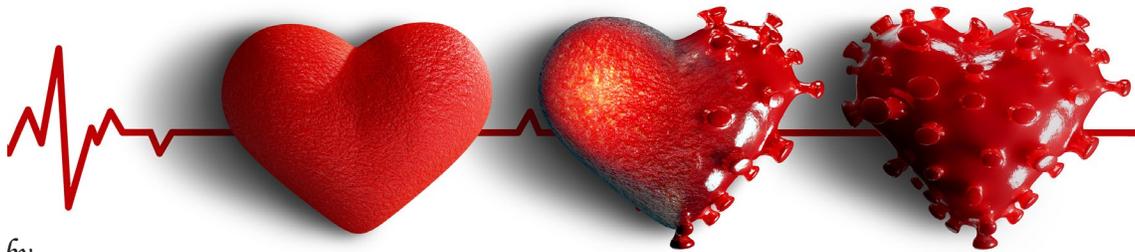


Coronavirus Quandaries for Patients with Cardiovascular Disease



by

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Part I – Is Grandpa at High Risk for the Coronavirus?

Arie was heading down to her basement to start her online coursework and stopped in the kitchen to grab a cup of coffee to take with her. Her mom, sitting at the kitchen table, looked up from her phone. “The one silver lining to all of this COVID-19 pandemic is having you home early from school. I hope we can hang out later!”

“I’d love to Mom, but my classes are still ongoing. I want to keep my grades up this semester and it’s sort of hard in the new online format for some classes. It’s just not the same as being on campus. Maybe this weekend we can watch a movie?”

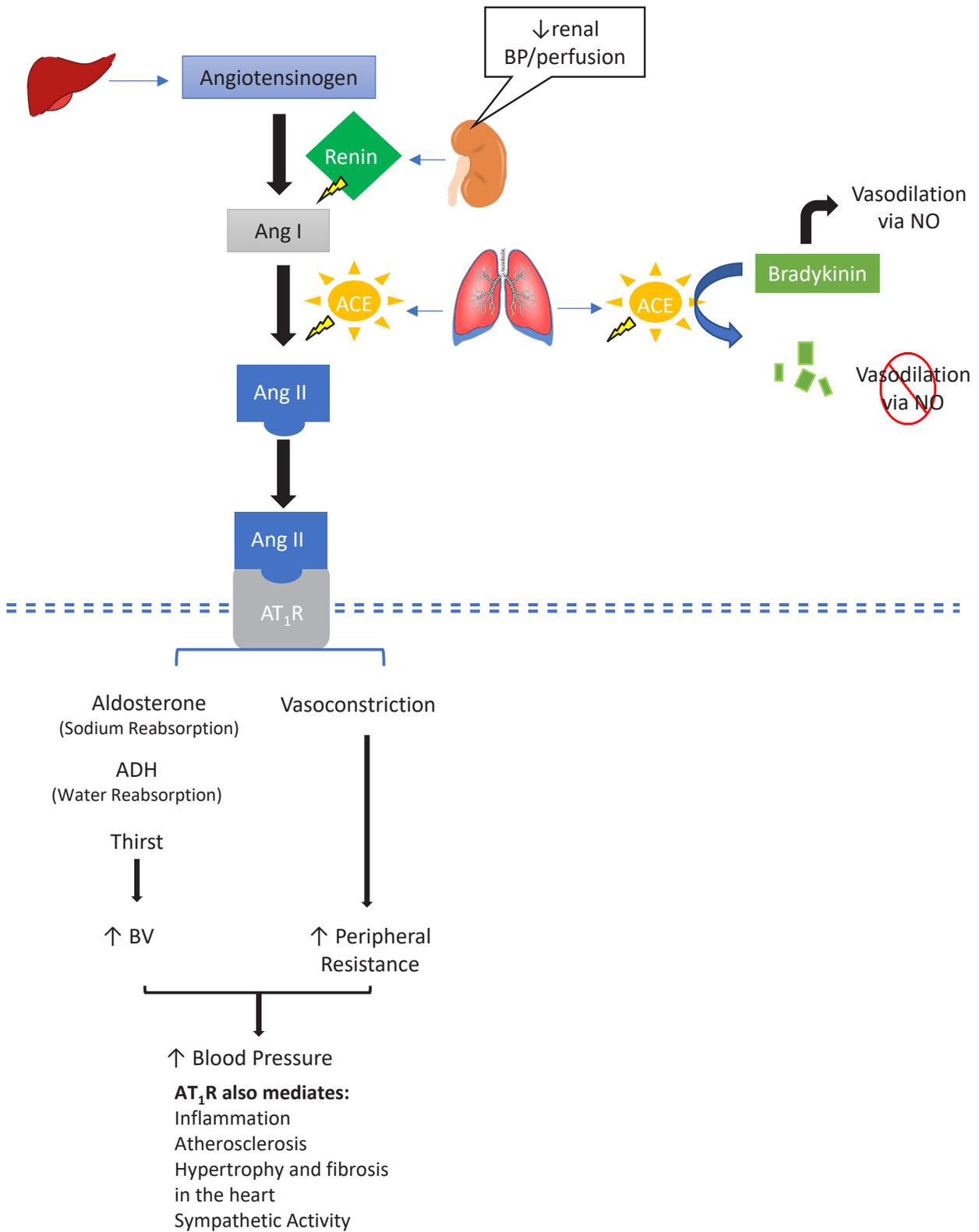
“My daughter, little miss smarty pants! Hey, your Aunt Charlotte just sent me this Instagram warning saying people on blood pressure medications should stop taking them because it can make the COVID-19 infection worse. Your grandfather takes medication for his hypertension and heart failure. I wonder if we need to do something... Are we putting him at greater risk?”

