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**Endothelial progenitor cells in cardiovascular diseases**

Lee PSS *et al*. Endothelial progenitor cells in cardiovascular diseases

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**Abstract**

Endothelial dysfunction has been associated with the development of atherosclerosis and cardiovascular diseases. Adult endothelial progenitor cells (EPCs) are derived from hematopoietic stem cells and are capable of forming new blood vessels through a process of vasculogenesis. There are studies which report correlations between circulating EPCs and cardiovascular risk factors. There are also studies on how pharmacotherapies may influence levels of circulating EPCs. In this review, we discuss the potential role of endothelial progenitor cells as both diagnostic and prognostic biomarkersas well as how cardiovascular pharmacotherapies may affect endothelial progenitor cells and how EPCs can be used directly and indirectly as a therapeutic agent. We will also evaluate the challenges facing EPC research and how these may be overcome.

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**Key words**: Endothelial progenitor cells; Cardiovascular diseases; Hypertension; Diabetes; Dyslipidemia; Therapy; Stents

**Core tip**: Our review summarises on the important associations between endothelial progenitor cells, cardiovascular risks, drugs and diseases. Current pharmacotherapies may enhance endothelial progenitor cells cell number and function. These and the evolving endothelial progenitor cell-based therapies may be important in the future treatment of cardiovascular diseases.

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**INTRODUCTION**

Cardiovascular diseases (CVD) are the leading cause of mortality in both developed and developing countries[1]. Angiogenesis, the formation of new blood vessels, has attracted interest in the field of cardiology. It was believed that angiogenesis could only occur by the new blood vessels sprouting out of pre-existing vessels. Under physiological conditions, vascular endothelium secretes substances that alter vascular tone and “defend” the vessel wall from inflammatory cell infiltration, thrombus formation, and vascular smooth muscle cell proliferation[2]. Indeed, endothelial damage has been implicated in atherosclerosis, thrombosis and hypertension. The balance between endothelial injury and recovery is important for reducing cardiovascular events[3]. However, mature endothelial cells possess limited regenerative capacity. There is growing interest in circulating endothelial progenitor cells (EPCs) as they may maintain endothelial integrity, function, and postnatal neovascularization[2].

**EPCS**

Differentiation of mesodermal cells to angioblasts and subsequent endothelial differentiation is thought to exclusively happen in embryonic development. This concept is overturned when Asahara and colleagues published in 1997 that purified CD34-positive hematopoietic progenitor cells from adults can differentiate *ex vivo* to an endothelial phenotype. These EPCs showed expression of various endothelial markers and are incorporated into neovessels at sites of ischemia[4].

EPCs appear to be a heterogenous group of cells originating from multiple precursors within the bone marrow and present in different stages of endothelial differentiation in peripheral blood. For this reason, the precise characterization of EPCs is difficult because many of the cell surface markers used in phenotyping are shared by hematopoietic stem cells and by adult endothelial cells[5].

Currently, EPCs are defined as cells positive for both hematopoietic stem cell marker such as CD34 and an endothelial marker protein such as VEGFR2. CD34 is not exclusively expressed on hematopoietic stem cells but also on mature endothelial cells. Other studies have used more immature hematopoietic stem cell marker CD133 and demonstrated that purified CD133-positive cells can differentiate to endothelial cells *in vitro*[6]. CD133, also known as prominin or AC133, is a highly conserved antigen with unknown biological activity, which is expressed on hematopoietic stem cells but is absent on mature endothelial cells and monocytic cells[7]. Thus, CD133+VEGFR2+ cells more likely reflect immature progenitor cells, whereas CD34+VEGFR2+ may represent shedded cells of the vessel wall[7]. Controversy remains with respect to the identification and the origin of endothelial progenitor cells which are isolated from peripheral blood mononuclear cells by cultivation in medium favoring endothelial differentiation.

**TYPES OF EPCS**

Although the markers for identification of EPC populations vary between studies, it has been agreed that there are lineage and functional heterogeneities within the EPC population. There are at least two different types of EPCs: the early and late EPCs. Early EPCs are usually referred as the angiogenic EPC population obtained from short-term cultures of 4-7 d *in vitro*. These early EPCs do form colony forming units (CFU) and they possess many endothelial characteristics such as harbouring markers of CD31, TIE2 andVEGFR2[4]. Jonathan Hill and colleagues have reported negative correlation between EPCs, measured by CFU and Framingham risk score in 45 men with various cardiovascular risks. They also reported positive correlation between CFU and brachial flow-mediated dilation, a measure of endothelial function[8]. Late EPCs, often called out-growth EPCs, have different growth patterns and are usually obtained from long term cultures of at least 2-3 wk *in vitro*. Outgrowth EPCs possess additional endothelial characteristics such as VE-cadherin and von Willebrand factor in addition to CD31, CD133, CD34 and VEGFR2[3]. These outgrowth EPCs will further differentiate into mature endothelial cells for angiogenesis and vasculogenesis. These two types of cells have distinct morphology: the early EPCs are spindle in shape (Figure 1) while outgrowth EPC has a cobblestone-like shape (Figure 2).

