European Journal of Internal Medicine

The spike effect of acute respiratory syndrome coronavirus 2 and coronavirus disease 2019 vaccines on blood pressure☆

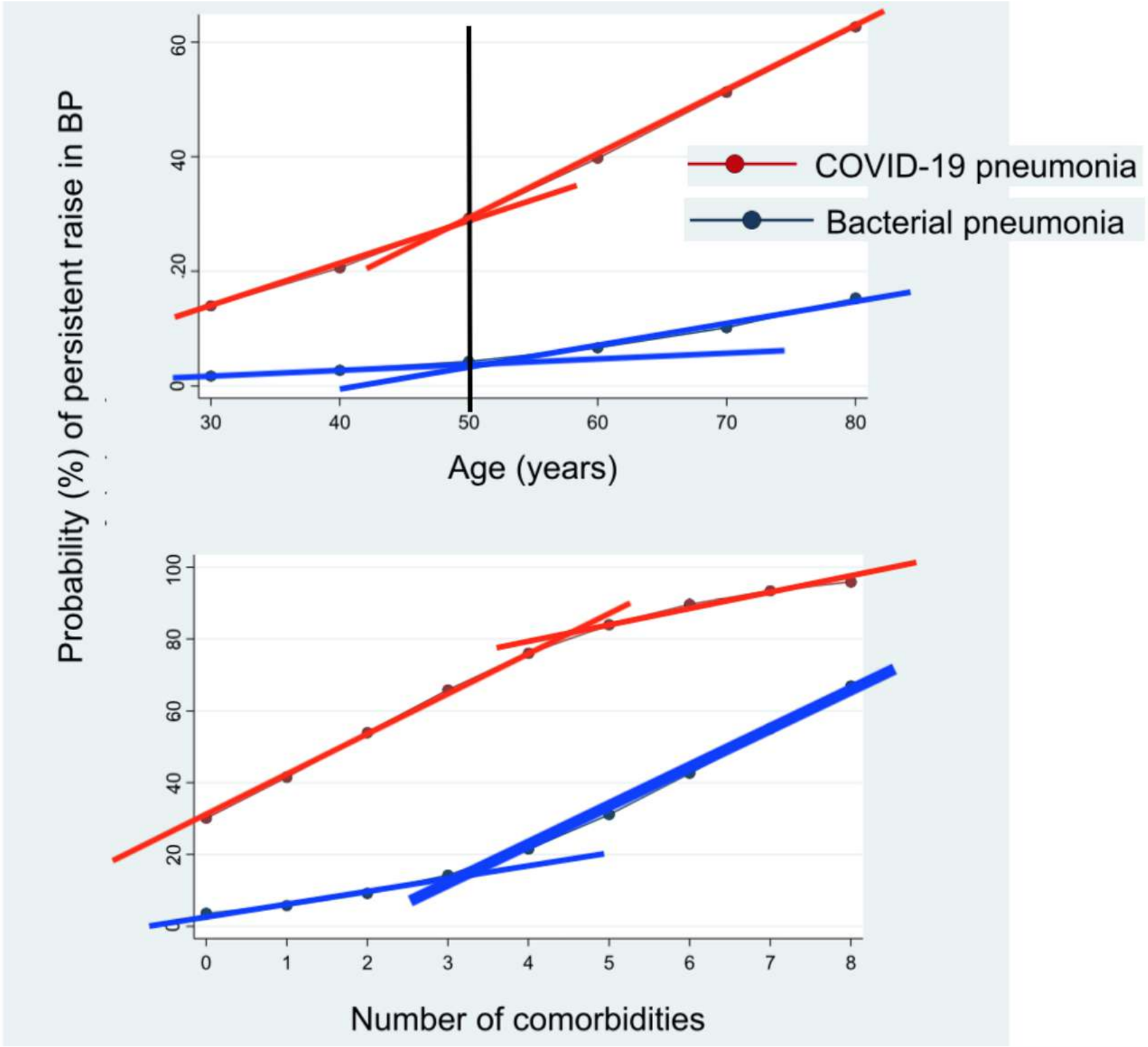
coronavirus disease 2019 vaccines on blood pressure☆

