Physician connect

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Dear Doctor,
Greetings from Micro Labs Limited. We are happy to bring you **'Physician connect'** which contains latest and interesting news in the field of Medicine.

This issue contains

- Renin-Angiotensin System Blockers and the COVID-19 Pandemic
- Efficacy of catheter-based renal denervation in the absence of antihypertensive medications: SPYRAL HTN-OFF MED study
- Atorvastatin Reduces Vascular Events: SPARCL Trial

Should you require any specific article or medical information, please feel free to contact us at medicalservices@microlabs.in
Looking forward to your valuable feedback

Best Regards,
Medical Team, Micro Labs Limited

Renin-Angiotensin System Blockers and the COVID-19 Pandemic

COVID-19 Pandemic has caused a significant health burden across the globe. Although the major current focus of public health authorities is to develop a coordinated global response to prepare health systems to meet this unprecedented challenge, a corollary concern has been identified that is of particular interest to clinicians and investigators with a major interest in hypertension.

Hypertension, coronary heart disease, and diabetes mellitus, particularly in elderly people, increase susceptibility to SARS-CoV-2 infection. Given that ACE2 (angiotensin-converting enzyme 2) is the receptor that allows coronavirus entry into cells, the idea has come up that pre existing use of renin-angiotensin system (RAS) blockers might increase the risk of developing a severe and fatal SARSCoV-2 infection.

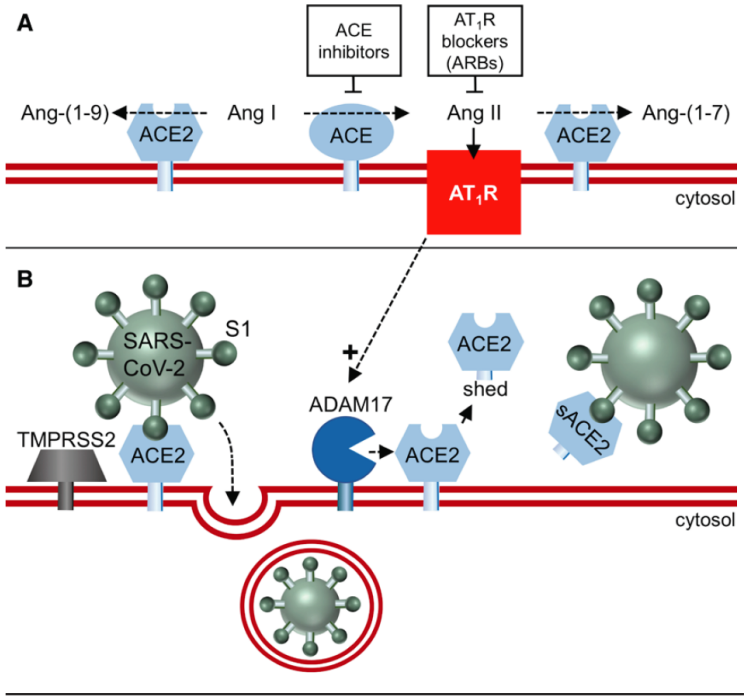


Figure. The carboxypeptidase ACE2 (angiotensin-converting enzyme 2) converts Ang II (angiotensin II) to Ang-(1–7) and Ang I to Ang-(1–9) **(A),** yet is not blocked by ACE (angiotensin-converting enzyme) inhibitors, which prevent the conversion of Ang I to Ang II. ACE2 also binds and internalizes SARSCov-2 (severe acute respiratory syndrome coronavirus-2**; B),** after priming by the serine protease TMPRSS2 (transmembrane protease, serine 2). Shedding of membrane-bound ACE2 by a disintegrin and metalloprotease 17 (ADAM17) results in the occurrence of soluble (s) ACE2, which can no longer mediate SARSCov- 2 entry and which might even prevent such entry by keeping the virus in solution. AT1R (Ang II, via its type 1 receptor) upregulates ADAM17, and AT1R blockers (ARBs) would prevent this.

