Biomarkers of Organ Dysfunction

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Achieving Excellence in Sepsis Diagnosis: A Workshop

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University of Toronto

Disclosures

I am speaking from an island that is the traditional and unceded territory of the Abegweit Mi'kmaq First Nation.

Commercial: Chair, DSMB AM Pharma

Academic: Chair, International Forum for Acute Care Trialists

Biomarkers of Sepsis

Great answers …

… what is the question?

Uses of a Biomarker

Prognostication: **Prediction of risk of organ dysfunction**

Diagnosis: **Early recognition of organ dysfunction**

Monitoring: **Response to therapy and resolution of organ dysfunction**

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

"Life-threatening organ dysfunction caused by a dysregulated host response to infection"

The Multiple Organ Dysfunction Syndrome (MODS)

- Physiologic insufficiency
- Resulting from tissue injury:
  - Infectious
  - Inflammatory
  - Iatrogenic
- Measured as both deranged function and use of external support

Table 2. *Sequential Organ Failure Assessment (SOFA) score*[10]

Organ system		Score				
		0	1	2	3	4
Respiratory	*PaO_2/FiO_2 (kPa)*	≥ 53.3	< 53.3	< 40	< 26.7	< 13.3
Renal	*Creatinine (µmol/l)*	< 110	110-170	171-299	300-440	> 440
Hepatic	*Bilirubin (µmol/l)*	< 20	20-32	33-101	102-204	> 204
Haematological	*Platelets x10³/µl*	≥ 150	< 150	< 100	< 50	< 20
Neurological	*Glasgow Coma Score*	15	13-14	10-12	6-9	< 6
Cardiovascular		MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine < 5 or dobutamine	Dopamine 5.1-15, epinephrine ≤ 0.1 or norepinephrine ≤ 0.1[A]	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1[A]

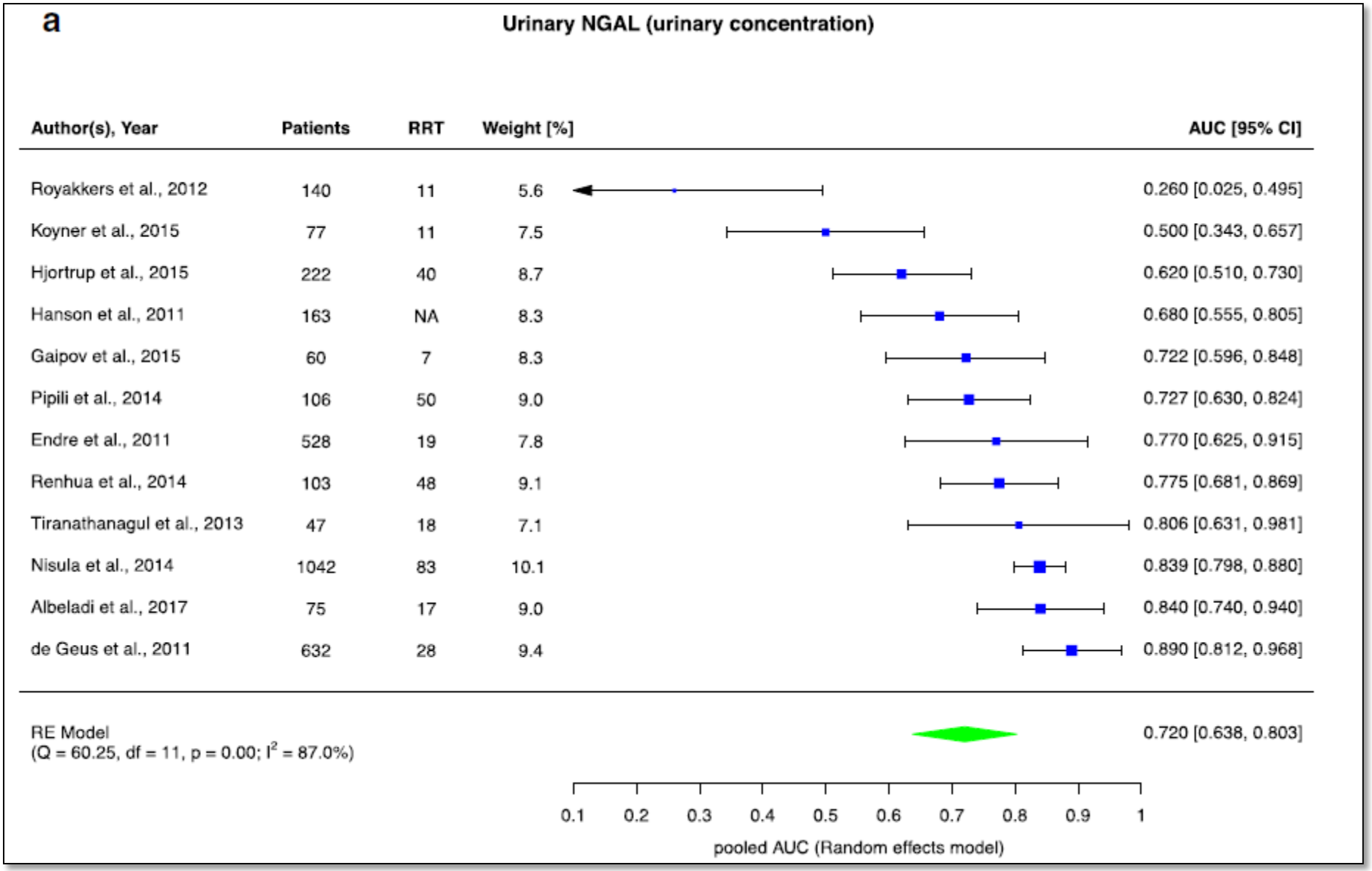
[A]Adrenergic agents (µg/kg/min) given for at least 1 hour.
MAP = mean arterial pressure.