“That seems suspicious, Mom. You can’t believe everything you read on social media. Anyone can post anything they want on there. Grandpa needs his anti-hypertension medication to make it easier on his heart. It works to lower his blood volume and blood pressure, which will decrease his afterload, increase his stroke volume, and decrease the workload on his heart,” spouted Arie.

“I have no idea what you just said,” Arie’s mom replied turning back to her phone. “I just googled it, and it’s a real thing in the news too. People are citing information from *The Lancet*. That’s a medical journal, right? I don’t get how blood pressure medication relates to this new coronavirus.”

“Mom, I just learned all about blood pressure regulation in my anatomy and physiology class. I’ll explain it to you. Let’s start with a picture” (Figure 1, next page).

Figure 1. Classical renin-angiotensin-aldosterone system. (Modified from Patel *et al.*, 2014)



Questions

1. Explain the relationship between blood volume and blood pressure.
2. List the functions of the hormones/enzyme listed below:
 - *Aldosterone*
 - *Renin*
 - *Antidiuretic Hormone (ADH)*
3. Heart failure is when the heart cannot eject enough blood to meet the body's oxygen and blood demand. Describe what would be the expected response from the RAAS (renin-angiotensin-aldosterone system) system in a patient with heart failure.
4. How is RAAS upregulation detrimental to heart failure patients over time?
5. How does the sodium ion influence blood volume and blood pressure?
6. Give three examples of pathologies in which there is an upregulation of RAAS. Next to each one explain your reasoning.
7. How would high levels of angiotensin II (Ang II) affect someone with hypertension?

Part II – Grandpa’s Medications

“Now, what about your grandfather’s medications? He’s taking lisinopril and furosemide. How do those interact with your RAAS system on this diagram that you’ve made?” asked Mom.

“My professor, Dr. Sven, did mention how certain medications disrupt the system and lower blood pressure, which is why grandpa is on these medications. But I’m not sure what drug classes those particular medications belong to.” Arie picked up her iPhone and said, “Hey Siri! What is lisinopril?”

An automated friendly voice boomed, “Lisinopril is a medication of the angiotensin-converting enzyme inhibitor class used to treat high blood pressure, heart failure and after heart attacks. For high blood pressure it is usually a first line treatment...” (Wikipedia, Lisinopril, 2020).

“Ah! Lisinopril is an ACE inhibitor, and furosemide is a diuretic. Ok, now I get it. Let me show you how these drugs disrupt the RAAS pathway and lower Grandpa’s blood pressure.”

