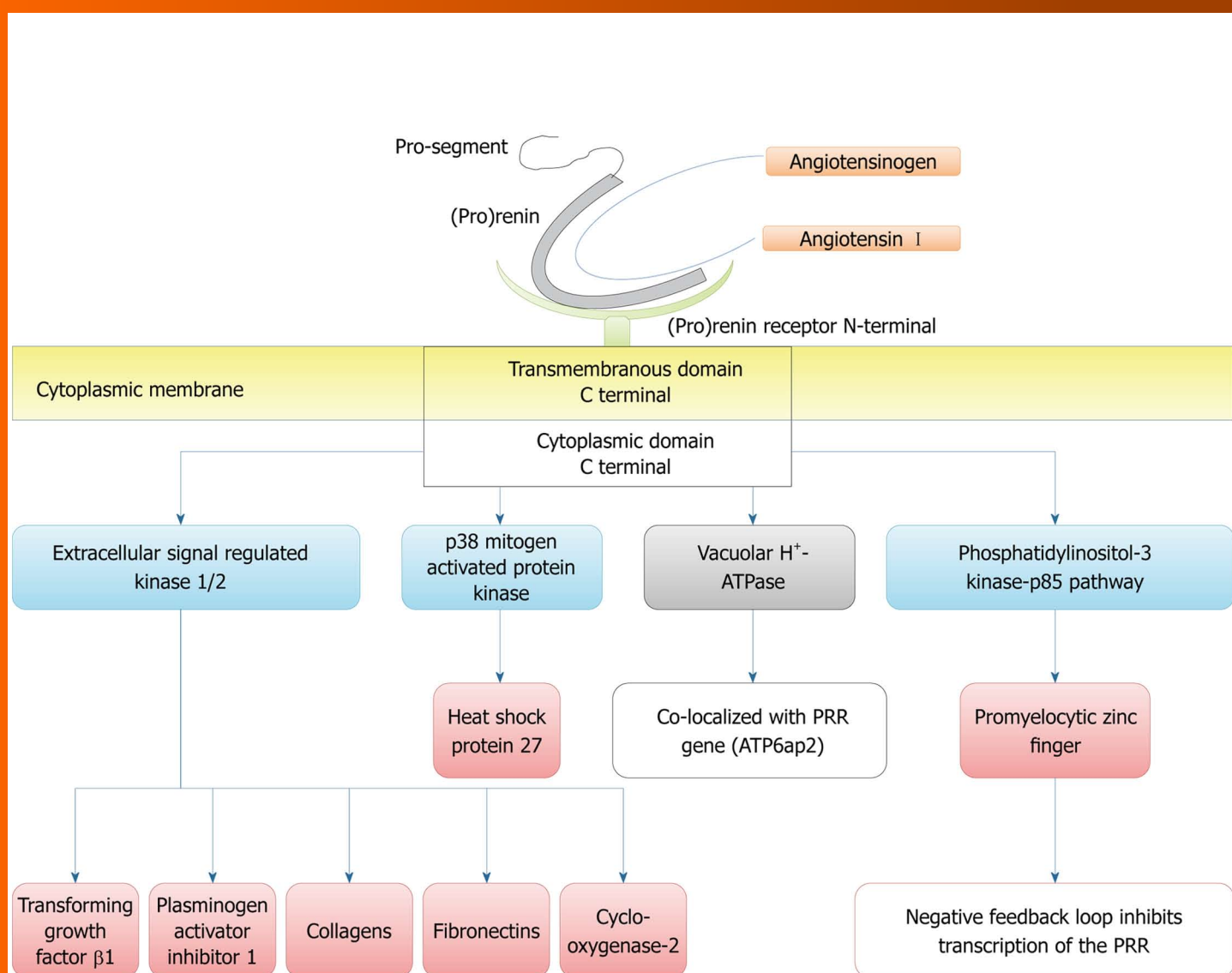


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Current status of aggressive blood pressure control

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Abstract

The concept of treatment of hypertension has gone through wide swings over the years. From ignoring blood pressure (BP) treatment initially, to aggressive BP control recently. As newer and more effective drugs were developed, it was possible to lower BP to very low levels. However, recent studies have shown that aggressive BP control might not be in the best interest of the patient. Low levels of diastolic BP (DBP) have been associated with increased cardiovascular events, a situation known as the J-curve effect. This has been seen mostly with low DBP, since the coronary arteries are perfused during the diastolic phase of the cardiac cycle. Due to an autoregulatory mechanism, the heart is protected against wide fluctuations of BP. However, the presence of coronary heart disease, hypertension, especially with left ventricular hypertrophy, shift the curve to higher BP levels and makes the heart more liable to DBP fluctuations. The J-Curve effect has been reported by most investigators, but not by others. Recently, a J-Curve effect has been observed with systolic BP (SBP), as well. In contrast to the heart, the brain is very infrequently subjected to J-curve effect, and in contrast to the heart, the brain's blood flow autoregulation depends mostly on the SBP. A Medline search of the English literature on this subject was conducted between 1992 and 2010 and 11 pertinent articles were selected. These articles with collateral literature will be discussed in this concise review.

INTRODUCTION

The concept of hypertension treatment has gone through severe extremes over the years. The basic premise for these was the original concept that hypertension is an essential condition and therefore should not be treated. The term “essentielle hypertonie”, i.e. essential hypertension, was first quoted by the German physician Frank E in 1911 and continues to be used today^[1]. Because of this concept, treatment of hypertension was resisted and several prominent academic physicians admonished primary care physicians who attempted to treat hypertension^[2-4]. Statements such as, “The greatest danger to anyone with high blood pressure (BP) lies in its discovery, because then some fool is certain to try to reduce it” by Hay^[2] in England, and “For mild benign hypertension, or BP below 200/100 mmHg, there is no indication for use of hypertensive drugs” by Friedberg^[4] in the US, were not unusual. However, as time progressed, and more effective treatments for hypertension were available, physicians began to treat the condition. The great impetus for treatment were the pivotal Veterans Administration studies conducted under Ed Freis which showed that lowering the BP reduced strokes, heart failure and kidney

failure^[5]. Subsequent studies showed the benefits of BP lowering with respect to stroke, kidney and cardiovascular disease complications which led to National and International guidelines recommending reduction of BP to < 140/90 mmHg for uncomplicated hypertension or < 130/80 mmHg for subjects with concomitant diabetes mellitus, coronary heart disease (CHD) or chronic kidney disease^[6-8]. However, recent large outcomes trials have found that more aggressive control of BP may cause a J-curve effect, especially in patients with preexisting CHD and lead to increased cardiovascular morbidity and mortality^[9,10]. For this review, a Medline search of the English literature was conducted from 1992 to 2010 and 11 pertinent articles were selected. These articles with collateral literature will be discussed in this concise review, as they pertain to aggressive BP control and the incidence of cardiovascular and stroke complications.

J-CURVE PHENOMENON AND CARDIOVASCULAR COMPLICATIONS

The J-curve phenomenon describes an inverse relationship between low diastolic BP (DBP) and cardiovascular morbidity and mortality. It was originally described by Stewart^[11] in 1979 where 169 well matched hypertensive patients were treated and followed for 6.25 years. At the end of the study, the incidence of myocardial infarction was 5 times higher in the patients with DBP < 90 mmHg, compared with those with a DBP 100-109 mmHg ($P < 0.01$). Similar observations were reported later by Cruickshank *et al*^[12], on 902 hypertensive patients treated with atenolol in combination with other drugs, and were followed for a mean of 6.1 years. They observed a J-curve relationship between a DBP of 85-90 mmHg, and myocardial infarction and death in patients with ischemic heart disease, and the cardiovascular complications rose on either side of the DBP range. Several other investigators followed with similar results^[13-25]. In a review by Farnett *et al*^[14], of 13 studies comprising 48000 hypertensive subjects treated for a minimum of 1 year, they observed a definite J-curve effect between a DBP of 85 mmHg and cardiovascular morbidity and mortality, but not stroke. They also found that the J-curve effect was steeper in patients with preexisting ischemic heart disease and in older hypertensive patients. In most older studies the J-curve effect has been observed with a low DBP. However, 2 recent large clinical outcomes trials have observed a J-curve effect with low SBP besides low DBP, and cardiovascular and stroke complications^[9,10]. In these studies, a J-curve effect was observed with SBP \leq 130 mmHg, and a DBP \leq 80 mmHg. In the International Verapamil-Trandolapril study (INVEST), 22576 hypertensive patients with CHD were randomized into 2 treatment regimens, a calcium channel blocker-based regimen (verapamil), or a β -blocker-based regimen (atenolol) and were followed for 24 mo^[9]. In this study, the adjusted models for the time of primary outcome (all-cause death, non-fatal myocardial infarction, and non-fatal stroke), the

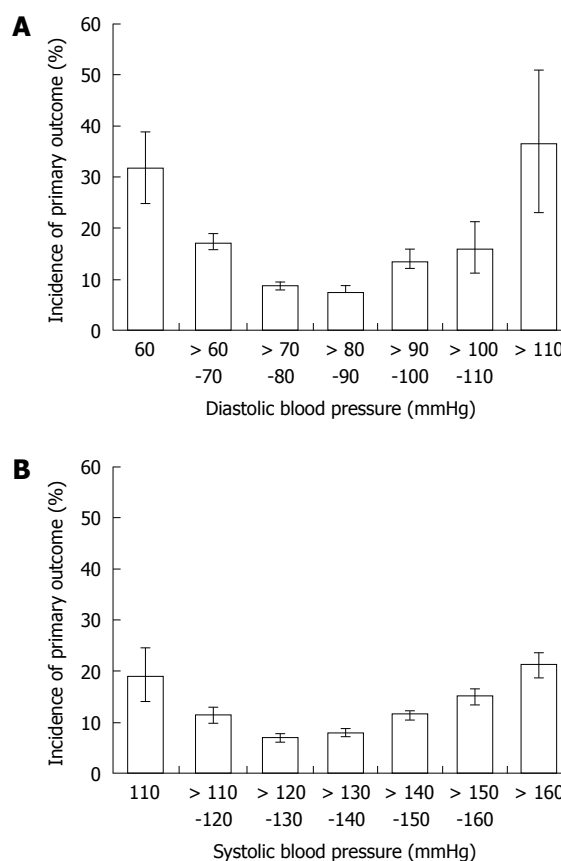


Figure 1 The J-curve effect for diastolic and systolic blood pressure and the first occurrence of all cause death, non-fatal myocardial infarction and non-fatal stroke. Adapted and modified with permission^[9].

nadir of BP for the J-curve effect was 129/74 mmHg (Figure 1). The incidence of stroke was much less than that of myocardial infarction and correlated with low SBP, whereas the incidence of myocardial infarction was correlated with low DBP. The other study is a sub-analysis of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) Study. In this study, 25620 high risk patients aged 55 years or older were equally randomized into 3 treatment regimens, telmisartan 80 mg/d, ramipril 10 mg/d, or their combination and were followed for 56 mo^[10]. A J-curve effect was observed with a SBP \leq 130 mmHg for myocardial infarction, but not for stroke (Figure 2). With respect to DBP, the highest risk for myocardial infarction occurred with an average initial DBP of 67 mmHg^[10]. All studies showing a J-curve effect are summarized in Table 1.

STUDIES WITH NO CLEAR EVIDENCE BETWEEN DBP AND J-CURVE EFFECT

Although the great majority of studies have demonstrated a J-curve effect between cardiovascular complications and DBP, there are several studies where such an effect has not been clearly demonstrated^[26-31]. These studies are summarized in Table 2. Coope *et al*^[27] did not observe any increase in cardiovascular complications with decreases

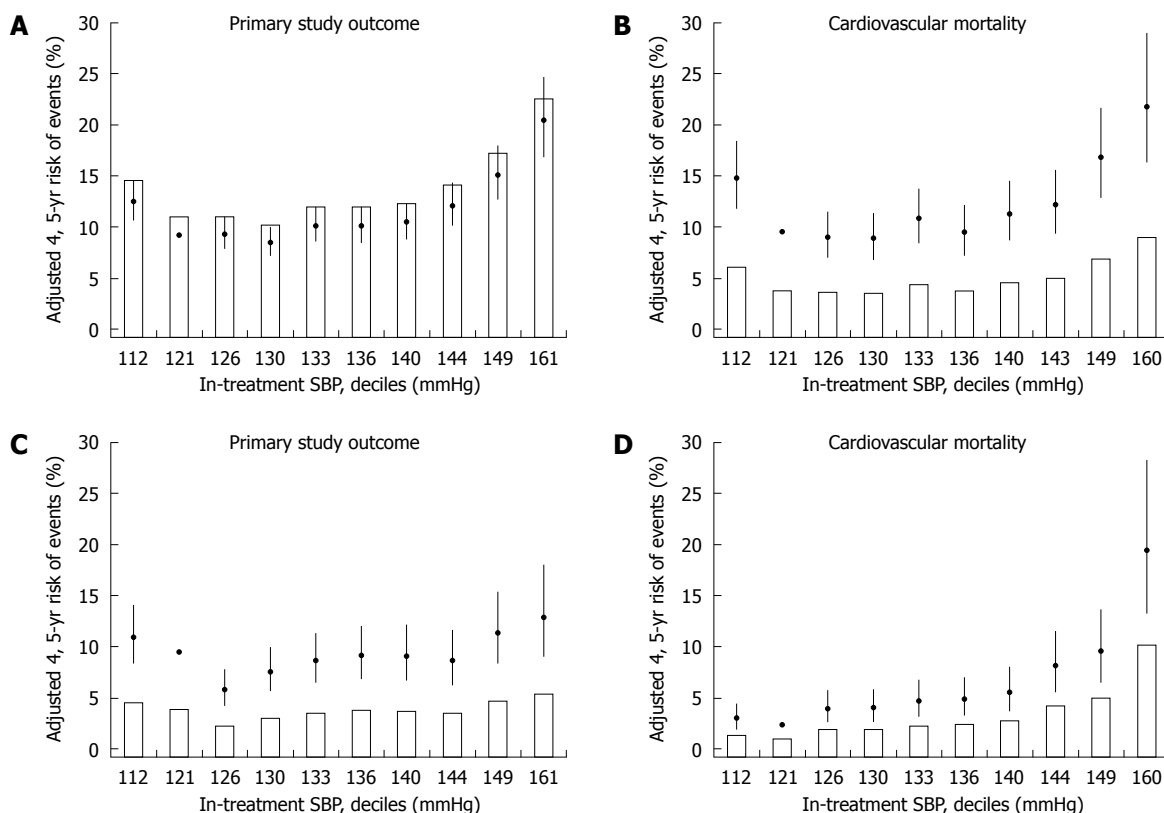
Table 1 Clinical trials demonstrating a J-curve effect for myocardial infarction, but not for stroke

Author	Subjects	Age (yr)	Follow-up (yr)	Baseline (DBP mmHg)	CAD (present)	J-curve event		
						MI	Stroke	DBP (mmHg)
Messerli <i>et al</i> ^[9]	22 576	66	2.7	86	Yes	Yes	No	76-86
Sleight <i>et al</i> ^[10]	25 620	55	4.7	82	Yes	Yes	No	75-79
Stewart <i>et al</i> ^[11]	169	44	6.3	124	No	Yes	-	100-109
Cruickshank <i>et al</i> ^[12]	902	55	6.1	109	Yes	Yes	No	80-90
Waller <i>et al</i> ^[13]	3350	50	6.5	110	Yes	Yes	-	91-98
Fletcher <i>et al</i> ^[18]	2145	51	4.0	107	Yes	Yes	No	86-91
Alderman <i>et al</i> ^[19]	1765	51	4.2	102	Yes	Yes	No	84-88
Samuelsson <i>et al</i> ^[20]	686	52	12.0	106	Yes	Yes	No	81
McCloskey <i>et al</i> ^[21]	912	30-79	3-21	104	Yes	Yes	No	84
Lindblad <i>et al</i> ^[22]	2574	59	7.4	92	Yes	Yes	No	84
Pastor-Barriuso <i>et al</i> ^[23]	7830	54	15.0	82	No	Yes	No	80
Protogerou <i>et al</i> ^[24]	331	85	3-4	-	Yes	Yes	No	< 70
Fagard <i>et al</i> ^[25]	4695	70	1-8	85	Yes	Yes	No	70-75

CAD: Coronary artery disease; DBP: Diastolic blood pressure; MI: Myocardial infarction.

Table 2 Clinical trials without clear evidence of J-curve effect

Author	Subjects	Age (yr)	Follow-up (yr)	Baseline (DBP mmHg)	CAD (present)	J-curve effect MI	Stroke	DBP (mmHg)
Wilhelmsen <i>et al</i> ^[26]	6569	40-60	3.9	107	Yes	Yes ²	No	88-89
Coope <i>et al</i> ^[27]	884	60-79	4.4	98	Yes	Yes ¹	No	80-89
Lubsen <i>et al</i> ^[29]	7661	63.0	4.9	85	Yes	Yes ³	No	85
Psaty <i>et al</i> ^[30]	4702	72.6	6.7	71	No	No	No	62
Glynn/PHS ^[31]	22071	53.2	13.0	79	Yes	No	No	65
Glynn/WHHS ^[31]	39876	53.8	6.2	78	No	No	No	70

¹Present in female smokers; ²Present for trend; ³Present for trend. CAD: Coronary artery disease; DBP: Diastolic blood pressure; MI: Myocardial infarction.Figure 2 The J-curve effect for systolic blood pressure and the incidence of the primary outcome, cardiovascular mortality and stroke in treated hypertensive patients. Adapted with permission^[10].

in SBP or DBP. In contrast, strokes were decreased by 58%. Similar findings have also been reported by other investigators^[26-31]. In the physicians and women's studies conducted by Glynn *et al*^[31], no J-curve effect was noted. However, most of these studies were observational and were not designed to show whether there was a J-curve effect observed between DBP or SBP and cardiovascular complications.

HEMODYNAMIC INTERRELATIONSHIPS BETWEEN BP, CORONARY ARTERY BLOOD FLOW AND J-CURVE EFFECT

Pathophysiologically, there is no argument regarding the occurrence of a J-curve effect and cardiovascular complications, because a BP of 0 mmHg is associated with 100% cardiovascular mortality. The question is at what pathophysiologic BP range the J-curve occurs. Since coronary artery perfusion occurs during the diastolic phase of the cardiac cycle, there should be an association between DBP and coronary artery perfusion. Studies in the dog have shown that the flow to the coronary arteries ceases when the DBP drops to 50 mmHg or lower, depending on the complete vasodilation or not of the coronary vascular bed^[32,33]. In patients with hypertension and especially in those with left ventricular hypertrophy (LVH), there is an upward shift of the coronary perfusion pressure to 70 mmHg for hypertensive patients and 80-90 mmHg for those with hypertension and LVH, compared to normotensive controls of 60 mmHg, under maximum vasodilation with intravenous infusion of sodium nitroprusside^[34]. Below these pressures the coronary blood flow decreases and the oxygen extraction increases, especially in hypertensive patients with LVH^[34]. Studies in dogs with hypertension and LVH showed that the lower range of coronary autoregulation is severely impaired below a perfusion pressure of 40 mmHg for the subendocardial myocardium and predisposes it to severe ischemia or myocardial infarction^[35]. The normal epicardial coronary arteries are conductance vessels and do not provide any resistance to blood flow and there is no detectable pressure drop along their entire length^[36]. The coronary pressure autoregulation provides a relatively constant perfusion to the myocardium over a fairly wide perfusion pressures ranging from 45-125 mmHg^[37]. Consequently, the coronary pressure autoregulation will protect the myocardium over a fairly wide epicardial pressure changes. However, in patients with CHD, the autoregulation will be compromised and a fall in DBP might lower the perfusion pressure distal to the epicardial artery stenosis below a critical level at which the autoregulation is no longer functional and the fractional flow reserve will be compromised and may lead to myocardial ischemia and myocardial infarction. This is further aggravated with the coexistence of hypertension and LVH^[34,35]. Therefore, patients with CHD, hypertension and LVH are at a greater risk of manifesting a J-curve effect with low DBP than normal persons.

CEREBRAL BLOOD FLOW AUTOREGULATION

Like the heart, the brain also possesses the intrinsic ability to regulate its blood flow through a wide range of BP levels^[38]. Under normal conditions, the cerebral blood flow (CBF) autoregulation typically operates at mean arterial pressures (MAP) in the order of 60-150 mmHg^[38]. However, these limits are not entirely fixed, and can be moderated by sympathetic nervous system activity, the vascular renin-angiotensin system and arterial CO₂ tension. In contrast to the coronary circulation, which depends on DBP, the cerebral circulation depends mostly on SBP. In a recent study using transcranial Doppler imaging, CBF autoregulation varied between a MAP of 40 and 125 mmHg^[39]. These studies show that the CBF is not seriously affected by low DBP and could explain the lack of a J-curve effect regarding strokes at low DBP in contrast with cardiovascular complications. In a pivotal study, Strandgaard *et al*^[40] studied CBF autoregulation in either untreated or ineffectively treated severe hypertensive patients, effectively treated severe hypertensive patients, or normotensive controls, and found that the lower limit of CBF autoregulation was a MAP of 113 ± 17 , 96 ± 17 and 73 ± 9 mmHg, respectively, in the 3 groups. He concluded that CBF autoregulation is shifted to higher BP levels in untreated or ineffectively treated hypertensive patients compared with effectively treated hypertensives or normal controls, and also, that effective BP control in previously severe hypertensive patients, adjusts the CBF autoregulation towards normotensive controls^[40].

DISCUSSION

The treatment of hypertension has gone through major extremes over the years, from the early advice of prominent cardiologists not to attempt to treat the disease^[2-4], to recent national and international guidelines to treat hypertension aggressively and the "lower the better"^[6-8]. Initially hypertension was considered an essential condition for survival and the term "essentielle hypertonie" was coined by the German physician Frank in 1911^[1], which continues to be used today. The French used to refer to hypertension as "fièvre essentielle", which literally means essential condition, or an ailment of life that strives to delay death^[41]. However, as more effective and safe drugs were developed the treatment of hypertension was successful and led to significant reductions in cardiovascular complications and strokes. This success eventually led to more aggressive BP control. This aggressive BP control has resulted in a higher incidence of cardiovascular complications and strokes in recent large clinical outcomes trials^[9,10]. First, Stewart^[11] and later Cruickshank *et al*^[12] noted an increase in cardiovascular complications after lowering the DBP below a certain level and coined the term "J-curve effect". This effect was subsequently noted by several investigators^[13-25], but not by others^[26-31].

