I am quite shocked at the content and opinions expressed in this article.

This just-published article from a top researcher in the field (Paolo Raggi) is in direct contrast to Dr. Mandrola's twisting of the data – the title says it all *"Coronary calcium is all we need for risk assessment, yet we do not use it often enough"* https://www.atherosclerosis-journal.com/article/S0021-9150(19)30031-0/fulltext

Here are my thoughts on each of Dr. Mandrola's points:

On the scenario of a 55-year-old white man, Dr. Mandrola appears to have chosen the optimum case to minimize the perceived value of the scan. Let me throw out three alternative cases to illustrate how misleading he has been (all taken from the excellent paper https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3840900/)

- A 60-year-old white man with SBP of 120mmHg and Total Cholesterol / HDL ratio of 150/65 (*note that LDL is not used in the algorithms, rather the TC/HDL is required*). This man has a supposed 5% risk from the algorithm. However, if he gets a CAC scan result it changes the outlook dramatically – his 10-yr risk will be a trivial **1%** with CAC = 0, and **13%** with CAC >300

- A 55-year-old hispanic man with SBP of 140mmHg and Total Cholesterol / HDL ratio of 220/50. This man has a supposed 10% risk from the algorithm. However, if he gets a CAC scan result it changes the outlook dramatically – his 10-yr risk will be only **3%** with CAC = 0, and a huge **28%** with CAC >300

- A 75-year-old white man with SBP of 120mmHg and Total Cholesterol / HDL ratio of 170/80. This man has a supposed 10% risk from the algorithm. However, if he gets a CAC scan result it changes the outlook dramatically – his 10-yr risk will be only **2%** with CAC = 0, and **16%** with CAC >300

The lives of these people are important. These people and all the others are entitled to find out their real level of disease - and hence their real level of risk. Most especially considering that the scan is cheap, fast, non-invasive and only involves a trivial amount of radiation (<1mSv mostly in modern scanners).

After briefly nodding in the direction of lifestyle, the whole discussion then centers on statin treatment. This is most misleading. Firstly, the lifestyle changes by a patient motivated by a high score are far more important than acknowledged here. For example, a large proportion of "surprise high scorers" will have undiagnosed T2 diabetes. A high score can motivate the person and their doctor to explore further for this pathology, using OGTT and insulin testing. A recent human trial has demonstrated that remission of the disease can be achieved in over half of the cases with a specific and highly effective diet regime (https://blog.virtahealth.com/2yr-t2d-trial-outcomes-virta-nutritional-ketosis/**).** As T2 Diabetes is a massive causal driver for ASCVD, and one of the highest risk factors for MI – addressing and resolving this would have an enormous impact on the patient's

risk level going forward. This is just one example of many, where appropriate actions following a high CAC score would have more impact than even the drug-induced mitigation of risk.

On the following few statin and NNT centric paragraphs I will comment that this is about saving patient's lives, and not just numbers. That said I would again urge practitioners to review Raggi's short and powerfully informative paper here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3840900/ . I will just pluck a few jewels from it for illustration on the Statin and NNT question:

"…almost half of the patients with an indication for statins have no CAC [9], hence they are at extremely low risk and do not need drugs [10].

"We need to treat 549 patients without CAC for 5 years to save one cardiovascular event [12],while we can save one event treating 12 patients with a CAC score>100 [11]"

"Hong et al. [8] modeled the cost of treating every patient with an indication for statin therapy, against the selective treatment of patients with CAC on a screening chest CT. The cost of long-term care was the same for the 2 methods, leaving room for patients and their physicians to discuss the preferred approach in a shared decision-making fashion."

Given the above published points (and a lot more besides) – it appears to me that Dr. Mandrola has a pervasive anti-CAC bias all through his thinking. Also, that this bias manifests itself in an element of "cherry-picking" - to eke out any data which can be used against the technology.

The rest of Dr. Mandrola's article proceeds to cover some more distractions e.g. "there is no randomized control trial on CAC." I thought that we had heard the last of this particular obfuscation. RCT's are for drugs, not for diagnostic screening tests. There are no RCT's for the CVD risk algorithms, or for stress tests etc. Their utility is simply obvious – they identify problems and enable preventative action to be taken. Conflating drug treatment with assessment tools is downright devious.

On the data from the MESA cohort of 5,185 people, the chosen way to present the outcomes is again highly misleading. Because we need to focus heavily on saving people at risk, here is a better summary based on the heart attacks *which actually occurred in people flagged as higher risk, whether by the algorithm or the CAC scan or both:*

- 19 events occurred in people who were High risk in the calculator but Low/Med in the CAC
- 118 events occurred in people who were High risk in both the calculator and the CAC
- 76 events occurred in people who were Low/Med risk in the calculator but High in the CAC

The latter 76 people were appropriately flagged as heading for a future event (which indeed they went on to actually have). With the CAC result they could be empowered to take all actions possibly to prevent said event, most notably *correct* diet/lifestyle intervention but also of course targeted drug

treatment. If you scale up this study to the population level, these “glossed-over” high-risk 76 would represent millions of people in the same situation.

Dr. Mandrola’s point about the 5/6 “false positives” from CAC is bizarre. The people with high CAC are of course high risk – that’s a given. ***But that doesn’t mean that every single one of them will have an event!*** The absurdity here is that, if a CAC score reclassifies a person from say 4% to 16% then yes – of course 1/6 of these should have an event, and 5/6 will not have an event. That’s what 16% risk means! Dr. Mandrola’s logic here would lead to scrapping the risk calculators while we’re at it – because only 1 in 6 of the people with a 16% risk score would go on to have an event. The other 5/6 would not have an event – so the risk calculators are useless!

I could go on but I guess everyone will now see how data and logic can be manipulated to make a case against anything one has a bias against. In closing, please do read that Raggi paper – and be properly informed!