# SAVING LIFE AND LIMB

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*Many people with critical limb ischaemia have no option but to have the affected limb amputated. Can regenerative medicine offer an alternative?*

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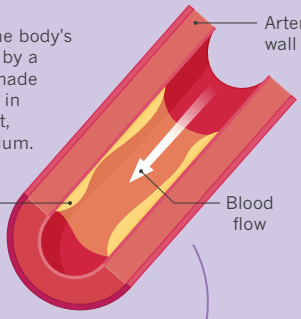
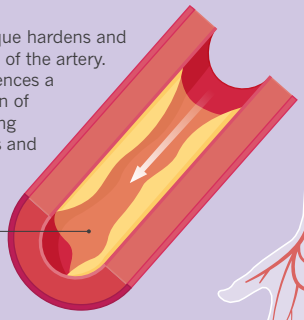
## A PROGRESSIVE DISEASE

Critical limb ischaemia (CLI) is the most severe form of a chronic cardiovascular condition called peripheral arterial disease, which is usually caused by atherosclerosis. Although CLI notably affects the limbs, the majority of patients will die from a heart attack or stroke[1].

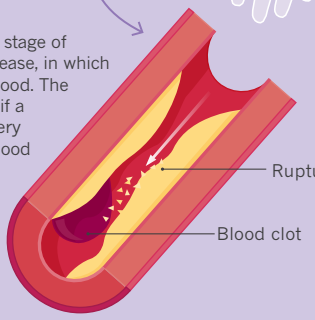
1 In atherosclerosis, the body's arteries are affected by a build-up of plaque made of substances found in the blood such as fat, cholesterol and calcium.




2 Over time, the plaque hardens and narrows the lumen of the artery. The patient experiences a gradual progression of symptoms, including tingling, numbness and pain in their limbs.

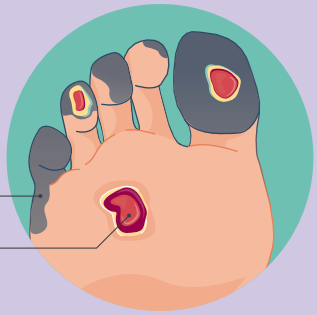



3 CLI is usually the end stage of peripheral arterial disease, in which a limb is starved of blood. The onset can be sudden if a plaque in a major artery ruptures, causing a blood clot that rapidly and severely restricts blood flow.




## EXTREME SYMPTOMS

The effects of CLI are usually most severe in the extremities of the affected limb.

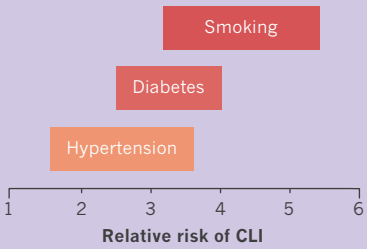





More than **50%** mortality within 5 years of CLI diagnosis[2].

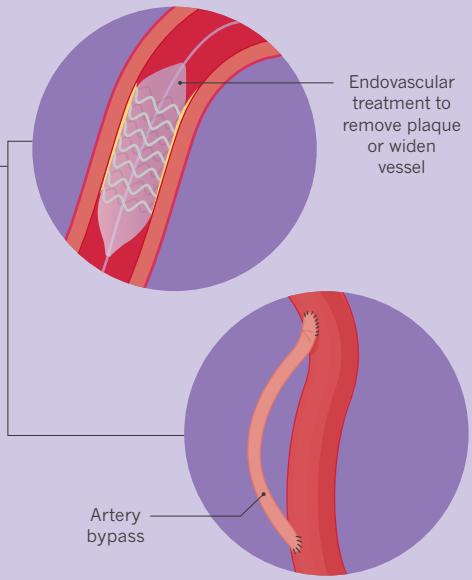
## GROWING PAIN

In Europe and the United States, there are 500–1,000 new cases of CLI per 1 million people each year[3]. The risk of developing CLI is increased for patients with certain risk factors, including hypertension, diabetes and smoking[1].




