Renin released from the kidneys, along the cascade of the renin–angiotensin–aldosterone axis, is a major regulator of blood pressure via the generation of angiotensin II and of body sodium and potassium via aldosterone release. Under normal conditions, renin decreases with age and higher blood pressure, whereas salt depletion stimulates renin release. In 1972, Brunner and Laragh first introduced the concept of classifying hypertensive patients according to plasma renin activity in relation to the daily sodium excretion. Among patients with essential hypertension, those with normal (57%) or high (16%) renin had an 11 and 14% frequency of heart attacks or strokes, respectively, whereas none of the low renin patients (27%) had such complications. Several subsequent studies noticed an increased risk of myocardial infarction, cardiovascular disease, or all-cause mortality with higher circulating renin levels, whereas none of the low renin patients (27%) had such complications. The initial report by Brunner and Laragh was cross-sectional, with cases of myocardial infarction or stroke occurring both before and after the renin profiling. Blumenfeld investigated patients admitted to an emergency department with a suspected cardiovascular or coronary events. Strong points of the Framingham cohort were the long follow-up, on average 7.1 years, of the patients, the large community-based cohort (3408 individuals), and the standardized conditions of the blood sampling, which minimized the influence of diurnal variability and body position on the renin level, and the sensitivity analyses dealing with the potential confounding by previous cardiovascular disease or antihypertensive drug treatment. The variability of the renin measurements was high, averaging (±SD) 28 ± 193 μU/mL in women and 32 ± 96 μU/mL in men. The Framingham investigators did not obtain repeat measurements of renin. They could therefore not correct for regression dilution bias, and might have underestimated the strength of the associations between outcome and renin. Finally, 1414 participants (41.5%) had their renin measurements taken while on antihypertensive drug treatment. None of the associations between mortality and renin reached significance in the untreated subjects.

The Framingham studies address some of the weaknesses of previous studies. The initial report by Brunner and Laragh was cross-sectional, with cases of myocardial infarction or stroke occurring both before and after the renin profiling. Blumenfeld investigated patients admitted to an emergency department with a suspected diagnosis of myocardial infarction before any acute treatment was administered. The plasma renin activity was 2.7-fold higher among confirmed cases than non-cases. As a continuous variable, plasma renin activity was the strongest independent factor associated with myocardial infarction. However, the renin secretion is under adrenergic control. Sympathetic arousal in patients with chest pain and the non-reported use of chronic background medication make Blumenfeld’s study difficult to interpret in terms of the long-term prognostic significance of renin. The sample size of the community-based Framingham study was larger than in any other cohort or case–control study. These reports included male middle-aged day-shift workers or selected patients with essential hypertension or a previous history of stroke. At variance with the continuous scale on which renin was measured, several researchers dichotomized the renin distribution.
arbitrary cut-off points to delineate subgroups increases the probability of false-positive results. For these reasons, none of the other studies\textsuperscript{2–4,7} match the external validity of the Framingham findings.\textsuperscript{6,8}

In our opinion, the Framingham findings\textsuperscript{6,8} do not lend support to the concept that high circulating renin levels might be a clinically significant predictor of myocardial infarction or mortality. In fact, Wang and co-workers\textsuperscript{8} demonstrated that among the new risk factors, the B-type natriuretic peptide and the urinary albumin-to-creatinine ratio outperformed renin in the prediction of mortality and that accounting for composite scores of these new biomarkers only resulted in a negligible improvement of risk stratification. The receiver operating characteristic (ROC) curves with the new biomarkers added to the conventional risk factors overlapped with the ROC estimates only based on the latter.\textsuperscript{6}

The positive association between myocardial infarction and renin in some studies\textsuperscript{2–3} has fuelled a lively and at times acid\textsuperscript{9} debate on the possible adverse effects of a reduction of salt intake at the level of the general population. Alderman summarized the hypothesized underlying mechanisms.\textsuperscript{10} Reduction of sodium intake by 100 mmol per day increases plasma renin activity three-fold. An inverse relationship of sodium/volume to renin release is part of the normal mechanism for control of blood pressure and urine flow. However, in addition, an activated renin–angiotensin–aldosterone system, particularly in the presence of hypertension, adversely affects the vascular endothelium, smooth muscle cells and inflammation associated with atherosclerotic lesions. The two Framingham reports\textsuperscript{6,8} help to put this dispute to rest. Moreover, the association between total mortality and renin weakening with time, as first reported in Parikh et al.\textsuperscript{[8]} and the lack of association between the risk of cardiovascular or coronary events and renin\textsuperscript{8} suggest a mechanism of reverse rather than direct causality. An editorial comment on the first human and animal studies of the association between cardiovascular complications and renin,\textsuperscript{11} published in 1972, already suggested that patients with advanced cardiovascular disease might have raised circulating renin levels, because of the renal involvement. Over more than 30 years, the argument therefore turned full circle. In contrast, what stood the test of time is the concept first raised by Laragh and co-workers\textsuperscript{1,12} and currently endorsed in most guidelines\textsuperscript{13} that high renin hypertension, mainly prevalent among young and white patients, as opposed to the elderly or patients of other ethnic groups, respectively, should be preferentially treated with inhibitors of the renin–angiotensin system.

**Acknowledgements**

The authors gratefully acknowledge the expert assistance of Mrs Sandra Covens.

**Conflict of interest:** none declared.

**References**