Crimson Publishers
Wings to the Research

Mini Review

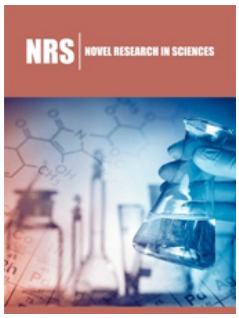
Angiotensin-Converting-Enzyme (ACE) One Receptor, Two Diseases COVID and Infrarenal Aortic Aneurysm: A Mini-Review

Masoud Mirzaie[1]*, Addicks JP[2], Kusnirova J[1], Akram M[3] and Fatehpur S[1]

[1]Department of Vascular Surgery, OWL, Klinikum Lippe University Hospital, Campus Lemgo, Germany

[2]Institute of Neuroradiology, OWL, Klinikum Lippe University Hospital, Campus Lemgo, Germany

[3]Department of Eastern, Medicine Government College University Faisalabad-Pakistan



***Corresponding author:** Masoud Mirzaie, Department of Vascular Surgery, OWL, Klinikum Lippe University Hospital, Campus Lemgo, Germany

Submission: June 29, 2021

Published: July 15, 2021

Volume 8 - Issue 3

How to cite this article: Masoud Mirzaie, Addicks JP, Kusnirova J, Akram M, Fatehpur S. Angiotensin-Converting-Enzyme (ACE) One Receptor, Two Diseases COVID and Infrarenal Aortic Aneurysm: A Mini-Review. Nov Res Sci. 8(3). NRS. 000690. 2021.
DOI: 10.31031/NRS.2021.08.000690

Introduction

The high morbidity and mortality caused by coronavirus disease 2019 (COVID-19) includes cardiovascular functional impairment. Evidence suggests that COVID infection causes symptomatic cardiac sufficiency in patients with preexisting cardiac disease and troponin elevation in critically ill patients [1-5]. The S1 subunit of the COVID virus S-glycoprotein functions as the Receptor-Binding Domain (RBD) for host cell entry [6]. The S2 subunit regulates both receptor recognition and fusion of viral and cellular membranes [7]. Angiotensin-Converting Enzyme 2 (ACE2) functions as a receptor for SARS-CoV-2. This results in the simultaneous binding of two S-glycoprotein trimers to an ACE2 dimer [8,9]. The cleavage of S2 subunit induced after binding itself leads to activation and uncaptured irreversible conformational change of gylcoprotein, facilitating membrane fusion [10].

Host proteases activated by SARS-CoV-2, such as cathepsin B, factor X, elastase, TMPRSS2 (Transmembrane Protease Serine 2), furin, etc., enhance S-glycoprotein priming and thus cell entry [11,12], which is inhibited by a serine protease inhibitor, mesylate combined with E-64d, an athepsin L/B inhibitor [13]. Binding of SARS-CoV-2 to the extracellular domains of transmembrane ACE2 proteins leads to downregulation of ACE2 expression [14,15]. From this, threapeutic approaches have already been developed by blocking the binding of SARS-CoV-2 to ACE2 receptors via inhibition of the Receptor Binding Domain (RBD) of the viral S protein [16-18]. In myocardial biopsies from patients after fatal COVID infection, in addition to myocardial fibrosis, a reduction in myocardial ACE2 expression was detected [19]. Expression of the ACE2 receptor in the heart, lung, gastrointestinal tract, and kidney, in conjunction with dysregulation of the renin-angiotensin system caused by binding of SARS co-virus to this receptor, explains the multiorgan attack, which can be lethal in the presence of comorbidities such as coronary artery disease, COPD, and diabetes [20-28].

The expression of ACE2 at the endothelium of the entire gastrointestinal tract forms the basis for enteric SARS-CoV-2 infection, the severity of which is directly related to the expression of ACE-II receptor [29,30].

It is not uncommon for gastrointestinal symptoms to appear earlier than respiratory manifestations [31-34]. The loss of ACE2 associated with hyperactivation of the ACE/Ang II/AT1R (angiotensin II type 1 receptor) axis not infrequently leads to disruptions in the

integrity of the gastrointestinal-blood barrier, which may promote septic courses [30-34]. Recent studies suggest that it is the gastrointestinal tract of SARS-CoV-2 patients that acts as a starting point for recurrent infections [35,36]. Apart from direct effects of SARS-CoV-2 infection on the gut, preexisting and exacerbating lung disease indirectly affects the gut microbiome [37-40].