Though endothelial dysfunction is associated with the development of atherosclerosis[9], the utility of EPCs as a prognostic marker is only recently been demonstrated In a study with 44 patients with coronary artery disease (CAD) and 33 patients with acute coronary syndrome (ACS) followed up for a median 10 mo duration, reduced number of EPCs was associated with a significantly higher incidence of cardiovascular events[10]. In another larger study with 519 patients with stable CAD, increased levels of endothelial progenitor cells were related to a reduced risk of death from cardiovascular causes, a first major cardiovascular event, revascularization and hospitalization[11].

However, issues in terms of isolation and identification of EPCs, especially in regards to the characterization or specific cell surface markers of these cells still unresolved. In addition, number and/or functionality of EPCs do not adequately describe cardiovascular disease risks. These limitations may be attributable to the inconsistent definitions of EPCs, the number of existing cardiovascular risk factors in different patient populations and the interaction between EPCs and other hematopoietic progenitor, inflammatory cells or platelets. There is also evidence of varied levels of circulating EPCs are present in a time dependent manner[12]. Therefore, depending on when sampling occur, EPC numbers and functions may be different.

***Peripheral arterial disease***

Peripheral arterial disease (PAD) is a manifestation of advanced atherosclerosis and affects 20% of the population aged over 65 years. Since PAD is associated with endothelial dysfunction, but there have been limited and inconsistent data available on the number and functional capacity of EPCs in PAD. Fadini and colleagues first demonstrated that number of EPCs, marked by CD34+/CD133+/KDR+ are significantly decreased in diabetic patients with PAD than diabetics alone[13]This finding was further supported by another paper from Fadini where they reported significantly lower CD34+/KDR+ EPCs in PAD patients compared to healthy controls[14].. A recent study also reported lower CD34+ count in patients with peripheral vascular disease compared to patients with abdominal aortic aneurysm[10]. On the other hand, several studies have documented increased number and functionality of EPCs in PAD patients compared to controls[14] (Table 1). Both studies have reported poor angiogenic response to ischaemia and EPC differentiation in PAD patients, together with reduced angiogenesis and low EPC levels[13,14]. In PAD, EPC mobilization can occur through inflammation and matrix metalloproteinase-mediated mechanisms[15]. Membrane type 1 matrix metalloproteinase (MT1-MMP) can contribute to vascular remodeling and regulate mobilization of CD34+ progenitor cells while pentraxin-3 is predominantly produced by vascular endothelium and is considered to reflect inflammatory status of endothelium[15]. There appeared to be increased number of EPCs and pentraxin-3 and decreased MT1-MMP in PAD patients compared to healthy controls[15]. Furthermore, cardiovascular events were also significantly correlated with decreased EPC levels and increased oxidative stress. In contrast, the number of EPCs wasshown to be significantly higher in severe PAD patients compared to healthy subjects[16]. These contrasting results may be present due to the different severity of PAD patients recruited in the study and methodological differences in measuring EPC population which can complicate interpretation of data. It is also possible that when PAD is only mild, EPC levels correlate to the poor vascular health. However, in severe PAD an elevated number of circulating EPCs may reflect mobilization from the bone marrow to repair endothelial damage. More studies are warranted to investigate these discrepancies in EPC and PAD.

***CAD***

Presence and extent of endothelial dysfunction predicts the outcome in patients with cardiovascular risk factors and in patients with coronary artery disease. Since endothelial progenitor cells possess the ability to home to sites of vascular injury, there is emerging interest in the therapeutic use of EPCs related to angiogenesis. In patients with CAD, EPCs isolated had impaired migratory response and a negative correlation of EPCs with the severity of CAD[17]. This was likely a result of endothelial dysfunction in patients with CAD[17], impaired coronary blood flow regulation and the strong association with risk factors for CAD. These risk factors may interfere with signaling pathways regulating EPC mobilization and differentiation such as those involving granulocyte-stimulating colony stimulating factor (GM-CSF) or VEGF. Impaired migratory response, affected by downregulation of VEGF may be contributed by VEGFR2. In addition, several studies documented decreased number of EPCs in CAD patients[18-21]. Circulating EPCs are also significantly lower in patients with progression of CAD angiographically[21]. Exhaustion of endothelial progenitor cells in the bone marrow, reduced nitric oxide bioavailability and long term statin treatment in CAD can also contribute to reduced number and impairment of EPCs[20]. However, there are contrasting studies which reported increased number of EPCs in angiographically significant CAD patients. A significant correlation was observed between the maximum stenosis severity and the number of EPCs from these patients[22].Werner and colleagues also observed an inverse association between the level of circulating EPCs and the risk of cardiovascular events among patients with angiographically documented CAD[23] The differences in the methodologies are likely to account for the different results. In addition, low frequency of EPCs in circulation and types of EPCs harvested may also contribute to the differences. Moreover, EPC population may represent a heterogenous population of endothelial progenitors with differing proliferative capacity. Despite these controversies, in patients with CAD, the circulating numbers of EPCs appears to predict cardiovascular outcome[23] (Table 2).

