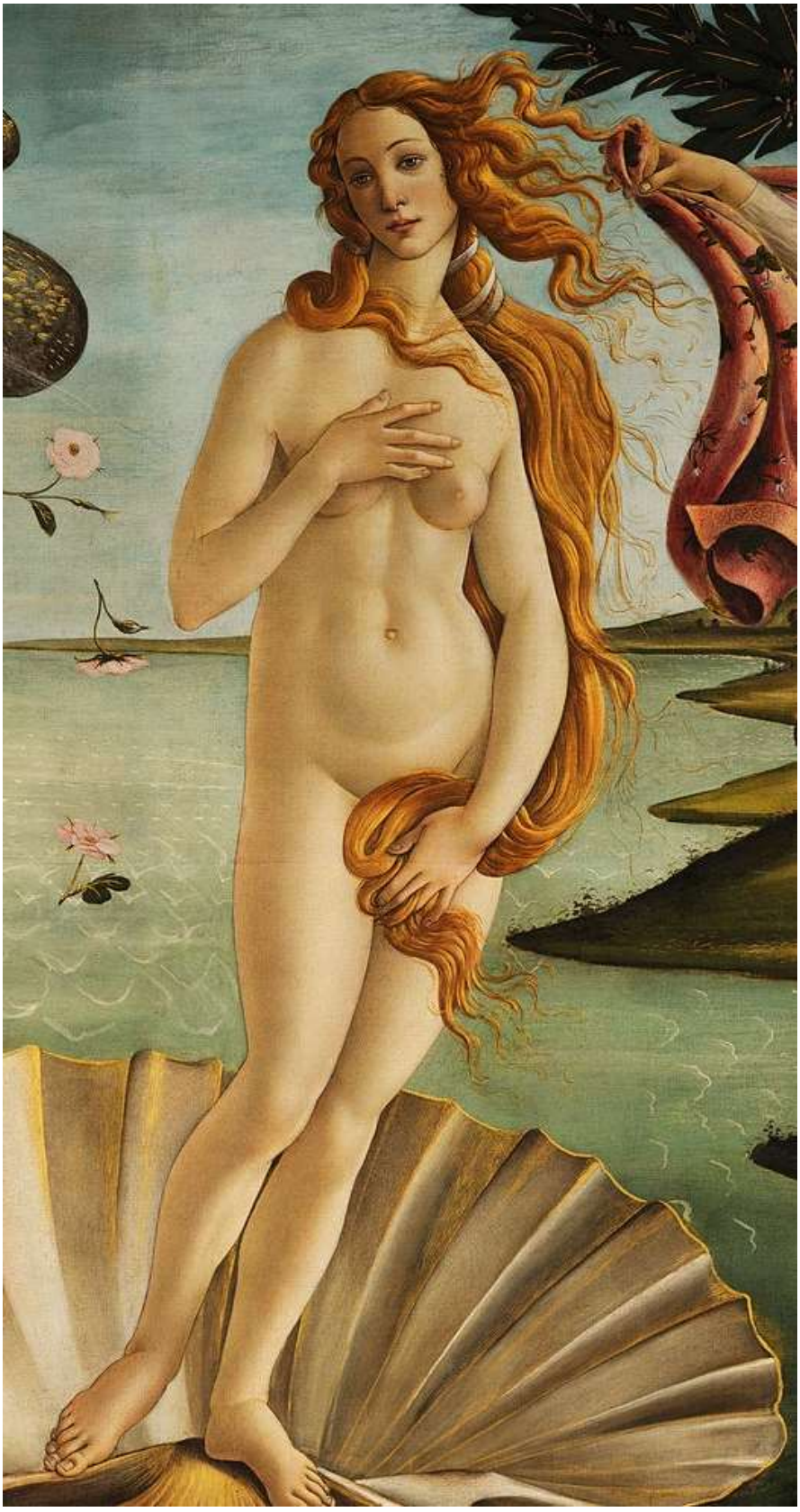
THE NORTHERN HOSPITAL

TISSUE PLASMINOGEN ACTIVATOR



"The Birth of Venus", (Detail) Tempera on canvas, Sandro Boticelli, c. 1485. Galleria degli Uffizi, Florence.

