The role of angiotensin-converting enzyme 2 in coronaviruses/influenza viruses and cardiovascular disease

Li Chen and Guang Hao

1Georgia Prevention Institute, Department of Medicine, Medical College of Georgia, Augusta University, Augusta, Georgia, USA; and 2Department of Epidemiology, School of Medicine, Jinan University, Guangzhou 510632, China

Abstract

Angiotensin-converting enzyme 2 (ACE2) has emerged as a key regulator of the renin–angiotensin system in cardiovascular (CV) disease and plays a pivotal role in infections by coronaviruses and influenza viruses. The present review is primarily focused on the findings to indicate the role of ACE2 in the relationship of coronaviruses and influenza viruses to CV disease. It is postulated that the risk of coronavirus or influenza virus infection is high, at least partly due to high ACE2 expression in populations with a high CV risk. Coronavirus and influenza virus vaccine usage in high CV risk populations could be a potential strategy to prevent both CV disease and coronavirus/influenza virus infections.

Keywords

Angiotensin-converting enzyme 2 • Cardiovascular disease • Coronaviruses • Influenza viruses

Background

The renin–angiotensin system (RAS) plays a critical role in maintaining normal cardiovascular (CV) functions and contributes to a spectrum of CV diseases, such as hypertension, coronary heart disease, myocarditis, and congestive heart failure.1 Generally, the RAS is composed of angiotensinogen, renin, angiotensin II (Ang II), Ang II receptors (AT1 and AT2 receptors), and angiotensin-converting enzyme (ACE).2,3 ACE is ubiquitously present in many cell types, tissues, and organs. ACE is an ectoenzyme that plays a role in the generation of Ang II by catalysing the extracellular conversion of the decapeptide Ang I.4 In the past two decades, a new homologue of the enzyme, termed angiotensin-converting enzyme 2 (ACE2), was identified, and ACE2 can convert Ang II to Ang(1-7) or convert Ang I to Ang(1-9).5,6 Although Ang II increases blood pressure (BP), Ang(1-7) is a vasodilator, and the ACE2/Ang(1-7) axis has been suggested to act as a natural damping mechanism for the activation of the classical RAS.7

Besides its crucial role in CV disease, ACE2 has also been considered as a functional potential coronavirus [including severe acute respiratory syndrome (SARS) coronavirus, human coronavirus NL63 (HCoV-NL63), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also called 2019-nCoV] receptor that binds directly to the viral spike protein.8–11 In addition, ACE2 plays an important role in acute lung injury induced by influenza viruses, such as H1N1, H5N1, and H7N9,12–14 suggesting that ACE2 still has unexpected facets with clinical implications.

CV diseases are the most common non-communicable diseases globally.15 In addition, emerging viral infections also represent a major global public health concern,16–18 such as coronavirus disease 2019 (COVID-19, caused by SARS-CoV-2) in China19 and 2009 H1N1 in the USA and Canada.20 ACE2 could be a novel therapeutic target for CV diseases and a potential target for the treatment of coronaviruses and influenza viruses. The present review is primarily focused on the findings indicating the role of ACE2 in the relationship of coronaviruses and influenza viruses to CV disease (Figure 1).

Coronaviruses/influenza viruses and CV diseases

Both influenza viruses and coronaviruses are typically contagious viruses that cause respiratory disease. Coronaviruses are members of the subfamily Coronavirinae, in the Coronaviridae family and the Nidovirales order, including four genera—Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus.21 Coronaviruses cause respiratory and intestinal infections in animals and humans. They were not considered to be highly pathogenic to humans until the outbreak of SARS in 2003. Six human-infecting types of coronaviruses were discovered before 2019. Two highly pathogenic viruses [SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV)] cause severe respiratory syndromes in humans, and the other four human coronaviruses (HCoV-NL63,
In atherosclerosis-prone apolipoprotein E knockout mice, ACE2 deficiency results in augmented vascular inflammation, and the inactivation of ACE2 by short hairpin RNA has been shown to decrease BP and improve cardiac function with inhibition of cardiac and renal fibrosis in spontaneously hypertensive rats.50 The key role of ACE2 in the progressive deterioration of cardiac remodelling and systolic dysfunction has further been found in humans.51 Circulating ACE2 activity increases with increasing vascular tone, which suggests that elevated ACE2 may be a compensatory response to hypertension.52 Ohtsuki et al. reported that the up-regulation of the ACE2 gene in the left ventricular myocardium of patients with severe heart failure was associated with the degree of left ventricular dilation and may thereby constitute an important adaptive mechanism to retard the progression of adverse left ventricular remodelling.53 Studies with recombinant human ACE2 have shown beneficial cardiac effects.49,50

