Results of the IMMEDIATE (*Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care*) Trial: A Double-Blinded Randomized Controlled Trial of Intravenous Glucose, Insulin & Potassium (GIK) for Acute Coronary Syndromes in Emergency Medical Services

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Disclosure / Conflict of Interest

There are no commercial, financial or other relationships related to the subject of this presentation that may create any potential conflict of interest.

Carl Apstein, MD, FACC

The IMMEDIATE Trial investigators would like to thank and honor the memory of Carl Apstein, MD, whose groundbreaking basic research was a foundation for this study, and whose vision, energy, good humor, and persistence were critical to the initiation of this study.

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Background: Mechanisms of GIK Cardiac Protection

Experimental studies show that GIK myocardial metabolic support, *started immediately in cardiac ischemia, followed by reperfusion*

- Improves glucose, glycogen, and energy metabolism, and mantains cellular ATP levels
- Supports cardiac function and delays necrosis
- Decreases plasma and cellular free fatty acid (FFA) levels

  (FFAs damage membranes, cause arrhythmias, waste oxygen)
- Preserves myocyte potassium (anti-arrhythmic)

Background: Rationale for Placebo-Controlled Trial of Very Early Emergency Medical Service (EMS) Use of GIK

- Experimental studies have shown the greatest benefit by GIK when started very early in ischemia, and yet
  - Prior trials have given GIK at the hospital, once AMI or STEMI is documented, on order of 6 hours after ischemia onset
  - Prior trials for STEMI have not started GIK *before* reperfusion
- Prior GIK trials for AMI/STEMI have not been placebo-controlled
- The best way to translate experimental results into clinical practice is by having paramedics give GIK to patients with ACS immediately, in the community

Study Purpose

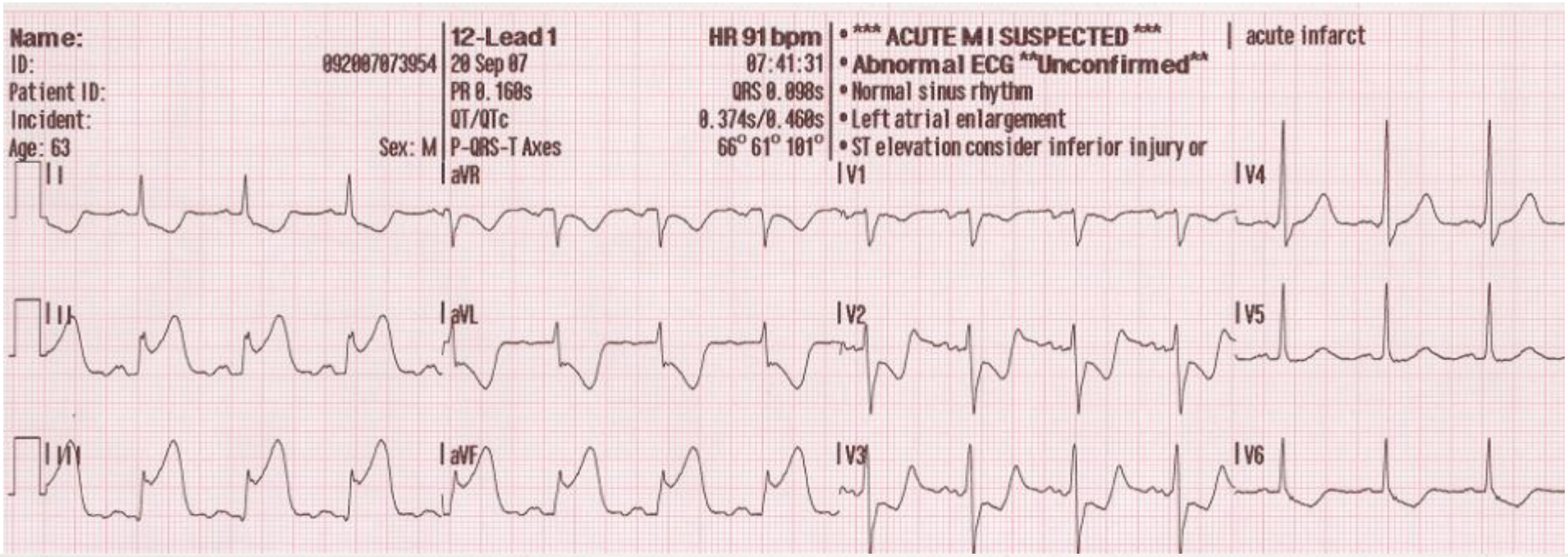
This trial investigated two types of potential benefit of GIK:

- *Protection of the myocardium from ischemia,* which should
  - limit progression to MI
  - reduce ultimate infarct size
- *Prevention of arrhythmias and cardiac arrest that occur very early in ACS/AMI,* associated with elevated free fatty acids

Methods: Basic Features of Study Design

- *Very early use of GIK* (30% glucose + 50U insulin + 80mEq KCL per liter @1.5 ml/kg/hr) initiated by paramedics, continued by ED physicians for continued use in-hospital for a total 12 hours
- *Placebo-controlled double-blinded* randomized clinical trial,
- An *effectiveness trial* rather than the usual efficacy trial
- Use of GIK for *acute coronary syndromes* (not just AMI/STEMI)
- To help paramedics best identify patients with ACS, *EMS use of predictive instrument decision support printed on ECGs*

Ambulance ECG with ACI-TIPI and TPI Decision Support



Name:
ID: 092007073954
Patient ID:
Incident:
Age: 63 Sex: M

Primary symptom: Chest pain/left arm pain
Blood Pressure: 130 / 79
Diabetes: No
Hypertension: Yes
Symptom Onset : 1:15

