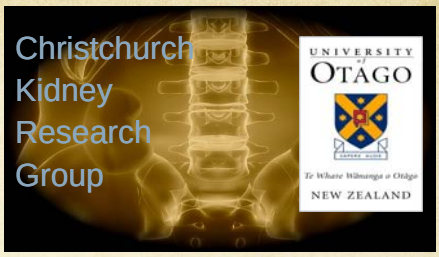

EPO, Statins and Stuff we already have – Does any of it help in AKI?

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ASN Denver Nov 2010

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- Summary of AKI interventions & Results
- Selected Outcomes:
  - Statins
  - Natriuretic Peptides
  - Fenoldapam
  - EPO
  - N-Acetylcysteine
  - Rolofylline
- Problems with Current Trials
- Future Potential

Some old, Some new Treatments

Pathology	Treatment
Vasoconstriction	Vasodilators (CO, ANP Fenoldapam, ET-antag)
Apoptosis/Necrosis	Inhibitors of caspase , p-53, PARP; EPO, minocycline
Inflammation/Oxidation	α-MSH, iNOS-inhibition, APC, statins
Growth Factor Decrease	EPO, HGF, (IGF-1)
Sepsis	ethyl pyruvate, APC

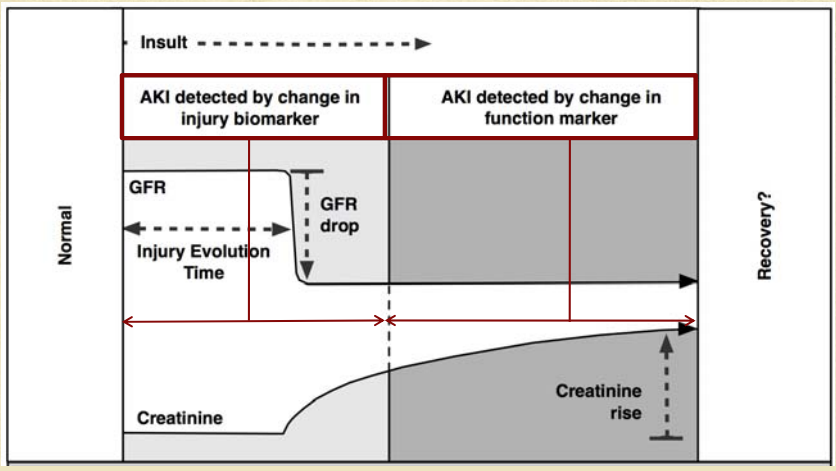
AKI Pharmaceutical Trials

- PubMed Search strategy for prevention or intervention trials excluding contrast-induced AKI
- Only randomised, placebo-controlled, single agent studies with n>30 selected
- 967 trials detected, 917 excluded: yield 50

