Outcome Measures:
A Critical Care Perspective

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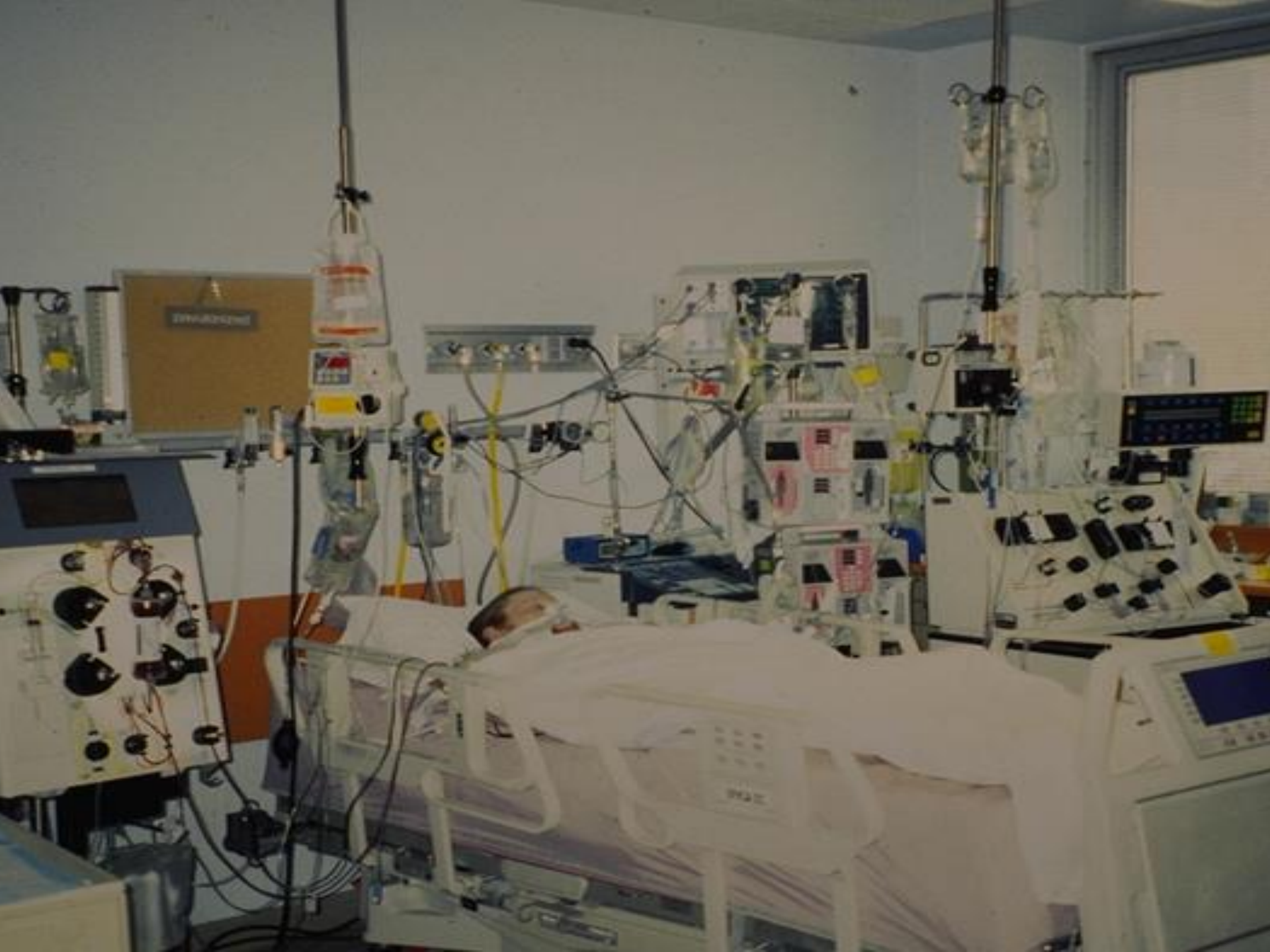
COMET V,
Calgary, Alberta
May 20, 2015

St. Michael's Hospital

University of Toronto



Challenges

- Multiple complex interventions
- Expectation of mortality benefit
- Substantial short and long term morbidity
- Outcomes heavily dependent on physician practice

Most Cited Trials in Critical Care

Author	Journal	Year	Focus	Citations/Yr
van den Berghe	NEJM	2001	Glucose	334
Rivers	NEJM	2001	EGDT	317
NICE/SUGAR	NEJM	2009	Glucose	310
PROWESS	NEJM	2001	APC	274
ARMA	NEJM	2000	Ventilation	271
VISEP	NEJM	2008	Glucose/Starch	217
Van den Berghe	NEJM	2006	Glucose	201
6S	NEJM	2012	Starch	192
CHEST	NEJM	2012	Starch	157
TRICC	NEJM	1999	Transfusion	140
CORTICUS	NEJM	2008	Steroids	137

CCCTG
Canadian Critical Care Trials Group

Founded 1989

- **>60 active research programs**
- **>200 publications**
- **16 in *New England Journal of Medicine***

ANZICS Clinical Trials Group

- Founded 1994
- 9 papers in NEJM

ARDSnet

PETAL NETWORK
Prevention & Early Treatment of Acute Lung Injury

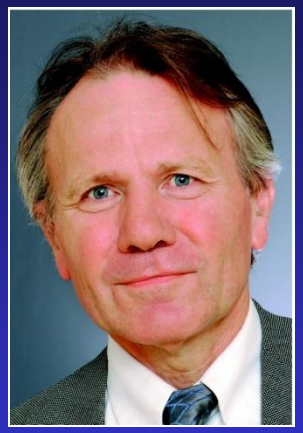
- NIH-funded
- 6 papers in *New England Journal of Medicine*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

