







RESEARCH ARTICLE

Enhancement of EPC migration by high-dose lisinopril is superior compared to captopril and ramipril [version 1; peer review: awaiting peer review]

Yudi Her Oktaviono ¹, Hanang Anugrawan Ahmad¹, Makhyan Jibril Al Farabi ¹, Parama Gandhi ¹, Caesar Lagaliggo Givani², Indah Sari Purna Lumeno³, Yusuf Azmi ⁴

¹Department of Cardiology and Vascular Medicine, Airlangga University, Soetomo Academic and General Hospital, Surabaya, East Java, 60825, Indonesia

²Department of Internal Medicine, Airlangga University, Soetomo Academic and General Hospital, Surabaya, East Java, 60825, Indonesia

³Postgraduate Degree, Hassanudin University, South Sulawesi, 90245, Indonesia

⁴Faculty of Medicine, Airlangga University, Surabaya, East Java, 60825, Indonesia

V1 First published: 11 Jan 2021, 10:15
<https://doi.org/10.12688/f1000research.26395.1>

Latest published: 11 Jan 2021, 10:15
<https://doi.org/10.12688/f1000research.26395.1>

Abstract

Background: Angiotensin-converting enzyme (ACE) inhibitors have been shown to promote endothelial progenitor cell (EPC) function. However, the efficacies of different ACE inhibitors in improving the migratory capabilities of EPCs in coronary artery disease (CAD) patients is unclear. This study compared the effectiveness of captopril, lisinopril, and ramipril toward the migration capability of impaired EPCs from CAD patients.

Methods: We isolated peripheral blood mononuclear cells (PBMCs), separated EPCs from PBMCs, and divided them into an untreated group (control) and treated groups of captopril, lisinopril, and ramipril at doses of 1mM, 10mM, and 100mM. EPC migration was evaluated using the Boyden chamber assay. Analysis of variance (ANOVA) was performed using SPSS 25.0.

Results: This study showed that treatment with captopril, lisinopril, and ramipril starting at the lowest dose (1 mM) increased EPC migration ($65,250 \pm 6,750$ cells; $60,750 \pm 5,030$ cells; and $49,500 \pm 8,400$ cells, respectively) compared to control ($43,714 \pm 7,216$ cells).

Increased migration of EPCs was observed by increasing the treatment dose to 10 mM with captopril, lisinopril, and ramipril ($90,000 \pm 16,837$ cells; $79,071 \pm 2,043$ cells; and $64,285 \pm 11,824$ cells, respectively). The highest EPC migration was shown for lisinopril 100 mM ($150,750 \pm 16,380$ cells), compared to captopril and ramipril at the same dose ($105,750 \pm 8,112$ cells and $86,625 \pm 5,845$ cells, respectively).

Conclusions: Captopril, ramipril, and lisinopril were shown to increase

Open Peer Review

Reviewer Status AWAITING PEER REVIEW

Any reports and responses or comments on the article can be found at the end of the article.

EPC migration in a dose-dependent manner. Low-dose (1 mM) and medium-dose (10 mM) captopril had a larger effect on EPC migration than lisinopril and ramipril. Meanwhile, high-dose lisinopril (100mM) had the highest migration effect, suggesting it may be preferable for promoting EPC migration in CAD patients.

Keywords

ACE Inhibitors, Coronary artery disease, Endothelial progenitor cells, Migration

Corresponding author: Yudi Her Oktaviono (yoktaviono@gmail.com)

Author roles: **Oktaviono YH:** Conceptualization, Data Curation, Funding Acquisition, Resources, Supervision, Writing – Review & Editing; **Ahmad HA:** Investigation, Methodology, Project Administration, Resources, Visualization; **Al Farabi MJ:** Data Curation, Formal Analysis, Investigation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Gandi P:** Investigation, Resources, Software, Validation; **Givani CL:** Data Curation, Formal Analysis, Writing – Original Draft Preparation, Writing – Review & Editing; **Lumeno ISP:** Resources, Validation, Writing – Review & Editing; **Azmi Y:** Data Curation, Formal Analysis, Writing – Original Draft Preparation

Competing interests: No competing interests were disclosed.

Grant information: This work was supported by the Indonesian Endowment Fund for Education (Lembaga Pengelola Dana Pendidikan) [PRJ-1084/LPDP.3/2017].

