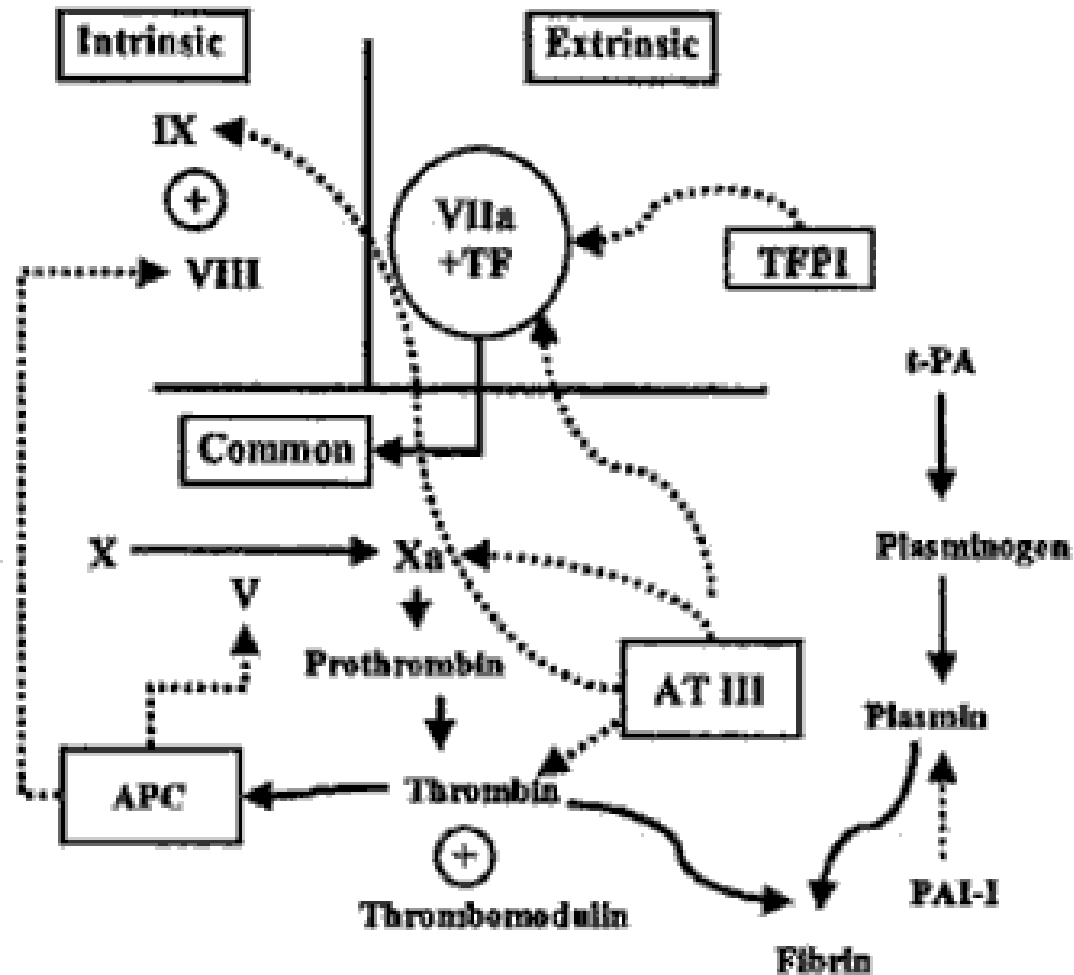


# THROMBOLYTICS IN ACS

**Dr. Tawfiq Almezeiny**  
**MD FRCPC (CCM)**

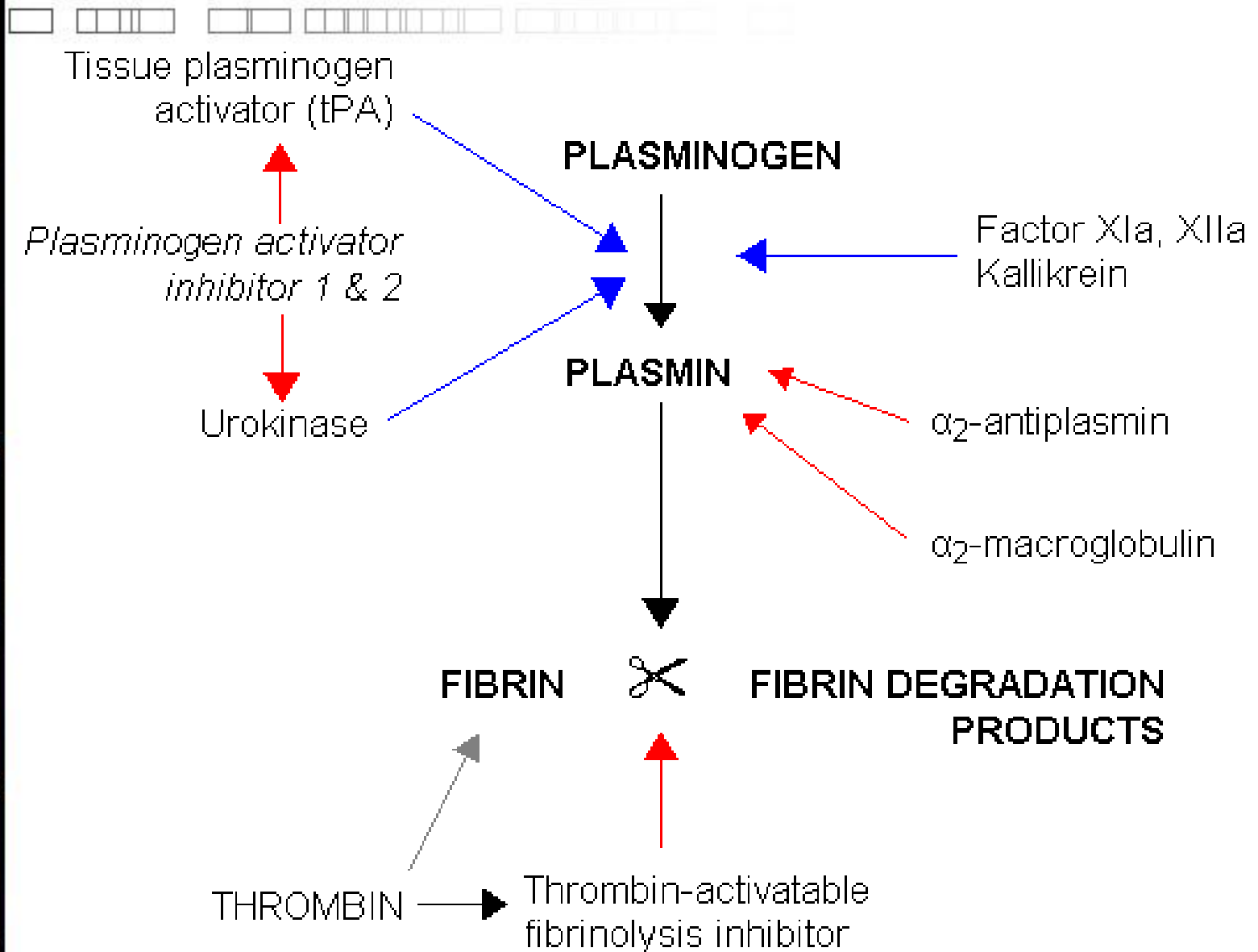


# Coagulation Vs Fibrinolysis



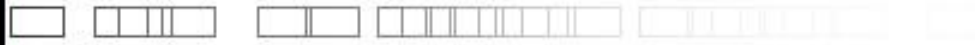


# Coagulation Vs Fibrinolysis





# Meeting the patient

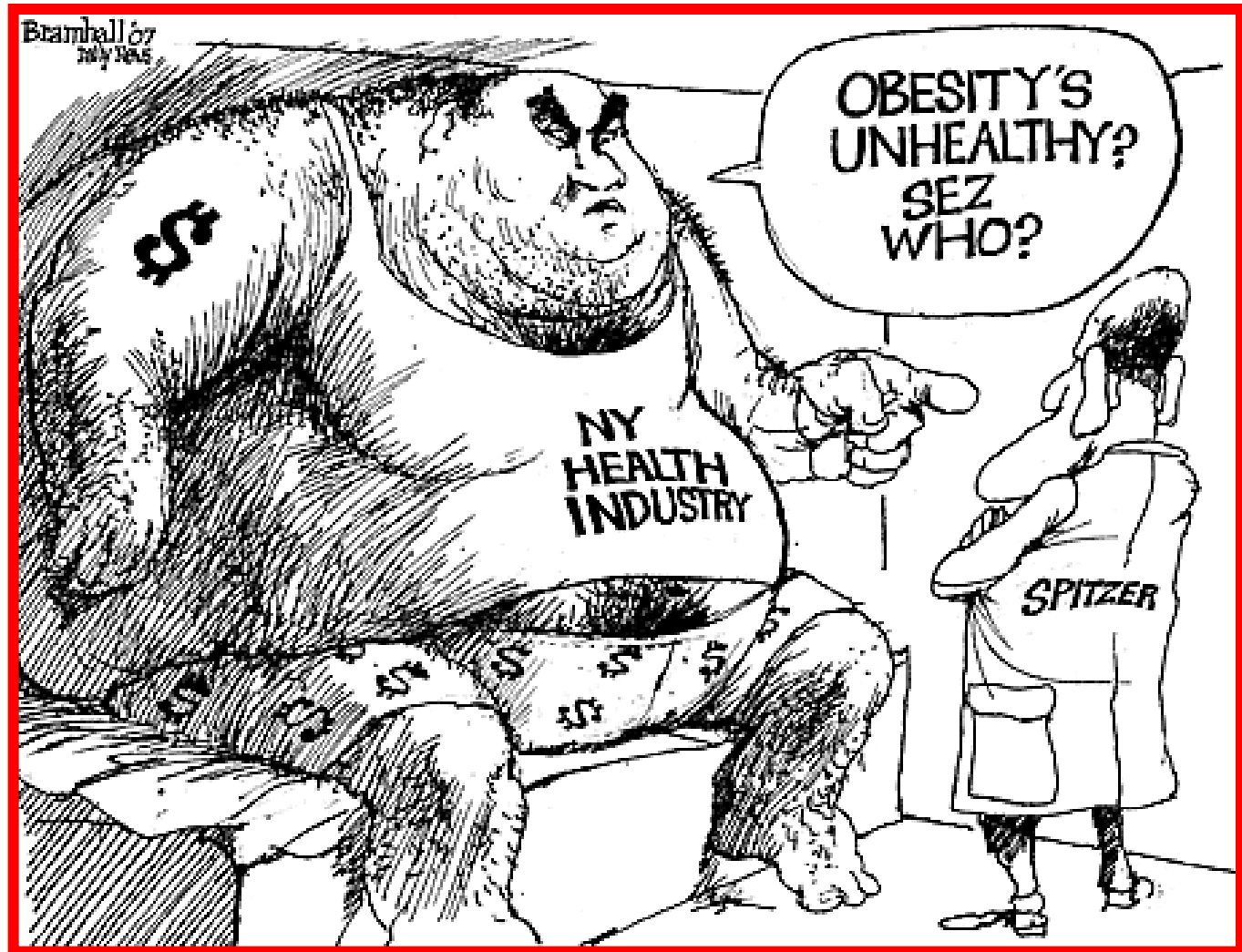
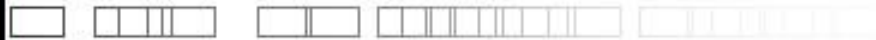


- Diagnosis ( ECG Criteria)
- Timing of onset of symptoms
- Questionnaire about contraindications.
- Consent ( written)

