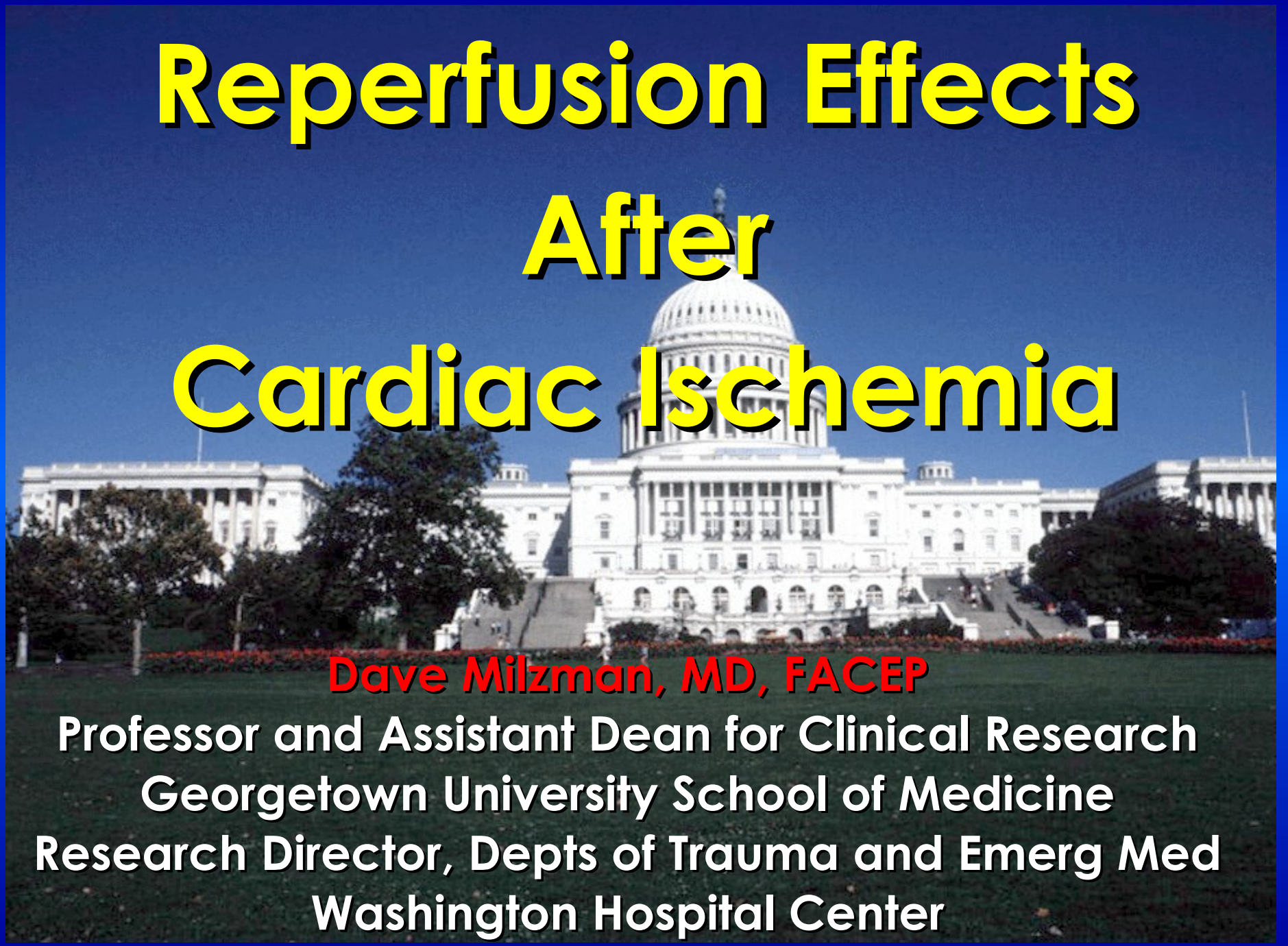
Reperfusion Effects After Cardiac Ischemia



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Universal Definition of Myocardial Infarction

Kristian Thygesen; Joseph S. Alpert; Harvey D. White;
on behalf of the Joint ESC/ACCF/AHA/WHF Task Force
for the Redefinition of Myocardial Infarction

Table 1 Clinical classification of different types of myocardial infarction

Type 1 Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2 Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
Type 3 Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a Myocardial infarction associated with PCI
Type 4b Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5 Myocardial infarction associated with CABG

JACC
2009;54:2205-41.

Survival from Out Of Hospital Cardiac Arrest < 10%, < 2%

Barriers to improving survival after cardiac arrest:

(1) Extremely Narrow Time Window (< 2-4 Minutes) To Begin Resuscitation Or Never Effective.

(2) The Limited Hemodynamic Capability Of Current Resuscitation To Achieve Circulation Required to Reverse Ischemia Of Critical Organs, CPR NOT PERFECT

(3) The Tissue Injury—known As Reperfusion Injury—
From Uncontrolled Reintroduction Of Oxygen After Ischemia