- **Markers of physiologic dysfunction?**
- **Markers of therapeutic intervention?**

Measures of Physiologic Derangement (MOD Score)

Respiratory	**PaO_2/FIO_2 ratio**
Cardiovascular	**Pressure-adjusted rate = HR X CVP/MAP**
Renal	**Creatinine**
Hematologic	**Platelets**
Hepatic	**Bilirubin**
CNS	**Glasgow Coma Scale**

- Marshall, *Crit Care Med* 23:1638, 1995



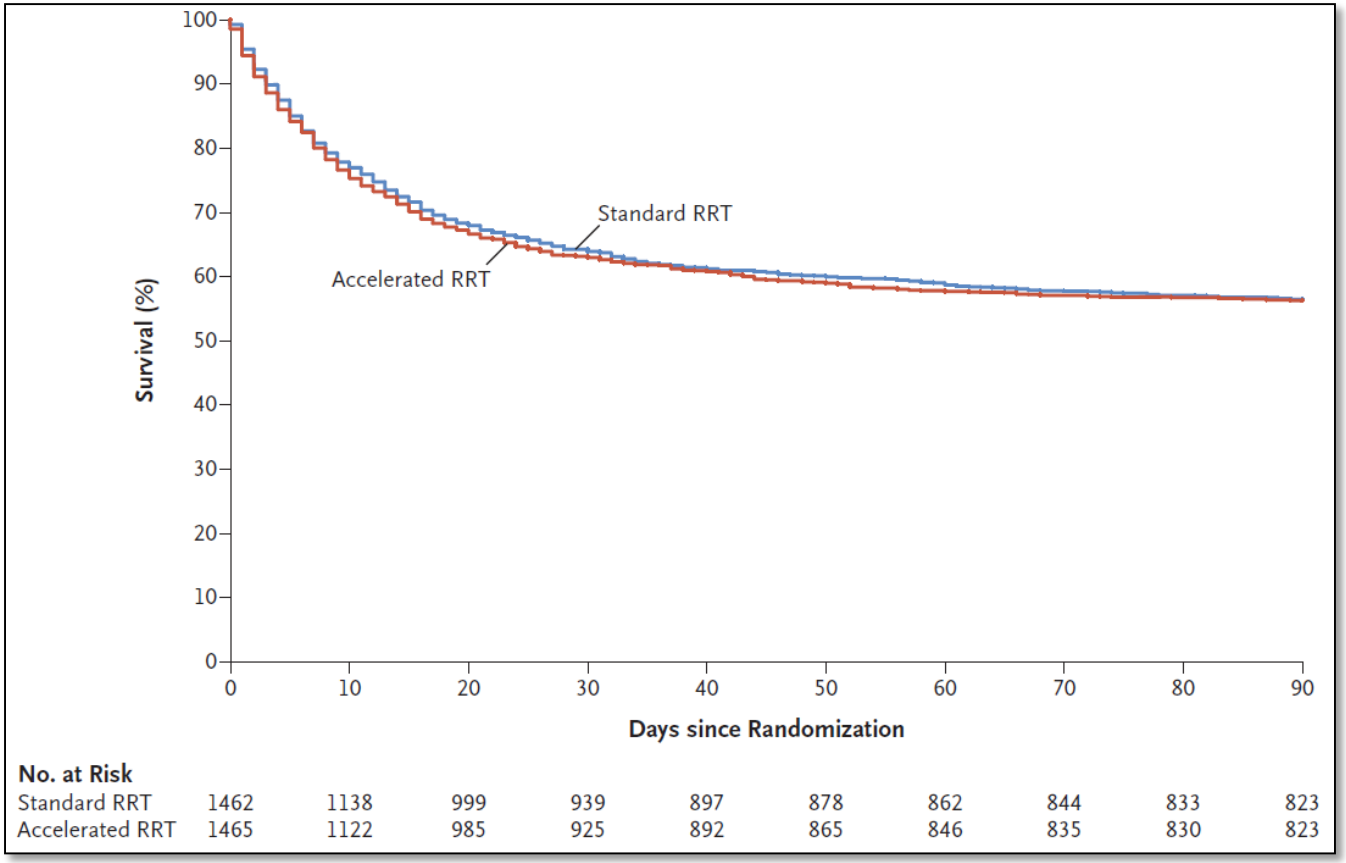
- Klein, *Intensive Care Med* 44:323, 2018