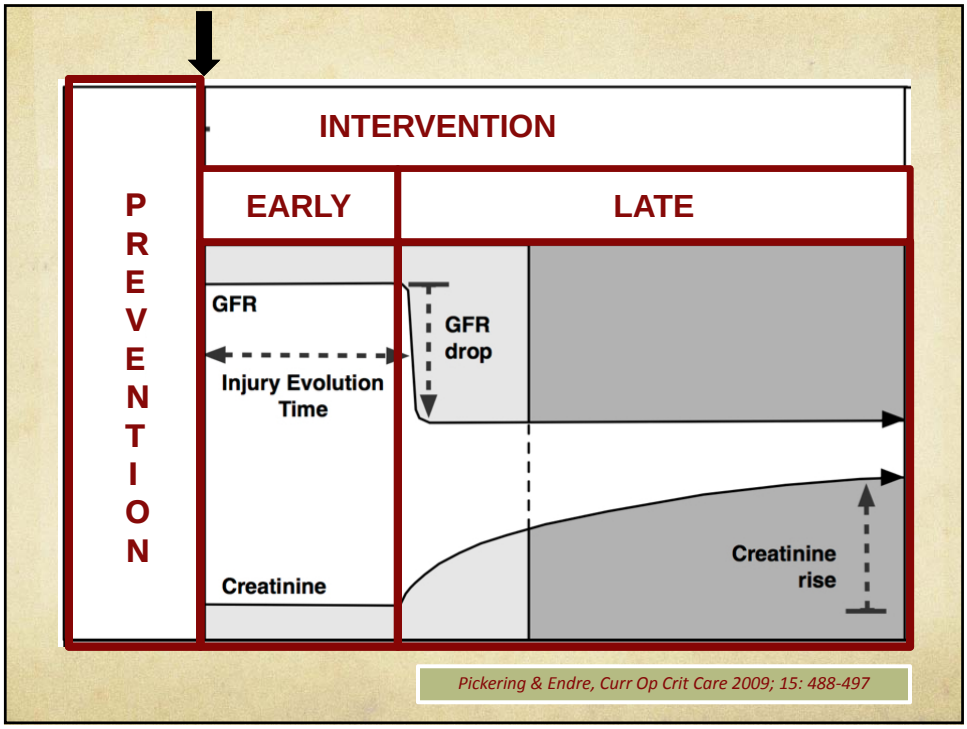
Definitions

- Prevention: Prior to Insult
- Intervention: After Insult
  - Early — Prior to increase in Creatinine
  - Late — After increase in Cr (or decrease UO)

Timing and AKI



Pickering & Endre, Curr Op Crit Care 15:488-497, 2009



AKI Pharmaceutical Trials Summary

- **Positive outcomes for 15 trials:**
  - **Prevention:** ANP(1), BNP (1), EPO (1), Fenoldopam (2), mannitol (1)
  - **Early Intervention:** alkaline phosphatase (1), ANP(1), Fenoldopam (2), IGF-1 (1), sodium nitroprusside (1)
  - **Late Intervention:** ANP(1), IgG (1), rolofylline (1)

AKI Pharmaceutical Trials Summary

- **Negative outcomes for 35 trials:**
- **Prevention:** BNP (1), dopamine (4), ethyl pyruvate (1), Fenoldopam (2), mannitol (3), NAC (8), theophylline(1)
- **Early Intervention:** ANP(1), BNP (1), dopamine (1), EPO (1), IGF-1 (1), NAC (1)
- **Late Intervention:** ANP(3), Fenoldopam (1), Furosemide (1), IGF-1 (1), rolofylline (1), triiodothyronine (1), thyroxine (1)
- **Harm as outcome in 2 (of these) trials:**
  - **Prevention:** mannitol (1)
  - **Late Intervention:** thyroxine (1)

Data will be summarised and individual trial outcomes will be discussed for:

- ANP & BNP
- IgF-1
- EPO
- Fenoldopam
- Rolofylline

- And for the
- retrospective analyses of renoprotection by Statins

Natriuretic Peptides: ANP, BNP

- Renal and Systemic Vasodilators
- Inhibit sodium reabsorption
- Prevent AKI in animal experiments
- Synthetic analogues not successful in clinical trials
- Initiation and end points in clinical trials all differ
- **Recombinant h-ANP and BNP warrant further trials for prevention and early intervention**

EPO

Trial	Patients	n	AKI	
ß-EPO Endre 2010 Kidney Int	AKI	163	NS p= 0.40 (RAVC, AKIN, RIFLE)	Early Intervention (BM-triaged)
ß-EPO Song 2009 Am J Nephrol	Post Cardiac Surgery	71	↓ p= 0. 0.035 (50% inc Cr /5 days	Prevention

Erythropoietin EPO

- Anti-apoptotic via JAK-STAT pathway
- Renoprotection, cardiac protection and neuroprotection against ischemic and toxic injury in animal studies
- Clinical protection in stroke now uncertain
- Clinical trials in cardiac ischemia, CIN prevention and renal transplantation underway
- **Further studies warranted for prevention or very early (<6hrs) treatment**