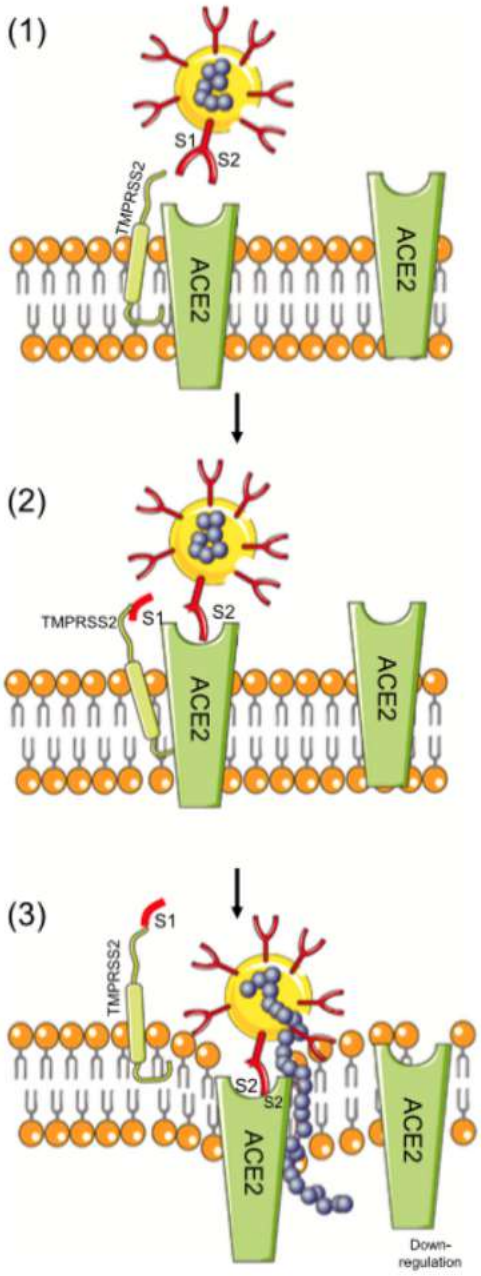
Fabio Angeli [a,b,*], Martina Zappa [a], Gianpaolo Reboldi [c], Giorgio Gentile [d], Monica Trapasso [e], Antonio Spanevello [a,b], Paolo Verdecchia [f]

ABSTRACT

Among the various comorbidities potentially worsening the clinical outcome in patients hospitalized for the acute respiratory syndrome coronavirus-2 (SARS-CoV-2), hypertension is one of the most prevalent. However, the basic mechanisms underlying the development of severe forms of coronavirus disease 2019 (COVID-19) among hypertensive patients remain undefined and the direct association of hypertension with outcome in COVID-19 is still a field of debate.

Experimental and clinical data suggest that SARS-CoV-2 infection promotes a rise in blood pressure (BP) during the acute phase of infection. Acute increase in BP and high in-hospital BP variability may be tied with acute organ damage and a worse outcome in patients hospitalized for COVID-19. In this context, the failure of the counter-regulatory renin-angiotensin-system (RAS) axis is a potentially relevant mechanism involved in the raise in BP. It is well recognized that the efficient binding of the Spike (S) protein to angiotensin converting enzyme 2 (ACE2) receptors mediates the virus entry into cells. Internalization of ACE2, downregulation and malfunction predominantly due to viral occupation, dysregulates the protective RAS axis with increased generation and activity of angiotensin (Ang) II and reduced formation of $Ang_{1,7}$. Thus, the imbalance between Ang II and Ang_{1-7} can directly contribute to excessively rise BP in the acute phase of SARS-CoV-2 infection. A similar mechanism has been postulated to explain the raise in BP following COVID-19 vaccination ("Spike Effect" similar to that observed during the infection of SARS-CoV-2). S proteins produced upon vaccination have the native-like mimicry of SARS-CoV-2 S protein's receptor binding functionality and prefusion structure and free-floating S proteins released by the destroyed cells previously targeted by vaccines may interact with ACE2 of other cells, thereby promoting ACE2 internalization and degradation, and loss of ACE2 activities.


Probability (%) of persistent raise in BP
0
20
40
60
30
40
50
60
70
80
Age (years)
COVID-19 pneumonia
Bacterial pneumonia
0
20
40
60
80
100
0
1
2
3
4
5
6
7
8
Number of comorbidities



First step:
the N-terminal portion of the viral protein unit S1 binds to a pocket of the ACE2 receptor.

Second step:
protein cleavage between the S1 and S2 units, operated by the receptor transmembrane protease serine 2 (TMPRSS2; structurally contiguous to ACE2 receptor).