Frank M. Brunkhorst, M.D., Christoph Engel, M.D., Frank Bloos, M.D., Ph.D., Andreas Meier-Hellmann, M.D., Max Ragaller, M.D., Norbert Weiler, M.D., Onnen Moerer, M.D., Matthias Gruendling, M.D., Michael Oppert, M.D., Stefan Grond, M.D., Derk Olthoff, M.D., Ulrich Jaschinski, M.D., Stefan John, M.D., Rolf Rossaint, M.D., Tobias Welte, M.D., Martin Schaefer, M.D., Peter Kern, M.D., Evelyn Kuhnt, M.Sc., Michael Kiehntopf, M.D., Christiane Hartog, M.D., Charles Natanson, M.D., Markus Loeffler, M.D., Ph.D., and Konrad Reinhart, M.D., for the German Competence Network Sepsis (SepNet)



German Sepsis Network

Scandinavian Critical Care Trials Group

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D., Anne B. Guttormsen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D., Gudmundur Klemenzson, M.D., Anders Åneman, M.D., Ph.D., Kristian R. Madsen, M.D., Morten H. Møller, M.D., Ph.D., Jeanie M. Elkjær, M.D., Lone M. Poulsen, M.D., Asger Bendtsen, M.D., M.P.H., Robert Winding, M.D., Morten Steensen, M.D., Pawel Berezowicz, M.D., Ph.D., Peter Søe-Jensen, M.D., Morten Bestle, M.D., Ph.D., Kristian Strand, M.D., Ph.D., Jørgen Wiis, M.D., Jonathan O. White, M.D., Klaus J. Thornberg, M.D., Lars Quist, M.D., Jonas Nielsen, M.D., Ph.D., Lasse H. Andersen, M.D., Lars B. Holst, M.D., Katrin Thormar, M.D., Anne-Lene Kjældgaard, M.D., Maria L. Fabritius, M.D., Frederik Mondrup, M.D., Frank C. Pott, M.D., D.M.Sci., Thea P. Møller, M.D., Per Winkel, M.D., D.M.Sci., and Jørn Wetterslev, M.D., Ph.D., for the 6S Trial Group and the Scandinavian Critical Care Trials Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Simvastatin in the Acute Respiratory Distress Syndrome

Daniel F. McAuley, M.D., John G. Laffey, M.D., Cecilia M. O'Kane, Ph.D., Gavin D. Perkins, M.D., Brian Mullan, M.B., T. John Trinder, M.D., Paul Johnston, M.B., Philip A. Hopkins, Ph.D., Andrew J. Johnston, M.D., Cliona McDowell, M.Sc., Christine McNally, B.A., and the HARP-2 Investigators, for the Irish Critical Care Trials Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*


BRICNet
Brazilian Research in Intensive Care Network


+CHINA
+CRITICAL
+CARE
+CLINICAL TRIALS GROUP

Emerging Groups

Latin American Critical Care Trials Investigators Network (LACCTIN)

Asian Critical Care Clinical Trials Group

Acute Care for Africa Research and Training (ACART)

What Is the Model?

- Led by clinician-investigators
- Questions defined by the investigator
- Culture of collegiality, inclusiveness, fun, and mentorship
- Commitment to scientific rigour

Influence of Organizational Model on Study Impact

Model	N	Median Citations/Year
Single site	116	6.8
2-5 sites	59	11.0
Ad hoc group	89	25.1 [a]
Trials group	44	44.1 [a,c]
Industry	85	12.3 [b]

[a] p<0.001 vs single site, [b] p<0.01 vs single site,
[c] p<0.01 vs industry

InFACT: a global critical care research response to H1N1

Published Online
November 10, 2009
DOI:10.1016/S0140-6736(09)61792-X

The H1N1 pandemic presents acute care researchers with an extraordinary challenge and an unprecedented opportunity. By early October, 2009, there had been more than 340 000 reported cases of H1N1 infection in 191 countries, with more than 4100 deaths.[1] WHO initially projected that up to 2 billion people could become infected with the virus over the next 2 years.[2] Although vaccination programmes and other factors should reduce this number, plausible estimates of the number of infected individuals who might benefit from admission to intensive care range from 200 000 to 10 million. Influenza killed at least 50 million people during the 1918 pandemic.[3] Today, with antibiotics and antiviral agents, mechanical ventilation, and the supportive measures available in intensive care, most of those deaths could have been prevented.

The mortality for H1N1-infected patients admitted to intensive care ranges from 10 to 40% over the first month,[4-8] and survivors spend a median of 2 weeks in the intensive care unit. To reduce this toll requires a better understanding of the epidemiology and clinical and treatment of severe H1N1 disease. In parallel, we will develop a biobank to facilitate studies of genetic susceptibility and clinical biology.

We are starting a programme of collaborative, investigator-led randomised trials of treatment strategies that target both the virus and the host response. Our initial three studies will evaluate inexpensive interventions that are available in both the developed and the developing world: corticosteroids and statins. They use adaptive designs to ensure that results can be quickly incorporated into practice, and that ineffective treatments are dropped. As measures of efficacy, they will measure survival of individual patients and the rapidity with which patients can be liberated from limited intensive-care resources.

We seek to reduce the consequences of severe H1N1 infection in the developed world, where available research infrastructure is most robust, and in the developing world, where the human toll is likely to be the greatest. To this end, we will catalogue international critical care capacity, and promote, mentor, and support clinical research activities in resource-poor areas.