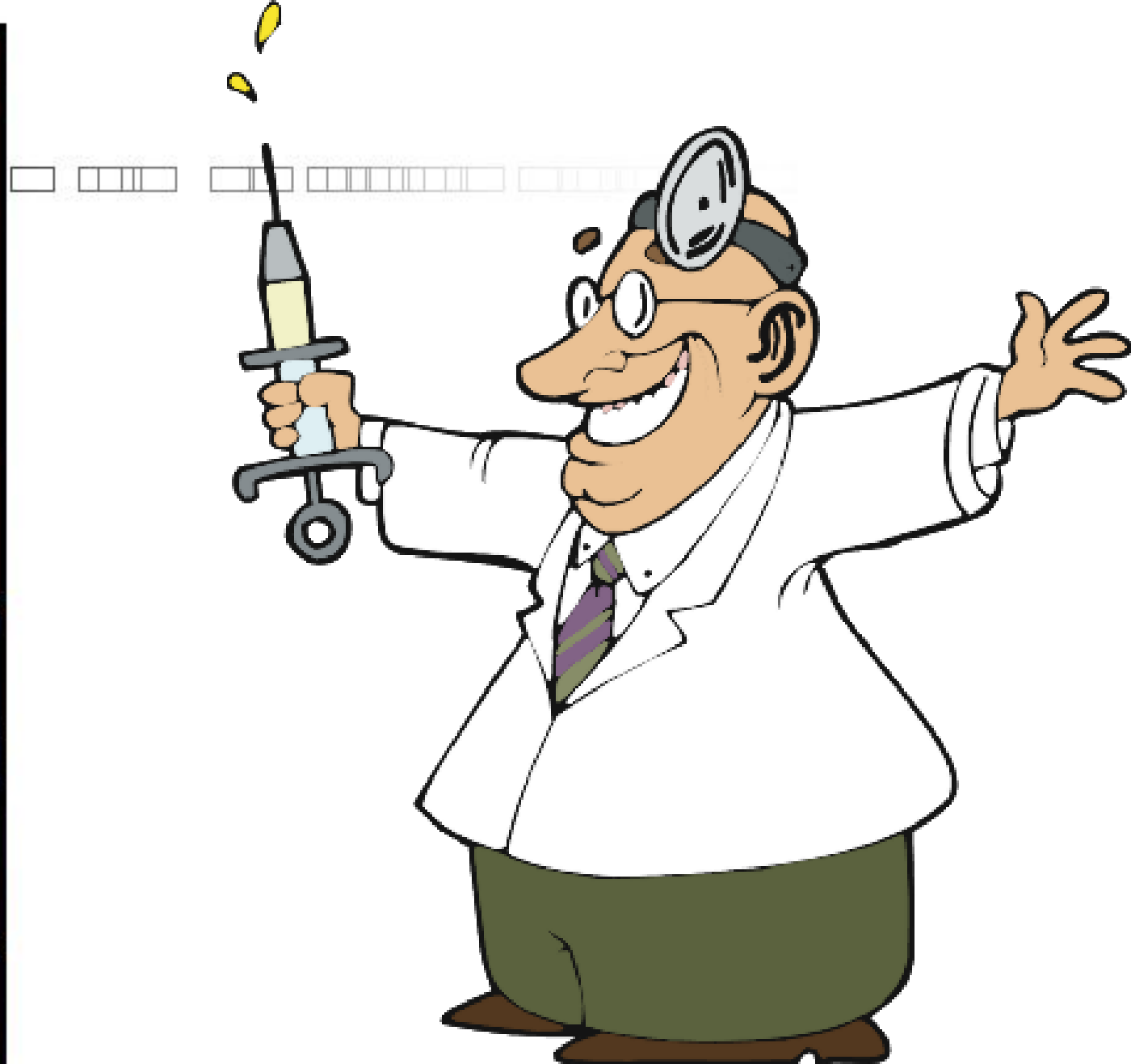
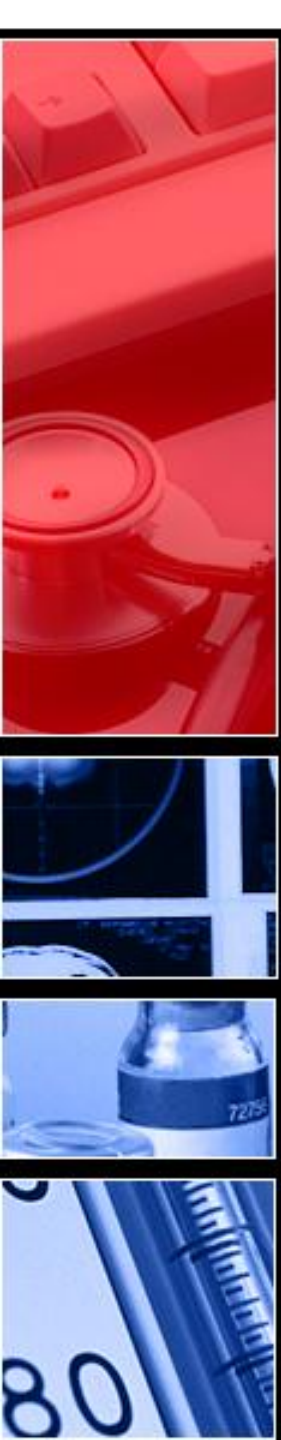




# Meeting the patient politely



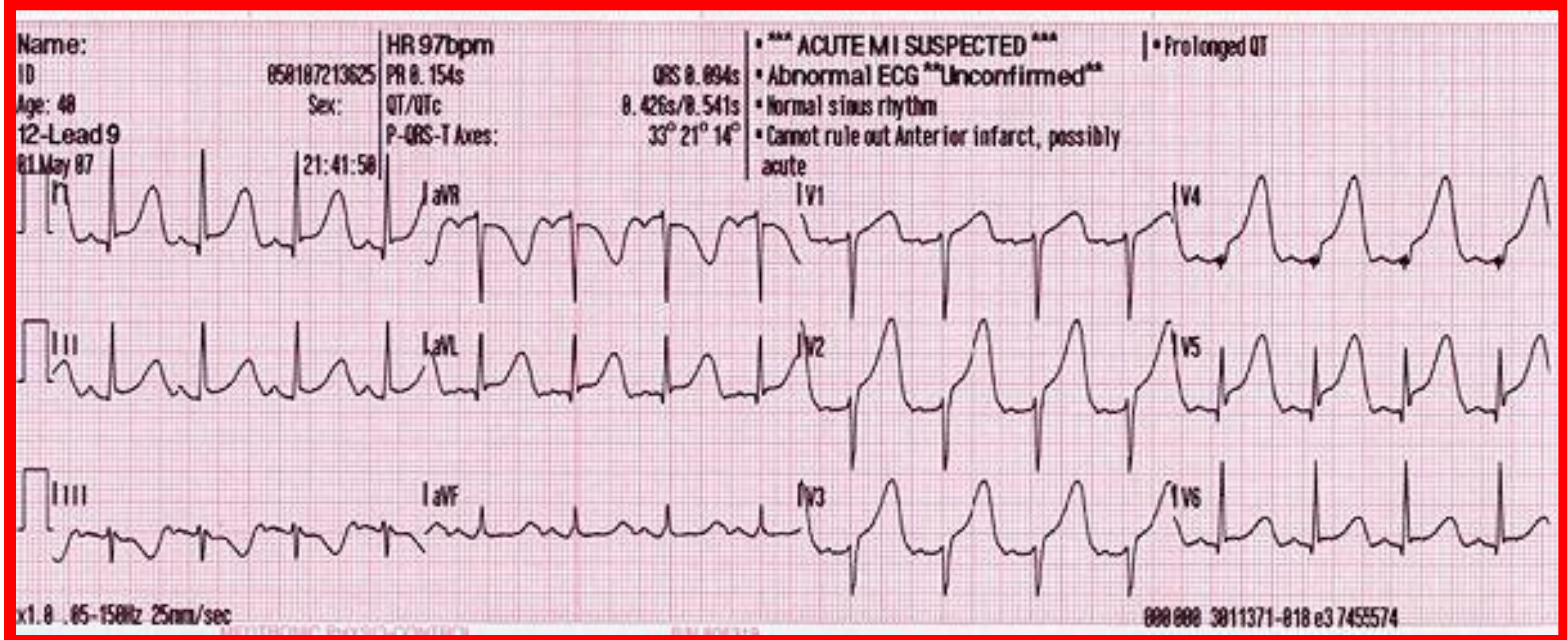






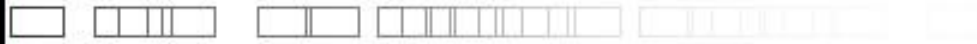
# CODE STEMI

- Expert cardiologist ( >75 PCI/year)
- Readily available cath lab (24 hours)
- Cardiac surgery service





# Reperfusion Therapy

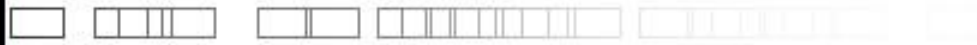


- Fibrinolytics
- PCI
- CABG





# Reperfusion Therapy



- Reopening of the infarct-related artery
- Salvage of the ischemic myocardium
- Reduce mortality and morbidity



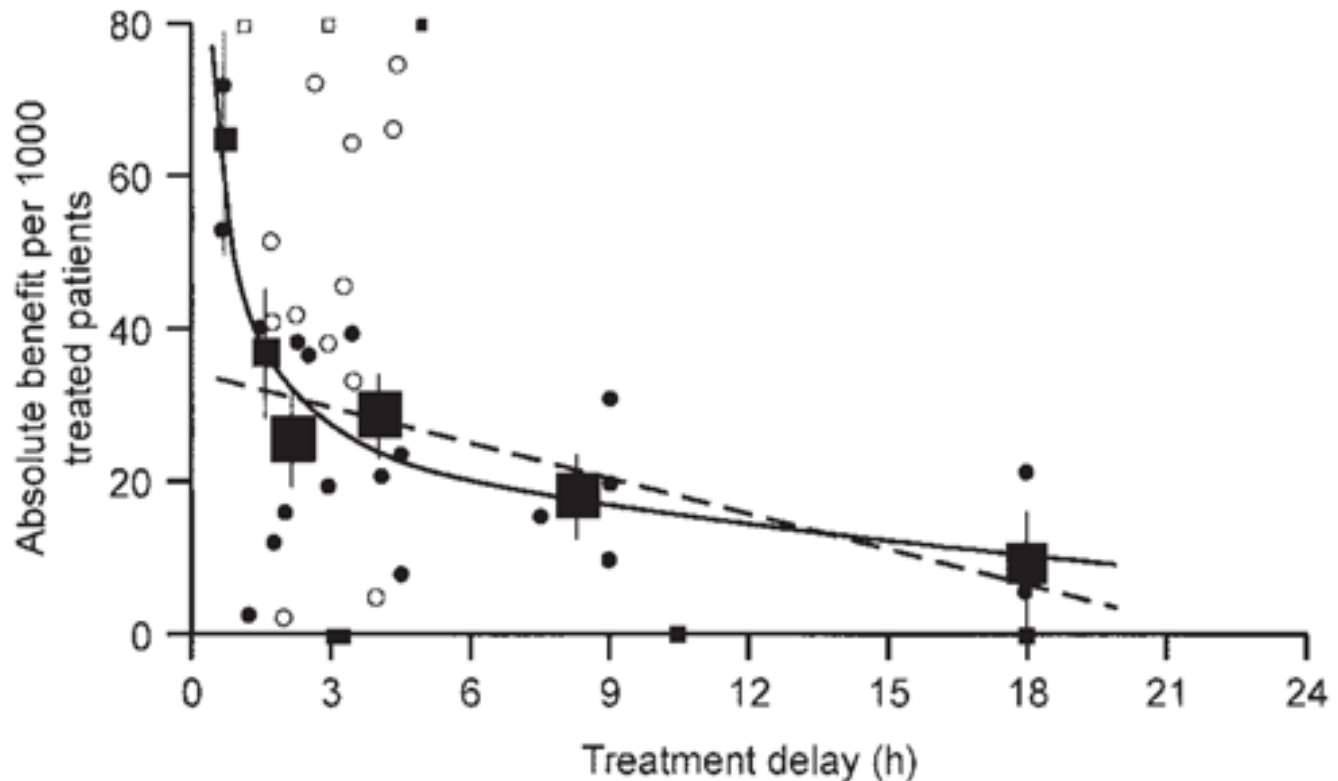


# Door-to-Needle time



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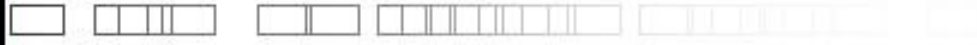


Source: JACC © 2007 American College of Cardiology Foundation





# Therapeutic agents



**streptokinase**

**Urokinase**

**T-Pa**

**r-PA**

**lanoteplase**

**TNK**

**APSAC**



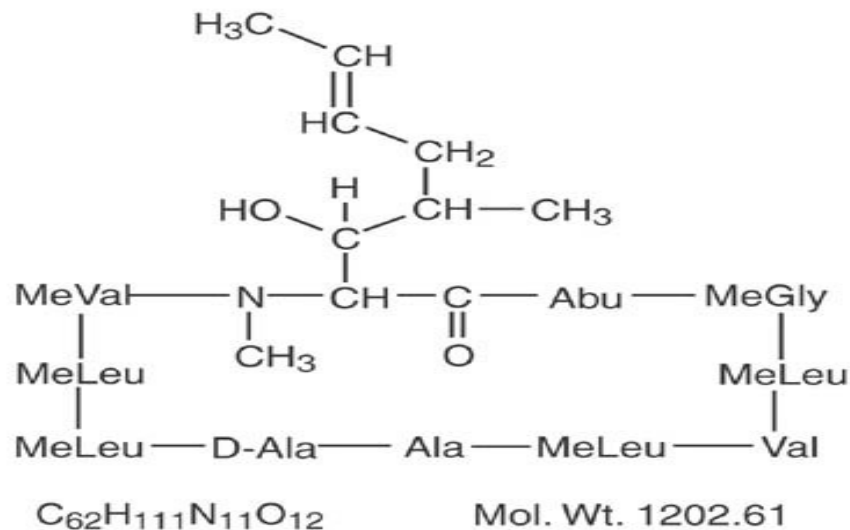
# Streptokinase

Discovered in 1930s

Dr. William Smith Tillett  
(1882–1974)



WILLIAM SMITH TILLETT M.D.

