

# Why is ACLF Drug Development Unique? Clinician Perspective

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# Decompensated Cirrhosis

- Similar to advanced metastatic cancer



**You're not acutely ill yet, but you've got potential!**

# What Do Clinicians Want?

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AD/ACLF Grade 1

ACLF Grade 2

ACLF Grade 3

Treatment to Achieve  
Reversal

Bridge to transplant

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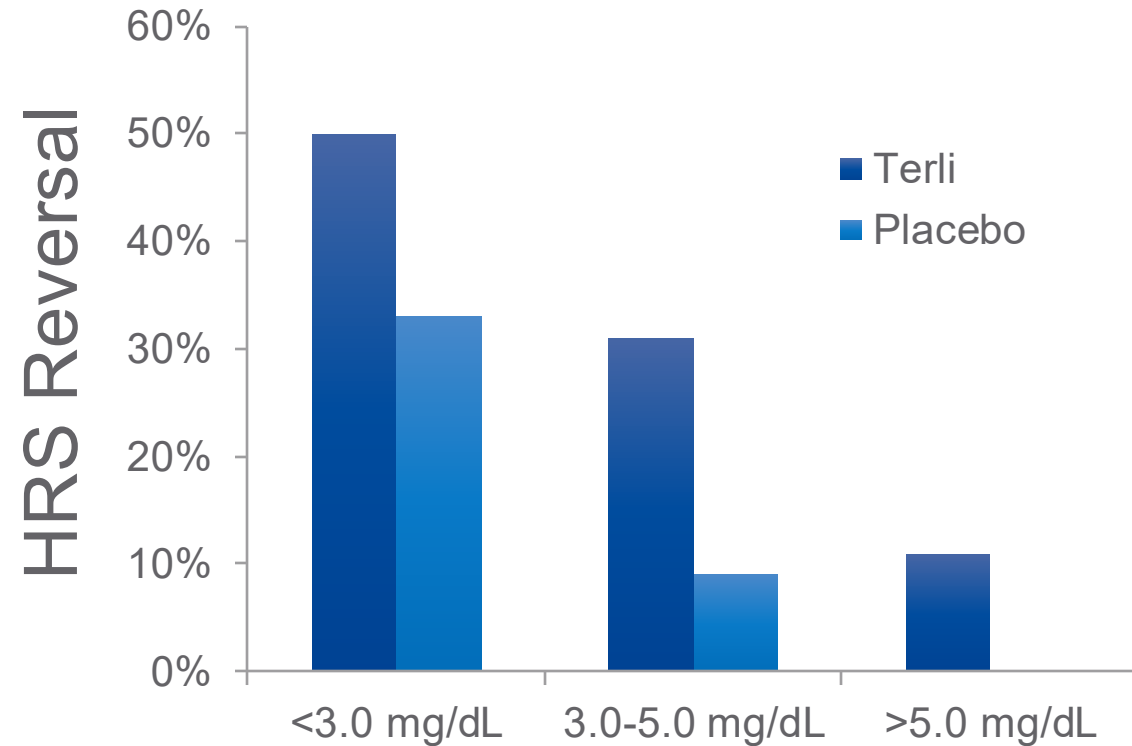
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Treatment to Remission  
Cure

Bridge to transplant  
Palliation to Prolong Life

# Organ Dysfunction / Failure Drug Development

- Terlipressin – drug development in US
  - Plagued by changing definition
  - Definition - difficult in practice
  - Definition did not allow early intervention
  - Early intervention improved outcome
- ACLF – what we need
  - ONE definition for everyone
  - Definition that is easy in practice
  - Definition that allows early intervention