What has transpired from these studies is that the heart is more vulnerable to BP changes, but not the brain, which has a much wider BP autoregulatory range. The coronary arteries are perfused during the diastolic phase of the cardiac cycle and are more vulnerable to low DBP and this situation is aggravated with the coexistence of CHD, hypertension and LVH where the coronary artery reserve is decreased^[34-37]. The question here is not whether there is a J-curve effect with low DBP, but what is a safe DBP that will provide benefits instead of increasing the risk of the treated patient. Regarding the guidelines advocating reduction of BP to < 140/90 mmHg for uncomplicated hypertensive patients and to < 130/80 mmHg for those who have coexisting CHD, diabetes or chronic kidney disease, there is no hard evidence for these recommendations as discussed by Zanchetti *et al*^[41,42], and these recommendations were mostly based on wisdom, and not facts. In addition, most clinical trials that have produced benefits from the treatment of hypertension, the BP was seldom lowered to below 140/90 mmHg. Support for these observations comes from a recent Japanese (JATOS) Study^[43]. In this study, 4418 older hypertensive Japanese patients were randomized to either an SBP reduction to < 140 mmHg ($n = 2212$) or to ≥ 140 mmHg ($n = 2206$) and followed for 2 years. At the end of the study, there was no difference in the primary endpoint of cardiovascular disease or renal failure between the 2 groups. If anything, a trend for higher cardiovascular complications was noted in the group randomized to SBP < 140 mmHg^[43]. Similar observations were recently reported from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which tested the aggressive SBP control in 4733 patients with type 2 diabetes mellitus^[44]. In this study the patients were randomized to SBP < 120 mmHg, or < 140 mmHg and were followed for 4.7 years. There was no difference between the aggressively and less aggressively treated groups with respect to cardiovascular events, and the more aggressively treated patients had significantly more side effects than the less aggressively treated patients. However, the incidence of strokes was significantly lower in the aggressively treated patients. Also, a subanalysis of 6400 diabetic patients from the INVEST study, showed that aggressive BP control was not associated with improved cardiovascular outcomes compared with the usual BP control. In addition, in their studies, Messerli *et al*^[9], and Sleight *et al*^[10], observed a J-curve effect for cardiovascular complications, for DBP < 80 mmHg and SBP < 130 mmHg. In a subanalysis of the PROVE IT-TIMI 22 trial^[45] in patients with acute coronary syndromes, a J-curve effect was noted for SBP and DBP of < 130 and < 80 mmHg, respectively. Based on the existing recommendations of professional guidelines for aggressive BP control and the recent evidence that aggressive BP control might not be beneficial, the caring physician may reach a quandary regarding decisions as to how aggressively he should treat his hypertensive patients. Since the recent evidence points towards a less aggressive control of BP, modera-

tion should be adapted. The classic Greeks used to say “ $\pi\alpha\nu \mu\epsilon\tau\rho\omicron\nu \alpha\rho\iota\sigma\tau\omicron\nu$ ” that is, “moderation is the best thing”. Regarding this matter, Mancia *et al*^[46] in a revised statement of the European Society of Hypertension guidelines stated, “On the basis of current data, it may be prudent to recommend lowering SBP/DBP to values within the range of 130-139/80-85 mmHg”. Along the same line of reasoning, Sleight *et al*^[10], proposed that “future trials should be designed to test the value of SBP lowering in high risk patients in the range of 130-150 mmHg”. To this point, Kannel *et al*^[47], caution against aggressive attempts to reduce a stubborn SBP of ≥ 140 mmHg in older individuals, because such attempts will further reduce the DBP, widen the pulse pressure (PP) and increase the cardiovascular complications. Wide PP is considered a significant afterload factor besides SBP in older individuals, causing structural cardiac changes and eventually heart failure. There is no doubt that additional prospective studies are needed to resolve this issue. Hopefully, the Systolic Blood Pressure Intervention Trial, which has similar design with the ACCORD study, with the exception that does not involve diabetic subjects, will provide the needed information when completed^[48].

In conclusion, based on the evidence presented, the onset of the J-curve effect with low BP is not uniform across all patients. Older and high risk patients with pre-existing CHD, diabetes and hypertension with LVH are more prone to develop the J-curve effect when their BP is decreased below a critical level. On the other hand, younger healthier individuals with uncomplicated hypertension can tolerate much lower BP without developing the J-curve effect. However, when physicians are dealing with older and high risk patients, they should refrain from aggressive BP treatment, and not lower their SBP and DBP < 130 and < 80 mmHg till new evidence becomes available.

REFERENCES

- 1 Frank E. *Deutsches Archiv Fur Klin Medizin* 1911; **103**: 397-412
- 2 Hay J. A British Medical Association Lecture on THE SIGNIFICANCE OF A RAISED BLOOD PRESSURE. *Br Med J* 1931; **2**: 43-47
- 3 White PD. Heart disease. 2nd ed. New York, NY: MacMillan Co., 1937
- 4 Friedberg CK. Diseases of the heart. Philadelphia, PA: WB Saunders Co., 1949
- 5 Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA* 1967; **202**: 1028-1034
- 6 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**: 1206-1252
- 7 Japanese Society of Hypertension. Guidelines for the management of hypertension (JSH 2004). *Hypertens Res* 2006; **29** (Suppl): 1-106
- 8 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina

- R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**: 1105-1187
- 9 **Messerli FH**, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006; **144**: 884-893
- 10 **Sleight P**, Redon J, Verdecchia P, Mancia G, Gao P, Fagard R, Schumacher H, Weber M, Böhm M, Williams B, Pogue J, Koon T, Yusuf S. Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study. *J Hypertens* 2009; **27**: 1360-1369
- 11 **Stewart IM**. Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension. *Lancet* 1979; **1**: 861-865
- 12 **Cruickshank JM**, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. *Lancet* 1987; **1**: 581-584
- 13 **Waller PC**, Isles CG, Lever AF, Murray GD, McInnes GT. Does therapeutic reduction of diastolic blood pressure cause death from coronary heart disease? *J Hum Hypertens* 1988; **2**: 7-10
- 14 **Farnett L**, Mulrow CD, Linn WD, Lucey CR, Tuley MR. The J-curve phenomenon and the treatment of hypertension. Is there a point beyond which pressure reduction is dangerous? *JAMA* 1991; **265**: 489-495
- 15 **D'Agostino RB**, Belanger AJ, Kannel WB, Cruickshank JM. Relation of low diastolic blood pressure to coronary heart disease death in presence of myocardial infarction: the Framingham Study. *BMJ* 1991; **303**: 385-389
- 16 **Hakala SM**, Tilvis RS, Strandberg TE. Blood pressure and mortality in an older population. A 5-year follow-up of the Helsinki Ageing Study. *Eur Heart J* 1997; **18**: 1019-23
- 17 **Messerli FH**, Panjath GS. The J-curve between blood pressure and coronary artery disease or essential hypertension: exactly how essential? *J Am Coll Cardiol* 2009; **54**: 1827-1834
- 18 **Fletcher AE**, Beevers DG, Bulpitt CJ, Butler A, Coles EC, Hunt D, Munro-Faure AD, Newson R, O'Riordan PW, Petrie JC. The relationship between a low treated blood pressure and IHD mortality: a report from the DHSS Hypertension Care Computing Project (DHCCP). *J Hum Hypertens* 1988; **2**: 11-15
- 19 **Alderman MH**, Ooi WL, Madhavan S, Cohen H. Treatment-induced blood pressure reduction and the risk of myocardial infarction. *JAMA* 1989; **262**: 920-924
- 20 **Samuelsson OG**, Wilhelmsen LW, Pennert KM, Wedel H, Berglund GL. The J-shaped relationship between coronary heart disease and achieved blood pressure level in treated hypertension: further analyses of 12 years of follow-up of treated hypertensives in the Primary Prevention Trial in Gothenburg, Sweden. *J Hypertens* 1990; **8**: 547-555
- 21 **McCloskey LW**, Psaty BM, Koepsell TD, Aagaard GN. Level of blood pressure and risk of myocardial infarction among treated hypertensive patients. *Arch Intern Med* 1992; **152**: 513-520
- 22 **Lindblad U**, Råstam L, Rydén L, Ranstam J, Isacsson SO, Berglund G. Control of blood pressure and risk of first acute myocardial infarction: Skaraborg hypertension project. *BMJ* 1994; **308**: 681-686
- 23 **Pastor-Barriuso R**, Banegas JR, Damián J, Appel LJ, Guallar E. Systolic blood pressure, diastolic blood pressure, and pulse pressure: an evaluation of their joint effect on mortality. *Ann Intern Med* 2003; **139**: 731-739
- 24 **Protogerou AD**, Safar ME, Iaria P, Safar H, Le Dudal K, Filipovsky J, Henry O, Ducimetière P, Blacher J. Diastolic blood pressure and mortality in the elderly with cardiovascular disease. *Hypertension* 2007; **50**: 172-180
- 25 **Fagard RH**, Staessen JA, Thijs L, Celis H, Bulpitt CJ, de Leeuw PW, Leonetti G, Tuomilehto J, Yodfat Y. On-treatment diastolic blood pressure and prognosis in systolic hypertension. *Arch Intern Med* 2007; **167**: 1884-1891
- 26 **Wilhelmsen L**, Berglund G, Elmfeldt D, Fitzsimons T, Holmgren H, Hosie J, Hörnkvist PE, Pennert K, Tuomilehto J, Wedel H. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. *J Hypertens* 1987; **5**: 561-572
- 27 **Coope J**, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. *Br Med J (Clin Res Ed)* 1986; **293**: 1145-1151
- 28 **Hasebe N**, Kido S, Ido A, Kenjiro K. Reverse J-curve relation between diastolic blood pressure and severity of coronary artery lesion in hypertensive patients with angina pectoris. *Hypertens Res* 2002; **25**: 381-387
- 29 **Lubsen J**, Wagener G, Kirwan BA, de Brouwer S, Poole-Wilson PA. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with symptomatic stable angina and hypertension: the ACTION trial. *J Hypertens* 2005; **23**: 641-648
- 30 **Psaty BM**, Furberg CD, Kuller LH, Cushman M, Savage PJ, Levine D, O'Leary DH, Bryan RN, Anderson M, Lumley T. Association between blood pressure level and the risk of myocardial infarction, stroke, and total mortality: the cardiovascular health study. *Arch Intern Med* 2001; **161**: 1183-1192
- 31 **Glynn RJ**, L'Italien GJ, Sesso HD, Jackson EA, Buring JE. Development of predictive models for long-term cardiovascular risk associated with systolic and diastolic blood pressure. *Hypertension* 2002; **39**: 105-110
- 32 **Bellamy RF**. Diastolic coronary artery pressure-flow relations in the dog. *Circ Res* 1978; **43**: 92-101
- 33 **Mosher P**, Ross J Jr, McFate PA, Shaw RF. Control of coronary blood flow by an autoregulatory mechanism. *Circ Res* 1964; **14**: 250-259
- 34 **Polesse A**, De Cesare N, Montorsi P, Fabbicchi F, Guazzi M, Loaldi A, Guazzi MD. Upward shift of the lower range of coronary flow autoregulation in hypertensive patients with hypertrophy of the left ventricle. *Circulation* 1991; **83**: 845-853
- 35 **Harrison DG**, Florentine MS, Brooks LA, Cooper SM, Marcus ML. The effect of hypertension and left ventricular hypertrophy on the lower range of coronary autoregulation. *Circulation* 1988; **77**: 1108-1115
- 36 **Pijls NH**, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, el Gamal MI. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation* 1995; **92**: 3183-3193
- 37 **Pijls NHJ**, De Bruyne B. Coronary pressure. Dordrecht: Kluwer Academic Publishers, 1997
- 38 **Paulson OB**, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990; **2**: 161-192
- 39 **Lucas SJ**, Tzeng YC, Galvin SD, Thomas KN, Ogoh S, Ainslie PN. Influence of changes in blood pressure on cerebral perfusion and oxygenation. *Hypertension* 2010; **55**: 698-705
- 40 **Strandgaard S**. Autoregulation of cerebral blood flow in hypertensive patients. The modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. *Circulation* 1976; **53**: 720-727
- 41 **Zanchetti A**, Amery A, Berglund G, Cruickshank JM, Hansson L, Lever AF, Sleight P. How much should blood pressure be lowered? The problem of the J-shaped curve. *J Hypertens Suppl* 1989; **7**: S338-S348

- 42 **Zanchetti A**, Grassi G, Mancia G. When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. *J Hypertens* 2009; **27**: 923-934
- 43 **JATOS Study Group**. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res* 2008; **31**: 2115-2127
- 44 **Cushman WC**, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**: 1575-1585
- 45 **Bangalore S**, Qin J, Sloan S, Murphy SA, Cannon CP. What is the optimal blood pressure in patients after acute coronary syndromes?: Relationship of blood pressure and cardiovascular events in the PRavastatin OR atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. *Circulation* 2010; **122**: 2142-2151
- 46 **Mancia G**, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, Cifkova R, Clément D, Coca A, Dominiczak A, Erdine S, Fagard R, Farsang C, Grassi G, Haller H, Heagerty A, Kjeldsen SE, Kiowski W, Mallion JM, Manolis A, Narkiewicz K, Nilsson P, Olsen MH, Rahn KH, Redon J, Rodicio J, Ruilope L, Schmieder RE, Struijker-Boudier HA, van Zwieten PA, Viigimaa M, Zanchetti A. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 2009; **27**: 2121-2158
- 47 **Kannel WB**, Wilson PW, Nam BH, D'Agostino RB, Li J. A likely explanation for the J-curve of blood pressure cardiovascular risk. *Am J Cardiol* 2004; **94**: 380-384
- 48 Systolic Blood Pressure Intervention Trial (SPRINT). Available from: URL: <http://clinicaltrials.gov/ct2/show/NCT01206062>

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Renin and cardiovascular disease: Worn-out path, or new direction?

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INTRODUCTION

A link between the kidney and left ventricular hypertrophy was reported by Richard Bright as early as 1836^[1], and was followed by the studies of Tigerstedt and Berman, who reported on the pressor effects of renal extracts and named the putative pressor renin in recognition of the organ of origin^[2,3]. Thus began the saga of the renin-angiotensin system (RAS) and its role in cardiovascular disease (CVD), a role which continues to evolve. A century of research has revealed that the RAS plays an important role in the regulation of blood pressure and the development of hypertension, atherosclerosis, heart failure, type 2 diabetes mellitus and renal disease^[4]. Renin is the first and rate limiting enzyme of the RAS cascade which leads to the production of various metabolites which function as key regulators of blood pressure, vascular tone, and salt and water balance, of which angiotensin II (Ang II) is the most studied (Figure 1). Current strategies to inhibit RAS for cardiovascular benefit include angiotensin converting enzyme (ACE) inhibitors, which block the conversion of angiotensin I (Ang I) to Ang II, and angiotensin receptor blockers (ARBs), which prevent the actions of Ang II, specifically on the angiotensin type 1 receptor, the receptor responsible for key adverse cardiovascular effects of Ang II (Figure 1). Both ACE inhibi-

Abstract

Inhibition of the renin angiotensin system has beneficial effects in cardiovascular prevention and treatment. The advent of orally active direct renin inhibitors adds a novel approach to antagonism of the renin-angiotensin system. Inhibition of the first and rate-limiting step of the renin angiotensin cascade offers theoretical advantages over downstream blockade. However, the recent discovery of the (pro)renin receptor which binds both renin and prorenin, and which can not only augment catalytic activity of both renin and prorenin in converting angiotensinogen to angiotensin I, but also signal intracellularly *via* various pathways to modulate gene expression, adds a significant level of complexity to the field. In this review, we will examine the basic and clinical data on renin and its inhibition in the context of cardiovascular pathophysiology.

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tors and ARBs are established antihypertensive agents, and have beneficial effects in systolic heart failure, atherosclerotic disease, diabetic nephropathy and renal disease^[4]. The discovery of the (pro)renin receptor (PRR), which binds both renin and its precursor, and the successful development of the first orally effective renin inhibitor has opened new avenues in the field of RAS and CVD. Renin inhibition, with the potential for augmented antagonism of RAS, could help to prevent the epidemic of CVD which continues unabated despite the use of ACE inhibitors and ARBs^[5].

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The first and the rate-limiting step in the RAS pathway is the conversion of angiotensinogen to Ang I by renin (Figure 1). Renin hydrolyzes the Leu10-Val11 bond of angiotensinogen, to generate the decapeptide Ang I [Ang-(1-10)]^[6]. ACE present in the endothelium and tissues, as well as non-ACE pathways such as chymase, cathepsin G, and kallikrein-like enzymes, convert Ang I to the octapeptide Ang II. Ang II, acting through its receptors, type 1 (ATR1) and type 2 (ATR2), is responsible for the acute and the chronic effects of RAS. Ang II promotes renal and systemic arteriolar constriction and reabsorption of sodium in the proximal segments of the nephron, effects which could be beneficial in acute injury by preservation of intravascular volume, maintenance of blood pressure and repair of vascular injury^[7]. However, chronic activation of ATR1 leads to abnormal gene expression and tissue remodeling, such as an increase in the synthesis of aldosterone by the adrenal zona glomerulosa, and increased expression of matrix proteins such as collagens I and III^[8] and fibronectin^[9,10]. In contrast, ATR2 stimulation provides cardiorenal protection through receptor-mediated vasodilatation, kinin-mediated anti-proliferative and pro-apoptotic effects in the heart and vasculature, and beneficial effects on sodium reabsorption by the proximal tubules of the kidney^[11].

As shown in Figure 1, there are other active metabolites that are products of the RAS, of which, Ang-(1-7)^[12,13] is the most important. Ang-(1-7) can be produced by the action of tissue endopeptidases especially neprilysin on Ang I^[14-16], or from Ang II by the action of angiotensin converting enzyme 2 (ACE2). Ang-(1-7) opposes the endogenous actions of tissue Ang II, provides cardiorenal protection by binding to the Mas protooncogene receptor^[17]. Apart from its anti-arrhythmogenic, antithrombotic and growth inhibitory effects, the most prominent effect of Ang-(1-7) is the inhibition of the Ang II-induced vasoconstriction^[18-20]. Ang-(1-7) is subsequently metabolized by ACE and aminopeptidases to inactive fragments Ang-(1-5), Ang-(1-4), Ang-(2-7) and Ang-(3-7)^[21]. Ang III [Ang-(2-8)] and Ang IV [Ang-(3-8)] are also produced by cleavage of Ang II. The functional role of Ang III and IV is relatively unclear, Ang III being a less potent stimulator than Ang II, and Ang IV playing a role in regulating

local blood flow to the brain^[22]. Ang-(1-12)^[20], a relatively new addition to the family of RAS effectors, is produced directly from angiotensinogen by a non-renin enzyme. It contains the 12 amino acids from the N-terminus of angiotensinogen and can act as a precursor for the generation of Ang II by chymase^[23].

PRORENIN RECEPTOR

Earlier research had shown that 2 proteins bind prorenin and renin, i.e. mannose 6-phosphate receptor (M6P-R)^[24,25] and renin binding protein^[26]. Renin bound to these receptors does not have any functional effect^[27,28]. For example, after binding of prorenin to M6P-R, the M6P-R/prorenin complex is internalized and activated to mature renin by proteolysis, but this intracellular renin is degraded and does not affect intra- or extracellular Ang II generation. In contrast to these earlier studies, Nguyen *et al.*^[29,30] discovered that renin binding to surface receptors on cultured human mesangial cells induced a hypertrophic effect and an increase in the expression of plasminogen activator inhibitor-1. Six years after their initial report, Dr Nguyen's group identified the specific receptor by expression cloning that eventually came to known as the (pro)renin receptor since it was found to bind both renin and prorenin^[31].

Biology of the prorenin receptor

The PRR is a 35 kDa protein consisting of 2 fragments: an extracellular soluble N-terminal domain and a C-terminal domain. The N-terminal (28 kDa) domain of the PRR specifically binds to renin and prorenin (Figure 2). The C terminal domain of the receptor has a cytoplasmic and a transmembrane domain^[31,32], and is homologous to a 8.9-kDa truncated protein termed M8-9 which was recently renamed ATP6ap2, and can associate with the vacuolar H(+)-ATPase, which plays an important role in acidification of urine^[33,34]. The presence of the PRR has also been demonstrated in the glomerular mesangium^[35], in the sub-endothelium of coronary and renal arteries, and in smooth muscle cells^[36]. The highest concentration of mRNA for PRR is seen in the heart, brain, placenta, with lower levels reported in the kidney and liver^[31].

Traditionally, human prorenin was considered as the enzymatically inactive biosynthetic precursor of renin^[37]. In addition to the juxtaglomerular cells of the kidneys (which also secrete renin) prorenin is secreted by reproductive organs, adrenal gland, eye and the submandibular gland^[38]. Two pathways of activation of prorenin to renin have been described: proteolytic and non-proteolytic. The proteolytic conversion of prorenin to renin occurs by the cleavage of the 43-amino acid N-terminal prosegment in juxtaglomerular cells to produce the active metabolite renin, an aspartyl protease^[39,40]. There are 2 forms in which the prorenin molecule exists: open and closed. It has been suggested that prorenin is a precursor renin with an amino acid chain (prosegment) that covers the cleft containing the active site and thus prevents access of an-

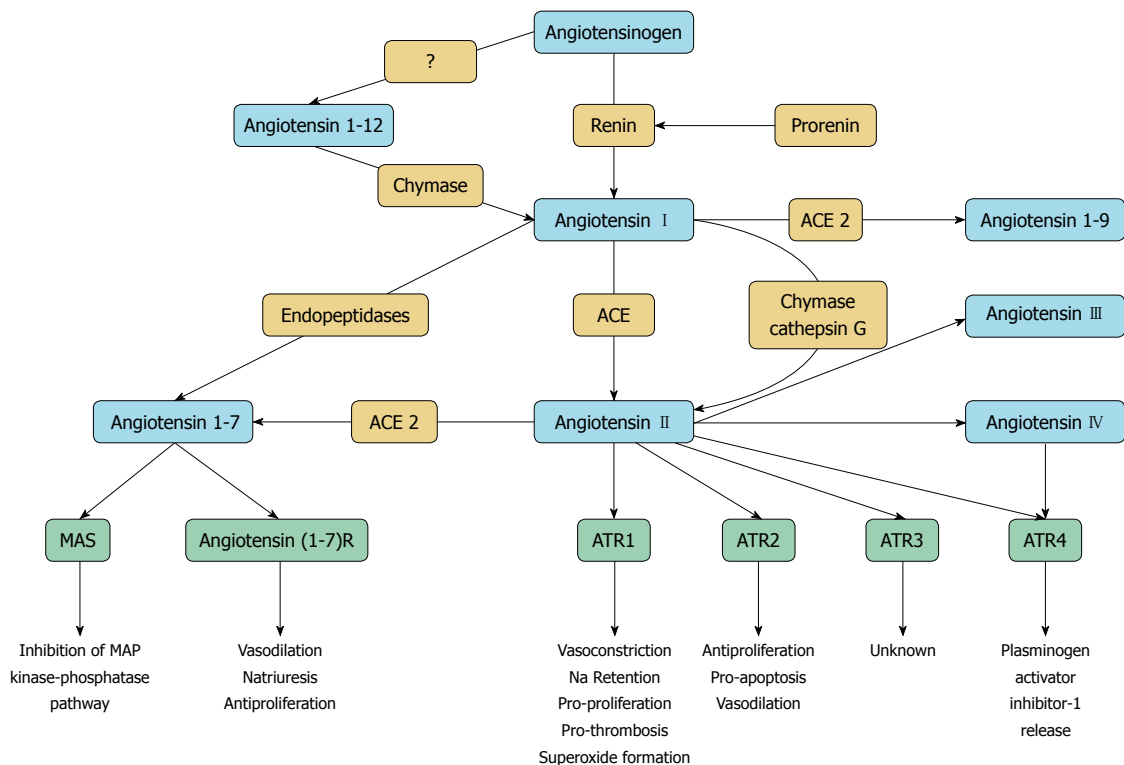


Figure 1 Schema of the renin-angiotensin system. ATR: Angiotensin II receptor; MAS: Mas proto-oncogene receptor; ACE: Angiotensin converting enzyme.