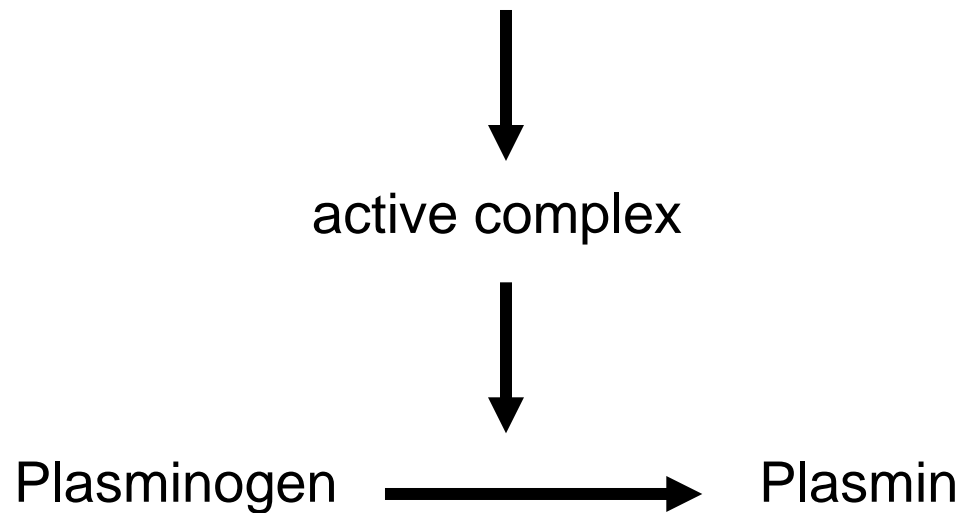




# streptokinase

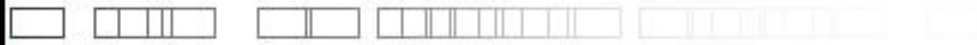


- Single chain polypeptide
- Derived from beta-hemolytic streptococci cultures
- Action: it binds to plasminogen





# streptokinase



- Dose : 1.5 million units over 60 minutes
- Adverse events : Bleeding  
Hypotension  
Allergic reaction





# streptokinase



- Allergic reaction

It can cause immunologic sensitization particularly with repeat administration

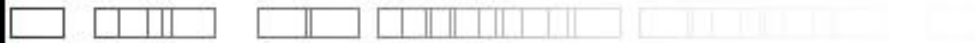
Major :  $< 1\%$

Minor :  $10\%$

Antistreptokinase antibodies remain for up to 7.5 years after exposure.



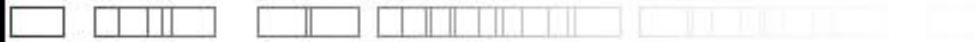
# Streptokinase



Route	onset	peak	duration
IV	immediate	rapid	4 Hours



# Alteplase ( t-PA )

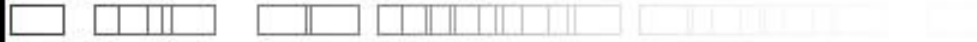


- Serine protease enzyme
- Produced by number of tissues including endothelial cells
- It is a Fibrin-Specific
- It binds to fibrin to form : Fibrin-tPA complex which has a great affinity to plasminogen
- This will lead to lysis





# Alteplase ( t-PA )

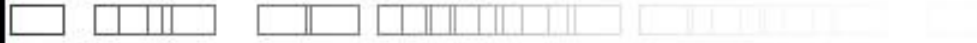


- t-PA is a poor enzyme in the absence of fibrin
- Non-fibrin- bound tPA in the systemic circulation does not activate plasminogen
- T 1/2 : short





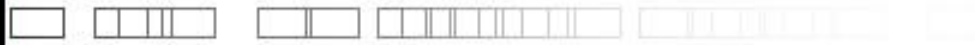
# Alteplase ( t-PA )



• Route	onset	peak	duration
• IV	30 min	60 min	unknown



# Reteplase ( r-PA )

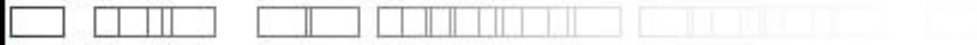


- Non-glycosylated form of tPA
- Is less fibrin specific than tPA
- But have longer half life 13 – 16 min
- In Trials : very similar results to tPA





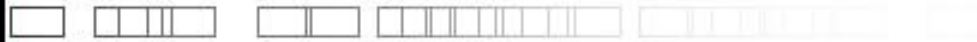
# Reteplase ( r-PA )



• Route	onset	peak	duration
• IV	30 min	30-90 min	48 hours



# Tenecteplase ( TNK – tPA )

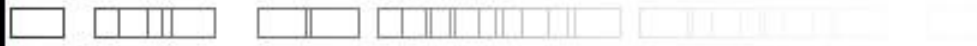


- Is multiple point – mutant form of tPA
- Longer plasma half life
- Single IV bolus injection
- 14 times more fibrin specific than tPA
- 80 fold higher resistance to PAI-1 than tPA
- In Trials : has LESS noncerebral bleeding rate





# Tenecteplase ( TNK – tPA )



• Route	onset	peak	duration
• IV	rapid	unknown	unknown



# Lanoteplase ( n- PA )



- is another mutant form of tPA
  - Longer circulation half life : 45 min
  - Greater fibrinolytic potency
  - But clinical trial fail to show this benefit in mortality
  - In-TIME trial : ( nPA to tPA in 15,078 patients)
    - mortality at 30 days : 6.8 to 6.6 %
    - mortality at 6 months : 8.7 to 8.8 %
- Hemorrhagic stroke is higher with nPA



# Other Fibrinolytic Agents



- Staphylokinase
- Anistreplase (APSAC)
- Urokinase
- Saruplase





# GISSI-2

Lancet 336 : 65 , 1990



- ***The Gruppo Italiano per lo studio della streptochinasi nell'infarto miocardico.***
- t-PA Vs Streptokinase in patients with AMI
- t-PA dose : 100 mg over 3 hours
- Results : No difference in mortality between the two group
- More strokes in the t-PA group 1.3 % to 1 %





# ISIS-3

Lancet 339:753 ,1992

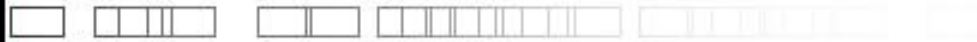


- Streptokinase Vs t-PA Vs APSAC
- 41,299 patients
- 24 hours after onset of symptoms
- No diagnostic ECG changes required
- Half of the patients received delayed S/Q Heparin
- Result : No difference among the three groups  
35-day Mortality  
6 months survival



# GUSTO – 1

NEJM 329:1615 , 1993



- Megatrial
- Hypothesis : early vessel potency is associated with a better outcome
- 41,000 patients

1. Accelerated tPA (90 min) + IV Heparin
2. Streptokinase + tPA (small dose) + IV Heparin
3. Streptokinase + IV Heparin
4. Streptokinase + S/Q Heparin



# GUSTO – 1

NEJM 329:1615 , 1993



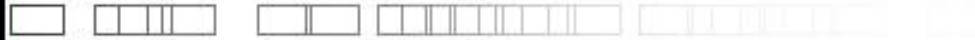
- Primary end point :30-day Mortality
- t-PA (90 min) is more aggressive than previous trials
- Subgroup analysis : Angiography assessment of the coronary blood flow ( TIMI flow 0- 3 )





# GUSTO – 1

NEJM 329:1615 , 1993



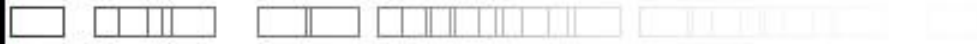
- Results :

1. Accelerated t-PA (with IV heparin) was the best.  
it reduces mortality by 15 %  
this was consistent with all subgroups :  
including elderly, Location of MI and Time from symptom onset



# GUSTO – 1

NEJM 329:1615 , 1993



- 2 . Strong relationship between TIMI flow and outcome

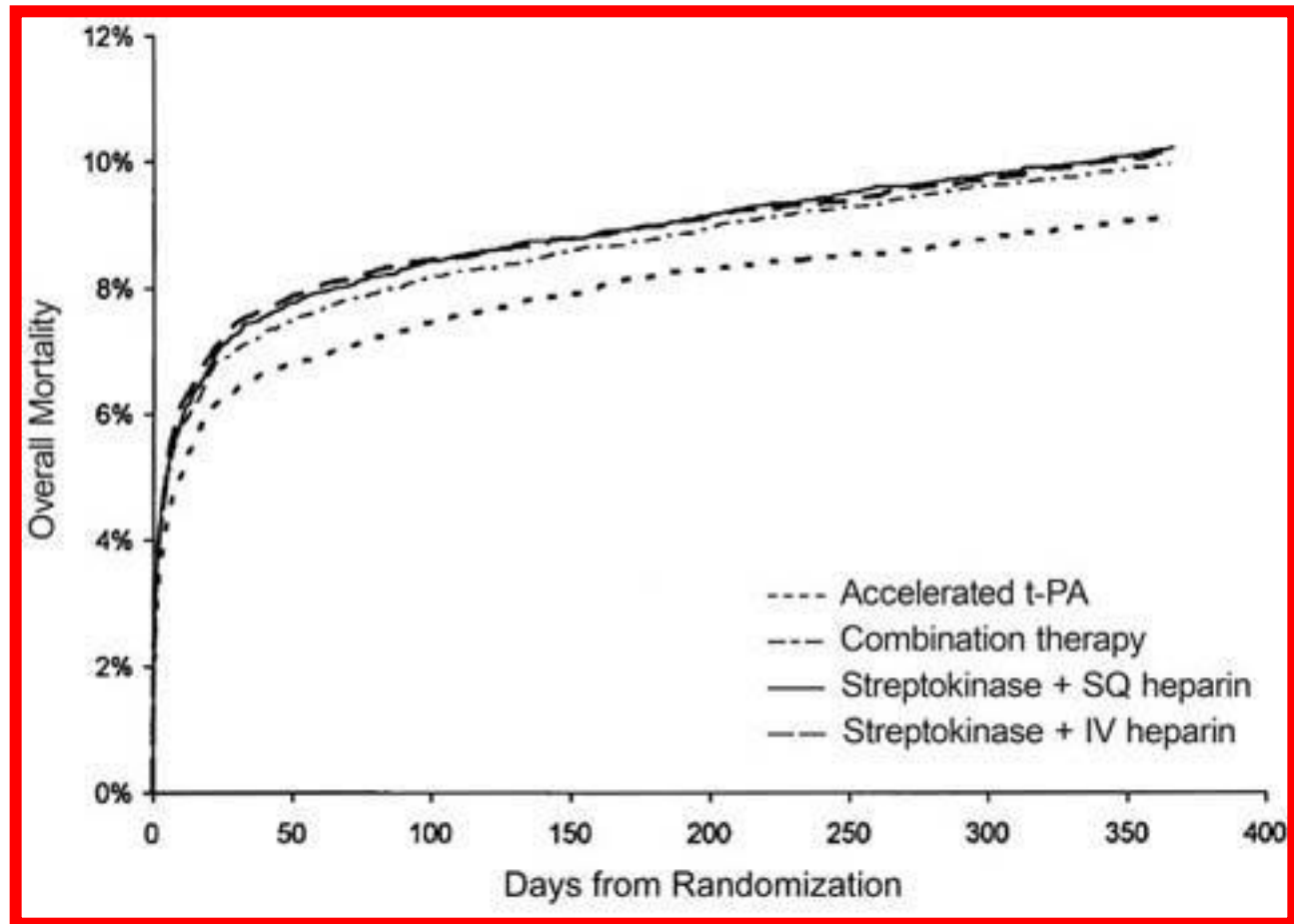
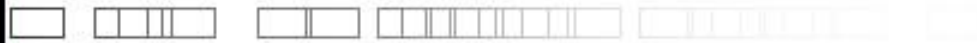
strong flow at 90 min ( TIMI grade 3 flow) had lower mortality rates than little or no flow

This findings was LOST by 180 min.