In addition, increased intestinal wall pathology as a consequence of Ang II-dependent hypertension has been demonstrated in both animal and human studies [41-43]. Similar pathologic gut wall changes have been noted in pulmonary diseases such as COPD and bronchial asthma [44-46]. Moreover, ACE-II deficiency may exacerbate intestinal wall pathology induced by diabetes mellitus in terms of dysbiosis associated with decreased levels of circulating angiogenic cells, hematopoietic cells with loss of reparative function, at least in animal models [47]. Thus, decreased enteric ACE2 expression induced by SARS-CoV-2 infection could similarly reduce circulating angiogenic cells and initiate the dysbiosis [47]. In the proteolysis and ectodomain shedding of ACE2, the membrane-bound protease TACE (TNF-α-converting enzyme), also known as ADAM-17 (A disintegrin and metalloproteinase 17), is of major importance [48-50].

The family of RAS consists of angiotensin-1-7(ANG (1-7), angiotensin-2-8 (ANG III), angiotensin-3-8 (ANG IV), and angiotensin-1-12 (ANG (1-12)). ANG (1-7), produced by the catalytic action of ACE2 on ANG II, abolishes the vasodilation induced by ANG II-AT1R. RAS angiotenins are of major importance insofar as ANG (1-9) arises from ANG-I through various carboxypeptidase enzymes such as carboxypeptidase A, cathepsin A, and ACE2. However, ANG represents a competitive inhibitor of ACE [51-60]. An important substrate for ADAM17 is Angiotensin-Converting Enzyme 2 (ACE2), cleavage of which by ADAM17 inactivates ACE2 itself, leading to reduced Ang (1-7) expression and increased angiotensin II retention [61-64]. This not only contributes to arterial hypertension but is involved in cardiovascular remodeling and other vascular diseases [65,66].

Angiotensin 1-7, through its protective effect by reducing oxidative stress and apoptosis, was able to reduce not only infarct size and neurological deficit after induced ischemia but also the risk of rupture of cerebral aneurysms in animal studies [67-78]. Because several studies have excluded a reduction in systolic arterial hypertension by Ang-1-7, the protective effect of Ang 1-7 cannot be related to the level of blood pressure [79-82]. Great importance is attached in the development of aneurysms not to the level of ACE-II expression but to the relative balance of AngII/Ang-(1-7) [83-86].

Deficiency of ACE2 promotes AngII-induced AAAs formation, which results from the reduction of Ang-(1-7) and consequently its protective effect [87,89]. Angiotensin type 1a receptors (AT1aR) are important for AngII-induced AAAs. Nevertheless, animal studies have demonstrated that AT1aR deficiency on endothelial cells and smooth muscle cells does not affect AngII-induced AAAs [89]. Future research will target cells that express ACE2 and control local angiotensin peptide concentrations [90]. Different mutations lead to increased plasma and tissue AngII levels via alterations in the expression level of ACE2 protein, resulting in cardiovascular disease [91-93]. The protective effect of Ang (1-7) on inflammation is achieved through inhibition of the resistin/Toll-like receptor 4 (TLR4)/MAPK/NF-kB signaling pathway. Indirectly, high variability of the TLR4 gene leads to the reduction of this protective effect [94-97].

Previous studies have found differential expression of ACE and ACE2 messengers in patients with thoracic aortic dissection and thoracic aneurysms, but a significant correlation to ACE I/D and ACE2 (A8790G) polymorphisms has not been demonstrated [98-101]. Thereby, the reports are very contradictory especially for ACE I/D polymorphism [101-105]. In abdominal aneurysms, a significant difference in genotype distribution and allele frequency was found only for ACE but not for AT1R and TGFBR1 polymorphisms. In this regard, the ACE DD genotype increased susceptibility to AAA, which was more significant when the ACE DD genotype and TGFBR1 6A allele were concurrent [106]. The influence of ACE DD genotype on the development of abdominal aortic anuerysms varies depending on ethnic origin. The association with CE I/D polymorphism occurred much more consistently [107-117].

A large study retrospectively examined the influence of 61 gene polymorphisms on BAA development. strong evidence was found for DAB2IP and LRP1, 9p21/CDKN2BAS, IL6R, LPA, LDLR, MMP3, and AGTR1 polymorphisms, and SORT1 [118-125]. Of course, a number of other polymorphisms and gene variants, such as the Marfan FBN1 gene on chromosome 15, transforming growth factor (TGF) β-signaling, play an important role in the development of the disease, TGFBR2, myosin heavy chain-11 (MYH11), and α-smooth muscle actin-2 (ACTA2) play a major role but are not the subject of this paper [126-130].

Conclusion

In summary, the role of ACE-II receptor as well as the RAS system goes far beyond blood pressure regulation. Its imbalance contributes to the pathophysiology and severity of cardiovascular disease. This role of the ACE-II receptor is either direct or indirect via ANg 1-7. Future research with RAS components based on nanotechnology opens new perspectives for the treatment of severe cardiovascular diseases.

Conflict of Interest

I hereby declare that there were no financial or other interests in the execution and evaluation of this work.