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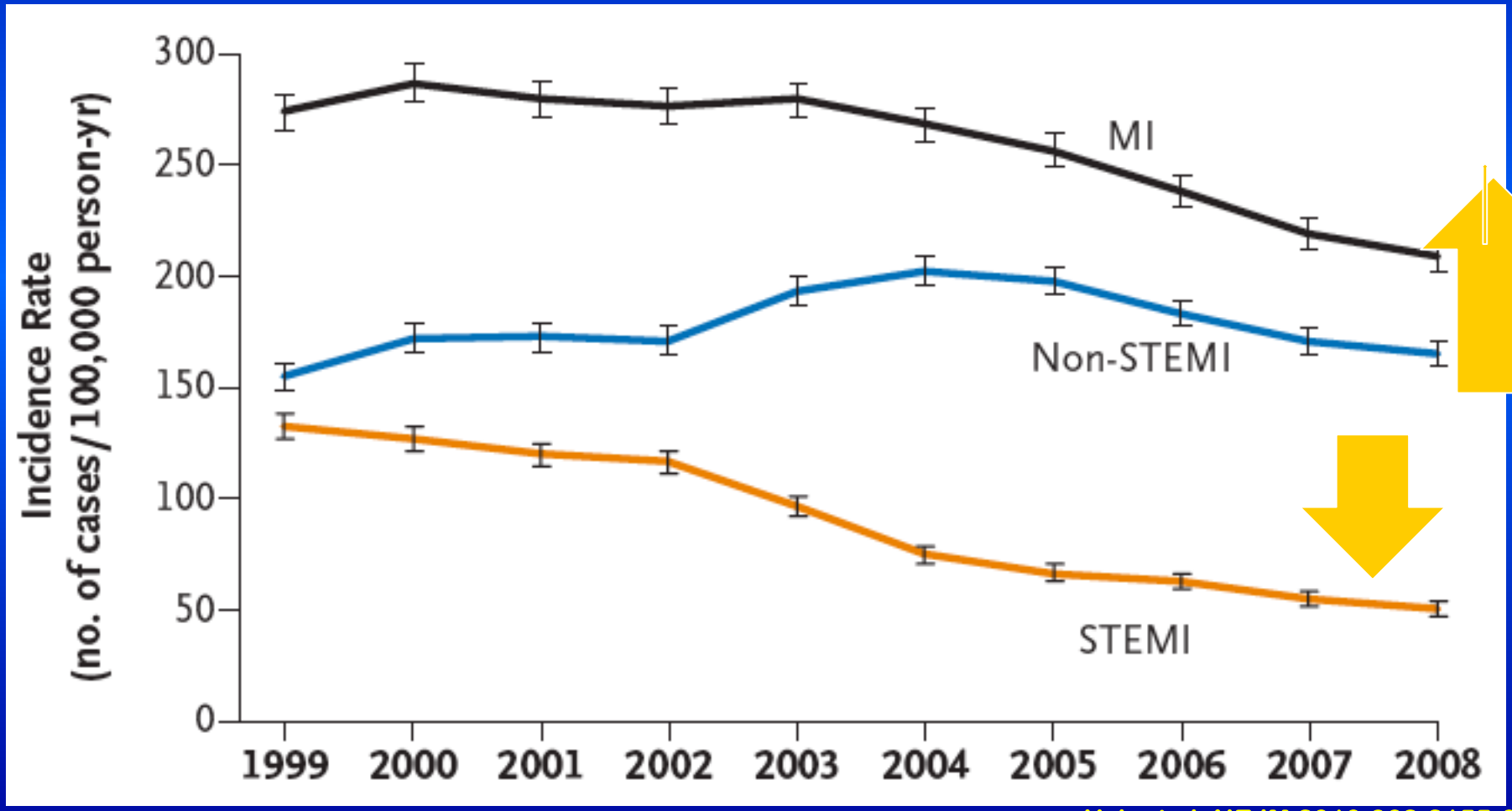
Limited Success to Reduce Injury

- TAKE AWAY MESSAGE:
- ***No Effective Therapies To Reduce Or Prevent Reperfusion Injury***
- Improved Understanding Of Pathophysiology
- Encouraging Preclinical Trials Of Multiple Agents,
- BUT……
- Most Of The Clinical Trials To Prevent Reperfusion Injury Have Been Disappointing

Population Trends in the Incidence and Outcomes of Acute Myocardial Infarction

Robert W. Yeh, M.D., Stephen Sidney, M.D., M.P.H., Malini Chandra, M.B.A., Michael Sorel, M.P.H., Joseph V. Selby, M.D., M.P.H., and Alan S. Go, M.D.



Yeh et al. NEJM 2010;362:2155-65.

Primary Reperfusion Therapy

- The Standard Of Care For The Treatment Of Acute Coronary Syndrome.

- PCI *(Percutaneous Coronary Intervention) And Thrombolysis*
- Prompt Restoration Of Blood Flow To Ischemic Myocardium Limits Infarct Size And Reduces Mortality

Primary Reperfusion Effects

- Return Of Blood Flow
- Can Also Result In Additional Cardiac Damage And Complications
- These Complications Are Reperfusion Injury
- **Such Damage Is More Likely When Reperfusion Is Delayed.**

- N Engl J Med 1987; 317:850.

Definition

- ***Reperfusion Injury***

- **Myocardial, Vascular, Or Electrophysiological Dysfunction**
- **That Is Induced By The Restoration Of Blood Flow To Previously Ischemic Tissue.**

When Does Cell Death Occur?

- **Difficult To Assess Ischemia And Reperfusion.**
- **Is Cell Death Irreversible After A Period Of Ischemia?**
- **Are Cells Still Salvageable At The Time Of Onset Of Reperfusion (Rosc)?**
- **Does Cell Death Occur During Reperfusion?**

Reperfusion Injury:

- Events Of Prolonged Ischemia Set The Biochemical Stage INCLUDES:

1. Decreased ATP Levels,
2. Elevated Reactive Oxygen/Nitrogen Species,
3. Reduced Electron Transport Cytochromes,
4. Intracellular Calcium (Ca2+) Overload.

Sudden Re-oxygenation

- Current Reperfusion Practice Introduces 0xygen Into This Dangerously Primed Biochemical Medium.
  - *Creates A Burst Of New Reactive Oxygen Species:*
- Lipid Oxidation, Mitochondrial Ca2+ Overload, Mitochondrial Permeability Transition,
- And Systemic Amplification Of Destructive Biochemical Cascades.

Reperfusion Injury: Treatment Theory

- Theoretically,
- Metabolic Strategies May Prevent
- Some Of These Destructive Cascades
- While Allowing Restoration Of Blood Flow
- And
- Promoting Long-term Neurologically Intact Survival

STEMI and Reperfusion Injury

1. Vascular Reperfusion Injury,
2. Stunning,
3. Reperfusion Arrhythmias

   All Occur In Patients With STEMI.