12-Lead 1
20 Sep 07
PR 0.160s
QT/QTc 0.374s/0.460s
P-QRS-T Axes 66° 61° 101°

HR 91 bpm
07:41:31

ACI-TIPI PREDICTED PROBABILITY OF ACUTE CARDIAC ISCHEMIA = 95%

Based on

- Age greater than 50; patient is male
- Patient has chief chest pain/discomfort or left arm pain as primary symptom
- Significant Q wave detected
- ST elevation of 0.2mV or more
- T waves elevated (hyperacute)

ACI-TIPI PROBABILITY INTENDED TO SUPPLEMENT CLINICIAN JUDGEMENT

THROMBOLYTIC PREDICTIVE INSTRUMENT (TPI)

TPI PREDICTED OUTCOMES:	WITHOUT / WITH THROMBOLYSIS
30-Day Mortality	11.4% / 2.6%
One-Year Mortality	14.0% / 5.5%
Cardiac Arrest within 48 Hrs.	6.4% / 4.2%
Thrombolysis-Related Intracranial Hemorrhage	0.5%
Thrombolysis-Related Other Major Bleeding	3.2%

NOTE: Consider above in context of patient contraindications to thrombolysis

PRELIMINARY - MD MUST REVIEW

Methods: Pre-Specified Endpoints

- Primary endpoint
  - Progression to MI confirmed by biomarkers and ECGs
- Major secondary endpoints
  - Pre- or in-hospital cardiac arrest or mortality
  - 30-day mortality (and 1-year mortality)
  - Hospitalization for heart failure or death within 30 days (and within 1 year)
- Biological mechanism cohort endpoints
  - Infarct size by sestamibi perfusion imaging at 30 days
  - LVEF by sestamibi gated SPECT at 30 days
  - Free fatty acid levels at infusion start, 6, and 12 hours

Methods: Inclusion Criteria

- Age 30 or older seen by EMS for symptoms consistent with ACS
- Paramedic judgment that clinical picture suggests ACS/AMI *and* prehospital 12-lead ECG has at least *one of the following*:
  - ACI-TIPI predicted probability of ACS of 75% or more
  - Thrombolytic predictive instrument (TPI) detection of STEMI
  - STEMI identified based on local EMS protocol

Methods: Exclusion Criteria

- HF evidenced by rales more than halfway up lung fields
- End stage renal failure requiring dialysis
- Language barrier or inability to understand informed consent
- Patient known to be pregnant

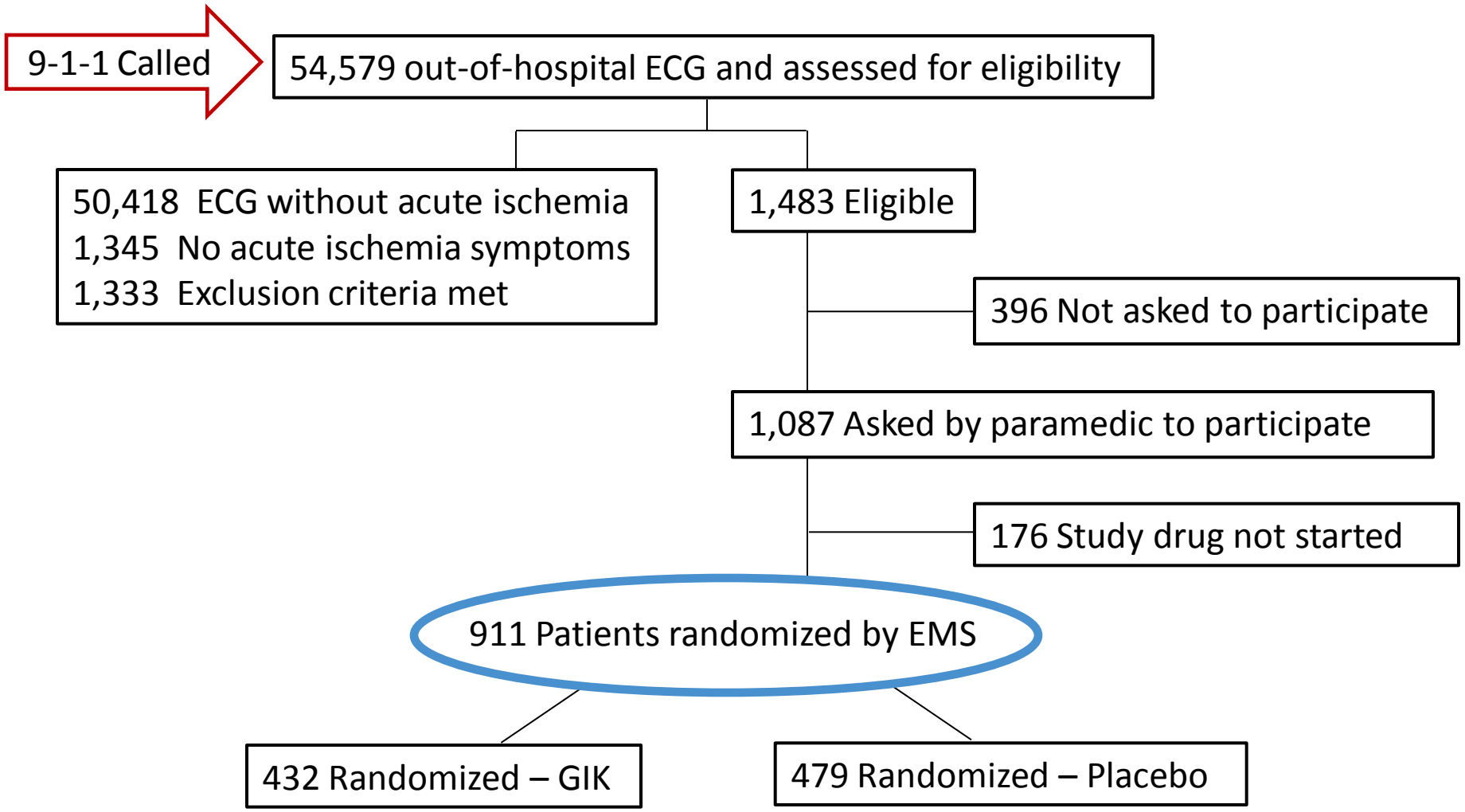
Methods: Enrollment and Oversight

- 36 EMS systems in 13 cities across the United States
- Trial used Exception from Informed Consent Requirements for Emergency Research (21CFR 50.24) procedures
  - Community consultation process
  - Information card read to patient by paramedic to get assent prior to randomization
  - Written consent when stable at receiving hospital
- Oversight by NIH-appointed DSMB