References

1. Shi S, Qin M, Shen B, Cai Y, Liu T, et al. (2020) Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 5(7): 802-810.

2. Guo T, Fan Y, Chen M, Wu X, Zhang L, et al. (2020) Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 5(7): 1-8.

3. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, et al. (2020) Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol 5(7): 819-824.

4. Li H, Liu L, Zhang D, Xu J, Dai H, et al. (2020) SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet 395(10235): 1517-1520.
5. Ruan Q, Yang K, Wang W, Jiang L, Song J (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 46(5): 846-848.
6. Tortorici MA, Veesler D (2019) Structural insights into coronavirus entry. Adv Virus Res 105: 93-116.
7. Yan R, Zhang Y, Li Y, Xia L, Guo Y, et al. (2020) Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 367(6485): 1444-1448.
8. Gallagher TM, Buchmeier MJ (2001) Coronavirus spike proteins in viral entry and pathogenesis. Virology 279(2): 371-374.
9. Simmons G, Zmora P, Gierer S, Heurich A, Pohlmann S (2013) Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research. Antiviral Res 100(3): 605-614.
10. Millet JK, Whittaker GR (2015) Host cell proteases: Critical determinants of coronavirus tropism and pathogenesis. Virus Res 202:120-134.
11. Yang J, Petitjean SJL, Koehler M, Zhang Q, Dumitru AC, et al. (2020) Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor. Nat Commun 4541.
12. Silva JS, Costa GD, Wang H, Ahmed S, Sun X, et al. (2017) Blunting of cardioprotective actions of estrogen in female rodent heart linked to altered expression of cardiac tissue chymase and ACE2. J Renin Angiotensin Aldosterone Syst 18(3): 1470320317722270.
13. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, et al. (2003) Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 426: 450-454.
14. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, et al. (2020) Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 181(2): 281-292.
15. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, et al. (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579: 270-273.
16. Wang K, Gheblawi M, Oudit GY (2020) Angiotensin converting enzyme 2: A double-edged sword. Circulation 142(5): 426-428.
17. Liu Y, Yang Y, Zhang C, Huang F, Wang F, et al. (2020) Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 63(3): 364-374.
18. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, et al. (2020) Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system celebrating the 20th anniversary of the discovery of ACE2. Circ Res 126(10): 1456-1474.
19. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, et al. (2009) SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest 39(7): 618-625.
20. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, et al. (2020) The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak-an update on the status. Mil Med Res 7(1): 11.
21. Lu R, Zhao X, Li J, Niu P, Yang B, et al. (2020) Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet 395(10224): 565-574.
22. Lau ST, Yu WC, Mok NS, Tsui PT, Tong WL, et al. (2005) Tachycardia amongst subjects recovering from severe acute respiratory syndrome (SARS). Int J Cardiol 100(1): 167-169.
23. Desai A, Boursiquot BC, Melki L, Wan EY (2021) Management of arrhythmias associated with COVID-19. Curr Cardiol Rep Curr Cardiol Rep 23(1): 2.
24. Wang D, Hu B, Hu C, Zhu F, Liu X, et al. (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 323(11): 1061-1069.
25. Guan WJ, Ni ZY, Hu Y (2020) China medical treatment expert group for Covid-19. N Engl J Med 382: 1708-1720.
26. Clerkin KJ, Fried JA, Raikhelkar J, Sayer J, Griffin JM, et al. (2020) Coronavirus disease 2019 (COVID-19) and cardiovascular disease. Circulation 141(20): 1648-1655.
27. Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, et al. (2012) ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature 487: 477-481.
28. Duan Y, Prasad R, Feng D, Beli E, Calzi SL, et al. (2019) Bone marrow-derived cells restore functional integrity of the gut epithelial and vascular barriers in a model of diabetes and ACE2 deficiency. Circ Res 125(11): 969-988.
29. Chan JF, Yuan S, Kok KH, To KKW, Chu H, et al. (2020) A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. Lancet 395(10223): 514-523.
30. Cheng PK, Wong DA, Tong LK, Ip SM, Lo ACT, et al. (2004) Viral shedding patterns of coronavirus in patients with probable severe acute respiratory syndrome. Lancet 363: 1699-1700.
31. Leung WK, To KF, Chan PK, Chan HLY, Wu AKL, et al. (2003) Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. Gastroenterology 125: 1011-1017.
32. Zhou J, Li C, Zhao G, Chu H, Wang D, et al. (2017) Human intestinal tract serves as an alternative infection route for Middle East respiratory syndrome coronavirus. Sci Adv 3(11): eaao4966.
33. Yeoa C, Kaushala S, Yeoa D (2020) Enteric involvement of coronaviruses: Is faecal-oral transmission of SARS-CoV-2 possible?. Lancet Gastroenterol Hepatol 5(4): 335-337.
34. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, et al. (2004) Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 203: 631-637.
35. Beli E, Yan Y, Moldovan L, Vieira CP, Gao R, et al. (2018) Restructuring of the gut microbiome by intermittent fasting prevents retinopathy and prolongs survival in *db/db* mice. Diabetes 67(9): 1867-1879.
36. Vallianou NG, Stratigou T, Tsagarakis S (2018) Microbiome and diabetes: Where are we now? Diabetes Res Clin Pract 146: 111-118.
37. Budden KF, Gellatly SL, Wood DL, Cooper MA, Morrison M, et al. (2017) Emerging pathogenic links between microbiota and the gut-lung axis. Nat Rev Microbiol 15(1): 55-63.
38. Iyer SN, Lu D, Katovich MJ, Raizada MK (1996) Chronic control of high blood pressure in the spontaneously hypertensive rat by delivery of angiotensin type 1 receptor antisense. Proc Natl Acad Sci USA 93(18): 9960-9965.
39. Santisteban MM, Qi Y, Zubcevic J, Kim S, Yang T, et al. (2017) Hypertension-linked pathophysiological alterations in the gut. Circ Res 120: 312-323.
40. Qi Y, Goel R, Kim S, Richards EM, Carter CS, et al. (2017) Intestinal permeability biomarker zonulin is elevated in healthy aging. J Am Med Dir Assoc 18: 810.e1-810.e4.
41. Sharma RK, Yang T, Oliveira AC, Lobaton GO, Aquino V, et al. (2019) Microglial cells impact gut microbiota and gut pathology in angiotensin II-induced hypertension. Circ Res 124: 727-736.
42. Syvanen M (2003) Churning out safer microbes for drug delivery. Nat Biotechnol 21(7): 758-759.