- Lethal Reperfusion Injury Of Potentially Salvageable Myocardium Remains Controversial In Experimental Animals And In Patients

STEMI and PCI and Reperfusion

- Reperfusion Increases The Cell Swelling That Occurs With Ischemia.
- Reperfusion Of The Myocardium In Which The Microvasculature Is Damaged Leads To The Creation Of A Hemorrhagic Infarct.
- *Fibrinolytic Therapy*
- *Appears More Likely To Produce Hemorrhagic Infarction---*
- *Than Catheter-based Reperfusion.*

Reperfusion Injury and Pathways

- 50% of Final Infarct Size May Be Attributable To Apoptosis /Death Signal-mediated Consequences Of Reperfusion Injury
- Many Molecular Mediators Of Death Signaling, With At Least 2 Separate Apoptotic Pathways

1. Intrinsic Pathway : Regulator Proteins Seen In B Cell Lymphoma
2. *Extrinsic Pathway: FAS Receptor, A Membrane-bound Member Of TNF Receptors -- Forms A Death-inducing Signaling Complex When It Interacts With An Appropriate Ligand*

Opportunities for additional myocardial salvage

- Opening An Occluded Vessel Restores Aerobic Metabolism And Function To Some Myocytes, Epicardial Flow Restoration Does Not Necessarily Equate To Microvascular Flow.
- 6% Of Myocardium May Show Evidence Of Microvascular Obstruction Even After Successful, Early Reperfusion
- Mechanisms Are Activated That Lead To Apoptosis Or Programmed Cell Death

Types of Reperfusion Injury

- (1) lethal reperfusion injury—APOPTOSIS
- reperfusion-induced death of cells that were still viable at the time of restoration of coronary blood flow
- .

Types of Reperfusion Injury

- (2) vascular reperfusion injury—progressive damage to the microvasculature so that there is an expanding area of no reflow and loss of coronary vasodilatory reserve;

Types of Reperfusion Injury

- (3) stunned myocardium—
- salvaged myocytes display a prolonged period of contractile dysfunction following restoration of blood flow
- because of reduced energy production
- *Can BE REVERSIBLE, with proper Resuscitation.*

Types of Reperfusion Injury

- (4) reperfusion arrhythmias—
- bursts of ventricular tachycardia
- and, Occasionally ventricular fibrillation—
- that occur within seconds of reperfusion.

Controlled Reperfusion was Better; Buckberg et al.

- Reduction Of Postischemic Myocardial Damage By Maintaining Arrest During Initial Reperfusion.Follette DM - *Surg Forum - 01-JAN-1977; 28: 28.*

Reducing Reperfusion Injury With Hypocalcemic, Hyperkalemic, Alkalotic Blood During Reoxygenation.Follette DM - *Surg Forum - 01-JAN-1978; 29: 284-6*

Protection Against Reperfusion Injury

- (1) Preservation Of Microvascular Integrity By Using Antiplatelet Agents And Antithrombins To Minimize Embolization Of Atheroembolic Debris
- (2) Prevention Of Inflammatory Damage
- (3) Metabolic Support Of The Ischemic Myocardium.

Protection Against Reperfusion Injury

- The Effectiveness Of Agents Directed Against Reperfusion Injury Rapidly Declines –
- *The Later They Are Administered After Reperfusion*
- No Beneficial Effect Is Detectable In Animal Models After 45 To 60 Minutes Of Reperfusion

Post-conditioning to Reduce Reperfusion Injury

- Definition - Introducing Brief Repetitive Episodes Of Ischemia Alternating With Reperfusion.
- Activates cellular protective mechanisms centering around prosurvival kinases.
  - also activated during ischemic preconditioning.

Post-conditioning to Reduce Reperfusion Injury

- Clinical studies in STEMI patients undergoing PCI Found:
- Postconditioning Protects The Human Heart And Is Associated With A Reduction In Infarct Size And Improvement In Myocardial Perfusion.

Reperfusion Arrhythmias

- Transient Sinus Bradycardia -- Inferior Infarcts At The Time Of Acute Reperfusion; Often Assoc W/ Some Degree Of Hypotension
- PVC , AIR, And Nonsustained Vtalso Commonly Follow Successful Reperfusion.
- ***Brief Electrical Storm At The Time Of Reperfusion Is Generally Innocuous***
- Indicate That No Prophylactic Antiarrhythmic Therapy Is Necessary When Fibrinolytics Are Prescribed.

Reprieve™ Endovascular Temperature Therapy System

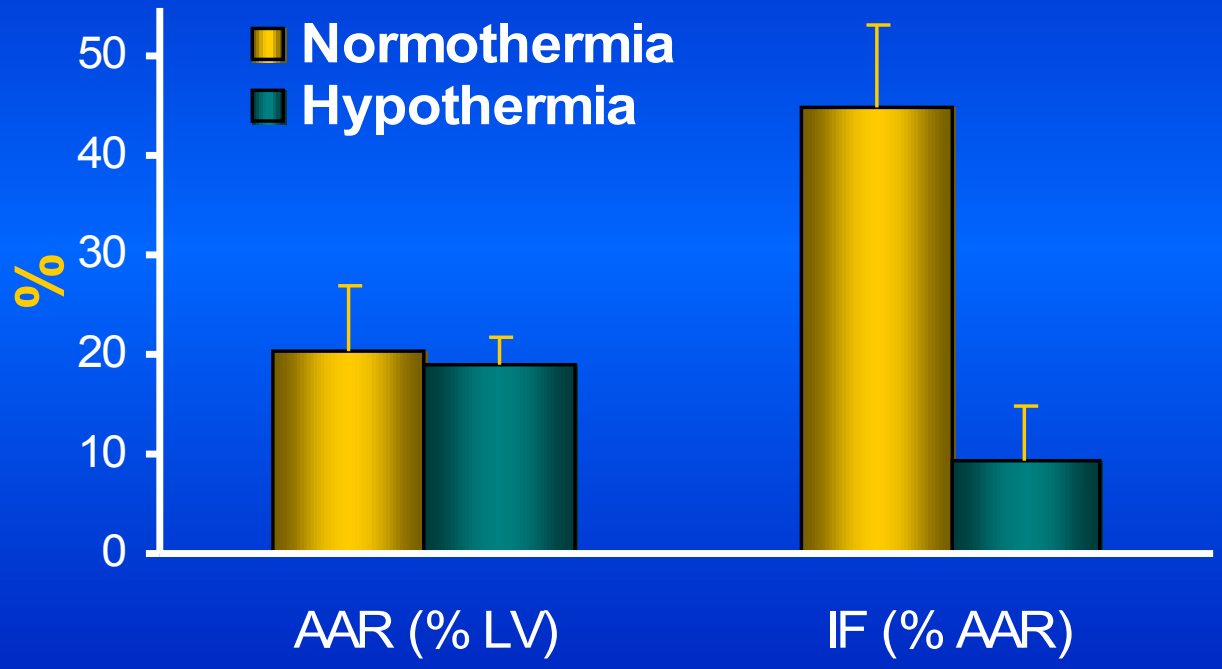
- Closed loop heat exchange catheter
- Catheter size: 10F
- Heat exchanger length: 25 cm
- Catheter coolant: sterile saline
- Placed in IVC via femoral vein

