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occurred in 12 (3 into the prohibitive risk category), whereas downgrading occurred in 14 patients (2 left the prohibitive risk category).

In conclusion, the results of the eyeball test did not match data from frailty testing in ~40% of elderly patients being considered for transcatheter therapy or cardiac surgery, leading to reclassification of surgical risk in approximately one-fourth of these patients. This indicates that providers systemically overestimated frailty with the eyeball test. Frailty is not a component of commonly used surgical risk calculators (e.g., European System for Cardiac Operative Risk Evaluation score, Society of Thoracic Surgeons predicted risk of mortality), and must be assessed clinically. Our findings demonstrate the incremental utility of objective methods of assessing frailty beyond the eyeball assessment, and these results will have implications for choice of surgical therapy in many patients with valvular heart disease.

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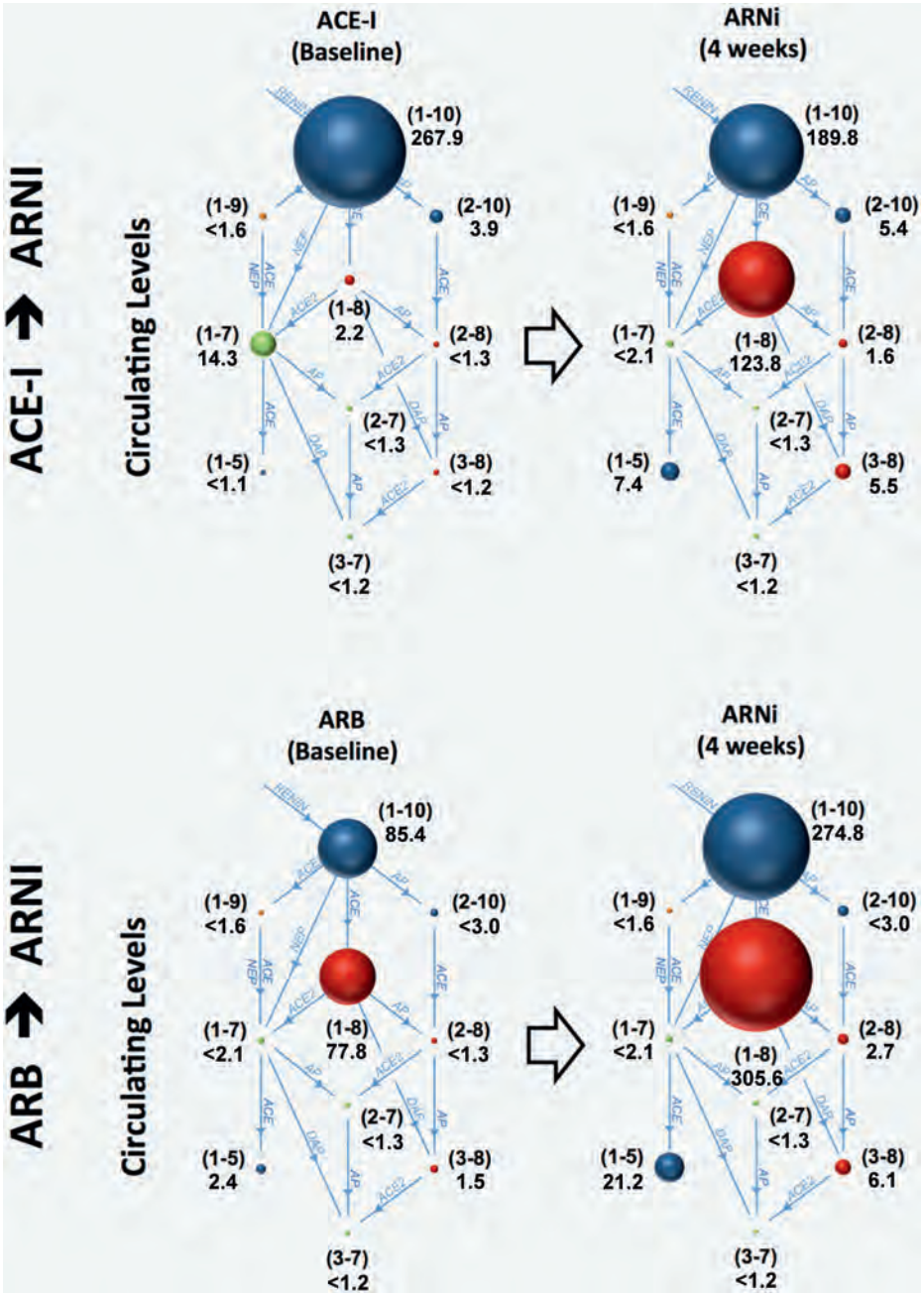
Renin-Angiotensin System Fingerprints of Heart Failure With Reduced Ejection Fraction

Blockade of the renin-angiotensin system (RAS) represents a cornerstone in the treatment of heart failure with reduced ejection fraction (HFrEF) (1). Beside established pharmacological therapy with angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin II type 1 receptor (AT1R) blocker (ARB), the combined inhibition of the angiotensin receptor and neprilysin (ARNI) has been proven beneficial in HFrEF and embedded in the treatment guidelines (1,2). RAS consists of an enzymatic cascade generating diverse angiotensin metabolites. Angiotensin II (AngII) (Ang1-8) exerts numerous detrimental effects by binding to its receptor AT1R promoting the progression of heart failure, whereas its actions on the type 2 receptor counteract AT1R mediated vasoconstriction, inflammation, and cellular growth signaling. The recent discovery of counter-regulatory peptides, including Ang1-7, or as meanwhile also suggested for Ang1-5 or Angiotensin IV (AngIV) (Ang3-8), changed our conception of RAS. Ang1-7 similarly promotes vasodilation and is able to downregulate AT1R. Although neprilysin (NEP) has pleiotropic effects on numerous vasoactive peptides, it is also an enzyme of RAS.