***Congestive heart failure***

It has been shown that endothelial dysfunction occur in patients with congestive heart failure (CHF). Despite these observations, limited data are available regarding the pattern of mobilization of EPCs and CD34+ cells during HF. In a study of EPC in HF, HF was associated with higher circulating EPC levels compared to healthy controls[27]. However, the severity of heart failure correlate with circulating EPCs inversely with significantly higher CD34+ counts in mild HF compared to severe HF[28]. CCF may result in hematopoietic progenitor cells migrating to the sites of damage to undergo progenitor cell differentiation. However a depletion of progenitor cells in the chronic stage of the disease could contribute to the biphasic bone marrow pattern of response to heart failure[28]. Consistent with numbers, colony forming unit, one of the functional capacities of EPCs is an independent predictor for outcomes in CHF and also negatively correlated with NYHA functional class[29]. Pertinent studies are summarized in Table 3.

**EFFECTS OF CARDIOVASCULAR-RELATED PHARMACOTHERAPIES ON EPCS**

The presence of conventional cardiovascular risk factors such as hypertension, dyslipidemia and diabetes and cardiovascular diseases are associated with endothelial injury and dysfunction. Experimental and clinical studies evaluate endothelial dysfunction as alterations of vasomotor function such as endothelium-dependent relaxations. Recent research on cell biology has identified circulating EPCs as a useful biomarker of endothelial function and integrity. Cardiovascular pharmacotherapies (Figure 3) have been shown in clinical studies to improve overall number and function of EPCs in patients with cardiovascular risks.

***Anti-hypertensive medications***

There are many classes of antihypertensives, which lower blood pressure by different mechanisms. Among the most widely used are angiotensin II receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs). They all have been shown to modulate EPC number and/or functions.

**ARBs:** Their main mechanism of action is to act on the renin-angiotensin-aldosterone system for treatment of hypertension. Several studies have explored the effect of ARBs in influencing the number and/or function of EPCs in both experimental and clinical hypertension. Three experimental studies using spontaneous hypertensive rats (SHR) have successfully demonstrated improved EPC number and function with ARB treatment[32-34]. In hypertension, endothelial damage can be caused by reactive oxygen species (ROS) secondary to the increased production of tissue angiotensin II. Since vascular NAD(P)H oxidase is a major source of ROS in the cardiovascular system, ARBs can significantly inhibited major components of NAD(P)H oxidase. Inhibition of oxidative stress in hypertension by ARBs correlated with improvement in EPC number and function[32-34]. These findings were separately validated in the clinical setting where similar improvement in EPC number and function were observed in healthy subjects and those with CAD[35,36] (Table 4). EPCs cultivated from healthy volunteers, treated in presence of telmisartan had significantly higher number and improved function of EPCs compared to cells not treated with telmisartan[35]. However, the increase of number and function of EPCs were inhibited by specific peroxisome proliferator-activated receptor-gamma (PPAR-γ) inhibitor, GW9662. This suggests that telmisartan-induced EPC proliferation is likely *via* the PPAR-γ-dependent pathway. Furthermore, it has also been shown that telmisartan is a ligand of PPAR-γ[37]. In a double-blinded study, CAD patients with no history of hypertension receiving 80 mg of telmisartan for 4 wk had significantly higher absolute number of EPCs compared to the placebo group. This was further supported by improvement in endothelial function in the treatment group[36]. The improvement on EPCs in these patients with CAD was independent from antihypertensive action of telmisartan, as reduction in blood pressure was not statistically different between groups. Therefore ARBs may be able to induce improvement in number and function of EPCs *via* pleotropic effects. The several mechanisms include inhibition of NAD(P)H oxidases and stimulation through the PPAR-γ pathway.

