

Prognostication of Cardiovascular Complications in Metabolic Syndrome Patients: The Role of Vistafin

Alexander E Berezin*

Professor, MD, PhD, Internal Medicine Department, State Medical University, 26, Mayakovsky Av., Zaporozhye, Postcode 69035, Ukraine

Abstract

Vistafin is insulin-mimicking adipocytokine secreted from visceral adipose tissue, which plays an essential role in a number of biological processes affected glucose uptake regulation, inflammation, immunity, insulin resistance, vascular calcification, capillary tube formation, endothelial cell function and angiogenesis. Circulating level of visfatin exhibits to be a sufficiently increased in MetS and Type 2 Diabetes Mellitus (T2DM) patients compared with healthy individuals. Several clinical studies have shown that serum visfatin may predict Cardiovascular (CV) disease and CV events in MetS and T2DM patients. The review summarizes the various aspects of the role of visfatin as biomarker of MetS compared with commonly used biomarkers, i.e. adiponectin, leptin, resistin, apelin. In future more investigations are needed to better understand the role of visfatin in dysmetabolic-related disease and its ability to predict CV complications in these patient populations.

Keywords: Metabolic Syndrome; Diabetes Mellitus; Biomarkers; Vistafin; Prognostication; Risk Stratification

***Corresponding Author:** Alexander E Berezin, Professor, MD, PhD, Internal Medicine Department, State Medical University, 26, Mayakovsky Av., Zaporozhye, Postcode 69035, Ukraine; E-mail: dr_berezin@mail.ru

Introduction

Metabolic Syndrome (MetS) is considered as a cluster of Cardiovascular (CV) and metabolic risk factors that appears to be highly prevalent and contributes to a rapidly growing medical and social problem worldwide [1, 2]. Although definitions of MetS are controversial and may include different metabolic conditions [3-5], recent clinical studies have shown that MetS closely associated with increased risk of diabetes mellitus, CV disease, cancer, obstructive sleep apnea, and musculoskeletal diseases [6-

10]. Moreover, there is a large body of epidemiological evidences suggesting that the genetic predisposition and co-morbidity of MetS could increase the risk of CV events and all-cause mortality, whereas MetS as crude factor does not mediate CV mortality [11, 12]. Recent clinical studies have shown that genetic predisposition in association with slightly elevated glucose levels may accelerate the development of atherosclerosis and increase the risk for CV disease in glucose-tolerant individuals [13, 14]. In this context, novel predictors of CV risk stratification are required and metabolic biomarkers might be useful in prognostication in patients with MetS beyond known CV disease. The aim of the mini review is summary of the various aspects of the role of visfatin as biomarker of MetS compared with commonly used biomarkers.

Biological Functionalities of Vistafin

Visfatin (known as pre-B-cell colony-enhancing factor - PBEF or nicotinamide phosphoribosyltransferase - NAMPT) is a newly discovered insulin-mimicking adipocytokine constitutively secreted from Visceral (VAT) and probably subcutaneous adipose tissue, as well as hepatocytes and it is thought to play a pivotal role in the pathogenesis of obesity and MetS [15, 16]. Visfatin exhibits both an intracellular enzymatic activity (nicotinamide phosphoribosyltransferase) leading to NAD synthesis and extracellular enzymatic activity that regulates cytokine function via the binding to its hypothetical receptor. As a result this molecule acts as with pleiotropic effector with variety spectrum of metabolic and stress responses affected insulin secretion in pancreatic beta-cells, immunity, inflammation and proliferation. It is known that visfatin may induce production of wide spectrum of cytokines, such as Tumor Necrotic Factor (TNF)-alpha, Interleukin (IL)-1beta, and IL-6.