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2021 Oktaviono YH *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Oktaviono YH, Ahmad HA, Al Farabi MJ *et al.* **Enhancement of EPC migration by high-dose lisinopril is superior compared to captopril and ramipril [version 1; peer review: awaiting peer review]** F1000Research 2021, 10:15 <https://doi.org/10.12688/f1000research.26395.1>

First published: 11 Jan 2021, 10:15 <https://doi.org/10.12688/f1000research.26395.1>

Introduction

Endothelial dysfunction and impaired endothelial regeneration are thought to play an important role in the pathogenesis of arteriosclerosis in coronary arterial disease (CAD)¹. Endothelial regeneration is not only fulfilled by resident endothelial cells but also repaired by endothelial progenitor cells (EPCs) originating from the bone marrow². EPCs are premature circulating cells, a specific subtype of hematopoietic stem cells that differentiate into endothelial cells *in situ* and promote neovascularization^{3,4}. Several studies have shown that in patients with CAD, there is a significant decrease in the number and migratory function of circulating EPCs, which leads to impaired neovascularization of ischemic tissue^{5,6}. Low EPC counts can predict severe endothelial dysfunction, cardiovascular events, and deaths from cardiovascular causes^{7,8}. It is suggested that intracellular damage and impaired redox balance in EPCs due to oxidative stress are the predisposes of imbalance in vascular pathology^{9,10}.

Angiotensin-converting enzyme (ACE) inhibitors are widely used in cardiovascular disease and have been shown to be associated with beneficial effects on EPCs in several *in vitro* and clinical studies¹¹⁻¹⁴. An animal study on mice with increased left ventricular pressure showed that ramipril increases the number and improves EPC migration¹². A clinical study in hypertensive patients showed that enalapril and zofenopril reduce EPC levels and prevent vascular damage and carotid intima-media thickening¹³. In a small clinical trial, administration of ramipril for four weeks in patients with stable CAD augments and increases the functional activity of EPCs, including migration, adhesion, and *in vitro* capacity of vasculogenesis¹⁵.

However, no studies have investigated the role of ACE inhibitors of captopril and lisinopril in relation to the EPCs. In addition, the comparison between different types of ACE inhibitors toward the impaired migration function of EPCs remains to be investigated. We aimed to evaluate the effects of captopril, lisinopril, and ramipril on EPCs migration from CAD patients.

Methods

Ethical statement

Our study protocol was approved by the Institutional Ethics Committee of Dr. Soetomo General Hospital (945/KEPK/II/2019). Informed consent for peripheral blood sampling procedures and participation in research studies was obtained from all patients before the blood was drawn. We have omitted all data that could reveal the identity of the patients.

Study population

In the present study, we used peripheral blood samples from the same participants and performed similar methodology to that described in our previous study¹⁶. From June 2018 to December 2018, we studied a total of eight patients with stable CAD who underwent coronary angiography. Only patients with the left main coronary artery stenosis of more than 50% or stenosis in other coronary arteries more than 70% were

recruited. To prevent the effects of myocardial ischemia on ECP kinetics, we excluded patients with a history of new-onset acute myocardial infarction. In addition, patients with anemia, diabetes, a history of percutaneous coronary intervention, or coronary artery bypass grafting were not included in the study. Physical examination was performed to determine body mass index (BMI) and to assess the vital signs. We also examined the lipid profile and performed echocardiography to assess left ventricular function. The characteristics of the study population are summarized in [Table 1](#).

Preparation of blood samples and mononuclear cell isolation

We collected 40 ml peripheral blood samples from the median cubital vein following WHO guidelines on drawing blood¹⁷. From freshly drawn heparinized blood, we isolated peripheral blood mononuclear cells (PBMCs) using Ficoll Histopaque 1077 (Sigma-Aldrich, USA). Briefly, peripheral blood was diluted 1:1 with phosphate buffer saline (PBS) + 2% fetal bovine serum (FBS) to a total volume of 30–35 ml. It was then carefully layered into 20 ml of Ficoll Histopaque 1077 (Sigma-Aldrich, USA) in a 50 ml conical tube. Subsequently, the tube was put into a centrifuge at 300xg for 30 minutes. The PBMC layer was obtained in the form of a buffy coat layer. Using a sterile plastic pipette, the PBMCs were carefully taken and put into another 50 ml conical tube. Furthermore, PBMC was added with PBS + 2% FBS in a ratio of 1: 1, then stirred until homogeneous and centrifuged at 300xg for 7 minutes. This step was repeated with the supernatant removed, 15 ml of PBS + 2% FBS was added to the precipitate formed at the bottom of the tube and centrifuged at 300xg for 7 minutes. Finally, the supernatant was removed, and the sediment was dissolved with a basal medium. Cells were concentrated up to 5×10^6 cells/ml.

Table 1. The characteristics of the study population.

Variable	Mean ± SD
Age (years)	54.50 ± 4.31
BMI (kg/m ²)	25.39 ± 2.13
Heart rate (times/minute)	86 ± 8.68
Systolic blood pressure (mmHg)	137.50 ± 24.35
Diastolic blood pressure (mmHg)	80 ± 7.56
Triglyceride (mg/dl)	97 ± 11.64
LDL (mg/dl)	145 ± 61.11
HDL (mg/dl)	35 ± 7.64
Total cholesterol (mg/dl)	200.50 ± 74.75
Left ventricle ejection fraction (%)	53.5 ± 4.11