43. Steidler L (2003) Genetically engineered probiotics. Best Pract Res Clin Gastroenterol 17: 861-876.

44. Bron PA, Kleerebezem M (2018) Lactic acid bacteria for delivery of endogenous or engineered therapeutic molecules. Front Microbiol 9: 1821.

45. Black RA, Rauch CT, Kozlosky CJ, Peschon JJ, Slack JL, et al. (1997) A metalloproteinase disintegrin that releases tumour-necrosis factor-alpha from cells. Nature 385(6618): 729-733.

46. Moss ML, Jin SL, Milla ME, Bickett DM, Burkhart W, et al. (1997) Cloning of a disintegrin metalloproteinase that processes precursor tumour-necrosis factor-alpha. Nature 385(6618): 733-736.

47. Black RA, White JM (1998) ADAMs: Focus on the protease domain. Curr Opin Cell Biol 10(5): 65465-65469.

48. Balakumar P, Jagadeesh G (2014) A century old renin-angiotensin system still grows with endless possibilities: AT1 receptor signaling cascades in cardiovascular physiopathology. Cell Signal 26(10): 2147-2160.

49. Chappell MC (2016) Biochemical evaluation of the renin-angiotensin system: the good, bad, and absolute? Am J Physiol Heart Circ Physiol 310: H137-H152.

50. Carey RM (2013) Newly discovered components and actions of the renin-angiotensin system. Hypertension 62: 818-822.

51. Coutinho DC, Foureaux G, Rodrigues KD, Salles RLA, Moraes PL, et al. (2014) Cardiovascular effects of angiotensin A: A novel peptide of the renin-angiotensin system. J Renin Angiotensin Aldosterone Syst 15: 480-486.

52. Ferreira AJ, Santos RA, Bradford CN, Mecca AP, Sumners C, et al. (2020) Therapeutic implications of the vasoprotective axis of the renin-angiotensin system in cardiovascular diseases. Hypertension 55(2): 207-213.

53. Ferrario CM (2010) New physiological concepts of the renin-angiotensin system from the investigation of precursors and products of angiotensin I metabolism. Hypertension 55(2): 445-452.

54. Haulica I, Bild W, Serban DN (2005) Angiotensin peptides and their pleiotropic actions. J Renin Angiotensin Aldosterone Syst 6(3): 121-131.

55. Jankowski V, Vanholder R, van der Giet M, Tölle M, Karadogan S, et al. (2007) Mass-spectrometric identification of a novel angiotensin peptide in human plasma. Arterioscler Thromb Vasc Biol 27(2): 297-302.

56. Ocaranza MP, Michea L, Chiong M, Lagos CF, Lavandero S, et al. (2014) Recent insights and therapeutic perspectives of angiotensin-(1-9) in the cardiovascular system. Clin Sci (Lond) 127(9): 549-557.

57. Pessôa SB, van der Lubbe N, Verdonk K, Roks AJ, Hoorn EJ, et al. (2012) Key developments in renin-angiotensin-aldosterone system inhibition. Nat Rev Nephrol 9(1): 26-36.