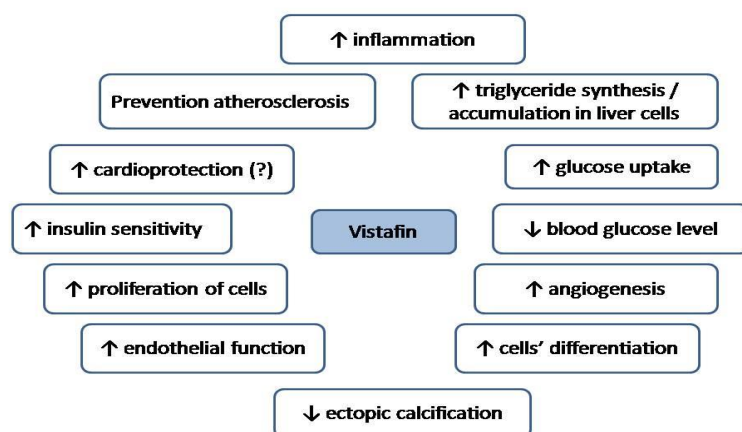
Visfatin is released from variety adipocytes, hepatocytes, activated mononuclears, and their elevated level can be found in the systemic circulation of patients with a obesity, inflammatory and rheumatic diseases, malignancy. Therefore, vistafin expression is up-regulated in sepsis, acute lung injury, inflammatory bowel disease, and myocardial infarction and plays a key role in the persistence of inflammation through its capacity to inhibit neutrophil apoptosis. The main regulator of release of vistafin is glucose and insulin [17]. In fact, concentrations of vistafin are increased by hyperglycaemia and lowered HDL-cholesterol level [18].

Visfatin acts via phosphorylation of p38 AMP-activated Protein Kinase (AMPK) in target cells that leads to an increase of phosphorylation of the insulin receptor, stimulation of glucose uptake through increased Glucose Transporter Type 4 (GLUT4) mRNA, and arise of the intracellular Ca^{2+} concentration in pancreatic β -cells [17]. Additionally, visfatin has stimulated the translocation of GLUT4 to the plasma membrane, and this effect was suppressed by AMPK α 2 inhibition [15]. Furthermore, visfatin has induced in dose-dependent manner endothelial proliferation and capillary tube formation via Vascular Endothelial Growth Factor (VEGF) and Matrix Metalloproteinases (MMP-2, MMP-9) production [19]. There are evidences regarding an ability of visfatin to activate endothelial NO synthase via Akt and MAP kinases, improves endothelial cell function and angiogenesis, prevent ectopic vascular calcification, as well as induces up-regulation of profibrotic molecules [20, 21].

Recent preclinical studies have shown that visfatin may improve insulin sensitivity and exert its hypocholesterolemic effects partially through up-regulation of the tyrosine phosphorylation of Insulin Receptor Substrate (IRS-1) protein and the mRNA levels of Peroxisome Proliferator-Activated Receptor- γ (PPAR- γ) and Sterol Regulatory Element-Binding Proteins 2 (SREBP-2) in the liver and adipose tissues [22, 23]. Overall, vistafin was found an autocrine regulator of sensitivity of target cells (cardiomyocytes, hepatocytes, adipocytes, muscle cells, etc.) to insulin action possibly through its effects on NAD biosynthesis. Moreover, pleiotropic component of biological function of this enzyme was defined too because of its molecular targets, i.e., IRS-1, PPAR- γ and SIRT6 are able to regulate transcription factors involved in pathways linked to glucose metabolism, inflammation, and proliferation / differentiation of

cells [24]. However, the pro-inflammatory action of visfatin cannot be prevented by IRS-1 blockade [25]. Thus, visfatin appears a direct contributor to vascular inflammation and endothelial dysfunction that are considered key features of atherothrombotic diseases linked to MetS (Figure 1).

Figure 1: Biological function of vistafin



Vistafin in Mets and Diabetes

Circulating level of visfatin demonstrates to be a sufficiently increased in MetS [26] and Type 2 Diabetes Mellitus (T2DM) patients compared with healthy individuals [27, 28]. In fact, visfatin mRNA levels were strongly correlated with pro-inflammatory gene expression including CD68 and tumor necrosis factor- α gene in both VAT and subcutaneous adipose tissues [28-30]. Interestingly, such component of MetS as insulin resistance and obesity was not associated with visfatin levels [27-31]. It has been suggested that elevated vistafin level could associate rather with inflammatory changes in blood than with metabolic disorders. However, visfatin expression is up-regulated in peripheral blood mononuclear cells received from obese type 2 diabetic patients compared to non-diabetic obese patients [32]. Thus indicates enhanced visfatin expression could relate to T2DM rather than obesity. Contrary, several clinical studies have revealed that circulating level of vistafin exhibits a negative correlation with visceral fat accumulation, insulin resistance and triglycerides, but it was found a negative correlation between vistafin and HDL cholesterol, this negative correlation completely disappeared after adjustment for lipid profile [31]. Authors concluded that visfatin level is an indicator of beneficial lipid profile in non-diabetic Caucasian subjects and that lipid metabolism might relate to visceral obesity and insulin resistance through vistafin expression in VAT. Borradaile and Pickering [32] reported that vistafin enables proliferating human endothelial