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

Isolation and culture of endothelial progenitor cells

To separate EPCs from PBMCs, we used standard protocols¹⁸. Briefly, PBMCs isolated from blood samples in a concentration of 5×10^6 cells/mL were collected in Stemline II Hematopoietic Stem Cell Expansion Medium (Sigma-Aldrich, USA) supplemented with endothelial basal medium (EBM) containing 40 ng/ml of vascular endothelial growth factor (VEGF) and 15% FBS. Then PBMCs were seeded in the six-well plate with fibronectin coating. The cultures were maintained with a humidified atmosphere at 37°C and 5% carbon dioxide. Forty-eight hours after seeding, we separated the medium liquid containing the non-adherent cells from the adherent cells attached to the bottom of the plate. All the medium liquid containing the non-adherent cells was collected into one tube, centrifuged with a spin at 300xg for 7 minutes, and the supernatant was discarded. The precipitate formed was dissolved with basal medium and supplement with a concentration of 1×10^6 cells/ml. We confirmed the cells as EPCs through immunofluorescence tests using fluorescein isothiocyanate (FITC) mouse anti-human CD34 monoclonal antibody (cat. no. 343604; Biologend, USA).

Treatment groups

Isolated EPCs were divided into three treatment groups and one negative control group. The treatment groups were divided into 1) captopril 1 μ M, 10 μ M, and 100 μ M; 2) lisinopril 1 μ M, 10 μ M, and 100 μ M; and 3) ramipril 1 μ M, 10 μ M, and 100 μ M. The cultures were maintained with a humidified atmosphere at 37°C and 5% carbon dioxide for 48 hours. Each data point represented the mean value of quadruplicate cultures.

Migration assay

We used the Boyden chamber migration assay to measure EPC migration. Briefly, migration chambers with 8 μ m pore-size filters were placed in 24-well plates. Using 1 mmol/L EDTA in PBS, isolated EPCs were detached and then centrifuged at 400xg for ten minutes. EPCs were seeded in the upper chamber (5×10^5 /ml in serum-free medium), and the lower compartment of the Boyden chamber was filled with endothelial basal medium. After 24 hours of incubation at 37°C, we scraped off non-migratory cells on the upper chamber with cotton swabs. The migration chamber was put into a new basal medium and added with 500 μ L of trypsin + EDTA 0.5% solution. After 10 minutes of incubation, we verified using a light microscope to ensure more than 90% of adhering cells were released from the lower surface of the migration chambers. For quantification, the cells were harvested and stained with trypan blue/Giemsa. Migrated EPCs were counted using an TC20 automated cell counter (Bio-Rad, USA).

Statistical analyses

Continuous data were presented as mean \pm SD. Multiple experimental group analysis of total migrated EPCs was performed using analysis of variance (ANOVA). A p-value of less than 0.05 was considered statistically significant. All statistical analysis was completed using SPSS version 25.0 for Windows.

Results

CD34 expression and migration capability of endothelial progenitor cells

CD34 is a positive marker for EPCs, and CD34 expression was found in the early to mature culture of EPCs. CD34 expression was characterized by the presence of green luminescence using a fluorescence microscope, indicating the presence of EPCs, as shown in Figure 1¹⁹. The migration capability of EPCs was evaluated by calculating the number of cells that moved from the upper chamber to the membrane facing the lower chamber with Giemsa staining (Figure 2).

ACE inhibitors increased endothelial progenitor cells migration

The number of EPC migrations in the captopril-treated group at different doses ($65,250 \pm 6,750$ cells at 1 mM; $90,000 \pm 16,837$ cells at 10mM; and $105,750 \pm 8112$ cells at 100 mM) was significantly higher than the control group ($43,714 \pm 7,216$ cells) ($p < 0.05$) (Figure 3). The number of EPC migrations in the lisinopril-treated group at different doses ($60,750 \pm 5,030$ cells at 1 mM; $79,071 \pm 2,043$ cells at 10mM; and $150,750 \pm 16,380$ cells at 100 mM) was significantly higher than the control group ($43,714 \pm 7,216$ cells) ($p < 0.05$) (Figure 4). The number of EPC migrations in the ramipril-treated group at different doses ($49,500 \pm 8,400$ cells at 1 mM; $64,285 \pm 11,824$ cells at 10mM; and $86,625 \pm 5,845$ cells at 100 mM) was significantly higher than the control group ($43,714 \pm 7,216$ cells) ($p < 0.05$) (Figure 5).

The increase in the migration of EPCs was consistent with the increase in the dose of ACE inhibitor. Captopril at doses of 1 mM and 10 mM had a higher migration effect than lisinopril and ramipril at the same doses ($p < 0.05$). Meanwhile,



Figure 1. CD34 expression was characterized by the presence of green luminescence in endothelial progenitor cell culture.