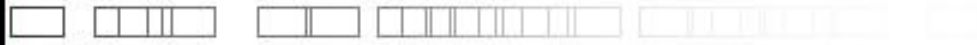


# Result from GUSTO trial





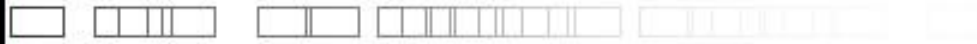
# GUSTO -3



- Multicenter 15,059 patients
- Compare r-PA to t-PA
- Mortality at 30 days : 7.47 to 7.27 %
- Incidence of stroke : 1.60 to 1.74 %
- Incidence of death or disabling stroke : 7.8 to 7.4 %
- Mortality at one year : 11.2 to 11.1 %



# GUSTO -3



- Mortality difference : 0.23 % with r-PA (this is not statistically significant)
- Except in those patients who present late > 4 hours : t-PA was superior to r-PA







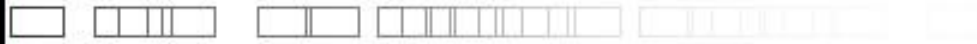
- 







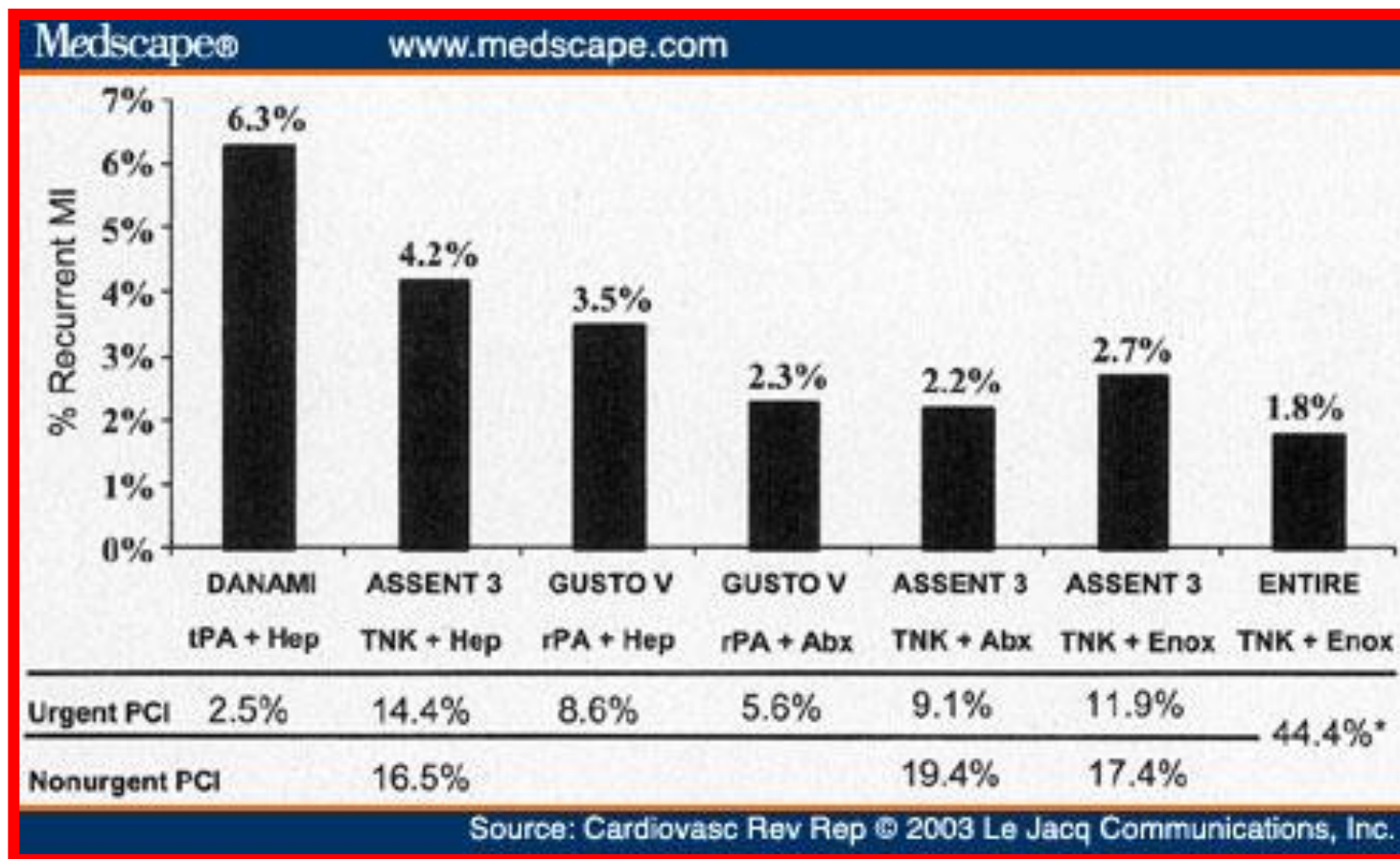
# ASSENT – II Trial



- Results :
  1. No difference in overall mortality (6.2%) or the rate of ICH ( 1.8 to 1.7 %)
  2. Mortality was slightly lower in those who present late > 4 hours
  3. Non-cerebral major bleeding is slightly more in the TNK group

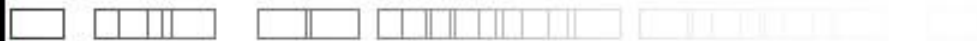


# Lytics and Other agents



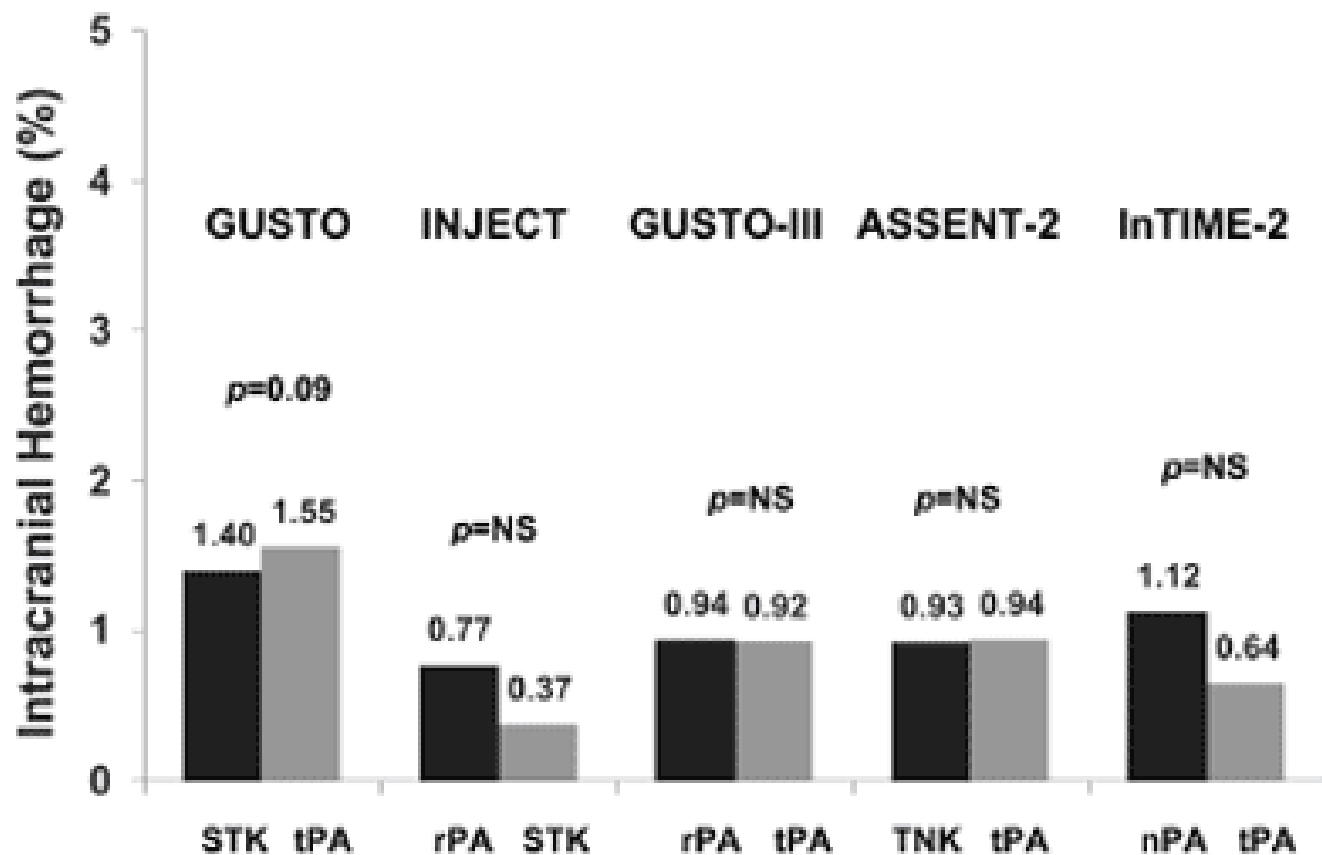


# Incidence of ICH



Medscape®

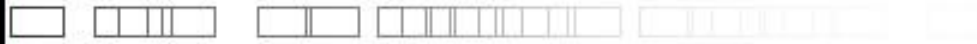
www.medscape.com



Source: Am J Geriatr Cardiol © 2003 Le Jacq Communications, Inc.



# Summary

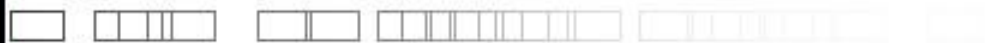


- 38 major clinical trials
- Efficacy and safety were similar to t-PA
- TNK has more favorable features; widely used in US centers
- N-PA has more incidence of cerebral hemorrhage in In-TIME-II trial.
- r-PA was not equivalent to t-PA in GUSTO-III trial .
- Streptokinase antigenicity had limited its use.

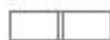




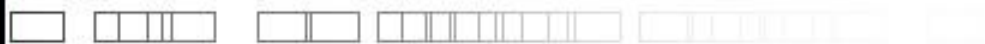




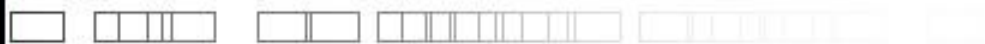




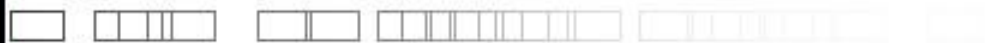




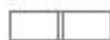




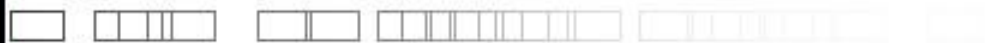




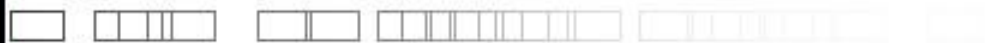




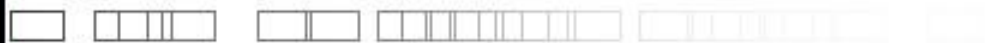




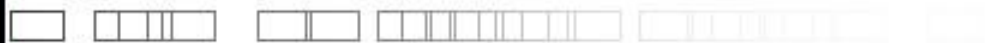




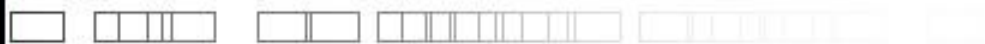




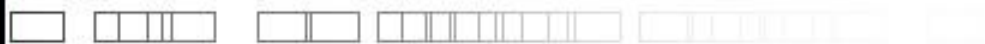




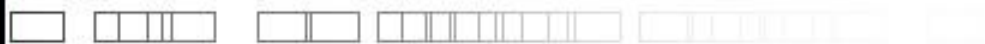




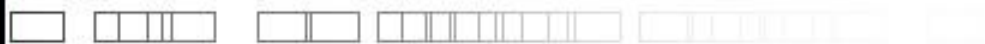








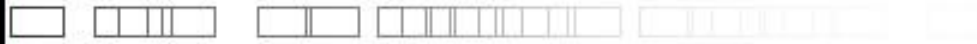








# Objectives



- Case presentation about a patient with Fulminant Hepatic Failure ( FHF ).
- General overview : FHF .
- Extracorporeal liver support.
- Molecular Adsorbent Recirculating System “**MARS**” .
- Example of relevant MARS RCT.



# History

18-years-old female

Previously healthy

Presented to the Emergency Department :

Vague abdominal pain and flatulence for two weeks

C/O Bilateral leg swelling for one day

No Hx of nausea,vomiting,diarrhea or weight loss

No Hx of dyspnea,palpitations  
or chest pain





# History



## Medications

- OCP for last four months

## Allergies

- Erythromycin

## Family Hx

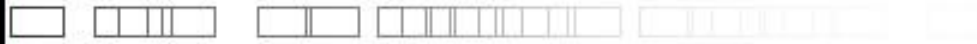
- Unremarkable

## Social Hx

- Unremarkable



# Examination

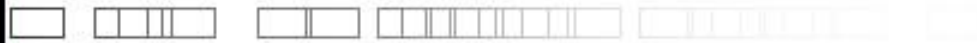


- Vital signs : normal
- Looked comfortable, not distressed
- Bilateral leg pitting edema
- Chest : NAD
- CVS : NAD





# Examination



## Abdomen

- distended
- Soft and non tender
- Large palpable mass occupying the majority of the abdominal cavity extending to the sebcostal margins,soft in consistency with rounded edges and a smooth surface. No bruit detected.