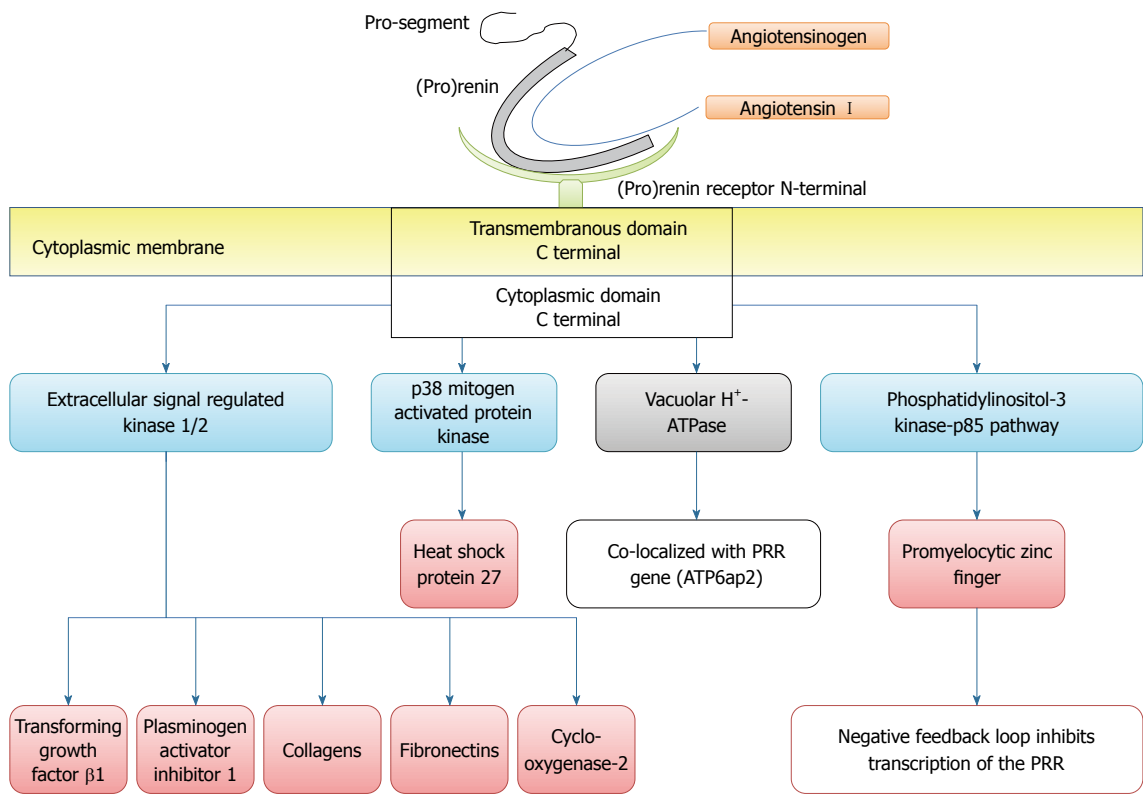


Figure 2 Signal transduction mediated by the (pro)renin receptor. PRR: (Pro)renin receptor.

giotensinogen (Figure 2), which is considered the closed conformation and accounts for 98% of prorenin under physiological conditions. However, at acidic pH prorenin

undergoes a conformational change to expose its active site^[41]. Interestingly, irrespective of whether renin or prorenin is present in the open (active) conformation

after binding to the PRR, they are capable of converting angiotensinogen to angiotensin I^[31,42].

Based on the mechanism of non-proteolytic activation of prorenin to renin, Suzuki *et al.*^[43], formulated the theory of “gate and the handle”. They proposed that the prosegment, which was termed the “handle region”, folds into an active site cleft of prorenin to prevent catalytic conversion of angiotensinogen to Ang I (Figure 2). They also proposed that any synthetic protein that mimics the handle region, i.e. handle region peptides (HRP), can bind to the catalytically active site of prorenin and prevent its non proteolytic activation (decoy hypothesis). This theory was later validated, albeit with limited success. HRP infusion normalized an elevated renal Ang II level in diabetic rats^[44]. Rat HRP infusion completely prevented the development of diabetic nephropathy in hemi-nephrectomized streptozocin-induced diabetic rats and also caused the regression of established diabetic nephropathy^[45,46]. HRP was also demonstrated to reduce cardiac Ang II levels and cardiac fibrosis in stroke-prone spontaneously hypertensive rats without affecting blood pressure^[47]. However, later studies showed that HRP failed to affect prorenin binding and prorenin-induced Ang I generation in vascular smooth muscle cells overexpressing the human PRR, even at relatively high concentration^[48]. Chronic HRP infusion also did not ameliorate target organ damage in Goldblatt hypertensive rats^[49]. Attempts to reproduce the effects of HRP *in vivo* were also unsuccessful^[50].

The role of tissue activation of PRR independent of the plasma concentration has been investigated in recent years. The level of prorenin in the human plasma is approximately 10-fold higher than that of renin (0.5 pmol/L)^[51]. The K_d value of PRR for prorenin and renin is 5 nmol/L and 20 nmol/L, respectively^[52,53]. In spite of the high concentration of prorenin in human plasma, its level is not adequate enough to bind to PRR. Thus, significant prorenin binding to its receptor occurs only at tissue sites where it is produced locally, i.e. in kidneys, ovaries, testis, adrenal gland, and eye^[39]. Similarly, the high renin concentration required to activate PRR may occur only in the kidneys.

Prorenin receptor signal transduction

The binding of the PRR by prorenin or renin triggers intracellular signaling and activates 3 main pathways (Figure 2). The most important of these, the extracellular signal-regulated kinase (ERK) 1/2 signaling pathway has been shown to be activated in mesangial cells^[30], vascular smooth muscle cells^[53], cardiomyocytes^[54] and renal tubular epithelial cells^[54,55] in an Ang II-independent manner. Signal transduction *via* the ERK pathway upregulates transforming growth factor β 1 gene expression^[56,57] as well as the genes coding for the plasminogen activator inhibitor-1^[56], collagens, fibronectin and cyclooxygenase-2^[58]. Ligand binding to PRR also activates the p38 mitogen-activated protein kinase (MAPK)-heat shock protein 27 cascade^[59,60] and the promyelocytic zinc finger protein-phosphatidylinositol-3-kinase-p85 α pathway^[61].

These varied signal transduction pathways are independent of Ang II generation and follow binding of both renin and prorenin to the PRR.

Other than signal transduction *via* the above-mentioned pathways, vacuolar H⁺-ATPase which has been co-localized with PRR has been shown to have a key role in urinary acidification^[34]. The gene for the PRR/ATP6ap2 component of the vacuolar H⁺-ATPase is conserved across a wide range of vertebrate and invertebrate species and mutation of the ATP6ap2 gene in zebrafish leads to their death early during development^[33]. Recently, cardiomyocyte specific ablation of Atp6ap2 has been shown to result in lethal heart failure^[62].

ALISKIREN

Initial renin inhibitors were peptides, and hence had poor bioavailability, rapid rates of elimination and weak antihypertensive activity. Therefore, they never entered the clinical arena^[63]. In 2003, by using a combination of molecular modeling and crystallographic analysis, Wood *et al.*^[64] designed a novel renin inhibitor, aliskiren [(2S,4S,5S,7S)-5-amino-N-(2-carbamoyl-2,2-dimethylethyl)-4-hydroxy-7-[[4-methoxy-3-(3-methoxypropoxy) phenyl]methyl]-8-methyl-2-(propan-2-yl)nonanamide], which did not require the extended peptide-like backbone of earlier inhibitors^[65,66]. The addition of various aromatic side chains dramatically increased its affinity for renin and increased its duration of action^[65]. Aliskiren is highly soluble in water (350 mg/mL at pH 7.4), and has a molecular weight of 609.8 Da (551.8 Da as the free base)^[64].

Pharmacokinetic properties

Aliskiren is rapidly absorbed through the oral route reaching a maximum plasma concentration within 1-3 h^[67,68]. However, it has low bioavailability: 2.4% in rats, 16% in marmosets, and approximately 2.6% in humans^[69]. The plasma half-life of aliskiren in rats, marmosets and humans is 23, 26 and 23-70 h respectively^[65,67,70-73]. When administered once daily, the steady state concentration of aliskiren is reached in 7-8 d^[67]. Food intake reduces C_{max} by 85% and area under the curve by 71%^[69]. Recently, concomitant administration of grapefruit, orange and apple juices (inhibitors of organic anion transporting polypeptide 2B1 influx transporter) with aliskiren have been shown to reduce the plasma aliskiren area under the curve by 61%, 62% and 63%, respectively^[74,75]. Thus, aliskiren should be taken carefully with regard to meals and in a routine manner to avoid any variability^[69]. Aliskiren is moderately bound to plasma proteins (47%-51%) in human plasma. However, the free plasma concentration of aliskiren is not affected by pathophysiological changes in protein concentration as occurs in chronic diseases. The volume of distribution of aliskiren is estimated as 135 L after a single 20 mg intravenous injection in healthy subjects indicating substantial extravascular distribution^[76].

In humans, only 20% of aliskiren is metabolized. The

major enzymes responsible for this appears to be cytochrome P450 (CYP) 3A4^[69,77]. Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C19, 2D6, 2E1 and CYP3A)^[66]. Age has a modest impact on aliskiren bioavailability in healthy volunteers^[68]. However, in clinical trials, the safety and tolerability was similar in the 2 groups^[67]. A pooled analysis of 7 clinical trials showed that the area under the curve and C_{max} were slightly lower in the healthy male (24%) than in the healthy female (30%) population, which was thought to be due to a lower bodyweight in females (66.0 kg) as compared to males (78.5 kg)^[69]. However, in clinical trials, there was no difference in blood pressure lowering efficacy, or safety and tolerability in women compared to men^[78]. Similarly, race does not significantly influence the pharmacokinetics of aliskiren^[67,69]. The dose of aliskiren does not need to be changed in the presence of hepatic and renal impairment though caution is advised in the presence of severe renal failure, particularly in those with sodium depletion^[69].

No clinically significant pharmacokinetic drug-drug interaction was noted with commonly used antihypertensives, such as ramipril, valsartan, amlodipine, hydrochlorothiazide, atenolol^[79,80], antihyperglycemic medications such as metformin and pioglitazone^[69], lipid-lowering agents such as lovastatin and fenofibrate, the cardiac glycoside digoxin^[81] or the antianginal drug isosorbide mononitrate. Co-administration of P-glycoprotein inhibitors like atorvastatin, ketoconazole or cyclosporine resulted in significant increases in aliskiren levels. Concomitant use of aliskiren with cyclosporine is not recommended.

Potential benefits of renin inhibition over traditional methods of RAS antagonism

An important reason for the suboptimal success of ACE inhibitors, ARB, aldosterone antagonists and their combination could be the phenomenon termed “ACE escape”. Even maximal doses of ACE inhibitors do not completely suppress the production of Ang II^[82], since ACE-independent pathways such as chymase, cathepsin G and kallikrein-like enzymes also contribute to Ang II production. In humans these alternate pathways may be responsible for up to one-third of Ang II. The importance of these pathways becomes even more important at the level of end organs especially heart^[83], kidney^[84] and the vascular endothelium^[85]. The other important rationale for ACE escape is a reactive rise (due to interruption of Ang II negative feedback) in plasma renin concentration (PRC) and more importantly plasma renin activity (PRA) (Table 1). An elevated PRA eventually leads to increased Ang II production, and is associated with an increased risk of major cardiovascular events, cardiovascular death, all-cause mortality and heart failure in high-risk patients with stable chronic vascular disease and/or diabetes^[86-88].

Renin inhibition, by inhibiting the first and rate limiting step in the RAS cascade, and by inhibiting the activity of elevated levels of renin, could lead to more complete blockade of the RAS than that obtained by the use of ACE inhibitors and ARBs. Although renin

Table 1 Effect of commonly used antihypertensives on effectors of the renin-angiotensin system

	PRC	PRA	Ang I	Ang II	Ang III	Ang IV	Ang-(1-7)
ACE-I	↑	↑	↑	↓	↓	↑	↑
ARB	↑	↑	↑	↓	↑	↓	↑
DRI	↑	↓	↓	↑	↓	↓	↓
Diuretics	↑	↑	↑	↑	Not known	Not known	↑/Not known
CCB	↔	↔	↔	↔	Not known	Not known	Not known
β blockers	↓	↓	↓	↓	Not known	Not known	↓/Not known

¹Effect shown with hydrochlorothiazide only; ²Effect shown with propranolol only. PRC: Plasma renin concentration; PRA: Plasma renin activity; Ang: Angiotensin; ACE-I: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers; DRI: Direct renin inhibitors; CCB: Calcium channel blockers.

inhibition leads to higher levels of PRC than seen with ACE inhibition or ARBs, PRA is considerably reduced. The concept has been validated by multiple clinical trials. In a crossover study of 12 mildly sodium depleted normotensive healthy human volunteers, aliskiren decreased PRA and urinary aldosterone levels compared with valsartan^[71]. Multiple studies have shown similar favorable comparisons with standard antihypertensives in sodium replete normotensive subjects as well as in mild to moderately hypertensive patients^[89-93]. However, Sealey and Laragh have questioned the long term efficacy of this approach^[94], postulating that the reactive increase in PRC might overcome the inhibitory effects of aliskiren, as evidenced by the fact that a few patients in clinical trials had a rise in blood pressure after administration of aliskiren. This issue was examined by Stanton *et al.*^[95], who performed a meta-analysis using data on 4877 patients enrolled in 8 randomized, double blind, placebo-and/or active-controlled trials. There were no significant differences in the frequency of increases in systolic (> 10 mmHg, $P = 0.30$) or diastolic (> 5 mmHg, $P = 0.65$) pressure among those treated with aliskiren (3.9% and 3.1%, respectively), angiotensin receptor blockers (4.0% and 3.7%), ramipril (5.7% and 2.6%), or hydrochlorothiazide (4.4% and 2.7%). Increases in blood pressure were considerably more frequent in the placebo group (12.6% and 11.4%, $P < 0.001$). In contrast, Nussberger *et al.*^[96] have demonstrated that the greatest blood pressure lowering effect of aliskiren occurred in patients with high baseline PRA, while its effects were considerably less pronounced in those with low PRA.

Another potential benefit of aliskiren relates to its prolonged half-life (23-70 h). Andersen *et al.*^[97] performed a randomized controlled trial in which aliskiren and ramipril were administered for 6 mo followed by a controlled withdrawal of the medications. The change in the level of PRA, PRC and control of the blood pressure 2 wk after the discontinuation of each medication was assessed. Four wk after stopping aliskiren-based therapy, PRA remained 52% below pre-treatment baseline in contrast

to the ramipril group in which PRA returned to baseline after 2 wk. In parallel with PRA, most of the blood pressure lowering effects of ramipril-based treatment disappeared 1 wk after stopping therapy. In contrast, median blood pressure values did not exceed 140/90 mmHg even at 4 wk after stoppage of aliskiren. The gradual return of BP towards baseline levels observed after stopping aliskiren-based therapy reflects the prolonged effects of aliskiren on PRA. In animal studies it has been demonstrated that aliskiren tends to substantially accumulate in the kidneys^[98]. The accumulation and slow release of aliskiren from the kidneys after stopping treatment may explain the persistent effects of aliskiren on PRA beyond the half-life of the drug^[99]. Prolonged suppression of PRA could be clinically beneficial especially in those patients whose compliance is inadequate.

Preclinical studies of aliskiren

Wood *et al.*^[100] were the first to demonstrate the benefit of aliskiren in lowering blood pressure in sodium depleted marmosets and spontaneously hypertensive rats. An important limitation for preclinical studies is the fact that renin is a species-specific enzyme. For example, the IC₅₀ of the oral human renin inhibitor aliskiren for rat renin is 100-fold the value for human renin (0.6 nM). A double transgenic rat model overexpressing human renin and angiotensinogen genes has been used to study the effects of renin inhibition on end organ protection^[101]. In this model, aliskiren (3 and 0.3 mg/kg per day administered subcutaneously) decreased blood pressure, albuminuria, and left ventricular hypertrophy, and improved survival^[102]. These effects were found to be as effective as high dose valsartan (10 mg/kg per day) and more prominent than low dose valsartan (1 mg/kg per day). In another study utilizing the same model, aliskiren attenuated increases in myocardial oxidant stress and fibrosis, while the ARB irbesartan demonstrated greater reductions in blood pressure and myocardial oxidant stress^[103]. Similarly, Whaley-Connell *et al.*^[104] demonstrated that aliskiren and irbesartan produced similar reductions in albuminuria and renal oxidant stress and RAS activation in this model. Aliskiren has recently been shown to provide protection against the development of doxorubicin-induced acute cardiomyopathy in rats^[105]. Pretreatment with aliskiren significantly reduced the rise in malondialdehyde levels and attenuated doxorubicin-induced inhibition of glutathione activity in the myocardium. Aliskiren has also been shown to improve cardiac function and remodeling after myocardial infarction independent of blood pressure control^[106], prevent the development of atherosclerosis in mice^[107], and improve systemic insulin resistance^[108] and pancreatic remodeling^[109] in transgenic Ren2 rat which overexpress tissue renin, and ameliorate chlorhexidine digluconate-induced peritoneal fibrosis in rats^[110].

The mechanisms of the putative beneficial effects of aliskiren on end organ protection are still a matter of debate. Not every tissue synthesizes renin locally, but depends on the extraction of renin from the blood^[111,112]. It

is possible that locally produced prorenin could generate Ang I. Also, as described before, the binding of renin or prorenin to their receptor also activates the MAPK/ERK-1/2 signaling pathway. The activation of the intracellular pathway is independent with no correlation with the production of the Ang II. So far, *in vitro* studies have failed to show any effects of aliskiren on blocking this signaling pathway, and aliskiren does not affect the binding of renin or prorenin to their receptor^[54,113,114]. Hence, based on current evidence, it could be surmised that the beneficial effects of aliskiren are most likely due to the prevention of the production of Ang II both at the systemic and local tissue level.

Effect of aliskiren in clinical hypertension

Aliskiren is an effective medication for the treatment of hypertension^[115]. Stanton *et al.*^[116] found that aliskiren reduced daytime ambulatory systolic pressure in a dose-dependent manner. In a pooled analysis of patients with mild to moderate hypertension, aliskiren 150 and 300 mg showed a mean reduction in systolic blood pressure of 8.7-13.0 mmHg and 14.1-15.8 mmHg respectively when compared with placebo (2.9-10.0 mmHg)^[117]. The mean reduction in diastolic blood pressure was 3.3-8.6 mmHg, 7.8-10.3 mmHg and 10.3-12.3 mmHg with placebo, 150 mg aliskiren and 300 mg aliskiren, respectively. The antihypertensive effect of aliskiren has been shown to be comparable in men and women^[77] and consistent across subgroups of age^[77], metabolic syndrome^[118,119] and obesity^[77].

The long pharmacological half-life of aliskiren makes it an ideal medication for once daily use. In a study involving 672 patients, the antihypertensive effect was maintained throughout a 24-h dosing period by 3 different doses of aliskiren (150, 300 and 600 mg)^[120]. The effect of a daily dose of aliskiren of 150 mg is comparable with irbesartan 150 mg/d^[121]. There is a minimal effect below the dose of 75 mg and a plateau of the dose response curve is reached at 300 mg. There is little or no additional blood pressure reduction with a higher dose of 600 mg. Overall, the tolerability profile of aliskiren is similar to that of placebo. The only adverse effect seen with aliskiren is diarrhea (9.5% with 600 mg; 2.3% with 300 mg; 1.2% with placebo). The higher occurrence of diarrhea is related to the high-unabsorbed fraction of the medication (77.5%)^[69].

The antihypertensive effect of aliskiren is comparable to that of standard antihypertensive medications including hydrochlorothiazide^[90], ramipril^[97,122], lisinopril^[123], losartan^[116], irbesartan^[121], valsartan^[124] and amlodipine^[92]. Furthermore, the antihypertensive effect of aliskiren has been found to be additive when combined with these medications. In large clinical trials, the effect of the combinations of aliskiren 300 mg with hydrochlorothiazide 25 mg^[90] and with valsartan 320 mg^[124] has been shown to have a synergistic effect. As a result, the US Food and Drug Administration has approved the use of the respective combinations in patients who are either not

adequately controlled with monotherapy or as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals. Apart from being a blocker of the RAS, the additive effect of aliskiren in combination with hydrochlorothiazide, valsartan and amlodipine may also be explained by its ability to suppress elevated PRA caused by diuretics, ACE inhibitors, ARB and vasodilators (Table 1).

Effectiveness of aliskiren on end-organ disease

Urine protein excretion in diabetic nephropathy is a predictor of non-fatal and fatal cardiovascular outcomes^[125,126]. It has been well demonstrated that patients with diabetic nephropathy have a high baseline serum prorenin level^[127]. Interestingly, these patients have normal or suppressed PRA levels^[128]. Prorenin has been proposed as a therapeutic target to slow the progression of diabetic nephropathy^[129]. In a randomized double-blind study which enrolled 599 diabetic patients with concomitant hypertension and nephropathy on standard treatment, the addition of aliskiren significantly reduced the urine albumin to creatinine ratio without a significant reduction in blood pressure^[130]. Also, aliskiren has proven to be a potent renal vasodilator with a pronounced natriuretic effect in normotensive individuals on a low sodium diet as compared to that induced by ACE inhibitors^[131]. Another study demonstrated that aliskiren increased renal plasma flow and glomerular filtration rate in healthy subjects^[132]. These studies suggest the renoprotective potential of aliskiren.

The Aliskiren in Left Ventricular Hypertrophy Trial was a non-inferiority trial in which 465 patients with hypertension, increased left ventricular wall thickness and body mass index $> 25 \text{ kg/m}^2$ were randomized to receive aliskiren 300 mg, losartan 100 mg, or their combination daily for 9 mo^[133]. Additional agents with the exception of β -blockers and other RAS modulators were allowed for optimal blood pressure control. After 34 wk of treatment, a significant reduction in left ventricular mass index was achieved by the combination of aliskiren and losartan (-6.4%), by aliskiren alone (-5.4%) and by losartan (-4.7%). However, the differences across the 3 groups were not statistically significant.

The Aliskiren Observation of Heart Failure Treatment trial (ALOFT) examined the effect of aliskiren (150 mg/d) on N-terminal pro-brain natriuretic peptide levels in patients with heart failure and class II-IV New York Heart Association symptoms^[134]. After 3 mo of treatment N-terminal pro-brain natriuretic peptide level was found to be reduced by $244 \pm 2025 \text{ pg/mL}$ with aliskiren ($P = 0.0106$) compared with an increase in the placebo group by $762 \pm 6123 \text{ pg/mL}$. The urinary aldosterone concentration was also reduced by aliskiren. The addition of aliskiren to standard therapy was well tolerated with a statistically nonsignificant increase in the rate of hypotension and hyperkalemia. This study suggested that aliskiren could modulate neurohumoral activation in heart failure when added to standard therapy.

The results of the ASPIRE study (Aliskiren Study in Post Myocardial Infarction Patients to Reduce Remodeling)^[135] were presented recently. This randomized controlled trial enrolled 820 patients who were within 1-6 wk of myocardial infarction and had a left ventricular ejection fraction of $< 45\%$ and an infarct size (segment length) of $> 20\%$. All the patients were receiving standard therapy including antiplatelet agents, statins, β -blockers and ACE inhibitors or ARBs. Patients were randomized to placebo or aliskiren 300 mg/d to examine the effect on the primary endpoint of change in left ventricular end systolic volume at week 36. There was no statistically significant difference between the 2 groups ($-3.5 \pm 16.3 \text{ mL}$ for placebo *vs* $-4.4 \pm 16.8 \text{ mL}$ for aliskiren). There was no difference in end diastolic volume, ejection fraction or cardiovascular outcomes between the 2 groups. There was a higher incidence of renal dysfunction, hypotension and hyperkalemia in the aliskiren group compared with the placebo, as well as a significant drop in blood pressure in the treatment group. This study raised some concerns about the use of aliskiren in post-myocardial infarction patients with systolic heart failure.

The recently reported Aliskiren and Valsartan to Reduce NT-proB-type natriuretic peptide *via* Renin-Angiotensin-Aldosterone-System Blockade (AVANT GARDE)-TIMI 43 Trial^[136] examined the hypothesis that early inhibition of the RAS in patients with normal ventricular systolic function but with elevated natriuretic peptides following an acute coronary syndrome would reduce ventricular stress as measured by N-terminal pro-brain natriuretic peptide levels. The effect of aliskiren, valsartan, and their combination was similar to placebo, while adverse events were more frequent in the treatment arm compared to placebo.

As described above, short- to intermediate-term studies have yielded mixed results on the effect of aliskiren on cardiovascular and other end organ protection. The ASPIRE HIGHER clinical trials program, a comprehensive group of 14 clinical trials, includes 4 large ongoing morbidity and mortality trials which may provide more conclusive answers on the role of direct renin inhibition in cardiovascular protection. The Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease Endpoints Trial (ALTITUDE) is evaluating the effect of aliskiren on cardiorenal end points in patients with type 2 diabetes and either renal or cardiovascular pathology. The Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE) Trial is examining the effect of aliskiren, enalapril and their combination in chronic systolic heart failure, while the Aliskiren Trial On Acute Heart Failure Outcomes (ASTRONAUT) Trial is evaluating the effect of aliskiren on outcomes in acute heart failure. The Aliskiren in Prevention of Later Life Outcomes (APOLLO) Trial will assess the effect of aliskiren on cardiovascular, functional and cognitive outcomes in an elderly population.