**ACEI:** Similar to ARBs, ACE inhibitors are used to treat hypertension and congestive heart failure through inhibition of angiotensin converting enzyme which is part of the renin-angiotensin-aldosterone system. Generally, there was positive trend towards improvement in EPC number[38] and function[38,39] with ACEI in patients with stable CAD and in hypertensive patients (Table 4). The administration of ramipril increased the number and improved the functional capacity of EPCs in patients with CAD within 1 wk of treatment. The improvement was further enhanced after 4 wk. Bradykinin B2- receptor pathway which activates endothelial nitric oxide synthase (eNOS) and involved in neovascularization of EPCs may have contributed to beneficial effects of Ramipril. Indeed, nitric oxide levels were increased *via* activation of bradykinin. This effect was independent of any impact on blood pressure[38]. Further comparison between enalapril and zofenopril has demonstrated that EPCs were increased after 1 and 5 years of followup[39]. ACE inhibition is reported to stimulate NO activity and decreases oxidative stress in human endothelial cells[40]. Zofenopril increases NO production in endothelium, decreases atherosclerotic development, and reduces ROS[41]. Similar to ARBs, ACE inhibition improves number and function of EPCs independent of blood pressure lowering effect and act via endothelial NO pathway.

**Calcium channel blockers:** Calcium channel blockers (CCBs) decrease blood pressure by inhibiting L-type voltage-gated calcium channels to decrease intracellular calcium. It acts on vascular smooth muscle to induce vasodilation and therefore decrease blood pressure. Preliminary results from two studies reported favourable outcomes on EPC number and function with CCBs in patients with essential hypertension[42,43] (Table 4). Men with stage 1 hypertension who were treated with nifedipine had significant improved number and angiogenic-related function of EPCs[42].The improvement may have been driven by increased VEGF release from vascular smooth muscle cells by nifedipine. It was also shown that nifedipine-treated EPCs had greater resistance to ROS-mediated oxidative stress and apoptosis. In addition, improvement of endothelial function by nifedipine may be partially due to increased proliferation and angiogenic activities of EPCs. Another CCB, barnidipine also demonstrated similar beneficial effect on EPCs in patients with essential hypertension[43]. Thus CCBs, alongside with ARBs and ACEI, may result in better vascular health in CAD patients with and without hypertension.

**CHOLESTEROL LOWERING MEDICATIONS**

***HMG-CoA reductase inhibitors (statins)***

Statins or HMG-CoA reductase inhibitors reduce cholesterol levels through inhibition of HMG-CoA reductase, an important enzyme in the synthesis of cholesterol in the liver. There is evidence to demonstrate that statins play an important role in the primary prevention of CVD[44]. The data on statins in primary and secondary therapy in CVD is overwhelmingly consistent. Different doses of different statins have been reported to be useful in increasing EPC number[45-50] and function[45,51] for treatment period of 3-16 wk. Studies have reported that statins exert beneficial effects on EPCs by enhancing EPC proliferation and differentiation *via* Akt pathway. This can result in activation of the eNOS pathway and r VEGF-induced endothelial cell migration[45,49] However, there was a study which reported contrasting outcome where 40 mg/d of statin long-term resulted in decrease EPC number and continuous statin therapy is inversely correlated with EPC number[52] (Table 5). It was put forth that EPCs may be unable to adequately respond to a continuously stimulus of chronic dose of statins. This may result in desensitization. However, function of EPCs measured by CFU was not altered by statin treatment. Though long term statin therapy may result in reduced EPC count, the beneficial effects of statin therapy in improving EPC function and endothelial function is consistently documented.

**ANTI-DIABETIC MEDICATIONS**

***Thiazolidinedione/Metformin***

Thiazolidinedione (TZD) and metformin are important oral medications in the management of type 2 diabetes mellitus. TZD activates peroxisome proliferator-activated receptors while metformin is a biguanide which is effective in reducing glucose production in the liver. Many clinical trials have compared the effects of both TZD and metformin on EPC number and/or function. Overall, TZD, metformin or combination of both drugs have been shown to be beneficial in improving EPC number and/or function in diabetic patients[53-57] (Table 6). In addition, pioglitazone was reported to decrease C-reactive protein (CRP) levels. Since increased EPC number was significantly correlated to lower CRP, pioglitazone may increase EPC number by attenuating the detrimental effects of CRP on EPCs [53,55,56]. Similar to ARBs, pioglitazone, a PPAR-γ agonist may be directly affecting EPCs through PPAR-γ receptors[53].