"There is a place in the woody vales of deepest Ida, far from the trodden paths and covered over with pine and holly... From there, reclining against a tree, I was looking forth upon the walls and lofty roofs of the Dardanian city, and upon the sea, when lo! It seemed to me that the earth trembled beneath my feet - I shall speak true words, though they will scarce have credit for truth - there appeared before my eyes, propelled on swift wings, the god Hermes!.. and at the self-same time, three glorious goddesses - Aphrodite, Pallas Athena, and Hera herself set down upon that verdant place. I was dumbstruck...chill tremors raised my hair on end, when the winged herald said "Lay aside your fear! You are to be the arbiter of beauty...pronounce which one deserves to vanquish the other two in this regard!" And, lest I should refuse, he laid command on me in the name of Zeus, then suddenly through the paths of ether he flew forth toward the stars...."

Ovid, "The Heroines" c. 15-25 B.C. E

There had never been such a celebration on Mount Olympus. All the gods had been invited to the marriage celebrations of the hero Peleus, ex Argonaut and Calydonian Boar hunter and the sea nymph, Thetis. All that is except for Eris, the goddess of discord. Greatly insulted Eris showed up anyway, but was told in no uncertain terms that she was not wanted. Angry and humiliated Eris departed, but not before tossing a beautiful golden apple into the middle of the crowed hall of the gods. On this apple was the inscription, "to the fairest". Almost immediately and undignified squabble broke out between the three most stunningly beautiful goddesses, Hera, wife of Zeus, Athena, the goddess of wisdom and war, and Aphrodite the goddess of love. Each, rather ungraciously overlooking the fact that the bride Thetis was herself very beautiful, claimed the golden apple. The arguments became so heated that an appeal was made to Zeus to arbitrate and to judge who was the fairest of the three. Needless to say, Zeus, as the husband of Hera, was extremely uncomfortable with having to make such a choice. He wisely refrained from making a decision, but this did not appease the goddesses, or any of the other gods, who by now were starting to takes sides with one or other of the three claimants to the golden apple. Before things got completely out of hand, Zeus proclaimed that a completely neutral judge must be found. His choice fell on a mortal, a certain Paris, who he spied on Earth, tending a flock of sheep. He ordered Hermes, the messenger, to escort Hera, Athena and Aphrodite to Earth, and to seek out Paris and instruct him to make the impossible judgment.

Now Paris in reality was no simple shepherd. He was actually the youngest son of a very powerful king, but he liked to get away from his father's court, which he felt was suffocating. He found pleasure in the open fields, in nature and tending one of his father's many flocks of sheep. One afternoon he was resting in a verdant paradise, lying back looking up into the sky, lost in his own thoughts. Suddenly the ground shook as if a great earthquake had gripped the land, and out of the blazing sun appeared the majestic figure of the god Hermes. Paris was terrified. The hairs stood up on the back of his neck. "Lay aside your fear, Paris!", the great god thundered. "You have been chosen by Zeus himself to be the arbiter of beauty...you must pronounce which one of these three, deserves to vanquish the other two in this regard!" At that point three of the most dazzlingly beautiful women he had even seen appeared before him. Each introduced themselves. The first, "I am Hera, sister and wife of Zeus himself. I am the most powerful goddess in all of Olympus". The second, "I am mighty Athena, the goddess of all wisdom and of war". The third, who seemed much gentler than the other two, and yet at the same time just as fiercely determined. "I am Aphrodite, the goddess of love". With these introductions over, the three goddesses began to disrobe before Paris, who could not believe what he was seeing.

Fist to display her charms was Hera, who haughtily pushed aside Athena and Aphrodite. She walked slowly towards him, while performing slow and sensuous pirouettes. Paris's heart was pounding, aroused at one moment but terrified the next in the presence of the Queen of the gods, whose eyes were fierce and angry. She came close to him and whispered in his ear, "Choose me and I will make you a great King with dominion over all the lands of the Earth".

Next Athena, flung her great shield and spear to the ground, then slowly unfastened her robe, which she let fall to the ground. She walked slowly toward Paris, arms aggressively and warlike placed on her hips. Paris's heart was pounding, aroused at one moment but terrified the next at her Amazonian form and bearing. She came close to him and whispered in his ear, "Choose me, and I will make you the greatest leader of armies the world has ever known. You will have great victories that will live forever in the memories of men".

Finally Aphrodite approached him. She was clothed in flowing translucent silks dyed in the flowers of Spring. In her hair she wore a garland of hyacinth, violets and crocus. Paris was consumed by the sweet scent of the flowers that adorned her body. Paris's heart was pounding, aroused at one moment but then almost swooned as the intoxicating scents of her flowers consumed him. She walked slowly towards him and whispered in his ear, "There is a certain mortal woman, whose beauty is equal to my own. Choose me and I will see to it that she will fall uncontrollably in love with you". At that moment she dropped her garments to the ground. Paris was so overcome at the vision before him, he was scarce able to breathe, let alone make any sort of coherent pronouncement.