cells to resist the oxidative stress of aging and of high glucose, and to productively use excess glucose to support replicative longevity and angiogenic activity. Based on these evidences authors concluded that visfatin is rate-limiting for NAD⁺ salvage from nicotinamide and confers resistance to oxidative stress via SIRT1. Takebayashi et al. (2007) [33] have reported serum visfatin level has closely associated in diabetic patients with vascular endothelial function. Similar data were received Pepene (2012) in polycystic ovary syndrome subjects [34]. Moreover, Malavazos et al. (2008) [35] have revealed that in patients with visceral obesity serum visfatin level has significantly correlated with plasminogen activator inhibitor-1 levels and prothrombotic state. Recently visfatin has shown to be associated with sVCAM-1 as a marker of endothelial dysfunction, activation of endothelium and vascular injury [36, 37]. There is evidence regarding an association between elevated vistafin level and the risk of asymptomatic atherosclerosis in obese and T2DM individuals [38]. Overall, this unique enzyme is considered an essential metabolic regulator in the NAD biosynthetic pathway with controversial capacities and various faces [39]. Visfatin may prevent apoptosis in T cells and mediates catabolic and pro-inflammation effect in individuals with rheumatic disease [40-43]. The pathophysiological significance and clinical value of this biomarker in dysmetabolic individuals are still not fully clear and they are required more investigation.

Vistafin and CV outcomes

The effects of vistafin on CV outcomes are controversial. This relates with multiple molecular effects of the molecules on target cells. By now, it is defined that vistafin may improves insulin resistance and might have an antidiabetic effect in MetS patients. Contrary, there are data that visfatin could link low-grading inflammation, thrombotic state, target organ damage, and CV clinical outcomes. In patients with known CV diseases visfatin was initially proposed as a clinical marker of atherosclerosis, endothelial dysfunction, chronic renal disease, and vascular damage, with a potential prognostic value [36, 37, 44-46]. In particularity, visfatin may be associated with clinical severity of aneurysmal subarachnoid hemorrhage and also have prognostic value for clinical outcomes [47]. Lu et al. (2009) [48] reported that serum visfatin level was an independent factor associated with ischemic stroke. Authors found that increasing concentrations of visfatin were independently and significantly

associated with a higher risk of ischemic stroke when concentrations were analyzed as both a quartile and a continuous variable. Moreover, circulating level of visfatin was associated with 6-month clinical outcomes including mortality and unfavorable outcome (modified Rankin Scale score >2) in the patients with ischemic stroke [49]. Indeed, plasma visfatin level was independently associated with acute coronary syndromes / acute myocardial infarction independent of well-known CV disease risk factors [50, 51]. Probably, vistafin could explain an influence of family history of diabetes on the patients' outcome [13, 14]. However, the studies depicted the predictive role of vistafin in CV outcomes are limited, whereas preliminary results of the investigations appear to be meaningful and scientifically interested.

Head-to-head comparison of vistafin with other metabolomics biomarkers

Recent clinical studies have shown that serum levels of adipocytokines, i.e. adiponectin, leptin, resistin, apelin and visfatin, were increased in dysmetabolic patients compared to healthy volunteers [11, 52]. All these biomarkers were associated with obesity, insulin resistance and various markers of glucose/lipid profile, inflammation and endothelial dysfunction. Whether vistafin appears to be better than novel biochemical risk factor for CV complications in MetS remains not clear. Accordingly, the predictive and discriminative role of vistafin in hypertension, atherosclerosis, ischemic heart disease, ischemic stroke and intracranial hemorrhage remains uncertain. Collectively, it is required more investigation regarding head-to-head comparison of vistafin with other metabolic biomarkers in predictive models.