***Dipeptidyl peptidase 4 inhibitors***

Dipeptidyl peptidase 4 (DPP4) inhibitors are new oral hypoglycemic agents and so there is limited data on their effects on EPCs.There is one study that reported increased EPC numberwith sitagliptin after 4 weeks of treatment compared to metformin[58] (Table 6). In addition, besides increased EPC levels, plasma stromal-derived factor-1α (SDF-1α) levels were also increased in patients who were on sitagliptin treatment for 4 wk[58]. The positive effect of DPP4 inhibitors on EPCs is likely driven by SDF-1α, a physiological substrate of DPP4 and a chemokine which can stimulate bone marrow mobilization of EPCs. SDF-1α is upregulated and, upon binding to its receptor CXCR4, stimulates the bone marrow to release EPCs. DPP4 inhibition increase circulating SDF-1α levels.

**EPCS AS A THERAPEUTIC POTENTIAL CANDIDATE IN CARDIOVASCULAR DISEASES**

***Endothelial progenitor cell capture stent***

The endothelial progenitor cell (EPC) capture stent is a device which uses the ability of bone marrow–derived EPCs to repair damaged arterial segments. The surface of EPC antibody consist of a covalently coupled polysaccharide intermediate coating with anti-human CD34 antibodies, is then attached to a stainless steel stent. Upon stent placement, the anti-human CD34 antibodies will therefore attract circulating EPCs to differentiate into mature endothelial cells to form a functional endothelium layer. This accelerated healing approach aims to decrease the risk of stent thrombosis and restenosis, as well as reduce prolonged dual antiplatelet therapy in these patients. Effectiveness and safety of this EPC capture stent have been tested in patients with de novo CAD[59-62] and STEMI[63-66] and generally these stents are feasible, safe and major adverse cardiac events (MACE) reported is between 4.2% to 16%. Despite this, there are also contradicting findings which suggest EPC capture stent is no better than conventional stents in reducing in-stent restenosis[61,62]. Preliminary results from a new anti-human CD133 coated coronary stent tested on a porcine model has demonstrated no difference in re-endothelialization or neointima formation with the use of CD133-stents. The existing low number of circulating CD133-positive cells may have result in lack of efficacy of these stents[67].

**Endothelial progenitor cell therapy**

Since the successful isolation of adult EPCs in 1997, we now know that bone marrow-derived EPCs may be mobilized to stimulate angiogenesis and may attenuate tissue ischemia for CAD and PAD. Initial pre-clinical studies have reported favourable improvement in left ventricular function in a rat model of myocardial infarction after intravenous injection of *ex vivo* expanded human CD34+ cells[68]. Furthermore, another study examined the effect of catheter-based, intramyocardial transplantation in a swine model of myocardial infarction provided encouraging outcomes in favouring the application of EPCs as a potential therapeutic therapy in clinical trials[63].

Recently, there have been several studies using intramyocardial transplantation of autologous CD34+ cells in patients with cardiovascular diseases, to improve cardiovascular outcomes.

In patients with refractory angina despite medically therapy with anti-anginal medications and undergoing several revascularization options including coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) intramyocardial transplantation of autologous CD34+ cells may be a feasible option. Phase I/II clinical trial[70] of 24 patients followed by Phase IIb[71] of 167 patients reported significant improvement in angina frequency and exercise tolerance. An ongoing RENEW study, a phase III trial of 444 patients will adequately examine the effect of intramyocardial transplantation of autologous CD34+ cells in patients with refractory angina[72]. Besides CAD, there was also a pilot study on the effect of autologous intramuscular injection of CD34+ in critical limb ischemia. The study found that CD34+ treatment reduced amputation rates[73].

**CONCLUSION**

Endothelial dysfunction secondary to various cardiovascular risk factors can lead to the development of atherosclerosis. As mature endothelial cells possess limited regenerative capacity, there is growing interest in circulating EPCs due to their acclaimed role in maintenance of endothelial integrity, function, and postnatal neovascularization. There has been increasing number of studies investigating effects of pharmacotherapies which cardiac patients tend to take, on EPC number and functions. EPC behavior and mechanisms are also elucidated in patients with CVD, including CAD, HF and PAD. Some studies showed conflicting results and this may be due to the varying definition of EPCs using different methods of identification, different timing of blood sampling, different severity of native disease and concomitant medication and comorbidities that may affect EPC number and functions. Besides a biological marker, EPCs have also been shown to be a useful prognostic marker in predicting events in patients with CAD. Lastly there are several promising studies to suggest EPCs as a novel therapy for CVDs[74]. However, due to the paucity of circulating cells, the effects of disease on cell quality, investigators need to be mindful of its possible limitations. Possible solutions include enhancing these cell numbers by increasing their mobilization or concentrating them before transplantation and improving their function using ex-vivo augmentation. Several pilot studies on animals have already shown encouraging results. Further translation to clinical practice is anticipated.