CONCLUSION

Renin inhibitors offer a novel method of RAS inhibition, alone and in combination with other antagonists of the RAS. Even though they are effective antihypertensive agents, the role of direct renin inhibition in cardiovascular protection is still a matter of debate. Although there are theoretical advantages of renin inhibitors in providing a greater degree of RAS suppression, the effect of elevated prorenin and renin levels through signal transduction *via* the PRR adds uncertainty to the overall effect of direct renin inhibition at the tissue level. Ongoing basic research and large randomized trials will shed more light on the role of this exciting new class of drug.

REFERENCES

- Bright R. Tabular view of the morbid appearances in 100 cases connected with albuminous urine: With observations. *Guy's Hosp Rep* 1836; **1**: 380-400
- Tigerstedt R, Bergman PG. Niere und Kreislauf. *Scand Arch Physiol* 1898; **8**: 223-271
- Basso N, Terragno NA. History about the discovery of the renin-angiotensin system. *Hypertension* 2001; **38**: 1246-1249
- Abassi Z, Winaver J, Feuerstein GZ. The biochemical pharmacology of renin inhibitors: implications for translational medicine in hypertension, diabetic nephropathy and heart failure: expectations and reality. *Biochem Pharmacol* 2009; **78**: 933-940
- Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010; **121**: 948-954
- James MN, Sielecki AR. Stereochemical analysis of peptide bond hydrolysis catalyzed by the aspartic proteinase penicillopepsin. *Biochemistry* 1985; **24**: 3701-3713
- Weber KT. Aldosterone in congestive heart failure. *N Engl J Med* 2001; **345**: 1689-1697
- Wolf G, Killen PD, Neilson EG. Intracellular signaling of transcription and secretion of type IV collagen after angiotensin II-induced cellular hypertrophy in cultured proximal tubular cells. *Cell Regul* 1991; **2**: 219-227
- Moriguchi Y, Matsubara H, Mori Y, Murasawa S, Masaki H, Maruyama K, Tsutsumi Y, Shibasaki Y, Tanaka Y, Nakajima T, Oda K, Iwasaka T. Angiotensin II-induced transactivation of epidermal growth factor receptor regulates fibronectin and transforming growth factor-beta synthesis via transcriptional and posttranscriptional mechanisms. *Circ Res* 1999; **84**: 1073-1084
- Tamura K, Nyui N, Tamura N, Fujita T, Kihara M, Toya Y, Takasaki I, Takagi N, Ishii M, Oda K, Horiuchi M, Umemura S. Mechanism of angiotensin II-mediated regulation of fibronectin gene in rat vascular smooth muscle cells. *J Biol Chem* 1998; **273**: 26487-26496
- Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell* 2001; **104**: 545-556
- Schiavone MT, Santos RA, Brosnihan KB, Khosla MC, Ferrario CM. Release of vasopressin from the rat hypothalamo-neurohypophyseal system by angiotensin-(1-7) heptapeptide. *Proc Natl Acad Sci USA* 1988; **85**: 4095-4098
- Santos RA, Brosnihan KB, Chappell MC, Pesquero J, Chrenicky CL, Greene LJ, Ferrario CM. Converting enzyme activity and angiotensin metabolism in the dog brainstem. *Hypertension* 1988; **11**: I153-I157
- Greene LJ, Spadaro AC, Martins AR, Perussi De Jesus WD, Camargo AC. Brain endo-oligopeptidase B: a post-proline cleaving enzyme that inactivates angiotensin I and II. *Hypertension* 1982; **4**: 178-184
- Welches WR, Santos RA, Chappell MC, Brosnihan KB, Greene LJ, Ferrario CM. Evidence that prolyl endopeptidase participates in the processing of brain angiotensin. *J Hypertens* 1991; **9**: 631-638
- Yamamoto K, Chappell MC, Brosnihan KB, Ferrario CM. In vivo metabolism of angiotensin I by neutral endopeptidase (EC 3.4.24.11) in spontaneously hypertensive rats. *Hypertension* 1992; **19**: 692-696
- Santos RA, Simoes e Silva AC, Maric C, Silva DM, Machado RP, de Buhr I, Heringer-Walther S, Pinheiro SV, Lopes MT, Bader M, Mendes EP, Lemos VS, Campagnole-Santos MJ, Schultheiss HP, Speth R, Walther T. Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas. *Proc Natl Acad Sci USA* 2003; **100**: 8258-8263
- Shenoy V, Ferreira AJ, Qi Y, Fraga-Silva RA, Díez-Freire C, Doobies A, Jun JY, Sriramula S, Mariappan N, Pourang D, Venugopal CS, Francis J, Reudelhuber T, Santos RA, Patel JM, Raizada MK, Katovich MJ. The angiotensin-converting enzyme 2/angiogenesis-(1-7)/Mas axis confers cardiopulmonary protection against lung fibrosis and pulmonary hypertension. *Am J Respir Crit Care Med* 2010; **182**: 1065-1072
- Chappell MC. Emerging evidence for a functional angiotensin-converting enzyme 2-angiotensin-(1-7)-MAS receptor axis: more than regulation of blood pressure? *Hypertension* 2007; **50**: 596-599
- Nagata S, Kato J, Sasaki K, Minamino N, Eto T, Kitamura K. Isolation and identification of proangiotensin-12, a possible component of the renin-angiotensin system. *Biochem Biophys Res Commun* 2006; **350**: 1026-1031
- Allred AJ, Diz DI, Ferrario CM, Chappell MC. Pathways for angiotensin-(1-7) metabolism in pulmonary and renal tissues. *Am J Physiol Renal Physiol* 2000; **279**: F841-F850
- Banegas I, Prieto I, Vives F, Alba F, de Gasparo M, Segarra AB, Hermoso F, Durán R, Ramírez M. Brain aminopeptidases and hypertension. *J Renin Angiotensin Aldosterone Syst* 2006; **7**: 129-134
- Prosser HC, Forster ME, Richards AM, Pemberton CJ. Cardiac chymase converts rat proAngiotensin-12 (PA12) to angiotensin II: effects of PA12 upon cardiac haemodynamics. *Cardiovasc Res* 2009; **82**: 40-50
- van Kesteren CA, Danser AH, Derkx FH, Dekkers DH, Lamers JM, Saxena PR, Schalekamp MA. Mannose 6-phosphate receptor-mediated internalization and activation of prorenin by cardiac cells. *Hypertension* 1997; **30**: 1389-1396
- Admiraal PJ, van Kesteren CA, Danser AH, Derkx FH, Sluiter W, Schalekamp MA. Uptake and proteolytic activation of prorenin by cultured human endothelial cells. *J Hypertens* 1999; **17**: 621-629
- Maru I, Ohta Y, Murata K, Tsukada Y. Molecular cloning and identification of N-acyl-D-glucosamine 2-epimerase from porcine kidney as a renin-binding protein. *J Biol Chem* 1996; **271**: 16294-16299
- Campbell DJ, Valentijn AJ. Identification of vascular renin-binding proteins by chemical cross-linking: inhibition of binding of renin by renin inhibitors. *J Hypertens* 1994; **12**: 879-890
- Sealey JE, Catanzaro DF, Lavin TN, Gahnm F, Pitarresi T, Hu LF, Laragh JH. Specific prorenin/renin binding (ProBP). Identification and characterization of a novel membrane site. *Am J Hypertens* 1996; **9**: 491-502
- Nguyen G, Delarue F, Berrou J, Rondeau E, Sraer JD. Specific receptor binding of renin on human mesangial cells in culture increases plasminogen activator inhibitor-1 antigen. *Kidney Int* 1996; **50**: 1897-1903

- 30 **Nguyen G**, Bouzahir L, Delarue F, Rondeau E, Sraer JD. [Evidence of a renin receptor on human mesangial cells: effects on PAII and cGMP]. *Nephrologie* 1998; **19**: 411-416
- 31 **Nguyen G**, Delarue F, Burcklé C, Bouzahir L, Giller T, Sraer JD. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest* 2002; **109**: 1417-1427
- 32 **Ludwig J**, Kerschler S, Brandt U, Pfeiffer K, Getlawi F, Apps DK, Schägger H. Identification and characterization of a novel 9.2-kDa membrane sector-associated protein of vacuolar proton-ATPase from chromaffin granules. *J Biol Chem* 1998; **273**: 10939-10947
- 33 **Advani A**, Kelly DJ, Cox AJ, White KE, Advani SL, Thai K, Connelly KA, Yuen D, Trogadis J, Herzenberg AM, Kuliszewski MA, Leong-Poi H, Gilbert RE. The (Pro)renin receptor: site-specific and functional linkage to the vacuolar H⁺-ATPase in the kidney. *Hypertension* 2009; **54**: 261-269
- 34 **Wagner CA**, Finberg KE, Breton S, Marshansky V, Brown D, Geibel JP. Renal vacuolar H⁺-ATPase. *Physiol Rev* 2004; **84**: 1263-1314
- 35 **Advani A**, Kelly DJ, Cox AJ, White KE, Advani SL, Thai K, Connelly KA, Yuen D, Trogadis J, Herzenberg AM, Kuliszewski MA, Leong-Poi H, Gilbert RE. The (Pro)renin receptor: site-specific and functional linkage to the vacuolar H⁺-ATPase in the kidney. *Hypertension* 2009; **54**: 261-269
- 36 **Zhang J**, Noble NA, Border WA, Owens RT, Huang Y. Receptor-dependent prorenin activation and induction of PAI-1 expression in vascular smooth muscle cells. *Am J Physiol Endocrinol Metab* 2008; **295**: E810-E819
- 37 **Hsueh WA**, Baxter JD. Human prorenin. *Hypertension* 1991; **17**: 469-477
- 38 **Krop M**, Danser AH. Circulating versus tissue renin-angiotensin system: on the origin of (pro)renin. *Curr Hypertens Rep* 2008; **10**: 112-118
- 39 **Reudelhuber TL**, Ramla D, Chiu L, Mercure C, Seidah NG. Proteolytic processing of human prorenin in renal and non-renal tissues. *Kidney Int* 1994; **46**: 1522-1524
- 40 **Sielecki AR**, Hayakawa K, Fujinaga M, Murphy ME, Fraser M, Muir AK, Carilli CT, Lewicki JA, Baxter JD, James MN. Structure of recombinant human renin, a target for cardiovascular-active drugs, at 2.5 Å resolution. *Science* 1989; **243**: 1346-1351
- 41 **Leckie BJ**, McGhee NK. Reversible activation-inactivation of renin in human plasma. *Nature* 1980; **288**: 702-705
- 42 **Gradman AH**, Pinto R, Kad R. Current concepts: renin inhibition in the treatment of hypertension. *Curr Opin Pharmacol* 2008; **8**: 120-126
- 43 **Suzuki F**, Hayakawa M, Nakagawa T, Nasir UM, Ebihara A, Iwasawa A, Ishida Y, Nakamura Y, Murakami K. Human prorenin has "gate and handle" regions for its non-proteolytic activation. *J Biol Chem* 2003; **278**: 22217-22222
- 44 **Ichihara A**, Hayashi M, Kaneshiro Y, Suzuki F, Nakagawa T, Tada Y, Koura Y, Nishiyama A, Okada H, Uddin MN, Nabi AH, Ishida Y, Inagami T, Saruta T. Inhibition of diabetic nephropathy by a decoy peptide corresponding to the "handle" region for nonproteolytic activation of prorenin. *J Clin Invest* 2004; **114**: 1128-1135
- 45 **Takahashi H**, Ichihara A, Kaneshiro Y, Inomata K, Sakoda M, Takemitsu T, Nishiyama A, Itoh H. Regression of nephropathy developed in diabetes by (Pro)renin receptor blockade. *J Am Soc Nephrol* 2007; **18**: 2054-2061
- 46 **Ichihara A**, Kaneshiro Y, Takemitsu T, Sakoda M, Nakagawa T, Nishiyama A, Kawachi H, Shimizu F, Inagami T. Contribution of nonproteolytically activated prorenin in glomeruli to hypertensive renal damage. *J Am Soc Nephrol* 2006; **17**: 2495-2503
- 47 **Ichihara A**, Kaneshiro Y, Takemitsu T, Sakoda M, Suzuki F, Nakagawa T, Nishiyama A, Inagami T, Hayashi M. Nonproteolytic activation of prorenin contributes to development of cardiac fibrosis in genetic hypertension. *Hypertension* 2006; **47**: 894-900
- 48 **Batenburg WW**, Krop M, Garrelds IM, de Vries R, de Bruin RJ, Burcklé CA, Müller DN, Bader M, Nguyen G, Danser AH. Prorenin is the endogenous agonist of the (pro)renin receptor. Binding kinetics of renin and prorenin in rat vascular smooth muscle cells overexpressing the human (pro)renin receptor. *J Hypertens* 2007; **25**: 2441-2453
- 49 **Müller DN**, Klanke B, Feldt S, Cordasic N, Hartner A, Schmieder RE, Luft FC, Hilgers KF. (Pro)renin receptor peptide inhibitor "handle-region" peptide does not affect hypertensive nephrosclerosis in Goldblatt rats. *Hypertension* 2008; **51**: 676-681
- 50 **Feldt S**, Maschke U, Dechend R, Luft FC, Müller DN. The putative (pro)renin receptor blocker HRP fails to prevent (pro)renin signaling. *J Am Soc Nephrol* 2008; **19**: 743-748
- 51 **Danser AH**, Derckx FH, Schalekamp MA, Hense HW, Riegger GA, Schunkert H. Determinants of interindividual variation of renin and prorenin concentrations: evidence for a sexual dimorphism of (pro)renin levels in humans. *J Hypertens* 1998; **16**: 853-862
- 52 **Nabi AH**, Kageshima A, Uddin MN, Nakagawa T, Park EY, Suzuki F. Binding properties of rat prorenin and renin to the recombinant rat renin/prorenin receptor prepared by a baculovirus expression system. *Int J Mol Med* 2006; **18**: 483-488
- 53 **Sakoda M**, Ichihara A, Kaneshiro Y, Takemitsu T, Nakazato Y, Nabi AH, Nakagawa T, Suzuki F, Inagami T, Itoh H. (Pro)renin receptor-mediated activation of mitogen-activated protein kinases in human vascular smooth muscle cells. *Hypertens Res* 2007; **30**: 1139-1146
- 54 **Saris JJ**, 't Hoen PA, Garrelds IM, Dekkers DH, den Dunnen JT, Lamers JM, Jan Danser AH. Prorenin induces intracellular signaling in cardiomyocytes independently of angiotensin II. *Hypertension* 2006; **48**: 564-571
- 55 **Advani A**, Kelly DJ, Cox AJ, White KE, Advani SL, Thai K, Connelly KA, Yuen D, Trogadis J, Herzenberg AM, Kuliszewski MA, Leong-Poi H, Gilbert RE. The (Pro)renin receptor: site-specific and functional linkage to the vacuolar H⁺-ATPase in the kidney. *Hypertension* 2009; **54**: 261-269
- 56 **Huang Y**, Noble NA, Zhang J, Xu C, Border WA. Renin-stimulated TGF- β 1 expression is regulated by a mitogen-activated protein kinase in mesangial cells. *Kidney Int* 2007; **72**: 45-52
- 57 **Huang Y**, Wongamorntham S, Kasting J, McQuillan D, Owens RT, Yu L, Noble NA, Border W. Renin increases mesangial cell transforming growth factor- β 1 and matrix proteins through receptor-mediated, angiotensin II-independent mechanisms. *Kidney Int* 2006; **69**: 105-113
- 58 **Kaneshiro Y**, Ichihara A, Takemitsu T, Sakoda M, Suzuki F, Nakagawa T, Hayashi M, Inagami T. Increased expression of cyclooxygenase-2 in the renal cortex of human prorenin receptor gene-transgenic rats. *Kidney Int* 2006; **70**: 641-646
- 59 **Ichihara A**, Suzuki F, Nakagawa T, Kaneshiro Y, Takemitsu T, Sakoda M, Nabi AH, Nishiyama A, Sugaya T, Hayashi M, Inagami T. Prorenin receptor blockade inhibits development of glomerulosclerosis in diabetic angiotensin II type 1a receptor-deficient mice. *J Am Soc Nephrol* 2006; **17**: 1950-1961
- 60 **Scheffé JH**, Neumann C, Goebel M, Danser J, Kirsch S, Gust R, Kintscher U, Unger T, Funke-Kaiser H. Prorenin engages the (pro)renin receptor like renin and both ligand activities are unopposed by aliskiren. *J Hypertens* 2008; **26**: 1787-1794
- 61 **Scheffé JH**, Menk M, Reinemund J, Effertz K, Hobbs RM, Pandolfi PP, Ruiz P, Unger T, Funke-Kaiser H. A novel signal transduction cascade involving direct physical interaction of the renin/prorenin receptor with the transcription factor promyelocytic zinc finger protein. *Circ Res* 2006; **99**: 1355-1366
- 62 **Kinouchi K**, Ichihara A, Sano M, Sun-Wada GH, Wada Y, Kurauchi-Mito A, Bokuda K, Narita T, Oshima Y, Sakoda M, Tamai Y, Sato H, Fukuda K, Itoh H. The (pro)renin receptor/ATP6AP2 is essential for vacuolar H⁺-ATPase assembly in murine cardiomyocytes. *Circ Res* 2010; **107**: 30-34
- 63 **Wood JM**, Cumin F, Maibaum J. Pharmacology of renin

- inhibitors and their application to the treatment of hypertension. *Pharmacol Ther* 1994; **61**: 325-344
- 64 **Wood JM**, Maibaum J, Rahuel J, Grütter MG, Cohen NC, Rasetti V, Rüger H, Göschke R, Stutz S, Fuhrer W, Schilling W, Rigollier P, Yamaguchi Y, Cumin F, Baum HP, Schnell CR, Herold P, Mah R, Jensen C, O'Brien E, Stanton A, Bedigian MP. Structure-based design of aliskiren, a novel orally effective renin inhibitor. *Biochem Biophys Res Commun* 2003; **308**: 698-705
 - 65 **Waldmeier F**, Glaenzel U, Wirz B, Oberer L, Schmid D, Seiberling M, Valencia J, Riviere GJ, End P, Vaidyanathan S. Absorption, distribution, metabolism, and elimination of the direct renin inhibitor aliskiren in healthy volunteers. *Drug Metab Dispos* 2007; **35**: 1418-1428
 - 66 **Buczko W**, Hermanowicz JM. Pharmacokinetics and pharmacodynamics of aliskiren, an oral direct renin inhibitor. *Pharmacol Rep* 2008; **60**: 623-631
 - 67 **Vaidyanathan S**, Jermany J, Yeh C, Bizot MN, Camisasca R. Aliskiren, a novel orally effective renin inhibitor, exhibits similar pharmacokinetics and pharmacodynamics in Japanese and Caucasian subjects. *Br J Clin Pharmacol* 2006; **62**: 690-698
 - 68 **Vaidyanathan S**, Reynolds C, Yeh CM, Bizot MN, Dieterich HA, Howard D, Dole WP. Pharmacokinetics, safety, and tolerability of the novel oral direct renin inhibitor aliskiren in elderly healthy subjects. *J Clin Pharmacol* 2007; **47**: 453-460
 - 69 **Vaidyanathan S**, Jarugula V, Dieterich HA, Howard D, Dole WP. Clinical pharmacokinetics and pharmacodynamics of aliskiren. *Clin Pharmacokinet* 2008; **47**: 515-531
 - 70 **Zhao C**, Vaidyanathan S, Yeh CM, Maboudian M, Armin Dieterich H. Aliskiren exhibits similar pharmacokinetics in healthy volunteers and patients with type 2 diabetes mellitus. *Clin Pharmacokinet* 2006; **45**: 1125-1134
 - 71 **Wuerzner G**, Azizi M. Renin inhibition with aliskiren. *Clin Exp Pharmacol Physiol* 2008; **35**: 426-430
 - 72 **Azizi M**, Ménard J, Bissery A, Guyenne TT, Bura-Rivière A, Vaidyanathan S, Camisasca RP. Pharmacologic demonstration of the synergistic effects of a combination of the renin inhibitor aliskiren and the AT1 receptor antagonist valsartan on the angiotensin II-renin feedback interruption. *J Am Soc Nephrol* 2004; **15**: 3126-3133
 - 73 **Nussberger J**, Wuerzner G, Jensen C, Brunner HR. Angiotensin II suppression in humans by the orally active renin inhibitor Aliskiren (SPP100): comparison with enalapril. *Hypertension* 2002; **39**: E1-E8
 - 74 **Tapaninen T**, Neuvonen PJ, Niemi M. Orange and apple juices greatly reduce the plasma concentrations of the OAT-P2B1 substrate aliskiren. *Br J Clin Pharmacol* 2010; Epub ahead of print
 - 75 **Tapaninen T**, Neuvonen PJ, Niemi M. Grapefruit juice greatly reduces the plasma concentrations of the OATP2B1 and CY-P3A4 substrate aliskiren. *Clin Pharmacol Ther* 2010; **88**: 339-342
 - 76 **Azizi M**, Webb R, Nussberger J, Hollenberg NK. Renin inhibition with aliskiren: where are we now, and where are we going? *J Hypertens* 2006; **24**: 243-256
 - 77 **Cheng JW**. Aliskiren: renin inhibitor for hypertension management. *Clin Ther* 2008; **30**: 31-47
 - 78 **Gradman AH**, Weir MR, Wright M, Bush CA, Keefe DL. Efficacy, safety and tolerability of aliskiren, a direct renin inhibitor, in women with hypertension: a pooled analysis of eight studies. *J Hum Hypertens* 2010; **24**: 721-729
 - 79 **Vaidyanathan S**, Valencia J, Kemp C, Zhao C, Yeh CM, Bizot MN, Denouel J, Dieterich HA, Dole WP. Lack of pharmacokinetic interactions of aliskiren, a novel direct renin inhibitor for the treatment of hypertension, with the antihypertensives amlodipine, valsartan, hydrochlorothiazide (HCTZ) and ramipril in healthy volunteers. *Int J Clin Pract* 2006; **60**: 1343-1356
 - 80 **Dieterle W**, Corynen S, Vaidyanathan S, Mann J. Pharmacokinetic interactions of the oral renin inhibitor aliskiren with lovastatin, atenolol, celecoxib and cimetidine. *Int J Clin Pharmacol Ther* 2005; **43**: 527-535
 - 81 **Vaidyanathan S**, Camenisch G, Schuetz H, Reynolds C, Yeh CM, Bizot MN, Dieterich HA, Howard D, Dole WP. Pharmacokinetics of the oral direct renin inhibitor aliskiren in combination with digoxin, atorvastatin, and ketoconazole in healthy subjects: the role of P-glycoprotein in the disposition of aliskiren. *J Clin Pharmacol* 2008; **48**: 1323-1338
 - 82 **Jorde UP**, Vittorio T, Katz SD, Colombo PC, Latif F, Le Jemtel TH. Elevated plasma aldosterone levels despite complete inhibition of the vascular angiotensin-converting enzyme in chronic heart failure. *Circulation* 2002; **106**: 1055-1057
 - 83 **Crackower MA**, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, Oliveira-dos-Santos AJ, da Costa J, Zhang L, Pei Y, Scholey J, Ferrario CM, Manoukian AS, Chappell MC, Backx PH, Yagil Y, Penninger JM. Angiotensin-converting enzyme 2 is an essential regulator of heart function. *Nature* 2002; **417**: 822-828
 - 84 **Schunkert H**, Ingelfinger JR, Dzau VJ. Evolving concepts of the intrarenal renin-angiotensin system in health and disease: contributions of molecular biology. *Ren Physiol Biochem* 1991; **14**: 146-154
 - 85 **Cooper ME**. The role of the renin-angiotensin-aldosterone system in diabetes and its vascular complications. *Am J Hypertens* 2004; **17**: 16S-20S; quiz A2-A4
 - 86 **Verma S**, Gupta M, Holmes DT, Teoh H, Xu L, Yusuf S, Lonn EM. Plasma renin activity is associated with increased cardiovascular events and mortality in the HOPE study [abstract]. *Circulation* 2009; **120**: S453
 - 87 **Alderman MH**, Ooi WL, Cohen H, Madhavan S, Sealey JE, Laragh JH. Plasma renin activity: a risk factor for myocardial infarction in hypertensive patients. *Am J Hypertens* 1997; **10**: 1-8
 - 88 **Muhlestein JB**, May HT, Bair TL, Prescott MF, Horne BD, Anderson JL. Association between baseline plasma renin activity and clinical outcomes in non-hypertensive patients with coronary artery disease. *J Hypertens* 2010; **28**: e384
 - 89 **Azizi M**, Ménard J, Bissery A, Guyenne TT, Bura-Rivière A. Hormonal and hemodynamic effects of aliskiren and valsartan and their combination in sodium-replete normotensive individuals. *Clin J Am Soc Nephrol* 2007; **2**: 947-955
 - 90 **Villamil A**, Chrysant SG, Calhoun D, Schober B, Hsu H, Matriciano-Dimichino L, Zhang J. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. *J Hypertens* 2007; **25**: 217-226
 - 91 **Geiger H**, Barranco E, Gorostidi M, Taylor A, Zhang X, Xiang Z, Zhang J. Combination therapy with various combinations of aliskiren, valsartan, and hydrochlorothiazide in hypertensive patients not adequately responsive to hydrochlorothiazide alone. *J Clin Hypertens* (Greenwich) 2009; **11**: 324-332
 - 92 **Drummond W**, Munger MA, Rafique Essop M, Maboudian M, Khan M, Keefe DL. Antihypertensive efficacy of the oral direct renin inhibitor aliskiren as add-on therapy in patients not responding to amlodipine monotherapy. *J Clin Hypertens* (Greenwich) 2007; **9**: 742-750
 - 93 **Uresin Y**, Taylor AA, Kilo C, Tschöpe D, Santonastaso M, Ibram G, Fang H, Satlin A. Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension. *J Renin Angiotensin Aldosterone Syst* 2007; **8**: 190-198
 - 94 **Sealey JE**, Laragh JH. Aliskiren, the first renin inhibitor for treating hypertension: reactive renin secretion may limit its effectiveness. *Am J Hypertens* 2007; **20**: 587-597
 - 95 **Stanton AV**, Gradman AH, Schmieder RE, Nussberger J, Sarangapani R, Prescott MF. Aliskiren monotherapy does not cause paradoxical blood pressure rises: meta-analysis of data from 8 clinical trials. *Hypertension* 2010; **55**: 54-60
 - 96 **Nussberger J**, Gradman AH, Schmieder RE, Lins RL, Chiang Y, Prescott MF. Plasma renin and the antihypertensive effect