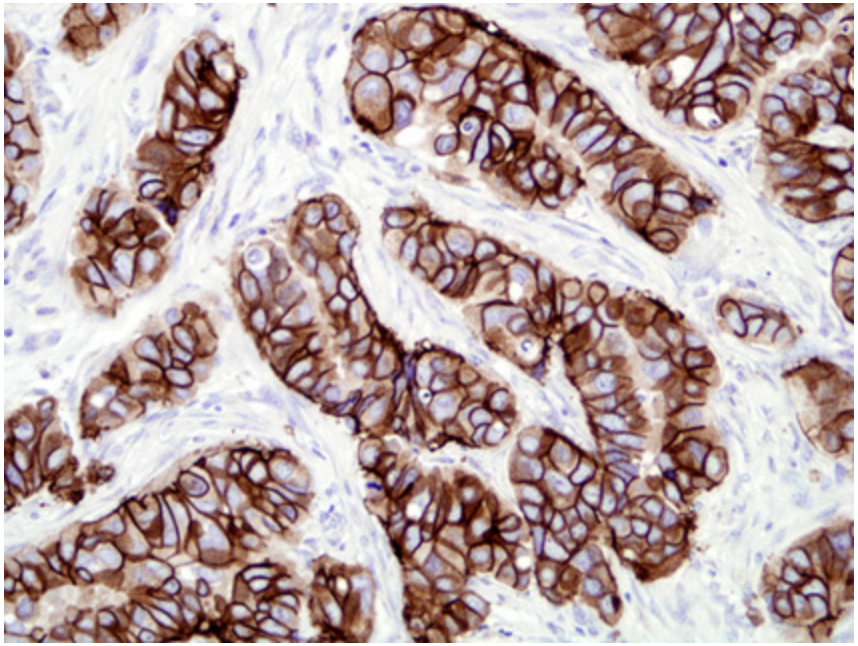
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

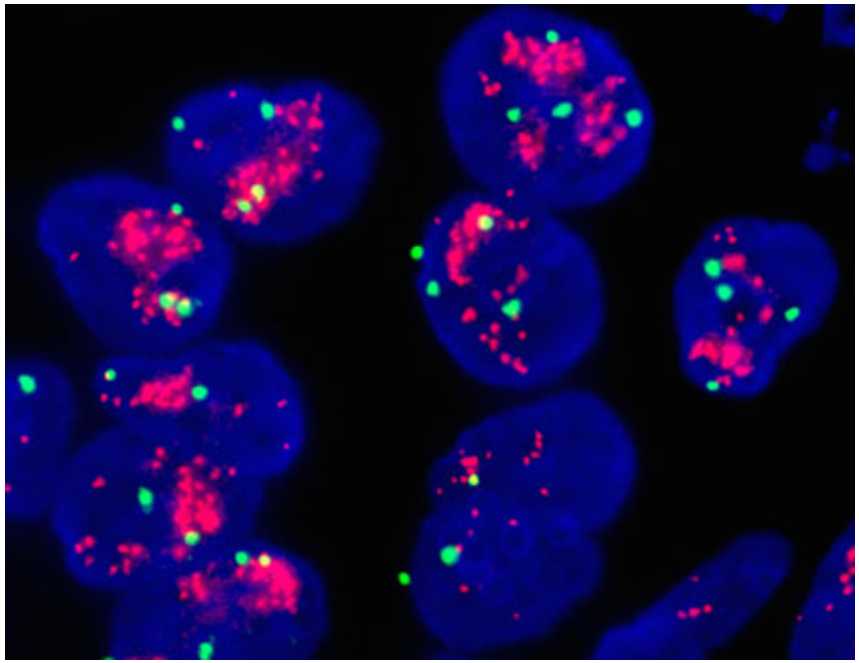
Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