Statins

- Animal studies show renoprotection after prevention: (eg Gueler J Am Soc Nephrol 2002: 13: 2288)
- No Prospective Study in AKI except in CIN (mixed results)
- Initially supported by retrospective human studies reviewing patients on statins vs those not during cardiovascular procedures (eg Khanal Am J Med 2005)
- Retrospective Analysis: 10648 patients undergoing CABG showed NO BENEFIT from prior statin use on AKI (RIFLE), RRT or cardiovascular outcome in propensity-matched groups
- Need 15,000 pts per group to find reduction in post-op RRT or mortality and 27,000 per group to exclude type II error!
- (Argalious, Anesth Analg 2010 111: 324)
- **Neither Initiation Nor Cessation Recommended**

  (Lameire, van Biesen, Hoste, Vanholder NDT 2009, 2: 1)

Fenoldopam

- Vasodilator (dopamine-1 agonist)
- Increases renal and splanchnic blood flow
- Prevents post operative decreases in creatinine clearance and reduced need for RRT
- Prevents AKI in many/most studies:
  - most underpowered
- May not prevent CIN
- **Warrants adequately powered RCTs for prevention and early intervention**

Rolofylline

- Selective adenosine A1-receptor antagonist
- Co-administration with loop diuretics enhanced diuresis while maintaining or improving renal function in large pilot study (n=301)
- Clinical trial (n=2033) in cardiac failure underway
- Late intervention did not prevent "persistent AKI" in Cardiac Failure
- **Preventive and early intervention studies are warranted**

Design Problems with AKI Trials 1

- **Timing - Most Interventions are Late:**
  - Inappropriate reliance on Creatinine
- **Poor Agent Selection:**
  - Preventive agents applied as Interventions
  - Interventions target one of multiple parallel processes
  - Agents not selected for phase of injury

Design Problems with AKI Trials 2

- **Heterogeneity ignored**:
  - Patients (onset, baseline function, comorbidity)
  - Aetiology of AKI (eg nephrotoxins vs underperfusion)
  - Consensus Definitions focus on stage of injury, ignore etiology and phase of renal injury
- **Varied and Inappropriate Outcome Measures:**
  - Treatment of Injury assessed from change in Function
  - Functional change assessed as a Categorical instead of Continuous variable
  - Hard outcomes better as as secondary outcomes
- **Underpowered**

Treatment Strategies: Empiricists vs Rationalists

- **based on assessment of risk**
- Empirical definitions and screening
- Cause and effect relationship not always understood, even when successful - cf statins for cardiovascular disease

Treatment of Risk

- **based on knowledge of disease**
- Critical exploration of pathophysiology
- Cause and effect pivotal to selecting treatment – eg antibiotics for infection, TNFα blockade in selected Rheumatoid arthritis

Treatment of Disease

Treatment Strategies in AKI: Empiricists vs Rationalists

- **Poor Study Design**
  - AKI Definition: wrong or consensus not used
  - Underpowered
  - Patient comorbidity and heterogeneity
  - Late intervention
  - Wrong and varied Outcome Measures

Need Larger and Better designed Trials

- **Non-Rational Intervention**
  - AKI Definition: Requires pathogenesis, phase
  - Wrong Triggers for Intervention: Timing should be based on phase of injury
  - Wrong Drugs for Phase of intervention (and targeting single of multiple pathways)
  - Wrong Outcome Measures

Need to Apply Existing and New Drugs Correctly

Interventions should be prioritised according to how closely they match:

- Knowledge of disease pathophysiology
- Measurability of short-term and long-term benefits
- Incidence of serious adverse effects
- Affordability

  - O'Donnell, J et al Prioritising health care funding. *Intern Med J.* 2005 Jul;35(7):409-12.