- of the orally active renin inhibitor aliskiren in clinical hypertension. *Int J Clin Pract* 2007; **61**: 1461-1468
- 97 **Andersen K**, Weinberger MH, Constance CM, Ali MA, Jin J, Prescott MF, Keefe DL. Comparative effects of aliskiren-based and ramipril-based therapy on the renin system during long-term (6 months) treatment and withdrawal in patients with hypertension. *J Renin Angiotensin Aldosterone Syst* 2009; **10**: 157-167
 - 98 **Feldman DL**, Jin L, Xuan H, Contrepas A, Zhou Y, Webb RL, Mueller DN, Feldt S, Cumin F, Maniara W, Persohn E, Schuetz H, Jan Danser AH, Nguyen G. Effects of aliskiren on blood pressure, albuminuria, and (pro)renin receptor expression in diabetic TG(mRen-2)27 rats. *Hypertension* 2008; **52**: 130-136
 - 99 **Gradman AH**, Kad R. Renin inhibition in hypertension. *J Am Coll Cardiol* 2008; **51**: 519-528
 - 100 **Wood JM**, Schnell CR, Cumin F, Menard J, Webb RL. Aliskiren, a novel, orally effective renin inhibitor, lowers blood pressure in marmosets and spontaneously hypertensive rats. *J Hypertens* 2005; **23**: 417-426
 - 101 **Ganten D**, Wagner J, Zeh K, Bader M, Michel JB, Paul M, Zimmermann F, Ruf P, Hilgenfeldt U, Ganten U. Species specificity of renin kinetics in transgenic rats harboring the human renin and angiotensinogen genes. *Proc Natl Acad Sci USA* 1992; **89**: 7806-7810
 - 102 **Pilz B**, Shagdarsuren E, Wellner M, Fiebeler A, Dechend R, Gratz P, Meiners S, Feldman DL, Webb RL, Garrelds IM, Jan Danser AH, Luft FC, Müller DN. Aliskiren, a human renin inhibitor, ameliorates cardiac and renal damage in double-transgenic rats. *Hypertension* 2005; **46**: 569-576
 - 103 **Whaley-Connell A**, Habibi J, Cooper SA, Demarco VG, Hayden MR, Stump CS, Link D, Ferrario CM, Sowers JR. Effect of renin inhibition and AT1R blockade on myocardial remodeling in the transgenic Ren2 rat. *Am J Physiol Endocrinol Metab* 2008; **295**: E103-E109
 - 104 **Whaley-Connell A**, Nistala R, Habibi J, Hayden MR, Schneider RL, Johnson MS, Tilmon R, Rehmer N, Ferrario CM, Sowers JR. Comparative effect of direct renin inhibition and AT1R blockade on glomerular filtration barrier injury in the transgenic Ren2 rat. *Am J Physiol Renal Physiol* 2010; **298**: F655-F661
 - 105 **Rashikh A**, Abul Kalam Najmi, Akhtar M, Mahmood D, Pillai KK, Ahmad SJ. Protective effects of aliskiren in doxorubicin-induced acute cardiomyopathy in rats. *Hum Exp Toxicol* 2011; **30**: 102-109
 - 106 **Westermann D**, Riad A, Lettau O, Roks A, Savvatis K, Becher PM, Escher F, Jan Danser AH, Schultheiss HP, Tschöpe C. Renin inhibition improves cardiac function and remodeling after myocardial infarction independent of blood pressure. *Hypertension* 2008; **52**: 1068-1075
 - 107 **Lu H**, Rateri DL, Feldman DL, Jr RJ, Fukamizu A, Ishida J, Oesterling EG, Cassis LA, Daugherty A. Renin inhibition reduces hypercholesterolemia-induced atherosclerosis in mice. *J Clin Invest* 2008; **118**: 984-993
 - 108 **Lastra G**, Habibi J, Whaley-Connell AT, Manrique C, Hayden MR, Rehmer J, Patel K, Ferrario C, Sowers JR. Direct renin inhibition improves systemic insulin resistance and skeletal muscle glucose transport in a transgenic rodent model of tissue renin overexpression. *Endocrinology* 2009; **150**: 2561-2568
 - 109 **Habibi J**, Whaley-Connell A, Hayden MR, DeMarco VG, Schneider R, Sowers SD, Karuparthi P, Ferrario CM, Sowers JR. Renin inhibition attenuates insulin resistance, oxidative stress, and pancreatic remodeling in the transgenic Ren2 rat. *Endocrinology* 2008; **149**: 5643-5653
 - 110 **Ke CY**, Lee CC, Lee CJ, Subeq YM, Lee RP, Hsu BG. Aliskiren ameliorates chlorhexidine digluconate-induced peritoneal fibrosis in rats. *Eur J Clin Invest* 2010; **40**: 301-309
 - 111 **van Kesteren CA**, Saris JJ, Dekkers DH, Lamers JM, Saxena PR, Schalekamp MA, Danser AH. Cultured neonatal rat cardiac myocytes and fibroblasts do not synthesize renin or angiotensinogen: evidence for stretch-induced cardiomyocyte hypertrophy independent of angiotensin II. *Cardiovasc Res* 1999; **43**: 148-156
 - 112 **Krop M**, de Bruyn JH, Derckx FH, Danser AH. Renin and prorenin disappearance in humans post-nephrectomy: evidence for binding? *Front Biosci* 2008; **13**: 3931-3939
 - 113 **Feldt S**, Batenburg WW, Mazak I, Maschke U, Wellner M, Kvakan H, Dechend R, Fiebeler A, Burckle C, Contrepas A, Jan Danser AH, Bader M, Nguyen G, Luft FC, Müller DN. Prorenin and renin-induced extracellular signal-regulated kinase 1/2 activation in monocytes is not blocked by aliskiren or the handle-region peptide. *Hypertension* 2008; **51**: 682-688
 - 114 **Sakoda M**, Ichihara A, Kurauchi-Mito A, Narita T, Kinouchi K, Murohashi-Bokuda K, Saleem MA, Nishiyama A, Suzuki F, Itoh H. Aliskiren inhibits intracellular angiotensin II levels without affecting (pro)renin receptor signals in human podocytes. *Am J Hypertens* 2010; **23**: 575-580
 - 115 **Musini VM**, Fortin PM, Bassett K, Wright JM. Blood pressure lowering efficacy of renin inhibitors for primary hypertension: a Cochrane systematic review. *J Hum Hypertens* 2009; **23**: 495-502
 - 116 **Stanton A**, Jensen C, Nussberger J, O'Brien E. Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren. *Hypertension* 2003; **42**: 1137-1143
 - 117 **Weir MR**, Bush C, Anderson DR, Zhang J, Keefe D, Satlin A. Antihypertensive efficacy, safety, and tolerability of the oral direct renin inhibitor aliskiren in patients with hypertension: a pooled analysis. *J Am Soc Hypertens* 2007; **1**: 264-277
 - 118 **Krone W**, Hanefeld M, Meyer HF, Jung T, Bartlett M, Yeh CM, Rajman I, Prescott MF, Dole WP. Comparative efficacy and safety of aliskiren and irbesartan in patients with hypertension and metabolic syndrome. *J Hum Hypertens* 2011; **25**: 186-195
 - 119 **White WB**, Anderson DR, Arora V, Bush C, Keefe DL. Antihypertensive effectiveness of the direct renin inhibitor aliskiren in patients with metabolic syndrome: a comparative analysis of 7219 patients from 10 randomized trials. *Eur Heart J* 2007; **28**: 868
 - 120 **Oh BH**, Mitchell J, Herron JR, Chung J, Khan M, Keefe DL. Aliskiren, an oral renin inhibitor, provides dose-dependent efficacy and sustained 24-hour blood pressure control in patients with hypertension. *J Am Coll Cardiol* 2007; **49**: 1157-1163
 - 121 **Gradman AH**, Schmieder RE, Lins RL, Nussberger J, Chiang Y, Bedigian MP. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation* 2005; **111**: 1012-1018
 - 122 **Duprez DA**, Munger MA, Botha J, Keefe DL, Charney AN. Aliskiren for geriatric lowering of systolic hypertension: a randomized controlled trial. *J Hum Hypertens* 2010; **24**: 600-608
 - 123 **Strasser RH**, Puig JG, Farsang C, Croket M, Li J, van Ingen H. A comparison of the tolerability of the direct renin inhibitor aliskiren and lisinopril in patients with severe hypertension. *J Hum Hypertens* 2007; **21**: 780-787
 - 124 **Oparil S**, Yarows SA, Patel S, Fang H, Zhang J, Satlin A. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet* 2007; **370**: 221-229
 - 125 **Brenner BM**, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345**: 861-869
 - 126 **Lewis EJ**, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345**: 851-860
 - 127 **Deinum J**, Rønn B, Mathiesen E, Derckx FH, Hop WC, Schalekamp MA. Increase in serum prorenin precedes onset

- of microalbuminuria in patients with insulin-dependent diabetes mellitus. *Diabetologia* 1999; **42**: 1006-1010
- 128 **Tuck ML**, Sambhi MP, Levin L. Hyporeninemic hypoaldosteronism in diabetes mellitus. Studies of the autonomic nervous system's control of renin release. *Diabetes* 1979; **28**: 237-241
 - 129 **Ichihara A**, Sakoda M, Mito-Kurauchi A, Itoh H. Activated prorenin as a therapeutic target for diabetic nephropathy. *Diabetes Res Clin Pract* 2008; **82** Suppl 1: S63-S66
 - 130 **Parving HH**, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* 2008; **358**: 2433-2446
 - 131 **Fisher ND**, Jan Danser AH, Nussberger J, Dole WP, Hollenberg NK. Renal and hormonal responses to direct renin inhibition with aliskiren in healthy humans. *Circulation* 2008; **117**: 3199-3205
 - 132 **Splenser AE**, Fisher ND, Danser AH, Hollenberg NK. Renal plasma flow: glomerular filtration rate relationships in man during direct renin inhibition with aliskiren. *J Am Soc Hypertens* 2009; **3**: 315-320
 - 133 **Solomon SD**, Appelbaum E, Manning WJ, Verma A, Berglund T, Lukashevich V, Cherif Papst C, Smith BA, Dahlöf B. Effect of the direct Renin inhibitor aliskiren, the Angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. *Circulation* 2009; **119**: 530-537
 - 134 **McMurray JJ**, Pitt B, Latini R, Maggioni AP, Solomon SD, Keefe DL, Ford J, Verma A, Lewsey J. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail* 2008; **1**: 17-24
 - 135 **Cleland JG**, Coletta AP, Buga L, Ahmed D, Clark AL. Clinical trials update from the American College of Cardiology meeting 2010: DOSE, ASPIRE, CONNECT, STICH, STOP-AF, CABANA, RACE II, EVEREST II, ACCORD, and NAVIGATOR. *Eur J Heart Fail* 2010; **12**: 623-629
 - 136 **Scirica BM**, Morrow DA, Bode C, Ruzyllo W, Ruda M, Oude Ophuis AJ, Lopez-Sendon J, Swedberg K, Ogorek M, Rifai N, Lukashevich V, Maboudian M, Cannon CP, McCabe CH, Braunwald E. Patients with acute coronary syndromes and elevated levels of natriuretic peptides: the results of the AVANT GARDE-TIMI 43 Trial. *Eur Heart J* 2010; **31**: 1993-2005

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Advantages and disadvantages of biodegradable platforms in drug eluting stents

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Several DES designs with biodegradable (BIO) polymers have been introduced in preclinical and clinical studies, including randomized trials. In this review, we analyze the clinical results from 6 observational and randomized studies with BIO polymers and discuss advantages and disadvantages of this new technology.

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Key words: Polymers; Drug eluting stents; Biodegradable polymers ; Stents; Thrombosis; Restenosis

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Abstract

Coronary angioplasty with drug-eluting stent (DES) implantation is currently the most common stent procedure worldwide. Since the introduction of DES, coronary restenosis as well as the incidence of target vessel and target lesion revascularization have been significantly reduced. However, the incidence of very late stent thrombosis beyond the first year after stent deployment has more commonly been linked to DES than to bare-metal stent (BMS) implantation. Several factors have been associated with very late stent thrombosis after DES implantation, such as delayed healing, inflammation, stent mal-apposition and endothelial dysfunction. Some of these adverse events were associated with the presence of durable polymers, which were essential to allow the elution of the immunosuppressive drug in the first DES designs. The introduction of erodable polymers in DES technology has provided the potential to complete the degradation of the polymer simultaneously or immediately after the release of the immunosuppressive drug, after which a BMS remains in place.

INTRODUCTION

A significant reduction in coronary restenosis rates has been observed with the introduction of drug-eluting stent (DES) technology during percutaneous coronary interventions (PCI)^[1-6]. During these years, we have also learned that some adverse effects, although rarely present, are more frequently associated with DES implantation^[7-14]; some of them can be linked to durable polymers, which were continually present in the first DES designs^[1-6]. Delayed healing, endothelial dysfunction, chronic arterial wall inflammation and late-acquired stent mal-apposition are more frequently linked with DES im-

plantation^[9-15]. All of these can increase the incidence of very late stent thrombosis that, although an uncommon event, was more frequently reported after DES implantation^[16-21]. Delayed loss of anti-restenotic efficacy was also reported with the first DES designs^[22,23]. Chronic arterial wall inflammation and endothelial dysfunction may be associated with the increased rate of target vessel revascularization (TVR) at a late stage, which has been found particularly in patients with complex lesions including those with diabetes^[24,25]. All of the above underscore the importance of this topic, especially after reports of increased rate of endothelial dysfunction after DES implantation as compared with bare-metal stent (BMS) implantation.

FIRST DES DESIGNS

Three main components were necessary to achieve a stable release of the drug in the first DES generation: the stent platform to scaffold the vessel, the polymer to deliver the immunosuppressive agent and the drug to inhibit neointimal growth.

Initially, sirolimus-eluting stents (SES; Cypher™, Cordis Co., Warren, NJ, USA) and paclitaxel-eluting stents (PES; Taxus™, Boston Scientific Co., Natick, MA, USA) were designed using permanent polymers such as poly(ethylene-co-vinyl acetate), poly(n-butyl methacrylate) and poly(styrene-*b*-isobutylene-*b*-styrene), which allowed controlled elution of the immunosuppressive agent. The SES design consists of a stainless steel platform coated with a permanent polymer containing sirolimus 140 µg/cm², 80% of which is released within 30 d. The PES design is also composed of a stainless steel platform with a permanent polymer coating combined with 1 µg/mm² paclitaxel; 10% of the paclitaxel is released within 2 wk after stent deployment, although 90% of it remains in the polymer forever^[24,26].

The presence of permanent polymers in the vessel arterial wall adds an additional factor that influences local responses and may alter processes involved in neointimal formation. Each polymer provokes a distinctive inflammatory response in animals, such as giant cell infiltration around the stent struts, and a progressive granulomatous and eosinophilic reaction^[23,27], which increase beyond the first year. These data support the perception that durable polymers in DES technology may provoke chronic inflammation and decreased efficacy.

BIODEGRADABLE POLYMERS IN DES TECHNOLOGY

The use of biodegradable (BIO) polymers, as opposed to durable polymers, in coronary stent technology has the advantages of a complete elution of drugs and a reduced inflammatory response, with the potential for decreasing the risk of late complications such as stent strut uncovering, mal-apposition, endothelial dysfunction and thrombosis^[5,7,9,10,28,29]. BIO polymers allow the complete release and elution of the immunosuppressive agent after

degradation of the polymer^[26,29]. Therefore, long-term antiplatelet therapy would not be required after the polymer completely disappeared. The most common BIO polymers are composed of polylactic acid (PLA), polyglycolide and poly(D,L-lactic-co-glycolic acid) (PLGA), which are completely metabolized into the body (breaking down into monomers, water and carbon dioxide) after fulfilling their purpose.

Several new stents with fully BIO polymers have been introduced using a variety of anti-proliferative agents such as sirolimus, tacrolimus, biolimus and paclitaxel. The safety and efficacy of these devices have been assessed clinically in first in man (FIM) and observational studies^[30-32]. For example, in the Paclitaxel In Stent Controlled Elution Study, the pharmacokinetics of the DES and not dose of the immunosuppressive agent appears to be associated with neointimal suppression and clinical outcome^[30]. However, an excess of late loss with a high rate of clinical angiographic restenosis and also a lack of reduction in stent thrombosis were reported in many of these FIM studies. A high inflammatory reaction due to major particle debris as a result of coating degradation, which was not simultaneous with drug release, was a major limitation for many of the first DES designs with BIO polymers. Therefore, to the best of our knowledge, only 6 DES with erodable polymers have randomized clinical data with enough patients to justify their introduction in clinical practice.

In the following paragraphs we will review and summarize the main findings from published randomized data of the Limus Eluted from a Durable *vs* Erodeable Stent Coating (LEADERS)^[28], NOBORI^[33,34], Individualized Drug Eluting Stent System to Abrogate Restenosis (ISAR)-TEST-3^[35] and TEST-4^[36,37] with sirolimus (rapamycin), PAIN'T (percutaneous intervention with BIO-polymer based paclitaxel-eluting or sirolimus-eluting *vs* bare stents for *de novo* coronary lesions)^[38] and EUCATAX^[39] trials. Study and stent design of each trial is described in Table 1.

LEADERS TRIAL

The LEADERS trial^[28] is the largest randomized trial with BIO polymer-coated stents. The study compared a PLA polymer loaded with Biolimus (Biolimus-eluting stent; BioMatrix Flex, Biosensors Inc, Newport Beach, CA, USA) *vs* a Cypher platform (SES). The BIO polymer was applied to the stent's abluminal surface only. After an initial burst of 40% of drug elution, complete drug release and polymer degradation was achieved over a period of 6 to 9 mo.

The LEADERS trial enrolled 1707 randomized patients, 807 included in the BIO polymer (BioMatrix Flex) and 850 in the durable polymer (Cypher) DES arms. The study included a large proportion of patients with acute coronary syndromes (55%) including ST elevation myocardial infarction (STEMI), multiple vessel disease (24%), previous PCI (36%) and vessel size < 2.75 mm (68%). At 9 mo of follow-up, all clinical endpoints met the criteria

Table 1 Comparison between published trials of biodegradable eluting stents

Name	Polymer	Stent design	Drug	Drug per stent length ($\mu\text{g}/\text{mm}^2$)	Polymer degradation	Drug release
ISAR-TEST-3 ^[35]	PLA	316L stainless steel microporus stent	Sirolimus	4.8	6-9 wk	28 d (95%)
ISAR TEST-4 ^[36]	PLA	316L stainless-steel microporus stent	Sirolimus	4.8	6-9 wk	28 d (95%)
NOBORI 1 ^[34]	PLA	Stainless-steel S-stent	Biolimus	15.6	9-12 mo	Two phases: immediately after stent implantation; sustained drug release over 9-12 mo
NOBORI CORE ^[33]	PLA	Stainless-steel S-stent	Biolimus	15.6	9-12 mo	Two phases: immediately after stent implantation; sustained drug release over 9-12 mo
LEADERS ^[28]	PLA	Flexible stainless- steel stent	Biolimus	15.6	6-9 mo	6-9 mo
PAINT ^[38]	PLA+ PLGA	316L stainless metallic platform	Paclitaxel and Sirolimus	6.4 (PES) 6.6 (SES)	7 mo	9-11 d (50%) 38 d (90%) 48 d (100%)
EUCATAX ^[39]	PLGA	Stainless steel open cell with glycocalix layer	Paclitaxel	11 to 43	6-8 wk	6-8 wk

PLA: Polylactic acid; PLGA: Polylactic-co-glycolic acid; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; ISAR: Individualized Drug Eluting Stent System to Abrogate Restenosis; LEADERS: Limus Eluted from a Durable *vs* Erodable Stent Coating.

of non-inferiority for the BioMatrix-Flex compared to Cypher, including the amount of late loss in the follow-up angiogram.

The incidence of all definitions of stent thrombosis was also similar between both DES designs (3.6% in BioMatrix-Flex and 3.3% in Cypher), although percent of uncovered (3.6% *vs* 39% in BioMatrix-Flex and Cypher, respectively, $P = 0.005$) or mal-apposed (0.3% *vs* 6.7% in BioMatrix-Flex and Cypher, respectively, $P = 0.04$) stent struts were significant higher in the Cypher stent arm. At 2 years of follow-up, the LEADERS trial also showed a superior outcome with BioMatrix in patients with STEMI as testified by the rates of major adverse cardiovascular events (MACCE; 8.1% for BioMatrix-Flex *vs* 19.3% for Cypher, $P < 0.01$); the incidence of stent thrombosis in this cohort of patients was significantly lower with BioMatrix-Flex compared with Cypher (2.6% *vs* 8.4%, respectively, $P < 0.05$).

In the short-term follow-up, there was a high incidence of non-STEMI in patients allocated to the BioMatrix-Flex polymer (5.4%), and a high incidence of stent thrombosis in patients with STEMI allocated to the SES arm.

NOBORI TRIAL

The Nobori stent (Terumo Co., Tokyo, Japan) uses a similar drug-polymer combination (Biolimus/PLA) as the one in BioMatrix in the LEADERS trial. In this trial^[33,34], 243 patients were randomized in a 2:1 ratio between Biolimus with BIO polymer stents (Nobori) and paclitaxel with durable polymer stents (Taxus).

At 9 mo of follow-up, the use of a DES with BIO polymer compared with the Taxus Liberte DES significantly reduced the amount of late loss and angiographic restenosis. Furthermore, although not powered to detect clinical differences, the incidence of target lesion revascularization (TLR) and TVR were also significantly

better with the Nobori stent design. Remarkably, stent thrombosis was not seen in the erodable polymer arm compared with 4.4% in the Taxus Liberte arm. There was a small sample size, a short-term outcome and a high rate of stent thrombosis in the Taxus Liberte arm.

