, Fagin J. A paradigm for restenosis based on cell biology: clues for the development of new preventive therapies. *J Am Coll Cardiol* 1991;17:758-69.
2. Holmes DR Jr, Vlietstra RE, Smith HC, Vetrovec GW, Kent KM, Cowley MJ, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol* 1984;53:77-C81
3. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994;31:489-95.
4. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I. A randomised comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994;331:496-501.
5. Mintz GS, Hoffmann R, Mehran R, Pichard AD, Kent KM, Satler LF, et al. In-stent restenosis: The Washington Hospital Center experience. *Am J Cardiol* 1998;81(Suppl)7A:7-13E.
6. Libby P, Schwartz D, Brogi E, Tanaka H, Clinton SK. A cascade model for restenosis. A special case of atherosclerosis progression. *Circulation* 1992;86(Suppl):III47-52.
7. Liu MW, Roubin GS, King SB 3rd. Restenosis after coronary angioplasty: potential biologic determinants and role of intimal hyperplasia. *Circulation* 1989;79:1374-87.
8. Desmet W, Vrolix M, De Scheeder I, Van Lierde J, Willems JL, Piessens J. Angiotensin-converting enzyme inhibition with fosinopril sodium in the prevention of restenosis after coronary angioplasty. *Circulation* 1994;89:385-92.
9. Weintraub WS, Bocuzzi SJ, Klein JL, Kosinski AS, King SB 3rd, Ivanhoe R, et al. Lack of effect of lovastatin on restenosis after coronary angioplasty. *N Engl J Med* 1994;331:1331-7.
10. Leaf A, Jorgensen MB, Jacobs AK, Cote G, Schoenfeld DA, Scheer J, et al. Do fish oils prevent restenosis after coronary angioplasty? *Circulation* 1994;90:2248-57.
11. Pepine CJ, Hirshfeld JW, Macdonald RG, Henderson MA, Bass TA, Goldberg S, et al. A controlled trial of corticosteroids to prevent restenosis after coronary angioplasty. *Circulation* 1990;81:1753-61.
12. Keefe JH Jr, McCallister BD, Bateman TM, Kuhnlein DL, Ligon RW, Hartzler GO. Ineffectiveness of colchicine for the prevention of restenosis after coronary angioplasty. *J Am Coll Cardiol* 1992;19:1597-600.
13. Hermans WR, Rensing BJ, Strauss BH, Serruys PW. Prevention of restenosis after percutaneous transluminal coronary angioplasty: the search for a "magic bullet". *Am Heart J* 1991;122:171-87.
14. Powell JS, Clozel JP, Muller RK, Kuhn H, Hefti F, Hosang M, et al. Inhibitors of angiotensin-converting enzyme prevent myointimal proliferation after vascular injury. *Science* 1989;245:186-8.
15. Van Belle E, Bauters C, Wernert N, Delcayre C, Piraube C, Dupuis B, et al. Reduction of neointimal hyperplasia with perindopril after experimental angioplasty is associated with inhibition of the c-jun and c-fos oncogenes. *J Am Coll Cardiol* 1994;23 (Abstract suppl)395A.
16. Faxon DP. Effect of high dose angiotensin-converting enzyme inhibition on restenosis: final results of the MARCATOR Study, a multicenter, double-blind, placebo-controlled trial of cilazapril. *J Am Coll Cardiol* 1995;2:362-9.

17. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. *Circulation* 1991;14:1849-65.
  18. Campbell-Boswell M, Robertson AL Jr. Effects of angiotensin II and vasopressin on human smooth muscle cells in vitro. *Exp Mol Pathol* 1981;35:265-76.
  19. Blaes N, Boissel JP. Growth-stimulating effect of catecholamines on rat aortic smooth muscle cells in culture. *J Cell Physiol* 1983;116:167-72.
  20. Nakaki T, Nakayama M, Yamamoto S, Kato R. Alpha-1 adrenergic stimulation and beta-2 adrenergic inhibition of DNA synthesis in vascular smooth muscle cells. *Mol Pharmacol* 1990;27:30-6.
  21. Van Belle E, Bauters C, Wernert N, Hamon M, McFadden EP, Racadot A, et al. Neointimal thickening after balloon denudation is enhanced by aldosterone and inhibited by spironolactone, and aldosterone antagonist. *Cardiovasc Res* 1995;29:27-32.
  22. Antoniucci D, Valenti R, Santora GM, Bolognese L, Trapani M, Cerisano G, et al. Restenosis after coronary stenting in current clinical practice. *Am Heart J* 1998;35:510-8.
  23. Meyer WJ 3rd, Nichols NR. Mineralocorticoid binding in cultured smooth muscle cells and fibroblasts from rat aorta. *J Steroid Biochem* 1981;14:1157-68.
  24. Lombes M, Oblin ME, Gasc JM, Baulieu EE, Farman N, Bonvalet JP. Immunohistochemical and biochemical evidence for a cardiovascular mineralocorticoid receptor. *Circ Res* 1992;71:503-10.
  25. Mikami H, Ogiwara T, Ohde H, Katahira K, Kohara K, Kumahara Y. Direct vascular effects of 19-hydroxyandrostenedione. *Methods Find Exp Clin Pharmacol* 1989;11:241-8.
  26. Purdy RE, Weber MA, Drayer JJ. Vasoconstrictor effects of aldosterone in isolated vascular tissue. *Clin Exp Hypertens A* 1982;4:1583-91.
  27. Couture R, Regoli D. Vascular reactivity to angiotensin and noradrenaline in rats maintained on a sodium free diet or made hypertensive with desoxycorticosterone acetate and salt (DOCA/salt). *Clin Exp Hypertens* 1980;2:25-43.
  28. Bockman CS, Jeffries WB, Pettinger WA, Abel PW. Enhanced release of endothelium-derived relaxing factor in mineralocorticoid hypertension. *Hypertension* 1992;20:304-13.
  29. Ward MR, Kanellakis P, Ramsey D, Funder J, Bobik A. Eplerenone suppresses constrictive remodeling and collagen accumulation after angioplasty in porcine coronary arteries. *Circulation* 2001;104:467-72.
  30. Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. *J Am Coll Cardiol* 1993;21:15-25.
  31. Clemmons DR. Interaction of circulating cell-derived and plasma growth factors in stimulating cultured smooth muscle cell replication. *J Cell Physiol* 1984;121:425-30.
  32. Libby P, Edelman E. Restenosis: Involvement of growth factors and cytokines. In: Topol EJ, editor. *Textbook of Interventional Cardiology*. Philadelphia: WB Saunders Co, 1999:346-57.
  33. Schwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE, et al. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. *J Am Coll Cardiol* 1992;19:267-74.
  34. Schwartz RS. Animal models of human coronary restenosis. In: Topol EJ, editor. *Textbook of Interventional Cardiology*. Philadelphia: WB Saunders Co, 1999:358-78.
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