As Paris gathered his composure, terrifying thoughts ran through his mind. Whichever goddess he chose, would mean that he instantly made enemies of the other two. No god, let alone mortal had ever faced a more difficult choice. For a moment he though he must choose Hera, as she was the wife of Zeus. But unlike his father, the king, he was far happier in simple pleasurable pursuits than in ruling over great empires. He almost chose Athena, but then reflected his choice would be more out of fear of the goddess than anything else. And besides, unlike his older brother, he knew he was no soldier. For Paris the stunning vision of the third goddess, was enough for him to decide. He finally announced that "Aphrodite was the fairest of the three". Hera and Athena were outraged. They both flew back to Olympus, vowing that Paris would deeply regret his choice. Aphrodite graciously thanked him. She then whispered in his ear. "Be patient, Paris. Before the year is done, your father will send you and your brother to Sparta on a diplomatic mission. There you will meet the woman I promised you. The instant your eyes meet, she will fall in love with you. Her name is Helen".

The princely youth, who liked to play at shepherd boy, was forced to make the most difficult decision any mortal had to make. Whatever choice he made would bring him unimaginable gifts, but this could only be at unimaginable cost. By choosing Aphrodite he gained Helen of Sparta, who became Helen of Troy. But in so doing Paris earned the hatred of Hera and Athena, who took the side of the Greeks in the ensuing disastrous ten year Trojan War. The price of Helen's hand would be the destruction of his family and his home city.

Tissue plasminogen activator, like the golden apple of Eris is potentially a most dangerous agent indeed. It can effect the most wondrous results, but it also has a darkly sinister side. The decision to use it may on occasions, seem as difficult a decision as the Judgment of Paris!

TISSUE PLASMINOGEN ACTIVATOR

Introduction

Tissue Plasminogen Activator (tPA or rtPA - trade name "**Alteplase**"), is a tissue plasminogen activator that is produced by **recombinant DNA** technology.

It is used in a variety of life-threatening thromboembolic events, including:

- **STEMI**
- **Massive pulmonary embolism**
- **Acute ischaemic stroke.**

Its major complication is **bleeding** which can be lethal in the case of intracerebral bleeds in particular.

Classification

The fibrinolytic agents can be classified as;

1. Fibrin non-specific agents:
    - **Streptokinase** (given as an infusion), now no longer used.
    - **Urokinase** (given as an infusion on occasions by interventional radiologists for arterial clots).
2. Fibrin-specific agents:
    - **Reteplase** (given as two IV bolus doses, 30 minutes apart)
    - **Alteplase** (tPA, given as an IV infusion)
    - **Tenecteplase**, (given as a single IV dose)

The fibrin specific drugs primarily accumulate onto established thrombus and results in an effective local degradation of fibrin while minimizing the inducing of a generalized systemic fibrinolytic state.

SK had a number of serious disadvantages:

- Anaphylaxis, as it is a protein derivative derived from bacterial sources. Aboriginal and Torres Straight Islanders are more prone to this, possibly as a result of a relatively high incidence of previous sensitizing streptococcal infection.
- Previous use of SK precludes further use in the future, not only because of the risk of allergic reaction but also due to the development of neutralizing antibody decreasing subsequent effectiveness.

- It must be given as an infusion, (as opposed to bolus dosing for reteplase and tenecteplase)

The fibrin specific agents are now the preferred thrombolytic agents.

Preparation

Vials:

- Containing 50 mg of lyophilised alteplase powder (as well as polysorbate 80, arginine and phosphoric acid) plus 50 ml solvent and transfer cannula.

Mechanism of Action

Alteplase (recombinant tissue plasminogen activator) is chemically identical to endogenous tissue-type plasminogen activator.

It is synthesised using the complementary DNA (cDNA) for natural human tissue type plasminogen activator.

It is a serine protease that converts plasminogen to plasmin, which then catalyses the breakdown of fibrin.

Clot-selectivity is thought to be due to the activation of plasminogen *within* the thrombus (in preference to circulating plasminogen), which then initiates local fibrinolysis and hence clot dissolution.

Pharmacokinetics

Absorption:

- tPA is given as a peripheral intravenous infusion or intra-arterially.

Distribution:

- Distribution approximates that of the plasma volume

Metabolism:

- tPA is rapidly cleared from circulating plasma primarily by the liver.

