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Big-Endothelin-1 as a prognostic and diagnostic marker

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The endothelin system (Endothelin-1) is a key regulator in cardiovascular (CV) disease and heart failure. Further, heart failure frequently coincides with renal disease. NT-proBNP is the currently established biomarker for the prognosis and diagnosis of heart failure. However, renal dysfunction may limit the clinical application of NT-proBNP to the diagnosis of heart failure.
We have examined the incremental value of the propeptide of Endothelin-1, Big-ET-1, in predicting total and CV mortality and death due to heart failure (HF) next to the well-established CV risk marker N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP). Further, we have examined whether Big Endothelin-1 (Big-ET-1) might be a suitable biomarker for the diagnosis of HF with preserved ejection fraction (HFpEF) in patients with chronic kidney disease (CKD), next to NT-proBNP.
Our analysis was conducted in 2829 participants from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study who were referred for coronary angiography. During the median observation period of 9.9 years, 843 (29.8 %) participants died. Among these, 523 (18.5 %) patients died from cardiovascular causes. Of these, 125 (4.4 %) died as a consequence of HF. From the entire study population, 439 patients were diagnosed with HFpEF.
Big-ET-1 was significantly and independently associated with total and CV mortality and death due to HF. Big-ET-1 held incremental predictive value for the prognosis of death due to HF, next to NT-proBNP. We have also found that the conjunct use of Big-ET-1 and NT-proBNP improves the risk stratification of patients with intermediate to high risk of cardiovascular death and death due to HF.
The examinations with regard to renal dysfunction have revealed that the NT-proBNP plasma level were increased exponentially with declining GFR, while Big-ET-1 plasma levels increased only in a moderate and linear fashion. In patients without CKD, a NT-proBNP cut-off point at 250 pg/mL was suitable for the discrimination between HFpEF and patients without HF. When the GFR was less than 60 mL/min/1.73m², the NT-proBNP cut-off point had to be raised to 750 pg/mL for a good discrimination of HFpEF from patients without heart failure. A cut-off point at 0.85 fmol/mL allowed to distinguish patients with HFpEF from persons without HF, independently of GFR.
Our investigations have shown that Big-ET-1 is an independent predictor of total and CV mortality and death due to CHF. The additional measurement of Big-ET-1 improves the risk stratification of patients with intermediate to high risk of cardiovascular death and HF. NT-proBNP was a good indicator of suspected HF. While for NT-proBNP, different cut-off points have to be considered in the diagnosis of HFpEF, a single cut-off point of the Big-ET-1 plasma value at 0.85 fmol/mL was appropriate to the diagnosis of HFpEF, regardless of the presence or absence of CKD. Finally, we have developed a risk stratification algorithm for patients affected with both, HFpEF and CKD, and have shown that Big-ET-1 improved the diagnosis of HFpEF in patients with chronic kidney disease, next to NT-proBNP.