58. Reiss K, Saftig P (2009) The "a disintegrin and metalloprotease" (ADAM) family of sheddases: Physiological and cellular functions. Semin Cell Dev Biol 20(2): 126-137.

59. Sriramula S, Haque M, Majid DS, Francis J (2008) Involvement of tumor necrosis factor-alpha in angiotensin II-mediated effects on salt appetite, hypertension, and cardiac hypertrophy. Hypertension 51(5): 1345-1351.

60. Zhang J, Patel MB, Griffiths R, Mao A, Song YS, et al. (2014) Tumor necrosis factor-α produced in the kidney contributes to angiotensin II-dependent hypertension. Hypertension 64(6): 1275-1281.

61. Kroetsch JT, Levy AS, Zhang H, Aschar-Sobbi R, Lidington D, et al. (2017) Constitutive smooth muscle tumour necrosis factor regulates microvascular myogenic responsiveness and systemic blood pressure. Nat Commun 8: 14805.

62. Xia H, Sriramula S, Chhabra KH, Lazartigues E (2013) Brain angiotensin-converting enzyme type 2 shedding contributes to the development of neurogenic hypertension. Circ Res 113(9): 1087-1096.

63. Xu J, Sriramula S, Xia H, Moreno-Walton L, Culicchia F, et al. (2017) Clinical relevance and role of neuronal AT1Receptors in ADAM17-mediated ACE2 shedding in neurogenic hypertension. Circ Res 121(1): 43-55.

64. Silva PRA, Kung DK, Mitchell IJ, Alenina N, Bader M, et al. (2014) Angiotensin 1-7 reduces mortality and rupture of intracranial aneurysms in mice. Hypertension 64(2): 362-368.

65. Sampaio WO, Henrique de Castro C, Santos RA, Schiffrin EL, Touyz RM (2007) Angiotensin-(1-7) counterregulates angiotensin II signaling in human endothelial cells. Hypertension 50(6): 1093-1098.

66. Su Z, Zimpelmann J, Burns KD (2006) Angiotensin-(1-7) inhibits angiotensin II-stimulated phosphorylation of map kinases in proximal tubular cells. Kidney Int 69(12): 2212-2218.

67. McCollum LT, Gallagher PE, Ann Tallant E (2012) Angiotensin-(1-7) attenuates angiotensin II-induced cardiac remodeling associated with upregulation of dual-specificity phosphatase 1. Am J Physiol Heart Circ Physiol 302(3): 801-810.

68. Pena Silva RA, Heistad DD (2014) Promising neuroprotective effects of the angiotensin-(1-7)-angiotensin-converting enzyme 2-mas axis in stroke. Exp Physiol 99(2): 342-343.

69. Jiang T, Gao L, Shi J, Lu J, Wang Y, et al. (2013) Angiotensin-(1-7) modulates renin-angiotensin system associated with reducing oxidative stress and attenuating neuronal apoptosis in the brain of hypertensive rats. Pharmacol Res 67(1): 84-93.

70. Jiang T, Gao L, Zhu XC, Yu JT, Shi JQ, et al. (2013) Angiotensin-(1-7) inhibits autophagy in the brain of spontaneously hypertensive rats. Pharmacol Res 71: 61-68.

71. Jiang T, Gao L, Guo J, Lu J, Wang Y, et al. (2012) Suppressing inflammation by inhibiting the NF-κB pathway contributes to the neuroprotective effect of angiotensin-(1-7) in rats with permanent cerebral ischaemia. Br J Pharmacol 167(7): 1520-1532.

72. Mecca AP, Regenhardt RW, O'Connor TE, Joseph JP, Raizada MK, et al. (2011) Cerebroprotection by angiotensin-(1-7) in endothelin-1-induced ischaemic stroke. Exp Physiol 96: 1084-1096.

73. Regenhardt RW, Desland F, Mecca AP, Pioquinto DJ, Afzal A, et al. (2013) Anti-inflammatory effects of angiotensin-(1-7) in ischemic stroke. Neuropharmacology 71: 154-163.

74. Regenhardt RW, Mecca AP, Desland F, Chinni PFR, Ludin JA, et al. (2014) Centrally administered angiotensin-(1-7) increases the survival of stroke-prone spontaneously hypertensive rats. Exp Physiol 99(2): 442-453.

75. Benter IF, Ferrario CM, Morris M, Diz DI (1995) Antihypertensive actions of angiotensin-(1-7) in spontaneously hypertensive rats. Am J Physiol 269: 313-319.

76. Costa Ma, Ma LV, Gomez Ka, Nakagawa P, Peña C, et al. (2010) Angiotensin-(1-7) upregulates cardiac nitric oxide synthase in spontaneously hypertensive rats. Am J Physiol Heart Circ Physiol 299(4): H1205-H1211.