Third step:
after the cleavage of the viral protein by TMPRSS2, the viral S2 unit undergoes a conformational rearrangement driving the fusion between the viral and cellular membrane, with subsequent entry of the virus into cell, release of its content, replication, and infection of other cells.

Fig. 3. Steps of SARS-CoV-2 entry process. The main step after the invasion of SARS-CoV-2 is binding to membranal ACE2 receptor; see text for details. **Legend:** ACE2=angiotensin-converting enzyme 2 receptor.

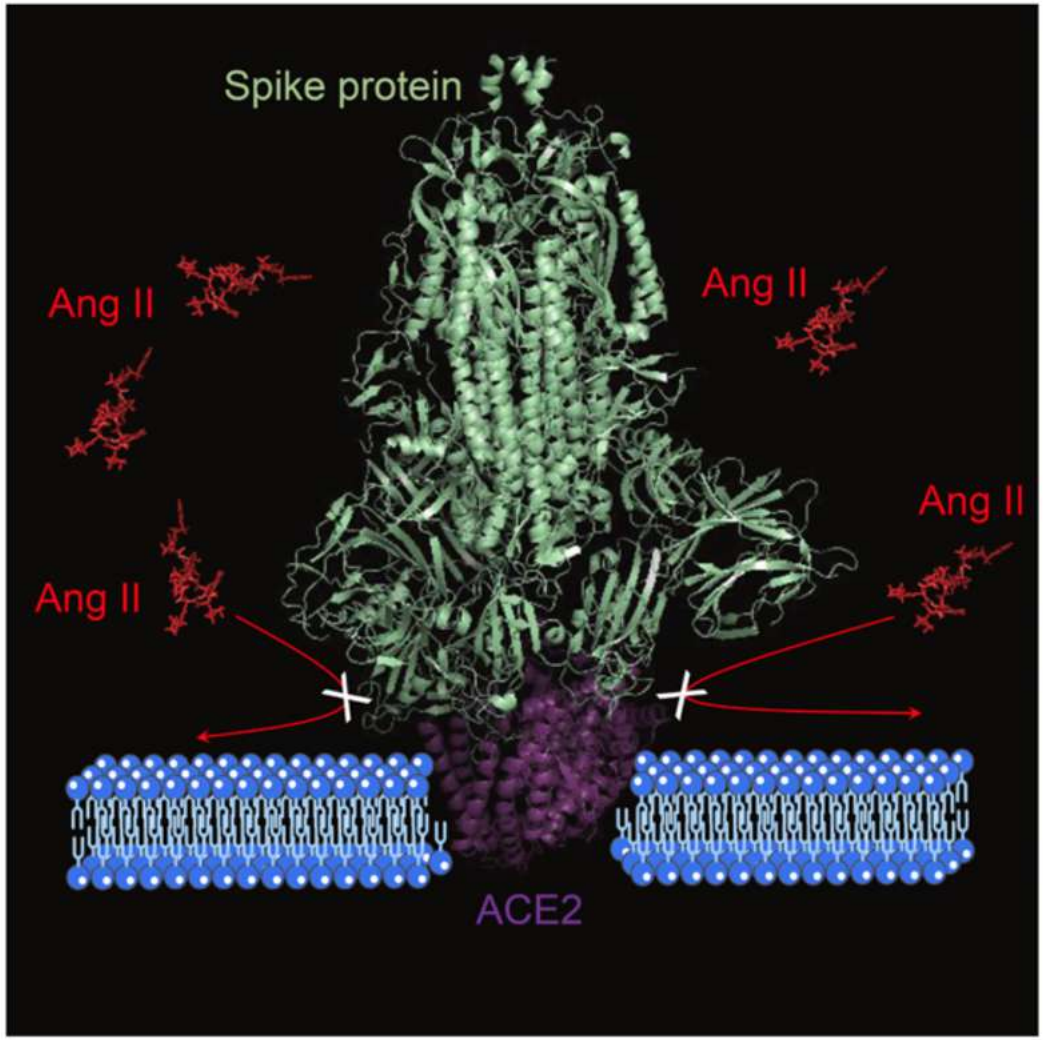


Fig. 5. The effect of binding of the Spike protein to ACE2 on the dysregulation of the renin-angiotensin system with increased generation and activity of Ang II (loss of ACE2 activity). **Legend:** ACE2=angiotensin-converting enzyme 2 receptor; Ang=angiotensin.