# Investigations

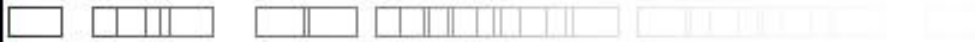
- CXR : NAD
- LFT: elevated bilirubin  
and enzymes

U/S :  
large mass arising from the left adnexa  
,cystic in nature.





# Admission



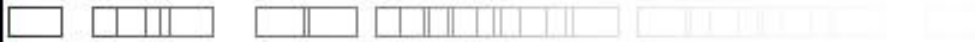
- Admission under gynecology
- Internal medicine consult

• <b>LFT</b>	day one	day two
--------------	---------	---------

- |               |            |            |
|---------------|------------|------------|
| • <b>Bili</b> | <b>52</b>  | <b>104</b> |
| • <b>ALT</b>  | <b>289</b> | <b>337</b> |
| • <b>GGT</b>  | <b>150</b> | <b>176</b> |
| • <b>ALP</b>  | <b>57</b>  | <b>61</b>  |
| • <b>Hb</b>   | <b>116</b> | <b>97</b>  |



# In-Patient Progress



## Investigations

- **CBC** Hb 97, WBC 11.3, Plt 160
- Alb 25
- Alfa feto-protein 300
- B HCG was negative
- HBV and HCV serology : negative
- HAV : positive





# COURSE AT THE OCH



## CT scan of the abdomen:

large left ovarian heterogeneous mass with cystic component .

multiple septations, fat and calcification.  
causing mass effect on the IVC and bowel.

Moderate amount of ascites.

**Normal appearing liver.**





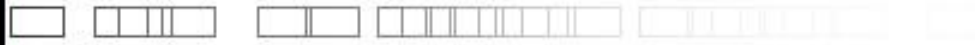








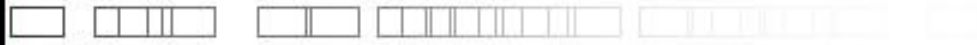
# Course : First week



- patient became jaundiced.
- INR was 5.2
- 2 units of FFP received
- Impression was liver failure secondary to IVC compression by the mass
- Urgent surgery is planned



# Course : first week

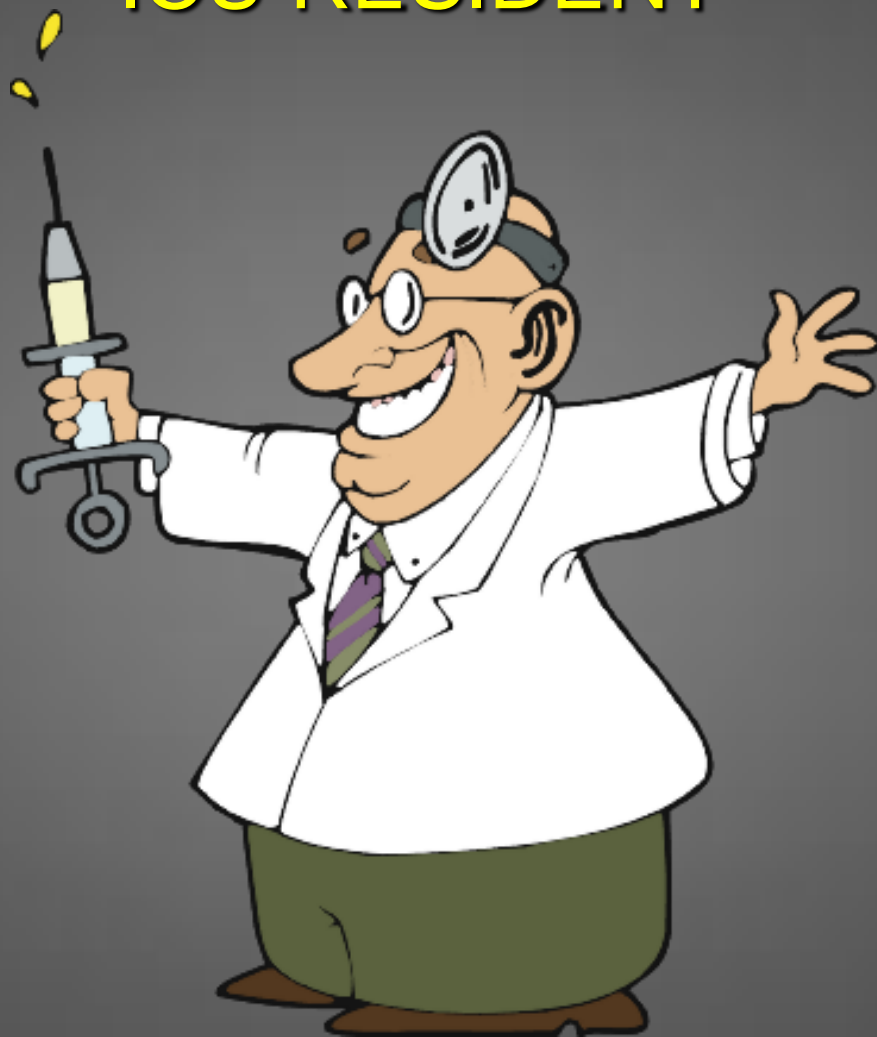


- Hematology and Anesthesia consulted
- Booked for tumor excision and staging
- ICU consulted : respiratory distress after transfusion of 3 units of FFP





# ICU RESIDENT





# ICU FELLOW



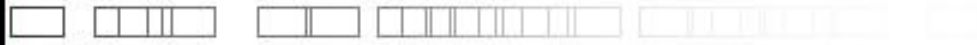


# ICU STAFF !





# ICU ASSESMENT



- Alert and oriented
- BP 136/94 HR 110 SAT 96% on 6L of oxygen
- RR 18





# ICU Admission

- **Investigations**

Hb 58, WBC 36.6, PLT 179, INR 3.42

Bili 687, fibrinogen was normal

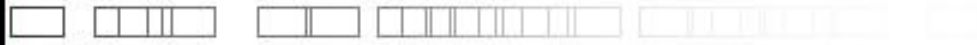
Lactate 7.9

ABG → metabolic acidosis





# Progress in ICU



- Respiratory failure → intubated
- 4 units of PRBC and 6 units of FFP transfused
- crystalloids
- BP remained stable through out resuscitation
- Post transfusion INR 1.62 and Hb 80
- **Second CT abdomen**  
no change in tumor size, no IVC or hepatic vascular obstruction, but increased ascites



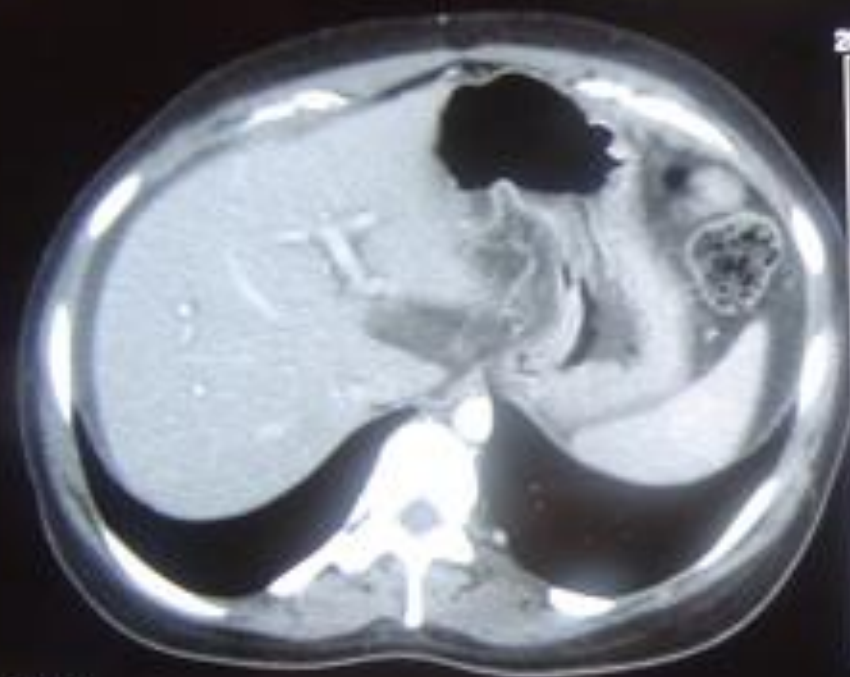


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ABD PEL  
Series 2

Ottawa Hospital Civic Campus  
LightSpeed16 CT99\_OC0  
FFS  
512 x 512 x 16  
CT ABD & PELVIS CONTRA

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ABDOM PELVIS C+  
Series 2

Ottawa Hospital General Camp  
LightSpeed Plus CT01\_OC  
FF  
512 x 512 x  
CT ABDOM



20 cm

L

STANDARD  
KV 120  
mA 300  
Tilt: 0  
Slice: 5 Loc: 140.695

P

W:350 L:40 HU



20 cm

STANDARD  
KV 120  
mA 200  
Tilt: 0  
Slice: 5 Loc: 40.095

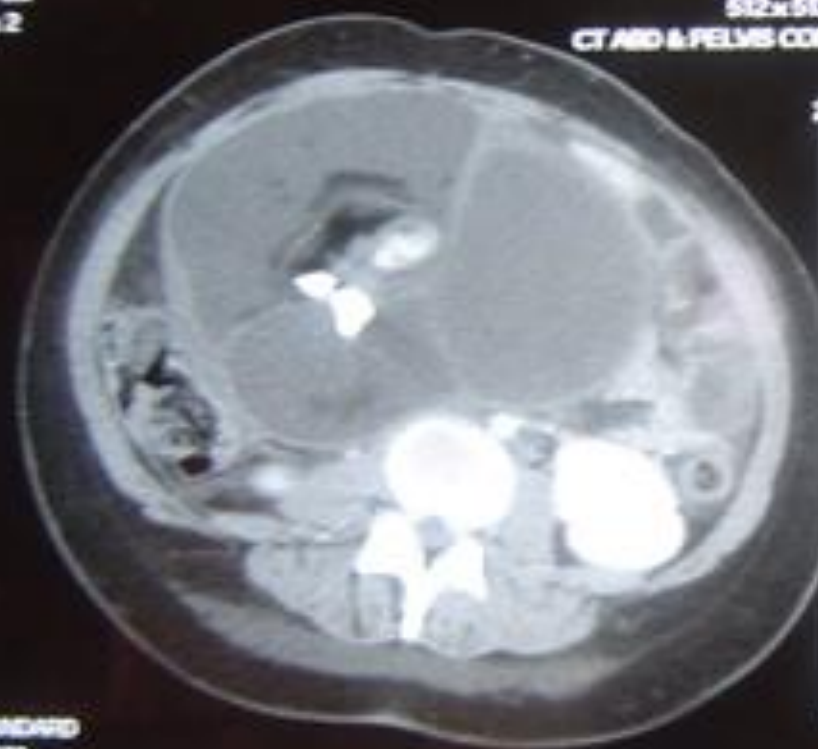
P

W:400 L:50



FTS 17-Mar-2005 10:09  
Ac: 200411180010001  
ABD PEL  
Series 2

Ottawa Hospital Chic Campus FTS 25-Mar-2005 04:14  
LightSpeed16 CT00\_OCD Ac: 200405047050000  
FFS ABDOME PELVIS C+  
512x512x16 Series 2  
CT ABD & PELVIS CONTRA



STANDARD  
kV 120  
mA 200  
TR: 0  
Slice 5 Loc 70885

P

W:500 L:401 H:1000

Ottawa Hospital General Camp FTS 25-Mar-2005 04:14  
LightSpeed Plus CT01\_OCD Ac: 200405047050000  
FFS ABDOME PELVIS C+  
512x512x16 Series 2  
CT ABDOME



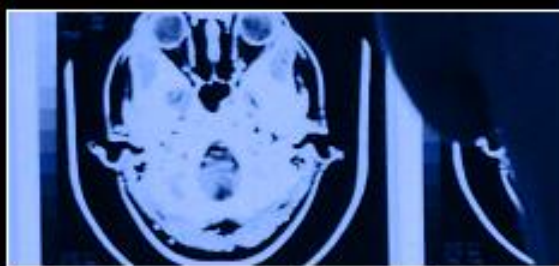
STANDARD  
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mA 200  
TR: 0  
Slice 5 Loc 236

W:400 L:511 H:1000





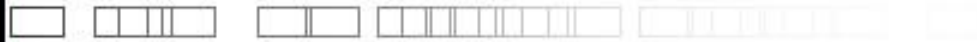




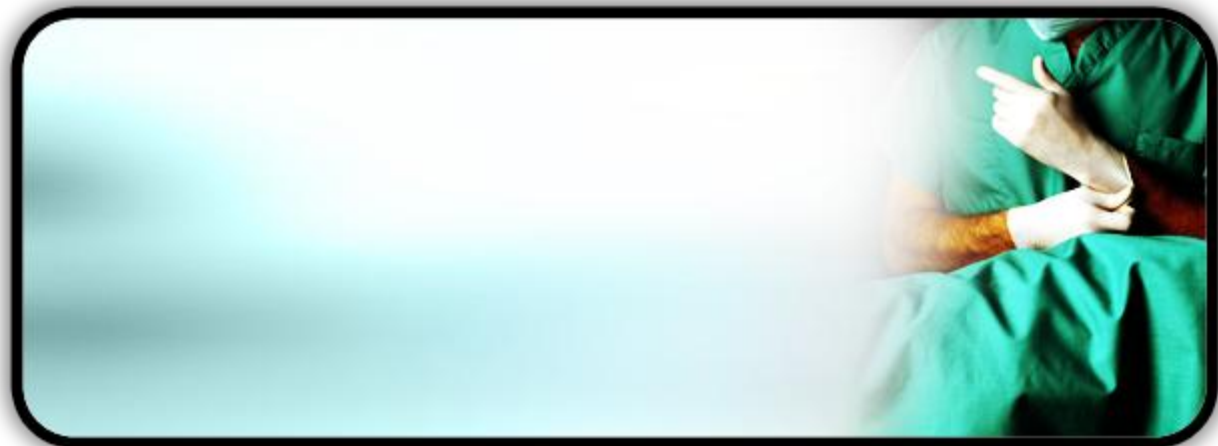
To : OR !