Conclusion

In conclusion, vistafin participates in pathophysiology of several dysmetabolic state including MetS, T2DM, obesity, and plays an important role in predicting CV disease and CV events. However, there are not sufficient evidence regarding advantages of vistafin compared other metabolic biomarkers (adiponectin, leptin, resistin, apelin) in risk stratification of patients with MetS. Whether visfatin would be eventually become a component of guided-biomarker medical care of dysmetabolic patients remains to be established. More investigations are needed to better understand the role of vistafin in dysmetabolic-related disease.

References

- Alberti KG, Zimmet P, Shaw J. Metabolic syndrome - a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med*. 2006; 23(5): 469–80.
- Zabetian A, Hadaegh F, Azizi F. Prevalence of metabolic syndrome in Iranian adult population, concordance between the IDF with the ATPIII and the WHO definitions. *Diabetes Res Clin Pract*. 2007; 77(2): 251–7.
- Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-97
- Alberti KG, Zimmet P, Shaw J. The metabolic syndrome - a new worldwide definition. *Lancet*. 2005; 366: 1059-62.
- Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735-52
- Cho LW. Metabolic syndrome. *Singapore Med J*. 2011; 52(11):779–85.
- Sanghera DK, Been L, Ortega L, Wander GS, Mehra NK, Aston CE, et al. Testing the association of novel meta-analysis-derived diabetes risk genes with type II diabetes and related metabolic traits in Asian Indian Sikhs. *J Hum Genet*. 2009; 54: 162–168.
- Vijayan VK. Morbidities associated with obstructive sleep apnea. *Expert Rev Respir Med*. 2012;6:557–66
- Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic Syndrome and Risk of Cancer: A systematic review and meta-analysis. *Diabetes Care*. 2012;35(11):2402-2411
- Sun K, Liu J, Lu N, Sun H, Ning G. Association between metabolic syndrome and bone fractures: a meta-analysis of observational studies. *BMC Endocrine Disorders*. 2014; 14: 13. doi:10.1186/1472-6823-14-13.
- Dallmeier D, Larson MG, Vasan RS, et al. Metabolic syndrome and inflammatory biomarkers: a community-based cross-sectional study at the Framingham Heart Study. *Diabetology & Metabolic Syndrome*. 2012; 4: 28.
- Zuliani G, Morieri ML, Volpato S, et al. Insulin resistance and systemic inflammation, but not metabolic syndrome phenotype, predict 9 years mortality in older adults. *Atherosclerosis*. 2014; 235(2): 538-545. doi:10.1016/j.atherosclerosis.2014.05.959.
- Pannaciuoli N, De Pergola G, Ciccone M, Rizzon P, Giorgino F, Giorgino R. Effect of family history of type 2 diabetes on the intima-media thickness of the common carotid artery in normal-weight, overweight, and obese glucose-tolerant young adults. *Diabetes Care*. 2003; 26(4):1230-4.
- Ciccone MM, Scicchitano P, Cameli M, Cecere A, Cortese F, Dentamaroet I et al. Endothelial Function in Pre-diabetes, Diabetes and Diabetic Cardiomyopathy: A Review. *J Diabetes Metab* 2014; 5:364. doi:10.4172/2155-6156.1000364
- Imai SI. Nicotinamide phosphoribosyl transferase (NAMPT): a link between NAD biology, metabolism, and diseases. *Curr Pharm Design* 2009;15:20–8
- Garten A, Petzold S, Barnikol-Oettler A, Körner A, Thasler WE, Kratzsch J, Kiess et al. Nicotinamide phosphoribosyltransferase (NAMPT/PBEF/visfatin) is constitutively released from human hepatocytes. *Biochem Biophys Res Commun*. 2010; 391(1):376-81.
- Haider DG, Schaller G, Kapiotis S, Maier C, Luger A, Wolzt M. The release of the adipocytokine visfatin is regulated by glucose and insulin. *Diabetologia*. 2006; 49: 1909–14.
- Hug C, Lodish HF. Medicine. Visfatin: a new adipokine. *Science*. 2005; 307:366–367
- Garten A, Petzold S, Schuster S, Körner A, Kratzsch J, Kiess W. Nampt and its potential role in inflammation and type 2 diabetes. *Handb Exp Pharmacol*. 2011; 203:147-64.
- Adya R, Tan BK, Punna A, et al. Visfatin induces human endothelial VEGF and MMP-2/9 production via MAPK and PI3K/Akt signalling pathways: novel insights into visfatin-induced angiogenesis. *Cardiovasc Res* 2008; 78:356–65
- Lovren F, Pan Y, Shukla PC, Quan A, Teoh H, Szmítko PE, et al. Visfatin activates eNOS via Akt and MAP kinases and improves endothelial cell function and angiogenesis in vitro and in vivo: translational implications for atherosclerosis. *Am J Physiol Endocrinol Metab*. 2009; 296(6): E1440-9.
- Sun Q, Li L, Li R, Yang M, Liu H, Nowicki MJ, et al. Over expression of visfatin/PBEF/Nampt alters whole-body insulin sensitivity and lipid profile in rats. *Ann Med*. 2009; 41(4):311-20.