ACE2 and CV disease

ACE2 has emerged as a key regulator of the RAS.19 Increasing evidence suggests that ACE2 plays a protective role in CV disease and other pathologies.49 In atherosclerosis-prone apolipoprotein E knockout mice, ACE2 deficiency results in augmented vascular inflammation, and the inflammatory response contributes to increased atherosclerotic plaque formation.41 In animal studies, Sarkissian et al. found that cardiac overexpression of ACE2 exerted a protective influence on the heart during myocardial infarction by preserving cardiac function, left ventricular wall motion, and contractility.42 Yamamoto et al. reported that ACE2 gene knockdown resulted in severe cardiac dysfunction (i.e. reduced contractility, increased hypertrophy, and dilation).43 In addition, ACE inhibitors and AT1 receptor antagonists, which have been proven to be beneficial for the treatment of myocardial infarction and heart failure, increase ACE2 gene expression, attenuate ACE2 gene down-regulation, and normalize AT1 receptor expression in the myocardium post-myocardial infarction.34–46 Loss of ACE2 enhances adverse remodelling and susceptibility to pressure and volume overload.54 Human recombinant ACE2 suppresses myocardial hypertrophy, fibrosis, inflammation, and BP.47 Feng et al. reported that ACE2 overexpression reduced Ang II-induced cardiac hypertrophy partially through a decrease in sympathetic drive in syn-hACE2 transgenic mice.48 Wysocki et al. found that, during Ang II infusion, recombinant human ACE2 effectively degraded Ang II and, in the process, normalized BP.49 One of the ACE2 activators, xanthone, has been demonstrated to decrease BP and improve cardiac function with inhibition of cardiac and renal fibrosis in spontaneously hypertensive rats.50 The key role of ACE2 in the progressive deterioration of cardiac remodelling and systolic dysfunction has further been found in humans.51 Circulating ACE2 activity increases with increasing vascular tone, which suggests that elevated ACE2 may be a compensatory response to hypertension.52 Ohtsuki et al. reported that the up-regulation of the ACE2 gene in the left ventricular myocardium of patients with severe heart failure was associated with the degree of left ventricular dilation and may thereby constitute an important adaptive mechanism to retard the progression of adverse left ventricular remodelling.53 Studies with recombinant human ACE2 have shown beneficial cardiac effects.49,50

Coronaviruses/influenza viruses and ACE2

Human ACE2 is an endothelium-bound carboxymonoepitopeptide with a single active site catalytic region whose expression is limited mainly to endothelial cells of the arteries, arterioles, and venules in various organs including the heart, lungs, and kidneys.52 Loss of ACE2 leads to age-
dependent cardiomyopathy and kidney disease, while also enhancing pulmonary, cardiac, and renal injuries. On the other hand, ACE2 was identified as a functional SARS coronavirus receptor. ACE2 and the AT2 receptor protect mice from SARS coronavirus-induced acute respiratory distress syndrome, whereas ACE, Ang II, and the AT1a receptor promote the impairment of lung function in mice models. Kuba et al. provided the genetic proof that ACE2 is a crucial SARS-CoV receptor in vivo, and SARS-CoV infections and the spike protein of SARS-CoV reduce ACE2 expression. This study also found that blocking the renin–angiotensin pathway can attenuate the worsened acute lung injury induced by the injection of SARS-CoV spike protein in mice. Furthermore, antibodies directed against ACE2 and soluble ACE2 molecules and derivatives were demonstrated to be capable of blocking SARS-CoV infection. Like SARS-CoV, HCoV-NL63 also employs ACE2 as a receptor for cellular entry. Wevers and Hoek found that HCoV-NL63 infection induced a reduction of cellular ACE2 expression. Tseng et al. demonstrated that transgenic mice expressing hACE2 were highly susceptible to SARS-CoV infection, resulting in a wide spectrum of clinical manifestations, including death, depending upon the transgenic lines. Letko and Munster first demonstrated that SARS-CoV-2 used the same cell entry receptor, ACE2, as SARS-CoV, and subsequent studies also confirmed this result.