Caution: Investigational Device. Limited by federal (USA) law to investigational use

TCT 2003

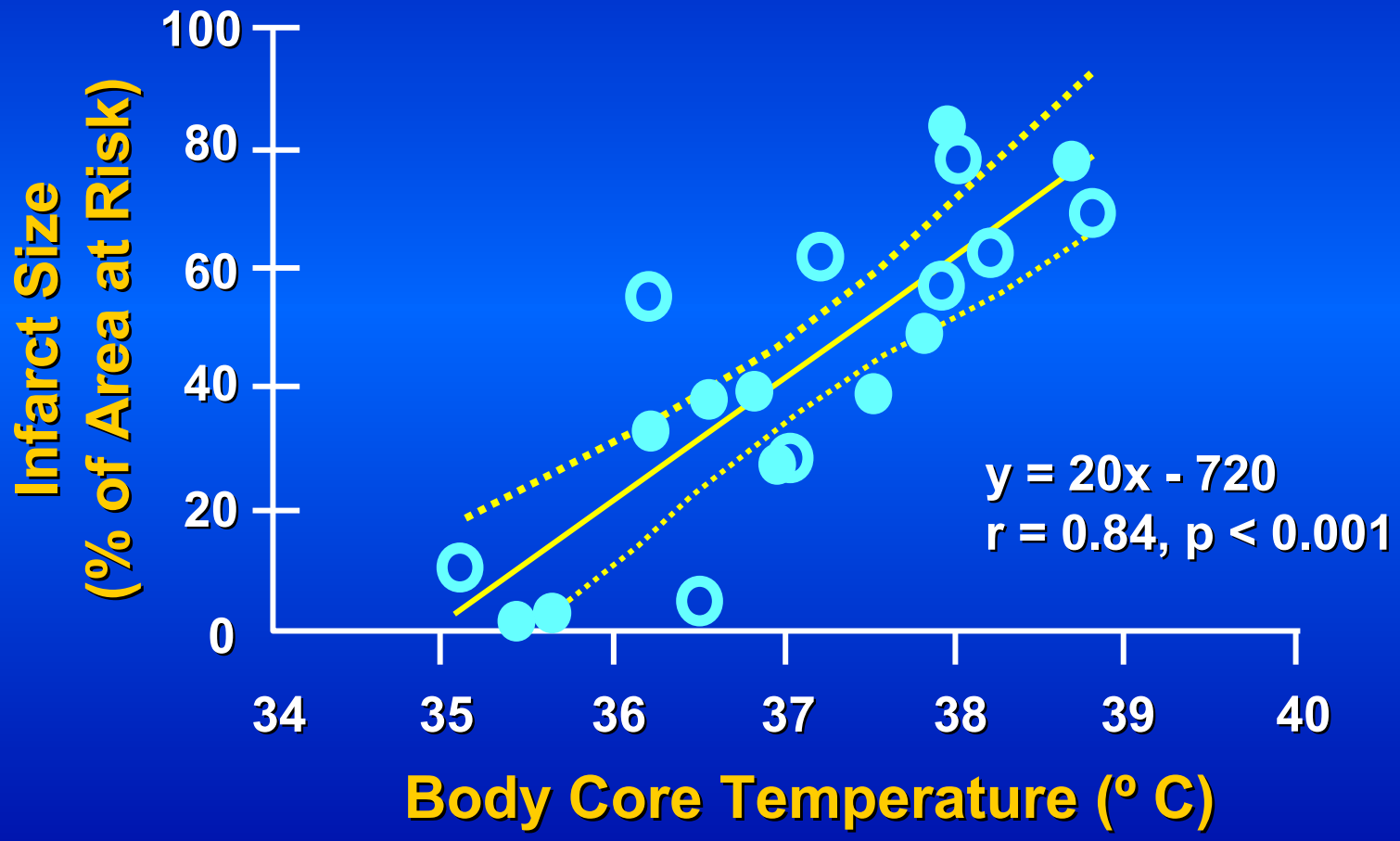
Radiant MEDICAL

Effect of Myocardial Temperature on Infarct Size



Dae M, Am J Physiol Heart Circ Physiol 2002; 28: H1584

Effect of Myocardial Temperature on Infarct Size



Duncker et al. AJP 1996; 270:H1189-99

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Study Design

