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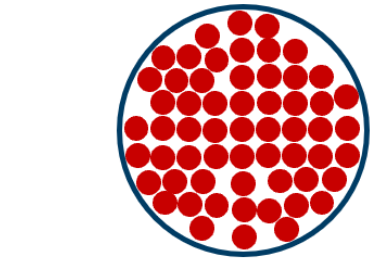
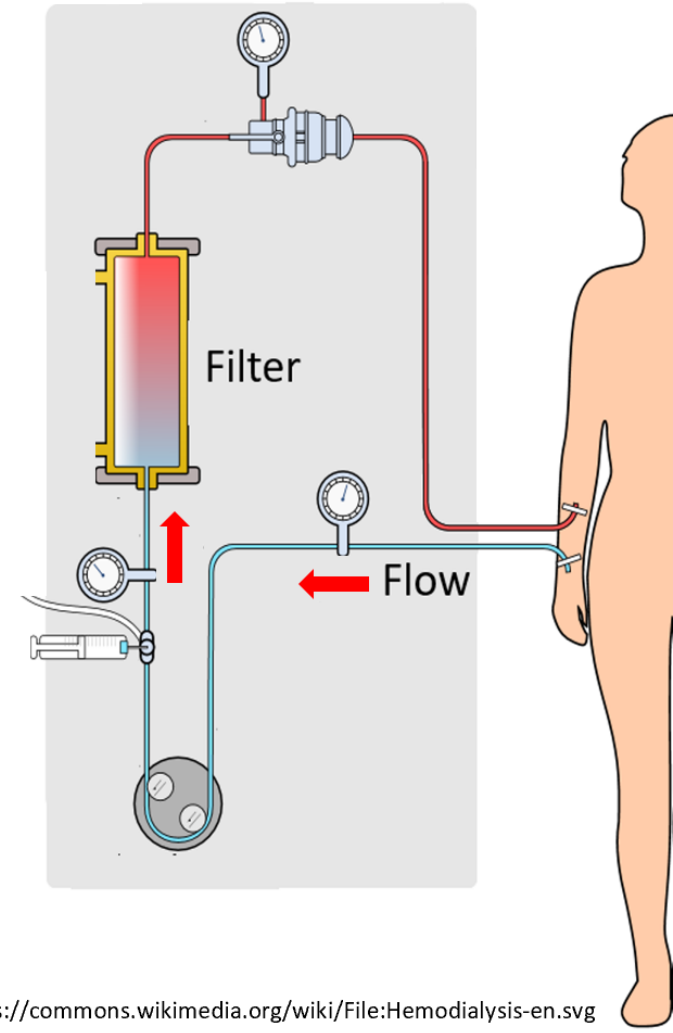
Regional Anticoagulant Satisfies Unmet Need

- Patients with sudden kidney failure are placed on an artificial kidney machine, **which is dialysis 24/7**, called continuous renal replacement therapy (CRRT).
- The machine circulates blood outside the patient, through a dialysis filter, and then returns blood to the patient.
- Exposure of blood to the dialysis filter causes clotting.
- Niyad™ is an anticoagulant for the dialysis filter.
- Blood clots cause:
  - More frequent filter changes
  - Increased blood loss, increased transfusions
  - Delayed/prolonged treatment time
  - Places a burden on doctors and nurses
- Niyad™ reduces blood clots in the machine.