  Its half-life is only **5 minutes.**

Indications

The major indications for use in the ED include:

1. STEMI:
   - If unable to access percutaneous intervention in a timely manner.
2. Pulmonary embolism:

- Massive pulmonary embolism with hypotension
- Massive pulmonary embolism with cardiac arrest
- *Consider* in sub-massive embolism with significant right ventricular strain.

3. Acute Ischaemic stroke:
   - Within 4.5 hours for anterior circulation strokes
   - May be considered up to 12 hours for posterior circulation strokes

Precautions-Contraindications [1]

Absolute contraindications:

Risk of bleeding:

- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed head or facial trauma within 3 months
- Suspected aortic dissection (including new neurological symptoms)

Risk of intracranial haemorrhage:

- Any prior intracranial haemorrhage
- Ischaemic stroke within 3 months
- Known structural cerebral vascular lesion (e.g. arteriovenous malformation)
- Known malignant intracranial neoplasm (primary or metastatic)

Relative contraindications:

Risk of bleeding:

- Current use of anticoagulants: the higher the international normalised ratio (INR), the higher the risk of bleeding
- Non-compressible vascular punctures
- Recent major surgery (within 3 weeks)
- Traumatic or prolonged (more than 10 minutes) cardiopulmonary resuscitation
- Recent (within 4 weeks) internal bleeding (e.g. gastrointestinal or urinary tract hemorrhage)

- Active peptic ulcer

Risk of intracranial haemorrhage:

- History of chronic, severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (more than **180 mm Hg** systolic or more than **110 mm Hg** diastolic)
- Ischaemic stroke more than 3 months ago, dementia, or known intracranial abnormality not covered in absolute contraindications

Other:

- Pregnancy

Adverse Effects

These include:

1. **Bleeding events:**
    - The most serious bleeding event is intracerebral bleeding which may be lethal.
    - GIT bleeding may also be lethal
2. Allergic reactions, (true IgE mediated allergic reactions are rare with tPA)
3. Angioedema:
    - Angioedema is an uncommon, but well documented complication of tPA.
    - The mechanism is thought to be related to plasmin activation of bradykinin.[3] The reaction is more likely to occur if the patient is taking concomitant ACE inhibitors as this also predisposes to increased levels of bradykinin, (**see Appendix II below**).
    - Airway threatening angioedema in a patient who has just been given tPA, represents a particularly challenging scenario in the ED, in view of the possible need for a surgical airway!

Dosing

STEMI:

Less than 65 kg	**Over 65 kg**
15 mg IV stat	15 mg IV stat

Then 0.75 mg/kg IV over 30 minutes *Then* 0.5 mg/kg IV over 60 minutes	*Then* 50 mg IV over 30 minutes *Then* 35 mg IV over 60 minutes

Massive and submassive PE: [1]

Less than 65 kg	**Over 65 kg**
Total Dose: 1.5 mg/kg (max 100 mg) IV Give 10 mg as bolus over 1 minute *Then* Remainder of dose IV over 2 hours	Give 10 mg IV as bolus over 1 to 2 minutes *Then* 90 mg IV over 2 hours

Cardiac arrest:

Specifically in the situation of PEA due to known PE

Give:

- **50 mg tPA administered as a rapid IV push over 1 minute while CPR is ongoing.**

The *timely* administration of 50 mg of tPA in 1 minute in patients with PEA due to confirmed PE is highly safe and effective leading to restoration of spontaneous circulation in the majority of such patients.

tPA may also be considered in PEA where there the patient has not responded to conventional management and there is a high suspicion of PE.

Subsequently 5000 units of heparin is given as an IV bolus, and the patient is started on an initial maintenance infusion of heparin at 10 U/kg per hour.

Despite chest compressions and other invasive manoeuvres during CPR, bleeding complications during the PEAPETT trial were surprisingly minimal.

Acute ischaemic stroke:

Total dose: 0.9 mg/kg, up to maximum of 90 mg IV

Give 10% of dose as bolus over 1 minute

Then

90% of dose over 60 minutes

Both bolus dose and infusion should be prepared before bolus is given, as the half-life of rtPA is only 5 minutes. The infusion should start immediately after the bolus was given.

tPA must not be mixed with other drugs, fluids or blood products. Patients must therefore have a dedicated cannula for rtPA administration and a second IV cannula for other drugs

Both bolus dose and infusion should be prepared before the bolus dose is given, as the half-life of rtPA is only 5 minutes. The infusion should start immediately after the bolus was given.