23. Sommer G, Garten A, Petzold S, Beck-Sickingher AG, Blüher M, Stumvoll M, et al. Visfatin/PBEF/Nampt: structure, regulation and potential function of a novel adipokine. *Clin Sci (Lond)*. 2008; 115(1):13-23.
24. Burgos ES. NAMPT in regulated NAD biosynthesis and its pivotal role in human metabolism. *Curr Med Chem*. 2011; 18(13): 1947-61.
25. Romacho T, Azcutia V, Vázquez-Bella M, Matesanz N, Cercas E, Nevado J, et al. Extracellular PBEF/NAMPT/visfatin activates pro-inflammatory signalling in human vascular smooth muscle cells through nicotinamide phosphoribosyltransferase activity. *Diabetologia*. 2009; 52(11): 2455-63.
26. Filippatos TD, Derdemezis CS, Gazi IF, et al. Increased plasma visfatin levels in subjects with the metabolic syndrome. *Eur J Clinical Investigation*. 2008; 38(1):71–72
27. Revollo JR, Körner A, Mills KF, Satoh A, Wang T, Garten A, et al. Nampt/PBEF/Visfatin regulates insulin secretion in beta cells as a systemic NAD biosynthetic enzyme. *Cell Metab*. 2007; 6(5):363-75.
28. Stastny J, Bienertova-Vasku J, Vasku A. Visfatin and its role in obesity development. *Diabetes Metab Syndr*. 2012; 6(2): 120-4.
29. Tanaka T, Nabeshima Y. Nampt/PBEF/Visfatin: a new player in beta cell physiology and in metabolic diseases? *Cell Metab*. 2007; 6(5): 341-3.
30. Pfützner A, Hanefeld M, Lübken G, Weber MM, Karagiannis E, Köhler C, et al. Visfatin: a putative biomarker for metabolic syndrome is not influenced by pioglitazone or simvastatin treatment in nondiabetic patients at cardiovascular risk - results from the PIOSTAT study. *Horm Metab Res*. 2007; 39(10): 764-8.
31. Wang P, van Greevenbroek MM, Bouwman FG, Brouwers MC, van der Kallen CJ, Smit E, et al. The circulating PBEF/NAMPT/visfatin level is associated with a beneficial blood lipid profile. *Pflugers Arch*. 2007; 454(6):971-6.
32. Laudes M, Oberhauser F, Schulte DM, et al. Visfatin/PBEF/Nampt and resistin expressions in circulating blood monocytes are differentially related to obesity and type 2 diabetes in humans. *Hormone and Metabolic Research*. 2010; 42(4): 268–273
33. Borradaile NM, Pickering JG. Nicotinamide phosphoribosyltransferase imparts human endothelial cells with extended replicative lifespan and enhanced angiogenic capacity in a high glucose environment. *Aging Cell*. 2009; 8(2): 100-12.
34. Takebayashi K, Suetsugu M, Wakabayashi S, Aso Y, Inukai T. Association between plasma visfatin and vascular endothelial function in patients with type 2 diabetes mellitus. *Metabolism*. 2007; 56(4):451–458.
35. Pepene CE. Evidence for visfatin as an independent predictor of endothelial dysfunction in polycystic ovary syndrome. *Clinical Endocrinology*. 2012;76(1):119–125
36. Malavazos AE, Ermetici F, Cereda E, et al. Epicardial fat thickness: relationship with plasma visfatin and plasminogen activator inhibitor-1 levels in visceral obesity. *Nutrition, Metabolism and Cardiovascular Diseases*. 2008;18(8):523–530
37. Yilmaz MI, Saglam M, Carrero JJ, et al. Serum visfatin concentration and endothelial dysfunction in chronic kidney disease. *Nephrology Dialysis Transplantation*. 2008; 23(3): 959–965
38. Axelsson J, Witasp A, Carrero JJ, et al. Circulating levels of Visfatin/pre-B-cell colony-enhancing factor 1 in relation to genotype, GFR, body composition, and survival in patients with CKD. *American Journal of Kidney Diseases*. 2007; 49(2): 237–244
39. Tan H, Zhong M, Gong H, Wang S, Zhang Y, Zhang W. Increased serum visfatin in patients with metabolic syndrome and carotid atherosclerosis. *Clinical Endocrinology*. 2008; 69(6):878–884
40. Imai S. Nicotinamide phosphoribosyltransferase (Nampt): a link between NAD biology, metabolism, and diseases. *Curr Pharm Des*. 2009; 15(1):20-8.
41. Chang YC, Chang TJ, Lee WJ, Chuang LM. The relationship of visfatin/pre-B-cell colony-enhancing factor/nicotinamide phosphoribosyltransferase in adipose tissue with inflammation, insulin resistance, and plasma lipids. *Metabolism*. 2010; 59(1): 93-9.
42. Nowell M, Evans L, Williams A. PBEF/NAMPT/visfatin: a promising drug target for treating rheumatoid arthritis? *Future Med Chem*. 2012; 4(6): 751-69.
43. Yang S, Ryu JH, Oh H, Jeon J, Kwak JS, Kim JH, et al. NAMPT (visfatin), a direct target of hypoxia-inducible factor-2 α , is an essential catabolic regulator of osteoarthritis. *Ann Rheum Dis*. 2015; 74(3): 595-602.