The STARRT-AKI Investigators, for the Canadian Critical Care Trials Group, the Australian and New Zealand Intensive Care Society Clinical Trials Group, the United Kingdom Critical Care Research Group, the Canadian Nephrology Trials Network, and the Irish Critical Care Trials Group*





HER2/Neu Immunostaining



HER2/Neu fluorescence in situ hybridization (FISH)

Are there markers of a biologic process resulting in deranged physiology?

- Enhanced innate immunity/oxidative injury
- Impaired adaptive immunity – enhanced infectious risk
- Altered host-microbial homeostasis
- Altered apoptosis
- Endothelial dysfunction
- Metabolic reprogramming

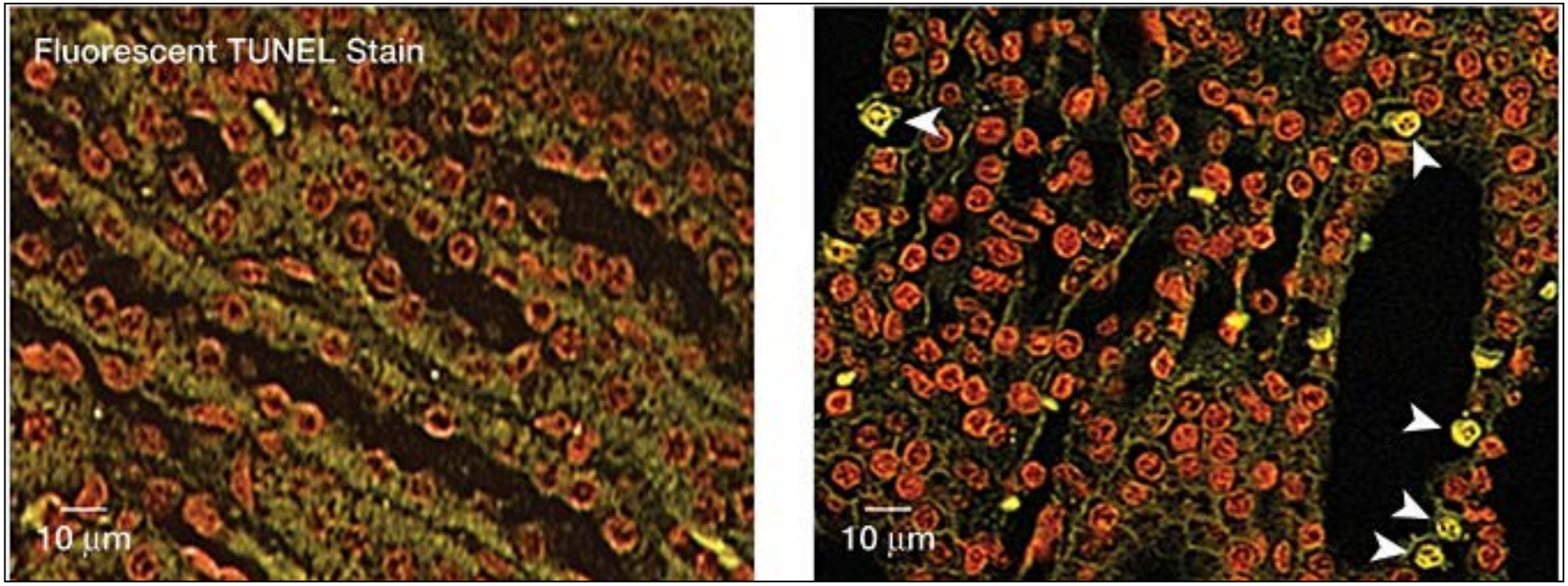
Kuiper et al. BMC Nephrology 2014, 15:126
http://www.biomedcentral.com/1471-2369/15/126