Questions

1. Explain why ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) are prescribed to treat hypertension and heart failure.
2. A drug that amplifies the effect of bradykinin would have what effect? What diseases could it be prescribed to treat?
3. Would a patient taking an ARB have the same vasodilation effect via bradykinin as a patient taking an ACE inhibitor?
4. Spironolactone is a drug that blocks the aldosterone receptor in the renal collecting tubule. How would the sodium and potassium levels in the urine change after a patient is placed on spironolactone? Based on these changes, what are possible metabolic adverse effects of the drug?
5. Approximately 20% of hypertensive patients have abnormally high plasma renin activity. What drug class should these patients respond to?
6. Twenty percent (20%) of hypertensive patients have low renin plasma activity yet still respond to drugs that interfere with the RAAS pathway. What other components of the RAAS mechanism may the drug be working through to lower blood pressure?

Part III – Does Grandpa’s Medication Increase His COVID-19 Risk?

“Wow, honey, I’m impressed! You really are starting to understand these medical matters. All of those tuition dollars are paying off, eh? But unless I missed it, your explanation of the RAAS system doesn’t talk about this, A-C-E-2 that’s in the news for being important for the COVID-19 infection and heart patients,” Arie’s mom said.

“Hmm... You’re right.” Arie was perplexed as she started to flip the pages in her physiology textbook. “I don’t know, we never discussed ACE2. My anatomy and physiology live office hour is starting soon and I’ll ask my professor about it,” Arie replied.

“That would be great. I don’t think this is just a social media spoof to mess with people and have them stop taking their meds; who would do that anyway!? I’m scrolling through Google News and here are some of the headlines:

“Can taking a certain type of high blood pressure medication worsen COVID-19 infections?”

–*Boston 25 News*, March 19, 2020 (Morelli, 2020)

“ACE inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19, paper suggests”

–*Science Daily*, March 23, 2020 (Louisiana State University Health Sciences Center, 2020)

“High blood pressure and diabetes medication taken by 13 million Americans could raise the risk of serious coronavirus symptoms, scientists say”

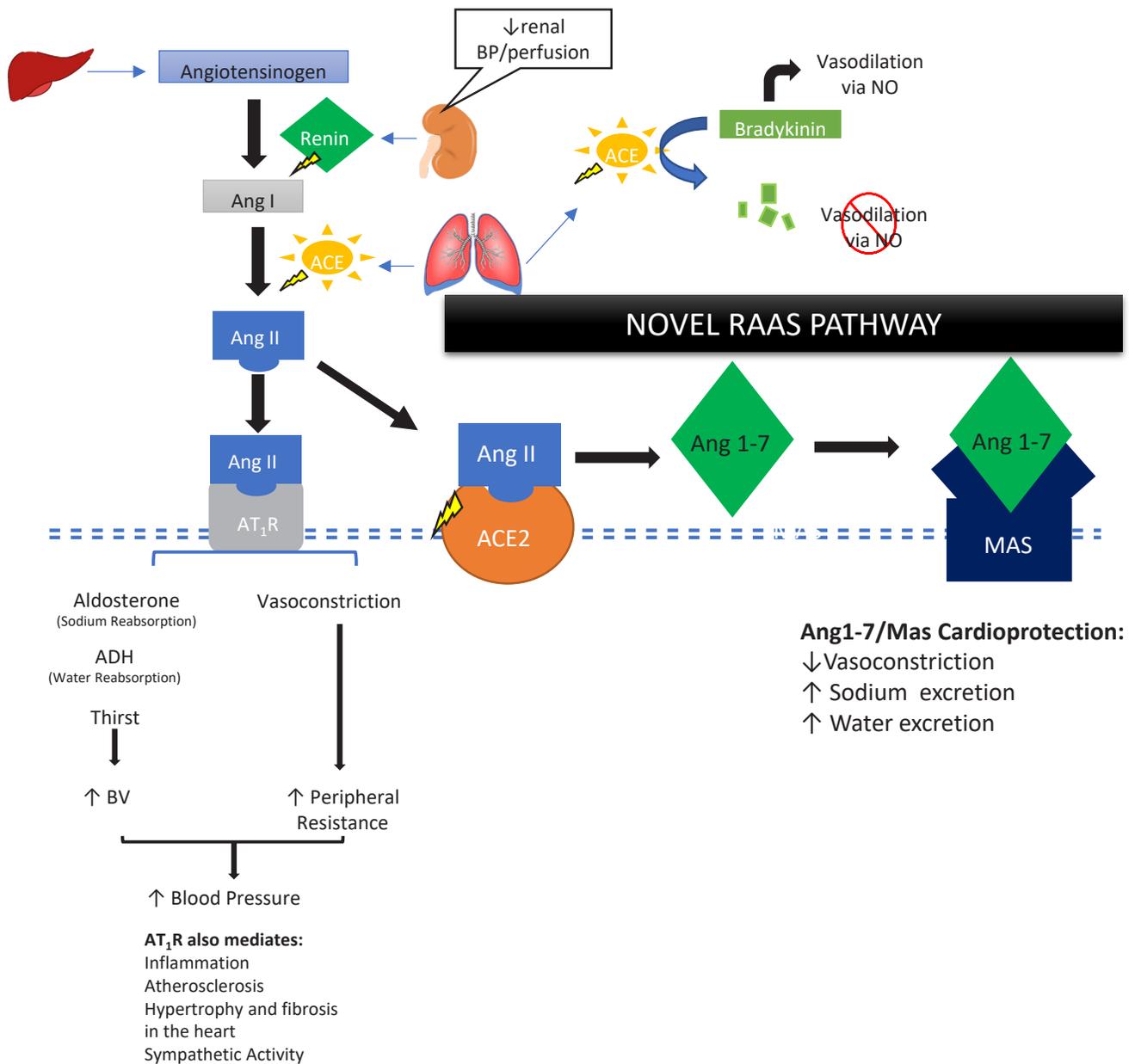
–*DailyMail.com*, March 13, 2020 (Kekatos, 2020)

