Background: Remodelling of the extracellular matrix (ECM) is a hallmark of heart failure (HF). Our previous analysis of the secretome of murine cardiac fibroblasts returned ADAMTS5 (a disintegrin and metalloproteinase with thrombospondin motifs 5) as one of the most abundant proteases. ADAMTS5 cleaves chondroitin sulphate proteoglycans (CSPGs) such as versican. The contribution of ADAMTS5 and its substrate versican to HF is unknown. Methods: Versican remodelling was assessed in mice lacking the catalytic domain of ADAMTS5 (Adamts5 Cat). Proteomics was applied to study ECM remodelling in left ventricular samples from HF patients, with a particular focus on the effects of common medications used for the treatment of HF. Results: Versican and versikine, an ADAMTS-specific versican cleavage product, accumulated in ischemic HF patients. Versikine was also elevated in a porcine model of cardiac ischemia/reperfusion injury and in murine hearts after angiotensin II (Ang II) infusion. In Adamts5 Cat mice, Ang II infusion resulted in an aggravated versican build-up and hyaluronic acid disarrangement, accompanied by reduced levels of integrin beta 1, filamin A and connexin 43. Echocardiographic assessment of Adamts5 Cat mice revealed a reduced ejection fraction and an impaired global longitudinal strain upon Ang II infusion. Cardiac hypertrophy and collagen deposition, however, were similar to littermate controls. In a proteomics analysis of a larger cohort of cardiac explants from ischemic HF patients (n=65), the use of beta-blockers was associated with a reduction in ECM deposition, with versican being among the most pronounced changes. Subsequent experiments in cardiac fibroblasts confirmed that beta1-adrenergic receptor stimulation increased versican expression. Despite similar clinical characteristics, HF patients treated with beta-blockers had a distinct cardiac ECM profile. Conclusions: Our results in animal models and patients suggest that ADAMTS proteases are critical for versican degradation in the heart, and that versican accumulation is associated with impaired cardiac function. A comprehensive characterisation of the cardiac ECM in ischemic HF patients revealed that beta-blockers may have a previously unrecognized beneficial effect on the cardiac CSPG content.