A simultaneous measurement of multiple systemic angiotensin peptides has only recently become available using mass spectrometry technology. This study aimed to explore the effects of therapy conversion to ARNI on systemic RAS patterns. Blood samples of stable chronic HFrEF patients were collected 4 h after the ingestion of morning medication including the RAS blocker at baseline (ACE-I: n = 6 and ARB: n = 6) and 6 weeks after therapy conversion to ARNI. ACE-I therapy was withheld for 72 h before the initiation of ARNI. In the case or ARB, ARNI was started without washout as recommended. Blood samples were immediately stabilized for the determination of circulating angiotensin levels by mass spectrometry (Attoquant Diagnostics, Vienna, Austria). N-terminal pro-B-type natriuretic peptide and active renin concentration were determined simultaneously. Moreover, plasmatic NEP activity was measured directly by a novel approach—a kinetic assay using Ang1-10 as the natural substrate of NEP and measuring the formation of its product Ang1-7 by mass spectrometry.

FIGURE 1 RAS Fingerprints of HFrEF Patients With Former ACE-I (n = 6) or ARB (n = 6) Therapy Converted to ARNI



The renin-angiotensin system (RAS) peptide cascade is illustrated as a pedigree starting at Ang1-10. Each intersection represents a specific peptide fragment symbolized by colored spheres, the amino acid sequence is indicated by numbers in brackets. Main responsible enzymes involved in the reactions are annotated at the conjunction lines. Size of spheres and numbers beside represent absolute concentrations of angiotensins (pg/ml, median values) analyzed by mass spectrometry. Ang1-10 – angiotensin I (AngI); Ang1-8 – Angiotensin II (AngII); Ang2-8 – Angiotensin III (AngIII); Ang3-8 – Angiotensin IV (AngIV). ACE-I = angiotensin-converting enzyme inhibitor; AP = aminopeptidase; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; DAP = diaminopeptidase; HFrEF = heart failure with reduced ejection fraction; NEP = neprilysin.

NEP activity was significantly reduced after therapy conversion to ARNI (68.7 [interquartile range (IQR): 45.9 to 169.6] ng[Ang1-7]/ml/h vs. 35.9 [IQR: 17.1 to 48.2] ng[Ang1-7]/ml/h; p = 0.004), confirming an efficient uptake of the drug. Likewise NT-proBNP levels decreased significantly (1,933 [IQR: 862 to 3,134] pg/ml vs. 1,309 [IQR: 469 to 2,184] pg/ml; p = 0.041) in line with observations from the clinical study (2). Interestingly there was a trend for higher renin levels after induction of ARNI (425 [IQR: 33 to 944] μIE/ml vs. 1,016 [IQR: 132 to 2,016] μIE/ml; p = 0.071). RAS fingerprints are displayed in **Figure 1**. For the converted ACE-I group a significant increase in AngII, Ang1-5, and AngIV was apparent. When converting from ARB to ARNI (introduction of NEP inhibition [NEPi]), the proportions of angiotensins remained similar. However, patients displayed higher concentrations of all systemic angiotensins on ARNI with significantly higher levels of the downstream metabolites Ang1-5 and AngIV.

Although NEP is principally a membrane-bound endopeptidase, the detection of therapy response in plasma suggests that circulating NEP might serve as surrogate for systemic NEP actions and that soluble NEP may be a useful biomarker in HFrEF, as already discussed (3). The introduction of NEPi was not associated with qualitative alterations in systemic RAS patterns but rather with elevation of all angiotensins. The profound clinical benefits of NEPi may lie in its net effects on the interplay of vasoactive peptides, yet it seems that NEPi also triggers RAS activation. Potential controversial effects of NEPi have long been discussed before the conduction of the PARADIGM-HF (Angiotensin-Neprilysin Inhibition versus Enelapril in Heart Failure) trial, and pharmacokinetic data showed that also LCZ696 (ARNI) leads to a significant dose-dependent elevation of AngII but also renin in healthy volunteers (4). RAS activation affects all angiotensin metabolites equally, including AngII and Ang1-7, which in their higher concentration could exert beneficial RAS effects alongside an efficient AT1R blockade. Excess of the downstream angiotensins as AngIV, which is discussed to exert vasoprotective properties, may further enhance beneficial ARNI effects.

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Circulating Long Noncoding RNAs in Personalized Medicine

Response to Pioglitazone Therapy in Type 2 Diabetes

Pioglitazone is a thiazolidinedione insulin sensitizer that improves left ventricle (LV) diastolic function in patients with type 2 diabetes mellitus (T2DM) (1). Unfortunately, the clinical use of pioglitazone is limited by the risk of adverse effects (2). Predictive tools are essential to monitor therapeutic effectiveness. Long noncoding RNAs (lncRNAs) are novel biomarkers of cardiac dysfunction (3). Nonetheless, no study has investigated the use of circulating lncRNAs as biomarkers of therapeutic efficiency. Here, we hypothesize that pre-treatment levels of circulating lncRNAs predict the response to pioglitazone therapy.

The PIRAMID (Pioglitazone Influence on tRiglyceride Accumulation in the Myocardium In Diabetes) study was a prospective intervention designed to evaluate the effect of pioglitazone on myocardial