Methods: Analysis

- Sample size calculation projected the need for 800 evaluable participants for 90% power to detect a 20% reduction in progression to MI (from 56% to 44%)
- Blinded adjudication of endpoints by Clinical Events Committee
- Logistic regression for comparisons of dichotomous endpoints
- Cox proportional hazards regressions for time-to-event endpoints
- Statistical testing used 2-sided 0.05 level of significance
- Three analytic cohorts
  - Intention-to-treat (ITT)
  - Presenting with ST elevation
  - Biological mechanism

Results: Screening and Enrollment of Participants



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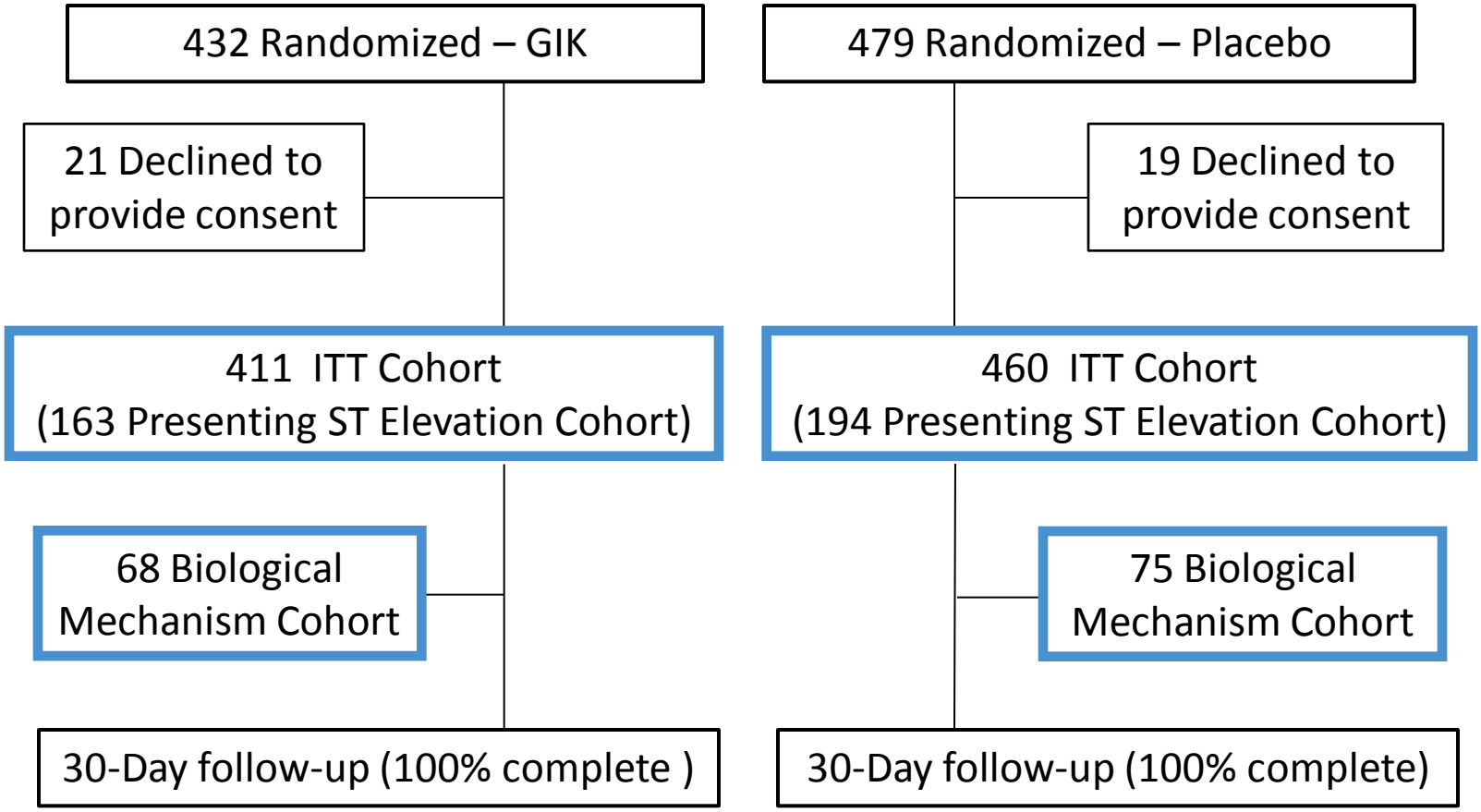

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Results: Presenting Characteristics (N=871)

	GIK (n=411)	Placebo (n=460)
Age (mean, yrs)	64	63
Men	73%	70%
White/Black/Hispanic (%)	82/13/11%	87/9/13%
Chest pain chief complaint	87%	85%
Shortness of breath chief complaint	4%	4%
Pre-hospital systolic BP (mean, mmHg)	143	143
Pre-hospital HR (mean, BPM)	87	87
History of DM	29%	26%
History of HF	17%	17%
History of MI	37%	35%