ISAR-TEST-3 AND -TEST-4 TRIALS

ISAR-TEST-3 trial

The ISAR-TEST-3 trial^[35] enrolled 605 patients randomized to a BIO polymer stent loaded with sirolimus, a sirolimus polymer-free stent and a sirolimus with permanent polymer stent (Cypher; Cordis, Florida, USA). The BIO polymer was completely absorbed within 6 to 9 wk after stent deployment, whereas 100% of sirolimus was released within the first 30 d. The main finding of this study was that the BIO polymer stent was not inferior to the Cypher stent in safety and efficacy, whereas the polymer-free stent was inferior in terms of efficacy to the other 2 DES designs.

This study had a small sample size, a short-term outcome and, in this DES stent design, the BIO polymer remains in place after the drug is completely eluted, therefore inflammatory reactions by the polymer itself cannot be excluded.

ISAR-TEST-4 trial

The ISAR-TEST-4 trial^[36] enrolled 2603 patients randomized to a BIO polymer DES (1299) or a permanent polymer DES (1304). In the latest group, 652 patients were treated with a Cypher stent and 652 with Xience V (Abbott Vascular, Abbott Park, IL, USA). At 1 year of follow-up, there were no differences in angiographic and clinical endpoints among patients treated with a BIO or permanent polymer, and the stent clearly met the non-inferiority test in both cases.

Two years follow-up of this trial was recently pre-

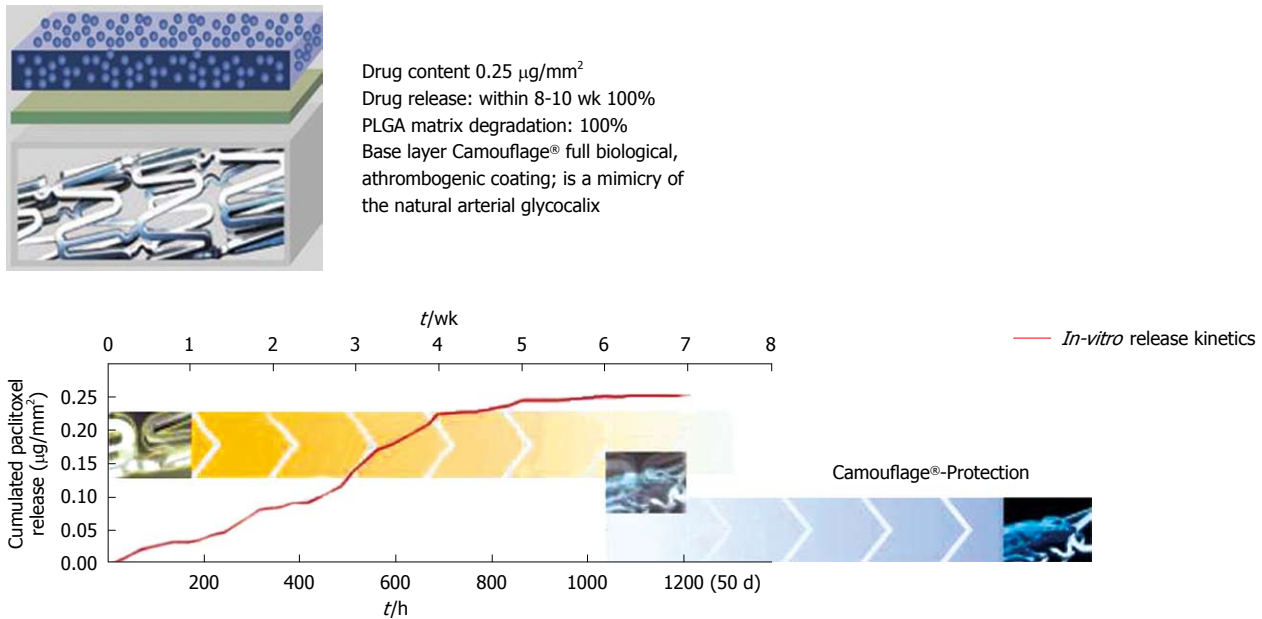


Figure 1 EUCATAX design and characteristics. PLGA: Poly(D,L-lactic-co-glycolic acid).

sented^[37], and a sustained equivalence in the incidence of safety/efficacy end points between BIO and permanent polymer DES designs was seen. The incidence of stent thrombosis was similar in both study arms.

This study had a short-term outcome and the same concerns regarding the BIO polymer DES design described above for ISAR-TEST-3.

PAINT TRIAL

The PAINT trial^[38] compared 2 DES with the same BIO polymer but with a different immunosuppressive drug (paclitaxel or sirolimus) *vs* a BMS design; 274 patients were randomly assigned to paclitaxel with BIO polymer ($n = 111$), sirolimus with BIO polymer ($n = 106$) and BMS ($n = 57$). All stents had the same laser cut stainless steel platform. Both paclitaxel and sirolimus were released in approximately 48 d, whereas complete polymer degradation occurred only after 7 mo.

Both DES designs had less late loss and TVR compared with the BMS, whereas SES had a lower late loss but similar 1-year clinical outcome compared with PES. All-cause death, MI and stent thrombosis were similar in the 3 groups.

The study had a small sample size, short period of follow-up, greater amount of in stent late loss with both BIO polymers in comparison with historical studies with the same drugs but a permanent polymer. Although the study did not show any significant differences in stent thrombosis rate among the different groups, this event occurred in 1.9% of each DES design compared with zero in the BMS arm. Finally, taking into consideration that release of the drug and degradation of the polymer was not simultaneous, similar concerns with this stent design can be applied to those described in the ISAR-TEST studies.

EUCATAX TRIAL

The rationale and purpose of the EUCATAX trial^[39] was to compare the efficacy and safety of a new PES dual coated with a BIO polymer and glycocalyx against an equivalent BMS (Eucatech AG, Reinholden; Germany). A FIM study was previously conducted^[40].

The PES is a stainless steel open cell (strut thickness 85 μm) modular design with 3 connecting fins *per modulo*. The double coating includes a BIO polymer as the platform for paclitaxel elution and a glycocalyx to increase hemocompatibility. The glycocalyx layer is a symmetric coating that uses camouflage nanotechnology. The BIO polymer is PLGA, which forms an asymmetric coating with a thickness of 2.5 μm on the luminal side and 5 μm on the abluminal side. Paclitaxel is loaded into the polymer, at a concentration of 11 to 43 μg depending on the stent length. The camouflage nanocoating^[41] is coated with hemo-heparin, which is a polymer-analogous modified heparin that lacks an active anticoagulation effect due to removal of the sulfate groups. On top of this hemo-heparin coat, the bio-absorbable polyester polymer PLGA serves as the carrier of the paclitaxel. In this stent design, degradation of the polymer occurred simultaneously with the elution of the drug at 6 to 8 wk after deployment. Therefore, according to the manufacturers, neither the drug nor the polymer remained in place (Figure 1).

The study included 422 patients (9.1% of those screened) and randomized 211 patients to the PES arm and 211 to the BMS arm (Figure 2). The population included diabetes in 23.5%, a reference vessel diameter size < 2.75 mm in 60%, multi-vessel disease in 60%, and acute coronary syndrome in 60%.

Cumulative clinical events at 18.3 ± 7.3 mo are shown in Figure 3. Cumulative cardiac events such as death,

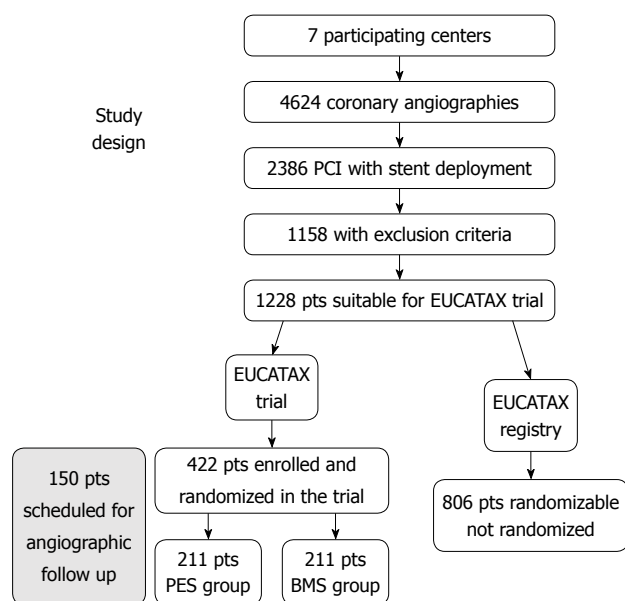


Figure 2 EUCATAX randomized trial design. Modified from Rodriguez *et al.*^[39]. Pts: Patients; PCI: Percutaneous coronary interventions; PES: Paclitaxel eluting stent; BMS: Bare-metal stent.

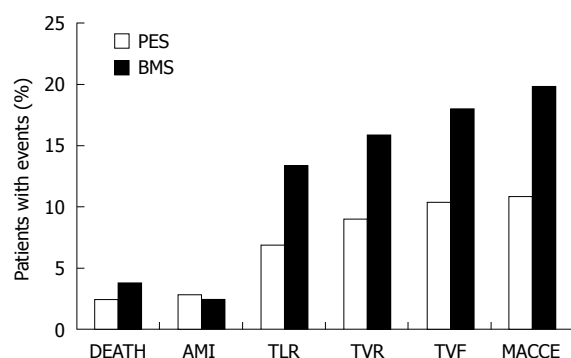


Figure 3 Results at 18 mo. EUCATAX trial. AMI: Acute myocardial infarction; MACCE: Major adverse cardiovascular events; TVF: Target vessel failure; TLR: Target lesion revascularisation; TVR: Target vessel revascularisation; PES: Paclitaxel-eluting stents; BMS: Bare-metal stent.

cardiac death, MI and stroke were similar, although PES showed a lower incidence of TLR and TVR driving a significant reduction in target vessel failure (TVF) and MACCE compared with the BMS design, and both were the major end points of the study. The incidence of any stent thrombosis was 1.4% in the PES group and 1.9% in the BMS group. Interestingly, beyond 1 year, no patient in the PES arm suffered stent thrombosis.

Baseline and follow-up angiographic findings are shown in Table 2. Follow-up angiography was performed in all 150 patients scheduled. In segment late luminal loss was 0.50 mm in the PES group and 0.94 mm in the BMS group ($P = 0.001$). The binary restenosis rate was 13.2% (13/98 lesions) in the PES arm and 34% (30/88 lesions) in the BMS arm ($P < 0.001$). Intravascular ultrasound showed no difference in late incomplete stent mal-apposition between groups (Table 2), although the incidence of late incomplete mal-apposition in the proximal seg-

Table 2 Quantitative coronary analysis for both groups in the EUCATAX trial n (%)

	PES	BMS	P value
Baseline QCA analysis			
Reference diameter (mm)	2.75 ± 0.5	2.85 ± 0.5	0.086
Minimal luminal diameter (mm)	0.86 ± 0.4	0.85 ± 0.5	0.780
Lesion length (mm)	16.2 ± 6.1	15.6 ± 6.3	0.410
Stent diameter (mm)	21.7 ± 5.6	20.0 ± 4.8	0.160
Stent size (mm)	2.96 ± 0.4	2.93 ± 0.5	0.780
Immediately Post PCI QCA analysis			
Reference diameter (mm)	2.91 ± 0.44	2.96 ± 0.43	0.340
Minimal luminal diameter (mm)	2.68 ± 0.42	2.72 ± 0.43	0.400
Follow up QCA analysis			
Reference diameter (mm)	2.75 ± 0.48	2.75 ± 0.36	0.990
Minimal luminal diameter (mm)	2.16 ± 0.51	1.81 ± 0.75	0.007
Stenosis diameter (%)	27.4 ± 29.8	39.6 ± 23.9	0.005
Acute gain	1.82 ± 0.47	1.87 ± 0.62	0.450
Net gain	1.30 ± 0.49	0.93 ± 0.63	0.002
Late loss (in-stent)	0.52 ± 0.59	0.94 ± 0.70	0.002
Late loss (in-segment)	0.50 ± 0.56	0.91 ± 0.69	0.001
Angiographic restenosis	13 (13.2)	31 (35.2)	0.001
Follow up intravascular ultrasound analysis			
Stent length (mm)	21.7 ± 5.6	20.0 ± 4.8	0.160
Stent size (mm)	2.96 ± 0.4	2.93 ± 0.5	0.780
Incomplete stent apposition	5 (11.1)	9 (24.3)	0.150
Proximal segment	1 (2.2)	8 (21.6)	0.015
Body segment	2 (4.4)	1 (2.7)	1.000
Distal segment	2 (4.4)	0 (0.0)	0.500

QCA: Quantitative coronary analysis; PCI: Percutaneous coronary intervention; BMS: Bare-metal stent.

ment of the stent was significantly in favor of the PES group ($P = 0.015$).

The study had a small sample size, a short-term outcome and a higher amount of late loss.

SUMMARY AND PERSPECTIVE

Since the introduction of the first DES designs, we have a strong clinical evidence for their significant benefits in terms of reduction of angiographic and clinical restenosis, which has been the Achilles heel of PCI during the past 30 years. However, although uncommon, we have also identified the potential deleterious effects of late and very late stent thrombosis associated with the implantation of these devices. Therefore, we clearly understand the complex process of designing the ideal DES, in which a combination of safety and efficacy should be the main goal.

Currently, we clearly recognize the advantages and disadvantages of the first DES designs in comparison with BMS, either in short- or long-term outcomes. However, little is known about the new DES generation in comparison with either BMS or the first DES designs. In the current review we report the short-term outcomes of new DES designs with BIO polymers either with respect to the first DES or to BMS designs. The results from these trials are presented in Table 3. Theoretically, BIO polymers have the advantage of complete degradation of

Table 3 Comparison between published trials of biodegradable eluting stents

Name	Stent design	Cardiac death	Cardiac death or MI	MI	TVR	TLR
LEADERS ^[28]	Biomatrix	2.1	6.7	5.8	7.8	6.5
	Cypher	2.7	6.6	4.6	9.9	7.4
	Nobori	0.0	-	4.7	7.1	0.0
NOBORI ^[34]	Taxus	0.0	-	8.6	14.3	2.9
ISAR-TEST-3 ^[35]	Biodegradable polymer stent	2.0	2.5	1.5	-	5.9
	Permanent polymer sirolimus	2.0	3.5	2.0	-	7.9
	Polymer free sirolimus	2.0	4.0	2.5	-	12.9
ISAR-TEST-4 ^[36]	Biodegradable polymer	2.8	6.3	4.3	13.7	8.8
	Control ¹	3.2	6.2	4.1	13.9	9.4
EUCATAX ^[39]	PES	1.9	4.7	2.8	8.2	6.1
	BMS	1.9	4.3	2.4	15.0	12.6

¹Control reflects results of Cypher (Cordis, Florida, USA) or Xience (Abbott Vascular, Abbott Park, IL, USA). MI: Myocardial infarction; TVR: Target vessel revascularization; TLR: Target lesion revascularization; ISAR: Individualized Drug Eluting Stent System to Abrogate Restenosis.

the polymer together with the immunosuppressive agent that was loaded on it, after which only a BMS remains in place. Thus, all side effects related to durable polymers would be avoided or minimized with this type of coating. Requirements for dual antiplatelet therapy over a long period, mandatory with SES and PES with durable polymers, would now be necessary only within the period before polymer degradation. Long-term antiplatelet therapy is one of the major limitations for Cypher and Taxus implantation, especially in older patients or in patients with concomitant non-cardiac vascular or non-vascular illness requiring surgery. Consequently, there is plenty scope to improve the safety profile of the first DES generation; however, are these new stents with BIO polymers the answers to our concerns?

If we look at the results from the randomized LEADERS^[28] and NOBORI^[34] trials, with stent designs that share an identical polymer and drug, we do not see any advantage in terms of efficacy and safety in comparison with the old SES design. Even though the LEADERS study met the criteria for non-inferiority for the BioMatrix-Flex stent at 12 mo of follow-up, if we exclude the subgroup of patients with STEMI, we do not see any advantages in terms of safety in relation to the SES with a durable polymer (Cypher). Furthermore, the rate of non-STEMI reported in this trial with a BIO polymer stent (BioMatrix-Flex) design appears to be higher than we would expect. In addition, analysis from the subgroup of patients with STEMI had the bias of a high number of stent thromboses in the Cypher arm (over 8%), which was never reported in any randomized study in patients with STEMI with this DES design in the first year of follow-up^[42].

The ISAR-TEST-4 trial^[36] also reported a randomized head-to-head comparison between a BIO polymer SES vs 2 different durable coating DES designs, Cypher and Xience V. The ISAR BIO DES design had sirolimus completely released within the first 29 d, although the polymer disappeared between 6 and 9 wk after stent deployment. Therefore, the polymer in the stent remained in place around 1 mo after the release of the drug. For this reason, we cannot discard some adverse effects re-

lated to the polymer, free of drug, during that time. One- and two-year outcomes of this positive non-inferiority trial did not demonstrate any safety or efficacy advantage compared with the durable polymer arms, and the incidence of stent thrombosis was similar in all groups. Also, a late luminal catch up loss phenomenon between 8 mo and 2 years was reported in the ISAR-TEST-4 trial with the BIO polymer stent, a finding which was also commonly reported after implantation of SES (Cypher) with a durable polymer^[37]. Taking into account that the drug and the polymer did not simultaneously disappear, an inflammatory response to coating breakdown cannot be discarded with this stent design.

In the PAINT trial^[38], in both BIO stent designs the polymer remained in place for several months after the drug was completely eluted; therefore, an inflammatory response in response to the polymer itself and during the degradation process should be strongly considered.

In the EUCATAX trial^[39], the BIO DES design allowed the polymer and the immunosuppressive drug to disappear simultaneously in the first 6 to 8 wk after deployment of the stent; beyond that time, a BMS with camouflage nanocoating remained in place. The camouflage nanocoating design has been linked with the safety outcome in promoting stent re-endothelialization and seems very useful in patients with a high-risk thrombotic profile such as STEMI or who underwent non-cardiac surgery soon after stent deployment. Interestingly, in a previous study with this kind of coating, intravascular ultrasound in patients with STEMI did not detect late acquired stent mal-apposition during follow-up angiography^[43].

If we compare the EUCATAX with the LEADERS trial, which share similar clinical and angiographic inclusion criteria, excluding a significant lower late loss in favor of the LEADERS stent designs, the dual DES coating of EUCATAX showed similar rates of cardiac events including TLR, TVR and MI, although in the EUCATAX trial a trend of lower rates of MI and stent thrombosis were seen (Table 4). However, the down side of the last study was the large amount of late loss determined in the late angiography study with the EUCATAX stent design, which was higher than we expected (Table 2). Thus, we

Table 4 Comparison of baseline characteristics and follow up angiographic and clinical results from the randomized LEADERS^[28] and EUCATAX^[39] trials

Patients characteristics	BioMatrix	Cypher	EucaTax	P values
No. of patients	857	850	211	
Age (yr)	65 ± 11	65 ± 11	63.8 ± 10.2	0.32
Male gender	75.0	75.0	83.4	0.62
Hypertension	74.0	73.0	64.0	0.46
Diabetes mellitus	26.0	23.0	23.2	0.49
Hypercholesterolemia	65.0	68.0	56.9	0.36
Smoking	24.0	25.0	21.3	0.68
Previous MI	32.0	33.0	20.4	0.02
Previous PCI	36.0	37.0	35.5	0.93
Multi vessel disease	37.0	32.0	55.0	< 0.001
Clinical presentation				
Acute coronary syndrome	55.0	56.0	59.7	0.80
Lesions per patient				
> 1 lesion	29.0	22.0	26.1	0.09
Small vessels ¹	68.0	69.0	60.3	0.45
Procedural characteristics				
Stents per lesion	1.3 ± 0.7	1.3 ± 0.7	1.36 ± 0.5	0.38
Stent length per lesion (mm)	24.7 ± 15.5	24.6 ± 14.8	21.7 ± 5.6	0.006
Angiographic follow-up				
In-stent late loss	0.08 ± 0.4	0.15 ± 0.4	0.52 ± 0.6	< 0.001
Stent thrombosis ²				
Overall stent thrombosis	3.6	3.3	1.4	0.28
Definite ST				
0-30 d	1.6	1.6	0.5	0.43
> 30 d-12 mo	0.4	0.5	0.9	0.52
0 d-12 mo	2.0	2.0	1.4	0.82
Efficacy endpoints at 12 mo				
Any TLR	6.5	7.4	6.1	0.63
Any TVR	7.8	9.9	8.2	0.23
Safety endpoints at 12 mo				
All causes of death	3.2	3.3	2.4	0.80
Cardiac death	2.1	2.7	1.9	0.66
Myocardial infarction	5.8	4.6	2.8	0.11
Cardiac death or MI	6.7	6.6	4.7	0.46

¹Small vessel was defined as any vessel diameter with less than 2.75 mm;

²Stent thrombosis definition by the Academic Research Consortium. MI: Myocardial infarction; PCI: Percutaneous coronary intervention; RVD: Reference vessel diameter; QCA: Quantitative coronary angiography; MLD: Minimal luminal diameter; DS: Diameter stenosis; TLR: Target lesion revascularization; TVR: Target vessel revascularization.

cannot exclude an inflammation process as a result of a crack in the PLGA coating, suggesting a possible breakdown of the polymer during the degradation process. We have to recognize that the degradation process of the BIO polymers is not always uniform; in poorly vascularized areas this process is likely to be slow, whereas in inflammatory areas it may be accelerated; consequently, if the drug elutes faster than the polymer, the advantage of the BIO polymer disappears.

CONCLUSION

Introduction of completely BIO instead of durable polymers has the potential to avoid or minimize some of the side effects related to the first DES designs. One year follow-up results from these randomized trials have demon-

strated similar safety/efficacy profiles with this new DES technology using BIO polymers when compared with durable polymer designs (LEADERS and ISAR trials). However, these similarities do not mean any superiority in terms of reduction of stent thrombosis, the Damocles sword of the first DES technology. Equivalency in efficacy requires longer follow-up assessment.

Dual coating technology using an antithrombotic layer behind the PLGA coating is promising in terms of safety, although its value in terms of efficacy is questionable and needs further assessment. Consequently, the complex process of designing a DES with BIO polymers remains a challenge.