Heparinisation:

Heparinisation should commence concurrently in patients receiving thrombolysis for cardiac or PE indications.

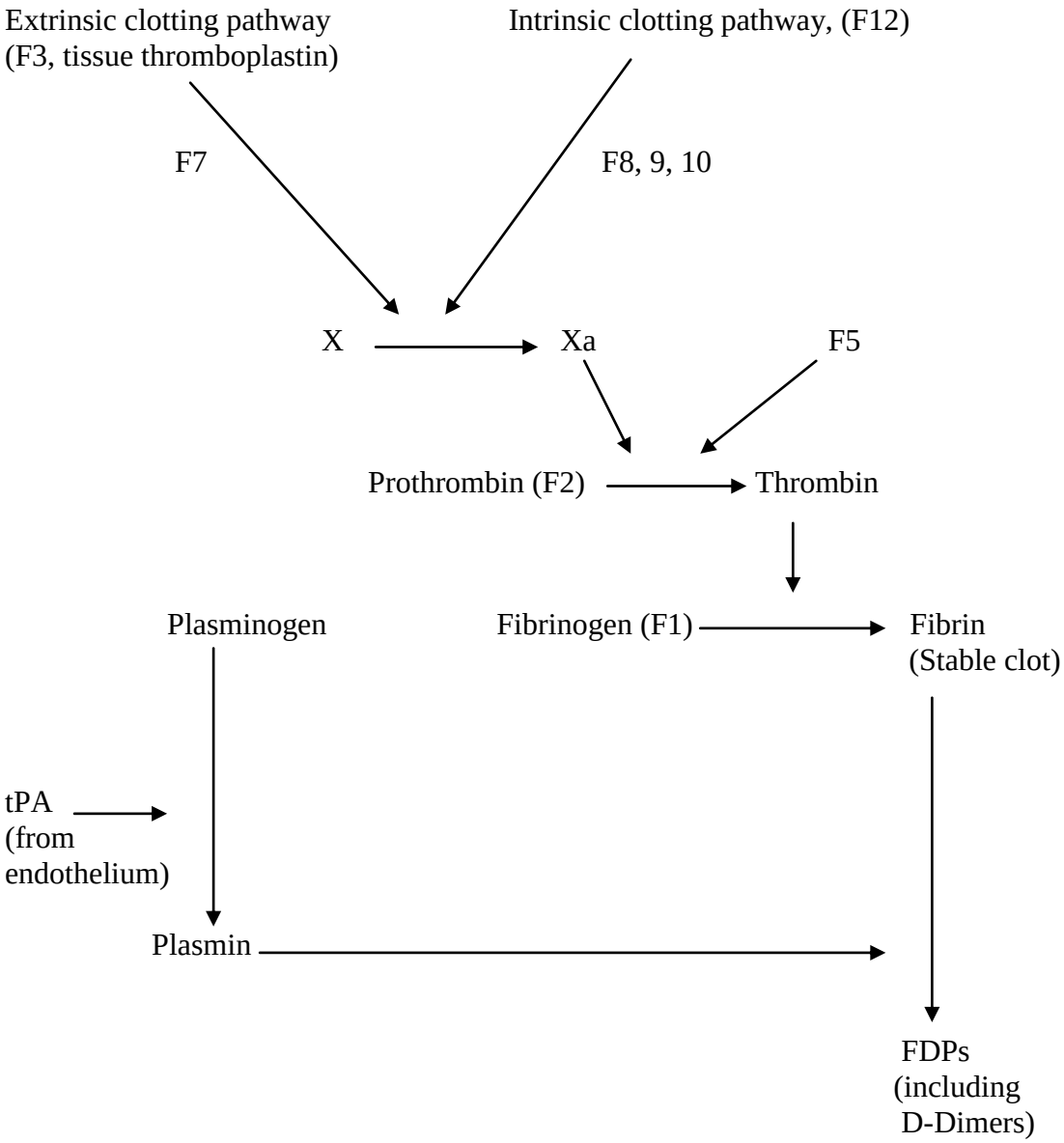
It **must not** be commended for **24 hours** after thrombolysis for acute ischemic stroke.