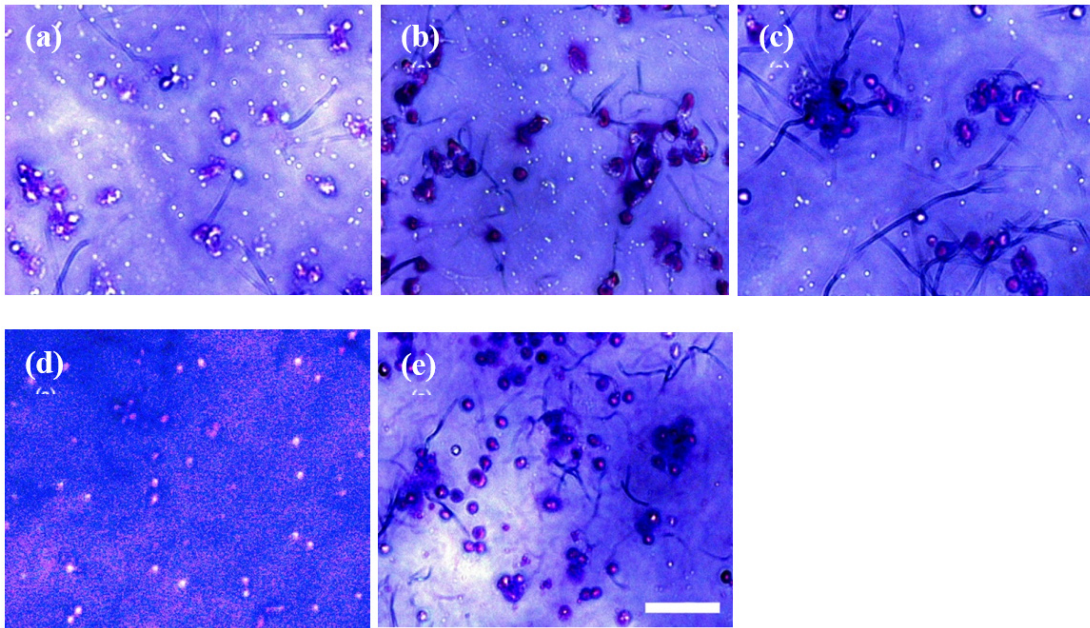


Figure 2. Light-inverted microscope view of endothelial progenitor cells under 48 h-treatment of (a) 100 mM captopril, (b) 100 mM lisinopril, (c) 100 mM ramipril, (d) negative control (medium only), and (e) positive control (100 ng/mL VEGF). White bar represents 100μm.

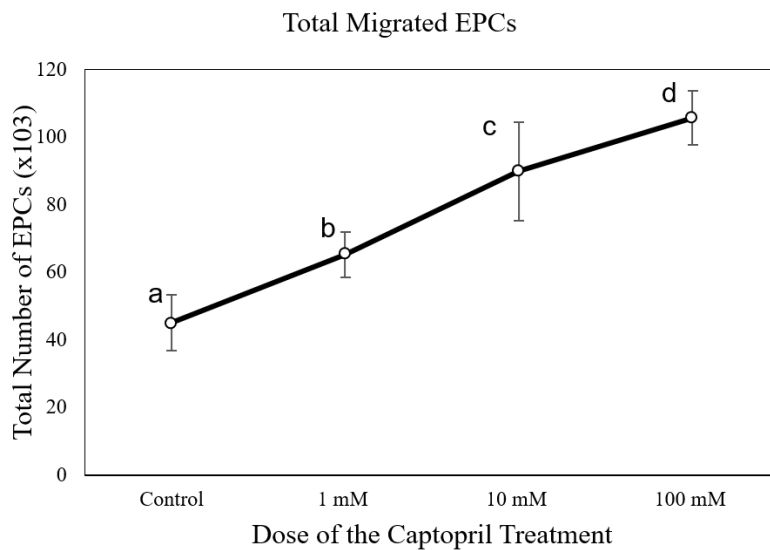


Figure 3. Total migrated endothelial progenitor cells (EPCs) on increasing dose of captopril treatment. Total migrated cells are expressed as mean ± SD (n = 4). Different annotations (a,b,c,d) denounce significant difference in ANOVA test (p<0.05).

lisinopril at a dose of 100mM had the highest migration effect (p < 0.05) (Figure 6).

Discussion

In this present study, we demonstrated that captopril, lisinopril, and ramipril therapy in EPC cultures from CAD patients was associated with improved migration of EPCs. This study showed

that ACE inhibitor treatment increases EPCs migration in a dose-dependent manner. At the doses of 1 mM and 10 mM, there was no significant difference in EPCs migration between captopril and lisinopril. However, both of them exceeded the results of ramipril at the same dose. Meanwhile, lisinopril at the dose of 100 mM had a superior outcome compared to captopril and ramipril at the same dose.