## CURRENT TREATMENTS

The gold standard in treatment for CLI is surgery to unblock or widen the obstructed blood vessel, or to bypass it through another vessel.



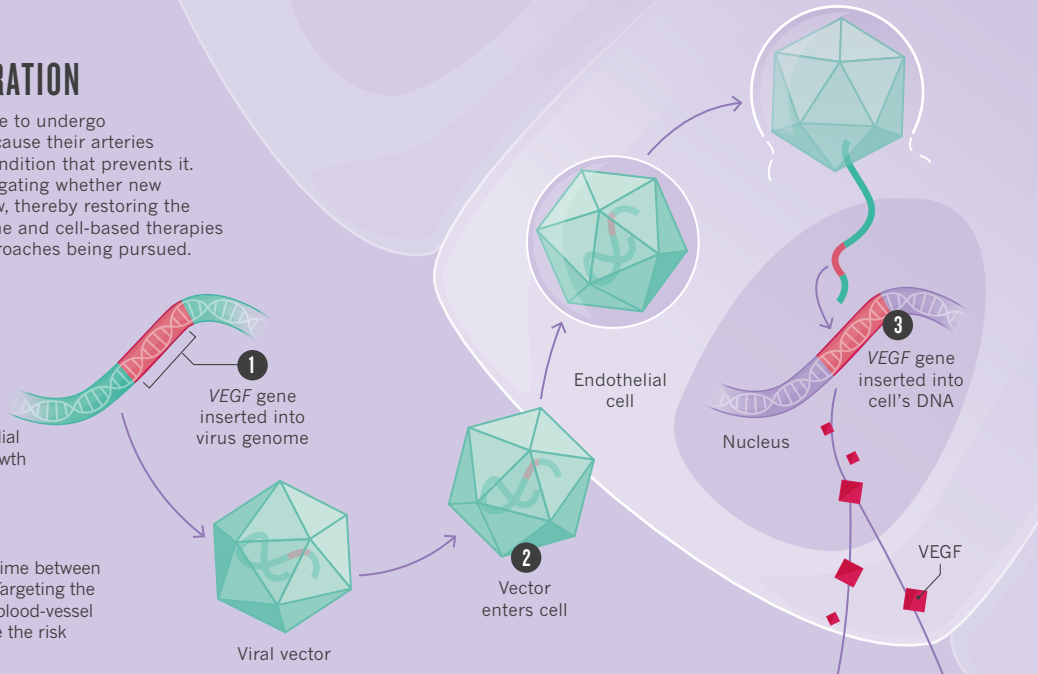
# RESCUE THROUGH REGENERATION

Up to 30% of people[4] with CLI are unable to undergo surgical treatments for the condition because their arteries are too calcified or they have another condition that prevents it. As an alternative, researchers are investigating whether new blood vessels can be encouraged to grow, thereby restoring the supply of blood to the affected limb. Gene and cell-based therapies are the main regenerative-medicine approaches being pursued.

## GENE THERAPY

A modified virus or other vector is used to insert genes into the cells that line the inner wall of the blood vessel. These genes encode proteins, such as vascular endothelial growth factor (VEGF), that promote the growth of new blood vessels.