Acute MI < 6 hours
Anterior MI
Inferior MI with reciprocal changes

Primary PCI

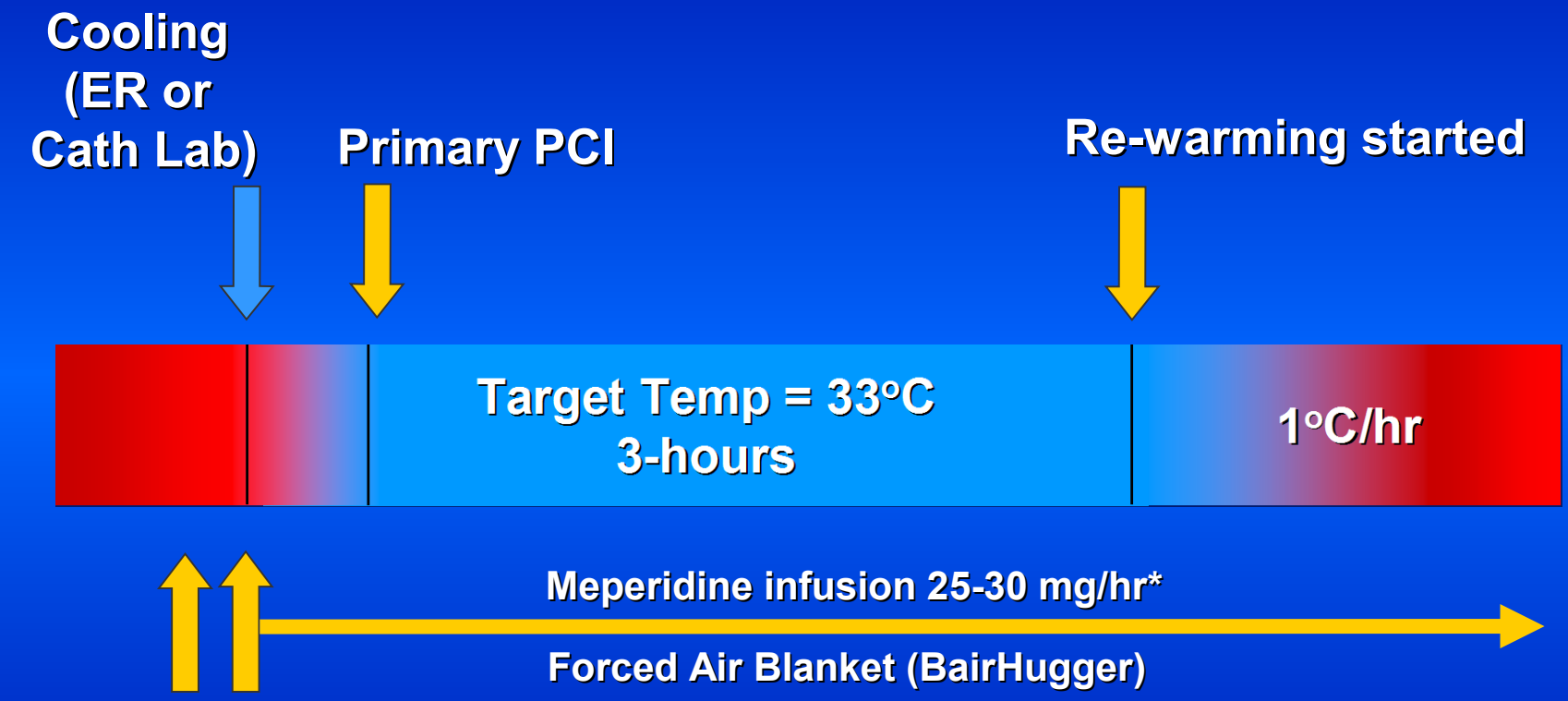
Primary PCI & Endovascular Cooling

Infarct size 30-days (SPECT)
MACE 30-days

Major Exclusion Criteria:

- Previous MI within one month
- Cardiogenic shock
- Hypersensitivity to hypothermia, buspirone, or meperidine
- IVC filter in situ