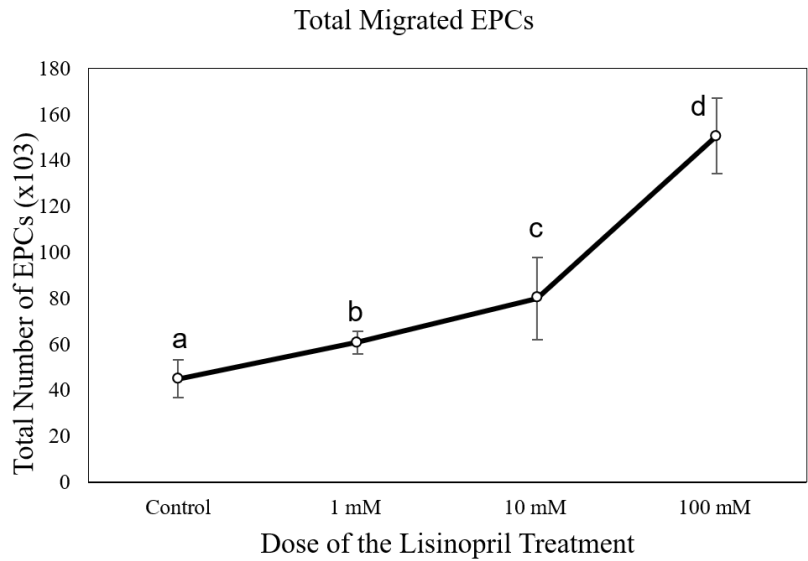


Figure 4. Total migrated endothelial progenitor cells (EPCs) on increasing dose of lisinopril treatment. Total migrated cells are expressed as mean ± SD (n = 4). Different annotations (a,b,c,d) denounce significant difference in ANOVA test (p<0.05).

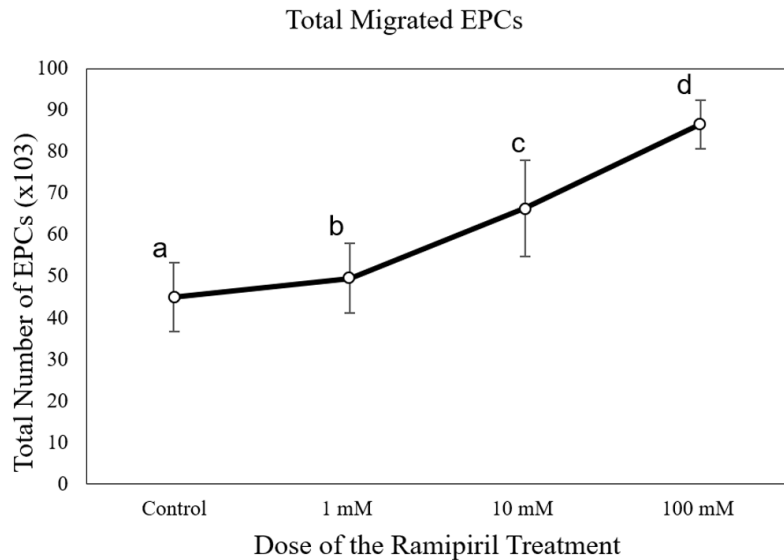


Figure 5. Total migrated endothelial progenitor cells (EPCs) on increasing dose of ramipiril treatment. Total migrated cells are expressed as mean ± SD (n = 4). Different annotations (a,b,c,d) denounce significant difference in ANOVA test (p<0.05).

Circulating EPCs are derived from hematopoietic stem cells produced in the bone marrow, which can repair endothelial dysfunction through endogenous mechanisms. In patients with CAD, the number and migration capacity of EPCs are decreased, and thus they are unable to maintain adequate endothelial stability^{6,20–22}. During ischemic conditions, EPCs are known to play an essential role in reendothelization and neovascularization. Animal and clinical studies have shown that EPCs

contribute up to 25% of newly formed vascular endothelial cells after ischemic conditions^{23,24}.

Several pharmacological agents have reported the beneficial effects on EPCs, such as HMG-CoA reductase inhibitors/statin^{25,26}, one of which has been demonstrated by our previous study¹⁶, peroxisome proliferator-activated receptor (PPAR) agonists²⁷, dihydropyridine calcium channel blocker²⁸, and angiotensin