77. Grobe JL, Mecca AP, Lingis M, Shenoy V, Boloton TA, et al. (2007) Prevention of angiotensin II-induced cardiac remodeling by angiotensin-(1-7). Am J Physiol Heart Circ Physiol 292(2): 736-742.

78. Grobe JL, Mecca AP, Mao H, Katovich MJ (2006) Chronic angiotensin-(1-7) prevents cardiac fibrosis in doca-salt model of hypertension. Am J Physiol Heart Circ Physiol 290(6): 2417-2423.

79. Iyer SN, Averill DB, Chappell MC, Yamada K, Allred AJ, et al. (2000) Contribution of angiotensin-(1-7) to blood pressure regulation in salt-depleted hypertensive rats. Hypertension 36(3): 417-422.

80. Santos RAS, Simoes e Silva AC, Maric C, Silva DMR, Machado RP, et al. (2003) Angiotensin-(1-7) is an endogenous ligand for the g protein-coupled receptor Mas. Proc Natl Acad Sci USA 100: 8258-8263.

81. Shenoy V, Ferreira AJ, Qi Y, Silva RAF, Freire CD, et al. (2010) The angiotensin-converting enzyme 2/angiogenesis-(1-7)/mas axis confers cardiopulmonary protection against lung fibrosis and pulmonary hypertension. Am J Respir Crit Care Med 182(8): 1065-1072.

82. Tesanovic S, Vinh A, Gaspari TA, Casley D, Widdop RE (2010) Vasoprotective and atheroprotective effects of angiotensin (1-7) in apolipoprotein e-deficient mice. Arterioscler Thromb Vasc Biol 30(8): 1606-1613.

83. Ferreira AJ, Bader M, Santos RA (2012) Therapeutic targeting of the angiotensin-converting enzyme 2/angiotensin-(1-7)/Mas cascade in the renin-angiotensin system: A patent review. Expert Opin Ther Pat 22(5): 567-574.

84. Rateri DL, Moorleghen JJ, Knight V, Balakrishnan A, Howatt DA, et al. (2012) Depletion of endothelial or smooth muscle cell-specific angiotensin ii type 1a receptors does not influence aortic aneurysms or atherosclerosis in ldl receptor deficient mice. PLoS One 7(12): e51483.

85. Cassis LA, Rateri DL, Lu H, Daugherty A (2007) Bone marrow transplantation reveals that recipient AT1a receptors are required to initiate angiotensin II-induced atherosclerosis and aneurysms. Arterioscler Thromb Vasc Biol 27(2): 380-386.

86. Wysocki J, Ye M, Soler MJ, Gurley SB, Xiao HD, et al. (2006) ACE and ACE2 activity in diabetic mice. Diabetes 55(7): 2132-2139.

87. Yamamoto K, Ohishi M, Katsuya T, Ito N, Ikushima M, et al. (2006) Deletion of angiotensin-converting enzyme 2 accelerates pressure overload-induced cardiac dysfunction by increasing local angiotensin II. Hypertension 47(4): 718-726.

88. Rabelo LA, Todiras M, Souza NV, Qadri F, Szijártó IA, et al. (2016) Genetic deletion of ACE2 induces vascular dysfunction in C57BL/6 mice: Role of nitric oxide imbalance and oxidative stress. PLoS One 11(4): e0150255.

89. Eden JS, Rockett R, Carter I, Rahman H, de Ligt J, et al. (2020) An emergent clade of SARS-CoV-2 linked to returned travellers from Iran. Virus Evolution 6(1).

90. Santos SHS, Andrade JMO, Fernandes LR, Sinisterra RDM, Sousa FB, et al. (2013) Oral Angiotensin-(1-7) prevented obesity and hepatic inflammation by inhibition of resistin/TLR4/MAPK/NF-κB in rats fed with high-fat diet. Peptides 46: 47-52.

91. Ioana M, Ferwerda B, Farjadian S, Ioana L, Ghaderi A, et al. (2012) High variability of TLR4 gene in different ethnic groups in Iran. Innate Immun 18(3): 492-502.

92. Totura AL, Whitmore A, Agnihothram S, Schäfer A, Katze MG, et al. (2015) Toll-like receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. mBio 6(3).

93. Li Y, Hu J, Qian H, Gu J, Meng W, et al. (2014) Novel findings: Expression of angiotensin-converting enzyme and angiotensin-converting enzyme 2 in thoracic aortic dissection and aneurysm. J Renin Angiotensin Aldosterone Syst 16(4): 1130-1134.

94. Tiret L, Rigat B, Visvikis S, Breda C, Corvol P, et al. (1992) Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin I-converting enzyme (ACE) gene controls plasma ACE levels. Am J Hum Genet 51(1): 197-205.

