**Title:** The End of Heart Disease: Next Generation Therapeutics for Atherosclerosis

**Body:**

Heart disease and stroke are the leading causes of death globally, and in the United States, they are responsible for more death than all cancers combined [1]. Sharing atherosclerosis as an underlying cause, both heart disease and stroke are dependent upon the buildup of ‘plaque’ into an atherosclerotic lesion behind the endothelial layer of the blood vessel wall [2]. These plaques are formed when low density lipoprotein cholesterols accumulate in the space, become oxidized or otherwise modified, are devoured by white blood cells called macrophages until they become gluttonous foam cells that accumulate and die, becoming the plaque [2]. Although it can be exacerbated by environmental factors, this plaque buildup is a continuous consequence of our imperfect metabolism operating normally, otherwise known as intrinsic aging.

Current clinically available treatments for atherosclerosis, both pharmaceutical and mechanical, are aimed at either:

● Slowing down the rate of development of atherosclerosis (statins and cholesterol drugs)[3]

● Reducing the immediate risk of blood clots (stent placement, angioplasty, endarterectomy)[3]

● Removing small blood clots (thrombolytic medicines)[4]

● Reducing blood pressure (aspirin, calcium channel blockers)[3,4]

● Overall health management (cut smoking, healthy eating, exercise)[3]

Some of these approaches have shown limited efficacy in recent analyses. Stenting [5], for example, was found not to significantly improve the risk of ischemic cardiovascular events or mortality in a recent meta-analysis. But even the most impactful of the approaches listed above suffer from the same problem as the least – they cannot undo atherosclerosis. Reversal of atherosclerosis is essential if we are ever to truly beat heart disease, but it is widely regarded as impossible with current therapies. Harboring this belief, many clinicians, researchers, and regulatory authorities mistakenly neglect this approach.

Interestingly, macrophages themselves are capable of reducing the size of atherosclerotic plaques through efferocytosis, whereby they engulf and clear apoptotic macrophages within early atherosclerotic lesions [6]. This process inevitably fails in more advanced atherosclerosis and exacerbates the problem of the ‘necrotic cores’ [6]. Nevertheless, intravascular ultrasound has shown that a partial regression in atherosclerosis is possible in individuals when proper management of cardiovascular risk factors including diabetes, hypertension, dyslipidemia, and smoking is implemented [7,1]. This suggests that under the right conditions reversal of atherosclerosis is possible.

Several groups are also developing drugs that can clear atherosclerotic plaques. Cyclarity Therapeutics is one such group, who engineered a cyclodexterin (a cyclic carbohydrate) called UDP-003 capable of binding with high-affinity to 7-ketocholesterol, taking it into its hydrophobic core so it may be cleared from foam cells [8]. In 2021, Cyclarity was awarded an Innovation Passport through the ‘Innovative Licensing and Access Pathway’ in the UK, and Phase I trials are scheduled to start there in 2024 [8].

The approach of another group, Repair Biotechnologies, derives inspiration from *Mycobacteria*, which are capable of degrading cholesterols that macrophages cannot [9]. The genetic code of these cholesterol-degrading Mycobacterial enzymes was given to human macrophages, allowing them to produce the enzymes for themselves [9]. Macrophages engineered by this ‘Cholesterol-Degrading Platform’ (CDP) have been shown to reduce atherosclerotic plaques by 48% in mice [10].

The therapeutic reversal of atherosclerosis, while in the early stages of development and clinical acceptance, has the potential to meaningfully impact the landscape of heart disease and stroke in a way current therapies simply cannot.

Healthcare practices are notoriously slow to change, sometimes taking decades for new discoveries to benefit the patient due to delays in guideline changes caused by a number of factors. Such factors include disagreements between professional societies, the reluctance of doctors to change their clinical practices, and even a lack of time for doctors to update their knowledge base [1]. The core sentiment driving this stagnation is concern about patient safety, a concern that paradoxically undermines that safety through delayed reform. We see this in the failure to rapidly develop and implement the clinical use of therapies and drugs that reverse atherosclerosis. Patients, physicians, policy makers, and the public should be aware that such therapies are on the way and that anything that can be done to hasten their arrival would save countless lives.

**References:**

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