- *Lancet*, 375:11, 2010

InFACT Members

- AMC Amsterdam
- ANZICS CTG
- ARDSNet
- BRIC Net
- CCCTG
- CRISMA
- Chinese CCTG
- ESICM CTG
- George Institute
- GIVITI
- Hellenic Sepsis Group
- ICNARC
- ICCTG
- ICS UK CTG
- LASI
- REVA Network
- Scandinavian CTG
- Scottish CTG
- SepNet
- SOAP Investigators
- TRIGERSEP
- USCIITG

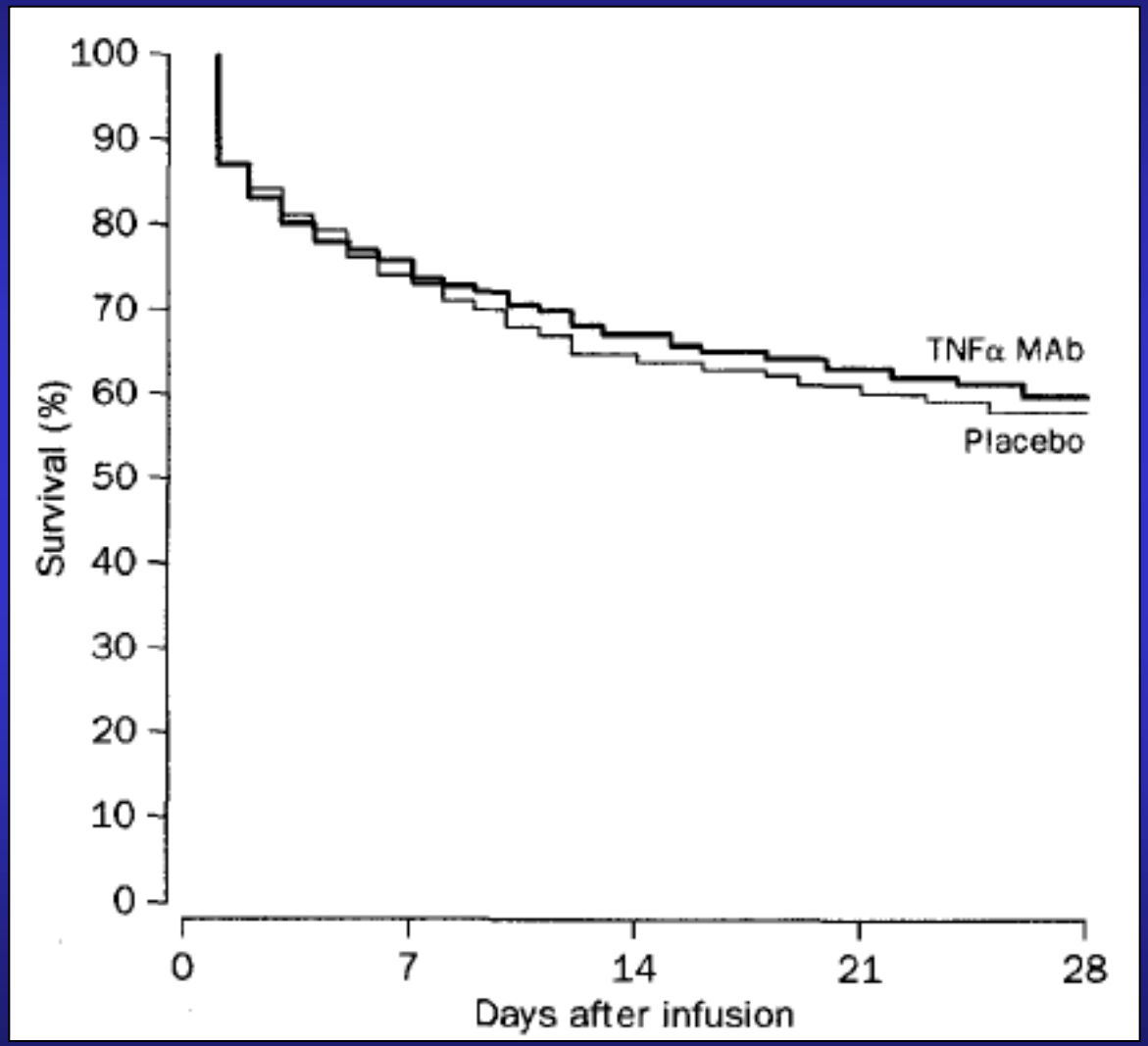
Outcome Measures Working Group

1. Create a framework for outcome measures
2. Establish domains within this framework
3. Compile core outcome measure sets
4. Understand performance of existing measures
5. Develop and validate new measures

