

**Table SI.** The most common renin-angiotensin system-related disorders

Disorders	Mechanism	Reference
<i>Cardiovascular</i>		
Hypertension	↑ ACE/Ang II/ AT1 axis, ↑ ACE2/Ang (1-7)/Mas axis	Han W et al., 2020 (65)
Heart failure	↓ AT1 receptor, ↑ cytokines and NO	Kurabayashi M et al., 1997 (66)
Post-MI	↑ Ang II; interstitial fibrosis, hypertrophy of myocardium ↑ Ang II; ROS; enlarge infarct size	Sun Y., 2010 (67)
OSAS	Hypoxia; ↑ RAS; ↑ muscle atrophy and fibrosis	Ahmad M et al., 2017 (68)
<i>Cerebrovascular</i>		
Stroke	↑ Ang II/AT1 axis; HT-induced pathology ↑ Ang II/AT1 axis (brain); vasoconstriction, proinflammatory, profibrotic and oxidative stress in the parenchyma	Saavedra JM, 2017 (69) Arroja MM et al., 2016 (70)
<i>Renal</i>		
Chronic kidney disease	↑ RAAS activity; ↑ sodium retention; ↑ blood pressure	Mishima E et al., 2019 (71)
<i>Metabolic</i>		
Diabetes mellitus	↑ SNS hyperactivity; ↑ renin; sodium retention, vasoconstriction ↑ SNS hyperactivity; ↓ muscle blood flow; ↓ glucose uptake	Thorp AA et al., 2015 (72)
Metabolic syndrome	IR; ↑ insulin; SNS overactivity ↑ RAAS; ↑ circulating plasma volume, sodium retention Intra-abdominal adipocytes; ↑ Angiotensinogen, aldosterone	Hausberg M et al., 1995 (73) Tanaka M, 2020 (74) Thorp AA et al., 2015 (72)
<i>Pulmonary</i>		
COPD	Chronic hypoxia, proinflammatory mediators in the lung (e.g. IL-6, TNF-α); ↑ Ang II/AT1 axis, ↑ ACE activity, ↑ AT1 receptor; bronchoconstriction, fibrosis, vasoconstriction and endothelial dysfunction	Vasileiadis IE et al., 2018 (75)
<i>Neurodegenerative</i>		
Alzheimer's disease	↓ Ang IV; ↓ AT4 receptor ↓ Ang (1-7)/Mas axis	Kehoe PG, 2018 (76)
Multiple sclerosis	↓ Ang II, ↑ ACE, ↓ ACE2 (cerebrospinal fluid); alteration of the intrathecal RAS	Kawajiri M et al., 2009 (77)
Parkinson's disease	↑ Ang II/AT1 axis ↑ Dopaminergic cell death ↓ Ang (1-7)	Labandeira-García JL et al., 2014 (78) Rocha NP et al., 2016 (79)

NO: nitric oxide; ROS: reactive oxygen species; IR: insulin resistance; SNS: sympathetic nervous system; OSAS: obstructive sleep apnoea syndrome; MI: myocardial infarction; HT: hypertension; COPD: chronic obstructive pulmonary disease; ACE: angiotensin converting enzyme; RAS: renin-angiotensin system; RAAS: renin-angiotensin-aldosterone system; Ang: angiotensin; AT1: angiotensin II type 1; AT4: Angiotensin II type 4.