In experimental mouse models, Zou et al. found that infection with highly pathogenic avian influenza A H5N1 virus results in a down-regulation of ACE2 expression in the lung and increased serum Ang II levels. Genetic inactivation of ACE2 causes severe lung injury in H5N1-challenged mice, confirming the role of ACE2 in H5N1-induced lung pathologies. Yang et al. reported that ACE2 could mediate the severe acute lung injury induced by influenza A (H7N9) virus infection in an experimental mouse model. Moreover, ACE2 deficiency worsened the disease pathogenesis markedly, mainly by targeting the AT1 receptor. This result is consistent with a study by Huang et al., who found that plasma Ang II levels were linked to H7N9-induced disease severity and predicted a fatal outcome in H7N9 patients. Myocardial injury has been observed during coronavirus infection. Pulmonary infection with human SARS-CoV in mice led to an ACE2-dependent myocardial infection, and myocardial damage was found in patients who had SARS-CoV in their hearts. Thus, the use of cardio-protective medications is essential. The effects of ACE inhibitor (ACEI) treatment during coronaviruses/influenza virus infections in humans is unclear. However, angiogenic activity against SARS-CoV and SARS-CoV-2 in vitro. Hu et al. identified N-(2-aminoethyl)-1 aziridine-ethanamine as a novel ACE2 inhibitor that was effective in blocking the SARS coronavirus spike protein-mediated cell fusion. A case study found that treatment with an ACEI together with plasma exchange improved the condition of a patient with scleroderma renal crisis complicated with thrombotic microangiopathy triggered by influenza B virus infection. Another case study of a woman positive for H1N1 and with severe acute left ventricular failure found that aggressive initial therapy followed by beta-blockers and ACEIs led to restoration of the patient’s left ventricular function and an associated marked improvement in symptoms. Angiotensin II receptor blockers (ARBs), a first-line therapy of hypertension, could inhibit the actions of Ang II through selective binding of AT1 receptors in vascular smooth muscle, and are effective in lowering BP and preventing major CV outcomes. Previous studies suggest that ARBs could up-regulate ACE2 in both rats and humans. A recent commentary suggested that ARB could be used as a therapy for reducing the aggressiveness and mortality from coronavirus infections. There is now an urgent need to study the effect of ACEI and ARB treatment during coronavirus/influenza virus infections in humans.

Coronavirus/influenza virus vaccines and CV disease prevention

Vaccination constitutes the primary approach for controlling influenza. In recent decades, numerous advances have been made in the development of vaccines against influenza viruses, such as the replacement of inactivated whole-virus vaccines with split or subunit vaccines, which comprise less reactogenic alternatives. The majority of available annual trivalent influenza vaccines contain two influenza A strains (H1N1 and H3N2) and only one influenza B virus. More recently, inactivated quadrivalent vaccines containing both Victoria and Yamagata lineages of type B IV have become available. Several epidemiological and clinical studies have demonstrated the beneficial effects of the influenza vaccine in patients with CV disease. In a meta-analysis of randomized clinical trials, Udell et al. reported that the use of the influenza vaccine was associated with a lower risk of major adverse CV events. In another meta-analysis including eight trials with 12,029 participants, Clar et al. reported that influenza vaccination may reduce CV mortality and combined CV events in patients with CV disease. Furthermore, a recent meta-analysis including six cohort studies and 179,158 participants also confirmed that influenza vaccination was associated with a significant decrease in all-cause mortality in patients with heart failure.