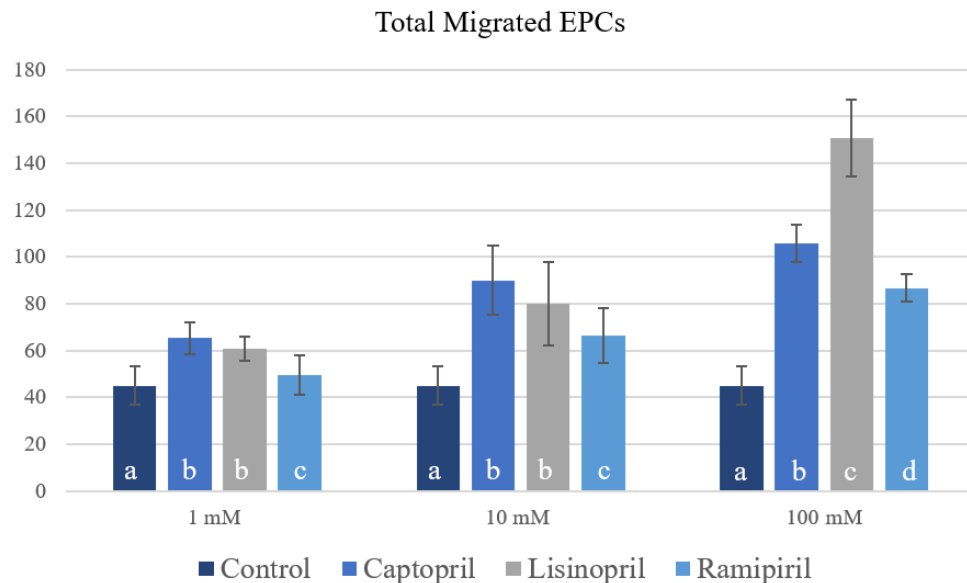


Figure 6. Total migrated endothelial progenitor cells (EPCs) on increasing dose of captopril, lisinopril and ramipiril. Total migrated cells are expressed as mean \pm SD (n = 4). Different annotations ^(a,b,c,d) denounce significant difference in ANOVA test (p<0.05).

II receptor antagonists (ARB)²⁹. Antioxidative agents with anti-inflammatory properties, such as ginsenoside, salvanolic acids, berberine, Ginkgo biloba, resveratrol, and puerarin, also have been found to increase the number or functional activity of EPCs³⁰. ACE inhibitors, which are widely used in cardiovascular therapy, such as for hypertension and congestive heart failure, may have a potential role in restoring the role of EPCs in repair, healing, and neovascularization^{11,31}. Several studies have demonstrated the role of ACE inhibitors in increasing the number and function of EPCs in patients with hypertension and stable CAD^{13,15}. Each of the ACE inhibitors has a different chemical functional group, which may explain the varying effects of different ACE inhibitor types in several studies, either *in vitro* or *in vivo*. Sulfhydryl-containing ACE inhibitors are known to be the most effective compared to other types of ACE inhibitors^{31–34}. Captopril has one sulfhydryl group, and zofenopril has two sulfhydryl groups to coordinate the zinc ion of the active side, whereas lisinopril, ramipril, and enalapril do not have sulfhydryl groups^{35–38}. Sulfhydryl-containing ACE inhibitors can reduce oxidative stress and stimulate nitric oxide (NO) activity in human endothelial cells³⁹ and patients with primary hypertension⁴⁰. *In vitro* studies have shown that zofenopril is more effective compared to enalapril in preventing foam cell formation and thereby slowing atherosclerosis. In addition, zofenopril can also reduce reactive oxygen species and increase NO production in the endothelium^{37,41–44}.

The finding that ACE inhibition therapy augmented the number of circulating EPCs in patients with CAD, and also enhanced

EPCs functional activity, may provide a novel strategy to improve neovascularization and reendothelialization after ischemia, thereby providing a therapeutic concept to improve EPC numbers and functions in patients with CAD.

Conclusion

Captopril, ramipril, and lisinopril were shown to increase EPC migration in a dose-dependent manner. Low-dose (1 mM) and medium-dose (10 mM) captopril had a larger effect on EPC migration than lisinopril and ramipril. Meanwhile, high-dose lisinopril (100mM) had the highest migration effect, suggesting it may be preferable for promoting EPC migration in CAD patients.

Data availability

Underlying data

Figshare: Dataset for Enhancement of EPC migration by high-dose lisinopril is superior compared to captopril and ramipril. <https://doi.org/10.6084/m9.figshare.13130303.v2>¹⁹

This project contains the following underlying data:

- Transwell_Migration_Assay_Dataset.xlsx
- Image Repository.zip (original, unedited microscopy images in JPG format)
- Clinical and demographic data of study population.docx