Grabbing a banana from the counter, Arie started for the stairs. “Don’t worry, I’m on it Mom!”

Arie logged into her computer. “Hi Dr. Sven! I have a question. I’m hearing in the news that the COVID-19 virus is more deadly for people with high blood pressure and heart disease. There are some people saying that these patients should stop taking their medications and switch to other ones. This affects my grandfather, so I wanted to learn about it. I was reviewing the RAAS system for blood pressure regulation, but I’m not seeing the links between the virus and what we learned. Can you explain it?”

“Insightful question, Arie! Since this is a point of interest right now, I’ve extended our diagram of the RAAS system to explain a more novel part, which has really been worked out in the last 20 years (Figure 2, next page). Basically, RAAS has to be regulated, right? We just don’t want Ang II to go unchecked -raising blood volume and blood pressure! Like most physiological systems, there is a negative regulator. It’s called ACE2. ACE2 cleaves Ang II, deactivating it. As it does this, it makes a new peptide called Ang1-7. ACE2 and Ang1-7 are thought to be cardioprotective because they downregulate AT1R and Ang II. Additionally, Ang1-7 has its own receptor called Mas, which when activated leads to vasodilation by nitric oxide,” said Dr. Sven. “Both branches of the pathway work to maintain homeostatic balance for our blood pressure.”

Figure 2. Novel RAAS regulation pathway. (Modified from Patel *et al.*, 2014)



Questions

1. What is a negative regulator? What is serving as a negative regulator in the RAAS pathway?
2. As ACE2 cleaves Ang II what happens to blood pressure and why?
3. If a patient has high levels of ACE2, what is expected to happen to their Ang II and Ang 1-7 levels?
4. ACE2 and Ang 1-7 are referred to as being “cardioprotective.” Why would this be?
5. ACE2 is cleaved by proteases and released as a soluble or plasma protein. Plasma ACE2 is associated with cardiovascular disease risk factors and is elevated in type 1 diabetics, hypertensive patients, and patients with kidney disease. Hypothesize why “tissue” (cell membrane bound) ACE2 is cardioprotective, but plasma ACE2 is associated with disease.
6. Using the diagram of the novel RAAS pathway (Figure 2), identify where new or experimental drugs can assist in decreasing hypertension within the novel RAAS pathway.
7. SARS-CoV-2 uses the ACE2 inhibitor to enter cells. Would an increase of tissue ACE2 increase the likelihood of infection with SARS-CoV-2? Make a hypothesis and explain your reasoning.