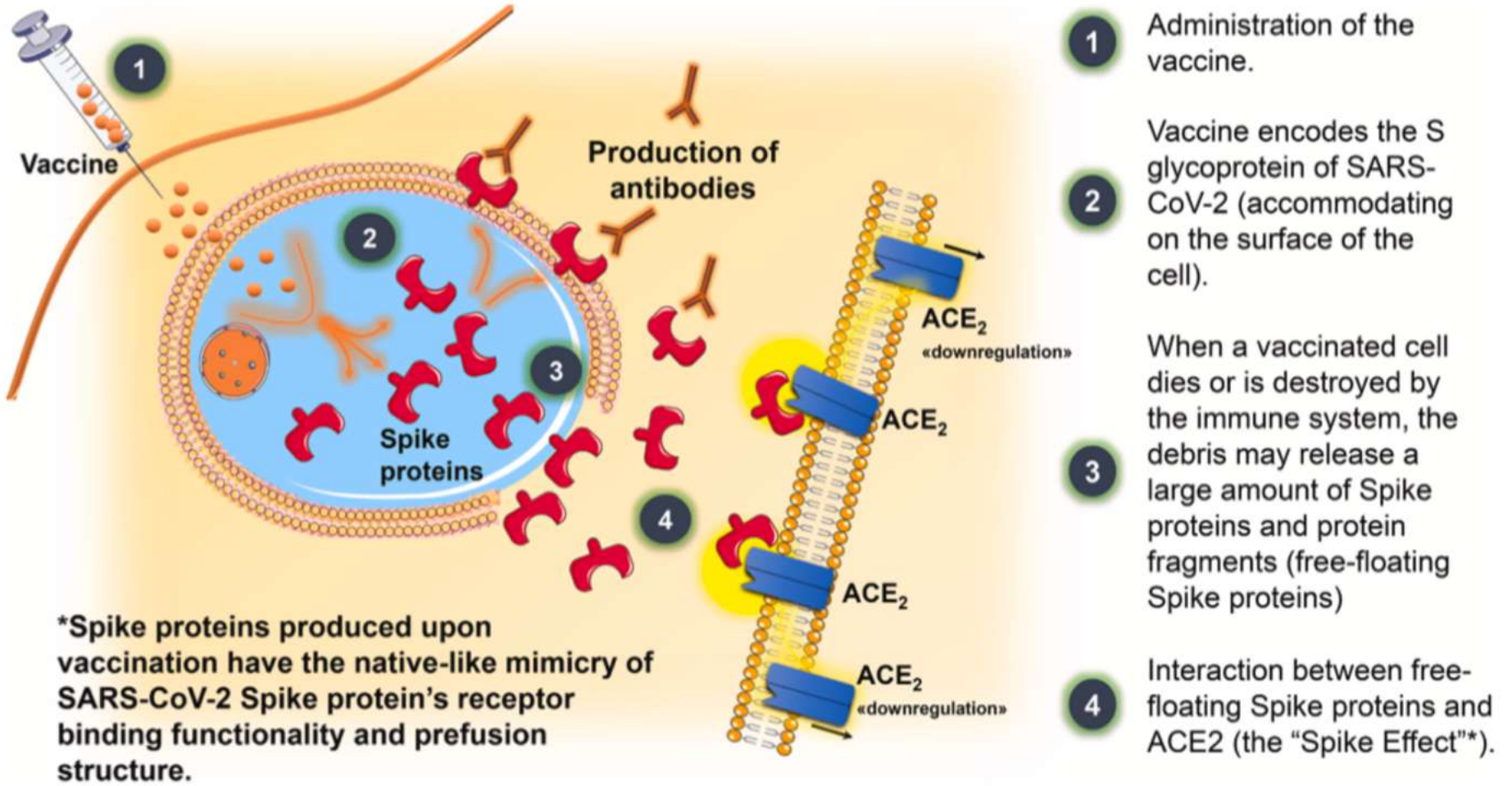


Fig. 6. Schematic mechanism of action of COVID-19 vaccines and their potential cardiovascular effects throughout the interaction between free-floating Spike proteins and ACE2 receptors. **Legend:** ACE2=angiotensin-converting enzyme 2 receptor; SARS-CoV-2= severe acute respiratory syndrome coronavirus-2.