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

References

- Ross R: **Atherosclerosis—an inflammatory disease.** *N Engl J Med.* 1999; **340**(2): 115–126.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Endtmann C, Ebrahimian T, Czech T, et al.: **Angiotensin II impairs endothelial progenitor cell number and function in vitro and in vivo: implications for vascular regeneration.** *Hypertension.* 2011; **58**(3): 394–403.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Asahara T, Masuda H, Takahashi T, et al.: **Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization.** *Circ Res.* 1999; **85**(3): 221–228.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Hu Y, Foteinos G, Xiao Q, et al.: **Rapid endothelial turnover in atherosclerosis-prone areas coincides with stem cell repair in apoE-deficient mice.** *Atherosclerosis.* 2008; **199**(2): 467.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Oktaviano YH, Sargowo D, Widodo MA, et al.: **Proliferation of Peripheral Blood-derived Endothelial Progenitor Cells from Stable Angina Subjects.** *Indones Biomed J.* 2014; **6**(2): 91.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Vasa M, Fichtlscherer S, Aicher A, et al.: **Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease.** *Circ Res.* 2001; **89**(1): E1–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Werner N, Wassmann S, Ahlers P, et al.: **Endothelial progenitor cells correlate with endothelial function in patients with coronary artery disease.** *Basic Res Cardiol.* 2007; **102**(6): 565–571.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Werner N, Kosiol S, Schiegl T, et al.: **Circulating endothelial progenitor cells and cardiovascular outcomes.** *N Engl J Med.* 2005; **353**(10): 999–1007.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Loomans CJM, De Koning EJP, Staal FJT, et al.: **Endothelial progenitor cell dysfunction in type 1 diabetes: another consequence of oxidative stress?** *Antioxid Redox Signal.* 2005; **7**(11–12): 1468–1475.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Rehman J, Li J, Orschell CM, et al.: **Peripheral blood “endothelial progenitor cells” are derived from monocyte/macrophages and secrete angiogenic growth factors.** *Circulation.* 2003; **107**(8): 1164–1169.
[PubMed Abstract](#) | [Publisher Full Text](#)
- You D, Cochain C, Loinard C, et al.: **Combination of the angiotensin-converting enzyme inhibitor perindopril and the diuretic indapamide activate postnatal vasculogenesis in spontaneously hypertensive rats.** *J Pharmacol Exp Ther.* 2008; **325**(3): 766–773.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Müller P, Kazakov A, Jagoda P, et al.: **ACE inhibition promotes upregulation of endothelial progenitor cells and neoangiogenesis in cardiac pressure overload.** *Cardiovasc Res.* 2009; **83**(1): 106–114.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Cacciatore F, Bruzzese G, Vitale DF, et al.: **Effects of ACE inhibition on circulating endothelial progenitor cells, vascular damage, and oxidative stress in hypertensive patients.** *Eur J Clin Pharmacol.* 2011; **67**(9): 877–883.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Wang CH, Verma S, Hsieh IC, et al.: **Enalapril increases ischemia-induced endothelial progenitor cell mobilization through manipulation of the CD26 system.** *J Mol Cell Cardiol.* 2006; **41**(1): 34–43.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Min TQ, Zhu CJ, Xiang WX, et al.: **Improvement in endothelial progenitor cells from peripheral blood by ramipril therapy in patients with stable coronary artery disease.** *Cardiovasc Drugs Ther.* 2004; **18**(3): 203–209.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Oktaviano YH, Al Farabi MJ, Meuthia F, et al.: **Rosuvastatin is Superior Compared to Simvastatin and Atorvastatin to Induce Endothelial Progenitor Cells Migration.** *J Clin Diagnostic Res.* 2019; **13**(5): OC05–OC08.
[PubMed Abstract](#) | [Publisher Full Text](#)
- World Health Organization (WHO): **WHO guidelines on drawing blood: best practices in phlebotomy.** World Health Organization. 2010.
[Reference Source](#)
- Bueno-Betí C, Novella S, Lázaro-Franco M, et al.: **An affordable method to obtain cultured endothelial cells from peripheral blood.** *J Cell Mol Med.* 2013; **17**(11): 1475–1483.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Al Farabi MJ: **Dataset for Enhancement of EPC migration by high-dose lisinopril is superior compared to captopril and ramipril.** *figshare.* Dataset. 2020.
<http://www.doi.org/10.6084/m9.figshare.13130303.v2>
- Fadini GP, Coracina A, Baesso I, et al.: **Peripheral blood CD34⁺KDR⁺ endothelial progenitor cells are determinants of subclinical atherosclerosis in a middle-aged general population.** *Stroke.* 2006; **37**(9): 2277–2282.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Liguori A, Fiorito C, Balestrieri ML, et al.: **Functional impairment of hematopoietic progenitor cells in patients with coronary heart disease.** *Eur J Haematol.* 2008; **80**(3): 258–264.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Briguori C, Testa U, Riccioni R, et al.: **Correlations between progression of coronary artery disease and circulating endothelial progenitor cells.** *FASEB J.* 2010; **24**(6): 1981–1988.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Murayama T, Tepper OM, Silver M, et al.: **Determination of bone marrow-derived endothelial progenitor cell significance in angiogenic growth factor-induced neovascularization in vivo.** *Exp Hematol.* 2002; **30**(8): 967–972.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Suzuki T, Nishida M, Futami S, et al.: **Neoendothelialization after peripheral blood stem cell transplantation in humans: a case report of a Tokaimura nuclear accident victim.** *Cardiovasc Res.* 2003; **58**(2): 487–492.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Llevadot J, Murasawa S, Kureishi Y, et al.: **HMG-CoA reductase inhibitor mobilizes bone marrow–derived endothelial progenitor cells.** *J Clin Invest.* 2001; **108**(3): 399–405.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Landmesser U, Engberding N, Bahlmann FH, et al.: **Statin-induced improvement of endothelial progenitor cell mobilization, myocardial neovascularization, left ventricular function, and survival after experimental myocardial infarction requires endothelial nitric oxide synthase.** *Circulation.* 2004; **110**(14): 1933–1939.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Gensch C, Clever YP, Werner C, et al.: **The PPAR-gamma agonist pioglitazone increases neoangiogenesis and prevents apoptosis of endothelial progenitor cells.** *Atherosclerosis.* 2007; **192**(1): 67–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Passacualle G, Desideri G, Croce G, et al.: **Nifedipine improves the migratory ability of circulating endothelial progenitor cells depending on manganese superoxide dismutase upregulation.** *J Hypertens.* 2008; **26**(4): 737–746.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Bahlmann FH, de Groot K, Mueller O, et al.: **Stimulation of endothelial progenitor cells: a new putative therapeutic effect of angiotensin II receptor antagonists.** *Hypertension.* 2005; **45**(4): 526–529.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lin CP, Lin FY, Huang PH, et al.: **Endothelial progenitor cell dysfunction in cardiovascular diseases: role of reactive oxygen species and inflammation.** *Biomed Res Int.* 2013; **2013**: 845037.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Napoli C, Cicala C, D'Armiento FP, et al.: **Beneficial effects of ACE-inhibition with zofenopril on plaque formation and low-density lipoprotein oxidation in watanabe heritable hyperlipidemic rabbits.** *Gen Pharmacol.* 1999; **33**(6): 467–477.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Candido R, Jandeleit-Dahm KA, Cao Z, et al.: **Prevention of accelerated atherosclerosis by angiotensin-converting enzyme inhibition in diabetic apolipoprotein E-deficient mice.** *Circulation.* 2002; **106**(2): 246–253.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Sun YP, Zhu BQ, Browne AE, et al.: **Comparative effects of ACE inhibitors and an angiotensin receptor blocker on atherosclerosis and vascular function.** *J Cardiovasc Pharmacol Ther.* 2001; **6**(2): 175–181.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Chobanian AV, Haudenschild CC, Nickerson C, et al.: **Antiatherogenic effect of captopril in the Watanabe heritable hyperlipidemic rabbit.** *Hypertension.* 1990; **15**(3): 327–331.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Unger T: **The role of the renin-angiotensin system in the development of cardiovascular disease.** *Am J Cardiol.* 2002; **89**(2A): 3A–9A; discussion 10A.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Kowala MC, Grove RI, Aberg G: **Inhibitors of angiotensin converting enzyme decrease early atherosclerosis in hyperlipidemic hamsters. Fosinopril reduces plasma cholesterol and captopril inhibits macrophage-foam cell accumulation independently of blood pressure and plasma lipids.** *Atherosclerosis.* 1994; **108**(1): 61–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Buikema H, Monnik SH, Tio RA, et al.: **Comparison of zofenopril and lisinopril to study the role of the sulfhydryl-group in improvement of endothelial dysfunction with ACE-inhibitors in experimental heart failure.** *Br J Pharmacol.* 2000; **130**(8): 1999–2007.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Predel HG, Düsing R, Bäcker A, et al.: **Combined treatment of severe essential hypertension with the new angiotensin converting enzyme inhibitor ramipril.** *Am J Cardiol.* 1987; **59**(10): 143D–148D.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Jacoby DS, Rader DJ: **Renin-angiotensin system and atherothrombotic diseases: from genes to treatment.** *Arch Intern Med.* 2003; **163**(10): 1155–64.
[PubMed Abstract](#) | [Publisher Full Text](#)