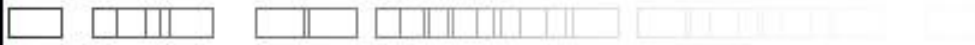
# Post-op (first few hours)



- RESP
  - PCV 25/PEEP 10, RR 25, Vt 475cc, 7.23/39/61/16 on FIO2 .90, desats to 85% with suctioning/movement
- CVS
  - 85/55, 90NSR, CVP 21, periphery cool but good cap refill
- GU
  - U/O 10-20cc/hr
- GI
  - Strange liver, dusky edematous bowel, distended.







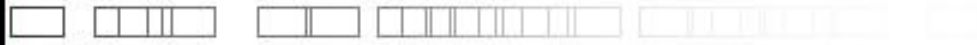
- Bloodwork:

- HGB 88, Plts 122, WBC 20.3
- INR 2.2, PTT 35, Fibrinogen 2.1, DD 2879
- Lytes N, Glu 3.1, Cr 145
- Lactate 7.3
- Ammonia 60, Bili 534, Alb 23
- Lipase 109H, ALP 25, GGT 47,
- AST 173H, ALT 33

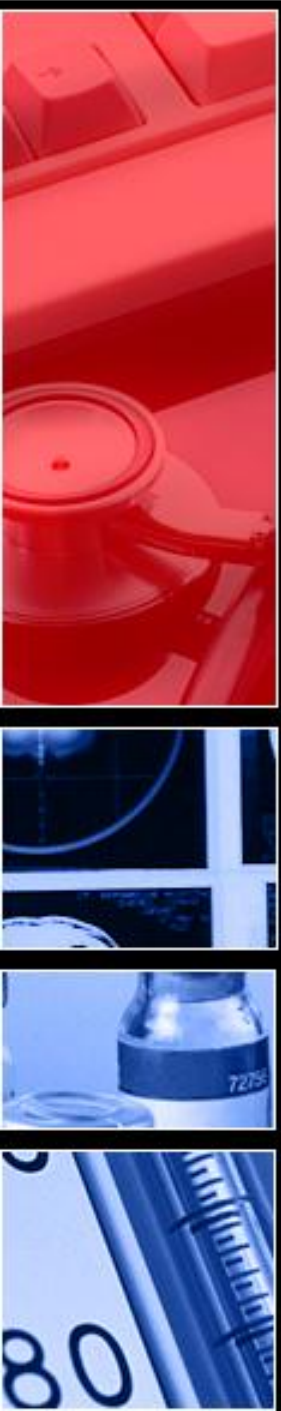




# ISSUES

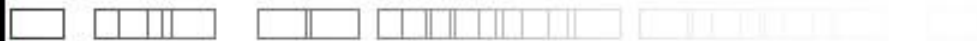


- 18yo, previously healthy, no family Hx
- Ventillation
- Hemodynamic status
- Acute renal failure
- Coagulopathy/DIC/Hemolysis
- Liver Dysfunction





# Ventillation



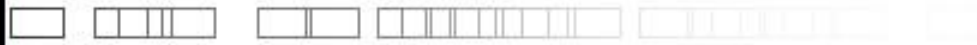
- PCV 25/PEEP 10, RR 25, Vt 475cc  
7.23/39/61/16 FIO<sub>2</sub> .85, desats to 85% with  
suctioning/movement
- CXR: bilateral patchy infiltrates,  
air-bronchograms and effusions.  
Very little aerated lung







# Ventilation



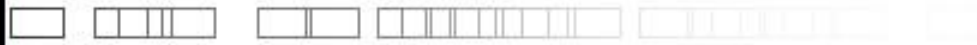
- **APRV**

airway pressure release ventilation

- 7.32/34/62/18 FIO<sub>2</sub> .80
- Tolerated well, but unclear role for prolonged ventilation



# Ventillation



- **HFOV**

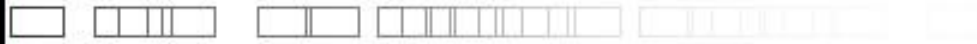
High Frequency Oscillation – 5hz

- Mean Paw from 32 to 24
- In 12 hours –  
7.31/39/95/19 FIO<sub>2</sub> .3
- CXR: better

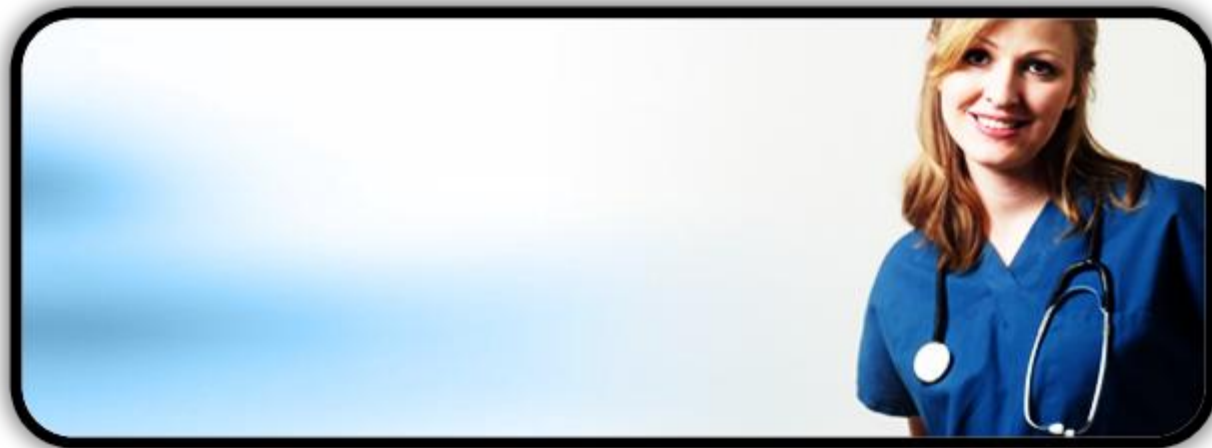




# Perfusion



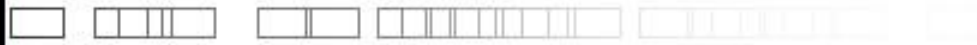
- Lactate **7.3** (from 9.0 pre-op) gradually improved to **5.6**
- pH 7.23 gradually to **7.32**
- ScVO<sub>2</sub> : **72%**
- Echo - normal systolic/diastolic f(x)
- Clinically - perfusion adequate







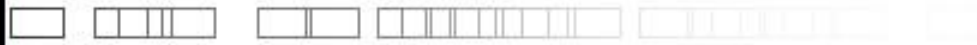
# Perfusion



- BP 80/40, MAP 60, HR 80, CVP 16
- Norepinephrine titrated to MAP>65
  - Initially 0.02ug/kg/min, within 12 hours up to 0.3
- Lactate from 5.6 to 9.7
- Flushed, yet cool periphery
- Abdomen distended, ABXR: non-specific
- T 38.4



# Renal Failure



- Cr
  - 69 one day pre-op
  - 233 POD#1
- Ongoing metabolic acidosis
- U/O slowed from 20cc/hr to 5cc/hr







# Liver Failure

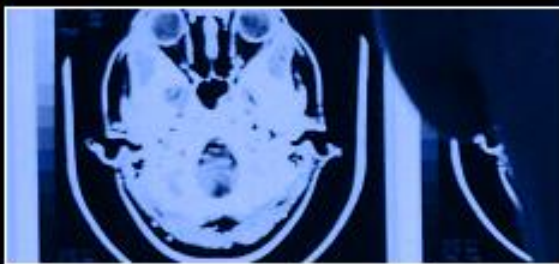
Test	Day 1	Day 10
ALT	289H	64
AST	475H	173H
GGT	176H	49
Bili	52H	810 (direct 455)
Alb	25L	Transfused
INR	5.2	Transfused
Glu	3.6	D50W



# Liver Failure W/U

- Hepatitis C/B/E/A-IgM -neg
- Fe 23 (norm), ferritin 1016 (high), (TIBC 23 (low), Sat 100% (high) - (3/19)
- Hemosiderin – negative
- IgG, IgM – normal
- parvovirus B19, EBV, CMV, HHV - pending
- Urine/stool parasites - pending
- mycoplasma, Q fever, syphilis, streptococcus, brucella, leptospira, bartonella serology pending
- Ceruloplasmin, 24hr urine for Cu - pending
- Alpha 1 antitrypsin – pending
- Biopsy – risk vs. benefit





# Fulminant Hepatic Failure



# Complications of Fulminant Hepatic Failure

- Encephalopathy
- Cerebral Edema
- Renal Failure
- Coagulopathy
- Infection/Sepsis
- Pulmonary Edema
- Metabolic Derangements
  - acid/base, blood sugars, electrolytes



# Hepatic Encephalopathy



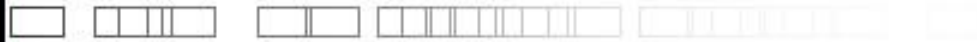
## Ammonia Hypothesis

- Ammonia is produced by the breakdown of nitrogenous substances by enterocytes and colonic bacteria
- The liver metabolizes it to urea and glutamine
- Increased serum ammonia is seen in 60-90% of encephalopathic patients and therapies aimed at reduction of levels are clinically effective
- However, this link is not always true





# Cerebral Edema

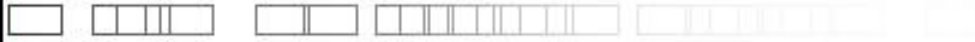


- In grade IV encephalopathy, 80% risk of developing edema and raised ICP
- Raised ICP and brainstem herniation is the primary cause of death in FHF
- Clinical signs of increased ICP:
  - Cushing's triad
  - Abnormal pupils
  - Decerebrate posturing
  - Seizure activity





# Cerebral Edema



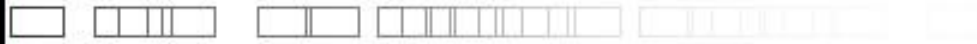
## Pathophysiology

- Extracellular/Vasogenic
  - disruption of the BBB, leaking of protein and fluid into the interstitium
- Intracellular/Cytotoxic
  - failure of the membrane Na/K pump, accumulation of osmolytes





# Extracorporeal Liver Support

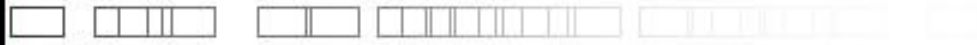


- Aim: is to provide temporary liver function
- Bridge to liver transplant.
- Recovery of native liver function.
- Donor graft is not always readily available.
- Not all patient are candidate for transplant.
- Decision to transplant is not always straightforward.





# Extracorporeal Liver Support



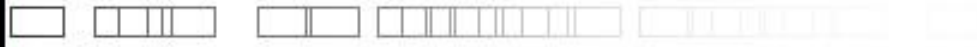
- Aim: is to provide temporary liver function
- Bridge to liver transplant
- Recovery of native liver function
- Two types:

**Biological**      and      **Non-Biological**





# Non-Biological Liver Support

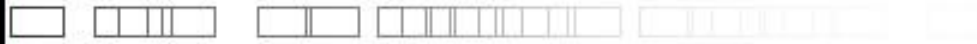


- MARS
- PLEX





# MARS

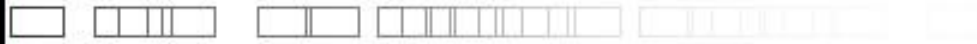


- Molecular adsorbent recirculation system “MARS”
- Also called : (ECAD) Extracorporeal Albumin Dialysis
- Treat both liver failure and renal failure.
- It exposes the patient ultrafiltrate to an albumin-rich solutions across a membrane.