Endovascular Cooling Protocol



*Meperidine bolus 12.5-25mg for shivering

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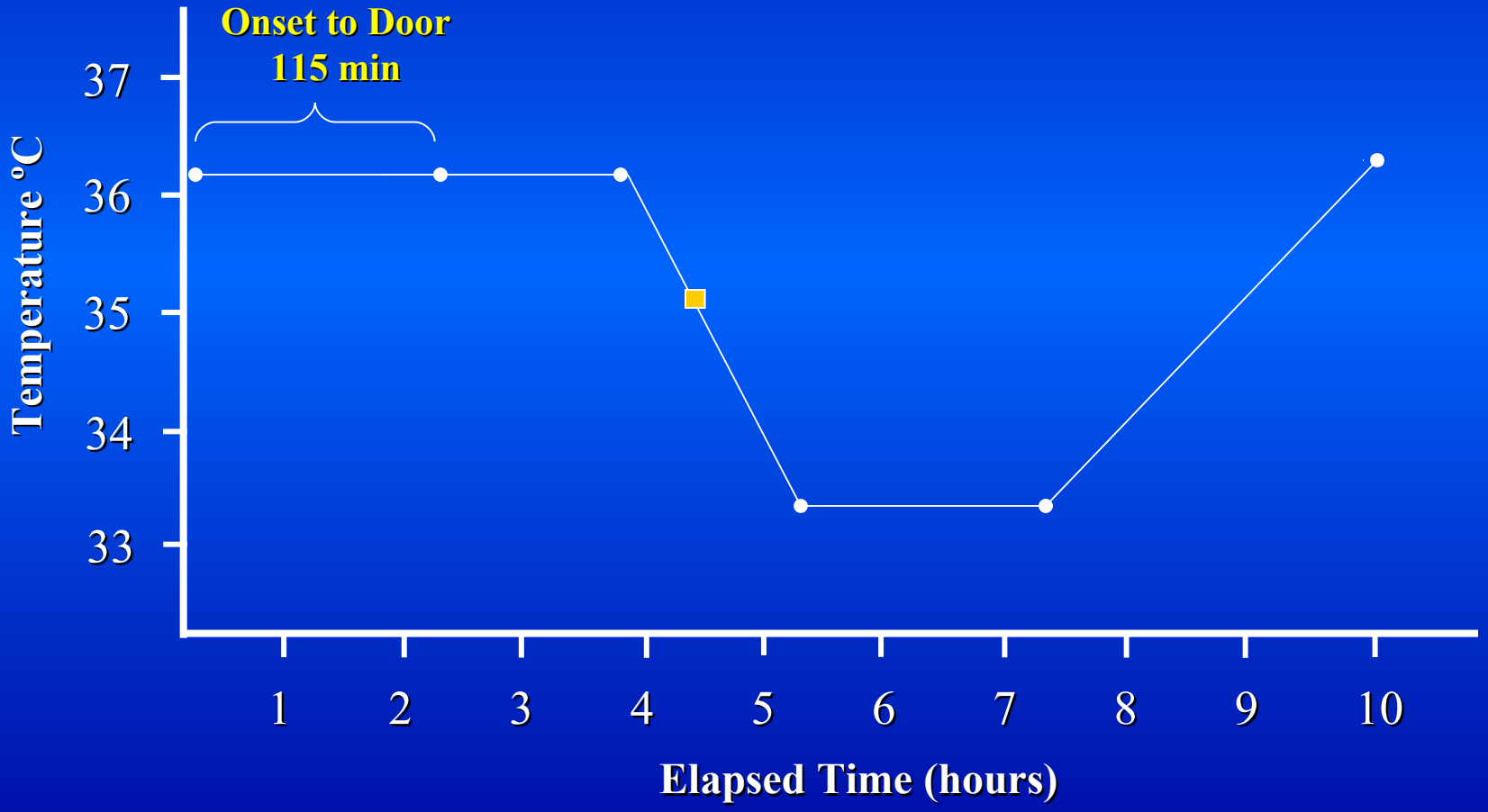
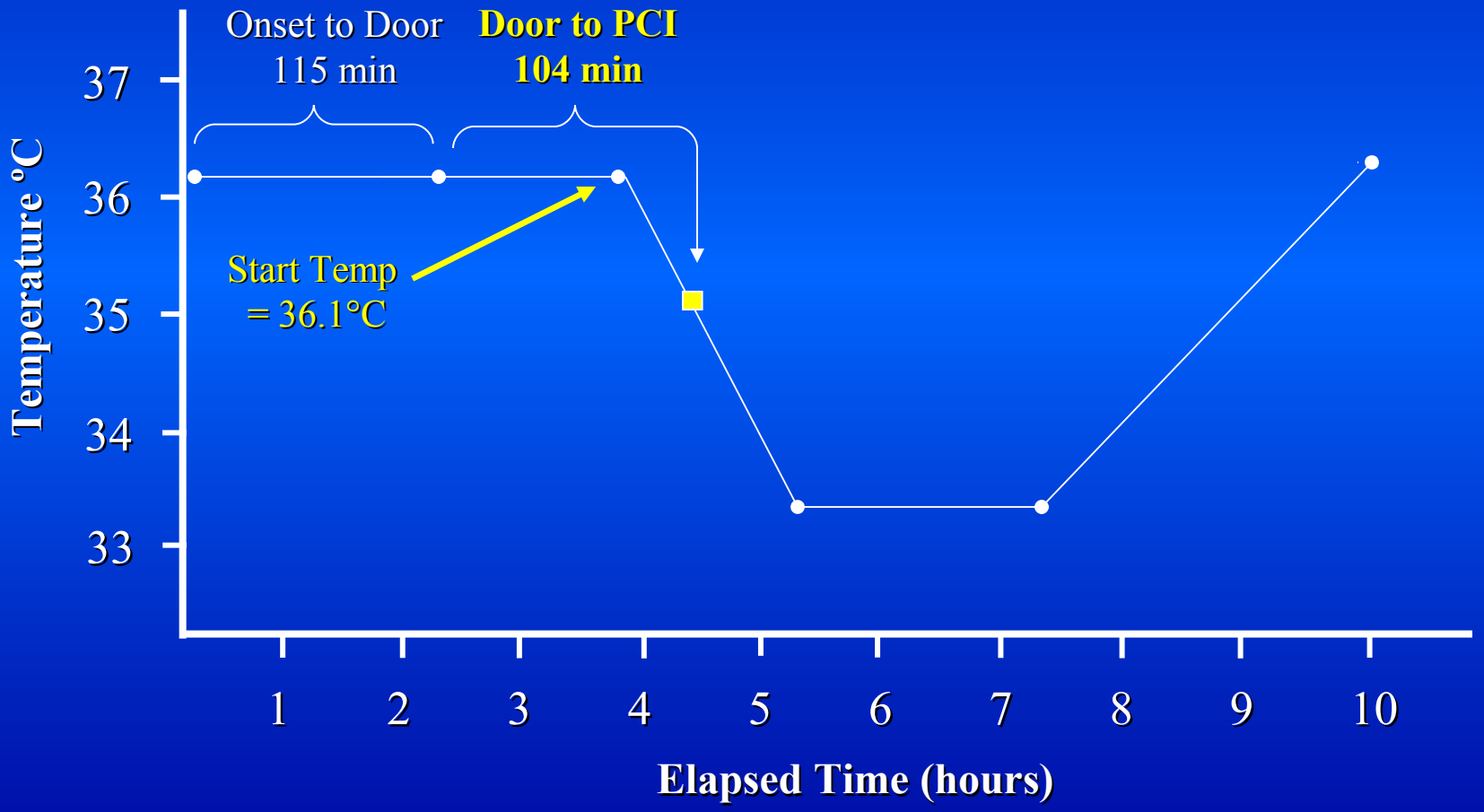
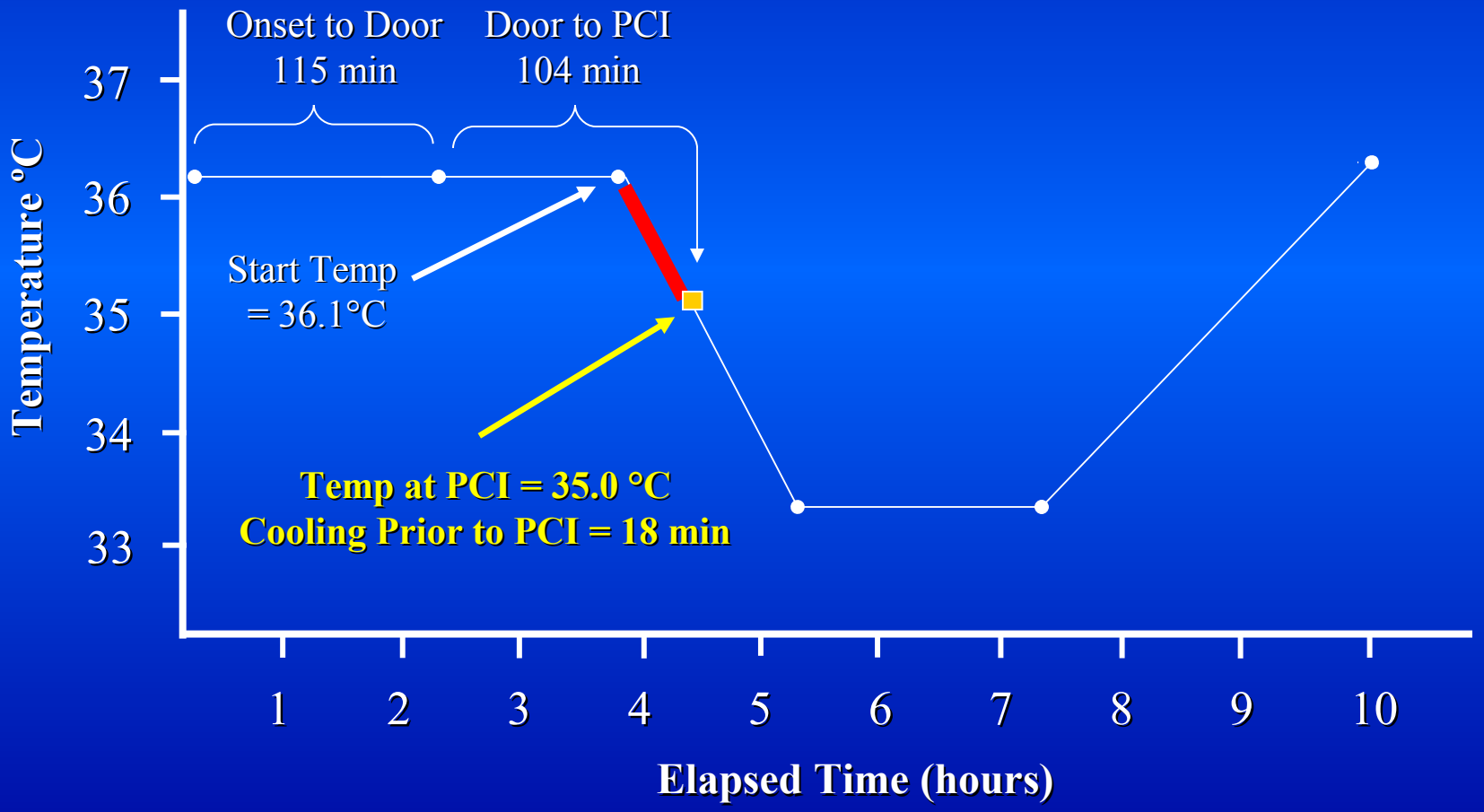
Procedural Results - Cooling