REFERENCES

- 1 **Sousa JE**, Costa MA, Abizaid AC, Rensing BJ, Abizaid AS, Tanajura LF, Kozuma K, Van Langenhove G, Sousa AG, Falotico R, Jaeger J, Popma JJ, Serruys PW. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation* 2001; **104**: 2007-2011
- 2 **Morice MC**, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; **346**: 1773-1780
- 3 **Moses JW**, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; **349**: 1315-1323
- 4 **Grube E**, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U, Russell ME. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation* 2003; **107**: 38-42
- 5 **Colombo A**, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 2003; **108**: 788-794
- 6 **Stone GW**, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004; **350**: 221-231
- 7 **Virmani R**, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tsepili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 2004; **109**: 701-705
- 8 **Togni M**, Windecker S, Cocchia R, Wenaweser P, Cook S, Billinger M, Meier B, Hess OM. Sirolimus-eluting stents associated with paradoxical coronary vasoconstriction. *J Am Coll Cardiol* 2005; **46**: 231-236
- 9 **Hong MK**, Mintz GS, Lee CW, Park DW, Park KM, Lee BK, Kim YH, Song JM, Han KH, Kang DH, Cheong SS, Song JK, Kim JJ, Park SW, Park SJ. Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. *Circulation* 2006; **113**: 414-419
- 10 **Kotani J**, Awata M, Nanto S, Uematsu M, Oshima F, Minamiguchi H, Mintz GS, Nagata S. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. *J Am Coll Cardiol* 2006; **47**: 2108-2111
- 11 **Joner M**, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E,

- Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006; **48**: 193-202
- 12 **Meier P**, Zbinden R, Togni M, Wenaweser P, Windecker S, Meier B, Seiler C. Coronary collateral function long after drug-eluting stent implantation. *J Am Coll Cardiol* 2007; **49**: 15-20
 - 13 **Finn AV**, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, Gold HK, Virmani R. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation* 2007; **115**: 2435-2441
 - 14 **Nakazawa G**, Finn AV, Joner M, Ladich E, Kutys R, Mont EK, Gold HK, Burke AP, Kolodgie FD, Virmani R. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. *Circulation* 2008; **118**: 1138-1145
 - 15 **Cook S**, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, Vogel R, Hess O, Meier B, Windecker S. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation* 2007; **115**: 2426-2434
 - 16 **McFadden EP**, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004; **364**: 1519-1521
 - 17 **Iakovou I**, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005; **293**: 2126-2130
 - 18 **Spertus JA**, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, Messenger JC, Khanal S, Peterson ED, Bach RG, Krumholz HM, Cohen DJ. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation* 2006; **113**: 2803-2809
 - 19 **Rodriguez AE**, Mieres J, Fernandez-Pereira C, Vigo CF, Rodriguez-Alemparte M, Berrocal D, Grinfeld L, Palacios I. Coronary stent thrombosis in the current drug-eluting stent era: insights from the ERACI III trial. *J Am Coll Cardiol* 2006; **47**: 205-207
 - 20 **Rodriguez AE**, Rodriguez-Granillo GA, Palacios IF. Late stent thrombosis: the Damocles's sword of drug eluting stents? *EuroIntervention* 2007; **2**: 512-517
 - 21 **Daemen J**, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Jüni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 2007; **369**: 667-678
 - 22 **Byrne RA**, Iijima R, Mehili J, Pinieck S, Bruskina O, Schömig A, Kastrati A. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. *JACC Cardiovasc Interv* 2009; **2**: 291-299
 - 23 **Finn AV**, Nakazawa G, Kolodgie FD, Virmani R. Temporal course of neointimal formation after drug-eluting stent placement: is our understanding of restenosis changing? *JACC Cardiovasc Interv* 2009; **2**: 300-302
 - 24 **Jiménez-Quevedo P**, Sabaté M, Angiolillo DJ, Costa MA, Alfonso F, Gómez-Hospital JA, Hernández-Antolín R, Bañuelos C, Goicolea J, Fernández-Avilés F, Bass T, Escaned J, Moreno R, Fernández C, Macaya C. Vascular effects of sirolimus-eluting versus bare-metal stents in diabetic patients: three-dimensional ultrasound results of the Diabetes and Sirolimus-Eluting Stent (DIABETES) Trial. *J Am Coll Cardiol* 2006; **47**: 2172-2179
 - 25 **Grube E**, Dawkins K, Guagliumi G, Banning A, Zmudka K, Colombo A, Thuesen L, Hauptman K, Marco J, Wijns W, Joshi A, Mascioli S. TAXUS VI final 5-year results: a multicentre, randomised trial comparing polymer-based moderate-release paclitaxel-eluting stent with a bare metal stent for treatment of long, complex coronary artery lesions. *EuroIntervention* 2009; **4**: 572-577
 - 26 **Kukreja N**, Onuma Y, Daemen J, Serruys PW. The future of drug-eluting stents. *Pharmacol Res* 2008; **57**: 171-180
 - 27 **Finn AV**, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K, Skorija K, Weber DK, Gold HK, Virmani R. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation* 2005; **112**: 270-278
 - 28 **Windecker S**, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Jüni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008; **372**: 1163-1173
 - 29 **Rodriguez AE**. Emerging drugs for coronary restenosis: the role of systemic oral agents the in stent era. *Expert Opin Emerg Drugs* 2009; **14**: 561-576
 - 30 **Aoki J**, Ong AT, Abizaid A, den Heijer P, Bonnier H, McClean DR, Verheye S, Belardi J, Condado JA, Pieper M, Sousa JE, Bressers M, Symons J, Litvack F, Sianos G, Serruys PW. One-year clinical outcome of various doses and pharmacokinetic release formulations of paclitaxel eluted from an erodable polymer - Insight in the Paclitaxel In-Stent Controlled Elution Study (PISCES). *EuroIntervention* 2005; **1**: 165-172
 - 31 **Onuma Y**, Serruys P, den Heijer P, Joesoef KS, Duckers H, Regar E, Kukreja N, Tanimoto S, Garcia-Garcia HM, van Beusekom H, van der Giessen W, Nishide T. MAHOROBA, first-in-man study: 6-month results of a biodegradable polymer sustained release tacrolimus-eluting stent in de novo coronary stenoses. *Eur Heart J* 2009; **30**: 1477-1485
 - 32 **Han Y**, Jing Q, Xu B, Yang L, Liu H, Shang X, Jiang T, Li Z, Zhang H, Li H, Qiu J, Liu Y, Li Y, Chen X, Gao R. Safety and efficacy of biodegradable polymer-coated sirolimus-eluting stents in "real-world" practice: 18-month clinical and 9-month angiographic outcomes. *JACC Cardiovasc Interv* 2009; **2**: 303-309
 - 33 **Ostojic M**, Sagic D, Beleslin B, Jung R, Perisic Z, Jagic N, Nedeljkovic M, Mangovski L, Milosavljevic B, Stojkovic S, Orlic D, Antonic Z, Miloradovic V, Topic D, Paunovic D. First clinical comparison of Nobori -Biolimus A9 eluting stents with Cypher -Sirolimus eluting stents: Nobori Core nine months angiographic and one year clinical outcomes. *EuroIntervention* 2008; **3**: 574-579
 - 34 **Chevalier B**, Silber S, Park SJ, Garcia E, Schuler G, Suryapranata H, Koolen J, Hauptmann KE, Wijns W, Morice MC, Carrie D, van Es GA, Nagai H, Detiege D, Paunovic D, Serruys PW. Randomized comparison of the Nobori Biolimus A9-eluting coronary stent with the Taxus Liberté paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries: the NOBORI 1 trial--Phase 2. *Circ Cardiovasc Interv* 2009; **2**: 188-195
 - 35 **Mehilli J**, Byrne RA, Wiecek A, Iijima R, Schulz S, Bruskina O, Pache J, Wessely R, Schömig A, Kastrati A. Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. *Eur Heart J* 2008; **29**: 1975-1982
 - 36 **Byrne RA**, Kastrati A, Kufner S, Massberg S, Birkmeier KA, Laugwitz KL, Schulz S, Pache J, Fusaro M, Seyfarth M, Schömig A, Mehilli J. Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial.

- Eur Heart J* 2009; **30**: 2441-2449
- 37 **Byrne RA**, Kastrati A. Biodegradable polymer limus-eluting stents are noninferior to permanent polymer-based stents: the ISAR-TEST-4 trial. *Interv Cardiol* 2010; **2**: 267-273
 - 38 **Lemos PA**, Moulin B, Perin MA, Oliveira LA, Arruda JA, Lima VC, Lima AA, Caramori PR, Medeiros CR, Barbosa MR, Brito FS Jr, Ribeiro EE, Martinez EE. Randomized evaluation of two drug-eluting stents with identical metallic platform and biodegradable polymer but different agents (paclitaxel or sirolimus) compared against bare stents: 1-year results of the PAINT trial. *Catheter Cardiovasc Interv* 2009; **74**: 665-673
 - 39 **Rodriguez AE**, Vigo CF, Delacasa A, Mieres J, Fernandez-Pereira C, Bernardi V, Bettinoti M, Rodriguez-Granillo AM, Rodriguez-Granillo G, Santaera O, Curotto V, Rubilar B, Tronje J, Palacios IF, Antoniucci D. Efficacy and safety of a double-coated paclitaxel-eluting coronary stent: The EUCATAX trial. *Catheter Cardiovasc Interv* 2011; **77**: 335-342
 - 40 **Ozbek C**, Mailänder C, Schilling U, Bach R. Clinical efficacy of a DE stent after an electively planned percutaneous coronary intervention under "real-life" conditions: prospective registry (first-in-man data). *Clin Hemorheol Microcirc* 2008; **39**: 311-321
 - 41 **Hoffmann M**, Horres R, Keller R, Baumann H. Isolation and characterisation of endothelial cell surface heparan sulphate from whole bovine lung for coating of biomaterials to improve haemocompatibility. In: Chiellini E, Sunamoto J, Migliaresi C, Ottenbrite RM, Cohn D, editors. Biomedical polymers and polymer therapeutics. New York, Boston, Dordrecht, London, Moscow: Kluwer Academic Publishers, 2002: 213-226
 - 42 **Kastrati A**, Dibra A, Spaulding C, Laarman GJ, Menichelli M, Valgimigli M, Di Lorenzo E, Kaiser C, Tierala I, Mehilli J, Seyfarth M, Varenne O, Dirksen MT, Percoco G, Varricchio A, Pittl U, Syväanne M, Suttorp MJ, Violini R, Schömig A. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. *Eur Heart J* 2007; **28**: 2706-2713
 - 43 **Perez G**, Rodriguez-Granillo AM, Mieres J, Llauro C, Rubilar B, Risau G, Fernandez-Pereira C, Rodriguez AE. New coating stent design for patients with high-risk coronary lesions for thrombotic events: early and long-term results of the Camouflage registry. *J Invasive Cardiol* 2009; **21**: 378-382

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Benefit of stem cells and skeletal myoblast cells in dilated cardiomyopathies

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Abstract

Although some authors suggest that there is mitotic division in the heart, most cardiomyocytes do not have the capacity to regenerate after myocardial infarction and when this occurs there is a deterioration of contractile function, and if the area of infarction is extensive ventricular remodeling may occur, leading to the development of heart failure. Cell transplantation into the myocardium with the goal of recovery of cardiac function has been extensively studied in recent years. The effects of cell therapy are based directly on the cell type used and the type of cardiac pathology. For myocardial ischemia in the hibernating myocardium, bone marrow cells have functional benefits, however these results in transmural fibrosis are not evident. In these cases there is a benefit of implantation with skeletal myoblasts, for treating the underlying cause of disease, the loss of cell contractility.

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INTRODUCTION

Congestive heart failure is the common final pathway for patients with ischemic and non-ischemic cardiomyopathies. Therapeutic options mainly target the consequences of heart failure, such as fluid overload and neurohumoral activation, which are known to have long term deleterious effects^[1]. However, improvement in ventricular contractility by restoration of cardiomyocyte contractile capacity has not been an issue until recently^[2].

Although some authors have shown evidence of mitotic division of cardiomyocytes, scar formation following myocardial injury leads to remodeling and permanent loss of ventricular contractility^[3]. Not surprisingly, attempts to restore ventricular contraction in ischemic cardiomyopathy by cell transplantation have emerged as a feasible therapeutic option.

The beneficial effect of cellular transplantation in the full range of cardiomyopathies remains to be investigated. The most appropriate cell type to be used for each dilated cardiomyopathy will probably vary, since mechanisms of myocardial damage are different. In this article we will first review the characteristics of some of the cells that have been studied as appropriate for transplantation either in ischemic or non-ischemic cardiomyopa-

thies. In addition, we will review some experimental and human studies in different types of non-ischemic dilated cardiomyopathies.

CHARACTERISTICS OF DIFFERENT CELLS

Myoblasts

Skeletal myoblast transplantation has been shown to be effective in many experimental^[4-7] and clinical^[8] studies. These cells differentiate into viable muscle fibers within the scarred tissue and they seem to be less prone to ischemia compared to cardiomyocytes^[9].

In a phase I clinical trial, Hagège *et al.*^[8] evaluated 10 patients with severe post-infarct ventricular dysfunction who received autologous myoblasts cultured for 16 d after being taken from the thigh. The authors demonstrated a recovery of function in areas previously akinetic and non-viable, but the mechanism of improvement was not completely understood. They hypothesized that it could happen either by a change in cell phenotype, since they expressed slow myosin instead of fast myosin, or simply by colonizing the infarcted area with new contractile cells and avoiding further dysfunction^[8]. However, the high incidence of ventricular arrhythmias in patients who received myoblasts was of major concern.

Paradoxically, in the phase II randomized, placebo-controlled trial Myoblast Autologous Grafting in Ischemic Cardiomyopathy by the same investigators, there were no statistically significant differences between the treatment and placebo groups in terms of ventricular arrhythmias (all the patients had received an implantable cardioverter-defibrillator). However, the study was ended early after an analysis by an independent data-monitoring board indicated that the trial was unlikely to show that treatment would be superior to placebo in terms of functional improvements in heart regional wall motion or global ventricular function (data presented at the Scientific session of the American Heart Association, Chicago, 2006)^[10].

In conclusion, there is still controversy on whether myoblast transplantation is a good option, at least as sole treatment. Potential pitfalls of this strategy are the lack of morphological differentiation into cardiomyocytes and also the absence of an intercalated disc between transplanted cells and the native adult cardiomyocytes, suggesting there may be no synchronicity in contraction between these types of cell.

Bone-marrow stem cells

Adult stem cells are pluripotent^[11]. They have the ability to differentiate into specific cells depending on the surrounding tissue and factors. The differentiation capacity of bone marrow cells is not completely understood. Some studies have shown that these cells are able to differentiate into cardiomyocytes^[12] but in another study only neoangiogenesis was seen and left ventricular ejection fraction deteriorated similarly in the transplanted and control groups (from $42\% \pm 5\%$ to $30\% \pm 4\%$ and

from $40\% \pm 4\%$ to $31\% \pm 1\%$, respectively, $P = 0.86$)^[13]. In fact, different results have been observed according to the studied model.

In a model of myocardial infarction, Orlic *et al.*^[14] have demonstrated the beneficial effect of bone marrow cell injection in the border of the infarcted myocardium shortly after coronary ligation. In this tissue, proliferating myocytes and vascular structures were noted. Bone marrow cells were transplanted in an area with viable myocardium, and not scar tissue, and this may explain why they differentiated into cardiomyocytes. In a clinical trial, Wollert *et al.*^[15] evaluated patients with acute myocardial infarction who, after acute treatment with percutaneous transluminal coronary angioplasty, were randomized to standard clinical treatment alone or standard treatment and bone marrow cell transplantation. Ventricular function significantly improved in patients who received cells, in comparison to those who did not.

In patients with established fibrosis, results are conflicting. Perin *et al.*^[16] showed that transendocardial injection of autologous mononuclear bone marrow cells in patients with end-stage ischemic heart disease improves perfusion and mechanical function of the injected segments. However, different results were demonstrated by Marzullo^[17], who demonstrated by scintigraphy that bone marrow cells can improve perfusion but not contraction. The author evaluated patients with a coronary artery bypass graft who had cells injected in the area of fibrosis. In areas where reperfusion was achieved after grafting, improvement was seen in perfusion and contraction. On the other hand, in areas where cell injection was performed, compared with culture medium only, an improvement in perfusion was seen.

Combined transplantation

The idea of using a combination of skeletal myoblasts and cells derived from the bone marrow is based on the concept of providing angio-muscular regeneration and not only isolated muscular or angiogenic regeneration. Our group has evaluated transplantation of co-cultured myoblasts and mesenchymal stem cells (MSC) in a rat model of myocardial infarction, and it was effective in improving ventricular function, with development of new skeletal muscular fibers and new blood vessels in the region of myocardial fibrosis^[18]. Our results with co-culture in Chagasic cardiomyopathy are described in the next section^[19].

CELL TRANSPLANTATION IN NON-ISCHEMIC DILATED CARDIOMYOPATHY

Experimental studies

While animal models of ischemia and myocardial infarction can be easily reproduced, models of non-ischemic dilated cardiomyopathy are lacking. In an interesting myocarditis model, where rats are immunized with porcine cardiac myosin resulting in severe heart failure, Nagaya *et al.*^[20] evaluated the effect of MSC on induction of myogenesis and angiogenesis. They isolated MSC from bone marrow aspirates, cultured them for 5 wk, then injected

cells or vehicle into the myocardium. Some engrafted MSCs were positive for the cardiac markers desmin, cardiac troponin T, and connexin-43, whereas others formed vascular structures and were positive for von Willebrand factor or smooth muscle actin. Compared with the control group, MSC transplantation significantly increased capillary density and ventricular maximum dp/dt, decreased the collagen volume of the myocardium and decreased left ventricular end diastolic pressure. Authors suggested that MSC transplantation improved cardiac function not only by induction of myogenesis and angiogenesis, but also by inhibition of myocardial fibrosis.

In a similar model of dilated cardiomyopathy, Werner *et al.*^[21] investigated the effect of spleen-derived endothelial progenitor cells injected by the femoral vein. These cells reduced the myocardial damage induced by experimental myocarditis and resulted in improvement in cardiac performance as shown by echocardiography. This late finding was consistent with a thicker left ventricular wall compared with the control group as demonstrated by histopathology. Another interesting finding was that endothelial progenitor cells from rats with dilated cardiomyopathy were compromised in their ability to bind immobilized fibronectin, cultured endothelial cells and cardiomyocytes as compared with progenitor cells from healthy rats, suggesting a whole dysfunctional state.

Working with CHF147 Syrian hamsters, a strain characterized by a δ -sarcoglycan deficiency that phenotypically features the human setting of primary dilated cardiomyopathy, Pouly *et al.*^[22] transplanted autologous tibial myoblasts and found an increment of 26% in fractional area change of transplanted hamsters compared with a reduction of 6% in control animals (fractional area change is an echo parameter commonly applied to evaluate ventricular function in murine models of heart failure). Engrafted myotubes were detected by immunohistochemistry in all myoblast transplanted hearts, suggesting that the functional benefits of myoblast transplantation seen in ischemic cardiomyopathies might also extend to non-ischemic cardiomyopathies.

As Chagasic cardiomyopathy caused by the hemoflagellate protozoa *Trypanosoma cruzi* infection has been one of the leading causes of heart disease in Latin America for decades, animal models of this disease have been developed to better evaluate new therapeutic options. Nevertheless, studies of cell transplantation in these experimental models are still lacking. In a mouse model, Soares *et al.*^[23] demonstrated that bone marrow cells injected intravenously migrated to the heart and caused a significant reduction in inflammatory infiltrates and in interstitial fibrosis. Cell therapy induced massive apoptosis of myocardial inflammatory cells. The effect was the same when injected bone marrow cells were obtained from normal or infected mice. Because ventricular function was not assessed, it remains to be proved whether these beneficial histological effects with mononuclear cells transplantation is translated into ventricular function improvement in models of Chagas disease.

Also in a rat model of Chagas disease, our group has evaluated the transplantation of co-cultured skeletal myoblasts and mesenchymal cells derived from bone marrow. As previously described, we had successfully tested this approach in a rat model of myocardial infarction. Because physiopathology in Chagas disease resembles the findings in chronic ischemic cardiomyopathy, with fibrosis and ischemia, we hypothesized that simultaneous transplantation of co-cultured MSC and skeletal myoblasts could be an effective approach in this disease.

To develop the rat model, we infected Wistar rats with trypomastigotes (infective form of *Trypanosoma cruzi*) and after 8 mo the animals which developed dilated cardiomyopathy (left ventricular ejection fraction < 37%) were included in the study. Autologous skeletal myoblasts were isolated from muscle biopsy, and MSC from bone marrow aspirates were co-cultured *in vitro* for 14 d. Rats were randomly assigned to receive subepicardial injection of co-culture of skeletal myoblast and MSC or culture medium as control. Cells were injected into the anterior and lateral left ventricular wall. One month after the procedure, the ejection fraction remained unchanged in the control group ($36.7\% \pm 3.6\%$ to $37.4\% \pm 6.7\%$, $P = 0.7684$) but was enhanced in the treated group ($30.1\% \pm 5.7\%$ to $51.8\% \pm 6.6\%$, $P < 0.0001$). We also found a reduced left ventricular end diastolic and systolic volumes in those rats receiving the cells. No change was observed in the control group. Histological analysis of the control group demonstrated a high degree of fibrosis, a feature of Chagas disease. In the treated group, skeletal muscle cells, with myotubular characteristics, endothelial cells, and formation of new vessels were identified in the epicardium where cells were transplanted. The musculoskeletal origin was confirmed by positive fast myosin immunostaining in the treated group. In conclusion, the combined cellular transplantation with myoblasts and MSC is functionally effective in the model of Chagas disease ventricular dysfunction.

Cellular transplantation has also been evaluated in a model of doxorubicin-induced cardiomyopathy. Ishida *et al.*^[24] performed the study in rats that randomly received bone marrow mononuclear cells, saline or no injection but a sham operation. After 4 wk of cells delivery through thoracotomy, ventricular function and diameters were evaluated by echocardiography. Systolic left ventricular diameter was smaller and fractional shortening was larger in the transplanted group. Beneficial effects of cellular transplantation were confirmed by Langendorff apparatus that revealed greater peak systolic pressure and lower end diastolic pressure in hearts from the transplant group.

Human studies

Experience with cellular transplantation in non-ischemic cardiomyopathies is still in a very preliminary phase, and bone marrow cells have been widely used for this. Lago *et al.*^[25] performed the transplantation of bone marrow stem cells into 8 patients with non-ischemic cardiomyopathy, deploying cells directly into coronary arteries. The

ejection fraction significantly increased from 18.3 ± 7 to $26.4\% \pm 10\%$ ($P < 0.005$) and left ventricular diastolic diameter showed a non significant decrease. Symptoms were significantly improved, as demonstrated by a reduction on functional class (NYHA) from 2.5 ± 0.8 to 1.4 ± 0.5 ($P < 0.001$). Another important issue addressed in this study was safety of the procedure: no mortality or major complications were observed.

Other studies have evaluated different routes for cell transplantation. Ghodsizad *et al.*^[26] reported the case of a 58-year-old man with end stage non-ischemic cardiomyopathy who received bone marrow cells by the transepi-myocardial route through a minimally invasive surgery approach. Six months after the procedure, echocardiography and cardiac magnetic resonance showed improvement of left ventricular contractility. By a similar approach, mini anterior-left thoracotomy, Kalil *et al.*^[27] transplanted mononuclear cells into the myocardium of 8 patients with dilated idiopathic cardiomyopathy. Evaluation of cardiac performance was performed by magnetic resonance before, 4, 6 and 8 mo after transplantation. Despite an improvement in the first 4 mo, the ejection fraction returned to basal values after 8 mo, suggesting only a transient beneficial effect.

Cellular transplantation has also been tested in patients with Chagas disease. This may be an interesting option for those patients with more advanced stages, particularly when heart transplantation seems to be the only option. It is worth recalling that heart transplantation has some peculiar implications in Chagas disease. First, most patients affected by the disease live in poor areas in developing countries, where the cost of heart transplantation is high and may be unaffordable. Second, immunosuppression treatment may reactivate Chagas infection compromising short-term and long-term prognosis^[28].

Vilas-Boas *et al.*^[29] studied 28 class III and IV patients with Chagas disease, all receiving optimized clinical treatment. Mononuclear bone marrow cells were delivered by intracoronary injection. After 60 d of transplantation there was an increase in ejection fraction ($20.1\% \pm 6.8\%$ to $23\% \pm 9\%$, $P = 0.02$), NYHA class (3.1 ± 0.3 to 1.8 ± 0.5 , $P < 0.0001$) and distance walked in 6 min, with no augmentation in the incidence of ventricular tachycardia. Their data demonstrated that injection of bone marrow mononuclear cells is feasible and may be effective in patients with heart failure resulting from Chagas disease.

Paracrine effects

In some situations after cell transplantation, there is a clinical improvement in patients, but without confirmation in laboratory tests. Lionetti *et al.*^[30] support the hypothesis that autocrine and paracrine mechanisms mediated by factors released by resident cardiac cells could play a key role in the repair of heart failure. Such signals may influence the function of cardiac stem cells through various mechanisms, among which the most studied are the survival of cardiomyocytes and angiogenesis. It is known that chemical, mechanical or genetic activation of cardiac cells can release peptides to protect tissues against ischemic injury.

CONCLUSION

Despite recent efforts described in this review, the real benefit of cellular transplantation in heart failure, especially caused by non-ischemic cardiomyopathies, is still far from being determined. Considering the experience of the last few years, we believe that different cardiomyopathies will benefit from different cell types. As myocardial perfusion is preserved in most non-ischemic cardiomyopathies, we believe that, in this group, myoblast transplantation may be an interesting and physiological approach by providing new and effective muscle fibers. However, this is just a hypothesis waiting to be tested.