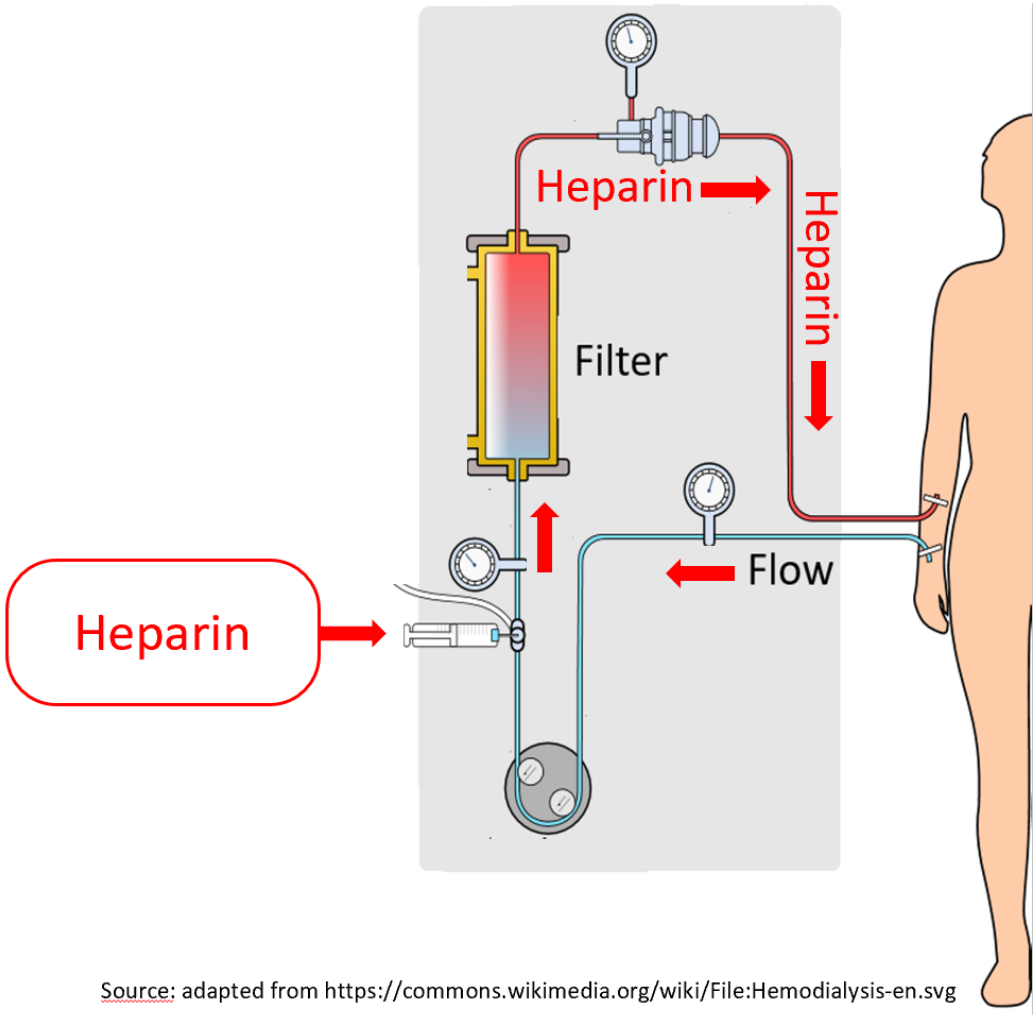
Cross Section of Hollow Fiber Filter



Source: adapted from https://commons.wikimedia.org/wiki/File:Hemodialysis-en.svg

Standard of Care – Heparin

- Heparin is a systemic anticoagulant.
- Since the dialysis filter does not remove heparin, clinicians fear over anticoagulating the patient.
- Heparin is contraindicated in patients at risk of bleeding.
- **Patients can develop heparin resistance and heparin induced thrombocytopenia (HIT).**
- Heparin is used in about 35% of CRRT patients.
- FDA granted **Breakthrough Designation** for patients that are intolerant to heparin or are at risk of bleeding.