To date, no vaccine has been developed to prevent SARS-CoV-2 or other coronavirus infections. Scientists across the world are racing to develop a vaccine, which is also a promising tool to prevent CV disease, for the coronavirus to tackle the outbreak of COVID-19.

Conclusions and future prospects

A role for ACE2 in involvement in vascular protective actions has been postulated. We therefore hypothesize that the risk of coronavirus or influenza virus infection is high among the CV disease-susceptible population, at least partly due to high ACE2 expression in this population, which needs to be confirmed in the future. Our hypotheses suggest that more protection should be employed for patients with CV disease. Coronavirus or influenza virus vaccine usage in the high CV risk population could be a potential strategy to prevent both CV disease and coronavirus/influenza virus infections. Furthermore, there is an urgent need to develop a vaccine for coronavirus prevention and control, and it will be important to evaluate the effect of coronavirus vaccines on CV protection.

Conflict of interest: none declared.

References

1. Wu CH, Mohammadmoradi S, Chen JZ, Sawada H, Daugherty A, Lu HS. Renin-angiotensin system and cardiovascular functions. Arterioscler Thromb Vasc Biol 2018;38:e108-e116.
2. Lu H, Cassis LA, Kooi CW, Daugherty A. Structure and functions of angiotensinogen. Hypertens Res 2016;39:492–500.
3. Dostal DE, Baker KM. The cardiac renin-angiotensin system: conceptual, or a regulator of cardiac function? Circ Res 1999;85:443-450.
4. Fleming I. Signaling by the angiotensin-converting enzyme. Circ Res 2006;98:887–896.
5. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE, Acton S. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res 2000;87:e1–e9.
26. Salamatbakhsh M, Mobaraki K, Sadeghimohammadi S, Ahmadzadeh J. The global burden of COVID-19 and its impact on the global burden of neurological disease. Nat Rev Neurol 2020;16:875–879.

27. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, Si H-R, Zhu Y, Li B, Huang C, et al. Clinical features of 199 novel coronavirus infections in Wuhan, China. Nat Med 2020;26:854–859.

28. Zou Z, Yan Y, Shu Y, Gao R, Sun Y, Li X, Ju X, Liang Z, Liu Q, Zhuo Y, Guo F, Bai T, Han Z, Zhu J, Zhou H, Huang F, Li F, Li H, Li N, Li D, Jin N, Penninger JM, Jiang C. Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. Nat Commun 2014;5:3594.

29. Yang P, Gu H, Zhao Z, Wang W, Cao B, Lai C, Yang X, Zhang L, Duan Y, Zhang S, Chen W, Zhen W, Cai M, Penninger JM, Jiang C. Wang X. Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. Sci Rep 2014;4:7027.

30. Liu X, Yang N, Tang J, Liu S, Luo D, Qian X, Wang X. Downregulation of angiotensin-converting enzyme 2 by the neuraminidase protein of influenza A (H1N1) virus. Virus Res 2014;185:64–71.

31. Zhao P, Yang X-L, Wang X-G, Gu H, Zhu B, Zhang L, Zhang W, Shi H-R, Zhu Y, Li B, Huang C-L, Chen H-D, Chen J, Luo Y, Guo H, Jiang R-D, Liu M-Q, Chen Y, Shen X-R, Wang Z, Zheng X-S, Zhao K, Chen QJ, Deng F, Liu L-L, Yan B, Zhan F-X, Wang Y-Y, Xiao G-F, Shi Z-L. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. bioRxiv 2020;2020.2020.02.19:4952.

32. Munoz LS, Garcia MA, Gordon-Lippin E, Parra B, Pardo CA. Emerging viral infections and their impact on the global burden of neurological disease. Semin Neurol 2018;38:163–175.

33. Liu L, Zhang M, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, Alabdullatif M, Rather P, et al. Clinical aspects of pandemic 2009 influenza A (H1N1) virus. Nat Rev Microbiol 2009;7:112–120.