Results: Time from Ischemic Symptom Onset to EMS Start of Study Drug Infusion

	GIK (n=411)	Placebo (n=460)
Time from symptom onset to study drug (median, mins [IQR])	90 [50-159]	90 [52-159]
Time from symptom onset to study drug		
0-30 mins	6%	4%
31-60 mins	25%	27%
61-90 mins	15%	16%
91-180 mins	17%	18%
181-360 mins	12%	12%
361 mins-24 hrs	9%	8%
Patients received primary PCI	48%	45%

Results: ITT Cohort
Hospital and 30-Day Endpoints

	GIK (n=411)	Placebo (n=460)	Risk Ratio (95% CI)	*P* Value
Progression to MI	49%	53%	0.88 (0.66-1.13)	0.28

Results: ITT Cohort
Hospital and 30-Day Endpoints

	GIK (n=411)	Placebo (n=460)	Risk Ratio (95% CI)	*P* Value
Progression to MI	49%	53%	0.88 (0.66-1.13)	0.28
30-Day Mortality	4%	6%	0.72 (0.40-1.29)	0.27

Results: ITT Cohort
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	GIK (n=411)	Placebo (n=460)	Risk Ratio (95% CI)	*P* Value
Progression to MI	49%	53%	0.88 (0.66-1.13)	0.28
30-Day Mortality	4%	6%	0.72 (0.40-1.29)	0.27
Cardiac Arrest or Hospital Mortality	4%	9%	0.48 (0.27-0.85)	0.01
Cardiac Arrest	4%	6%	0.56 (0.30-1.07)	0.08
Hospital Mortality	3%	5%	0.62 (0.31-1.24)	0.18

Results: ITT Cohort
Hospital and 30-Day Endpoints

	GIK (n=411)	Placebo (n=460)	Risk Ratio (95% CI)	*P* Value
Progression to MI	49%	53%	0.88 (0.66-1.13)	0.28
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Cardiac Arrest	4%	6%	0.56 (0.30-1.07)	0.08
Hospital Mortality	3%	5%	0.62 (0.31-1.24)	0.18
30-Day Mortality or Hospitalization for HF	6%	8%	0.73 (0.43-1.23)	0.24

Results: Cohort Presenting with ST Elevation Hospital and 30-Day Endpoints

	GIK (n=163)	Placebo (n=194)	Risk Ratio (95% CI)	*P* Value
Progression to MI	85%	89%	0.74 (0.40-1.38)	0.34

Results: Cohort Presenting with ST Elevation Hospital and 30-Day Endpoints

	GIK (n=163)	Placebo (n=194)	Risk Ratio (95% CI)	*P* Value
Progression to MI	85%	89%	0.74 (0.40-1.38)	0.34
30-Day Mortality	5%	8%	0.63 (0.27-1.49)	0.29

Results: Cohort Presenting with ST Elevation Hospital and 30-Day Endpoints

	GIK (n=163)	Placebo (n=194)	Risk Ratio (95% CI)	*P* Value
Progression to MI	85%	89%	0.74 (0.40-1.38)	0.34
30-Day Mortality	5%	8%	0.63 (0.27-1.49)	0.29
Cardiac Arrest or Hospital Mortality	6%	14%	0.39 (0.18-0.82)	0.01
Cardiac Arrest	6%	11%	0.49 (0.23-1.03)	0.06
Hospital Mortality	4%	7%	0.49 (0.18-1.31)	0.16

Results: Cohort Presenting with ST Elevation Hospital and 30-Day Endpoints

	GIK (n=163)	Placebo (n=194)	Risk Ratio (95% CI)	*P* Value
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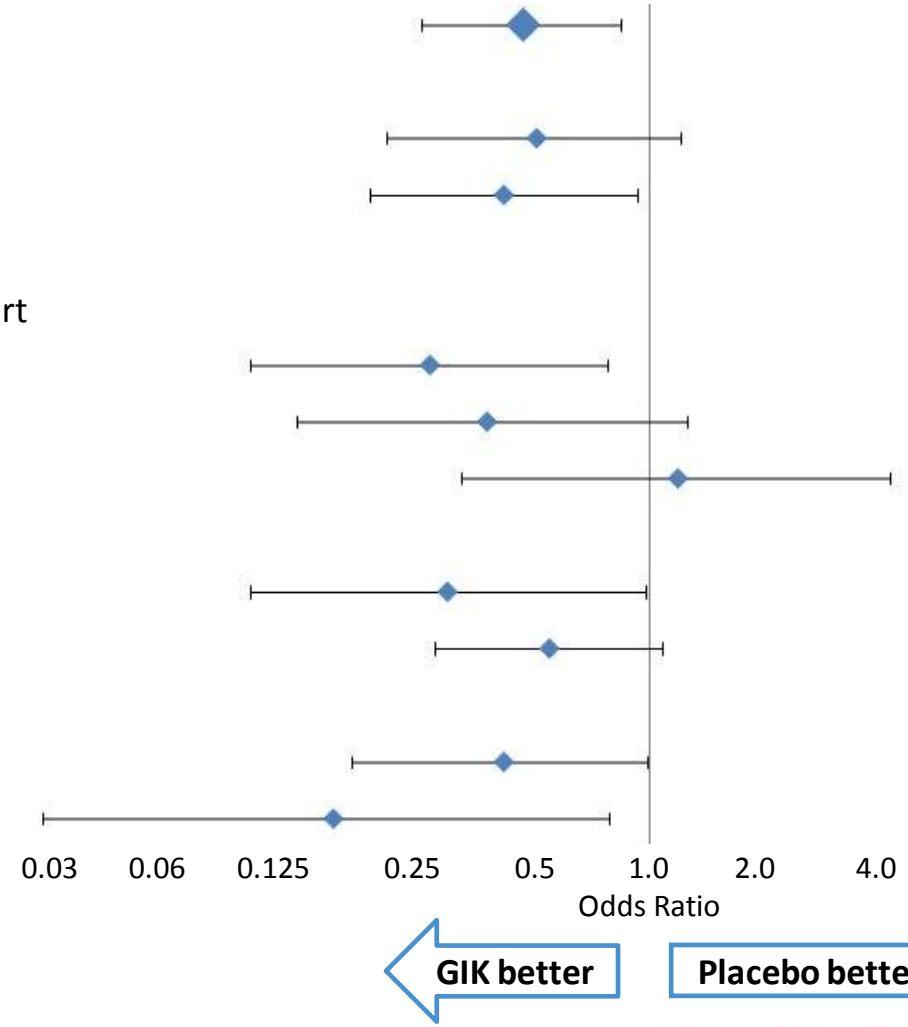
Cardiac Arrest	6%	11%	0.49 (0.23-1.03)	0.06
Hospital Mortality	4%	7%	0.49 (0.18-1.31)	0.16
30-Day Mortality or Hospitalization for HF	6%	10%	0.56 (0.25-1.23)	0.15