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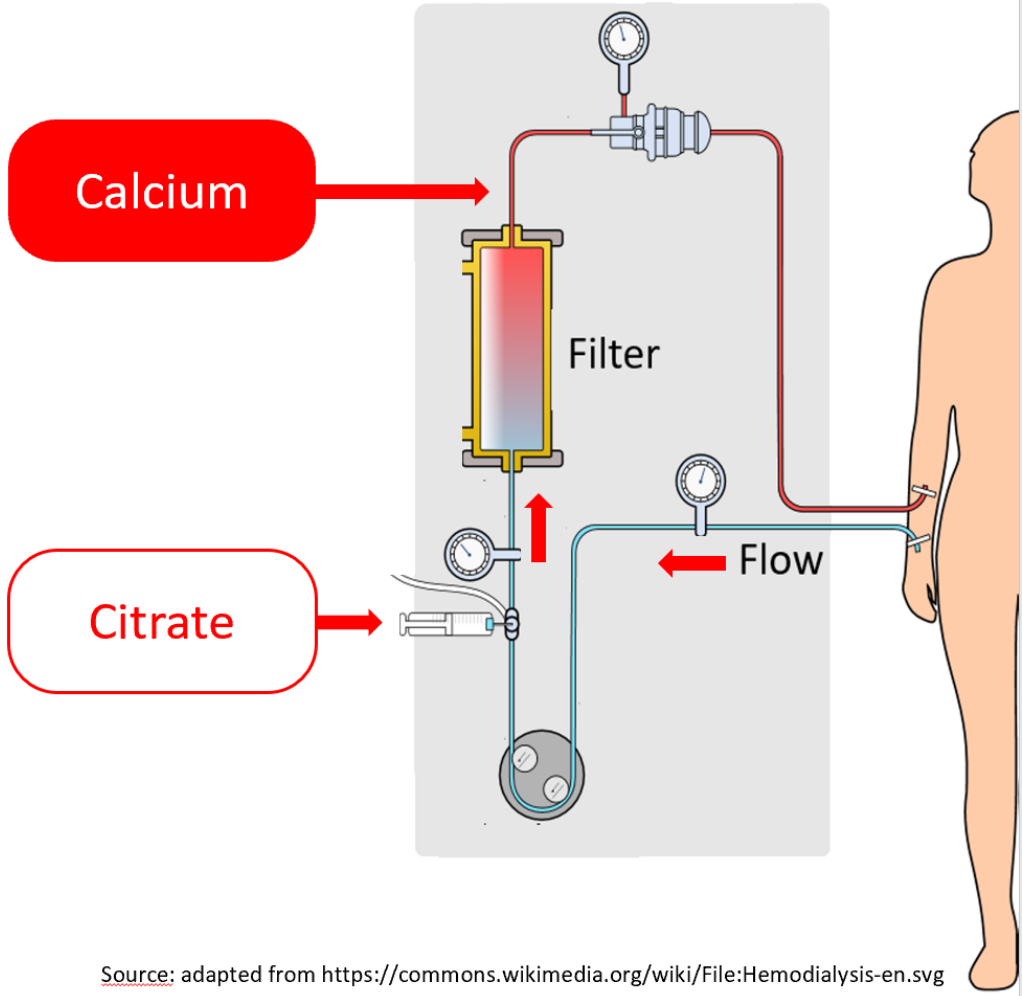
Current Alternative to Standard of Care – Citrate

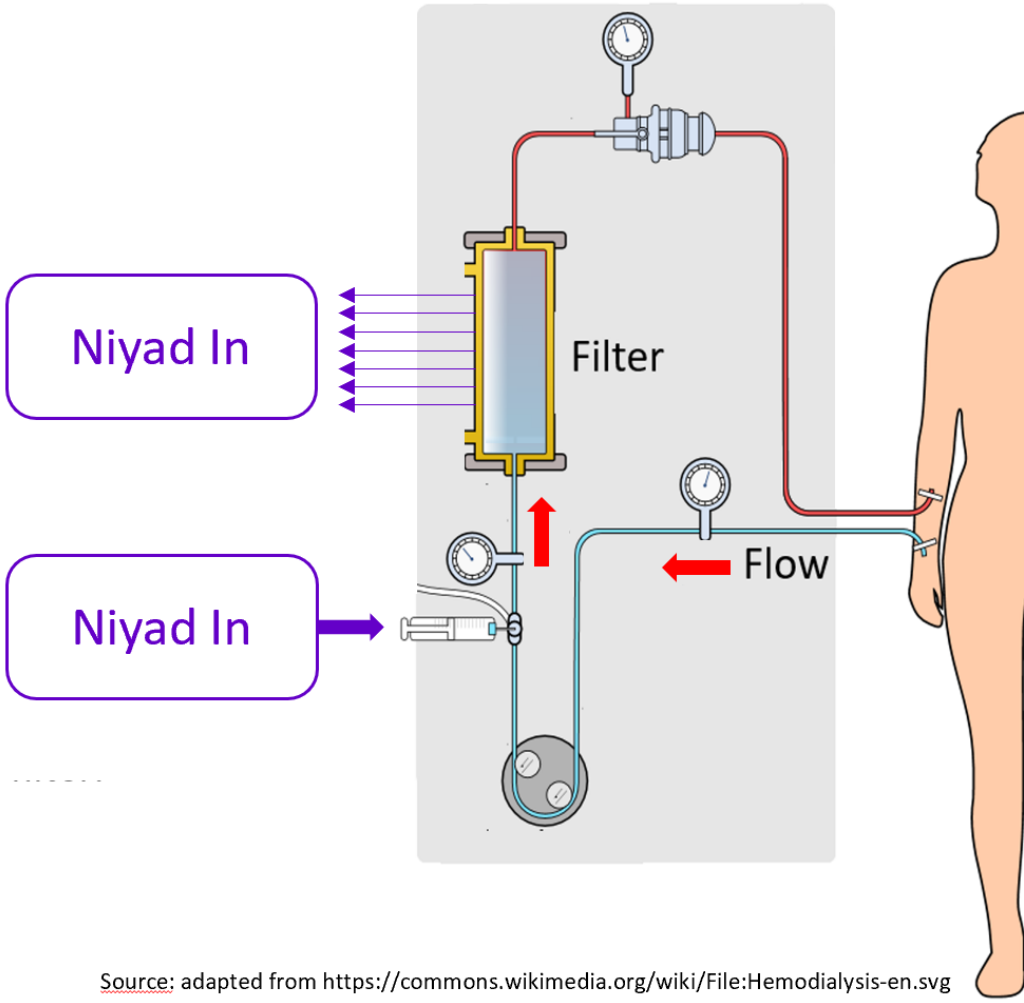
- The use of citrate in CRRT is not approved by the FDA
- Use of citrate requires simultaneous and precise infusion of calcium as a reversal agent (Citrate's Achilles' heel)
- Use of citrate:
  - May experience pump asynchrony
  - Requires frequent blood sampling for monitoring of ionized calcium
  - Is labor intensive and requires advanced training
  - Calcium is frequently on FDA's drug shortage list
  - Citrate is contraindicated in patients with liver failure (43% of AKI patients)
- Used at 40% of hospitals in US, but overall in only 5% of patients