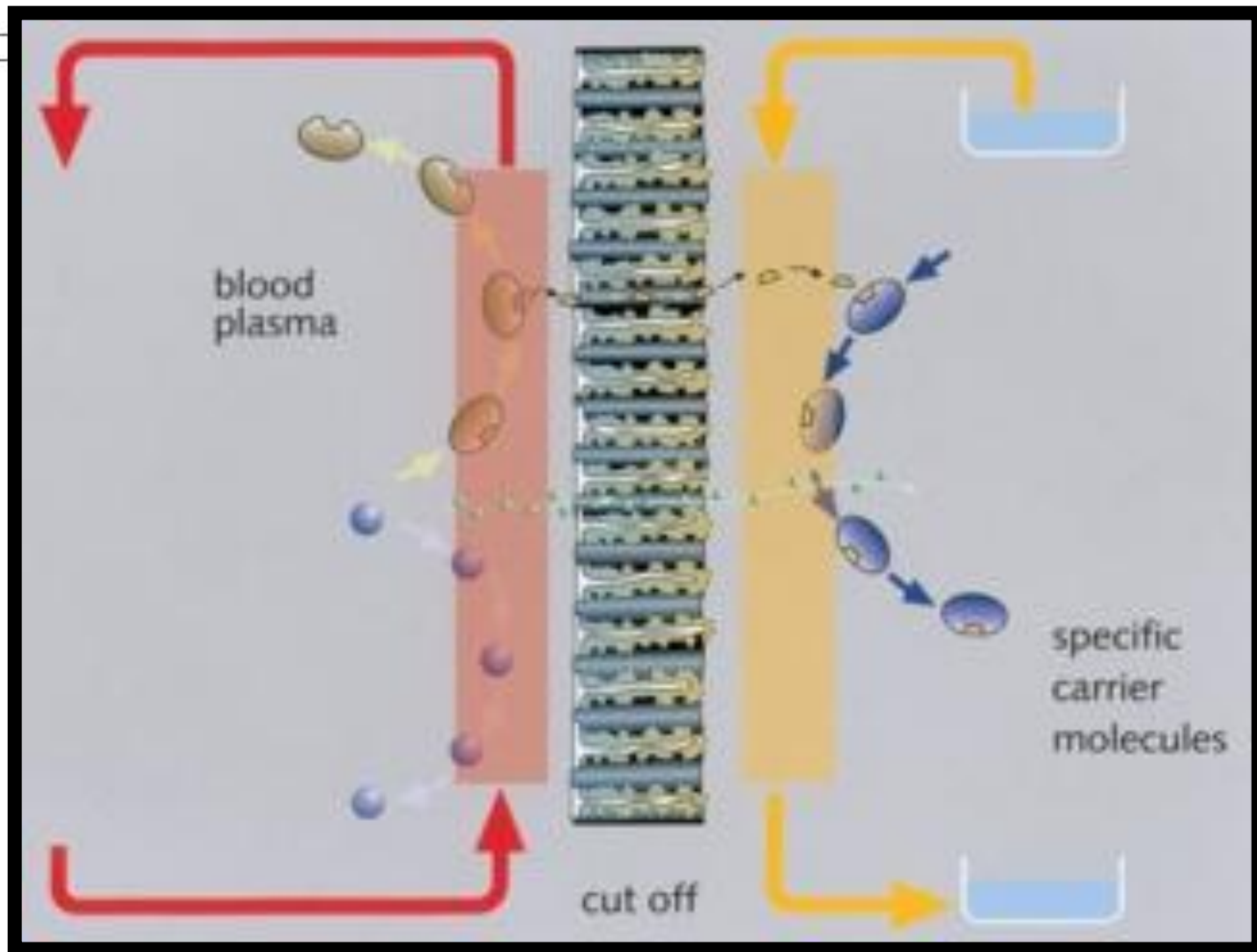
# MARS



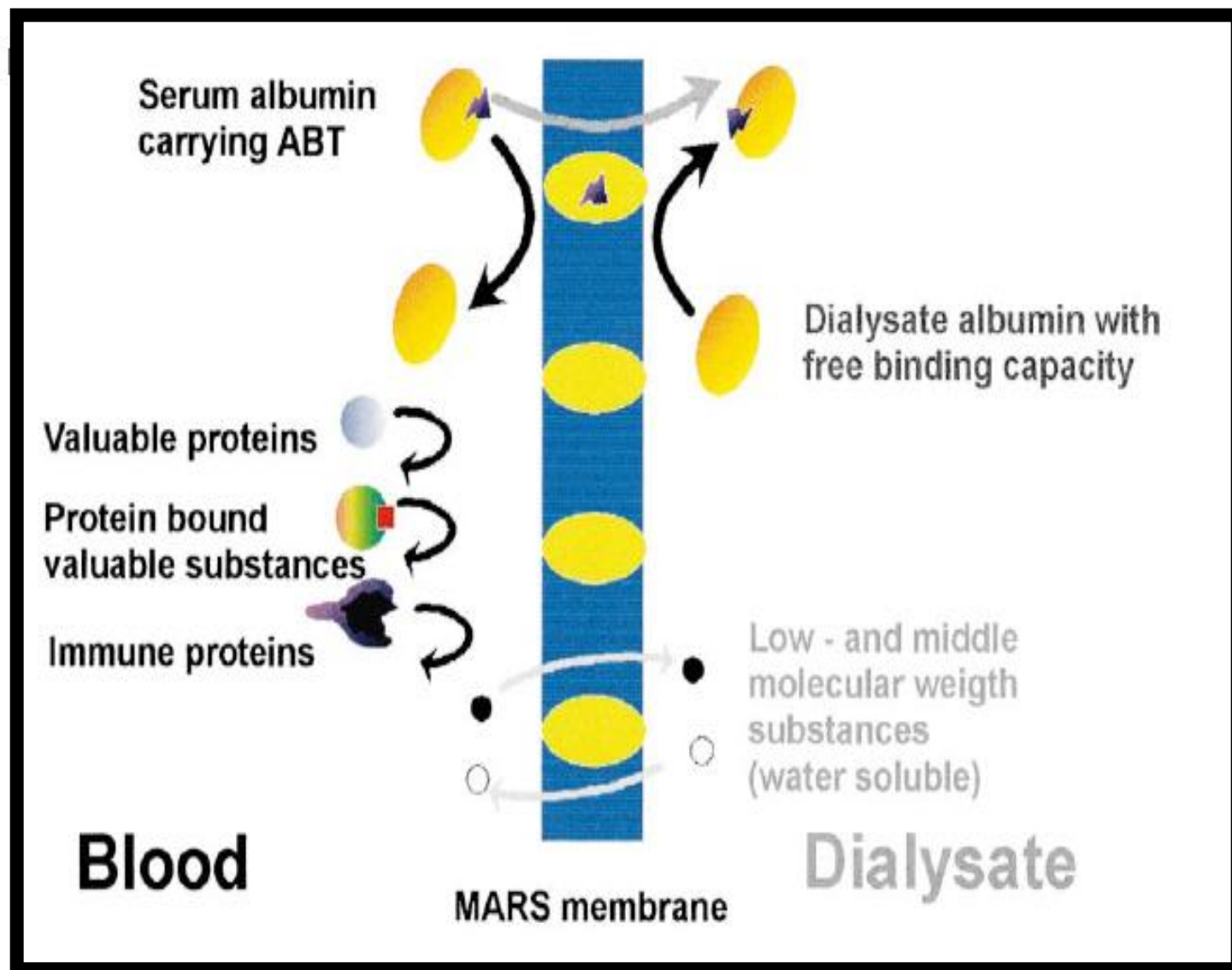
Assumption that bilirubin and other albumin-bound substances and toxins will move across a concentration gradient from the patient to a circulating **25%** albumin solutions.

Then , the ultrafiltrate cross through another cartridge to undergo conventional renal dialysis.

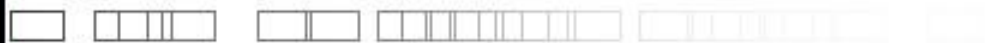








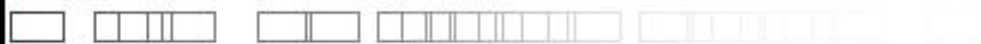












# Improvement of Hepatorenal Syndrome With Extracorporeal Albumin Dialysis MARS: Results of a Prospective, Randomized, Controlled Clinical Trial

*Steffen R. Mitzner,\* Jan Stange,\* Sebastian Klammt,\* Teut Risler,†  
Christiane M. Erley,† Brigitte D. Bader,† Elke D. Berger,† Werner Lauchart,†  
Piotr Peszynski,\* Jens Freytag,\* Heiko Hickstein,\* Jan Looock,\*  
Johannes-Mathias Löhr,\* Stefan Liebe,\* Jörg Emmrich,\* Gero Korten,\*  
and Reinhard Schmidt\**



*Journal of liver transplantation May, 2002*



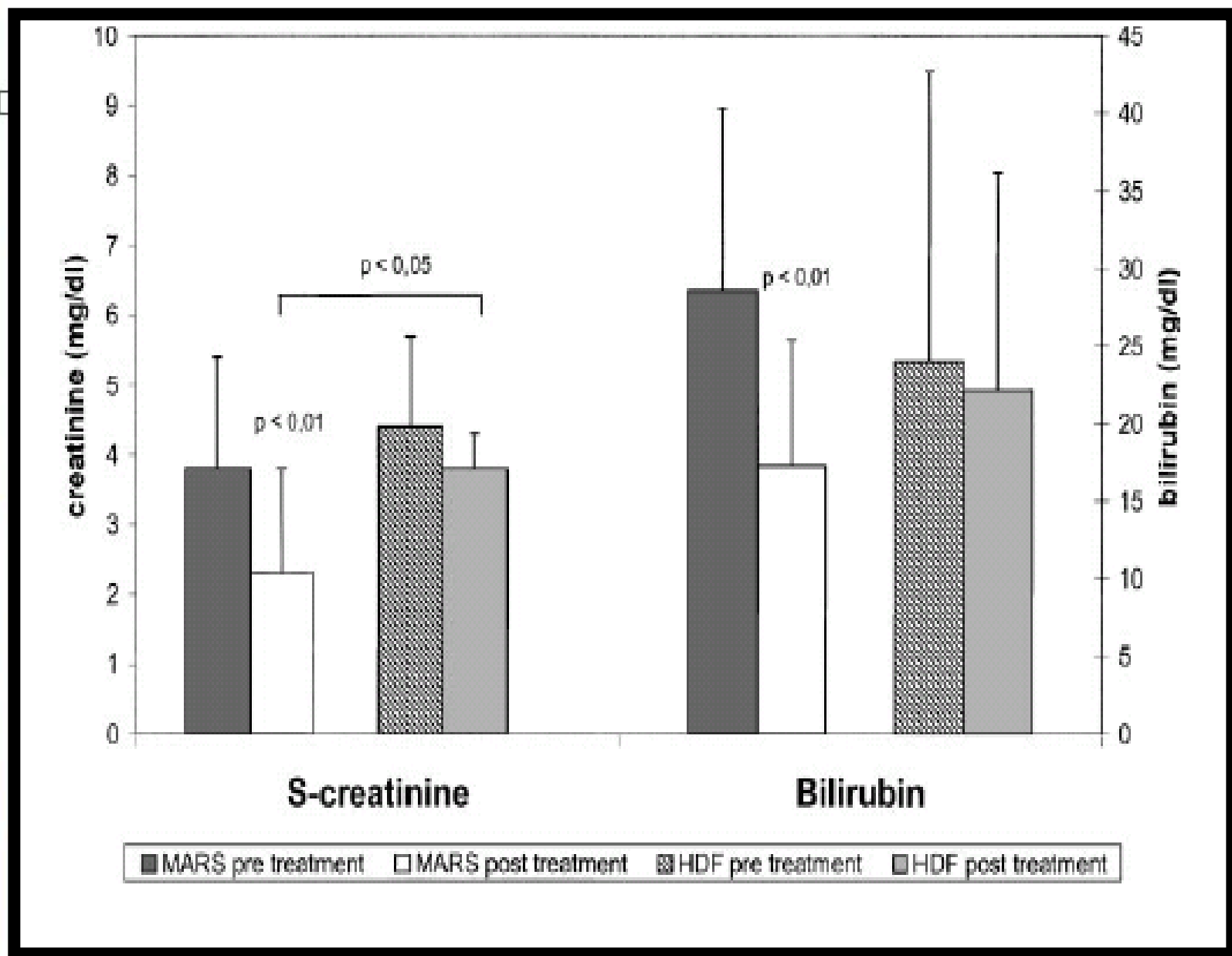


**Table 2.** Inclusion and Exclusion Criteria for the Prospective, Controlled, Clinical Trial of MARS Treatment of Patients With HRS