44. Bao JP, Chen WP, Wu LD. Visfatin: a potential therapeutic target for rheumatoid arthritis. *J Int Med Res*. 2009; 37(6): 1655-61.
45. Wang JX, Hou Y, Ruan SP, Wang J, Hu XM. Plasma visfatin, a possible prognostic marker in aneurysmal subarachnoid hemorrhage. *Peptides*. 2013; 50:8-12.
46. Romacho T, Sánchez-Ferrer CF, Peiró C. Visfatin/Nampt: an adipokine with cardiovascular impact. *Mediators Inflamm*. 2013; 2013: 946427.
47. Kadoglou NPE, Sailer N, Moumtzouoglou A, et al. Visfatin (Nampt) and ghrelin as novel markers of carotid atherosclerosis in patients with type 2 diabetes. *Experimental and Clinical Endocrinology and Diabetes*. 2010;118(2):75–80
48. Lu LF, Yang SS, Wang CP, et al. Elevated Visfatin/Pre-B-cell colony-enhancing factor plasma concentration in ischemic stroke. *Journal of Stroke and Cerebrovascular Diseases*. 2009; 18(5): 354–359.
49. Yin CG, Jiang L, Tang B, Zhang H, Qian Q, Niu GZ. Prognostic significance of plasma visfatin levels in patients with ischemic stroke. *Peptides*. 2013; 42: 101-4.
50. Liu SW, Qiao SB, Yuan JS, Liu DQ. Association of plasma visfatin levels with inflammation, atherosclerosis and acute coronary syndromes (ACS) in humans. *Clin Endocrinol (Oxf)*. 2009; 71(2):202-7.
51. Yu TH, Lu LF, Hung WC, et al. Circulating visfatin level at admission is associated with occlusion of the infarct-related artery in patients with acute ST-segment elevation myocardial infarction. *Acta Cardiologica Sinica*. 2011; 27(2):77–85.
52. Wang P, Vanhoutte PM, Miao CY. Visfatin and cardio-cerebro-vascular disease. *J Cardiovascular Pharmacology*. 2011; 59(1): 1-9.