95. Rigat B, Hubert C, Corvol P, Soubrier F (1992) PCR detection of the insertion/deletion polymorphism of the human angiotensin converting enzyme gene (DCP1) (dipeptidyl carboxypeptidase 1). Nucl Acids Res 20(6): 1433.

96. Zhong J, Yan Z, Liu D, Ni Y, Zhoa Z, et al. (2006) Association of angiotensin-converting enzyme 2 gene A/G polymorphism and elevated blood pressure in Chinese patients with metabolic syndrome. J Lab Clin Med 147(2): 91-95.

97. Kalay N, Caglayan O, Hetal A, Ozdogru I, Dogan A, et al. (2009) The deletion polymorphism of the angiotensin-converting enzyme gene is associated with acute aortic dissection. Tohoku J Exp Med 219(1): 33-37.

98. Jing Q, Wang X, Ma Y, Yang M, Huang G, et al. (2013) Angiotensin-converting enzyme I/D polymorphism and the risk of thoracic aortic dissection in Chinese Han population. Mol Biol Rep 40(2): 1249-1254.

99. Huang LG, Liu DB, Wang HQ (2014) Angiotensin-converting enzyme I/D polymorphism and aortic aneurysm risk: A meta-analysis. Interact Cardiovasc Thorac Surg 19(5): 782-787.

100. Tangurek B, Ketenci B, Ozay B, Ozer N, Yilmaz H, et al. (2008) Lack of association between angiotensin converting enzyme gene polymorphism and type I aortic dissection. J Intl Med Res 36(4): 714-720.

101. Lucarini L, Sticchi E, Sofi F, Pratesi G, Pratesi C, et al. (2009) ACE and TGFBR1 genes interact in influencing the susceptibility to abdominal aortic aneurysm. Atherosclerosis 202(1): 205-210.

102. Song Y, Miao R, Wang H, Qin X, Zhang Y, et al. (2015) Meta-analysis of the association between angiotensin-converting enzyme I/D polymorphism and aortic aneurysm risk. J Renin Angiotensin Aldosterone Syst 16(4): 1125-1129.

103. Pola R, Gaetani E, Santoliquido A, Gerardino L, Cattani P, et al. (2001) Abdominal aortic aneurysm in normotensive patients: Association with angiotensin-converting enzyme gene polymorphism. Eur J Vasc Endovasc Surg 21(5): 445-449.

104. Fatini C, Pratesi G, Sofi F, Pratesi C, Gensini GF, et al. (2005) ACE DD genotype: A predisposing factor for abdominal aortic aneurysm. Eur J Vasc Endovasc Surg 29(3): 227-232.

105. Jones GT, Thompson AR, van Bockxmeer FM, Hafez H, Cooper JA, et al. (2008) Angiotensin II type 1 receptor 1166C polymorphism is associated with abdominal aortic aneurysm in three independent cohorts. Arterioscler Thromb Vasc Biol 28(4): 764-770.

106. Korcz A, Stecyna JM, Gabriel M, Drabarczyk MZ, Pawlaczyk K, et al. (2009) Angiotensin-converting enzyme (ACE, I/D) gene polymorphism and susceptibility to abdominal aortic aneurysm or aortoiliac occlusive disease. J Surg Res 153(1): 76-82.

107. Obukofe B, Sayers RD, Thompson J, Sandford RM, London NJM, et al. (2010) Is there an association between angiotensin converting enzyme (ACE) genotypes and abdominal aortic aneurysm? Eur J Vasc Endovasc Surg 40(4): 457-460.

108. Lesauskaite V, Marsalkiene SG, Tamosiunas A, Benetis R (2011) Protective effects of angiotensin-converting enzyme I/I and matrix metalloproteinase-3 6A/6A polymorphisms on dilatative pathology within the ascending thoracic aorta. Eur J Cardiothorac Surg 40(1): 23-27.

109. Foffa I, Murzi M, Mariani M, Mazzone AM, Glauber M, et al. (2012) Angiotensin-converting enzyme insertion/deletion polymorphism is a risk factor for thoracic aortic aneurysm in patients with bicuspid or tricuspid aortic valves. J Thorac Cardiovasc Surg 144(2): 390-395.

110. Pisano C, Maresi E, Balistreri CR, Candore G, Merlo D, et al. (2012) Histological and genetic studies in patients with bicuspid aortic valve and ascending aorta complications. Interact Cardiovasc Thorac Surg 14(3): 300-306.

111. Balistreri CR, Pisano C, Candore G, Maresi E, Codispoti M, et al. (2013) Focus on the unique mechanisms involved in thoracic aortic aneurysm formation in bicuspid aortic valve versus tricuspid aortic valve patients: Clinical implications of a pilot study. Eur J Cardiothorac Surg 43(6): 180-186.