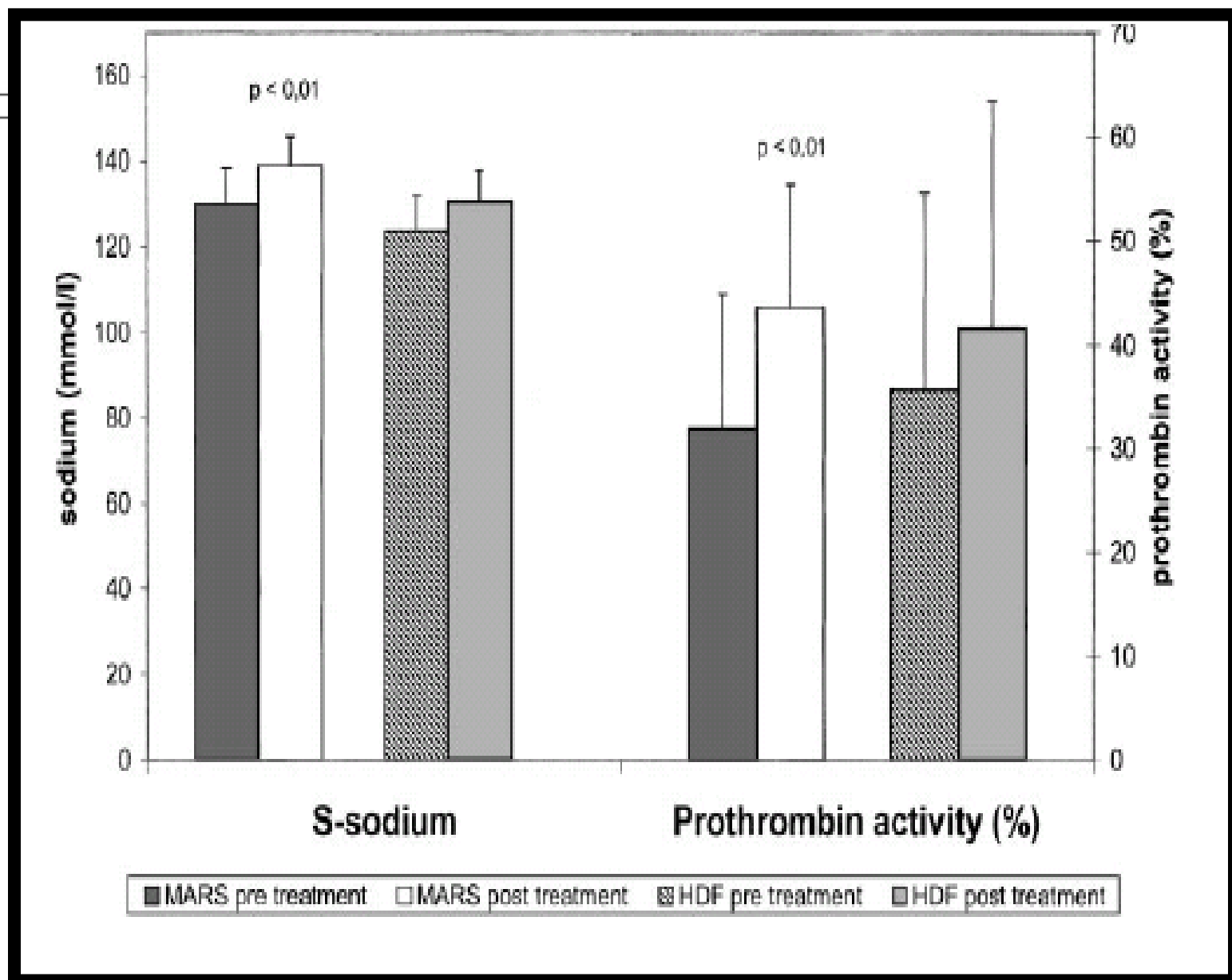
Inclusion Criteria	Exclusion Criteria
HRS	FHF
Serum creatinine $>1.5$ mg/dL	Sepsis unresponsive to antibiotic treatment
Oliguria $<500$ mL/d	Severe acute hemorrhages
Urine sodium $<20$ mmol/L	Malignancies
CVP $>8$ cm H <sub>2</sub> O	Obstructive/chronic renal failure
Need of hemodialysis/filtration treatment	Pregnancy
Age 18-60 yr	Severe cardiopulmonary disease
Informed consent	
Chronic liver failure (3 of 4 criteria)	
Ultrasonic signs of chronic damage	
Impaired synthesis function (hypoalbuminemia $<30$ g/L, prolonged prothrombin time (quick value $<70\%$ ), AT III $<70\%$ , serum cholinesterase $<40$ $\mu$ mol/s/L or $<2.3$ kU/L)	
Hyperbilirubinemia ( $>15$ mg/dL)	
Hepatic encephalopathy (grade I-IV)	

Abbreviations: CVP, central venous pressure; AT III, anti-thrombin III.

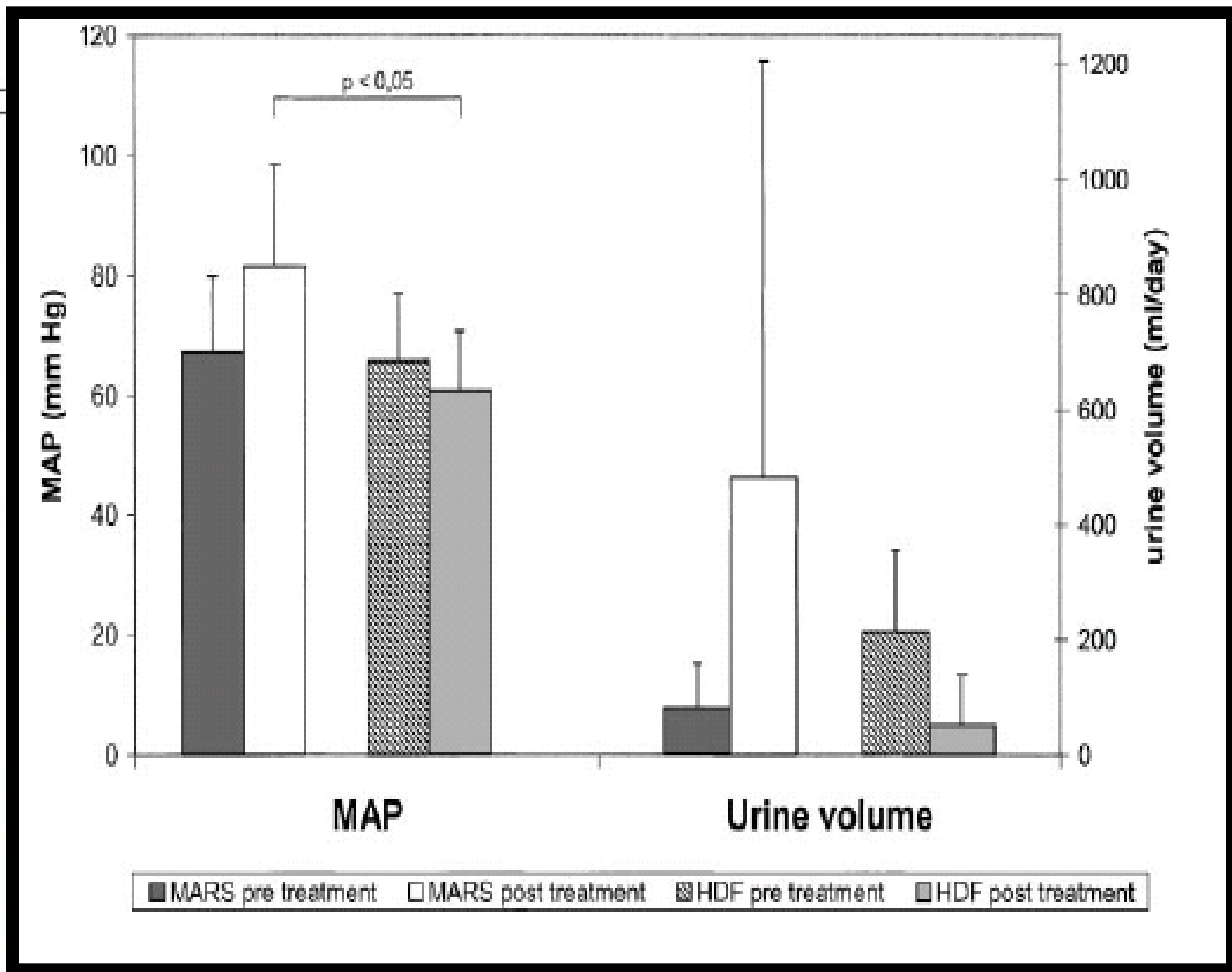




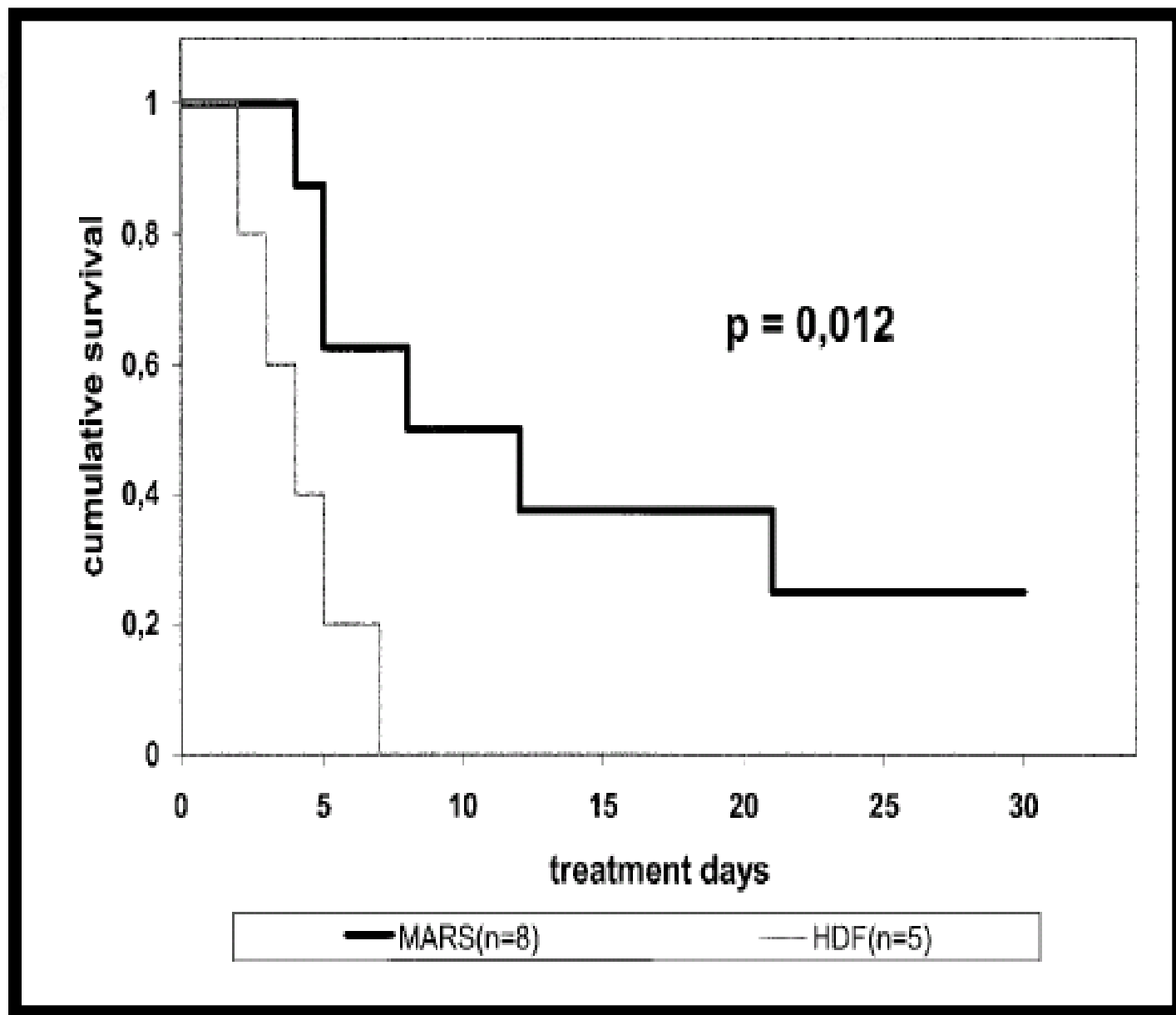




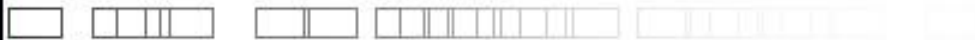












QuickTime™ and a  
TIFF (LZW) decompressor  
are needed to see this picture.



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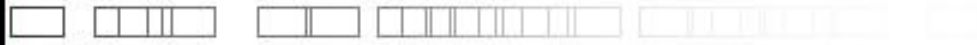


QuickTime™ and a  
TIFF (LZW) decompressor  
are needed to see this picture.





# Summary about MARS



- Cost
- Need of liver transplant center
- RCT : Not easy to conduct ,Sample size
- FDA approval for safety and efficacy
- Anticoagulation : heparin or citrate
- ?Role of MARS in : Acute - AoCHF - Post liver resection