Bleeding complications:

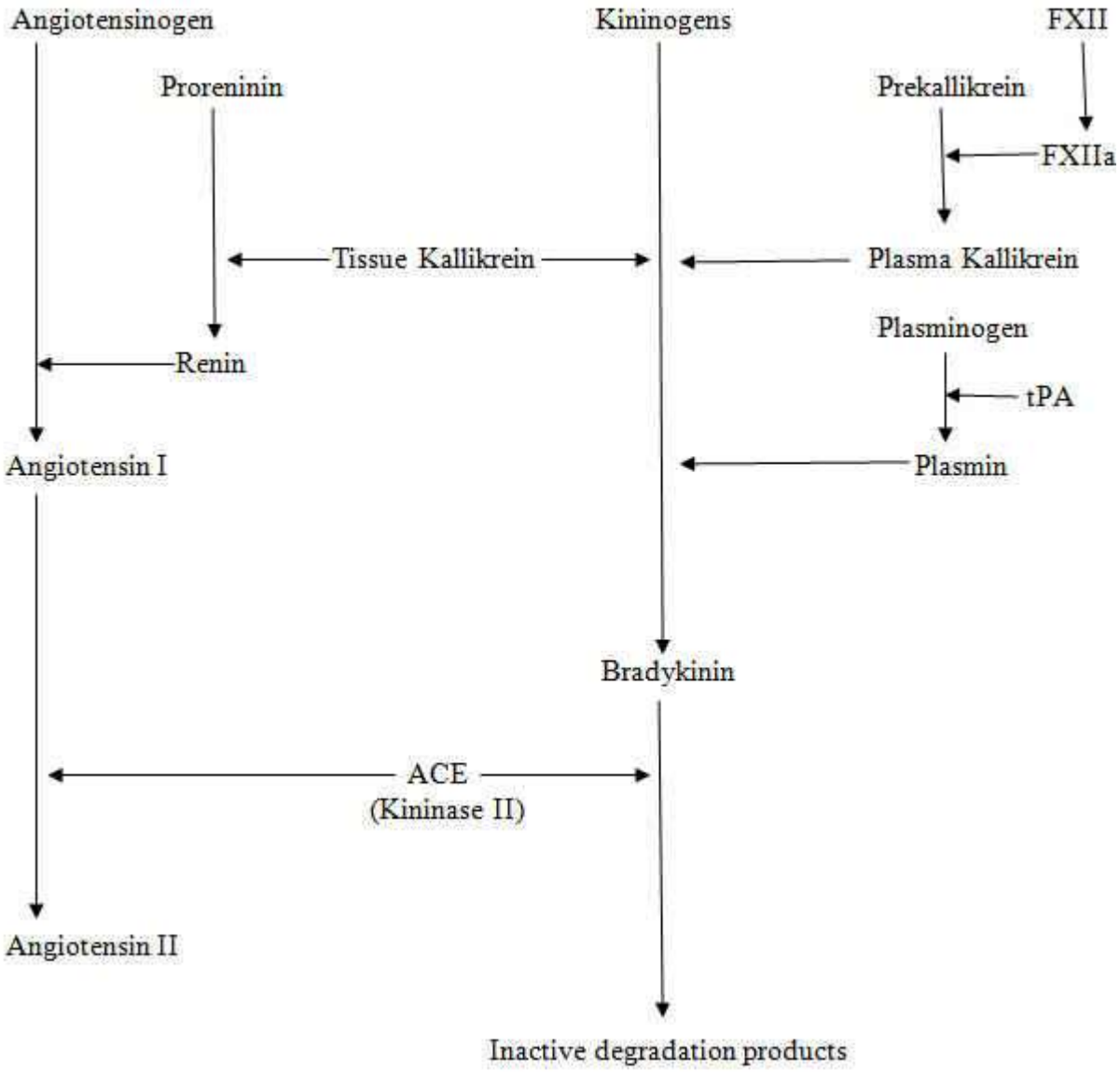
In the event of neurological deterioration, the infusion must be stopped if still running and a CT brain should be performed immediately to look for intracerebral bleeding.

Appendix 1

The coagulation cascade and fibrinolytic system:



Appendix 2



Biochemical pathways, demonstrating some of the relationships between tissue plasminogen, bradykinin and ACE, in the pathogenesis of angioedema.

References

1. Alteplase in eTG complete, November 2015

2. Mohsen Sharifi, Jeremy Berger et al. Pulseless electrical activity in pulmonary embolism treated with thrombolysis (the "**PEAPETT**" study). American Journal of Emergency Medicine: 29 June 2016.

    - DOI: http://dx.doi.org/10.1016/j.ajem.2016.06.094.

3. Giuseppe Molinaro at al. Biochemical Basis of Angioedema Associated With Recombinant Tissue Plasminogen Activator Treatment An In Vitro Experimental Approach. *Stroke*. 2002; 33:1712-1716.

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