34. Wysocki J, Ye M, Rodriguez E, Gonzalez-Pacheco FR, Barrios C, Evora K, Schuster RK, Lamkins AJ, Gubala V, Ostrov DA, Raizada MK. Structure-based identification of angiotensin II-dependent inhibitors of angiotensin-converting enzyme 2. J Biol Chem 2016;291:7018–7029.

35. Parajuli N, Ramprasath T, Patel VB, Wang W, Putko B, Mori J, Oudit GY. Targeting angiotensin-converting enzyme 2: a central regulator for cardiovascular disease. Curr Hypertens Rep 2010;12:170–175.

36. Battle D, Wysocki J, Khan MS. Vascular angiotensin-converting enzyme 2: lord of the ring? Circ Res 2010;107:822–824.

37. Tikellis C, Bernardi S, Burns WC. Angiotensin-converting enzyme 2 as a new therapeutic target for cardiovascular disease. Can J Physiol Pharmacol 2009;87:507–513.

38. Chen N, Zhou M, Dong X, Qu J, Gong F, Lu Y, Qiu Y, Wang J, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–513.

39. Xia H, Lazartiges E. Angiotensin-converting enzyme 2: central regulator for cardiovascular disease. Curr Hypertens Rep 2010;12:170–175.

40. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Ocaranza MP, Godoy I, Jalil JE, Varas M, Collantes P, Pinto M, Roman M, Ramirez C, Copaja M, Diaz-Araya G, Castro P, Lavandero S. Enalapril attenuates downregulation of angiotensin-converting enzyme 2 in the late phase of ventricular dysfunction in myocardial infarcted rat. Hypertension 2006;48:572–578.

41. Tikellis C, Bernardi S, Burns WC. Angiotensin-converting enzyme 2 from a regulatory and therapeutic perspective. Curr Opin Nephrol Hypertens 2011;20:62–68.

42. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, Alabdullatif M, Rather P, et al. Clinical aspects of pandemic 2009 influenza A (H1N1) virus. Nat Med 2009;15:222–233.

43. Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: is there a causal relationship? Heart 2002;87:712–716.

44. Madjid M, Aboshady I, Awan I, Litovsky S, Casscells SW. Influenza and cardiovascular disease: is there a causal relationship? Tex Heart Inst J 2004;31:8–13.

45. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Ocaranza MP, Godoy I, Jalil JE, Varas M, Collantes P, Pinto M, Roman M, Ramirez C, Copaja M, Diaz-Araya G, Castro P, Lavandero S. Enalapril attenuates downregulation of angiotensin-converting enzyme 2 in the late phase of ventricular dysfunction in myocardial infarcted rat. Hypertension 2006;48:572–578.

46. Parajuli N, Ramprasath T, Patel VB, Wang W, Putko B, Mori J, Oudit GY. Targeting angiotensin-converting enzyme 2 as a new therapeutic target for cardiovascular diseases. Can J Physiol Pharmacol 2014;92:558–565.

47. Parajuli N, Ramprasath T, Patel VB, Wang W, Putko B, Mori J, Oudit GY. Targeting angiotensin-converting enzyme 2 as a new therapeutic target for cardiovascular diseases. Can J Physiol Pharmacol 2014;92:558–565.

48. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005;112:2650–2610.

49. Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB, Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. Hypertension 2004;43:970–976.

50. Parulji N, Ramprasaath T, Patel VB, Wang W, Putko B, Mori J, Oudit GY. Targeting angiotensin-converting enzyme 2 as a new therapeutic target for cardiovascular diseases. Can J Physiol Pharmacol 2014;92:558–565.

51. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005;112:2650–2610.

52. Parulji N, Ramprasaath T, Patel VB, Wang W, Putko B, Mori J, Oudit GY. Targeting angiotensin-converting enzyme 2 as a new therapeutic target for cardiovascular diseases. Can J Physiol Pharmacol 2014;92:558–565.

53. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005;112:2650–2610.