40. Napoli C, Bruzzese G, Ignarro LJ, *et al.*: **Long-term treatment with sulfhydryl angiotensin-converting enzyme inhibition reduces carotid intima-media thickening and improves the nitric oxide/oxidative stress pathways in newly diagnosed patients with mild to moderate primary hypertension.** *Am Heart J.* 2008; **156**(6): 1154.e1-8.
[PubMed Abstract](#) | [Publisher Full Text](#)
41. Cominacini L, Pasini A, Garbin U, *et al.*: **Zofenopril inhibits the expression of adhesion molecules on endothelial cells by reducing reactive oxygen species.** *Am J Hypertens.* 2002; **15**(10 Pt 1): 891-895.
[PubMed Abstract](#) | [Publisher Full Text](#)
42. Evangelista S, Manzini S: **Antioxidant and cardioprotective properties of the sulphhydryl angiotensin-converting enzyme inhibitor zofenopril.** *J Int Med Res.* 2005; **33**(1): 42-54.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. de Nigris F, D'Armiento FP, Somma P, *et al.*: **Chronic treatment with sulfhydryl angiotensin-converting enzyme inhibitors reduce susceptibility of plasma LDL to *in vitro* oxidation, formation of oxidation-specific epitopes in the arterial wall, and atherogenesis in apolipoprotein E knockout mice.** *Int J Cardiol.* 2001; **81**(2-3): 107-115; discussion 115-6.
[PubMed Abstract](#) | [Publisher Full Text](#)
44. Scribner AW, Loscalzo J, Napoli C: **The effect of angiotensin-converting enzyme inhibition on endothelial function and oxidant stress.** *Eur J Pharmacol.* 2003; **482**(1-3): 95-99.
[PubMed Abstract](#) | [Publisher Full Text](#)

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research