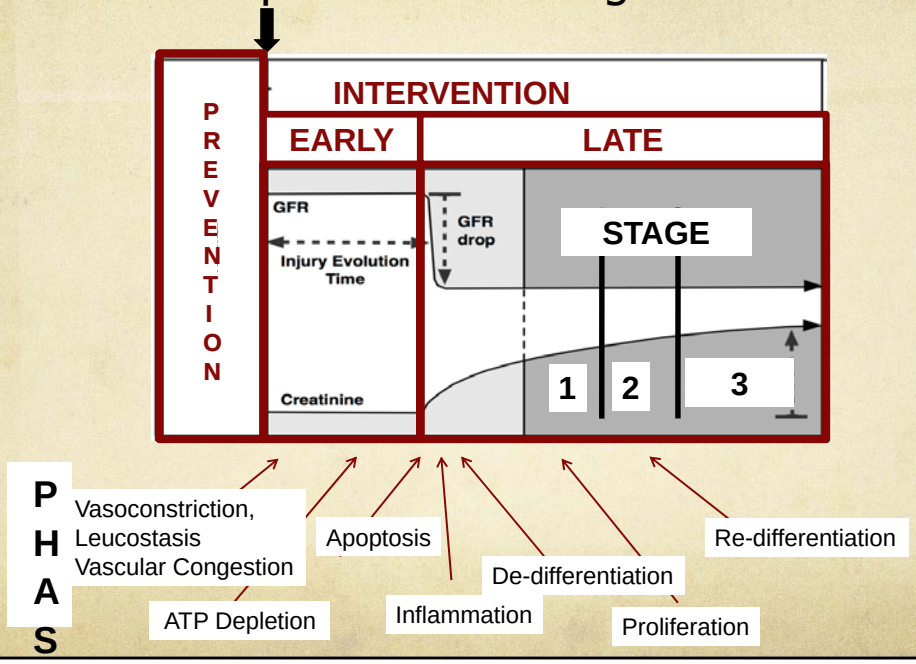
Contrast-Induced Nephropathy (CIN)

- Definition of CIN differs from RIFLE and AKIN
  - Usual: 25% increase above baseline Creatinine or absolute increase 0.5 mg/dl assessed 48 to 72 hours post procedure
- In 32,161 hospitalised patients over 5 days who did not receive contrast: >50% showed an increase in Cr >25% and more than 40% showed an increase >0.4mg/dl.
  (Newhouse AJR 2008, 191:376)
- **"Prevention studies relying on small changes in Creatinine need to be interpreted with caution"**
  (Lameire NDT 2009, 2:1-10)

Design Problems with AKI Trials

- Most trials **Underpowered**
- Outcome Measures: Treatment of **Injury** assessed from change in **Function**
- Outcome Measures: Functional change assessed as **Categorical** instead of **Continuous** variable
- Agents: **Preventive** agents applied as **Interventions**
- Intervention designed to treat only one of many multiple and probably parallel processes: **Phase** of injury does not equal functional **Stage**

Concept: Phase vs Stage of AKI



In General, AKI Trials Need:

- Definition of AKI to include biomarkers and causation
- Early detection of AKI
- Detection of phase of renal injury
- Time, cause and phase-specific intervention
- Outcome measures to reflect treatment

Old Drugs warranting adequately powered RCTs:

Definite:

- rhANP, rhBNP
- fenoldapam

Probable:

- EPO

Possible

- rolofylline
- IgF-1

Require:

- Prevention or Early Intervention (not Late)
- Triaging and Timing of Early intervention should include urine and plasma biomarkers of injury
- EPO initiation within 6 hours of injury (or as prevention)
- Adequate Power

Acknowledgements

- Christchurch Kidney Research Group:
  John Pickering, Jill Robinson, Maryam Nejat,
  Azrina Md Ralib, Jan Mehrtens, Seton Henderson, Geoff Shaw, Peter George,
  Dunedin: Rob Walker, John Schollum,
  Robyn Hutchison, Jenny Bedford, John Leader
- Heath Research Council NZ, Lottery Health New Zealand, University of Otago Research Fund