Dissolving blood clot clots effectively and safely (Fibrinolysis)

Fibrinolysis is the body's defense against the build-up of fibrin (clots) needed to arrest bleeding and to repair the daily wear and tear injuries to the blood vessel inner surface. This same enzyme system is used in the treatment of blood clots, which are the triggering cause of heart attacks and of 85% of strokes, which are the leading causes of death and disability world-wide.

Fibrinolysis was misunderstood to only involve tPA
Unfortunately, when therapeutic fibrinolysis was begun 30 years ago, only one of the two enzymes, called activators, involved in fibrinolysis had been identified. Therefore, only this one, called tPA, was used in therapy. Remarkably, tPA alone remains the way fibrinolysis is manage to the present day.

By contrast, we now know that tPA's function in nature is limited to the initiation of fibrinolysis, analogous to the function of the starter of a car. As with the starter, tPA alone has never been very effective and tPA also has been associated with serious hemorrhagic side effects.

In nature, when a clot forms in an artery, tPA that is stored in the vessel wall is released, binds to the clot and iniates its fibrinolysis. Any tPA remaining is eliminated within minutes, since tPA causes bleeding. After this tPA initiation of fibrinolysis, the second activator in blood, called uPA, continues and completes dissolution of the clot. The tPA does 1/3 of the job and uPA does 2/3.

The two activators together are much more effective and also safer than tPA alone, since much lower doses than with tPA are required.

Due to tPA, fibrinolysis became discredited and replaced by angioplasty (PCI)
The inadequate results of fibrinolysis with tPA alone resulted in fibrinolysis being replaced by PCI as the treatment of choice for heart attack, and PCI is increasingly being used in stroke as well. However, PCI is a technically demanding procedure that is time-consuming, requires hospitalization, and is costly. As a result, optimal salvage of heart or brain function, which requires that circulation be restored within 1-2 hours of a heart attack or stroke, cannot be achieved in most patients. Only fibrinolysis can open a blocked artery sufficiently rapidly, but this requires fibrinolysis with a sequential combination of tPA and uPA, as in nature, rather than tPA alone.

Therapeutic fibrinolysis with tPA combined with uPA has been validated
This natural, sequential combination was once tested in 101 heart attack patients who were given a mini dose of tPA (5% of its standard dose) which was followed by 90 minute infusion of uPA, mimicking nature's sequence in which uPA in the circulation completes the process. A complete clot dissolution in the coronary artery occurred in 82% of the patients and the mortality rate was only 1%. This result compares with a coronary opening rate of 45% and a mortality rate of 6.3% in

the best of the tPA alone studies. This study was published in 1995 in a leading heart journal but was never repeated.

When PCI is used as the primary treatment for heart attack, the mortality is about 5%. However, PCI can cause dislodgement of the clot by the catheter with fragments blocking the peripheral coronary circulation out of reach of the catheter; only reachable by fibrinolysis.

Prospects for the future
Unfortunately, the company that was developing uPA abandoned it after the 101 patient trial, and uPA has not been on the US market since then. More recently, as single site mutant of uPA has been developed which is more stable at therapeutic concentrations. It has completed preclinical testing is scheduled to start clinical trials in heart attack and stroke in the latter half of 2018. A sequential combination of a mini-bolus of tPA followed by mutant uPA will be used.

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Fibrin-specific and effective clot lysis requires both plasminogen activators and for them to be in a sequential rather than simultaneous combination.
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