During the spread of the severe acute respiratory syndrome coronavirus-2, some reports of data still emerging and in need of full analysis indicate that certain groups of patients are at risk of COVID-19. This includes patients with hypertension, heart disease, diabetes mellitus, and clearly the elderly. Many of those patients are treated with renin angiotensin system blockers. Because the ACE2 (angiotensin-converting enzyme 2) protein is the receptor that facilitates coronavirus entry into cells, the notion has been popularized that treatment with renin-angiotensin system blockers might

increase the risk of developing a severe and fatal severe acute respiratory syndrome coronavirus-2 infection.

ACE2 in its full-length form is a membrane-bound enzyme, whereas its shorter (soluble) form circulates in blood at very low levels. As a mono-carboxypeptidase, ACE2 contributes to the degradation of several substrates including angiotensins I and II. ACE (angiotensin-converting enzyme) inhibitors do not inhibit ACE2 because ACE and ACE2 are different enzymes. Although angiotensin II type 1 receptor blockers have been shown to upregulate ACE2 in experimental animals, the evidence is not always consistent and differs among the diverse angiotensin II type 1 receptor blockers and differing organs. Moreover, there are no data to support the notion that ACE inhibitor or angiotensin II type 1 receptor blocker administration facilitates coronavirus entry by increasing ACE2 expression in either animals or humans. Indeed, animal data support elevated ACE2 expression as conferring potential protective pulmonary and cardiovascular effects.

- ACE2 (angiotensin-converting enzyme 2) is the receptor that allows coronavirus entry into cells.
- ACE2 in its full-length form is a membrane-bound enzyme, whereas its shorter (soluble) form circulates in blood at very low levels.
- ACE inhibitors **do not** inhibit ACE2 because ACE and ACE2 are entirely different enzymes.
- Although angiotensin II type 1 receptor blockers have been suggested to upregulate ACE2, the evidence is not fully consistent and differs per angiotensin II type 1 receptor blocker and per organ.
- There are no data supporting that ACE inhibitors or angiotensin II type 1 receptor blockers facilitate coronavirus entry by increasing ACE2 expression.
- Treatment with RAS blockers should not be discontinued because of concerns with coronavirus infection based on the currently available evidence.
- ***At Present There Is No Evidence to Abandon Renin-Angiotensin System Blockers***

Source: Danser AHJ, [published online ahead of print, 2020 Mar 25]. Hypertension. 2020; doi:10.1161/HYPERTENSIONAHA.120.15082

Efficacy of catheter-based renal denervation in the absence of antihypertensive medications: SPYRAL HTN-OFF MED study

Catheter-based renal denervation has significantly reduced blood pressure in previous studies. Following a positive pilot trial, the SPYRAL HTN-OFF MED (SPYRAL Pivotal) trial was designed to assess the efficacy of renal denervation in the absence of antihypertensive medications.

In this international, prospective, single-blinded, sham-controlled trial, done at 44 study sites in Australia, Austria, Canada, Germany, Greece, Ireland, Japan, the UK, and the USA, hypertensive patients with office systolic blood pressure of 150 mm Hg to less than 180 mm Hg were randomly assigned 1:1 to either a renal denervation or sham procedure. The primary efficacy endpoint was baseline-adjusted change in 24-h systolic blood pressure and the secondary efficacy endpoint was baseline-adjusted change in office systolic blood pressure from baseline to 3 months after the procedure. We used a Bayesian design with an informative prior, so the primary analysis combines evidence from the pilot and Pivotal trials. The primary efficacy and safety analyses were done in the intention-to-treat population

SPYRAL Pivotal showed the superiority of catheter-based renal denervation in reducing the BP.