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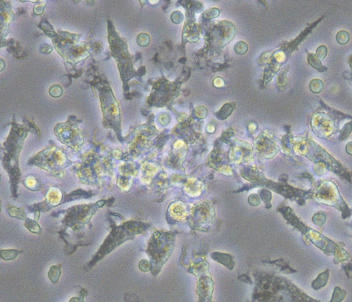
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**Figure 1 Colony forming unit isolated from human peripheral blood mononuclear cells using commercial colony forming unit-hill assay.**



**Figure 2 Cobble-shaped outgrowth endothelial progenitor cells from human peripheral blood at day 14.**



**Figure 3 Cardiovascular-related pharmacological therapies which may affect number and function of endothelial progenitor cells.**

Angiotensin II Receptor Blockers (ARBs)

* Losartan
* Candesartan
* Telmisartan
* Valsartan

Angiotensin Converting Enzyme Inhibitors (ACEI)

* Ramipril
* Enalapril
* Zofenopril

Calcium Channel Blockers (CCBs)

* Nifedipine
* Barnidipine

HMG-CoA Reductase Inhibitors (Statins)

* Atorvastatin
* Rosuvastatin
* Pravastatin

Biguanide

* Metformin

Thiazolidinedione (TZDs)

* Pioglitazone

Dipeptidyl Peptidase 4 Inhibitors (DPP4I)

* Sitagliptin

**Table 1 Effect of peripheral arterial disease on endothelial progenitor cells**

|  |  |  |  |
| --- | --- | --- | --- |
| Ref. | Subjects | EPCs (Number/Function) | Findings |
| Fadini *et al* [13] | 55 diabetic without PAD; 72 diabetic with PAD | CD34+/CD133+/ KDR+ | CD34+/CD133+/ KDR+ is significantly lower in diabetics with PAD compared to diabetics alone |
| Fadini *et al* [14] | 15 healthy controls; 30 PAD | CD34+/KDR+ | CD34+/KDR+ is significantly lower in patients with PAD than controls |
| Delva *et al* [16] | 24 healthy controls; 45 PAD | CFU  CD133+, CD34+, CD34+/KDR+ | CFU is significantly increased in patients with PAD compared to controls  CD34+ and CD133+ are significantly decreased in patients with PAD compared to controls  No difference between groups for CD34+/KDR+ |
| Morishita *et al* [15] | 22 healthy controls; 48 PAD | CD34+/CD133+/ KDR+ | CD34+/CD133+/ KDR+ is significantly higher in PAD compared to controls |

AAA: Abdominal aortic aneurysm; EPC: Endothelial progenitor cells; PAD: Peripheral arterial disease.

**Table 2 Effect of coronary artery disease on endothelial progenitor cells**

|  |  |  |  |
| --- | --- | --- | --- |
| Ref. | Subjects | EPCs (Number/Function) | Findings |
| Vasa *et al* [17] | 9 healthy controls; 45 CAD | CD34+/KDR+ (flow cytometry)  Migratory activity | Both CD34+/KDR+ and migratory activity were impaired in patients with CAD compared to controls |
| Eizawa *et al* [18] | 36 healthy controls; 34 stable CAD | CD34+ (flow cytometry) | CD34+ is significantly decreased in patients with stable CAD |
| Wang *et al* [19] | 44 controls; 35 mild CAD; 25 severe CAD | CD34+/KDR+ (flow cytometry)  Migratory activity | CD34+/KDR+ is the lowest in severe CAD followed by mild CAD  Migratory activity is also impaired in CAD patients |
| Liguori *et al* [20] | 15 healthy controls; 40 CHD | CFU  CD34+ (flow cytometry)  Migratory activity | CFU, CD34+ and migratory capacity were significantly impaired in patients with CHD  CHD is the main predictor which impair CFU capacity |
| Briguori *et al* [21] | 136 CAD | CFU  CD34+/KDR+ (flow cytometry) | Low levels of CFU and CD34+/KDR+ predict CAD progression |
| Guven *et al* [22] | 24 controls; 24 CAD | CD34+ (flow cytometry) | CD34+ EPC is significantly elevated in CAD patients compared to controls  EPCs is also positively correlated with maximum stenosis |
| Werner *et al* [23] | 90 CHD | CFU  CD34+/KDR+ (flow cytometry) | CD34+/KDR+ and CFU positively correlate with endothelium-dependent vasodilation (acetylcholine infusion) |

CAD: Coronary artery disease; CFU: Colony forming unit; CHD: Coronary heart disease; EPC: Endothelial progenitor cells.