112. Bradley DT, Badger SA, McFarland M, Hughes AE (2016) Abdominal aortic aneurysm genetic associations: Mostly false? A systematic review and meta-analysis. Eur J Vasc Endovasc Surg 51(1): 64-75.

113. Yoon S, Tromp G, Vongpunsawad S, Ronkainen A, Juvonen T, et al. (1999) Genetic analysis of MMP3, MMP9, and PAI-1 in Finnish patients with abdominal aortic or intracranial aneurysms. Biochem Bioph Res Com 265(2): 563-568.

114. Helgadottir A, Gretarsdottir S, Thorleifsson G, Holm H, Pattel RS, et al. (2012) Apolipoprotein(a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism. J Am Coll Cardiol 60(8): 722-729.

115. Gretarsdottir S, Baas AF, Thorleifsson G, Holm H, Heijer MD, et al. (2010) Genome-wide association study identifies a sequence variant within the DAB2IP gene conferring susceptibility to abdominal aortic aneurysm. Nat Genet 42: 692-697.

116. Bown MJ, Jones GT, Harrison SC, Wright BJ, Bumpstead S, et al. (2011) Abdominal aortic aneurysm is associated with a variant in low-density lipoprotein receptor-related protein 1. Am J Hum Genet 89: 619-627.

117. Harrison SC, Smith AJP, Jones GT, Swerdlow DI, Rampuri R, et al. (2012) Interleukin 6 receptor pathways in abdominal aortic aneurysm. Eur Heart J 34(48): 3707-3716.

118. Jones GT, Bown MJ, Gretarsdottir S, Romaine SPR, Helgadottir A, et al. (2013) A sequence variant associated with Sortilin-1 (SORT1) on 1p13.3 is independently associated with abdominal aortic aneurysm. Hum Mol Genet 22(14): 2941-2947.

119. Helgadottir A, Thorleifsson G, Magnusson KP, Grétarsdottir S, Steinthorsdottir V, et al. (2008) The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. Nat Genet 40(2): 217-224.

120. Pannu H, Fadulu TV, Papke CL, Scherer S, Liu Y, et al. (2007) MYH11 mutations result in a distinct vascular pathology driven by insulin-like growth factor 1 and angiotensin II. Hum Mol Genet 16(20): 2453-2462.

121. Guo DC, Pannu H, Fadulu TV, Papke CL, Yu RK, et al. (2007) Mutations in smooth muscle α-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. Nat Genet 39(12): 1488-1493.

122. Guo DC, Regalado ES, Gong L, Duan X, Cortez RLPS, et al. (2016) LOX mutations predispose to thoracic aortic aneurysms and dissections. Circ Res 118(6): 928-934.

123. Guo DC, Gong L, Regalado ES, Cortez RLPS, Zhao R, et al. (2015) MAT2A mutations predispose individuals to thoracic aortic aneurysms. Am J Hum Genet 96(1): 170-177.

124. Regalado ES, Guo DC, Villamizar C, Avidan N, Gilchrist D, et al. (2011) Exome sequencing identifies SMAD3 mutations as a cause of familial thoracic aortic aneurysm and dissection with intracranial and other arterial aneurysms. Circ Res 109(6): 680-686.

125. Guo DC, Regalado E, Casteel DE, Cortez RLPS, Gong L, et al. (2013) Recurrent gain-of-function mutation in PRKG1 causes thoracic aortic aneurysms and acute aortic dissections. Am J Hum Genet 93(2): 398-404.

126. Guo DC, Regalado ES, Minn C, Fadulu VT, Coney J, et al. (2011) Familial thoracic aortic aneurysms and dissections identification of a novel locus for stable aneurysms with a low risk for progression to aortic dissection. Circ Cardiovasc Genet 4(1): 36-42.

127. Kuang SQ, Martinez MO, Guo DC, Gong L, Regalado ES, et al. (2016) FOXE3 mutations predispose to thoracic aortic aneurysms and dissections. J Clin Invest 126(3): 948-961.

128. Regalado E, Medrek S, Fadulu VT, Guo DC, Pannu H, et al. (2011) Autosomal dominant inheritance of a predisposition to thoracic aortic aneurysms and dissections and intracranial saccular aneurysms. Am J Med Genet A 155A(9): 2125-2130.

129. Milewicz DM, Regalado E (1993) Thoracic aortic aneurysms and aortic dissections. In Gene Reviews® Pagon RA, Adam MP, Ardinger HH (Eds.), University of Washington, Seattle, USA.

130. Milewicz DM, Regalado ES (2015) Use of genetics for personalized management of heritable thoracic aortic disease: How do we get there? J Thorac Cardiovasc Surg 149(2): 3-5.