From June 25, 2015, to Oct 15, 2019, 331 patients were randomly assigned to either renal denervation (n=166) or a sham procedure (n=165). The primary and secondary efficacy endpoints were met, with posterior probability of superiority more than 0·999 for both. The treatment difference between the two groups for 24-h systolic blood pressure was −3·9 mm Hg (Bayesian 95% credible interval −6·2 to −1·6) and for office systolic blood pressure the difference was −6·5 mm Hg (−9·6 to −3·5). No major device-related or procedural-related safety events occurred up to 3 months.

SPYRAL Pivotal showed the superiority of catheter-based renal denervation compared with a sham procedure to safely lower blood pressure in the absence of antihypertensive medications.

Source: Bohm M et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. ACC 2020.

Atorvastatin Reduces Vascular Events: SPARCL Trial

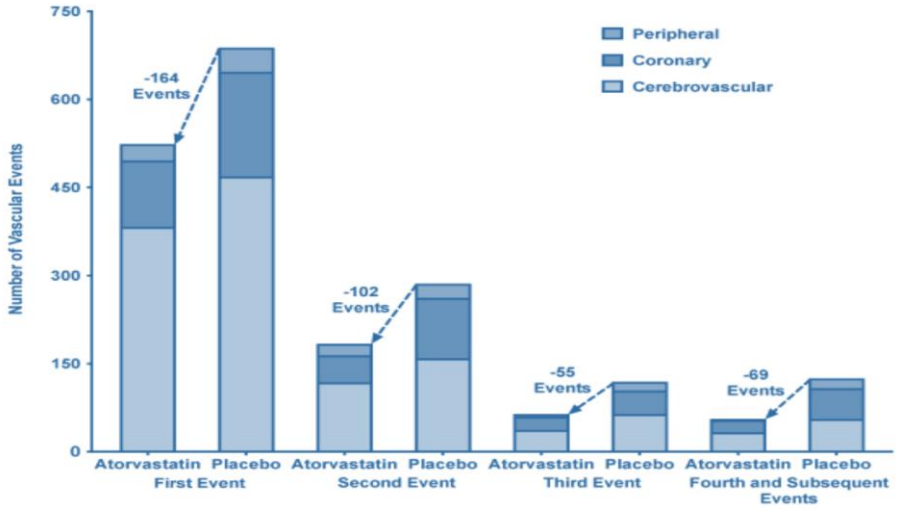
The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial compared atorvastatin with placebo in 4,731 participants with recent stroke or transient ischemic attack and no known coronary heart disease. Atorvastatin reduced the first occurrence of stroke and the first occurrence of a composite of vascular events.

This post hoc analysis assessed the occurrence of all (first and subsequent) vascular events and the effect of atorvastatin to reduce these events by vascular territory (cerebrovascular, coronary, or peripheral) in SPARCL. Treatment effects on total adjudicated vascular events, overall and by vascular territory, were

summarized by marginal proportional hazards models. Vascular event rates were estimated for each treatment group with cumulative incidence functions.

> Atorvastatin reduced the first occurrence of stroke and the first occurrence of a composite of vascular events.

The placebo group had an estimated 41.2 first and 62.7 total vascular events per 100 participants over six years. There were 164 fewer first and 390 fewer total vascular events in the atorvastatin group (total events hazard ratio 0.68, 95% confidence interval 0.60 to 0.77). The total events reduction included 177 fewer cerebrovascular, 170 fewer coronary, and 43 fewer peripheral events. Over six years, an estimated 20 vascular events per 100 participants were avoided with atorvastatin treatment. In participants with recent stroke or transient ischemic attack, the total number of vascular events prevented with atorvastatin was more than twice the number of first events prevented. Total event reduction provides a comprehensive metric to capture the totality of atorvastatin clinical efficacy in reducing disease burden after stroke or transient ischemic attack.



Source: Szarek M et al. Atorvastatin Reduces First and Subsequent Vascular Events Across Vascular Territories in the SPARCL Trial. ACC 2020.