BMC Nephrology

RESEARCH ARTICLE Open Access

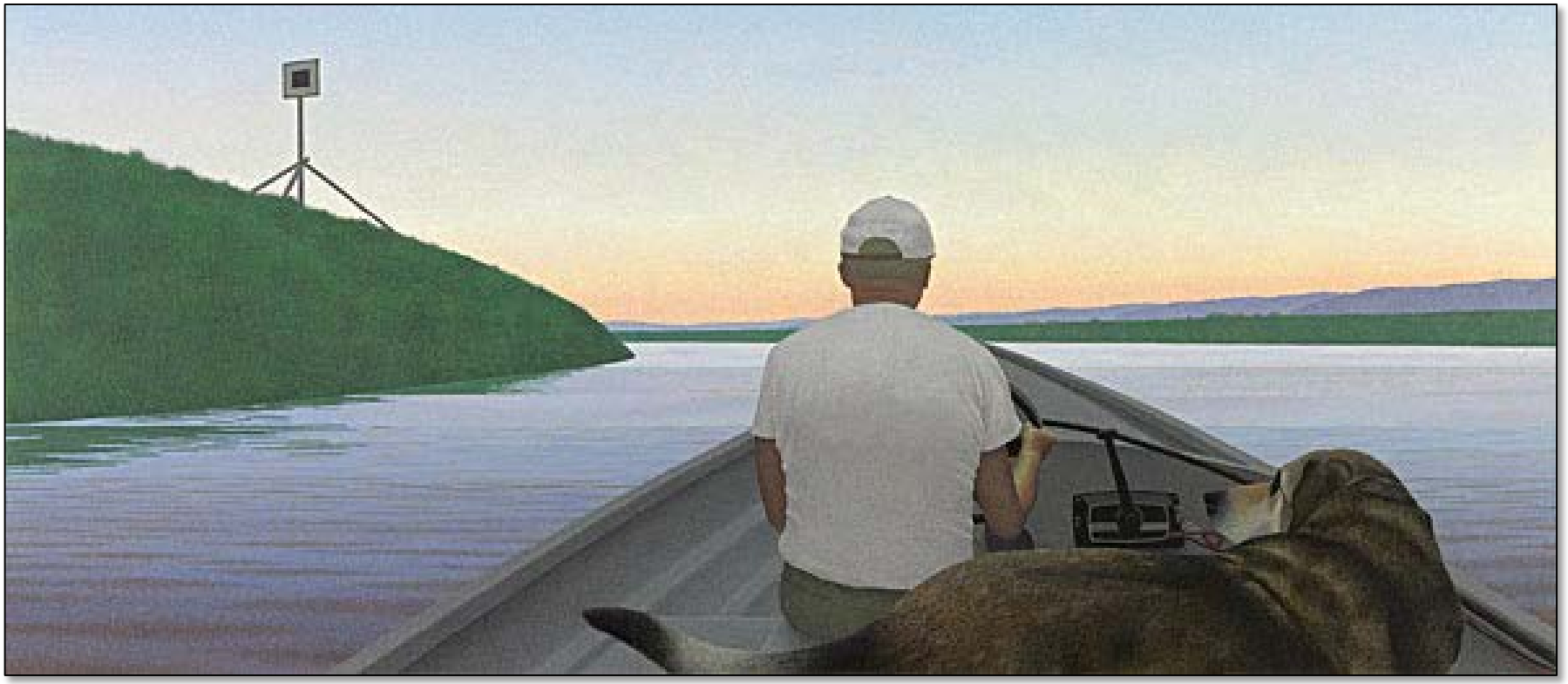
Injurious mechanical ventilation causes kidney apoptosis and dysfunction during sepsis but not after intra-tracheal acid instillation: an experimental study

Jan Willem Kuiper[1,2*], AB Johan Groeneveld[3], Jack J Haitsma[2], Lonneke Smeding[4], Mark PV Begieneman[5], Serge Jothy[6], Rosanna Vaschetto[2,7,8] and Frans B Plötz[9]



Conclusions

- **Organ dysfunction is an outcome**
- **Its biologic underpinnings are poorly understood**
- **Its roots lie in both biology and clinical practice**
- **The concept of a biomarker is premature**



- Alex Colville 1920 - 2013

Thank you!