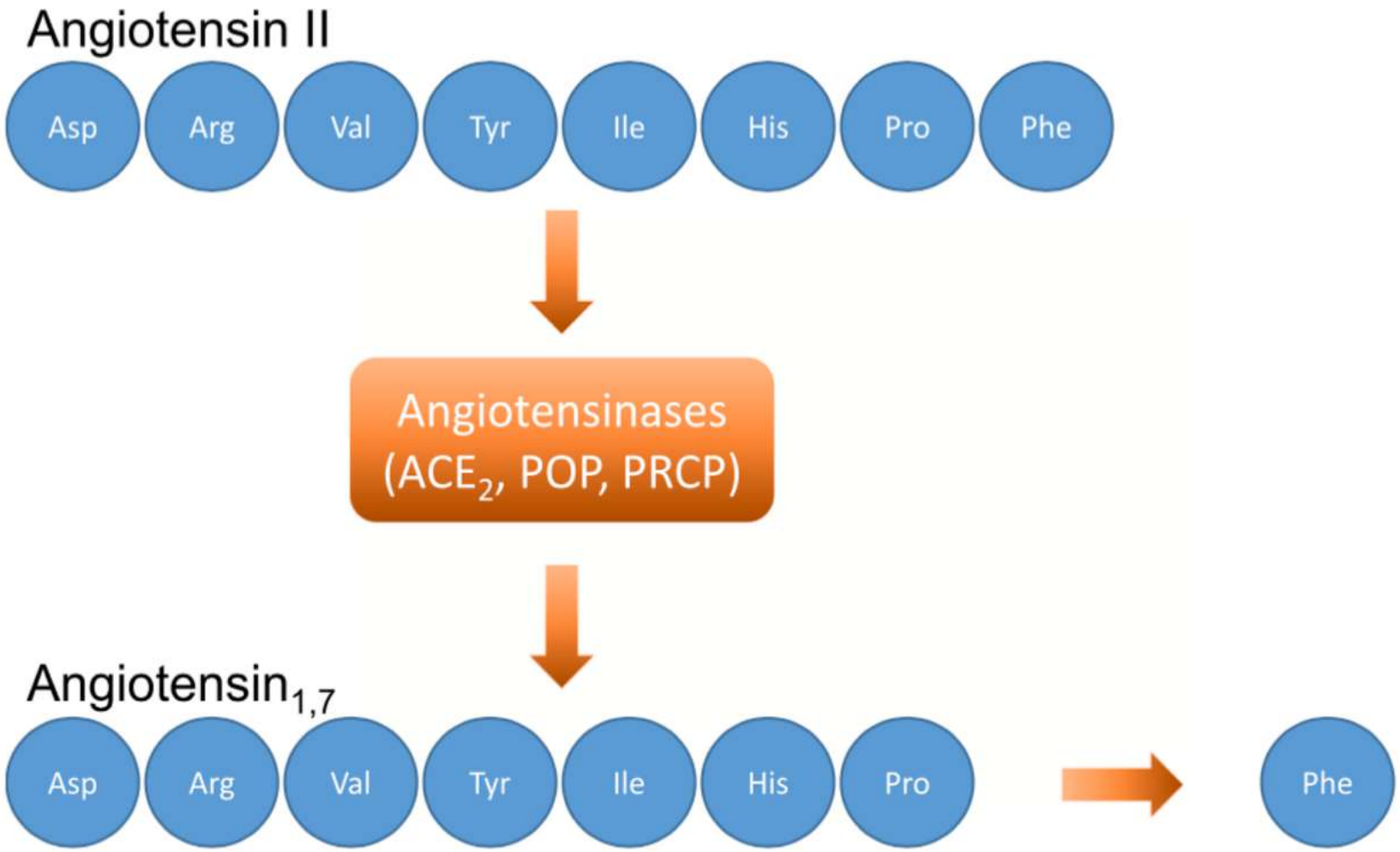


Fig. 4. Angiotensin$_{1,7}$ formation. Angiotensin$_{1,7}$ is formed by the action of the angiotensin-converting enzyme 2 (and other angiotensinases, including POP and PRCP) by the cleavage of an amino acid from Angiotensin II. **Legend:** ACE2=angiotensin-converting enzyme 2 receptor; POP=prolyl oligopeptidase; PRCP=prolyl carboxypeptidases.