Part IV – Coronavirus Quandaries for Patients with Cardiovascular Disease

“Ok, thank you for the explanation. I’ve seen the ACE2 receptor mentioned in the news articles about the hypertension medications worsening COVID-19 infection. But how are the two linked?” asked Arie as she intently studied her new diagram (Figure 2) of the novel RAAS components.

“Well, simply put, viruses have a key to enter a door on their host cell. Once they open the door, it allows them to infect the cell. In more advanced terms, the SARS-CoV-2 virus, which causes COVID-19, has proteins on its viral envelope that need to find a specific binding partner on its host cell. Coronaviruses, like SARS-CoV-2, have what’s called the coronavirus S (spike) protein on their viral envelop. This binds to the ACE2 receptor and allows the virus to begin its mechanism to enter and infect the host cell. So the S protein is the key and ACE2 is the door,” explained Dr. Sven.

“Makes sense,” thought Arie. “So people on ACE inhibitors or ARBs are decreasing the effect of Ang II. What would that do to ACE2 and viral infection?”

“Good question! And that is what the medical community is grappling with right now. There have been commentaries and opinion papers on the topic published in science journals to quickly alert the medical community to the hypotheses as to why patients with hypertension, diabetes and cardiovascular disease have severe COVID-19 infections and higher mortality. Commentaries and opinion papers use past work or studies and the current experience of investigators. But because they are meant to get the ideas out quickly, they generally do not use the scientific method to investigate the hypothesis.”

Dr. Sven continued, “There is evidence in animals and humans that treatment with ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs) increase ACE2. Thus, some scientists and clinicians hypothesize that patients taking these drugs may be raising their ACE2 levels, and therefore more ‘doors’ for COVID-19 to bind to and infect. They reason that this may be why these patients have a more severe COVID-19 infection and worse outcomes. On the other hand, there have been studies done where ACEi and ARBs have been used and there is no measurable increase in ACE2.”

Arie was quiet for a moment while she considered Dr. Sven’s explanation. Then, with an exasperated sigh she started to think out loud. “Well, what are people supposed to do? The science is confusing, the news articles are confusing. It seems risky to put out there that people should be wary of the medications that they need, but at the same time, is it their medications that are putting them at high risk? My mom wants to know what to do for my grandfather who takes an ACEi and I don’t know what to tell her!”

“Well, the last part is easy; tell your mom to always call the prescribing physician before making any changes to any medication. In fact, at least twelve medical associations have come out and stated that they feel patients on these medications should stay on their ACEi or ARBs until more evidence is available or unless they are advised to switch by their physician. Now as for the science, it is important to remember the types of scientific communications and the weight given to each kind by the scientific community. And the quandary of it all, well that’s the interesting part of science and why we want you to learn to think critically. You are learning the physiology so you can apply it to answering questions to better serve patients someday.”

Later, Arie explained what she had learned to her mom. They decided the best course of action was to call the grandfather’s cardiologist, Dr. Smith, and ask his advice.

“Thank you for calling,” said Dr. Smith. “I’ve received a lot of concerned calls from my patients about what they are hearing and reading in the media concerning the COVID-19. What we know from data is that patients with cardiovascular diseases are at more risk, and also the infection may damage the cardiovascular system in some patients. However, because we are in the midst of the pandemic, we have no clear clinical data yet as to whether ACE inhibitors or angiotensin receptor blockers would make the infection worse. There are experts speculating that it might, because animal studies show that the drugs increase ACE2, a receptor the virus uses to enter cells. To make matters more confounding, in other viral pneumonias, ACEi and ARBs have reduced lung injury. Ultimately, to date, we have no data to go on for COVID-19. That’s why many medical associations, like the American Heart Association, have issued statements saying the best course of action is to not change medications unless there is a clinical reason to do so. And

that is what I'm telling my patients; until we see a randomized control trial, we are just guessing. There is a risk to patients if they stop using their medications. Halting heart failure therapy can lead to a decline of cardiac performance, which can worsen the heart failure and possibly increase mortality" (American Heart Association, 2020).