***The field is ripe for drug development***

# Organ Dysfunction / Failure Drug Development

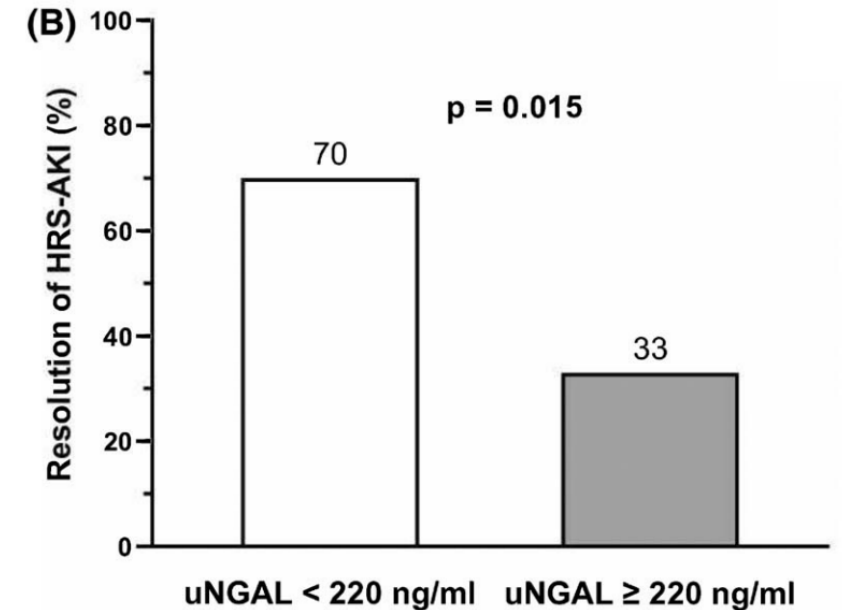
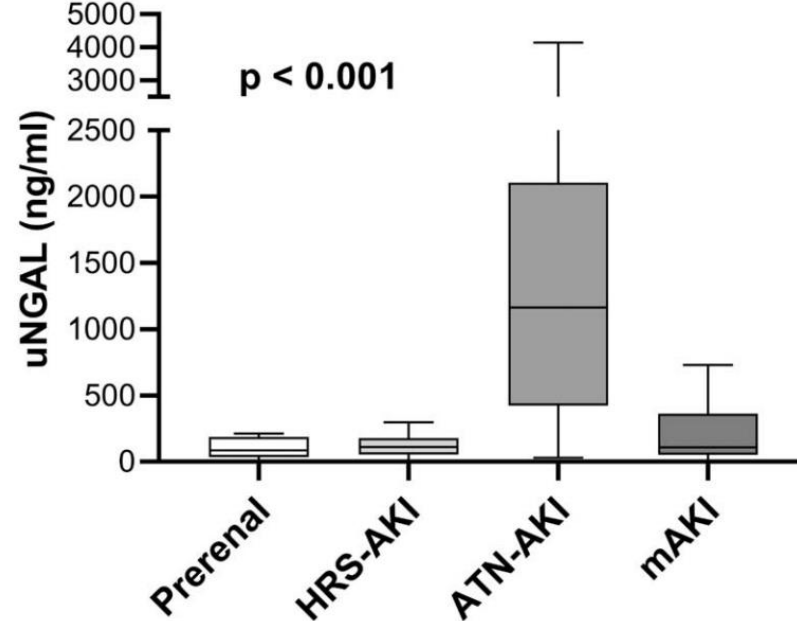
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- **What went well** in Terlipressin drug development in US:
  - Easy access to medical monitor to facilitate confirmation of meeting enrollment criteria
    - If we waited the pt may not meet criteria
  - Sharing of best practices at meetings to optimize enrollment
  - Sharing of data -- allowed investigators to educate practice partners, hospitalists & referral doctors
- **What went poorly:**
  - The inclusion and exclusion criteria were too long & complicated
  - Required a baseline creatinine within last 14 day
  - You had to enroll within 6 hours of the creatinine being drawn
    - 5 am labs – result @ 9am...
  - Could not *realistically* screen and enroll the patient on the same day
    - Needless delay decreased probability of response
  - Endpoint = Confirmed HRS response – logistical problem with hospital discharge...

# Drug Development & Biomarker Development/Validation



- This could have made Terlipressin drug development better...
- Is incredibly important in a potentially heterogenous disease like ACLF



*We need to choose patients that will benefit the MOST from EACH drug.*

# We must dive into ACLF now

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- ACLF is an orphan disease
  - High mortality
  - No accepted therapy other than liver transplant
- Because of the acuity of deterioration & severity of systemic inflammation
  - Unique space
  - Urgency for drug and therapeutic development
  - Given the recent consensus – timing is now...