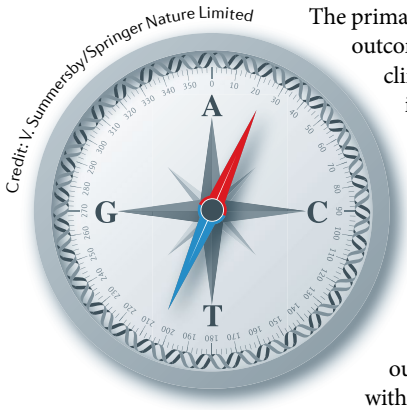

Credit: V. Summersby/Springer Nature Limited

The primary combined outcome of net adverse clinical events occurred in 5.1% of the genotype-guided group and 5.9% of the standard-therapy group ($P<0.001$ for noninferiority). The rate of the primary bleeding outcome was lower with genotype-guided therapy than with standard therapy (9.8% versus 12.5%; HR 0.78, 95% CI 0.61–0.98, $P=0.04$).

The investigators highlight the feasibility of the genotype-guided approach in clinical practice. "The mean time to obtaining genetic results after randomization was just 3 h," says Danny Claassens. "We were therefore able to adjust the [antiplatelet] treatment, if necessary, within 1 day."

Gregory B. Lim

> The rate of the primary bleeding outcome was lower with genotype-guided therapy

ORIGINAL ARTICLE Claassens, D. M. F. et al. A genotype-guided strategy for oral $P2Y_{12}$ inhibitors in primary PCI. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1907096 (2019)


Credit: Getty/iMrSquid

subsequently validated using CCTA scans from 1,575 patients enrolled in the SCOT-HEART trial, and was shown to significantly improve the predictive value of traditional risk-prediction tools for MACE.

The capacity of the FRP to detect unstable coronary plaques was also assessed. The FRP was significantly higher in patients with acute myocardial infarction (AMI) and remained unchanged 6 months after the index event, unlike the FAI, which decreased dramatically after AMI, suggesting that FAI is a more dynamic biomarker of inflammation, whereas FRP captures more static changes.

Together, these findings indicate that both FRP and FAI are complementary tools for the prediction of adverse cardiac events.

Karina Huynh

> both FRP and FAI are complementary tools for the prediction of adverse cardiac events

ORIGINAL ARTICLE Oikonomou, E. K. et al. A novel machine learning-derived radiotranscriptomic signature of perivascular fat improves cardiac risk prediction using coronary CT angiography. *Eur. Heart J.* https://doi.org/10.1093/eurheartj/ehz592 (2019)

HEART FAILURE

The search for an effective HFpEF treatment continues


Credit: V. Summersby/Springer Nature Limited

The highly anticipated PARAGON-HF trial results, presented at the ESC Congress 2019, indicate that the angiotensin receptor–neprilysin inhibitor sacubitril–valsartan does not have a significant benefit in reducing the risk of hospitalizations for heart failure or death from cardiovascular causes in patients with heart failure with preserved ejection fraction (HFpEF). The trial narrowly missed statistical significance for the primary outcome, but suggests a heterogeneous effect of sacubitril–valsartan, with potential benefit in certain patients such as those with 'mid-range' left ventricular ejection fraction (LVEF) and women.

Sacubitril–valsartan is currently approved for the treatment of patients with heart failure with reduced ejection fraction (HFrEF) on the basis of data from PARADIGM-HF. "Although HFpEF accounts for up to 50% of people with heart failure, we have no proven treatment," explains the PARAGON-HF investigator John McMurray. "PARAGON-HF is the latest and largest attempt to find an effective therapy, testing sacubitril–valsartan," he adds. The trial included 4,822 patients (52% women) with NYHA class II–IV heart failure, LVEF ≥45%, high natriuretic peptides levels and structural heart disease, who were randomly assigned to receive sacubitril–valsartan or valsartan.

Fewer primary outcome events (hospitalizations for heart failure or death from cardiovascular causes) occurred with sacubitril–valsartan treatment than with valsartan treatment (894 versus 1,009 events), but the overall result narrowly missed statistical significance (rate ratio of 0.87, 95% CI 0.75–1.01, $P=0.059$). Therefore, subsequent analyses were considered to be exploratory. The benefit trend was driven by a 15% reduction in hospitalizations for heart failure, with no differences in death from cardiovascular causes. Secondary outcomes suggested an improvement in clinical condition with sacubitril–valsartan. At 8 months, more patients in the sacubitril–valsartan group than in the valsartan group had improvements in the NYHA class (15.0% versus 12.6%) and an improvement of ≥5 points in the Kansas City Cardiomyopathy Questionnaire score. Renal function decline occurred less frequently in the sacubitril–valsartan group (1.4% versus 2.7%). Sacubitril–valsartan was associated with higher rates of hypotension and angio-oedema, but lower rates of elevated creatinine or potassium levels than valsartan.

Interestingly, sacubitril–valsartan had a significant benefit in two prespecified subgroups: patients in the lower LVEF range studied (45–57%) and women. In patients with LVEF ≤57%, sacubitril–valsartan led to a 22% reduction in the rate of the primary outcome compared with valsartan. "This finding makes sense as we know sacubitril–valsartan is highly effective in people with HFrEF (LVEF ≤40%) and other drugs effective for HFrEF also show efficacy in patients in the lower part of the HFpEF LVEF range," explains McMurray. In women, sacubitril–valsartan reduced the rate of the primary outcome by 27.5%.

"The regulatory agencies and guideline committees will have to review the data and consider whether there is enough evidence to recommend use of sacubitril–valsartan in some patients with HFpEF, such as those with a LVEF below normal," says McMurray. "We need to do more analysis of the very interesting finding of the possibly greater benefit in women, especially as HFpEF is the predominant type of heart failure in women."

Irene Fernández-Ruiz

ORIGINAL ARTICLE Solomon, S. D. et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1908655 (2019)