54. Parulji N, Ramprasaath T, Patel VB, Wang W, Putko B, Mori J, Oudit GY. Targeting angiotensin-converting enzyme 2 as a new therapeutic target for cardiovascular diseases. Can J Physiol Pharmacol 2014;92:558–565.
55. Han DP, Penn-Nicholson A, Cho MW. Identification of critical determinants on ACE2 for SARS-CoV entry and development of a potent entry inhibitor. Virology 2006;350:15–25.

56. Dijkstra R, Jebeink MF, Dejis M, Milewska A, Pyrc K, Buelow E, van der Bijl A, van der Hoek L. Replication-dependent downregulation of cellular angiotensin-converting enzyme 2 protein expression by human coronavirus NL63. J Gen Virol 2012;93:1924–1929.

57. Wevers BA, Hoek Lvd. Renin–angiotensin system in human coronavirus pathogenesis. Future Virol 2010;5:145–161.

58. Tseng CT, Huang C, Newman P, Wang N, Narayanay K, Watts DM, Makino S, Packard MM, Zaki SR, Chan TS, Peters CJ. Severe acute respiratory syndrome coronavirus infection of mice transgenic for the human angiotensin-converting enzyme 2 virus receptor. J Virol 2007;81:1162–1173.

59. San Y, Wang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. J Virol 2020:10.1128/JVI.00127-20.

60. Hoffmann M, Kleine-Weber H, Krüger N, Müller M, Drosten C, Pöhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. bioRxiv 2020:2020.2001.2031.929942.

61. Bao L, Deng W, Huang B, Gao H, Ren L, Wei Q, Yu P, Xu Y, Liu J, Qi F, Qu Y, Wang W, Li F, Lv Q, Xue J, Gong S, Liu M, Wang G, Wang S, Zhao L, Liu P, Zhao L, Ye F, Wang H, Zhou W, Zhu N, Zhen W, Yu H, Zhang X, Song Z, Guo L, Chen L, Wang C, Wang Y, Wang X, Xiao Y, Sun Q, Li H, Zhu F, Ma C, Yan L, Yang M, Han J, Xu W, Tan W, Peng X, Lin Q, Wu G, Qin C. The pathogenicity of 2019 novel coronavirus in NACE2 transgenic mice. bioRxiv 2020:2020.2002.2007.939389.

62. Huang F, Guo J, Zou Z, Liu J, Cao B, Zhang S, Li H, Wang W, Sheng M, Liu S, Pan J, Bao C, Zeng M, Xiao H, Qian G, Hu X, Chen Y, Chen Y, Zhao Y, Liu Q, Zhou H, Zhu J, Gao H, Yang S, Liu X, Zheng X, Yang J, Diao H, Cao H, Wu Y, Zhao M, Tan S, Guo D, Zhang X, Ye Y, Wu W, Xu Y, Penninger JM, Li D, Gao GF, Jiang C, Li L. Angiotensin II plasma levels are linked to disease severity and predict fatal outcomes in H7N9-infected patients. Nat Commun 2014;5:3595.

63. Peng YD, Meng K, Guan HQ, Leng L, Zhu RR, Wang BY, He MA, Cheng LX, Huang K, Zeng QT. [Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV]. Zhongguo xin xue guan bing za zhi 2020;48:E004.

64. He XW, Lai J, Jiang D, Wang MW, Li Y, Xiao ZC, Xu C, Li SS, Zeng HS. [Impact of complicated myocardial injury on the clinical outcome of severe or critically ill COVID-19 patients]. Zhongguo xin xue guan bing za zhi 2020;48:E011.

65. Lei C, Fu W, Qian K, Li T, Zhang S, Ding M, Hu S. Potent neutralization of 2019 novel coronavirus by recombinant ACE2-Ig. bioRxiv 2020:2020.2001.2007.939976.

66. Huentelman MJ, Zubcevic J, Hernandez Prada JA, Xiao X, Dimitrov DS, Raizada MK, Ostrov DA. Structure-based discovery of a novel angiotensin-converting enzyme 2 inhibitor. Hypertension 2004;44:903–906.