Results: ITT Cohort Subgroups of Clinical Interest for Cardiac Arrest or Hospital Mortality

ITT Subgroup	Odds Ratio (95% CI)	*P* Value
All	0.48 (0.27-0.85)	0.01
Age: < 65 years	0.52 (0.22-1.21)	0.13
Age: ≥ 65 years	0.43 (0.20-0.94)	0.04
Time from symptom onset to study drug start		
0 - 1 hour	0.28 (0.10-0.79)	0.02
> 1 hour - 6 hours	0.39 (0.13-1.25)	0.11
> 6 hours	1.18 (0.34-4.06)	0.79
Diabetic	0.31 (0.10-0.99)	0.05
Not Diabetic	0.56 (0.29-1.09)	0.09
STEMI, Primary PCI	0.43 (0.18-1.00)	0.05
STEMI, Not Primary PCI	0.16 (0.03-0.80)	0.03



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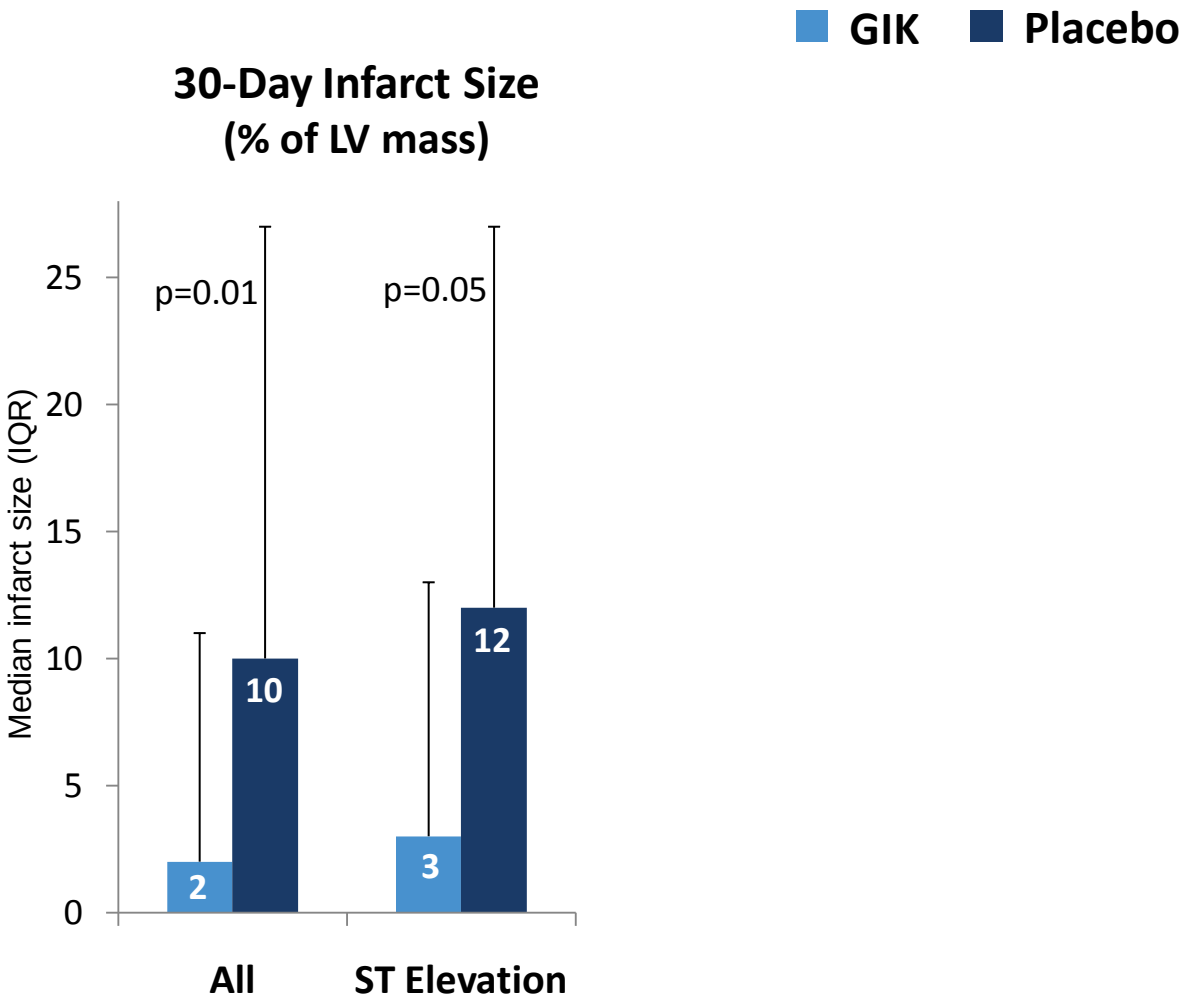
Results: Biological Mechanism Cohort (N=153)
30-Day Infarct Size, LVEF, and Free Fatty Acid Levels