"Yes, I've learned all about the ACE2 receptor today. Thank you for your opinion, Dr. Smith. This is truly the coronavirus quandary for cardiovascular disease," said Arie.

Questions

1. There are conflicting studies on whether ACEi and ARBs increase ACE2. How can studies using the same drug classes have different outcomes? Brainstorm reasons why these studies might not be comparable.
2. Does an increase in ACE2 on the cell's surface mean there will be more viral infection? Explain.
3. Knowing that the SARS viruses use ACE2 to infect cells, brainstorm possible pharmacological interventions that could exploit this relationship. List any possible adverse effects suspected with how it might interfere with RAAS.
4. After talking with Arie's family, Dr. Smith read an article in *JAMA Cardiology* (Madjid *et al.*, 2020) highlighting cardiovascular complications experienced by patients in previous coronavirus and influenza epidemics. The review article explained potential mechanisms by which these viral infections can lead to increased risks of myocardial infarction, heart failure and arrhythmias. Dr. Smith must weigh this information against the reports of ACEi and ARBs negatively affecting COVID-19 infection. Give your opinion as to how Dr. Smith should advise his patients with existing cardiovascular disease and explain your rationale.

Part V – Headlines, News and the Hierarchy of Scientific Evidence

The SARS-CoV-2/COVID-19 crisis and pandemic has highlighted the different types of scientific literature and communication. Unfortunately, when reported in the media and news, there can be a lack of clarity on where the “scientific” information has come from and what type of study it’s based upon. The science community uses various types of scientific studies for various means. The types of studies carry differing strengths of evidence depending on how data is gathered. Additionally, there are various types of scientific literature that are used to quickly disseminate experiences, opinions, untested hypotheses, etc., so the scientific/medical community can discuss and consider these ideas quickly. The idea that hypertensive patients taking ACEi and ARBs may be at a greater risk for COVID-19 illness is one such example. The public was quickly made aware of the information from media sources without a clear understanding of the strength of the evidence supporting the hypothesis. Figure 3 is a diagram of the hierarchy of evidence pyramid showing the various strengths of evidence that a study can generate for a given hypothesis.

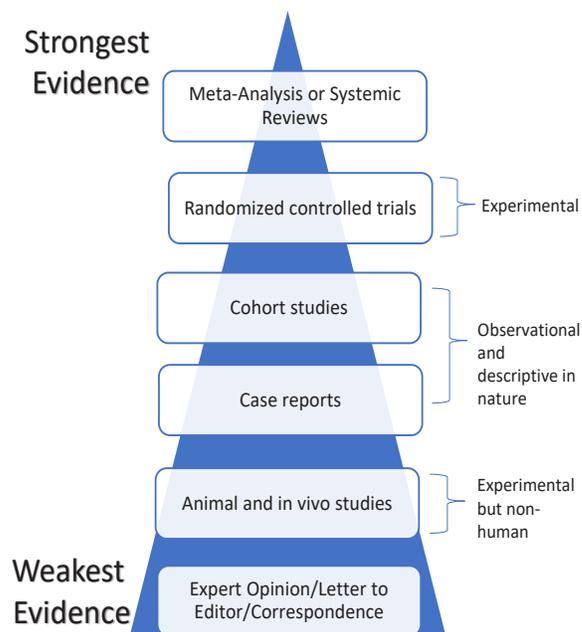


Figure 3. Hierarchy of evidence pyramid. (Modified from Anon., 2016)

Questions

1. What are the advantages/disadvantages of the various types of scientific studies? Explain each study’s placement along the hierarchy of evidence pyramid.
2. During a time of crisis like the SARS-CoV-2 pandemic, what type of study is the most feasible to do and why?
3. What types of studies do you believe formed the foundation for the hypothesis that ACEi and ARBs might increase the severity of COVID-19 infection and why?
4. Why were the first scientific reports on the SARS-CoV-2/COVID-19 infections case and cohort studies?
5. Why would clinicians and medical associations want to quickly issue statements for patients not to change their medications based on the reports?

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