A Conceptual Framework

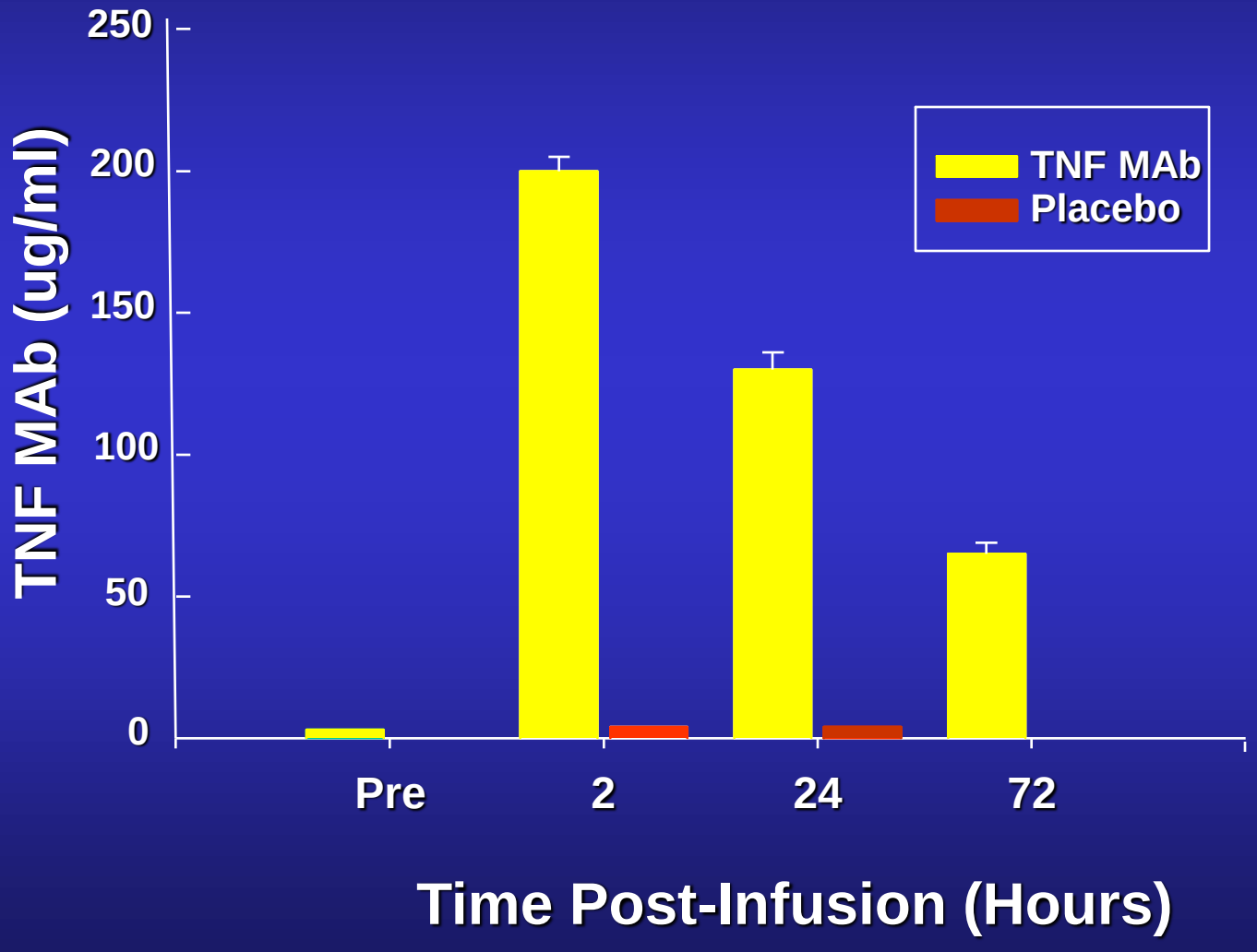
1. **Does it work?** Biologic and physiologic activity
2. **Does it help?** Patient-centred benefit
3. **Should we use it?** Risks, benefits, costs
4. **Can we study it?** Feasibility, compliance, recruitment rates