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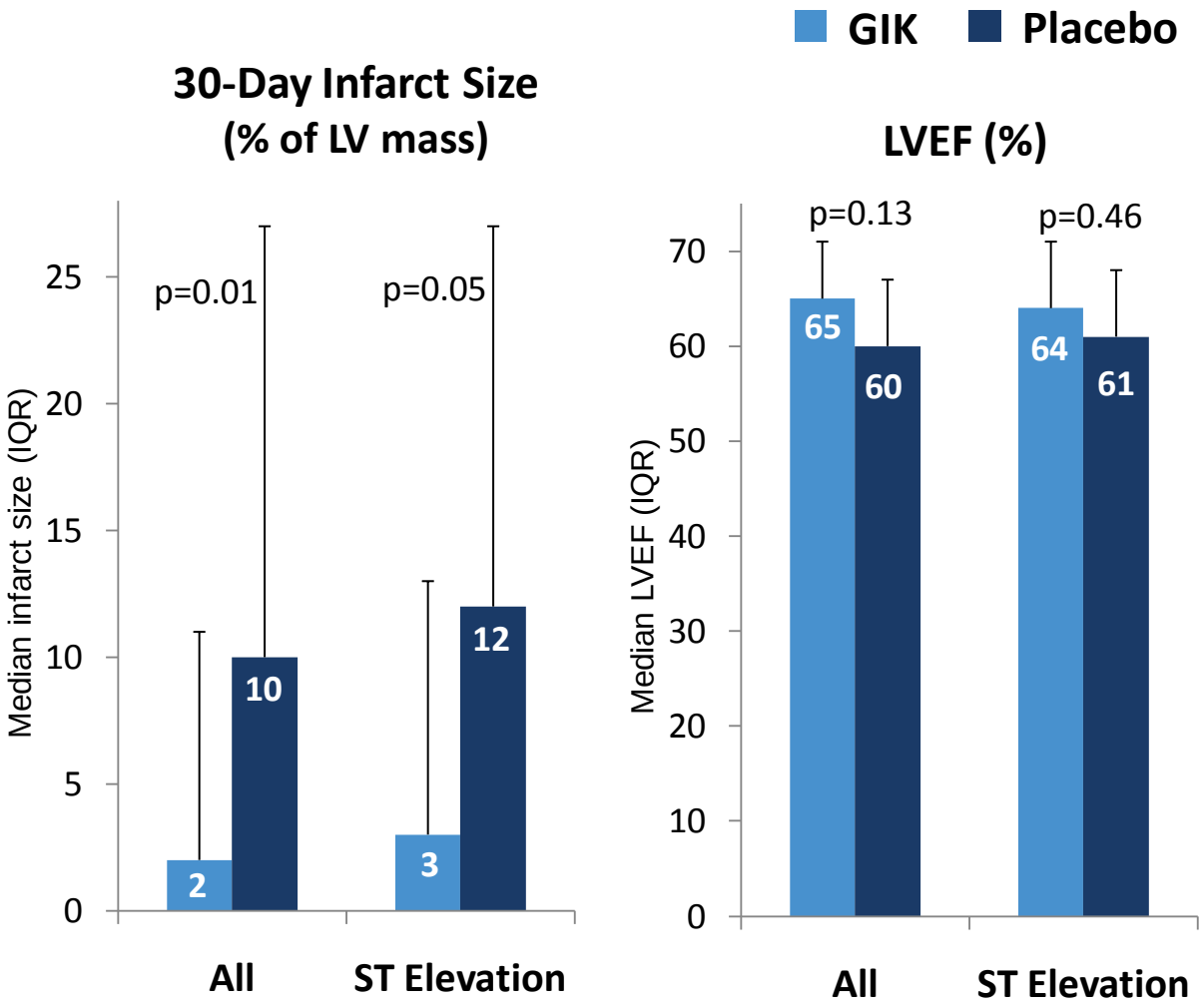

