Title: AHA 22 Highlights With Dr Joseph Hill

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- My name is Joseph Hill. I'm Professor of Medicine in Molecular biology at the University of Texas Southwestern Medical Centre in Dallas, Texas. Chief of Cardiology and I'm the Editor in Chief of Circulation. I've been asked to provide my own perspective on some of the highlights of the American Heart Association Scientific Sessions 2022. These are my own personal views.
And others may select other clinical trials, but there were two exciting trials, exciting for me focusing on gene editing. One focusing on the gene coding for transthyretin in patients with transthyretin amyloidosis and cardiomyopathy. The therapy was well-tolerated. And the transthyretin levels dropped drastically as expected.
And there was another study coming from Verve Therapeutics where they extended their efficacy and safety evaluations in non-human primates targeting PCSK9 as also in mouse models to focus on mechanisms. They tracked these non-human primates out for almost 500 days. There was an early transaminitis as has been seen before, but that resolved quickly. The procedure was well-tolerated. There was a profound and enduring drop in both PCSK9 and LDL cholesterol. And there was after careful evaluation no evidence of off-targeting editing. It's quite exciting.
Another study entitled, IRONMAN which contributed to the steady drumbeat of evidence that administration of iron during exacerbations of heart failure provides benefit here. It decreased the risk of subsequent hospitalisation as well as cardiovascular death.
One study entitled, "OCEAN -DOSE" studied olpasiran, which is a small interfering siRNA molecule targeting LP. A randomised double-blind placebo-controlled trial phase two in almost 300 subjects with established atherosclerotic cardiovascular disease and elevated LP levels found that a dose as little as 75 milligrammes administered every 12 weeks was well-tolerated and reduced LP levels by more than 95% in these subjects with established atherosclerotic cardiovascular disease.
Another important study published simultaneously in the New England Journal entitled, EMPA-Kidney addressed the question of SGLT2 inhibition therapy and its impact on individuals with chronic kidney disease. They studied individuals with an eGFR in the range of 20 to 45 more or less and tracked nearly 6,600 of them with this depressed EFR. And in summary, they found that the rate of development of end stage renal disease was diminished in the empagliflozin group. The rate of hospitalisation for any cause was similarly lower in that group. And there were no stratifications across different subsets of individuals. In other words, across a wide range of subjects with chronic kidney disease who are risk of disease progression empagliflozin actually led to lower risk of progression of kidney disease and lower risk of death from cardiovascular causes relative to placebo.
Finally, the last study I'll highlight is one entitled, ISCHEMIA-EXTENDed. We're all familiar with the now quite famous ISCHEMIA study that evaluated an initial invasive versus an initial conservative management strategy for patients with chronic coronary disease and moderate to severe ischemia after ruling out left main disease and so forth. It had been reported previously that there was no major difference in most outcomes at a median of

three years in the invasive arm versus the conservative arm. And in this study, they took these subjects out and followed them for essentially another three years. All-cause mortality, again, was not different between the randomised treatment groups.
There was a lower seven-year rate of cardiovascular mortality with an initial invasive strategy, but a higher seven-year rate of non-cardiovascular mortality compared with the conservative strategy. A little bit of a puzzle. There was no heterogeneity of treatment effect across the different pre-specified subgroups. So again, consistent with largely with what had been reported at three years. There was no difference in all-cause mortality with an initial invasive strategy compared with an initial conservative strategy, but there was a lower risk of cardiovascular mortality and higher risk of non-cardiovascular mortality with an initial invasive strategy.
So that is just a few of the exciting late-breaking clinical trials that were released at this year's AHA Scientific Sessions. The first one in three years now taking place face-to-face in Chicago, Illinois. Those are the studies that I personally found the most exciting. And I hope that my summary is helpful for you. Thank you.