REFERENCES

- 1 Carraway EA, Rayburn BK. Device therapy for remodeling in congestive heart failure. *Curr Heart Fail Rep* 2007; **4**: 53-58
- 2 Guarita-Souza LC, Carvalho KA, Rebelatto C, Senegaglia A, Hansen P, Furuta M, Miyague N, Francisco JC, Olandoski M, Faria-Neto JR, Oliveira SA, Brofman PR. Cell transplantation: differential effects of myoblasts and mesenchymal stem cells. *Int J Cardiol* 2006; **111**: 423-429
- 3 Kajstura J, Leri A, Finato N, Di Loreto C, Beltrami CA, Anversa P. Myocyte proliferation in end-stage cardiac failure in humans. *Proc Natl Acad Sci USA* 1998; **95**: 8801-8805
- 4 Ghostine S, Carrion C, Souza LC, Richard P, Bruneval P, Vilquin JT, Pouzet B, Schwartz K, Menasché P, Hagege AA. Long-term efficacy of myoblast transplantation on regional structure and function after myocardial infarction. *Circulation* 2002; **106**: I131-I136
- 5 Scorsin M, Hagege A, Vilquin JT, Fiszman M, Marotte F, Samuel JL, Rappaport L, Schwartz K, Menasché P. Comparison of the effects of fetal cardiomyocyte and skeletal myoblast transplantation on postinfarction left ventricular function. *J Thorac Cardiovasc Surg* 2000; **119**: 1169-1175
- 6 Taylor DA, Atkins BZ, Hungspreugs P, Jones TR, Reedy MC, Hutcheson KA, Glower DD, Kraus WE. Regenerating functional myocardium: improved performance after skeletal myoblast transplantation. *Nat Med* 1998; **4**: 929-933
- 7 Dorfman J, Duong M, Zibaitis A, Pelletier MP, Shum-Tim D, Li C, Chiu RC. Myocardial tissue engineering with autologous myoblast implantation. *J Thorac Cardiovasc Surg* 1998; **116**: 744-751
- 8 Hagege AA, Marolleau JP, Vilquin JT, Alhéritière A, Peyrard S, Duboc D, Abergel E, Messas E, Mousseaux E, Schwartz K, Desnos M, Menasché P. Skeletal myoblast transplantation in ischemic heart failure: long-term follow-up of the first phase I cohort of patients. *Circulation* 2006; **114**: I108-I113
- 9 Eckert P, Schnackerz K. Ischemic tolerance of human skeletal muscle. *Ann Plast Surg* 1991; **26**: 77-84
- 10 Menasché P. Scientific session of the American Heart Association. Chicago, 2006
- 11 Verfaillie CM. Adult stem cells: assessing the case for pluripotency. *Trends Cell Biol* 2002; **12**: 502-508
- 12 Deb A, Wang S, Skelding KA, Miller D, Simper D, Caplice NM. Bone marrow-derived cardiomyocytes are present in adult human heart: A study of gender-mismatched bone marrow transplantation patients. *Circulation* 2003; **107**: 1247-1249
- 13 Bel A, Messas E, Agbulut O, Richard P, Samuel JL, Bruneval P, Hagege AA, Menasché P. Transplantation of autologous fresh bone marrow into infarcted myocardium: a word of caution. *Circulation* 2003; **108** Suppl 1: I1247-I1252
- 14 Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, McKay R, Nadal-Ginard B, Bodine DM, Leri A, Anversa P. Bone marrow cells regenerate infarcted myocardium. *Nature* 2001; **410**: 701-705

- 15 **Wollert KC**, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C, Fichtner S, Korte T, Hornig B, Messinger D, Arseniev L, Hertenstein B, Ganser A, Drexler H. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet* 2004; **364**: 141-148
- 16 **Perin EC**, Dohmann HF, Borojevic R, Silva SA, Sousa AL, Mesquita CT, Rossi MI, Carvalho AC, Dutra HS, Dohmann HJ, Silva GV, Belém L, Vivacqua R, Rangel FO, Esporcatte R, Geng YJ, Vaughn WK, Assad JA, Mesquita ET, Willerson JT. Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. *Circulation* 2003; **107**: 2294-2302
- 17 **Marzullo P**. Nuclear imaging after cell implantation. *Int J Cardiol* 2004; **95** Suppl 1: S53-S54
- 18 **Souza LC**, Carvalho KA, Rebelatto C, Senegaglia A, Furuta M, Miyague N, Hansen P, Francisco JC, Olandowski M, Brofman PR. Combined transplantation of skeletal myoblasts and mesenchymal cells (cocultivation) in ventricular dysfunction after myocardial infarction. *Arq Bras Cardiol* 2004; **83**: 294-299; 288-293
- 19 **Guarita-Souza LC**, Carvalho KA, Witowicz V, Rebelatto C, Senegaglia A, Hansen P, Miyague N, Francisco JC, Olandowski M, Faria-Neto JR, Brofman P. Simultaneous autologous transplantation of cocultured mesenchymal stem cells and skeletal myoblasts improves ventricular function in a murine model of Chagas disease. *Circulation* 2006; **114**: I120-I124
- 20 **Nagaya N**, Kangawa K, Itoh T, Iwase T, Murakami S, Miyahara Y, Fujii T, Uematsu M, Ohgushi H, Yamagishi M, Tokudome T, Mori H, Miyatake K, Kitamura S. Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy. *Circulation* 2005; **112**: 1128-1135
- 21 **Werner L**, Deutsch V, Barshack I, Miller H, Keren G, George J. Transfer of endothelial progenitor cells improves myocardial performance in rats with dilated cardiomyopathy induced following experimental myocarditis. *J Mol Cell Cardiol* 2005; **39**: 691-697
- 22 **Pouly J**, Hagège AA, Vilquin JT, Bissery A, Rouche A, Bruneval P, Duboc D, Desnos M, Fiszman M, Fromes Y, Menasché P. Does the functional efficacy of skeletal myoblast transplantation extend to nonischemic cardiomyopathy? *Circulation* 2004; **110**: 1626-1631
- 23 **Soares MB**, Lima RS, Rocha LL, Takyia CM, Pontes-de-Carvalho L, de Carvalho AC, Ribeiro-dos-Santos R. Transplanted bone marrow cells repair heart tissue and reduce myocarditis in chronic chagasic mice. *Am J Pathol* 2004; **164**: 441-447
- 24 **Ishida M**, Tomita S, Nakatani T, Fukuhara S, Hamamoto M, Nagaya N, Ohtsu Y, Suga M, Yutani C, Yagihara T, Yamada K, Kitamura S. Bone marrow mononuclear cell transplantation had beneficial effects on doxorubicin-induced cardiomyopathy. *J Heart Lung Transplant* 2004; **23**: 436-445
- 25 Abstracts of the 55th Annual Scientific Session of the American College of Cardiology, March 11-14, 2006, Atlanta, Georgia, USA. *J Am Coll Cardiol* 2006; **47**: 1A-384A
- 26 **Ghodsizad A**, Ruhparwar A, Marktanner R, Borowski A, Mohammad Hasani MR, Poll L, Vshivkov I, Stoldt V, Voelkel T, Piechaczek C, Burchardt ER, Stocksclaeder M, Sucker C, Gams E, Klein HM. Autologous transplantation of CD133+ BM-derived stem cells as a therapeutic option for dilative cardiomyopathy. *Cytotherapy* 2006; **8**: 308-310
- 27 **Kalil RA**, Ott D, Sant'Anna R, Dias E, Marques-Pereira JP, Delgado-Cañedo A, Nardi NB, Sant'Anna JR, Prates PR, Nesralla I. Autologous transplantation of bone marrow mononuclear stem cells by mini-thoracotomy in dilated cardiomyopathy: technique and early results. *Sao Paulo Med J* 2008; **126**: 75-81
- 28 **Stolf NA**, Higushi L, Bocchi E, Bellotti G, Auler JO, Uip D, Amato Neto V, Pileggi F, Jatene AD. Heart transplantation in patients with Chagas' disease cardiomyopathy. *J Heart Transplant* 1987; **6**: 307-312
- 29 **Vilas-Boas F**, Feitosa GS, Soares MB, Mota A, Pinho-Filho JA, Almeida AJ, Andrade MV, Carvalho HG, Dourado-Oliveira A, Ribeiro-dos-Santos R. [Early results of bone marrow cell transplantation to the myocardium of patients with heart failure due to Chagas disease]. *Arq Bras Cardiol* 2006; **87**: 159-166
- 30 **Lionetti V**, Bianchi G, Recchia FA, Ventura C. Control of autocrine and paracrine myocardial signals: an emerging therapeutic strategy in heart failure. *Heart Fail Rev* 2010; **15**: 531-542

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Cardiac mass in a patient with colorectal cancer: "Not all that glitters is gold!"

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INTRODUCTION

Mitral valve calcification (MVC) is a degenerative abnormality of the cardiac fibrous skeleton that occurs mainly in elderly individuals^[1]. Caseous calcification of the mitral annulus (CCMA) is a less well known and rarely described entity representing a variant of MVC, typically located in the posterior mitral annulus^[2] that should be included in the differential diagnosis of intracardiac masses. It is found in 0.6% of patients with MVC and 0.06% of all echocardiographic studies^[3]. In necropsy studies, its prevalence raises to 2.7%^[1]. It is more prevalent in the elderly, in women and in patients undergoing dialysis. Histopathologic analysis of this entity reveals an amorphous basophilic fluid, surrounded by macrophages (mainly) and lymphocytes. This condition carries a benign prognosis. Surgery may be rarely needed due to hemodynamic compromise^[4,5]. The association of colorectal cancer (CC) with CCMA has not been described previously.

CASE REPORT

A 74-year-old woman with a history of hypertension was admitted to our department with non ST-elevation myocardial infarction. Standard medical treatment was promptly initiated and a coronary angiogram was per-

Abstract

When performing echocardiography in a 74-year-old woman admitted with non ST elevation myocardial infarction and concomitant colorectal cancer (CC), a dense calcification of the mitral annulus was detected. Differential diagnosis between secondary metastasis and other etiologies of cardiac masses was essential for staging and therapeutic decision-making. Multimodality imaging with echocardiography alongside a computed tomography scan and cardiac magnetic resonance was crucial for the final diagnosis of caseous calcification of the mitral annulus (CCMA). CCMA is briefly reviewed and some possible explanations for the previously undescribed association of CC with CCMA are suggested.

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Key words: Pathologic calcification; Mitral valve; Colorectal cancer; Cardiac metastasis

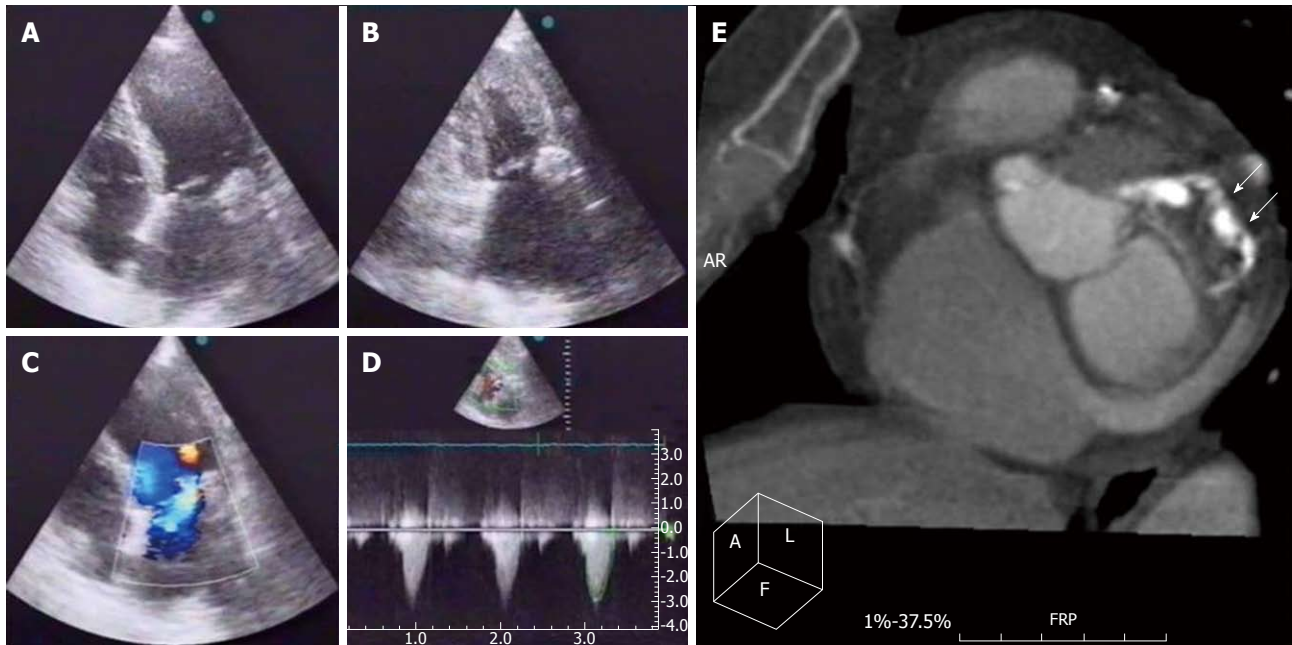


Figure 1 Pre-discharge transthoracic echocardiogram. Apical 4C (panel A) and 2C (panel B) showing a 2.3 cm × 2.0 cm round echodense mass at the posterior side of the mitral annulus, grade II mitral regurgitation (panel C) and moderate aortic stenosis (peak gradient 33 and medium 21 mmHg) (panel D); E: Cardiac assessment with 16-slice multidetector row computed tomography (Philips Brilliance 16 using electrocardiographic triggering, endovenous contrast enhancement and multiplanar and volumetric reconstruction), a peripherally calcified, round 2.5 cm × 3.0 cm mass with decreased signal on the inside can be seen in the posterior part of the mitral annulus (arrows).

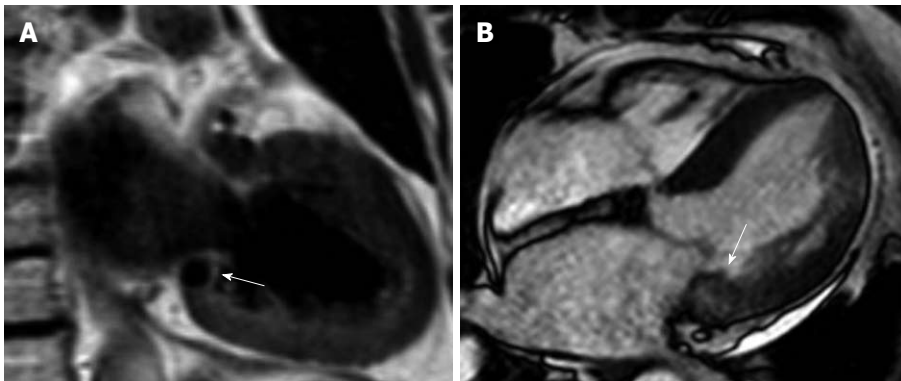


Figure 2 Cardiac magnetic resonance images (Philips 1.5 Tesla MRI scanner). A: A well defined dark mass (arrow) is near the posterior mitral valve leaflet in a T1 weighted sequence, suggestive of calcification; B: In steady state free precession images, the mass (arrow) appears only slightly darker than the normal myocardium, with a well defined intramyocardial border.

formed at 48 h of evolution. Two-vessel coronary artery disease was diagnosed and complete revascularization with 3 bare-metal stents was accomplished by staged percutaneous procedures. A heavily calcified mitral annulus, moderate mitral regurgitation and ejection fraction of 77% were found on the left ventriculogram. The patient had a favorable outcome (Killip class 1). A pre-discharge transthoracic echocardiogram (TTE) (Figure 1A-D) showed moderate enlargement of the left atrium, grade II mitral regurgitation and good left ventricular systolic function. A 2.3 cm × 2.0 cm round echodense mass was found at the posterior side of the mitral annulus adjacent to the atrial side of the posterior leaflet. Fibrocalcification of the aortic valve with moderate stenosis (peak gradient 33 and

medium 21 mmHg) was also described. Blood calcium levels and renal function were normal.

Meanwhile, in order to better clarify the persistent microcytic hypochromic anemia (8.6 g/dL hemoglobin, mean globular volume 79 fL) diagnosed during her initial admission, an endoscopic study of the gastrointestinal tract was conducted. An invasive, well differentiated mucinous colorectal adenocarcinoma was detected 20 cm away from the anal margin.

In order to perform cancer staging, the nature of the cardiac mass had to be elucidated. During a routine chest computed tomography (CT) scan for cancer staging, a cardiac CT evaluation was performed (Figure 1E) (suggestive of CCMA). Further evaluation by cardiac magnetic

resonance revealing absence of vascular flow within the mass, and the presence of a dark signal in T1 weighted sequences was also consistent with calcification (Figure 2A). In steady state free precession images, the mass appeared only slightly darker than the normal myocardium, with a well defined intramyocardial border (Figure 2B). Along with the TTE, these data suggested a diagnosis in favor of a CCMA. Therefore, as no hepatic, pulmonary or other type of metastasis was found in cancer staging (T4N0M0 - Stage II), left hemicolectomy was successfully performed and the patient was discharged 9 d later.

After 24 mo, the patient is currently stable, with no relapse of cancer nor progression of mitral valve disease (NYHA I and similar findings in follow-up TTE).

DISCUSSION

Although there are only 9 reports of the association of CC with cardiac metastasis^[6], when faced with a patient with CC and a cardiac mass, this is a possible diagnosis, that may be frequently overlooked (metastasis to the heart occurred in 10.7% out of 1,029 autopsy cases in which a malignant neoplasm had been diagnosed^[7]). Other possibilities to consider would be a myxoma^[8], other types of tumor^[9,10], an organized thrombus or abscess. An abscess would be clinically unlikely and the other possibilities could be excluded by the typical presentation of the CCMA that we found. Even though TTE was almost diagnostic by itself, this patient had to undergo chest CT for cancer staging, and cardiac CT along with magnetic resonance imaging were helpful for mass characterization and exclusion of other potential etiologies, and for diagnosis confirmation^[11,12].

An accurate diagnosis was of utmost importance in this patient, since it changed both treatment and prognosis. Unlike cardiac metastasis, CCMA has a good prognosis and does not require cardiac surgery, unless it causes mitral stenosis or symptomatic and severe mitral regurgitation. Additionally, the absence of cardiac metastasis turned this into a stage II colorectal cancer, eligible for curative surgical treatment, instead of a stage IV (metastatic).

We may wonder if this association of CC and CCMA is a mere coincidence or if there is any kind of circulating substance produced by the CC that led to increased cal-

cium deposition in the heart. Triple simultaneous involvement of the heart (calcification of coronary vessels, mitral and aortic valves) is unusual in this context. The possibility of a common link between aortic stenosis and coronary heart disease has been described before^[13], but nothing has been said about CCMA as a part of this continuum.

REFERENCES

- 1 **Pomerance A.** Pathological and clinical study of calcification of the mitral valve ring. *J Clin Pathol* 1970; **23**: 354-361
- 2 **Harpaz D, Auerbach I, Vered Z, Motro M, Tobar A, Rosenblatt S.** Caseous calcification of the mitral annulus: a neglected, unrecognized diagnosis. *J Am Soc Echocardiogr* 2001; **14**: 825-831
- 3 **Novaro GM, Griffin BP, Hammer DF.** Caseous calcification of the mitral annulus: an underappreciated variant. *Heart* 2004; **90**: 388
- 4 **Minardi G, Manzara C, Pulignano G, Pino PG, Pavaci H, Sordi M, Musumeci F.** Caseous calcification of the mitral annulus with mitral regurgitation and impairment of functional capacity: a case report. *J Med Case Reports* 2008; **2**: 205
- 5 **Fernandes RM, Branco LM, Galrinho A, Timóteo AT, Tavares A, Feliciano J, Oliveira R, Fiarresga A, Mamede A, Banazol N, Roquette J, Ferreira RC.** Caseous calcification of the mitral annulus. A review of six cases. *Rev Port Cardiol* 2007; **26**: 1059-1070
- 6 **Choi PW, Kim CN, Chang SH, Chang WI, Kim CY, Choi HM.** Cardiac metastasis from colorectal cancer: a case report. *World J Gastroenterol* 2009; **15**: 2675-2678
- 7 **Klatt EC, Heitz DR.** Cardiac metastases. *Cancer* 1990; **65**: 1456-1459
- 8 **Nuño IN, Kang TY 4th, Arroyo H, Starnes VA.** Synchronous cardiac myxoma and colorectal cancer: a case report. *Tex Heart Inst J* 2001; **28**: 215-217
- 9 **Kato M, Nakatani S, Okazaki H, Tagusari O, Kitakaze M.** Unusual appearance of mitral annular calcification mimicking intracardiac tumor prompting early surgery. *Cardiology* 2006; **106**: 164-166
- 10 **de Vrey EA, Scholte AJ, Krauss XH, Dion RA, Poldermans D, van der Wall EE, Bax JJ.** Intracardiac pseudotumor caused by mitral annular calcification. *Eur J Echocardiogr* 2006; **7**: 62-66
- 11 **Monti L, Renifilo E, Profili M, Balzarini L.** Cardiovascular magnetic resonance features of caseous calcification of the mitral annulus. *J Cardiovasc Magn Reson* 2008; **10**: 25
- 12 **Blankstein R, Durst R, Picard MH, Cury RC.** Progression of mitral annulus calcification to caseous necrosis of the mitral valve: complementary role of multi-modality imaging. *Eur Heart J* 2009; **30**: 304
- 13 **Lung B.** Interface between valve disease and ischaemic heart disease. *Heart* 2000; **84**: 347-352

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Meetings

Events Calendar 2011

January 25
 Moving towards a national strategy
 for Chronic Obstructive Pulmonary
 Disease
 London, United Kingdom

February 24-26
 Abdominal Obesity 2011 -
 2nd International Congress on
 Abdominal Obesity
 Buenos Aires, Argentina

February 25-27
 CardioRhythm 2011
 Hong Kong, China

March 19-26
 Cardiology Update: Caribbean
 Cruise
 San Diego, CA, United States

March 25
 Cardiology for General Practice
 London, United Kingdom

April 1-2
 11th Annual Spring Meeting on
 Cardiovascular Nursing
 Brussels, Belgium

April 14-16
 EuroPREvent 2011
 Genova, Switzerland

April 30-May 4
 ATC 2011 - 2011 American
 Transplant Congress
 Philadelphia, United States

May 11-14
 3th Radiochemotherapy and
 Brachiththerapy Congress & 6th

Medical Physycs Meeting
 Córdoba, Argentina

May 15-18
 ICNC10 - Nuclear Cardiology and
 Cardiac CT
 Amstedan, The Netherlands

May 19-20
 Adult Cardiovascular Pathology
 London, United Kingdom

May 20-22
 XXIX NATIONAL CARDIOLOGY
 CONGRESS
 Córdoba, Argentina

May 20-22
 4th Meeting Uremic Toxins and
 Cardiovascular Disease
 Groningen, The Netherlands

May 21-24
 Heart Failure Congress 2011
 Gothenburg, Sweden

June 2-5
 CODHy 2011 - The 1st Asia Pacific
 Congress on Controversies to
 Consensus in Diabetes, Obesity and
 Hypertension
 Shanghai, China

June 26-29
 EHRA EUROPACE 2011
 Madrid, Spain

June 29-July 1
 Hands-on Cardiac Morphology -
 Summer Edition
 London, United Kingdom

August 27-31
 ESC 2011 - European Society of
 Cardiology Congress 2011
 Paris, France

October 23-26
 9th International Congress on
 Coronary Artery Disease
 Venecia, Italy



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- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaobua Zazhi* 1999; **7**: 285-287

In press

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID: 2516377 DOI: 10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI: 10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI: 10.1136/bmj.325.7357.184]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI: 10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI: 10.1097/00003086-200208000-00026]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRS A Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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- 12 **Breedlove GK**, Schorffheide AM. Adolescent pregnancy. 2nd ed. Wicczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean \pm SD or mean \pm SE.

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Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as *v* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h; blood glucose concentration, *c* (glucose) 6.4 \pm 2.1 mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 24.5 μ g/L; CO₂ volume fraction, 50 mL/L CO₂, not 5% CO₂; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, etc. Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1949-8462/g_info_20100312200347.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg 1*, *c myc*, *c fos*, etc.

Restriction enzymes: *EcoRI*, *HindI*, *BamHI*, *Kho I*, *Kpn I*, etc.

Biology: *H. pylori*, *E. coli*, etc.

Examples for paper writing

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