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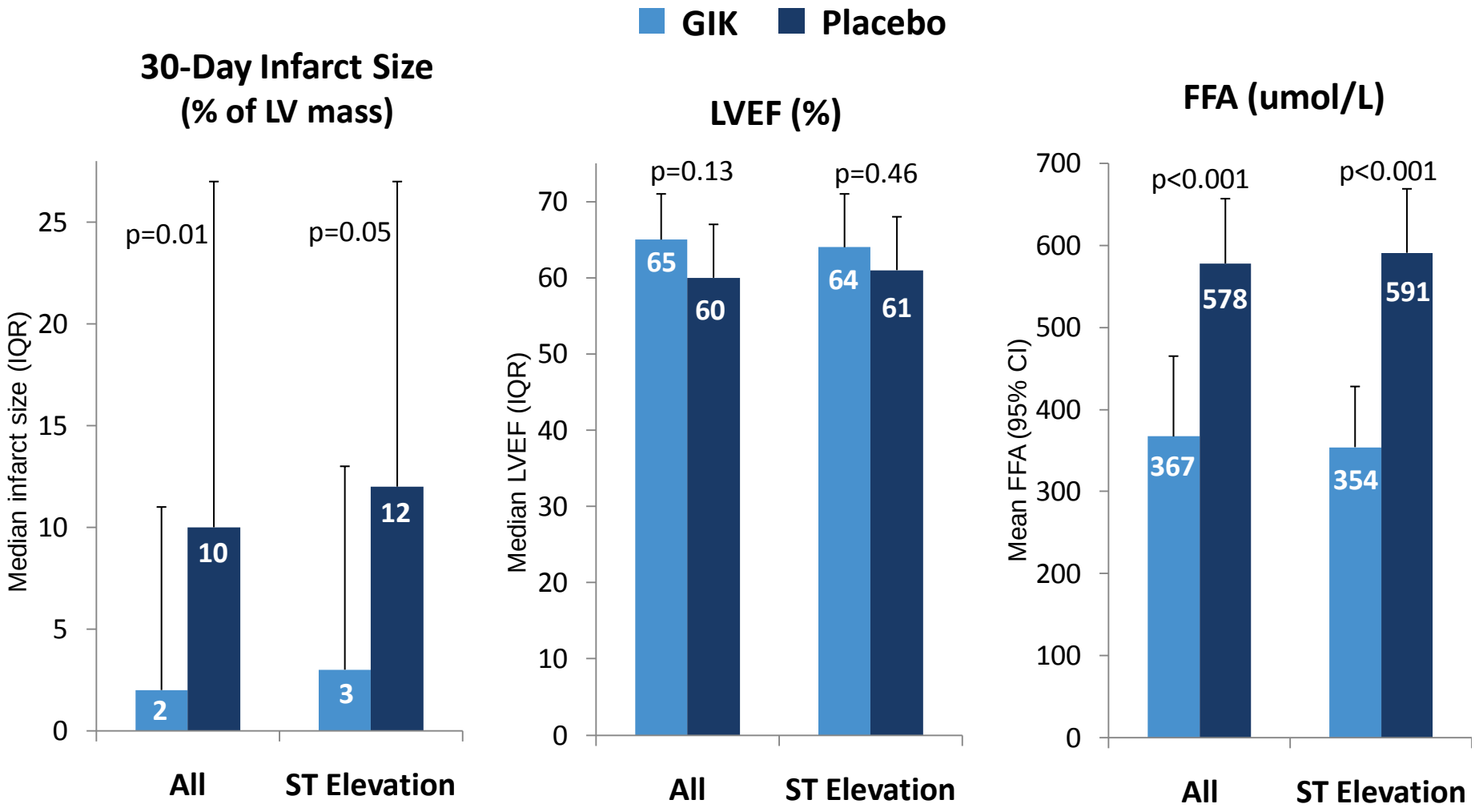

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Results: ITT Cohort Selected Safety Endpoints

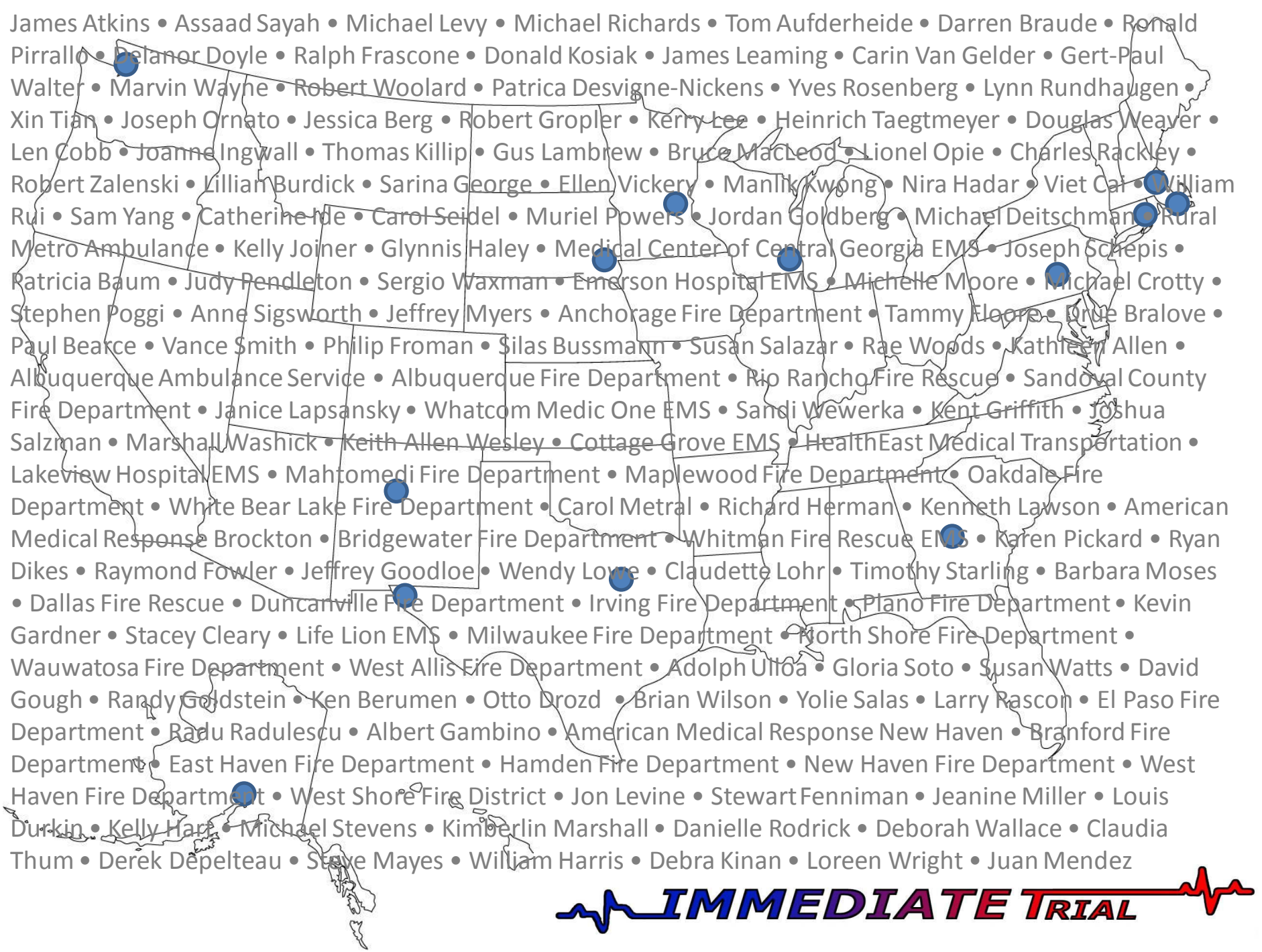
	GIK (n=411)	Placebo (n=460)	P value
Serious Adverse Events	7%	9%	0.26
Heart Failure	2%	3%	0.47
All Participants			
Any K+ > 5.5 mEq/L	4%	2%	0.10
Any K+ $\leq$ 3.5 mEq/L	25%	30%	0.10
Any glucose >300 mg/dL	21%	10%	< 0.001
Participants with Diabetes			
Any glucose >300 mg/dL	44%	29%	0.02
Participants without Diabetes			
Any glucose >300 mg/dL	11%	3%	< 0.001