NORASEPT: Anti-TNF Mab for Sepsis

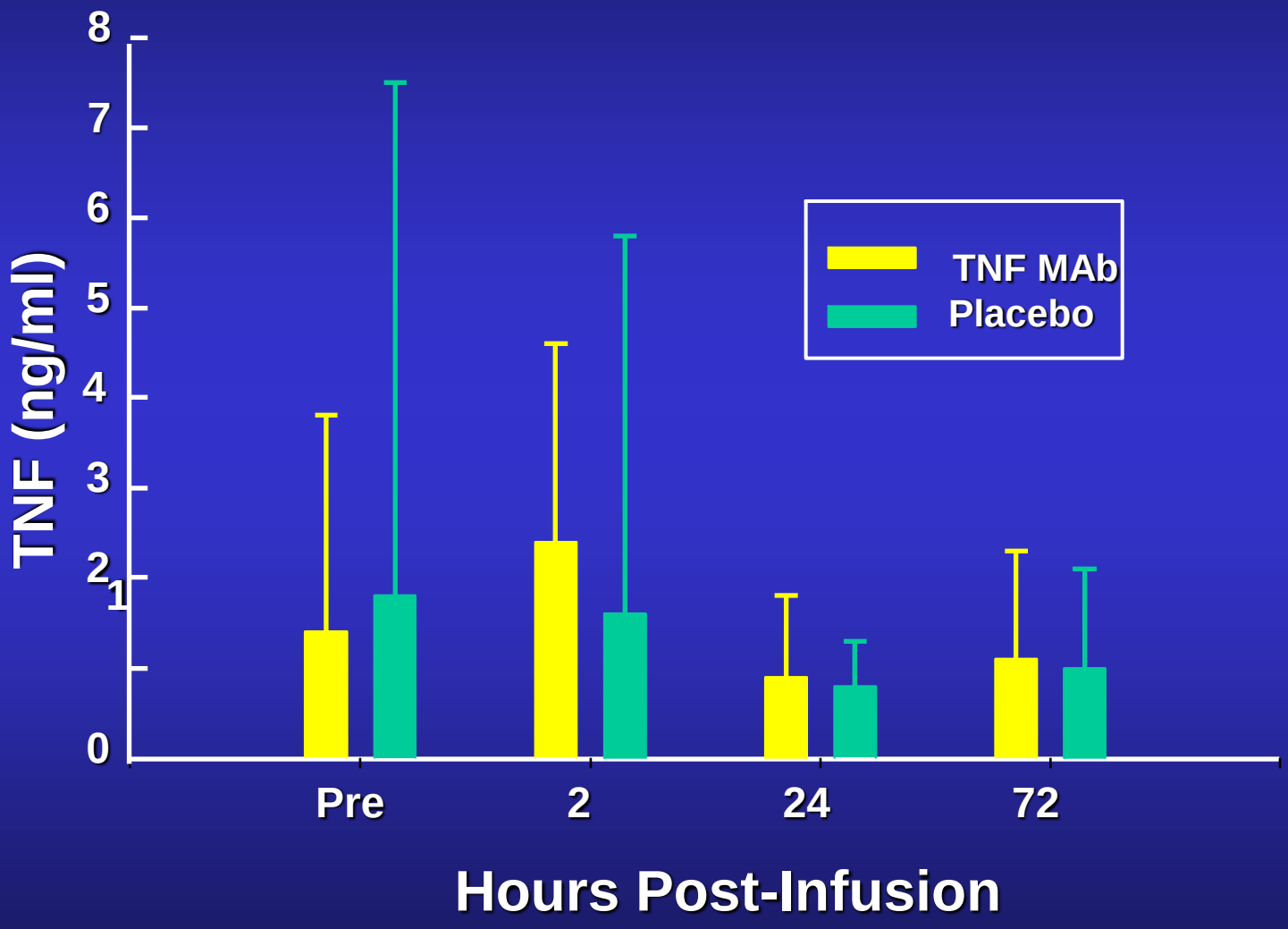


- *Lancet* 351:929, 1998

NORASEPT II:
Antibody Levels Following Drug Infusion

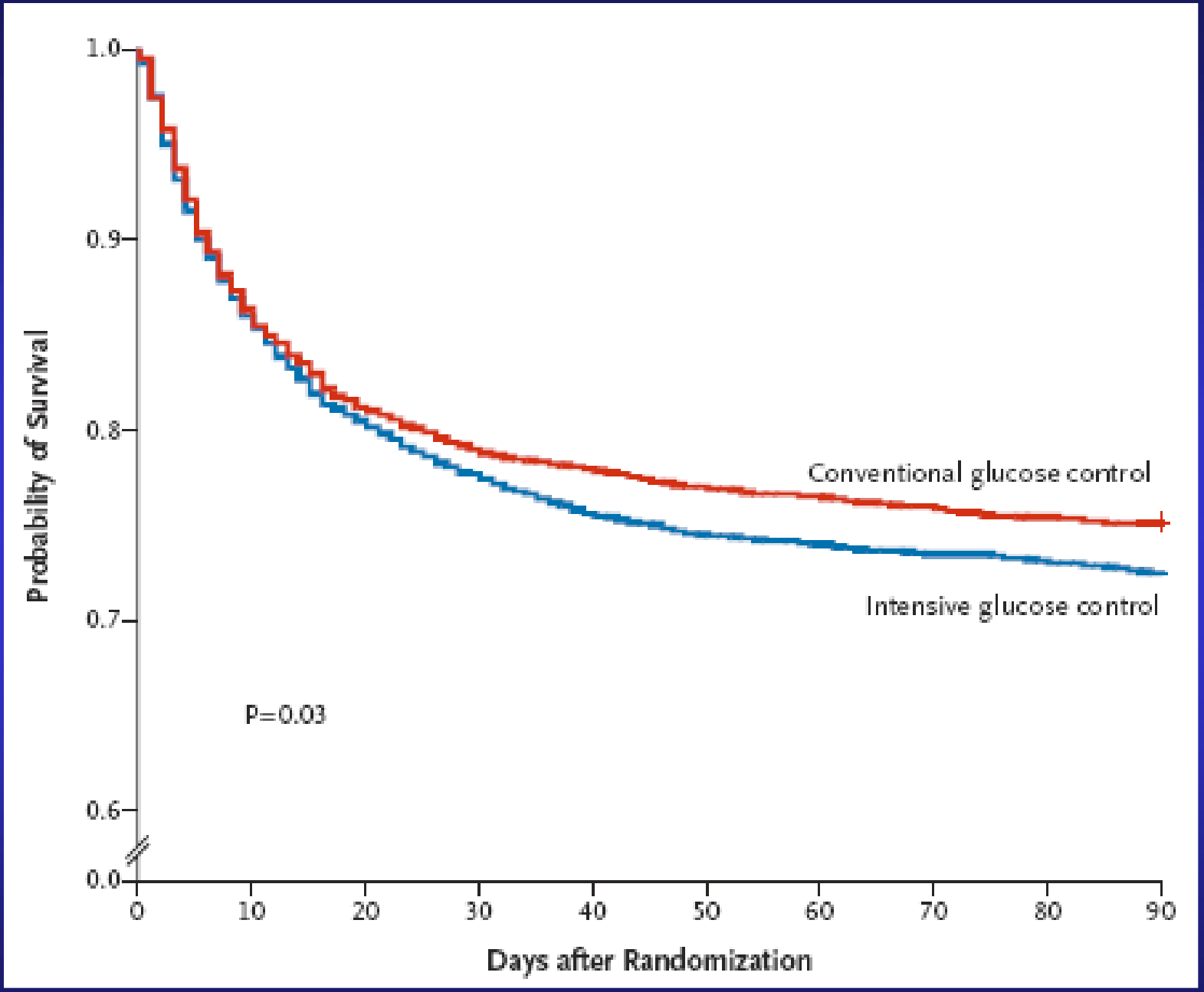


TNF Levels Following Infusion



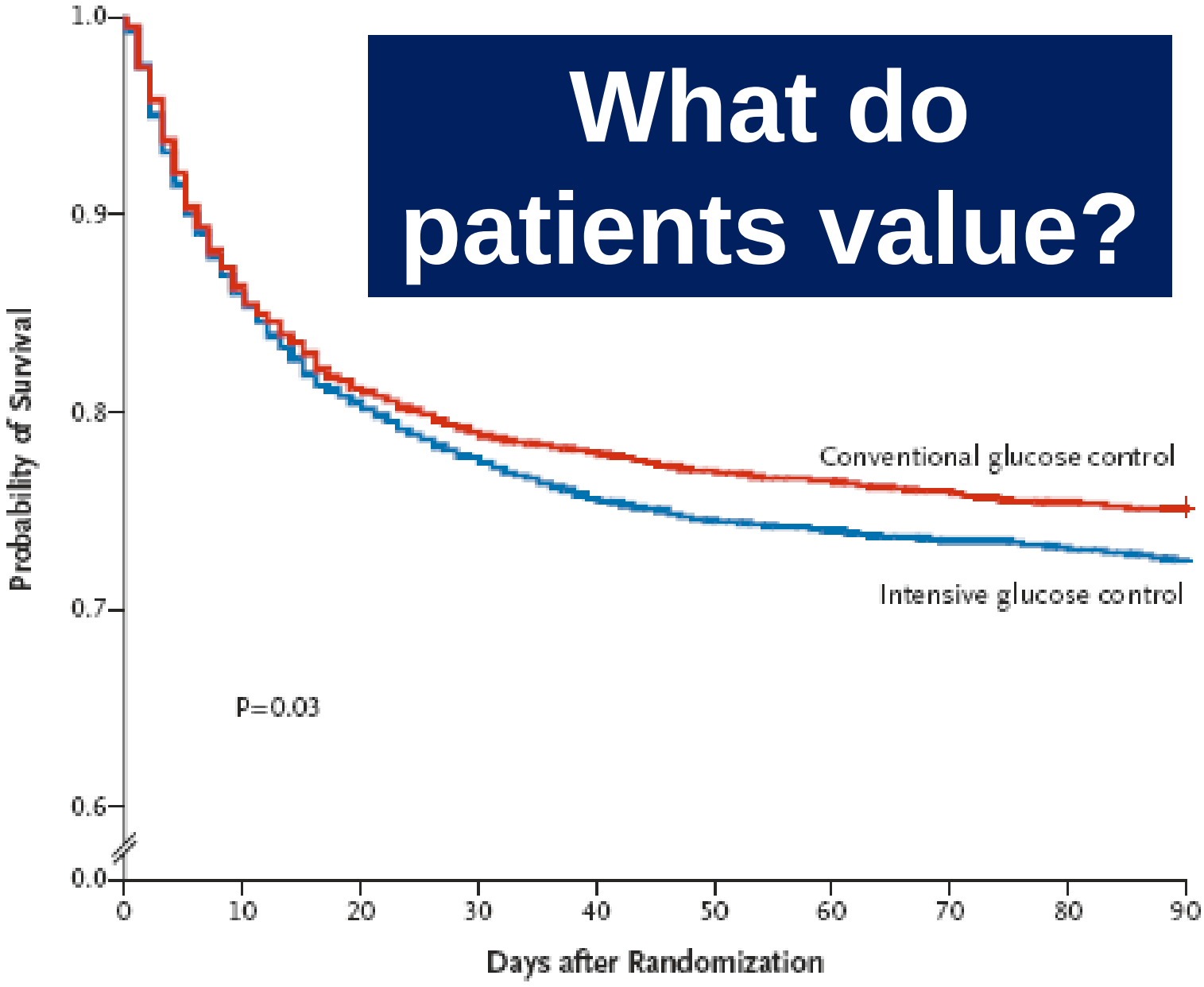
Does It Help?

- Improved survival
- Reduced discomfort/pain
- Reduced acute morbidity
- More rapid recovery
- More complete recovery



Finfer, *N Engl J Med* 360:1283, 2009

What do patients value?



Finfer, *N Engl J Med* 360:1283, 2009

Integrating Mortality and Morbidity Outcomes

Using Quality-adjusted Life Years in Critical Care Trials

Niall D. Ferguson[1,2,3], Damon C. Scales[1,4], Ruxandra Pinto[4], M. Elizabeth Wilcox[1,2,3], Deborah J. Cook[5,6,7,8], Gordon H. Guyatt[5,6,7], Holger J. Schünemann[5,6,7], John C. Marshall[1,9,10], Margaret S. Herridge[1,2,3], and Maureen O. Meade[5,6,7,8]; for the Canadian Critical Care Trials Group

[1]Interdepartmental Division of Critical Care Medicine, [2]Division of Respirology, Department of Medicine, [3]University Health Network and Mount Sinai Hospital, [4]Sunnybrook Health Science Centre, [9]Department of Surgery, and [10]St. Michael's Hospital, The University of Toronto, Toronto, Ontario, Canada; and [5]Department of Medicine, [6]Department of Clinical Epidemiology and Biostatistics, [7]CLARITY Research Team, and the [8]Critical Care Medicine Program, McMaster University, Hamilton, Ontario, Canada

How to measure morbidity

- length of stay
- organ failure
- intensity of therapy
- location in health care system