Source: adapted from https://commons.wikimedia.org/wiki/File:Hemodialysis-en.svg

Benefits of Niyad™

- Kidney Disease Improving Global Outcome (KDIGO) **Clinical Practice Guidelines** for Acute Kidney Injury recommend using anticoagulation during RRT.
- There is no suitable anticoagulant available.
- Solution: Niyad™ provides anticoagulation without the shortcomings of heparin or citrate.
- No contraindications for Niyad™ :
  - Can be used in patients at risk of bleeding, whereas heparin can not
  - Can be used in patients with liver failure, whereas citrate can not
- Fewer filter changes, less blood loss, fewer transfusions, more importantly – lower cost of doctor and nursing time (the decision makers in selecting an anticoagulant)



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Patient Population – Acute Kidney Injury (AKI)

- The etiology of AKI is often sepsis, pneumonia, multi-organ dysfunction syndrome, major surgery, and others.
- Safety
  - Nafamostat, the active ingredient in Niyad™, has been used for more than 30 years in Japan and 15 years in South Korea as an anticoagulant for dialysis circuits.
  - Safety of the product is well documented in numerous publications as well as the JADER database.
  - The most common adverse events observed are hyperkalemia, hyponatremia, nausea/vomiting, and hypersensitivity – all of which are addressable in the use environment.
- Use of the product is documented in clinical notes and medical records in the ICU.

Product Description

Niyad™ in RRT

- FDA agreed to regulate Niyad™ as a device because it anticoagulates blood outside the patient.
- Niyad™, the active ingredient:
  - Small molecule, broad spectrum, protease inhibitor
  - Inhibits thrombin at the platelet thrombin receptor, PAR1
  - Short systemic circulation half-life (~8 minutes), making it ideally suited as a regional anticoagulant in extracorporeal circuits.
- When Niyad™ is administered into the RRT circuit, blood becomes anticoagulated.
- Niyad™'s small molecular weight (347 Da) allows a significant portion to be removed via filtration.
- The amount of Niyad™ that is returned to the patient is very low and is rapidly metabolized. Thus, the anticoagulation effect of Niyad™ is primarily limited to the RRT circuit.

Directions for Use

Preparation of the dialysis circuit

- Prime the dialysis filter according to the manufacturer's instructions with Niyad™.

Maintenance of anticoagulation of the dialysis circuit

- Prepare a solution of Niyad™
  - Add WFI or 5 % dextrose for injection to the Niyad™ vial.
  - Repeat above step for a second vial.
- Add the contents of the two reconstituted vials to 0.9 % saline for injection.
- Measure the activated clotting time (ACT) using a celite system. Titrate the dose up or down to achieve the desired the level of anticoagulation.

CRRT Coding

1. What is the patient demographic for the device?
    a. Patients undergoing CRRT that are intolerant to heparin OR are at a risk of bleeding.
2. What percentage of pivotal study subjects should be from the "Breakthrough Population" vs. "non-Breakthrough Population"?
    a. 100 %

Summary

- Niyad™ provides anticoagulation for patients in the ICU undergoing CRRT.
- There are no FDA-approved products for regional anticoagulation of the extracorporeal circuit, especially if the patient is intolerant to heparin OR at risk of bleeding.
- FDA granted Breakthrough Device Designation.