**Table 3 Summary of clinical trials: Effect of heart failure on endothelial progenitor cells**

|  |  |  |  |
| --- | --- | --- | --- |
| Ref. | Subjects | EPCs (Number/Function) | Findings |
| Valgimigli *et al* [27] | 45 healthy controls; 91 CHF | CD34+, CD34+/CD133+/ KDR+ (flow cytometry) | CD34+ and CD34+/CD133+/ KDR+ are significantly elevated in CHF patients compared to controls  EPC number is negatively correlated with NYHA functional class |
| Nonaka-Sarukawa *et al* [28] | 22 healthy controls; 16 mild CHF; 10 severe CHF | CD34+ (flow cytometry) | CD34+ is significantly higher in mild CHF compared to severe CHF |
| Michowitz *et al* [29] | 107 CHF | CFU | CFU is the independent predictor for CHF  CFU is also negatively correlated with NYHA functional class |

EPC: Endothelial progenitor cells; CHF: Congestive heart failure; CFU: Colony forming unit; NYHA: New York Heart Association.

**Table 4 Effect of anti-hypertensive medications on endothelial progenitor cells**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Ref. | Subjects | Drugs | Duration | EPCs (Number/Function) | Findings |
| **Angiotensin II receptor blockers** | | | | | |
| Yao *et al* [32] | 42 SHR-SP rats | Losartan  (10mg/kg per day)  *vs*  Placebo | 2 wk | CFU  CD34+ (flow cytometry)  Migratory activity | Losartan improved EPC number and function from SHR-SP rats compared to WKY rats |
| Yu *et al* [33] | 18 SHR-SP rats | Candesartan  (1mg/kg per day)  *vs*  Tempol, Trichlormethiazide | 2 wk | CFU | The highest CFU count was observed in candesartan treatment group |
| Yoshida *et al*[34] | 12 SHR-SP rats | Valsartan (300mg/l)  *vs*  Hydralazine | 2 wk | CFU  Migratory activity | Treatment with valsartan has stimulated increase in CFU and migration activity in SHR-SP rats compared to hydralazine-treated rats |
| Honda *et al* [35] | 15 healthy controls | Telmisartan (1µM)  *vs*  Valsartan | 4 d | CFU  Proliferation activity | CFU and EPC proliferative activity are significantly increased in cells treated with telmisartan *in vitro* |
| Pelliccia *et al* [36] | 40 CAD | Telmisartan (80 mg per day)  *vs*  Placebo | 4 wk | CD34+/CD45-/ KDR+ (flow cytometry) | CD34+/CD45-/ KDR+ is significantly elevated in patients treated with telmisartan |
| **Angiotensin converting enzyme inhibitors** | | | | | |
| Min *et al* [38] | 20 CAD | Ramipril (5 mg per day)  *vs*  Placebo | 4 wk | EPC number  Migratory activity  Proliferation activity  Adhesion activity | There was 1.5 fold increase in EPC number after 1 wk of treatment  Followed by 2.5 fold increase in EPC count after 4 wk  Migration, proliferation and adhesion activities were also significantly improved with ramipril |
| Cacciatore *et al* [39] | 36 HT | Enalapril (20 mg per day)  *vs*  Zofenopril (30 mg/d) | 1 year and 5 years | CFU  Migratory activity | Increased CFU count for both treatment groups at 1 year and 5 years  No difference for migratory activity |
| **Calcium channel blockers** | | | | | |
| Sugiura *et al* [42] | 37 HT | Nifedipine (20 mg per day)  *vs*  Untreated | 4 wk | CD34+/CD133+ (flow cytometry)  Migratory activity | EPC number and function were significantly improved in the nifedipine group |
| De Ciuceis *et al* [43] | 29 essential HT | Barnidipine (20 mg per day)  *vs*  Hydrochlorothiazide (25 mg per day) | 3 and 6 mo | EPC number | EPC number was significantly elevated in patients treated with barnidipine compared to hydrochlorothiazide |

CAD: Coronary artery disease; CFU: Colony forming unit; EPC: Endothelial progenitor cells; HT: Hypertension; SHR-SP: Spontaneous hypertensive rats-stroke prone; WKY: Wistar-Kyoto.

