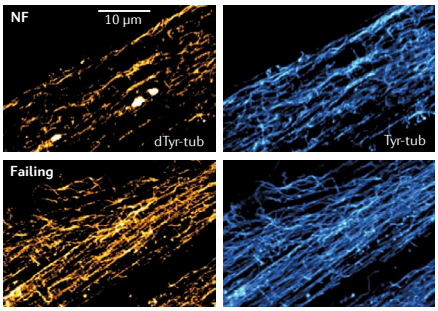
HEART FAILURE

# Targeting the cytoskeleton in heart failure

New insights into the mechanisms of heart failure suggest that detyrosination, a microtubule post-translational modification that increases the mechanical resistance of the cytoskeleton, is a potential therapeutic target. "Suppressing detyrosination … reduced the stiffness of myocytes isolated from patients with heart failure, and improved the magnitude and kinetics of both myocyte contraction and relaxation," says lead study investigator Benjamin Prosser.

Prosser and colleagues used mass spectrometry, super-resolution imaging, and single-cell mechanical assays to assess cardiomyocytes isolated from left ventricular samples from patients with heart failure of various aetiologies and severity and from individuals with non-failing hearts. Failing cardiomyocytes had upregulation and stabilization of the cytoskeleton, specifically microtubules, intermediate filaments, and associated proteins, compared with non-failing cardiomyocytes. The microtubule network in failing cardiomyocytes was dense and heavily detyrosinated, which led to increased cardiomyocyte stiffness and impaired contractility, and these features were independent of disease origin.

Suppression of microtubule detyrosination with pharmacological or genetic approaches reduced the stiffness of failing cardiomyocytes and restored 40–50% of the lost contractile function. "We saw marked improvements in relaxation kinetics particularly in cardiomyocytes from patients with diastolic dysfunction, raising the possibility that a microtubule-based intervention could one day be used for treating patients with heart failure with preserved ejection fraction, a burgeoning patient population that lacks any viable therapeutic interventions," remarks Prosser. Compounds for manipulating detyrosination have been approved by the FDA, but Prosser cautions that the long-term safety and efficacy of this approach must be examined.




Credit: Detyrosinated tubulin (dTyr-tub) and tyrosinated tubulin (Tyr-tub) in microtubule networks from non-failing (NF) and failing cardiomyocytes. Reprinted from Chen, C. Y. et al. Suppression of detyrosinated microtubules improves cardiomyocyte function in human heart failure. *Nat. Med.* https://doi.org/10.1038/s41591-018-0046-2 (2018).

"Preclinical studies in small and large animal models are next on the docket," says Prosser, "but we must be careful to select the appropriate animal models that accurately reflect the cytoskeletal phenotypes of patient populations to avoid repeating the mistakes of the past."

*Irene Fernández-Ruiz*

**ORIGINAL ARTICLE** Chen, C. Y. et al. Suppression of detyrosinated microtubules improves cardiomyocyte function in human heart failure. *Nat. Med.* https://doi.org/10.1038/s41591-018-0046-2 (2018)
**FURTHER READING** Kim, G. H. et al. Reverse remodelling and myocardial recovery in heart failure. *Nat. Rev. Cardiol.* **15**, 83–96 (2018)

AORTIC DISEASES

# AAA: to screen or not to screen?

Screening programmes for abdominal aortic aneurysm (AAA) have been introduced in the UK and Sweden on the basis of clinical trials showing the beneficial effect of this approach in reducing mortality from AAA. A study now calls these programmes into question by revealing that screening did not contribute to the reduction of AAA mortality in Sweden since the programme implementation, and could even be harmful.

AAA incidence has dramatically decreased in the UK and Sweden in the past 30 years. "Because of the rapidly changing epidemiology of AAA, the clinical trials on AAA screening are outdated and the effects of screening in contemporary populations are unknown," explains study investigator Minna Johansson. In this retrospective, registry-based, cohort study, the investigators assessed the incidence of AAA and of disease-specific mortality and surgery in men aged 65 years who were screened for the disease between 2006 and 2009, compared with non-screened, age-matched men. "In Sweden, the screening programme was introduced stepwise, county by county; this offered a unique possibility to compare contemporary screened and non-screened men of the same age," says Johansson.

Mortality from AAA decreased >70% between the early 2000s and 2015 in men aged 65–74 years, in both screening and control cohorts, and the study only reported an additional, non-significant reduction of 24% with screening. Other factors, notably the reduction in the prevalence of smoking, might therefore explain the reduction in AAA mortality. In addition, the odds of being diagnosed with AAA and of having surgery were higher in the screening cohort than in the control group. Altogether, the results indicated that for every 10,000 men screened, 2 men avoided death from AAA but 49 men were overdiagnosed and 19 underwent avoidable surgery.


Credit: V. Summersby/Macmillan Publishers Limited

> "Given the substantially less favourable benefit-to-harm balance found in this study, the AAA screening programme should be revalidated."

Given the substantially less favourable benefit-to-harm balance found in this study, the AAA screening programme should be revalidated.

"When we invite asymptomatic citizens to an intervention, we must be reasonably certain that this intervention causes more good than harm. It is doubtful whether this is the case for AAA screening," concludes Johansson.

*Alexandra Le Bras*

**ORIGINAL ARTICLE** Johansson, M. et al. Benefits and harms of screening men for abdominal aortic aneurysm in Sweden: a registry-based cohort study. *Lancet* **391**, 2441–2447 (2018)