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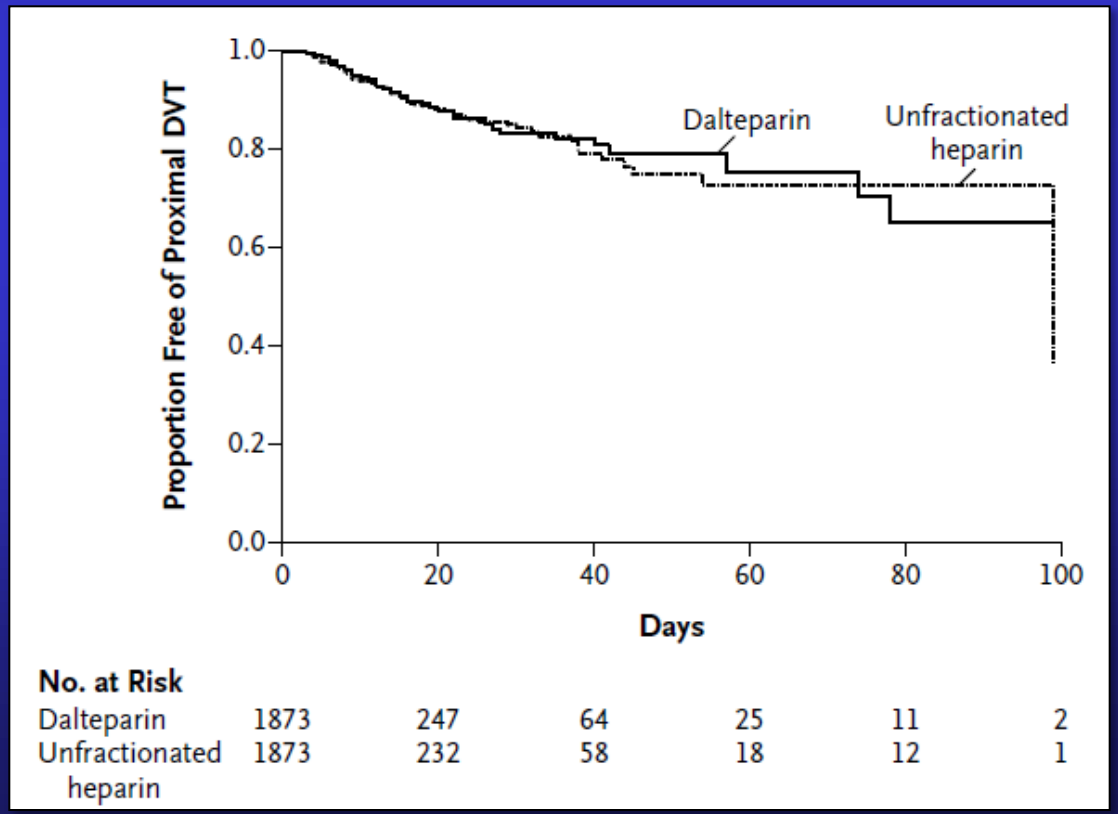
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dalteparin versus Unfractionated Heparin in Critically Ill Patients

The PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group

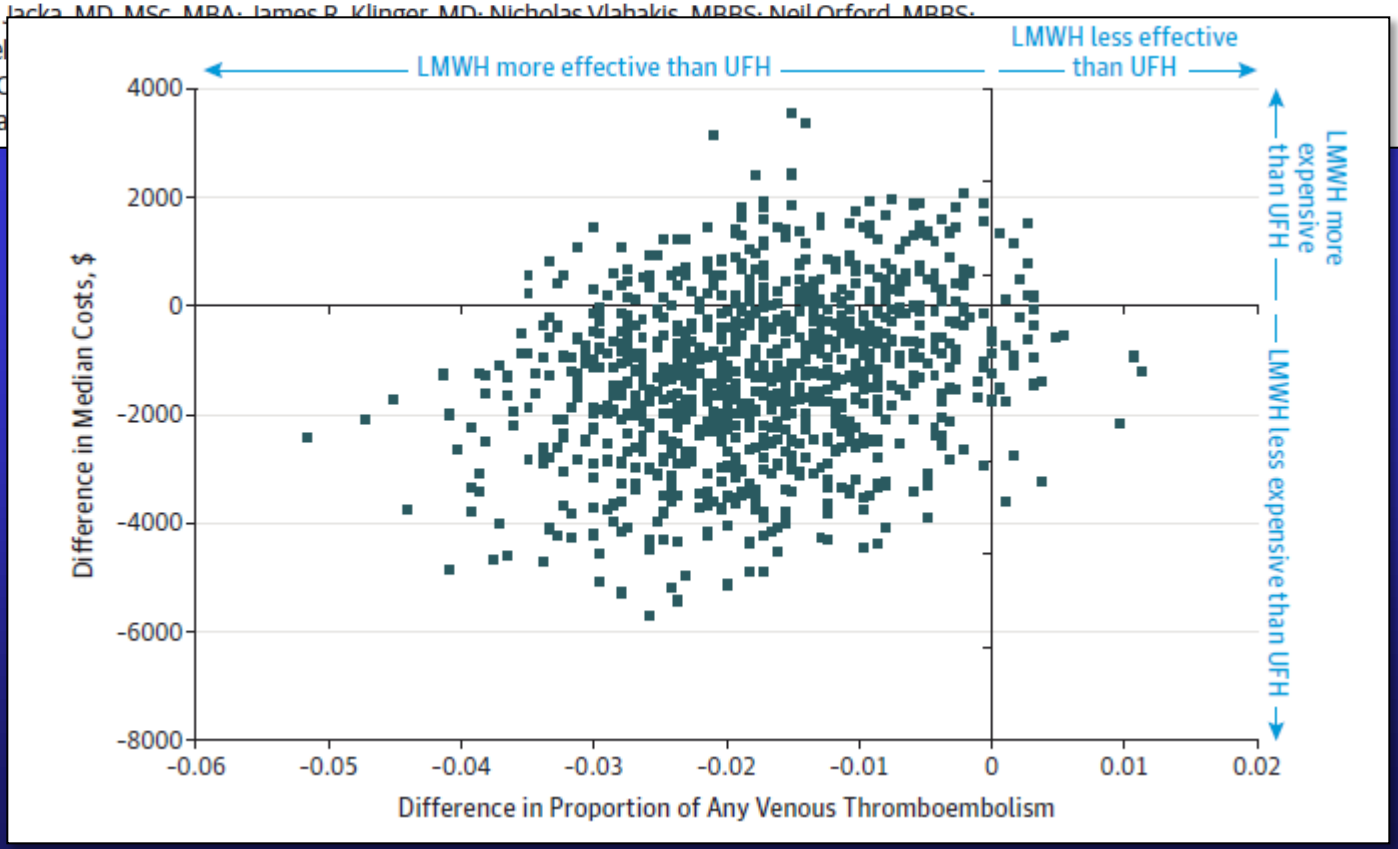
- *N Engl J Med* 364:1305, 2011



Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Cost-effectiveness of Dalteparin vs Unfractionated Heparin for the Prevention of Venous Thromboembolism in Critically Ill Patients

Robert A. Fowler, MDCM, MS; Nicole Mittmann, MSc, PhD; William Geerts, MD, MSc; Diane Heels-Ansdell, MSc; Michael K. Gould, MD, MS; Gordon Guyatt, MD; Murray Krahn, MD, MSc; Simon Finfer, MD; Ruxandra Pinto, PhD; Brian Chan, BSc; Orges Ormanidhi, MSc; Yaseen Arabi, MD; Ismael Qushmaq, MD; Marcelo G. Rocha, MD; Peter Dodek, MD, MHSc; Lauralyn McIntyre, MD, MSc; Richard Hall, MD, PhD; Niall D. Ferguson, MD, MSc; Sangeeta Mehta, MD; John C. Marshall, MD; Christopher James Doig, MD, MSc; John Muscedere, MD; Michael J Jacka, MD, MSc, MBA; James R. Klinger, MD; Nicholas Vlahakis, MBBS; Neil Orford, MBBS; Ian Seppel
Deborah C
Australia a



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AATICC Pilot Study

Feasibility Proportion of eligible patients who are consented and randomized

Acceptability Proportion of randomized patients who remain in assigned treatment arm

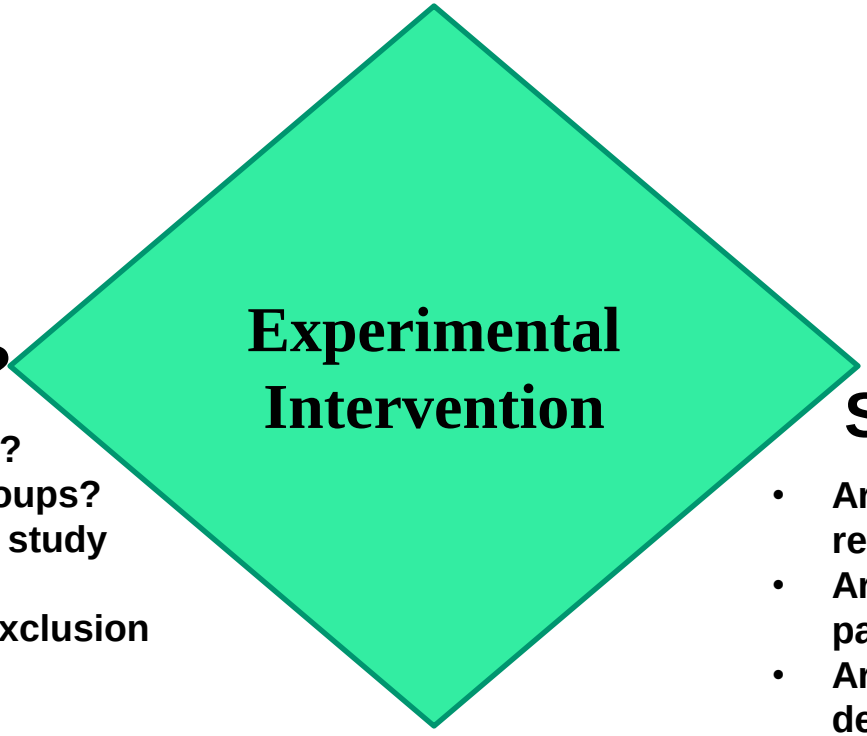
Acceptability: Major Protocol Violations

Empiric Antibiotics	0/6
Placebo	6/6*

* p=0.005

The Patient: Does it help?

- Is survival increased?
- Is recovery accelerated?
- Are symptoms attenuated
- Are long term outcomes improved



The Investigator

Can we study it?

- Can we recruit patients?
- Can we differentiate groups?
- Will clinicians maintain study groups?
- Are the inclusion and exclusion criteria appropriate?

Society

Should we use it?

- Are costs reasonable in relation to benefits?
- Are side effects acceptable to patients?
- Are outcomes acceptable to decision-makers?

The Intervention: Does it Work?

- Is the intervention biologically active in vivo?
- What are its biochemical and physiologic effects?
- What is the optimal dose and duration of therapy to maximize these effects?

InFACT

Core Outcome Measure Sets

- Mechanical ventilation
- Closed head injury
- Subarachnoid hemorrhage
- Sedation
- Sepsis

InFACTGlobal.org