**Table 5 Effect of HMG-CoA reductase inhibitors (statins) on endothelial progenitor cells**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Ref. | Subjects | Drugs | Duration | EPCs (Number/Function) | Findings |
| Vasa *et al*[45] | 15 CAD | Atorvastatin (40 mg per day) | 4 wk | CD34+/KDR+ (flow cytometry)  Migratory activity | CD34+/KDR+ was significantly increased after 4 wk of therapy  Migration activity was also significantly improved after 4 wk of treatment |
| Leone *et al*[46] | 40 STEMI | Atorvastatin (80 mg per day)  *vs*  Atorvastatin  (20 mg per day) | 16 wk | CD34+/KDR+ (flow cytometry) | Patients who took 80 mg of atorvastatin had higher CD34+/KDR+ than those who took 20 mg atorvastatin |
| Spadaccio *et al*[47] | 50 CAD | Atorvastatin (20 mg per day)  *vs*  placebo | 3 wk | CD34+/CD133+ (flow cytometry) | Atorvastatin has significantly elevated EPC count after 3 wk |
| Erbs *et al*[48] | 42 CHF | Rosuvastatin (40 mg per day)  *vs*  Placebo | 12 wk | CD34+/KDR+ (flow cytometry) | Rosuvastatin significantly increase EPC count compared to placebo |
| Tousoulis *et al*[49] | 60 SHF | Rosuvastatin (10 mg per day)  *vs*  Allopurinol (300mg per day) | 4 wk | CD34+/KDR+, CD34+/CD133+/ KDR+ (flow cytometry) | CD34+/KDR+ and CD34+/CD133+/ KDR+ are improved with rosuvastatin treatment compared to allopurinol |
| Huang *et al* [50] | 100 healthy controls; 100 ICM | Atorvastatin  (10 mg per day)  *vs*  Atorvastatin  (40 mg per day) | 1 year | CD34+ (flow cytometry) | CD34+ count was significantly elevated in patients under 40 mg atorvastatin after 1 year |
| Paradisi *et al* [51] | 20 healthy controls | Pravastatin  (40 mg per day)  *vs*  Placebo | 8 wk | CFU  Tubule formation assay | CFU was increased by 31% in pravastatin group compared to placebo  No difference was observed for tubule formation assay between groups |
| Hristov *et al* [52] | 209 CAD  (Without statin, *n* = 65, Statin 10/20 mg/d, *n* = 101, statin 40 mg/d, *n* = 43) | Statin (10/20 mg per day) or 40 mg per day  *vs*  Untreated | 8 wk | CFU  CD34+/KDR+ (flow cytometry) | 40 mg/d of statin treatment has significantly decreased EPC number  Continuous statin therapy inversely correlated with EPC number |

CAD: Coronary artery disease; CFU: Colony forming unit; CHF: Congestive heart failure; EPC: Endothelial progenitor cells; ICM: Ischaemic cardiomyopathy; SHF: Systolic heart failure; STEMI: ST-elevated myocardial infarction.

**Table 6 Effect of anti-diabetic medications on endothelial progenitor cells**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Ref. | Subjects | Drugs | Duration | EPCs (Number/function) | Findings |
| **Thiazolidinedione/metformin** | | | | | |
| Wang *et al* [53] | 36 type 2 diabetes | Metformin + Pioglitazone (30 mg per day)(*n* = 24)  *vs*  Metformin (n=12) | 8 wk | CD34+/KDR+ (flow cytometry)  Migratory activity | Both EPC number and migration activity improved with combination of metformin and pioglitazone |
| Werner *et al* [54] | 54 CAD | Pioglitazone (45 mg per day)  *vs*  Placebo | 4 wk | CFU  CD34+ (flow cytometry) | Improved EPC number and CFU count with pioglitazone treatment |
| Makino *et al* [55] | 34 type 2 diabetes | Pioglitazone (15-30 mg per day) | 24 wk | CD34+ (flow cytometry) | Number of CD34+ increased steadily at 12 weeks and continued to increase after 24 weeks of pioglitazone |
| Esposito *et al* [56] | 110 type 2 diabetes | Pioglitazone (15-45 mg per day) (*n* = 55)  *vs*  Metformin (1000-2000 mg per day) (*n* = 55) | 24 wk | CD34+/KDR+ (flow cytometry) | Significant improvement in CD34+/KDR+ in patients who took pioglitazone compared to metformin |
| Liao *et al* [57] | 51 healthy controls; 46 type 2 diabetes | Metfomin (1700-2550 mg per day) | 16 wk | CD45-/CD34+/KDR+ (flow cytometry) | EPC number is significantly lower in type 2 diabetic patients and significantly improved after metformin |
| **Dipeptidyl peptidase 4 inhibitors** | | | | | |
| Fadini *et al*[58] | 32 type 2 diabetes | Sitagliptin (100 mg per day) (*n* = 16)  *vs*  Metformin (*n* = 16) | 4 wk | CD34+/KDR+ (flow cytometry) | EPC number in sitagliptin group has significantly improved compared to metformin group by 2 fold |

CAD: Coronary artery disease; CFU: Colony forming unit; EPC: Endothelial progenitor cells.