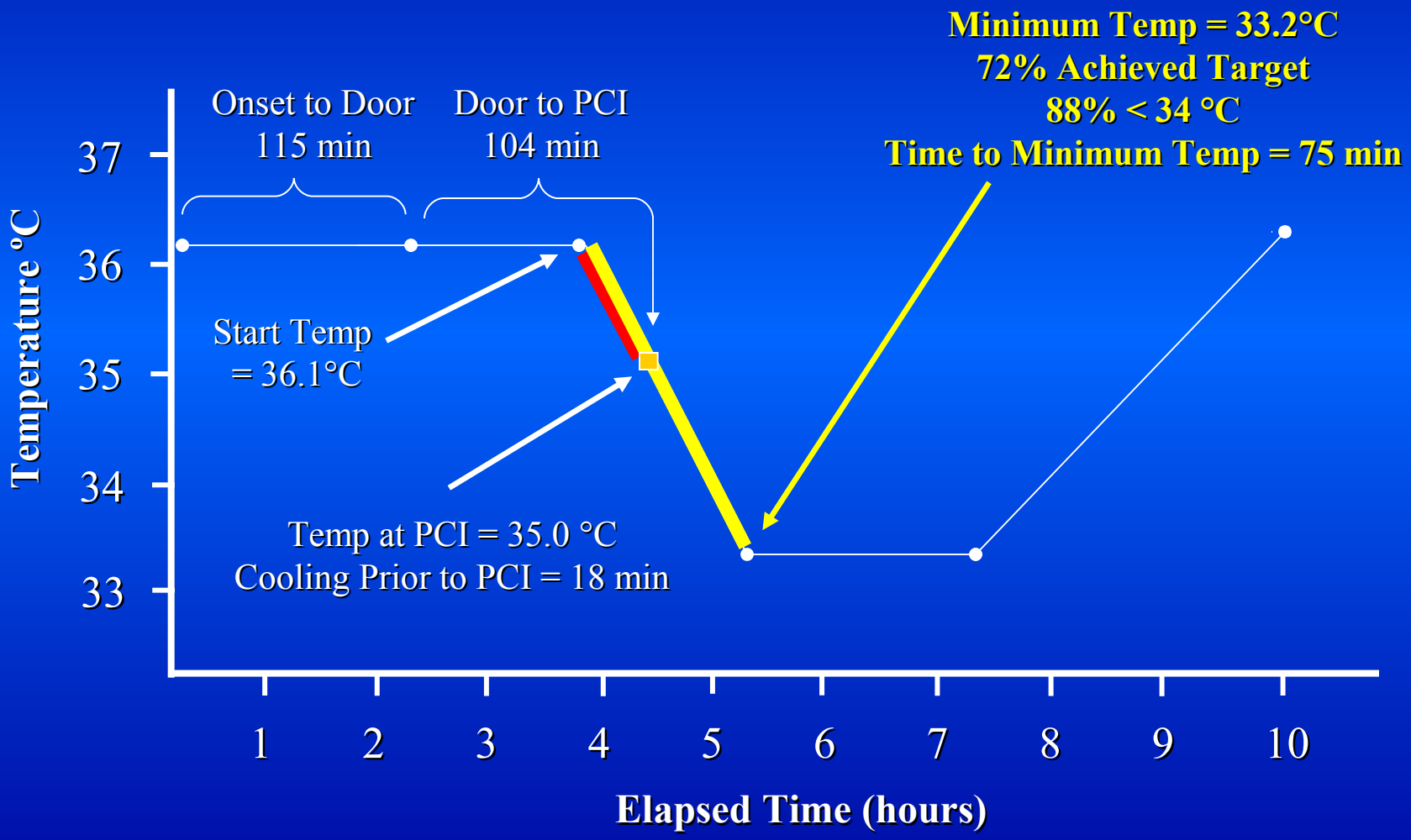
Procedural Results - Cooling



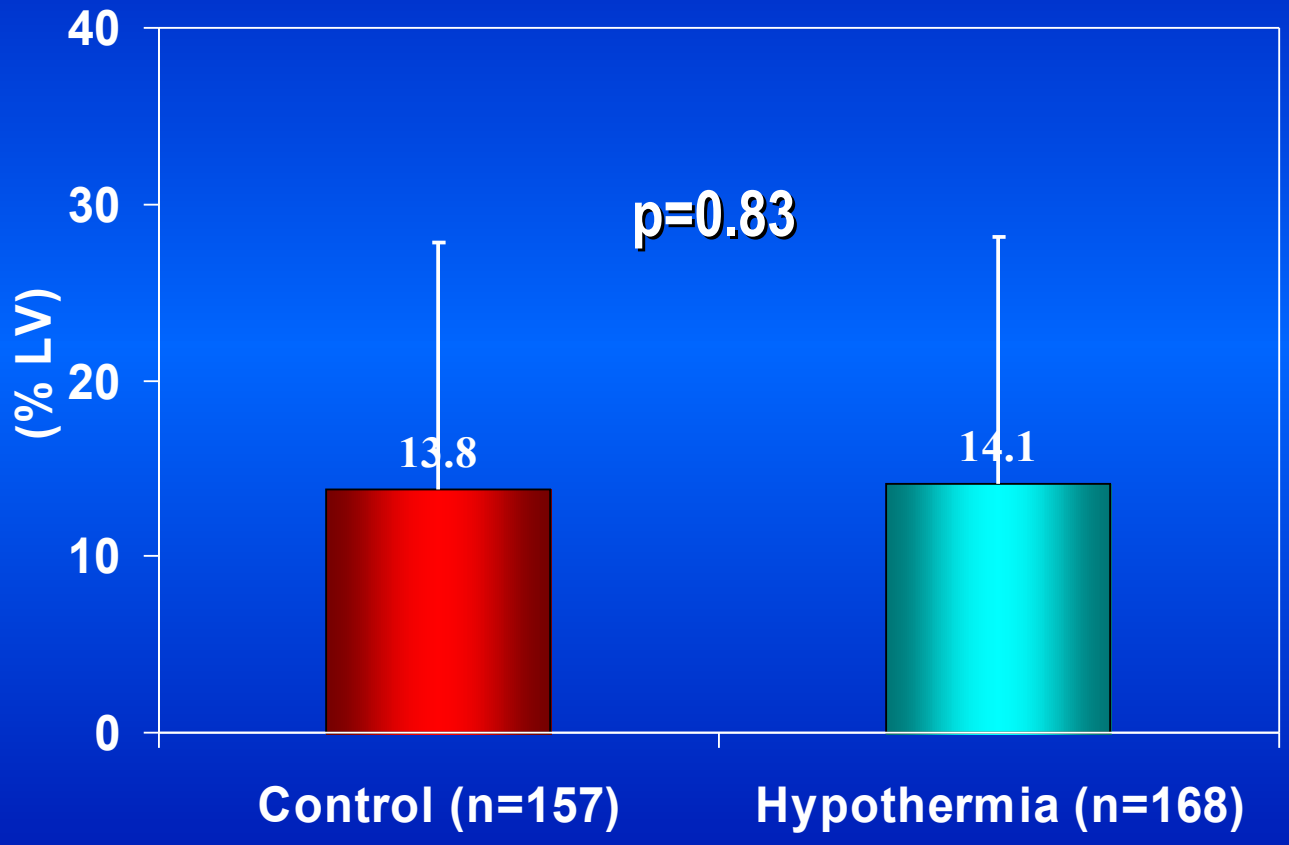
Procedural Results - Cooling



Procedural Results - Cooling



Primary Effectiveness Endpoint:
Infarct Size at 30-days



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ECPB Controlling

Reperfusion Improves Survival

- Emergency Cardiopulmonary Bypass: A Promising Rescue Strategy for Refractory Cardiac Arrest

No Intervention Has Reduced Reperfusion Injury in RCT in Humans

The quest for interventions that could prevent or mitigate reperfusion injury has prompted an intense scientific pursuit for decades.

This pursuit has broadened our understanding of the underlying pathogenic processes

The growing evidence identifying mitochondria as effectors and targets of reperfusion injury is bringing renewed hope that novel and more effective interventions could be developed for resuscitation from cardiac arrest.

Critical Care Clinics – 2012:28; 2