67. Shimizu T, Iwamoto N, Okamoto M, Endo Y, Tsuji S, Takata A, Igawa T, Umeda M, Fukui S, Sumiyoshi R, Kitamura M, Koga T, Kawashima SY, Ichinose K, Tamai M, Nalamra H, Onguchi T, Nakamura H, Origuchi T, Nishino T, Kawakami A. Scleroderma renal crisis complicates with thrombotic microangiopathy triggered by influenza B virus infection. Intern Med 2019;58:641–445.

68. Constopoulos C, Benson A, Prasad S, Ghuran A. Diagnostic dilemmas in cardiology. BMJ Case Rep 2012;doi:10.1136/bcr-2012-006521.

69. Burnier M. Angiotensin II type 1 receptor blockers. Circulation 2001;103:904–912.

70. Salvador GL, Marmentini VM, Cosma WR, Junior EL. Angiotensin-converting enzyme inhibitors reduce mortality compared to angiotensin receptor blockers: systematic review and meta-analysis. Eur J Prev Cardiol 2017;24:1914–1924.

71. Klimas J, Olvedy M, Odchindov-Mazkovicova K, Kruzliak P, Carayiannis A, Markevich S, Krtiscek F, Krenke P, Ochonickij P. Perinatally administered losartan augments renal ACE2 expression but not cardiac or renal Mas receptor in spontaneously hypertensive rats. J Cell Mol Med 2015;19:1965–1974.

72. Furushashi M, Miyawaki N, Mitaka T, Fuseya T, Ishimura S, Ohno K, Shibata S, Tanaka M, Watanabe Y, Akazaka H, Ohnishi H, Yoshida H, Takazawa H, Sato S, Ura N, Shimamoto K, Mura T. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. Am J Hypertens 2015;28:15–21.

73. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res 2020:10.1002/ddr.21656.

74. Trucchi C, Paganino C, Amicizia D, Orsi A, Tisa V, Piazza MF, Icardi G, Ansaloni F. Universal influenza virus vaccines: what needs to happen next? Expert Opin Biol Ther 2019;16:671–683.

75. Tisa V, Barberis I, Faccio V, Paganino C, Trucchi C, Martini M, Ansaloni F. Quadrivalent influenza vaccine: a new opportunity to reduce the influenza burden. J Prev Med Hyg 2016;57:E28–E33.

76. Rudenko L, Kneleve I, Krolokola E, Stepanova E, Rokston A, Donina S, Pizarrova M, Grigorjeva E, Kryshen K, Mushkynan A, Makarov M, Sparrow EG, Torelli G, Kieny MP. Rationale for vaccination with trivalent or quadrivalent live attenuated influenza vaccines: protective vaccine efficacy in the ferret model. PLoS One 2018;13:e0208028.

77. Ambrose CS, Levin MJ. The rationale for quadrivalent influenza vaccines. Hum Vaccin Immunother 2012;8:81–88.

78. Wu HH, Chang YY, Kuo SC, Chen YT. Influenza vaccination and secondary prevention of cardiovascular disease among Taiwanese elders—a propensity score-matched follow-up study. PLoS One 2019;14:e0219172.

79. Fukuta H, Goto T, Wakami K, Kamiya T, Ohbe N. The effect of influenza vaccination on mortality and hospitalization in patients with heart failure: a systematic review and meta-analysis. Heart Fail Rev 2019;24:109–114.

80. Udell JA, Zsivi R, Bhatt DL, Keshkar-Jarvimi M, Gaughan F, Phrommintikul A, Ciszewski A, Valoli H, Hoffman EB, Farkouh ME, Cannon CP. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. JAMA 2013;310:1711–1720.

81. Clar C, Oseni Z, Flowers N, Keshkar-Jarvimi M, Rees K. Influenza vaccines for preventing cardiovascular disease. Cochrane Database Syst Rev 2015;5:CD005050.

82. Rodrigues BS, David C, Costa J, Ferreira JJ, Pinto F, Caldeira D. Influenza vaccination in patients with heart failure: a systematic review and meta-analysis of observational studies. Heart 2020;106:350–357.