Limitations

- Primary endpoint progression to MI was not significantly different between groups -- favorable results based on pre-specified major secondary endpoints, biologically consistent with the GIK benefit seen in pre-clinical studies
- Absolute numbers of clinical endpoints were relatively small
- Reduction in infarct size results, although consistent with experimental studies of early GIK, based on the relatively small biological mechanism cohort
- Understanding of the long-term effects of GIK on HF and mortality will require longer follow-up, underway

Conclusions

- Immediate EMS administration of GIK *very early* in the course of ACS and STEMI, consistent with preclinical research, can be done in a wide range of communities and EMS systems
- Progression to infarction, the primary endpoint, was not prevented, but infarct size was significantly diminished
- Composite endpoint of cardiac arrest or acute mortality was significantly reduced, and FFA levels were lower, consistent with the proposed FFA link to arrhythmias
- Risks and side effects rates from GIK are very low, and GIK is inexpensive, potentially available in all communities, and deserves further evaluation in trials for widespread EMS use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IMMEDIATE TRIAL

ONLINE FIRST

Out-of-Hospital Administration of Intravenous Glucose-Insulin-Potassium in Patients With Suspected Acute Coronary Syndromes

The IMMEDIATE Randomized Controlled Trial

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Context Laboratory studies suggest that in the setting of cardiac ischemia, immediate intravenous glucose-insulin-potassium (GIK) reduces ischemia-related arrhythmias and myocardial injury. Clinical trials have not consistently shown these benefits, possibly due to delayed administration.

Objective To test out-of hospital emergency medical service (EMS) administration of GIK in the first hours of suspected acute coronary syndromes (ACS).

Design, Setting, and Participants Randomized, placebo-controlled, double-blind effectiveness trial in 13 US cities (36 EMS agencies), from December 2006 through July 31, 2011, in which paramedics, aided by electrocardiograph (ECG)-based decision support, randomized 911 (871 enrolled) patients (mean age, 63.6 years; 71.0% men) with high probability of ACS.

Intervention Intravenous GIK solution (n=411) or identical-appearing 5% glucose placebo (n=460) administered by paramedics in the out-of-hospital setting and continued for 12 hours.

Main Outcome Measures The prespecified primary end point was progression of ACS to myocardial infarction (MI) within 24 hours, as assessed by biomarkers and ECG evidence. Prespecified secondary end points included survival at 30 days and a composite of prehospital or in-hospital cardiac arrest or in-hospital mortality, analyzed by intent-to-treat and by presentation with ST-segment elevation.

Results There was no significant difference in the rate of progression to MI among patients who received GIK (n=200; 48.7%) vs those who received placebo (n=242; 52.6%) (odds ratio [OR], 0.88; 95% CI, 0.66-1.13; *P*=.28). Thirty-day mortality was 4.4% with GIK vs 6.1% with placebo (hazard ratio [HR], 0.72; 95% CI, 0.40-1.29; *P*=.27). The composite of cardiac arrest or in-hospital mortality occurred in 4.4% with GIK vs 8.7% with placebo (OR, 0.48; 95% CI, 0.27-0.85; *P*=.01). Among patients with ST-segment elevation (163 with GIK and 194 with placebo), progression to MI was 85.3% with GIK vs 88.7% with placebo (OR, 0.74; 95% CI, 0.40-1.38; *P*=.34); 30-day mortality was 4.9% with GIK vs 7.7% with placebo (HR, 0.63; 95% CI, 0.27-1.49; *P*=.29). The composite outcome of cardiac arrest or in-hospital mortality was 6.1% with GIK vs 14.4% with placebo (OR, 0.39; 95% CI, 0.18-0.82; *P*=.01). Serious adverse events occurred in 6.8% (n=28) with GIK vs 8.9% (n=41) with placebo (*P*=.26).

Conclusions Among patients with suspected ACS, out-of-hospital administration of intravenous GIK, compared with glucose placebo, did not reduce progression to MI. Compared with placebo, GIK administration was not associated with improvement in 30-day survival but was associated with lower rates of the composite outcome of cardiac arrest or in-hospital mortality.

Trial Registration clinicaltrials.gov Identifier: NCT00091507

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EXPERIMENTAL AND CLINICAL studies have shown intravenous glucose-insulin-potassium (GIK) to have 2 types of benefits in cardiac ischemic syndromes. One is protecting against myocardial injury by providing metabolic support to ischemic myocardium, which should limit progression of unstable angina pectoris to myocardial infarction (MI), lessen infarct size,

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