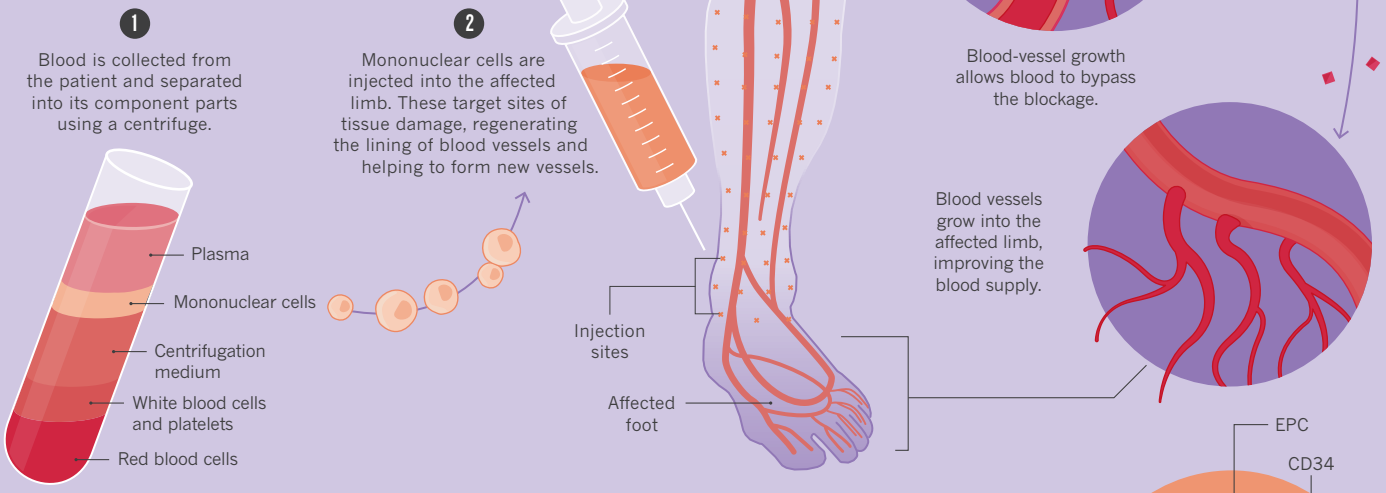
So far, gene therapies have been shown to improve wound healing in patients, but do not considerably prolong the length of time between diagnosis with CLI and limb amputation[5]. Targeting the correct cells is crucial because promoting blood-vessel formation in healthy tissues might increase the risk of tumours.




## CELL THERAPY

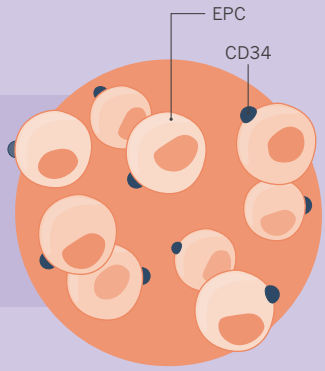
Cells from the patient are used to supply substances that promote blood-vessel formation and boost the growth of new arteries to the affected limb. Cell therapy seems to provide a more sustained and targeted release of such substances than gene therapy.

Small phase I and phase II clinical trials have shown that cell-based therapies are safe and improve wound healing, but the trials were not large enough to detect any improvements in delaying amputation[4].




## NEXT STEPS

Efforts to optimize cell-based therapies for CLI are under way. One approach is to increase the proportion of a type of mononuclear cell called endothelial progenitor cells (EPCs), which have a role in blood-vessel regeneration, in the injected cells. This is achieved by selecting cells that express the protein CD34 on their surface. A small 2009 trial[6] showed that people who received such CD34-expressing cells showed improvements in pain scores and in the distance that they could walk. A larger trial is being planned in Japan for later this year to test whether the therapy can delay or prevent the need for amputation.




Sources: 1. Davies, M. G. *Methodist Debakey Cardiovasc. J.* **8,** 10–14 (2012). 2. Teraa, M., Conte, M. S., Moll, F. L. & Verhaar, M. C. *J. Am. Heart Assoc.* **5,** e002938 (2016). 3. Norgren, L. *et al. J. Vasc. Surg.* **45,** S5–S67 (2007). 4. Samura, M. *et al. J. Transl. Med.* **15,** 49 (2017). 5. Belch, J. B. *et al. Lancet* **377,** 1929–1937 (2011). 6. Kawamoto, A. *et al. Stem Cells* **27,** 2857–2864 (2009).